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Exploiting the Maitland–Japp reaction: a synthesis of (±)-centrolobine☆

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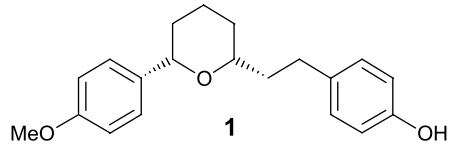
Abstract—Application of our one-pot, three-component variation of the Maitland–Japp reaction has led to the formation of a tetrahydropyran-4-one, which was converted in three steps to the antiparasitic and antibiotic natural product (±) centrolobine.

1. Introduction

(−)-Centrolobine **1** was isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile*.[1,2] Recently, (−)-centrolobine **1** and related natural products, have been shown to be active against *Leishmania amazonensis promastigotes*; a parasite associated with *leishmaniasis*, a major health problem in Brazil.[3,4]



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Leishmania is a parasitic disease transmitted by the sand fly, and is related to Indian dum dum fever. Once in its human host, the parasite attacks the spungiform organs of the body, especially the liver and spleen, where the initial symptoms include a high fever, meaning that the disease is often mistaken for malaria. If the parasite attacks the skin, similar symptoms to leprosy arise, again, often leading to the wrong treatment being given to the patient. For the past 80 years, the only available drug for this distressing disease has been the pentavalent antimonials, which have been recently, linked to cardiac and renal toxicity.[3] It is for this reason that Leon and co-workers, conducted a screen of traditional remedies from the Amazon rainforest to find new anti-leishmanial compounds.[3,4] Interestingly, (−)-centrolobine **1** had already been shown to be one of the active ingredients in a herbal tea made from the wood of *Centrolobum robustum* that is used by the native peoples of the Amazon as a tonic cure for a variety of ailments.

(−)-Centrolobine **1** is a 2,6 *cis*-substituted tetrahydropyran and its simple structure has made it a test-bed for pyran-forming methodologies in recent years. The structure of **1** was proven with the synthesis of the racemic methyl ether in 1964,[1] but it was not until 2002, that the absolute configuration was assigned by the asymmetric total synthesis of **1** by Colobert and co-workers.[5,6] Three further, asymmetric syntheses followed from the groups of Rychnovsky,[7] Evans[8] and Cossy.[9]

The first, total synthesis by Colobert et al.[5] featured the reduction of a β-ketosulfoxide followed by an intramolecular cyclisation and yielded the natural product in nine steps. The second synthesis by Rychnovsky[7] utilised a Prins cyclisation as the key step and furnished (−)-centrolobine in seven steps. A synthesis by Evans,[8] formed the tetrahydropyran ring by an intramolecular reductive etherification strategy and provided the natural product in five steps from aldehyde **5**. Finally, Cossy reported a four step synthesis of (−)-centrolobine in an overall yield of 7%.[9]

2. Results and discussion

We were of the opinion that the existing syntheses of centrolobine were either unduely long or produced centrolobine in an unacceptably low yield, and that our renaissance of the Maitland–Japp reaction may provide a way to synthesise centrolobine in a more expedient and higher yielding

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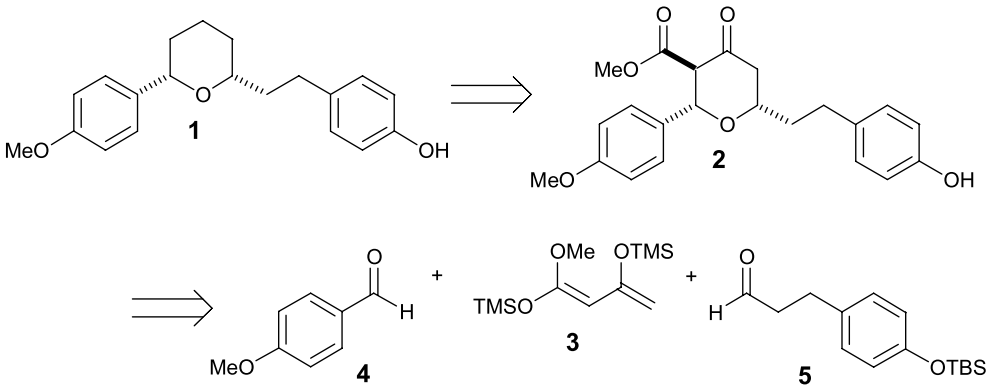


