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A Cycloadditive Route to Trifluoromethyl-substituted Aminoalcohols

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Abstract: A synthetic approach to the title compounds is described, involving the 1,3-dipolar cycloaddition of nitrones to trifluoromethyl-substituted alkene derivatives, followed by reductive ring opening of the so obtained isoxazolidines.

Isoxazolidines and 4,5-dihydroisoxazoles are important classes of heterocycles;[1] they possess significant masked functionalities that, on unmasking, give rise to several new functional groups.[2] Most of them are easily prepared by 1,3-dipolar cycloaddition of nitrones and nitrile oxides to olefins.[3,4] Moreover, if stereochemistry can be controlled during the cycloaddition, it can be maintained during the transformation into open-chain compounds.[5] Since common and inexpensive chemicals serve as starting materials and the experimental conditions are simple, these heterocycles can be used as central intermediates in a strategy to prepare complex heteroatom-substituted carbon chains.

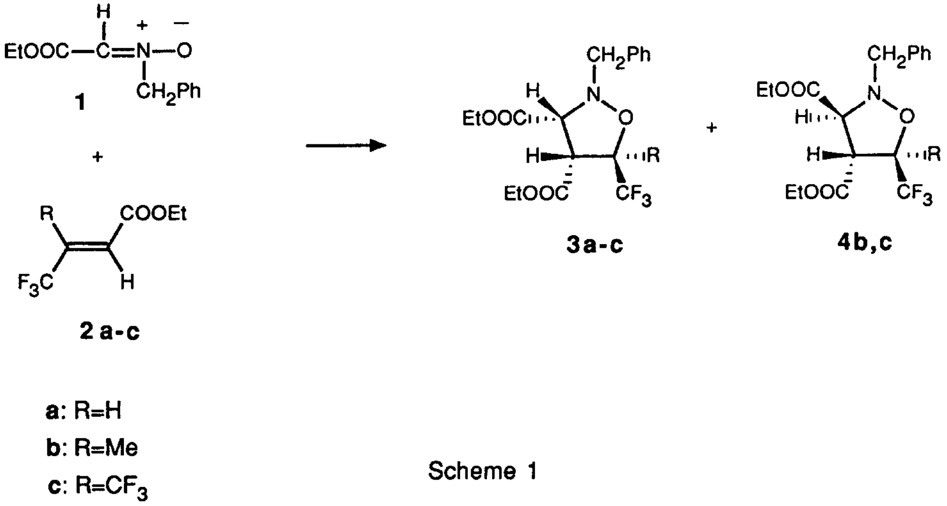
A limited number of examples exist in the literature, where nitrile oxides[6] and nitrones[7] are successfully used in cycloadditions to olefins bearing fluorine atoms or trifluoromethyl groups directly bonded to sp^2 carbon of the olefin.

In our continuing interest in developing strategies to fluoroorganic compounds from fluorosubstituted esters,[8] we have studied 1,3-dipolar cycloadditions to trifluorosubstituted acrylic esters[9] and β-diketones.[10] In this paper we report the cycloaddition of

N-benzyl-*C*-ethoxycarbonylnitrone **1** to trifluorocrotonic esters **2a-c**, and the elaboration of the cycloadducts into trifluoromethyl-substituted open-chain compounds of potential biological interest.[11]

RESULTS AND DISCUSSION

Nitrone **1** was prepared according to a literature method from ethyl glyoxylate and *N*-benzylhydroxylamine.[12] It was refluxed in toluene with equimolar amounts of alkene derivatives **2a-c** until disappearance of the nitrone moiety. The reaction products were separated by flash chromatography; the results are illustrated in Scheme 1 and the Table.

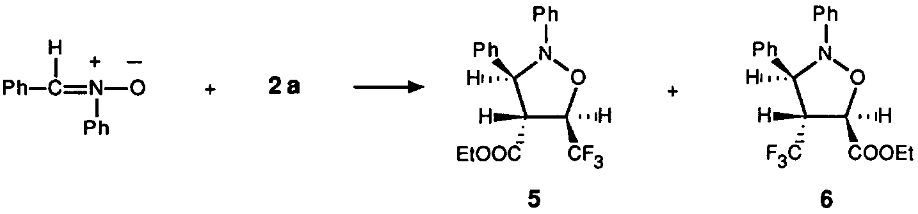


Scheme 1

Table. Reaction of Nitrone **1** with Alkenes **2**

Substrate	Time(h)	Products	Yield %
2a	5	**3a**	72
2b	60	**3b**	23
		4b	47
2c	8	**3c**	33
		4c	35

The full regioselectivity of these reactions is in contrast to that previously observed in the cycloaddition of *C,N*-diphenylnitrone to 4,4,4-trifluorocrotonate **2a**, where the two regioisomeric isoxazolidines **5** and **6** were obtained in 55:45 ratio.[9a]

