acid[10] (0.248 g, 0.61 mmol), *N*-hydroxybenzotriazole (0.107 g, 7 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.144 g, 7 mmol) under ice-cooling. The mixture was stirred at 0 °C for 30 min and then at room temperature for 15 h. After the addition of water (20 mL) and sodium methyldithiocarbamate (0.182 g, 1.4 mmol) under ice-cooling, the mixture was stirred at room temperature for 2 h. Insoluble materials were removed by filtration and the filtrate was subjected to chromatography on Amberlite XAD-2. Elution with 5% ethanol, followed by lyophilization, gave **8** (135 mg, 36.0%) as a colorless powder: IR (KBr) 3430, 1770, 1730, 1670, 1630, 1530, 1250, 1150, 1080 cm^{-1}; NMR (D_2O) δ 1.45 (9 H, s, $C(CH_3)_3$), 1.53 (6 H, s, $C(CH_3)_2$), 5.58 (1 H, d, J = 5 Hz, C_3-H), 6.98 (1 H, s, proton at position 5 of the thiazole ring).

***cis,rac*,(*Z*)-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]-α,α-dimethylacetic Acid (9).** To **8** (0.131 g, 0.25 mmol) was added trifluoroacetic acid (5 mL) under ice-cooling, and the mixture was stirred for 2.5 h. The mixture was evaporated to dryness under reduced pressure, and the residue was subjected to chromatography on Dowex 50W (H^+ form, 20 mL). Elution with water gave the fractions containing **9**, which were combined and concentrated to 20 mL. The concentrate was rechromatographed on Amberlite XAD-2. Elution with 5% ethanol, followed by lyophilization, gave **9** (68 mg, 60.3%) as a colorless powder: IR (KBr) 3400, 1770, 1680, 1640, 1270, 1240, 1180, 1050 cm^{-1}; NMR (D_2O) δ 1.551 (3 H, s, CH_3), 1.559 (3 H, s, CH_3), 4.606 (1 H, ddt, J = 24.4, 5.6, 2.9 Hz, C_2-H), 4.71–5.35 (2 H, m, CH_AH_BF, not clearly assigned), 5.606 (1 H, d, J = 5.9 Hz, C_3-H), 7.160 (1 H, s, proton at position 5 of the thiazole ring).

Anal. Calcd for $C_{13}H_{16}F_1N_5O_8S_2 \cdot 1.5H_2O$: C, 32.50; H, 3.99; N, 14.58. Found: C, 32.46; H, 3.98; N, 14.83.

***cis,rac*,(*Z*)-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]acetic Acid 4-Nitrophenylmethyl Ester Monosodium Salt (10).** A mixture of **7** (0.296 g, 0.84 mmol) and 10% palladium/charcoal (300 mg) in dimethylformamide (7 mL) was stirred under hydrogen at room temperature for 45 min. The catalyst was filtered off and washed with dimethylformamide (6 mL). To the combined filtrate and washings were added 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[(*p*-nitrobenzyloxycarbonyl)methoxy]imino]acetic acid[13] (0.365 g, 0.8 mmol), *N*-hydroxybenzotriazole (0.123 g, 0.8 mmol), and *N,N'*-dicyclohexylcarbodiimide (0.165 g, 0.8 mmol) under ice-cooling. The mixture was stirred at 0 °C for 30 min and than allowed to stand overnight at room temperature. After being cooled to 0 °C, the mixture was diluted with water (20 mL) and, then sodium methyldithiocarbamate (0.210 g, 1.6 mmol) was added. After being stirred at room temperature for 2 h, the mixture was subjected to chromatography on Amberlite XAD-2. Elution with 5% ethanol, followed by lyophilization, gave **10** (206 mg, 43.5%) as a colorless powder: IR (KBr) 3430, 1760, 1670, 1270, 1250, 1050 cm^{-1}; NMR (D_2O) δ 4.85 (2 H, s, OCH_2CO), 5.20 (2 H, s, OCH_2Ph), 6.84 (1 H, s, proton at position 5 of the thiazole ring).

***cis,rac*,(*Z*)-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]acetic Acid (11).** A mixture of **10** (0.205 g, 3.5 mmol) and 10% palladium/charcoal (200 mg) in water (15 mL) was stirred under hydrogen at room temperature for 1.5 h. The catalyst was filtered off and washed with water. The combined filtrate and washings were adjusted to pH 8 with aqueous sodium bicarbonate. The solution was subjected to chromatography on Amberlite XAD-2. Elution with water gave the fractions containing **11**. After the pH was adjusted to 3 with dilute hydrochloric acid, the solution was concentrated to 30 mL. The concentrate was subjected to chromatography on Dowex 50W (H^+ form). Elution with water gave the fractions containing **11**. After concentration to 40 mL, the material was rechromatographed on Amberlite XAD-2. Elution with water, followed by lyophilization, gave **11** (75.5 mg, 48.7%) as a colorless powder: IR (KBr) 3400, 1770, 1675, 1640, 1240, 1050 cm^{-1}; NMR (D_2O) δ 4.589 (1 H, ddt, J = 24.2, 5.6, 2.9 Hz, C_2-H), 4.70–5.01 (2 H, m, CH_AH_BF, not clearly assigned), 4.861 (2 H, s, OCH_2), 5.615 (1 H, d, J = 5.6 Hz, C_3-H), 7.191 (1 H, s, proton at position 5 of the thiazole ring).

(13) Takeda. Jpn. Kokai Tokkyo Koho 57-131758, 1982.

Anal. Calcd for $C_{11}H_{12}FN_5O_8S_2 \cdot 2H_2O$: C, 28.64; H, 3.50, N, 15.18. Found: C, 28.84; H, 3.55; N, 15.10.

Acknowledgment. We are grateful to Dr. K. Morita of this division for encouragement throughout this work. Thanks are also due to Dr. M. Kondo of this division for in vitro antibacterial testing.

