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Synthesis of γ-Hydroxy α,β-Unsaturated Amides by Base-Induced Isomerization of Epoxy Amides

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Abstract: Treatment of 3,4-epoxyamides with LDA affords γ-hydroxy-α,β-unsaturated amides, usually with high *(E)*-selectivity. The 3,4-epoxyamides were prepared by the epoxidation of β,γ-unsaturated amides with *meta*-chloroperbenzoic acid. © 1998 Elsevier Science Ltd. All rights reserved.

The contiguous trifunctionality of γ-hydroxy α,β-unsaturated amides is found in a variety of natural products, including the macrocyclic anti-inflammatory depsipeptide salinamide B.[1] The enzymatic oxidation of porphobilinogen by porphobilinogen oxidase affords a cyclic γ-hydroxy α,β-unsaturated amide;[2] related systems formed during the photooxidation of *tert*-butylpyrroles are relevant to phototherapy used in the treatment of neonatal jaundice.[3] Related is the saturated and conformationally constrained γ-hydroxy amide portion of the antibiotic TAN-868A whose geometry resembles the *(E)*-4-hydroxy-2-alkenamides herein prepared. Additionally, many macrolide antibiotics such as cytochalasin B[4b,5] possess a γ-hydroxy α,β-unsaturated ester unit of defined alkene geometry, and the ability to synthesize aza analogues (*i.e.* γ-hydroxy α,β-unsaturated amidic units) could usefully enhance the therapeutic potential of the former compounds.

The chiral hydroxymethine unit attached to the β-position of γ-hydroxy α,β-unsaturated amides can have a powerful stereodirecting influence on 1,4-additions,[6] and the contiguous trifunctionality provides versatility as synthetic intermediates. Despite this, routes to γ-hydroxy α,β-unsaturated amides are neither extensive nor of established generality. They have been prepared by the reaction of aldehydes with sulfoxonium ylides, but the latter depends upon the availability of the appropriate isocyanate.[7] Another route uses hydrogenation over Lindlar's catalyst of γ-hydroxy alkynamides, but the latter were prepared by metallation of an alkyne and reaction with methyl chloroformate, an addition that proceeded typically in 40% or lower yields.[8] One γ-hydroxy α,β-unsaturated amide was prepared by the cobalt(II) porphyrin catalyzed monohydration of an α,β,γ,δ-unsaturated amide.[9]

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This manuscript is dedicated to Professor Alan Katritzky on the occasion of his 70th birthday

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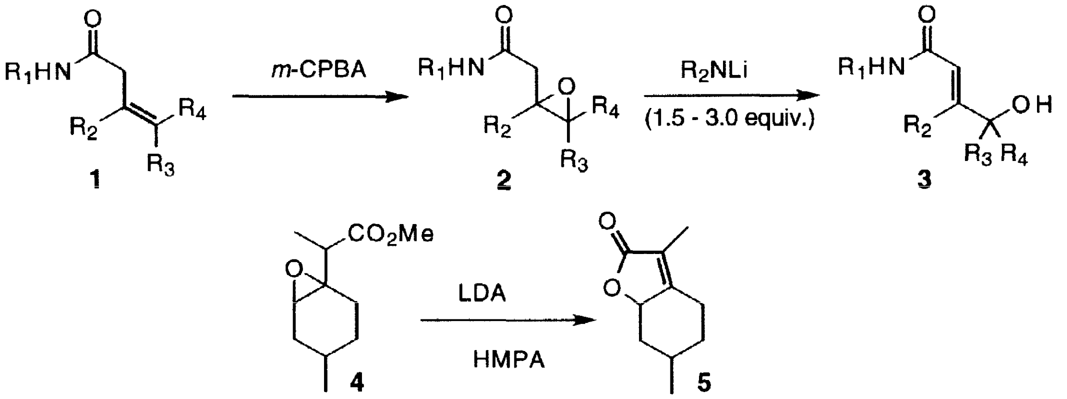
We describe here a new two-step synthesis of γ-hydroxy α,β-unsaturated amides from β,γ-unsaturated amides (Scheme 1). The route does not require any particular substitution or functionality, unlike the best alternative route which uses specifically the *N*-methoxy-*N*-methyl substituent;[10] the NH hydrogen atom(s) of primary or secondary amides does not interfere with the epoxide cleavage. The procedures are simple, and *(E)*-stereoselectivity is preferred or exclusive (Table 1). The required α-deprotonation, effected by the acidity of the carboxamide group, runs contrary to the normal regioselectivity of ring-opening of unfunctionalized unsymmetrical epoxides,[11] which arises by proton abstraction at the *less* (or least) substituted carbon atom, owing to the substantial steric requirements of the base.[11b] While an analogy can be drawn with isolated examples of the base-induced opening of epoxy esters,[12] the present work discloses a useful *distinction*: the epoxy amides afford amidic products, *not lactams*, when the *(Z)*-amides are formed. In contrast, the esters are prone to cyclization to the lactones (*e.g.* **4** to **5**).[12b] Unlike the present work with amides, there appears to be no report of the formation of the corresponding *(Z)*-hydroxy unsaturated esters by means of epoxide cleavage.