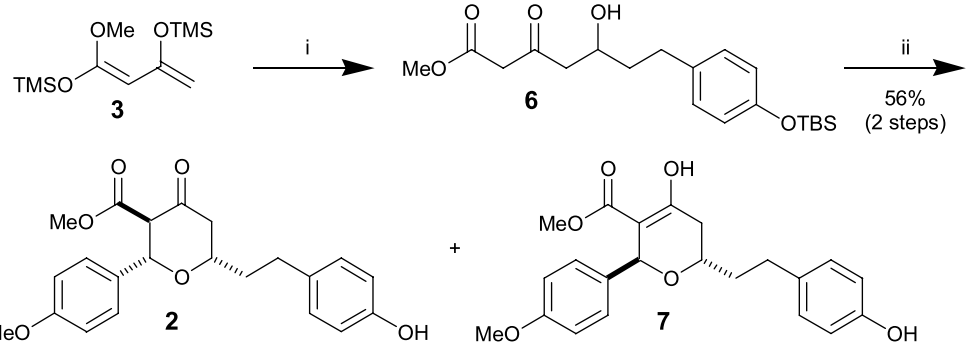
Scheme 1. Retrosynthetic analysis of centrolobine.

manner. Retrosynthetically, it was hypothesised that centrolobine **1** could be obtained by reduction and decarboxylation of the tetrahydropyran-4-one **2**, which would be the result of the Lewis acid mediated Maitland–Japp reaction of Chan's diene **3** and the two aldehydes **4** and **5** (Scheme 1).

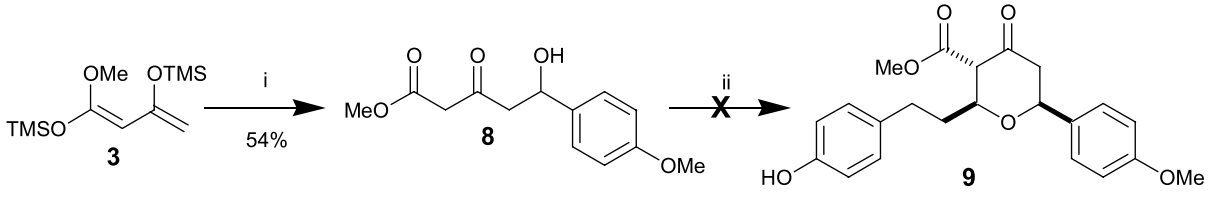
2.1. The two-pot construction of tetrahydropyran-4-one 2

Initially, construction of the tetrahydropyran-4-one **2** by our original two-pot procedure was investigated.[10] It was decided to use aldehyde **5** as the aldol reaction coupling partner, as it had been used previously as a starting point in Evans' synthesis of centrolobine.[8] Aldehyde **5** was prepared according to the procedure of Jones[11] and was subjected to a Mukaiyama aldol reaction with Chan's diene **3**, to give aldol adduct **6**, which was used without any further, purification. With the δ-hydroxy β-ketoester **6** in hand, the boron trifluoride mediated pyran-forming reaction was investigated. Pyran formation appeared to be rapid by TLC analysis but prolonged reaction times were necessary to effect in situ TBS deprotection. This led to the isolation of two diastereomeric tetrahydropyran-4-ones **2** and **7** in a 1.0:0.6 ratio and in a combined overall yield of 56% from the aldehyde **5** (Scheme 2).

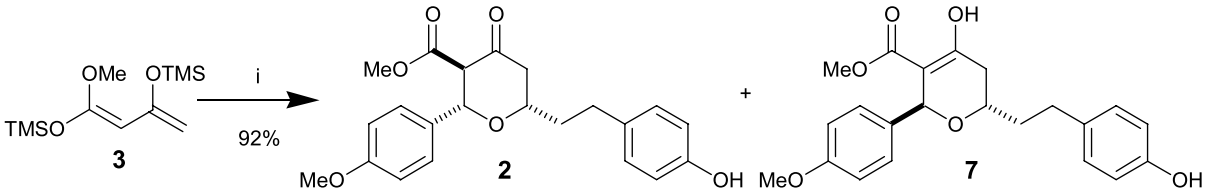
In an attempt to increase, the yield and the selectivity of the Maitland–Japp cyclisation reaction, it was decided to investigate introduction of the side chains in the reverse order, to give pyranone **9**. Therefore, aldol adduct **8** was synthesised in an unoptimised 54% yield by reaction of Chan's diene **3** with anisaldehyde **4**. The cyclisation reaction between **8** and the aldehyde **5** was attempted under the standard boron trifluoride diethyl etherate mediated conditions,[10] however, none of the desired product **9** was isolated. In a further, experiment it was found that the δ-hydroxy β-ketoester **8** was unstable to the Lewis acidic reaction conditions (Scheme 3), probably as the hydroxyl centre is activated by the 4-methoxy group on the aromatic ring.