Registry No. (±)-*cis*-**1**, 88946-30-9; (±)-*cis*-**1** (amine), 88946-38-7; (±)-*cis*-**2**, 88946-31-0; (±)-*cis*-**3**, 88124-54-3; (±)-*cis*-**4**, 88946-32-1; (±)-*cis*-**5**, 88946-33-2; (±)-*cis*-**6**, 89015-35-0; (±)-*cis*-**7**, 88946-34-3; (±)-*cis*-**8**, 88946-35-4; (±)-*cis*-**9**, 86455-21-2; (±)-*cis*-**10**, 88946-36-5; (±)-*cis*-**11**, 88946-37-6; OMB–NH_2, 20781-20-8; $FtCH_2COCl$, 6780-38-7; FCH_2CH_2OH, 371-62-0; 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-(methoxyimino)acetyl chloride hydrochloride, 65243-22-3; 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[1-methyl-1-[(*tert*-butyloxy)carbonyl]ethoxy]imino]-acetic acid, 79656-47-6; 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[[(*p*-nitrobenzyloxy)carbonyl]methoxy]imino]acetic acid, 84208-28-6.

Sulfazecin Analogues. Preparation of 4-(Trifluoromethyl)-1-sulfo-2-azetidinone Derivatives

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Received August 24, 1983

The recently discovered sulfazecin and monobactam antibiotics are monocyclic β-lactams activated by an N-1 sulfonate substituent.[1,2] Aztreonam, a member of this new group of compounds that contains a methyl substituent in the 4-position of the β-lactam ring, has excellent activity against Gram-negative bacteria and is currently being evaluated in the clinic.[3] It is suggested in the literature that an increase in the reactivity of the β-lactam ring correlates well with antibacterial activity.[4] We reasoned that replacing the hydrogens of the 4-methyl group with fluorine atoms, which are strongly electronegative, would cause the β-lactam to be even more susceptible to nucleophillic attack. Thus, we hoped that replacing the methyl group by trifluoromethyl would have a good effect on antibacterial activity. In the preceding note by Ochiai and collaborators, this hypothesis was successfully tested by the preparation of the very active antibacterials, 4-(fluoromethyl)-3-(acylamino)-1-sulfo-2-azetidinones.[5] In the present paper, we describe the preparation of 3-(acylamino)-1-sulfo-2-azetidinones with *cis*- and *trans*-4-trifluoromethyl substituents.

During the course of this work, an alternate procedure for the preparation of these compounds was reported by Kronenthal et al.[6]

(1) Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature (London)* **1981**, *289*, 590.

(2) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. *Nature (London)* **1981**, *291*, 489.

(3) Sykes, R. B.; Bonner, D. P.; Bush, K.; Georgopapadakou, N. H. *Antimicrob. Agents Chemother.* **1982**, *21*, 85.

(4) Boyd, D. B. "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1, pp 437.

(5) Yoshioka, K.; Miyawaki, T.; Kishimoto, S.; Matsuo, T.; Ochiai, M., preceding note in this issue.

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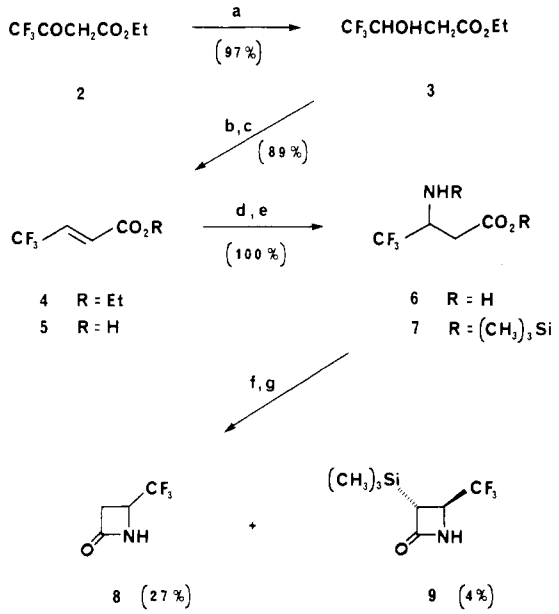
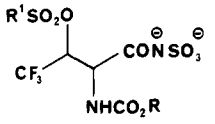
0022-3263/84/1949-1430$01.50/0

Scheme I[a]



[a] (a) 5% Pd/C, H_2, 125 °C, 1500 psi; (b) DEAD, Ph_3P, Et_2O; (c) 1 N NaOH, THF; (d) NH_3, 100 °C; (e) $(CH_3)_3SiCl$, Et_3N, PhH; (f) MeMgBr, Et_2O; (g) CH_3OH, 50 °C.

Initially we modeled our approach to the 4-trifluoromethyl compounds after the excellent method described by Floyd et al. for the preparation of *N*-sulfo-2-azetidinones.[7,8] However, attempted cyclizations of 1[9] led either



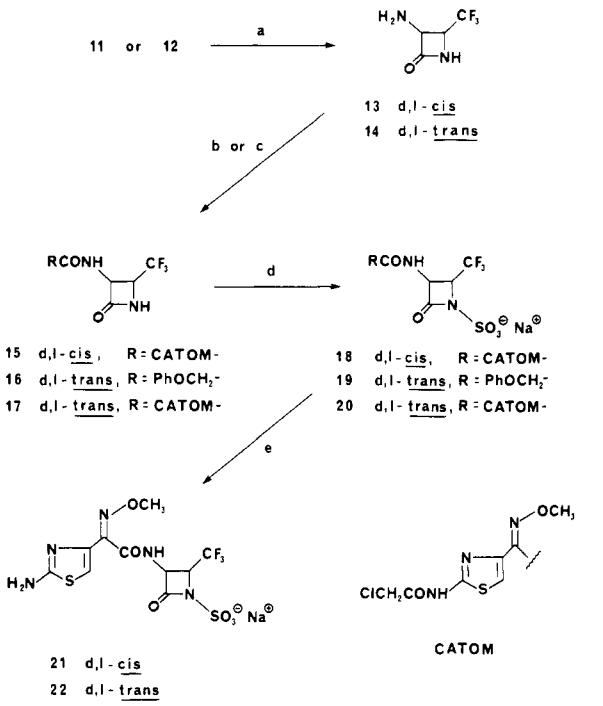
1

to unreacted starting material ($R^1 = CH_3$) or mixtures in which the main product was that of elimination of sulfonate (R^1 = *p*-CH_3Ph, *p*-NO_2Ph, or CF_3). Although small amounts of β-lactam products were observed in reactions of the triflates ($R^1 = CF_3$), this finding was not investigated further due to the complexity of the reaction mixtures.

Alternatively, it was found possible to form the 4-(trifluoromethyl)-2-azetidinone from a β-amino acid, effecting N_1–C_2 bond formation by treatment of the bis(trimethylsilyl) derivative with a Grignard reagent. This approach is outlined in Scheme I.

