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THE PREPARATION AND REACTIONS OF 1-LITHIO-ALKYLAMINO-1-LITHIO-OXY-ALLENE DERIVATIVES

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Abstract—The reaction of secondary α-keto-amide 2,4,6-tri-iso-propylbenzenesulphonylhydrazones with n-butyllithium generated, via a modified Shapiro reaction, the title carbanions [RCH=C=C(O⁻)N̄R¹]. These reacted at carbon with deuterium oxide, aldehydes, and ketones and are therefore most useful for the introduction of acrylate functionality.

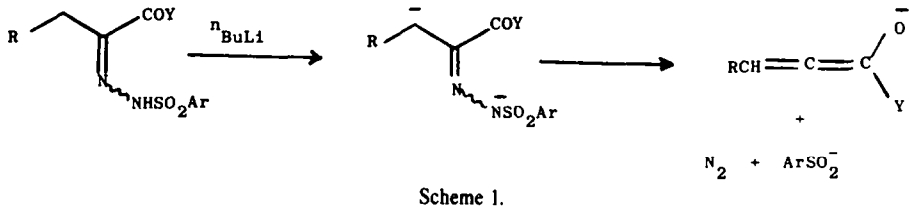
Recently we have described, in communication form, the preparation and reactions of 1 - lithio - oxy - 1 - lithio - amino - allenes.[1] Herein we report experimental details of this work. Anions derived from 1,1 - dihetero - substituted allenes (**1**) are most useful for the introduction of acrylate functionality.[2,3] Marino's reagent (**2**), prepared via hex - 1 - ynylcopper and ethyl 2 - bromoacrylate, deserves particular mention.[2]

We considered that the anions (**1**, X=O⁻) should be available from α-keto-carboxylic acids (Y=O⁻), -esters (Y=OR¹), or -carboxamides (Y=N̄R¹) via the Shapiro reaction[4] (Scheme 1). The preparation and use of α - bromo - α,β - unsaturated esters would thereby be avoided. The α - keto - acids (**3**),[5] ethyl pyruvate, and α - keto - amides (**4** and **5**) were converted into their respective 2,4,6 - tri - iso - propylbenzenesulphonylhydrazones[6] (trisylhydrazones)[7] (55–100%). The superiority of trisylhydrazones in the Shapiro reaction is emphasised elsewhere.[7,8] Secondary α - keto - amide trisylhydrazones (**6** and **7**) are especially attractive being readily available from the reaction of cyclohexyl or methyl isonitrile with acetyl or hexanoyl chloride,[9] water, and 2,4,6 - tri - iso - propylbenzenesulphonylhydrazine in sequence, usually in one pot.

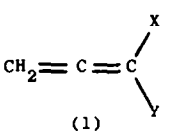
The attempted metallation of ethyl pyruvate trisylhydrazone (**9**) using lithium di - iso - propylamide followed by n- or t-butyllithium were unsuccessful. Only the adducts (**12a** and **b**) (**32**, 31%) were formed. Attempted metallation of the α - keto - acid trisylhydrazones (**10**) gave intractable mixtures. Since the primary α - keto - amide trisylhydrazone (**11**) gave only 2 - diazoheptanamide (**13**) (54%), clearly C–H deprotonation could not have taken place.

Although the Shapiro reaction could not be applied to α - keto - esters or -acids, secondary α - keto - amides proved versatile precursors. The trisylhydrazones (**6a** and **7a** and **b**) but not (**6b**) reacted cleanly (Scheme 1, Y=N̄–c–C_6H_{11} or N̄Me) with n-butyllithium at −78° in 1,2 - dimethoxyethane to give the trianions (**14a** and **b** and **15**) as bright orange solutions or suspensions. Formation of trianion (**14a**) was authenticated by allylation or propylation giving trisylhydrazones (**8a**; 70%) and (**8b**; 38%). In general, trianion (**14a**) alkylations were unsatisfactory: trisylhydrazone (**8b**) was accompanied by hydroxy - trisylhydrazone (**8c**; 14%). It is most reasonable that (**8c**) was formed via electron transfer and the aza-ene (**16**).

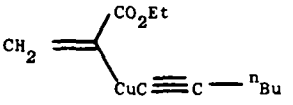
On warming up to 25°, the orange trianions (**14a** and **b** and **15**) decomposed. As expected the self-indicating sequential loss of the arenesulphinate anion and nitrogen gave the allenic dianions (**17** and **18a** and **b**) as pale yellow suspensions. It is most reasonable to assume allenic character since the cation is lithium.[10] The allenic dianions (**17** and **18a** and **b**) were efficiently captured by deuterium oxide, aldehydes, or ketones giving adducts (**19**; 59–82%), (**20**; 21–62%) and (**21**; 34–64%). Formation of the deuterio-acrylamide (**19a**) was accompanied by a minor product (7%) possibly the trisylhydrazone dimer (**22**). Acetone and hexadeuterio - acetone partially protonated (38%) (or deuterated 24%) dianion (**18a**). Dianion (**18a**) gave exclusively the E - deuterio - amide (**20a**) or *Z*-hydroxy - alkylamide (**20c**) with deuterium oxide or acetone respectively. The assignment of geometry clearly followed from the NMR spectra; the proton *cis* to the amide substituent resonated at lower field than the *trans*. Exclusive formation of the *Z*-isomer of **20c** is consistent with steric approach control.[10] Since the deuterio-amide (**20a**) was exclusively *trans*, we suspect that deuteration of dianion (**18a**) occurred initially on nitrogen thereby permitting a later transition state. Reactions of dianions (**18a** and **b**) with propenal (exclusive 1,2-addition), propanal and 2,2 - dimethyl - 4R - formyl - 1,3 - dioxolan[11] gave mixtures of the *E* and *Z* geometric isomers



Scheme 1.



(1)



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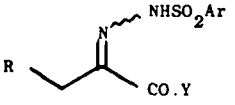
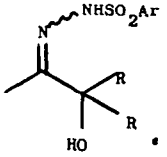


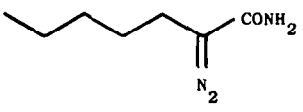
$RCH_2CO.CO.Y$

(3a) R = H, Y = OH
(3b) R = $^{n}C_{13}H_{27}$, Y = OH
(4) R = ^{n}Bu, Y = NH_2
(5a) R = H, Y = NH-c-C_6H_{11}
(5b) R = ^{n}Bu; Y = NH-c-C_6H_{11}
(5c) R = H, Y = NHMe
(5d) R = ^{n}Bu, Y = NHMe

(6a) R = H, Y = NH-c-C_6H_{11}
(6b) R = H, Y = NHMe
(7a) R = ^{n}Bu, Y = NH-c-C_6H_{11}
(7b) R = ^{n}Bu, Y = NHMe
(8a) R = CH_2=$CHCH_2$, Y = NH-c-C_6H_{11}
(8b) R = ^{n}Pr, Y = NH-c-C_6H_{11}
(8c) R = OH, Y = NH-c-C_6H_{11}
(9) R = H, Y = OEt
(10a) R = H, Y = OH
(10b) R = $^{n}C_{13}H_{27}$, Y = OH
(11) R = ^{n}Bu, Y = NH_2

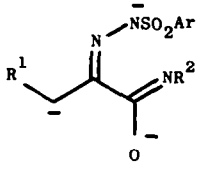


(12a) R = ^{n}Bu
(12b) R = ^{t}Bu

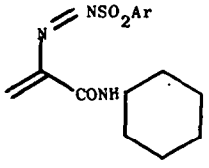


(13)

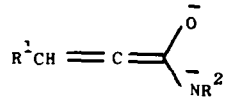
Ar = 2,4,6-(^{iso}Pr)$_3C_6H_2$



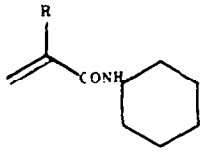
(14a) R^1 = H, R^2 = c-C_6H_{11}
(14b) R^1 = ^{n}Bu, R^2 = c-C_6H_{11}
(15) R^1 = ^{n}Bu, R^2 = Me



(16)



(17) R^1 = H, R^2 = c-C_6H_{11}
(18a) R^1 = ^{n}Bu, R^2 = c-C_6H_{11}
(18b) R^1 = ^{n}Bu, R^2 = Me



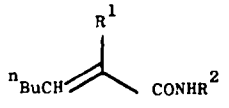
(19a) R = D
(19b) R = CH_2OH
(19c) R = CH(OH)Et
(19d) R = CH(OH)CH=CH_2
(19e) R = C(OH)Me_2
(19f) R = CH(OH)dlox
(19g) R = H

(*E*:*Z*, 4:3–4:1). By analogy[12] the principle diastereoisomer produced from 2,2 - dimethyl - 4R - formyl - 1,3 - dioxolan and dianions (**17** and **18b**) was assigned as erythro. erythro.