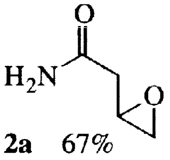
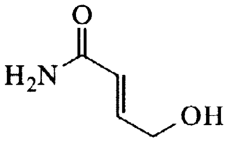
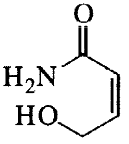
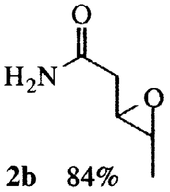
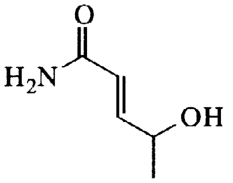
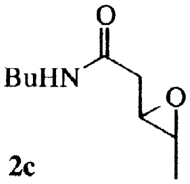
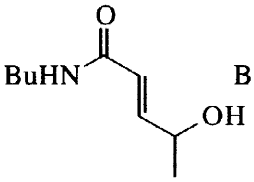
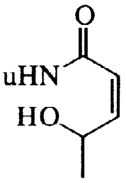
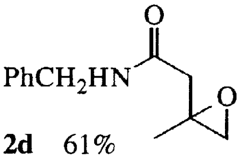
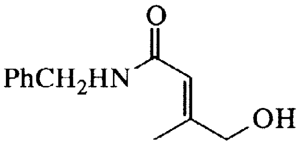
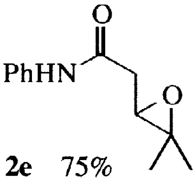
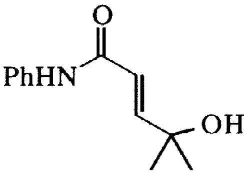
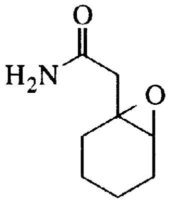
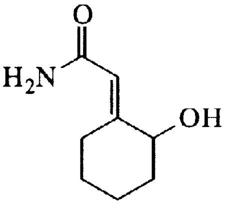
Scheme 1



The conditions to give satisfactory yields of products in part reflect the relative ease of deprotonation of the epoxy amide, and in part the thermodynamic stability of the γ-hydroxy α,β-unsaturated amide. The effect of steric hindrance is seen in entry 4, as compared with the unsubstituted epoxide in entry 1. Comparison of entry 4 with entry 5 indicates that substitution at the β-position hinders access of the base; that is supported by entry 6, requiring a long reaction period owing to β-substitution (as part of the cyclohexane ring). For entry 6, when the reaction was performed at 0 °C or above, nucleophilic displacements occurred, resulting in a much lower yield of **3f** (20%). In contrast with entry 1, entry 3 shows that the *(Z)-isomer can be obtained in substantial quantity simply by using a bulky N-substituent.* The assignments of the *(E)*- and *(Z)*-isomers of the 4-hydroxy-2-alkenamides were consistent with the expected larger coupling constants for the *trans*-alkenic hydrogen atoms (17.0 Hz and 14.0 Hz for amides ***(E)*-3a** and ***(Z)*-3a** respectively; and 14.5 Hz and 12.0 Hz, for the amides ***(E)*-3c** and ***(Z)*-3c**.

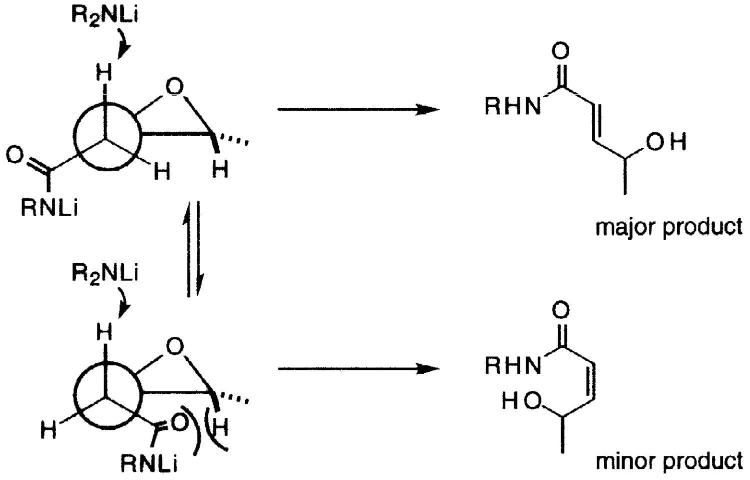
The base-promoted isomerization of epoxides provides a useful route to a variety of alcohols, though not invariably allylic alcohols,[13] and in acyclic cases there can be less positional control of deprotonation, resulting in mixtures. Allylic epoxides typically gave 1:1 *(E)*:*(Z)* mixtures.[13,14] Both solvent[15] and the nature

