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Asymmetric synthesis of β,β-difluoroamino acids via cross-coupling and Strecker reactions

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Abstract

β,β-Difluoroamino acids were synthesized from commercially available ethyl bromodifluoroacetate using cross-coupling and Strecker reactions as key steps. The coupling reaction of aryl iodides with ethyl bromodifluoroacetate gave the corresponding coupling products, which were transformed to 2-difluoromethyl-1,3-oxazolidines in two steps. Boron trifluoride etherate promoted Strecker reaction of 2-difluoromethyl-1,3-oxazolidines gave α-amino nitriles in good yields and diastereoselectivities. After removal of chiral auxiliary and hydrolysis of the nitrile group, β,β-difluorophenylalanine was obtained with 73% ee. Partial racemization occurred during the hydrolysis of nitrile group.

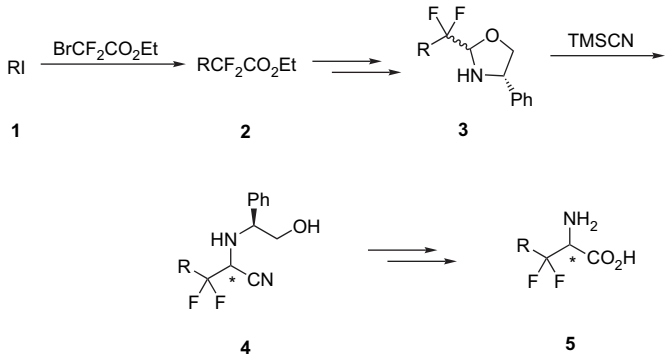
Keywords: Fluorinated amino acid; Bromodifluoroacetate; Cross-coupling reaction; Strecker reaction

1. Introduction

Fluorinated amino acids have gained an important position in the synthesis of compounds exhibiting interesting properties for bioorganic application.[1] Among them, *gem*-difluoroamino acids and their derivatives have been the subject of considerable research because the CF_2/CH_2 transposition has been recognized as a valuable tool in the blockage of metabolic process. β,β-Difluorophenylalanine is an attractive unnatural amino acid target because of its biological and pharmacological properties.[2] Two synthetic methods for this fluorinated amino acid have been developed by direct fluorination. One utilized the ring-opening reaction of 2-carboxyl-1-phenyl-1-azirine with hydrogen fluoride pyridine and optically active isomers were prepared by enzymatic hydrolysis.[3] The other employed a lengthy route containing twice *vic*-bromofluorination at the beginning and there was no stereoselectivity during the construction of the chiral center.[4] Therefore it is necessary to develop more efficient strategies for the synthesis of β,β-difluorophenylalanine and its derivatives. In this paper we report a convenient asymmetric synthesis of β,β-difluoroamino acids starting from ethyl bromodifluoroacetate and aryl iodides.

2. Results and discussion

The synthetic route is shown in Scheme 1. The crossing-coupling reaction of aryl halides **1** with ethyl bromodifluoroacetate



Scheme 1.

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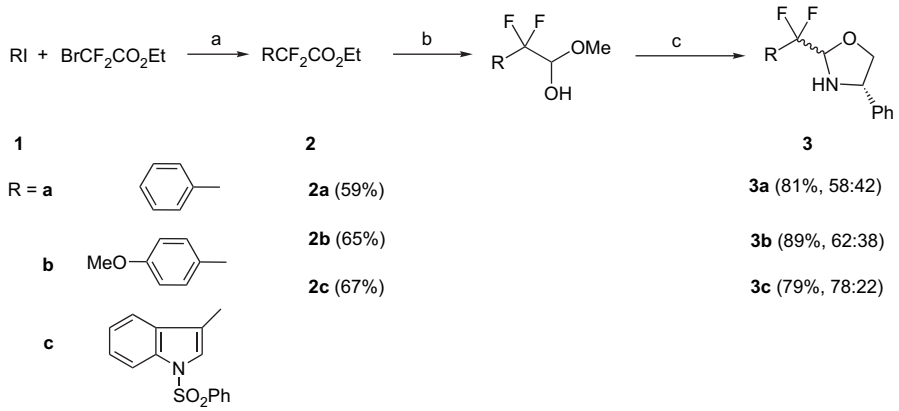