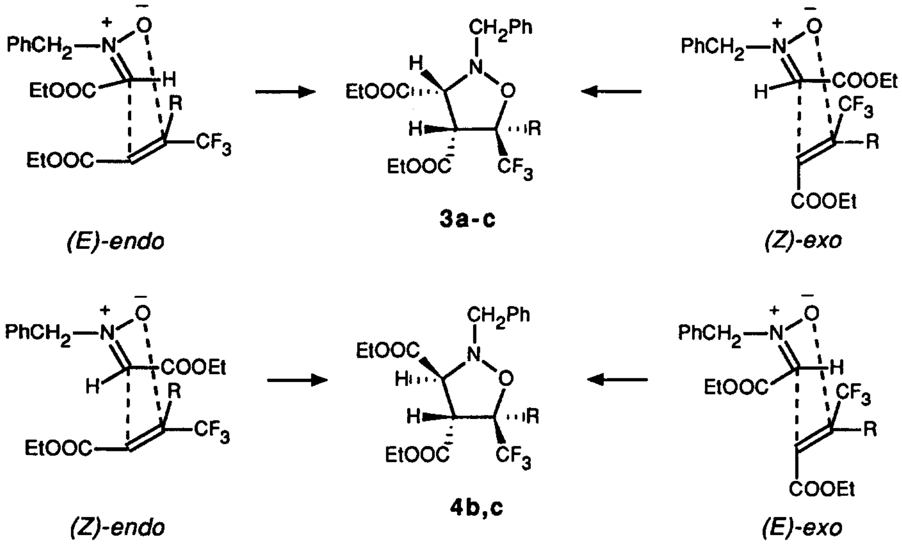


However, such a behaviour is in agreement with the reported 1,3-dipolar cycloadditions of nitrone **1** to some different mono- and disubstituted alkenes,[12,13] where only one regioisomer is formed.

Some remarks can be made about the stereochemical course of the reactions. Nitrone **1** is present in C_6D_6 solution at room temperature, as shown by NMR data, as a *ca.* 1.5:1 mixture of the *E*- and *Z*-stereoisomers, in agreement with the literature data.[14,(#)] So it is possible that either or both stereoisomers are involved in the cycloaddition.[15]

(#)The assignment of the *E*- and *Z*- configurations has been made from the NOE enhancements observed by irradiation of the benzylic protons and observation of the vinylic proton (ca. 5% enhancement for the *Z*- isomer and less than 1% for the *E*-isomer). It must be stressed that during the NOE experiment some transfer of magnetization has been observed between the *E*- and *Z*- benzylic protons. Transfer of magnetization occurs when the nuclei belonging to different species are in fast exchange on the relaxation time scale. We have observed a great variability of the transfer extent from sample to sample, meaning that the presence of impurities in solution play an important role on the *E*- and *Z*- exchange rate.

As illustrated in Scheme 2, the H-3,H-4-*cis* isoxazolidines **3** could be formed by the *E*-nitrone reacting in an *endo*-way, or by the *Z*-nitrone in an *exo*-way. Similarly, the H-3,H-4-*trans* isoxazolidines **4** could be formed by the *Z*-nitrone reacting in an *endo*-way, or by the *E*-nitrone in an *exo*-way.



Scheme 2

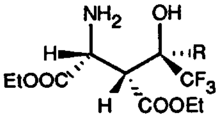
In the case of 4,4,4-trifluorocrotonate **2a**, only the H-3,H-4-*cis* isoxazolidine **3a** was obtained: the formation of this single isomer may be accounted for by the 1,3 steric interaction between the ethoxycarbonyl group of the nitrone and the bulky trifluoromethyl group of the dipolarophile. In contrast, the presence of an additional methyl or trifluoromethyl group on the β-carbon of the alkene moiety (substrates **2b** and **2c**) may induce a superimposing steric effect, which levels the difference between the two directions of approach, thus leading to mixtures of diastereoisomers.

Finally, it must be noted that in isoxazolidines **3a,b** and **4b** the stereochemistry of the starting alkene is maintained,in line with the intrinsic *cis*-stereospecificity of concerted 1,3-dipolar cycloadditions.

Isoxazolidines **3** and **4** were hydrogenated at atmospheric pressure and at room temperature with palladium hydroxide as a catalyst,[16] affording in 5h the corresponding 1,3-aminoalcohols **7** and **8** in high yields. Being the hydrogenolysis reaction stereoselective,[5] the relative configurations of the stereogenic centres were not affected by this process. These compounds may be regarded as 3-functionalised aspartic acid diethyl esters: from the stereochemical point of view, compounds **7** and **8** belong respectively to the *threo* and *erythro* series.

By way of the same hydrogenation procedure, we also converted isoxazolidines **5** and **6** into the corresponding opened products **9** and **10**.

