Nitrone Cycloaddition: An Approach to the Cyclophane Alkaloid (±)-Lythranidine[1]

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The synthesis of (±)-lythranidine **1**, a cyclophane alkaloid from *Lythrum anceps* Makino, involves three interesting problems. These are the construction of the 17-membered ring, the formation of the *trans*-2,6-dialkylpiperidine and the establishment of the correct relative stereochemistry at the four asymmetric centres (C-3, C-5, C-9, C-11). In our approach to the synthesis of this alkaloid, the *trans*-dialkylpiperidine was formed *via* a nitrone cycloaddition reaction. Cyclisation to give the 17-membered ring was achieved using tris(triphenylphosphine)nickel(0), prepared *in situ* from bis(triphenylphosphine)nickel dichloride, and the di-iodide **9**. Deprotection of macrocyclic biaryl **10** gave the (C-3, C-11) epimer of (±)-lythranidine.

Over 40 alkaloids have been isolated from the Lythraceae family of plants.[1] They have been classified into five structural types,[2] representative alkaloids of which are shown in structures **A**–**E**.

The laboratory synthesis of (±)-lythranidine **1**, an alkaloid extracted from *Lythrum anceps* Makino, involves three interesting problems. These are the construction of the 17-membered ring, the formation of the *trans*-2,6-dialkylpiperidine and the establishment of the correct relative stereochemistry at the four asymmetric centres (C-3, C-5, C-9, C-11). To date only one synthesis of (±)-lythranidine has been published.[3]

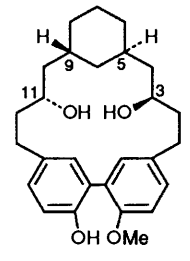
In our approach, we proposed to set up the *trans*-2,6-dialkylpiperidine of lythranidine by using a nitrone cycloaddition reaction. Formation of the biaryl linkage to give the 17-membered ring would occur at a later stage in the synthesis. An additional feature to this approach is that the cycloaddition of nitrones to alkenes gives ultimately 1,3-amino alcohols in a stereocontrolled fashion. Epimerisation of the alcohols would therefore furnish the natural product.

exo-Addition[4] of 4-(*p*-benzyloxyphenyl)but-1-ene† to 3,4,5,6-tetrahydropyridine 1-oxide in boiling chloroform smoothly gave the isoxazolidine **2**. Oxidation with *m*-chloroperoxybenzoic acid (MCPBA) gave a mixture of isomeric nitrones. Subsequent cycloaddition with 4-(*p*-benzyloxyphenyl)-but-1-ene afforded the isoxazolidine **3** in 31% yield.

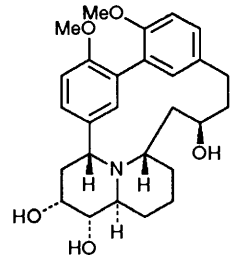
Earlier work has established[4] that cycloaddition of terminal alkenes to 2,3,4,5-tetrahydropyridine 1-oxide takes place in the *exo*-mode leading, by analogy, to the stereochemistry shown in structure **2**. These isoxazolidines, when treated with MCPBA, give a mixture of isomeric nitrones.[5] This contrasts with the observation by Tufariello *et al.*[4] that isoxazolidines prepared from Δ^1-pyrroline 1-oxides could be oxidised with MCPBA to give exclusively one regioisomer (Scheme 1). Oxidation of these isoxazolidines with MCPBA, followed by cycloaddition with a terminal alkene, however, has been shown to give the *trans*-substituted piperidine.

Reductive cleavage of the N–O bond with zinc/10 mol dm^{-3} acetic acid yielded the symmetrical dialkylpiperidine **4**. Benzoylation of the nitrogen and acetylation of the hydroxy groups gave the fully protected amido diacetate **5**.

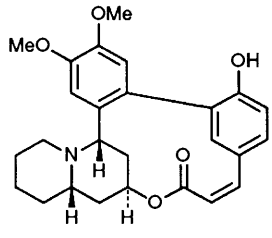
Of the methods available for forming a bond between two aromatic rings,[6] the Ullmann reaction[7] has been one of the most widely used. The traditional reaction conditions consist of heating an aryl halide in the presence of finely divided copper without solvent at high temperature. The high temperatures needed for this reaction reduce its utility for the synthesis of complex natural products. The use of zero-valent nickel in place of copper, on the other hand, has been reported to give biaryls in high yield at low temperatures (~50 °C),[8] and it is by this method that we proposed to form the biaryl bond in our synthesis of (±)-lythranidine. The conventional Ullmann



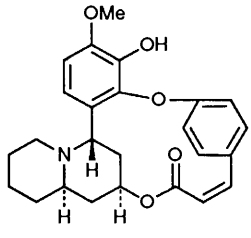
1 **A** Lythranidine



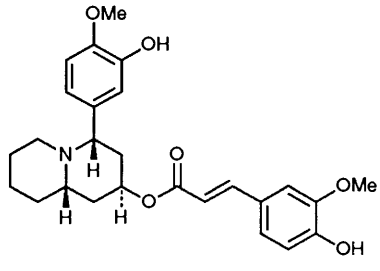
B Lythrancine-1



C Lythrine

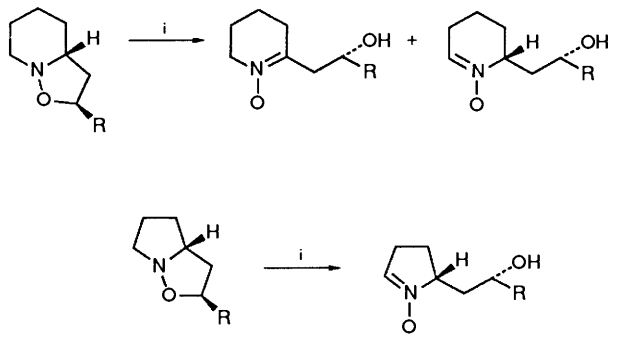


D Lagerine



E Abresoline

† An analogous study using 4-(*p*-methoxyphenyl)but-1-ene proved unsuccessful, giving a complex mixture in the cycloaddition reaction following the MCPBA oxidation.



