Synthesis of α-Hydroxy-β-triflamido Carboxylic Esters through Ring-Opening of Alkoxycarbonyl Oxiranes

Vittoria Lupi,*[a] Domenico Albanese,[a] Dario Landini,[a] Davide Scaletti,[a] Michele Penso*[b]

[a] Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Venezian 21, 20133 Milano, Italy
Fax +39(02)50314159; E-mail: vittoria.lupi@unimi.it

[b] CNR- Istituto di Scienze e Tecnologie Molecolari (ISTM), via Golgi 19, 20133 Milano, Italy
E-mail: michele.penso@istm.cnr.it

Received 7 December 2004; revised 27 January 2005

Abstract: The oxirane ring of 3-alkyl- and 3-arylglycidic esters has been opened with trifluoromethanesulfonamide ($TfNH_2$) under solid-liquid heterogeneous conditions. The corresponding α-hydroxy-β-triflamido esters were produced in good yields, in a regio- and stereoselective fashion. Several reaction parameters, such as the nature of the base, the presence of a phase transfer catalyst and/or a solvent have been examined.

Key words: regioselectivity, stereoselectivity, ring-opening, epoxides, amino acids

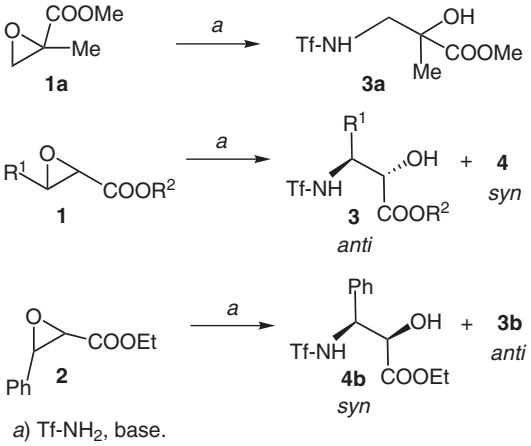
β-Amino-α-hydroxy acids show interesting pharmacological properties and are also important intermediates in the synthesis of biologically active molecules,[1] e.g. the well known anti-tumor agent taxol[2] (containing a 2*R*,3*S*-3-phenylisoserine unit); bestatin[3] (a derivative of 3-benzylisoserine), which is a potent suppressor of *Pseudomonas aeruginosa* infection and of tumorigenesis in esophageal adenocarcinoma; amastatin[4] (derived from 3-isopropylisoserine), like bestatin, has been used to improve the action of some bioactive peptides by inhibiting their degradation by aminopeptidases; or kynostatin 272,[5] which is one of the more promising new drugs for the treatment of AIDS.

The protocols commonly used for the preparation of β-amino-α-hydroxy acid derivatives, i.e. the ring-opening reactions of glycidic esters by a source of nucleophilic nitrogen,[6] like ammonia, amines or azides, often lack regioselectivity and hence large amounts of the by-product α-amino-β-hydroxy ester derivatives accompany the target compounds. Furthermore, even if the S_N2 antiperiplanar opening is favored and hence the *anti*-β-amino-α-hydroxy esters are the main or the sole products, several procedures suffer from a low degree of stereoselectivity and both *anti*- and *syn*-isomers are produced.

This report summarizes the results that we obtained by investigating the reactivity, under different conditions, of a set of glycidic esters **1a**–**h**, **2** (Scheme 1) by nucleophilic ring-opening with trifluoromethanesulfonamide ($TfNH_2$) to give the corresponding *N*-trifluoromethanesulfonyl-α-amino-β-hydroxy esters.

SYNTHESIS 2005, No. 10, pp 1675–1681
Advanced online publication: 07.04.2005
DOI: 10.1055/s-2005-865285; Art ID: Z23104SS

In preceding papers we have reported the ring-opening of alkyl- or aryl-substituted oxiranes by trifluoroacetamide[7] and sulfonamides,[8] under solid-liquid phase transfer catalysis (SL-PTC) conditions, using catalytic amounts of anhydrous potassium carbonate as a base. The results of this research were the starting point for performing a series of nucleophilic ring-opening reactions of glycidic esters by $TfNH_2$ (Table 1).



a) Tf-NH_2, base.

1,3,4	R^1	R^2	1,3,4	R^1	R^2
b	Ph	Et	**f**	C_5H_{11}	Et
c	4-NO_2-C_6H_4	Et	**g**	*c*-C_6H_{11}-CH_2	Et
d	4-Cl-C_6H_4	Et	**h**	4-NO_2-C_6H_4	*t*-Bu
e	4-MeO-C_6H_4	Et			

Scheme 1

It is interesting to note that the reaction in dioxane at 90 °C, with excess $TfNH_2$ in the presence of catalytic amounts (0.1 mol equiv) of triethylbenzylammonium chloride (TEBA) as phase transfer agent, and potassium carbonate gave the *anti*-α-hydroxy-β-triflamido ester **3b** in 53% yield (entry 2), whereas the use of a stoichiometric amount of K_2CO_3 (entry 3) resulted in decomposition of the starting material. The epoxy ester **1a** (entry 1), which is the unique example of a C-3 unsubstituted starting material, gave almost complete conversion under the above PTC conditions to the corresponding β-amino-α-hydroxy ester. The reaction of 4-nitro-phenyl glycidates **1c** and **1h** (entries 4 and 5) required very long reaction times for the

Table 1 Ring-Opening of Alkyl Glycidates **1** by $TfNH_2$ under SL-PTC Conditions[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]	Product	Yield (%)[b]
1	**1a**	7	**3a**	95	–	–
2	**1b**	46	**3b**	53	**4b**	2
3	**1b**	25[c]	**3b**	24	**4b**	–
4	**1c**	120	**3c**	40	**4c**	6
5	**1h**	120	**3h**	38	**4h**	29
6	**1f**	7	**3f**	33	**4f**	33

[a] Glycidate **1** (1 mol), $TfNH_2$ (2 mol), K_2CO_3 (0.1 mol), TEBA (0.1 mol), dioxane, 90 °C.
[b] Isolated yield.
[c] Using an increased amount of K_2CO_3 (1 mol).

reaction to reach completion. In addition, the epoxy ring of the *t*-butyl ester **1h** (entry 5), owing to the higher steric hindrance close to the reaction center, was opened with a lower stereoselectivity (**3h/4h**, 1.3:1) than that found in the ring-opening of the corresponding ethyl ester **1c** (**3c/4c**, 6.7:1, entry 4). Finally, complete loss of stereoselectivity was found in the opening of the 3-pentyl derivative **1f** (entry 6).

