ORGANIC LETTERS

1999
Vol. 1, No. 7
977−980

First Highly Diastereoselective Synthesis of *syn* α-Methyl β-Fluoroalkyl β-Amino Esters

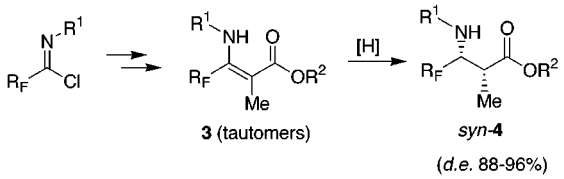
Santos Fustero,* Belén Pina, Marta García de la Torre, Antonio Navarro, Carmen Ramírez de Arellano, and Antonio Simón

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46100-Burjassot (Valencia), Spain

santos.fustero@uv.es

Received June 30, 1999

ABSTRACT



A new two-step approach for the diastereoselective synthesis of the *syn* α-methyl β-fluoroalkyl β-amino esters 4 has been developed. This approach is based on the chemical reduction of the fluorinated β-enamino esters 3, which have been previously obtained from imidoyl chlorides 1 and lithium ester enolates, with $ZnI_2/NaBH_4$ as the reducing agent. The process takes place with high *syn* diastereoselectivity and good to excellent yields. A metal-chelated six-membered model has been suggested to explain the stereochemical outcome of the reduction reaction.

The study of the chemistry and biological activity of β-amino acids has aroused considerable interest during the last two decades.[1] The α-methyl derivatives are recognized as an especially attractive class of β-amino acids; they have been found (e.g. 2-methyl-3-aminopentanoic acid) to be framework components for several biologically active cyclic peptides which have been isolated from marine organisms and which have antifungal, antineoplasic, or cytotoxic properties.[1c,2] These substrates also display enhanced resistance toward protease enzymes when incorporated into peptidic sequences.[1,2] Useful synthetic approaches have already been reported for the synthesis of α-substituted β-amino acids;[1] most of them have involved alkylation reactions of the corresponding α-unsubstituted β-amino acids,[1,3] conjugate additions of chiral amines to appropriate α,β-unsaturated acid derivatives,[4] or enzymatic resolution of racemic α-alkyl β-amino acids.[5] However, much less attention has been given to the stereoselective reduction of α-alkyl β-enamino acid derivatives, although Palmieri[6] and, more recently, Lhommet[7] have described convenient proce-

(1) Reviews: (a) Cole, D. *Tetrahedron* **1994**, *50*, 9517. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (d) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

(2) (a) Pettit, G. R.; Kamano, Y.; Kizu, H.; Dufresne, C.; Herald, C. L.; Bontems, R. J.; Schmidt, J. M.; Boettner, F. E.; Nieman, R. A. *Heterocycles* **1989**, *28*, 553. (b) Carter, D. C.; Moore, E. R.; Mynderse, J. S.; Niemczura, W. P.; Todd, J. S. *J. Org. Chem.* **1984**, *49*, 236. (c) Fernández, R.; Rodríguez, J.; Quiñoa, E.; Riguera, R.; Muñoz, L.; Fernández-Suarez, M.; Debitus, C. *J. Am. Chem. Soc.* **1996**, *118*, 11635. (d) Hu, T.; Panek, J. J. *J. Org. Chem.* **1999**, *64*, 3000.

(3) See for example: (a) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103. (b) Juaristi, E.; Escalante, J. *J. Org. Chem.* **1993**, *58*, 2282 and literature cited therein. (c) Braschi, I.; Cardillo, J.; Tomasini, C.; Venezia, R. *J. Org. Chem.* **1994**, *59*, 7792. (d) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455. (e) Sewald, N.; Hiller, K.; Körner, H.; Findeisen, M. *J. Org. Chem.* **1998**, *63*, 7263.

(4) (a) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109. (b) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1994**, *59*, 649. (c) Enders, D.; Bettray, W.; Raabe, G.; Runsik, J. *Synthesis* **1994**, 1322.

(5) Cardillo, G.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1996**, *61*, 8651.

(6) (a) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328. (b) Palmieri, G.; Cimarelli, C. *J. Org. Chem.* **1996**, *61*, 5557.

(7) (a) David, O.; Blot, J.; Bellec, Ch.; Fargeau-Bellasoued, M. C.; Haviari, G.; Célérier, J. P.; Lhommet, G.; Gramain, J. C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122. (b) See also: Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170. (c) For asymmetric hydrogenation of α-unsubstituted β-enamino acid derivatives, see: Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.

