Stereoselective Synthesis of Fluorinated Isoxazolidines and 2,3-Dihydroisoxazoles: A Cycloadditive Route to Enantiomerically Pure Amino Fluoro Alcohols

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3-(Fluoroalkyl)isoxazolidines **6** and -2,3-dihydroisoxazoles **8** have been obtained in enantiomerically pure form with good diastereoselectivity by 1,3-dipolar cycloaddition of diethyl fumarate and dimethylacetylene dicarboxylate, respectively, to the chiral fluorinated nitrone (*R*)-**5**. The latter has been prepared from the β-fluoromethyl-β-oxo sulfoxide (R_S)-**1**, by a synthetic sequence where the chiral and enantiomerically pure sulfinyl function acts as a removable source of chirality. Reductive opening of isoxazolidines **6** then afforded amino fluoromethyl diols **7** in good yields.

The synthesis of fluoro-substituted heterocycles has received a great deal of attention in recent years, because the peculiar biological activity of many of these compounds makes them effective as antifungal, antiviral, and antitumor agents.[1] However, although a great number of achiral fluoro heterocycles have been described, only a few enantiomerically pure, selectively fluorinated derivatives have been prepared by asymmetric synthesis.[2]

One of the most powerful tools for the construction of five-membered heterocyclic systems with defined substitution patterns are 1,3-dipolar cycloadditions,[3] owing to their remarkable stereocontrol: One of the key features of the reaction is the possibility of transferring the stereochemical information present on the dipole or on the dipolarophile moiety to the newly formed stereocentres of the heterocyclic ring.[4]

In the context of an ongoing research program on the synthesis of optically active fluoroorganic compounds with a sulfinyl group acting as a chiral auxiliary,[5] we described the preparation of some fluoro-substituted 4,5-dihydroisoxazoles and isoxazolidines. These were obtained by 1,3-dipolar cycloaddition of nitrile oxides and nitrones with fluorinated alkene dipolarophiles bearing a chiral and optically pure sulfinyl group, such as vinyl or allyl sulfoxides.[6] These heterocycles are also versatile templates in organic synthesis, since their N−O bond can be reductively cleaved, affording open-chain compounds such as β-hydroxy ketones and 1,3-amino alcohols.[4a] In the examples described, the fluorinated substituent and the sulfinyl chiral auxiliary both reside on the dipolarophile moiety. Since asymmetric 1,3-dipolar cycloadditions of nitrones can also be efficiently performed when a chiral substituent is properly sited on the nitrone,[4e] rather than on the dipolarophile, it appeared interesting to consider a chiral and enantiomerically pure fluorinated nitrone as the cycloaddition counterpart, in order to exploit the synthetic potential of its reaction with dipolarophiles. It must be added that, to the best of our knowledge, only an achiral *C*-trifluoromethyl nitrone has been described in the literature.[7] Whilst a recent paper deals with chiral fluoro-substituted nitrones[8] used in intermolecular cycloadditions, some examples of such nitrones have been reported in intramolecular applications, but they have never been isolated.[9] In order to achieve the desired synthesis, we decided to use chiral and enantiomerically pure fluorinated β-oxo sulfoxides[5] as starting materials, due to their easy availability and great potential.

We report here the synthesis of the chiral and enantiomerically pure β-fluoromethyl nitrone **5**, exploiting the sulfinyl function of the β-oxo sulfoxide **1** as the primary source of chirality. Also described are its reaction with typical dipolarophiles, such as diethyl fumarate and dimethyacetylene dicarboxylate, which allowed the preparation of isoxazolidines **6** and 2,3-dihydroisoxazoles **8** with good diastereoselectivity. Isoxazolidine rings **6** were then reductively opened, affording fluoromethyl aminodiols **7**.

Results and Discussion

β-Fluoromethyl-β-oxo sulfoxide (R_S)-**1**, easily available through the condensation of the lithium salt of methyl *p*-tolyl sulfoxide with ethyl fluoroacetate,[10] was reduced to the β-hydroxy sulfoxide (2*S*,R_S)-**2** with diisobutylaluminium hydride with high diastereoselectivity[11] (Scheme 1). By treatment of the latter alcohol with benzyl bromide, the *O*-benzyl derivative (2*S*,R_S)-**3** was then obtained in good yield.[12] The sulfinyl function of compound (2*S*,R_S)-**3** was then removed by Pummerer rearrangement[13] performed with trifluoroacetic anhydride and $HgCl_2$,[14] to give the aldehyde (*R*)-**4**, that was not isolated. By direct treatment[9] of the crude mixture with *N*-benzylhydroxylamine hydrochloride, the stable, chiral and enantiomerically pure (vide

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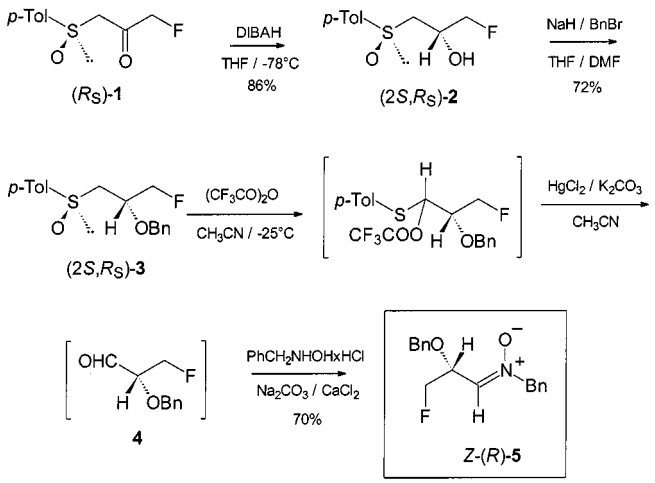
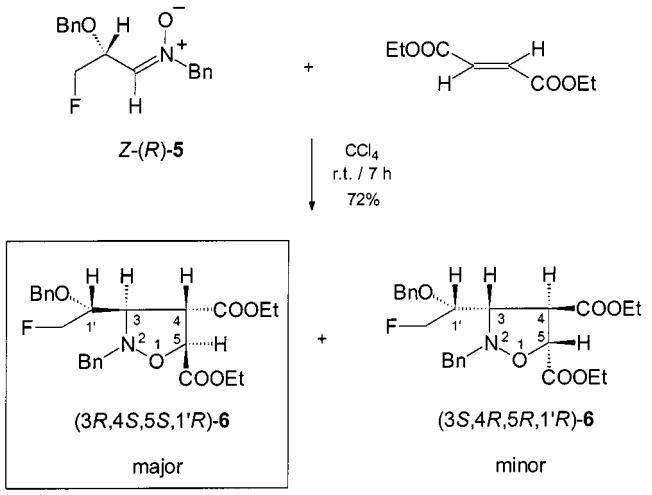
infra) nitrone (*R*)-**5** was obtained in 70% yield. The (*Z*) form was assigned to the nitrone, on the basis of NOE (3%) observed between the benzylic hydrogen atoms at a chemical shift of δ = 4.86 and the olefinic hydrogen at δ = 6.71.[8]