Table 1. Preparation of 4-Hydroxy-2-alkenamides from 3,4-Epoxy Amides

	3,4-Epoxy amides	Temperature (°C)	Time (h)	4-Hydroxy-2-alkenamides (isolated yields)
1.	 **2a** 67%	0	2	 ***(E)*-3a** 63%  ***(Z)*-3a** 9%
2.	 **2b** 84%	-84	5.5	 **3b** 83%
3.	 **2c** 80%	-78	1.5	 ***(E)*-3c** 67%  ***(Z)*-3c** 24%
4.	 **2d** 61%	15	26	 **3d** 47%
5.	 **2e** 75%	15	4	 **3e** 83%
6.	 **2f** 67%	-10	168	 **3f** 62%

of the base[16] can be crucial in obtaining regioselective product formation; in benzene at reflux, 1-methyl-1-cycloheptene oxide affords a mixture of two allylic alcohols and 2-methylcycloheptanone.[15] In contrast, the epoxy amides in Table 1 isomerize to products of a single constitution in every case, as with epoxy amides, but differ from the latter in that *(Z)*-stereoisomers have been isolated, and in their reluctance to form lactams. The *trans*-selectivity can be rationalized by invoking a concerted process of *syn*-deprotonation and ring opening (Scheme 2).[12,17]

Scheme 2



In conclusion, an efficient and simple route to γ-hydroxy α,β-unsaturated amides has been developed that depends upon the carboxamide group overriding the usual kinetic deprotonation of unsymmetrical epoxides. No protective groups are required, and the process is more general than most methods that have been previously described.

EXPERIMENTAL

General: All melting points were determined on a microscope hot-stage apparatus. ^{1}H and ^{13}C NMR spectra were run on a Bruker AM-250 instrument at 250 and 68.8 MHz respectively. Microanalytical data were obtained on a Perkin Elmer 2400 CHN elemental analyser. Mass spectra were obtained on a Kratos MS-25 or Fisons Prospec 3000 instrument. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR instrument. Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualized using an alkaline $KMnO_4$ spray or by ultraviolet light. Flash column chromatography was performed using Sorbsil C60 40/60A silica gel. Petroleum ether (40-60 fraction) and ethyl acetate were distilled before use; tetrahydrofuran was distilled over sodium and benzophenone; dichloromethane was distilled over calcium hydride. Evaporation refers to the removal of solvent under reduced pressure.

3-Butenamide,[18] *(E)*-3-pentenamide,[19] and 4-methyl-3-pentenenitrile,[20] and cyclohexene-1-acetamide[21] were prepared according to literature procedures.

Preparation of 3-Alkenoic acids: General Procedure. To a solution of the 3-alkenenitrile (0.12 mol) in dichloromethane (50 mL) cooled in an ice-bath were added 30% w/v aqueous hydrogen peroxide (0.60 mmol), tetra-*n*-butylammonium iodide (0.60 mol), and an aqueous solution of 20% w/v sodium hydroxide (0.36 mol). The mixture was allowed to warm to 20 °C and vigorously stirred. Progress of the reaction was monitored by TLC; when the nitrile could no longer be detected, the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL) to remove the phase transfer catalyst. The aqueous layer was acidified with dilute hydrochloric acid, extracted with dichloromethane (5 x 30 mL) and the combined organic layers dried (Na_2SO_4). Evaporation of the solvent afforded the 3-alkenoic acid.

***(E)*-3-Pentenoic acid.** (*E*)-3-Pentenenitrile was hydrolyzed over 5 days as described above to give ***(E)*-3-pentenoic acid** as a clear yellow liquid (84%) bp 192-200 °C/760 mmHg), (lit bp[22] 66 °C/4 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.68 (3H, dd, *J* = 6.0, 1.0 Hz), 3.06 (2H, dd, *J* = 6.0, 1.5 Hz), 5.45-5.68 (2H, m), 11.80 (1H, bd s); ^{13}C NMR ($CDCl_3$) δ 17.8 (q), 37.8 (t), 121.9 (d), 130.0 (d), 179.0 (s).

3-Methyl-3-butenoic acid. 3-Methyl-3-butenenitrile was hydrolyzed over 6 days as described above to give **3-methyl-3-butenoic acid** as a clear colourless liquid (38%), bp 90-95 °C /53mmHg), (lit bp[23] 85 °C/20 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.82 (3H, t, *J* = 2.0 Hz), 3.06 (2H, s), 4.90 (2H, dt, *J* = 15.5, 2.0 Hz), 10.92 (1H, bd s); ^{13}C NMR ($CDCl_3$) δ 22.3 (q), 43.1 (t), 115.3 (s), 137.9 (t), 178.0 (s).

4-Methyl-3-pentenoic acid. 4-Methyl-3-pentenenitrile was hydrolyzed over 72 h as described above to give **4-methyl-3-pentenoic acid** as a clear yellow liquid (68%), bp 160-162 °C/53 mmHg), (lit bp[24] 101-102 °C/10 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.63 (3H, d, *J* = 1.5 Hz), 1.74 (3H, d, *J* = 1.5 Hz), 3.06 (2H, dt, *J* = 7.0, 1.5 Hz), 5.27 (2H, tt, *J* = 7.0, 1.5 Hz), 11.20 (1H, bd s); ^{13}C NMR ($CDCl_3$) δ 23.9 (q), 25.6 (q), 33.6 (t), 115.0 (d), 136.2 (s), 179.2 (s).

