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Enantioselective Routes toward 1β-Methylcarbapenems from Chiral Aziridines

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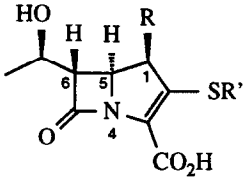
Abstract: *This paper describes two enantioselective aziridine-based routes toward 1β-methylthienamycin,* **2**, *and related carbapenems, the key steps being completely regioselective ring-opening reactions of the chiral aziridines* **7** *and* **10** *with* $AlMe_3$.

A major breakthrough in the field of β-lactam antibiotics was heralded by the discovery[1a] of thienamycin (**1a**). The extraordinary broad-spectrum antibacterial activity of this precious material provided the impetus for a chemical tour de force in the form of a large-scale, multi-step, total synthesis of the antibiotic and its chemically more stable derivative imipenem (**1b**) in the Merck Sharp & Dohme laboratories[1b]. Since then, thienamycin and related carbapenems have continued to fire the imagination of organic chemists[1c,2].

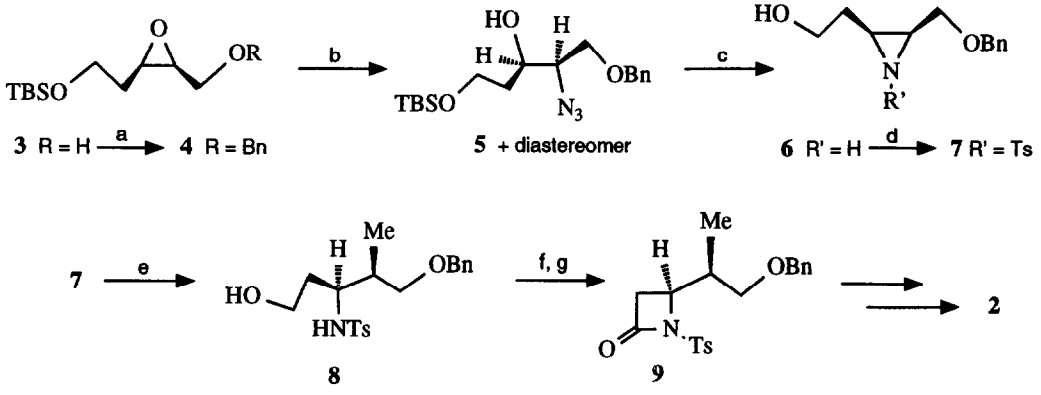


1a R = H, R' = $CH_2CH_2NH_2$
1b R = H, R' = $CH_2CH_2NHCH{=}NH$
2 R = Me, R' = $CH_2CH_2NH_2$

Clinically, a major problem with carbapenems such as **1a** and **1b** is the ease with which they are metabolized by renal dehydropeptidase-I (DHP-I). Co-administration of an enzyme inhibitor is thus necessary, and these drawbacks have prompted a search, via chemical modification, for less fragile structures which retain the antibacterial activity of the parent molecule; the 1β-methyl derivative **2** appears to be highly promising in this respect[3c], since it is biologically more active than thienamycin and is highly resistant to hydrolysis by DHP-I.

For the organic chemist, the four contiguous stereogenic centres of **2** provide a synthetic challenge of some complexity, the C-5 centre being that which is usually secured first. Installation of the C-6 (*R*)-hydroxyethyl moiety of all three carbapenems shown above has been achieved[3a,b;4] in stereoselective fashion via sequential aldol reaction (between a suitable β-lactam enolate and acetaldehyde), oxidation, and reduction. For **2**, this protocol is particularly attractive[3b] if the 1β-methyl group is already in place, and a variety of techniques has been described[3d,e] for stereocontrol at C-1.

Our own approach to the enantioselective synthesis of carbapenems[5a,b] relies on the regioselective ring-opening of suitably substituted 2,3-aziridino alcohols. These chiral intermediates are readily available in enantiomerically pure (or highly enriched) form via the corresponding oxiranes which are themselves the products of Sharpless asymmetric epoxidation[6] of allylic alcohols. In the preceding paper[7] we showed that trimethylaluminium is a nucleophile which displays complete regioselectivity in the ring-scission of certain 2,3-disubstituted aziridines carrying a benzyloxymethyl side-chain, and we proposed that a Lewis acid-base pairing of the reagent and the aforementioned substituent was of prime importance for the regiochemical outcome. We now demonstrate that this methodology provides a simple solution to the stereochemical problem posed by the C-1 and C-5 stereocentres of **2** (Scheme 1).