Scheme 1. Synthesis of nitrone (*R*)-**5** from β-fluoromethyl-β-oxo sulfoxide (R_S)-**1**

Nitrone (*R*)-**5** was then treated with two typical symmetrical dipolarophiles. The reaction of the nitrone with a 3:1 molar ratio of diethyl fumarate was performed in CCl_4; after 7 h stirring at room temperature, the two diastereoisomeric isoxazolidines (3*R*,4*S*,5*S*,1′*R*)-**6** (major) and (3*S*,4*R*,5*R*,1′*R*)-**6** (minor) were isolated in a 5.5:1 ratio from the crude reaction mixture by flash column cromatography, in 72% overall yield (Scheme 2).



Scheme 2. 1,3-Dipolar cycloaddition of nitrone (*R*)-**5** with diethyl fumarate

The structure and the absolute stereochemistry of compounds **6** were determined by analysis of their ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra and NOE experiments (see Experimental section and Figure 1) and by chemical evidence. In both the diastereoisomeric compounds, (3*R*,4*S*,5*S*,1′*R*)-**6** and (3*S*,4*R*,5*R*,1′*R*)-**6**, mutual NOEs were observed between 3-H and 5-H, which must therefore be disposed on the same side of the ring in the two molecules. The *anti* configuration of 4-H with respect to 5-H, and therefore also with 3-H, follows from the stereoconservative mechanism of 1,3-dipolar cycloadditions,[3] being *trans*-configured in the starting olefin, diethyl fumarate. In the major isomer, (3*R*,4*S*,5*S*,1′*R*)-**6**, the C-3 side chain assumes the preferred configuration shown in Figure 1, as evidenced by the NOEs observed between 1′-H and the *N*-CH_2 protons, between the fluorine atom and 3-H but not with 4-H, and the smaller enhancements observed for the CH_2F protons with respect to the OCH_2 ones by irradiation of 4-H. All these findings require that the chirality of C-3, C-4, and C-5 is (*R*,*S*,*S*), respectively, being (*R*) the absolute configuration of C-1′. In the minor isomer (3*S*,4*R*,5*R*,1′*R*)-**6**, the smaller NOEs observed for the OCH_2 protons with respect to the CH_2F ones by irradiation of 4-H, together with the lack of sizable NOEs between 1′-H and the *N*-CH_2 protons, and the enhancements of both 3-H and 4-H by irradiation of the fluorine atom indicate that the C-3 side chain preferentially adopts the conformation depicted in Figure 1, thus confirming that the ring carbon atoms have opposite chirality. It must be noted that a progressive addition of the optically active shift reagent Eu(TFC)$_3$, {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]europium(III)}, to a $CDCl_3$ solution of major-**6** showed no doubling of ^{1}H-NMR signals. This fact showed the enantiomeric purity of compound major-**6** to be ≥ 95% and therefore also demonstrated the enantiomeric purity of its precursor nitrone (*R*)-**5**.

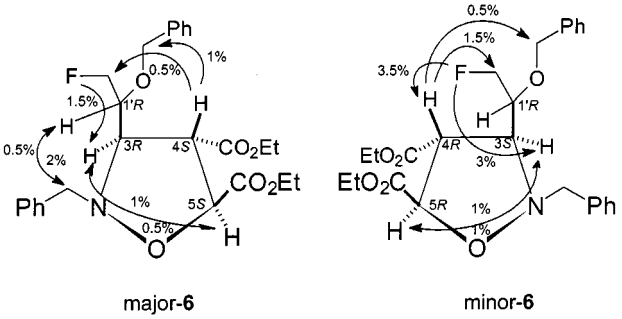
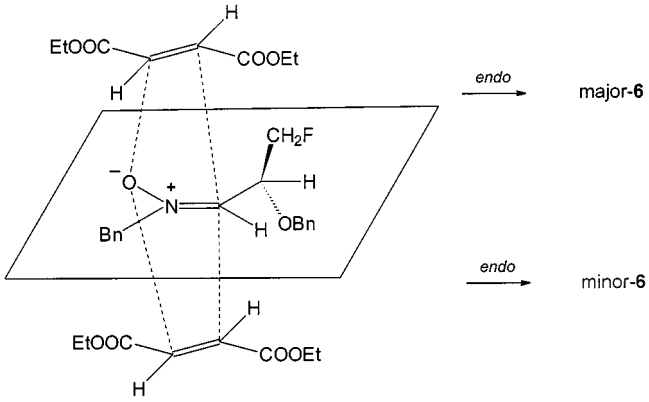


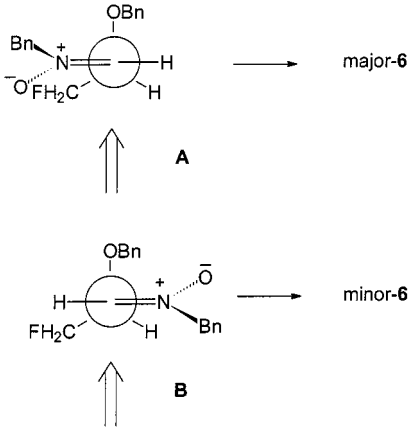
Figure 1. Selected NOEs in isoxazolidines **6**

