Stereocontrol by the Carbon-Fluorine Bond and Its Application to Asymmetric Synthesis of 3-Fluoro β-Lactams

John T. Welch,* Koichi Araki,† Robert Kawecki, and John A. Wichtowski

University at Albany, State University of New York, Albany, New York 12222

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Optically active 3-fluoro-β-lactams **4** and **5** were prepared via a ketene-imine cycloaddition reaction using fluoroacetyl chloride and an imine derived from (*R*)-glyceraldehyde acetonide. The high stereoselectivity observed can be rationalized as a consequence of stereoelectronic effects. Deprotonated β-lactams **4** and **12** were reacted with alkylating agents to give exclusively cis-3-alkyl-substituted derivatives of 3-fluoro β-lactams. The directed aldol reaction of β-lactams **4** and **12** with aldehydes and ketones provides *cis*-3-hydroxyalkyl derivatives with high stereoselectivity; however, diastereoisomeric control was not maintained at the hydroxylated carbon atom. The desired stereochemistry in the side chain was achieved by reduction of 3-acetyl-3-fluoro β-lactam **22**. The lithium enolates of β-lactams **4** and **12** have been investigated by low-temperature ^{19}F NMR studies.

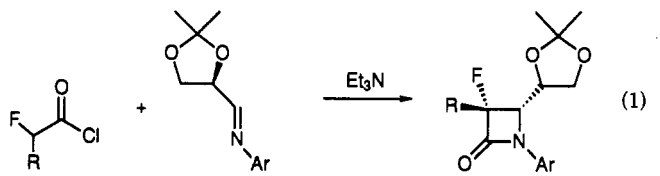
The need for ever more potent and effective β-lactam antibiotics as well as more effective adjuvant β-lactamase inhibitors has motivated synthetic chemists to prepare new functionalized azetidinones.[1] In spite of these efforts, relatively few approaches to the synthesis of fluorinated azetidinones have been reported.[2] These strategies usually depend upon fluorination of an intact β-lactam or involve synthesis of the fluorinated β-lactam molecule in a nonstereocontrolled manner from fluorinated building blocks. Fluorination strategies include reaction of 6-diazopenicillanate or 7-diazocephalosporinate with pyridinium polyhydrogen fluoride[2a,b] or with *N*-bromosuccinimide and tetrabutylammonium dihydrogen trifluoride.[2c] Fluorination of 6α-hydroxy derivatives was possible using (diethylamino)sulfur trifluoride,[2c] and only very recently, it was reported that 3-fluoroazetidinones are formed by the pyrolysis of fluorinated thiazolidinones, prepared via anodic fluorination with triethylamine-hydrogen fluoride.[2d] The building block approach has involved the cycloaddition of hexafluoropropene to nitrones to give a 3-fluoro-3-(trifluoromethyl) β-lactams,[2e] the cyclization of α,α-difluoro-β-bromopropionamides[2f] or β-hydroxyamides[2g] to form 3,3-difluoro-substituted β-lactams, or the Reformatsky reaction of methyl difluoroiodoacetate with imines.[2h] We have found that while ester α-fluoroenolates condense with imines to give 3-fluoro-2-azetidinones in moderate yield and in a nonstereoselective manner,[2i] the fluoroketene-imine condensation reaction is a highly stereoselective method for the preparation of cis-substituted fluoro β-lactams.[2i]

We now report the first highly enantioselective synthesis of 3-fluoro-substituted β-lactams via the fluoroketene-imine condensation reaction. Although the condensation of acid chlorides with imines to form β-lactams has been known since Staudinger's discovery,[3] the remarkable selectivity of this process with fluorinated ketenes was unanticipated. Previously, the synthesis of these materials in optically active form was very difficult or inefficient.[2]

Since β-lactams are useful optically active synthons,[4] the elaboration of the fluorinated azetidinone products by stereoselective alkylation and aldol reactions is also described. As reported here, 3-fluoro β-lactams may serve as versatile building blocks for the asymmetric synthesis of fluorinated sugars or amino acids whose importance in biological applications or materials science is well documented.[5]

Results and Discussion

Synthesis of the Optically Active 3-Fluoro β-Lactams. When fluoroacetyl chloride[6] (**1**) is allowed to react with optically active imine **3** obtained from *p*-anisidine and (*R*)-glyceraldehyde acetonide, a single diastereoisomer of 3-fluoro-2-azetidinone **4** is formed in 68% yield and in an ee not less than 99% (eq 1). The absolute stereochem-



(1)

1 R=H, **2** R=Ph; **3** Ar = 4-MeOPh; **4** R=H, **5** R=Ph

† Visiting Research Chemist, Mitsubishi Petrochemical Co.

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(3) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51-123.

(4) E.g.: Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770-774. Manhas, M. S.; Van der Veen, J. M.; Wagle, D. R.; Hedge, V. R.; Bari, S. S.; Kosarych, Z.; Ghosh, M.; Krishnan, L. *Ind. J. Chem.* **1986**, *25B*, 1095-1104 and references cited therein.

(5) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; J. Wiley: New York, 1991. (b) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, D.C., 1991. (c) Abeles, R. H.; Alston, T. A. *J. Biol. Chem.* **1990**, *265*, 16705-16708.

(6) **Caution**: Fluoroacetyl chloride and the sodium fluoroacetate used in its preparation are fatal poisons affecting the central nervous system causing epileptic convulsions. α-Fluorocarboxylic acid chlorides were handled with extreme caution in an efficient fume hood.

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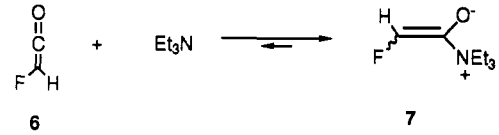
istry of this product was confirmed by single-crystal X-ray diffraction studies.

Both ketene cycloaddition to the imine or acylation of the imine followed by ring closure have been proposed as possible mechanisms for formation of 2-azetidinones by this process.[1a] Both of these proposals are supported by spectroscopic investigations.[7] Our attempts, as well as recent investigations by Dolbier,[8] to detect free fluoroketene (6) failed. Low-temperature ^{19}F NMR studies of a mixture of fluoroacetyl chloride and triethylamine indicated formation of a zwitterionic intermediate 7 that may be in equilibrium with free fluoroketene whose concentration is too low to be observable (eq 2). However,

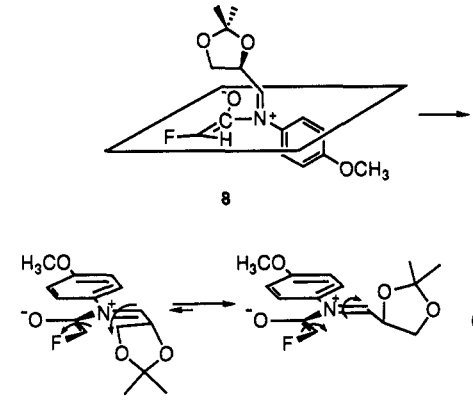


6 7 (2)

the formation of fluorocyclobutanones on treatment of cyclopentadiene[8,9] with 1, under the reaction conditions described above, clearly involves the reaction of fluoroketene, even if fluoroketene has only limited stability. Recent ab initio studies on the fluoroketene molecule seem to confirm the high destabilizing effect of fluorine.[10]

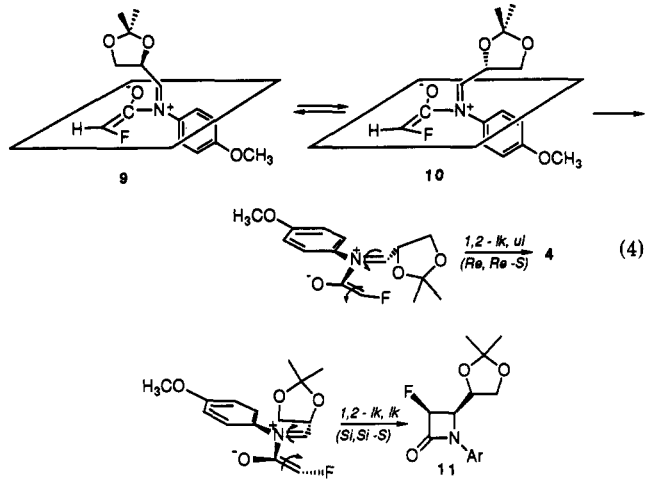
Although the reaction of the optically active aldimine derived from glyceraldehyde acetonide with α-substituted acid chlorides was reported nearly 10 years ago,[11] the origin of the outstanding stereocontrol associated with the reactions of this imine is still not clearly understood. β-Lactams bearing a variety of substituents at the C-3 carbon atom (e.g., azido, phthalimido, methoxy, phenoxy, benzyloxy, acetoxy, or allyloxy) have been formed with a cis configuration in the ring.[11,12] Despite the pronounced differences in steric demand by these substituents, diastereoisomeric excesses higher than 99% have been reported. In our case, the product also has cis stereochemistry; however, the lack of steric control elements in fluoroketene suggests rather that stereoelectronic effects are involved.

The high stereoselectivity observed may be rationalized as a consequence of the anti addition of the imine 3 to a single face of fluoroketene (6). The intermediate zwitterionic species 8 is postulated to collapse with 1,2-*lk,ul* topicity, i.e., antiperiplanar to the adjacent carbon–oxygen bond, via a conrotatory ring closure to form 4 for stereoelectronic reasons[11a] (eq 3). While a cycloaddition process with 1,2-*lk,ul* topicity is possible from the product of initial attack by the imine 3 syn to fluorine,[13] such an attack would require either the unlikely reaction of the *Z*-imine or rapid isomerization of the C–N double bond



(3)

in zwitterionic species 9 to form the reactive intermediate[14] 10 that may be stabilized by intramolecular hydrogen bonding[7c,15a] (eq 4). Since conrotatory ring closure under



(4)

stereoelectronic control can proceed from either of two equally likely conformations, as there are no apparent steric constraints, both cis diastereoisomers 11 and 4 should be formed. Our inability to detect the formation of 11 requires that each step of this process proceeds with excellent stereochemical control. The stereoselectivity of the ketene–imine cycloaddition is normally attributed to anti attack of the imine on a ketene bearing a sterically demanding substituent, e.g., alkyl, chloro, azido, phthalimido, etc.[15] While it is possible that this reaction may be exquisitely sensitive to steric effects, the nonsterically demanding nature of fluorine suggests that the stereochemical outcome of the investigated reaction is most likely controlled by stereoelectronic factors. The stereoselective formation of 3-fluoro-3-phenyl β-lactam 5 is in agreement with the suggested mechanism. The propensity for the reaction to proceed via anti attack on the fluoroketene may be an especially effective demonstration

(7) (a) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792–3796. (b) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, *34*, 3167–3170. (c) Bolognese, A.; Diurno, M. V.; Mazzoni, O.; Giordano, F. *Tetrahedron* **1991**, *47*, 7417–7428.

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(13) Attack syn to fluorine would be predicted by the proposals of Cieplak (see: Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447–8462. Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875–5876. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552) and would be consistent with the cycloaddition reactions of fluoroallene described by Dolbier (Dolbier, W. R., Jr. *Acc. Chem. Res.* **1991**, *24*, 65–69).

(14) This type of isomerization is priviledged for imines with a substituent on the sp^2 carbon atom that can stabilize positive charge (e.g., Ph, OMe, SMe).