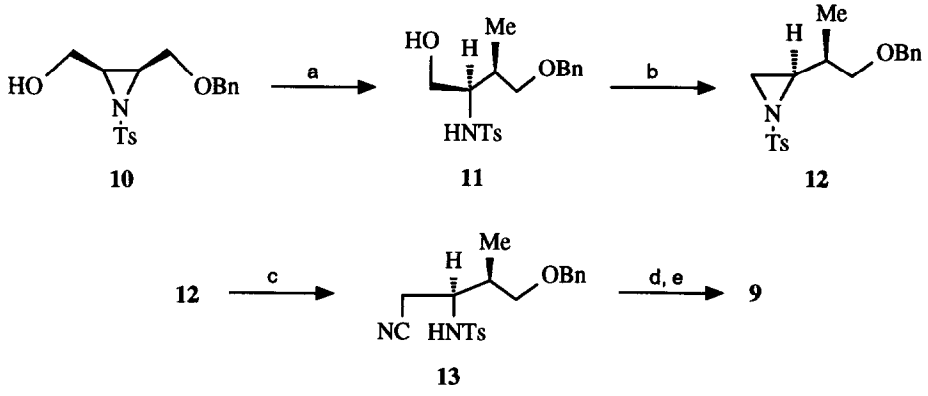
Scheme 1. TBS=$SiMe_2{}^tBu$; Bn=$CH_2C_6H_5$; Ts=paratoluenesulfonyl. (a) NaH, BrBn, Bu_4NI, THF, 90%; (b) NaN_3,NH_4Cl, $MeOCH_2CH_2OH/H_2O$, 80°C, 80%; (c) MsCl, pyridine, 0°C, 92% then $LiAlH_4$, THF, 50°C, 50%; (d) TsCl, pyridine, 0°C, 97%; (e) $AlMe_3$, toluene, reflux, 65%; (f) Jones oxidation, -20°C, 80%; (g) DCC, 4-pyrrolidinopyridine (cat.), CH_2Cl_2, RT, 60%.

The starting material (**3**, Scheme 1) was available in 80-90% yield from Sharpless epoxidation of (Z)-5-^{t}butyldimethylsilyloxy-2-penten-1-ol according to the procedure of Tamm[8], with the exception that diethyl (+)-L-tartrate was used as the source of chirality. The alcohol function was then protected[8] as the benzyl ether, **4**. Using the enantiomers of **3** and **4** Tamm and co-workers[8] deduced, from the results of chemical correlations, that the epoxy alcohol was of at least 95% optical purity, but direct comparison with our materials was not possible since no optical rotation data were reported for the enantiomers of **3** or **4**. We found, however, that the e.e. of **3** could be determined easily by high-field ^{1}H NMR spectroscopic analysis of the corresponding Mosher ester[9], and that in our hands the Sharpless epoxidation yielded material of 90-95% optical purity. Epoxide **4** was then ring-opened (with inversion) by azide to give a mixture of regioisomeric azido-alcohols (**5**) which were converted to their mesylates. Exposure of the mesylates to $LiAlH_4$ in THF at 50°C then accomplished (i) reduction of the azide groups,

(ii) ring-closure to the aziridine, and (iii) removal of the silyl protective group[10] in a single operation which furnished **6** in good overall yield from **5**. Selective N-tosylation of **6** delivered chiral aziridine **7**, thus setting the stage for the key ring-opening reaction.

On the basis of our earlier results[7] from ring-opening reactions of aziridines akin to **7** we felt quite confident that trimethylaluminium would attack the heterocycle at the carbon atom proximal to the benzyloxymethyl substituent, and we were pleased to find that this was indeed the case. From the reaction of **7** and excess trimethylaluminium in refluxing toluene, the sulfonamide **8** was isolated in acceptable yield as a single regioisomer. (The other regioisomer could not be detected in the high-field ^{1}H NMR spectrum of the crude product). After careful Jones oxidation of **8**, the resultant N-tosyl β-amino acid was subjected to our previously described[5b,11] ring-closure conditions to give the desired azetidinone **9** with relative and absolute stereochemistry matching C-1 and C-5 of **2**. As noted above, highly stereoselective methods are available[3b] for the introduction of the two remaining stereocentres of the carbapenem.