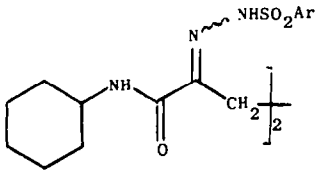
The dianion intermediates (**23** and **24**) (either used *in situ* or prepared by deprotonation of **19d**, **21a** or **21b**) reacted rapidly with electrophiles at the alkoxide substituent and more slowly on the amide nitrogen. Thus, the derivatives (**25** and **26**) (55–81%) were readily obtained.

Attempted hydrolyses of the adducts (**19d**, **20e** or **21b**) were unsuccessful; (**19d**) and methanolic potassium hydroxide gave (**27**) (72%) and all other reactions intractable mixtures or starting materials. The tertiary amides (**26b** and **d**) reacted with iodine in aqueous tetrahydrofuran[13] to give the expected iodolactones (**28a**) 32% based on **7b** *E*:*Z*, 2:1) and **28b** (77% based on **21b**, *E* ≫ *Z*).

The allenic dianions (**17** and **18**) are clearly versatile intermediates. The Shapiro reaction provides the most convenient synthesis of such acrylate precursors. Application to the construction of β-lactams[14] and the obtusilactones[15] are current objectives.

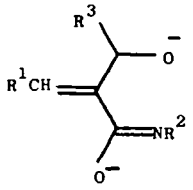


(20a) R^1 = D, R^2 = c-C_6H_{11}
(20b) R^1 = H, R^2 = c-C_6H_{11}
(20c) R^1 = C(OH)Me_2, R^2 = c-C_6H_{11}
(20d) R^1 = (C(OH)$(CD_3)_2$, R^2 = c-C_6H_{11}
(20e) R^1 = CH(OH)CH=CH_2, R^2 = c-C_6H_{11}
(21a) R^1 = CH(OH)Et, R^2 = Me
(21b) R^1 = CH(OH)CH=CH_2, R^2 = Me
(21c) R^1 = CH(OH)diox, R^2 = Me

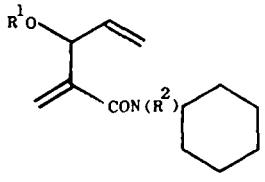


(22)

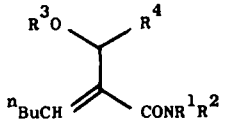
diox-CHO = 2,2-dimethyl-4R-formyl-1,3-dioxolan

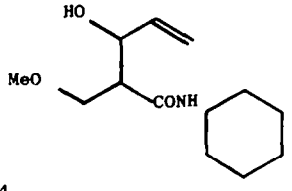


(23) R^1 = H, R^2 = c-C_6H_{11}, R^3 = CH=CH_2
(24a) R^1 = ^{n}Bu, R^2 = Me, R^3 = Et
(24b) R^1 = ^{n}Bu, R^2 = Me, R^3 = CH = CH_2



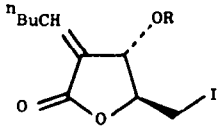
(25a) R^1 = R^2 = Me
(25b) R^1 = ^{t}BuMe$_2$Si;
R^2 = Me
(25c) R^1 = ^{t}BuMe$_2$Si, R^2 = H





(26a) R^1 = R^2 = R^3 = Me, R^4 = Et
(26b) R^1 = R^2 = R^3 = Me, R^4 = CH=CH_2
(26c) R^1 = R^3 = Me, R^2 = H, R^4 = CH=CH_2
(26d) R^1 = R^2 = Me, R^3 = ^{t}BuMe$_2$Si, R^4 = CH=CH_2

(27)



(28a) R^1 = Me
(28b) R^1 = ^{t}BuMe$_2$Si

EXPERIMENTAL

IR spectra were recorded as Nujol mulls or liquid films. NMR spectra were recorded in $CDCl_3$. All reagents and solvents were thoroughly purified by standard methods.[16] All reactions were carried out under argon; bath temps are recorded. Work up refers to evaporation, dilution with water and extraction (2x) with organic solvent, drying (Na_2SO_4) and rotary evaporation. Chromatography refers to flash chromatography[17] on Merck Kieselgel H using a solvent gradient (the weight of adsorbent is given in parenthesis). Plc was carried out on Merck Kieselgel GF_{254}. DME refers to 1,2-dimethoxethane.

Preparation of trisylhydrazones

The ketone, 2,4,6 - tri - iso - propylbenzenesulphonylhydrazine[6] (0.95–1.05 equiv) and as catalyst, conc HCl (method A) or Amberlite IR-120 (H) resin (method B) or no catalyst (method C) were stirred at 25° until complete reaction. Evaporation and recrystallisation gave: *ethyl 2-oxopropanoate* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* **9** (method B) (86%), m.p. 135–7° (from aqueous EtOH), ν_{max} 3230, 1710, and 1705 cm^{-1}, δ 2.05 (3H, s, MeC=N) and 8.48 (1H, br, s), *m/e* 396 (M^+) and 189 (base) (Found: C, 60.54; H, 8.28; N, 7.20. $C_{20}H_{32}N_2O_4S$ Requires: C, 60.58; H, 8.13; N, 7.06%); *2-oxohexadecanoic acid* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* (**10b**) (method A) (100%), oil, ν_{max} 3700–2500, 3200, 1695 and 1602, δ 2.3–2.7 (2H, m, CH_2C=N), 8.35–8.55 (1H, s), and 8.75–8.85 (1H, s), *m/e* 268 and 251 (base) (Found: C, 67.58; H, 9.93; N, 5.05. $C_{31}H_{54}N_2O_4S$ Requires: C, 67.59; H, 9.88; N, 5.08%) *2-oxopropanoic acid* 2,4,6 - *tri - iso - propylbenzenesulpnonylhydrazone* (**10a**) (method C) was obtained as an impure solid m.p. 142° (from diethyl ether and light petroleum), ν_{max} 3250–3190, 3200–2300 and 1700 cm^{-1}, δ 2.1 (3H, s, MeC=N), 8.75–9.25 (2H, br, m), *m/e* 323 $(M-CO_2H)^+$ and 189 (base); *2-oxoheptanamide* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* (**11**) (method A) (95%), m.p. 141–147° (from aqueous MeOH), ν_{max} 3475, 3255, 3200 and 1695 cm^{-1}, δ 2.35–2.65 (2H, m, 3-CH_2), 5.5–5.8 and 6.5–6.7 (2H, m, NH_2), and 8.7–9.0 (1H, m, NH), *m/e* 268 and 189 (base) (Found: C, 62.65; H, 8.99; N, 10.00; $C_{22}H_{37}N_3O_3S$ Requires: C, 62.38; H, 8.80; N, 9.92%); N-*cyclohexyl - 2 - oxopropanamide* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* (**6a**) (method B) (93%), m.p. 161–3° (from aqueous MeOH), ν_{max} 3410, 3155 and 1655 cm^{-1}, δ 2.02 (3H, s, 3-Me), and 6.4–6.8 (1H, m, NHCO), *m/e* 449 (M^+) and 204 (base) (Found: C, 64.04; H, 8.82; N, 9.36. $C_{24}H_{39}N_3O_3S$ Requires: C, 64.11; H, 8.74; N, 9.35%).

