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The Facile Construction of Indole Alkaloid Models: A Tandem Cascade Approach for the Synthesis of a Model for Pseudocopsinine.

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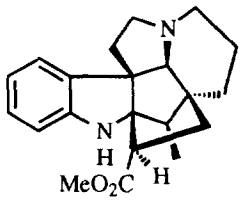
Abstract: A short and concise route to the pseudocopsinine skeleton is reported which relies on a tandem radical cascade to furnish five fused rings in one step.

INTRODUCTION

The indole alkaloids are widely distributed in nature and possess equally wide ranging biological activity.[1] We have been interested in the construction of indole alkaloids for several years[2] and we now report in full on our model studies leading to the synthesis of pseudocopsinine (1). Pseudocopsinine (1) was isolated by a Russian group led by Yunusov from *Vinca erecta*.[3] The original structure proposed was incorrect, but X ray analysis by Andrianov[4] proved the structure (1) for pseudocopsinine.



(1)

In our retrosynthetic analysis of (1) we proposed a tandem radical induced cyclisation[5] (Scheme 1).

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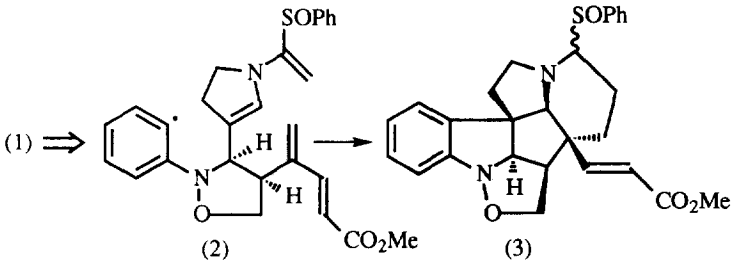
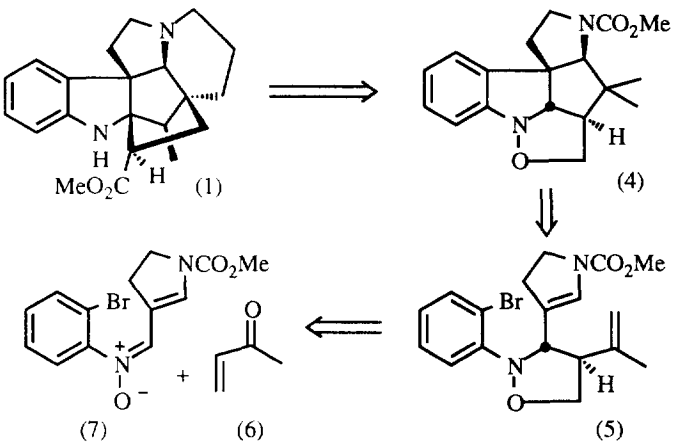


Scheme 1

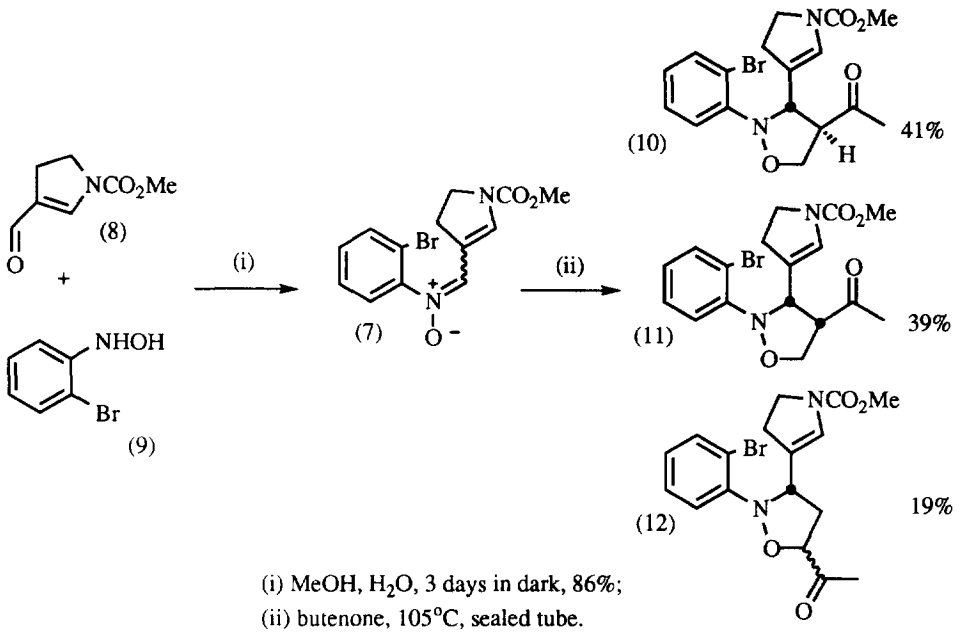
In order to test our hypothesis we considered the model cyclisation shown in scheme 2.



Scheme 2

RESULTS AND DISCUSSION

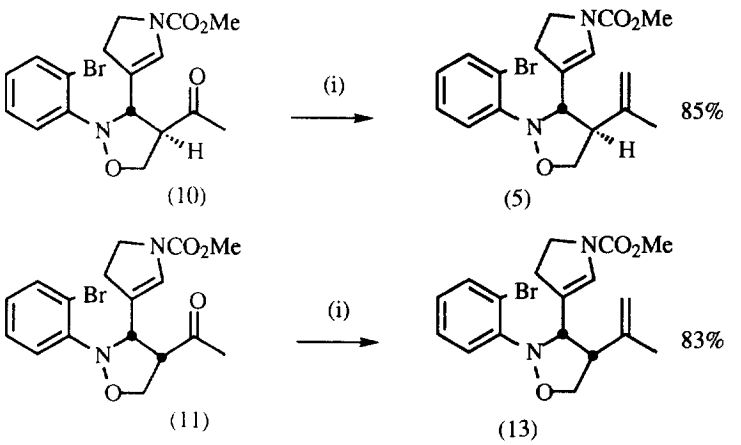
To construct the heterocycle (5) we required the nitrone (7)[6] which was synthesised by reaction of the pyrroline aldehyde (8)[7] with *o*-bromophenylhydroxylamine (9).[8] The nitrone (7) reacted smoothly with butenone to afford the *anti*-adduct (10) as a colourless gum and the *syn*-adduct (11) as a white solid. The undesired regioadducts were also isolated in low yield (Scheme 3).



