Asymmetric Fluorination of Enolates with Nonracemic *N*-Fluoro-2,10-Camphorsultams

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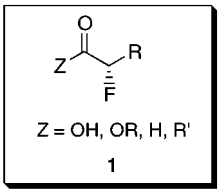
The asymmetric "electrophilic" fluorination of tertiary enolates by nonracemic *N*-fluoro-2,10-camphorsultams **3** affords quaternary α-fluoro carbonyl compounds in modest yield and ee. The highest asymmetric induction was observed for the fluorination of the sodium enolate of 2-methyl-1-tetralone (**8a**) by (−)-*N*-fluoro-2,10-(3,3-dichlorocamphorsultam) (**3b**) to give (*S*)-(+)-2-fluoro-2-methyl-1-tetralone (**9a**) in 70% ee. The absolute configuration was established by X-ray crystallography of the corresponding diastereomeric *β*-hydroxy sulfoximine prepared from (±)-**9a** and the Johnson reagent. The asymmetric induction exhibited by **3** is opposite to that of the closely related enolate hydroxylation reagents nonracemic (camphorylsulfonyl)oxaziridines **4**. The *N*-fluoro sultams **3** were prepared by fluorination (10% F_2/N_2) of the corresponding sultams **5**.

The stereoselective replacement of hydrogen and hydroxyl groups by fluorine in biologically active molecules is a common strategy for enhancing biological activity and studying enzyme mechanism. Fluorine uniquely influences the basicity, acidity, and nonbonding interactions of neighboring groups because of its extreme electronegativity.[1,2] Replacement of hydrogen by fluorine is often regarded as an isosteric substitution despite the fact that their van der Waals radii are different (1.20 vs 1.47 Å).[3,4] The similarity of typical C−F and C−O bond lengths (1.39 vs 1.43 Å) and the possibility that fluorine may function as a weak hydrogen bond acceptor suggest that replacement of hydroxyl by fluorine in bioactive compounds would result in useful analogues.[1,5] Furthermore the high C−F bond strength often protects fluorine from metabolic transformations. For these reasons, plus the importance of chirality in pharmacologically and biologically active molecules, the synthesis of enantiomerically pure fluoroorganic molecules is of significance.[6]

Recent efforts have focused on the asymmetric synthesis of fluoroorganic molecules where at least one of the chiral centers bears a fluorine. Of particular interest are nonracemic α-fluoro carbonyl compounds **1**, which are fluorine analogues of the α-hydroxy carbonyl moiety found in many biologically active compounds.[7,8] Not only do α-fluoro carbonyl compounds exhibit biological activity, but they have also found utility as enzyme inhibitors,[8] and in the study of enzyme mechanisms.[8] Furthermore, nonracemic α-fluoro carbonyl compounds are important building blocks for the asymmetric construction of bioactive materials[8,9b,10] and ferroelectric devices.[11]



Z = OH, OR, H, R'

1

Optically active α-fluoro acids **1** (Z = OH) have been prepared by enzyme-catalyzed kinetic resolution of α-fluoro esters[12] and 2-fluoro-2-substituted malonic esters.[13]

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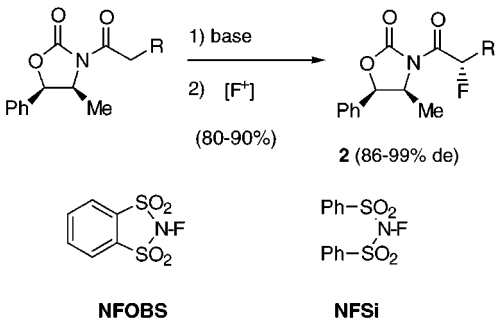
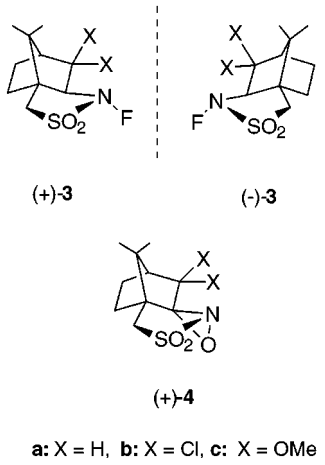
Fluorodeamination of chiral α-amino acids with retention of configuration[14] using HF-pyridine/sodium nitrite has also been described.[15] Treatment of enantiomerically enriched α-hydroxy acids with fluoroamines[16] and diethylaminosulfur trifluoride (DAST)[10a,14,17] likewise gives these compounds, but with varying degrees of success. Ethyl (*R*)-fluorohexanoate was prepared in 91% ee by conversion of corresponding α-hydroxy ester to the mesylate followed by nucleophilic displacement with fluoride ion.[17a]

The diastereoselective fluorination of chiral enolates with electrophilic fluorination reagents[6c,18] and the enantioselective amide acetal Claisen rearrangement described by Welch[19] are other useful sources of α-fluoro carbonyl compounds. In this regard we have shown that the highly diastereoselective (85−99%) fluorination of chiral imide enolates with *N*-fluoro-*o*-benzenedisulfonimide (NFOBS)[20] and *N*-fluorobenzenesulfonimide (NFSi)[20] is a particularly general route to these materials.[21] However, a disadvantage of any chiral auxiliary based asymmetric synthesis is the necessity of preparing and eventually removing the auxiliary without epimerization. Indeed some racemization occurred in the alkaline hydrolysis of **2**, but removal of the auxiliary was accomplished without racemization by reduction to the *β*-fluorohydrin.[21]



An enantioselective fluorinating reagent for the reagent-controlled asymmetric fluorination of prochiral enolates to α-fluoro carbonyl compounds in high ee's and predictable stereochemistry would be of considerable value. The first "electrophilic" asymmetric fluorinating reagent was (−)-*N*-fluoro-2,10-camphorsultam (**3a**) prepared by Differding and Lang in 1988.[22] However, the ee's and yields for enolate fluorinations with this reagent were generally poor (vide infra). Enantiopure *N*-fluoro-*N*-tosylamines also give low to moderate ee's (2−54%) for the fluorination of tertiary enolates.[23] Another reagent, a nonracemic aminofluorosulfurane, a nucleophilic source of fluorine, also gave low ee's (16%) in the kinetic resolution of 2-(trimethylsiloxy)propanoate.[24] In connection with our interest in the asymmetric synthesis of α-fluoro carbonyl compounds **1** we describe details of a synthetic and mechanistic study of the asymmetric fluorination of enolates using nonracemic *N*-fluorocamphorsultams **3**.[25] This work is related to our studies on the asymmetric hydroxylation of prochiral enolates using the closely related (camphorylsulfonyl)oxaziridine **4**[26] because the chiral recognition mechanisms are likely to be similar and the precursors of **4** are the precursors of **3** (Scheme 1).