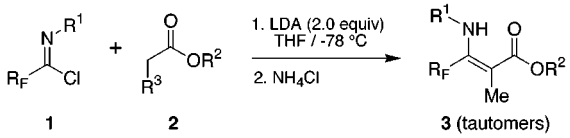
10.1021/ol990774o CCC: $18.00
Published on Web 09/09/1999

dures for the diastereoselective reduction of cyclic and acyclic α-substituted β-enamino esters to β-amino esters[6,7] or γ-amino alcohols[6a] with good to moderate diastereoselectivity.

In addition, the synthesis of fluorinated organic molecules has received considerable attention recently due to the unique biological properties imparted by the fluorine atom,[8] as well as their utility in industrial and pharmaceutical applications, including drug design and mechanistic and metabolic investigations.[9] In connection with ongoing investigations into the synthesis and reactivity of fluorinated 1,3-difunctionalized derivatives,[10] we report here a new and efficient two-step approach to fluorinated *syn* α-methyl β-amino esters **4** by means of diastereoselective reduction of previously synthesized fluorinated β-enamino esters **3**.[11] In sharp contrast to their nonfluorinated derivatives[1−7] very little is known about the synthesis and pharmacological utility of the corresponding β-fluoroalkyl β-amino acids;[12] particularly rare are descriptions of methods for preparing α-substituted β-fluoroalkyl β-amino acids. To the best of our knowledge, the literature includes only four synthetic routes for the diastereoselective synthesis of these substrates. In 1993,[13] Kitazume reported the first example of an α-alkyl β-difluoromethyl β-amino acid synthesis by means of condensation of difluoroacetaldimine with enol silyl ethers. More recently, Bégué[14] and Uneyama[15] have independently described alternative two-step routes to *syn* and *anti* (3-fluoroalkyl)-isoserinates. The Staudinger reaction of ketenes to give fluorinated aldimines, followed by acidic methanolysis of the azetidones initially formed,[14] and diastereoselective reduction of α-hydroxy β-imino esters previously obtained by means of base-catalyzed intramolecular rearrangement of imino ethers[15] are respectively the strategies developed by the aforementioned authors. Finally, Soloshonok's group[16] has very recently reported an elegant chemoenzymatic approach to α,β-disubstituted fluorinated β-amino acids. This strategy is based on a diastereoselective biomimetic transamination of α-alkyl β-keto carboxylic esters to generate the required fluorinated α-methyl β-amino moiety. The drawback to this process, as with most of the aforementioned methods (de 15−36%),[13,14] is the low to moderate stereocontrol observed (de <40%).[16]

In our method we began by synthesizing the starting fluorinated β-enamino esters **3** as previously described:[11] namely, by treating imidoyl chlorides **1**[17] with lithium enolates of alkyl propanoates **2-Li** in dry tetrahydrofuran (THF) at −78 °C. This gave rise to the expected α-methyl β-enamino esters **3**, isolated in high yields as a mixture of enamino and imino tautomers as shown in Table 1.

Table 1. Fluorinated α-Methyl β-Enamino Esters **3** Obtained from **1** and **2**



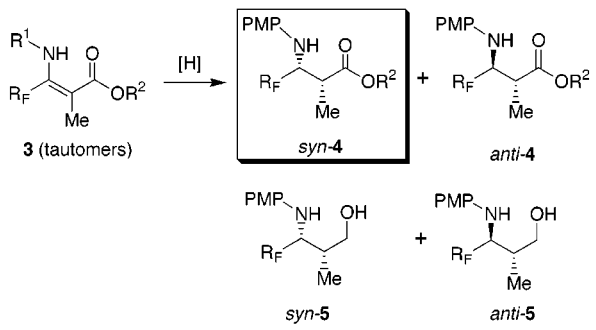
1 2 3 (tautomers)

entry[a]	R_F	R^2	product[b]	imino/enamino ratio[c]	yield (%)[d]
1	CF_3	Me	**3a**	60/40	92
2	CF_3	Et	**3b**	40/60	87
3	CF_3	*t*-Bu	**3c**	30/70	91
4	CF_2Cl	Me	**3d**	10/90	72
5	CF_3CF_2	Me	**3e**	84/16	71

[a] All reactions were carried out on a 8.0 mmol scale. [b] R^1 = *p*-$MeOC_6H_4$ (PMP) and R^3 = Me in all cases. [c] Imino/enamino tautomer ratio estimated by ^1H and ^{19}F NMR on the crude mixture. [d] Isolated yield.