Encouraged by these preliminary results, in order to optimize the reaction conditions, we modified several parameters for the ring-opening reaction using ethyl *trans*-3-phenylglycidate (**1b**) as a model substrate (Table 2). No improvements were observed when cesium carbonate was utilized as the base (entry 2), instead of K_2CO_3. Changing the base for lyophilized sodium carbonate (entry 3) produced comparable yields of **3b** in shorter reaction times. An analogous reaction, carried out without TEBA (entry 4) showed a very low reaction rate. In contrast, good results were obtained by operating in the absence of solvent (entry 5) and the product **3b** was isolated in 75% yield. Moreover, in the absence of solvent, the PTC did not effect the reaction rate and in fact, it promoted the formation of by-products, as highlighted by the higher yield of **3b** obtained in the non-catalyzed ring-opening reaction (entry 6).

These results were partially reported in a preceding communication,[9] which indicated that the ring-opening of glycidic esters is more efficient if carried out in the presence of a catalytic amount of base, without any solvent. Following this rule, **1b** was subjected to ring-opening with $TfNH_2$ with a range of different inorganic, anhydrous bases and salts (Table 3) as well as several organic bases (Table 4).

Carbonates of alkaline and alkaline-earth metals (Table 3, entries 1–4) are the most efficient bases (Na >> K = Cs = Ca). Sodium acetate itself (entry 5) acted in part as a nucleophile and opened the oxirane ring. Potassium and cesium fluoride must be used in stoichiometric quantities, as the formation of hydrogen fluoride, during the reaction, produced the corresponding alkali metal hydrogendifluoride $M^+HF_2^-$ (Scheme 2), a non-basic species.

Table 2 Ring-Opening of **1b** by $TfNH_2$ under SL-PTC Conditions[a]

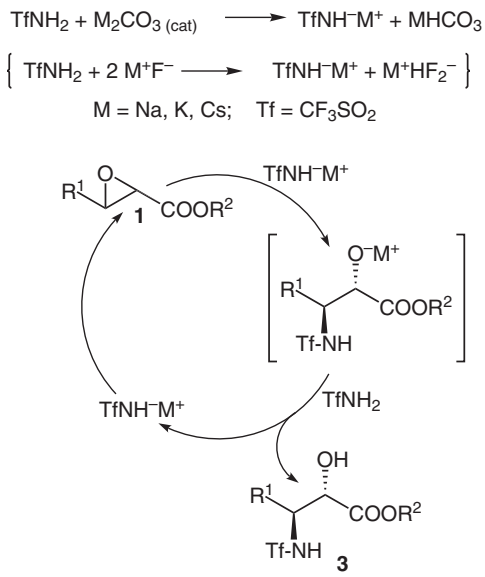
Entry	Base	Time (h)	**3b** (%)[b]	**4b** (%)[b]
1	K_2CO_3	46	53	2
2	Cs_2CO_3	33	58	2
3	Na_2CO_3	30	56	3
4	Na_2CO_3	48	18[c]	–
5	Na_2CO_3	7	75[d]	3
6	Na_2CO_3	7	80[e]	7
7	$KHCO_3$	89	12[f]	–

[a] Glycidate **1b** (1 mol), $TfNH_2$ (2 mol), base (0.1 mol), TEBA (0.1 mol), dioxane, 90 °C.
[b] Isolated yield.
[c] Without TEBA.
[d] Without solvent.
[e] Without TEBA and solvent.
[f] Together with **1b** (81%).

Table 3 Ring-Opening of Glycidic Ester **1b** under Heterogeneous Conditions without a Solvent: Effect of the Inorganic Base[a]

Entry	Base	Time (h)	**3b** (%)[b]	**4b** (%)[b]
1	Na_2CO_3	7	80	7
2	K_2CO_3	20	69	5
3	Cs_2CO_3	21	67	6
4	$CaCO_3$	23	71	6
5	NaOAc	21	63[c]	–
6	KF[d]	8	62	–
7	CsF[d]	15	45	–
8	LiI[e]	15	51	–

[a] Glycidate **1b** (1 mol), $TfNH_2$ (2 mol), base (0.1 mol), 90 °C.
[b] Isolated yield.
[c] Together with ethyl *anti*-3-acetoxy-2-hydroxy-3-phenyl-propionate (10%).
[d] Using an increased amount of base (1 mol).
[e] Using an increased amount of base (0.2 mol).



Scheme 2

Among the ring-opening reactions carried out with an organic base (Table 4), the best results were obtained with DBU (entry 1). Analogous yields, in slightly longer reaction times, were obtained with hindered amines, such as Hunig's base (entry 2) and diisopropylamine (entry 3), whereas widely used pyridine (entry 5) and 4-dimethylaminopyridine (entry 6) were less efficient.