Scheme 1 *Reagent:* i, MCPBA

reaction, and its low-temperature variants, results in the biaryl bond being formed at the position from which the halide is displaced. We therefore needed to prepare the di-iodide **7**.

Treatment of compound **5** with thallium(III) trifluoroacetate in trifluoroacetic acid (TFA) followed by aqueous KI[9] gave an intractable tar. A model study using 4-benzyloxytoluene also gave no identifiable products although treatment of 4-methoxytoluene in a similar fashion gave 3-iodo-4-methoxytoluene in 5% yield. It is likely that the strong mineral acid used as solvent for this reaction is responsible for the decomposition observed. Reaction of 4-benzyloxy- and 4-methoxy-toluene with silver(I) trifluoroacetate and iodine in dichloromethane gave the 3-iodoaromatic in 54 and 56% yield, respectively. The silver(I) trifluoroacetate/iodine method therefore seemed the most promising for our purposes.

Treatment of compound **5** with silver(I) trifluoroacetate/iodine (4 mol equiv.) for 40 h at room temperature gave the mono-iodinated product **6** in 81% yield. The availability of this product led us to consider other methods used to form biaryl bonds. Photolysis of aryl iodides has been reported to give biaryls[10] in moderate yield. Irradiation of compound **6** in acetonitrile gave the biaryl in low yield, together with considerable decomposition. Treatment of compound **5** with 10 mol equiv., or compound **6** with another 4 mol equiv., of silver(I) trifluoroacetate/iodine afforded the di-iodide **7**.

Reaction of the di-iodide with the zero-valent nickel complex, formed by the reduction of bis(triphenylphosphine)nickel dichloride with zinc in the presence of triphenylphosphine, resulted in de-iodination to give compound **5** in 54% yield. The observation of de-iodination implies that the intermediate diarylnickel complex formed but that closure to give the macrocycle was slow, possibly due to steric hindrance of the benzyl protecting groups. In order to lower steric hindrance we turned our attention to the methyl-protected amido diacetate **8**.

Hydrogenolysis of the benzyl protecting groups in compound **5** and methylation of the resulting diphenol gave compound **8** in 96% overall yield. Treatment of compound **8** with 8 mol equiv. of silver(I) trifluoroacetate/iodine gave di-iodide **9** in 83% yield. Reaction of this di-iodide with the zero-valent nickel complex at 55 °C furnished a mixture of biaryl **10** (55%), de-iodinated material **8**, and mono- and di-iodinated compounds in trace amounts. ^{13}C NMR spectroscopy showed the biaryl to be a mixture of isomers (due to the chiral biaryl axis) in the ratio 3:1.

Treatment of compound **10** with methanolic potassium carbonate gave the crystalline macrocyclic amido diol **11** in 99% yield as a mixture of isomers. Recrystallisation from dichloromethane/light petroleum, however, gave a single compound, as seen by NMR spectroscopy. Treatment of this compound with diethyl azodicarboxylate (DEAD), triphenylphosphine and either benzoic, formic or acetic acid in diethyl ether or dichloromethane afforded the starting material **11** as well as diethyl hydrazinedicarboxylate and triphenylphosphine oxide. The latter two compounds are by-products of the Mitsunobu inversion procedure,[11] and so partial inversion may have occurred.

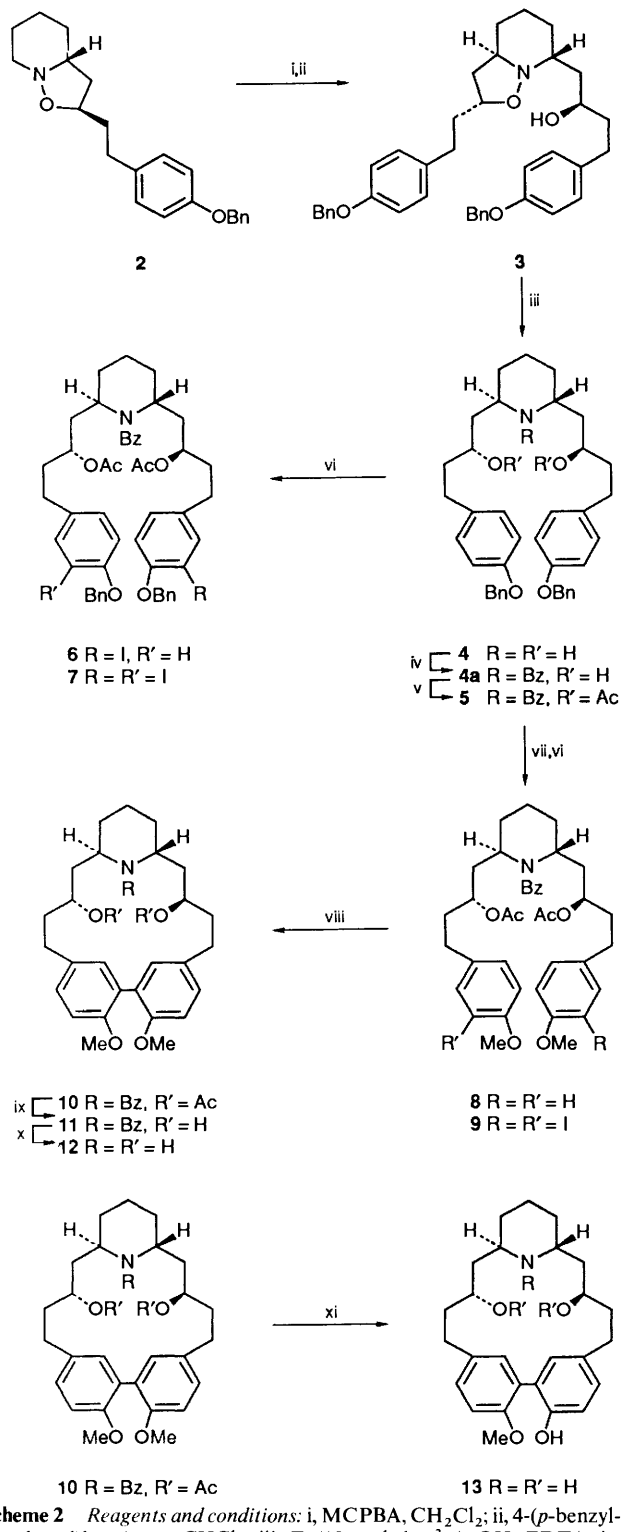
Reduction of compound **11** with $LiAlH_4$ and hydrogenolysis gave the amino diol **12**. Treatment of compound **10** with diisobutylaluminium hydride (DIBAL) (with a view to fully deprotecting the amido diacetate in one step[12]) gave a product corresponding to **11** (TLC). Interestingly, treatment of the crude product from this reaction with $LiAlH_4$ and hydrogenolysis as above resulted in monodemethylation to give the (C-3, C-11) epimer of (±)-lythranidine, compound **13** (Scheme 2).