(i) MeOH, H_2O, 3 days in dark, 86%;
(ii) butenone, 105°C, sealed tube.

Scheme 3

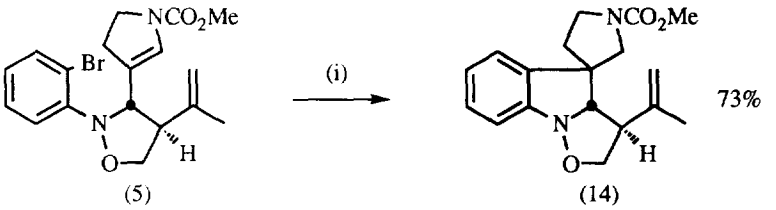
Wittig methylenation of (10) and (11) proceeded smoothly at low temperature to give the radical cyclisation precursors (5) and (13) respectively (Scheme 4).



(i) $Ph_3P{=}CH_2$, THF, -78°C

Scheme 4

Our initial radical cyclisation studies focussed on the *anti*-diastereomer (5). Treatment of (5) with tri-n-butyltin hydride in refluxing benzene led to the isolation of a single product (14) in 73% yield. Spectroscopic analysis of (14) revealed that monocyclisation had occurred exclusively (Scheme 5) in a manner analogous to the findings of Jones.[9]

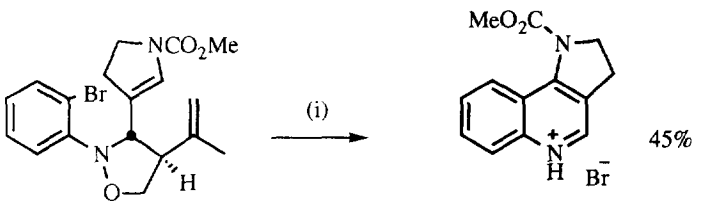


(5) (14)

(i) Bu_3SnH, AIBN, benzene, Δ, syringe pump.

Scheme 5

Reaction conditions were varied in order to induce the second cyclisation. When the cyclisation precursor (5) was treated with *tris*(trimethylsilyl)silane[10] in boiling toluene, the quinoline (15) was isolated in 45% yield (Scheme 6).

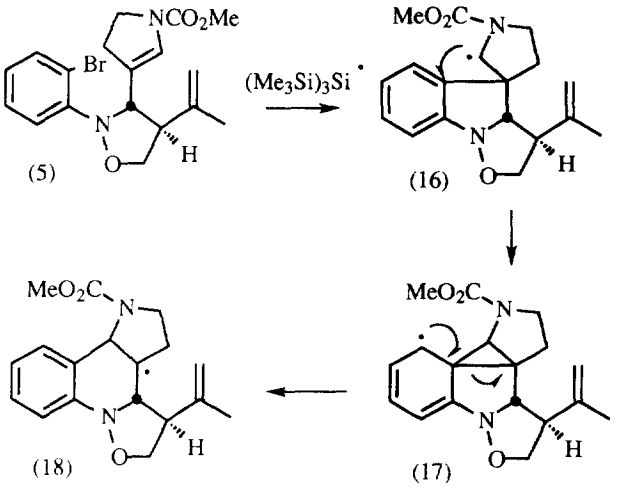


(5) (15)

(i) $(Me_3Si)_3SiH$, AIBN, toluene, Δ, syringe pump.

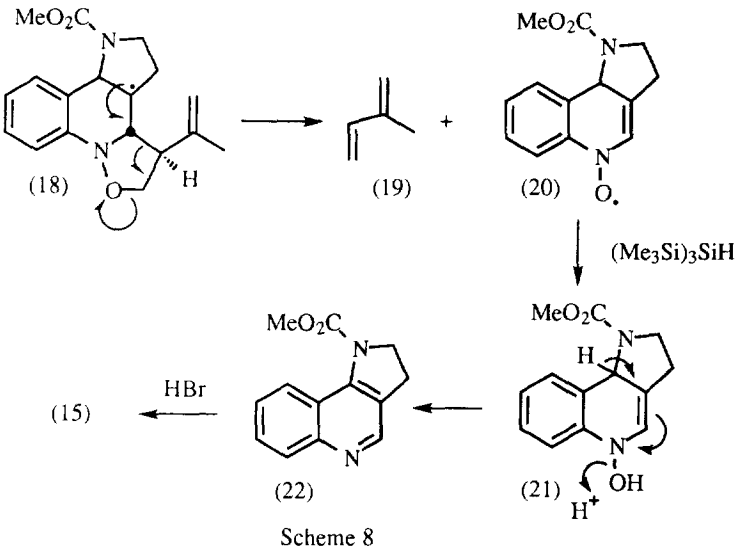
Scheme 6

Formation of (15) is an interesting observation and may be due to a slower hydrogen atom transfer[11] to the spirocyclic radical (18) from *tris*(trimethylsilyl)silane (Scheme 7).



Scheme 7

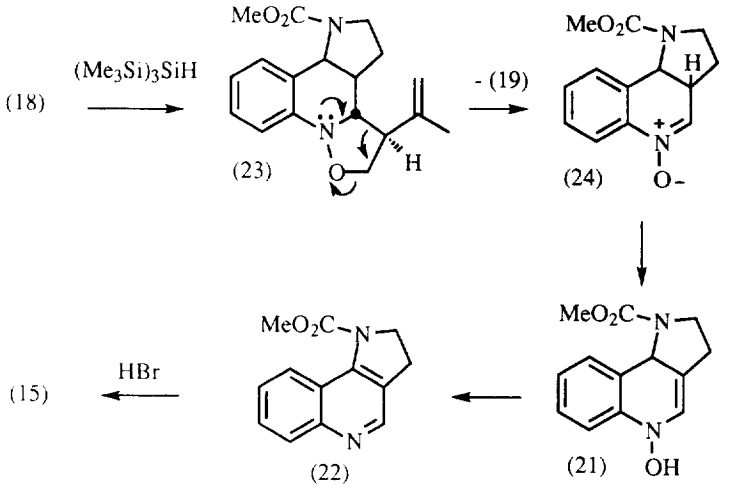
Equilibration of the radical (16) to the thermodynamically more stable system (18)[12] would be favoured in the presence of a relatively poor hydrogen atom donor. At least two mechanistic pathways are now open for the formation of the quinolinium salt (15). A radical fragmentation pathway is shown in scheme 8.