Preparation of the amino acid **6** has been reported,[10] but several improvements in the procedure are noted below. Of the possible methods for eliminating water from **3** [e.g., boric anhydride (55%),[11] phosphorus pentoxide (60%),[12] or via the triflate (80%)[12]], it was found most convenient to form **4** quantitatively by treatment with diethyl azodicarboxylate/triphenylphosphine.[13] In addition, amidolysis of the unsaturated acid **5** in a bomb at 100 °C gave an essentially quantitative yield of the amino acid **6**.

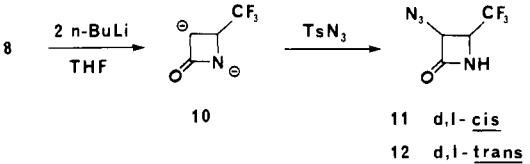
Scheme II[a]



[a] (a) 10% Pd/C, H_2, THF; (b) $PhOCH_2COCl$, Et_3N, THF; (c) [2-[(chloroacetyl)amino]-4-thiazolyl](methoxyimino)-acetic acid, NHBT, DCC, DMF; (d) SO_3·DMF followed by Dowex (Na^+); (e) CH_3NHCS_2Na, H_2O.

Direct cyclization of **6** to form **8** failed. However, application of the trimethylsilyl modification of the Breckpot β-lactam synthesis proved to be successful.[14] Thus, methylmagnesium bromide cyclization of the bis(silyl) compound **7** gave **8** in 27% yield. The C-silylated product **9** (4%) was also isolated, presumably a result of trimethylsilyl transfer to the enolate of the *N*-trimethylsilyl derivative of **8**.

With the desired 4-(trifluoromethyl)-2-azetidinone in hand, introduction of the 3-acylamino group was considered. This group, which is present in most β-lactam antibacterials, is deemed essential for activity. This transformation was accomplished in stepwise fashion, first introducing an azide group by treatment of the dianion **10** with tosyl azide to give a 30% yield of *cis*- and *trans*-3-azido-4-(trifluoromethyl)-2-azetidinones (**11** and **12**) in a ratio of 1:3.[15,16] The isomers were separated by silica gel chromatography, and the structure assignment was based on the magnitude of the coupling constant between H3 and H4 ($J_{3,4}$ = 2 Hz for trans and 5.5 Hz for cis).[17]



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(8) Routes involving introduction of the trifluoromethyl group onto a performed β-lactam moiety were unsuccessful. For example, treatment of a 4-carboxy-2-azetidinone with SF_4 resulted in destruction of the β-lactam ring.

(9) Compound **1** was synthesized from the known 2-amino-3-hydroxy-4,4,4-trifluorobutyramide: Walborsky, H. M.; Baum, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 187.

(10) Walborsky, H. M.; Baum, M. E. *J. Org. Chem.* **1956**, *21*, 538.

(11) Walborsky, H. M.; Schwarz, M. *J. Am. Chem. Soc.* **1953**, *75*, 3241.

(12) Unpublished results.

(13) Mitsonobu, O. *Synthesis* **1981**, 1.

(14) (a) Birkofer, L.; Schramm, J. *Justus Liebigs Ann. Chem.* **1975**, 2195. (b) Breckpot, R. *Bull. Soc. Chim. Belg.* **1923**, *32*, 412.

(15) For reactions of azetidinone dianions, see: Durst, T.; Van Den Elzen, R.; Legault, R. *Can. J. Chem.* **1974**, *52*, 3206. Depres, J.; Greene, A. E.; Crabbe, P. *Tetrahedron Lett.* **1978**, 2191.

(16) For examples of azide transfer from tosyl azide, see: Kuhlein, K.; Jensen, H. *Justus Liebigs Ann. Chem.* **1974**, 369.

(17) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941. Luche, J. L.; Kagan, H. B.; Pathasarathy, R.; Tsoucaris, G.; deRango, C.; Zelwer, C. *Tetrahedron* **1968**, *24*, 1275.

Conversion of **11** or **12** to acylamino derivatives was accomplished as shown in Scheme II. Thus, catalytic reduction (10% Pd/C) of either compound in THF yielded the cis or trans amino compounds **13** and **14**, respectively. These amines were then acylated directly to yield amides **15–17**. For example, treatment of either **13** or **14** with [2-[(chloroacetyl)amino]-4-thiazolyl](methoxyimino)acetic acid in the presence of 1-hydroxybenzotriazole (NHBT) and *N,N'*-dicyclohexylcarbodiimide (DCC) gave the cis amide **15** (65%) or the trans amide **17** (88%), respectively.[18] On the other hand, acylation of **14** with phenoxyacetyl chloride in the presence of triethylamine gave **16** (55%). Sulfonation of **15–17** with *N,N*-dimethylformamide–sulfur trioxide complex[7] gave the *N*-sulfo compounds **18–20** in 60–70% yield. Removal of the chloroacetyl group from **18** and **20** was achieved in 55–60% yield with sodium methyldithiocarbamate, giving the aminothiazoles **21** and **22**.[19]

Compounds **19**, **21**, and **22** were tested for in vitro antibacterial activity. The phenoxyacetyl analogue **19** is essentially devoid of activity while the aminothiazole compounds exhibit weak activity against Gram-negative bacteria, the cis isomer **21**, being slightly more active than the trans isomer **22**. This is to be contrasted with the corresponding substances having a 4-methyl or 4-fluoromethyl substituent which show good antibacterial activity.[5,20]

Although the biological results were disappointing, our original premise regarding the chemical reactivity of a trifluoromethyl-substituted β-lactam proved to be correct. Thus, compound **19** has a half-life of 3.5 h in biological buffer[21] while the methyl analogue has a half-life of 298 h. Consequently, as suggested earlier in the literature,[21] higher chemical reactivity of the β-lactam is not a sufficient prerequiste for improved antibacterial activity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were measured on a Digilab FTS 15-E spectrometer. ^{1}H NMR were recorded on a Varian XL-100-FT spectrometer with $Si(CH_3)_4$ as the internal standard. ^{19}F NMR were recorded on a Varian XL-100-FT spectrometer with $CFCl_3$ as the internal standard. Mass spectra were recorded on a VG ZAB-1F spectrometer by using the FAB (positive ion, glycerol matrix) technique. Preparative liquid chromatography was carried out on a Waters Prep 500 instrument using the support and eluant indicated.