N-*Cyclohexyl - 2 - oxoheptanamide* 2,4,6 - *Tri - iso - propylbenzenesulphonylhydrazone* (**7a**)

n-Hexanoyl chloride (1.36 g) and cyclohexyl isonitrile (1.09 g) were heated together at 65° for 50 min and cooled to 0°. Aqueous (6 ml) acetone (6 ml) was added and after 2 hr at 0° to 25° general work up [diethyl ether] and azeotropic evaporation with toluene (2 × 10 ml) gave the crude (**5b**). This (method A) gave the *amide trisylhydrazone* (**7a**) (4.30 g, 85%), m.p. 140–3° (from aqueous EtOH), ν_{max} 3380, 3130 and 1637 cm^{-1}, δ 2.1–3.1 (3H, m, 3-CH_2, p-$CHMe_2$), 6.4–6.7 (1H, m, NHCO), 7.15 (2H, s), and 8.3–8.6 (1H, m, NNH), *m/e* 267 and 189 (base) (Found: C, 66.50; H, 9,51; N, 8.35. $C_{28}H_{47}N_3O_3S$ Requires: C, 66.50; H, 9.37; N, 8.31%).

N - *Methyl - 2 - oxoheptanamide* 2,4,6 - *Tri - iso - propylbenzenesulphonylhydrazone* (**7b**)

In the same way, methyl isonitrile (0.63 g) and n-hexanoyl chloride (1.35 g) gave the *amide sulphonylhydrazone* (**7b**) (3.95 g, 91%), m.p. 174–80° (from aqueous MeOH), ν_{max} 3390, 3130, 1658 and 1656 cm^{-1}, δ2.3–3.1 (3H, m, 3-CH_2, p-$CHMe_2$), 2.77 (3H, d, J 4.5 Hz, NMe), 6.4–6.8 (1H, m, NHCO), and 9.5 (1H, s, NNH), *m/e* 438 $(M+H)^+$, and 189 (base) (Found: C, 63.25; H, 9.12; N, 9.56. $C_{23}H_{39}N_3O_3S$ Requires: C, 63.12; H, 8.98; N, 9.60%).

N - *Methyl - 2 - oxopropanamide* 2,4,6 - *Tri - iso - propylbenzenesulphonylhydrazone* (**6b**)

Methyl isonitrile (0.46 g) and acetyl chloride (813 mg) in CH_2Cl_2 (1 ml) were refluxed for 30 min and cooled to 0°. Aqueous (7.5 ml) THF (7.5 ml) was added, followed after 70 min by MeOH (20 ml), 2,4,6 - tri - iso - propylbenzenesulphonylhydrazine (3.07 g) and conc HCl (2 drops). After 70 min, dilution with water precipitated a solid. This was washed with water and light petroleum, chromatographed (20 g, eluant CH_2Cl_2: Et_2O 1:0–0:1) and crystallised from aqueous MeOH to give the *amide sulphonylhydrazone* **6b** (2.15 g, 55%), m.p. 174°, ν_{max} 3415, 3050 and 1667 cm^{-1}, δ 2.0 (3H, s, 3-Me), 2.77 (3H, d, J 5 Hz, NMe), 6.5–6.8 (1H, m, NHCO), and 8.37 (1H, s, NNH), *m/e* 268 and 189 (base) (Found: C, 59.76; H, 8.27; N, 10.99. $C_{19}H_{31}N_3O_3S$ Requires: C, 59.81; H, 8.19; N, 11.01%).

Reaction of the ester sulphonylhydrazone (**9**) *with lithium di - iso - propylamide and n - butyllithium*

The ester **9** (397 mg) was dissolved in DME (5 ml) and the soln cooled to −75°. Lithium di - iso - propylamide [from di - iso - propylamine (0.20 ml) and n-BuLi (1.3 M, 1.0 ml) in DME (2 ml)] was added, and the light yellow soln treated with n-BuLi (1.3 M, 2.2 ml). The orange soln was warmed to −68° over 15 min, recooled to −78° and treated with 1 - bromohexane (0.60 ml). The orange soln was warmed to −60° over 3 hr, quenched with glacial AcOH (0.32 g) in water (2 ml) and warmed up to 25°. Work up (CH_2Cl_2), chromatography (20 g, eluant CH_2Cl_2) and plc (1 development with CH_2Cl_2: Et_2O 9:1) gave 3 - (*n - butyl*) - 3 - *hydroxyheptan - 2 - one* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* **12a** (146 mg, 32%) m.p. 146–8° (from EtOH and water), ν_{max} 3480, 3225, 1170, 1158, 1050 and 1042 cm^{-1}, δ 0.5–1.8 (18H, m), 1.28 (18H, 2d, J 7 Hz), 1.76 (3H, s, 1-Me), 2.9 (1H, septet, J 7 Hz), 3.8 (1H, s, OH), 4.24 (2H, septet, J 7 Hz), 7.16 (2H, s) and 7.9 (1H, s, NH) *m/e* 466 (M^+) 409, 267, 186, 143 (base), 127, and 57 (Found: C, 66.83; H, 9.82; N, 5.89. $C_{26}H_{46}N_2O_3S$ Requires: C, 66.91; H, 9.93; N, 6.00%).

Reaction of the ester sulphonylhydrazone (**9**) *with lithium di - iso - propylamide and t - butyllithium*

As in the previous example, reaction of **9** (388 mg) with lithium di - iso - propylamide and t - BuLi followed by allyl bromide and work up gave E, Z - 3 - *t - butyl - 4,4 - dimethyl - 3 - hydroxypentan - 2 - one* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* **12b** (142 mg, 31%), m.p. 209–210° (from aqueous MeOH), ν_{max} 3435, 3238, 1332, 1167 and 1155 cm^{-1}, δ 0.88 and 0.95 (18H, 2s, ^{t}Bu), 1.1–1.4 (18H, m), 1.85 and 2.02 (3H, 2s, 1-Me), 2.95 (1H, m), 4.3 (2H, m), 4.47 (1H, s, OH), 7.15–7.2 (2H, 2s), and 7.75 (1H, s, NH), *m/e* 463, 451, 409 (base), 367, 267, 189 and 57 (Found: C, 66.91; H, 9.83; N, 5.98. $C_{26}H_{46}N_2O_3S$ Requires: C, 66.91; H, 9.93; N, 6.00%).

Reaction of the amide sulphonylhydrazone (**11**) *with n-Butyllithium*

Compound **11** (435 mg) was dissolved in DME (10 ml) and the soln cooled to −78°. n-BuLi (1.4 M, 4.0 ml) was added, the yellow soln warmed up to 25° over 100 min and quenched with D_2O (0.50 ml). Work up (CH_2Cl_2) and chromatography (12 g, eluant Et_2O) gave *2-diazoheptanamide* **13** (86 mg, 54%) m.p. 82–4° (from CH_2Cl_2 and light petroleum), ν_{max} 3355, 3180, 2080, 1660, 1590 and 1410 cm^{-1}, δ 0.76–1.1 (3H, t, 7-Me), 1.2–1.8 (6H, m), 2.3 (2H, t, J 8 Hz, 3-CH_2), and 5.7–6.3 (2H, br s, NH), *m/e* 155 (M^+), 127, 98 (base), 59, 44 and 41 (Found: C, 54.35; H, 8.46; N, 26.83. $C_7H_{13}N_3O$ Requires: C, 54.18; H, 8.44; N, 27.07%).