Scheme 2. (a) Cu, DMSO, 55 °C. (b) $NaBH_4$, MeOH, −55 °C. (c) (*S*)-phenylglycinol, PPTS, toluene, Dean Stark distillation.

was used to prepare α,α-difluoroesters **2**,[5] which was next transformed to oxazolidines **3**. Strecker reaction of **3** afforded the corresponding amino nitriles **4**. Removal of the chiral auxiliary of **4** followed by hydrolysis gave title compound **5**.

Iodobenzene (**1a**), 4-iodoanisole (**1b**), and 3-iodo-1–phenylsulfonyl-1*H*-indole (**1c**) were chosen as starting materials, which may finally be converted to difluorinated analogs of important natural phenylalanine, tyrosine, and tryptophan (Scheme 2). In the presence of copper powder, the cross-coupling reaction of **1** and ethyl bromodifluoroacetate took place readily in DMSO under mild conditions to give α,α-difluoroesters **2** in good yields. Reduction of **2** with $NaBH_4$ in methanol gave the corresponding methyl hemiacetals, which were not stable enough for purification by column chromatography and were condensed with (*S*)-phenylglycinol directly to give oxazolidines **3**, the stable equivalents of the corresponding imines.[6,7]

A stereoselective approach to α-amino nitriles was developed by Brigaud et al. using Lewis acid promoted Strecker reaction of 2-trifluoromethyl-1,3-oxazolidines.[7] Under similar conditions, diastereomeric mixture of oxazolidines **3** was allowed to react with trimethylsilyl cyanide in the presence of $BF_3\cdot OEt_2$ and α-amino nitriles **4** were obtained in high yields with good diastereoselectivities (Scheme 3). The absolute configuration of the major product was determined by X-ray crystallographic studies (Fig. 1).[8] The formation of an iminium ion intermediate has been proposed for the good diastereoselectivity of the above Strecker reaction.[7] The existence of the intermediate in our reaction was partially proved by a simple NMR experiment. When $BF_3\cdot OEt_2$ was added to a $CDCl_3$ solution of **3a**, new signals appeared for protons of imine in its ^1H NMR spectrum. Therefore the nucleophilic attack took place mainly from the *Si* face to give major diastereomer with (*S*,*S*) configuration due to the hindering effect of phenyl in the iminium ion intermediate (Fig. 2).[9]

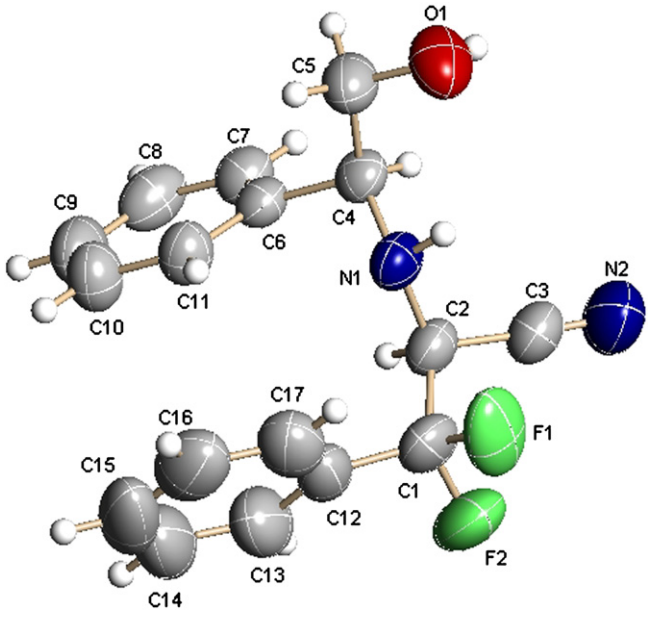
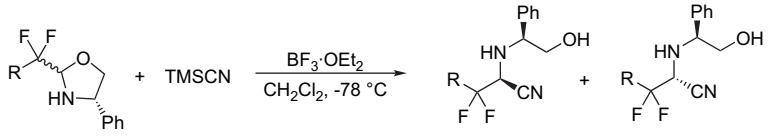


Figure 1. ORTEP of the crystal structure of **4a** (major isomer).