From the mechanistic point of view, both isoxazolidines **6** result from a 100% *endo* attack of the alkene dipolarophile on the (*Z*)-nitrone **5** (Scheme 3): Such total *endo* selectivity may be ascribed to the steric interaction in the transition state between one of the ethoxy groups of diethyl fumarate and the bulky C substituent of the nitrone, that leads them in an *anti* relationship in the cycloadducts. The facial diastereoselectivity shown in the cycloaddition in favour of the major isomer (3*R*,4*S*,5*S*,1′*R*)-**6** could be explained by comparison between the two preferred conformations of the nitrone in the transition state. These conformations can reasonably be assumed to be the same as those proposed by DeShong for structurally related nitrones,[15] referring to Felkin-Ahn models[16] (Scheme 4). As suggested by Ahn, the polarized carbon−oxygen bond is orthogonal to the plane of the nitrone, thus excluding any conformation where the C substituent is perpendicular to

the double bond. The attack of the dipolarophile takes place preferably onto conformation **A**, which is expected to be the more reactive conformer, since the approach of the dipolarophile to the nitrone carbon atom avoids interactions with the bulky C substituent, thus leading to the major cycloadduct (3*R*,4*S*,5*S*,1′*R*)-**6**.



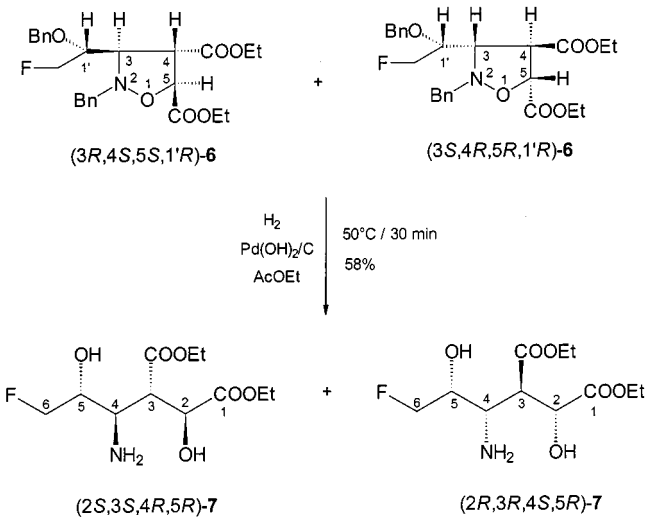
Scheme 3. Proposed model for the total *endo* selectivity of the cycloaddition



Scheme 4. Preferred conformations of the nitrone (*R*)-**5** in the transition state

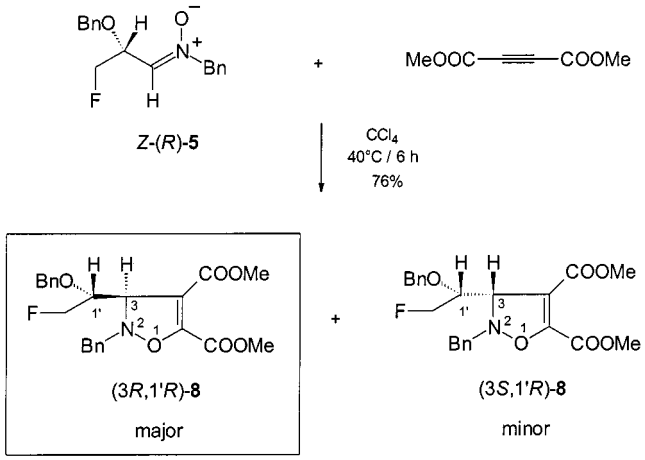
In order to obtain open-chain compounds, the 5.5:1 mixture of isoxazolidines **6** was subsequently hydrogenated in ethyl acetate at atmospheric pressure in the presence of $Pd(OH)_2$:[17] After 30 min of stirring at 50°C, the two diastereoisomeric amino diols (2*S*,3*S*,4*R*,5*R*)-**7** (major) and (2*R*,3*R*,4*S*,5*R*)-**7** (minor) were isolated in a 5:1 ratio by flash column cromatography in 58% overall yield (Scheme 5). As evidenced by spectral and analytical data (see Experimental Section), the reductive cleavage of the N−O bond was accompanied by a concomitant complete debenzylation, thus allowing the deprotection of both the amino and the hydroxy functions.

The reaction of nitrone (*R*)-**5** with a 20% molar excess of dimethylacetylene dicarboxylate was performed in CCl_4 at 40°C: After stirring for 6 h, the two diastereoisomeric 2,3-dihydroisoxazoles (3*R*,1′*R*)-**8** (major) and (3*S*,1′*R*)-**8** (minor) were isolated in a 2:1 ratio from the crude reaction



Scheme 5. Catalytic hydrogenation of isoxazolidines **6**

mixture by flash column cromatography, in 76% overall yield (Scheme 6). The stereochemistry of the two 2,3-dihydroisoxazoles **8** was tentatively assigned on the basis of chemical-shift criteria, since no significant NOE enhancements were observed. In fact, in the major isomer the CH_2F protons resonate at a lower field with respect to the corresponding protons of the minor isomer and the OCH_2 protons at a higher field. This behaviour may be attributed to the shielding effect exerted by the C-4−C-5 double bond, in the hypothesis that in 2,3-dihydroisoxazoles **8** the C-3 side chain assumes the same preferred conformation adopted in the corresponding isoxazolidines **6**. Furthermore, such stereochemistry should also follow from the observed general behaviour of the same nitrone with structurally related ethylene and acetylene dipolarophiles.[3][4] The lower reactivity of dimethylacetylene dicarboxylate with respect to diethyl fumarate reflects the general behaviour with nitrones of acetylenic dipolarophiles, compared to ethylenic ones.[4a]



Scheme 6. 1,3-Dipolar cycloaddition of nitrone (*R*)-**5** with dimethylacetylene dicarboxylate

Conclusion

In conclusion, an efficient general route to chiral fluorinated nitrones has been described: Starting from properly fluoro-substituted β-oxo sulfoxides and different *N*-alkylhydroxylamines, a wide variety of such nitrones can be prepared. On considering the great deal of unsaturated molecules that can be used as dipolarophiles, there is clear evidence that the described method is a valid and effective route to a wide variety of chiral, selectively fluorinated isoxazolidine and 2,3-dihydroisoxazole systems of potential biological interest. The reductive opening of the obtained heterocycles can then efficiently allow the preparation of highly functionalized and enantiomerically pure fluorinated amino alcohols.

