Monobactams: Stereoselective Synthesis of *trans*-3-Amino- and 3-Acylamino-4-trifluoromethyl-2-azetidinones

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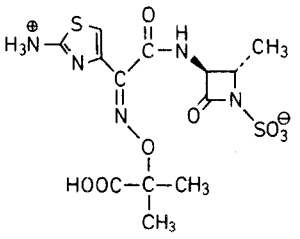
An improved synthesis of *trans*-3-amino-4-trifluoromethyl-2-azetidinone (**7**), a precursor of *trans*-4-trifluoromethyl monobactams such as **9** and **10**, is described.

Recently, much attention has been focused on the total synthesis of monocyclic β-lactam antibiotics such as Aztreonam (**1**), because of their excellent activity against Gram-negative bacteria[1,2]. In the course of our program directed to the synthesis of Aztreonam analogues, we explored methodologies for the preparation of fluorinated derivatives of **1**, which seemed particularly attractive because of their expected enhanced reactivity towards nucleophilic attack at the β-lactam ring[3]. The recent publication[4] dealing with the synthesis of *cis*- and *trans*-4-trifluoromethyl monobactams such as **9** and **10**, prompted us to report our independent and more direct approach to *trans*-**7** which is a precursor of **9** and **10**[4].

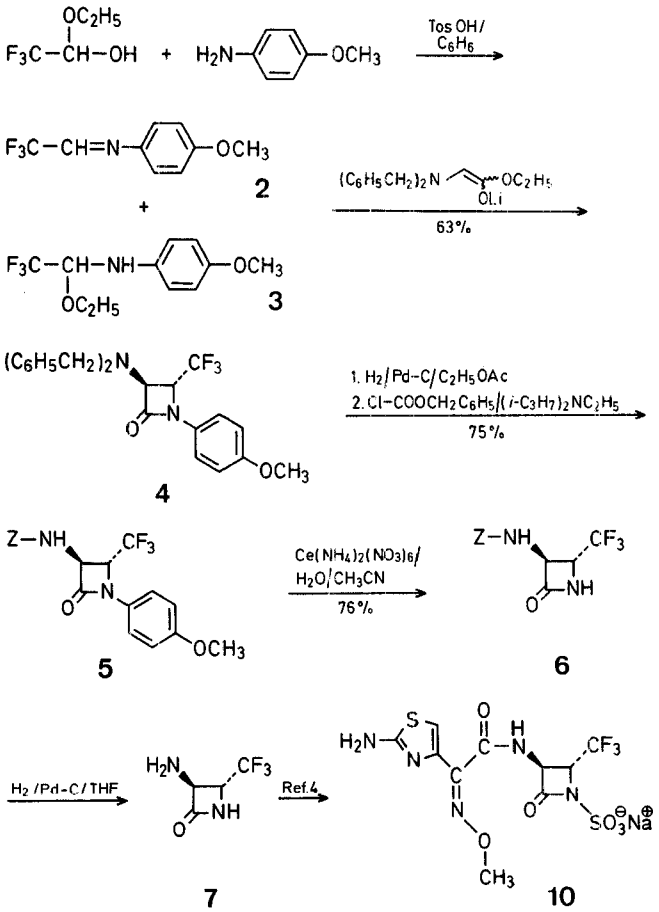
Among the various methods now available for the formation of β-lactam rings, the one involving simultaneous closure of the N/C-2 and C-3/C-4 bonds appears particularly straightforward. This can be accomplished by interaction of an imine with an acyl chloride[5], with a trimethylsilylketene acetal under Lewis acid catalysis[6], or with an ester enolate[7]. The latter method seemed particularly attractive for our purposes in view of its general tendency to give stereoselectively *trans*-β-lactams. Therefore, we planned to prepare *N*-(2,2,2-trifluoroethylidene)-4-methoxyaniline (**2**) and to react it with the enolate of a suitably protected glycinate. Attempted preparation[8] of imine **2** by reaction of commercially available trifluoroacetaldehyde ethyl hemiacetal and 4-methoxyanil-

