Synthesis of 3-Methyleneazetidin-2-one Derivatives from α-Keto-amides

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Several α-methyleneazetidin-2-one derivatives (CH_2=C·CO·NR^1·CHR^2, R^1 = cyclohexyl, $PhCH_2$; R^2 = H, Me, Et, Pr^n, *etc.*) were prepared from the 2-(2,4,6-tri-isopropylbenzenesulphonylhydrazones) of primary α-ketoamides ($CH_3COCONHR^1$) using the Shapiro reaction. Thus, trimetallation of these hydrazone derivatives at −78 °C and warming to between −10 and +25° C gave the allenic dianions [CH_2=C=C(O^-)N^-R]. Reaction of these with the aldehydes (R^2CHO), followed by toluene-4-sulphonyl chloride or -sulphonic anhydride, gave the title β-lactams.

α-Methylene and α-ethylidene β-lactams (1a) and (1b) are potentially useful intermediates for the construction of carbapenem antibacterial agents. For example, Corbett and Eglington [1] reported the conversion of the MM17880 derivative (2) into the antibiotic PS-5 (3), as well as related reactions. This transformation involved the elimination of the ethyl sulphate anion from compound (2) giving the (*E*)-ethylidene derivative (4); subsequent borohydride reduction and deprotection gave compound (3). Several syntheses of simple monocyclic α-methylene-β-lactams (1a) have recently been reported.[2-5] These preparations have utilised either late α-methylenylation on preformed β-lactams [2] or reactions *via* masked acrylamide units.[3-5] Both Kay [3] and Ban [4] have shown that these α-methylene-β-lactams undergo conjugate addition of thiol and amine nucleophiles. Herein we report details of our method for the preparation of the α-methylene-β-lactams (5), (6), and (14) from primary α-keto-amides *via* the Shapiro reaction.[6] This synthesis proceeds *via* the dianions (11) and thus uses masked acrylamide functionality.

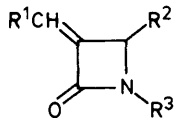
Elsewhere [7] we have reported that primary α-keto-amide 2-(2,4,6-tri-isopropylbenzenesulphonylhydrazones) (9) (trisylhydrazones [8]) were metallated by n-butyl-lithium in tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME) solution at −78° C to give the trianions (10). On warming to room temperature, these decomposed with the elimination of the arenesulphinate anion and nitrogen to give the allenic dianions (11). Addition of aldehydes (or ketones) then gave the derived hydroxy-acrylamides (12). We anticipated that these alcohols (12) should be readily transformed into the α-methylene-β-lactams (14) by remetallation with n-butyl-lithium followed by toluene-4-sulphonylation. Initial arenesulphonylation at oxygen would give the anions (13) which would then cyclise *in situ* (Scheme).

The α-keto-amide trisylhydrazones (9) were prepared using either the condensation of acetyl chloride with cyclohexyl isonitrile,[9] or the reaction of a primary amine with pyruvoyl chloride,[10] and subsequent reaction with trisylhydrazine.[7] Both the *N*-cyclohexyl and *N*-benzyl products (9a, b) were metallated with n-butyl-lithium [7] at −78 °C to give the highly coloured trianions (10a) (orange solution) and (10b) (purple solution). On warming to between −10 °C and room temperature, the allenic dianions (11a, b) were formed. This process was self-indicating since nitrogen was evolved and the dianions were also coloured: (11a) (yellow suspension) and (11b) (claret solution). As detailed elsewhere [7] these dianions (11a, b) reacted smoothly with several aldehydes with instant discharge of colour. Work-up gave the hydroxy-acrylamide derivatives (12a—g), (7a), and (8a) (see Table). After chromatographic purification, these amides were remetallated with n-butyl-lithium and the mixtures treated with toluene-4-sulphonyl chloride or -sulphonic anhydride. Work-up gave the β-lactams (5), (6), and (14). In one case, that of compound (12d) with toluene-4-sulphonyl chloride, the chloro-acrylamide (15a) (32%) was isolated as a by-product. The β-lactams (5) and (14) were fully authenticated by microanalyses and spectral data. Of particular interest was the fact that they all exhibited a carbonyl band in their i.r. spectrum at 1 730—1 760 cm^{-1}. In three cases the intermediate toluene-4-sulphonates (7b), (8b) (crude), and (15b) were isolated. Both compounds (7b) and (15b) were fully characterised. By reaction with sodium hydride, the toluene-4-sulphonates (8b) and (15b) were cyclised to afford the β-lactams (6) and (14a) (19 and 92%, respectively).

Table. Preparation of trisylhydrazones (9), acrylamides (12), β-lactams (14), and related compounds

Product	R^1	R^2	% Yield
(5)			65
(6)			19
(7a)			46 [a]
(7b)			43
(8a)			14 [a]
(9a)	cyclohexyl		93 [a]
(9b)	$PhCH_2$		64
(9c)	Bu^t		66
(9d)	$CH_2CH{=}CH_2$		54
(9e)	Bu^tMe_2Si		30
(9f)	Ph_3C		80
(12a)	cyclohexyl	H	59 [a]
(12b)	cyclohexyl	Me	74
(12c)	cyclohexyl	Et	80 [a]
(12d)	cyclohexyl	Pr	83
(12e)	cyclohexyl	$[CH_2]_6CH_3$	70
(12f)	$PhCH_2$	Me	57
(12g)	$PhCH_2$	Et	58
(12h)	Bu^t	Et	45
(14a)	cyclohexyl	H	60
(14b)	cyclohexyl	Me	64
(14c)	cyclohexyl	Et	68
(14d)	cyclohexyl	Pr^n	55
(14e)	cyclohexyl	$[CH_2]_6CH_3$	57
(14f)	$PhCH_2$	Me	51
(14g)	$PhCH_2$	Et	60
(15a)			32
(15b)			69

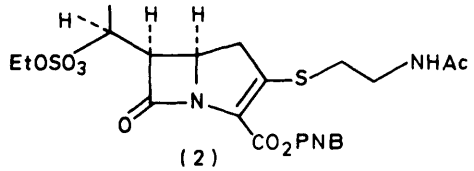
[a] Reference 7.



