A strategy for the synthesis of popolohuanone E: formal total synthesis of (±)-arenarol

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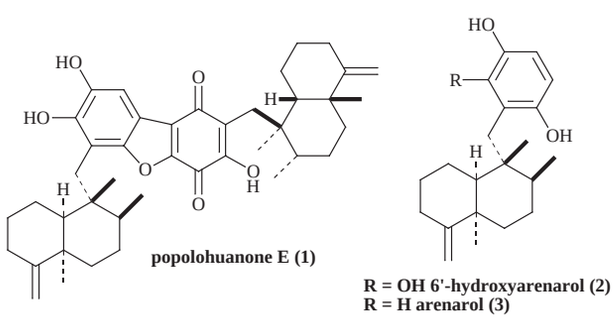
A strategy for the synthesis of popolohuanone E, an oxidatively dimerised arenarol derivative with selective cytotoxic behaviour against non-small cell human lung cancer cells, is described. A known route for the diastereoselective synthesis of the *cis*-decalin was followed and the subsequent formation of the hindered benzylic bond was illustrated by a formal synthesis of (±)-arenarol. The analogous route directed towards the total synthesis of popolohuanone E is described, along with preliminary model studies concerning the formation of the homo-biaryl nucleus.

Introduction

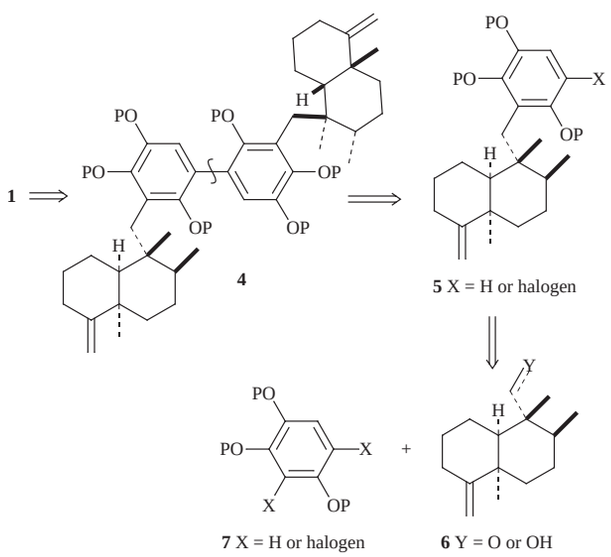
Popolohuanone‡ E (**1**) is an oxidatively dimerised arenarol



Popolohuanone E (**1**) and structures of related compounds

derivative that was isolated from a Pohnpei sponge *Dysidea* sp. Compound **1** is a potent inhibitor of topoisomerase II and shows selective cytotoxicity against the A549 non-small cell human lung cancer cell line.[1] The structure of **1** was elucidated by mass spectral and nuclear magnetic resonance data[1] supported by those reported for analogues.[2] The scarcity (4×10^{-4}% of dried sponge) and tedious isolation of this natural product, coupled with its high anti-cancer activity and complex structure prompted us to design a potentially efficient stereocontrolled synthesis of **1**. It has been proposed that **1** may be formed from the oxidative dimerisation of the as yet unreported 6′-hydroxyarenarol (**2**).[1] The total synthesis of **1** has not been achieved yet, but there have been reports, concerning the synthesis of a related compound arenarol **3**, in racemic[3] and enantioselective form,[4] which is closely related to the proposed biogenetic precursor **2**. The syntheses of avarol and avarone, *trans*-fused decalin systems with structural similarity to **2** and **3**, have also been reported.[5,6] Due to the recent activity in this area we wish to report our independent formal synthesis of racemic **3** and describe our studies towards the total synthesis of out ultimate target **1**.