Scheme 1



Synthesis and Structure of *N*-Fluoro-2,10-camphorsultams. Preparation of the *N*-fluoro-2,10-camphorsultams (+)-**3** was accomplished by direct fluorination of the corresponding camphorsultams (+)-**5a**−**c**[27] using 10% F_2/N_2 and are summarized in Table 1. Powdered NaF was added to scavenger HF. In addition to the *N*-fluoro sultam (+)-**3** two side products were observed, the (camphorylsulfonyl)imines **6** and in the case of (−)-**5b**, the (*N*,*N*-difluoroamino)camphorsulfonyl fluoride (−)-**7**. The optimum temperature for fluorination was −40 °C since lowering the temperature to −78 °C produced no reaction and higher temperatures resulted in decomposition. Somewhat higher yields; e.g. 10% were observed at lower molar concentrations of **5** (Table 1: compare entries 2 and 3, and 10 and 11), but had little effect on the formation of the side products. The imines **6** result from dehydrofluorination of **3** as evidenced by the fact that 15−20% of **6b** was obtained on treatment of **3b** under the fluorination conditions. As the polarity

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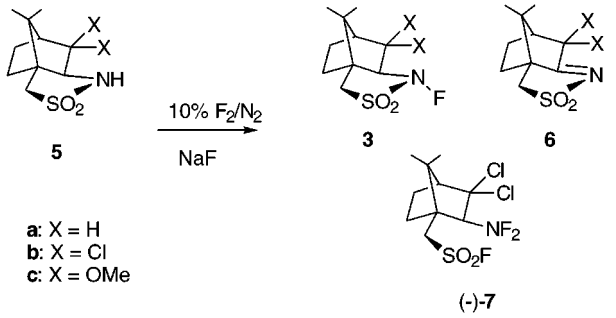
Table 1. Fluorination of Camphorsultams 5 to *N*-Fluorocamphorsultams 3 at −40 °C for 1.5 h

entry	sultam	conditions concentration/solvent	products (% yield)	δ ^{19}F ppm of **3** (J = Hz)
1	(−)-**5a** (X = H)	(0.1 M)/1:1 $CHCl_3$:$CFCl_3$	(+)-**3a** (67) [75%]	−65.5 (br,s)
2	(−)-**5b** (X = Cl)	(0.1 M)/1:1 $CHCl_3$:$CFCl_3$	(+)-**3b** (67), (+)-**6b** (13), (−)-**7** (5)	−53.9 d (48.4)
3		(0.2 M)/1:1 $CHCl_3$:$CFCl_3$	(+)-**3b** (56), **6b** (9), (−)-**7** (11)	
4	(+)-**5b** (X = Cl)	(0.2 M)/1:1 $CHCl_3$:$CFCl_3$	(−)-**3b** (56), **6b** (12), (−)-**7** (10)	
5		(0.4 M)/1:1 $CHCl_3$:$CFCl_3$	(−)-**3b** (58), **6b** (11), (−)-**7** (12)	
6		(0.2 M)/$CHCl_3$	(−)-**3b** (67), **6b** (7), (−)-**7** (11)	
7		(0.2 M)/4:5:1 $CHCl_3$:$CFCl_3$:EtOH	(−)-**3b** (35), **6b** (0), (−)-**7** (0)	
8	(+)-**5c** (X = OMe)	(0.2M)/1:1 $CHCl_3$:$CFCl_3$	(−)-**3c** (25), **6b** (35)	−55.6 d (44.0)
9	(−)-**5c** (X = OMe)	(0.2M)/1:1 $CHCl_3$:$CFCl_3$	(−)-**3c** (31), **6b** (40)	
10	(+)-**5c** (X = OMe)	(0.2M) $CHCl_3$	(−)-**3c** (42), **6b** (21)	
11	(+)-**5c** (X = OMe)	(0.6M) $CHCl_3$	(−)-**3c** (34), **6b** (33)	

of the solvent increased from $CHCl_3$:$CFCl_3$ to $CHCl_3$ the yield of the *N*-fluoro sultam increased, possibly due to the greater solubility of the starting material (Table 1: entries 4 and 6). The formation of byproducts **6** and **7** may involve fluorine radicals. Earlier studies on the fluorination of steroidal alkenes with F_2 indicated that the low yields observed in less polar solvents occurred from the generation of fluorine radicals resulting in undesirable reactions.[28] Rosen has presented evidence that addition of proton donors such as ethanol suppresses fluorine radical formation enhancing polar reactions.[29] Indeed fluorination of **5b** in the presence of ethanol completely eliminated the formation of **6b** and **7** (Table 1, entry 7). Unfortunately the yield of **3b** was only 35%. Products were isolated by flash chromatography after filtration and removal of the solvent. The *N*-fluoro-2,10-camphorsultams **3a**−**c** are stable white crystalline solids storable at room temperature for more than a year without noticeable deterioration and giving satisfactory elemental analyses.