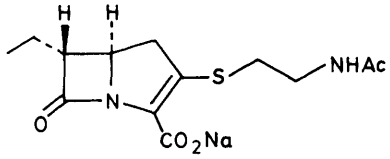
(1)

a ; R^1 = H R^2, R^3 various

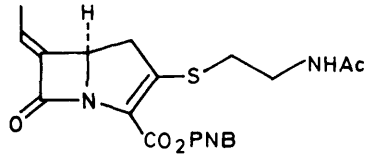
b ; R^1 = Me



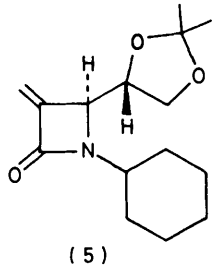
(2)



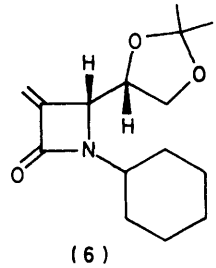
(3)



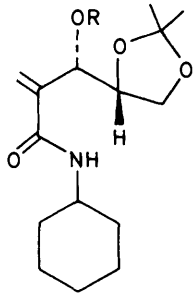
(4)



(5)



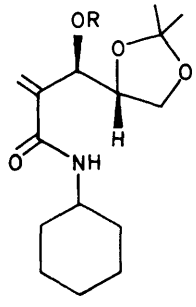
(6)



(7)

a ; R = H

b ; R = Ts



(8)

a ; R = H

b ; R = Ts

PNB = CH_2-C$_6$H$_4$-NO_2

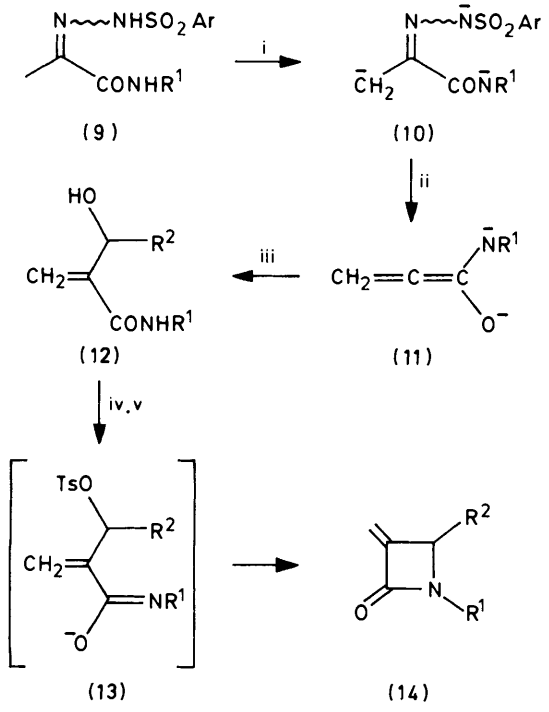
Ts = O_2S-C$_6$H$_4$-CH_3

Several alternative trisylhydrazones (9) were also examined. The *N*-t-butyl- (9c), *N*-allyl- (9d), and *N*-t-butyldimethylsilyl- (9e) trisylhydrazones all reacted with n-butyl-lithium to give, presumably, the yellow-green trianions (10c—e) and thence the dianions (11c—e). Dianion (11c) reacted with propanal to give the expected product (12h) albeit in poor (45%) yield. This disappointing result precluded cyclisation studies. Dianion (11d) reacted with n-butanal to give a complex mixture which probably contained the expected acrylamide adduct (12). The dianion (11e) reacted with n-octanal to give, on aqueous work-up, an adduct, probably (16); this could not be obtained in microanalytically pure form. It is most reasonable to suppose that the silyl protecting group was lost on work-up rather than on metallation since the hydrazone (17a) gave the α-diazo-amide (17b) on attempted trimetallation.[7] Finally, the attempted trimetallation of the trityl-trisylhydrazone (9f) using n-butyl-lithium in excess gave an intractable mixture of products Trianion formation had not taken place since recovered starting material (9f) on D_2O-quenching was not C-deuteriated. In all the trisylhydrazones (9) the C=N geometry was probably the same. This is fully consistent with the ^{1}H n.m.r. resonances, due to the CH_3C=N moiety, all occurring at *ca* δ 2.0.

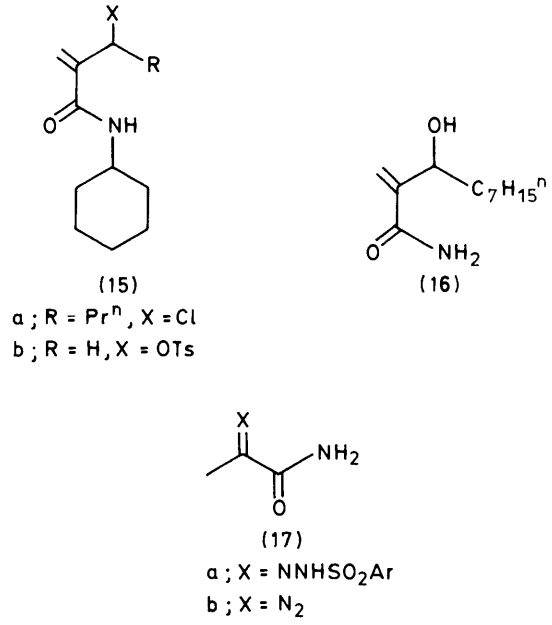
Since α-keto-amide are readily available compounds[9,11] the Shapiro reaction provides a convenient synthetic route to α-methylene-β-lactams. In this transformation several of the steps are self-indicating by colour change. This is both experimentally useful and aesthetically pleasing.

