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Article

The Preparation and Intramolecular Radical Cyclisation Reactions of Chiral Oxime Ethers

Susan E. Booth[a], *Paul R. Jenkins**[,a], *and Christopher J. Swain*[b]

[a]*Department of Chemistry, Leicester University, Leicester LE1 7RH, UK*
[b]*Merck, Sharp and Dohme, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

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O éter-oxima quiral **2** e o éster-oxima **4** foram preparados para alquilação e esterificação da oxina **1**. Hidroxiamina racêmica 6 e a hidroxiamina **10** foram sintetisadas a partir de N-hidroxipu-canimida e o álcool correspondente na presença de di etil azodicarboxilato, e os dois produtos convertidos nos éteres-oximas **7** e **11** respectivamente. As reações de ciclização radicalar intra-moleculares desses éteres e ésteres-oxima foram estudadas; a formação das alquil hidróxi-aminas **3**, **8** e **12** foi observada nas reações bem sucedidas.

Chiral oxime ether **2** and Oxime ester **4** have been prepared by alkylation and esterification of the oxime **1**. Racemic hydroxylamine **6** and chiral hydroxylamine **10** have been synthesised from N-hydroxysuccinimide and the corresponding alcohol in the presence of diethylazodicarboxylate, the two products were converted into the oxime ethers **7** and **11** respectively. The intramolecular radical cyclisation reactions of these oxime ethers and esters has been studied, successful reaction was observed to produce alkyl hydroxylamines **3**, **8** and **12**.

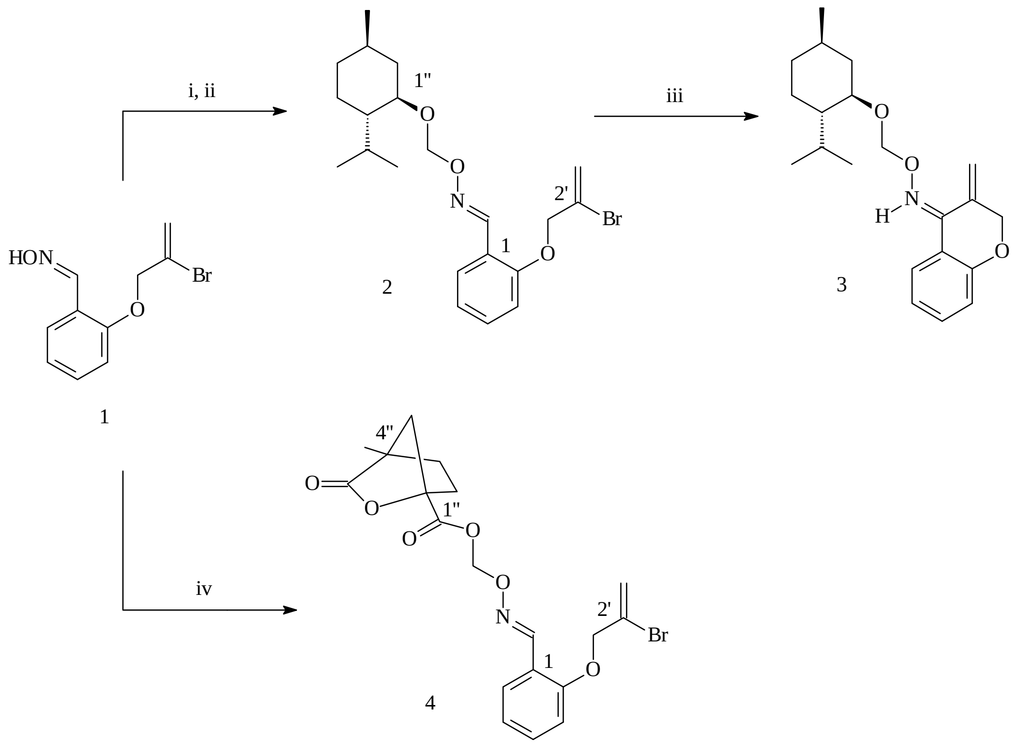
Keywords: *racemic hydroxylamines, oxime ester, intramolecular reactions, radical cyclizations, chiral oxime ether*

Introduction

The first example of the intramolecular addition of a radical to an oxime ether was published in 1983 by Corey and Pyne[1]. In this work a silyloxyalkyl radical was produced by the reaction of zinc and trimethyl silyl chloride on a carbonyl group which then attacks the oxime ether. The alkoxyaminyl radical which results from the cyclisation seems to have special stability which may be due to stabilisation of the nitrogen radical centre by the adjacent oxygen lone pair. Since this early work extensive studies have taken place in which alkyl radicals have been produced by reaction of a halide with tributyl tin hydride, or a related reductive method, which then undergo addition to the oxime ether usually, but not always in an intramolecular reaction[2]. In 1990 Enholm et al., reported the intramolecular additon of an alkenyl radical to an oxime ether, the sp^2 radical was generated by addition of Bu_3SnH to an alkyne[3]. Prompted by these studies we have recently reported a series of examples of intramolecular radical cyclisation reactions of oxime ethers[4]. An unusual rearrangement was also observed when the alkoxyamine products of the cyclisation were reduced with $LiAlH_4$ [5]. The next stage in this project was to modify the reaction to produce chiral products, we now wish to report our studies on this topic. The idea was to use a chiral hydroxylamine to produce a chiral oxime ether RCH=NOR*, nucleophilic attack on these compounds has received some attention in the literature[6], and has been the subject of a recent publication[7]. However, we know of no previous work on the addition of radicals to chiral oxime ethers of this type.