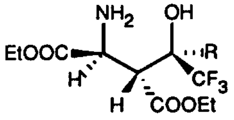
3a-c ⟶



7a-c

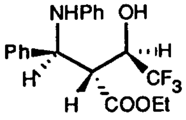
a: R=H
b: R=Me
c: R=CF_3

4b,c ⟶



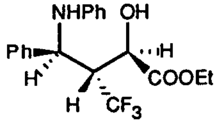
8b,c

5 ⟶



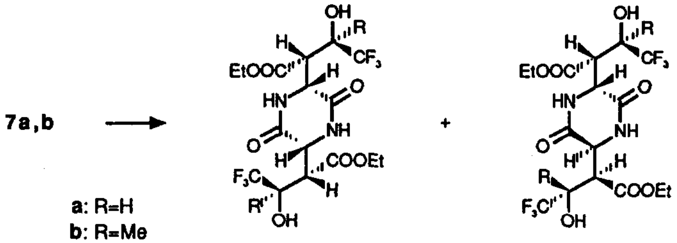
9

6 ⟶

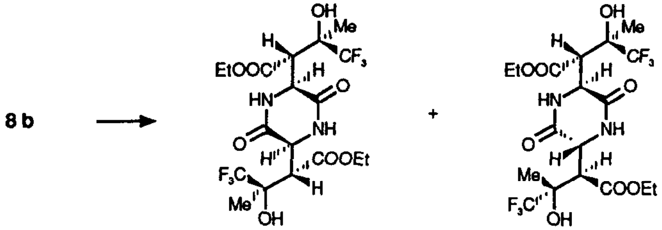


10

Compounds **7** and **8** were unstable upon heating or prolonged standing in solution at room temperature. It is known that α-amino acid esters easily convert into dioxopiperazines.[17] Compounds **7a,b** and **8b** formed, on heating at 50°C in chloroform solution for 15 min, the dioxopiperazines **11a,b** and **12b**, respectively, as mixtures of diastereoisomers.

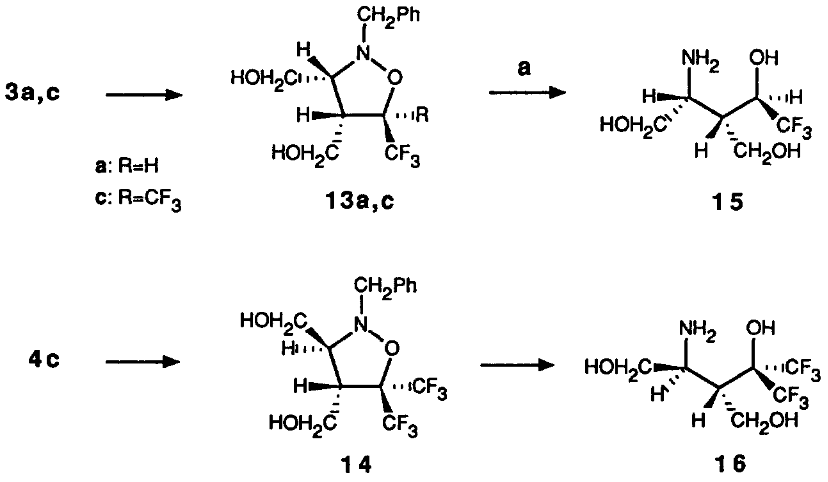


11a,b



12b

On the other hand, the treatment of isoxazolidines **3a,c** and **4c** with $LiAlH_4$ in mild conditions,[18] allowed the obtainment of the corresponding alcohols **13a,c** and **14** in good yields (Scheme 3).



Scheme 3

Subsequent hydrogenation of compounds **13a** and **14** in the presence of $Pd(OH)_2$ gave the polyhydroxylated trifluoromethyl-substituted open-chain products **15** and **16**.

STRUCTURAL ASSIGNMENTS

The regiochemistry of isoxazolidines 3 and 4 was determined from their proton NMR data, which show that the trifluoromethyl group is linked to carbon C-5 of the ring. In fact, all compounds 3 and 4 display two vicinal hydrogen atoms (coupling constants ca. 7-10 Hz) which were assigned to the H-3 and H-4 protons. The alternative regioisomer should bear the trifluoromethyl substituent at carbon C-4 of the ring and in this case no appreciable couplings should be observed between protons H-3 and H-5.

The stereochemistry of the ring substituents for isoxazolidines 3 and 4 was established mainly from homo- and heteronuclear Overhauser effects. In fact, the analysis of the vicinal coupling constants $J_{3,4}$ and $J_{4,5}$ did not result in an unambiguous configurational assignment of the chiral carbon atoms. In five-membered rings the coupling constants between vicinal *trans* pseudoaxial protons fall in the range 10-12 Hz depending on the electronegativity of the substituents, while those between *trans* pseudoequatorial protons range from 0 to 2 Hz.[19] In our case the coupling constants $^3J_{3,4}$ and $^3J_{4,5}$ for most of the isoxazolidines under examination display intermediate values (7-9 Hz), suggesting that some fast equilibrium between different ring conformations should exist.