The conversion of the fluorinated β-enamino esters **3** into the corresponding β-amino derivatives **4** was accomplished by means of diastereoselective chemical reduction, as outlined in Scheme 1 and Table 2. First, we studied the behavior of **3** toward sodium cyanoborohydride ($NaBH_3CN$) in a 4:1 mixture of THF and methanolic HCl as the solvent at room temperature. The process provided high yields of a *syn*/*anti* separable mixture of α-methyl β-fluoroalkyl β-amino esters **4**; however, only moderate diastereoselectivity (de 30−46%) was observed (entries 1, 11, and 13 in Table 2). Other reducing agents such as DIBAH, L-Selectride, *n*-Bu_4NBH_4,

Scheme 1



(8) (a) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (b) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, Wiley: Chichester, U.K., 1991. (d) German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*; Springer-Verlag: Berlin, Heidelberg, Germany, 1989.

(9) (a) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993. (b) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) Urban, J. J.; von Tersch, R. L. *J. Org. Chem.* **1999**, *64*, 3409 and literature cited therein.

(10) (a) Fustero, S.; Navarro, A.; Díaz, D.; de la Torre, M. G.; Asensio, A.; Sanz, F.; Liu González, M. *J. Org. Chem.* **1996**, *61*, 8849. (b) Fustero, S.; Navarro, A.; Asensio, A. *Tetrahedron Lett.* **1997**, *38*, 4891. Corrigenda: *Tetrahedron Lett.* **1997**, *38*, 6477. (c) Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210.

(11) Fustero, S.; Pina, B.; Simón Fuentes, A. *Tetrahedron Lett.* **1997**, *38*, 6771.

(12) Several fluorine-containing amino acids have been used in the design of protease and suicide inhibitors. See for example: *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, U.K., 1994.

(13) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302.

(14) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Thanh Nga, T. T. *J. Org. Chem.* **1997**, *62*, 8826 and literature cited therein.

(15) Uneyama, K.; Hao, J.; Amii, H. *Tetrahedron Lett.* **1998**, *39*, 4079.

Table 2. α-Methyl β-Fluoroalkyl β-Amino Esters **4** and γ-Amino Alcohols **5** Obtained by Reduction of **3**

entry	**3**[a]	[H]	reacn conditions	product **4** (**5**)	yield (%) of **4**[b] (*syn*/*anti*)[c]	yield (%) of **5**[b] (*syn*/*anti*)[c]
1	**3a**	$NaBH_3CN$	THF−MeOH·HCl (4:1), room temp, 4 h	**4a**	90 (67/33)	
2	**3a**	$NaBH_4$	$ZnBr_2$ (1.5 equiv), CH_2Cl_2, room temp, 20 h	**4a**	90 (93/7)	7 (99/1)
3	**3a**	$NaBH_4$	$ZnBr_2$ (1.5 equiv), CH_2Cl_2, Δ, 48 h	**4a (5a)**	43 (96/4)	57 (99/1)
4	**3a**	$NaBH_4$	$ZnCl_2$ (1.5 equiv), CH_2Cl_2, room temp, 48 h	**4a**	32 (90/10)	
5	**3a**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, room temp, 24 h	**4a (5a)**	90 (98/2)	10 (99/1)
6	**3a**	$NaBH_4$	ZnI_2 (1.5 equiv), CH_2Cl_2, Δ, 8 h	**4a** (**5a**)	73 (98/2)	27 (99/1)
7	**3a**	$Zn(BH_4)_2$	CH_2Cl_2, room temp, 24 h	**4a (5a)**	70 (96/4)	10 (99/1)
8	**3b**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, room temp, 48 h	**4b**	92 (98/2)	
9	**3c**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, room temp, 24 h	**4c**	71 (96/4)	
10	**3c**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, Δ, 24 h	**4c (5c)**	86 (97/3)	10 (99/1)
11	**3d**	$NaBH_3CN$	THF−MeOH·HCl (4:1), room temp, 4 h	**4d**	99 (65/35)	
12	**3d**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, Δ, 24 h	**4d**	98 (94/6)	
13	**3e**	$NaBH_3CN$	THF−MeOH·HCl (4:1), room temp, 5 h	**4e**	82 (73/27)	
14	**3e**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, room temp, 24 h	**4e**	30 (>95/5)	
15	**3e**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, Δ, 48 h	**4e (5e)**	36 (97/3)	20 (99/1)