The structure of the ring-opened product (*N*,*N*-difluoroamino)camphorsulfonyl fluoride (−)-**7** was determined on the basis of its spectral properties. In the ^{19}F NMR spectra of **7** the diastereotopic NF_2 fluorines appear at δ −144.5 and −164.2 ppm as doublets of a doublet coupled with the adjacent methine proton. Their chemical shifts are in accord with those previously reported for other amino difluorides.[30] The sulfonyl fluoride fluorine appears as a triplet at δ −147.1 ppm as a result of coupling with the nearby methylene group. Additional support for the structure of **7** is the report of a very similar ring-opened product obtained in the fluorination of 3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide.[31]

The degree of asymmetric induction exhibited by **3a**−**c** will be dependent in large part on the geometry at

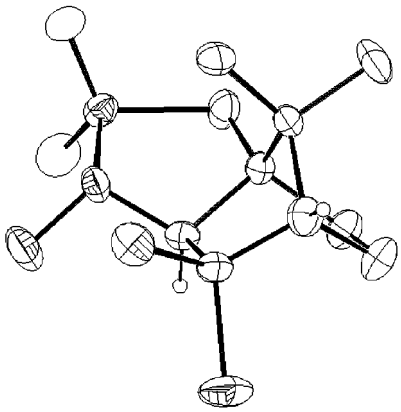
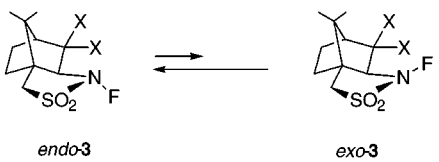


Figure 1. Computer-generated X-ray structure of (+)-**3b**.

nitrogen, which may be pyramidal or planar, and the fluorine's steric and electronic environment. Although electronegative atoms containing lone pairs of electrons (e.g. halogens) are known to increase the barrier to pyramidal inversion at nitrogen, sulfonyl groups frequently decrease it.[32] The fluorine atom in the ^{19}F NMR spectra of (+)-*N*-fluoro-camphorsultam (**3a**) at 22 °C appears as a broad singlet at −65.5 ppm relative to the standard ($CFCl_3$) rather than the expected doublet due to coupling with the adjacent proton. On cooling to 0 °C a second broad hump appeared at −54.0 ppm, and at −60 °C these peaks were resolved into two doublets at −66.4 (J = 48.8 Hz) and at −54.0 (J = 73.3 Hz) ppm. The relative intensities were 97:3. We interpret this to mean that (+)-**3a**, at ambient temperatures, exists as a rapidly equilibrating mixture of the *endo* and *exo* forms, but at −60 °C a nonequilibrating 97:3 *endo*/*exo* mixture. On the other hand the fluorine NMR spectra of the dichloro and dimethoxy *N*-fluoro sultams (+)-**3b** and (+)-**3c** were doublets at −53.9 (J = 48.4 Hz) and −55.6 (J = 44.0 Hz) ppm, respectively. On heating to 75 °C these absorptions remained doublets, indicating that these sultams exist exclusively in the sterically more favorable *endo* form.



The X-ray crystal structure of (+)-*N*-fluoro-2,10-(3,3-dichlorocamphorsultam) (**3b**), shown in Figure 1, con-

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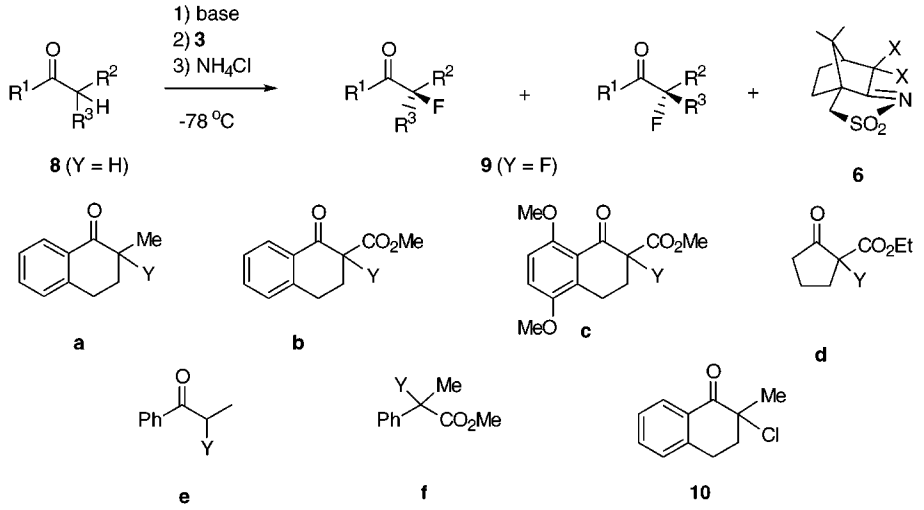
Scheme 2



firms that the fluorine atom occupies the *endo* position. The nitrogen atom is sp^3 hybridized and pyramidal as indicated by the C−N, N−S, and N−F bond angles of approximately 107° as well as the fact that it is out of the S, C, F plane by 0.57 Å.

Asymmetric Fluorinations. In a typical experiment 0.8−1.5 equiv of *N*-fluoro sultams **3a**−**c** were added to the preformed kinetic enolates of **8a**−**f** at −78 °C (Scheme 2). However, fluorination at this temperature was slow, and warming to 0 °C was required for completion in many cases. Products were identified by comparison with authentic samples and by ^{19}F NMR. The ee's were determined using the chiral shift reagent Eu(hfc)$_3$. These results are summarized in Table 2.