In Scheme 2 we describe an alternative route to **9**, based on the same ring-opening methodology, and featuring chiral aziridines at two stages in the reaction sequence. The starting material used here was racemic, but the Sharpless epoxy alcohol required for preparation of enantiomerically pure **10** is commercially available in the form of its 4-nitrobenzoate[12].



10 **11** **12**

Scheme 2. Bn=$CH_2C_6H_5$; Ts=paratoluenesulfonyl. (a) $AlMe_3$, toluene, 75°C, 92% (see ref. 7); (b) DEAD, PPh_3, THF, RT, 80%; (c) KCN, MeOH, 40°C, 82%; (d) 2M NaOH.aq., reflux, 98%; (f) see step (g) in Scheme 1.

As described in the preceding paper[7] $AlMe_3$ efficiently ring-opened **10** to give **11** as a single regioisomer. An intramolecular Mitsunobu reaction[13] then set up the new chiral aziridine **12** which was, as expected, attacked by cyanide exclusively at the less hindered site to yield **13**. Hydrolysis to the corresponding carboxylic acid was followed by ring-closure to the β-lactam as described above. The final product was identical (except for optical rotation) with the material prepared from aziridino alcohol **7**.

This "iterative" aziridine route is highly efficient in terms of regioselectivity (>99:1 for both ring-opening reactions) and chemical yield, delivering diastereomerically pure **9** from the readily available **10** in five steps and 35% overall yield.

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EXPERIMENTAL

General remarks. Unless stated otherwise, ^{1}H NMR spectra were run on a Varian XL 300 spectrometer. IR spectra were obtained for thin films or CH_2Cl_2 solutions on a Perkin-Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. Optical rotations were measured at ambient temperature on a Perkin-Elmer 241 polarimeter. Mass spectra were run on a Finnigan MAT INCOS 50 instrument (direct inlet; electron impact ionization). HPLC analyses were performed on a Waters Associates system (M 45 pump, R 401 differential refractometer) using mixtures of hexane and ethyl acetate as the mobile phase. Elemental analyses were performed by Analytische Laboratorien, Engelskirchen, Germany. Pyridine, toluene and dichloromethane were dried over calcium hydride and distilled under nitrogen before use. THF was distilled under nitrogen from purple solutions of Na/benzophenone. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Analytical TLC was run on Merck silica gel 60-F 254 plates, and spots were visualized by UV light and/or polyphosphomolybdic acid-heat. Moisture-sensitive reactions were carried out in flame- or oven-dried glassware.

Epoxides **3** and **4** were prepared according to the literature procedure for the enantiomeric compounds[8] (with the exception that (+)-DET was used in the Sharpless epoxidation) and had spectral data in accord with those reported. For **3**, material shown to be of 92% e.e. by 400 MHz ^{1}H and 376 MHz ^{19}F NMR spectroscopic analysis of the corresponding Mosher ester[9] had $[\alpha]_D$ +7.39° (*c*=1.01, CH_2Cl_2) while **4** had $[\alpha]_D$ +3.2° (*c*=1.00, CH_2Cl_2). Compound **11** was prepared as described previously[7].

Aziridine **6**. Epoxide **4** (4.73 g, 14.7 mmol) was dissolved with stirring under nitrogen in an 8:1 mixture of 2-methoxyethanol and water (90 mL). Sodium azide (5.73 g, 88 mmol) and ammonium chloride (1.57 g, 29.4 mmol) were added and the mixture was heated at 80°C for 10 h. The reaction mixture was then cooled and partitioned between ether and water, the layers were separated and the aqueous layer was extracted with ether. The combined organics were washed thrice with water and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (silica gel, 5 to 15% ether in pentane) to yield an inseparable 3:1 mixture of regioisomeric azido alcohols (^{1}H NMR analysis). Yield: 4.24 g ,80%. IR: 3500 cm^{-1} (b, OH); 2100 (s, azide); 1100 (s, OSi).