The only exception is $^3J_{3,4}$ for compound **4c** (10.7 Hz), which indicates that for this compound the two hydrogens H-3 and H-4 are essentially in a *trans* pseudoaxial orientation. Thus we have used the stationary nuclear Overhauser effects obtained by difference spectroscopy experiments as an alternative method for the ring configurational assignment.

The irradiation of the CF_3 group of **3a** resulted in enhancement of the signal for H-5 (9%), H-4 (4%) and H-3 (2%). The same experiment performed on the reduction product **13a** produced signal enhancements for H-5 (8%), H-4 (5%), H-3 (1%) and for the methylene protons of the CH_2OH-4 group (0.8%), while no effect was detected for the CH_2OH-3 protons. In addition, the irradiation of H-5 of compound **3a** had no effect upon the intensity of H-3, suggesting that the two protons are not spatially close. All these observations point to the conclusion that the trifluoromethyl group of **3a** is oriented *cis* to the protons H-3 and

H-4.

The same procedure has been used for the structural elucidation of the diastereoisomeric compounds **3b** and **4b**. The saturation of the CF_3 fluorine nuclei of **3b** caused enhancement of the signals of H-4 (9%) and H-3 (6%), while the irradiation of the CH_3 group produced only a small effect upon the intensity of H-4 (ca. 1%). The same experiments performed on the isomer **4b** led to the observation of NOE contacts at H-4 (11%) by irradiation of CF_3 group, and at H-3 (3%) and H-4 by saturation of the CH_3 group. These data unequivocally indicate that the CF_3 substituent is *cis* to H-3 and H-4 for **3b**, while it is oriented *cis* to H-4 and *trans* to H-3 for **4b**.

Compounds **3c** and **4c** possess two non-equivalent CF_3 groups. The irradiation of the high field CF_3 of **3c** generates NOE at H-4 (11%) and H-3 (4%), while the saturation of the low field CF_3 generates only a small NOE at H-4 (1.2%). These data clearly correspond to those expected for the *cis* arrangement of the two ethoxycarbonyl substituents. In the case of compound **4c**, the experiment performed on the high field CF_3 resulted in enhancement of the signals for H-4 (1.8%) and H-3 (2.1%), whereas that performed on the low field CF_3 produced a strong NOE only for H-4 (15%). These effects are in agreement with a *trans* configuration of H-3 and H-4, as already deduced from their coupling constant (10.7 Hz).

EXPERIMENTAL

M.p.s were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 177 spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^1H and ^{19}F NMR spectra were run on a Bruker AC 250 spectrometer. Chemical shifts are quoted in ppm with respect to internal TMS for proton and to external C_6F_6 for fluorine nuclei. The nuclear Overhauser effects were obtained from monodimensional NOE difference spectra, where one or more experiments were performed with the decoupler on-resonance and then subtracted from a control spectrum with the decoupler off-resonance.

Nitrone **1** was prepared according to a literature method.[12]

All new compounds gave satisfactory elemental analyses (C ±0.3, H ±0.25, N ±0.25) and correct molecular peaks in the mass spectra.

Reaction of Nitrone **1** *with Alkene* **2a**.

A solution of *N*-benzyl-*C*-ethoxycarbonylnitrone **1** (5.7 mmol) and ethyl 4,4,4-trifluorocrotonate **2a** (5.7 mmol) in toluene (40 ml) was refluxed for 5h. The solvent was removed under reduced pressure and the residue was crystallised from *n*-hexane to give (3*R**,4*R**,5*R**)-*2-benzyl-3,4-diethoxycarbonyl-5-trifluoromethylisoxazolidine* **3a** (72%), m.p. 70-71 °C; ν (Nujol) 1760 cm^{-1}; ^{1}H NMR (C_3D_6O) δ: 1.20 and 1.27 (6H, t, 2 OCH_2CH_3, *J*(CH_2,CH_3) 7.0 Hz), 4.05-4.30 (6H, m, 2 OCH_2CH_3 and NCH_2Ph), 4.25 (1H, t, H-4, *J*(H-3,H-4) 7.0, *J*(H-4,H-5) 7.0 Hz), 4.37 (1H, d, H-3), 4.89 (1H, dq, H-5, *J*(H-5,CF_3) 7.0 Hz), 7.25-7.35 (5H, m, C_6H_5); ^{19}F NMR (C_3D_6O) δ: -72.5 (broad s, CF_3).

Reaction of Nitrone **1** *with Alkene* **2b**.