Experimental

M.p.s were determined on a Kofler hot-stage and are uncorrected. I.r. spectra were recorded as Nujol mulls (solids) or films (liquids) (unless otherwise stated), and ^{1}H n.m.r. spectra



Scheme. *Reagents and conditions*: i, Bu^{n}Li (3.2—3.4 mol equiv.), −78 °C, DME or THF; ii, 25 °C, DME or THF; iii, R^2CHO, −78 °C, H_2O; iv, Bu^{n}Li (2 mol equiv.), −78 °C, THF; v, TsCl or Ts_2O, −78 to +25 °C. Ar = $C_6H_2Pr^i_3$-2,4,6. For (9)—(11), R^1 = (a) cyclohexyl; (b) CH_2Ph; (c) Bu^t; (d) $CH_2CH{=}CH_2$; (e) $SiMe_2Bu^t$; (f) CPh_3



in deuteriochloroform solution unless stated to the contrary. All reactions were carried out under dry argon or nitrogen using *freshly* dried and distilled reagents and solvents.[12] n-Butyl-lithium refers to the freshly titrated Aldrich reagent in *ca.* 1.0—1.6M hexane solution. Purification was carried out by flash chromatography [13] on Merck Kieselgel H (silica) or by preparative layer chromatography (p.l.c.) on Merck Kieselgel GF_{254} (developing solvent is given in parentheses). Light petroleum refers to the redistilled fraction with b.p. 40—60 °C. Organic extracts were dried over $MgSO_4$ or Na_2SO_4 before filtration and rotary evaporation was carried out at ≤40 °C.

Preparation of N-*Cyclohexyl*-2-*oxopropionamide and its Derived Trisylhydrazone* (9a).—A mixture of cyclohexylamine (3.5 g) and triethylamine (3.6 g) in diethyl ether (10 ml) was added to a stirred solution of pyruvoyl chloride [10] (3.67 g) in diethyl ether (50 ml) at −78 °C. After the solution had warmed to room temperature, water (20 ml) was added and the organic phase was separated, dried, and evaporated. Recrystallisation of the residue from dichloromethane–light petroleum gave *N*-cyclohexyl-2-oxopropionamide (2.97 g, 50%). This reacted, in the usual way,[7,14] with 2,4,6-tri-isopropylphenylsulphonylhydrazine to give the derived hydrazone (9a).[7]

Preparation of N-*t-Butyl*-2-*oxopropionamide and its Derived Trisylhydrazone* (9c).—In the same way, a solution of pyruvoyl chloride (2.65 g) in diethyl ether (20 ml) was condensed with t-butylamine (1.83 g) and triethylamine (2.5 g) in diethyl ether (10 ml) at −78 °C. After the mixture had warmed to room temperature it was washed in turn with water (20 ml), 10% hydrochloric acid (5 ml), and 1M sodium hydroxide (5 ml) and then dried, evaporated, and distilled to give oily N-*t-butyl*-2-*oxopropionamide* (1.15 g, 32%), b.p. 69 °C at 16 mmHg; $\nu_{max.}$ 3 380, 1 715, 1 675, 1 510, 1 450, 1 360, 1 225, and 1 110 cm^{-1}; δ 1.4 (9 H, s), 2.45 (3 H, s), and 6.8 (1 H, s); *m/z* 143 ($M^{+\cdot}$), 100, and 57 (Found: C, 58.75; H, 9.25; N, 9.65. $C_7H_{13}NO_2$ requires C, 58.7; H, 9.15; N, 9.8%).

To a solution of *N*-t-butyl-2-oxopropionamide (1.06 g) in dichloromethane was added 2,4,6-tri-isopropylphenylsulphonylhydrazine (2.2 g). The mixture was stirred overnight at room temperature and water (20 ml) was then added. The organic layer was separated, dried, and concentrated under reduced pressure. Recrystallisation of the product afforded the *title compound* (9c) (1.96 g, 66%), m.p. 157—158 °C (dichloromethane–light petroleum); $\nu_{max.}$ 3 390, 3 200, 1 660, 1 170, 860, 760, and 750 cm^{-1}; δ 1.38 (27 H, m), 2.08 (3 H, s), 3.0 (1 H, m), 4.36 (2 H, m), 6.7 (1 H, s), 7.33 (2 H, s), and 8.49 (1 H, s); *m/z* 424 ($M - H$)$^+$, 408, 268, 251, 233, 204, and 189 (Found: C, 62.45; H, 8.8; N, 9.9. $C_{22}H_{37}N_3O_3S$ requires C, 62.35; H, 8.8; N, 9.9%).

Preparation of N-(*Triphenylmethyl*)-2-*oxopropionamide* 2-(2,4,6-*Tri-isopropylbenzenesulphonylhydrazone*) (9f).—To a solution of pyruvoyl chloride (1.42 g) in diethyl ether (50 ml) at −78 °C was added a solution of triphenylmethylamine (3.40 g) and triethylamine (1.34 g) in diethyl ether (20 ml). After work-up as above the crude product was recrystallised from dichloromethane–light petroleum to afford *N*-(triphenylmethyl)-2-oxopropionamide (3.56 g, 76%), m.p. 139—140 °C; $\nu_{max.}$ (CH_2Cl_2) 3 380, 1 710, 1 680, 1 490, 1 440, 1 250, 1 185, 1 170, 760, 740, 700, and 630 cm^{-1}; δ 2.46 (3 H, s) and 7.2—7.28 (15 H, m); *m/z* 329 ($M^{+\cdot}$), 243, 182, and 105.

The amide (3.29 g) was converted into the *hydrazone* (9f) (5.0 g, 80%), m.p. 181—182 °C (from aqueous ethanol); $\nu_{max.}$ (CH_2Cl_2) 3 570, 3 500, 3 430, 1 695, 1 500, and 910 cm^{-1}; δ 1.06—1.33 (18 H, m), 1.93 (3 H, s), 2.93 (1 H, m), 4.13 (2 H, m), 7.16 (17 H, m), 8.08 (1 H, s), and 8.23 (1 H, s); *m/z* 313 and 243 (Found: C, 71.05; H, 7.25; N, 6.5. $C_{37}H_{43}N_3O_3S{\cdot}H_2O$ requires C, 70.8; H, 7.25; N, 6.7%).