In general the *N*-fluoro dichloro sultam **3b** gave better yields and ee's than did **3a**. This is most likely related to the greater reactivity of **3b** where fluorinations occurred at −78 °C vs rt for **3a**. The highest asymmetric induction was observed for the fluorination of the sodium enolate of 2-methyl-1-tetralone (**8a**) with **3b** affording the 2-fluoro-2-methyl-1-tetralone (**9a**) in 76% ee and 53% yield (Table 2; entry 6). For fluorination of β-ketone ester enolates **8b**−**c**, the ee's were more modest and in the range of 34−46% ee. The enolate of propiophenone (**8e**), the only secondary enolate studied, gave racemic **9e** (Table 2: entry 29). The fact that **9e** was racemic is undoubtedly related to the ease with which it under goes base-catalyzed epimerization under the reaction conditions as a consequence of the enhanced acidity of the α-fluoro proton.[21a,b,d] While fluorination yields were quite good for the *N*-fluoro-2,10-(3,3-dimethoxycamphorsultam) (**3c**) the asymmetric induction was dismal (<5%). As previoulsy observed for hydroxylations using the corresponding (camphorylsulfonyl)oxaziridines **4** the ee's of **9** were dependent upon the geometry of the enolate, the counterion, the structure of **3** as well as the reaction conditions (Table 2).[39]

A side-product isolated in 3−11% in the fluorination of the sodium enolate of **8a** was 2-chloro-2-methyl-2-tetralone (**10**) (Table 2: entries 4, 5, 10). As previously reported, this product arises from chlorination of the enolate by the dichlorocamphorsulfonimine **6b**[33] and can be completely suppressed by fluorination at −78 °C. Enolate induced H−F elimination of **3b** is responsible for the formation of **6b** which also reduces product yields. The reason the β-keto ester enolates of **8a**−**d** gave higher yields is probably related to their lower basicity resulting in less elimination. In addition to HF elimination, which destroys the enolate, it can also be quenched by the acidic α-imino protons in the sulfonimine **6a**. Indeed when the enolate of **8a** was treated with **6a** followed by a D_2O quench no incorporation of deuterium into **8a** was observed.

Absolute Configuration of 2-Fluoro-2-methyl-1-tetralone (9a). To design more effective enantioselective N−F fluorinating reagents an understanding of chiral recognition mechanism is important. This requires that the absolute configurations of the product α-fluoro carbonyl compounds be known. Because the active site structures of *N*-fluoro sultam (+)-**3** and oxaziridine (+)-**4** are similar it is anticipated that they will afford the same sense of asymmetric induction in the fluorination and hydroxylation of enolates. Consequently the enolate of 2-methyl-1-tetralone (**8a**) on fluorination by (+)-**3b** should give (*R*)-**9a**. To confirm this assumption (*R*)-(+)-hydroxy-2-methyl-1-tetralone (**11**), prepared in >95% ee by hydroxylation of the sodium enolate of **8a** with (+)-**4b**,[33] was treated with DAST.[34] This nucleophilic fluorinating reagent generally reacts with α-hydroxy carbonyl compounds with inversion of configuration,[34b,c] although a few examples are known where the configuration was retained.[35] Thus treatment of (+)-**11** with DAST gave (−)-**9a** in 20% yield and 70% ee. The major product, identified by comparison with an authentic material, was 2-methyl-1-naphthol (**12**) isolated in 54% yield (Scheme 3).[36] Unexpectedly, the signs of rotation of **9a** prepared

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(38) The X-ray structure of **14** will be published elsewhere.

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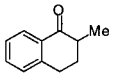
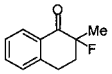
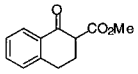
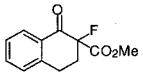
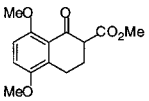
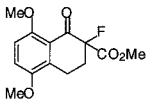
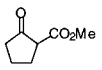
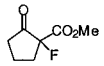
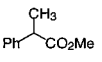
Table 2. Asymmetric Fluorination of Enolates Using *N*-Fluorocamphorsultams 3

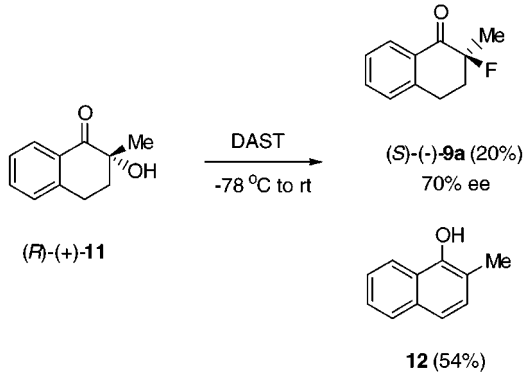
entry	Enolate	N-F Sultam[a]	Reaction Conditions Base[b]/Solvent/°C	Products % ee (config.) [% isolated yield]	$[\alpha]^{20}_D$ (*c* $CHCl_3$)
1	**8a** 	(+)-**3a** [X = H]	LDA/THF/-78 to rt	**9a**  35 (*S*) [<5][d]	
2			NaH/Et_2O/0 to rt	25 [28]	
3		(+)-**3b** [X = Cl]	LDA/THF/-78	10 [31]	
4			NaHMDS/THF/-78 to 0	67 (*S*) [41], **10** [11]	-20.4 (1.8)
5			$NaHMDS/Et_2O$/-78	6 (S) [51], **10** [3]	
6			NaHMDS/-78	76 (*S*) [53]	-21.5 (1.6)
7			NaHMDS/-78/HMPA	70 (*S*) [24]	
8			$LDA/ZnCl_2$/THF/-78 to rt	10 (*S*) [33]	
9		(-)-**3b** [X=Cl] (0.8)[e]	NaHMDS/THF[c]/-78	75 (*S*) [40]	+21.8 (1.5)
10		(-)-**3b** [X=Cl]	NaHMDS/THF/-78 to rt	65 (*S*) [50], **10** [7]	-20.3 (1.8)
11		(+)-**3c** [X = OMe]	NaHHDS/-78 to rt	<5 [61]	
12	**8b** 	(+)-**3a** [X=H]	NaHMDS/THF/-78 to rt	**9b**  14 [8]	
13		(+)-**3b** [X=Cl]	NaHMDS/THF/-78	25 [75]	
14			LDA/THF/-78	26 [25]	
15			KHMDS/THF[c]/-78	41 [90]	+6.12 (0.4)
16			LDA/THF[c]/-78	17 [87]	
17	**8c** 	(+)-**3a** [X = H]	NaH/Et_2O/0 to rt	**9c**  25 [28]	-2.88 (1.6)
18		(+)-**3b** [X = Cl]	NaHMDS/THF/-78 to rt	34 [22]	
18			NaHMDS/THF/0 to rt	26 [57]	+2.83 (2.1)
19			$NaHMDS/Et_2O$/-78 to rt	37 [85]	
20			NaH/Et_2O/0 to rt	46 [95]	+4.93 (1.4)
21			NaH/Et_2O[c]/0 to rt	40 [95]	
22			KHMDS/THF/-78	20 [28]	
23		(+)-**3c** [X = OMe]	NaHMDS/-78	14 [83]	
24			LDA/THF/-78 to 0	14 [76]	
25	**8d** 	(+)-**3a** [X=H]	NaH/Et_2O/0 to rt	**9d**  70 [63][d]	-18.5 (1.4)
26		(+)-**3b** [X=Cl]	NaHMDS/THF/-78 to rt	10 [41]	
27			NaH/Et_2O/-78 to rt	34 [59]	-9.5 (5.4)
28		(+)-**3c** [X= OMe]	NaH/Et_2O/-78	<5 [57]	
29	**8e** 	(+)-**3b** [X=Cl]	NaHMDS/THF/-78 to rt	**9e**  0 [41]	
30	**8f** 	(+)-**3a** [X=H]	LDA/THF/-78 to rt	**9f**  35 [< 10][d]	
31		(+)-**3b** [X=Cl]	LDA/THF/-78	29 [62]	
32			NaHMDS/THF/-78	33 [54]	+0.92 (1.1)
33		(+)-**3c** [X= OMe]	NaHMDS/THF/-78	< 5 [55]	