Preparation of N - *cyclohexyl - 2 - oxohex - 5 - enamide* 2,4,6 - *tri - iso - propylbenzenesulphonylhydrazone* (**8a**)

Compound **6a** (443 mg) was dissolved in DME (5 ml) and the soln cooled to −76°. Lithium di - iso - propylamide (from di - iso - propylamine (0.40 ml) and n-BuLi (1.3 M, 2.0 ml) in DME (2 ml)) was added, the soln stirred for 18 min and then treated with n-BuLi (1.3 M, 4.0 ml). The orange soln was warmed to −69° over 27 min recooled to −78°, quenched with allyl bromide (0.70 ml) and stirred for 3 hr. Glacial AcOH (0.60 g) in water (2 ml) was added and the soln warmed to 25°. Work up (CH_2Cl_2, diethyl ether), chromatography (20 g, eluant CH_2Cl_2: Et_2O 1:0–9:1) and recrystallisation of the residue from aqueous MeOH gave the *amide sulphonylhydrazone* **8a** (337 mg, 70%), m.p. 153–4°, ν_{max} 3400, 3170, 1660, 1520, 1342, 1175, 1160, 910 and 681 cm^{-1}, δ 1.0–2.1 (10H, m), 1.3 (18H, 2d, J 7 Hz), 2.05–3.15 (5H, m, 3,4-CH_2, p-$CHMe_2$), 3.4–3.9 (1H, m, HCN), 4.2 (2H, septet, J

7 Hz), 4.8–6.1 (3H, m, CH=CH$_2$), 6.3–6.7 (1H, br s, NH), 7.17 (2H, s, aryl-H), and 8.0–8.5 (1H, br s, NH), *m/e* 490 $(M+H)^+$, 251, 233, 204, 189 (base), 161, 112, 83, 67 and 55 (Found: C, 66.33; H, 8.97; N, 8.58. $C_{27}H_{43}N_3O_3S$ Requires: C, 66.22; H, 8.85; N, 8.58%); and the amide sulphonylhydrazone (**6a**) (106 mg, 24%) identical (tlc and NMR) with the starting material.

Reaction of the trianion (**14a**) *with* 1-*iodopropane*

Compound **6a** (448 mg) was dissolved in DME (5 ml) and the soln cooled to −75°. n-BuLi (1.0 M, 3.5 ml) was added, the soln warmed to −68° over 20 min and recooled to −75°. 1-Iodopropane (0.20 ml) was added, the suspension stirred to −65° over 165 min, quenched with glacial AcOH (0.35 g) in water (2 ml) and warmed to 25°. Work up (CH_2Cl_2) and chromatography (18 g, eluant CH_2Cl_2:Et_2O 1:0–4:1) gave E,Z - N - *cyclohexyl* - 2 - *oxohexanamide* 2,4,6 - *tri* - *iso* - *propylbenzenesulphonylhydrazone* **8b** (184 mg, 38%) m.p. 148–9° (from diethyl ether and light petroleum), ν_{max} (CCl_4) 3420, 3200, 1675, 1600, 1515, 1505, 1465, 1455, 1428, 1385, 1365, 1332, 1165, 1155, 1105, 1090 and 906 cm^{-1}, δ 0.7–2.0 (17H, m), 1.28 (18H, d, J 7 Hz, CHMe$_2$), 2.3–2.6 (2H, m, 3-CH$_2$), 2.88 (1H, septet, J 7 Hz, p-CHMe$_2$), 3.3–3.8 (1H, m, HCN), 4.15 (2H, septet, J 7 Hz, o-CHMe$_2$), 6.3–6.6 (1H, m, amide NH), 7.2 (2H, s, aryl-H), and 8.5 (1H, br s, NNH), *m/e* 492 $(M+H)^+$, 399 250 (base), 232, 189, 161, 149 and 114 (Found: C, 65.70; H, 9.35; N, 8.47. $C_{27}H_{45}N_3O_3S$ Requires: C, 65.95; H, 9.22; N, 8.35%); the amide sulphonylhydrazone **6a** (206 mg, 46%), identical (tlc and NMR) with the starting material; and N - *cyclohexyl* - 3 - *hydroxy* - 2 - *oxopropanamide* 2,4,6 - *tri* - *iso* - *propylbenzenesulphonylhydrazone* **8c** (63 mg, 14%) m.p. 134–6° (from diethyl ether and light petroleum), ν_{max} 3360, 3170, 1645, 1175 and 1160 cm^{-1}, δ 1.0–2.0 (10H, m), 1.26 (18H, 2d, J 7 Hz, CHMe$_2$), 2.9 (1H, septet, J 7 Hz, p-CHMe$_2$), 3.3–3.8 (1H, m, HCN), 4.1 (2H, septet, J 6.5 Hz, o-CHMe$_2$), 4.72 (2H, s, 3-CH$_2$), 6.5–6.8 (1H, m, amide NH), and 7.17 (2H, s, aryl-H), *m/e* 267, 251 (base), 233, 204, 189, 169, 149 and 126 (Found: C, 61.97; H, 8.65; N, 8.93. $C_{24}H_{39}N_3O_4S$ Requires: C, 61.90; H, 8.44; N, 9.02%).

Preparation of N - *cyclohexyl* - 2 - *deuterioprop* - 2 - *enamide* (**19a**)

Compound **6a** (445 mg) was dissolved in DME (5 ml) and the soln cooled to −78°. n-BuLi (1.0 M, 4.0 ml) was added, the soln warmed up to 25° over 100 min, and D_2O (0.50 ml) was added. Work up (CH_2Cl_2), chromatography (15 g, eluant CH_2Cl_2:Et_2O 1:0–4:1) and plc 1 development in Et_2O gave the *deuterio-amide* **19a** (82 mg, 54%), m.p. 102–3° (from CH_2Cl_2 and light petroleum), ν_{max} 3285, 1640, 1620 and 1553 cm^{-1}, δ 1.0–2.2 (10H, m), 3.6–4.1 (1H, m, HCN) 5.54 (1H, s, CH$_2$=C), 6.16 (1H, s, CH$_2$=C) and 6.6–7.0 (1H, m, NH), *m/e* 154 (M^+), 126, 111, 97, 73 (base), 57, 56 and 41 *ca.* 100% monodeuterated (Found: C, 69.95; N, 9.04. $C_9H_{14}{}^2HNO$ Requires: C, 70.09; N, 9.08%) and a solid possibly the sulphonylhydrazone **22** (29 mg, 7%) m.p. 142–144° (from aqueous MeOH at 0°), ν_{max} (CCl_4) 3420, 1680, 1170, 1158 and 910 cm^{-1}, δ 1.0–2.1 (24H, m), 1.24 (36H, 2d, J 7 Hz), 6.4–6.8 (2H, m, NH) and 7.17 (4H, s, aryl-H), *m/e* 451, 358, 268, 251, 233 (base), 204, 189, 175 and 161 (Found: C, 63.81; H, 8.85; N, 9.22. $C_{48}H_{76}N_6O_6S_2$ Requires: C, 64.25; H, 8.53; N, 9.35%). A subsequent preparation from **6a** (973 mg), DME (12 ml), n-BuLi (1.3 M, 5.4 ml) gave, on warming up to 25° over 2 hr, recooling to −78° and quenching with D_2O (0.50 ml) the deuterioamide **9a** 275 mg, 82%).

Preparation of N - *cyclohexyl* - 3 - *hydroxy* - 3 - *methyl* - 2 - *methylenebutanamide* (**19e**)

Compound **6a** (452 mg) was dissolved in DME (5 ml) and the soln cooled to −78°. n-BuLi (1.0 M, 4.0 ml) was added, the orange-red soln warmed to 25° over 100 min and quenched with acetone (0.20 ml). General work up (CH_2Cl_2), chromatography (19 g, eluant CH_2Cl_2: Et_2O 1:0–0:1) and plc (Et_2O) gave the *hydroxy-amide* **19e** (126 mg, 59%) as an oil, ν_{max} 3700–3120, 1655, 1608, 1535, 1455, 1155 and 1130 cm^{-1}, δ 1.0–2.4 (10H, m), 1.4 (6H, s, 3-Me), 3.3–4.0 (1H, m, HCN), 4.7 (1H, s, OH), 5.36 (1H, s, CH$_2$=), 5.52 (1H, s, CH$_2$=), and 6.5–6.9 (1H, br, NH), *m/e* 211 (M^+), 196, 193, 150, 114, 112 (base), 83, 67, 56 and 55 (Found: C, 68.12; H, 10.12; N, 6.42. $C_{12}H_{21}NO_2$ Requires: C, 68.21; H, 10.02; N, 6.63%).

Preparation of N - *cyclohexyl* - 3 - *hydroxy* - 2 - *methylenepent* - 4 - *enamide* (**19d**)

In the same way **6a** (2.73 g), n-BuLi (18.76 mmole), DME (25 ml) and acrolein (0.70 ml) (added at −78° and solution allowed to warm up to 25°) gave on chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–1:1) the hydroxy-amide **19d** (1.03 g, 81%), m.p. 87–9° (from diethyl ether and light petroleum), ν_{max} 3500–3150, 3285, 1655 and 1615 cm^{-1}, δ 0.9–2.2 (10H, m), 3.4–4.15 (2H, m, HCN, OH), 4.9–6.3 (6H, m), and 6.4–6.9 (1H, m, NH), *m/e* 209 (M^+), 192, 191, 180 (base), 110, 98, 83 and 56 (Found: C, 68.83; H, 9.29; N, 6.56. $C_{12}H_{19}NO_2$ Requires C, 68.87; H, 9.15; N, 6.69%).