Results and Discussion

We have previously reported the use of chloromethyl menthyl ether as a chiral OH protecting group useful in the measurement of the enantiomeric excess of intermediates in a synthetic sequence[8]. In seeking new applications for this reagent we deprotonated the oxime **1** (Scheme 1) with sodium hydride and alkylated the resulting alkoxide with chloromethyl menthyl ether in THF with DMPU to produce



Scheme 1. Reagents: i, NaH, DMPU, THF; ii, chloromethyl-(1R)-menthyl ether; iii, Bu_3SnH, AIBN, Benzene; iv, camphanic chloride, pyridine.

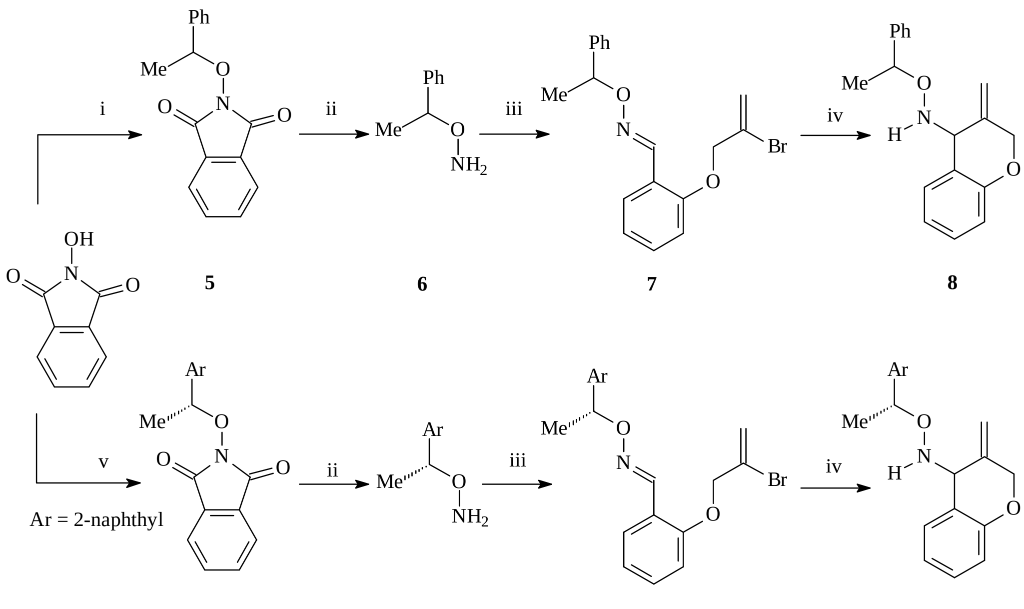
the chiral oxime ether **2** in 82% yield. Treatment of **2** with Bu_3SnH and AIBN gave alkoxyamine **3** in 78% yield as a 1:1 mixture of diastereoisomers as measured from the ^{13}C- and ^{1}H-NMR of the product. The lack of diasteroselectivity is not surprising in view of the fact that the oxime carbon is five bonds away from the chiral centre on the menthyl group. Four of these connecting bonds are single and so we would expect a wide variety of conformations to be present hence making effective chirality transfer more difficult.

It is well known that esters have a prefered conformation in which the acyl and alkoxy substituents are trans. We therefore attempted to restrict the conformational mobility of the system by preparing oxime ester by reaction of the oxime **1** with camphanic chloride and pyridine to produce the oxime ester **4** in 93% yield. Oxime esters have previously been used in Beckmann type rearrangements[10], radical cyclisation reactions have not been reported previously for the compounds. When the oxime ester **4** was treated with Bu_3SnH the starting material was consumed but no identifiable product was obtained. Clearly the chirality in oxime ethers **2** and **4** is too far away from the oxime carbon atom and the two formally diastereotopic faces of the oxime are not sufficiently different for selectivity to occur in the addition reaction. The closest we can get the stereogenic carbon to the oxime is to have it directly attatched to the nitrogen of the oxime, in order to achieve this objective we need to us a chiral oxime ether.

Oxime ethers are most conveniently prepared from alcohols and N-hydroxy succinimide following the method of Grochowski and Jurczac[11]. We therefore need to apply this method to chiral alcohols to produce chiral hydroxylamines. The first example in Scheme 2 is the reaction of racemic 1-phenyl ethanol with N-hydroxy succinimide to give the adduct **5** in 62% yield. The succinimide group is then removed by reaction with hydrazine to furnish the racemic 1-phenyl ethyl hydroxylamine **6** which was converted directly into the oxime ether **7**. Succesful intramolecular radical cyclisation of oxime **7** was achieved with Bu_3SnH and AIBN to produce the alkoxy amine **8** in 62% yield as a 1:1 mixture of diastereoisomers.