a) 1.5 equivalents of the N-F reagent used unless otherwised noted. b) 1.1 Equivalents of base used. c) Inverse addition. d) Reference 16. e) 0.8 equivalents of (-)-**3b** used

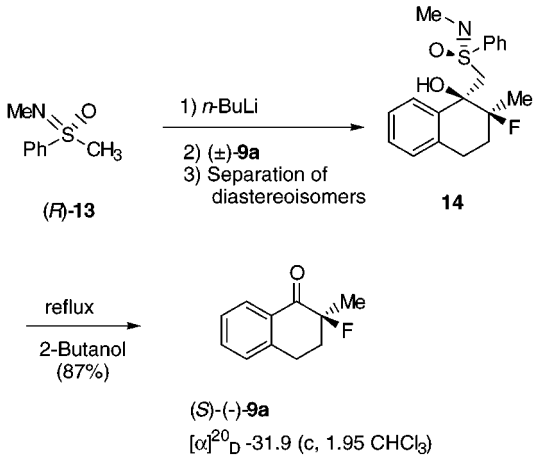
by fluorination of the enolate of **8a** with (+)-**3b** and by DAST treatment of (*R*)-**11** were the same; e.g. negative. This means that despite the apparent similarities in active site structures, (+)-**3** and (+)-**4** give different senses of asymmetric induction. This brings into question whether DAST actually reacts with (*R*)-**11** with inversion of configuration, particularly in light of the low yield and the fact that **11** is a tertiary hydroxyl group.

To unequivocally assign the structure of **9** it was necessary to prepare a solid derivative and determine its absolute configuration by X-ray analysis. Ideally suited for this purpose is the Johnson reagent, (*R*)-(−)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (**13**).[37] This reagent has been employed in the resolution of ketones which is based on its reversible addition to chiral ketones. Thus treatment of (*R*)-**13** with 1.1 equiv of *n*-BuLi at −78 °C gave the corresponding α-lithio derivative to which was added 1.0 equiv of racemic **9a** (Scheme 4). After quenching with aqueous NH_4Cl the *β*-hydroxy sulfoximine diastereoisomers were separated into two fractions by flash chromatography. The first fraction consisted of two diastereoisomers in a 1:5 ratio while the second fraction **14** was diastereomerically pure by NMR. X-ray crystal analysis of the latter fraction revealed that the fluorine stereocenter has the (*S*)-configuration.[38] (*S*)-(−)-2-Fluoro-2-methyl-1-tetralone (**9a**) was regenerated in 87% yield by

Scheme 3



Scheme 4

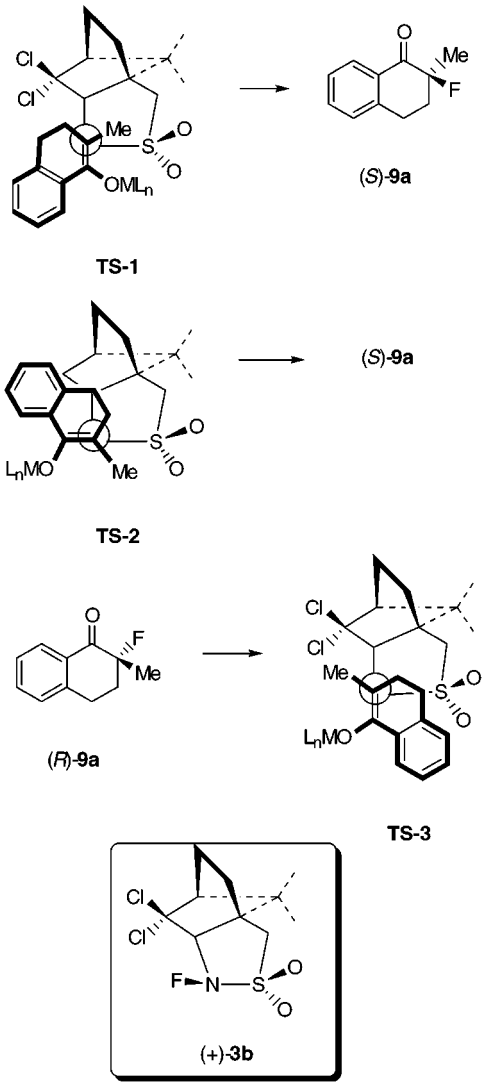


refluxing **14** in 2-butanol for 2 h. This result verifies that DAST reacts with (*R*)-(+)-**11** with inversion of configuration and that (+)-**3** and (+)-**4** give the opposite stereoinduction with enolates.