Ethyl (±)-4,4,4-Trifluoro-3-hydroxybutanoate (3). This was prepared by the procedure of Walborsky and Schwarz[11] from ethyl trifluoroacetoacetate (**2**) and isolated as a white waxy solid: yield 97%; mp 28–30 °C (lit.[11] bp 90–91 °C/50mm); IR ($CHCl_3$) ν_{max} 3610, 3470, 1726, 1325, 1280, 1174, 1133, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 2.68 (m, 2, J = 5.5, 6.5 Hz, C-2 protons), 4.01 (br s, 1, OH), 4.19 (q, 2, J = 7 Hz, $-CH_2O$), 4.44 (m, 1, J = 5.5, 6.5 Hz, $^3J_{HF}$ = 6 Hz, C_3 proton); ^{19}F NMR ($CDCl_3$) δ −80.4 (dm, $^3J_{HF}$ = 6.05, $^4J_{HF}$ = 2.2 Hz, CF_3).

Ethyl (*E*)-4,4,4-Trifluoro-2-butenoate (4). A mixture of the alcohol **3** (186 g, 1 mol) and triphenylphosphine (262 g, 1 mol) in anhydrous diethyl ether (1.0 L) was stirred at ambient temperature until complete solution occurred. The mixture was cooled to 0 °C and diethyl azodicarboxylate (174 g, 1 mol) was slowly added, forming a thick precipitate of Ph_3PO. The cooling bath was removed and the mixture stirred at room temperature overnight. The phosphine oxide was removed by filtration (279 g) and washed with diethyl ether (2 × 250 mL). The ether was removed from the combined filtrate and washings by distillation through a short column, and the unsaturated ester **4** was isolated as a colorless liquid by distillation (160.5 g, 96%): bp 110–112 °C (lit.[11] bp 114–115 °C); IR ($CHCl_3$) ν_{max} 1727, 1667, 1380, 1310, 1280, 1137, 1020, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3, J = 7 Hz, CH_3), 4.25 (q, 2, J = 7 Hz, $-CH_2-$), 6.49 (dq, 1, $J_{2,3}$ = 16, $^4J_{HF}$ = 1.5 Hz, =CHCO–), 6.76 (dq, $J_{2,3}$ = 16, $^3J_{HF}$ = 6.1 Hz, CF_3CH=); ^{19}F NMR ($CDCl_3$) δ −66.25 (dd, $^4J_{HF}$ = 1.5, $^3J_{HF}$ = 6.1 Hz, CF_3).

(*E*)-4,4,4-Trifluoro-2-butenoic Acid (5). To a stirred solution of ethyl (*E*)-4,4,4-trifluoro-2-butenoate (120 g, 0.714 mol) in tetrahydrofuran (1400 mL) was added 1 N sodium hydroxide (aqueous solution, 715 mL, 0.715 mol) and the resulting mixture stirred at ambient temperature for 1.5 h. The pH was adjusted to 2 with 1 N hydrochloric acid and the tetrahydrofuran was removed under vacuum. The resulting aqueous solution was saturated with sodium chloride and extracted with diethyl ether (4 × 1 L). The organic phase was washed with saturated aqueous sodium chloride and dried, and solvent was removed to afford **5** as a white crystalline solid (93 g, 93%): mp 54–55 °C (lit.[11] mp 54–55 °C); IR ($CHCl_3$) ν_{max} 2700, 2605, 2530, 1743, 1717, 1683, 1665, 1420, 1307, 1280, 1145, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.50 (dq, 1, $J_{2,3}$ = 15.5, $^4J_{HF}$ = 1.5 Hz, =CHCO–), 6.88 (dq, 1, $J_{2,3}$ = 15.5, $^3H_{HF}$ = 6.1 Hz, CF_3CH=), 11.85 (s, 1, CO_2H); ^{19}F NMR ($CDCl_3$) δ −66.5 (dd, $^3J_{HF}$ = 6.1, $^4J_{HF}$ = 1.5 Hz, CF_3).

(±)-3-Amino-4,4,4-trifluorobutanoic Acid (6). A solution of (*E*)-4,4,4-trifluoro-2-butenoic acid (14 g, 0.10 mol) in liquid ammonia (35 mL) in a glass-lined steel bomb was heated at 100 °C for 20 h. The ammonia was allowed to evaporate, ethanol (50 mL) was added, and the solution was concentrated to dryness. The residue was redissolved in ethanol (50 mL), concentrated to dryness, and then triturated with methylene chloride (50 mL), and the solvent was removed under vacuum. The resulting cream-colored solid was dried over phosphorus pentoxide to afford **6** (15.1 g, 100%): mp 180–182 °C (lit.[10] mp 180–181 °C); IR (KBr) ν_{max} 2980–2620, 2220, 1670, 1627, 1595, 1390, 1365, 1250, 1185, 1120 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.26 (dd, 1, J = 15.5, 9 Hz, $-HCH_ACO_2H$), 2.53 (dd, 1, J = 15.5, 4.5 Hz, $-H_BCHCO_2H$), 3.58 (m, 1, J = 9.0, 8.7, 4.5 Hz, CF_3CH), 5.15 (br s, 3, NH_2, CO_2H); ^{19}F NMR (MeSO-d_6) δ −76.63 (d, $^3J_{HF}$ = 8.7 Hz, CF_3).

Trimethylsilyl (±)-4,4,4-Trifluoro-3-[(trimethylsilyl)-amino]butanoate (7). A mixture of trimethylsilyl chloride (9.77 g, 11.5 mL, 90 mmol) and 3-amino-4,4,4-trifluorobutanoic acid (6.28 g, 40 mmol) in anhydrous benzene (40 mL) was stirred at ambient temperature for 30 min. To this suspension was slowly added a solution of triethylamine (9.3 g, 13.0 mL, 93 mmol) in benzene (15 mL), and the mixture was then refluxed for 4 h. The suspension was allowed to stand at room temperature overnight (aids filtration) and filtered through a Schlenk filter, and solvent was removed to afford the crude product **7** (11.5 g, 95%) as a pale yellow oil, which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9, $Si(CH_3)_3$), 0.30 (s, 9, $Si(CH_3)_3$), 2.31 (dd, 1, J = 14.5, 9.5 Hz, $-CHH_ACO$-), 2.73 (dd, 1, J = 14.5, 4 Hz, $-CH_BHCO$-), 3.68 (m, J = 9.5, 7.3, 4 Hz, CF_3CH); ^{19}F NMR ($CDCl_3$) δ −78.75 (d, $^3J_{HF}$ = 7.3 Hz, CF_3).

