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Asymmetric Synthesis of α,α-Difluoro-*β*-amino Acid Derivatives from Enantiomerically Pure *N-tert*-Butylsulfinimines

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Abstract: Addition of the Reformatsky reagent derived from ethyl bromodifluoroacetate to alkyl- and aryl-substituted *N-tert*-butylsulfinimines furnishes *β-tert*-butylsulfinamyl-*β*-substituted α,α-difluoroproponiates in diastereomeric ratios ranging from 80:20 to 95:5. The diastereomers are easily separated and the enantiomerically pure, protected *β*-amino esters are readily transformed to the corresponding acid, amide, and amine derivatives as useful synthons for medicinal chemistry targets.

Fluorinated *β*-amino acids have recently become of great interest in both medicinal and synthetic organic chemistry.[1-3] In general, the introduction of fluorine atoms in bioactive targets often produces significant changes in the physical properties, physiological activity, and metabolic profile of these compounds. For example, replacement of scissile amide bonds in peptides by a *gem*-difluoroketo group often leads to potent transition state analogue inactivators of serine proteases such as elastase.[1] The CH_2 to CF_2 transposition in the *β*-amino acid fragment of the naturally occurring antifungal tetrapeptide Rhodopeptin[4] (Figure 1) results in an improved toxicity profile for this class of compounds.[2] Fluorinated *β*-amino acids have also been incorporated in the side chain of analogues of docetaxel[3] (Figure 1).

In the latter two examples, the requisite *β*-branched α,α-difluoro-*β*-amino acid fragments were prepared via lengthy (6 to 8 step) racemic syntheses with resolution of the diastereomeric products after incorporation into the target core. So far we have encountered only one report in the current literature of stereoselective preparation of *β*-branched α,α-difluoro-*β*-amino acids.[5] The key transformation in that account is the addition of the Reformatsky reagent **1** derived from ethyl bromodifluoroacetate to chiral 1,3-oxazolidines derived from aldehydes and either phenylglycinol or 2-aminobutanol (Scheme 1). The method produces the difluoroazetidinone precursor to the *β*-amino acid fragment with excellent diastereoselection (85 to >99% de), but requires ring-opening of the intermediate azetidinone followed by reductive or hydrolytic cleavage of the chiral auxiliary to liberate the desired amino acid. In addition, subsequent transformations of the amino acid (for example, in peptide couplings) would require an additional protection step to block either the amine or carboxyl terminus. The chiral auxiliary would not serve as a suitable protecting group on nitrogen since it contains a reactive hydroxyl and it also does not eliminate the reactivity of that secondary nitrogen center.

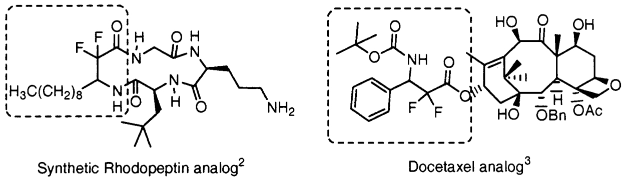
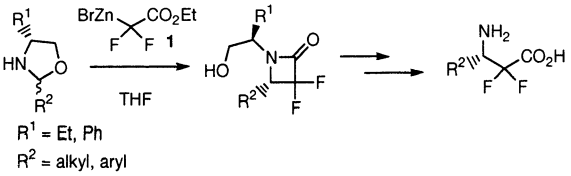


FIGURE 1. Natural product analogues containing α,α-difluoro-*β*-amino acid fragments.

SCHEME 1. α,α-Difluoro-*β*-amino Acids from Chiral Oxazolidinones[5]



Both Davis[6] and Ellman[7] have carried out extensive studies on the stereoselective addition of organometallic reagents (including Grignards, organolithiums, and acetate enolates) to enantiomerically pure sulfinimines. We reasoned that this methodology could be extended to the addition of Reformatsky-type reagents to chiral sulfinimines, given the literature precedent of addition of these reagents to aldimines.[8] We were particularly interested in the use of Ellman's *N-tert*-butylsulfinimine **2** since in the resulting adduct, the *N*-sulfinyl group has been found to be comparable in reactivity to a Boc group and in this context would play the dual role[7b] of chiral auxiliary and protecting group for subsequent transformations. Thus, copper sulfate-mediated condensation of commercial aldehydes **3a**−**e** with (*R*)-**2**[9] afforded the sulfinimines **4a**−**e** in good yield. The sulfinimines were treated with an excess (3 equiv) of the Reformatsky reagent **1**[10] at room