***N*-Butyl-(*E*)-3-pentenamide (1c).** To well-stirred (*E*)-3-pentenoic acid (3.90 g, 39.0 mmol) was added dropwise thionyl chloride (11.7 g, 98 mmol) over 5 min. The mixture was heated at 50 °C for 2 h, then allowed to cool and excess thionyl chloride removed under vacuum. The (*E*)-3-pentenoyl chloride so prepared was added in small portions with vigorous shaking after each addition, to a mixture of butylamine (2.90 g, 40 mmol) and 5% w/v aqueous sodium hydroxide (60 mL, 75 mmol). The aqueous layer was then extracted with dichloromethane (4 x 30 mL), the combined organic layers were dried (Na_2SO_4) and the solvent evaporated to give **amide 1c** as a cream solid (3.60 g, 58%), mp 32-35 °C (from butyl ether-petroleum ether); ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, *J* = 7.0 Hz), 1.26-1.50 (4H, m), 1.71 (3H, dd, *J* = 6.0, 1.5 Hz) 2.93 (2H, d, *J* = 6.0 Hz), 3.21 (2H, q, *J* = 6.5 Hz), 5.44-5.70 (3H, m). HRMS (EI) *m/e* calcd for $C_9H_{17}NO$ 155.1310, found 155.1316 (M^+).

***N*-(Benzyl)-3-methyl-3-butenamide (1d).** To a solution of 3-methyl-3-butenoic acid (0.60 g, 6.0 mmol) in dichloromethane (10 mL) cooled in an ice-bath was added dropwise oxalyl chloride (1.50 g, 12 mmol) in dichloromethane (10 mL) over 10 min. The mixture was stirred at 0 °C for 30 min then allowed to warm to 20 °C and stirred overnight. Evaporation gave a residue of 3-methyl-3-butenoyl chloride which was added in portions with vigorous shaking after each addition, to a mixture of benzylamine (0.77 g, 7.2 mmol) and 10% w/v aqueous sodium hydroxide (20 mL, 50 mmol). The precipitate was filtered and dried to give a pale yellow solid (0.54 g). The aqueous layer was then acidified and extracted with dichloromethane (4 x 30 mL), the combined organic layers were dried (Na_2SO_4) and evaporated to give a white solid (0.53 g). The two samples were combined and recrystallized from water to give **amide 1d** as white prisms (0.97 g, 86%) mp 43-45 °C; IR (nujol) 3285, 1640, 895 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.69 (3H, s), 2.88 (2H, s), 4.28 (2H, d, *J* = 6.0 Hz), 4.81 (2H, d, *J* = 12.5 Hz), 7.03 (1H, bd s), 7.11-7.26 (5H, m); ^{13}C NMR ($CDCl_3$) δ 22.4 (q), 43.6 (t), 46.1 (t), 115.7 (s), 127.5 (d), 127.7 (d), 127.7 (d), 128.7 (d), 128.7 (d), 138.2 (t), 140.2 (t) , 170.5 (s); LRMS (EI) *m/e* 189 (M^+, 14%), 174 (8), 91 (100); HRMS (EI) *m/e* calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1157 (M^+).

N-Phenyl-4-methyl-3-pentenamide (1e). To a solution of 4-methyl-3-pentenoic acid (1.0 g, 8.8 mmol) in dichloromethane (10 mL) cooled in an ice-bath was added dropwise oxalyl chloride (2.8 g, 22 mmol) in dichloromethane (10 mL) over 10 min. The mixture was stirred at 0 °C for 30 min then allowed to warm to 20 °C and stirred for 16 h. Evaporation gave 4-methyl-3-pentenoyl chloride which was added in portions, with vigorous shaking after each addition, to a mixture of aniline (0.90 g, 9.6 mmol) and 10% w/v aqueous sodium hydroxide (20 mL, 50 mmol). The precipitate was filtered and dried to give **amide 1e** as needles (1.4 g, 83%) mp 109-110 °C (from diethyl ether-petroleum ether) (lit. mp[25] 101 °C); ^{1}H NMR (CDCl$_3$) δ 1.71 (3H, d, J = 1.5 Hz), 1.84 (3H, d, J = 1.5 Hz), 3.11 (2H, d, J = 7.0 Hz), 5.38 (1H, tt, J = 7.0, 2.2 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.31 (2H, t, J = 8.0 Hz), 7.42 (1H, bd s), 7.49 (2H, d, J = 8.0 Hz).

3,4-Epoxybutanamide (2a). To a solution of 3-butenamide[18] (0.28 g, 3.3 mmol) in dichloromethane (10 mL) cooled in an ice-bath was added dropwise *meta*-chloroperbenzoic acid (0.84 g, 4.9 mmol) dissolved in dichloromethane (20 mL) over 10 min. The ice-bath was then removed and the mixture heated at reflux for 48 h. Evaporation gave a residue which was purified by column chromatography on silica using ethyl acetate eluent to afford **amide 2a** as prisms (0.22 g, 67%), mp 57-58 °C (from ethyl acetate-petroleum ether); IR (nujol) 3205, 1670, 865 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.27 (1H, dd, J = 15.0, 7.0 Hz), 2.38 (1H, dd, J = 15.0, 4.0 Hz), 2.54 (1H, t, J = 8.0 Hz), 2.89 (1H, t, J = 8.0 Hz), 3.23 (1H, ddd, J = 12.5, 4.5, 2.5 Hz), 6.32 (1H, bd s), 6.46 (1H, bd s); ^{13}C NMR (CDCl$_3$) δ 39.2 (t), 47.1 (t), 48.7 (d), 172.8 (s). Anal. Calcd for $C_4H_7NO_2$.0.5 H_2O: C, 43.73 H, 7.32; N, 12.72%; found: C, 43.83 H, 7.33; N, 12.28%.