Compound **4a** was chosen as an example for the following transformations. The chiral auxiliary of **4a** was removed by reacting with lead tetraacetate in a mixed solvent of dichloromethane and methanol. After hydrolysis of the nitrile group with



Scheme 3. Strecker reaction of **3** and TMSCN.

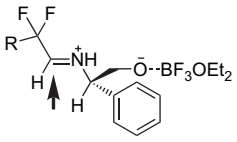
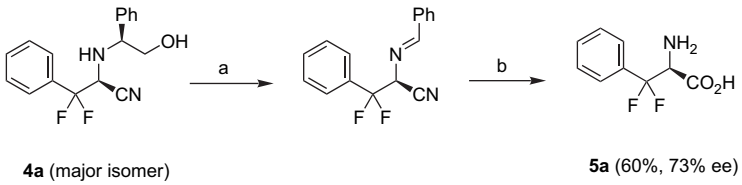


Figure 2.

(50 mL×3). The ethereal solution was washed with saturated NaCl solution and dried over Na_2SO_4. After removal of solvent, the crude product was added to a solution of (*S*)-phenylglycinol (685 mg, 5 mmol) and PPTS (20 mg) in toluene, and the resulted mixture was refluxed to remove water by azeotropic distillation until no water was separated. After



4a (major isomer) **5a** (60%, 73% ee)

Scheme 4. (a) $Pb(OAc)_4$, CH_2Cl_2/MeOH (2:1), 0 °C. (b) (1) concd HCl, 100 °C, 3 h; (2) Dowex H^+, 2% NH_4OH.

concentrated HCl and ion-exchange resin purification, β,β-difluorophenylalanine **5a** was obtained in 50% overall yield from **4a** (Scheme 4). The enantiomeric excess of **5a** was determined by NMR analysis of its methyl ester in the presence of $Eu(tfc)_3$.[3a] Unfortunately, only 73% ee was achieved. Partial racemization occurred during the hydrolysis of nitrile group, since complete racemization was observed when **4a** was treated with concentrated HCl solution for a long time.[4] Attempt to improve ee value by changing reaction temperature and hydrolytic media failed to give better result.

3. Conclusion

In summary, we have developed a short and efficient method for the synthesis of β,β-difluoroamino acids. The strategy employed easily available ethyl bromodifluoroacetate as the difluoromethylene precursor and the cross-coupling reaction of aryl iodides with ethyl bromodifluoroacetate and $BF_3\cdot OEt_2$ promoted Strecker reaction as key steps.

4. Experimental

4.1. General

Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra and high-resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 and a Finnigan MAT-8430 spectrometer, respectively. The known compounds **2a–c**[5] were prepared according to literature. The diastereomeric ratio of **3** and **4** was determined by ^{19}F NMR.

4.2. General procedure for the preparation of *3*

$NaBH_4$ (190 mg, 5 mmol) was added in portion to a solution of **2** (5 mmol) in MeOH (5 mL) at −60 °C. After addition, the reaction mixture was stirred for 1 h at −50 °C. Then 10 mL of 10% HCl was added and the mixture was extracted with ether removal of toluene under reduced pressure, the residue was purified by flash chromatography to give **3**.

4.2.1. (4S)-2-(Difluoro(phenyl)methyl)-4-phenyloxazolidine (*3a*)

Colorless oil. IR (film): ν 3363, 2887, 1452, 1103, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 1H), 3.38 (t, J=8.7 Hz, 0.42H), 3.64 (t, J=7.8 Hz, 0.58H), 4.00 (q, J=4.2 Hz, 0.58H), 3.99–4.18 (m, 1H), 4.44 (q, J=7.8 Hz, 0.42H), 5.21–5.24 (m, 1H), 7.22–7.35 (m, 5H), 7.43–7.47 (m, 3H), 7.60–7.64 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.8, −111.4 (AB, J_{AB}=250.7 Hz, 1.16F), −108.3, −111.4 (AB, J_{AB}=252.4 Hz, 0.84F); MS (*m/z*, %): 275 (M^+, 1), 148 (100); Anal. Calcd for $C_{16}H_{15}F_2NO$: C, 69.81; H, 5.49; N, 5.09. Found: C, 69.59; H, 5.57; N, 4.90.