The optimal reaction conditions were applied to glycidic esters bearing an aromatic ring (**1c**–**e**,**h** and **2**) or an alkyl group (**1f**,**g**) in the C-3 position (Scheme 1). All these substrates underwent reaction with an excess of $TfNH_2$ (2 mol equiv) in the presence of a catalytic amount of lyophilized sodium carbonate (0.1 mol equiv), at 90 or 120 °C, depending on the melting point of the starting glycidate and its reactivity (Table 5). The ring-opening of *trans*-3-(4-nitrophenyl) derivatives **1c** and **1h**, carrying a strong electron withdrawing group (EWG), proceeded with lower selectivity than those found for the reactions of the substrates **1b**, **1d**, and **1e**, possessing a weaker EWG (H, Cl, or OMe, respectively). Actually, while complete conversion of **1c** is achieved in four hours, *anti*-**3c** was isolated in less than 56% yield, even after prolonged reaction times (Table 5, entry 4). Furthermore, as found under PTC conditions, the presence of the large *t*-Bu group in **1h** leads to a reduction in stereoselectivity and **4h** was isolated in 19% yield. In contrast, **1b**, **1d**, and **1e** gave satisfactory yields (74–80%) in reasonable reaction times (entries 2, 5, and 6). The ring-opening of ethyl 3-pentyl-glycidate (**1f**) and ethyl 3-cyclohexylmethyl-glycidate (**1g**) at 90 °C required longer reaction times (entries 7 and 8) in order to attain good yields of the corresponding α-hydroxy-β-triflamido esters. However, such operating temperatures were required because the stereoselectivity of the nucleophilic attack on these esters decreased dramatically when the temperature was increased to 120 °C. Finally, the ester **1a** (entry 1) was also found to be very reactive under these

Table 4 Ring-Opening of Glycidic Ester **1b** Using Organic Bases, without Solvent[a]

Entry	Base	Time (h)	**3b** (%)[b]	**4b** (%)[b]
1	DBU	16	64	6
2	*i*-Pr_2NEt	22	65	–
3	*i*-Pr_2NH	22	64	9
4	Et_3N	12	48	–
5	Pyridine	21	46	–
6	DMAP	15	55	7

[a] Glycidate **1b** (1 mol), $TfNH_2$ (2 mol), organic base (0.2 mol), 90 °C.
[b] Isolated yield.

Table 5 Preparation of β-Triflamido-α-hydroxy Esters **3** and **4** (General Procedure)[a]

Entry	Substrate	T (°C)	Time (h)	Product	Yield (%)[b]	Product	Yield (%)[b]
1	**1a**	90	0.5	**3a**	98	–	–
2	**1b**	90	7	**3b**	80	**4b**	8
3	**2**[c]	120	4	**3b**	5	**4b**	77
4	**1c**	120	4	**3c**	56[d]	**4c**	4
5	**1d**	90	15	**3d**	80	**4d**	5
6	**1e**	90	0.5	**3e**	74	**4e**	3
7	**1f**	90	31	**3f**	64	**4f**	6
8	**1g**	90	30	**3g**	50	**4g**	12
9	**1h**	90	10	**3h**	51	**4h**	19

[a] Glycidate **1**, **2** (1 mol), $TfNH_2$ (2 mol), lyophilized Na_2CO_3 (0.1 mol).
[b] Isolated yield.
[c] See ref.[9]
[d] After 16 h, **3c** was isolated in only 43% yield.

conditions, giving 2-hydroxy-2-methyl-3-triflamidopropionate (**3a**) in almost quantitative yield.

The results as a whole indicate that, under the solid-liquid heterogeneous conditions employed, the ring-opening reaction of glycidates proceeds principally through the S_N2 antiperiplanar mechanism: *trans*-epoxy esters **1** produces the corresponding *anti*-α-hydroxy-β-triflamido esters **3** and only minor amounts of the *syn*-isomers **4** (e.g., **3b/4b**, 10:1), which are derived from the S_N1 reaction. Analogously, by the S_N2 mechanism the *cis*-glycidate **2** gave predominantly ester **4b** (**4b/3b**, 15:1). The carbocation formed in the monomolecular reaction is attacked by the nucleophile ($TfNH^-Na^+$) from the less crowded side, generating the *syn*-stereoisomer. This mechanism was confirmed also by the ring-opening of the highly hindered substrates **1g** and **1h**, which gave significant amounts of *syn*-isomers **4g** and **4h**. The monomolecular pathway is promoted by the acidity of triflamide (pK_a 9.7 in DMSO,[10] pK_a 6.3 in water[11]). In fact, when a stoichiometric amount of $TfNH_2$ was used, **1b** gave *anti*-**3b** (78%) as the sole product, even with a prolonged reaction time.[9] Furthermore, the ring-opening reactions show good regioselectivities. In fact, only the regioisomers **3** and **4** which result from nucleophilic attack on C-β were isolated and, by ^1H NMR spectroscopic analysis of the crude reaction mixture, very small quantities (≤1%) of the regioisomeric β-hydroxy-α-triflamido esters **5** and **6** were detected.

In conclusion, substituted glycidates underwent ring-opening by triflamide under solid-liquid heterogeneous conditions, without a solvent in the presence of catalytic amounts of lyophilized sodium carbonate as a base. The corresponding α-hydroxy-β-triflamido esters were synthesized in good stereoselectivity. This simple procedure is environmentally friendly since it does not require any organic solvent. Moreover, only catalytic amounts of a cheap and safe base are needed as the necessary nucleophile ($TfNH^-M^+$) is regenerated during the catalytic cycle (Scheme 2). In order to find the appropriate conditions for promoting the reversed stereochemical reaction pathway, i.e. the formation of the *syn*-isomers from the more available *trans*-glycidates, we are currently studying the ring-opening reaction of several *t*-butyl glycidates, both under heterogeneous and homogeneous conditions.

Melting points were determined on a Büchi 535 apparatus and are corrected. IR spectra were measured with a Perkin Elmer FT-IR spectrometer 1725X. ^1H and ^{19}F NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300.133 (^1H) or 282.407 (^{19}F) MHz; TMS (^1H) and $CDCl_3$ (^{19}F) were used as external references and δ are in ppm. Missing signals of several *syn*-stereoisomers **4** are hidden by signals of the corresponding *anti*-stereoisomers **3**, or they could not be unambiguously identified due to their low intensity. Reagent-grade commercially available reagents and solvents were used and dried, when required, before use. Petroleum ether (PE, 40–60 °C) was used for chromatography on silica gel (230–400 mesh). Alkaline metal carbonates were dried by heating at 140 °C under vacuum (0.05 mmHg) for 6 h. Analytical TLC was performed using Merck pre-coated silica gel F_{254} plates.

