Quinuclidine N-oxide (QNO) (1)

A magnetically stirred solution of quinuclidine (3g, 27mmol) in Et₂O (50ml) was cooled to -78°C. O₃ was passed through the solution for 3 hours (during which time a precipitate formed), before purging with N₂ for 5 minutes. The mixture was allowed to warm to ambient temperature before removing the Et₂O in vacuo affording QNO (3.26g, 95%) as a white solid to be used immediately or stored over P₂O₅ in a vacuum desiccator.

Lithiation of QNO

A suspension of QNO (0.5g, 3.94mmol) in THF (50ml) was subject to ultrasonic irradiation for 10 minutes before cooling to -78°C and adding a 1.3M solution of 'BuLi in hexane (3.33ml, 4.33mmol). The mixture was stirred at -78°C for an additional 30 minutes after which time a deep orange colour forms. Use of such a solution of Li-QNO is described in the following procedures.

Methyl 2-(nitromethyl)-3-phenylpropanoate (4)

A suspension of QNO (0.95g, 7.5mmol) in dry THF (50ml) was subject to ultrasonic radiation for 10 minutes under an atmosphere of N₂. The resulting suspension was magnetically stirred and cooled to -78°C before adding a 1.3M solution of 'BuLi in hexane (2.31ml, 3.0mmol). The solution was stirred for a further 30 minutes before adding methyl 3-nitropropanoate (2) (0.2g, 1.5mmol) in THF (2ml) and stirring at -78°C for a further 30 minutes. Benzyl bromide (0.37ml, 3.15mmol) was then added drop-wise and the resultant mixture allowed to warm to ambient temperature. Acetic acid (1ml) was added followed by water (10ml) and the phases were separated. The aqueous phase was re-extracted with Et₂O (3 x 15ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated to a yellow oil which was purified by flash column chromatography (loading and eluting with 40% ethyl acetate 60% hexane) to give afford the title product as a colourless oil (0.33g, 99%).

1H NMR (400MHz, CDCl₃) δ 7.33-7.28 (3H, m, aromatic); 7.16-7.09 (2H, m, aromatic) 4.67 (1H, dd, 1 of CH₂NO₂ J=9.0); 4.42 (1H, dd, 1 of CH₂NO₂ J=4.5); 3.74 (3H, s, OCH₃); 3.43 (1H, m, CHCO₂CH₃); 3.10 (1H, dd, 1 of CH₂Ph J=6.0); 2.79 (1H, dd, 1 of CH₂Ph J=9.0). 13C NMR (100MHz, CDCl₃) δ 172.5, 136.4, 129.0, 128.8, 127.4, 74.0, 52.5, 45.0, 35.1. IR (neat) 3076, 3056, 3023, 2955, 1739, 1550, 1494, 1435, 1376, 1245, 1200, 1172, 1099, 1075, 1040, 968, 843, 743 cm⁻¹. Acc. Mass (Cl+NH₃) calculated 241.11884, found 241.11860.

(Z)-1-(Hex-3-enyl)benzene (6)

QNO (1.94g, 15.3mmol) in THF (100ml) was lithiated under the described conditions above with 1.3M 'BuLi (2.38ml, 3.09mmol). The mixture was allowed to warm to -5°C before adding via a cannula to a suspension of the phosphonium salt (4) (1.41g, 3.07mmol) in THF (15ml) at -5°C. The resultant bright orange ylide suspension was allowed to warm to ambient temperature and stir for 2 hours before adding propionaldehyde (0.23ml, 3.26mmmol) and allowing the mixture to stir overnight. Saturated ammonium chloride (10ml) and water (50ml) were added and the phases separated. The aqueous phase was re-extracted with Et₂O (3 x 50ml) and the combined organics washed with water (50ml) and brine (50ml) before drying (MgSO₄), filtering and removing the solvents in vacuo. The crude solid was suspended in Et₂O and
triphenylphosphine oxide removed by filtration. The filtrate was concentrated in vacuo and purified by flash column chromatography (loading and eluting in hexane) affording alkene 5 as a colourless oil (0.32g, 65%).

1H NMR (400MHz, CDCl3) δ 7.14-7.33 (5H, m, aromatics); 5.35-5.43 (2H, m, CH2CHCH2); 2.60 (2H, t, PhCH2-CH2 J=7.7Hz); 2.30-2.39 (2H, m, PhCH2CH2); 1.93-2.04 (2H, m, CHCH2CH3); 0.92 (3H, t, CH3 J=6.8Hz). 13C NMR (100MHz, CDCl3) δ 142.12, 132.63, 132.29, 128.47, 128.26, 125.76, 36.14, 29.10, 20.56, 14.22. IR (neat) 3085, 3060, 3030, 3004, 2959, 2930, 2874, 2855, 1601, 1494, 1453, 1400, 1360,1329,1302, 1260, 1073, 1028, 900, 870,803, 769cm⁻¹.