The other example in Scheme 2 is the reaction of (S)-naphthyl ethanol with N-hydroxy succinimide and diethyl azodicarboxylate to furnish the (R) adduct **9** in 57% yield where inversion of configuration has occured in the substitution reaction. The succinimide group was again removed with hydrazine to yield the chiral hydroxylamine **10** which was converted directly into the chiral oxime ether **11** in 93% yield. Treatment of this oxime with Bu_3SnH and AIBN gave radical cyclisation in 68% yield to give the alkoxy amine **12** as a 1:1 mixture of diastereoisomers.

In conclusion chiral and racemic oxime ether derivatives have been prepared and subjected to intramolecular radical cyclisation reactions. This is the first study of this topic to the best of our knowledge. The lack of diastereoselectivity in the process was disappointing, however it is hoped that in the future asymmetric induction will be possible in this reaction.



Scheme 2. Reagents: i, PPh_3, racemic α-methylbenzyalcohol; ii, N_2H_4; iii, 2-(2-bromoallyloxy)-benzaldehyde, pyridine; iv, Bu_3SnH, AIBN, benzene; v, PPh_3, (S)-naphthyl ethanol.

Experimental

General

^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. ^{1}H-NMR (360 MHz and 250 MHz) and ^{13}C-NMR (90.5 MHz and 63.5 MHz) spectra were recorded on Bruker AM-360 and AM-250 spectrometers at Merck, Sharp and Dohme, Harlow. Standard mass spectra and accurate mass measurements were made at the SERC mass spectrometry centre, University College of Swansea. Elemental analysis was carried out by Butterworth Laboratories, Teddington, Middlesex. Infra-red spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Melting points were determined on a Kofler hotstage and are uncorrected.

Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). T.l.c. was performed on Merck aluminium sheets coated with silica gel 60 F_{254} (Art 5735).

Light petroleum (b.p. 40-60 °C) and ethyl acetate were distilled prior to use. THF was distilled from sodium metal in the presence of benzophenone.

(R) menthol and its derivatives are obtained from 1R, 2S, 5R-menthol.

2-(3-Bromoallyloxy)benzaldehyde-O-((R)-menthoxymethoxy)oxime 2

2-(3-Bromoallyloxy)benzaldehyde oxime **1** (500 mg, 1.95 mmol) in dry THF (1 cm^3) was added dropwise to a suspension of sodium hydride (56 mg, 2.34 mmol, 80% dispersion in mineral oil) in dry THF (10 cm^3) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (300 mg, 2.34 mmol). The solution was stirred at room temperature for 1 h followed by the addition of chloromethylmenthyl ether (600 mg, 2.93 mmol) in one portion. Stirring at room temperature was continued for 1 h. The reaction was quenched with water and the crude product extracted into diethyl ether. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C) (1:9, v/v) as eluent afforded **oxime ether 2** as a clear, colourless oil (678 mg, 82%); R_f (diethyl ether-light petroleum [b.p. 40-60 °C], 1:1, v/v) 0.35; $[\alpha]_D$ -64° (c. 6.5, CH_2Cl_2); $\nu_{max.}$ (film)/cm^{-1} 3060 w, 2940 s, 2910 s, 2860 s, 1635 w (C=N), 1600 m, 1570 w, 1560 w, 1480 m, 1450 s, 750 s; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.71-1.04 (12 H, m, H-4", H-7", H-8", H-9", H-10"), 1.17-1.42 (2 H, m, H-5" and H-2"), 1.62 (2 H, m, H-3"), 2.08-2.28 (2 H, m, H-6"), 3.47 (1 H, td, J 4.2, J 10.6, H-3"), 4.64 (2 H, dd, $J_{1',3'E}$ and $J_{1',3'Z}$ < 1.0, H-1'), 5.26 and 5.30 (2 H, AB quartet, J 7.7, OCH_2O), 5.66 (1 H, dt, $J_{3'Z,3'E}$ 2.0, H-3'Z), 5.96 (1 H, dt, H-3'E), 6.81 (1 H, d, $J_{3.4}$ 8.1, H-3), 6.97 (1 H, dd, $J_{5,4}$ 7.4, $J_{5,6}$ 7.7, H-5), 7.29 (1 H, td, $J_{4,6}$ 1.6, H-4), 7.85 (1 H, dd, H-6), 8.56 (1 H, s, CH=N) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 15.8 (C-7"), 21.1 (C-10"), 22.3 (C-9"), 23.1 (C-2"), 25.0 (C-8"), 31.5 (C-3"), 34.4 (C-1"), 41.3 (C-4"), 48.1 (C-6"), 71.9 (C-1'), 77.6 (C-5"), 95.9 (OCH_2O), 112.4 (C-3), 118.0 (C-3'), 121.1 (C-1), 121.6 (C-5), 126.6 (C-2'), 126.8 (C-4), 131.1 (C-6), 145.5 (CH=N), 155.6 (C-2) ppm; m/z (EI) 424/426 (MH^+, 2), 256/258 (2), 240/242 (4), 169 (8), 139 (48), 97 (22), 83

(100), 69 (40), 55 (58); (Found: MH^+, 424.1487. $C_{21}H_{34}BrNO_3$ requires MH^+, 424.1487).