Scheme 2. Reagents and conditions: (i) **5**, $TiCl_4$, CH_2Cl_2, -78 °C; (ii) anisaldehyde, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temperature, 24 h, 56% over two steps.



Scheme 3. Reagents and conditions: (i) anisaldehyde, $TiCl_4$, CH_2Cl_2, -78 °C, 54%; (ii) **5**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temperature.



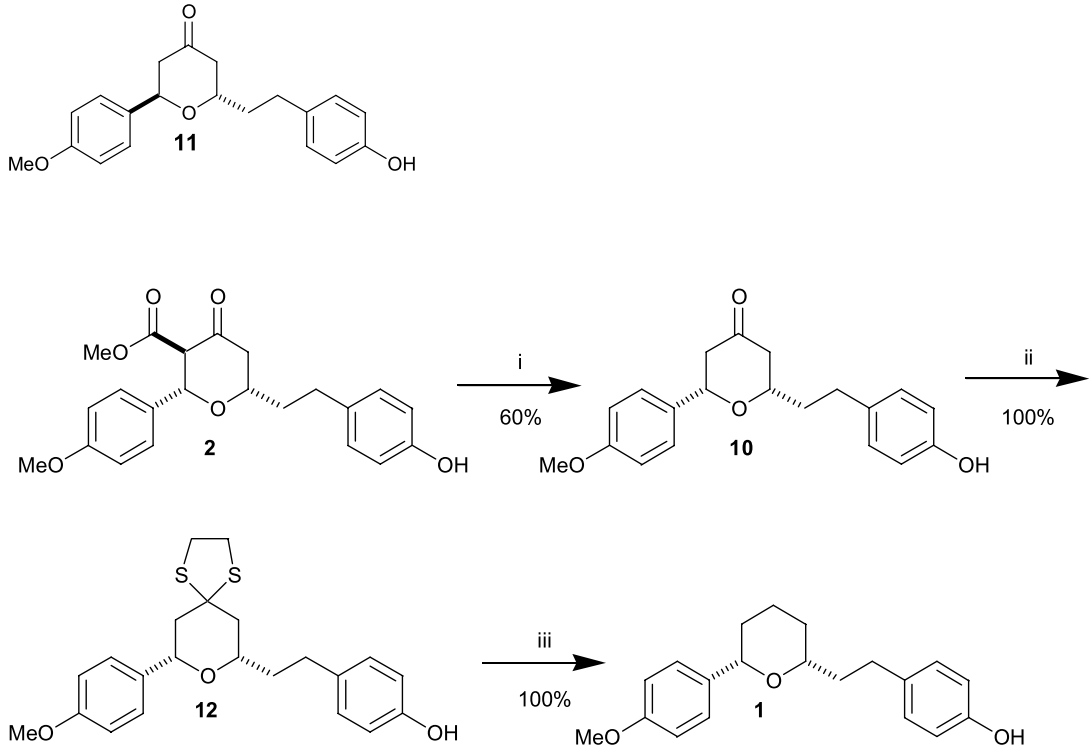
Scheme 4. Reagents and conditions: (i) $Yb(OTf)_3$, **5**, −78 °C, 1 h, then TFA, anisaldehyde, −78 °C to room temperature, 12 h, 92%.

2.2. The one-pot construction of tetrahydropyran-4-one 2

The one-pot pyran-forming methodology[12] was also applied to the synthesis of tetrahydropyran-4-one **2**.[13] It had previously been found that ytterbium (III) triflate favoured the formation of the 2,6 *cis*-isomer over the 2,6 *trans*-isomer, and using the optimised reaction conditions the 2,6 *cis*-isomer **2** was formed in a 2:1 ratio to the 2,6 *trans*-isomer **7** and in an excellent 92% yield (Scheme 4). It was possible to separate and then resubmit the *trans*-diastereomer to the reaction conditions and hence, re-equilibrate to a 2:1 mixture of **2**:**7**, thus, increasing the isolated yield of **2** to 82%.