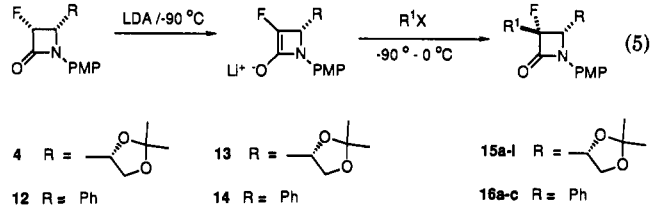
(15) Brady has suggested hydrogen bonding between the amino or the methoxy group from ketene and hydrogen attached to sp^2 carbon from imine in the zwitterion structure: (a) Brady, W. T.; Dad, M. M. *J. Org. Chem.* **1991**, *56*, 6118–6122. (b) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784–5791.

Table I. Stereoselective Alkylation of 3-Fluoro β-Lactams 4 and 12

entry	β-lactam	R^1X	product	yield, %
1	4	MeI	**15a**	99
2	12	MeI	**16a**	45
3	4	EtI	**15b**	78
4	4	$EtSO_3CF_3$	**15b**	46
5	12	EtI	**16b**	47
6	4	BnBr	**15c**	57
7	12	BnBr	**16c**	13
8	4	BuI	**15d**	56
9	4	*i*-PrI	**15e**	13
10	4	$CH_2{=}CHCH_2Br$	**15f**	80
11	4	$CH{\equiv}CCH_2Br$	**15g**	44
12	4	$BnOCH_2Cl$	**15h**	49
13	4	$MeOCH_2CH_2OCH_2Cl$	**15i**	38

of electrostatic effects or may be derived from secondary orbital interactions[16] which distort the LUMO of the fluoroketene[17] to favor reaction anti to fluorine. It is not possible to definitively exclude any mechanism, yet the selectivity of the process and the recognized difficulty in controlling enol or enolate geometry in the reactions of α-fluorinated carbonyl compounds argue against selective reactions of enolates that might be formed in stepwise processes.[18]

Alkylation of 3-Fluoro β-Lactams. The optically pure 3-fluoroazetidinone **4** as well as previously reported racemic 4-phenyl-substituted β-lactam **12**[2i] may be depro-



tonated with LDA at −90 °C and alkylated with no loss of stereochemical integrity at the fluorinated carbon as determined by ^{19}F NMR of the reaction mixture (see Table I). The yield varies depending on the nature of the alkylating agent.

The absolute stereochemistry of the products has been confirmed by single-crystal X-ray diffraction studies of **15c** followed by correlation with the fluorine–proton coupling constants of the remaining compounds. The vicinal coupling constant of fluorine to hydrogen at C-4 in cis-substituted products is very small (e.g., 3.4 Hz for **16a**) compared to the trans-β-lactam (12.0 Hz for *trans*-**16a**).

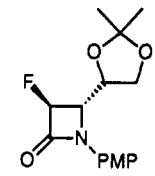
The alkylation reactions of fluorinated enolates[18a,b] and azaenolates[18c] previously have been found to lack stereoselectivity and efficiency even in those cases where control of enolate geometry is not problematic. In contrast to hydrocarbon chemistry, selective alkylation reactions were possible only when the fluorinated enolate benefited from additional stabilization such as that provided by sulphinyl[19] or phosphorus substitution.[20]

Table II. Aldol Reactions of 3-Fluoro β-Lactam 4[a]

entry	R^1	R^2	additive	products	diast ratio[b] 18:19	yield,[c] %
1	Me	H		**18a + 19a**	1:1.2	64
2	Et	H		**18b + 19b**	1:1.4	44
3	*i*-Pr	H		**18c + 19c**	1:1.4	33
4	*i*-Pr	H	$TiCl_4$	**18c + 19c**	1:1.3	30
5	*i*-Pr	H	$MgBr_2$	**18c + 19c**	1:1.3	35
6	*i*-Pr	H	$ZnCl_2$	**18c + 19c**	1:1.5	28
7	Ph	H		**18d + 19d**	1:1.5	45
8	*t*-Bu	H		**18e + 19e**	1:1.2	47
9	Me	Me		**18f**		85
10	Ph	Me		**18g + 19g**	1:3.7	44
11	$BuCH_2$	Me		**18h + 19h**	1:1.8	51

[a] Method A (see Experimental Section). [b] From ^{19}F NMR spectra of crude reaction mixture. [c] Isolated (not optimized) yield.

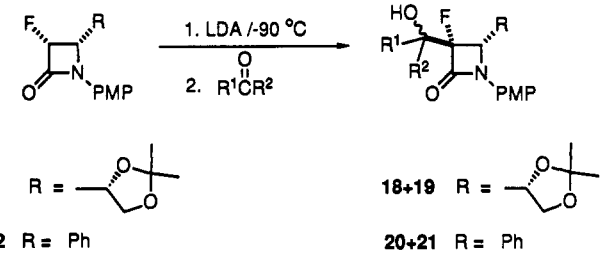
The very high stereoselectivity at C-3 in the ring is the result of the steric effects. The large substituent at C-4 directs electrophilic attack from the opposite face. Indeed, the trans diastereoisomer **17** was obtained with nonster-



17

ically demanding electrophiles such as D_2O or H_2O. Nevertheless, the cis–trans ratio was as high as 5:1 in this case. Further proof of the importance of steric interactions is illustrated by the methylation of the enolate of *trans*-3-fluoro β-lactam **17**, where the cis product **15a** is formed in more than 99% diastereoisomeric excess (de).[21]

Aldol Reaction of 3-Fluoro β-Lactams. The crucial 3-hydroxyalkyl side chain, as found in the important antibiotics thienamycin or carpetimycin,[22] can be introduced into 2-azetidinones by a directed aldol reaction of the lactam enolate.[23] When enolate **13**, generated by treatment of β-lactam **4** with LDA at −95 °C, was allowed to react with aldehydes or ketones, cis diastereoisomers **18** and **19** were obtained exclusively (Table II). Unfor-



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(17) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273–279.
(18) (a) Welch, J. T.; Eswarakrishnan, S.; Seper, K.; Samartino, J. S. *J. Org. Chem.* **1984**, *49*, 4720–4721. (b) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5403–5405. (c) Welch, J. T.; Seper, K. W. *J. Org. Chem.* **1988**, *53*, 2991–2999. (d) Welch, J. T.; Plummer, J. S.; Chou, T. S. *J. Org. Chem.* **1991**, *56*, 353–359. (e) Welch, J. T.; Yamazaki, T.; Plummer, J. S.; Gimi, R. *Tetrahedron Lett.* **1991**, *32*, 4267–4270.
(19) Bravo, P.; Resnati, G. *Tetrahedron Lett.* **1987**, *28*, 4865–4866.
(20) Burton, D. J.; Thenappan, A.; Yang, Z. Y. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, D.C., 1991; Chapter 7.
(21) The 3:1 mixture of cis and trans diastereoisomers, obtained by protonation of the enolate **13** and chromatography, was taken for this experiment.
(22) Ratcliffe, R. W.; Albers-Schonberg, G. The Chemistry of Thienamycin and Other Carbapenem Antibiotics. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 227–313.
(23) (a) DiNinno, F.; Beattie, T. R.; Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960–2965. (b) Hamlet, A. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 411–415. (c) Maruyama, H.; Hiraoka, T. *J. Org. Chem.* **1986**, *51*, 399–402. (d) Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1989**, *54*, 5736–5745. (e) Durst, T.; Sharma, M. K. *J. Org. Chem.* **1990**, *55*, 5525–5528.

Table III. Stereoselective Aldol Reaction of 3-Fluoro β-Lactam 12[a]

entry	R^1	R^2	products	diast ratio[b] 20:21	yield, %
1	Me	H	**20a + 21a**	1:1.3	52
2	Et	H	**20b + 21b**	1:2.0	67
3	Bu	H	**20c + 21c**	1:1.3	61
4	*i*-Pr	H	**20d + 21d**	1:1.1	70
5	Et_2CH	H	**20e + 21e**	1:1.2	63
6	*t*-Bu	H	**20f + 21f**	1:1.0	76
7	Ph	H	**20g + 21g**	1:1.1	52
8	Me	Me	**20h**		33
9	Et	Me	**20i + 21i**	1:1.6	51
10	*t*-Bu	Me	**20j + 21j**	1:57.0	73
11	$-(CH_2)_4-$		**20k**		69

[a] Method B (see Experimental Section). [b] From ^{19}F NMR spectra of crude reaction mixture.

tunately, the stereoselectivity in the side chain was poor even in the case of aldehydes with bulky substituents (entry 8, Table II). The racemic fluorolactam **12** was also utilized in aldol-type reactions with various carbonyl compounds (Table III). As in the case of the alkylation reactions, the aldol reactions proceeded with excellent diastereoselection with respect to the relative configuration at C-3 and C-4. The lack of stereocontrol at the newly formed hydroxy center suggests that this reaction might proceed through an extended open transition state in which there is no diastereofacial control of the approach of the aldehyde. The exchange of the lithium counterion for titanium, magnesium, or zinc did not influence the observed diastereoisomeric ratio (entries 4–6, Table II).

The relative stereochemistry between C-3 and C-4 of the product can be easily determined from ^{19}F NMR spectra. Only coupling (J_{HF} = 12–29 Hz) to hydrogen at C-1′ was observed (**18a–e**, **19a–e**), indicating cis substitution in the ring (the vicinal coupling constant of fluorine to the hydrogen at C-4 in the cis diastereoisomer was very small compared to the value for the trans derivative, vide supra).

Although the yields of the aforementioned aldol reactions were good as determined by the ^{19}F NMR spectra of the crude reaction mixture, isolation of analytically pure material was cumbersome in some cases.

The interesting reactivity of α-fluoro enolates **13** and **14** prompted us to investigate these species by NMR methods as there are only a few reports of such investigations of α-fluorocarbanions.[24] ^{19}F NMR spectrum of a THF solution of the enolate **13** recorded at −80 °C, showed two major peaks at δ −164 and −172 ppm ($CFCl_3$ ref) in a ratio of 1:1. Warming the carbanion solution resulted in broadening of the signal at δ −164 ppm until its disappearance at −35 °C. However, on recooling, this resonance reappeared (Figure 1). Behavior of this type, associated with disturbance of an equilibrium by temperature changes, has been postulated to exist between dimeric and tetrameric structures, with the dimers favored at low temperatures in THF solutions of organolithium compounds.[25] The signal at δ −172 ppm appeared to be a doublet with a 3-Hz coupling constant to hydrogen at C-4.

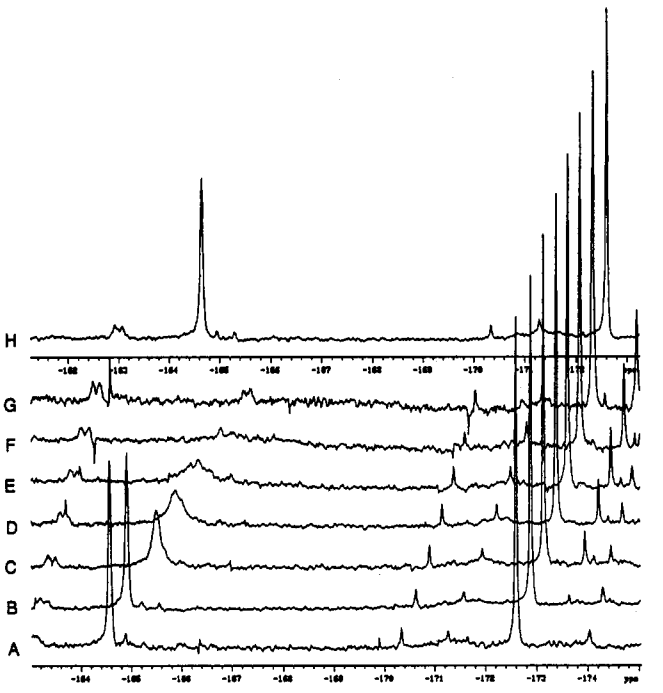
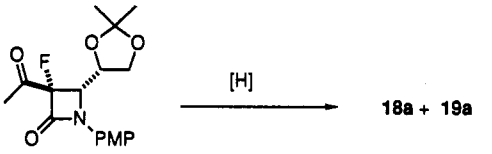


Figure 1. Low-temperature ^{19}F NMR spectra of the enolate **13** in THF solution: (A) −85 °C; (B) −80 °C; (C) −65 °C; (D) −60 °C; (E) −55 °C; (F) −45 °C; (G) −35 °C; (H) again −80 °C. Coupling constant to hydrogen at C-4 was not observed due to line broadening.