Experimental Section

General: Melting points (m.p.) are uncorrected and obtained with a capillary apparatus. − Polarimetric analyses were performed with JASCO IP-181 and PROPOL polarimeters. − Analytical thin-layer chromatography (TLC) were routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Flash chromatographies (FC) were performed with silica gel 60 (230−400 ASTM mesh). − ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were recorded with a Bruker AC 250L spectrometer, operating at 250.13, 62.89 and 235.35 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00), whilst C_6F_6 was used as external standard (δ_F = −162.90) for ^{19}F. Coupling constants are expressed in Hertz (Hz). In the ^{13}C-NMR signal assignment, capital letters refer to the pattern resulting from directly bonded (C,H) couplings and lower case letters to the one from (C,F) couplings. − Mass spectra were registered on a TSQ 70 Finnigan Mat three-stage quadrupole instrument. DIS (Direct Inlet System) was used for pure compounds. − Infrared spectra were performed using a Perkin−Elmer System 2000 FT-IR (scan range: 15600 cm^{-1}; combined scan direction). − Commercially available reagent-grade solvents were employed without purification. All reactions where anhydrous organic solvents were employed were performed under nitrogen, after flame-drying procedures of the glass apparatus. Compounds **1**[10], **2**[11], and **3**[12] were prepared as described previously.

Synthesis of the Fluorinated Nitrone (*R*)-5: A solution of trifluoroacetic anhydride (0.39 mL, 1.96 mmol) in CH_3CN was added dropwise to a solution of the *O*-benzyl derivative (2*S*,R_S)-**3** (300 mg, 0.98 mmol) and sym-collidine (0.29 mL, 2.16 mmol) in CH_3CN (3 mL), cooled at −25°C and stirred under nitrogen. The mixture was allowed to reach room temperature and, after total consumption of the substrate, it was cooled again at −10°C; solid K_2CO_3 was then added until pH = 7, then a solution of of $HgCl_2$ (800 mg, 2.94 mmol) in CH_3CN (4 mL) was added portionwise. A white precipitate formed slowly. The reaction mixture was allowed to reach room temperature, and stirring was continued for 2.5 h. The white solid was filtered through a Celite pad, and the filtrate was concentrated to dryness under reduced pressure. An attempt to isolate the intermediate aldehyde **4** as a pure compound was performed through purification of the crude reaction mixture by flash chromatography with an *n*-hexane/ethyl acetate (8:2) mixture as eluant. Only 2-benzyloxyprop-2-enal[18] was recovered in 55% yield: R_f = 0.40.− ^{1}H NMR ($CDCl_3$): δ = 4.88 (br. s, 2 H, OCH_2), 5.10 and 5.22 (d, *J* = 3.1 Hz, 2 H, C=CH_2), 7.1−7.4 (m, 5 H, ArH), 9.27 (s, 1 H, CHO). − MS (EI); *m*/*z* (%): 162 (8) $[M + H]^+$, 133 (23) $[C_9H_9O]^{+\cdot}$, 107 (8) $[C_7H_7O]^{+\cdot}$, 105 (10) $[C_7H_5O]^{+\cdot}$, 91 (100) $[C_7H_7]^{+\cdot}$. − IR (film): $\tilde{\nu}$ = 3034 cm^{-1} (ν_{CHArom}), 2927 (ν_{CH2}), 2854, 1705 (ν_{CHO}), 1613, 1456, 1311, 1261 ($\nu_{C=C}$), 1047, 872, 741, 698. − The crude intermediate aldehyde **4** (296 mg, 1.6 mmol) was suspended in methanol (10 mL) and the resulting slurry was added dropwise to a suspension of *N*-benzylhydroxylamine hydrochloride (0.808 g, 5.1 mmol), sodium carbonate (0.537 g, 5.1 mmol) and calcium chloride (0.562 g, 5.1 mmol) in methanol (4.5 mL). The mixture was stirred at room temp. for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate from 3:2 to 1:1) to give 320 mg of (*R*)-**5**: Yield 70%, m.p. 63°C. − R_f = 0.33. − $[\alpha]_D^{20}$ = +21.5 (*c* = 1.2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$) δ = 4.56 and 4.62 (br. d, *J* = 12.0 Hz, 2 H, OCH_2), 4.61 (ddd, *J* = 47.5, 9.7 and 4.1 Hz, 1H, CH_aF), 4.65 (ddd, *J* = 47.5, 9.7 and 2.8 Hz, 1 H, CH_bF), 4.86 (br. s, 2 H, NCH_2), 4.92 (dddd, *J* = 24.5, 5.9, 4.1 and 2.8 Hz, 1H, OCH), 6.71 (br. d, *J* = 5.9 Hz, 1 H, N=CH), 7.2−7.5 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$), δ = 69.49 (T, NCH_2); 72.49 (T, OCH_2); 73.69 (Dd, $^2J_{C,F}$ = 20.4 Hz, OCH); 81.44 (Td, $^1J_{C,F}$ = 173.9 Hz, CH_2F); 127.73 (D), 127.84 (D), 128.31 (D), 128.84 (D), 128.99 (D), 129.11 (D), 132.02 (S) and 137.15 (S); 135.60 (Sd, $^3J_{C,F}$ = 8.0 Hz, N=CH). − ^{19}F NMR ($CDCl_3$) δ = −230.65 (br. dt, *J* = 24.5 and 47.5 Hz, 1 F, CH_2F). − Selected NOE: {N=CH} enhanced NCH_2 (3%). − IR (KBr) $\tilde{\nu}$ = 3031 cm^{-1}, 2959, 1600 ($\nu_{C=N}$), 1455, 1169 (ν_{N-O}), 1027, 749, 700. − MS (EI); *m*/*z* (%): 288 (8) $[M + H]^+$, 181 (21) $[C_{10}H_{12}FNO]^{+\cdot}$, 161 (7) $[C_{10}H_{11}NO]^{+\cdot}$, 123 (6) $[C_7H_9NO]^{+\cdot}$, 105 (3) $[C_7H_7N]^{+\cdot}$, 91 (100) $[C_7H_7]^{+\cdot}$, 77 (8) $[C_6H_5]^{+\cdot}$. − $C_{17}H_{18}FNO_2$ (287.33): calcd. C 71.06, H 6.31, N 4.87; found C 70.95, H 6.40, N 4.76.