4-(2-(R)-Menthoxymethoxyamino)chroman-3-ylidene 3

2-(2-Bromoallyloxy)benzaldehyde-O-(2-(R)-menthoxymethoxy) oxime **2** (250 mg, 0.59 mmol) and tributyltin hydride (206 mg, 0.71 mmol) were dissolved in benzene (30 cm^3, 0.02 M dilution of **2**) and the solution degassed by bubbling a steady stream of nitrogen through it for 1 h. The solution was heated to reflux temperature under a nitrogen atmosphere and azobisisobutyronitrile (AIBN) (20 mg, 0.12 mmol) in benzene (10 cm^3) added over 10 h. Heating at reflux temperature was continued for a further 12 h. Benzene was evaporated *in vacuo* and the residue purified by chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C) (1:4, v/v) as eluent. A 1:1 mixture of diastereoisomers of **hydroxylamine 3** (159 mg, 78%) as a pale yellow oil. R_f (diethyl ether-light petroleum [b.p. 40-60 °C], 1:4, v/v) 0.47; ν_{max} (film)/cm^{-1} 3200 br, w, 3010 w, 2960 m, 2920 w, 2860 w, 1650 (C=N), 1600 w, 1590 m, 1580 w, 1480 m; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.68-1.04 (24 H, complex m, H-2', H-7', H-8', H-9' and H-10' in both diastereoisomers), 1.18-1.43 (4 H, m, H-5'and H-2' in both diastereoisomers), 1.62 (4 H, m, H-3' in both diastereoisomers), 1.98-2.31 (4 H, m, H-6' in both diastereoisomers), 3.29 (1 H, td, *J*4.2, 10.6, H-1' in diastereoisomer A), 3.35 (1 H, td, *J*4.3, 10.6, H-1' in diastereoisomer B), 4.44 (1 H, s, H-4 in diastereoisomer B), 4.47 (1 H, s, H-4 in diastereoisomer A), 4.49 (2 H, d, $J_{2x,2y}$ 12.0, H-2x in both diastereoisomers), 4.70 and 4.84 (2 H, AB q, *J*7.6, OCH_2O in diastereoisomer B), 4.75 and 4.86 (2 H, AB q, *J*7.5, OCH_2O in diastereoisomer A), 4.85 (2 H, d, H-2y in both diastereoisomers), 5.28 (2 H, s, H-E in both diastereoisomers), 5.33 (2 H, s, H-Z in both diastereoisomers), 6.84 (2 H, d, $J_{8,7}$ 8.2, H-8 in both diastereoisomers), 6.90 (2 H, t, $J_{6,5} = J_{6,7}$ 7.5, H-6 in both diastereoisomers), 7.15-7.27 (4 H, m, H-5 and H-7 in both diastereoisomers) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 15.9 (C-7'), 21.1 (C-10'), 22.3 (C-9'), 22.96 and 23.02 (C-4'), 25.3 (C-8'), 31.49 and 31.55 (C-5'), 34.31 and 34.35 (C-3'), 41.2 and 42.3 (C-6'), 48.1 and 48.2 (C-2'), 60.1 (C-4), 67.3 (C-2), 76.9 (C-1'), 96.5 and 98.0 (OCH_2O), 115.8 and 115.9 (C=CH_2), 116.9 and 117.0 (C-8), 119.87 and 119.93 (C-4a), 120.6 (C-6), 129.42 and 129.45 (C-7), 129.9 and 130.1 (C-5), 139.3 and 139.4 (C-3), 155.19 and 155.25 (C-8a); m/z (CI) 346 (MH^+, 7), 160 (6), 145 (100), 122 (4); (Found: MH^+, 346.2382. $C_{21}H_{31}NO_3$ requires MH^+, 346.2382).