***trans*-3,4-Epoxypentanamide (2b).** To a solution of *(E)*-3-pentenamide[19] (0.50 g, 5.0 mmol) in dichloromethane (5 mL) cooled in an ice-bath was added dropwise *meta*-chloroperbenzoic acid (1.74 g, 10.0 mmol) dissolved in dichloromethane (22 mL) over 20 min. The ice-bath was then removed and the mixture stirred at 20 °C for 2 days. The mixture was then cooled in an ice-bath for 10 min, potassium fluoride (0.87g, 15 mmol) added, and the suspension kept in the ice-bath for a further 10 min. The solid was filtered and the filtrate evaporated to give a residue which was purified by column chromatography on silica (ethyl acetate eluent) to give **amide 2b** as microprisms (0.49 g, 84%), mp 94-95 °C (from ethyl acetate-petroleum ether); IR (nujol) 3200, 1645, 855 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.32 (3H, d, J = 6.0 Hz), 2.29 (1H, dd, J = 15.5, 7.0 Hz), 2.65 (1H, dd, J = 15.5, 4.5 Hz), 2.86-2.92 (1H, m), 2.95-3.01 (1H, m), 5.72 (1H, bd s) 6.01 (1H, bd s); ^{13}C NMR (CDCl$_3$) δ 17.3 (q), 38.8 (t), 55.0 (d), 55.6 (d), 172.5 (s). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17%; found: C, 52.10; H, 7.68; N, 11.93%.

***trans*-N-Butyl-3,4-epoxypentanamide (2c).** To a solution of *N*-butyl-*(E)*-3-pentenamide (**1c**) (2.0 g, 13 mmol) in dichloromethane (15 mL) cooled in an ice-bath was added dropwise *meta*-chloroperbenzoic acid (4.50 g, 26.0 mmol) dissolved in dichloromethane (50 mL) over 20 min. The ice-bath was then removed and the mixture stirred for 20 °C at 40 h. Evaporation gave a residue which was purified by column chromatography on silica (1:1 ethyl acetate:petroleum ether as eluent) to afford **amide 2c** as microprisms (1.80 g, 80%), mp 36-38 °C (from toluene); IR (nujol) 3095, 1645, 860 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.85 (3H, t, J = 6.5 Hz), 1.27 (3H, d, J = 5.5 Hz), 1.23-1.48 (4H, m), 2.19 (1H, dd, J = 15.5, 7.0 Hz), 2.57 (1H, dd, J = 15.5, 4.5 Hz), 2.81 (1H, dq, J = 5.0, 2.5 Hz), 2.89-2.94 (1H, m), 3.20 (2H, q, J = 6.5 Hz), 5.94 (1H, bd s); ^{13}C NMR (CDCl$_3$) δ 13.7 (q), 17.3 (q), 20.0 (q), 31.5 (t), 39.2 (t), 39.3 (t), 55.0 (d), 55.9 (d), 169.5 (s). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18%; found: C, 62.92; H, 10.25; N, 8.12%.

***N*-Benzyl-3,4-epoxy-3-methylbutanamide (2d).** To a solution of *N*-benzyl-3-methylbutenamide **(1d)** (0.31 g, 1.6 mmol) in dichloromethane (10 mL) cooled in an ice-bath was added dropwise *meta*-chloroperbenzoic acid (0.56 g, 3.3 mmol) dissolved in dichloromethane (15 mL) over 10 min. The ice-bath was then removed and the mixture stirred for 20 °C at 48 h. Evaporation gave a residue which was purified by column chromatography on silica (1:1 ethyl acetate:petroleum ether as eluent) to afford **amide 2d** as microprisms (0.20 g, 61%), mp 63-65 °C (from chloroform); IR (nujol) 3290, 1635, 1500, 895 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, s), 2.31 (1H, d, *J* = 14.0 Hz), 2.58 (1H, d, *J* = 14.0 Hz), 2.66 (2H, q, *J* = 5.0 Hz), 4.38 (2H, d, *J* = 6.0 Hz), 6.33 (1H, bd s), 7.20-7.27 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.2 (q) 43.5 (t), 43.9 (t), 54.2 (t), 55.1 (s), 127.4 (d), 127.6 (d), 127.6 (d), 128.7 (d), 128.7 (d), 138.2 (s), 169.2 (s). LRMS (EI) *m/e* 205 (M$^+$, 12%), 106 (84), 91 (100); HRMS (EI) *m/e* calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1099 (M$^+$).