Reaction of Nitrone (*R*)-5 with Diethyl Fumarate: Neat diethyl fumarate (69 μL, 0.4 mmol) was added by syringe to a solution of nitrone (*R*)-**5** (100 mg, 0.3 mmol) in CCl_4 (7 mL) kept under nitrogen. The reaction mixture was stirred at room temperature for 3.5 h. Then a furher excess of diethyl fumarate (83 μL, 0.48 mmol) was added and the reaction was stirred for additional 3.5 h. The solvent was evaporated to dryness and ^{19}F- and ^{1}H-NMR analyses of the crude reaction mixture revealed a 5.5:1 mixture of isoxazolidines (3*R*,4*S*,5*S*,1′*R*)-/(3*S*,4*R*,5*R*,1′*R*)-**6**. The residue was purified by flash chromatography with an *n*-hexane/ethyl acetate (9:1) mixture as eluant to give 104 mg of compounds **6** as the only detectable epimeric mixture of compounds (72% overall yield, R_f = 0.35). Further flash purifications with a cyclohexane/ethyl acetate (9:1) mixture as eluant afforded the isolation of the two diastereoisomeric isoxazolidines **6** in enantiomerically and diastereomerically pure form.

(3*R*,4*S*,5*S*,1′*R*)-6 (Major): R_f = 0.37. − $[\alpha]_D^{20}$ = +19.4 (*c* = 0.6, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.27 and 1.31 (t, *J* = 7.1 Hz, 6 H, 2 OCH_2*Me*), 3.58 (dd, *J* = 6.6 and 4.3 Hz, 1 H, 3-H), 3.71 (dddd, *J* = 20.1, 6.6, 5.6, and 3.0 Hz, 1 H, 1′-H), 3.86 (dd, *J* = 5.7 and 4.3 Hz, 1 H, 4-H), 4.07 and 4.10 (br. d, *J* = 13.5 Hz, 2 H, NCH_2), 4.1−4.3 (m, 4 H, 2 O*C*H_2Me), 4.39 (ddd, *J* = 47.5, 10.1, and 5.6 Hz, 1 H, CH_aF), 4.59 (ddd, *J* = 47.2, 10.1, and 3.0 Hz, 1 H, CH_bF), 4.61 and 4.71 (br. d, *J* = 11.6 Hz, 2 H, OCH_2), 5.05 (d, *J* = 5.7 Hz, 1 H, 5-H), 7.2−7.5 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.09 and 14.21 (Q, 2 OCH_2*Me*); 53.90 (D, C-4); 60.59 (T, NCH_2); 61.78 and 61.86 (T, 2 O*C*H_2Me); 68.59 (Dd, $^3J_{C,F}$ = 7.2 Hz, C-3); 73.00 (T, OCH_2); 77.52 (Dd, $^2J_{C,F}$ = 18.5 Hz, C-1′); 78.55 (D, C-5); 83.16 (Td, $J_{C,F}$ = 171.5 Hz, *C*H_2F); 127.53 (D), 127.65 (D), 127.68 (D), 128.26 (D), 128.34 (D), 128.92 (D), 136.28 (S) and 137.89 (S) (ArC); 169.75 and 171.90 (S, 2 *C*O_2Et). − ^{19}F NMR ($CDCl_3$): δ = −231.40 (br. ddd, *J* = 47.5, 47.2, and

20.1 Hz, 1 F, CH_2F). − Selected NOEs ($CDCl_3$): {3-H} enhanced 4-H (2%), 5-H (1%), 2-CH_2 (2%), 1′-OCH_2 (0.5%) and 1′-CH_2 (1%); {4-H} enhanced 3-H (2%), 5-H (2.5%), 1′-H (2.5%), 1′-OCH_2 (1%) and 1′-CH_2 (0.5%); {5-H} enhanced 3-H (0.5%), 4-H (2%), and 2-CH_2 (1.5%); {1′-H} enhanced 4-H (3%), 2-CH_2 (0.5%), 1′-OCH_2 (2%) and 1′-CH_2 (1%); {2-CH_2} enhanced 3-H (10.5%), 5-H (9%) and 1′-H (2%); {1′-OCH_2} enhanced 3-H (0.5%), 4-H (0.5%) and 1′-H (2%); {F} enhanced 3-H (1.5%), 1′-H (2.5%), 1′-OCH_2 (0.5%) and 1′-CH_2 (7.5%). − IR (film): $\tilde{\nu}$ = 2984 cm^{-1}, 1735, 1455, 1372, 1218, 1097, 1030, 754, 699. − MS (EI): 460 (5) $[M + H]^+$, 386 (1) $[C_{22}H_{25}FNO_4]^+$, 307 (7) $[C_{16}H_{21}NO_5]^{+\cdot}$, 306 (40) $[C_{16}H_{20}NO_5]^+$, 280 (10) $[C_{14}H_{15}FNO_4]^+$, 260 (37) $[C_{11}H_{15}FNO_5]^+$, 164 (10) $[C_9H_7FNO]^+$, 91 (100) $[C_7H_7]^{+\cdot}$. − $C_{25}H_{30}FNO_6$ (459.51): calcd. C 65.35, H 6.58, N 3.05; found C 65.47, H 6.50, N 3.13.