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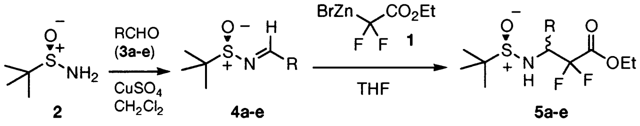
TABLE 1. Diastereoselective Addition of 1 to Chiral Sulfinimines 4a−e

entry	substrate	R	product	yield (%)[a]	dr[b]
1	**4a**	*i*-C_4H_9	**5a**	51	81:19
2	**4b**	*n*-C_3H_7	**5b**	55	80:20
3	**4c**	Ph	**5c**	82	90:10
4	**4d**	*c*-C_6H_{11}	**5d**	81	87:13
5	**4e**	2-thiazolyl	**5e**	58	95:5

[a] Isolated yields of diastereomeric mixtures. [b] Diastereomeric ratios determined by chiral HPLC.

SCHEME 2

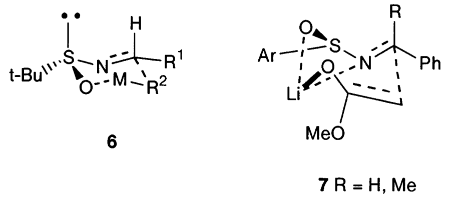


temperature for 18 h to afford the sulfinamide adducts **5a−e** in 51 to 82% yield (Scheme 2).

Both aryl- and alkyl-derived adducts were successfully prepared by this method (Table 1). The diastereomeric ratios of the adduct mixtures (shown in Table 1) were determined by chiral HPLC and ranged from 80:20 for simple alkyl side chains such as propyl (entry 2) to 95:5 for the 2-thiazolyl case (entry 5). By comparison, Ellman reports an 83:17 diastereomeric ratio for the addition of the lithium enolate of methyl acetate to sulfinimine **4c**[7b] in THF. Our diastereomeric ratio of 90:10 for adduct **5c** compares favorably with this result. Chiral HPLC methods were also required for isolation of the diastereomers on preparative scale.

To rationalize the origin of the observed diastereoselectivity of the reaction, we examined transition state models proposed by Ellman[11] and Davis[12] as shown in Scheme 3. For the addition of Grignard and alkyllithium reagents to *N*-*tert*-butylsulfinimines Ellman proposes the six-membered transition state **6** in which coordination of the metal M to the sulfinyl oxygen directs addition of the incoming R^2 group to the *Si* face of the sulfinimine with >80% stereoselectivity.[11] For the addition of lithium enolates to sulfinimines Davis proposes the modified eight-membered bicyclic transition state **7** in which the metal ion is coordinated to the sulfinyl oxygen, the imine nitrogen, and the enolate oxygen, again leading to delivery of the incoming nucleophile to the *Si* face.[12] It has long been debated whether the structure of the zinc enolate of an ester is better described as a C-metalated versus an O-metalated species.[13] Orsini and co-workers have shown that in solution the reagent formed from *tert*-butylbromoacetate and zinc exists as a dimer of the C-metalated species.[13] The Reformatsky reagent derived from ethyl bromodifluoroacetate has also been described as a C-metalated species.[14] However, it has been proposed that in the reaction of these zinc enolates with carbonyl compounds, the reagent dissociates and undergoes rate-determining conversion to the O-metalated species.[15] Finally, though the thermodynamically preferred sulfinimine is expected to be the *E* isomer, some amounts of the *Z* isomer may be generated in the reaction mixture. Ellman reports such isomerization in the reaction of Grignard reagents with sulfinimines derived from ketones.[11]

SCHEME 3. Ellman (6)[11] and Davis (7)[12] Transition State Models for the Addition of Organometallic Reagents to Chiral Sulfinimines[a]