A solution of *N*-benzyl-*C*-ethoxycarbonylnitrone **1** (2.4 mmol) and ethyl 3-methyl-4,4,4-trifluorocrotonate **2b** (2.4 mmol) in toluene (25 ml) was refluxed for 60h. The solvent was removed under reduced pressure and the residue was flash chromatographed on a silica gel column with *n*-hexane/ethyl acetate 85:15 as eluant. First fractions gave (3*R**,4*S**,5*S**)-*2-benzyl-3,4-diethoxycarbonyl-5-methyl-5-trifluoromethylisoxazolidine* **4b** (47%), m.p. 49-50 °C (from *n*-hexane); ν (Nujol) 1740 cm^{-1}; ^{1}H NMR (C_6D_6) δ: 0.72 and 0.83 (6H, t, 2 OCH_2CH_3, *J*(CH_2,CH_3) 7.0 Hz), 1.26 (3H, s, CH_3), 3.65-3.85 (4H, m, 2 OCH_2CH_3), 3.89 (1H, d, NCH_aH_bPh, *J*(H_a,H_b) 15.0 Hz), 4.37 (1H, d, H-3, *J*(H-3,H-4) 9.5 Hz), 4.41 (1H, d, H-4), 4.52 (1H, d, NCH_aH_bPh),7.0-7.5 (5H, m, C_6H_5); ^{19}F NMR (C_6D_6) δ: -81.0 (s, CF_3). Subsequent fractions gave (3*R**,4*R**,5*R**)-*Isomer* **3b** (23%), oil; ν (Film) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.28 (6H, t, 2 OCH_2CH_3, *J*(CH_2,CH_3) 7.0 Hz), 1.52 (3H,s, CH_3), 3.60 (1H, d, *J*(H-3,H-4) 7.6 Hz), 3.86 (1H, d, H-4), 4.08 (1H, d, NCH_aH_bPh, *J*(H_a,H_b) 14.5 Hz), 4.14-4.31 (4H, m, 2 OCH_2CH_3), 4.41 (1H, d, NCH_aH_bPh), 7.21-7.42 (5H, m, C_6H_5); ^{19}F NMR ($CDCl_3$) δ: -81.95 (s, CF_3).

Reaction of Nitrone **1** *with Alkene* **2c**.

A solution of *N*-benzyl-*C*-ethoxycarbonylnitrone **1** (2.4 mmol) and ethyl 3-trifluoromethyl-4,4,4-trifluorocrotonate **2c** (2.4 mmol) in toluene (25 ml) was refluxed for 8h. The solvent was removed under reduced pressure and the residue was flash chromatographed on a silica gel column with toluene/ethyl acetate 29:1 as eluant. First fractions gave (3*R**,4*S**)-*2-benzyl-3,4-diethoxycarbonyl-5,5-bis(trifluoromethyl)isoxazolidine* **4c** (35%), oil; ν (Film) 1750 cm^{-1}; ^{1}H NMR (C_3D_6O) δ: 1.26 and 1.27 (6H, t, 2 OCH_2CH_3, *J*(CH_2,CH_3) 7.0 Hz), 4.18 (1H, d, NCH_aH_bPh, *J*(H_a,H_b) 14.9 Hz), 4.16-4.32 (5H, m, 2 OCH_2CH_3 and H-3), 4.40 (1H, dq, H-4. *J*(H-3,H-4) 10.7, *J*(H-4,CH_3) 1.0 Hz), 4.58 (1H, d, NCH_aH_bPh), 7.25-7.44 (5H, m, C_6H_5); ^{19}F NMR (C_3D_6O) δ: -72.2 (q, CF_3-5 *cis* to H-4, *J*(CF_3,CF_3) 9.1 Hz), -68.5 (q, CF_3-5 *trans* to H-4).

Subsequent fractions gave *(3R*,4R*)-Isomer* **3c**, oil; ν (Film) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.20 and 1.21 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 3.61 (1H, d, H-3, *J*(H-3,H-4) 7.1 Hz), 3.92 (1H, d, H-4), 4.05-4.25 (5H, m, 2 OCH_2CH_3 and NCH_aH_bPh), 4.67 (1H, d, NCH_aH_bPh, $J(H_a,H_b)$ 15.0 Hz), 7.29 (5H, broad s, C_6H_5); ^{19}F NMR ($CDCl_3$) δ: -77.4 (q, CF_3-5 *cis* to H-4, $J(CF_3,CF_3)$ 11.5 Hz), -71.5 (q, CF_3-5 *trans* to H-4).

Hydrogenation of Isoxazolidines **3,4,5,6,13a,14**. *General Procedure.*

A solution of isoxazolidine **3,4,5,6,13a,14** (0.5 mmol) in ethyl acetate (15 ml) was hydrogenated at room temperature and at 1 atm for 5h in the presence of 20% $Pd(OH)_2/C$ (0.1 mmol). The catalyst was removed by filtration over celite and the solvent was evaporated under reduced pressure, affording 1,3-aminoalcohol **7,8,9,10,15,16**.