Scheme 8

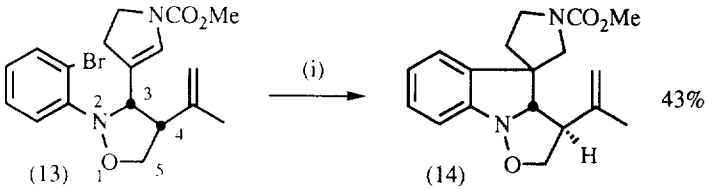
Fragmentation of (18) with loss of isoprene (19) would give rise to a nitrosyl radical (20) which could gain a hydrogen atom from *tris*(trimethylsilyl)silane and then eliminate water to form the quinoline (21). Reaction of water with *tris*(trimethylsilyl)silyl bromide would provide hydrogen bromide, resulting in the isolation of the salt (15). Alternatively quenching of the tertiary radical (18) with *tris*(trimethylsilyl)silane could

occur giving a tetrahydroquinoline intermediate (23). The tetrahydroquinoline (23) could undergo a retro [3+2] cycloaddition to form the nitrone (24) and isoprene (19). Tautomerism of the nitrone to the N-hydroxydihydroquinoline (21) with successive loss of water and reaction with hydrogen bromide would give the salt (15) (Scheme 9).



Scheme 9

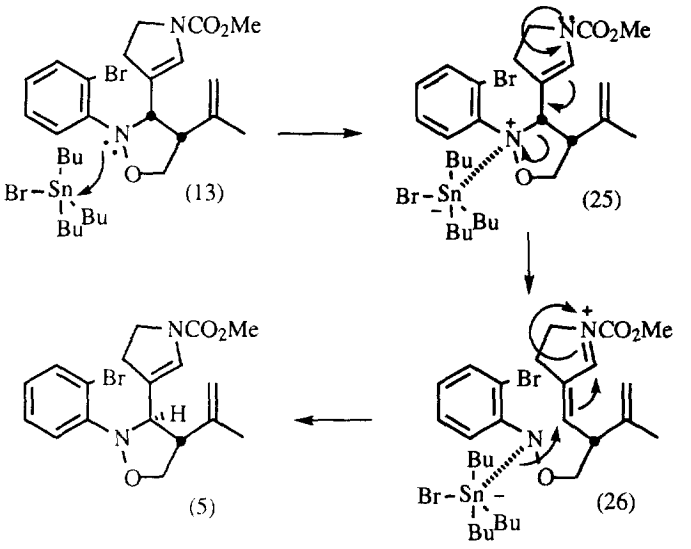
We next investigated the radical cyclisation chemistry of the *syn*-adduct (13). Radical induced cyclistion of (13) was attempted using the syringe pump technique for slow addition of tri-n-butyltin hydride to a solution of (13) in boiling benzene. The spirocyclic isoxazolidine product (14) was isolated in 43% yield yet to our surprise it was epimeric at C4 of the isoxazolidine ring with respect to the starting material (13) (Scheme 10).



(i) Bu_3SnH, AIBN, benzene, Δ, syringe pump.

Scheme 10

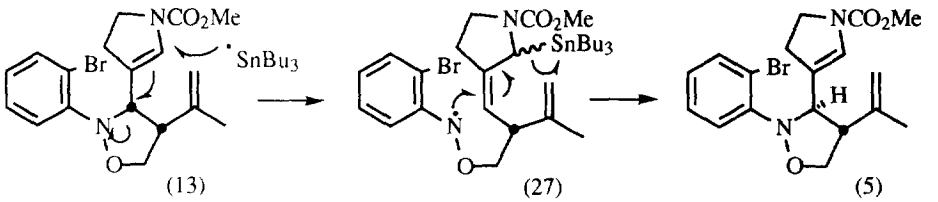
The formation of (14) is interesting and may be due to traces of tri-n-butyltin bromide in solution behaving like a Lewis acid (Scheme 11).



Scheme 11

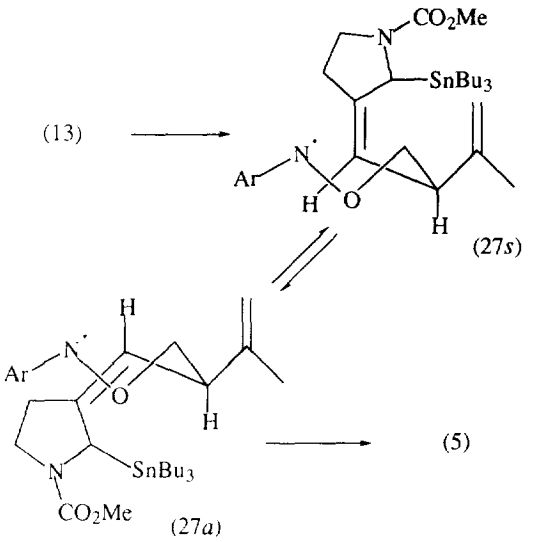
In the presence of tri-n-butyltin bromide a ring opening reaction of (13) to (26) could occur, which is enhanced by the mesomeric effect of the pyrroline nitrogen. Free rotation of the pyrrolinium ion (26) to its lowest energy conformer would allow cyclisation to the *anti*-isoxazolidine (5).

Another explanation for the formation of (5) from (13) relies on the addition of tri-n-butyltin radicals to the pyrroline double bond (Scheme 12).