4.2.2. (4S)-2-(Difluoro(4-methoxyphenyl)methyl)-4-phenyloxazolidine (*3b*)

Colorless oil. IR (film): ν 3363, 2889, 1616, 1518, 1254, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.55 (br, 1H), 3.40 (t, J=7.8 Hz, 0.38H), 3.64 (t, J=7.5 Hz, 0.62H), 3.84 (s, 3H), 4.01 (q, J=5.1 Hz, 0.62H), 4.13–4.19 (m, 1H), 4.44 (q, J=7.5 Hz, 0.38H), 5.10–5.21 (m, 1H), 6.95 (d, J=9.0 Hz, 2H), 7.24–7.34 (m, 5H), 7.52–7.56 (m, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −106.3, −110.0 (AB, J_{AB}=251.0 Hz, 1.24F), −116.8, −110.1 (AB, J_{AB}=252.7 Hz, 0.76F); MS (*m/z*, %): 306 (M^++1, 5.15), 157 (17.56), 149 (11.49), 148 (100.00), 121 (9.44), 120 (80.76), 103 (25.33); Anal. Calcd for $C_{17}H_{17}F_2NO_2$: C, 66.87; H, 5.61; N, 4.59. Found: C, 66.47; H, 5.80; N, 4.30.

4.2.3. (4S)-2-(Difluoro(1-(phenylsulfonyl)-1H-indol-3-yl)-methyl)-4-phenyloxazolidine (*3c*)

Yellow oil. IR (film): ν 3359, 2887, 1712, 1448, 1377, 1178, 1134, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.61 (br, 1H), 3.29 (t, J=8.4 Hz, 0.22H), 3.60 (t, J=7.5 Hz, 0.78H), 3.95–4.00 (m, 0.78H), 4.06–4.14 (m, 1H), 4.41–4.47 (m, 0.22H), 5.22–5.32 (m, 1H), 7.13–7.51 (m, 10H), 7.79–8.01 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −103.4, −105.4 (AB, J_{AB}=265.4 Hz, 1.56F), −103.6, −105.8 (AB, J_{AB}=267.7 Hz, 0.44F); MS (ESI, *m/z*, %):

455.2 (M^++1); Anal. Calcd for $C_{24}H_{20}F_2N_2O_3S$: C, 63.42; H, 4.44; N, 6.16. Found: C, 63.16; H, 4.50; N, 5.97.

4.3. General procedure for Strecker reaction

To a solution of oxazolidines **3** (0.5 mmol) in dichloromethane (5 mL) under nitrogen atmosphere were added cyanotrimethylsilane (99 mg, 1 mmol) and $BF_3 \cdot OEt_2$ (142 mg, 1 mmol) at −78 °C. The reaction mixture was stirred for 8 h. After warming to room temperature, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (25 mL). The aqueous layer was extracted with dichloromethane (3×25 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography gave pure major isomer of **4**.

4.3.1. (S)-3,3-Difluoro-2-[(S)-2-hydroxy-1-phenylethylamino]-3-phenylpropanenitrile (*4a*)

Colorless solid. Mp: 136–137 °C; $[\alpha]_D^{25}$ −136.3 (*c* 0.48, $CHCl_3$); IR (KBr): ν 3473, 1453, 1064, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70 (s, 1H), 2.60 (d, *J*=13.5 Hz, 1H), 3.48–3.54 (m, 1H), 3.74–3.88 (m, 2H), 4.04–4.09 (m, 1H), 7.03 (d, *J*=6.3 Hz, 2H), 7.23–7.28 (m, 3H), 7.44–7.56 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.3, −107.0 (AB, J_{AB}=250.1 Hz, 2F); MS (*m/z*, %): 303 (M^++H, 5), 271 (100); Anal. Calcd for $C_{17}H_{16}F_2N_2O$: C, 67.54; H, 5.33; N, 9.27. Found: C, 67.66; H, 5.18; N, 9.19.