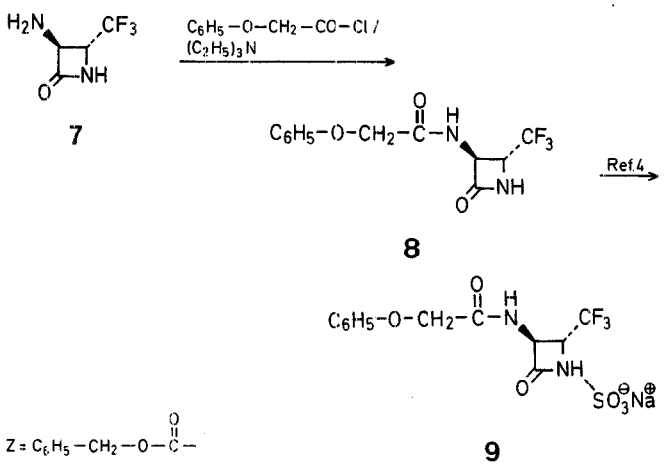


1 Aztreonam

ine led in 95% yield to a 6:4 mixture of the expected imine **2** and a by-product which was identified as **3** by ^{1}H- and ^{13}C-N.M.R. spectrometry. Although we found some difficulties in separating these products by bulb-to-bulb distillation, pure **2** could be obtained in 85% yield by treating this mixture with lithium diisopropylamide in tetrahydrofuran. The reaction of **2** with the lithium enolate of ethyl dibenzylaminoacetate[9] proceeded smoothly to give exclusively the *trans*-β-lactam **4** in good yield (69%). Alternatively, and more conveniently, **4** could be obtained directly in 63% yield, by treating the crude mixture of **2** and **3** with the enolate of ethyl dibenzylaminoacetate in the presence of an excess of lithium diisopropylamide (see Scheme)[10].

The attempted removal of the 4-methoxyphenyl group with ceric ammonium nitrate[11] at this stage failed because of extensive oxidative debenzylation. Thus, we converted **4** into the benzyloxycarbonyl derivative **5** by catalytic hydrogenolysis of the dibenzylamino group[12] (H_2/Pd-C/ethyl acetate; 83%) followed by reaction with benzyl carbonochloridate (diisopropylamine/dichloromethane, 90%). It is worth noting that ethanol or methanol could not be used as solvents in the hydrogenation step since they cause extensive cleavage of the β-lactam ring within a few hours at room temperature. This is in agreement with the higher reactivity of trifluoromethyl substituted β-lactams already observed[4]. Treatment of **5** with ceric ammonium nitrate gave the 1-unsubstituted derivative **6** (76%) which, upon reductive cleavage (H_2/Pd-C/tetrahydrofuran) of the benzyloxycarbonyl group, furnished **7**. The latter can be acylated *in situ* with various carboxylic acid derivatives. For example, acylation with phenoxyacetyl chloride gave **8** in 80% yield from **6** (27% overall yield from trifluoroacetaldehyde ethyl hemiacetal), which can be transformed, as previously described[4], into the





monobactam **9**. Unfortunately, both **9** and **10**, which have been already synthesized in three steps from **7**[4], were found to be devoid of significant anti-bacterial activity[4].

I.R. spectra were recorded with a Perkin-Elmer 257 spectrophotometer. N.M.R. spectra were recorded with a Varian FT-80 (80 MHz) instrument, using tetramethylsilane as internal standard. Microanalyses were performed with a Perkin-Elmer 240 instrument. 270-400 Mesh silica gel (Merck) was used for flash chromatography[13]. Dry solvents were obtained by distillation under an inert atmosphere: benzene was distilled from sodium metal; tetrahydrofuran from potassium metal in the presence of benzophenone; ethyl acetate from sodium carbonate; dichloromethane from phosphorus pentoxide. Organic extracts were dried with sodium sulfate and filtered before removal of the solvent under reduced pressure.

N-(2,2,2-Trifluoroethylidene)-4-methoxyaniline (2):

To a solution of trifluoroacetaldehyde ethyl hemiacetal (90% purity, Janssen; 3.52 ml, 27.3 mmol) and 4-methoxyaniline (3.30 g, 26.8 mmol) in dry benzene (50 ml), a catalytic amount of *p*-toluenesulfonic acid (150 mg, 0.9 mmol) is added. The resulting solution is refluxed while the water formed is removed through a Soxhlet apparatus filled with 3 Å molecular sieves. After 3 h, the reaction is complete, as judged by T.L.C., and the solution is treated with 1% aqueous sodium hydrogen carbonate solution (20 ml). The phases are separated and the aqueous layer is washed with ether (10 ml). After evaporation of the solvent, the organic extracts give a liquid which, upon bulb-to-bulb distillation at 80–130°C (oven temperature)/1 torr, furnishes a pale yellow liquid, identified as a 6:4 mixture of **2** and **3**; yield: 5.65 g (95%).