The ^7Li NMR spectrum of a THF solution of enolate **13** exhibited very broad resonances at 0.5 and 1.5 ppm (LiBr ref) presumably as a result of lithium exchange. Unfortunately, our attempts to obtain a ^{13}C NMR spectrum were hampered by low signal to noise ratios. The ^{19}F NMR spectrum of the enolate **14** at −80 °C exhibited a single resonance at δ −171 ppm. This signal was observed even after warming to −35 °C, but at temperatures greater than −65 °C additional resonances were detected. Interestingly, the alkylation and aldol reactions of 3-fluoro β-lactams were also cleaner and more efficient at temperatures below −65 °C.

Control of the stereochemistry in the side chain of 3-(hydroxyethyl) β-lactams was possible by stereoselective reduction[23b,d,e,26] of the 3-acetyl derivative **22** obtained by Swern oxidation of a mixture of the aldols **18a** and **19a**.[27]



22

Potassium tri-*sec*-butylborohydride (K-Selectride) (Aldrich), the reducing agent of choice for many 3-acetyl-

(24) ^{13}C NMR data of the carbanion obtained from fluoromethyl phenyl sulfoxide have been published: Najera, C.; Yus, M.; Hassig, R.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1100–1103. ^{19}F NMR data of the lithium enolate of *N,N*-dimethylfluoroacetamide was published by: Welch, J. T.; Eswarakrishnan, S. In *Fluorine-Containing Molecules. Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH Publishers: New York, 1988; p 135.

(25) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654. (b) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 6190–6198.

(26) (a) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208–2212. (b) Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V. *Tetrahedron* **1985**, *41*, 5871–5878. (c) Bateson, J. H.; Robins, A. M.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 29–35. (d) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129–1135. (e) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765–6767.

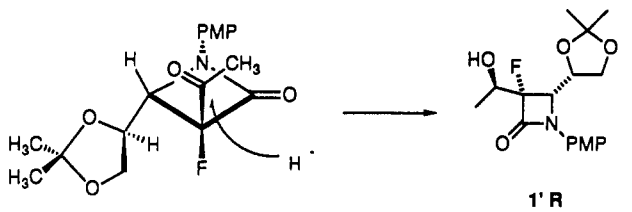
(27) Despite using different acetylating agents (acetic anhydride, acetyl chloride, ethyl acetate, *p*-nitrophenyl acetate) and bases (LDA, LHMDS) as well as employing an inverse addition procedure, all attempts at direct acetylation yielded complicated mixtures of byproducts.

Table IV. Stereoselective Reduction of 3-Acetyl-3-fluoro β-Lactam 22

entry	reducing agent	solvent	additive	temp, °C	diast ratio[a] 1′R:1′S	yield,[b] %
1	KBH(s-Bu)$_3$	THF		−78	4.0:1	41
2	KBH(s-Bu)$_3$	Et_2O	KI	25	1.7:1	31
3	LiBH(s-Bu)$_3$	THF		−78	8.7:1	47
4	LiBH(s-Bu)$_3$	THF		−95	12.0:1	29
5	i-Pr$_2$NEtBH$_3$	Et_2O	$Mg(CF_3CO_2)_2$	0	1:1.1	84
6	i-Pr$_2$NEtBH$_3$	THF	$ZnCl_2$	0	1.6:1	98
7	i-Pr$_2$NEtBH$_3$	THF	LiBr	0	2.9:1	85
8	LiBH(OEt)$_3$	THF		−78	6.0:1	85
9	LiBH(O-s-Bu)$_3$	THF		−78	6.5:1	77
10	LiAlH(O-t-Bu)$_3$	THF/Et_2O		−78	17.2:1	98[c]
11	$PhMe_2SiH$	CH_2Cl_2	$EtAlCl_2$	25	1:2.5	37

[a] From ^{19}F NMR spectra of crude reaction mixture after workup. [b] Calculated from ^{19}F NMR spectra (both diastereoisomers). [c] Isolated yield.

Scheme I



1′ R

substituted β-lactams,[26a,b] was ineffective in this case (Table IV). Even addition of potassium iodide did not improve diastereoselectivity. Lithium tri-*sec*-butylborohydride was much more stereoselective but the yield was not acceptable. Diisopropylethylamine–borane complex was not stereoselective even in the presence of magnesium, zinc, or lithium salts. Alkoxy-modified lithium borohydrides were efficient reducing agents, but the diastereomeric excesses observed were modest. The best result (89% de and 98% isolated yield) was achieved using commercially available lithium tri-*tert*-butoxyaluminohydride. Slow addition of the β-lactam solution was crucial for good stereoselectivity in this case. Recrystallization of the product from methylene chloride–hexane solution (2–3 times) yielded a single diastereoisomer.

The *R* configuration in the side chain was confirmed by single-crystal X-ray diffraction studies of the major diastereoisomer (after removal of the acetonide protection; compound **23**, see Experimental Section). According to the model proposed by Bouffard et al.,[26a] the stereochemical outcome of the reduction of **22** (entries 1–10, Table IV) was a result of a non-chelation-controlled reaction (Scheme I). Surprisingly, there was no difference in the sense of stereoselectivity using potassium and lithium tri-*sec*-butylborohydride, as is usually observed in such systems. A similar inconsistency was observed in the reduction of 3-acetyl-3-chloro β-lactam derivatives.[26c] This suggests that a halogen atom at C-3 dramatically changes the reactivity of such compounds.

Conclusions

The highly enantioselective formation of optically active 3-fluoro-2-azetidinones may be attributed to very efficient asymmetric induction in the ketene–imine cycloaddition reaction when fluoroacetyl chloride is treated with triethylamine in the presence of an imine derived from (*R*)-glyceraldehyde acetonide. This highly stereoselective process requires the reactive fluorinated intermediate to react very selectively in the absence of steric control elements. Alkylation and aldol reaction of 3-fluoro-β-lactams **4** and **12** give exclusively cis-substituted products. The optimized reduction of the 3-acetyl derivative **22** permits preparation of 1′*R* diastereoisomer **18a** in very good yield and 89% de. Studies of the use of 3-fluoro-β-lactams as optically active building blocks for the synthesis of fluorinated carbohydrates and amino acids are in progress and will be published elsewhere.

Experimental Section

^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 300, 75, and 282 MHz, respectively. ^{19}F NMR chemical shifts were referenced to $CFCl_3$. Low-temperature ^7Li NMR spectra were recorded at 117 MHz in THF solution with LiBr (1 M in THF) as an external standard. THF and diethyl ether were distilled from sodium in the presence of sodium benzophenone ketyl. Diisopropylamine was dried with calcium hydride. All aldehydes were distilled before use. Melting points were uncorrected. All reactions were carried out under an argon atmosphere. Lithium alkoxyborohydrides were freshly prepared from $LiBH_4$, and a stoichiometric amount of alcohol in THF at reflux (3 h). K- and L-Selectride (potassium or lithium tri-*sec*-butylborohydride) were purchased from Aldrich. Samples for low-temperature measurements were prepared in flame-dried 5-mm NMR tubes under an argon atmosphere in THF–C_6D_6 (10:1) solutions, using syringe techniques.

General Method for Ketene–Imine Condensation. To a dichloromethane solution (300 mL) of freshly prepared imine (147 mmol) and triethylamine (22.2 g, 220 mmol) was added dropwise a dichloromethane solution (30 mL) of α-fluorocarboxylic acid chloride (176 mmol) at room temperature with stirring. After overnight stirring, the reaction mixture was washed with water and saturated NaCl solution and dried with $MgSO_4$. Evaporation of the solvent gave solid that was recrystallized from ethanol (**4**, **12**) or purified by chromatography on silica gel (**5**).

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (4): yield 68%; mp 154–156 °C; $[\alpha]_D$ +77.9° (*c* = 1.5, $CHCl_3$); IR (KBr) 1749 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.55 (s, 3 H), 3.77–3.82 (m, 1 H), 3.80 (s, 3 H), 4.23–4.31 (m, 2 H), 4.40 (m, 1 H), 5.54 (dd, 1 H, *J* = 55.0, 5.0 Hz), 6.88 (m, 2 H), 7.66 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 26.7, 26.7, 55.5, 62.0 (d, *J* = 21.3 Hz), 66.6 (d, *J* = 6.5 Hz), 76.6 (d, *J* = 3.0 Hz), 90.3 (d, *J* = 221.3 Hz), 110.4, 114.1, 119.7, 130.5, 157.0, 160.4 (d, *J* = 22.2 Hz); ^{19}F NMR ($CDCl_3$) δ −202.1 (d, *J* = 55 Hz). Anal. Calcd for $C_{15}H_{18}FNO_4$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.87; H, 6.06; N, 4.71.

Crystal Data of 4.[28] $C_{15}H_{18}FNO_4$, orthorhombic, space group $P2_12_12_1$, *a* = 5.733(2) Å, *b* = 13.888(5) Å, *c* = 18.212(7) Å, *V* = 1450.1(9) Å^3, D_c = 1.353 g cm^{-3}, μ = 1.0 cm^{-1}, *Z* = 4, λ(Mo Kα) = 0.710 73 Å (graphite monochromator), *T* = 298 K. A Nicolet R3m/V diffractometer was used to collect 1992 reflections (0° < 2θ < 55°) on a colorless crystal, 0.15 × 0.15 × 0.80 mm^3. Of these, 1947 were unique and 854 observed ($|F_o| > 6\sigma|F_o|$). Lorentz and polarization correction factors were applied to the data. All the non-hydrogen atoms were located by direct methods. R = 0.051, R_w = 0.050, GOF = 1.549.

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-3-phenyl-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (5): yield 19%; mp 112–115 °C; $[\alpha]_D$ +75.2° (*c* = 1.5, $CHCl_3$); IR (KBr) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.53 (s, 3 H), 3.81 (s, 3 H), 3.86 (dd, 1 H, *J* = 6.4, 9.5 Hz), 4.3–4.4 (m, 2 H), 4.55 (m, 1 H), 6.91 (m, 2 H), 7.4–7.5 (m, 5 H), 7.76 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.0, 26.7, 55.5, 66.6 (d, *J* = 6.5 Hz), 69.0 (d, *J* = 25.2 Hz), 76.8 (d, *J* = 3.3 Hz), 100.7 (d, *J* = 219.5 Hz), 110.3, 114.2, 120.1, 125.3 (d, *J* = 8.7 Hz), 129.1, 129.9, 130.1 (d, *J* = 4.0 Hz), 133.4 (d, *J* = 22.9 Hz), 157.1, 161.5 (d, *J* = 25.5 Hz); ^{19}F NMR ($CDCl_3$) δ −167.1. Anal. Calcd for $C_{21}H_{22}FNO_4$: C, 67.92; H, 5.93; N, 3.77. Found: C, 67.93; H, 5.95; N, 3.72.