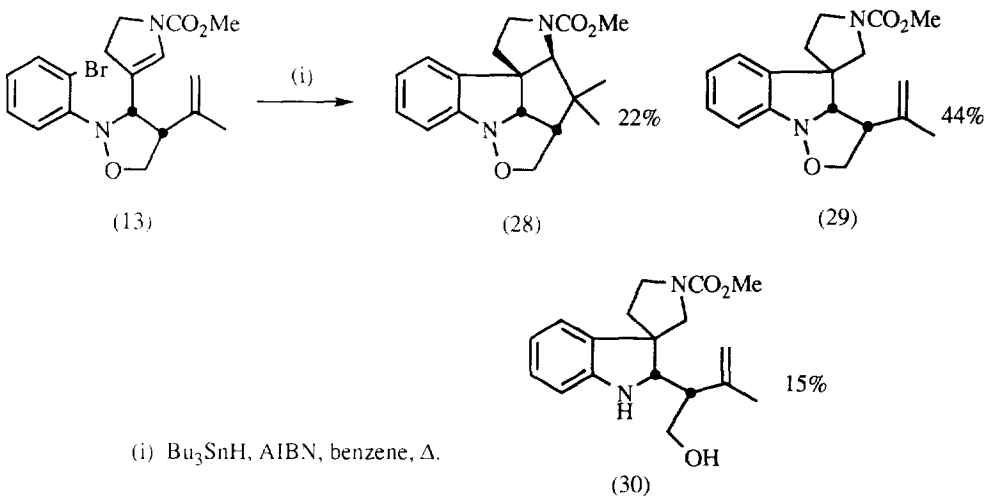
Scheme 12

Radical mediated ring opening of (13) would give rise to an intermediate nitrogen centred radical (27); rotation of the allylic stannane moiety in (27) to the lowest energy conformer followed by cyclisation would furnish the *anti*-isoxazolidine (5) (Scheme 13).



Scheme 13

In order to prevent prolonged exposure of the radical precursor (13) to tri-n-butyltin bromide, which could possibly be responsible for the observed stereo-randomisation, it was decided to premix all the reagents together in benzene and heat them at reflux. To our delight the desired tandem cyclisation occured giving the pentacyclic model (28) for pseudocopsinine synthesis together with other products (Scheme 14).



Scheme 14

Although the isolated yield of (28) was only 22%, the brevity of construction more than compensates for this low yielding step. The formation of the amino alcohol (30) is interesting and demonstrates the potential

utility of stannanes for the cleavage of N-O bonds.[13] Further work on the use of tandem reactions for the construction of indole alkaloids will appear in full.

EXPERIMENTAL

General: Tetrahydrofuran (THF) and Et_2O were distilled under argon from sodium benzophenone just prior to use. Dichloromethane (DCM), benzene, toluene, diisopropylamine and triethylamine were distilled from calcium hydride and used immediately. All reactions involving organometallic reagents were conducted under an atmosphere of argon in dry flasks. Chromatography was carried out using Sorbsil C60 40/60H grade silica gel according to the procedure described by Still.[14] Analytical thin layer chromatography was performed on Macherey Nagel Sil G/UV254 precoated silica plates. Compounds were visualised using alkaline potassium permanganate solution, acidic ceric sulfate solution or UV fluorescence. IR spectra were recorded using a Perkin Elmer 298 spectrometer as films on NaCl plates unless otherwise noted. NMR spectra were recorded at 400MHz (^1H) and 100MHz (^{13}C) on a Jeol EX400 spectrometer or at 250MHz (^1H) and 63MHz (^{13}C) on a Bruker WM250 spectrometer. Resonance multiplicities are abbreviated as follows d=doublet, t=triplet, s=singlet, br=broad, q=quartet (quaternary in 13C), m=multiplet. Mass spectra were recorded at the EPSRC Mass Spectrometry Service Centre at the University of Swansea or on a VG Micromass 7070F high resolution instrument. All melting points were recorded on an Electrothermal melting point apparatus and are uncorrected.

Z&E-N'-(2-Bromophenyl)-1-methoxycarbonyl-2-pyrroline-3-carbaldimine N'-oxide (7). 1-Methoxycarbonyl-2-pyrroline-3-carboxaldehyde[7] (8) (2.11g, 13.6mmol) and 2-bromophenylhydroxylamine[8] (9) (2.57g, 13.6mmol) were dissolved in mixture of methanol / water (1:1, 66ml) and left to stir under an atmosphere of argon in the dark for 3 days. The nitrone precipitate was a yellow solid (3.79g, 86%), which was filtered and washed with ether. Further purification was unnecessary. ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 3.0 (br m, 2H), 3.80 (s, 3H), 3.90 (br t, 2H, J=9.4Hz), 7.12 (s, 1H), 7.28 (dt, 1H, J=2.1 & 7.8Hz), 7.40 (dt, 1H, J=1.3 & 7.7Hz), 7.50 (dd, 1H, J=1.6 & 7.8Hz), 7.65 (dd, 1H, J=1.3 & 7.9Hz), 8.55 (br s, 0.3H), 8.68 (br s, 0.7H). ^{13}C nmr (62.9 MHz, $CDCl_3$ with DEPT 135 @ 20°C): δ = 28.785 + 29.930 (t), 45.258 (t), 52.962 (q), 112.012 (s), 116.540 (s), 125.869 (d), 128.229 (d), 130.342 (d), 133.580 (d), 135.975 (d), 147.234 (s), 152.557 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3044, 2955, 1708, 1574. CIMS, m/e (rel.intensity): 328 (10%), 327 (100%, $[M+H]^+$), 326 (12%), 325 (100%, $[M+H]^+$), 311 (30%), 309 (35%). HRMS: Calcd. for $C_{13}H_{13}BrN_2O_3$ ($[M+H]^+$): 325.018772; found 325.0188. Melting point: 172-173°C.