Preparation of N - *cyclohexyl* - 3 - *hydroxy* - 2 - *methylene-propanamide* (**19b**)

In the same way **6a** (1.847 g), n-BuLi (1.34 M, 9.2 ml), DME (20 ml) and paraformaldehyde (0.50 g) (added at 0° and warmed to 25° during 30 min) gave, on chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–1:1) and plc (2 developments in Et_2O), the *hydroxyamide* **19b** (446 mg, 59%), m.p. 77–78° (from diethyl ether and light petroleum), ν_{max} 3320, 3295, 1663, 1625, 1615 and 1548 cm^{-1}, δ 1.0–2.1 (10H, m), 3.65–4.2 (2H, m, HCN, OH), 4.4 (2H, d, J 6 Hz, 3-CH$_2$), 5.5 (1H, s, CH$_2$=C), 5.88 (1H, s, CH$_2$=C), and 6.7–7.15 (1H, br, s, NH), *m/e* 183 (M^+), 166, 140, 122, 102 (base), 85 and 56 (Found: C, 65.54; H, 9.37; N, 7.51. $C_{10}H_{17}NO_2$ Requires: C, 65.54; H, 9.35; N, 7.64%).

Preparation of N - *cyclohexyl* - 3 - *hydroxy* - 2 - *methylenepentanamide* (**19c**)

In the usual way, **6a** (1.434 g), DME (15 ml), n-BuLi (1.34 M, 7.5 ml) and propanal (0.40 ml) (added at −78° and soln warmed up to 25°) gave, on chromatography (19 g, eluant CH_2Cl_2:Et_2O 1:0–7:3), the *hydroxy-amide* **19c** (538 mg, 80%), m.p. 98–101° (from light petroleum then CH_2Cl_2–light petroleum), ν_{max} 3460, 3280, 1655, 1610 and 1540 cm^{-1}, δ 0.9 (3H, t, J 7 Hz, 5-Me), 1.0–2.1 (12H, m), 3.3–4.9 (3H, m, 3-CH, HCN, OH), 5.35 (1H, s, CH$_2$=C), 5.76 (1H, s, CH$_2$=C) and 6.3–7.1 (1H, m, NH), *m/e* 211 (M^+), 193, 182, 130, 112 (base), 110 and 56 (Found: C, 68.43; H, 10.03; N, 6.41. $C_{12}H_{21}NO_2$ Requires: C, 68.21; H, 10.02; N, 6.63%).

Preparation of N - *cyclohexyl* - 2 - *methylene* - 3,4,5 - *trihydroxypentanamide* 4,5 - *acetonide* (**19f**)

Compound **6a** (970 mg) was dissolved in DME (12 ml) and the soln cooled to −78°. n-BuLi (1.3 M, 5.3 ml) was added, the soln warmed to 25° over 130 min and recooled to −78°. Freshly distilled 4R - 2,2 - dimethyl - 4 - formyl - 1,3 - dioxolan[11] (0.30 ml) was added, the soln stirred for 30 min and warmed to 25°. Work up (diethyl ether), chromatography (18 g, eluant CH_2Cl_2:Et_2O 1:0–3:2) and plc. (1 development in Et_2O) gave **19g** (80 mg, 24%), ν_{max} 3280, 1653, 1618 and 1550 cm^{-1}, δ 1.0–2.1 (10H, m), 3.6–4.4 (1H, br, HCN), 5.55–5.7 (1H, 4s, 3-CH$_2$), 5.8–6.4 (1H, NH) and 6.15–6.3 (2H, 3s, 2-CH, 3-CH$_2$), *m/e* 153 (M^+), 110, 72 (base) and 55; 3S, 4R, N - *cyclohexyl* - 2 - *methylene* - 3,4,5 - *trihydroxypentanamide* 4,5 - *acetonide* **19f** (280 mg, 46%) m.p. 96–7° (from diethyl ether and light petroleum), $[\alpha]_{589}^{20}$ −7.0 (*C*=0.23, CH_2Cl_2), ν_{max} 3400, 3315, 1653, 1617 and 1545 cm^{-1}, δ 1.0–2.1 (10H, m), 1.35 (3H, s, MeCO), 1.43 (3H, s, MeCO), 3.6–4.4 (6H, br, CH$_2$CHCHOH, HCN), 5.62 (1H, s, CH=C), 5.82 (1H, s, CH$_2$=C) and 6.25–6.6 (1H, br, NH), *m/e* 283 (M^+) 268, 183, 182, 117, 101 (base) and 83 (Found: C, 63.87; H, 9.07; N, 4.83. $C_{15}H_{25}NO_4$ Requires: C, 63.58; H, 8.89; N, 4.94%); and 3R, 4R - N - *cyclohexyl* - 2 - *methylene* - 3,4,5 - *trihydroxypentanamide* 4,5 - *acetonide* **19f** (87 mg, 14%), m.p. 80–1° (from diethyl ether and light petroleum), $[\alpha]_{589}^{20}$ −37° (C = 0.225, CH_2Cl_2), ν_{max} 3430, 3360, 1658, 1620, 1612 and 1528 cm^{-1}, δ 1.0–2.1 (10H, m), 1.35 (3H, s, MeCO), 1.45 (3H, s, MeCO), 3.4–3.6 (1H, m, OH), 3.7–4.4 (5H, m, CH$_2$CHCH, HCN), 5.55 (1H, s, CH$_2$=), 5.95 (1H, s, CH$_2$=) and 6.7–6.9 (1H, br, NH), *m/e* 283 (M^+), 268, 183, 182, 144, 101 (base), 100 and 83 (Found: C, 63.84; H, 9.12; N, 4.79. $C_{15}H_{25}NO_4$ Requires: C, 63.58; H, 8.89; N, 4.94%).

Preparation of E - (N - *cyclohexyl*) - 2 - *deuteriohept* - 2 - *enamide* (**20a**)

Compound **7a** (507 mg) was dissolved in DME (5 ml) and the

soln cooled to −78°. n-BuLi (1.34 M, 3.6 ml) was added, the soln warmed to −50° over 40 min, to 25° over 110 min, recooled to −70°, quenched with D_2O (0.50 ml) and warmed to 25°. Work up (diethyl ether), chromatography (20 g, eluant CH_2CH_2:Et_2O 1:0–9:1) and plc (1 development in CH_2CH_2:Et_2O 16:1) gave the E - *deuterio* - *amide* **20a** (130 mg, 62%) m.p. 106–9° (from diethyl ether and light petroleum), ν_{max} 3290, 1654, 1620 and 1547 cm^{-1}, δ 0.7–1.1 (3H, br, 7–CH₃), 1.1–3.0 (16H, m), 3.4–4.2 (1H, m, HCN), 5.8–6.4 (1H, m, NH) and 6.75 (1H, br t, J 6 Hz, CH=), *m/e* 210 (M^+), 181, 167, 153, 129 (base), 112 and 56, *ca.* 100% monodeuteriated (Found: C, 74.46; H, 11.24; N, 6.66. $C_{13}H_{22}{}^2HNO$ Requires: C, 74.24; N, 6.66%).