(±)-4-(Trifluoromethyl)-2-azetidinone (8). To a solution of the trimethylsilyl ester **7** (11 g, 0.037 mol) in anhydrous diethyl ether (50 mL), at −20 °C, was added dropwise a solution of methylmagnesium bromide (20 mL, 3 M solution in diethyl ether, 60 mmol). The reaction was stirred at −20 °C for 3 h and then stirred at room temperature for 3 h and allowed to stand overnight. The reaction mixture was cooled to −10 °C and the pH adjusted to 3 with 2 N aqueous hydrochloric acid saturated with ammonium chloride. Water was added to just dissolve the precipitated salts, and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 75 mL), and the combined organic phase was washed with saturated sodium chloride (2 × 75 mL) and dried (Na_2SO_4) and solvent removed to afford a yellow oil. The oil was heated in methanol (25 mL) at 50 °C for 2 h, and solvent was removed to afford a solid which TLC showed to be a mixture of two compounds. Purification by preparative liquid chromatography (silica; 5% diethyl ether, dichloromethane) afforded 4-(trifluoromethyl)-2-azetidinone (**8**) (1.36 g, 27%) as a white powdery solid: mp 52–54 °C; IR ($CHCl_3$) ν_{max} 3420, 1790,

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1280, 1176, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.05 (dd, 1, $J_{3,3}$ = 15, $J_{3,4}$ = 3 Hz, H-3 proton, cis to CF_3), 3.26 (dd, 1, $J_{3,3}$ = 15, $J_{3,4}$ = 4.5 Hz, H-3 proton, trans to CF_3), 4.09 (m, 1, $^3J_{HF}$ = 6, $J_{3,4}$ = 4.5, $J_{3,4}$ = 3 Hz, H-4), 6.98 (br s, 1, NH); ^{13}C NMR ($CDCl_3$) (^{1}H decoupled) δ 39.83 (d, $^3J_{CF}$ = 2 Hz, C-4), 47.32 (q, $^2J_{CF}$ = 92.5 Hz, C-3), 124.33 (q, $^1J_{CF}$ = 277.85 Hz, CF_3), 166.39 (s, C-2); ^{19}F NMR ($CDCl_3$) δ −78.24 (d, $^3J_{HF}$ = 6 Hz, CF_3). Anal. Calcd for $C_4H_4F_3NO$: C, 34.55; H, 2.90; N, 10.07. Found: C, 34.30; H, 3.08; N, 10.17.

The second compound, isolated as a white solid, was identified as *trans*-4-(trifluoromethyl)-3-(trimethylsilyl)-2-azetidinone (**9**) (0.3 g, 4%): mp 84–86 °C; IR ($CHCl_3$) ν_{max} 3407, 1773, 1280, 1250, 1165, 1155, 875, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9, $Si(CH_3)_3$), 2.92 (d, 1, J = 2.5 Hz, H-3), 3.78 (dq, 1, $^3J_{HF}$ = 5.5, J = 2.5 Hz, H-4), 6.28 (br s, 1, NH); ^{19}F NMR ($CDCl_3$) δ −77.99 (d, $^3J_{HF}$ = 5.5 Hz, CF_3). Anal. Calcd for $C_7H_{12}F_3NOSi$: C, 39.80; H, 5.73; N, 6.63. Found: C, 40.02; H, 5.66; N, 6.53.

***trans*,*rac*-3-Azido-4-(trifluoromethyl)-2-azetidinone (12) and *cis*,*rac*-3-Azido-4-(trifluoromethyl)-2-azetidinone (11).** To a stirred solution of 4-(trifluoromethyl)-2-azetidinone (**8**) (1.39 g, 0.010 mol) in anhydrous tetrahydrofuran (60 mL) at 0 °C was slowly added *n*-butyllithium (12.5 mL of a 1.6 M solution in hexane, 0.020 mol). The mono anion (addition of first 6.2 mL of base solution) was colorless, but as soon as the dianion started to form, the solution turned a deep red color. The mixture was stirred at 0 °C for 60 min and then cooled to −78 °C. A solution of tosyl azide (1.97 g, 0.010 mol) in anhydrous tetrahydrofuran (15 mL) was added dropwise, and the mixture was stirred at −78 °C for 1 h and then at −50 °C for 2 h. Trimethylsilyl chloride (3.25 g, 3.84 mL, 0.030 mol) was added, and the mixture was stirred at −50 °C for 1 h. The temperature was then raised slowly to ambient temperature, and the mixture was then heated at 50 °C for 8 h. The solvent was removed under vacuum, the residue was dissolved in diethyl ether (300 mL), and the organic phase was washed successively with water (3 × 100 mL) and saturated aqueous sodium chloride (2 × 100 mL) and dried ($MgSO_4$). Removal of the solvent gave a red oil, which was purified by preparative chromatography (silica, dichloromethane/hexane/ethyl acetate, 70:15:15, as the eluant) to afford *trans*-3-azido-4-(trifluoromethyl)-2-azetidinone (**12**) (0.38 g, 22%) as an amber colored oil and *cis*-3-azido-4-(trifluoromethyl)-2-azetidinone (**11**) (0.15 g, 8%) as a slightly impure (contains some **8**) yellow oil. **12**: ^{1}H NMR ($CDCl_3$) δ 3.25 (ddq, 1, $^3J_{HF}$ = 6, $J_{3,4}$ = 2, $J_{1,4}$ = 0.5 Hz; H-4), 4.75 (d, 1, J = 2 Hz, H-3), 7.03 (br resonance, 1, NH). **11**: ^{1}H NMR ($CDCl_3$ δ 4.17 (m, 1, $^3J_{HF}$ = 6, $J_{3,4}$ = 5.5 Hz, H-4), 5.00 (dd, $J_{1,3}$ = 0.5, $J_{3,4}$ = 5.5 Hz, H-3), 7.15 (br resonance, 1, NH).