4-[2-(2-Bromophenyl)-4S*-acetyl-isoxazolidin-3R*-yl]-2,3-dihydropyrrole-1-carboxylic acid methyl ester (10) & 4-[2-(2-bromophenyl)-4R*-acetyl-isoxazolidin-3R*-yl]-2,3-dihydropyrrole-1-carboxylic acid methyl ester (11) & 4-[2-(2-bromophenyl)-5S* & 5R*-acetyl-isoxazolidin-3R*-yl]-2,3-dihydropyrrole-1-carboxylic acid methyl ester (12). The nitrone (7) (3.00g, 9.20mmol) and freshly distilled butenone (4.0ml, 3.37g, 48mmol) were stirred in a sealed glass tube, which was heated to 105°C under an argon atmosphere for 30 minutes. As the nitrone reacted, it dissolved and the reaction was complete when all the solid had disappeared. The excess methyl vinyl ketone was removed *in vacuo* to yield the crude mixture of products (3.65g, 100%), which analysed as three spots by

tlc. Trituration of the crude reaction mixture from a solution in ether yielded the *syn*-isomer (11) as a white powder. Compounds (10) and (12) were separated *via* chromatography (SiO_2, 1:1 petrol / ether). The first eluted compounds proved to be a mixture of *syn*- and *anti*-forms of the 5-substituted isoxazolidine (12) (693mg, 19%). ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 2.4 (br m, 3H), 2.6 (br m, 4H), 3.65 (2xs, 3H), 3.8 (br m, 2H), 4.25 (m, 1H), 4.7 (m, 1H), 6.39 + 6.42 + 6.49 (3xbr s, 1H), 6.9-7.1 (m, 1H), 7.4 (m, 3H). ^{13}C nmr (62.9 MHz, $CDCl_3$ with DEPT 135 @ 20°C): δ = 25.815 (q), 28.619 + 29.331 (t), 34.570 + 36.000 (t), 45.829 (t), 52.489 (q), 60.814 + 65.117 (d), 80.898 + 82.786 (d), 118.8 (s), 121.463 + 122.148 (d), 127 to 129 (multiple d), 133.150 + 133.484 (d), 147.261 (s), 152.577 + 153.098 (s), 209.823 (s). The next fraction to elute contained the *syn*- form of the 4-substituted isoxazolidine (11) (1.42g, 39%). ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 2.18 (s, 3H), 2.75 (br m, 2H), 3.75 (s, 3H), 3.75 (br m, 3H), 4.49 (dd, 1H, J=7.9 & 9.6Hz), 4.59 (t, 1H, J=8.4Hz), 5.04 + 5.11 (2xbr d, 1H, J=7.3Hz), 6.55 + 6.70 (2xbr s, 1H), 6.98 (m, 1H), 7.28 (m, 2H), 7.56 (d, 1H, J=7.8Hz). ^1H nmr (250MHz, $CDCl_3$ @ 50°C): δ = 2.18 (s, 3H), 2.75 (br m, 2H), 3.72 (s, 3H), 3.74 (br m, 3H), 4.43 (dd, 1H, J=7.9 & 9.4Hz), 4.55 (t, 1H, J=8.5Hz), 5.08 (br d, 1H, J=7.5Hz), 6.60 (br s, 1H), 6.94 (m, 1H), 7.28 (m, 2H), 7.56 (dd, 1H, J=1.4 & 7.8Hz).^{13}C nmr (62.9 MHz, $CDCl_3$ with DEPT 135 @ 20°C): δ = 29.457 + 30.133 (t), 30.316 (q), 45.661 (t), 52.395 (q), 57.454 (d), 65.243 (d), 67.853 (t), 112.590 (s), 117.828 (s), 118.312 (d), 125.285 (d), 127.829 (d), 128.309 + 129.006 (d), 133.701 (d), 147.897 (s), 152.279 + 153.089 (s), 202.162 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3052, 2954, 2897, 1702, 1652, 1585. HRMS: Calcd. for $C_{17}H_{19}BrN_2O_4$ ($[M]^+$): 394.052812; found: 394.0529. Melting point: 129-130°C.

The final fraction to elute as a clear viscous gum (1.49g, 41%) was the *anti*-4-substituted isoxazolidine (10). ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 2.22 (s, 3H), 2.75 (br m, 2H), 3.53 (m, 1H), 3.70 (s, 3H), 3.75 (br m, 2H), 4.30 (m, 1H), 4.40 (m, 1H), 4.79 + 4.84 (2xbr d, 1H, J=4.3Hz), 6.45 + 6.56 (2xbr s, 1H), 6.99 (dt, 1H, J=1.6 & 7.7Hz), 7.27 (dt, 1H, J=1.2 & 8.3Hz), 7.41 (dd, 1H, J=1.5 & 8.1Hz), 7.52 (br d, 1H, J=8.2Hz). ^1H nmr (250MHz, $CDCl_3$ @ 50°C): δ = 2.20 (s, 3H), 2.70 (br m, 2H), 3.50 (m, 1H), 3.70 (s, 3H), 3.75 (br m, 2H), 4.28 (t, 1H, J=8.4Hz), 4.38 (dd, 1H, J=5.8 & 8.3Hz), 4.82 (d, 1H, J=4.5Hz), 6.50 (br s, 1H), 6.96 (dt, 1H, J=1.7 & 7.7Hz), 7.24 (dt, 1H, J=1.5 & 7.7Hz), 7.40 (dd, 1H, J=1.7 & 8.1Hz), 7.45 (dd, 1H, J=1.4 & 8.0Hz). ^{13}C nmr (62.9 MHz, $CDCl_3$ with DEPT 135 @ 20°C): δ = 28.963 (q), 28.689 + 29.739 (t), 45.741 (t), 52.576 (q), 60.343 (d), 65.249 (d), 67.761 (t), 116.289 (s), 118.826 + 119.083 (s), 121.180 (d), 126.525 (d), 127.981 (d), 128.140 + 128.986 (d), 133.360 (d), 146.392 (s), 152.510 + 153.161 (s), 204.322 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3062, 2953, 2855, 1702, 1654, 1585. CIMS, m/e (rel. intensity): 397 (10%, $[M+H]^+$), 395 (10%, $[M+H]^+$), 311 (11%), 309 (11%), 224 (20%). HRMS: Calcd. for $C_{17}H_{19}BrN_2O_4$ ($[M]^+$): 394.052812; found: 394.0529.

4-[2-(2-Bromophenyl)-4S*-isopropenyl-isoxazolidin-3R*-yl]-2,3-dihydropyrrole-1-carboxylic acid methyl ester (5).