(2R,2αR*,3R*)-3-amino-2-(α-hydroxy-β,β,β-trifluoroethyl)butanedioic acid diethyl ester* **7a**: (82%), oil; ν (Film) 3400, 3300, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.25 and 1.28 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 3.42 (1H, t, H-2, *J*(H-2,H-3) 5.0 Hz, *J*(H-2,H-2α) 5.0 Hz), 3.92 (1H, d, H-3), 3.8-4.2 (3H, broad, NH_2 and OH), 4.10-4.37 (4H, m, 2 OCH_2CH_3), 4.68 (1H, dq, H-2α, $J(H\text{-}2\alpha,CF_3)$ 8.0 Hz).

(2R,2αR*,3R*)-3-amino-2-(α-hydroxy-α-methyl-β,β,β-trifluoroethyl)-butanedioic acid diethyl ester* **7b**: (93%), oil; ν (Film) 3400, 3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.27 and 1.31 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 1.41 (3H, s, CH_3), 3.26 (1H, d, H-2, *J*(H-2,H-3) 4.0 Hz), 4.05 (1H, d, H-3), 4.08-4.35 (4H, m, 2 OCH_2CH_3), 3.0-4.5 (3H, broad, NH_2 and OH); ^{19}F NMR ($CDCl_3$) δ: -82.0 (s, CF_3).

(2R,3R*)-3-amino-2-[α-hydroxy-β,β,β-trifluoro-α-(trifluoromethyl)-ethyl]butanedioic acid diethyl ester* **7c**: (91%), oil; ν (Film) 3400, 3300, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.27 and 1.29 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.2 Hz), 3.49 (1H, d, H-2, *J*(H-2,H-3) 3.6 Hz), 4.28-4.32 (5H, m, 2 OCH_2CH_3 and H-3), 4.2-5.3 (3H, broad, NH_2 and OH); ^{19}F NMR ($CDCl_3$) δ: -75.0 and -76.7 (2 CF_3 groups, q, $J(CF_3,CF_3)$ 10.5 Hz).

(2R,2αR*,3S*)-3-amino-2-(α-hydroxy-α-methyl-β,β,β-trifluoroethyl)-butanedioic acid diethyl ester* **8b**: (88%), oil; ν (Film) 3400, 3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.29 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 1.51 (3H, s, CH_3), 3.16 (1H, d, H-2, *J*(H-2,H-3) 9.6 Hz), 4.09 (1H, d, H-3), 4.1-4.25 (4H, m, 2 OCH_2CH_3), 3.5-4.7 (3H, broad, NH_2 and OH); ^{19}F NMR ($CDCl_3$) δ: -82.8 (s, CF_3).

(2R,3S*)-3-amino-2-[α-hydroxy-β,β,β-trifluoro-α-(trifluoromethyl)-ethyl]butanedioic acid diethyl ester* **8c**: (84%), oil; ν (Film) 3380, 3300, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.26 and 1.30 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.1 Hz), 3.40 (1H, dq, H-2, *J*(H-2,H-3) 10.5 Hz, $J(H\text{-}2, CF_3)$ 1.1 Hz), 4.08-4.42 (4H, m, 2 OCH_2CH_3), 4.38 (1H, d, H-3); ^{19}F NMR

($CDCl_3$) δ: -73.8 and -77.4 (2 CF_3, q, *J*(CF_3,CF_3) 10.0 Hz).

(2R,2αS*,3R*)-3-hydroxy-2-[α-phenyl-α-(phenylamino)methyl]-4,4,4-trifluorobutanedioic acid diethyl ester* **9**: (71%), m.p. 103 °C (from *n*-hexane); ν (Nujol) 3400, 3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.87 (3H, t, OCH_2CH_3, *J*(CH_2,CH_3) 7.0 Hz), 3.20 (1H, t, H-2, *J*(H-2,H-2α) 9.0 Hz, *J*(H-2,H-3) 9.0 Hz), 3.81 (2H, q, OCH_2CH_3), 4,68 (1H, dq, H-3, *J*(H-3,CF_3) 7.0 Hz), 4.88 (1H, d, H-2α), 5.2 (1H, broad, NH and OH), 6.7-7.2 (10H, m, 2 C_6H_5).

(2R,3R*,4S*)-2-Hydroxy-4-phenyl-4-phenylamino-3-trifluoromethyl-butanoic acid ethyl ester* **10**: (64%), m.p. 97-98 °C (from *n*-hexane); ν (Nujol) 3400, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.13 (3H, t, OCH_2CH_3, *J*(CH_2,CH_3) 7.0 Hz), 2.7-3.9 (3H, m, H-2,H-3,H-4), 3.78 (2H, q, OCH_2CH_3), 5.05 (2H, broad, NH and OH), 6.4-7.6 (10H, m, 2 C_6H_5).