Non-4-yn-2-ol (8)
A suspension of QNO (3.86g, 30.39mmol) in dry THF (100ml) was lithiated with a 1.57M solution of tBuLi in hexane (3.87ml, 6.08mmol) under identical conditions to those described above. The solution was warmed to 0°C before adding 1-hexyne (0.5g, 6.08mmol) and allowing to warm to ambient temperature. At this point the reaction mixture was cooled to -78°C before adding propylene oxide (0.44ml, 6.26mmol) and allowing the mixture to warm to ambient temperature and stir for a further 2 hours. 10% acetic acid (30ml) was added and the phases separated before re-extracting the aqueous phase with Et2O (2 x 50ml). The organics were combined and washed with water (50ml), saturated NaHCO3 (50ml) and brine (50ml) before drying (MgSO4) filtering and concentrating in vacuo to a colourless liquid (0.46g, 55%).

1H NMR (400MHz, CDCl3) δ 0.82 (3H, t, CH3CH2); 1.23 (3H, d, CH3CH(OH)CH2); 1.33-1.58 (4H, m, CH3CH2CH2); 1.85-1.99 (1H, bs, OH); 2.12 (2H, q, CH2CH2CC); 2.20-2.39 (2H, m, CCCH2CH(OH)CH3); 3.85-3.9 (1H, m CHOH).

13C NMR (100MHz, CDCl3) δ 13.91, 18.76, 22.30, 22.54, 29.82, 30.04, 31.14, 31.46, 66.93. IR (neat) 3359, 2958, 2872, 1458, 1430, 1376, 1355, 1327, 1115, 1085, 940cm⁻¹.

3-Allyl-tetrahydropyran-2-one (10)
QNO (0.45g, 3.58mmol) in THF (25ml) was lithiated with a 1.3M solution of tBuLi in hexane (2.75ml, 3.58mmol) under the previously described conditions. A 1M solution of δ-valerolactone (9) (0.67ml, 3.58mmol) in THF (3.6ml) was added over 1 hour keeping the temperature at -78°C. The resulting mixture was allowed to stir for a further 20 minutes before allyl bromide (0.37ml, 4.3mmol) in THF (2ml) was added drop-wise. The reaction mixture was then warmed to -30°C and stirred for an additional 2 hours. Saturated ammonium chloride (3ml) and water (20ml) were added and the mixture allowed to warm to ambient temperature. The phases were separated and the aqueous phase was re-extracted with DCM (3 x 25ml). The combined organic solutions were combined, dried (Na2SO4), filtered and the solvents were removed in vacuo to afford a yellow oil purified by flash column chromatography (compound pre-adsorbed onto silica using DCM, column eluted with 5% EtOAc, 95% hexane) yielding the product as a colourless oil (0.45g, 89%).

1H NMR (400MHz, CDCl3) δ 5.8-5.9 (1H, m, CH2CHCH2); 5.05-5.1 (2H, m, CH2CHCH2); 4.25-4.31 (2H, m, OCH2CH2); 2.65-2.73 (1H, m, 1 of CH2CHCH2); 2.55-2.6 (1H, m, C(O)CHCH2); 2.3-2.35 (1H, m, 1 of CH2CHCH2); 2.05-2.11 (1H, m, 1 of C(O)CHCH2); 1.90-1.95 (2H, m, OCH2CH2); 1.55 (1H, m, 1 of C(O)CHCH2). 13C NMR
(S)-3-[1,3] Dithian-2-yl-5-isopropenyl-2-methylcyclohexanone (14)

QNO (0.5g, 4.33mmol) in THF (10ml) was subject to ultrasonic radiation for 10 minutes, cooled to –78°C before adding 1.25M tBuLi in hexane (0.70ml, 0.88mmol). The mixture was stirred for 30mins at this temperature before adding 1,3-dithiane (0.104g, 0.87mmol) in THF (2ml). The mixture was allowed to warm to room temperature before cooling back down to –78°C and adding carvone (0.135g, 0.9006mmol). The mixture was allowed to warm to room temperature and stir overnight. Saturated aqueous ammonium chloride (5ml) and water (10ml) were added. The mixture was partitioned between Et₂O (10ml) and H₂O (10ml). The aqueous phase was re-extracted with more Et₂O and the organics combined and dried over MgSO₄, filtered before concentrating in vacuo to give a yellow oil. This was purified by flash column chromatography (gradient elution, hexane to 10% EtOAc in hexane), yielding the title product as a yellow oil (0.22g, 93%).

1H NMR (400MHz CDCl₃) δ 1.18 (3H, d, CH(CH₃)CO), 1.40 (3H, s, CCH₃), 1.41-2.68 (8H, m, 6 cyclohexane H’s and CH₂CH₂S), 2.75-2.88 (4H, m, 2 x SCH₂), 3.95 (1H, d, SCHS), 4.60-4.68 (2H, m, CH₂CCH₃). 13C NMR (100MHz CDCl₃) δ 21.16, 21.97, 26.06, 27.85, 30.66, 30.87, 40.77, 40.96, 41.67, 42.35, 51.80, 55.11, 112.37, 146.78. IR (neat) 3083, 2971, 2923, 2888, 1707, 1642, 1450, 1434, 1368, 1328, 1247, 1207, 1142, 1110, 1058, 960, 898, 802cm⁻¹. m/z (Cl+NH₃) (M+H)⁺ calculated 271.11902, found 271.11974.