(3*S*,4*R*,5*R*,1′*R*)-6 (Minor): R_f = 0.33. − ^1H NMR ($CDCl_3$/[D_6]benzene, 1:2): δ = 1.28 (t, *J* = 7.1 Hz, 6 H, 2 OCH_2*Me*), 3.66 (dddd, *J* = 20.2, 6.7, 5.4, and 3.6 Hz, 1 H, 1′-H), 3.68 (ddd, *J* = 6.7, 4.7, and 1.2 Hz, 1 H, 3-H), 3.77 (dd, *J* = 5.7 and 4.7 Hz, 1 H, 4-H), 4.12 and 4.15 (br. d, *J* = 13.5 Hz, 2 H, N*CH*$_2$), 4.21 and 4.23 (q, *J* = 7.1 Hz, 4 H, 2 O*CH*$_2$Me), 4.55 (ddd, *J* = 47.1, 10.5, and 5.4 Hz, 1 H, CH_aF), 4.56 (ddd, *J* = 47.3, 10.5, and 3.6 Hz, 1 H, CH_bF), 4.60 and 4.63 (br. d, *J* = 11.7 Hz, 2 H, O*CH*$_2$), 4.99 (d, *J* = 5.7 Hz, 1 H, 5-H), 7.2−7.4 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$) δ = 14.09 and 14.21 (Q, 2 OCH_2*Me*); 53.18 (D, C-4); 61.30 (T, NCH_2), 61.78 and 61.86 (T, 2 O*C*H_2Me); 68.19 (Dd, $^3J_{C,F}$ = 6.9 Hz, C-3); 72.95 (T, OCH_2); 78.29 (Dd, $^2J_{C,F}$ = 18.5 Hz, C-1′); 78.70 (D, C-5); 83.53 (Td, $^1J_{C,F}$ = 171.0 Hz, *C*H_2F); 127.45 (D), 127.67 (D), 127.83 (D), 128.26 (D), 128.34 (D), 128.84 (D), 136.48 (S), and 137.73 (S) (ArC); 169.43 and 171.80 (S, 2 *C*O_2Et). − ^{19}F NMR ($CDCl_3$): δ = −230.45 (br. ddd, *J* = 47.3, 47.1, and 20.2 Hz, 1 F, CH_2F). − Selected NOEs ($CDCl_3$/[D_6]benzene, 1:2): {3-H} enhanced 4-H (1%), 5-H (1%), 1′-H (2%), 2-CH_2 (2%), 1′-OCH_2 (1%) and 1′-CH_2 (1%); {4-H} enhanced 3-H (1%), 5-H (2%), 1′-H (3%), 1′-OCH_2 (0.5%) and 1′-CH_2 (1.5%); {5-H} enhanced 3-H (1%), 4-H (2.5%) and 2-CH_2 (1.5%); {1′-H} enhanced 3-H (1%), 4-H (2.5%), 1′-OCH_2 (2%) and 1′-CH_2 (1.5%); {2-CH_2} enhanced 3-H (11%) and 5-H (11.5%); {1′-OCH_2} enhanced 3-H (2%) and 1′-H(3%); {1′-CH_2} enhanced 4-H (3.5%) and 1′-H (3%); {F} enhanced 3-H (3%), 4-H (3.5%), 1′-H (6%), 1′-OCH_2 (1.5%) and 1′-CH_2 (10.5%). − IR (film): $\tilde{\nu}$ = 2928.21 cm^{-1}, 2365, 1734 (ν_{COO}), 1456, 1374, 1265, 1218, 1098, 1029, 757. − MS (EI); *m*/*z* (%): 460 (5) $[M + H]^+$, 386 (20) $[C_{22}H_{25}FNO_4]^+$, 306 (20) $[C_{16}H_{20}NO_5]^+$, 280 (5) $[C_{14}H_{15}FNO_4]^+$, 260 (20) $[C_{11}H_{15}FNO_5]^+$, 165 (8) $[C_9H_8FNO]^{+\cdot}$, 91 (100) $[C_7H_7]^{+\cdot}$. − $C_{25}H_{30}FNO_6$ (459.51): calcd. C 65.35, H 6.58, N 3.05; found C 65.27, H 6.66, N 3.15.

Catalytic Hydrogenation of Isoxazolidines 6: A solution of the 5.5:1 mixture of isoxazolidines **6** (95 mg, 0.21 mmol) in ethyl acetate (8 mL) was hydrogenated at atmospheric pressure and at 50°C for 30 min in the presence of 20% $Pd(OH)_2$/C (30 mg). The catalyst was removed by filtration through a Celite pad, and the solvent was removed under reduced pressure. The residue was flash-chromatographed on a silica gel column with a toluene/EtOH (4:1) mixture as eluant, affording amino diols **7** (58% yield).

(2*S*,3*S*,4*R*,5*R*)-7 (Major): $[\alpha]_D^{20}$ = −54.3 (*c* = 0.2, CH_3OH). − M.p. 112−113°C ($CHCl_3$/AcOEt, 9:1). − ^1H NMR (CD_3OD + D_2O): δ = 1.27 (t, *J* = 7.2 Hz, 6 H, 2 Me), 3.50 (dd, *J* = 8.6 and 3.7 Hz, 1 H, 3-H), 3.78 (dddd, *J* = 21.5, 5.1, 4.4, and 4.1 Hz, 1 H, 5-H), 3.99 (dd, *J* = 4.4 and 3.7 Hz, 1 H, 4-H), 4.17 and 4.18 (q, *J* = 7.2 Hz, 4 H, 2 OCH_2), 4.39 (ddd, *J* = 47.3, 10.0, and 4.1 Hz, 1 H, C*H*HF), 4.41 (ddd, *J* = 47.3, 10.0, and 5.1 Hz, 1 H, CH*H*F), 4.52 (d, *J* = 8.6 Hz, 1 H, 2-H). − ^{13}C NMR (CD_3OD) δ = 14.53 (Q, 2 Me), 47.83 (D, C-3), 57.07 (Dd, $^3J_{C,F}$ = 5.5 Hz, C-4), 62.10 (T, 2 OCH_2), 70.90 (D, C-2), 71.76 (Dd, $^2J_{C,F}$ = 19.0 Hz, C-5), 85.44 (Td, $^1J_{C,F}$ = 170.0 Hz, C-6), 172.11 and 177.52 (S, 2 CO). − ^{19}F NMR (CD_3OD): δ = −230.75 (dt, *J* = 21.5 and 47.3 Hz, CH_2F). − IR (KBr): $\tilde{\nu}$ = 3451 cm^{-1}, 3341 (ν_{OH}, ν_{NH}), 1708 (ν_{COO}). − MS (FAB/Xe); *m*/*z* (%): 282 (25) $[M + H]^+$, 244 (20) $[C_{11}H_{18}NO_5]^+$, 236 (85) $[C_9H_{15}FNO_5]^+$, 218 (63) $[C_9H_{13}FNO_4]^+$, 190 (45) $[C_8H_{12}O_5]^{+\cdot}$, 172 (78) $[C_7H_{12}O_4]^{+\cdot}$, 91 (100) $[C_3H_6FNO]^{+\cdot}$. − $C_{11}H_{20}FNO_6$ (281.28): calcd. C 46.97, H 7.17, N 4.98; found C 46.84, H 7.06, N 5.07.