The following N.M.R. data for **3** were obtained by subtracting the spectra of pure **2** (see below) from those of the mixture.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.19 (dt, 3H, J = 7 Hz, 1.1 Hz, CH_2CH_3); 3.75 (br. q, 2H, J = 7 Hz, CH_2CH_3); 3.76 (s, 3H, OCH_3); 4.75–5.05 (m, 1H, CH—CF_3); 6.78 ppm (s, 4 H_{arom}).

^{13}C-N.M.R. ($CDCl_3$): δ = 15.09 (CH_2CH_3); 55.64 (OCH_3); 64.90 (CH_2CH_3); 84.12 (q, J = 33 Hz, CH—CF_3); 114.98, 116.89 (C_{arom}); 123.10 (q, J = 283 Hz, CF_3); 138.32, 154.15 ppm [H_3CO—C, $C(OC_2H_5)$NH—C].

A solution of this mixture of **2** and **3** (1.90 g, 8.57 mmol) in dry tetrahydrofuran (6 ml) is treated at −20°C with a 0.4 normal solution of lithium diisopropylamide in 3/1 tetrahydrofuran/*n*-hexane containing few crystals of 2,2'-bipyridyl, until the solution remains red (8.8 ml, 3.52 mmol). After 30 min, the solution is treated with 1% aqueous sodium hydrogen carbonate solution (10 ml) and diluted with ether (30 ml). The phases are separated and the organic layer, after evaporation of the solvent, gives a crude liquid residue which, upon bulb-to-bulb distillation at 70–120°C (oven temperature)/0.08 torr furnishes pure **2** as a pale yellow liquid; yield: 1.48 g (85%).

$C_9H_8F_3NO$	calc.	C 53.21	H 3.97	N 6.89
(203.16)	found	53.4	4.1	6.7

I.R. (neat): ν = 1600, 1580, 1500, 1355, 1285, 1250, 1155, 1135, 1030, 890, 830, 765 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.84 (s, 3H, OCH_3); 6.60–7.50 (m, 4 H_{arom}); 7.83 ppm (dq, 1H, J = 3.7 Hz, 1.2 Hz, CH—CF_3).

^{13}C-N.M.R. ($CDCl_3$): δ = 119.46 (q, J = 273 Hz, CF_3); 114.64, 123.23 (C_{arom}); 144.15 (q, J = 38 Hz, CH—CF_3); 140.03, 160.53 ppm (O—C, N—C).

Trans-1-(4-Methoxyphenyl)-3-dibenzylamino-4-trifluoromethyl-2-azetidinone (4):

A solution of ethyl dibenzylaminoacetate (5 g, 17.6 mmol) in dry tetrahydrofuran (20 ml) is added dropwise at −60 °C to a 0.5 normal solution of lithium diisopropylamide in 2.5/1 tetrahydrofuran/_n_-hexane containing few crystals of 2,2′-bipyridyl (38.7 ml, 19.36 mmol). After stirring for 20 min at the same temperature, a solution of the 6:4 mixture of **2** and **3** (3.90 g, 17.6 mmol) in tetrahydrofuran (10 ml) is added. The temperature is raised to −20 °C and then more lithium diisopropylamide solution is added until the solution remains red (15 ml). After additional stirring for 30 min at 0 °C, the solution is treated with aqueous 30% ammonium chloride solution (10 ml) to pH 8, diluted with ether (50 ml), and the phases are separated. The organic phase, after evaporation of the solvent, leaves a crude product which is purified by flash chromatography[13] (ether/_n_-hexane) to give **4** as a white solid; yield: 4.88 g (63%); m.p. 132–134 °C (ether/_n_-pentane).