Molecular recognition for the asymmetric hydroxylation of acyclic and cyclic ketone enolates by (camphorylsulfonyl)oxaziridine derivatives **4** has been interpreted in terms of "open" or "nonchelated" transition states.[26,39,40] Based on the structure−reactivity trends, it was argued that the primary transition-state control element is steric in origin, as observed for other enantioselective oxidations by these reagents. It was further assumed that regardless of the actual solution structure of the enolate the enolate−oxygen metal aggregate was the sterically most demanding group in the vicinity of the enolate C−C bond.[33,39] While this model has proven to be a useful predictor of enolate hydroxylation stereochemistry, a few exceptions have been noted. These include the hydroxylation of a β-ketoester enolate used in the synthesis of the AB segment of daunomycin[41] and an eight-membered cyclic lactone enolate employed in the synthesis of (+)-lauercin.[42] However, these exceptions may not be due to a flawed model, but rather to the difficulty in evaluating the relevant nonbonded interactions.

Applying the enolate-hydroxylation model to the asymmetric fluorination of the 2-methyl-1-tetralone (**8a**) enolate requires the reasonable assumption that the enolate

Scheme 5



attacks the F−N bond in an S_N2 fashion as proposed for enolate hydroxylations by oxaziridines (Scheme 5).[43] In support of the S_N2 mechanism for "electrophilic" fluorination by N−F reagents is the fact that rearranged products were not detected in the fluorination of citronellic ester enolate as would be expected of an ET mechanism involving radical species.[44] Beak has also shown that the aryl bromide−alkyllithium exchange reaction either proceeds through a trigonal bipyramid structure or an S_N2 transition state.[45] In **3** fluorine is more exposed and in a less sterically encumbered environment than is the oxygen atom in **4** (Figure 1). For the *N*-fluoro sultam **3** this results in reduced asymmetric induction compared to **4**; e.g. 70 vs 95%, respectively. This means that the steric factors which made **TS-3** of lowest energy for enolate hydroxylations is apparently of less importance for enolate fluorinations. In this regard **TS-1** and **TS-2** are favored because (+)-**3b** give (*S*)-**9a** in 70−75% ee. Furthermore, in **TS-2** there is the possibility of a stabiliz-

(40) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.
(41) Davis, F. A.; Clark, C.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1994**, *59*, 1184.
(42) Burton, J. W.; Clar, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
(43) Bach, R. D.; Andres, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613.
(44) Differding, E.; Ruegg, G. M.; Lang, L. W. *Tetrahedron Lett.* **1991**, *32*, 1779.
(45) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420.

ing metal enolate chelation with the sulfonyl oxygens.[43,46] However, enolate fluorinations in the presence of HMPA, known to disrupt metal chelation,[47] failed to diminish the ee of **9a** (Table 2: entry 7).

In summary electrophilic asymmetric fluorination of tertiary enolates by *N*-fluoro-2,10-camphorsultams **3** afforded quaternary α-fluoro carbonyl compounds in modest yield and ee. The sense of asymmetric induction exhibited by these reagents is opposite that for the closely related (camphorylsulfonyl)oxaziridine **4** hydroxylating reagents.

Experimental Section

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 μm) purchased from Analtech Inc. TLC plates were visualized with UV, in an iodine chamber or with phosphomolybdic acid unless noted otherwise. THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

Substrates **8** were purchased from Aldrich Chemical Co. and used without additional purification unless otherwise noted. Sultams **5a**−**c** were prepared by reduction of the corresponding (camphorsulfonyl)imines **6** with $NaBH_4$ as previously described.[27,48]

Fluorinations was carried out in the apparatus recommended by Matheson Gas Products for the handling of dilute concentrations of F_2/N_2. For a related apparatus see ref 49. ***Caution: Fluorine is a poisonous, corrosive gas which is a powerful oxidant.***

(+)-*N*-Fluoro-2,10-(3,3-dichlorocamphorsultam) (3b). In a 50 mL two-necked round-bottomed flask fitted with a Teflon septum, a Teflon adapter with a Teflon outlet tube attached to a soda lime tower, and a Teflon O-ring to hold the Teflon tube was placed a solution of 3.0 g (10.6 mmol) of (+)-2,10-(3,3-dichlorocamphorsultam) (**5b**) in dry chloroform (50 mL). To this solution was added 2.1 g (50 mmol) of NaF, dried overnight under high vacuum. The reaction flask was cooled to −40 °C (dry ice−acetonitrile bath), and dry nitrogen gas was passed into the solution. After 10 min, the N_2 flow was stopped and fluorine gas (10% in N_2) was introduced into the solution. The flow rate of F_2 was maintained at 60 mL/min, and the reaction was continued until complete as indicated by TLC (1.0−1.5 h). The fluorine gas flow was stopped, and the reaction mixture was purged with N_2 for 15 min. The solution was filtered, and the filtrate was washed with 20 mL of $CHCl_3$ and concentrated to give an oil which was purified by column chromatography (CH_2Cl_2/*n*-pentane eluant, 70:30) to give 2.13 g (67%) of (+)-**3b**: mp 161−162 °C; $[\alpha]^{20}_D = +16.4$ ($c = 1.3$, $CHCl_3$); IR (KBr) cm^{-1} 2990, 1407, 1279, 1197, 1065; ^1H NMR($CDCl_3$) δ 1.07 (s, 3 H), 1.46 (s, 3 H), 1.70−2.13 (m, 3 H), 2.31−2.43 (m, 1 H), 2.61 (d, $J = 4.2$, 1 H), 3.36 (q_{AB}, $J_1 = 14.1$ Hz, $J_2 = 25.7$ Hz, 2 H), 4.01 (d, $J = 44.9$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.2, 25.5, 31.9, 47.9, 48.0, 50.0, 61.8, 83.7, 91.6; ^{19}F NMR ($CDCl_3$) δ −53.9 (d, $J = 48.4$ Hz). Anal. Calcd for $C_{10}H_{14}Cl_2FNO_2S$: C, 39.75; H, 4.67. Found: C, 39.63; H, 4.65.