Crystal Data of 5.[28] $C_{21}H_{22}NO_4F$, orthorhombic space group $P2_12_12_1$, *a* = 6.248(3) Å, *b* = 7.863(6) Å, *c* = 39.46(4) Å, *V* = 1938(3) Å^3, D_c = 1.273 g cm^{-3}, μ = 0.9 cm^{-1}, *Z* = 4, λ(Mo Kα) = 0.710 73 Å (graphite monochromator), *T* = 298 K. A Nicolet R3m/V diffractometer was used to collect 2455 reflections (0° < 2θ < 55°) on a colorless crystal, 0.15 × 0.15 × 0.80 mm^3. Of these, 2402 were unique and 1164 observed ($|F_o| > 6\sigma|F_o|$). Lorentz and polarization correction factors were applied to the data. All the non-hydrogen atoms were located by direct methods. *R* = 0.088, R_w = 0.091, GOF = 3.51.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-4-phenyl-2-azetidinone (12)**: yield 78%; mp 166–168 °C; IR (KBr) 1742 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H), 5.27 (dd, 1 H, *J* = 5.1, 3.1 Hz), 5.70 (dd, 1 H, *J* = 5.1, 44.6 Hz), 6.82 (m, 2 H), 7.29 (m, 2 H), 7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 55.4, 61.5 (d, *J* = 23.1 Hz), 91.4 (d, *J* = 227.1 Hz), 114.5, 118.9, 127.7, 128.9, 129.2, 130.0, 131.9, 156.8, 160.5 (d, *J* = 23.8 Hz); ^{19}F NMR ($CDCl_3$) δ −199.2 (d, *J* = 44.6 Hz). Anal. Calcd for $C_{16}H_{14}FNO_2$: C, 70.85; H, 5.17; N, 5.17. Found: C, 70.71; H, 5.25; N, 5.02.

General Procedure for Alkylation of 3-Fluoro β-Lactams. To a solution of lithium diisopropylamide (3.4 mmol) in 10 mL of THF at −90 °C was added a THF solution (7 mL) of 3-fluoro β-lactam (1.76 mmol) at such a rate that the temperature did not exceed −85 °C. After 5 min, 3.2 mmol of the appropriate alkylating agent was added dropwise at −90 °C. The reaction mixture was allowed to warm gradually to 0 °C and was quenched with saturated ammonium chloride, followed by extraction with methylene chloride. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was then purified by silica gel chromatography (hexane–ethyl acetate).

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-3-methyl-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15a): yield 99%; mp = 114–115 °C; $[\alpha]_D$ +82.9° (*c* = 1.5, $CHCl_3$); IR (KBr) 1754 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.55 (s, 3 H), 1.71 (d, 3 H, *J* = 23.0 Hz), 3.78 (m, 1 H), 3.80 (s, 3 H), 4.01 (dd, 1 H, *J* = 3.9, 8.3 Hz), 4.28 (ddd, 1 H, *J* = 2.5, 6.5, 8.8 Hz), 4.37 (m, 1 H), 6.88 (m, 2 H), 7.68 (m, 2 H); ^{13}C NMR δ 18.9 (d, *J* = 26.7 Hz), 24.9, 26.7, 55.5, 66.5 (d, *J* = 4.6 Hz), 68.1 (d, *J* = 21.1 Hz), 76.7 (d, *J* = 3.0 Hz), 98.8 (d, *J* = 216.6 Hz), 110.2, 114.1, 119.8, 130.5 (d, *J* = 4.1 Hz), 156.9, 162.6 (d, *J* = 24.3 Hz); ^{19}F NMR ($CDCl_3$) δ −164.9 (q, *J* = 23.9 Hz). Anal. Calcd for $C_{16}H_{20}FNO_4$: C, 62.13; H, 6.52; N, 4.53. Found: C, 61.84; H, 6.64; N, 4.60.

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-ethyl-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15b): yield 78%; mp 112–114 °C; $[\alpha]_D$ +98.1° (*c* = 1.58, $CHCl_3$); IR (KBr) 1748 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, *J* = 7.7 Hz), 1.34 (s, 3 H), 1.53 (s, 3 H), 1.9–2.15 (m, 2 H), 3.74 (m, 1 H), 3.78 (s, 3 H), 4.03 (dd, 1 H, *J* = 3.6, 8.7 Hz), 4.24 (ddd, 1 H, *J* = 2.5, 6.2, 8.7 Hz), 4.36 (m, 1 H), 6.86 (m, 2 H), 7.66 (m, 2 H); ^{13}C NMR δ 7.32 (d, *J* = 5.9 Hz), 24.9, 26.0 (d, *J* = 26.2 Hz), 26.7, 55.4, 66.1 (d, *J* = 20.8 Hz), 66.6 (d, *J* = 6.5 Hz), 76.8 (d, *J* = 5.2 Hz), 101.4 (d, *J* = 221.1 Hz), 110.1, 114.1, 119.7, 130.6 (d, *J* = 2.1 Hz), 156.9, 162.6 (d, *J* = 26.1 Hz); ^{19}F NMR ($CDCl_3$) δ −172.58 (t, *J* = 28.5 Hz). Anal. Calcd for $C_{17}H_{22}FNO_4$: C, 63.14; H, 6.86; N, 4.33. Found: C, 62.97; H, 7.00; N, 4.29.

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-benzyl-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15c): yield 57%; mp 120 °C; $[\alpha]_D$ +187.2° (*c* = 2.0, $CHCl_3$); IR (KBr) 1752 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.41 (s, 3 H), 2.77 (dd, 1 H, *J* = 8.8, 6.8 Hz), 3.11 (dd, 1 H, *J* = 14.7, 32.0 Hz), 3.39 (t, 1 H, *J* = 14.7 Hz), 3.79 (s, 3 H), 3.86 (ddd, 1 H, *J* = 2.3, 8.8, 6.2 Hz), 4.08 (dd, 1 H, *J* = 3.9, 8.1 Hz), 4.24 (m, 1 H), 6.86 (m, 2 H), 7.25–7.36 (m, 5 H), 7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.5, 38.4 (d, *J* = 23.0 Hz), 55.5, 65.6 (d, *J* = 21.0 Hz), 76.5 (d, *J* = 3.1 Hz), 66.1 (d, *J* = 3.1 Hz), 100.4 (d, *J* = 221.3 Hz), 109.9, 114.1, 120.0, 128.0, 128.8, 130.2, 130.5 (d, *J* = 2.0 Hz), 133.1 (d, *J* = 3.1 Hz), 156.9, 162.4 (d, *J* = 24.3 Hz); ^{19}F NMR ($CDCl_3$) δ −169.7 (dd, *J* = 14.3, 32.0 Hz). Anal. Calcd for $C_{22}H_{24}FNO_4$: C, 68.54; H, 6.28; N, 3.64. Found: C, 68.51; H, 6.29; N, 3.48.

Crystal Data for 15c.[28] $C_{22}H_{24}FNO_4$, monoclinic $P2_1$, *a* = 6.374(1) Å, *b* = 20.099(3) Å, *c* = 8.023(2) Å, β = 91.13(2)°, *V* = 1027.6(3) Å^3, D_c = 1.246 g cm^{-3}, μ = 0.86 cm^{-1}, *Z* = 2, λ(Mo Kα) = 0.710 73 Å (graphite monochromator), *T* = 298 K. A Nicolet R3m/V diffractometer was used to collect 2657 reflections (0° < 2θ < 55°) on a colorless crystal, 0.15 × 0.25 × 0.30 mm^3. Of these, 2451 were unique and 1398 observed ($|F_o| > 6\sigma|F_o|$). Lorentz and polarization correction factors were applied to the data. All the non-hydrogen atoms were located by direct methods. *R* = 0.069, R_w = 0.072, GOF = 1.97.

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-butyl-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15d): yield 56%; mp 110–112 °C; $[\alpha]_D$ +81.0° (*c* = 1.68, $CHCl_3$); IR (KBr) 1749 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, *J* = 7.0 Hz), 1.2–1.6 (m, 4 H), 1.35 (s, 3 H), 1.55 (s, 3 H), 1.9–2.1 (m, 2 H), 3.77 (dd, 1 H, *J* = 6.3, 8.8 Hz), 3.79 (s, 3 H), 4.26 (ddd, 1 H, *J* = 2.5, 7.0, 8.8 Hz), 4.37 (m, 1 H, *J* = 1.5 Hz), 6.88 (m, 2 H), 7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.7, 24.9, 25.0, 26.7, 32.6 (d, *J* = 22.8 Hz), 55.5, 66.4 (d, *J* = 21.0 Hz), 66.6 (d, *J* = 5.0 Hz), 76.8 (d, *J* = 3.2 Hz), 101.0 (d, *J* = 219.5 Hz), 110.1, 114.1, 119.8, 130.6 (d, *J* = 2.0 Hz), 156.8, 162.7 (d, *J* = 24.0 Hz); ^{19}F NMR ($CDCl_3$) δ −170.9 (t, *J* = 21.2 Hz). Anal. Calcd for $C_{19}H_{26}FNO_4$: C, 64.94; H, 7.46; N, 3.99. Found: C, 64.87; H, 7.67; N, 3.85.

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-3-isopropyl-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15e): yield 13%; mp 104–106 °C; $[\alpha]_D$ +87.7° (*c* = 0.81, $CHCl_3$); IR (KBr) 1749 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.07 (d, 3 H, *J* = 6.8 Hz), 1.14 (d, 3 H, *J* = 6.9 Hz), 1.35 (s, 3 H), 1.54 (s, 3 H), 2.1–2.3 (m, 1 H), 3.80 (s, 3 H), 3.75 (dd, 1 H, *J* = 7.3, 9.1 Hz), 4.06 (dd, 1 H, *J* = 4.0, 8.3 Hz), 4.23 (ddd, 1 H, *J* = 2.4, 7.0, 9.1 Hz), 4.37 (m, 1 H), 6.87 (m, 2 H), 7.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, *J* = 5.5 Hz), 16.6 (d, *J* = 5.5 Hz), 16.6 (d, *J* = 5.9 Hz), 25.1, 26.7, 31.1 (d, *J* = 23.6 Hz), 55.5, 64.2 (d, *J* = 20.7 Hz), 66.7 (d, *J* = 5.0 Hz), 77.1 (d, *J* = 5.0 Hz), 103.4 (d, *J* = 223.6 Hz), 110.0, 114.1, 119.8, 130.4 (d, *J* = 4.0 Hz), 156.6; ^{19}F NMR ($CDCl_3$) δ −177.6 (d, *J* = 18.0 Hz). Anal. Calcd for $C_{18}H_{24}FNO_4$: C, 64.08; H, 7.17; N, 4.15. Found: C, 63.85; H, 7.03; N, 3.88.