(2R,3R*,4R*)-2-amino-4-hydroxy-3-hydroxymethyl-5,5,5-trifluoro-pentan-1-ol* **15**: (92%), oil; ν (Film) 3300 cm^{-1}; ^1H NMR (C_3D_6O) δ: 3.16 (1H, dt, H-2, *J*(H-2,H-3) 4.5 Hz, *J*(H-2,CH_2OH) 4.5 and 9.5 Hz), 3.5-4.10 (10H, m, 2 CH_2OH, H-3, OH-4, and NH_2), 4.31 (1H, qd, H-4, *J*(H-3,H-4) 6.0 Hz, *J*(H-4,CF_3) 8.0 Hz); ^{19}F NMR (C_3D_6O) δ: -71.9 (CF_3, d, *J*(CF_3,H-4) 8.0 Hz).

(2R,3S*)-2-amino-4-hydroxy-3-hydroxymethyl-5,5,5-trifluoro-4-trifluoromethylpentan-1-ol* **16**: (78%), oil; ν (Film) 3300 cm^{-1}; ^1H NMR (C_3D_6O) δ: 2.42 (1H, broad q, H-3, *J*(H-2,H-3) *ca.* 6 Hz), 2.95 (3H, broad, 3 OH), 3.44 (1H, m, H-2), 3.61 (1H, dd, $H-1_a$), *J*($H-1_a$,$H-1_b$) 7.0 Hz, J_{gem} 10.5 Hz), 3.89 (2H, d, CH_2OH-3, *J*(CH_2,H-3) 6.0 Hz), 3.92 (1H, dd, $H-1_b$, *J*($H-1_b$,H-2) 4.5 Hz); ^{19}F NMR (C_3D_6O) δ: -67.9 and -71.6 (2 CF_3, q, *J*(CF_3,CF_3) 9.5 Hz).

Preparation of Alcohols **13a,c** *and* **14**. *General Procedure.*

To a cooled solution (0°C) of isoxazolidine **3a,c** and **4c** (0.7 mmol) in dry diethyl ether (5 ml) $LiAlH_4$ (0.85 mmol) was added. After stirring at 0°C for 30 min, 2M HCl was slowly added; the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure, affording alcohol **13a,c** and **14**.

(3R,4R*,5R*)-2-benzyl-3,4-dihydroxymethyl-5-trifluoromethyl-isoxazolidine* **13a**: (83%), m.p. 94-95 °C (from di-isopropyl ether); ν (Nujol) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.51 (1H, broad s, OH), 2.66 (1H, broad s, OH), 3.15 (1H, m, H-4), 3.37 (1H, q, H-3, *J*(H-3,H-4) 7.0 Hz, *J*(H-3,CH_2OH) 6.0 and 5.0 Hz), 3.69 and 3.74 (2H, m, CH_2OH-3, J_{gem} 11.7 Hz), 3.91 (2H, d, CH_2OH-4, *J*(H-4,CH_2) 6.0 Hz), 3.96 (1H, d, NCH_aH_b, *J*(H_a,H_b) 13.2 Hz), 4.17 (1H, d, NCH_aH_b), 4.22 (1H, qd, H-5, *J*(H-5,H-4) 7.0 Hz, *J*(H-5,CF_3) 7.0 Hz), 7.25-7.39 (5H, m, C_6H_5); ^{19}F NMR ($CDCl_3$) δ: -78.8 (d, CF_3, *J*(CF_3,H-5) 7.0 Hz).

(3R*,4R*)-2-benzyl-3,4-dihydroxymethyl-5,5-bis(trifluoromethyl)-isoxazolidine **13c**: (89%), oil; ν (Film) 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.95 (2H, broad s, 2 OH), 3.45-3.58 (2H, m, H-3 and H-4), 3.63 and 3.88 (2H, dd, CH_2OH, J_{gem} 11.0, J_{vic} 4.0 and 7.0 Hz), 3.96 and 4.12 (2H, broad m, CH_2OH), 4.10 (1H, d, NCH_aCH_b, $J(H_a,H_b)$ 14.0 Hz), 4.21 (1H, d, NCH_aH_b), 7.28-7.42 (5H, m, C_6H_5); ^{19}F NMR ($CDCl_3$) δ: -70.4 and -76.1 (2 CF_3, q, $J(CF_3,CF_3)$ 9.3 Hz).
(3R*,4S*)-2-benzyl-3,4-dihydroxymethyl-5,5-bis(trifluoromethyl)-isoxazolidine **14**: (91%), oil; ν (Film) 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.51 (2H, broad s, 2 OH), 3.07 (ddd, H-4, J(H-3,H-4) 10.0 Hz, J(H-4,CH_2OH-4) 5.5 and 2.5 Hz), 3.25 (1H, ddd, H-3, J(H-3,CH_2OH-3) 4.5 and 9.7 Hz), 3.63 (1H, dd, CH_aH_bOH-4, J_{gem} 12.0 Hz), 3.78 (1H, dd, CH_aH_bOH-4), 3.66 (1H, dd, CH_aH_bOH-3, J_{gem} 11.0 Hz), 4.09 (1H, dd, CH_aH_bOH-3), 4.09 (1H, d, NCH_aH_b, J_{gem} 14.7 Hz), 4.24 (1H, d, NCH_aH_b), 7.25-7.40 (5H, m, C_6H_5); ^{19}F NMR ($CDCl_3$) δ: -72.6 and -77.2 (2 CF_3, q, $J(CF_3,CF_3)$ 9.5 Hz).