Glycidates **1a** and **1b** are commercially available, whereas ethyl 3-(4-nitrophenyl)oxirane-2-carboxylate (**1c**),[12] ethyl 3-(4-chlorophenyl)oxirane-2-carboxylate (**1d**),[13] ethyl 3-(4-methoxyphenyl)oxirane-2-carboxylate (**1e**),[14] ethyl 3-pentyloxirane-2-carboxylate (**1f**)[15] and *tert*-butyl 3-(4-nitrophenyl)oxirane-2-carboxylate (**1h**)[16] were prepared, according to the literature, from the corresponding aldehyde through the Darzens reaction with the appropriate 2-bromo- or 2-chloroacetate. Ethyl 3-cyclohexylmethyloxirane-2-carboxylate (**1g**) was prepared by MCPBA epoxidation, in the presence of catalytic amounts of bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide,[6f] ethyl (*E*)-4-cyclohexyl-but-2-enoate[17] which was prepared by the Horner–Emmons reaction of cyclohexyl-acetaldehyde[18] with $(EtO)_2P(O)CH_2CO_2Et$. *cis*-3-Phenyl-oxirane-2-carboxylate **2** was prepared by a multistep protocol from benzoyl acetate.[19] The *anti*-isomer **3b** was prepared by an independent literature procedure.[6g] The regioisomer (*R*,*S*)-*syn*-3-hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-2-aminopropionate (**6b**) was prepared from commercial (*R*,*S*)-*syn*-3-phenylserine as described below. The relative configuration of the ester **4b** and of the regioisomer (*R*,*S*)-*anti*-3-hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-2-aminopropionate (**5b**) were assigned by comparative ^1H NMR analysis of the corresponding proton signals. In addition, comparison of the chemical shifts and coupling constants of the new compounds with those of **3b** and **4b**, permitted assignment of the identity of **3c–h** and **4c–h**.

Trifluoromethanesulfonamide

Following a literature method,[20] a mixture of trifluoromethanesulfonic anhydride (12 g, 42.5 mmol) and aq NH_3 (30%; 300 mL) was stirred at 0 °C for 30 min and then left at –10 °C for 24 h. After the work-up described in the literature, triflamide was purified by sublimation under vacuum (0.02 mmHg) and isolated (5.51 g, 87%) as a white solid.

Mp 117–119 °C (lit.[20] 117–118 °C).

IR (nujol): 3390, 3279 (NH), 1377 (SO_2) cm^{-1}.

^{19}F NMR ($CDCl_3$): δ = –79.39 (s).

Ethyl (2*RS*,3*SR*)-3-Cyclohexylmethyloxirane-2-carboxylate (1g)

To a soln of ethyl (*E*)-4-cyclohexylbut-2-enoate (400 mg, 2.04 mmol) and bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl)sulfide (72 mg, 0.2 mmol) in DCE (4.5 mL), MCPBA (70%, 754 mg, 3.06 mmol) was added. The reaction mixture was stirred under reflux for 4 h, then a further portion of MCPBA (137 mg, 0.56 mmol) was added, and stirring and heating were continued for 20 h (TLC analysis). After cooling to r.t., the crude mixture was filtered, the solvent was removed under vacuum and the residue was diluted with Et_2O (3 mL), washed with a soln of Na_2SO_3 (1.5 M; 3 mL), and then with a sat. soln of $NaHCO_3$ (3 mL). The organic layer was dried over $MgSO_4$, filtered, the solvent was removed under vacuum, and the residue purified by flash chromatography on silica gel (Et_2O–PE, 1:15). Ester **1g** was isolated (313 mg, 72%) as a colorless oil.

IR (film): 1731 (C=O), 1288 and 848 (COC) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.29 (t, 3 H, *J* = 7.3 Hz, OCH_2CH_3), 1.45–1.79 (m, 13 H, *c*-$C_6H_{11}CH_2$), 3.10–3.21 (m, 2 H, H-2, H-3), 4.22 (q, 2 H, *J* = 7.3 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{20}O_3$ (212.1): C, 67.89; H, 9.50. Found: C, 67.74; H, 9.48.

α-Hydroxy-β-triflamido Esters 3; General Procedure

In a dried flask, a heterogeneous mixture of the glycidate **1** (1 mmol), lyophilized Na_2CO_3 (11 mg, 0.1 mmol), and trifluoromethanesulfonamide (298 mg, 2 mmol) was stirred at 90–120 °C until the starting material was no longer detectable (TLC analysis). After cooling to r.t., the crude product was diluted with CH_2Cl_2 (5

mL), filtered through celite (0.5 g), CH_2Cl_2 was removed under vacuum, and the residue purified by flash chromatography on silica gel.

Methyl 2-Hydroxy-2-methyl-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (3a)

Methyl 2-methyloxirane-2-carboxylate (**1a**; 116 mg) was subjected to the procedure described above at a temperature of 90 °C for 0.5 h. Flash chromatography (EtOAc–PE, 1:3) gave **3a** (260 mg, 98%) as a white solid.

Mp 70–71 °C.

IR (nujol): 3315 (NH), 1750 (C=O), 1372 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.44 (s, 3 H, CH_3-2), 3.36 (dd, 1 H, *J* = 13.2, 8.0 Hz, H-3), 3.50 (br s, 1 H, OH), 3.63 (dd, 1 H, *J* = 13.2, 3.9 Hz, H-3), 3.85 (s, 3 H, OCH_3), 5.51 (dd, 1 H, *J* = 8.0, 3.9 Hz, NH).