Preparation of N-*Benzyl*-2-*oxopropionamide* 2-(2,4,6-*Tri-isopropylbenzenesulphonylhydrazone*) (9b).—Pyruvoyl chloride [10] (2.4 g) was added dropwise to a stirred solution of benzylamine (2.2 g) and triethylamine (2.3 g) in diethyl ether (20 ml) at −78 °C. The mixture was allowed to warm to room

temperature and the resultant solid was filtered off and leached with diethyl ether. Evaporation of the combined filtrate and washings gave an oily solid (2.6 g). An aliquot (1.5 g) was stirred ovrenight with a solution of 2,4,6-tri-isopropylphenylsulphonylhydrazine (2.5 g) in dichloromethane (30 ml). Evaporation and recrystallisation from aqueous ethanol gave the *title hydrazone* (9b) (3.5 g, 64%) as a white, amorphous solid, m.p. 174—175 °C; $\nu_{max.}$ 3 350 and 1 650 cm^{-1}; δ 1.2 (18 H, 2 × d, each *J* 7 Hz), 2.0 (3 H, s), 2.6—3.0 (1 H, m), 3.9—4.3 (2 H, m), 4.4 (2 H, d, *J* 6 Hz), 7.1 (2 H, s), 7.2 (5 H, s), 8.0br (1 H, m), and 8.2 (1 H, s); *m/z* $M^{+\cdot}$ peak absent, 268, 251, 233, 221, and 204 (Found: C, 65.6; H, 7.85; N, 9.0. $C_{25}H_{35}N_3O_3S$ requires C, 65.6; H, 7.7; N, 9.2%).

Preparation of N-*Allyl*-2-*oxopropionamide* 2-(2,4,6-*Tri-isopropylbenzenesulphonylhydrazone*) (9d).—*N*-Allyl-2-oxopropionamide, prepared in the usual way, was obtained as an oil (50%), b.p. 120 °C at 20 mmHg; $\nu_{max.}$ ($CHCl_3$) 3 410, 3 310, 1 720, 1 680, 1 520, 1 355, 1 170 and 810 cm^{-1}; δ 2.5 (3 H, s), 3.88—4.11 (2 H, m), 5.11—5.44 (2 H, m), 5.66—6.15 (1 H, m), and 7.1 (1 H, s); *m/z* 127 ($M^{+\cdot}$) (Found: $M^{+\cdot}$, 127.0636. $C_6H_9NO_2$ requires *M*, 127.0633).

The *hydrazone* (9d) was prepared in the usual way (54%), m.p. 173 °C (from dichloromethane–light petroleum); $\nu_{max.}$ ($CHCl_3$) 3 380, 3 170, 1 660, 1 170, 1 095, 905, and 735 cm^{-1}; δ 1.26 (18 H, d, *J* 7 Hz), 2.0 (3 H, s), 2.93 (1 H, m), 3.86 (2 H, m), 4.22 (2 H, m), 4.97—5.33 (2 H, m), 5.55—6.08 (1 H, m), 6.8 (1 H, s), 7.17 (2 H, s), and 8.25 (1 H, s); *m/z* 283, 265, 251, and 235 (Found: C, 61.55; H, 8.1; N, 10.25. $C_{21}H_{33}N_3O_3S$ requires C, 61.9; H, 8.15; N, 10.3%).

Preparation of N-(*t-Butyldimethylsilyl*)-2-*oxopropionamide* 2,4,6-*Tri-isopropylbenzenesulphonylhydrazone* (9e).—To a solution of pyruvoyl chloride (1.31 g) in diethyl ether (30 ml) at −78 °C was slowly added a solution of triethylamine (1.10 g) and t-butyldimethylsilylamine [15] (1.31 g) in diethyl ether (10 ml). After the addition was complete the reaction mixture was allowed to warm to room temperature. The triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure. **Very rapid** column chromatography on silica (30 g; eluant dichloromethane) afforded *N*-(t-butyldimethylsilyl)-2-oxopropionamide (1.32 g, 65%) which was purified further by sublimation at 100 °C and 20 mmHg, m.p. 51.5—53.5 °C; $\nu_{max.}$ 3 360, 3 270, 1 720, 1 235, 830, and 780 cm^{-1}; δ 0.27 (6 H, s), 0.99 (9 H, s), and 2.39 (3 H, s); *m/z* 202 $(M + H)^{+\cdot}$.

This α-keto-amide (770 mg) and 2,4,6-tri-isopropylphenylsulphonylhydrazine (1.11 g) were stirred in dichloromethane (20 ml) at room temperature overnight. The solvent was removed under reduced pressure; **rapid** column chromatography of the residue on silica (30 g; eluant dichloromethane) afforded the *title compound* (9e) (580 mg, 30%) as a white, crystalline solid, m.p. 101—103 °C (from dichloromethane–light petroleum); $\nu_{max.}$ 3 380, 3 230, 1 670, 1 160, 840, and 680 cm^{-1}; δ 0.18 (6 H, s), 0.85 (9 H, s), 1.2—1.38 (18 H, m), 2.02 (3 H, s), 2.73—3.15 (1 H, m), 4.08—4.47 (2 H, m), 6.31 (1 H, s), 7.24 (2 H, s), and 8.38 (1 H, s) (Found: C, 60.1; H, 8.9; N, 8.75. $C_{24}H_{43}N_3O_3SSi$ requires C, 59.8; H, 9.0; N, 8.7%).

Preparation of N-*Cyclohexyl*-3-*hydroxy*-2-*methylenehexanamide* (12d) and *Related Reactions.*—To a solution of the hydrazone (9a) (449 mg) in DME (15 ml) at −78 °C was added n-butyl-lithium (3.3 mmol). The orange-red solution was allowed to warm to room temperature (60 min), during which time it became golden-yellow in colour. After being stirred at room temperature for 30 min the mixture was cooled to −78 °C and freshly redistilled n-butanal (0.09 ml) was added. The reaction mixture was allowed to rewarm to room temperature (15 min) and the solvent was then removed under reduced pressure. The residue was partitioned between water (10 ml) and diethyl ether (20 ml). The ethereal layer was separated, dried, and concentrated under reduced pressure. Chromatography of the residue on silica (10 g; eluant dichloromethane) afforded the *title compound* (12d) (118 mg, 83%) as a white, crystalline solid, m.p. 103—104 °C (from dichloromethane–light petroleum); $\nu_{max.}$ 3 360, 3 300, 1 655, 1 620, and 1 540 cm^{-1}; δ 0.9—2.1 (17 H, m), 3.66—4.11 (2 H, m), 4.22—4.53 (1 H, m), 5.4 (1 H, s), 5.75 (1 H, s), and 6.9 (1 H, d, *J* 8 Hz); *m/z* 225 ($M^{+\cdot}$) and 207 $(M - H_2O)^{+\cdot}$ (Found: C, 69.2; H 10.4; N, 6.1. $C_{13}H_{23}NO_2$ requires C, 69.3; H, 10.3; N, 6.2%).