Methyl triphenylphosphonium bromide (1.17g, 3.29mmol) was stirred as a white suspension in dry tetrahydrofuran (48ml) under an atmosphere of argon at room temperature. *n*-Butyllithium (2.53ml of 1.2M solution in hexanes, 3.04mmol) was added dropwise at 20°C and the white solid disappeared to give a red solution. The reaction mixture was allowed to stir at 20°C for 1 hour before being cooled to -78°C. The ketone (10) (1.00g, 2.53mmol) in THF (10ml) was added dropwise and the previously red solution turned pale orange. The reaction mixture was removed from the cold bath and allowed to warm to room temperature over a period of

1 hour before being quenched by the addition of saturated $NH_4Cl_{(aq)}$ (10ml). The two layers were partitioned and the aqueous layer was further extracted using ether (3x75ml). All the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo . The crude product was purified via chromatography (SiO_2, 1:1 ether / pentane) to yield a colourless gum (850mg, 85%). ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 1.82 (s, 3H), 2.65 (br m, 2H), 3.33 (m, 1H), 3.68 (s, 3H), 3.70 (br m, 2H), 4.01 (br t, 1H, J=7.8Hz), 4.27 (br t, 1H, J=8.4Hz), 4.43 + 4.47 (2xbr d, 1H, J=5.4 & 6.1Hz), 4.86 (br s, 2H), 6.34 + 6.45 (2xbr s, 1H), 6.97 (dt, 1H, J=1.6 & 7.6Hz), 7.27 (dt, 1H, J=1.4 & 7.7Hz), 7.44 (d, 1H, J=8.1Hz), 7.51 (d, 1H, J=7.9Hz). ^{13}C nmr (62.9 MHz, $CDCl_3$ with DEPT 135 @ 20°C): δ = 19.696 (q), 28.619 + 29.554 (t), 45.666 (t), 52.509 (q), 55.530 (d), 67.268 (d), 70.276 (t), 113.373 (t), 115.832 + 116.399 (s), 119.476 + 120.023 (s), 120.023 + 121.253 (d), 125.940 (d), 127.913 (d), 127.913 + 128.702 (d), 133.321 (d), 142.571 (s), 147.026 (s), 152.516 + 153.097 (s). ν_{max} (CCl_4) / cm^{-1}: 3076, 2956, 1715, 1650, 1588. HRMS: Calcd. for $C_{18}H_{21}BrN_2O_3$ ($[M]^+$): 392.073547; found: 392.0739.

4-[2-(2-Bromophenyl)-4R*-isopropenyl-isoxazolidin-3R*-yl]-2,3-dihydropyrrole-1-carboxylic acid methyl ester (13).

A white suspension of methyl triphenylphosphonium bromide (936g, 2.62mmol) was stirred in dry tetrahydrofuran (60ml) under an atmosphere of argon at room temperature. *n*-Butyllithium (1.26ml of 2.5M solution in hexanes, 3.14mmol) was added dropwise at 20°C to give a red solution. The reaction mixture was stirred at 20°C for 1 hour and then cooled to -78°C. The ketone (11) (936mg, 2.36mmol) in THF (5ml) was added dropwise and the previously red solution turned pale orange. The reaction mixture was removed from the cold bath and allowed to warm to room temperature over a period of 1 hour before being quenched by the addition of saturated $NH_4Cl_{(aq)}$ (20ml). The two layers were partitioned and the aqueous layer was extracted using ethyl acetate (3x50ml). All the organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The olefin product was isolated as a white solid (770mg, 83%) from the crude residue *via* chromatography (SiO_2, 1:1 ether / pentane). ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 1.76 (s, 3H), 2.80 (br m, 2H), 3.24 (br q, 1H, J=9Hz), 3.71 (s, 3H), 3.80 (br m, 2H), 4.22 (dd, 1H, J=7.1 & 10.8Hz), 4.55 (m, 3/2H), 4.65 (br d, 1/2H, J=6.6Hz), 4.77 (br s, 1H), 4.94 (br s, 1H), 6.62 + 6.72 (2xbr s, 1H), 6.74 (dt, 1H, J=2.3 & 7.5Hz), 7.28 (m, 2H), 7.53 (d, 1H, J=8.0Hz). ^1H nmr (250MHz, $CDCl_3$ @ 50°C): δ = 1.75 (s, 3H), 2.75 (br m, 2H), 3.28 (br q, 1H, J=9.0Hz), 3.70 (s, 3H), 3.75 (br m, 2H), 4.17 (dd, 1H, J=7.2 & 10.5Hz), 4.49 (dd, 1H, J=7.1 & 8.9Hz), 4.62 (br d, 1H, J=6.7Hz), 4.78 (br s, 1H), 4.94 (q, 1H, J=1.2), 6.63 (br s, 1H), 6.90 (dt, 1H, J=1.9 & 7.5Hz), 7.22 (dd, 1H, J=1.4 & 8.1Hz), 7.30 (dt, 1H, J=1.8 & 8.1Hz), 7.56 (dd, 1H, J=1.4 & 7.9Hz). ^{13}C nmr (62.9 MHz, $CDCl_3$ with DEPT 135 @ 20°C): δ = 23.511 (q), 30.575 + 31.428 (t), 45.872 (t), 49.864 (q), 52.523 (d), 66.694 (d), 69.687 (t), 112.948 + 113.117 (t), 119.004 (d), 125.099 (d), 127.830 (d), 127.830 + 128.495 (d), 133.724 (d), 139.455 (s), 149.498 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3047, 2982, 2955, 1701, 1654, 1586. HRMS: Calcd. for $C_{18}H_{21}BrN_2O_3$ ($[M]^+$): 392.073547; found: 392.0736. Melting point: 64-66°C.

(3R,3aS,4R or 4S)-3-(1-Methylvinyl)-2,3,3a,4-tetrahydro-isoxazolo [2,3-a] indole-4-spiro-3'-pyrrolidine-1'-carboxylic acid methyl ester (14).