^{19}F NMR ($CDCl_3$): δ = –77.70 (s).

Anal. Calcd for $C_6H_{10}F_3NO_5S$ (265.0): C, 27.17; H, 3.80; N, 5.28. Found: C, 27.10; H, 3.69; N, 5.41.

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (3b) and Ethyl (*R*,*S*)-*syn*-2-Hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (4b)

Ethyl (2*RS*,3*SR*)-3-phenyl-oxirane-2-carboxylate (**1b**; 192 mg) was subjected to the procedure described above at a temperature of 90 °C for 7 h. Flash chromatography (EtOAc–PE, 1:3) gave **3b** (273 mg, 80%) as a white solid and **4b** (27 mg, 8%) as a white solid.[9]

3b

Mp 91–92 °C.

IR (nujol): 3321 (NH), 1747 (C=O), 1358 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.23 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 3.15 (d, 1 H, *J* = 5.6 Hz, OH), 4.05–4.21 (m, 2 H, OCH_2CH_3), 4.63 (dd, 1 H, *J* = 5.6, 3.5 Hz, H-2), 4.99 (dd, 1 H, *J* = 9.6, 3.5 Hz, H-3), 6.21 (d, 1 H, *J* = 9.6 Hz, NH), 7.24–7.34 (m, 5 H, Ar).

^{19}F NMR ($CDCl_3$): δ = –78.18 (s).

Anal. Calcd for $C_{12}H_{14}F_3NO_5S$ (341.1): C, 42.23; H, 4.13; N, 4.10. Found: C, 42.08; H, 4.05; N, 4.20.

4b

Mp 85–86 °C.

IR (nujol): 3318 (NH), 1750 (C=O), 1361 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.37 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 3.28 (d, 1 H, *J* = 2.9 Hz, OH), 4.28–4.41 (m, 2 H, OCH_2CH_3), 4.43 (dd, 1 H, *J* = 2.9, 1.9 Hz, H-2), 5.07 (dd, 1 H, *J* = 9.8, 1.9 Hz, H-3), 5.91 (d, 1 H, *J* = 9.8 Hz, NH), 7.32–7.39 (m, 5 H).

^{19}F NMR ($CDCl_3$): δ = –78.06 (s).

Anal. Calcd for $C_{12}H_{14}F_3NO_5S$ (341.1): C, 42.23; H, 4.13; N, 4.10. Found: C, 42.12; H, 4.05; N, 4.15.

(*R*,*S*)-*anti*-3-Hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-2-aminopropionate (5b)

(^1H NMR and ^{19}F NMR analyses of the crude product)

^1H NMR ($CDCl_3$): δ = 4.48 (dd, 1 H, *J* = 9.5, 3.9 Hz, H-2), 5.20 (d, 1 H, *J* = 3.9 Hz, H-3).

^{19}F NMR ($CDCl_3$): δ = –77.80 (s).

(*R*,*S*)-*syn*-3-Hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-2-aminopropionate (6b)

(^1H NMR and ^{19}F NMR analyses of the crude product)

^1H NMR ($CDCl_3$): δ = 4.24 (d, 1 H, *J* = 2.7 Hz, H-2), 5.32 (d, 1 H, *J* = 2.7 Hz, H-3).

^{19}F NMR ($CDCl_3$): δ = –78.15 (s).

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-3-(4-nitrophenyl)-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (3c) and Ethyl (*R*,*S*)-*syn*-2-Hydroxy-3-(4-nitrophenyl)-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (4c)

Ethyl (2*RS*,3*SR*)-3-(4-nitrophenyl)-oxirane-2-carboxylate (**1c**; 237 mg), was subjected to the procedure described above at a temperature of 120 °C for 4 h. Flash chromatography (EtOAc–PE, 1:2) gave an inseparable mixture of **3c** and **4c** (232 mg, 60%; 97:3) as a yellow solid.

IR (nujol): 3340 (NH), 1740 (C=O), 1515, 1333 (NO_2), 1352 (SO_2) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}F_3N_2O_7S$ (386.0): C, 37.31; H, 3.39; N, 7.25. Found: C, 36.92; H, 3.31; N, 7.36.

3c

^1H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 3.34 (br s, 1 H, OH), 4.08–4.23 (m, 2 H, OCH_2CH_3), 4.69 (d, 1 H, *J* = 3.5 Hz, H-2), 5.11 (d, 1 H, *J* = 3.5 Hz, H-3), 6.50 (br s, 1 H, NH), 7.48 (d, 2 H, *J* = 8.7 Hz, Ar), 8.19 (d, 2 H, *J* = 8.7 Hz, Ar).

^{19}F NMR ($CDCl_3$): δ = –78.08 (s).

4c

^1H NMR ($CDCl_3$): δ = 1.19 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 4.50 (d, 1 H, *J* = 3.6 Hz, H-2), 5.31 (d, 1 H, *J* = 3.6 Hz, H-3), 7.53 (d, 2 H, *J* = 8.7 Hz, Ar), 8.22 (d, 2 H, *J* = 8.7 Hz, Ar); NH, OH and OCH_2CH_3 protons are hidden.

^{19}F NMR ($CDCl_3$): δ = –77.65 (s).

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-3-(4-chlorophenyl)-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (3d) and Ethyl (*R*,*S*)-*syn*-2-Hydroxy-3-(4-chlorophenyl)-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (4d)

Ethyl (2*RS*,3*SR*)-3-(4-chlorophenyl)-oxirane-2-carboxylate (**1d**; 227 mg) was subjected to the procedure described above at a temperature of 90 °C for 15 h. Flash chromatography (EtOAc–PE, 1:3) gave an inseparable mixture of **3d** and **4d** (319 mg, 85%; 94:6) as a white solid.

IR (nujol): 3320 (NH), 1738 (C=O), 1343 (SO_2) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}ClF_3NO_5S$ (375.0): C, 38.36; H, 3.49; N, 3.73. Found: C, 37.99; H, 3.44; N, 3.79.