***trans*,*rac*-*N*-[2-(Trifluoromethyl)-4-oxo-3-azetidinyl]-2-phenoxyacetamide (16).** A solution of *trans*-3-azido-4-(trifluoromethyl)-2-azetidinone (**12**) (0.35 g, 0.00194 mol) in anhydrous tetrahydrofuran (20 mL) was hydrogenated over 10% palladium on carbon (0.35 g) until TLC indicated complete disappearance of starting material (1.5 h). The catalyst was filtered off, and triethylamine (0.216 g, 0.00214 mol) was added to the stirred, cooled (0 °C) solution. Phenoxyacetyl chloride (0.398 g, 0.0023 mol) in anhydrous tetrahydrofuran (8 mL) was added dropwise and the mixture stirred for 1 h at 0 °C. The mixture was then stirred at ambient temperature for 16 h. The tetrahydrofuran was removed under reduced pressure, dichloromethane (200 mL) was added, and the organic solution was washed successively with water (2 × 80 mL), 1 N aqueous hydrochloric acid (1 × 80 mL), and saturated aqueous sodium chloride (1 × 80 mL) and dried ($MgSO_4$) and solvent removed. Preparative chromatography (silica; dichloromethane/ethyl acetate/hexane, 3:1:1) afforded *trans*-*N*-[2-(trifluoromethyl)-4-oxo-3-azetidinyl]-2-phenoxyacetamide (**16**) (0.31 g, 55%) as a white powdery solid: mp 143–145 °C; IR (KBr) ν_{max} 3250, 1784, 1677, 1600,1544, 1295, 1244, 1175, 1150, 1080, 1055, 756, 695 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.35 (dq, 1, $^3J_{HF}$ = 7, $J_{3,4}$ = 2.5 Hz, H-4), 4.56 (s, 2, -OCH_2CO), 4.87 (dd, J = 8, $J_{3,4}$ = 2.5 Hz, H-3), 7.00 (m, 3, OPh), 7.32 (m, 2, OPh), 8.93 (d, 1, J = 8 Hz, -NHC-3), 8.98 (s, 1, NH); ^{19}F NMR (Me_2SO-d_6) δ −74.8 (d, $^3J_{HF}$ = 7 Hz, CF_3). Anal. Calcd for $C_{12}H_{11}F_3N_2O_3$: C, 50.01; H, 3.85; N, 9.72. Found: C, 50.15; H, 3.97; N, 9.66.

***trans*,*rac*,(*Z*)-2-[(Chloroacetyl)amino]-α-(methoxyimino)-*N*-[2-(trifluoromethyl)-4-oxo-3-azetidinyl]-4-thiazoleacetamide (17).** A solution of the *trans*-azido(trifluoromethyl)azetidinone **12** (0.27 g, 0.0015 mol) in anhydrous tetrahydrofuran (20 mL) was hydrogenated over 10% palladium on carbon (0.2 g) until TLC indicated the complete disappearance of starting material (1.5 h). The catalyst was removed by filtration, anhydrous dimethylformamide (10 mL) was added, and the tetrahydrofuran was removed under reduced pressure. To this solution was added [2-[(chloroacetyl)amino]-4-thiazolyl](methoxyimino)acetic acid (0.417 g, 0.0015 mol) and *N*-hydroxybenzotriazole hydrate (0.23 g, 0.0015 mol) and the mixture cooled to 0 °C. Dicyclohexylcarbodiimide (0.34 g, 0.0016 mol) was added, and after being stirred at 0 °C for 1 h the reaction mixture was stirred at ambient temperature for 18 h. The dicyclohexylurea (0.32 g) was removed by filtration, ethyl acetate (50 mL) was added, and the organic phase washed successively with water (3 × 20 mL), saturated sodium bicarbonate (1 × 20 mL) and saturated sodium chloride (1 × 20 mL) and dried (Na_2SO_4). Removal of solvent gave a pale yellow solid (0.65 g), which NMR showed to contain some DMF and the urea. The residue was dissolved in hot ethyl acetate, filtered, and precipitated out with hexane to afford the desired product **17** (0.55 g, 88%) as a creamy white powder: mp 139–141 °C; IR (KBr) ν_{max} 3330–3280, 1775, 1683, 1550, 1280, 1185, 1150, 1045 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.91 (s, 3, OCH_3), 4.35 (m, 1, $^3J_{HF}$ = 6.9, $J_{3,4}$ = 2.2, H-4), 4.40 (s, 2, -CH_2Cl), 4.93 (dd, 1, $J_{3,4}$ = 2.2, J = 8 Hz, H-3), 7.44 (s, 1, thiazole), 9.12 (s, 1, NH at N-1), 9.50 (d, 1, J = 8 Hz, NH at C_3), 12.84 (br s, 1, -OCNH thiazole); ^{19}F NMR (Me_2SO-d_6) δ −78.76 (d, $^3J_{HF}$ = 6.9 Hz, CF_3). The ^{1}H NMR and microanalysis indicated that traces of the urea were present.

***cis*,*rac*,(*Z*)-2-[(Chloroacetyl)amino]-α-(methoxyimino)-*N*-[2-(trifluoromethyl)-4-oxo-3-azetidinyl]-4-thiazoleacetamide (15).** This compound was prepared by application of the above procedure to the *cis*-3-azido-4-(trifluoromethyl)-2-azetidinone (**11**). The product was purified by preparative liquid chromatography (silica, ethyl acetate/dichloromethane, 55:45) to afford **15** as a pale cream powder (65%): mp 227–228 °C; IR (KBr) ν_{max} 3400, 3285, 1785, 1677, 1550, 1270, 1155, 1047 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.83 (s, 3, OCH_3), 4.35 (s, 2, CH_2Cl), 4.49 (dq, 1, $J_{3,4}$ = 4.5 Hz, $^3J_{HF}$ = 6.5 Hz, H-4), 5.55 (dd, 1, $J_{3,4}$ = 4.5, J = 9.0 Hz, H-3), 7.31 (s, 1, thiazole proton), 9.01 (s, 1, NH, β-lactam N), 9.60 (d, 1, J = 9.0 Hz, NH at C-3), 12.85 (s, 1, NH at C-2 of thiazole); ^{19}F NMR (Me_2SO-d_6) δ −71.08 (d, $^3J_{HF}$ = 6.5 Hz, CF_3); mass spectrum (positive ion FAB, glycerol matrix), calcd for $C_{12}H_{12}ClF_3N_5O_4S$ (M + H) 414.0250 (found 414.0289). Anal. Calcd for $C_{12}H_{11}ClF_3N_5O_4S$ (0.2 ethyl acetate): C, 35.64; H, 2.94; N, 16.31. Found: C, 35.81; H, 2.93; N, 16.54.