***N*-Phenyl-3,4-epoxy-4-methylpentanamide (2e).** To a solution of *N*-phenyl-4-methyl-3-pentenamide **(1e)** (0.20 g, 1.06 mmol) in dichloromethane (20 mL) cooled in an ice-bath was added dropwise *meta*-chloroperbenzoic acid (0.36 g, 2.1 mmol) dissolved in dichloromethane (15 mL) over 10 min. The ice-bath was then removed and the mixture stirred at 0 °C for 48 h. Evaporation gave a residue which was purified by column chromatography on silica (1:2 ethyl acetate:petroleum ether as eluent) to afford **amide 2e** as an oily solid (0.17 g, 75%); IR ($CHCl_3$) 3140 1665, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.41 (3H, s), 2.51 (1H, dd, *J* = 15.0, 5.0 Hz), 2.73 (1H, dd, *J* = 15.0, 8.0 Hz), 3.20 (1H, dd, *J* = 7.0, 4.5 Hz), 6.90 (1H, bd s), 7.08 (1H, t, *J* = 7.0 Hz), 7.29 (2H, t, *J* = 7.5 Hz), 7.51 (2H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 18.8 (q), 24.5 (q), 37.3 (t), 59.7 (s), 60.5 (d), 120.2 (d), 124.5 (d), 124.5 (d), 129.0 (d), 129.0 (d), 137.7 (s), 168.8 (s). LRMS (EI) *m/e* 205 (M$^+$, 73%), 119 (28), 93 (100), 85 (22); HRMS (EI) *m/e* calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1099 (M$^+$).

1-(2-Acetamido)-7-oxa-bicyclo[4.1.0]heptane (2f). To a solution of 1-cyclohexene-1-acetamide[21] (0.23 g, 1.65 mmol) in dichloromethane (6 mL) cooled in an ice-bath was added dropwise *meta*-chloroperbenzoic acid (0.57 g, 3.3 mmol) dissolved in dichloromethane (15 mL) over 10 min. The ice-bath was then removed and the mixture stirred at 20 °C for 16 h. Evaporation gave a residue which was purified by column chromatography on silica (ethyl acetate as eluent) to give **amide 2f** as cream prisms (0.17 g, 67%), mp 107-108 °C (from propan-2-ol). IR (nujol) 3190, 1660, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17-1.50 (4H, m), 1.72-2.05 (4H, m), 2.31 (1H, d, *J* = 14.0 Hz), 2.58 (1H, d, *J* = 14.0 Hz), 3.11 (1H, t, *J* = 2.5 Hz), 5.59 (1H, bd s), 6.15 (1H, bd s); ^{13}C NMR ($CDCl_3$) δ 19.2 (t), 19.7 (t), 24.4 (t), 27.9 (t), 44.6 (t), 57.9 (s), 59.2 (d), 172.4 (s). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03%; found: C, 61.52; H, 8.53; N, 8.99%.

***(E)*- and *(Z)*-4-Hydroxy-2-butenamide (3a).** To a solution of freshly distilled diisopropylamine (0.40 g, 4.0 mmol) in freshly distilled THF (10 mL) under an atmosphere of nitrogen, and cooled to 0 °C in an ice-bath was added a solution of *n*-butyllithium in hexane (1.5 mL, 2.5 M, 3.8 mmol). The solution of LDA was stirred for 40 min prior to addition of amide **2a** (0.16 g, 1.6 mmol) dissolved in freshly distilled THF (15 mL). The mixture was stirred 0 °C under an atmosphere of nitrogen. Progress of the reaction was monitored by TLC; upon disappearance of the epoxide spot after 2 h, water (3.5 mL) was added and the mixture allowed to warm to 20 °C. The organic and aqueous layers were separated and the aqueous layer extracted with dichloromethane (5 x 20 mL). Propan-2-ol (20 mL) was then added to the aqueous layer which was dried

(Na_2SO_4) and the removed under rotary evaporation to give an 87:13 mixture of *(E)*- and *(Z)*-isomers of **amide (3a)** as cream microprisms (0.12 g, 72%); IR (nujol) 3350, 1680, 1590, 1100, 965 cm^{-1}; for *(E)*-**3a**: ^{1}H NMR (CD_3OD) δ 4.22 (2H, dd, *J* = 4.5, 2.5 Hz), 6.20 (1H, dt, *J* = 17.0, 2.5 Hz), 6.86 (1H, dt, *J* = 17.0, 4.0 Hz); ^{1}H NMR (CD_3OD) δ 62.1 (t), 122.8 (d), 145.7 (d), 170.9 (s): data for *(Z)*-**3a**: ^{1}H NMR (CD_3OD) δ 4.17 (2H, dd, *J* = 4.5, 2.5 Hz), 6.02 (1H, dt, *J* = 14.0, 3.0 Hz), 6.63 (1H, dt, *J* = 14.0, 4.0 Hz); ^{13}C NMR (CD_3OD) δ 62.4 (t), 128.2 (d), 142.5 (d), 175.5 (s). MS m/z (EI+) 101 (M+ 6%), 84 (M+ -OH, 41), 72 (M+ -CO -H, 100); HRMS 101.0479 ($C_4H_7NO_2$ requires 101.0477).