In the same way the hydrazone (9a) reacted with (i) n-octanal to give N-*cyclohexyl*-3-*hydroxy*-2-*methylenedecanamide* (12e) (70%), m.p. 84.5—85.5 °C (from dichloromethane–light petroleum); $\nu_{max.}$ (CH_2Cl_2) 3 300, 1 650, 1 610, 1 520, 1 185, and 1 125 cm^{-1}; δ 0.8—2.0 (25 H, m), 3.62—4.04 (2 H, m), 4.15—4.68 (1 H, m), 5.4 (1 H, s), 5.77 (1 H, s), and 6.9 (1 H, d, *J* 8 Hz); *m/z* 263 $(M - H_2O)^{+\cdot}$, 220, and 164 (Found: C, 72.55; H, 11.25; N, 4.85. $C_{17}H_{31}NO_2$ requires C, 72.55; H, 11.1; N, 5.0%) and with (ii) acetaldehyde to give N-*cyclohexyl*-3-*hydroxy*-2-*methylenebutyramide* (12b) (74%), m.p. 100—102 °C (from dichloromethane–light petroleum); $\nu_{max.}$ 3 350, 3 300, 1 660, 1 615, 1 530, 1 110, and 930 cm^{-1}; δ 1.0—2.05 (13 H, m), 3.4—3.93 (1 H, m), 4.04—4.26 (1 H, m), 4.46—4.77 (1 H, m), 5.42 (1 H, s), 5.72 (1 H, s), and 6.9 (1 H, s); *m/z* 197 ($M^{+\cdot}$), 182, 179, 136, and 98 (Found: C, 67.0; H, 9.85; N, 6.95. $C_{11}H_{19}NO_2$ requires C, 66.95; H, 9.7; N, 71.%).

The hydrazone (9b) similarly reacted with n-butyl-lithium in DME at −78 °C [deep-purple trianion (10b)] [claret-coloured dianion (11b) on warming to −10 °C] and subsequently with with (i) acetaldehyde (−78 °C) to give N-*benzyl*-3-*hydroxy*-2-*methylenebutyramide* (12f) (57%), m.p. 45.5—46.5 °C; $\nu_{max.}$ 3 260, 1 660, 1 615, 1 115, 935, 740, and 705 cm^{-1}; δ 1.35 (3 H, d, *J* 7 Hz), 3.2 (2 H, s), 4.5 (2 H, d, *J* 6 Hz), 4.6 (1 H, m), 5.45 (1 H, s), 5.8 (1 H, s), and 7.35 (5 H, s); *m/z* 205 ($M^{+\cdot}$), 187, 114, 106, 91, and 43 (Found: C, 69.85; H, 7.45; N, 6.55. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.35; N, 6.8%); and (ii) propanal (−78 °C) to give N-*benzyl*-3-*hydroxy*-2-*methylenevaleramide* (12g) (58%), m.p. 60.5—61.5 °C; $\nu_{max.}$ 3 290, 1 655, 1 620, 995, 935, and 705 cm^{-1}; δ 0.8—2.0 (6 H, m), 3.4—3.8 (1 H, m), 4.2 (1 H, m), 4.4 (2 H, d, *J* 6 Hz), 5.35 (1 H, s), 5.8 (1 H, s), and 7.3 (5 H, s); *m/z* 219 ($M^{+\cdot}$), 201, 190, 167, 106, and 91 (Found: C, 71.25; H, 7.9; N, 6.35. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%).

Preparation of 1-*Cyclohexyl*-3-*methyleneazetidin*-2-*one* (14a).—A solution of the amide (12a) (142 mg) in THF (10 ml) was cooled to −78 °C. n-Butyl-lithium (1.61 mmol) was added and the solution was warmed to 0 °C. Toluene-4-sulphonyl chloride (236 mg) was added and the solution stirred overnight at 25 °C and was then evaporated to dryness. The residue was dissolved in water (10 ml) and the solution was extracted with diethyl ether (2 × 20 ml); the extract was dried, evaporated to dryness, and separated by p.l.c. (one development with diethyl ether, eight developments with dichloromethane) to give the methylene β-lactam (14a) [3] (77 mg, 60%) as an oil, $\nu_{max.}$ 2 930, 2 855, 1 745, 1 668, 1 628, 1 530, 1 467, 1 452, 1 390, 1 364, 1 350, 1 318, 1 259, 1 223, 1 110, 1 083, 993, 966, 918, 890, 793, and 728 cm^{-1}; δ 1.0—2.1 (10 H, m), 3.45—4.05 (1 H, m, HCN), 3.8 (2 H, d, *J* 1 Hz, 4-H_2), 5.25 (1 H, m, *J* 1 Hz, C*H*H=), and 5.85 (1 H, m, *J* 1.5 Hz, CH*H*=); *m/z* 165 ($M^{+\cdot}$), 122, 84, 81, and 55 (Found: C, 72.4; H, 9.4; N, 8.35%; $M^{+\cdot}$, 165.1152. Calc. for $C_{10}H_{15}NO$: C, 72.7; H, 9.15; N, 8.5%; *M*, 165.1154).

Preparation of 1-*Cyclohexyl*-4-*methyl*-3-*methyleneazetidin*-2-*one* (14b).—To a solution of the amide (12b) (81 mg) in

THF (10 ml) at −78 °C was added n-butyl-lithium (0.91 mmol). The mixture was allowed to warm to 0 °C and was then recooled to −78 °C. A solution of toluene-4-sulphonyl chloride (100 mg) in dry THF (5 ml) was added and the reaction mixture was allowed to warm to room temperature overnight. Work-up and separation by p.l.c. (dichloromethane) afforded the *title compound* (14b) (47.6 mg, 64%) as a viscous oil, $\nu_{max.}$ (CH_2Cl_2) 1 730, 1 510, 1 370, 1 250, 1 100, 1 030, 980, 920, and 890 cm^{-1}; δ 1.1—2.05 (13 H, m), 3.31—3.93 (1 H, m), 3.93—4.36 (1 H, m), 5.00 (1 H, s), and 5.53 (1 H, s); *m/z* 197 ($M^{+\cdot}$), 136, and 98 (Found: C, 74.05; H, 9.7; N, 8.0%; $M^{+\cdot}$, 179.1310. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.55; N, 7.8%; *M*, 179.130).