2-(2-Bromoallyloxy)benzaldehyde-O-camphanic oxime 4

2-(3-Bromoallyloxy)benzaldehyde oxime **1** (500 mg, 1.95 mmol) and camphanic chloride (507 mg, 2.34 mmol) were stirred for 30 min at room temperature in pyridine (2 cm^3). The reaction mixture was diluted with water (10 cm^3) and the product was extracted into diethyl ether. The organic phase was washed with hydrochloric acid (2 M), water and dried ($MgSO_4$). Column chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C) (7:3. v/v) as eluent yielded the **oxime ether 4** (791 mg, 93%) as needles, m.p. 88-89 °C (from ethanol). (Found: C, 55.01; H, 5.19; N, 3.32. $C_{20}H_{22}BrNO_5$ requires C, 55.04; H, 5.09; N, 3.21); $[\alpha]_D$ -6° (c. 2.24, CH_2Cl_2); R_f (diethyl ether-light petroleum [b.p. 40-60 °C], 7:3. v/v) 0.38; $\nu_{max.}$ (CH_2Cl_2)/cm^{-1} 2990 w-2860 w, 1780 s and 1710 s (C=O), 1630 w; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.67 (3 H, s, Me), 1.14 (3 H, s, Me), 1.15 (3 H, s, Me), 1.74 (1 H, ddd, $J_{3a'',2a''}$ 4.1, $J_{3a'', 2b''}$ 9.3, $J_{3a'',3b''}$ 13.3, H-3a''), 1.99 (1 H, ddd, $J_{2b'',3b''}$ 4.5, $J_{2b'', 2a''}$ 15.0, H-2b''), 2.15 (1 H, ddd, $J_{3b'',2a''}$ 10.7, H-3b''), 2.55 (1 H, ddd, H-2a''), 4.72 (2H, s, H-1'), 5.73 (1 H, d, $J_{3'E,3'Z}$ 1.8, H-4'Z), 5.99 (1 H, d, H-3'E), 6.01 (1 H, d, $J_{3,4}$ 8.4, H-3), 7.04 (1 H, dd, $J_{5,4}$ 7.4, $J_{5,6}$ 7.8, H-5), 7.45 (1 H, ddd, $J_{4,6}$ 1.6, H-4), 8.00 (1 H, dd, H-6), 8.93 (1 H, s, C*H*=N) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 9.7 (Me), 16.68 (Me), 16.72 (Me), 28.9 (C-3''), 30.9 (C-2''), 54.66 (*C*Me_2), 54.7 (C-4''), 72.1 (C-1'), 90.5 (C-1''), 112.7 (C-3), 118.5 (C-1), 118.8 (C-3'),121.8 (C-5), 126.1 (C-2'), 128.0 (C-4), 133.5 (C-6), 153.7 (*C*H=N), 156.7 (C-2), 164.9 (C-5''), 178.0 (*C*=O) ppm; m/z (CI) 436 (MH^+, 2), 255 (12), 216 (100), 160 (38), 137 (5), 120 (15), 109 (8) (Found: MH^+, 436.076. $C_{20}H_{22}BrNO_5$ requires MH^+ 436.076).

Reaction of 2-(2-Bromoallyloxy)benzaldehyde O-camphanic oxime 4 with tributyltin hydride and AIBN

A solution of AIBN (23 mg, 0.014 mmol) in benzene (10 cm^3) was added dropwise over 8 h to a solution of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime **4** (300 mg, 0.68 mmol) and tributyltin hydride (240 mg, 0.83 mmol) in dry deoxygenated benzene (34.4 cm^3, 0.02 M dilution of **4**) heated at reflux temperature. Heating was continued for a further 5 h. Benzene was evaporated under reduced pressure but analysis of the crude product mixture revealed in excess of ten components that could not be isolated. All starting material was consumed.

N-(α-Methylbenzyloxy)phthalimide 5

To a stirred solution of N-hydroxyphthalimide (1.00 g, 6.13 mmol), triphenylphosphine (1.61 g, 6.13 mmol) and α-methylbenzylalcohol (0.75 g, 6.13 mmol) in THF (30 cm^3) under a nitrogen atmosphere was slowly added diethylazodicarboxylate (1.17 g, 6.74 mmol). The reaction mixture was stirred at room temperature for 24 h. THF was evaporated *in vacuo*. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C)(1:1, v/v) as eluent afforded the **phthalimide 5** (1.01 g, 62%) as plates, m.p. 89-91 °C (from light petroleum [b.p. 60-80 °C]); (Found: C, 71.86; H, 4.92; N, 5.27. $C_{16}H_{13}NO_3$ requires C, 71.90; H, 4.92; N, 5.24); R_f (dichloromethane-light petroleum [b.p. 40-60 °C] 1:1, v/v) 0.43; ν_{max} (CH_2Cl_2)/cm^{-1} 3080-2820 w, 1785 s, 1725 s, 1460 m, 1370 s, 1185 s; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.70 (3 H, d, *J* 6.5, CH_3), 5.49 (1 H, q, PhC*H*Me-), 7.26-7.36 (3 H, m, H-*o* and H-*p* in PhCH(Me)O-), 7.50 (2 H, m, H-*m* in PhCH(Me)O-), 7.69 (4 H, m, phthalimide protons) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 20.4 (CH_3), 85.0 (Ph*C*HMe-), 123.3 (phthalimide), 127.5 (C-*o* in PhCH(Me)O-), 128.3 (C-*m* in PhCH(Me)O-), 128.7 (phthalimide), 128.9 (C-*p* in PhCH(Me)O-), 134.2 (phthalimide), 138.9 (C' in PhCH(Me)O-), 163.7 (C-1 and C-3) ppm; m/z (EI) 268 (MH^+, 13), 164 (13), 105 (100), 90 (31); (Found: $[M+NH_4]^+$, 285.1239. $C_{16}H_{13}NO_3$ requires $[M+NH_4]^+$, 285.1239).