3d

^1H NMR ($CDCl_3$): δ = 1.24 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 3.17 (d, 1 H, *J* = 5.4 Hz, OH), 4.09–4.20 (m, 2 H, OCH_2CH_3), 4.62 (dd, 1 H, *J* = 5.4, 3.5 Hz, H-2), 4.97 (dd, 1 H, *J* = 9.3, 3.5 Hz, H-3), 6.21 (d, 1 H, *J* = 9.3 Hz, NH), 7.20 (d, 2 H, *J* = 8.5 Hz, Ar), 7.31 (d, 2 H, *J* = 8.5 Hz, Ar).

^{19}F NMR ($CDCl_3$): δ = –78.12 (s).

4d

^1H NMR ($CDCl_3$): δ = 1.37 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 3.37 (d, 1 H, *J* = 5.4 Hz, OH), 4.35 (dd, 2 H, *J* = 7.2, 1.5 Hz, OCH_2CH_3), 4.38 (d, 1 H, *J* = 1.9 Hz, H-2), 5.03 (d, 1 H, *J* = 1.9 Hz, H-3); NH and Ar protons are hidden.

^{19}F NMR ($CDCl_3$): δ = –78.07 (s).

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-3-(4-methoxyphenyl)-*N*-(trifluoromethane-sulfonyl)-3-aminopropionate (3e) and Ethyl (*R*,*S*)-*syn*-2-Hydroxy-3-(4-methoxyphenyl)-*N*-(trifluoromethane-sulfonyl)-3-aminopropionate (4e)

Ethyl (2*RS*,3*SR*)-3-(4-methoxyphenyl)-oxirane-2-carboxylate (**1e**; 222 mg) was subjected to the procedure described above at a tem-

perature of 90 °C for 0.5 h. Flash chromatography (EtOAc–PE, 2:5) gave an inseparable mixture of **3e** and **4e**, (286 mg, 77%; 96:4) as a white solid.

IR (nujol): 3344 (NH), 1753 (C=O), 1350 (SO_2) cm^{-1}.

Anal. Calcd for $C_{13}H_{16}F_3NO_6S$ (371.1): C, 42.05; H, 4.34; N, 3.77. Found: C, 42.85; H, 4.44; N, 3.85.

3e

^1H NMR ($CDCl_3$): δ = 1.36 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 3.45 (d, 1 H, *J* = 3.5 Hz, OH), 3.81 (s, 3 H, OCH_3), 4.34 (q, 2 H, *J* = 7.2 Hz, OCH_2CH_3), 4.39–4.41 (m, 1 H, H-2), 5.01 (dd, 1 H, *J* = 9.6, 1.8 Hz, H-3), 6.24 (d, 1 H, *J* = 9.6 Hz, NH), 6.89 (d, 2 H, *J* = 8.7 Hz, Ar), 7.30 (d, 2 H, *J* = 8.7 Hz, Ar).

^{19}F NMR ($CDCl_3$): δ = –78.06 (s).

4e

^1H NMR ($CDCl_3$): δ = 1.24 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 3.22 (d, 1 H, *J* = 6.0 Hz, OH), 3.78 (s, 3 H, OCH_3), 4.08–4.18 (m, 2 H, OCH_2CH_3), 4.61 (dd, 1 H, *J* = 6.0, 3.4 Hz, H-2), 4.94 (dd, 1 H, *J* = 9.6, 3.4 Hz, H-3), 6.30 (d, 1 H, *J* = 9.6 Hz, NH), 6.83 (d, 2 H, *J* = 6.6 Hz, Ar), 7.17 (d, 2 H, *J* = 6.6 Hz, Ar).

^{19}F NMR ($CDCl_3$): δ = –78.10 (s).

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-*N*-(trifluoromethanesulfonyl)-3-aminooctanoate (3f) and Ethyl (*R*,*S*)-*syn*-2-Hydroxy-*N*-(trifluoromethanesulfonyl)-3-aminooctanoate (4f)

Ethyl (2*RS*,3*SR*)-3-pentyl-oxirane-2-carboxylate (**1f**; 186 mg) was subjected to the procedure described above at a temperature of 90 °C for 31 h. Flash chromatography (Et_2O–PE, 2:5) gave an inseparable mixture of **3f** and **4f** (235 mg, 70%; 91:9) as a white solid.

IR (nujol): 3326 (NH), 1742 (C=O), 1339 (SO_2) cm^{-1}.

Anal. Calcd for $C_{11}H_{20}F_3NO_5S$ (335.1): C, 39.40; H, 6.01; N, 4.18. Found: C, 39.85; H, 6.32; N, 4.07.

3f

^1H NMR ($CDCl_3$): δ = 0.86 (t, 3 H, *J* = 6.9 Hz, H-8), 1.19–1.33 (m, 6 H, H-5, H-6, H-7), 1.28 (t, 3 H, *J* = 6.9 Hz, OCH_2CH_3), 1.43–1.62 (m, 2 H, H-4), 3.51 (br s, 1 H, OH), 3.86 (dt, 1 H, *J* = 10.3, 3.1 Hz, H-3), 4.23–4.34 (m, 2 H, OCH_2CH_3), 4.40 (d, 1 H, *J* = 3.1 Hz, H-2), 5.95 (br s, 1 H, NH).

^{19}F NMR ($CDCl_3$): δ = –78.20 (s).

4f

^1H NMR ($CDCl_3$): δ = 4.17 (d, 1 H, *J* = 3.3 Hz, H-3); the other protons are hidden.

^{19}F NMR ($CDCl_3$): δ = –77.97 (s).