The mixture of azido alcohols (4.04 g, 11.1 mmol) was dissolved with stirring under nitrogen in dry pyridine (50 mL) and the solution cooled to 0°C before addition of mesyl chloride (1.04 mL, 13.3 mmol). The reaction mixture was allowed to reach room temperature overnight and was then poured into

ether. The resultant mixture was extracted with several portions of $CuSO_4$.aq., the organic phase was washed with water and dried over Na_2SO_4, and the solvents were removed to yield an inseparable 3:1 mixture of azido mesylates which was purified by flash chromatography (silica gel, 5 to 20% ether in pentane). Yield: 4.52 g, 92 %. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.35 (m; phenyl); 4.95 (m; C<u>H</u>OMs, minor regioisomer); 4.80 (m; C<u>H</u>OMs, major isomer); 4.55 (2xAB, J=12.5 Hz; benzyl); 3.91-3.68 (m; C<u>H</u>$_2$OBn, C<u>H</u>$_2$OSi, C<u>H</u>N_3); 3.06 (2xs; mesyl Me); 1.90-1.70 (m; C<u>H</u>$_2$C<u>H</u>$_2$OSi); 0.89 (2xs; ^{t}Bu); 0.05 (2xs; $SiMe_2$). IR: 2107 (s; azide); 1361 (s; mesyl); 1176 (s; mesyl).

The mixture of mesylates (0.372 g, 0.84 mmol) was dissolved with stirring under nitrogen in dry THF (10 mL) and the solution was cooled to 0°C before addition of lithium aluminium hydride (0.096 g, 2.5 mmol) The resultant mixture was allowed to reach room temperature over 2 h and was then heated at 50°C overnight. The mixture was cooled and the reaction was quenched by careful addition of water. A solution of NH_4Cl.aq. was added and the mixture was stirred vigorously for 10 min. before being filtered through a Celite pad. The filter cake was washed thoroughly with ethyl acetate, the combined organics were dried over Na_2SO_4, the solvents were removed *in vacuo* at as low a temperature as possible (the aziridine is volatile) and the residue was purified by flash chromatography (silica gel, 10% MeOH in EtOAc) to yield **6** (0.087 g, 50%). Due to the volatility of the aziridine, no attempt was made to free the material completely of solvent, and thus no reliable optical rotation data or elemental analysis were obtained. ^{1}H NMR: 7.35 (5H, m; phenyl); 4.55 (2H, AB, J=12,5; benzyl); 3.81 (2H, m; C<u>H</u>$_2$OH); 3.69 (1H, dd, J=11, 5.9; C<u>H</u>OBn); 3.43 (1H, dd, J=11, 7; C<u>H</u>OBn); 2.33 (4H, m; aziridine, N<u>H</u>, O<u>H</u>); 1.71 (2H, m; C<u>H</u>$_2$C<u>H</u>$_2$OH). IR: 3500-3200 (b, s; OH, NH).

N-tosyl aziridine **7**. Aziridine **6** (0.05 g, 0.24 mmol) was dissolved with stirring under nitrogen in dry pyridine (3 mL) and the solution was cooled to 0°C before addition of tosyl chloride (0.046 g, 0.24 mmol). The mixture was stirred at 0°C for 20 min. and then worked up as described above for the mesylates. Flash chromatography (silica gel, 40 to 75% ether in pentane) yielded pure **7** (0.084 g, 97%). ^{1}H NMR: 7.85 and 7.32 (each 2H, AA'BB', J_{AB}= 8.4; tosyl); 7.36-7.29 (3H, m; phenyl); 7.18 (2H, m; phenyl); 4.41 (2H, AB, J=12.5; benzyl); 3.73 (2H, m; C<u>H</u>$_2$OH); 3.56 (1H, dd, J=10.5, 6; C<u>H</u>OBn); 3.51 (1H, dd, J= 10.5, 6.1; C<u>H</u>OBn); 3.09 (1H, m, J_{cis}= 6.3; aziridine); 3.01 (1H, m, J_{cis}= 6.3; aziridine); 2.43 (3H, s; tosyl Me); 2.28 (1H, bt, J=6; O<u>H</u>); 1.86 (1H, m; C<u>H</u>CH$_2$OH); 1.57 (1H, m; C<u>H</u>CH$_2$OH). IR: 3300 (b; OH); 1315 (s; sulfonamide); 1162 (s; sulfonamide). $[\alpha]_D$ -18.5° (*c*=1.00, CH_2Cl_2). MS (70 eV): m/z 361 (M^+, 2%); 155 (12%); 91 (100%). Anal. Calcd. for $C_{19}H_{23}NO_4S$: C, 63.13%; H,6.41. Found: C, 63.12; H, 6.53.