O-(α-Methyl)benzylhydroxylamine 6

N-(α-Methylbenzyloxy)phthalimide **5** (290 mg, 1.09 mmol) and hydrazine monohydrate (54 mg, 1.09 mmol) were heated at reflux temperature in ethanol (5 cm^3) for 2 h. The reaction mixture was poured into 3% sodium carbonate solution and the product extracted with diethyl ether. R_f (dichloromethane-light petroleum [b.p 40-60 °C], 1:1, v/v) 0.20. The **hydroxylamine 6** was used without purification.

2-(2-Bromoallyloxy)benzaldehyde-O-(α-Methyl)benzyloxime 7

2-(2-Bromoallyloxy)benzaldehyde (225 mg, 0.93 mmol) and O-(α-methyl)benzylhydroxylamine **6** (150 mg, 1.12 mmol) were stirred overnight at room temperature in pyridine (5 cm^3). Pyridine was removed under reduced pressure. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C) (1:1, v/v) as eluent yielded a single isomer of the **oxime ether 7** as a clear colourless oil (246 mg,73%); R_f (dichloromethane-light petroleum [b.p. 40-60 °C], 1:1, v/v) 0.52; ν_{max} (film)/cm^{-1} 3060 w, 3010 w, 2990 m, 2910 w, 2860 w, 1635 m, 1600 s, 1570 w, 1480 s, 1450 s; δ_H (300 MHz, $CDCl_3$,Me_4Si) 1.61 (3 H, d, *J* 6.6, Me), 4.60 (2 H, t, $J_{1',3'Z} = J_{1',3'E}$ 1.3, H-1'), 5.35 (1 H, q, PhC*H*(Me)O-), 5.64 (1 H, dt, $J_{3'Z,3'E}$ 2.2, H-3'Z), 5.94 (1 H, dt, H-3'E), 6.77 (1 H, d, $J_{3,4}$ 8.4, H-3), 6.91 (1 H, dd, $J_{5,4}$ 7.5, $J_{5,6}$ 7.7, H-5), 7.20-7.40 (6 H, m, H-4 and H-*o*, H-*m* and H-*p* in PhCH(Me)O-), 7.74 (1 H, dd, $J_{6,4}$ 1.7, H-6), 8.61 (C*H*=N) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 21.9 (Me), 71.9 (C-1'), 81.2 (Ph*C*H(Me)O-), 112.5 (C-3), 118.0 (C-3'), 121.5 (C-1), 121.6 (C-5), 126.4 (C-*m* in PhCH(Me)O-), 126.5 (C-2'), 126.7 (C-4), 127.4 (C-*p* in PhCH(Me)O-), 128.2 (C-*o* in PhCH(Me)O-), 130.8 (C-6), 143.1 (C' in PhCH(Me)O-), 144.3 (*C*H=N), 155.4 (C-2) ppm; m/z (CI) 360/362 (MH^+, 100), 256/258 (7), 242 (28), 160 (15), 145 (15), 122 (23), 105 (22), 94 (2); (Found: MH^+, 360.0599. $C_{18}H_{18}BrNO_2$ requires MH^+, 360.0599).

4-(α-Methylbenzoxyamino)chroman-3-ylidene 8

2-(2-Bromoallyloxy)benzaldehyde-O-(α-methyl)benzyloxime **7** (125 mg, 0.35 mmol) and tributyltin hydride (122 mg, 0.42 mmol) were dissolved in dry benzene (18 cm^3, 0.02 M dilution of **7**) and the solution degassed for 1 h. The reaction mixture was heated to reflux temperature and a solution of AIBN (12 mg, 0.07 mmol) in dry benzene (10 cm^3) added over 8 h. Heating was continued for 18 h. Benzene was removed under reduced pressure. Chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C)(1:9, v/v) as eluent afforded a 1:1 mixture of diastereoisomers of the **hydroxylamine 8** as a pale yellow oil (59 mg, 61%); R_f (diethyl ether-light petroleum [b.p. 40-60 °C], 1:4, v/v) 0.36; ν_{max} (CH_2Cl_2)/cm^{-1} 3080 w, 2960-2900 m, 2805 w, 1640 m, 1610 m, 1570 w, 1485 s, 1240 s; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.44 (3 H, d, *J* 6.6, Me in isomer A), 1.52 (3 H, d, *J* 6.6, Me in isomer B), 4.30 (1 H, d, $J_{2ax,2eq}$ 11.5, H-2ax in isomer B), 4.40 (1 H, s, H-4 in isomer b), 4.48 (1 H, s, H-4 in isomer A), 4.50-4.55 (2 H, m, H-2eq in isomer B and H-2ax in isomer A), 4.76-4.84 (2 H, m, C*H*Me in isomers A and B), 4.88 (1 H, dd, $J_{2eq,Z}$ 1.1, $J_{2eq,2ax}$ 11.7, H-2eq in isomer A), 5.23 (1 H, s, H-E in isomer B), 5.34 (2 H, m, H-E in isomer A and H-Z in isomer B), 5.41 (1 H, d, H-Z in isomer A), 6.77-6.90 (2 H, m, H-8 in isomers A and B), 7.07-7.29 (2 H, m, H-6 in isomers A and B), 7.40-7.48 (4 H, m, H-5 and H-7 in isomers A and B), 7.70-7.83 (10 H, m, H-*o*, H-*m* and H-*p* in $PhCH_2$ in isomers A and B) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 23.9 and 24.9 (Me), 58.6 and 58.7 (C-4), 69.3 and 69.9 (C-2), 81.5 and 81.6 (*C*H(Me)Ph), 116.9 and 117.1 (C=*C*H_2), 120.7 and 120.8 (C-8), 120.8 and 121.1 (C-4a), 126.0 and 126.2 (C-6), 127.1 and 127.2 (C-*p* in $PhCH_2$), 127.8 and 127.9 (C-*m* in $PhCH_2$), 128.1 and 128.2 (C-*o* in $PhCH_2$), 128.5 and 128.6 (C-7), 129.7 and 129.8 (C-5), 143.5 and 143.8 (C' in $PhCH_2$), 145.0 and 145.1 (C-3), 155.1 and 155.4 (C-8a) ppm.