Preparation of 2,5-Dioxopiperazines **11a,b** and **12b**. _General Procedure._

A solution of 1,3-aminoalcohol **7a,b** and **8b** (0.2 mmol) in chloroform (5 ml) was heated at 50°C for 15 min. After cooling at room temperature, the so-formed precipitate was filtered, affording 2,5-dioxopiperazine **11a,b** and **12b**.
11a: (45%), m.p. 203-205 °C (from chloroform); ν (Nujol) 3340, 3290, 1730, 1660 cm^{-1}; ^{1}H NMR (C_2D_6SO) (mixture of two diastereoisomers in _ca._ 7:3 ratio) δ (major diastereoisomer): 1.14 (6H, t, 2 OCH_2CH_3, $J(CH_3,CH_2)$ 7.0 Hz), 3.47 (2H, d, CHCO, J(CHCO,$CHCF_3$) 7.5 Hz), 3.92-4.20 (4H, m, 2 OCH_2CH_3), 4.59 (2H, s, CHNH), 4.77 (2H, m, $CHCF_3$), 6.98 (2H, d, 2 OH, J($CHCF_3$,OH) 5.5 Hz), 7.81 (2H, s, 2 NH); δ (minor diastereoisomer): 1.14 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 3.40 (2H, d, CHCO, J(CHCO,$CHCF_3$) 7.0 Hz), 3.92-4.20 (4H, m, 2 OCH_2CH_3), 4.32 (2H, s, CHNH), 4.77 (2H, m, $CHCF_3$), 7.60 (2H, broad s, 2 OH), 7.98 (2H, s, 2 NH); ^{19}F NMR (C_2D_6SO) δ: -72.7 (CF_3, d, major diast., $J(CF_3,H)$ 6.0 Hz), -72.85 (CF_3, d, minor diast., $J(CF_3,H)$ 6.0 Hz).
11b: (41%), m.p. 163-165 °C (from chloroform); ν (Nujol) 3350, 3300, 1730, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$ + C_2D_6SO) (mixture of two diastereoisomers in _ca._ 7:3 ratio) δ (major diastereoisomer): 1.28 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 1.51 (6H, s, 2 CH_3), 3.54 (2H, d, CHCO, J(CHCO,CHNH) 4.0 Hz), 4.05-4.34 (4H, m, 2 OCH_2CH_3), 4.57 (2H, broad s, CHNH), 6.50 (2H, broad s, 2 OH), 7.30 (2H, s, 2 NH); δ (minor diastereoisomer): 1.28 (6H, t, 2 OCH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 1.51 (6H, s, 2 CH_3), 3.65 (2H, d, CHCO, J(CHCO,CHNH) 3.5 Hz), 4.05-4.34 (4H, m, 2 OCH_2CH_3), 4.57 (2H, broad s, CHNH), 6.65 (2H, broad s, 2 OH), 7.51 (2H,

s, 2 NH); ^{19}F NMR ($CDCl_3$ + C_2D_6SO) δ: -81.0 (CF_3, s, major diast.), -81.5 (CF_3, s, minor diast.).

12b: (38%), m.p. 179-181 °C (from chloroform); ν (Nujol) 3340, 3300, 1730, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$ + C_2D_6SO) (mixture of two diastereoisomers in *ca.* 65:45 ratio) δ (major diastereoisomer): 1.29 (6H, t, 2 OCH_2CH_3, $J(CH_3,CH_2)$ 7.0 Hz), 1.49 (6H, s, 2 CH_3), 3.45 (2H, d, CHCO, J(CHCO,C*H*NH) 4.0 Hz), 4.05-4.32 (4H, m, 2 OCH_2CH_3), 4.46 (2H, d, C*H*NH), 7.37 (2H, s, 2 OH), 8.42 (2H, s, 2 NH); δ (minor diastereoisomer): 1.29 (6H, t, 2 OCH_2CH_3, $J(CH_3,CH_2)$ 7.0 Hz), 1.52 (6H, s, 2 CH_3), 3.20 (2H, d, CHCO, J(CHCO,C*H*NH) 10.0 Hz), 4.05-4.32 (4H, m, 2 OCH_2CH_3), 4.69 (2H, d, C*H*NH), 7.37 (2H, s, 2 OH), 8.20 (2H, s, 2 NH); ^{19}F NMR ($CDCl_3$ + C_2D_6SO) δ: -75.20 (CF_3, s, major diast.), -75.26 (CF_3, s, minor diast.).

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