4.3.2. (S)-3,3-Difluoro-2-[(S)-2-hydroxy-1-phenylethylamino]-3-(4-methoxyphenyl)propanenitrile (*4b*)

Yellow oil. $[\alpha]_D^{25}$ −90.8 (*c* 1.10, $CHCl_3$); IR (film): ν 3493, 3339, 1613, 1518, 1328, 1256, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.04 (s, 1H), 2.57 (d, *J*=12.9 Hz, 1H), 3.45–3.55 (m, 1H), 3.72–3.81 (m, 2H), 3.86 (s, 3H), 4.03–4.08 (m, 1H), 6.95 (d, *J*=9.0 Hz, 2H), 7.07–7.10 (m, 2H), 7.23–7.28 (m, 3H), 7.41 (d, *J*=7.8 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −97.2, −104.5 (AB, J_{AB}=249.0 Hz, 2F); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.5, 137.0, 128.9, 128.5, 127.7, 127.6, 127.5, 124.7 (t, *J*=25.6 Hz), 118.7 (t, *J*=249.2 Hz), 115.8, 113.8, 67.2, 62.7, 55.5, 55.2 (t, *J*=33.6 Hz); MS (ESI, *m/z*, %): 333 (M^++1); HRMS Calcd for $C_{18}H_{19}F_2N_2O_2$ (M+1): 333.1410; Found: 333.14091.

4.3.3. (S)-3,3-Difluoro-2-[(S)-2-hydroxy-1-phenylethylamino]-3-[1-(phenylsulfonyl)-1H-indol-3-yl]-propanenitrile (*4c*)

Yellow oil. $[\alpha]_D^{25}$ −72.2 (*c* 1.00, $CHCl_3$); IR (film): ν 3336, 2930, 1449, 1380, 1190, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.05 (s, 1H), 2.78 (d, *J*=12.6 Hz, 1H), 3.42–3.49 (m, 1H), 3.70–3.75 (m, 1H), 3.88–4.00 (m, 1H), 4.02–4.08 (m, 1H), 6.88–7.59 (m, 11H), 7.89–8.03 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −93.6, −103.0 (AB, J_{AB}=260.8 Hz, 2F); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 136.6, 134.7, 134.5, 129.6, 128.8, 128.5, 127.5, 127.0, 126.8 (t, *J*=8.2 Hz), 126.4, 125.7, 124.2, 120.4, 117.7 (t, *J*=219.0 Hz), 115.4, 115.0, 114.4, 113.7, 66.9, 62.7, 54.3 (t, *J*=31.2 Hz); MS (ESI, *m/z*, %): 504.2 (M+Na^+); HRMS Calcd for $C_{25}H_{21}F_2N_3O_3S$ (M+Na): 504.1154; Found: 504.11639.

4.4. The preparation of *5a*

To a solution of **4a** (151 mg, 0.5 mmol) in 5 mL of MeOH and 10 mL of CH_2Cl_2 was added $Pb(OAc)_4$ (332 mg, 0.75 mmol) at 0 °C. After 30 min of stirring at 0 °C, the reaction mixture was poured into an aqueous phosphoric acid buffer solution (15 mL) at room temperature and then filtered on Celite. The aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was mixed with 5 mL of concentrated HCl, and the mixture was stirred for 3 h at 100 °C. After cooling to room temperature, the reaction mixture was extracted with ether (30 mL), and the aqueous solution was concentrated under reduced pressure to give the crude product. Pure **5a** was obtained after purification with ion-exchange resin.