Alcohol **8**. N-tosyl aziridine **7** (0.327 g, 0.9 mmol) was dissolved with stirring under nitrogen in dry toluene (10 mL) and a 2M solution of $AlMe_3$ in hexane (5.9 mL, 11.8 mmol) was added dropwise via syringe. The mixture was then heated under reflux for 24 h (reaction monitored by HPLC), cooled, and diluted with ether. The resultant mixture was added *slowly* via cannula to a vigorously stirred ice-cold solution of NH_4Cl.aq. After 10 min. the mixture was filtered through a pad of Celite, the filter-cake was washed with fresh ether and the combined organics were dried over $MgSO_4$. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (silica gel, 75% ether in pentane) to yield

8 as a colourless oil (0.220 g, 65%). ^{1}H NMR: 7.76 and 7.31 (each 2H, AA'BB', J_{AB}= 8.5; tosyl); 7.40-7.21 (5H, m; phenyl); 5.81 (1H, d, J=8.3; NH); 4.40 (2H, s; benzyl); 3.95 (1H, bm; CHOH); 3.68 (1H, bm; CHOH); 3.43 (1H, m; CHN); 3.27 (1H, t, J=10; CHOBn); 3.21 (1H, dd, J=10, 4.9; CHOBn); 2.68 (1H, bt, J=6.5; OH); 2.43 (3H, s; tosyl Me); 1.67 (2H, m; $CHCH_3$, $CHCH_2OH$); 1.33 (1H, m; $CHCH_2OH$); 0.64 (3H, d, J=7; Me). IR: 3345 (b; OH); 3325 (b; NH); 1330 (s; sulfonamide); 1160 (s; sulfonamide). $[\alpha]_D$ -27.9° (*c*=0.98, CH_2Cl_2). MS: 377 (M^+, 1%); 268 (2%); 228 (19%); 155 (18%); 91 (100%). Anal. Calcd. for $C_{20}H_{27}NO_4S$: C, 63.63%; H, 7.21. Found: C, 63.89; H, 7.04.

Oxidation of **8**. To a solution of **8** (0.084 g, 0.2 mmol) in acetone (4 mL) at -20°C was added Jones reagent (1.87M, 0.32 mL, 0.6 mmol). The resultant mixture was stirred at -20°C for 2 h, the reaction was quenched by addition of Na_2SO_3.aq. and the solution poured into EtOAc. The phases were separated, the aqueous phase was extracted with fresh EtOAc, and the combined organics were washed with water and then dried over $MgSO_4$. The solvents were removed *in vacuo* to yield the crude N-tosyl β-amino acid (0.069 g, 80%) which was pure according to ^{1}H NMR spectroscopic analysis. This material was used directly in the next step. ^{1}H NMR: 7.72 and 7.30 (each 2H, AA'BB', J_{AB}= 8; tosyl); 7.39-7.20 (5H, m; phenyl); 5.69 (1H, d, J=8; NH); 4.39 (2H, s; benzyl); 3.66 (1H, m; CHN); 3.27 (2H, m; CH_2OBn); 2.51 (1H, dd, J=13, 6.9; $CHCO_2H$); 2.40 (3H, s; tosyl Me) overlapping (1H, m; $CHCO_2H$); 1.90 (1H, m; $CHCH_3$); 0.80 (3H, d, J=7; Me).