(2*R*,3*R*,4*S*,5*R*)-7 (Minor): $[\alpha]_D^{20}$ = +25.6 (*c* = 0.1, CH_3OH). − ^1H NMR (CD_3OD + D_2O): δ = 1.28 (t, *J* = 7.2 Hz, 6 H, 2 Me), 3.39 (dd, *J* = 8.3 and 3.9 Hz, 1 H, 3-H), 3.79 (ddt, *J* = 15.3, 3.6, and 5.8 Hz, 1 H, 5-H), 4.01 (dd, *J* = 3.9 and 3.6 Hz, 1 H, 4-H), 4.17 and 4.18 (q, *J* = 7.2 Hz, 4 H, 2 CH_2), 4.38 (dd, *J* = 47.1 and 5.8 Hz, 2 H, CH_2F), 4.54 (d, *J* = 8.3 Hz, 1 H, 2-H). − ^{13}C NMR (CD_3OD): δ = 14.53 (Q, 2 Me), 50.18 (D, C-3), 56.97 (Dd, $^3J_{C,F}$ = 5.5 Hz, C-H), 62.11 (T, 2 OCH_2), 70.87 (D, C-2), 71.85 (Dd, $^2J_{C,F}$ = 19.8 Hz, C-5), 85.16 (Td, $^1J_{C,F}$ = 170.6 Hz, C-6), 171.93 and 177.90 (S, 2 CO). − ^{19}F NMR (CD_3OD) δ = −227.68 (dt, *J* = 15.3 and 47.1 Hz, CH_2F). − MS (FAB/Xe); *m*/*z* (%): 282 (55) $[M + H]^+$, 244 (48) $[C_{11}H_{18}NO_5]^+$, 236 (82) $[C_9H_{15}FNO_5]^+$, 198 (42) $[C_9H_{12}NO_4]^+$, 190 (45) $[C_8H_{12}O_5]^{+\cdot}$, 170 (100) $[C_7H_{10}O_4]^{+\cdot}$, 91 (78) $[C_3H_6FNO]^{+\cdot}$. − $C_{11}H_{20}FNO_6$ (281.20): calcd. C 46.97, H 7.17, N 4.98; found C 47.09, H 7.08, N 4.86.

Reaction of Nitrone (*R*)-5 with Dimethylacetylene Dicarboxylate: Neat dimethylacetylene dicarboxylate (61 μL, 0.5 mmol) was added by syringe to a solution of nitrone (*R*)-**5** (120 mg, 0.4 mmol) in CCl_4 (8.5 mL) under nitrogen. The reaction mixture was stirred at 40°C for 6 h. The solvent was evaporated to dryness and the residue was purified by flash chromatography with an *n*-hexane/ethyl acetate (4:1) mixture as eluant to give 2,3-dihydroisoxazoles (3*R*/*S*,1′*R*)-**8** as the only detectable 2:1 epimeric mixture of compounds: 129 mg (76% yield); R_f = 0.35.

(3*R*,1′*R*)-8 (Major): ^1H NMR ($CDCl_3$): δ = 3.64 and 3.88 (s, 6 H, 2 OMe), 3.85 (ddt, *J* = 19.0, 4.8, and 4.5 Hz, 1 H, 1′-H), 3.94 and 4.27 (br. d, *J* = 12.9 Hz, 2 H, NCH_2), 4.47 (dd, *J* = 4.8 and 1.3 Hz, 1 H, 3-H), 4.48 and 4.61 (br. d, *J* = 11.7 Hz, 2 H, OCH_2), 4.55 (dd, *J* = 47.5 and 4.5 Hz, 2 H, CH_2F), 7.1−7.5 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 51.96 and 53.23 (Q, 2 OMe); 63.58 (T, NCH_2); 69.29 (Dd, $^3J_{C,F}$ = 9.2 Hz, C-3); 72.66 (T, OCH_2); 79.16 (Dd, $^2J_{C,F}$ = 18.5 Hz, C-1′); 82.92 (Td, $^1J_{C,F}$ = 170.2 Hz, CH_2F); 106.95 (S, C-4); 127.86 (D), 128.27 (D), 128.39 (D), 128.46 (D), 128.60 (D), 129.63 (D), 134.33 (S) and 137.74 (S) (ArC); 152.02 (S, C-5); 159.06 and 162.62 (S, 2 *C*O_2Me). − ^{19}F NMR ($CDCl_3$): δ = −231.35 (br. dt, *J* = 19.0 and 47.5 Hz, 1 F, CH_2F). − MS (EI); *m*/*z* (%): 430 (1) $[M + H]^+$, 410 (2) $[C_{23}H_{24}NO_6]^+$, 409 (4) $[C_{23}H_{23}NO_6]^{+\cdot}$, 370 (1) $[C_{21}H_{21}FNO_4]^+$, 353 (4) $[C_{17}H_{20}FNO_6]^{+\cdot}$, 276 (8) $[C_{14}H_{14}NO_5]^+$, 218 (5) $[C_{12}H_{12}NO_3]^+$, 185 (18) $[C_7H_7NO_5]^{+\cdot}$, 156 (6) $[C_5H_2NO_5]^+$, 91 (100) $[C_7H_7]^{+\cdot}$. − $C_{23}H_{24}FNO_6$ (429.45): calcd. C 64.33, H 5.63, N 3.26; found C 64.43, H 5.55, N 3.18.