Sodium *trans*,*rac*-2-(Trifluoromethyl)-4-oxo-3-[(phenoxyacetyl)amino]-1-azetidinesulfonate (19). A dimethylformamide solution of sulfur trioxide–dimethylformamide complex (4.42 mL of a 1.13 M solution, 5 mmol) was added to a solution of the azetidinone **16** (0.226 g, 0.79 mmol), and the resulting mixture was stirred at 0 °C for 66 h (monitered by TLC). Pyridine (0.394 g, 5 mmol) was added and the mixture stirred at 0 °C for 15 min. The mixture was added dropwise into vigorously stirred anhydrous diethyl ether (100 mL) and stirred for 1.5 h at ambient temperature. The ether was decanted from the gummy solid, which was then stripped of all remaining solvent under vacuum. To the residue were added Dowex 50W (Na form, 20 g wet) and water (40 mL), and the mixture was stirred at room temperature for 2 h. The resin was filtered off, and the filtrate was lyophilized to afford a mixture (0.71 g) of product and sodium sulfate. Preparative chromatography (C-18 reverse phase) using 22% methanol in water as the eluant afforded, after removal of methanol and lyophilisation, the desired sodium salt **19** (0.22 g, 72%) as a white powder: mp 128–130 °C; IR (KBr) ν_{max} 1790, 1686, 1600, 1533, 1499, 1290, 1247, 1187, 1057 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.41 (dq, 1, $^3J_{HF}$ = 6.2, $J_{2,3}$ = 2.8 Hz, H-2), 4.56 (s, 2, -OCH_2CO-), 4.93 (dd, 1, $J_{2,3}$ = 2.8, J = 8.5 Hz, H-3), 6.90–7.10 (m, 3, OPh), 7.24–7.46 (m, 2, OPh), 9.13 (d, 1, J = 8.5 Hz, NH); ^{19}F NMR (Me_2SO-d_6) δ −72.08 (d, $^3J_{HF}$ = 6.2 Hz, CF_3); mass spectrum (positive ion FAB, glycerol matrix), calcd for $C_{12}H_{10}F_3N_2O_6SNa_2$ (M + Na) 413.0007 (found 413.0003). Anal. Calcd for $C_{12}H_{10}F_3N_2O_6SNa$: C, 36.93; H, 2.58; N, 7.18. Found: C, 36.60; H, 2.83; N, 7.66.

Sodium *trans*,*rac*,(*Z*)-3-[[[2-[(Chloroacetyl)amino]-4-thiazolyl](methoxyimino)acetyl]amino]-2-(trifluoromethyl)-4-oxo-1-azetidinesulfonate (20). This compound was prepared by application of the above procedure to **17**. The product

was purified by preparative liquid chromatography (C-18 reverse phase, 20% methanol–water) to afford **20** as a white powdery solid (60%): mp 210–213 °C; IR (KBr) ν_{max} 1790, 1680, 1547, 1290, 1262, 1191, 1050 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.90 (s, 3, OCH_3), 4.33 (dq, 1, $^3J_{HF}$ = 6.1, $J_{2,3}$ = 2.5 Hz, H-2), 4.37 (s, 2, $ClCH_2$-), 4.91 (dd, 1, J = 2.5, 8 Hz, H-3), 7.41 (s, 1, thiazole proton), 9.57 (d, 1, J = 8 Hz, NH), 12.84 (br s, 1, -HN-thiazole); ^{19}F NMR (Me_2SO-d_6) δ −72.0 (d, $^3J_{HF}$ = 6.14 Hz, CF_3); mass spectrum (positive ion FAB, glycerol matrix), calcd for $C_{12}H_{11}ClF_3N_5O_7S_2Na$ (M + H) 515.9631 (found 515.9595). Anal. Calcd for $C_{12}H_{10}ClF_3N_5O_7S_2Na$: C, 27.94; H, 1.95; N, 13.58. Found: C, 28.11; H, 2.24; N, 13.88.

Sodium *cis,rac*,(*Z*)-3-[[[2-[(Chloroacetyl)amino]-4-thiazolyl](methoxyimino)acetyl]amino]-2-(trifluoromethyl)-4-oxo-1-azetidinesulfonate (18). This compound was prepared by application of the preceding method utilizing the appropriate azetidinone, **15**. Purification was accomplished by preparative liquid chromatography (C-18 reverse phase, 20% methanol–water) to afford **18** as a white lyophilized powder (62%): mp 181–184 °C; IR (KBr) ν_{max} 1792, 1685, 1551, 1290, 1273, 1190, 1172, 1055 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.87 (s, 3, OCH_3), 4.40 (s, 2, $ClCH_2$), 4.58 (dq, 1, $^3J_{HF}$ = 6.5, $J_{2,3}$ = 5.5 Hz, H-2), 5.56 (dd, 1, $J_{2,3}$ = 5.5, J = 8.5 Hz, H-3), 7.35 (s, 1, thiazole proton), 9.63 (d, 1, J = 8.5 Hz, NH), 12.94 (s, 1, thiazole-NH-); ^{19}F NMR (Me_2SO-d_6) δ −67.8 (d, $^3J_{HF}$ = 6.5 Hz, CF_3); mass spectrum (positive ion FAB, glycerol matrix), calcd for $C_{12}H_{11}ClF_3N_5O_7S_2Na$ (M + H) 515.9631 (found 515.9621). Anal. Calcd for $C_{12}H_{10}ClF_3N_5O_7S_2Na$ (0.5 H_2O): C, 27.46; H, 2.11; N, 13.34. Found: C, 27.50; H, 2.17; N, 13.49.