***(E)*-4-Hydroxy-2-pentenamide** (**3b**). To a solution of freshly distilled diisopropylamine (0.44 g, 4.3 mmol) in freshly distilled THF (15 mL) under an atmosphere of nitrogen, and cooled to 0 °C in an ice-bath was added a solution of *n*-butyllithium in hexane (2.0 mL, 2.5 M, 5.0 mmol). The solution of LDA was stirred at 0 °C for 40 min. It was then cooled in ethyl acetate/liquid nitrogen, and a solution of amide **2b** (0.20 g, 1.7 mmol) in freshly distilled THF (30 mL) added, the temperature being maintained at -84 °C for 5.5 h under an atmosphere of nitrogen. Water (5 mL) was then added and the mixture was allowed to warm to 20 °C. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (4 x 30 mL). All the organic layers were combined, dried (Na_2SO_4) and evaporated to give a yellow oil. Recrystallization afforded **amide 3b** as needles (0.114 g, 83%), mp 119-120 °C (from ethanol-dichloromethane); IR (nujol) 3370, 3185, 1670, 1575, 1145, 990 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.27 (3H, d, *J* = 6.0 Hz), 4.38 (1H, ddq, *J* = 6.0, 5.5, 1.5 Hz), 6.10 (1H, dd, *J* = 15.0, 1.5 Hz), 6.78 (1H, dd, *J* = 15.0, 5.5 Hz); ^{13}C NMR (CD_3OD) δ 22.1 (q), 66.6 (d), 118.4 (d), 152.2 (d), 170.4 (s). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17%; found: C, 52.00; H, 7.82; N, 11.87%.

***(E)*- and *(Z)*-*N*-Butyl-(*E*)-4-hydroxy-2-pentenamide** (**3c**). To a solution of amide **2c** (0.20 g, 1.2 mmol) in freshly distilled THF (6 mL) kept at -78 °C in a bath of acetone/solid carbon dioxide, and under an atmosphere of nitrogen, was added lithium diisopropylamide in hexanes (1.5 mL, 2.5 M, 3.8 mmol). The mixture was stirred at -78 °C for 1.5 h. Water (10 mL) was then added and the mixture was allowed to warm to 20 °C. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The aqueous layer was then acidified and extracted with dichloromethane (4 x 30 mL). All of the combined organic layers were dried over sodium sulfate, evaporated, and the residue subjected to chromatography on silica (1:1 ethyl acetate:petroleum ether as eluent) to give ***(E)*-amide** (**3c**) (0.137 g, 67%) as an orange oil; IR (neat) 3300, 3090, 1670, 1555, 1150, 975 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 0.91 (3H, t, *J* = 7.0 Hz), 1.31-1.55 (4H, m), 1.32 (3H, d, *J* = 7.0 Hz) 3.81 (2H, q, *J* = 6.5 Hz), 4.48 (1H, ddd, *J* = 7.0, 5.0, 1.5 Hz), 5.71 (1H, bd s), 6.00 (1H, dd, *J* = 14.5, 1.5 Hz), 6.83 (1H, dd, *J* = 14.5, 5.5 Hz); ^{13}C NMR ($CHCl_3$) δ 13.7 (q), 20.1 (t), 22.7 (q), 31.5 (t), 39.3 (t), 66.8 (d), 121.9 (d), 146.9 (d), 166.5 (s); LRMS (EI) *m/e* 171 (M^+, 28%), 153 (52), 111 (100); HRMS (EI) *m/e* calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1257; and ***(Z)*-amide** (**3c**) (47 mg, 24%) as a brown oil; IR (neat) 3300, 3090, 1655, 1560, 1060, 735 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 0.85 (3H, t, *J* = 7.0 Hz), 1.23-1.48 (4H, m), 1.26 (3H, d, *J* = 7.0 Hz), 3.22 (2H, q, *J* = 6.5 Hz), 4.68 (1H, ddq, *J* = 7.0, 5.5, 1.5 Hz), 4.78 (1H, bd s), 5.72 (1H, dd, *J* = 12.0, 1.5 Hz), 6.05 (1H, dd, *J* = 12.0, 5.5 Hz), 6.51 (1H, bd s); ^{13}C NMR ($CHCl_3$) δ 13.7 (q), 20.1 (t), 22.7 (q), 31.4 (t), 39.5 (t), 64.6 (d), 122.9 (d), 149.5 (d), 166.7 (s); LRMS (EI) *m/e* 171 (M^+, 40%), 153 (80), 110 (100); HRMS (EI) *m/e* calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1262.