To a solution of (5) (200mg, 0.509mmol) in freshly distilled, degassed benzene (25ml) heated at reflux under an atmosphere of argon was added a solution of freshly distilled tri-n-butyltin hydride (164ml, 178mg, 0.611mmol) and azaisobutyronitrile (10mg, 0.06mmol) in benzene (10ml) dropwise over 18 hours *via* syringe pump. When the addition was complete, the heating was continued for a further hour, and then the reaction mixture was allowed to cool. The crude mixture was concentrated *in vacuo* and purified chromatographically (SiO_2, 1:1 ether / pentane) to yield a colourless gum (117mg,73%). ^1H nmr (400MHz, $CDCl_3$ @ 20°C): δ = 1.82 (s, 3H), 2.37 (t, 2H, J=7.0Hz), 3.05 (m, 1H), 3.28 + 3.33 (2xd, 1H, J=11.0Hz), 3.50 (m, 1H), 3.75 (m, 8H), 4.83 (t, 1H, J=1.4Hz), 4.85 (s, 1H), 7.13 (m, 3H), 7.53 (d, 1H, J=7.3Hz). ^1H nmr (250MHz, $CDCl_3$ @ 50°C): δ = 1.81 (s, 3H), 2.36 (t, 2H, J=7.8Hz), 3.01 (q, 1H, J=7.8Hz), 3.29 (d, 1H, J=10.9Hz), 3.50 (m, 1H), 3.67 (s, 3H), 3.70 (m, 5H), 4.83 (m, 1H), 4.86 (s, 1H), 7.08 (m, 3H), 7.53 (d, 1H, J=1.9 & 7.3Hz). ^{13}C nmr (100.4 MHz, $CDCl_3$ with DEPT 90 & 135 @ 20°C): δ = 18.489 (q), 31.016 + 32.004 (t), 45.281 + 45.647 (t), 52.468 (d), 52.596 (q), 53.566 (s), 58.357 + 58.741 (t), 71.982 + 72.164 (t), 76.736 + 76.864 (d), 113.514 + 113.715 (t), 115.708 (d), 122.475 + 122.566 (d), 124.706 (d), 128.894 + 129.004 (d), 132.204 (s), 143.543 + 143.762 (s), 151.077 (s), 155.357 + 155.631 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3076, 2954, 2880, 1704, 1640, 1608, 1594. HRMS: Calcd. for $C_{18}H_{22}N_2O_3$ ($[M]^+$): 314.163043; found: 314.1639.

2,3-Dihydro-pyrrolo [3,2-c] quinoline-1-carboxylic acid methyl ester hydrobromide (15).

To a solution of (5) (200mg, 0.509mmol) in freshly distilled, degassed toluene (25ml) heated at reflux under an atmosphere of argon was added a solution of freshly distilled *tris*(trimethylsilyl)silane (188ml, 152mg, 0.611mmol) and azaisobutyronitrile (10mg, 0.06mmol) in toluene (10ml) dropwise over 18 hours *via* syringe pump. When the addition was complete, the heating was continued for a further hour, before being allowed to cool. The crude mixture was concentrated *in vacuo* and purified chromatographically (SiO_2, 1:1 ether / pentane) to yield a yellow gum (70mg, 45%). ^1H nmr (250MHz, $CDCl_3$ @ 20°C): δ = 3.12 (m, 2H), 3.83 (s, 3H), 3.98 (m, 2H), 6.91 (d, 1H, J=8Hz), 7.01 (t, 1H, J=8Hz), 7.27 (t, 1H, J=8Hz), 7.58 (d, 1H, J=8Hz), 8.08 (br s, 1H). ^{13}C nmr (100.4 MHz, $CDCl_3$ with DEPT 90 & 135 @ 20°C): δ = 26.709 + 27.625 (t), 46.697 + 47.319 (t), 53.226 + 53.573 (q), 117.965 (s), 119.977 (d), 126.122 (d), 128.225 (d), 132.833 (d), 138.689 + 139.958 (s), 150.740 (s), 156.041 (d), 185.906 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3054, 2956, 1715, 1654, 1620, 1575. EIMS, m/e (rel. intensity): 310 (52%, $[M]^+$), 309 (40%,$[M-H]^+$), 308 (50%, $[M]^+$), 307 (35%,$[M-H]^+$), 229 (100%,$[M-Br]^+$). HRMS: Calcd. for $C_{13}H_{13}BrN_2O_2$ ($[M]^+$): 310.01412; found: 310.0144.

(2aR,2bR,3aR,6aS)-3,3-Dimethyl-2a,3,3a,4,5,6-hexahydro-2H-cyclopenta [b] pyrrolo [5,4,3a-cd] isoxazolo [2,3-a] indole-4-carboxylic acid methyl ester (28) & (3R,3aR, 4S)-3-(1-methylvinyl)-2,3,3a,4-tetrahydro-isoxazolo [2,3-a] indole-4-spiro-3'-pyrrol-idine-1'-carboxylic acid methyl ester (29) & 3-methoxy carbonyl-6,7-benzo-9-[2-(1-hydroxyl-3-methyl-3- butenyl)] 3-aza-8-azo [4,4] nonane (30).

To AIBN (34mg, 0.203mmol) and freshly distilled tri-*n*-butyltin hydride (415mg, 383ml, 1.42mmol) under an atmosphere of argon was added a solution of the *syn*- olefin (13) (400mg, 1.02mmol) in freshly distilled and degassed benzene (48ml). The reaction mixture was heated at reflux for 2 hours after which time all the starting