(3*R*,4*S*,4′*S*)-3-Allyl-*N*-(*p*-anisyl)-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15f): yield 80%; mp 110 °C; $[\alpha]_D$ +107.4° (*c* = 1.75, $CHCl_3$); IR (KBr) 1752 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.52 (s, 3 H), 2.5–2.9 (m, 2 H), 3.7 (m, 1 H), 3.78 (s, 3 H), 4.06 (dd, 1 H, *J* = 4.0, 8.2 Hz), 4.22 (ddd, 1 H, *J* = 2.4, 6.7, 8.9 Hz), 4.36 (m, 1 H, *J* = 1.3 Hz), 5.26 (d, 1 H, *J* = 4.4 Hz), 5.30 (d, 1 H, *J* = 11.6 Hz), 5.7–5.9 (m, 1 H), 6.86 (m, 2 H), 7.66 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 26.5, 36.8 (d, *J* = 24.3 Hz), 55.3, 65.6 (d, *J* = 22.9 Hz, C-4), 66.5 (d, *J* = 4.9 Hz), 76.6 (d, *J* = 3.6 Hz), 99.8 (d, *J* = 221.3 Hz), 110.0, 113.9, 119.7, 121.3, 129.0 (d, *J* = 5.8 Hz), 130.3 (d, *J* = 4.0 Hz), 156.8, 162.0 (d, *J* = 24.5 Hz); ^{19}F NMR ($CDCl_3$) δ −170.5 (dd, *J* = 15.6, 29.5 Hz). Anal. Calcd for $C_{18}H_{22}FNO_4$: C, 64.45; H, 6.62; N, 4.18. Found: C, 64.32; H, 6.53; N, 4.11.

(3*R*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-3-propargyl-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15g): yield 44%; oil; $[\alpha]_D$ +122.5° (*c* = 1.73, $CHCl_3$); IR (KBr) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.55 (s, 3 H), 2.15 (t, 1 H, *J* = 2.5 Hz), 2.78–3.02 (m, 2 H), 3.79 (s, 3 H), 3.99 (dd, 1 H, *J* = 6.3, 8.9 Hz), 4.23–4.32 (m, 2 H), 4.35–4.41 (m, 1 H), 6.88 (m, 2 H), 7.67 (m, 2 H); ^{13}C-NMR δ 23.0 (d, *J* = 29.6 Hz), 25.0, 26.7, 55.5, 66.0 (d, *J* = 21.3 Hz), 66.6 (d, *J* = 5.1 Hz), 72.8, 75.8 (d, *J* = 8.9 Hz), 76.6 (d, *J* = 3.4 Hz), 98.4 (d, *J* = 225.7 Hz), 110.2, 114.1, 120.0, 130.1, 157.1, 161.0 (d, *J* = 24.6 Hz); ^{19}F NMR ($CDCl_3$) δ −169.9 (dd, *J* = 13.0, 24.5 Hz). Anal. Calcd for $C_{18}H_{20}FNO_4$: C, 64.86; H, 6.01; N, 4.20. Found: C, 64.71; H, 6.21; N, 4.05.

(3*S*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-[(benzyloxy)methyl]-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15h): yield 49%; mp 66–68 °C; $[\alpha]_D$ +72.1° (*c* = 1.97, $CHCl_3$); IR (KBr) 1750

(28) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.54 (s, 3 H), 3.7–4.0 (m, 3 H), 3.79 (s, 3 H), 4.2–4.3 (m, 2 H), 4.37 (m, 1 H), 4.58 (d, 1 H, J = 12.6 Hz), 4.65 (d, 1 H, J = 12.6 Hz), 6.88 (m, 2 H), 7.25–7.35 (m, 5 H), 7.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.7, 25.0, 55.5, 65.0 (d, J = 22.9 Hz), 66.6 (d, J = 5.1 Hz), 67.9 (d, J = 25.9 Hz), 74.0, 76.5 (d, J = 3.4 Hz), 99.8 (d, J = 222.5 Hz), 110.2, 114.1, 119.9, 127.8, 128.1, 128.6, 130.5 (d, J = 4.0 Hz), 137.0, 157.0, 160.3 (d, J = 25.0 Hz); ^{19}F NMR ($CDCl_3$) δ −178.2 (dd, J = 11.4, 28.4 Hz). Anal. Calcd for $C_{23}H_{26}FNO_5$: C, 66.48; H, 6.31; N, 3.37. Found: C, 66.41; H, 6.34; N, 3.36.

(3*S*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-3-[(2-methoxyethoxy)-methyl]-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (15i): yield 38%; oil; $[\alpha]_D$ +78.5° (c = 1.86, $CHCl_3$); IR (KBr) 1757 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.54 (s, 3 H), 3.34 (s, 3 H), 3.51–3.52 (m, 2 H), 3.66–3.8 (m, 4 H), 3.79 (s, 3 H), 3.90–3.97 (m, 2 H), 4.20–4.25 (m, 1 H), 4.3–4.4 (m, 2 H), 6.87 (m, 2 H), 7.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.0, 26.6, 55.4, 59.0, 64.8 (d, J = 21.2 Hz), 66.6 (d, J = 6.7 Hz), 69.4 (d, J = 26.1 Hz), 71.7, 71.9, 76.5 (d, J = 3.1 Hz), 99.9 (d, J = 222.1 Hz), 110.2, 114.0, 119.9, 130.5, 156.9, 160.8 (d, J = 23.3 Hz); ^{19}F NMR ($CDCl_3$) δ −178.2 (dd, J = 10.7, 28.0 Hz). Anal. Calcd for $C_{19}H_{26}FNO_6$: C, 59.53; H, 6.79; N, 3.66. Found: C, 59.37; H, 6.89; N, 3.66.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-methyl-4-phenyl-2-azetidinone (16a)**: yield 45%; mp 142–144 °C; IR (KBr) 1746 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.82 (d, 3 H, J = 21.8 Hz), 3.74 (s, 3 H), 4.99 (d, 1 H, J = 3.4 Hz), 6.81 (m, 2 H), 7.28 (m, 2 H), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.5 (d, J = 26.2 Hz), 55.4, 67.9 (d, J = 24.6 Hz), 99.4 (d, J = 221.3 Hz), 114.4, 118.9, 127.5, 128.8, 129.0, 130.1, 132.5, 156.6, 162.8 (d, J = 25.4 Hz); ^{19}F NMR ($CDCl_3$) δ −162.2 (q, J = 21.8 Hz). Anal. Calcd for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N, 4.90. Found: C, 71.26; H, 5.80; N, 4.64.

***cis*-*N*-(*p*-Anisyl)-3-ethyl-3-fluoro-4-phenyl-2-azetidinone (16b)**: yield 47%; mp 167–168 °C; IR (KBr) 1747 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3 H, J = 7.2 Hz), 2.10 (m, 2 H), 3.75 (s, 3 H), 5.03 (d, 1 H, J = 3.4 Hz), 6.80 (m, 2 H), 7.28 (m, 2 H), 7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 7.4 (d, J = 4.7 Hz), 25.9 (d, J = 23.8 Hz), 55.5, 66.3 (d, J = 24.4 Hz), 102.1 (d, J = 224.4 Hz), 114.4, 119.8, 127.5, 128.8, 128.9, 130.2, 132.7, 156.7, 162.8 (d, J = 25.3 Hz); ^{19}F NMR ($CDCl_3$) δ −171.1 (dd, J = 3.4 Hz). Anal. Calcd for $C_{18}H_{18}FNO_2$: C, 72.24; H, 6.02; N, 4.68. Found: C, 72.20; H, 6.07; N, 4.78.

***cis*-*N*-(*p*-Anisyl)-3-benzyl-3-fluoro-4-phenyl-2-azetidinone (16c)**: yield 13%; mp 172–174 °C; IR (KBr) 1744 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 3.30 (dd, 1 H, J = 29.2, 14.6 Hz), 3.50 (dd, 1 H, J = 15.2, 14.6 Hz), 3.74 (s, 3 H), 5.06 (d, 1 H, J = 4.2 Hz), 6.77 (d, 2 H), 6.96 (m, 3 H), 7.22 (m, 2 H), 7.27 (m, 2 H), 7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 38.4 (d, J = 24.2 Hz), 55.4, 65.2 (d, J = 24.4 Hz), 101.2 (d, J = 226.8 Hz), 114.4, 119.1, 127.3, 127.6, 128.6, 128.7, 130.0, 130.2, 132.3, 133.6, 156.7, 162.4 (d, J = 25.4 Hz); ^{19}F NMR ($CDCl_3$) δ −165.9 (dd, J = 29.2, 15.2 Hz). Anal. Calcd for $C_{23}H_{20}FNO_2$: C, 76.44; H, 5.58; N, 3.88. Found: C, 76.56; H, 5.73; N, 3.72.

Deuteriation of β-Lactam 4. The solution of β-lactam 4 (0.175 g, 0.6 mmol) in THF (2.5 mL) was added to the LDA (1.2 mmol) in THF (2.5 mL) at −100 °C. The reaction mixture was kept at this temperature for 5 min, and then 0.6 mL of water-d_2 (99.96% D) was added at −100 °C. After 5 min, the mixture was warmed to room temperature and 15 mL of benzene was added. The organic layer was separated, dried ($MgSO_4$), and evaporated to give 0.170 g crystals. ^{19}F NMR ($CDCl_3$) showed 75% of *cis*-3-deuterioazetidinone, δ −202.8 (br s), 6% of starting material 4, δ −202.1 (d, J = 55 Hz), and 16% of *trans*-3-deuterio-3-fluoroazetidinone 17, δ −197.5 (dt, J = 11 Hz). The same experiment was repeated with H_2O.

(3*S*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (17): ^{1}H NMR δ 1.31 and 1.36 (s, 3 H), 1.49 (s, 3 H), 3.79 (s, 3 H), 3.7–4.4 (m, 4 H), 5.33 (dd, J = 55.4, 1.5 Hz, 1 H), 6.87 (m, 2 H), 7.65 (m, 2 H); ^{13}C NMR δ 25.0, 26.6, 55.5, 62.4 (d, J = 24 Hz), 66.1 (d, J = 4 Hz), 76.6, 92.4 (d, J = 219 Hz), 110.8, 114.4, 120.1, 130.5, 157.0, 160.0 (d, J = 24 Hz); ^{19}F NMR δ −196.9 (dd, J = 55, 13 Hz).

General Procedure for Aldol Reaction of 3-Fluoro β-Lactams. Method A. *n*-Butyllithium (1.0 mL, 2.4 mmol, in hexane) was added to the solution of diisopropylamine (0.24 g, 2.4 mmol) in THF (5 mL) at −25 °C. This mixture was kept for 30 min at this temperature and cooled to −100 °C. The solution of β-lactam 4 (0.35 g, 1.2 mmol) in THF (6 mL) was added slowly at −95 °C. After 5 min, a solution of carbonyl compound (1.8 mmol) in THF (1.5 mL) was added at −95 °C. The reaction mixture was kept for 5 min at this temperature and quenched with saturated NH_4Cl solution. After being warmed to room temperature, the organic layer was separated and the water layer was extracted twice with methylene chloride. Organic extracts were dried with $MgSO_4$. Evaporation of the solvent often gave solid that was recrystallized from a methylene chloride–hexane solution. In other cases the crude products were purified by chromatography on silica gel using methylene chloride/methanol (100:1) as an eluant. Additives (see Table II) were added to enolate 13 as a solution (1.4 mmol in 6 mL of THF) at −95 °C.

Method B. To a THF solution (7 mL) of lithium diisopropylamide (1.5 mmol) at −90 °C was added 3-fluoro β-lactam 12 (0.75 mmol) in THF (6 mL) at such a rate that the temperature did not exceed −85 °C. After 5 min, an excess of the appropriate carbonyl compound (3.6 mmol) was added rapidly at −90 °C. The reaction mixture was allowed to warm gradually to room temperature and was quenched with saturated ammonium chloride, followed by extraction with methylene chloride. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was then purified by silica gel chromatography (dichloromethane–ethyl acetate).