With a reasonably efficient route to the desired 2,6 *cis*-isomer **2** in hand, the final stages of the synthesis were investigated. Decarboxylation of the pyranone **2** was attempted using LiOH, however, the product of a retro-Michael reaction was formed exclusively, rather than that, of decarboxylation. Decarboxylation was achieved by use of LiOH and H_2O_2, which provided **10** in 60% yield. The remaining mass balance of the reaction was an enone arising from a retro-Michael reaction. We rationalised that the less basic, more nucleophilic hydroperoxide anion favoured saponification of the methyl ester via nucleophilic attack at the carboxyl group, rather than enolate formation, which led to the competing retro-Michael reaction. For the purposes of comparison and to establish that epimerisation at the C6 position had not taken place during the decarboxylation process, the 2,6 *trans*-isomer **11** was formed by decarboxylation of the *trans* pyranone **7** using the same $LiOH/H_2O_2$ conditions employed for the *cis*-isomer **2**. The two compounds, **10** and **11**, had markedly different ^1H NMR spectra with **10** having an ABX system with $J^3=10.7$, 3.4 Hz for H2 coupling to H3α and H3β, and $J^3=10.7$, 3.8 Hz for H6 coupling to H5α and H5β, indicating the 2,6 *cis* stereochemistry whereas **11** had $J^3=5.7$, 5.4 Hz for H6 coupling to H5α and H5β, consistent with a 2,6 *trans* structure in rapid conformational equilibrium. The fact that no epimerisation occurred during the decarboxylation of either pyranone indicates that, under these conditions, decarboxylation is more facile than the retro-Michael reaction and that the decarboxylation of **7** must proceed via tautomerisation of **7** to its keto-tautomer.

The final synthetic challenge was to effect the reduction of the carbonyl of **10** to a methylene group. The first method investigated was the Wolff–Kischner reaction, but upon work-up this was found to have returned only starting



Scheme 5. Reagents and conditions: (i) H_2O_2, LiOH, THF, H_2O, room temperature, 5 h, then 70 °C, 30 min, then room temperature, 12 h, 60%; (ii) $HSCH_2CH_2SH$, $BF_3\cdot OEt_2$, CH_2Cl_2, room temperature, 100%; (iii) Raney nickel, H_2, EtOH, 30 °C, 100%.

material. Analysis by TLC suggested that the hydrazone was formed readily, which implied that the base-mediated elimination was the problematic step. The phenolic hydroxyl group would have been deprotonated under the reaction conditions giving an anionic species that would perhaps be less susceptible to elimination of the hydrazone. With the failure of the Wolff–Kischner reaction it was decided to effect the carbonyl removal in two steps via formation of the dithiane. To this end the carbonyl in **10** was treated with ethane dithiol and boron trifluoride diethyl etherate to give the dithiane **12** in quantitative yield. Raney Nickel reduction of **12** proceeded under an atmosphere of hydrogen at 70 °C to give (±)-centrolobine **1** quantitatively (Scheme 5).

3. Conclusions

We have applied our variation of a one-pot, three-component Maitland–Japp reaction to the synthesis of (±)-centrolobine. The synthesis was achieved in four steps and in 50% yield from aldehyde **5**, which compares extremely favourably with those syntheses already reported.

4. Experimental

4.1. General

All melting points are uncorrected. Reaction progress was monitored using glass-backed TLC plates pre-coated with silica UV_{254} and visualised by using either UV radiation (254 nm), ceric ammonium molybdate or anisaldehyde stains. Column chromatography was performed using silica gel 60 (220–240 mesh), with the solvent systems indicated in the relevant experimental procedures. Dichloromethane was distilled from calcium hydride, tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl, dimethyl formamide was stirred with calcium hydride and distilled prior to use. Benzene, DMSO and MeCN were all distilled from calcium hydride prior to use. Hexane was distilled prior to use. All other reagents were used as received from commercial suppliers unless stated otherwise in the appropriate text.

4.2. The two-pot procedure for the synthesis of 4-hydroxy-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 2 and 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)tetrahydro-pyran-3-carboxylic acid methyl ester 7

To a solution of 3-(4-*tert*-butyldimethlsilyloxyphenyl) propanal **5** (264 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added titanium tetrachloride (111 μL, 1.00 mmol). The black solution was stirred for 2 min and then Chan's diene **3** (570 μL, 2.00 mmol) was added over a 1 min period. The black solution was stirred at −78 °C for 1 h and then 5% aq, $NaHCO_3$ soln (20 mL) was added and the reaction allowed to warm to room temperature. The solution was taken up in Et_2O (30 mL) and washed with 5% aq, $NaHCO_3$ soln (3×30 mL), and brine (2×30 mL), dried ($MgSO_4$), and concentrated in vacuo. The product **6** was used without further purification in the next reaction.