Experimental

250 MHz ^1H and 62.9 MHz ^{13}C NMR spectra were recorded with a Bruker AM 250 spectrometer. *J*-Values are given in Hz. Short-column chromatography[13] and dry-column flash chromatography used Merck Kieselgel 60H (Merck No. 7736), and flash chromatography[14] used Camlab Kieselgel 60, 230–400 mesh. IR spectra were recorded with a Perkin-Elmer 881 spectrometer, as liquid films unless otherwise stated. High-resolution accurate mass spectra were determined at the SERC Mass Spectroscopy Centre, University College, Swansea. Light petroleum refers to that fraction boiling in the range 40–60 °C.

trans-8-[2-(p-*Benzyloxyphenyl*)*ethyl*]-9-*oxa*-1-*azabicyclo*-[4.3.0]*nonane* **2**.—A solution of *N*-hydroxypiperidine (3.47 g, 34 mmol) in dry dichloromethane (30 cm^3) was stirred with yellow mercury(II) oxide (24.7 g, 114 mmol) for 30 min. Magnesium sulphate (2.5 g) was added and the slurry was filtered through a plug of Celite and $MgSO_4$ with the aid of dichloromethane (130 cm^3). The solvent was removed under reduced pressure and was replaced with chloroform (50 cm^3). The solution was treated with 4-(4-benzyloxyphenyl)but-1-ene (1.88 g, 7.8 mmol) and refluxed under nitrogen for 24 h, after which the cooled solution was washed successively with 2 mol dm^{-3} HCl (100 cm^3) and saturated aq. $NaHCO_3$ (100 cm^3), dried over $MgSO_4$, filtered, and evaporated. Chromatography over flash silica and elution with 10–50% ether–hexane gave the *product* **2** (2.16 g, 81%) as a pale yellow oil, which solidified on storage; ν_{max}/cm^{-1} 3034, 2859, 1613, 1585, 1513, 1455, 1028, 834, 731 and 696; δ_H(250 MHz; $CDCl_3$) 1.59–2.15 (10 H, m), 2.15–2.39 (1 H, app q), 2.39–2.58 (1 H, m), 2.58–2.87 (3 H, m), 3.37–3.73 (1 H, br s), 4.00–4.19 (1 H, br s), 5.00 (2 H, s, CH_2Ph), 6.88 and 7.11 (4 H, ABq, ArH) and 7.20–7.65 (5 H, ArH) [Found: C, 78.0; H, 8.1; N, 4.15%; (M^+ + 1), 338. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.06; N, 4.15%; (M^+ + 1), 338].

(2R*,6R*,8R*)-8-[2-(p-*Benzyloxyphenyl*)*ethyl*]-2-[(2′R*)-4-(p-*benzyloxyphenyl*)-2-*hydroxybutyl*]-9-*oxa*-1-*azabicyclo*-[4.3.0]*nonane* **3**.—To a stirred solution of the isoxazolidine **2** (5.85 g, 17.3 mmol) in dichloromethane (100 cm^3) at 0 °C was added a solution of MCPBA (80%; 3.74 g, 17.3 mmol) in dichloromethane (70 cm^3) during 20 min. After the addition the mixture was stirred at room temp. for 1 h. The solution was washed with saturated aq. $NaHCO_3$ (2 × 100 cm^3), dried over $MgSO_4$, filtered and evaporated. Chloroform (50 cm^3) and 4-(4-benzyloxyphenyl)but-1-ene (6.78 g, 28 mmol) was added and the solution was refluxed under nitrogen for 40 h. Chromatography over 60H silica and elution with hexane–80% diethyl ether–hexane gave the *isoxazolidine* **3** as a solid (3.32 g, 31.3%). Recrystallisation from ethyl acetate–light petroleum gave an amorphous powder (m.p. 107–108 °C); ν_{max}(KBr disc)/cm^{-1} 3337, 3033, 2918, 1609, 1582, 1381, 1241, 1075, 906, 738 and 696; δ_H(250 MHz; $CDCl_3$) 1.19–2.16 (13 H, m), 2.21–2.46 (1 H, app q), 2.49–3.00 (5 H, m), 3.49–3.73 (1 H, br s), 3.86–4.14 (1 H, m), 4.16–4.41 (1 H, m), 4.65–4.97 (1 H, br m, OH), 5.08 (4 H, s, 2 × $PhCH_2$), 6.92 and 7.13 (8 H, 2 overlapping ABq,



Scheme 2 *Reagents and conditions*: i, MCPBA, CH_2Cl_2; ii, 4-(*p*-benzyloxyphenyl)but-1-ene, $CHCl_3$; iii, Zn/10 mol dm^{-3} AcOH, EDTA; iv, BzCl, Et_3N; v, Ac_2O, py, DMAP; vi, CF_3CO_2Ag, CH_2Cl_2; then I_2–$CHCl_3$; vii, 5% Pd/C, H_2, MeOH; then K_2CO_3, MeI, acetone; viii, $(PPh_3)_2NiCl_2$, Zn, DMF, PPh_3; ix, K_2CO_3, MeOH; x, $LiAlH_4$, THF; then 5% Pd/C, H_2, MeOH; xi, DIBAL, THF; then $LiAlH_4$, THF; 5% Pd/C, H_2, MeOH