(R)-N-(2-(2-naphthyl)ethoxy)phthalimide 9

Diethylazodicarboxylate (2.22 g, 12.75 mmol) was added dropwise to a stirred solution of (S)-α-methyl-2-naphthalenemethanol (2.00 g, 11.61 mmol), N-hydroxyphthalimide (1.89 g, 11.61 mmol) and triphenylphosphine (3.05 g, 11.61 mmol) in THF (50 cm^3) under a nitrogen atmosphere. The reaction was left stirring at room temperature for 72 h. THF was evaporated under reduced pressure. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C)(2:1, v/v) as eluent afforded the **phthalimide 9** (2.10 g, 57%) as needles, m.p. 105-106 °C (from diethyl ether); (Found: C, 75.84; H, 4.89; N, 4.45. $C_{20}H_{15}NO_3$ requires C, 75.69; H, 4.76; N, 4.41); R_f (dichloromethane-light petroleum [b.p. 40-60 °C], 1:1, v/v) 0.38; ν_{max} (CH_2Cl_2)/cm^{-1} 3080-2820 w, 1780 s, 1720 s, 1460 m, 1370 s, 1180 s; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.77 (3 H, d, *J* 6.5, Me), 5.67 (1 H, q, ArC*H*Me-), 7.41 (2 H, m, H-7" and H-6"), 7.60 (4 H, m, phthalimide protons), 7.80 (5 H, m, H-1", H-3", H-4", H-5" and H-8") ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 20.6 (Me), 85.1 (Ar-C*H*Me-), 123.1 (C-4 and C-7), 124.7 (C-3"), 126.0 (C-6"), 126.2 (C-7"), 127.9 (C-4"), 127.5 (C-1"), 127.9 (C-5"), 128.1 (C-8"), 128.6 (phthalimide), 132.7 (C-8a"), 133.4 (C-4a"), 134.1 (phthalimide), 136.4 (C-2"), 163.6 (phthalimide) ppm; m/z (EI) 317 (M^+, 1), 155 (100), 127 (12), 115 (8), 104 (10), 76 (13); (Found: M^+, 317.1050. $C_{20}H_{15}NO_3$ requires M^+, 317.1050).

(R)-O-2-(2-naphthyl)ethylhydroxylamine 10

(R)-N-(2-(2-naphthyl)ethoxy)phthalimide **9** (670 mg, 2.11 mmol) and hydrazine monohydrate (106 mg, 2.11 mmol) were heated at reflux temperature in ethanol (5 cm^3) for 2 h. The reaction mixture was poured into 3% sodium carbonate solution and the product extracted with diethyl ether. R_f (dichloromethane-light petroleum (b.p 40-60 °C)(1:1, v/v) 0.38. The **hydroxylamine 10** was used without purification.