$C_{25}H_{23}F_3N_2O_2$	calc.	C 68.17	H 5.26	N 6.36
(440.46)	found	68.4	5.25	6.35

I.R. ($CHCl_3$): ν = 1760, 1305, 1160, 1130 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.79 (s, 3H, OCH_3); 3.72, 3.93 (AB system, 4H, J = 13.6 Hz, N—CH_2—C_6H_5); 4.35 (dq, 1H, J = 5.6 Hz, 2.0 Hz, CH—CF_3); 4.48 (d, 1H, J = 2.0 Hz, CH—N); 6.85 (d, 2H, J = 8.7 Hz, 2H _ortho_ to OCH_3); 7.10–7.45 ppm (m, 12 H_{arom} + 2H _meta_ to OCH_3)

trans-_N_-(4-Methoxyphenyl)-3-benzyloxycarbonylamino-4-trifluoromethyl-2-azetidinone (5):

A solution of **4** (4 g, 9.08 mmol) in dry ethyl acetate (100 ml) is hydrogenated over 10% palladium on charcoal (500 mg, 0.47 mmol) for 3 days at room temperature. Removal of the catalyst by filtration, and evaporation of the solvent gives a crude product which is purified by flash chromatography[13] (ether/_n_-hexane) to give pure _trans_-1-(4-methoxyphenyl)-3-amino-4-trifluoromethyl-2-azetidinone as a white solid; yield: 1.97 g (83%); m.p. 105.5–107.5 °C.

$C_{11}H_{11}F_3N_2O_2$	calc.	C 50.77	H 4.26	N 10.77
(260.2)	found	50.9	4.3	10.6

I.R. ($CHCl_3$): ν = 3665, 3400, 1760, 1600, 1500, 1400, 1275, 1160 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.94 (s, 2H, NH_2); 3.78 (s, 3H, OCH_3); 4.20 (dq, 1H, J = 5.6 Hz, 1.9 Hz, CH—CF_3); 4.39 (d, 1H, J = 1.9 Hz, CH—N); 6.89 (d, 2H, J = 9.2 Hz, 2H _ortho_ to OCH_3); 7.31 ppm (d, 2H, J = 9.2 Hz, 2H _meta_ to OCH_3).

A solution of this compound (1.93, 7.42 mmol) and diisopropylethylamine (2.84 ml, 16.32 mmol) in dry dichloromethane (12 ml) is treated at 0 °C with a solution of benzyl carbonochloridate (95% purity, Janssen; 1.23 ml, 8.16 mmol) in dichloromethane (8 ml). The resulting solution is stirred at 0 °C for 30 min and at 27 °C for 40 min, quenched with aqueous 30% ammonium chloride solution (10 ml) to pH 7.5, and the phases are separated. Evaporation to dryness affords a solid which, upon flash chromatography[13] (ether/_n_-hexane), gives pure **5** as a white solid; yield: 2.64 g (90%); m.p. 112–114 °C.

$C_{19}H_{17}F_3N_2O_4$	calc.	C 57.87	H 4.34	N 7.10
(394.35)	found	57.8	4.3	7.0

I.R. ($CHCl_3$): ν = 3440, 1775, 1725, 1600, 1500, 1160, 1130 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.78 (s, 3H, OCH_3); 4.50–4.90 (m, 2H, CH—N. CH—CF_3); 5.11 (s, 2H, $CH_2C_6H_5$); 5.63 (d, 1H, J = 6.9 Hz, NH); 6.88 (d, 2H, J = 9.1 Hz, 2H _ortho_ to OCH_3); 7.10–7.50 ppm (m, 7H, 5 H_{arom} + 2H _meta_ to OCH_3).

trans-3-Benzyloxycarbonylamino-4-trifluoromethyl-2-azetidinone (6):

A solution of ceric ammonium nitrate (10.51 g, 19.17 mmol) in water (64 ml) is added dropwise in 7 min at 0 °C to a solution of **5** (2.52 g, 6.39 mmol) in acetonitrile (60 ml). The resulting solution is stirred for 20 min at 0 °C, and then diluted with water (100 ml), and extracted with ethyl acetate (2 × 100 ml). The organic phase is washed with 5% sodium hydrogen carbonate solution (30 ml), 10% sodium sulfite solution (30 ml), 5% sodium hydrogen carbonate solution (30 ml), and brine (30 ml). The organic extracts are treated for 1 h with active charcoal, filtered through a Celite cake, and evaporated to dryness to give a solid, which is purified by crystallisation (ethyl acetate/ether) to give **6**; yield: 1.40 g (76%); m.p. 139–142 °C.