ArH) and 7.24–7.59 (10 H, m, ArH); δ_C(62.9 MHz; $CDCl_3$) 18.52 (CH_2), 25.51 (br, CH_2), 29.40, 31.14 and 31.24 (3 × CH_2), 35.56 (br, CH_2), 37.34 (CH_2), 39.12 (br, CH_2), 40.04 (CH_2), 39.12 (3 × br CH_2), 56.66 (CH), 59.68 (br, CH), 68.33 (CH), 70.13 (PhCH_2), 75.59 (CH), 114.8 and 114.87 (CH *ortho* to OBn), 127.45, 127.84, 127.87, 128.52, 128.54 and 129.38 (6 × arom CH), 134.11, 135.18, 137.30 and 137.40 (4 × arom Cquat) and 156.96 and 157.14 (2 × arom Cquat) (Found: C, 79.1; H, 7.7; N, 2.4. $C_{39}H_{45}NO_4$ requires C, 79.15; H, 7.66; N, 2.37%).

(2R*,6R*)-2,6-*Bis*-[(2R*)-4-(p-*benzyloxyphenyl*)-2-*hydroxybutyl*]*piperidine* **4**.—The isoxazolidine **3** (3.21 g, 5.42 mmol) and ethylenediaminetetraacetic acid (13.11 g, 54 mmol) were dissolved in an ethanol (160 cm^3)–10 mol dm^{-3} acetic acid (160 cm^3) mixture and heated to reflux. Zinc dust (2.82 g, 43 mmol) was added cautiously and the mixture was heated at reflux for 30 min. The cooled solution was neutralised with aq. NH_4OH (*d* 0.880) and extracted with chloroform (5 × 200 cm^3). The organic phase was dried over $MgSO_4$, filtered, and evaporated to give a solid. Recrystallisation from ethyl acetate–light petroleum gave the *product* **4** as an amorphous powder (2.37 g, 74%) (m.p. 110–112 °C); ν_{max}(Nujol)/cm^{-1} 3368, 2926, 2856, 1610, 1582, 1174, 1023, 822, 738 and 696; δ_H(250 MHz; $CDCl_3$) 1.11–1.51 (4 H, m), 1.51–2.11 (10 H, m), 2.46–3.05 (4 H, m, 2 × ArCH_2), 3.05–4.19 (5, H, br m, NH, 2 × CHN, 2 × CHOH), 5.05 (4 H, s, 2 × PhCH_2), 6.94 and 7.16 (8 H, ABq, ArH) and 7.27–7.73 (10 H, m, ArH); δ_C(62.9 MHz; $CDCl_3$) 19.96, 31.57, 32.06, 39.10, 39.60 (5 × CH_2), 47.29 (CH), 68.56 (CH), 70.14 (PhCH_2), 114.89 (arom CH *ortho* to OBn), 127.46, 127.86, 128.55 and 129.36 (4 × arom CH) and 134.83, 137.35 and 157.06 (3 × arom Cquat) [Found: C, 79.0; H, 7.8; N, 2.4%; (M^+ + 1), 594. $C_{39}H_{47}NO_4$ requires C, 78.89; H, 7.98; N, 2.36%; (M^+ + 1), 594].

(2R*,6R*)-1-*Benzoyl*-2,6-bis-[(2R*)-4-(p-*benzylhydroxyphenyl*)-2-*hydroxybutyl*]*piperidine* **4a**.—A solution of amino diol **4** (2.68 g, 4.5 mmol) in benzene (50 cm^3) at 0 °C was stirred and treated with triethylamine (0.69 cm^3, 1.1 mol equiv.) and benzoyl chloride (0.52 cm^3, 1.1 mol equiv.) under nitrogen for 8 h. The solution was washed successively with 2 mol dm^{-3} HCl (2 × 100 cm^3) and saturated aq. $NaHOC_3$ (2 × 100 cm^3), dried over $MgSO_4$, filtered and evaporated. Chromatography over 60H silica and elution with chloroform gave the amide **4a** (1.716 g, 55%). Another component (1.1 g, 31%), identified as the amido monobenzoate, was also isolated. This was treated with methanolic KOH to give the *amide* **4a** (824 mg, overall yield 2.54 g, 81%); ν_{max}/cm^{-1} 3408, 3064, 2865, 1608, 1510, 1453, 1413, 830, 739 and 696; δ_H(250 MHz; $CDCl_3$) 1.35–2.22 (14 H, m), 2.32–2.89 (4 H, br s), 3.11–3.65 (2 H, br s), 3.89–4.46 (2 H, br s), 5.05 (4 H, s, 2 × PhCH_2), 6.92 and 7.08 (8 H, ABq, ArH) and 7.19–7.60 (15 H, m, ArH); δ_C(62.9, MHz; $CDCl_3$), 16.18, 27.26, 30.91, 39.07 and 41.84 (5 × CH_2), 67.60 (br CH), 70.12 (PhCH_2), 114.85 (CH *ortho* to OBn), 126.59–129.56 (6 × arom CH), 134.43, 137.25, 137.81 and 157.09 (4 × arom Cquat) and 174.0 (C=O) (Found: C, 79.2; H, 7.4; N, 2.0. $C_{46}H_{51}NO_5$ requires C, 79.50; H, 7.32; N, 2.06%).