(1*R-exo*)-(−)-2-(*N*,*N*-difluoroamino)-7,7-dimethylbicyclo-[2.2.1]heptane-1-methanesulfonyl Fluoride (7). This compound was isolated as a byproduct of the fluorination of (+)-**5b** (10%): mp 105−106 °C; $[\alpha]^{20}_D = -20.2$ ($c = 1.4$, $CHCl_3$); IR (KBr) cm^{-1} 2992, 1492, 1407, 1210; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.40 (s, 3 H), 1.93−2.12 (m, 2 H), 2.32−2.40 (m, 1 H), 2.61−2.64 (m, 1 H), 3.33−3.42 (m, 1 H), 3.76−3.82 (m, 1 H), 4.37 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.6, 23.0, 24.7, 30.7, 51.9, 52.0, 52.3, 62.4, 90.4 (m); ^{19}F NMR ($CDCl_3$) δ −144.5 (dd, $J_1 = 613.7$ Hz, $J_2 = 33$ Hz, 1 F), −147.1 (t, $J = 8.8$ Hz, 1 F), −164.2 (dd, $J_1 = 613.7$ Hz, $J_2 = 24.2$ Hz, 1 F). Anal. Calcd for $C_{10}H_{14}Cl_2F_3NO_2S$: C, 35.31; H, 4.15. Found: C, 35.42; H, 4.04.

(+)-*N*-Fluoro-2,10-(3,3-dimethoxycamphorsultam) (3c). The typical procedure for the preparation of (+)-**3b** was followed, eluant: Et_2O/*n*-pentane, 50:50; yield 34%; mp 154−156 °C, $[\alpha]^{20}_D$ +49.6 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1} 3006.5, 1342.1, 1156.8, 106.4; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 1.27 (s, 3 H), 1.55−1.91 (m, 5 H), 2.19 (d, $J = 4.2$ Hz, 1 H), 3.06−3.42 (m, 2 H), 3.18 (s, 3H), 3.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 108.3, 76.4, 76.3, 50.0, 48.3, 48.2, 48.0, 46.9, 46.8, 33.5, 21.0, 20.6; ^{19}F NMR ($CDCl_3$) δ −55.6 (d, $J = 44.0$ Hz). Anal. Calcd for $C_{12}H_{20}FNO_4S$: C, 49.13; H, 6.87. Found: C, 49.04; H, 7.25.

Determination of Enantiomeric Purity. The enantiomeric purity of the α-fluoro carbonyl compounds were determined by chiral shift reagent experiments using increasing amounts of [(3-heptafluoropropyl)hydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$].

General Procedure for Asymmetric Fluorination of Carbonyl Enolates 8 Using *N*-Fluoro Camphorsultams (3). In a 25-mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 3 mL of freshly distilled THF containing 0.4 mmol of **3**. The reaction flask was cooled to −78 °C (dry ice−acetone bath), and 0.6 mL (0.6 mmol, 1.5 equiv based on the carbonyl compound) of a 1.0 M solution of either LDA, NaHMDS, or KHMDS in THF was added. The mixture was then stirred for 5 min at −78 °C, warmed to 0 °C, stirred for an additional 45 min, and cooled to −78 °C. A solution of the *N*-fluorocamphorsultam **3** (1.1 mmol) in 3 mL of THF was quickly added to the reaction mixture. After the reaction was complete, as indicated by TLC, the reaction mixture was quenched by addition of aqueous NH_4Cl (3 mL), ether (10 mL) at −78 °C was added, and the solution was warmed to room temperature. The aqueous layer was extracted with ether (2 × 5 mL), the combined organic phases were washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$), and concentrated to give an oil that was purified by preparative TLC (8% EtOAc in pentane). Products were identified by comparison with authentic samples and/or literature values.

(−)-2-Fluoro-2-methyl-1-tetralone (9a): (50%), oil, 76% ee $[\alpha]^{20}_D = -21.5$ (*c* 1.6, $CHCl_3$); CD spectrum: molecular ellipticity [*Q*] (*c* 3.21, C_2H_5OH), 21 °C; $[Q]_{325}$ −2833°; ^{19}F NMR ($CDCl_3$) δ −154.4 (m). Its spectral properties were in agreement with literature values.[50,51]

(+)-2-Carbomethoxy-2-fluoro-1-tetralone (9b): (90%), oil; 41% ee, $[\alpha]^{20}_D = +6.12$ (*c* 2.0, $CHCl_3$); IR (NaCl) 1765 and 1695 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51−2.85 (m, 2 H), 3.0−3.28 (m, 2 H), 3.85 (s, 3 H), 7.23−7.41 (m, 2 H), 7.50−7.60 (m, 1 H), 8.05−8.11 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 31.6, and 32.0 (d, $J = 22.2$), 53.0, 91.7, and 94.8 (d, $J = 194.3$ Hz), 127.3, 128.5, 128.8, 130.4, 134.6, 142.1, 167.6 and 168.0 (d, $J = 25.8$ Hz), 188.3 and 188.6 (d, $J = 18.1$ Hz); ^{19}F NMR ($CDCl_3$) δ −156 (m). Anal. Calcd for $C_{12}H_{11}FO_3$: C, 64.86; H, 4.95. Found: C, 64.41; H, 4.78.

(+)-2-Carbomethoxy-5,8-dimethoxy-2-fluoro-1-tetralone (9c): (95%), oil; 46% ee $[\alpha]^{20}_D$ +4.93 (*c* 1.4, $CHCl_3$); IR (NaCl) 1762 and 1686 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48−2.78 (m, 2 H), 3.00−3.09 (t, $J = 6.0$ Hz, 2 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 6.79−6.87 (d, $J = 9.06$ Hz, 1 H); 7.01−7.09 (d, $J = 9.06$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.9, 22.9 and 23.2 (d, $J = 18.3$ Hz), 30.2 and 30.5 (d, $J = 19.0$ Hz), 52.8,

(46) For examples of metal chelation involving sulfonyl oxygens see: Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396. Hellwinkel, D.; Lenz, R.; Lammerzahl, F. *Tetrahedron* **1983**, *39*, 2073. Giblin, G. M. P.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1987**, 207. Hollstein, W.; Harms, K.; Marsch, M.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1287.