To a stirred mixture of 5-hydroxy-3-oxo-7-(4-tertbutyldimethlsilyloxyphenyl) heptanoic acid methyl ester **6** (1.00 g, 2.63 mmol) in CH_2Cl_2 (40 mL) at room temperature was added anisaldehyde (383 μL, 3.16 mmol) followed by boron trifluoride diethyletherate (333 μL, 2.63 mmol). The yellow solution was stirred at room temperature for 48 h and was then taken up in Et_2O (60 mL) and washed with brine (2×30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:10 EtOAc–petroleum ether) gave **2** and **7** in a ratio of 1.0:0.6 in favour of **2** (566 mg, 56%).

Compound **2**. Oil ν_{max} (film) 3598, 2955, 2930, 1744 (C═O), 1714 (C═O), 1614, 1514, 1251, 1176 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.32 (2H, d, J=8.4 Hz), 7.00 (2H, d, J=8.4 Hz), 6.89 (2H, d, J=8.8 Hz), 6.74 (2H, d, J=8.4 Hz), 5.37 (1H, br s), 4.81 (1H, d, J=10.7 Hz), 3.81 (3H, s), 3.81 (1H, dddd, J=11.2, 7.4, 4.4, 2.4 Hz), 3.62 (1H, d, J=10.7 Hz), 3.60 (3H, s), 2.70–2.64 (2H, m), 2.56 (1H, dd, J=14.6, 2.4 Hz), 2.46 (1H, dd, J=14.6, 11.2 Hz), 2.03 (1H, m), 1.85 (1H, m) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.0, 168.0, 154.0, 133.0, 130.9, 129.4, 128.1, 115.3, 114.0, 80.4, 76.0, 55.2, 46.9, 37.8, 30.9, 30.2 ppm; *m/z* (CI+) 384 (40%, M^+), 325 (33%, M^+–CO_2Me), 107 (100%, $MeOPh^+$); HRMS: found (M^+), 384.1561. $C_{22}H_{24}O_6$ requires (M^+) 384.1573.

Compound **7**. Oil ν_{max} (film) 3354, 2924, 2853, 1714 (C═O), 1612, 1414, 1259, 1216, 1173, 1097, 1031 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 12.29 (1H, s), 7.28 (2H, d, J=8.8 Hz), 6.93 (2H, d, J=8.8 Hz), 6.68 (2H, d, J=8.8 Hz), 6.61 (2H, d, J=8.3 Hz), 5.64 (1H, s), 3.88 (3H, s), 3.65 (3H, s), 3.52 (1H, m), 2.60 (1H, ddd, J=13.7, 8.3, 4.9 Hz), 2.40–2.30 (2H, m), 2.22 (1H, dd, J=18.1, 3.9 Hz), 1.81 (1H, dddd, J=17.1, 14.1, 7.8, 4.9 Hz), 1.62 (1H, dddd, J=17.1, 11.7, 8.3, 3.4 Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.2, 171.0, 159.2, 153.5, 133.1, 133.1, 129.8, 129.5, 115.0, 113.5, 99.0, 72.4, 64.7, 55.3, 51.6, 37.6, 34.8, 30.2 ppm; *m/z* (TOF ES+) 448 (69%, M^++Na+CH_3CN), 407 (100%, M^++Na), 385 (36%, M^++H); HRMS: found (M^++Na), 407.1459. $C_{22}H_{24}O_6$ requires (M^++Na) 407.1471.

4.3. The one-pot procedure for the synthesis of 4-hydroxy-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 2 and 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)tetrahydro-pyran-3-carboxylic acid methyl ester 7

To a suspension of ytterbium (III) triflate (310 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added 3-(4-*tert*-butyldimethlsilyloxyphenyl) propanal **6** (130 mg, 0.50 mmol) followed by Chan's diene (285 μL, 1.00 mmol). The white mixture was stirred at −78 °C for 180 min and then trifluoroacetic acid (158 μL, 2 mmol) was added followed by the anisaldehyde (75 μL, 0.60 mmol). The mixture was warmed to room temperature over 5 min and then stirred at room temperature for 5 h. The mixture was then diluted with Et_2O (40 mL) and washed with 5% aq, $NaHCO_3$ soln, (3×30 mL) and brine (2×30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:10 EtOAc–petroleum ether)

pyran products **2** (115 mg, 60%) and **7** (62 mg, 32%), which were spectroscopically identical to those made via the method above.