(2R*,6R*)-2,6-Bis-[(2R*)-2-*acetoxy*-4-(p-*benzyloxyphenyl*)-*butyl*]-1-*benzoylpiperidine* **5**.—A solution of amido diol **4a** (570 mg, 0.82 mmol) in dry pyridine (20 cm^3) was treated with acetic anhydride (2 cm^3, 21 mmol) and 4-dimethylaminopyridine (DMAP) (60 mg, 0.5 mmol). The solution was stirred under nitrogen for 24 h. Chloroform (50 cm^3) was added and the solution was washed successively with 2 mol dm^{-3} HCl (100 cm^3), saturated aq. $NaHCO_3$ (100 cm^3), water (50 cm^3) and saturated brine (100 cm^3), dried over $MgSO_4$, filtered and evaporated. Chromatography over 60H silica and elution with chloroform gave the *amido acetate* **5** as a pale yellow oil (614 mg, 96%); ν_{max}/cm^{-1} 3034, 2935, 2865, 1728, 1638, 1610, 1582, 1509, 1026, 736 and 697; δ_H(250 MHz; $CDCl_3$) 1.46–1.95 (10 H, m), 1.95–2.19 (2 H, m), 2.05 (6 H, s, OAc), 2.19–2.81 (6 H, m), 3.46–3.76 (2 H, br s, 2 × CHN), 4.76–4.97 (2 H, br s, 2 × CHOAc), 5.03 (4 H, s, 2 × PhCH_2), 6.92 and 7.05 (8 H, ABq, ArH) and 7.16–7.76 (15 H, m, ArH); δ_C(62.9 MHz; $CDCl_3$)

19.11 (CH_2), 21.27 (OAc), 28.19, 30.37, 36.12 and 36.90 (4 × CH_2), 52.92 (br, CH), 70.10 (Ph*C*H_2), 71.86 (br CH), 114.89 (arom CH *ortho* to OBn), 133.82, 137.32, 137.83 and 157.12 (4 × arom Cquat), 170.00 (C=O, acetate) and 173.00 (C=O, amide) (Found: M^+, 782.4053. $C_{50}H_{55}NO_7$ requires M, 782.405 64).

Iodination of Amino Diacetate **5**.—A solution of amido diacetate **5** (331 mg, 0.42 mmol) in dry dichloromethane (10 cm^3) was treated with silver trifluoroacetate (410 mg, 1.84 mmol). The slurry was stirred under nitrogen for 10 min. A solution of iodine (241 mg, 1.9 mmol) in chloroform (14 cm^3) was added dropwise during 10 min. The resulting pale yellow slurry was stirred under nitrogen for 40 h at room temperature. The slurry was filtered through a plug of Celite with the aid of chloroform, and evaporated to give a brown glass. Chromatography over 60H silica and elution with 50% ethyl acetate–dichloromethane gave the *mono-iodinated compound* **6** (313 mg, 81%); δ_H(250 MHz; $CDCl_3$) 1.41–1.86 (10 H, m), 2.03 (6 H, s, OAc), 1.86–2.19 (3 H, m), 2.19–2.65 (6 H, m), 3.46–3.70 (2 H, br s), 4.73–4.95 (2 H, br s), 5.00 (4 H, s, 2 × Ph*C*H_2), 6.73 (2 H, d, *J* 12.2), 6.86 (1 H, d, *J* 12, CH *meta* to iodine), 6.95–7.08 (3 H, m, arom including CH *para* to iodine), 7.19–7.49 (15 H, ArH) and 7.54 (1 H, d, *J* 2.7, CH *ortho* to iodine); δ_C(62.9 MHz; $CDCl_3$), 19.10 (CH_2), 21.29 (2 × OAc), 28.21, 30.10, 30.57, 35.88 (×2) and 36.89 (6 × CH_2), 52.76 (2 × br, CH, CHNCH), 70.02 and 70.96 (2 × Ph*C*H_2), 71.74 and 71.96 (2 × *C*HOAc), 86.85 (CI), 112.80 (arom CH *ortho* to OBn on iodinated ring), 114.87 (arom CH *ortho* to OBn), 126.94–129.98 (10 × arom CH), 133.74, 136.08, 136.73, 137.31 and 137.84 (5 × arom Cquat), 139.09 (CH *ortho* to iodine), 155.53 and 157.09 (arom Cquat), 170.45 (C=O, acetate) and 173.78 (C=O, amide) [Found: (M^+ + 1), 908.2976 (FAB). $C_{50}H_{55}NIO_7$ requires *m/z*, 908.302 327].

Photolysis of Compound **6**.—A solution of compound **6** (50 mg, 0.05 mmol) in dry acetonitrile (2 cm^3) was irradiated in a quartz cell with a 400 W bulb for 2.5 h. Solvent was removed under reduced pressure. Chromatography over 60H silica and elution with 5% ethyl acetate–dichloromethane gave the biaryl (5 mg, 12%); δ_H(250 MHz; $CDCl_3$) 2.05 (6 H, s, 2 × OAc), 1.43–2.19 (12 H, m), 2.19–2.89 (6 H, m), 3.46–3.78 (2 H, br s, C*H*NC*H*), 4.70–5.00 (2 H, br s, 2 × C*H*OAc), 5.14 (4 H, s, 2 × Ph*C*H_2) and 6.81–7.89 (21 H, m); δ_C(62.9 MHz; $CDCl_3$), 19.11 (CH_2), 21.28 (OAc), 28.19, 30.53, 30.98, 36.15 and 36.92 (5 × CH_2), 52.89 (2 × br, CH, CHNCH), 68.49 (2 × Ph*C*H_2), 71.97 (*C*HOAc), 117.20, 122.01, 122.99, 124.60, 126.93, 127.55, 128.37, 128.61 and 129.30 (9 × arom CH), 130.20, 131.51, 135.00, 137.74 and 153.01 (5 × arom Cquat), 170.57 (C=O, acetate) and 173.87 (C=O, amide) [Found: (M^+ + 1), 780.390 102 4 (FAB). $C_{50}H_{54}NO_7$ requires *m/z*, 780.389 99].