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-4-cyclohexyl-*N*-(trifluoromethanesulfonyl)-3-aminobutanoate (3g) and Ethyl (*R*,*S*)-*syn*-2-Hydroxy-4-cyclohexyl-*N*-(trifluoromethanesulfonyl)-3-aminobutanoate (4g)

Ethyl (2*RS*,3*SR*)-3-cyclohexylmethyl-oxirane-2-carboxylate (**1g**, 212 mg) was subjected to the procedure described above at a temperature of 90 °C for 30 h. Flash chromatography (Et_2O–PE, 2:5) gave an inseparable mixture of **3g** and **4g**, (224 mg, 62%; 81:19) as a colorless oil.

IR (film): 3332 (NH), 1751 (C=O), 1337 (SO_2) cm^{-1}.

Anal. Calcd for $C_{13}H_{22}F_3NO_5S$ (361.1): C, 43.21; H, 6.14; N, 3.88. Found: C, 43.15; H, 6.06; N, 3.98.

3g

H NMR ($CDCl_3$): δ = 0.60–1.01 (m, 2 H, H-cyclo), 1.16–1.50 (m, 8 H, H-cyclo), 1.31 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 1.63–1.72 (m, 3 H, H-4, CH-cyclo), 3.20 (br s, 1 H, OH), 4.00 (dt, 1 H, *J* = 10.8, 2.9 Hz, H-3), 4.22–4.36 (m, 2 H, OCH_2CH_3), 4.39 (d, 1 H, *J* = 2.9 Hz, H-2), 5.51 (br s, 1 H, NH).

^{19}F NMR ($CDCl_3$): δ = –78.10 (s).

4g

^1H NMR ($CDCl_3$): δ = 1.29 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 4.17 (d, 1 H, *J* = 3.5 Hz, H-3); the other protons are hidden.

^{19}F NMR ($CDCl_3$): δ = –77.74 (s).

Ring-Opening under SL-PTC Conditions; Typical Procedure *t*-Butyl (*R*,*S*)-*anti*-2-Hydroxy-3-(4-nitrophenyl)-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (3h) and *t*-Butyl (*R*,*S*)-*syn*-2-Hydroxy-3-(4-nitrophenyl)-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (4h)

To a dried flask containing a dioxane solution (2 mL) of *t*-butyl (2*RS*,3*SR*)-3-(4-nitrophenyl)-oxirane-2-carboxylate (**1h**) (265 mg, 1 mmol), $TfNH_2$ (298 mg, 2 mmol) and TEBA (23 mg, 0.1 mmol) was added anhyd K_2CO_3 (14 mg, 0.1 mmol). The reaction mixture was stirred at 90 °C for 120 h (TLC analysis). After cooling to r.t., the crude mixture was diluted with CH_2Cl_2 (5 mL), filtered through celite (0.5 g), the solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc–PE, 1:4) to give an inseparable mixture of **3h** and **4h** (261 mg, 67%; 55:45) as a yellow solid.

IR (nujol): 3352 (NH), 1735 (C=O), 1506, 1339 (NO_2), 1360 (SO_2) cm^{-1}.

Anal. Calcd for $C_{14}H_{17}F_3N_2O_7S$ (414.1): C, 40.58; H, 4.14; N, 6.76. Found: C, 40.43; H, 4.20; N, 6.88.

3h

^1H NMR ($CDCl_3$): δ = 1.36 (s, 9 H, *t*-BuO), 4.58 (d, 1 H, *J* = 3.6 Hz, H-2), 5.03 (d, 1 H, *J* = 3.6 Hz, H-3), 7.53 (d, 2 H, *J* = 8.7 Hz, Ar), 8.21 (d, 2 H, *J* = 8.7 Hz, Ar); NH and OH protons are hidden.

^{19}F NMR ($CDCl_3$): δ = –78.06 (s).

4h

^1H NMR ($CDCl_3$): δ = 1.27 (s, 9 H, *t*-BuO), 3.30 (br s, 1 H, OH), 4.40 (d, 1 H, *J* = 3.4 Hz, H-2), 5.28 (d, 1 H, *J* = 3.4 Hz, H-3), 6.40 (br s, 1 H, NH), 7.58 (d, 2 H, *J* = 8.7 Hz, Ar), 8.25 (d, 2 H, *J* = 8.7 Hz, Ar).

^{19}F NMR ($CDCl_3$): δ = –77.57 (s).

Ring-Opening in the Presence of an Organic Base; Typical Procedure

In a dried flask, a mixture of ethyl (2*RS*,3*SR*)-3-phenyl-oxirane-2-carboxylate (**1b**) (192 mg, 1 mmol), DBU (30 mg, 0.2 mmol), and trifluoromethanesulfonamide (298 mg, 2 mmol) was stirred at 90 °C for 16 h (TLC analysis). After cooling to r.t., the crude mixture was diluted with CH_2Cl_2 (5 mL) and washed with acidic water (2 × 3 mL). The organic phase was dried over sodium sulfate, evaporated to dryness under vacuum and purified by flash chromatography on silica gel (EtOAc–PE, 1:3). An inseparable mixture of **3b** and **4b** was isolated (239 mg, 70%; 91:9) as a white solid.

Ethyl (*R*,*S*)-*anti*-2-Hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-3-aminopropionate (3b)

In a dried flask, a solution of ethyl (*R*,*S*)-*anti*-2-hydroxy-3-phenyl-3-aminopropionate (209 mg, 1.0 mmol), which was prepared by reduction of ethyl (*R*,*S*)-*anti*-3-azido-2-hydroxy-3-phenylpropionate,[6g] triethylamine (101 mg, 1.0 mmol), and trifluoromethanesulfonic anhydride (282 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 1 h (TLC analysis, EtOAc–PE, 1:3). The crude product was washed with water (2 × 2 mL) and the organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporat-

ed under vacuum. Ester **3b** was isolated (276 mg, 81%) as a white solid.

Mp 91–92 °C.

^{1}H NMR and ^{19}F NMR spectra match those of **3b** prepared by the previous method.