7 R = H, Me

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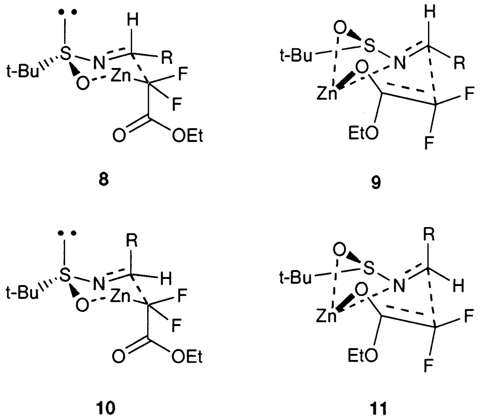
SCHEME 4



The transition states **8−11** shown in Scheme 4 reflect consideration of all these factors, namely a six- versus eight-membered transition state, a C-metalated versus O-metalated form of **1**, and the *E* versus *Z* isomers of the sulfinimine. Transition states **8** and **9** would give rise to the same stereochemical outcome of addition to the *Si* face of the sulfinimine, i.e., yielding the (*R*) isomer. Transition states **10** and **11** would give rise to the opposite outcome of addition to the *Re* face, i.e., yielding the (*S*) isomer; hence the facial selectivity of the addition would be predicted to be the same regardless of whether the reaction proceeds through the six-membered or eight-membered transition state, and would thus be solely dependent on sulfinimine geometry. One would predict that larger R groups on the sulfinimine would favor the *E* isomer (transition states **8** and **9**) and would result in improved selectivity for the (*R*)-diastereomer of the adduct, with the minor (*S*)-diastereomer arising from the less favorable *Z*-sulfinimine (transition states **10** and **11**).

As illustrated in Table 1, the highest diastereomeric ratios are obtained with the more bulky aryl or cycloalkyl R groups (entries 3−5). To determine the absolute configuration at C-3, the major diastereomer of adduct

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(10) Reagent **1** was prepared from zinc powder and ethyl bromodifluoroacetate in THF.

(11) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883−8904.

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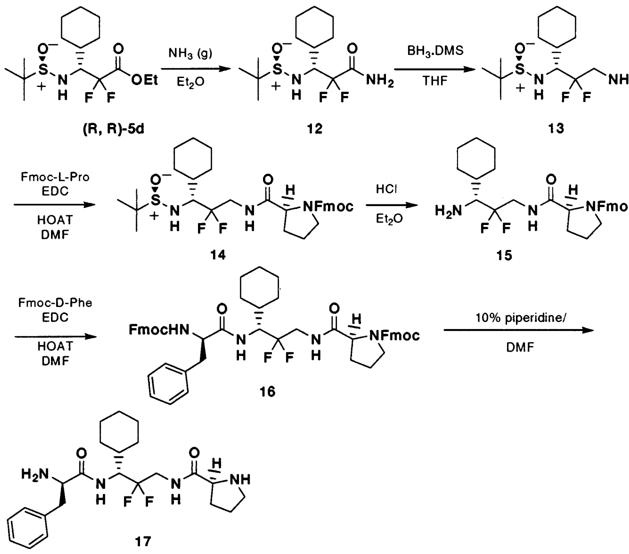
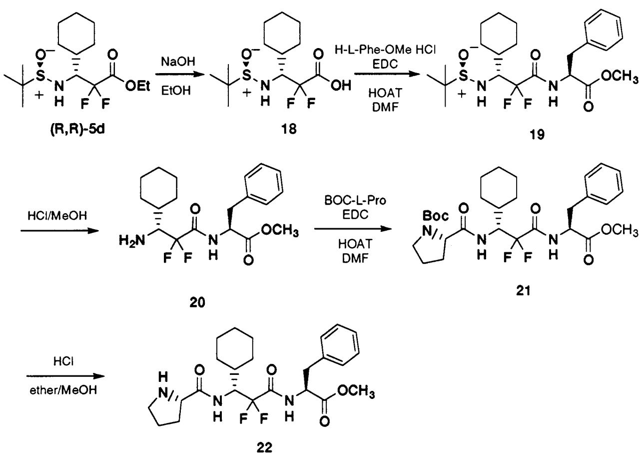
SCHEME 5



SCHEME 6



5d was converted to the crystalline primary amide **12** by ammonolysis (Scheme 5). X-ray crystallographic analysis of **12** shows the absolute configuration at the newly formed stereocenter to be *R*.[16] The stereochemical results presented in Table 1 are therefore consistent with the analysis presented above, in that either transition state model **8** or **9** correctly predicts the observed configuration at C-3 of the major diastereomer (Scheme 4).