(2R*,6R*)-2,6-Bis-[(2R*)-2-*acetoxy*-4-(4-*benzyloxy*-3-*iodophenyl*)*butyl*]-1-*benzoylpiperidine* **7**.—Silver trifluoroacetate (5.5 g, 25 mmol, 10.4 mol equiv.) was added in one portion to a solution of the amido diacetate **5** (1.87 g, 2.4 mmol) in dry dichloromethane (50 cm^3) and the mixture was stirred under nitrogen for 5 min. A solution of iodine (1.724 g, 13.6 mmol, 5.6 mol equiv.) in chloroform (100 cm^3) was added dropwise during 40 min. The slurry was stirred for 48 h and then filtered through a plug of Celite with the aid of dichloromethane (500 cm^3). The solvent was removed to give a brown foam. Chromatography over 60H silica and elution with 5% ethyl acetate–dichloromethane gave the *product* **7** as a foam (1.496 g, 60%); ν_{max}/cm^{-1} 2967, 2930, 2672, 1771, 1728, 1644, 1522, 946, 907 and 812; δ_H(250 MHz; $CDCl_3$) 1.43–1.84 (10 H, m), 1.84–2.00 (2 H, m), 2.08 (6 H, s, OAc), 2.11–2.41 (2 H, m), 2.41–2.70 (4 H, m), 3.43–3.76 (2 H, br s, C*H*NC*H*), 4.67–5.00 (2 H, br s, 2 × C*H*OAc), 5.11 (4 H, s, 2 × Ph*C*H_2), 6.76 (2 H, d, *J* 12.3, CH *meta* to I), 7.00 (2 H, dd, *J* 12.3, 2.7, CH *para* to I), 7.19–7.67 (15 H, m, ArH) and 7.54 (2 H, d, *J* 2.7, arom CH *ortho* to I); δ_C(62.9 MHz; $CDCl_3$) 18.96 (CH_2), 21.24 (OAc), 28.07, 30.08, 35.86 and 36.93 (4 × CH_2), 52.75 (br, CH, CHNCH), 71.08 (Ph*C*H_2), 71.82 (*C*HOAc), 86.85 (CI), 112.83 (CH *meta* to I), 126.90, 127.04, 127.83, 128.52 and 128.70 (5 × arom CH), 129.22 (CH *para* to I), 129.97 (arom. CH), 136.11, 136.72 and 137.79 (3 × arom Cquat), 139.12 (CH *ortho* to I), 155.58 (arom Cquat), 170.50 (C=O, acetate) and 173.78 (C=O, amide) [Found: (M^+ + 1), 1034.198 803 (FAB). $C_{50}H_{54}NI_2O_7$ requires *m/z*, 1034.198 936].

Attempted Cyclisation of Compound **7**.—Bis(triphenylphosphine)nickel dichloride (90 mg, 0.13 mmol), zinc (60 mg, 1 mmol), and triphenylphosphine (70 mg, 0.26 mmol) were placed in an oven-dried Schlenk tube. *N*,*N*-Dimethylformamide (DMF) (5 cm^3) was added and the Schlenk tube was evacuated and filled with nitrogen three times. The flask was heated to 50 °C for 30 min during which time the solution became dark red (from deep blue). The substrate (104 mg, 0.1 mmol) in DMF (5 cm^3) was added under nitrogen pressure and the solution was stirred under nitrogen at 50 °C. After 90 min the solution became pale green although overnight the dark red solution reappeared. After 22 h the solution was poured into 2 mol dm^{-3} HCl (50 cm^3) and extracted with chloroform (3 × 50 cm^3). The extracts were diluted with diethyl ether (100 cm^3), and the organic phase was washed successively with water (100 cm^3) and saturated brine (100 cm^3), dried over $MgSO_4$, filtered, and evaporated. Chromatography over 60H silica and elution with 5% ethyl acetate–dichloromethane gave the amido acetate **5**.

(2R*,6R*)-2,6-*Bis*-[(2R*)-2-*acetoxy*-4-(p-*methoxyphenyl*)*butyl*]-1-*benzoylpiperidine* **8**.—A solution of amido diacetate **7** (1.838 g, 2.35 mmol) in 50% methanol–diethyl ether mixture (50 cm^3) was hydrogenated over 5% Pd/C (200 mg) at atmospheric pressure for 90 min. The slurry was filtered through a plug of Celite with the aid of diethyl ether. The solvent was removed and replaced with acetone (60 cm^3). K_2CO_3 (5 g) and iodomethane (3 cm^3, 48 mmol) and the mixture was refluxed and stirred for 4 h. The acetone was removed under reduced pressure and replaced with chloroform (50 cm^3) and water (50 cm^3). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 50 cm^3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Chromatography over 60H silica and elution with chloroform gave the *product* **8** (1.425 g, 96%) as a foam; $\nu_{max}(CHCl_3)/cm^{-1}$ 3002, 2942, 1727, 1632, 1510, 1442, 1373, 1239, 1028 and 823; δ_H(250 MHz; $CDCl_3$) 1.38–1.65 (2 H, m), 1.65–1.86 (8 H, m), 1.86–1.97 (2 H, m), 2.03 (6 H, s, 2 × OAc), 2.11–2.43 (2 H, br s), 2.43–2.70 (4 H, m), 3.46–3.67 (2 H, br s), 3.81 (6 H, s, 2 × OMe), 4.67–5.00 (2 H br s), 6.78 and 7.00 (8 H, ABq, ArH) and 7.27–7.54 (5 H, m, ArH); δ_C(62.9 MHz; $CDCl_3$) 19.08 (CH_2), 21.23 (OAc), 28.16, 30.50, 36.13 and 36.86 (4 × CH_2), 52.85 (br, CH), 55.23 (OMe), 71.96 (CH), 113.82 (CH *ortho* to OMe), 126.62, 128.62, 129.15 and 129.83 (4 × arom CH), 133.46 and 137.82 (2 × arom Cquat), 157.86 (arom. Cquat *para* to OMe), 170.53 (C=O, acetate) and 173.84 (C=O, amide) (Found: M^+, 629.335. $C_{38}H_{47}NO_7$ requires M, 629.335 215).