Preparation of N - *cyclohexyl* - 2 - (2 - *hydroxyprop* - 2 - *yl)hept* - 2 - *enamide* (**20c**)

Compound **7a** (502 mg) was dissolved in DME (6 ml) and the soln cooled to −78°. n-BuLi (1.34 M, 5.0 ml) was added and the orange soln warmed up to 25° over 155 min. The resulting yellow soln was recooled to −78°, quenched with acetone (0.40 ml) and warmed up to 25°. Work up (diethyl ether), chromatography (21 g, eluant CH_2Cl_2:Et_2O 1:0–9:1) and plc (developed in CH_2Cl_2:Et_2O 4:1), gave E - N - *cyclohexylhept* - 2 - *enamide* **20b** (80 mg, 38%), m.p. 108–110° (from diethyl ether and light petroleum), ν_{max} 3295, 1665, 1620, 1547 and 984 cm^{-1}, δ 0.75–2.6 (19H, m), 3.5–4.1 (1H, m, HCN), 5.4–6.6 (1H, m, NH), 5.7 (1H, d, J 15 Hz, 2–CH) and 6.78 (1H, dt, J 15, 7 Hz, 3–CH), *m/e* 209 (M^+), 180, 166, 152, 128 (100%), 111 and 55 (Found: C, 74.35; H, 11.23; N, 6.67. $C_{13}H_{23}NO$ Requires: C, 74.59; H, 11.07; N, 6.69%); and the Z-*hydroxyamide* (**20c**) (56 mg, 21%), m.p. 73–4° (from diethyl ether and light petroleum), ν_{max} 3360, 3290, 1648, 1615, 1540, 1355 and 1168 cm^{-1}, δ 0.7–1.1 (3H, m, 7–Me), 1.1–2.5 (16H, m), 1.5 (6H, s, MeCO), 3.4–4.0 (1H, m, HCN), 4.1 (1H, br s, OH), 5.4–5.9 (1H, m, NH) and 5.63 (1H, t, J 7 Hz, HC=C), *m/e* 267 (M^+), 252 (base), 249, 206, 168, 153 and 82 (Found: C, 72.05; H, 11.22; N, 5.29. $C_{16}H_{29}NO_2$ Requires: C, 71.86; H, 10.93; N, 5.24%).

Preparation of N - *cyclohexyl* - 2 - (1 - *hydroxyprop* - 2 - *enyl)hept* - 2 - *enamide* (**20e**)

In the same way, **7a** (512 mg), DME (6 ml), n-BuLi (1.34 M, 5 ml) and acrolein (0.35 ml) gave, on chromatography (21 g, eluant CH_2Cl_2:Et_2O 1:0–9:1), the E,Z - *hydroxy* - *amide* **20e** (135 mg, 51%) as an oil, ν_{max} 3290, 1655, 1610, 1540 and 1448 cm^{-1}, δ 0.7–2.4 (19H, m), 3.3–4.2 (1H, m, HCN), 4.5–4.8 (1H, m, OH), 4.93–6.5 (4H, m, vinyl H including 6.4 J 7 Hz, E 3–CH) and 6.55–7.15 (1H, m, NH), *m/e* 265 (M^+), 248, 247, 234 (base), 128 and 55 (Found: C, 72.12; H, 10.52; N, 5.05. $C_{16}H_{27}NO_2$ Requires: C, 72.41; H, 10.25; H, 5.28%).

Preparation of Z - (N - *cyclohexyl*) - 2 - (*hexadeuterio* - 2 - *hydroxyprop* - 2 - *yl)hept* - 2 - *enamide* (**20d**)

In the same way, **7a** (507 mg), DME (5 ml), n-BuLi (1.34 M, 5.0 ml) and d_6-acetone (0.35 ml; added at −65°), gave, on chromatography (21 g, eluant CH_2Cl_2:Et_2O 1:0–9:1) and plc (2 developments in CH_2Cl_2:Et_2O 9:1) gave the E- **20a** (51 mg, 24%) and the Z- **20d** (104 mg, 38%), m.p. 77–79° (from Et_2O–light petroleum), ν_{max} 3360, 3280, 2220, 1645, 1610 and 1540 cm^{-1}, δ 0.7–2.5 (19H, m), 3.4–4.2 (1H, m, HCN), 4.13 (1H, br s, OH), 5.44–6.0 (1H, br s, NH) and 5.64 (1H, t, J 7 Hz, HC=C), *m/e* 273 (M^+), 253 (base), 212, 156, 89 and 56 (Found: C, 70.48; N, 5.10. $C_{16}H_{23}{}^2H_6NO_2$ Requires: C, 70.28; N, 5.12%).

Preparation of 2 - (1 - *hydroxypropyl*) - N - *methylhept* - 2 - *enamide* (**21a**)

In the same way, **7b** (440 mg), DME (10 ml), n-BuLi (1.34 M, 3.8 ml) and propanal (0.20 ml) gave, on chromatography (18 g, eluant CH_2Cl_2:Et_2O 1:0–3:2) and plc (3 developments in Et_2O), an oil probably the E:Z (4:3) - *hydroxy* - *amide* **21a** (128 mg, 64%), ν_{max} 3320, 1665, 1620 and 1550 cm^{-1}, δ 0.75–1.1 (6H, m), 1.1–1.9 (6H, m, 2'–CH_2, 5,6–CH_2), 2.0–2.4 (2H, m, 4–CH_2), 2.8 (3H, 2d, J 4.5 Hz, NMe), 4.0–6.5 (3H), 4.0 (t, J 7 Hz, Z1'–CH), 4.1–4.4 and 4.8–5.2 (2m, OH), 4.55 (t, J 7 Hz, E1'–CH), 5.6 (t, J 8 Hz, Z CH=C), 6.35 (t, J 8 Hz, E CH=C) and 6.8–7.1 and 7.4–7.7 (1H, 2m, NH), *m/e* 199 (M^+) 181, 170 (base) 139, 112, 81, 67 and 59 (Found: M^+ 199.1573. $C_{11}H_{21}NO_2$ Requires: M^+ 199.1572). A sample of **21a** (195 mg) was dissolved in THF (10 ml) and the soln cooled to −78°. n-BuLi (1.3 M, 1.8 ml) was added, the soln was warmed to 25°, quenched with MeI (3.0 ml) and stirred for 4 d. Work up (diethyl ether), chromatography (16 g, eluant Et_2O:CH_2Cl_2 0:1–1:4) and plc (2 developments with Et_2O) gave N,N - *dimethyl* - 2 - (1 - *methoxypropyl)hept* - 2 - *enamide* **26a** (141 mg, 63%) as an oil. ν_{max} 1660, 1630, 1393, 1268, 1130, 1108 and 1084 cm^{-1}, δ 0.8–1.1 (6H, m, MeCH₂), 1.1–1.55 (4H, m, 6,5, –CH_2), 1.6–1.9 (2H, m, 2'–CH_2), 2.15–2.4 (2H, m, 4–CH), 2.95 (6H, s, NMe_2), 3.25 (3H, s, OMe), 3.9 (1H, t, J 7 Hz, 1'–CH) and 5.45 (1H, 2t, J 8 Hz, CH=C, E and/or Z?), *m/e* 227 (M^+), 212, 195 (base), 112 and 88 (Found: C, 69.02; H, 11.42; N, 6.11. $C_{13}H_{25}NO_2$ Requires: C, 68.68; H, 11.08; N, 6.16%).

Preparation of 2 - (1 - *hydroxyprop* - 2 - *enyl*) - N - *methylhept* - 2 - *enamide* (**21b**)

Hydrazone **7b** (879 mg) was suspended in DME (24 ml) and cooled to −78°. n-BuLi (1.34 M, 10.0 ml) was added, the suspension warmed to −30° over 75 min, to 25° over 40 min, recooled to −62°, quenched with acrolein (0.65 ml) and warmed to 25°. Work up (diethyl ether), chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–1:1) and plc (developed in Et_2O) gave the E,Z - *hydroxy* - *amide* **21b** (198 mg, 50%) as an oil, R_f 0.35, 0.33 (diethyl ether), ν_{max} 3320, 1655, 1610, and 1548 cm^{-1}, δ 0.7–1.1 (3H, m, 7–CH_3), 1.10–1.65 (6H, m, 5,6–CH_2), 1.9–2.5 (2H, m, 4–CH_2), 2.8 (3H, 2d, J 5 Hz, NMe), 4.6–4.9 (1H, m, OH), 4.9–6.6 (4H, m, CH_2=CHCH), 5.65 (t, J 7 Hz, Z 3–CH), 6.4 (t, J 7 Hz, E 3–CH) and 6.4–7.55 (1H, m, NH), *m/e* 197 (M^+), 180, 168, 166 (base), 140, 99 and 58 (Found: C, 66.51; H, 9.92; N, 6.65; M^+, 197.1412. $C_{11}H_{19}NO_2$ Requires: C, 66.97; H, 9.71; N, 7.10%; M^+, 197.1416).