[a] All reactions were carried out on a 2.0 mmol scale. [b] Yields of the crude mixture. Isolated yield: *syn*-**4a** (81%); *syn*-**4b** (81%); *syn*-**4c** (70%); *syn*-**4d** (80%); *syn*-**4e** (30%). [c] The *syn*/*anti* diastereoisomer ratios for **4** and **5** were determined on the crude reaction mixtures by ^{19}F NMR.

and $NaBH(OAc)_3$ and catalytic hydrogenation (Pd/C) were much less efficient with regard to chemical yield and stereoselectivity.

Next, we examined the use of sodium borohydride ($NaBH_4$) in the presence of different zinc halides as chelating agents. The reactions were carried out in dry CH_2Cl_2 as the solvent at room temperature, and the process worked extremely well, providing mainly the *syn* α-methyl β-fluoroalkyl β-amino esters **4** in high yields and, in general, with excellent diastereoselectivity (entries 5, 8, 10, 12, and 15 in Table 2).

It is worth noting that, on some occasions, especially when the reduction reaction was performed at higher temperature and/or for long reaction times, we also observed the formation of variable amounts of the corresponding γ-amino alcohols **5**, which were isolated almost exclusively as single *syn* diastereoisomers (*syn*/*anti* = 99/1) (Scheme 1 and Table 2).

The best results were obtained by employing an excess (3.0 equiv) of anhydrous ZnI_2 as the chelating agent and CH_2Cl_2[18] as the solvent, as shown in Table 2. In contrast, other zinc salts such as $ZnBr_2$ (entry 2, Table 2) and, particularly, $ZnCl_2$ (entry 4, Table 2) were less effective. In addition, the use of $Zn(BH_4)_2$ as the reducing agent instead of the system $ZnI_2/NaBH_4$ yielded slightly lower diastereoisomeric ratios and chemical yields (entry 7, Table 2). The replacement of the methyl group in R^2 by ethyl or *tert*-butyl groups did not affect the stereoselectivity to a significant degree (entries 8−10, Table 2). However, the use of the pentafluoroethyl species **3e**, instead of trifluoromethyl (**3a**−**c**) or chlorodifluoromethyl (**3d**) derivatives, resulted not only in a lower chemical yield but also in an increasing amount of γ-amino alcohol **5e** (entries 14 and 15, Table 2).

Compounds **4**[19] and **5** were easily separated by means of flash chromatography, and they showed spectroscopic (^1H, ^{13}C, and ^{19}F NMR), analytical, and/or HRMS data in agreement with the proposed structure.[20] Further corroboration for the correct configuration assignments for these derivatives (**4** or **5**) was unambiguously obtained by X-ray crystallographic analyses. Because we were unable to obtain adequate single crystals for the major diastereoisomer (2*R**,3*R**)-**4**, the relative stereochemistry of the two newly chiral created centers was determined for the fluorinated

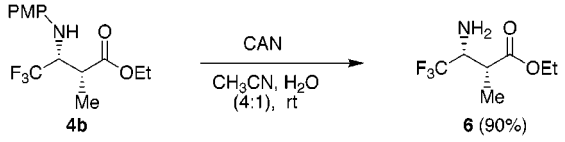
(16) (a) Soloshonok, V. A.; Soloshonok, I. V.; Kukhar, V. P.; Svedas, V. K. *J. Org. Chem.* **1998**, *63*, 1878 and literature cited therein. For the biocatalytic and enantioselective biomimetic version with α-unsubstituted β-fluoroalkyl β-amino acids, see: (b) Soloshonok, V. A.; Soloshonok, I. V.; Ono, T. *J. Org. Chem.* **1997**, *62*, 7538 and literature cited therein.

(17) Uneyama, K.; Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H. *J. Org. Chem.* **1993**, *58*, 32.

(18) Others solvents such as diethyl ether (Et_2O) or tetrahydrofuran (THF) gave poorer results.