4.3.1. 2,6-*cis*-6-(2-(4-Hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-4-oxo-tetrahydropyran 10. To a solution of 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-tetrahydro-pyran-3-carboxylic acid methyl ester **2** (70 mg, 0.18 mmol) in THF/H_2O (4:1, 2 mL) at room temperature was added hydrogen peroxide (90 μL, 0.72 mmol) followed by lithium hydroxide (9 mg, 0.28 mmol). The solution was stirred at 60 °C for 2 h and then taken up in Et_2O (30 mL) and washed with 5% aq, sodium metabisulfite soln, (3× 330 mL), and brine (2×20 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (1:10 EtOAc–petroleum ether) gave the title compound **10** as an oil (36 mg, 60%) ν_{max} (film) 3414, 2856, 1714 (C=O), 1660, 1514, 1444, 1250, 1032 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.31 (2H, d, J=8.4 Hz), 7.03 (2H, d, J=8.4 Hz), 6.93 (2H, d, J=8.8 Hz), 6.74 (2H, d, J=8.8 Hz), 4.92 (1H, s), 4.56 (1H, dd, J=10.7, 3.8 Hz), 3.82 (3H, s), 3.71 (1H, dddd, J=10.7, 8.1, 4.3, 3.4 Hz), 2.77 (1H, ddd, J=14.1, 9.5, 5.5 Hz), 2.71 (1H, ddd, J=14.1, 8.5, 7.7 Hz), 2.61 (1H, ddd, J=14.5, 3.8, 1.3 Hz), 2.57 (1H, dd, J=14.5, 10.7 Hz), 2.44 (1H, ddd, J=14.1, 3.4, 1.3 Hz), 2.39 (1H, dd, J=14.1, 10.7 Hz), 2.04 (1H, dddd, J=13.6, 8.5, 8.1, 5.5 Hz), 1.84 (1H, dddd, J=13.6, 9.4, 7.7, 4.3 Hz) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.2 (s), 159.3 (s), 153.8 (s), 133.5 (s), 133.0 (s), 129.5 (d), 127.0 (d), 115.2 (d), 114.0 (d), 112.7 (s), 78.2 (d), 76.1 (d), 55.3 (q), 49.3 (t), 47.7 (t), 38.1 (t) ppm; m/z (CI+) 326 (38%, M^+), 107 (30%, $C_6H_4OMe^+$) 84 (100%); HRMS: found (M^+), 326.1505. $C_{20}H_{22}O_4$ requires (M^+) 326.1518.

4.3.2. 2,6-*trans*-6-(2-(4-Hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-4-oxo-tetrahydropyran 11. To a solution of 4-hydroxy-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester **7** (40 mg, 0.10 mmol) in THF/H_2O (1 mL, 4:1), was added hydrogen peroxide (75 μL, 0.416 mmol) followed by lithium hydroxide (7 mg, 0.166 mmol). The reaction was stirred at room temperature for 5 h. No change was seen by TLC analysis so the temperature was raised to 70 °C for 3 h and the reaction was then stirred for a further, 15 h at room temperature. The reaction mixture was taken up in ether (30 mL), and then washed with 5% aq sodium metabisulfite soln, (3×20 mL), and brine (2×20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:10 EtOAc–petroleum ether) gave the title compound **11** as an oil (21 mg, 65%) ν_{max} (film) 3598, 3019, 2929, 2856, 1714 (C=O), 1612, 1514, 1181, 1034 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.29 (2H, d, J=8.8 Hz), 6.94 (2H, J=8.4 Hz), 6.89 (2H, d, J=8.8 Hz), 6.69 (2H, d, J=8.4 Hz), 5.24 (1H, dd, J=5.7, 5.4 Hz), 4.73 (1H, br s), 3.89 (1H, m), 3.82 (3H, s), 2.84 (1H, ddd, J=14.9, 5.4, 1.1 Hz), 2.79 (1H, ddd, J=14.9, 5.7, 1.1 Hz), 2.69 (1H, ddd, J=14.1, 9.6, 5.0 Hz), 2.54–2.48 (2H, m), 2.35 (1H, ddd, J=14.5, 7.6, 1.1 Hz), 1.96 (1H, dddd, J=18.4, 14.1, 9.2, 5.0 Hz), 1.67 (1H, dddd, J=18.4, 14.2, 7.3, 4.2 Hz) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.4, 159.4, 133.5, 132.1, 129.5, 128.4, 115.2, 114.0, 114.0, 73.4, 70.6, 55.3, 47.3, 45.9, 36.7, 30.6 ppm; m/z (CI+) 326 (83%, M^+), 205 (10%, M^+–$CH_2CH_2C_6H_4OH$) 134 (80%), 107 (30%, $C_6H_4OMe^+$); HRMS: found (M^+), 326.1509. $C_{20}H_{22}O_4$ requires (M^+) 326.1518.