Preparation of 1-*Cyclohexyl*-4-*ethyl*-3-*methyleneazetidin*-2-*one* (14c).—A solution of the amide (12c) (413 mg) in THF (15 ml) was cooled to −78 °C. n-Butyl-lithium (4.15 mmol) was added and the solution was warmed to 25 °C during 20 min and was then recooled to −78 °C. A solution of toluene-4-sulphonyl chloride (625 mg) in THF (16 ml) was added dropwise during 15 min and the reaction mixture was warmed to 25 °C, stirred for 15 h, and evaporated to dryness. The usual work-up and chromatography of the residue on silica (16 g) [gradient elution; dichloromethane–diethyl ether (1 : 0—9 : 1)] gave the *methylene* β-*lactam* (14c) (258 mg, 68%) as an oil, $\nu_{max.}$ 2 960, 2 930, 2 858, 1 750, 1 704, 1 465, 1 453, 1 387, 1 368, 1 353, 1 323, 1 305, 1 269, 1 260, 1 107, 1 081, and 913 cm^{-1}; δ 0.97 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.0—2.1 (10 H, m), 1.75 (2 H, q, *J* 7 Hz, MeCH_2), 3.3—3.7 (1 H, m, HCN), 3.95—4.2 (1 H, m, 4-H), 5.05 (1 H, s, CH*H*=), and 5.57 (1 H, s, C*H*H=); *m/z* 193 ($M^{+\cdot}$), 178, 164, 150, 112, and 67. An analytical sample was prepared by short-path distillation, b.p. *ca.* 100 °C at 0.2 mmHg (Found: C, 74.7; H, 10.2; N, 7.2%; $M^{+\cdot}$, 193.1467. $C_{12}H_{19}NO$ requires C, 74.55; H, 9.9; N, 7.25%; *M*, 193.1467).

Preparation of 1-*Cyclohexyl*-3-*methylene*-4-*propylazetidin*-2-*one* (14d).—(*a*) To a solution of the amide (12d) (112 mg, 0.5 mmol) in dry THF (10 ml) at −78 °C was added n-butyl-lithium (1.1 mmol). The mixture was allowed to warm to 0 °C (15 min) and was recooled to −78 °C. A solution of toluene-4-sulphonic anhydride (220 mg) in dry THF (2 ml) was then added at −78 °C. After the mixture had warmed to room temperature overnight it was poured into water (10 ml) and extracted with diethyl ether (2 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure. P.l.c. of the residue (dichloromethane) afforded the *title compound* (14d) (55.6 mg, 55%) as a viscous oil, $\nu_{max.}$ (CH_2Cl_2) 1 730, 1 700, 1 370, 1 250, 1 105, 1 070, 985, 950, 920, and 890 cm^{-1}; δ 0.85—2.05 (17 H, m), 3.33—3.73 (1 H, m), 3.97—4.25 (1 H, m), 5.06 (1 H, m), and 5.27 (1 H, m); *m/z* 207 ($M^{+\cdot}$), 164, and 126 (Found: C, 74.85; H, 10.4; N, 6.7. $C_{13}H_{21}NO$ requires C, 75.3; H, 10.2; N, 6.75%).

(*b*) To a solution of the amide (12d) (225 mg, 1 mmol) in dry THF (10 ml) at −78 °C was added n-butyl-lithium (2.2 mmol). After the solution had warmed to 0 °C and had been recooled to −78 °C, a solution of toluene-4-sulphonyl chloride (480 mg) in dry THF (2 ml) was added. The mixture was allowed to warm to room temperature overnight and was then poured into water (10 ml) and extracted with diethyl ether (2 × 25 ml). The combined organic extracts were dried and concentrated under reduced pressure. Column chromatography of the residue on silica (15 g; eluant light petroleum–dichloromethane 2 : 1) afforded first 3-*chloro*-N-*cyclohexyl*-2-*methylenehexanamide* (15a) (79.8 mg, 32%), m.p. 92—94 °C (from dichloromethane–light petroleum); $\nu_{max.}$ 3 410, 1 650, 1 620, 1 490, 1 445, 1 200, and 1 100 cm^{-1}; δ 0.85—2.1 (17 H, m), 3.60—4.06 (1 H, m), 4.82 (1 H, t, *J* 6 Hz), 5.57 (1 H, s), 5.68 (1 H, s), and 6.05br (1 H, d, *J* 10 Hz); *m/z* 245, 243 ($M^{+\cdot}$), 208, 162, and 126 (Found: C, 64.2; H, 9.25; N, 5.7. $C_{13}H_{22}ClNO$ requires C, 64.05; H, 9.1; N, 5.75%) and then the β-lactam (14d) (88 mg, 42%), identical with the previous sample.

Preparation of 1-*Cyclohexyl*-4-*heptyl*-3-*methyleneazetidin*-2-*one* (14e).—To a solution of amide (12e) (295.5 mg) in dry THF (15 ml) at −78 °C was added n-butyl-lithium (2.46 mmol) and the mixture was allowed to warm to 0 °C. After being recooled to −78 °C the mixture was treated with a solution of toluene-4-sulphonic anhydride (456.4 mg) in dry THF (5 ml). The reaction mixture was allowed to warm to room temperature overnight whence work-up in the usual way and p.l.c. (dichloromethane) of the residue afforded the *title compound* (14e) (148 mg, 57%), $\nu_{max.}$ (CH_2Cl_2) 1 730, 1 700, 1 450, 1 360, 920, and 890 cm^{-1}; δ 0.80—2.05 (25 H, m), 3.31—3.71 (1 H, m), 4.04—4.18 (1 H, m), 5.04 (1 H, s), and 5.6 (1 H, s); *m/z* 263 ($M^{+\cdot}$), 178, 164, and 138 (Found: C, 77.15; H, 11.35; N, 5.25%; $M^{+\cdot}$ 263.2257. $C_{17}H_{29}NO$ requires C, 77.5; H, 11.1; N, 5.3%, *M*, 263.2249).