material had been consumed. The crude reaction mixture was concentrated *in vacuo* and the tin residues were removed[15] by dissolving the crude material in a mixture of ethyl acetate (3ml), water (125ml) and potassium fluoride dihydrate (350mg). The white precipitate formed was filtered through a plug of Celite®. The filtrate was dried (MgSO4), filtered, concentrated *in vacuo* and purified *via* chromatography (SiO_2 2:1 pentane / ether).
The first fraction (30mg) was a complex mixture of compounds. The second fraction was a colourless gum and analysed as the product of tandem radical cyclisation (28) (72mg, 22%). ^{1}H nmr (400MHz, $CDCl_3$ @ 20°C): δ = 1.08 (br s, 4.5H), 1.20 (br s, 1.5H), 2.35 (br m, 2H), 3.05 (dt, 1H, J=7.9 & 11.3Hz), 3.35 (dt, 1H, J=2 & 10Hz), 3.68 + 3.74 (2xs, 3H), 3.88 (dd, 1H, J=7.8 + 8.9Hz), 3.85 (br m, 2H), 4.10 + 4.21 (2xbr s, 1H), 4.36 (d, 1H, J=8.1Hz), 7.00 (d, 1H, J=7.5Hz), 7.15 (d, 2H, J=8Hz), 7.29 (br t, 1H, J=8Hz). ^{1}H nmr (250MHz, $CDCl_3$ @ 50°C): δ = 1.07 (br s, 3H), 1.12 (br s, 3H), 2.30 (br m, 2H), 3.03 (dt, 1H, J=7.9 & 11.1Hz), 3.35 (dd, 1H, J=8.9 & 11.1Hz), 3.70 (br m, 1H), 3.70 (s, 3H), 3.85 (dd, 1H, J=7.7 + 8.8Hz), 3.90-4.08 (br m, 2H), 4.16 (br s, 1H), 4.34 (d, 1H, J=8.2Hz), 7.01 (d, 1H, J=7.5Hz), 7.18 (d, 2H), 7.28 (m, 1H). ^{13}C nmr (100.4 MHz, $CDCl_3$ with DEPT 90 & 135 @ 20°C): δ = 24.890 + 25.128 (q), 25.475 (q), 36.923 + 37.746 (t), 45.775 (s), 49.451 + 49.871 (t), 52.359 + 52.633 (q), 63.642 + 63.917 (d), 63.258 + 64.227 (s), 66.879 (t), 78.346 +78.584 (d), 80.431 + 79.754 (d), 119.823 (d), 121.414 + 121.524 (d), 127.376 + 127.431 (d), 128.930 (d), 141.074 + 141.257 (s), 149.724 (s), 155.777 + 155.923 (s). ν_{max} ($CDCl_3$) / cm^{-1}: 2958, 1706, 1648, 1592, 1454. EIMS, m/e (rel. intensity): 314 (55%, $[M]^+$), 229 (100%). HRMS: Calcd. for $C_{18}H_{22}N_2O_3$ ($[M]^+$): 314.163043; found: 314.1630. The third fraction was a white solid (141mg, 44%), whose spectroscopic data were consistant with the monocyclised product (29). ^{1}H nmr (400MHz, $CDCl_3$ @ 20°C): δ = 1.33 (s, 3H), 2.35 (m, 1H), 2.60 (m, 1H), 3.29 (br d, 1H, J=10.8Hz), 3.42 (m, 1H), 3.63 + 3.65 (2xs, 3H), 3.70 (m, 4H), 3.97 (m, 1H), 4.08 (br t, 1H, J=8.2Hz), 4.67 (s, 1H), 4.80 (t, 1H, J=1.5Hz), 7.03 (m, 2H), 7.15 (d, 1H, J=8.0Hz), 7.25 (m, 1H). ^{1}H nmr (250MHz, $CDCl_3$ @ 50°C): δ = 1.35 (s, 3H), 2.31 (m, 1H), 2.57 (m, 1H), 3.31 (br d, 1H, J=10.8Hz), 3.39 (br q, 1H, J=8.4Hz), 3.66 (s, 3H), 3.65 (m, 4H), 3.97 (d, 1H, J=9.3Hz), 4.08 (dd, 1H, J=8.0 & 8.6Hz), 4.63 (s, 1H), 4.78 (t, 1H, J=1.5Hz), 7.03 (m, 2H), 7.12 (d, 1H, J=8.0Hz), 7.23 (m, 1H). ^{13}C nmr (100.4 MHz, $CDCl_3$ with DEPT 90 & 135 @ 20°C): δ = 21.964 (q), 28.730 + 29.773 (t), 45.665 + 46.049 (t), 52.322 (q), 52.450 (d), 52.743 + 53.108 (s), 60.350 + 60.680 (t), 71.762 + 71.872 (t), 76.334 (d), 115.397 + 115.617 (d), 116.732 + 116.952 (t), 121.505 (d), 124.688 (d), 128.839 (d), 134.399 + 134.709 (s), 141.275 + 141.458 (s), 150.693 (s), 155.686 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3054, 2986, 2954, 1700, 1460. CIMS, m/e (rel. intensity): 315 (3%, $[M+H]^+$), 297 (20%), 285 (100%), 231 (70%). HRMS: Calcd. for $C_{18}H_{23}N_2O_3$ ($[M+H]^+$): 315.170868; found: 315.1709. Melting point: 124-125°C. The final product to elute was isolated as a colourless gum and analysed as the monocyclised and N-O bond cleaved product (30) (48mg, 15%). ^{1}H nmr (400MHz, $CDCl_3$ @ 20°C): δ = 1.73 (m, 1H), 1.85 (s, 3H), 2.27 (m, 1H), 2.68 (br m, 1H), 3.74 + 3.77 (2xs, 3H), 3.65 (br m, 9H), 5.05 (s, 1H), 5.16 (s, 1H), 6.60 (d, 1H, J=7.7Hz), 6.72 (t, 1H, J=7.3Hz), 6.97 (m, 1H), 7.05 (t, 1H, J=7.7Hz). ^{13}C nmr (100.4 MHz, $CDCl_3$ with DEPT 90 & 135 @ 20°C): δ = 20.921 + 21.379 (q), 30.303 + 31.108 (t), 44.348 + 44.751 (t), 50.914 + 51.152 (d), 52.578 (q), 52.340 + 53.291 (s), 54.827 + 55.138 (t), 60.862 + 61.009 (t), 63.222 + 63.533 (d), 109.179 (d), 115.178 + 115.507 (t), 119.219 (d), 122.182 (d), 128.107 (d), 136.721 (s), 143.945 + 144.073 (s), 147.877 (s), 155.503 (s). ν_{max} (CH_2Cl_2) / cm^{-1}: 3403, 3074, 2956, 2888, 1688, 1610, 1486. CIMS, m/e (rel. intensity): 317 (5%, $[M+H]^+$), 297 (15%), 285 (35%), 231 (100%). HRMS: Calcd. for $C_{18}H_{25}N_2O_3$ ($[M+H]^+$): 317.1865518; found: 317.1865.

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