4.4.1. (S)-2-Amino-3,3-difluoro-3-phenylpropanoic acid (*5a*)

White solid. Mp: 170–171 °C. $[\alpha]_D^{25}$ −47.6 (*c* 0.22, 1.2 N HCl); IR (KBr): ν 3012, 1639, 1601, 1513, 1066, 1034 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 4.26 (dd, J_1=20.4 Hz, J_2=6.3 Hz, 1H), 7.38–7.44 (m, 5H); ^{19}F NMR (282 MHz, D_2O): δ −93.5, −108.6 (AB, J_{AB}=247.0 Hz, 2F); ^{13}C NMR (75 MHz, D_2O): δ 66.8 (t, *J*=27.2 Hz), 122.3 (t, *J*=247.1 Hz), 128.3 (t, *J*=6.4 Hz), 128.8, 131.3, 132.3 (t, *J*=24.5 Hz), 167.2; MS (ESI, *m/z*, %): 202.2 (M^+); HRMS Calcd for $C_9H_{10}F_2NO_2$: 202.0674; Found: 202.0673.

4.4.2. Determination of ee value of compound *5a*

$SOCl_2$ (1 mL) was added dropwise to a solution of **5a** (10 mg, 0.05 mmol) in methanol (5 mL) under stirring at −10 °C. The mixture was allowed to warm up to room temperature and then refluxed for 24 h. After removal of methanol and excess $SOCl_2$, the residue was dissolved in saturated aqueous $NaHCO_3$ solution (5 mL) and stirred for 0.5 h. The reaction mixture was extracted with ether (20 mL×3). The ethereal layer was combined and washed with saturated aqueous NaCl solution (30 mL), dried over Na_2SO_4, and concentrated in vacuum. The crude product was directly dissolved in $CDCl_3$ and $Eu(tfc)_3$ (18 mg, 0.02 mmol) was added to the solution. The ee value of **5a** could be easily determined by its ^{19}F NMR spectrum.

Acknowledgements

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References and notes

1. (a) Qiu, X. L.; Meng, W. D.; Qing, F. L. *Tetrahedron* **2004**, *60*, 6711; (b) Sutherkand, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621; (c) Kukhar,

V. P.; Soloshonok, V. A. *Fluorine Containing Amino Acids: Synthesis and Properties*; Wiley: New York, NY, 1995.
2. (a) Okuda, K.; Seila, A. C.; Strobel, S. A. *Biochemistry* **2005**, *44*, 6675; (b) Chen, H.; Cong, L. N.; Li, Y. H.; Yao, Z. J.; Wu, L.; Zhang, Z. Y.; Bruke, T. R.; Quon, M. J. *Biochemistry* **1999**, *38*, 384; (c) Chen, L.; Wu, L.; Otaka, A.; Smyth, M. S.; Rouer, P. P.; Rurke, T. R.; den Hertog, J.; Zhang, Z. Y. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 976; (d) Frogier, P. R. T.; Tran, T. T.; Viani, S.; Condom, R.; Guedj, R. *Antiviral Chem. Chemother.* **1994**, *5*, 372.
3. (a) Ayi, A. I.; Guedj, R.; Septe, B. *J. Fluorine Chem.* **1995**, *73*, 165; (b) Khéribet, R.; Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5333.
4. Schlosser, M.; Brügger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron* **2004**, *60*, 7731.
5. (a) Sato, K.; Kawata, R.; Ama, F.; Omote, M.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **1999**, *47*, 1013; (b) Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Wallace, D. J.; Davies, A. J.; Kennedy, D. J.; Dolling, U. H. *Tetrahedron Lett.* **2002**, *50*, 9271.
6. (a) Higashiyama, K.; Ishii, A.; Mikami, K. *Synlett* **1997**, 1381; (b) Higashiyama, K.; Ishii, A.; Miyamoto, F.; Mikama, K. *Tetrahedron Lett.* **1998**, *39*, 1199; (c) Higashiyama, K.; Ishii, A.; Miyamoto, F.; Mikami, K. *Chem. Lett.* **1998**, 119; (d) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461.
7. (a) Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827; (b) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 7075.
8. Crystallographic data (excluding structure factors) for structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 626441. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44(0) 1223 336033 or email: deposit@ccdc.cam.ac.uk].
9. (a) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179; (b) Dave, R. H.; Hosangadi, B. D. *Tetrahedron* **1999**, *55*, 11295.