Preparation of (4S)-1-*Cyclohexyl*-4-(2,2-*dimethyl*-1,3-*dioxolan*-4S-*yl*)-3-*methyleneazetidin*-2-*one* (5).—A solution of the amide (7a) (237 mg) in THF (10 ml) was cooled to −78 °C. n-Butyl-lithium (2.01 mmol) was added and the suspension was stirred for 5 min, warmed to 25 °C, and then recooled to −78 °C. A solution of toluene-4-sulphonyl chloride (309 mg) in the THF (11 ml) was added dropwise during 15 min and the mixture was warmed to 25 °C and stirred for 15 h. The usual work-up and chromatography on silica (18 g; gradient elution with dichloromethane–diethyl ether (1 : 0—9 : 1) as eluant] gave the β-*lactam* (5) (145 mg, 65%) as an oil, $\nu_{max.}$ 3 000, 2 940, 2 865, 1 760, 1 460, 1 387, 1 365, 1 355, 1 262, 1 216, 1 158, 1 068, and 850 cm^{-1}; δ 1.1—2.0 (10 H, m), 1.38 (3 H, s, Me), 1.47 (3 H, s, Me), 3.55—3.7 (1 H, m, HCN), 3.73—3.82 (1 H, dd, *J* 6 and 6 Hz, CH*H*O), 4.04—4.24 (total 3 H, m, NCHCHCH), 5.1 (1 H, m, C*H*H=), and 5.68 (1 H, t, *J* 1 Hz, CH*H*=); *m/z* 265 ($M^{+\cdot}$), 250, 207, 164, 101, and 83. An analytical sample was purified by short-path distillation, b.p. *ca.* 180 °C at 0.3 mmgH; $[\alpha]_{589}^{22}$ +36.6° (*c* 0.235, dichloromethane) (Found: C, 68.2; H, 8.95; N, 5.3%; $M^{+\cdot}$, 265.1679. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.75; N, 5.3%; *M*, 265.1678).

Preparation of (4R)-1-*Cyclohexyl*-4-(2,2-*dimethyl*-1,3-*dioxolan*-4S-*yl*)-3-*methyleneazetidin*-2-*one* (6).—A solution of the amide (8a) (115 mg) in the THF (10 ml) was cooled to −78 °C. n-Butyl-lithium (1.04 mmol) was added and the suspension was stirred for 5 min, warmed to 25 °C, and then recooled to −78 °C. A solution of toluene-4-sulphonyl chloride (190 mg) in THF (12 ml) was added during 15 min and the solution was warmed to 25 °C and stirred for 20 h. The usual work-up gave the crude tosylate (8b) (*ca.* 90%) and the β-lactam (6) (105 mg) as an inseparable mixture, $\nu_{max.}$ 1 740, 1 660, 1 625, and 1 600 cm^{-1}; δ 2.45 (3 H, s), 5.2 (1 H, d, *J* 6 Hz, *H*COTs), 5.65 (1 H, s), and 5.8 (1 H, s). The crude material was dissolved in THF (5 ml), the mixture was treated with sodium hydride (15 mg), and the suspension was stirred for 76 h. The usual work-up and p.l.c. [five developments with dichloromethane–diethyl ether (9 : 1), three developments with light petroleum–diethyl ether (1 : 1)] of the residue gave the β-*lactam* (6) (20 mg, 19%) as an oily solid, m.p. 55—58 °C; $[\alpha]_{589}^{21}$ −8.3 (*c* 0.42, dichloromethane); $\nu_{max.}$ (CCl_4) 2 995, 2 940, 2 860, 1 760, 1 455, 1 415, 1 385, 1 375, 1 360, 1 352, 1 318, 1 267, 1 210, 1 170, 1 165, 1 120, 1 067, and 924 cm^{-1}; δ 1.15—2.0 (10 H, m), 1.35 (3 H, s, Me), 1.45 (3 H, s, Me), 3.4—3.55 (1 H, m, HCN), 3.8—3.9 (1 H, dd, *J* 6 and 7 Hz, C*H*HO), 4.05—4.12 (1 H, dd, *J* 6 and 7 Hz, CH*H*O), 4.3—4.42 (total 2 H, m, NCHCH), 5.21 (1 H, t,

J 0.5 Hz, C*H*H=), and 5.63 (1 H, t, *J* 0.5 Hz, CH*H*=); *m/z* 265 ($M^{+\cdot}$), 250, 164, 108, 101, and 83 (Found: C, 67.85; H, 8.95; N, 5.3%, $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.75; N, 5.3%).

Preparation of (3S,4R)-N-*Cyclohexyl*-4,5-*dihydroxy*-2-*methylene*-3-(p-*tolylsulphonyloxy*)*valeramide Acetonide* * (7b). —A solution of the hydroxy-amide (7a) (38 mg) in THF (5 ml) was cooled to −78 °C. n-Butyl-lithium (0.67 mmol) was added and the solution warmed to 25 °C, treated with toluene-4-sulphonyl chloride (132 mg), stirred for 10 min, and quenched with water (5 ml). The usual work-up and p.l.c. of the residue (diethyl ether) gave the *amido-tosylate* (7b) (25 mg, 43%), m.p. 97—98 °C (from diethyl ether–light petroleum); $\nu_{max.}$ ($CHCl_3$) 3 435, 2 930, 2 860, 1 670, 1 630, 1 602, 1 500, 1 453, 1 374, 1 355, 1 170, 1 150, 1 110, 1 097, 1 075, 965, 942, 910, and 890 cm^{-1}; δ 1.0 − 2.05 (10 H, m), 1.3 (total 6 *H*, s, $OCMe_2$), 2.45 (3 H, s, Ar*Me*), 3.55—4.15 (total 3 H, m, CH_2O and HCN), 4.4 (1 H, q, *J* 7 Hz, 4-H), 5.25 (1 H, d, *J* 7 Hz, 3-H), 5.25—5.9br (1 H, NH), 5.55br (1 H, s, C*H*H=), 5.66br (1 H, s, CH*H*=), and 7.25—7.4 and 7.7—7.9 (total 4 H, m, ArH); *m/z* 437 ($M^{+\cdot}$), 422, 182, 101, 91, and 59 (Found: C, 60.35; H, 7.25; N, 3.2. $C_{22}H_{31}NO_6S$ requires C, 60.4; H, 7.15; N, 3.2%).