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(1′-hydroxyethyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18a and 19a): yield 64%; mp 145–148 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) (1′*S*) δ 1.35 (s, 3 H), 1.45 (d, J = 6.0 Hz, 3 H), 1.53 (s, 3 H), 3.4 (br s, 1 H), 3.78 (s, 3 H), 3.85–4.40 (m, 5 H), 6.85 (m, 2 H), 7.64 (m, 2 H) and (1′*R*) 1.29 (d, J = 6.4 Hz, 3 H), 1.33 (s, 3 H), 1.51 (s, 3 H), 3.13 (br s, 1 H), 3.77 (s, 3 H), 3.86 (m, 1 H), 4.15–4.40 (m, 4 H), 6.86 (m, 2 H), 7.64 (m, 2 H); ^{13}C NMR (1′*R*) δ 17.0 (d, J = 6 Hz), 25.1, 26.6, 55.4, 62.9 (d, J = 21 Hz), 66.5 (d, J = 25 Hz), 66.6 (d, J = 4 Hz), 76.6 (d, J = 3 Hz), 102.3 (d, J = 221 Hz), 110.2, 114.1, 120.0, 130.2 (d, J = 4 Hz), 157.0, 161.6 (d, J = 23 Hz) and (1′*S*) 17.3 (d, J = 5 Hz), 19.2, 25.0, 55.4, 64.4 (d, J = 21 Hz), 66.4 (d, J = 25 Hz), 66.7 (d, J = 6 Hz), 76.6, 101.7 (d, J = 226 Hz), 110.1, 114.0, 120.0, 130.4 (d, J = 4 Hz), 156.9, 161.8 (d, J = 23 Hz); ^{19}F NMR (1′*R*) δ −177.3 (d, J = 12 Hz) and (1′*S*) −187.5 (d, J = 17 Hz). Anal. Calcd for $C_{17}H_{22}FNO_5$: C, 60.18; H, 6.49. Found: C, 59.99; H, 6.59.

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(1′-hydroxypropyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18b and 19b): yield 44%; mp 122–124 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^{1}H NMR δ 1.04 and 1.07 (t, J = 7.3 Hz, 3 H), 1.35 (s, 3 H), 1.53 (s, 3 H), 1.60 and 1.90 (m, 2 H), 2.6 (br s, 1 H), 3.85–4.40 (m, 5 H), 3.79 (s, 3 H), 6.86 (m, 2 H), 7.66 (m, 2 H); ^{13}C NMR δ 10.1, 23.7 (d, J = 7 Hz), 25.0, 26.6, 55.4, 63.3 (d, J = 21 Hz), 66.7 (d, J = 5 Hz), 72.0 (d, J = 24 Hz), 76.7, 102.3 (d, J = 223 Hz), 110.2, 114.1, 119.9, 130.2 (d, J = 4 Hz), 157.0, 161.6 (d, J = 23 Hz) and 10.1, 24.2 (d, J = 4 Hz), 25.1, 26.6, 55.4, 64.4 (d, J = 21 Hz), 66.7 (d, J = 5 Hz), 71.8 (d, J = 23 Hz), 76.7, 101.7 (d, J = 224 Hz), 110.1, 114.0, 120.0, 130.4 (d, J = 4 Hz), 156.9, 161.8 (d, J = 23 Hz); ^{19}F NMR δ −176.4 (d, J = 12 Hz) and −186.1 (d, J = 18 Hz). Anal. Calcd for $C_{18}H_{24}FNO_5$: C, 61.19; H, 6.80; N, 3.97. Found: C, 60.92; H, 6.83; N, 3.89.

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(1′-hydroxy-2′-methylpropyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18c and 19c): yield 33%; mp 118–121 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^{1}H NMR δ 1.05 (m) and 1.47 (d, J = 7.1 Hz, 6 H), 1.35 (s, 3 H), 1.52 and 1.53 (s, 3 H), 2.06 and 2.23 (m, 1 H), 2.2 (br s, 1 H), 3.65–4.40 (m, 5 H), 3.80 (s, 3 H), 6.87 (m, 2 H), 7.66 and 7.67 (m, 2 H); ^{13}C NMR δ 17.2 (d, J = 3 Hz), 19.2, 20.3 (d, J = 4 Hz), 25.1, 29.9 (d, J = 3 Hz), 55.5, 64.0 (d, J = 21 Hz), 66.5 (d, J = 7 Hz), 72.2 (d, J = 25 Hz), 76.7, 102.8 (d, J = 222 Hz), 110.1, 114.1, 119.9, 130.4 (d, J = 4 Hz), 156.9, 161.4 (d, J = 23 Hz) and 17.5, 20.4 (d, J = 4 Hz), 25.1, 26.6, 30.0, 55.5, 65.1 (d, J = 21 Hz), 66.7 (d, J = 5 Hz), 75.1 (d, J = 24 Hz), 76.7, 102.7 (d, J = 226 Hz), 110.0, 114.0, 120.0, 130.5 (d, J = 4 Hz), 156.9, 161.5 (d, J = 23 Hz); ^{19}F NMR δ −173.4 (d, J = 12 Hz) and −184.6 (d, J = 25 Hz). Anal. Calcd for $C_{19}H_{26}FNO_5$: C, 62.13; H, 7.08; N, 3.81. Found: C, 62.17; H, 7.08; N, 4.00.

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(1′-hydroxybenzyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18d and 19d): yield 45%; mp 176–177 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^1H NMR δ 1.24 (s, 3 H), 1.38 (s, 3 H), 2.44 (dd, *J* = 8.8, 7.4 Hz, 1 H), 3.25 (d, *J* = 4.8 Hz, 1 H), 3.78 (s, 3 H), 4.18 (m, 1 H), 4.32 (dd, *J* = 8.8, 4.4 Hz, 1 H), 5.19 (dd, *J* = 4.8, 10 Hz, 1 H), 6.83 (m, 2 H), 7.4 (m, 5 H), 7.64 (m, 2 H); ^{13}C NMR δ 25.2, 26.5, 55.4, 62.7 (d, *J* = 21 Hz), 65.7 (d, *J* = 5 Hz), 69.9 (d, *J* = 28 Hz), 76.3 (d, *J* = 3 Hz), 101.3 (d, *J* = 224 Hz), 109.8, 114.0, 120.0, 126.9, 128.4, 128.9, 130.3, 135.5 (d, *J* = 5 Hz), 156.9, 162.1 (d, *J* = 23 Hz); ^{19}F NMR δ −176.9 (d, *J* = 12 Hz). Second diastereoisomer: mp 158–162 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^1H NMR δ 1.31 (s, 3 H), 1.47 (s, 3 H), 3.0 (br s, 1 H), 3.54 (dd, *J* = 9.2, 6.8 Hz, 1 H), 3.75 (s, 3 H), 4.08 (m, 1 H), 4.13 (dd, *J* = 9.2, 3.7 Hz, 1 H), 4.33 (m, 1 H), 5.21 (d, *J* = 14.1 Hz, 1 H), 6.76 (m, 2 H), 7.3 (m, 5 H), 7.49 (m, 2 H); ^{13}C NMR δ 25.0, 26.6, 55.4, 63.0 (d, *J* = 21 Hz), 66.4 (d, *J* = 5 Hz), 72.9 (d, *J* = 24 Hz), 76.4 (d, *J* = 5 Hz), 101.7 (d, *J* = 226 Hz), 110.1, 113.9, 120.1, 126.9, 128.5, 129.0, 129.7 (d, *J* = 4 Hz), 135.5 (d, *J* = 65 Hz), 157.0, 161.3 (d, *J* = 24 Hz); ^{19}F NMR δ −178.1 (d, *J* = 17 Hz). Anal. Calcd for $C_{22}H_{24}FNO_5$: C, 65.84; H, 5.99; N, 3.49. Found: C, 65.61; H, 6.11; N, 3.35.

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(2′,2′-dimethyl-1′-hydroxypropyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18e and 19e): yield 47%; mp 133–136 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^1H NMR δ 1.08 and 1.11 (s, 9 H), 1.34 (s, 3 H), 1.50 and 1.52 (s, 3 H), 2.3 (br s, 1 H), 3.3–4.5 (m, 5 H), 3.80 (s, 3 H), 6.87 (m, 2 H), 7.65 and 7.66 (m, 2 H); ^{13}C NMR δ 25.2, 26.6, 26.9, 35.8, 55.45, 64.7 (d, *J* = 21 Hz), 66.6 (d, *J* = 3 Hz), 76.7, 77.8 (d, *J* = 24 Hz), 104.1 (d, *J* = 230 Hz), 109.8, 114.0, 120.0, 130.4, 156.9, 161.4 (d, *J* = 24 Hz) and 19.1, 25.1, 26.9, 35.2, 55.45, 64.6 (d, *J* = 21 Hz), 66.4 (d, *J* = 5 Hz), 76.8, 78.1 (d, *J* = 27 Hz), 103.7 (d, *J* = 223 Hz), 110.0, 114.1, 119.9, 130.4, 156.9, 161.2 (d, *J* = 23 Hz); ^{19}F NMR δ −171.2 (d, *J* = 6 Hz) and −182.8 (d, *J* = 29 Hz). Anal. Calcd for $C_{20}H_{28}FNO_5$: C, 62.99; H, 7.35; N, 3.67. Found: C, 62.82; H, 7.42; N, 3.65.

(3*S*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-fluoro-3-(2′-hydroxy-2′-propyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18f): yield 85%; mp 135–136 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^1H NMR δ 1.35 (s, 3 H), 1.37 (d, *J* = 2 Hz, 3 H), 1.53 (s, 3 H), 1.43 (d, *J* = 2.2 Hz, 3 H), 3.70 (br s, 1 H), 3.80 (s, 3 H), 3.8–4.4 (m, 4 H), 6.87 (m, 2 H), 7.67 (m, 2 H); ^{13}C NMR δ 23.9 (d, *J* = 6 Hz), 24.7 (d, *J* = 3 Hz), 25.1, 26.6, 55.4, 63.2 (d, *J* = 20 Hz), 66.7 (d, *J* = 6 Hz), 70.8 (d, *J* = 24 Hz), 76.9 (d, *J* = 3 Hz), 103.5 (d, *J* = 226 Hz), 110.0, 114.0, 119.9, 130.2 (d, *J* = 5 Hz), 156.9, 161.6 (d, *J* = 23 Hz); ^{19}F NMR δ −180.6. Anal. Calcd for $C_{18}H_{24}FNO_5$: C, 61.19; H, 6.80; N, 3.97. Found: C, 60.95; H, 7.00; N, 3.88.

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(1′-hydroxy-1′-phenylethyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18g and 19g): yield 44%; mp 166–168 °C; IR ($CHCl_3$) 1758 cm^{-1} (C=O); ^1H NMR δ 1.20 (s, 3 H), 1.29 (s, 3 H), 1.90 (s, 3 H), 2.70 (br s, 1 H), 3.77 (s, 3 H), 3.7–4.2 (m, 4 H), 6.82 (m, 2 H), 7.3–7.4 (m, 5 H), 7.64 (m, 2 H); ^{13}C NMR δ 23.7 (d, *J* = 5 Hz), 25.3, 26.4, 55.4, 62.9 (d, *J* = 21 Hz), 65.4 (d, *J* = 4 Hz), 72.9 (d, *J* = 25 Hz), 76.3 (d, *J* = 5 Hz), 103.1 (d, *J* = 228 Hz), 109.5, 113.9, 120.1, 126.0 (d, *J* = 4 Hz), 128.3, 128.4, 130.4 (d, *J* = 4 Hz), 141.7, 156.8, 162.0 (d, *J* = 23 Hz); ^{19}F NMR δ −177.7. **19g**: ^1H NMR δ 1.30 (s, 3 H), 1.44 (s, 3 H), 1.85 (s, 3 H), 3.32 (br s, 1 H), 3.69 (s, 3 H), 3.9–4.4 (m, 4 H), 6.70 (m, 2 H), 7.1–7.3 (m, 5 H), 7.59 (m, 2 H); ^{13}C NMR δ 24.2 (d, *J* = 4 Hz), 25.0, 26.5, 55.3, 63.5 (d, *J* = 21 Hz), 66.7 (d, *J* = 4 Hz), 74.5 (d, *J* = 22 Hz), 76.6 (d, *J* = 3 Hz), 103.5 (d, *J* = 228 Hz), 110.0, 113.7, 120.0, 125.9, 128.0, 128.1, 129.6 (d, *J* = 4 Hz), 139.9 (d, *J* = 4 Hz), 156.8, 161.6 (d, *J* = 24 Hz); ^{19}F NMR δ −180.4. Anal. Calcd for $C_{23}H_{26}FNO_5$: C, 66.51; H, 6.27; N, 3.37. Found: C, 66.47; H, 6.39; N, 3.38.