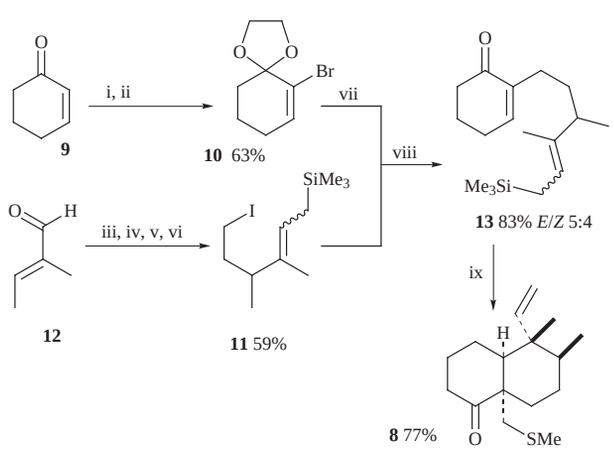
Retrosynthetically we can view **4** as a reduced form of **1** (Scheme 1). A potential synthesis can then be simplified to the intermolecular biaryl coupling of two molecules of **5**. Simple benzofuran quinone systems have been prepared by the ceric ammonium nitrate oxidation of trimethoxybenzenes[7] followed by acidic rearrangement[7] or exposure to ultra-violet irradiation.[8] Monomer **5** can be most easily derived from the *cis*-fused decalin **6** and a suitable aromatic partner **7**.



Scheme 1 Retrosynthetic plan

Results and discussion

We chose to synthesise the *cis*-fused decalin fragment according to slight modifications of the procedure of Tokoroyama.[9] This led to *cis*-decalin **8** (Scheme 2), from which we could synthesise



Scheme 2 *Reagents and conditions*: i, Br_2, Et_3N, $CHCl_3$, 0 °C, 55 min; ii, $HOCH_2CH_2OH$, CSA, PhH, 80 °C, 14 h; iii, Me_3SiCH_2MgCl, Et_2O, 0 °C, 30 min; iv, $Hg(OAc)_2$, $CH_2CHOCH_2CH_3$, 33 °C, 48 h, then PhMe, 110 °C, 2 h; vi, $NaBH_4$, EtOH, rt, 1 h; vii, Imid, Ph_3P, I_2, MeCN, rt, 3.5 h; vii, Bu^sLi, THF–HMPA (~10:1), **11**, −78 °C, 20 h; viii, HCl (aq.), THF, rt, 4.5 h; ix, $TiCl_4$, $ClCH_2SMe$, CH_2Cl_2, 0 °C, 1 h

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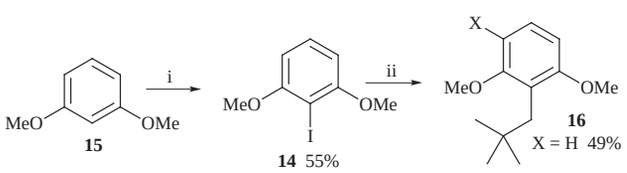
‡ From *popolohua* meaning *purplish blue as the sea* in Hawaiian.

a variety of coupling partners for the potentially difficult formation of the sterically hindered benzylic bond. Cyclohexenone **9** was brominated, treated with base to eliminate HBr and then protected under standard conditions to give the ketal **10** according to the outlined literature procedure in an overall yield of 63%.[10] The anion generated from lithium–halogen exchange of **10** with two equivalents of *sec*-butyllithium was quenched with the electrophile **11**. Alkyl halide **11** was derived from treatment of tiglic aldehyde [(*Z*)-2-methylbut-2-enal, **12**] with a Peterson Grignard reagent Me_3SiCH_2MgCl. The resultant allylic alcohol was then subjected to a Claisen rearrangement; reduction of the resultant aldehyde followed by conversion of the hydroxy function to an iodide function gave **11** in 59% overall yield from tiglic aldehyde. The use of a one pot iodination using triphenylphosphine, iodine and imidazole in acetonitrile was found to increase substantially the overall yield of these transformations as opposed to using the reported[9] two step procedure of mesylation followed by treatment with sodium iodide. Treatment of the coupled product with aqueous hydrochloric acid to remove the ketal protecting group gave **13** in 83% yield from **11** as a 5:4 mixture of *E*/*Z* isomers. Intramolecular Hosomi–Sakurai cyclisation of the allylsilane mixture, mediated by titanium tetrachloride with *in situ* trapping of the resultant enolate with $ClCH_2SMe$, stereoselectively formed the described *cis*-decalin **8** in the same yield of 77% as reported in the literature.[9]