Sodium *trans,rac*,(*Z*)-3-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-(trifluoromethyl)-4-oxo-1-azetidinesulfonate (22). To a stirred solution of the chloroacetyl-protected aminoazetidinone, **20**, (0.112 g, 0.22 mmol) in water (4 mL) at 5 °C was added sodium methyldithiocarbamate[19] (0.0323 g, 0.22 mmol). After being stirred at room temperature for 2 h, the mixture was purified by preparative liquid chromatography (C-18 reverse phase, 100% water) to afford, after lyophilization, the title compound **22** (0.052 g, 55%) as a white powder: mp 252–255 °C; IR (KBr) ν_{max} 3440, 3340, 1792, 1673, 1617, 1533, 1392, 1290, 1272, 1189, 1125, 1053 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.84 (s, 3, OCH_3), 4.32 (dq, 1, $^3J_{HF}$ = 6.8, $J_{2,3}$ = 2.5 Hz, H-2), 4.87 (dd, 1, $J_{2,3}$ = 2.5, J = 8.5 Hz, H-3), 6.69 (s, 1, thiazole proton), 7.17 (br s, 2, NH_2), 9.46 (d, 1, J = 8.5 Hz, NH); ^{19}F NMR (Me_2SO-d_6) δ −72.05 (d, $^3J_{HF}$ = 6.8 Hz, CF_3); mass spectrum (positive ion FAB, glycerol matrix,) calcd for $C_{10}H_9F_3N_5O_6S_2Na_2$ (M + Na) 461.9742 (found 461.9716). Anal. Calcd for $C_{10}H_9F_3N_5O_6S_2Na{\cdot}2H_2O$: C, 25.43; H, 2.77; N, 14.82. Found: C, 25.65; H, 2.44; N, 14.35.

Sodium *cis,rac*,(*Z*)-3-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-(trifluoromethyl)-4-oxo-1-azetidinesulfonate (21). This was prepared by removal of the chloroacetyl protecting group from **18** as outlined for the corresponding trans analogue. Purification by preparative liquid chromatography (C-18 reverse phase, 100% water) followed by lyophilization afforded the desired amino compound **21** (62%) as a white powder: mp 249–252 °C; IR (KBr) ν_{max} 3400, 1790, 1680, 1620, 1530, 1395, 1290, 1270, 1190, 1145, 1053, cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.98 (s, 3, OCH_3), 4.52 (dq, 1, $^3J_{HF}$ = 6.9, $J_{2,3}$ = 5.5 Hz, H-2), 5.50 (dd, 1, $J_{2,3}$ = 5.5, J = 8.5 Hz, H-3), 6.57 (s, 1, thiazole proton), 7.14 (br s, 2, NH_2), 9.45 (d, 1, J = 8.5 Hz, -CONH-); ^{19}F NMR (Me_2SO-d_6) δ −68.81 (d, $^3J_{HF}$ = 6.9 Hz, CF_3); mass spectrum (positive ion FAB, glycerol matrix), calcd for $C_{10}H_{10}F_3N_5O_6S_2Na$ (M + H) 439.9922 (found 439.9893). Anal. Calcd for $C_{10}H_9F_3N_5O_6S_2Na{\cdot}2.5H_2O$: C, 24.80; H, 2.91; N, 14.46. Found: C, 24.68; H, 2.90; N, 14.34.

Stability Studies on 19 and Its Nonfluorinated Analogue. Deuterated "biological buffer solution" was prepared in D_2O essentially as described in the literature,[21] being 0.27 M in Na_2DPO_4 and 0.065 M in KD_2PO_4. The buffer had a pD of 7.4. Solutions containing 15 μmol of the appropriate β-lactam in 0.5 mL of deuterated buffer were maintained in NMR tubes at 37 °C. The fluorinated compound **19** was monitored by ^{19}F NMR whereas the nonfluorinated analogue was followed by monitoring the CH_3 group shift by ^{1}H NMR.

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Registry No. **2**, 372-31-6; (±)-**3**, 88968-78-9; **4**, 25597-16-4; **5**, 406-94-0; (±)-**6**, 88968-79-0; (±)-**7**, 88968-80-3; (±)-**8**, 88968-81-4; (±)-**9**, 88968-82-5; (±)-**11**, 88968-83-6; (±)-**12**, 88968-84-7; (±)-**13**, 88968-85-8; (±)-**14**, 88968-86-9; (±)-**15**, 88968-87-0; (±)-**16**, 88968-88-1; (±)-**17**, 89015-85-0; (±)-**18**, 88968-89-2; (±)-**19**, 88968-90-5; (±)-**20**, 89015-86-1; (±)-**21**, 88968-91-6; (±)-**22**, 89015-87-2; $CATOMCO_2H$, 64486-18-6; $PhOCH_2COCl$, 701-99-5.

Selective Reduction of Monosubstituted Nitrobenzenes to Anilines by Dihydrolipoamide–Iron(II)

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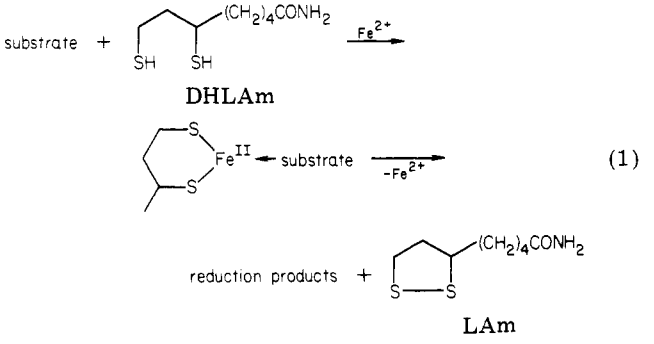
Lipoamide (LAm) works as a coenzyme in acyl transfer and redox reactions in living systems, undergoing the following redox reaction: LAm ⇌ dihydrolipoamide (DHLAm). We have recently reported[1,2] that hydroxylamine derivatives, azo-, azoxy-, and nitrobenzenes were reduced by DHLAm–Fe(II) through coordination of substrates to a complex of DHLAm–Fe(II) under weakly basic conditions as shown in eq 1. The peculiar reactivity of



(1)

DHLAm–Fe(II) is interesting in connection with electron transfer of iron–sulfur proteins such as ferredoxins.[3,4] In spite of extensive studies of iron–sulfur complexes as models for nonheme iron proteins, these complexes have not yet seen practical application in synthetic organic chemistry.

Because of the synthetic versatility of aryl nitro compounds, their direct reduction constitutes one of the best routes to the important aromatic amines. Reagents for the reduction of aromatic nitro compounds to the corresponding anilines by classical methods (catalytic hydrogenations, Clemmensen-type reductions, Birch reduction, metal (salts) reductions, etc.) are useful, but these methods have poor selectivity for some functional groups and usu-

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