$C_{12}H_{11}F_3N_2O_3$	calc.	C 50.01	H 3.85	N 9.72
(288.23)	found	49.85	3.9	9.55

I.R. ($CHCl_3$): ν = 3420, 1800, 1725, 1600, 1500, 1165, 1150, 1120, 1015 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 4.35 (dq, 1H, J = 6.4 Hz, 2.2 Hz, CH—CF_3); 4.67 (dd, 1H, J = 8.2 Hz, 2.2 Hz, CH—C=O); 5.15 (s, 2H, CH_2); 5.60 (d, 1H, J = 8.2 Hz, NH—COO); 6.37 (br. s, 1H, NH—$CHCF_3$); 7.36 ppm (s, 5 H_{arom}).

trans-3-Phenoxyacetylamino-4-trifluoromethyl-2-azetidinone (8):

A solution of **6** (200 mg, 0.694 mmol) in freshly distilled tetrahydrofuran) (10 ml) is hydrogenated over 10% palladium on charcoal (30 mg, 0.028 mmol) at room temperature for 3 h. The catalyst is filtered off, the filtrate is treated with dry triethylamine (0.097 ml, 0.833 mmol), phenoxyacetyl chloride (0.115 ml, 0.833 mmol), and the mixture is then stirred overnight. Most of the tetrahydrofuran is then evaporated under reduced pressure, ethyl acetate (30 ml) is added, and the solution is washed with 0.1 normal hydrochloric acid (20 ml) and brine (15 ml) to give a product which, after flash chromatography[13] (ether/_n_-hexane), furnishes pure **8** as a white solid; yield: 160 mg (80%); m.p. 141–145 °C.

$C_{12}H_{11}F_3N_2O_3$	calc.	C 50.01	H 3.85	N 9.72
(288.23)	found	50.15	3.95	9.7

I.R. (KBr): ν = 3250, 1780, 1670, 1535, 1290, 1240, 1170, 1145, 750, 690 cm^{-1}.

^{1}H-N.M.R. (acetone-d_6): δ = 4.49 (dq, 1H, J = 6.2 Hz, 2.4 Hz, CH—CF_3); 4.59 (s, 2H, CH_2); 5.05 (dd, 1H, J = 8.3 Hz, 2.4 Hz, CH—C=O); 6.85–7.50 (m 5 H_{arom}); 8.02 (s, 1H, NH—CH—CF_3); 8.50 ppm (d, 1H, J = 8.3 Hz, NH—CO—CH_2).

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[1] Cimarusti, C.M. et al *Tetrahedron* **1983**, *39*, 2577 and references therein.
[2] Mattingly, P.G., Miller, M.J., Cooper, R.D.G., Daugherty, B.W. *J. Org. Chem.* **1983**, *48*, 3556 and references therein.
[3] Yoshioka, K. et al. *J. Org. Chem.* **1984**, *49*, 1427.
[4] Bevilacqua, P.F., Keith, D.D., Roberts, J.L. *J. Org. Chem.* **1984**, *49*, 1430.
[5] Mukerjee, A.K., Srivastava, R.C. *Synthesis* **1973**, 327.
[6] Ojima, I., Inaba, S., Yoshida, K. *Tetrahedron Lett.* **1977**, 3643.
[7] Gluchowsy, C., Cooper, L., Bergbreiter, D.E., Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.
[8] Newman, H., Moon, E.L. *J. Org. Chem.* **1964**, *29*, 2063.
[9] Scolastico, C., Conca, E., Prati, L., Guanti, G., Banfi, L., Berti, A., Farina, P., Valcavi, U. *Synthesis* **1985**, in press.
[10] Here only one enantiomeric form is arbitrarily shown, although racemates were obtained.
[11] Kronenthal, D.R., Han, C.Y., Taylor, M.K. *J. Org. Chem.* **1982**, *47*, 2765.
[12] Guanti, G., Banfi, L., Narisano, E., Scolastico, C. *Tetrahedron Lett.*, **1984**, *25*, 4693.
[13] Still, W.C., Kahn, H., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.