(*R*,*S*)-*syn*-3-Hydroxy-3-phenyl-*N*-(trifluoromethanesulfonyl)-2-aminopropionate (6b)

Hydrogen chloride was bubbled into a solution of commercially available (*R*,*S*)-*syn*-3-phenylserine trihydrate (3.60 g, 15.3 mmol) in anhyd EtOH (36 mL). The solution was stirred under reflux for 1 h (TLC analysis, MeOH–CH_2Cl_2, 1:9). After cooling to r.t., the crude mixture was concentrated under vacuum, Et_2O (20 mL) was added, and (*R*,*S*)-*syn*-3-hydroxy-3-phenyl-2-aminopropionate hydrochloride was crystallized as a white solid, which was isolated by filtration (2.10 g, 56%).

Mp 184–185 °C (dec.) [lit.[21] 186 °C (dec.)].

In a dried flask, a mixture of (*R*,*S*)-*syn*-3-hydroxy-3-phenyl-2-aminopropionate hydrochloride (1.95 g, 8.0 mmol) and Et_3N (1.74 g, 16.0 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 1 h, then trifluoromethanesulfonic anhydride (4.51 g, 16.0 mmol) was added and the mixture was stirred for a further 1 h (TLC analysis, EtOAc–PE, 1:3). The crude mixture was washed with water (2 × 10 mL) and the organic layer was dried over $MgSO_4$, filtered, and the solvent evaporated under vacuum. Ester **6b** was isolated (2.14 g, 78%) as a white solid.

Mp 89–90 °C.

IR (nujol): 3320 (NH), 1746 (C=O), 1358 (SO_2) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.23 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 3.14 (br s, 1 H, OH), 4.24 (d, 1 H, *J* = 2.7 Hz, H-2), 4.28 (d, 2 H, OCH_2CH_3), 5.32 (d, 1 H, *J* = 2.7 Hz, H-3), 6.22 (br s, 1 H, NH), 7.34–7.44 (m, 5 H, Ar).

^{19}F NMR ($CDCl_3$): δ = –78.15 (s).

Anal. Calcd for $C_{12}H_{14}F_3NO_5S$ (341.1): C, 42.23; H, 4.13; N, 4.10. Found: C, 42.06; H, 4.08; N, 4.14.

Acknowledgment

Financial support from the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR), Consiglio Nazionale delle Ricerche (CNR) and Fondo per gli Investimenti della Ricerca di Base (FIRB) are gratefully acknowledged.

References

(1) (a) Andruszkiewicz, R. *Pol. J. Chem.* **1998**, *72*, 1. (b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.
(2) (a) Shigemori, H.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 245. (b) Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. *Prog. Chem. Org. Nat. Prod.* **2002**, *84*, 53. (c) Kingston, D. G. I. *Chem. Commun.* **2001**, 867.
(3) (a) Chen, X.; Wang, S.; Wu, N.; Yang, C. S. *Curr. Cancer Drug Targets* **2004**, *4*, 267. (b) Koch, M. A.; Breinbauer, R.; Waldmann, H. *Biol. Chem.* **2003**, *384*, 1265. (c) DuBois, R. N. *J. Natl. Cancer Inst.* **2003**, *95*, 1028.
(4) (a) Bernkop-Schnurch, A. *J. Controlled Release* **1998**, *52*, 1. (b) de Godoy, M. A. F.; Dunn, S.; Rattan, S. *Gastroenterology* **2004**, *127*, 127. (c) Ben-Sasson, S. A.; Cohen, E. US Patent 2004146549, **2004**; *Chem. Abstr.* **2004**, *141*, 162351.
(5) Davis, D. A.; Read-Connole, E.; Pearson, K.; Fales, H. M.; Newcomb, F. M.; Moskovitz, J.; Yarchoan, R. *Antimicrob. Agents Chemother.* **2002**, *46*, 402.
(6) (a) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (b) Bhatia, B.; Jain, S.; De, A.; Bagchi, I.; Iqbal, J. *Tetrahedron Lett.* **1996**, *37*, 7311. (c) Alcaide, B.; Biurrun, C.; Martínez, A.; Plumet, J. *Tetrahedron Lett.* **1995**, *36*, 5417. (d) Hashiyama, T.; Inoue, H.; Takeda, M.; Murata, S.; Nagao, T. *Chem. Pharm. Bull.* **1985**, *33*, 2348. (e) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* **2000**, 311. (f) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1. (g) Legters, J.; van Dienst, E.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 69.
(7) Albanese, D.; Landini, D.; Penso, M. *Tetrahedron* **1997**, *53*, 4787.
(8) Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* **1999**, *55*, 6387.
(9) Penso, M.; Albanese, D.; Landini, D.; Lupi, V. *Chem. Lett.* **2001**, 400.
(10) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305.
(11) Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094.
(12) Martynov, V. F.; Ol'man, G. *Zh. Obshch. Khim.* **1958**, *28*, 592.
(13) Ayi, A. I.; Remli, M.; Condom, R.; Guedj, R. *J. Fluorine Chem.* **1981**, *17*, 565.
(14) Martynov, V. F.; Ol'man, G. *Zh. Obshch. Khim.* **1957**, *27*, 1881.
(15) Della Pergola, R.; Di Battista, P. *Synth. Commun.* **1984**, *14*, 121.
(16) Bachelor, F. W.; Bansal, R. K. *J. Org. Chem.* **1969**, *34*, 3600.
(17) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557.
(18) Stratakis, M.; Nencka, R.; Rabalakos, C. *J. Org. Chem.* **2002**, *67*, 8758.
(19) Hoffmann, R. V.; Kim, H.-O. *J. Org. Chem.* **1991**, *56*, 6759.
(20) Burdon, J.; Farazmand, I.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1957**, 2574.
(21) Elphimoff-Felkin, I.; Felkin, M. H.; Tchoubar, B.; Welvart, M. Z. *Bull. Soc. Chim. Fr.* **1952**, 252.