(3*S*,1′*R*)-8 (Minor): ^1H NMR ($CDCl_3$): δ = 3.62 and 3.91 (s, 6 H, 2 OMe), 3.88 and 4.32 (br. d, *J* = 12.6 Hz, 2 H, NCH_2), 3.90 (dddd, *J* = 12.0, 6.5, 5.5, and 2.5 Hz, 1 H, 1′-H), 4.12 (ddd, *J* = 46.7, 9.6, and 5.5 Hz, 1 H, CH_aF), 4.30 (br. d, *J* = 2.5 Hz, 1 H, 3-H), 4.39 (ddd, *J* = 47.2, 9.6, and 6.5 Hz, 1 H, CH_bF), 4.53 and 4.66 (br. d, *J* = 11.9 Hz, 2 H, OCH_2), 7.1−7.5 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 51.64 and 52.93 (Q, 2 OMe); 63.66 (T, NCH_2); 68.72 (Dd, $^3J_{C,F}$ = 7.5 Hz, C-3); 73.60 (T, OCH_2); 75.66 (Dd, $^2J_{C,F}$ = 18.5 Hz, C-1′); 82.92 (Td, $^1J_{C,F}$ = 170.2 Hz, CH_2F); 104.22 (S, C-4); 127.72 (D), 128.27 (D), 128.39 (D), 128.48 (D), 128.60 (D),

130.01 (D), 134.01 (S), and 137.65 (S) (ArC); 153.77 (S, C-5); 159.33 and 162.41 (S, 2 CO_2Me). – ^{19}F NMR ($CDCl_3$): δ = −229.51 (br. ddd, J = 47.2, 46.7, and 12.0 Hz, 1 F, CH_2F).

[1] M. J. Silvester, *Aldrichim. Acta* **1991**, *24*, 31; *Biomedical Aspects of Fluorine Chemistry* (Ed.: R. Filler, A. Kobayashi), Elsevier, New York, **1992**; M. J. Silvester, *Adv. Heterocycl. Chem.* **1994**, *59*, 1; K. Burger, U. Wucherpfennig, E. Brunner, *Adv. Heterocycl. Chem.* **1994**, *60*, 1; *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards* (Ed.: G. Resnati, V. A. Soloshonok), Tetrahedron Symposium-in-Print No. 58, *Tetrahedron* **1996**, *52*, 1.

[2] P. Bravo, G. Resnati, *Tetrahedron: Asymmetry* **1990**, *1*, 661; *Fluorine in Bioorganic Chemistry* (Ed.: J. T. Welch, S. Eswarakrishnan), Wiley, New York, **1991**.

[3] *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1990**.

[4] [4a] K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, New York, **1988**. – [4b] R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, *Gazz. Chim. Ital.* **1989**, *119*, 253. – [4c] M. Cinquini, F. Cozzi, "Stereoselective Synthesis" in *Methods Org. Chem. (Houben-Weyl)*, **1995**, vol. E21c, ch. 1.6.1.2, p. 2953. – [4d] M. Frederickson, *Tetrahedron* **1997**, *53*, 403. – [4e] K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863.

[5] P. Bravo, A. Farina, M. Frigerio, S. V. Meille, F. Viani, *Tetrahedron: Asymmetry* **1994**, *5*, 987 and references therein; P. Bravo, L. Bruché, M. Frigerio, F. Viani, M. Zanda, *Phosphorus Sulfur Silicon* **1994**, *95–96*, 399; P. Bravo, M. Zanda, "Asymmetric Synthesis of Fluoro Organic Compounds via Chiral Sulfoxide Chemistry" in *Enantiocontrolled Synthesis of Fluoro Organic Compounds: Stereochemical Challenges and Biomedical Targets* (Ed.: V. A. Soloshonok), Wiley, Chichester, in press.

[6] P. Bravo, L. Bruché, A. Farina, G. Fronza, S. V. Meille, A. Merli, *Tetrahedron: Asymmetry* **1993**, *4*, 2131; P. Bravo, L. Bruché, G. Fronza, A. Merli, *Gazz. Chim. Ital.* **1994**, *124*, 275; A. Arnone, P. Bravo, L. Bruché, P. Seresini, *J. Chem. Res.* **1996**, (*S*) 198; A. Arnone, P. Bandiera, P. Bravo, L. Bruché, M. Zanda, *Gazz. Chim. Ital.* **1996**, *126*, 773; P. Bravo, L. Bruché, P. Seresini, M. Zanda, A. Arnone *J. Heterocycl. Chem*. **1997**, *34*, 489; A. Arnone, P. Bandiera, P. Bravo, L. Bruché, M. Zanda, *Synth. Commun.* **1998**, *28*, 2665.

[7] K. Tanaka, M. Oshuga, Y. Sugimoto, Y. Okafuji, K. Mitsuhashi, *J. Fluorine Chem.* **1988**, *39*, 39.

[8] M. Ihara, Y. Tanaka, N. Takahashi, Y. Tokunaga, K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3043.

[9] A. Arnone, M. Cavicchioli, A. Donadelli, G. Resnati, *Tetrahedron: Asymmetry* **1994**, *5*, 1019; A. Arnone, P. Bravo, A. Donadelli, G. Resnati, *Tetrahedron* **1996**, *52*, 131; A. Arnone, P. Bandiera, P. Bravo, L. Bruché, M. Zanda, *Gazz. Chim. Ital.* **1996**, *126*, 773; A. Arnone, F. Blasco, G. Resnati, *Tetrahedron* **1997**, *53*, 17513.

[10] P. Bravo, E. Piovosi, G. Resnati, S. De Munari, *Gazz. Chim. Ital.* **1988**, *118*, 115.

[11] P. Bravo, G. Resnati, *Tetrahedron Lett.* **1987**, *28*, 4865.

[12] P. Bravo, E. Piovosi, G. Resnati, *J. Chem. Soc., Perkin Trans. 1* **1989**, 1201.

[13] H. Sugihara, R. Tanikaga, A. Kaji, *Synthesis* **1978**, 881.

[14] P. Bravo, M. Frigerio, G. Resnati, *J. Org. Chem.* **1990**, *55*, 4216.

[15] P. DeShong, C. M. Dicken, J. M. Leginus, R. R. Whittle, *J. Am. Chem. Soc.* **1984**, *106*, 5598.

[16] M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett*. **1968**, 2199; N. T. Anh, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61.

[17] P. Bravo, L. Bruché, G. Fronza, G. Zecchi, *Tetrahedron* **1992**, *48*, 9775.

[18] C. R. Davies, J. S. Davies, *J. Chem. Soc., Perkin Trans. 1* **1976**, 2390; Y.-S. Hon, F.-J. Chang, L. Lu, W.-C. Lin, *Tetrahedron* **1998**, *54*, 5233.

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