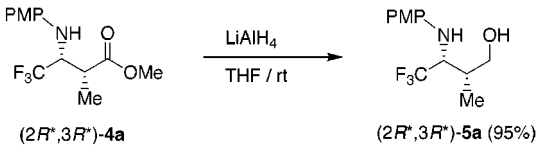
(19) **General Procedure for the Synthesis of α-Methyl β-Fluoroalkyl β-Amino Esters 4.** To a solution of anhydrous zinc iodide (1.91 g, 6.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added the corresponding α-methyl β-fluoroalkyl β-enamino ester **3** (2.0 mmol). The resulting mixture was stirred at the same temperature for 1 h, and then $NaBH_4$ (0.375 g, 10 mmol) was added, also at 0 °C. The solution was allowed to reach room temperature and then monitored by means of TLC. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 × 20 mL). The organic layers were combined, washed with brine, and dried over sodium sulfate. After filtration, the solvents were removed under reduced pressure to provide the crude reaction mixture **4** and/or **5**. Purification was carried out as indicated in each case. (2*R**,3*R**)-**4b**: flash chromatography (*n*-hexanes−EtOAc (7:1)) on silica gel (R_f = 0.3) gave a yellow solid (81%); mp 40−42 °C; ^1H NMR (400 MHz) 1.09 (t, *J* = 8.7 Hz, 3H), 1.20 (d, *J* = 4.4 Hz, 3H); 2.84 (m, 1H), 3.51 (br d, *J* = 6.5 Hz, 1H), 3.64 (s, 3H), 3.40 (q, *J* = 4.4 Hz, 2H), 4.30−4.40 (m, 1H), 6.60 (d, *J* = 5.7 Hz, 2H), 6.68 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz) 11.4 (q), 13.8 (q), 39.6 (d), 55.5 (q), 58.2 (q, $^2J_{CF}$ = 28.1 Hz), 61.1 (t), 114.7 (d), 115.6 (d), 125.7 (q, $^1J_{CF}$ = 283.0 Hz), 140.0 (s), 153.2 (s), 172.7 (s); ^{19}F NMR (376 MHz) −73.5 (d, J_{FH} = 8.0 Hz); HRMS calcd for $C_{13}H_{18}F_3NO_3$ 305.1238, found 305.1251. Anal. Calcd for $C_{13}H_{18}F_3NO_3$: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.10; H, 5.96; N, 4.57.

(20) Further conversion of **4** into the N-unprotected β-amino esters **6** has been carried out by standard procedures. Thus, for example, treatment of **4b** with ceric ammonium nitrate (CAN) in CH_3CN-H_2O (1:1) as the solvent afforded to (2*R**,3*R**)-**6** in 90% overall yield:



γ-amino alcohol derivative (2*R**,3*R**)-**5a**,[21] which was obtained in excellent overall yield by means of $LiAlH_4$/THF reduction of the diastereomerically pure α-methyl β-trifluoromethyl β-amino ester **4a** as outlined in Scheme 2. The

Scheme 2



(2*R**,3*R**)-**4a** (2*R**,3*R**)-**5a** (95%)

stereochemical outcome of the reduction reaction of **3** to the major diastereoisomer *syn*-**4** can be easily understood if it is assumed that hydride attacks the imino carbon from the opposite side (*si* face) of the α-methyl group (*ul*-1,2-addition), since ZnI_2 coordinates with both ester carbonyl oxygen and the nitrogen imino group in a six-membered metal chelate (Figure 1).

In summary, the first effective diastereoselective synthesis of *syn* α-methyl β-fluoroalkyl β-amino esters **4** and γ-amino alcohols **5** by means of chemical reduction of the corresponding β-enamino esters **3** has been developed. The process works well, it is very simple and inexpensive, and easily available starting materials are used. We feel this new

(21) Full details of the X-ray structure of (2*R**,3*R**)-**5a** will be published in a full account of this work.

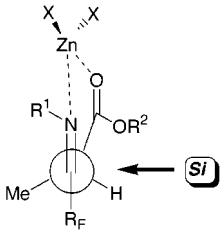


Figure 1.

strategy to fluorinated β-amino esters will be convenient for the enantioselective synthesis of these and other related systems. Further studies along these lines are in progess.

Acknowledgment. We thank the Dirección General de Investigación Científica y Técnica (DGES PB97-0760-C02-01) for financial support. B.P., M.G.T., and A.N. are indebted to the Generalitat Valenciana, the Fundación Ramón Areces, and the Universidad de Valencia for predoctoral fellowships.

Supporting Information Available: Text giving spectroscopic data and experimental details for **3a**−**e**, *syn*-**4a**−**e**, *anti*-**4a**, **5a**,**e**, and **6** and an ORTEP drawing of *syn*-**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990774O