Preparation of N,N - *dimethyl* - 2 - (1 - *methoxyprop* - 2 - *enyl)hept* - 2 - *enamide* (**26b**)

Compound **7b** (876 mg) was suspended in DME (20 ml) and the suspension cooled to −78°. n-BuLi (1.34 M, 10.0 ml) was added, the suspension was warmed to 25° over 2 hr, recooled to −78° and quenched with acrolein (0.60 ml). n-BuLi (1.34 M, 6.0 ml) was added, the soln warmed to 25° over 20 min, quenched with MeI (5.0 ml) and stirred for 3 d. Work up (diethyl ether) and chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–4:1) gave the E:Z (2:1) - *hydroxy* - *amide* **26** (266 mg, 59%) as an oil, ν_{max} 1635 cm^{-1}, δ 0.75–1.05 (3H, m, 7–CH_3), 1.05–1.7 (4H, m, 5,6–CH_2), 1.8–2.5 (2H, m, 4–CH_2), 3.0 (6H, br s, NMe_2), 3.32 (3H, br s, MeO), 4.3–4.5 (2H), 4.32 (d, J 8 Hz, Z 1'–CH), 4.5 (d, J 8 Hz, E 1'–CH) and 5.05–6.2 (4H, m, CH=C), *m/e* 225 (M^+), 210, 194, 180 (base), 121, 72 and 71 (Found: C, 69.19; H, 10.42; N, 5.97. $C_{13}H_{23}NO_2$ Requires: C, 69.29; H, 10.29; N, 6.22%).

Preparation of N - *methyl* - Z - 2 - (*pentylidene*) - 3,4,5 - *trihydroxypentanamide* 4,5 - *acetonide* (**21c**)

Compound **7b** (878 mg) was suspended in DME (20 ml) and the suspension cooled to −78°. n-BuLi (1.22 M, 11.0 ml) was added, the suspension was warmed to 25° over 110 min, quenched with 4R - 2,2 - dimethyl - 4 - formyl - 1,3 - dioxolan[11] (0.40 ml) and stirred for 10 min. Work up (diethyl ether), chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–3:2) and plc (3 developments in Et_2O) gave 3S,4R - N - *methyl* - Z - 2 - (*pentylidene*) - 3,4,5 - *trihydroxypentanamide* 4,5 - *acetonide* **21c** (116 mg, 21%) m.p. 68–9° (from diethyl ether and petroleum), $[\alpha]_{589}^{20}$ + 17° (C=0.13, CH_2Cl_2), ν_{max} 3345 and 3150, 1655, 1620, 1505, 1418, 1342, 1312, 1268, 1218, 1158, 1062, 1033 and 854 cm^{-1}, δ 0.8–1.1 (3H, br, MeCH₂), 1.2–1.6 (4H, m), 1.4 (6H, 2s, MeCO), 2.1–2.4 (2H, m, CH_2C=), 2.9 (3H, d, J 5 Hz, NMe), 4.05–4.35 (3H, m, 4–CH, 5–CH_2), 4.4 (1H, br t, J 7 Hz, 3–CH), 5.1 (1H, d, J 8 Hz, OH), 6.4 (1H, t, J 8 Hz, HC=) and 6.6–6.90 (1H, m, NH), *m/e* 272 (M + H)$^+$ 256, 171, 170 (base), 101 and 58 (Found: C, 61.71; H, 9.33; N, 5.06. $C_{14}H_{25}NO_4$ Requires: C, 61.97; H, 9.29; N, 5.16%); and an oil probably containing isomeric **21c** (69 mg, 13%), ν_{max} 3210, 1670, 1625, 1550 and 1068 cm^{-1}, δ 0.8–1.1 (3H, m, MeCH₂) 1.2–1.6 (4H, m), 1.38 (6H, m, MeCO), 2.0–2.45 (2H, m, CH_2C=), 2.90 (3H, overlapping d, J 4 Hz, NMe), 3.5–4.5 (3H, m, 4–CH, 5–CH_2), 4.65–4.75 and 5.75–6.0 (1H, m, 3–CH), 6.00–6.45 and 7.2–7.6 (1H, br, NH) and 6.55, 6.65 and 6.8 (1H, 3t, HC=), *m/e* 272 (M^+ + H), 271 (M^+), 256, 171, 170 (base), 141, 111 and 101.

Preparation of N - *cyclohexyl* - 3 - *hydroxy* - 2 - (*methoxymethyl*)*pent* - 4 - *enamide* (**27**)

Hydroxy-amide **19d** (134 mg) and powdered KOH (152 mg) were suspended in MeOH (2 ml) and the soln stirred for 14 d. Work up (AcOH, diethyl ether) and plc (1 development in Et_2O) gave the *hydroxy* - *amide* **17** (111 mg, 72%) m.p. 84° (from Et_2O and light petroleum), ν_{max} 3280, 1630, 1550 and 1118 cm^{-1}, δ 1.00–2.05 (10H, m), 2.1–2.6 (1H, m, 2–CH), 3.3 (3H, s, MeO), 3.6 (2H, d, J 6 Hz, MeOCH_2), 3.6–4.8 (2H, m, HCN, OH) and 4.9–6.6 (5H, m, CH_2=CHCH, NH), *m/e* 241 (M^+), 226, 224, 184 (base), 154, 104, 72 and 57 (Found: C, 64.65; H, 9.76; N, 5.80. $C_{13}H_{23}NO_3$ Requires: C, 64.70; H, 9.61; N, 5.81%).

Preparation of (±) - 4,5 - *trans* E,Z - 5 - *iodomethyl* - 4 - *methoxy* - 3 - *pentylidenetetrahydrofuran* - 2 - *one* (**28a**)

Compound **7b** (2.143 g) was suspended in DME (40 ml) and the suspension cooled to −78° n-BuLi (1.34 M, 25 ml) was added, the suspension warmed to 25° over 2 h, recooled to −78°. and quenched with acrolein (1.0 ml). The soln was stirred for 10 mm, quenched with MeI (10.0 ml), warmed to 25° and stirred for 3 d. Work up (diethyl ether) and chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–7:3) gave the crude **26b**. I_2 (1.35 g) was added, the mixture suspended in THF (20 ml) and water (20 ml), stirred for 15 hr and saturated with sodium thiosulphate. Work up (diethyl ether) chromatography (20 g, eluant CH_2Cl_2) and plc (1 development in CH_2Cl_2) gave the *Z-iodolactone* **28a** (164 mg, 10%) as an oil, ν_{max} (CCl_4) 1775, 1678, 1470, 1370, 1195, 1180, 1132, 1116, 1082 and 1000 cm^{-1}, δ 0.65–0.95 (3H, m, MeCH_2), 1.05–1.6 (4H, m), 2.50–2.85 (2H, m, CH_2C=), 3.2 (3H, s, MeO), 3.2–3.45 (2H, m, CH_2I), 4.15 (1H, br d, J 4.5 Hz, 4–CH), 4.35–4.6 (1H, m, 5–CH) and 6.43 (1H, t, J 7 Hz, HC=), *m/e* 324 (M^+) 292, 197 (base), 165, 154 and 84 (Found: C, 40.97; H, 5.43. $C_{11}H_{17}IO_3$ Requires: C, 40.76; H, 5.28%); and the E-*iodolactone* **20a** (345 mg, 22%) as an oil, ν_{max} 1770, 1680, 1182, 1145, 1112, 1102, 1082, 1056, 1002, 732 cm^{-1}, δ 0.7–1.1 (3H, m, MeCH_2), 1.20–1.75 (4H, m), 2.45 (2H, *ca.* q, J 8 Hz, CH_2C=), 3.38 (3H, s, OMe), 3.4–3.6 (2H, m, CH_2I), 4.5–4.75 (2H, m, 4–CH, 5–CH) and 6.88 (1H, t, J 8 Hz, HC=), *m/e* 324 (M^+), 292, 282, 197 (base), 165, 154 and 84 (Found: M^+ 324.0223. $C_{11}H_{17}IO_3$ Requires: M^+, 324.0224).