(47) For recent studies on the influence of HMPA on anion aggregation see: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448. Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.

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(49) Purrington, S. T.; Woodard, D. J. *J. Org. Chem.* **1991**, *56*, 142.

(50) Differding, E.; Lang, R. W. *Helv. Chim. Acta* **1989**, *72*, 1248.

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55.9 and 56.2 (d, J = 18.3 Hz), 92.3 and 95.4 (d, J = 194.4 Hz), 110.3, 116.7, 120.3, 133.5, 149.8, 155.0, 167.8 and 168.2 (d, J = 25.8 Hz), 187.5 and 187.8 (d, J = 18.4 Hz); ^{19}F NMR ($CDCl_3$) δ −155 (m). Anal. Calcd for $C_{14}H_{15}FO_5$: C, 59.57; H, 5.32. Found: C, 59.28; H, 5.22.

(−)-2-Carboethoxy-2-fluorocyclopentanone (9d): (62%), oil; 34% ee $[\alpha]^{20}_D$ −9.5 (*c* 5.24, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ −164. Its spectral properties were in agreement with literature values.[52]

(+)-2-Fluorophenylpropanone (9e): (41%), oil; racemic; ^{19}F NMR ($CDCl_3$) δ −172.4 (m). Its spectral properties were in agreement with literature values.[52]

(+)-Ethyl 2-fluoro-2-phenylpropionate (9f): (54%), oil; 33% ee $[\alpha]^{20}_D$ +0.92 (*c* 1.1, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ −152. Its spectral properties were in agreement with literature values.[53]

Formation of (S)−(−)-2-Methyl-2-fluoro-1-tetralone (9a) Using Diethylaminosulfur Trifluoride (DAST). In a 25 mL oven-dried two-necked flask equipped with a rubber septum, an argon bubbler, and a magnetic stirring bar was placed 0.10 g (0.57 mmol) of (*R*)-(+)-2-hydroxy-2-methyl-1-tetralone[33] (**11**, 95% ee) in CH_2Cl_2 (3 mL). The reaction mixture was cooled to −78 °C, and 0.138 g (0.86 mmol) of DAST was added dropwise *via* syringe. After the addition was complete, the reaction mixture was warmed to room temperature, and aqueous sat. NH_4Cl (1 mL) was added dropwise after the reaction was complete (TLC). The solution was diluted with diethyl ether (10 mL), extracted with water (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. Purification by prep TLC (8% ethyl acetate in pentane eluant) gave 0.02 g (20%) of **9a**, 70% ee, $[\alpha]^{20}_D$ −20.8 (*c* 1.8, $CHCl_3$).

2-Methyl-1-naphthol (12). This compound was isolated in 54% yield from the DAST reaction described in the preceding section: mp 63−65 °C [lit.[36] 64−66 °C]; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3 H), 5.08 (br s, exchangeable with D_2O, 1 H), 7.22−7.71 (m, 5 H), 8.10−8.18 (m, 1 H).

Preparation of β-Hydroxy Sulfoximine (14). In a 25 mL oven-dried two-necked flask equipped with a rubber septum, an argon bubbler, and a magnetic stirring bar was placed 0.170 g (1 mmol) of (*R*)-(−)-*N*,*S*-dimethyl-S-phenylsulfoximine in THF (5 mL) at −78 °C. *n*-BuLi (2.5 M in hexane, 0.44 mL, 1.1 mmol) was added to the reaction mixture, it was stirred at room temperature for 15 min, the yellow solution was cooled to −78 °C, and 0.178 g (1 mmol) of (±)-**9** in THF (1 mL) was added. The mixture was stirred for 45 min at −78 °C, quenched with saturated NH_4Cl (1 mL), and diluted with ether (10 mL). The organic phase was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash chromatography (ether/*n*-hexane, 1:4) to give 0.016 g (10%) of **9**, 0.11 g of fraction I and 0.122 g of fraction II (65% I+II). Fraction I proved to be a mixture of two diastereomers in a ratio of 1:5 by ^{19}F NMR (δ −146.6 major, δ −151.0 minor). Fraction II, a single diastereoisomer, was crystallized from CH_2Cl_2 and ether; mp: 124−5 °C; $[\alpha]^{20}_D$ 12.5 (*c* 1.13 $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ −149.7; ^{1}H NMR ($CDCl_3$), δ 7.75−6.80 (m, 9 H), 3.53 (d, J = 14.7 Hz, 1 H), 3.35 (d, J = 15.0, Hz 1 H,), 2.96 (m, 1 H), 2.73−2.66 (m, 4 H, includes 3 H at 2.70), 2.37−2.29 (m, 1 H), 2.21−2.10 (m, 1 H), 1.83 (d, J = 23.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142−127 97.9 (d, J = 174 Hz), 62.4 (d, J = 4.0 Hz), 45.6, 31.5 (d, J = 22.4 Hz), 29.5, 25.7 (d, J = 4.0 Hz), 22.7 (d, J = 26.4 Hz). Anal. Calcd for $C_{21}H_{30}FNO_2S$: C, 66.68; H, 6.38; N, 4.03. Found: C, 65.44; H, 6.35; N; 3.86.

Thermolysis of β-Hydroxysulfoximine 14. In a single-necked round-bottomed flask equipped with a magnetic stir bar and reflux condenser was placed 0.088 g (0.25 mmol) of **14** in 2-BuOH (10 mL). The solution was refluxed for 2 h at which time the solvent was concentrated, and the residue was purified by flash chromatography to give 0.011 g (87%) of **9a**: $[\alpha]^{20}_D$ −31.9 (*c* 1.95, $CHCl_3$).

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Supporting Information Available: X-ray crystal structure data for (+)-**4b** and **14** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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