4.3.3. 4-Dithiane-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-tetrahydropyran 12. To a solution of 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-4-oxo-tetrahydropyran **10** (20 mg, 0.061 mmol), in CH_2Cl_2 (1 mL), was added ethane dithiol (5.6 μL, 0.07 mmol), followed by boron trifluoride etherate (8.5 μL, 0.06 mmol). The solution was stirred at room temperature for 20 min then taken up in Et_2O (30 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the title compound as an oil (25 mg, 100%). ν_{max} (film) 3389, 2922, 2852, 1814, 1613, 1442, 1248, 1176, 1033 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.31 (2H, d, J=8.8 Hz), 7.03 (2H, d, J=8.8 Hz), 6.89 (2H, d, J=8.8 Hz), 6.73 (2H, d, J=8.8 Hz), 4.52 (1H, dd, J=11.1, 2.0 Hz), 3.80 (3H, s), 3.67 (1H, dddd, J=11.1, 6.7, 4.4, 2.0 Hz), 3.37–3.35 (4H, m), 2.77 (1H, ddd, J=14.0, 9.9, 5.6 Hz), 2.67 (1H, ddd, J=14.0, 9.6, 6.7 Hz), 2.31 (1H, ddd, J=13.5, 2.4, 2.4 Hz), 2.15 (1H, dd, J=13.5, 11.1 Hz) 2.15 (1H, ddd, J=13.5, 4.1, 2.0 Hz) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 159.0 (s), 153.7 (s), 134.3 (s), 134.2 (s), 129.5 (d), 127.3 (d), 115.2 (d), 113.8 (d), 78.1 (d), 76.4 (d), 65.8 (s), 55.4 (q), 49.7 (t), 47.4 (t), 39.3 (t), 37.9 (t), 37.8 (t), 30.8 (t) ppm; m/z (CI+) 402 (47%, M^+), 309 (100%, M^+-PhOH), 135 (45%), 107 (91%, $C_6H_4OMe^+$); HRMS: found (M^+), 402.1315. $C_{22}H_{26}O_3S_2$ requires (M^+) 402.1323.

4.3.4. (±) Centrolobine 1. To a solution of 4-dithiane-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-tetrahydropyran **12** (20 mg, 0.05 mmol) in EtOH (2 mL), was added Raney nickel (150 mg, 50% slurry in H_2O). The heterogeneous mixture was heated at 35 °C for 18 h under an atmosphere of H_2 and then passed through celite. The solvent was removed under reduced pressure to give (±) centrolobine as a white solid (15 mg, 100%) The data were in agreement with the literature values.[5–8] Mp 87–89 °C (lit.[1,5,6] 85–87 °C); ν_{max} (film) 3348, 2924, 2851, 1613, 1514, 1454, 1246, 1174, 1080, 1035, 827 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.31 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.8 Hz), 6.88 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.8 Hz), 4.29 (1H, dd, J=11.1, 2.0 Hz), 3.80 (3H, s), 3.44 (1H, dddd, J=12.6, 6.4, 4.7, 1.8 Hz), 2.73 (1H, m), 2.65 (1H, m), 1.95–1.22 (8H, m) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 158.7, 153.5, 135.9, 134.7, 129.6, 127.2, 115.1, 113.7, 79.1, 77.2, 55.4, 38.4, 33.4, 31.3, 30.8, 24.1 ppm; m/z (TOF ES+) 335 (50%, M^+ +Na), 233 (100%); HRMS: found (M^+ +Na), 335.1623. $C_{20}H_{24}O_3$ requires (M^+ + Na) 335.1626.

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