Preparation of N - *cyclohexyl* - 3 - *methoxy* - N - *methyl* - 2 - *methylenepent* - 4 - *enamide* (**25a**)

Hydroxy-amide **19d** (255 mg) was dissolved in THF (6 ml) and the soln cooled to −78°. n-BuLi (1.34 M, 2.0 ml) was added, the soln warmed to 25° over 15 min, quenched with MeI (1.0 ml) and stirred for 2 d. Evaporation and chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–7:3) gave the *methoxy* - *amide* **25a** (235 mg, 81%) as an oil, ν_{max} 1620, 1457, 1413, 1085 and 925 cm^{-1}, δ 1.0–2.0 (10H, m), 2.80 (3H, s, NMe), 3.30 (3H, s, OMe), 4.1–4.55 (1H, m, HCN) and 4.9–6.0 (6H, m, HC=, 3–CH) *m/e* 237 (M^+), 222 (base), 206, 162, 140, 124, 112 and 55 (Found: C, 70.58; H, 9.94; N, 5.75. $C_{14}H_{23}NO_2$ Requires: C, 70.85; H, 9.77; N, 5.90%).

Preparation of 2 - (1 - *methoxyprop* - 2 - *enyl*) - N - *methylhept* - 2 - *enamide* (**26c**)

E, Z-Hydroxy-amide **21b** (138 mg) and t-BuOK (78 mg) were suspended in CH_2Cl_2 (5 ml) and MeI (5 ml). The suspension stirred for 40 min and then evaporated. Purification by plc (2 developments in Et_2O) gave mainly the E - *methoxy* - *amide* **26c** (81 mg, 55%) as an oil, ν_{max} 3370, 1670, 1630 and 1540 cm^{-1}, δ 0.73–1.1 (3H, m, MeCH_2), 1.15–1.6 (4H, m), 1.93–2.55 (2H, m, CH_2C=), 2.8 (3H, d, J 4.5 Hz, NMe), 3.33 (3H, s, OMe), 4.63–6.26 (4H, m, CH_2=CHCH), 6.7–7.4 (1H, m, NH) and 6.93 (1H, t, J 7.5 Hz, 2–C=CH), *m/e* 211 (M^+), 196, 180, 179, 166 (base) 71 and 58 (Found: C, 68.18; H, 10.20; N, 6.70. $C_{12}H_{21}NO_2$ Requires C, 68.21; H, 10.02; N, 6.63%).

Preparation of 3 - (*t* - *butyldimethylsilyloxy*) - N - *cyclohexyl* - N - *methyl* - 2 - *methylenepent* - 4 - *enamide* (**25b**)

Hydroxy-amide **19d** (62 mg) was dissolved in THF (5 ml) and the soln cooled to −78°. n-BuLi (1.34 M, 0.60 ml) was added, the soln warmed to 25°, recooled to −78° and then quenched with t-butylchlorodimethylsilane (103 mg) in THF (5 ml). The soln was warmed to 60° for 30 min, cooled to 25°, quenched with MeI (4.0 ml) and stirred for 3 d. Work up (CH_2Cl_2) and plc (3 developments in CH_2Cl_2:Et_2O 9:1) gave the derived **25c** (77 mg, 80%) as an oil, ν_{max} 3330, 1655, 1610 and 1528 cm^{-1}, δ 0.07 (3H, s, MeSi), 0.10 (3H, s, MeSi), 0.90 (9H, s, ^{t}Bu), 1.0–2.05 (10H, m), 3.5–4.0 (1H, m, HCN), 4.9–6.1 (5H, m, CH_2=CHCH, 2–C=CH), 5.9 (1H, m, 2–C=CH) and 6.5–6.85 (1H, m, NH), *m/e* 323 (M^+), 308 and 266 (base), 184 and 75. A sample of **25c** (74 mg) was dissolved in THF (5 ml). NaH (40 mg, excess) was added, the suspension stirred for 10 min, treated with MeI (3 ml) and stirred for 3 d. Work up (CH_2Cl_2) gave the *silyl* - *amide* **25b** (77 mg, 100%) as an oil, ν_{max} 1650, 1624 and 1072 cm^{-1}, δ 0.07 (6H, s, MeSi), 0.92 (9H, s, ^{t}Bu), 1.0–2.1 (10H, m), 2.8 (3H, s, NMe), 3.3–3.9 (1H, m, HCN), 4.96–6.0 (3H, m, CH_2=CH), 5.0 (1H, s, 2–C=CH), 5.15 (1H, d, J 16 Hz, 3–CH) and 5.3 (1H, s, 2–C=CH), *m/e* 337 (M^+), 322, 280, 198, 73 and 55 (Found: C, 67.83; H, 10.75; N, 4.34. $C_{19}H_{35}NO_2Si$ Requires: C, 67.60; H, 10.45; N, 4.15%).

Preparation of 2 - [(*t* - *butyldimethylsilyloxy*)*prop* - 2 - *enyl*] - N,N - *dimethylhept* - 2 - *enamide* (**26d**)

Hydroxy-amide (*E*:*Z*- ratio high) **21b** (567 mg) was dissolved in THF (20 ml) and the soln cooled to −78°. n-BuLi (1.4 M, 5.0 ml) was added, the soln warmed to 25° and then recooled to −78°. t-Butylchlorodimethylsilane (1.0 g) in THF (4 ml) was added, the soln was warmed to reflux for 30 min and then evaporated. Work up (diethyl ether) gave a crude residue which was dissolved in THF (20 ml). NaH (1.5 g, excess) and imidazole (1 crystal) were added, the suspension treated with MeI (15 ml) stirred for 5 d and quenched with water (15 ml). Work up (CH_2Cl_2) and chromatography (20 g, eluant CH_2Cl_2:Et_2O 1:0–9:1) gave mainly the E - (*vide infra*)*silyl* - *amide* **26d** (717 mg, 77%) as an oil, ν_{max} 1630, 1390, 1080, 1065, 838 and 778 cm^{-1}, δ 0.05 (6H, s, MeSi), 0.7–1.05 (3H, br, MeCH_2), 0.86 (9H, s, ^{t}Bu), 1.1–1.6 (4H, m), 2.0–2.5 (2H, m, CH_2C=), 3.05 (6H, s, NMe_2) and 5.0–6.6 (5H, m, HC=, 3–CH), *m/e* 325 (M^+), 310, 268 (base), 180, 102 and 73 (Found: C, 66.60; H, 11.11; N, 4.24. $C_{18}H_{35}NO_2Si$ Requires: C, 66.40; H, 10.84; N, 4.30%).

Preparation of (±) - 4,5 - trans - 4 - (*t* - *butyldimethylsilyloxy*) - 5 - *iodomethyl* - 3 - *pentylidenetetrahydrofuran* - 2 - *one* (**28b**)

Silyl-amide (*E* ≫ *Z*) **26d** (211 mg) was dissolved in THF (5 ml) and water (4 ml). I_2 (0.50 g) was added and the soln stirred for 20 hr. Work up (sodium thiosulphate soln, diethyl ether) and chromatography (20 g, eluant CH_2Cl_2 1:0–1:1) gave mainly the E - *iodo* - *lactone* **28b** (202 mg, 70%) as an oil, ν_{max} 1774, 994 and 835 cm^{-1}, δ 0.1 (3H, s, SiMe), 0.2 (3H, s, SiMe), 0.8–1.05 (3H, m, MeCH_2), 0.9 (9H, s, ^{t}Bu), 1.1–1.7 (4H, m), 2.35 (2H, q, J 8 Hz, CH_2C=), 3.3–3.55 (2H, m, CH_2I), 4.4 (1H, m, 5–CH), 4.96 (1H, d, J 4 Hz, 4–CH) and 6.7 (1H, t, J 8 Hz, HC=), *m/e* 424 (M^+), 423, 409, 367, 297, 240 (base), 211 and 197 (Found: C, 45.62; H, 7.04; $(M-H)^+$, 423.0847. $C_{16}H_{29}IO_3Si$ Requires: C, 45.28; H, 6.89%; $(M-H)^+$, 423.0854).

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