(1′*R*,3*S*,4*S*,4′*S*)- and (1′*S*,3*S*,4*S*,4′*S*)-*N*-(*p*-anisyl)-3-fluoro-3-(2′-hydroxy-2′-heptyl)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (18h and 19h): yield 51%; mp 126–128 °C; IR ($CHCl_3$) 1756 cm^{-1} (C=O); ^1H NMR δ 0.87 (t, *J* = 6.7 Hz, 3 H), 1.25–1.50 (m, 8 H), 1.35 (s, 3 H), 1.37 (d, *J* = 2.1 Hz, 3 H), 1.53 (s, 3 H), 1.81 (br s, 1 H), 3.80 (s, 3 H), 3.8–4.4 (m, 5 H), 6.88 (m, 2 H), 7.67 (m, 2 H); ^{13}C NMR δ 14.0, 20.9 (d, *J* = 6 Hz), 22.6, 25.2, 26.6, 26.7, 32.2, 35.4, 55.4, 63.1 (d, *J* = 23 Hz), 66.7 (d, *J* = 5 Hz), 72.7 (d, *J* = 23 Hz), 77.0 (d, *J* = 3 Hz), 104.3 (d, *J* = 226 Hz), 110.1, 114.0, 120.0, 130.2 (d, *J* = 4 Hz), 156.9, 161.8 (d, *J* = 23 Hz) and 14.1, 19.2, 20.4 (d, *J* = 3 Hz), 22.2, 25.2, 26.6, 32.3, 36.3 (d, *J* = 5 Hz), 55.4, 63.1 (d, *J* = 23 Hz), 66.7 (d, *J* = 5 Hz), 72.7 (d, *J* = 28 Hz), 77.0 (d, *J* = 3 Hz), 104.4 (d, *J* = 227 Hz), 110.1, 114.0, 120.0, 130.2 (d, *J* = 4 Hz), 156.9, 161.9 (d, *J* = 23 Hz); ^{19}F NMR δ −179.7 and −180.9. Anal. Calcd for $C_{22}H_{32}FNO_5$: C, 64.55; H, 7.82; N, 3.42. Found: C, 64.61; H, 7.96; N, 3.41.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(1′-hydroxyethyl)-4-phenyl-2-azetidinone (20a and 21a)**: yield 52%; mp 106–108 °C; IR (KBr) 1754 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.42 (d, *J* = 6.3 Hz) and 1.44 (d, 3 H, *J* = 5.9 Hz), 3.0 and 3.1 (br s, 1 H), 3.73 (s, 3 H), 4.32 (m, 1 H), 5.31 (d, *J* = 3.3 Hz) and 5.40 (d, 1 H, *J* = 4.1 Hz), 6.78 and 6.80 (m, 2 H), 7.27 and 7.28 (m, 2 H), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.9 (d, *J* = 4.9 Hz) and 17.4, 55.3, 62.65 (d, *J* = 22.6 Hz) and 63.2 (d, *J* = 24.5 Hz), 66.2 (d, *J* = 28.5 Hz) and 67.1 (d, *J* = 27.5 Hz), 102.6 (d, *J* = 226.2 Hz) and 102.8 (d, *J* = 225.3 Hz), 114.3 and 114.4, 119.0 and 119.1, 127.6, 128.7, 128.8 and 128.85, 129.7 and 129.9, 132.3 and 132.4, 156.7 and 156.7, 161.4 (d, *J* = 24.1 Hz) and 161.82 (d, *J* = 22.7 Hz); ^{19}F NMR ($CDCl_3$) δ −176.15 (d, *J* = 11.8 Hz) and −181.2 (d, *J* = 17.9 Hz). Anal. Calcd for $C_{18}H_{18}FNO_3$: C, 68.56; H, 5.75; N, 4.44. Found: C, 68.32; H, 6.00; N, 4.42.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(1′-hydroxypropyl)-4-phenyl-2-azetidinone (20b and 21b)**: yield 67%; mp 108–112 °C; IR (KBr) 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.3 Hz) and 1.09 (t, 3 H, *J* = 6.8 Hz), 1.63 and 1.78 (m, 2 H), 3.01 (d, *J* = 4.9 Hz) and 3.26 (d, *J* = 6.8 Hz), 3.73 (s, 3 H), 4.04 (m, 1 H), 5.32 (d, *J* = 3.3 Hz) and 5.41 (d, 1 H, *J* = 3.1 Hz), 6.78 and 6.79 (m, 2 H), 7.27 and 7.28 (m, 2 H), 7.37 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.1 and 10.3, 24.1 (d, *J* = 3.6 Hz) and 24.5, 55.4, 63.1 (d, *J* = 22.6 Hz) and 63.3 (d, *J* = 22.8 Hz), 71.4 (d, *J* = 26.9 Hz) and 72.4 (d, *J* = 26.3 Hz), 102.7 (d, *J* = 226.4 Hz) and 102.9 (d, *J* = 227.0 Hz), 114.4 and 114.5, 119.1 and 119.2, 127.7 and 127.8, 128.8, 128.8 and 128.9, 129.9 and 130.0, 132.4 and 132.5, 156.8 and 156.8, 161.6 (d, *J* = 24.0 Hz) and 162.2 (d, *J* = 24.7 Hz); ^{19}F NMR ($CDCl_3$) δ −175.4 (d, *J* = 11.8 Hz) and −180.1 (d, *J* = 12.5 Hz). Anal. Calcd for $C_{19}H_{20}FNO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.06; H, 6.32; N, 4.10.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(1′-hydroxypentyl)-4-phenyl-2-azetidinone (20c and 21c)**: yield 61%; mp 92–96 °C; IR (KBr) 1754 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, *J* = 7.1 Hz), 1.40 (m, 2 H), 1.66 (m, 2 H), 1.98 (d, *J* = 5.0 Hz) and 2.10 (d, 1 H, *J* = 7.3 Hz), 3.76 (s, 3 H), 4.13 (m, 1 H), 5.28 (d, *J* = 3.9 Hz) and 5.36 (d, 1 H, *J* = 4.0 Hz), 6.80 and 6.82 (m, 2 H), 7.27 and 7.29 (m, 2 H), 7.38 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.4 and 22.4, 27.7 and 27.8, 30.4 (d, *J* = 5.7 Hz) and 30.9, 55.4, 63.0 (d, *J* = 24.4 Hz) and 63.5 (d, *J* = 24.4 Hz), 70.7 (d, *J* = 27.1 Hz) and 71.3 (d, *J* = 26.4 Hz), 102.5 (d, *J* = 226.4 Hz) and 102.8 (d, *J* = 225.6 Hz), 114.4 and 114.5, 119.1, 127.7, 128.8, 128.9 and 129.0, 129.9 and 130.0, 132.3 and 132.4, 156.7 and 156.8, 161.3 (d, *J* = 25.8 Hz) and 161.6 (d, *J* = 24.2 Hz); ^{19}F NMR ($CDCl_3$) δ −174.88 (d, *J* = 18.3 Hz) and −179.83 (d, *J* = 12.9 Hz). Anal. Calcd for $C_{21}H_{24}FNO_3$: C, 70.57; H, 6.77; N, 3.92. Found: C, 70.48; H, 6.60; N, 3.86.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(1′-hydroxy-2′-methylpropyl)-4-phenyl-2-azetidinone (20d and 21d)**: yield 70%; mp 122–123 °C; IR (KBr) 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.01 (d, *J* = 7.2 Hz) and 1.03 (d, *J* = 6.9 Hz) and 1.06 (d, *J* = 6.8 Hz) and 1.08 (d, 6 H, *J* = 6.9 Hz), 2.13 (m, 1 H, m), 2.69 (d, *J* = 6.0 Hz) and 2.81 (d, 1 H, *J* = 7.3 Hz), 3.73 and 3.74 (s, 3 H), 3.90 (ddd, *J* = 6.0, 6.0, 14.5 Hz) and 3.99 (ddd, 1 H, *J* = 6.0, 7.3, 12.6 Hz), 5.28 (d, *J* = 4.1 Hz) and 5.43 (d, 1 H, *J* = 4.7 Hz), 6.76 (d, *J* = 9.4 Hz) and 6.79 (d, 2 H, *J* = 9.4 Hz), 7.25 and 7.28 (m, 2 H), 7.38 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.5 and 18.0, 19.7 and 20.0, 30.1 and 30.2, 55.4, 63.7 (d, *J* = 24.8 Hz) and 64.3 (d, *J* = 23.2 Hz), 74.1 (d, *J* = 28.0 Hz) and 76.4 (d, *J* = 24.8 Hz), 102.8 (d, *J* = 228.7 Hz) and 103.1 (d, *J* = 228.8 Hz), 114.4 and 114.5, 119.1 and 119.2, 128.1 and 128.3, 128.8 and 128.8, 129.0 and 129.1, 129.9, 132.3 and 132.5, 156.7 and 156.8, 161.7 (d, *J* = 25.7 Hz) and 162.3 (d, *J* = 24.6 Hz); ^{19}F NMR ($CDCl_3$) δ −177.40 (d, *J* = 14.5 Hz) and −178.25 (d, *J* = 12.6 Hz). Anal. Calcd for $C_{20}H_{22}FNO_3$: C, 69.95; H, 6.46; N, 4.08. Found: C, 70.19; H, 6.66; N, 3.83.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(1′-hydroxy-2′-ethylbutyl)-4-phenyl-2-azetidinone (20e and 21e)**: yield 63%; mp = 133–136 °C; IR (KBr) 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz) and 0.91 and 0.93 (t, *J* = 7.9 Hz) and 0.94 (t, 6 H, *J* = 7.4 Hz), 1.48 (m) and 1.69 (m, 5 H), 2.69 (d, *J* = 6.6 Hz) and

2.44 (d, 1 H, J = 7.4 Hz), 3.73 and 3.74 (s, 3 H), 4.14 (ddd, J = 6.6, 6.6, 17.3 Hz) and 4.22 (ddd, 1 H, J = 6.6, 7.4, 14.6 Hz), 5.25 (d, J = 4.0 Hz) and 5.45 (d, 1 H, J = 4.7 Hz), 6.78 and 6.79 (m, 2 H), 7.26 and 7.27 (m, 2 H), 7.39 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.1 and 11.2 and 11.4, 20.5 and 20.8, 21.8 and 22.2, 42.3 and 42.4, 55.4, 63.9 (d, J = 22.7 Hz) and 64.4 (d, J = 22.9 Hz), 71.2 (d, J = 24.5 Hz) and 73.0 (d, J = 25.0 Hz), 103.0 (d, J = 229.9 Hz) and 103.3 (d, J = 228.7 Hz), 114.4 and 114.5, 119.1 and 119.2, 128.0 and 128.2, 128.8 and 128.8, 129.0 and 129.1, 129.9 and 130.0, 132.3 and 132.6, 156.7 and 156.8, 161.6 (d, J = 24.2 Hz) and 162.16 (d, J = 24.2 Hz); ^{19}F NMR ($CDCl_3$) δ −178.14 (d, J = 17.3 Hz) and −178.58 (d, J = 14.6 Hz). Anal. Calcd for $C_{22}H_{26}FNO_3$: C, 71.13; H, 7.06; N, 3.77. Found: C, 70.74; H, 6.78; N, 3.73.