(2R*,6R*)-2,6-*Bis*-[(2R*)-2-*acetoxy*-4-(3-*iodo*-4-*methoxyphenyl*)*butyl*]-1-*benzoylpiperidine* **9**.—Silver trifluoroacetate (4.12 g, 18.6 mmol, 8 mol equiv.) was added in one portion to a solution of amido acetate **8** (1.476 g, 2.34 mmol) in dry dichloromethane (50 cm^3). After 5 min, a solution of iodine (2.38 g, 18.7 mmol) in chloroform (100 cm^3) was added and the mixture was stirred for 3 h at room temperature. The slurry was filtered through a plug of Celite with the aid of dichloromethane (500 cm^3). Solvent was removed under reduced pressure and

chromatography over 60H silica and elution with dichloromethane–5% ethyl acetate–dichloromethane gave the *product* **9** (1.716 g, 83%) as a foam; $\nu_{max}(CHCl_3)/cm^{-1}$ 2973, 1729, 1630, 1490, 1439, 1372, 876 and 707; δ_H(250 MHz; $CDCl_3$) 1.38–1.81 (10 H, m), 1.81–1.97 (2 H, m), 2.03 (6 H, s, OAc), 2.11–2.57 (6 H, m), 3.38–3.65 (2 H, br s), 3.81 (6 H, s, 2 × OMe), 4.57–5.05 (2 H, br s), 6.65 (2 H, d, *J* 12.1, CH *meta* to I), 7.03 (2 H, dd, *J* 12.1 and 2.6, CH *para* to I), 7.24–7.43 (5 H, m, ArH) and 5.51 (2 H, d, *J* 2.6 CH *ortho* to I); δ_C(62.9 MHz; $CDCl_3$) 19.01 (CH_2), 21.27 (OAc), 28.13, 30.01, 35.89 and 36.87 (4 × CH_2), 52.75 (br, CH), 56.41 (OMe), 71.73 (CH), 85.92 (CI), 110.94 (CH *ortho* to OMe), 126.88, 128.68, 129.31 and 129.95 (4 × arom CH), 135.67 and 137.78 (2 × arom Cquat), 139.01 (CH *ortho* to I), 156.42 (arom. Cquat), 170.45 (C=O, acetate) and 173.75 (C=O, amide) (Found: M^+, 881.128 557 3. $C_{38}H_{45}NI_2O_7$ requires M, 881.128 51).

Cyclisation of Compound **9**.—Bis(triphenylphosphine)nickel dichloride (418 mg, 0.64 mmol), zinc (70 mg, 1 mmol), triphenylphosphine (171 mg, 0.65 mmol), and dry DMF (20 cm^3) were placed in a Schlenk tube, which was then evacuated and filled with nitrogen three times. The flask was heated to 50 °C for 30 min during which time the solution became dark red. A solution of the substrate (250 mg, 0.28 mmol) in DMF (5 cm^3) was added and the mixture was stirred under a flow of argon for 21 h at 50 °C. The cooled solution was evaporated to give a black oil, 2 mol dm^{-3} HCl (150 cm^3) was added and the solution was extracted with diethyl ether (3 × 50 cm^3). The extracts were washed with brine (100 cm^3), dried over $MgSO_4$, filtered, and evaporated. Chromatography over 60H silica and elution with dichloromethane–5% diethyl ether–dichloromethane gave the *biaryl* **10** (98 mg, 55%) as a 3:1 mixture of diastereoisomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 2932, 2860, 1723, 1627, 1499, 1446, 1024, 943 and 908; δ_H(250 MHz; $CDCl_3$) 1.19–2.27 (13 H, m), 2.05 (6 H, 2 s, 2 × OAc), 2.27–3.11 (5 H, m), 3.11–3.38 (1 H, br s), 3.38–4.00 (6 H, 4 s, Me), 4.00–4.32 (1 H, br s), 4.46–5.05 (3 H, 3 overlapping br s) and 6.43–7.73 (11 H, m); δ_C(62.9 MHz; $CDCl_3$) 20.87 (br, OAc), 52.71 and 54.42 (br CH), 55.96 and 55.87 (OMe), 70.95, 71.95, 72.68 and 73.58 (*C*HOAc), 111.62, 111.98 and 113.82 (CH *ortho* to OMe), 137.44, 137.62 and 137.84 (Cquat, biaryl), 155.52, 155.40 and 155.78 (Cquat *para* to OMe), 170.21, 170.52, 170.77 and 171.32 (C=O, acetate) and 173.65 and 173.85 (C=O, amide) (Found: M^+, 627.3195. $C_{38}H_{45}NO_7$ requires M, 627.319 565).

Hydrolysis of Biaryl **10**.—K_2CO_3 (2.5 g) was added to a solution of the biaryl (314 mg, 0.5 mmol) in methanol (50 cm^3) and the solution was stirred for 18 h. The methanol was removed under reduced pressure and was replaced with chloroform (50 cm^3) and water (50 cm^3). The organic phase was separated and the aq. phase was extracted with chloroform (3 × 50 cm^3). The combined organics were washed with brine, dried over $MgSO_4$, and evaporated. Chromatography over 60H silica and elution with chloroform gave the *product* **11** as a solid. Recrystallisation from dichloromethane–light petroleum gave an amorphous powder (269 mg, 99%), m.p. 232–234 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 3398, 3023, 2940, 1633, 1590, 1501, 1464, 1134, 1065, 707 and 647; δ_H(250 MHz; CD_3OD), 1.08–2.32 (14 H, m), 2.32–3.21 (4 H, m), 3.21–3.79 (4 H, m), 3.71 and 3.79 (6 H, 2 s, OMe), 4.10–4.36 (1 H, br s) and 6.61–7.63 (11 H, m) (Found: C, 73.6; H, 7.5; N, 2.5%; M^+, 543.2985. $C_{34}H_{41}NO_5 \cdot 0.5H_2O$ requires C, 73.91; H, 7.61; N, 2.54%; M, 543.298 445).