(R)-2-(2-Bromoallyloxy)benzaldehyde-O-2-(2-naphthyl)ethyloxime 11

(R)-O-2-(2-naphthyl)ethylhydroxylamine **10** (400 mg, 2.14 mmol) and 2-(2-bromoallyloxy)benzaldehyde (430 mg, 1.78 mmol) were stirred in pyridine (5 cm^3) at room temperature overnight. Pyridine was removed under reduced pressure. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C)(1:1, v/v) as eluent afforded the **oxime ether 11** as a clear, colourless oil (677 mg, 93%); R_f (dichloromethane-light petroleum [b.p. 40-60 °C], 1:1, v/v) 0.51; $[\alpha]^D$ +7.42° (c. 4.58, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3045 w, 2970 s, 2910 m, 2860 w, 1635 m, 1600 s, 1540 w, 1480 s, 750 s; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.68 (3 H, d, *J* 6.6, Me), 4.55 (2 H, t, $J_{1',3'Z}$=$J_{1',3'E}$ 1.2, H-1'), 5.51 (1 H, q, OC*H*(Me)naphth), 5.64 (1 H, dt, $J_{3'Z,3'E}$ 2.1, H-3'Z), 5.90 (1 H, dt, H-3'E), 6.69 (1 H, d, $J_{3,4}$ 8.2, H-3), 6.87 (1 H, dd, $J_{5,4}$ 7.5, $J_{5,6}$ 7.7, H-5), 7.19 (1 H, ddd, $J_{4,6}$ 1.7, H-4), 7.41 (2 H, m, H-6" and H-7"), 7.51 (1 H, dd, H-6), 7.71-7.81 (5 H, m, H-1", H-3", H-4", H-5" and H-8"), 8.60 (1 H, s, *H*C=N) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 21.9 (Me), 71.8 (C-1'), 81.3 (O*C*H(Me)naphth), 112.4 (C-3), 118.0 (C-3'), 121.4 (C-1), 121.4 (C-5), 124.6 (C-3"), 125.1 (C-6"), 125.6 (C-7"), 125.9 (C-4"), 126.5 (C-2'), 126.7 (C-4), 127.6 (C-1"), 127.9 (C-5"), 128.0 (C-8"), 130.8 (C-6), 132.8 (C-8a"), 133.2 (C-4a"), 140.6 (C-2"), 144.4 (*C*=N), 155.4 (C-2) ppm; m/z (EI) 410/412 (MH^+, 2), 256/258 (2), 155 (100), 141 (2), 127 (15); (Found: MH^+, 410.0756. $C_{22}H_{20}BrNO_2$ requires MH^+, 410.0756).

4-[2-(R)-(2-naphthyl)ethoxyamino]chroman-3-ylidene 12

(R)-2-(2-Bromoallyloxy)benzaldehyde O-(2)-(2-naphthyl)ethyloxime **11** (300 mg, 0.73 mmol) and tributyltin hydride (256 mg, 0.88 mmol) were dissolved in benzene (37 cm^3, 0.02 M dilution of **11**) and the solution was degassed with a steady stream of nitrogen for 1 h. The solution was heated to reflux temperature and a solution of AIBN (24 mg, 0.15 mmol) in benzene (10 cm^3) was added over 8 h *via* a syringe pump. Benzene was evaporated *in vacuo*. Chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C)(1:9, v/v) as eluent afforded the **hydroxylamine 12** (165 mg, 68%) as a 1:1 mixture of diastereoisomers A and B, seen as a clear, colourless oil. R_f (diethyl ether-light petroleum [b.p. 40-60 °C], 1:9, v/v) 0.17; $\nu_{max.}$ (CH_2Cl_2)/cm^{-1} 3250 br. w, 1600 m, 1580 s, 1480 s, 1460 s, 1240 s, 1070 s; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.36 (3 H, d, *J* 6.6, Me in diastereoisomer A), 1.43 (3 H, d, *J* 6.5, Me in B), 4.35 (1 H, d, $J_{2ax,2eq}$ 11.6, H-2ax in A), 4.37 (1 H, s, H-4 in A), 4.43 (1 H, s, H-4 in B), 4.51 (1 H, d, $J_{2ax,2eq}$ 11.6, H-2ax in B), 4.55 (1 H, d, H-2eq in A), 4.62 (2 H, 2 overlapping q, MeC*H* in A and B), 4.84 (1 H, d, H-2eq in B), 5.22 (1 H, s, C=C$H_a$$H_b$ in A), 5.30 (2 H, 2 x s, C=C$H_a$$H_b$ in A and C=C$H_a$$H_b$ in B), 5.32 (2 H, br. s, N*H* in A and B), 6.78 (4 H, m, H-3 and H-5 in A and B), 7.00-7.23 (4 H, m, H-4 and H-6 in A and B), 7.42 (6 H, m, H-7', H-6' and H-3' in A and B), 7.75 (8 H, m, H-1', H-4', H-5' and H-8' in A and B) ppm; δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 21.0 (Me), 21.6 (Me), 60.1 and 10.4 (C-4), 67.2 and 67.3 (C-2), 81.0 and 81.9 (*C*HMe), 115.7 and 116.1 (C=*C*H_2), 116.8 (C-8), 119.8 and 120.3 (C-4a), 120.4 and 120.5 (C-6), 126.3 (C-5), 126.7 and 127.3 (C-7), 127.4 (*C*H), 127.5 (*C*H), 128.1 (2 x *C*H), 128.3 (*C*H), 128.5 (*C*H), 129.4 (2 x *C*H), 130.0 (*C*H), 132.7 (*C*H), 132.9 (*C*H), 137.0 (C-3), 139.1 (*C*), 139.6 (*C*), 143.0(*C*), 143.6 (*C*), 155.1 and 155.2 (C-4a), 168.6 (2 x C-8a) ppm [NB: the C atoms in the naphthyl group could not be assigned unambiguously]; m/z (CI) 332 (MH^+, 22) 188 (8), 171 (5), 155 (39), 145 (100), 128 (2); (Found: MH^+, 332.1651. $C_{22}H_{21}NO_2$ requires MH^+, 332.1651).

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