As an example of the utility of the method, (*R*,*R*)-**12** was reduced with borane to obtain the monoprotected diamine fragment **13** (Scheme 5). EDC coupling to Fmoc-proline provided peptide **14**, which was subjected to mild acidic conditions (4 M HCl−Et$_2$O, rt, 30 min) to remove the sulfinyl group followed by EDC coupling to Fmoc-D-phenylalanine and Fmoc removal to afford the pseudotripeptide **17**, in which a substituted 2,2-difluoro-1,3-diaminopropyl fragment has been inserted as a linker (Scheme 5).

Alternatively, ester (*R*,*R*)-**5d** was hydrolyzed to the corresponding acid **18** (Scheme 6), which was then coupled to phenylalanine methyl ester. Cleavage of the sulfinyl group followed by a second peptide coupling to Boc-proline and BOC removal afforded the tripeptide **22**, which now bears an α,α-difluoro-β-amino acid linker (Scheme 6).

In summary, we have developed a highly convergent, stereoselective route to β-branched α,α-difluoro-β-amino esters via reaction of the Reformatsky reagent derived from ethyl bromodifluoroacetate with chiral *N*-*tert*-butylsulfinimines. The diastereomeric adducts are readily purified by chiral HPLC and the *tert*-butylsulfinyl group serves as a sturdy protecting group on nitrogen during subsequent transformations of the ester moiety. These adducts provide the corresponding carboxylic acids as well as novel monoprotected 2,2-difluoro-1,3-diaminopropane fragments (in 2 steps), both of which undergo facile peptide coupling reactions. The ease of manipulation of these sulfinamide adducts should render this method readily applicable to solid-phase peptide synthesis.

Experimental Section[17]

***N*-(1-Cyclohexylmethylidene)-2-methylpropane-2-sulfinamide (4d).** To a solution of *R*-(+)-2-methyl-2-propanesulfinamide (**2**, 2.7 g, 22.3 mmol) in CH_2Cl_2 (30 mL) was added copper sulfate (17.8 g, 111.4 mmol) and molecular sieves. A solution of cyclohexane carboxaldehyde (**3d**, 5.0 g, 44.6 mmol) in CH_2Cl_2 (7 mL) was then added dropwise. The mixture was stirred at room temperature for 18 h. The resulting mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo giving the crude product, which was purified by silica gel chromatography (gradient elution with hexane to 1:9 ethyl acetate/hexane to 1:1 ethyl acetate/hexane) to afford **4d** as a clear oil (85% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, $J = 4.8$ Hz, 1 H), 2.47−2.46 (m, 1 H), 1.89−1.68 (m, 5 H), 1.37−1.24 (m, 5 H), 1.19 (s, 9 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.85, 56.57, 44.17, 29.48, 26.05, 25.53, 22.48; FTIR (cm^{-1}) 2925 and 2849 (C−H), 1618 (C=N), 1086 (S=O), 687 (C−S); HRMS (FAB) calculated for $(C_{11}H_{22}NOS)^+$ (M + H) 216.1417, found 216.1446.