Preparation of N-*Cyclohexyl*-2-*methylene*-3-(p-*tolylsulphonyloxy*)*propionamide* (15b).—The hydroxy-amide (12a) (46 mg), powdered potassium hydroxide (28.5 mg), and toluene-4-sulphonyl chloride (48 mg) were stirred in diethyl ether (1 ml) at −20 °C for 48 h. The mixture was filtered and the filtrate was evaporated to dryness. P.l.c. (diethyl ether–dichloromethane 1 : 4) of the residue gave the *title toluene*-4-*sulphonate* (15b) (42 mg, 45%), m.p. 72—73 °C; $\nu_{max.}$ (CH_2Cl_2) 3 435, 1 670, 1 510, 1 355, 1 175, 1 100, and 940 cm^{-1}; δ 1.2—2.3 (11 H, m), 2.45 (3 H, s), 4.75 (2 H, s), 5.65 (1 H, s), 5.85 (1 H, s), 7.0br (1 H, s), and 7.4 and 7.85 (total 4 H, ABq, *J* 8 Hz); *m/z* 337 ($M^{+\cdot}$), 321, 294, 256, 249, and 239 (Found: C, 60.5; H, 7.05; N, 4.0. $C_{17}H_{23}NO_4S$ requires C, 60.5; H, 6.85; N, 4.15%). Repetition of the reaction on a 1.68 mmol scale gave the toluene-4-sulphonate (15b) in 69% yield.

Alternative Preparation of 1-*Cyclohexyl*-3-*methyleneazetidin*-2-*one* (14a).—The foregoing toluene-4-sulphonate (15b) (20 mg) was added to a mixture of oil-free (dichloromethane) sodium hydride (50%, 3 mg) and trihexylmethylammonium iodide (2.4 mg) in dichloromethane (2.5 ml). After being vigorously stirred overnight the mixture was filtered and the filtrate was chromatographed on silica (eluant dichloromethane) to give the title β-lactam (14a) (9 mg, 92%), identical with an authentic sample.

Preparation of 1-*Benzyl*-4-*methyl*-3-*methyleneazetidin*-2-*one* (14f).—The *title azetidin*-2-*one*, prepared in a similar manner to the β-lactam (14e), was obtained as an oil (51%), $\nu_{max.}$ (CH_2Cl_2) 1 745, 1 675, 1 515, 1 500, 1 380, 1 350, 1 105, 1 080, 925, and 900 cm^{-1}; δ 1.25 (3 H, d, *J* 6.5 Hz), 4.0 (1 H, m), 4.26 and 4.74 (total 2 H, ABq, *J* 16 Hz, ArCH_2), 5.1 (1 H, s), 5.65 (1 H, s), and 7.3 (5 H, s); *m/z* 187 ($M^{+\cdot}$), 172, 133, 105, and 91 (Found: C, 76.7; H, 7.25; N, 7.45%; $M^{+\cdot}$, 187.0997. $C_{12}H_{13}NO$ requires C, 77.0; H, 7.0; N, 7.5%; *M*, 187.0997).

Preparation of 1-*Benzyl*-4-*ethyl*-3-*methyleneazetidin*-2-*one* (14g).—The title β-*lactam*, prepared in analogous manner to compound (14e), was obtained as an oil (60%), $\nu_{max.}$ 1 745, 1 695, 1 495, 1 450, 1 385, 1 355, 1 305, 1 265, 1 100, 1 075, 1 025, 925, 795, 730, and 700 cm^{-1}; δ 0.88 (3 H, t, *J* 7 Hz), 1.65 (2 H, m), 3.94 (1 H, t, *J* 6 Hz), 4.2 and 4.78 (total 2 H, ABq, *J* 16 Hz, ArCH_2), 5.13 (1 H, s), 5.7 (1 H, s), and 7.3 (5 H, s, ArH); *m/z* 201 ($M^{+\cdot}$), 186, 172, 158, 144, 133, 104, 91, and 84 (Found: $M^{+\cdot}$, 201.1151. $C_{13}H_{15}NO$ requires *M*, 201.1154).

Preparation of N-*t-Butyl*-3-*hydroxy*-2-*methylenevaleramide* (12h).—To a soluton of the hydrazone (9c) (425 mg, 1 mmol) in dry DME (20 ml) at −78 °C was added n-butyl-lithium (3.29 mmol). The lime-yellow-coloured solution was slowly allowed to warm to room temperature (1 h) and was then recooled to −78 °C. Freshly distilled propanol (66 mg) was added to the mixture which was then allowed to warm to room temperature (15 min). Work-up in the usual way and p.l.c. of the residue (diethyl ether–dichloromethane 1 : 9) afforded the *title compound* (12h) (83 mg, 45%) as a viscous oil, $\nu_{max.}$ (CH_2Cl_2) 3 300, 1 715, 1 620, and 1 500 cm^{-1}; δ 0.93 (3 H, t, *J* 7 Hz), 1.36 (9 H, s), 1.4—1.8 (2 H, m), 4.15 (2 H, m), 5.28 (1 H, m), 5.68 (1 H, m), and 6.8 (1 H, s); *m/z* 185 ($M^{+\cdot}$), 167, 156, 100, and 58 (Found: $M^{+\cdot}$, 185.1416. $C_{10}H_{19}NO_2$ requires *M*, 185.1416).

Attempted Preparation of the Dianion (11e).—In the usual way, the trisylhydrazone (9e) (481 mg) was treated with n-butyl-lithium (5 mmol) in DME (30 ml) at −78 °C (lime-green solution); the mixture was allowed to warm to room temperature and was then recooled to −78 °C and quenched with n-octanal. Work-up and chromatography on silica (8g; eluant diethyl ether–dichloromethane 1 : 5) gave a crude oil, probably the amide (16) (94 mg, 47%), $\nu_{max.}$ (CH_2Cl_2) 3 550, 3 530, 3 500, 3 410, 3 370, 1 680, 1 635, and 1 590 cm^{-1}; δ 0.85 (3 H, m), 1.2—1.8 (12 H, m), 3.0br (1 H, m), 4.35 (1 H, t, *J* 6 Hz), 5.5 (1 H, s), 5.88 (1 H, s), and 6.0—6.8br (2 H, NH_2).

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* Alternative name: (3S)-N-*Cyclohexyl*-3-(2,3-*dimethyl*-1,3-*dioxolan*-4R-*yl*)-2-*methylene*-3-(p-*tolylsulphonyloxy*)*propionamide*.

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