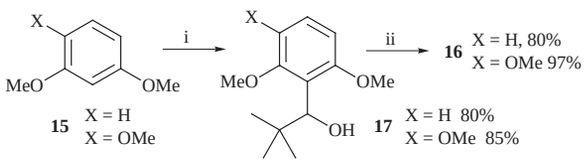
With the *cis*-decalin system **8** in hand we turned our attention to the formation of the hindered benzylic bond, flanked by two *ortho* methoxy groups and a quaternary centre. Our first attempts centred around a transition metal catalysed carbon–carbon bond formation. We investigated a model system which we believed contained the steric constraints that would be present in the natural system. We desired to couple neopentylmagnesium bromide with 2-iodo-1,3-dimethoxybenzene **14**, prepared by metallation and trapping with iodine of 1,3-dimethoxybenzene **15** (Scheme 3). Initial attempts at



Scheme 3 *Reagents and conditions*: i, BuLi, TMEDA, Et_2O, 35 °C, 24 h; I_2; ii, $(CH_3)_3CCH_2MgBr$, Pd(DPPF)Cl_2 cat., Et_2O, 35 °C, 24 h

using the chloro derivative failed despite evidence that aryl chlorides may be more reactive in these coupling reactions.[11] Eventually, after screening a variety of different catalysts, we found that the use of dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II)[12] in refluxing diethyl ether furnished the coupled product **16** in a modest yield of 49%.

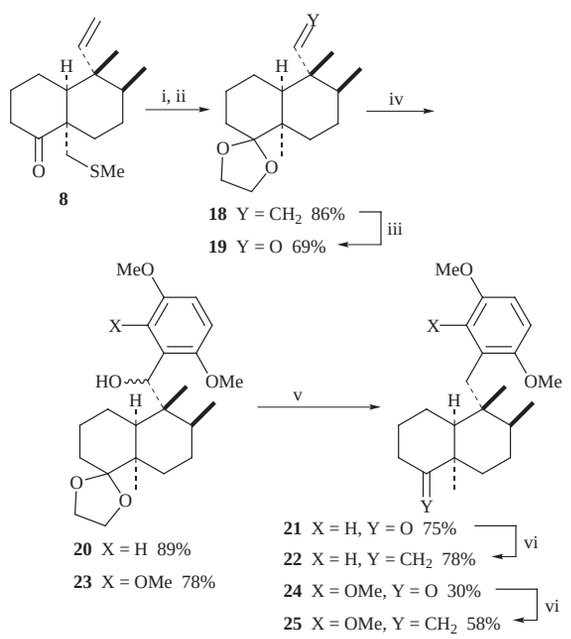
This yield was unacceptable for such an important convergent bond construction in our synthesis and coupled with the fact that we may have experienced difficulty in forming a neopentyl like halide from **8** we searched for a better strategy. It was after this decision that Weimer and Scott published their synthesis of arenarol where, after a similar disconnection, they joined 2,5-dimethoxyphenylmagnesium bromide with a neopentyl like iodide using a nickel catalyst in a similar yield.[3] Note that this coupling has only one *ortho* substituent on the aromatic partner. We envisaged an alternative strategy would be to reduce the benzylic alcohol obtained from the addition of a suitable aromatic nucleophile to the aldehyde **6** (Y = O), prepared from **8** by oxidative cleavage of the terminal alkene. In our model system 2,5-dimethoxyphenyllithium added to trimethyl acetaldehyde to give the benzylic alcohol **17** in 80% yield (Scheme 4). Direct hydrogenation of the benzylic alcohol§[13] or