(Ar)-O-*Methyl*-3,11-epi-*lythranidine* **12**.—A solution of amido diacetate **10** (140 mg, 0.22 mmol) in anhydrous tetrahydrofuran (THF) (5 cm^3) was added dropwise to a slurry of $LiAlH_4$ (71 mg, 1.87 mmol) in THF (15 cm^3). The slurry was stirred under nitrogen for 18 h at room temperature after which time the excess of $LiAlH_4$ was destroyed by the addition of water (1 drop). The slurry was filtered through a plug of sand with the aid of diethyl ether (500 cm^3). Solvent was removed and replaced with methanol (20 cm^3) and the substrate was hydrogenated over 5% Pd/C (41 mg) at atmospheric pressure for 18 h. The slurry was filtered through a plug of Celite with the aid of methanol and the solvent was removed under reduced pressure. Preparative TLC with 15% methanol–3% triethylamine–82% ethyl acetate gave the *product* **12**; crystallisation from ethyl acetate–light petroleum gave a powder (53 mg, 55%), m.p. 135–139 °C (indistinct); ν_{max}(KBr disc)/cm^{-1} 3361, 2934, 1607, 1500, 1438, 1364, 1132, 941, 812 and 748; δ_H(250 MHz; CD_3OD) 1.10–2.37 (16 H, m), 2.42–2.74 (2 H, m), 2.74–3.00 (2 H, m), 3.11–3.39 (2 H, m), 3.71 (6 H, 2 s, OMe), 3.50–3.95 (4 H, m) and 6.63–7.58 (6 H, m, ArH); δ_C(62.9 MHz; CD_3OD), 19.88, 30.18, 30.86, 30.95, 32.20, 40.09, 40.32 and 42.86 (8 × CH_2), 49.20 and 50.02 (CHNCH), 56.38 (2 × OMe), 66.48 and 67.57 (CHOH), 112.76 and 112.91 (2 × CH *ortho* to OMe), 129.66, 129.82, 132.09 and 133.87 (4 × arom CH), 134.35 and 135.08 (arom Cquat, biaryl) and 156.98 (2 × arom Cquat) (Found: M^+, 439.2723. $C_{27}H_{37}NO_4$ requires M, 439.272 235).

3,11-epi-*Lythranidine* **13**.—A solution of amido diacetate **10** (100 mg, 0.16 mmol) in anhydrous toluene (10 cm^3) at −78 °C was treated with DIBAL (1 mol dm^{-3} in toluene, 0.5 cm^3, 0.5 mmol). The solution was stirred at −78 °C for 1 h and then allowed to reach room temperature and was then stirred under nitrogen for 24 h. Excess of DIBAL was quenched by the addition of water and 2 mol dm^{-3} NaOH (1 cm^3). The aqueous phase was extracted with chloroform (4 × 10 cm^3). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated. TLC suggested that the product was the amido diol **11**. The product was dissolved in anhydrous THF and added to a slurry of $LiAlH_4$ (0.5 g) in THF (15 cm^3). The slurry was stirred overnight under nitrogen. Excess of $LiAlH_4$ was destroyed with water. The resulting slurry was filtered through a plug of sand with the aid of diethyl ether. Solvent was removed under reduced pressure to give a yellow oil. This was taken up into methanol and hydrogenated over 5% Pd/C at room temperature for 4 h, after which time the slurry was filtered through a plug of Celite with the aid of methanol. Solvent was removed to give a yellow glass. Crystallisation from dichloromethane–light petroleum gave an amorphous powder (52 mg); δ_H(250 MHz; $CDCl_3$) 1.16–1.37 (1 H, m), 1.37–2.00 (12 H, m), 2.00–2.10 (2 H, m), 2.16–2.34 (3 H, m), 2.53–2.76 (2 H, m), 2.76–3.00 (2 H, m), 3.53–3.74 (4 H, m), 3.79 (3 H, OMe), 6.82 (1 H, m), 7.00 (4 H, m) and 7.18 (1 H, m) (Found: M^+, 428. $C_{26}H_{35}NO_4$ requires M, 428).

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References

1 For a review, see E. Fujita and K. Fuji, *International Review of Science, Organic Chemistry Series 2*, ed. K. Wiesner, Butterworths, London, 1976, vol. 9, pp. 119–159.
2 K. Fuji, T. Yamada, E. Fujita and H. Murata, *Chem. Pharm. Bull.*, 1978, **26**, 2515.
3 K. Fuji, K. Ichikawa and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1066.
4 J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396; *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, 1984, vol. 2, p. 83; J. J. Tufariello and Sk. Asrof Ali, *Tetrahedron Lett.*, 1978, 4647; Sk. Asrof Ali, P. A. Senaratne, C. R. Illig, H. Meckler and J. J. Tufariello, *Tetrahedron Lett.*, 1979, 4167; E. Gossinger, *Monatsch. Chem.*, 1981,

112, 1017; C. Hootele, W. Ibebeke-Bomangwa, F. Driessens and S. Sabil, *Bull. Soc. Chim. Belg.*, 1987, **96**, 57; W. Ibebeke-Bomangwa and C. Hootele, *Tetrahedron*, 1987, **43**, 935; Sk. Asrof Ali and M. I. M. Wazeer, *J. Chem. Soc., Perkin Trans. 1*, 1988, 396.
5 W. Carruthers, P. Coggins and J. B. Weston, *J. Chem. Soc., Perkin Trans. 1*, 1990, in the press.
6 M. Sainsbury, *Tetrahedron*, 1980, **36**, 3327.
7 P. E. Fanta, *Synthesis*, 1974, 9.
8 M. F. Semmelhack, P. M. Helquist and L. D. Jones, *J. Am. Chem. Soc.*, 1971, **93**, 5908; M. F. Semmelhack, P. M. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. S. Ryono, J. G. Smith and R. D. Stauffer, *J. Am. Chem. Soc.*, 1981, **103**, 6460.
9 A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray and F. Kienzle, *J. Am. Chem. Soc.*, 1971, **93**, 4841.
10 R. K. Sharma and N. Kharasch, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 36.
11 O. Mitsunobu, *Synthesis*, 1981, 1.
12 J. Gutzwiller and M. Uskokovic, *J. Am. Chem. Soc.*, 1970, **92**, 204.
13 B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1967, 1869.
14 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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