Ethyl 3-[(*tert*-Butylsulfinyl)amino]-3-cyclohexyl-2,2-difluoropropanoate (5d).[18] To a suspension of zinc (~100 mesh powder, 2.73 g, 41.8 mmol) in anhydrous, degassed THF (27 mL) was added ethyl bromodifluoroacetic (5.36 mL, 41.8 mmol). The mixture was warmed to 30 °C, resulting in a vigorous exothermic reaction that gave a green-gray mixture. The oil bath was removed and additional ethyl bromodifluoroacetic (2.0 mL, 15.6 mmol) was added to consume the zinc. After cooling to room temperature, the resulting solution [ca. 3 equiv of Reformatsky reagent (**1**)] was cannulated into a solution of *N*-(1-cyclohexylmethylidene)-2-methylpropane-2-sulfinamide (**4d**, 3.0 g, 13.9 mmol) in anhydrous, degassed THF (15 mL). The reaction was stirred at room temperature under inert atmosphere for 18 h. The solvent was removed in vacuo, and the resulting oil was redissolved in ethyl acetate. To this solution was added 3% aqueous ammonium hydroxide. The resulting precipitate was removed by filtration. The filtrate layers were separated, and the aqueous layer was extracted twice more with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Silica gel chromatography (gradient elution with 1:5 ethyl acetate/hexane to ethyl acetate) afforded the diastereomeric mixture **5d** as a clear oil (3.70 g, 81%). The minor and major diastereomers eluted at 5.86 and 8.02 min respectively by analytical chiral HPLC (Chiralpak AD column eluting with 98:2 A/B, where A = hexane and B = 2-propanol); diastereomeric ratio 13:87. Data for the diastereomeric mixture **5d**:[19] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.38 (app q, $J = 7.2$ Hz, 2 H, from major diastereomer) and 4.30 (m, 2 H, from minor diaste-

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(16) See the Supporting Information.

(17) Full experimental details and compound characterization appear in the Supporting Information.

(18) Oven-dried glassware was used for the protocol described in this procedure.

reomer), 3.78−3.60 (m, 2 H), 3.49 (d, $J = 9.7$ Hz, 1 H, from minor diastereomer), 1.88−1.56 (m, 8 H), 1.37 (t, $J = 7.1$ Hz, 3 H), 1.26 (s, 9 H), 1.10−1.04 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 63.58, 63.46, 63.17, 62.84, 60.52, 57.33, 38.11, 31.06, 27.05, 26.50, 26.01, 23.09, 22.95, 21.16, 14.34, 14.00; FTIR (cm^{-1}) 2934 and 2857 (C−H), 1768 (C=O), 1096 (C−O), 1042 (S=O); HRMS (FAB) calculated for $(C_{15}H_{28}F_2NO_3S)^+$ (M + H) 340.1752, found 340.1770. The diastereomers were separated on preparative scale under the conditions described above and were characterized as follows: Minor diastereomer of **5d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (qd, $J = 2.8$, 7.2 Hz, 2 H), 3.75−3.64 (m, 1 H), 3.47 (d, $J = 10$ Hz, 1 H), 1.82−1.57 (m, 4 H), 1.67−1.61 (m, 4 H), 1.36 (t, $J = 7.2$ Hz, 3 H), 1.21 (s, 9 H), 1.31−1.13 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.11, 163.78, 163.47, 118.29, 115.76, 113.20, 64.12, 63.87, 63.65, 63.18, 57.01, 37.73, 30.91, 27.92, 26.65, 26.28, 25.94, 22.75, 14.13; FTIR (cm^{-1}) 2924 and 2850 (C−H), 1775 (C=O), 1069 (C−O), 1042 (S=O); HRMS (APCI) calculated for $(C_{15}H_{28}F_2NO_3S)^+$ (M + H) 340.1752, found 340.1735. Major diastereomer of **5d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.38 (app q, $J = 7.2$ Hz, 2 H), 3.74−3.63 (m, 2 H), 1.83−1.56 (m, 8 H), 1.40−1.03 (m, 6 H), 1.26 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 118.76, 115.36, 63.62, 57.46, 42.45, 26.01, 23.92, 22.34, 12.02, 10.44; FTIR (cm^{-1}) 2984 and 2857 (C−H), 1771 (C=O), 1097 (C−O), 1044 (S=O); HRMS (ES) calculated for $(C_{15}H_{28}F_2NO_3S)^+$ (M + H) 340.1752, found 340.1750.

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Supporting Information Available: Experimental procedures and full characterization including spectral data for compounds **4a**−**c**, **4e**, **5a**−**c, 5e**, and **12**−**22**, ^{1}H NMR spectra for compounds **4d** and **5d**, and X-ray crystal structure of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Peaks of the major and minor diastereomers overlap unless otherwise noted.