***N*-Benzyl-4-hydroxy-3-methyl-2-butenamide (3d)**. To a solution of freshly distilled diisopropylamine (46 mg, 0.45 mmol) in freshly distilled THF (8 mL) under an atmosphere of nitrogen, and cooled to 0 °C in an ice-bath was added a solution of *n*-butyllithium in hexane (0.20 mL, 2.5 M, 0.5 mmol). The solution of LDA was stirred at 0 °C for 40 min prior to addition of a solution of amide **2d** (75 mg, 0.37 mmol) in freshly distilled THF (7 mL). The mixture stirred at 15 °C for 26 h, under an atmosphere of nitrogen. Water (5 mL) was then added, the organic and aqueous layers were separated and the aqueous layer extracted with dichloromethane (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to give a brown oil which was subjected to chromatography on silica (1:1 ethyl acetate:petroleum ether as eluent) to give amide **3d** as a yellow oil. Recrystallization afforded amide **3d** (35 mg, 47%) as needles, mp 142-144 °C from toluene; IR ($CHCl_3$) 3300, 1660, 1555, 1495, 1080, 850 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.81 (3H, d, *J* = 0.5 Hz), 4.15 (1H, s), 4.38 (2H, d, *J* = 6.0 Hz), 5.63 (1H, d, *J* = 0.5 Hz), 6.31 (1H, bd s), 7.18-7.30 (5H, m); ^{13}C NMR ($CHCl_3$) δ 24.3 (q), 43.7 (t), 63.9 (t), 119.7 (d), 127.6 (d), 127.8 (d), 127.8 (d), 128.8 (d), 128.8 (d), 138.2 (s), 156.6 (s), 169.2 (s); LRMS (EI) *m/e* 205 (M^+, 24%), 187 (42), 106 (55), 91 (100); HRMS (EI) *m/e* calcd for $C_{12}H_{15}NO_2$ 205.1103; found 205.1099.

***N*-Phenyl-*(E)*-4-hydroxy-4-methyl-2-pentenamide (3e)**. To a solution of freshly distilled diisopropylamine (0.24 g, 2.4 mmol) in freshly distilled THF (10 mL) under an atmosphere of nitrogen, and cooled to 0 °C in an ice-bath was added a solution of *n*-butyllithium in hexane (0.96 mL, 2.5 M, 2.4 mmol). The solution of LDA was stirred at 0 °C for 40 min prior to addition of a solution of amide **2e** (0.163 g, 0.79 mmol) in freshly distilled THF (10 mL), and the mixture stirred at 20 °C for 4 h under an atmosphere of nitrogen. Water (5 mL) was then added, the organic and aqueous layers were separated and the aqueous layer extracted with dichloromethane (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to give a solid which was recrystallized from ethyl acetate to give amide **3e** as prisms (0.12 g, 80%) mp 182-183 °C from ethyl acetate, (lit. mp[26] 173-174 °C). IR (nujol) 3270, 3140, 1680, 1600, 1550, 1135, 955 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.30 (6H, s), 6.11 (1H, d, *J* = 15.5 Hz), 6.89 (1H, d, *J* = 15.5 Hz), 7.03 (1H, t, *J* = 8.0 Hz), 7.26 (2H, t, *J* = 8.0 Hz), 7.56 (2H, d, *J* = 8.0 Hz); ^{13}C NMR ($CHCl_3$) δ 29.3 (q), 29.3 (q), 71.3 (s), 121.4 (d), 121.7 (d), 125.4 (d), 125.4 (d), 129.9 (d), 129.9 (d), 139.9 (s), 153.3 (d), 166.8 (s). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%; found: C, 70.09; H, 7.28; N, 6.78%.

2-(2-Hydroxycyclohexylidene)-acetamide (3f). To a solution of freshly distilled diisopropylamine (0.29 g, 2.9 mmol) in freshly distilled THF (10 mL) under an atmosphere of nitrogen, and cooled to 0 °C in an ice-bath was added a solution of *n*-butyllithium in hexane (1.15 mL, 2.5 M, 2.9 mmol). The solution of LDA was stirred at 0 °C for 40 min, then cooled to -10 °C, prior to addition of a solution of amide **2f** (0.18 g, 1.2 mmol) in freshly distilled THF (15 mL) and the mixture was stirred at -10 °C for 13 days under an atmosphere of nitrogen. Water (5 mL) was added, the organic and aqueous layers were separated and the aqueous layer extracted with dichloromethane (6 x 20 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated. The residue was recrystallized from dichloromethane to give **amide 3f** as cream prisms (0.115 g, 62%), mp 156-158 °C; IR (nujol) 3320, 3125, 1680, 1610, 1090, 845 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.17-1.52 (4H, m), 1.92 (1H, dq, *J* = 13.0, 2.5 Hz), 2.04 (1H, m), 2.27 (1H, tdd, *J* = 13.0, 6.5, 3.0 Hz), 2.53 (1H, m), 2.84 (1H, dt, *J* = 13.0, 5.0 Hz), 4.62 (1H, ddd, *J* = 13.0, 7.0, 1.5 Hz), 5.68 (1H, s,); ^{13}C NMR ($CHCl_3$) δ 22.5 (t), 26.6 (t), 28.2 (t), 34.4 (t), 81.5 (d), 112.3 (d), 118.2 (s), 172.1 (s); LRMS (EI) *m/e* 155 (M^+, 1%), 137 (78), 109 (100); HRMS (EI) *m/e* calcd for $C_8H_{13}NO_2$ 155.0946; found 155.0954.

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