***cis*-*N*-(*p*-Anisyl)-3-(2′,2′-dimethyl-1′-hydroxypropyl)-3-fluoro-4-phenyl-2-azetidinone (20f and 21f)**: yield 76%; mp = 186–192 °C; IR (KBr) 1724 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.05 and 1.10 (s, 9 H), 2.94 (br s, 1 H), 3.72 (s, 3 H), 3.86 (dd, J = 22.3, 2.4 Hz) and 3.94 (dd, 1 H, J = 10.3, 6.4 Hz), 5.28 (d, J = 4.1 Hz) and 5.50 (d, 1 H, J = 4.4 Hz), 6.76 and 6.78 (m, 2 H), 7.24 and 7.25 (m, 2 H), 7.38 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 26.9, 26.9, 27.0 and 27.0, 35.5 (d, J = 2.1 Hz) and 35.7, 55.4, 63.72 (d, J = 23.3 Hz) and 65.4 (d, J = 23.0 Hz), 76.0 (d, J = 26.9 Hz) and 79.1 (d, J = 24.3 Hz), 103.4 (d, J = 234.4 Hz) and 104.0 (d, J = 229.8), 114.4, 119.22, 128.6 and 128.7, 128.8, 129.0 and 129.2, 129.8 and 123.0, 132.1 and 132.6, 156.7 and 156.8, 162.0 (d, J = 25.4 Hz) and 162.7 (d, J = 24.2 Hz); ^{19}F NMR ($CDCl_3$) δ −179.46 (d, J = 22.0 Hz) and −175.88 (d, J = 10.3 Hz). Anal. Calcd for $C_{21}H_{24}FNO_3$: C, 70.75; H, 6.77; N, 3.92. Found: C, 70.34; H, 6.64; N, 3.84.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(hydroxyphenylmethyl)-4-phenyl-2-azetidinone (20g and 21g)**: yield 52%; IR (KBr) 1741 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.89 (d, J = 3.6 Hz) and 3.22 (d, 1 H, J = 5.1 Hz), 3.72 and 3.74 (s, 3 H), 5.32 (d, J = 8.1 Hz) and 5.34 (d, 1 H, J = 9.0 Hz), 5.20 (d, J = 3.3 Hz) and 5.38 (d, 1 H, J = 3.6 Hz), 6.62–6.96 (m, 3 H), 7.06–7.72 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 55.0 and 55.1, 61.7 (d, J = 23.1 Hz) and 62.3 (d, J = 24.7 Hz), 69.3 (d, J = 29.8 Hz) and 72.2 (d, J = 26.2 Hz), 67.0 (d, J = 30.2 Hz), 102.2 (d, J = 226.8 Hz) and 102.6 (d, J = 227.4 Hz), 113.9 and 114.0, 118.7, 125.5, 126.6 (d, J = 4.0 Hz), 127.0, 127.2, 127.3, 127.4, 127.8, 128.0, 128.1, 128.3, 128.4, 129.4 and 129.9, 132.1, 132.4, 137.1 and 137.2, 138.4, 156.2, 161.0 (d, J = 23.9 Hz) and 163.0 (d, J = 24.4); ^{19}F NMR ($CDCl_3$) δ −173.59 and −175.16 (d, J = 9.0 Hz). Anal. Calcd for $C_{23}H_{20}FNO_3$: C, 73.20; H, 5.34; N, 3.71. Found: C, 72.93; H, 5.45; N, 3.47.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(2′-hydroxy-2′-propyl)-4-phenyl-2-azetidinone (20h)**: yield 33%; mp 181–182 °C; IR (KBr) 1735 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.52 (s, 3 H), 2.24 (s, 1 H), 3.74 (s, 3 H), 5.40 (d, 1 H, J = 3.6 Hz), 6.79 (m, 2 H), 7.28 (m, 2 H), 7.37 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 24.6, 55.4, 62.7 (d, J = 24.2), 71.1 (d, J = 25.2 Hz), 104.3 (d, J = 228.5 Hz), 114.4, 119.1, 127.8, 128.8, 128.8, 129.9, 132.7, 156.6, 161.62 (d, J = 24.1 Hz); ^{19}F NMR ($CDCl_3$) δ −176.4. Anal. Calcd for $C_{19}H_{20}FNO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.41; H, 6.12; N, 4.16.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(2′-hydroxy-2′-butyl)-4-phenyl-2-azetidinone (20i and 21i)**: yield 51%; mp 134–136 °C; IR (KBr) 1736 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 6.5 Hz) and 1.04 (t, 3 H, J = 6.7 Hz), 1.26 (br s, 1 H), 1.36 (d, J = 2.2 Hz) and 1.48 (d, 3 H, J = 2.1 Hz), 1.79 and 2.00 (m, 2 H), 3.76 (s, 3 H), 5.40 (d, J = 4.7 Hz) and 5.41 (d, 1 H, J = 4.9 Hz), 6.81 (m, 2 H), 7.28 (m, 2 H), 7.39 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 7.0, 20.4 (d, J = 1.8 Hz) and 20.5 (d, J = 1.9 Hz), 28.8 and 29.3, 55.4, 62.7 (d, J = 22.8 Hz) and 62.9 (d, J = 22.7 Hz), 73.3 (d, J = 25.6 Hz) and 73.4 (d, J = 23.8 Hz), 105.0 (d, J = 230.2 Hz) and 105.1 (d, J = 229.7 Hz), 114.4, 119.1, 127.9, 128.8, 128.9, 130.00, 132.7, 156.7, 161.6 (d, J = 24.2 Hz) and 161.8 (d, J = 23.5 Hz); ^{19}F NMR ($CDCl_3$) δ −176.16 and −176.69. Anal. Calcd for $C_{20}H_{22}FNO_3$: C, 69.95; H, 6.46; N, 4.08. Found: C, 69.77; H, 6.44; N, 4.05.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(2′-hydroxy-3′,3′-dimethyl-2′-butyl)-4-phenyl-2-azetidinone (20j and 21j)**: yield 73%; mp 204–206 °C; IR (KBr) 1732 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.39 (s, 3 H), 2.24 (s, 1 H), 3.73 (s, 3 H), 5.38 (d, 1 H, J = 4.3 Hz), 6.78 (m, 2 H), 7.26 (m, 2 H), 7.39 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.4, 26.7, 26.7, 38.3 (d, J = 2.1 Hz), 55.4, 64.3 (d, J = 24.6), 77.6 (d, J = 25.2 Hz), 107.4 (d, J = 233.3 Hz), 114.4, 119.2, 128.7, 129.1, 129.7, 132.6, 156.7, 161.6 (d, J = 25.6 Hz); ^{19}F NMR ($CDCl_3$) δ −170.9. Anal. Calcd for $C_{22}H_{26}FNO_3$: C, 71.14; H, 7.06; N, 3.77. Found: C, 67.59; H, 6.90; N, 3.53.

***cis*-*N*-(*p*-Anisyl)-3-fluoro-3-(1′-hydroxycyclopentyl)-4-phenyl-2-azetidinone (20k)**: yield 69%; mp 184–185 °C; IR (KBr) 1736 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 2 H), 1.85 (m, 4 H), 2.03 (m, 2 H), 2.31 (s, 1 H), 3.73 (s, 3 H), 5.37 (d, 1 H, J = 4.0 Hz), 6.78 (m, 2 H), 7.28 (m, 2 H), 7.38 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.4, 35.4 (d, J = 3.3 Hz), 35.9, 55.4, 63.7 (d, J = 22.7), 81.7 (d, J = 25.2 Hz), 103.7 (d, J = 228.3 Hz), 114.4, 119.0, 127.7, 128.7, 128.7, 129.9, 132.7, 156.6, 161.7 (d, J = 22.5 Hz); ^{19}F NMR ($CDCl_3$) δ −175.44. Anal. Calcd for $C_{21}H_{22}FNO_3$: C, 70.97; H, 6.24; N, 3.94. Found: C, 70.89; H, 6.31; N, 3.86.

(3*S*,4*S*,4′*S*)-*N*-(*p*-Anisyl)-3-acetyl-3-fluoro-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-azetidinone (22). Swern oxidation of the mixture of diastereoisomers **18a** and **19a** was performed under standard conditions[29] at −50 °C. Chromatography of the crude product on silica gel (methylene chloride/methanol (100:1)) gave pure compound **22**: yield 66%; mp 76–78 °C; $[\alpha]_D$ −5.9° (c = 1.3, $CHCl_3$); IR ($CHCl_3$) 1764, 1726 cm^{-1} (C=O); ^{1}H NMR δ 1.36 (s, 3 H), 1.53 (s, 3 H), 2.43 (d, J = 4.4 Hz, 3 H), 3.64 (m, 1 H), 3.80 (s, 3 H), 4.26 (m, 1 H), 4.41 (m, 1 H), 4.55 (dd, J = 3.2, 8.3 Hz, 1 H), 6.89 (m, 2 H), 7.64 (m, 2 H); ^{13}C NMR δ 25.0, 26.4, 26.5, 55.4, 63.8 (d, J = 20 Hz), 66.6 (d, J = 5 Hz), 76.0, 101.9 (d, J = 235 Hz), 110.7, 114.2, 120.1, 129.9, 157.3, 157.7 (d, J = 24 Hz), 199.1 (d, J = 29 Hz); ^{19}F NMR δ −177.9. Anal. Calcd for $C_{17}H_{20}FNO_5$: C, 60.53; H, 5.93; N, 4.15. Found: C, 60.50; H, 6.04; N, 4.12.

Reduction of 3-Acetyl-3-fluoro β-Lactam 22. Reactions were carried out on a 0.15 mmol scale. Conditions are detailed in Table IV. Standard workup (quenching with water, extraction with methylene chloride, drying with $MgSO_4$) was used.

Crystal Structure of 23.[28] Compound **18a** was purified by crystallization (three times), and the acetonide protection was removed. Crystals of the triol were grown from a chloroform, benzene, and methanol mixture. Crystal data: $C_{14}H_{18}FNO_5$, M = 299.3, monoclinic, space group $P2_1$, a = 6.053(2) Å, b = 7.922(4) Å, c = 15.330(6) Å, β = 99.27(3)°; V = 725.5 Å^3, Z = 2, D_c = 1.370 g cm^{-1}, μ = 1.1 cm^{-1}, λ(Mo Kα) = 0.710 73 Å, F(000) = 316, T = 298 K. A Nicolet R3m/V diffractometer was used to collect 1879 reflections ($3° < 2\theta < 55°$) on a colorless crystal 0.15 × 0.20 × 0.80 mm^3. Of these, 1789 were unique and 1298 were observed ($|F_o| > 6\sigma|F_o|$). Lorentz and polarization correction factors were applied to the data. The non-hydrogen atoms were located by direct methods. R = 0.058, R_w = 0.062, GOF = 2.125.

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