Azetidinone **9**. The crude acid from the previous step (0.069 g, 0.17 mmol) was dissolved with stirring under nitrogen in dry CH_2Cl_2 (1.5 mL). A catalytic amount of 4-pyrrolidinopyridine was added, followed by dicyclohexylcarbodiimide (DCC, 0.040 g, 0.19 mmol) and the resultant mixture was stirred at room temperature for 1 h. The precipitated DCU was filtered off, the filtrate was diluted with fresh CH_2Cl_2, and then washed once with water, once with 5% aqueous acetic acid, and finally with water. The organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo* to leave a residue which was purified by flash chromatography (75% ether in pentane). There was obtained 0.039 g (60%) of the azetidinone **9** as an oil. ^{1}H NMR: 7.85 and 7.31 (each 2H, AA'BB'; J_{AB}= 8; tosyl); 7.39-7.25 (5H, m; phenyl); 4.43 (2H, s; benzyl); 4.18 (1H, ddd, J=6.5(cis), 5, 3.5(trans); CHN); 3.54 (1H, dd, J=9.5, 4.9; CHOBn); 3.49 (1H, dd, J=9.5, 6; CHOBn); 3.09 (1H, dd, J=16, 3.5(trans); CHCO); 2.91 (1H, dd, J=16, 6.5(cis); CHCO); 2.44 (3H, s; tosyl Me); 2.33 (1H, tddd, J=7, 6, 5, 4.9; $CHCH_3$); 1.02 (3H, d, J=7; Me). IR: 1787 (s; C=O). $[\alpha]_D$ -36° (*c*=1.00, CH_2Cl_2). MS: M^+ not observed; 218 (M-tosyl; 2%); 190 (9%); 155 (8%); 91 (100%). Anal. Calcd. for $C_{20}H_{23}NO_4S$: C, 64.32%; H, 6.21. Found: C, 64.29; H, 6.08.

N-tosyl aziridine **12**. Compound **11** (see ref. 7; 0.125 g, 0.34 mmol) was dissolved with stirring under nitrogen in dry THF (4 mL). Triphenylphosphine (0.108 g, 0.41 mmol) was added, followed by diethyl azodicarboxylate (DEAD, 0.059 g, 0.34 mmol) and the reaction mixture was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, 20% ether in pentane) to yield the aziridine as an oil (0.095 g, 80%). ^{1}H NMR: 7.82 and 7.31 (each 2H, AA'BB', J_{AB}= 8; tosyl); 7.40-7.20 (5H, m; phenyl); 4.43 (2H, s; benzyl); 3.36 (1H, dd, J=10, 4.2; CHOBn); 3.30 (1H, dd, J=10, 7; CHOBn); 2.70 (1H, m; aziridine); 2.65 (1H, d, J_{cis}= 6.3, J_{gem}= 0; aziridine); 2.44 (3H, s; tosyl Me); 2.22 (1H, d, J_{trans}= 3.5; J_{gem}= 0; aziridine); 1.65 (1H,

m; C<u>H</u>CH$_3$); 0.79 (3H, d, J=7; Me). IR: 1321 (s; sulfonamide); 1161 (s; sulfonamide).

Nitrile **13**. The aziridine **12** (0.025 g, 0.07 mmol) was dissolved with stirring in methanol (2 mL) and potassium cyanide (0.047 g, 0.7 mmol) was added. The resultant mixture was heated at 40°C overnight and then cooled before the solvent was removed *in vacuo* to leave a residue which was purified by flash chromatography (silica gel, 40 to 75% ether in pentane). There was obtained **13** as an oil (0.022 g, 82%). ^{1}H NMR: 7.72 and 7.30 (each 2H, AA'BB', J_{AB}= 9; tosyl); 5.61 (1H, d, J=7; N<u>H</u>); 4.37 (2H, s; benzyl); 3.58 (1H, m; C<u>H</u>N); 3.30 (2H, d, J=6; C<u>H</u>$_2$OBn); 2.68 (1H, dd, J=17, 4.9; C<u>H</u>CN); 2.57 (1H, dd, J=17, 7.5; C<u>H</u>CN); 2.42 (3H, s; tosyl Me); 2.07 (1H, m; C<u>H</u>CH$_3$); 0.91 (3H, d, J=7; Me). IR: 2254 (m; CN); 1330 (s; sulfonamide); 1160 (s; sulfonamide).

Hydrolysis of **13**. The nitrile from the previous step (0.020 g, 0.05 mmol) was heated overnight in refluxing 2M NaOH.aq. (2 mL). The solution was then cooled in an ice bath and acidified by careful addition of conc. HCl. The resultant mixture was extracted with three portions of EtOAc and the combined organics were dried over $MgSO_4$. Removal of the solvent gave the pure acid (0.0192 g, 98%) which was spectroscopically identical with that prepared from **8**.

This material was subjected to the ring-closure reaction described above to give racemic azetidinone **9**, identical in all respects (except optical rotation) with that prepared previously.

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