Scheme 4 *Reagents and conditions*: i, BuLi, TMEDA, Et_2O; $(CH_3)_3CCHO$; ii, Et_3SiH, TFA, rt

its trifluoroacetate ester[14] under a variety of conditions failed or gave low yields. As the aromatic ring is electron rich we decided to perform an ionic hydrogenation by treating the benzylic alcohol with trifluoroacetic acid (TFA) and triethylsilane (Et_3SiH).[15] This led to the desired reduction in 80% yield. Repetition of this strategy with the corresponding 1,2,4-trimethoxyphenyl analogue proved just as effective (Scheme 4).¶

The *cis*-decalin system **8** was then transformed into the requisite aldehyde which required the reduction of the sulfide. Freshly prepared Raney nickel simultaneously reduced the terminal alkene, which has some precedent.[16] Alternate solvents did not preserve the alkene,[17] but deactivation of Raney nickel with acetone[16] produced a more selective reagent which removed the sulfide in the presence of the terminal alkene in 86% yield (Scheme 5). However, such was the reduced activity



Scheme 5 *Reagents and conditions*: i, Raney Ni, THF, 67 °C, 2 h; ii, $HOCH_2CH_2OH$, CSA, PhH, 80 °C, 14 h; iii, O_3, DCM–MeOH (3:1), −78 °C; iv, X = H 2,5-dimethoxyphenyllithium or X = OMe 2,3,5-trimethoxyphenyllithium, TMEDA, THF, 0 °C, 30 min; v, H_2 (1 atm), $Pd(OH)_2$/C cat., EtOAc, 72 h; vi, $Zn(CH_2ZnBr)_2$·THF, $TiCl_4$, CH_2Cl_2, rt, 20 h

of the Raney nickel that a ten fold excess by weight was required to complete the desired reaction. Standard ketal protection of the ketone in 97% yield gave **18** which upon ozonolysis of the terminal alkene in a dichloromethane–methanol mixture followed by reduction of the ozonide with triphenylphosphine gave aldehyde **19** in 69% yield. Reaction with *ortho*-lithiated-1,4-dimethoxybenzene gave the benzylic alcohol **20** in 89% yield as an inseparable, unquantifiable by NMR, mixture of diastereoisomers. Disappointingly, subjection to the ionic reducing system TFA–Et_3SiH gave a complex mixture of products possibly due to the sensitivity of the ketal protecting group. Recourse to standard hydrogenation conditions proved effect-

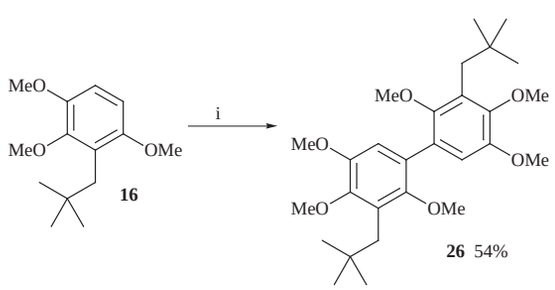
§ Although electron donating methoxy groups should accelerate this process.[22]

¶ Addition of the acid before the hydride donor leads to substantial 1,2-methyl migration.

ive and the reduced compound **21** was isolated as the ketone in 75% yield. Presumably some acetic acid is generated during the hydrogenation reaction which facilitates hydrolysis of the ketal and accelerates the reaction. Treatment with Nysted's reagent [$Zn(CH_2ZnBr)_2$·THF][18] and $TiCl_4$ gave the exocyclic alkene **22** in 78% yield, which had identical spectroscopic data to the intermediate prepared by Weimer and Scott in their total synthesis of arenarol.‖[3]

The progression of this synthesis towards popolohuanone E **1** has followed the route above. Addition of 2,3,6-trimethoxyphenyllithium to **19** resulted in formation of the benzylic alcohol **23** in 78% yield (Scheme 5). Reduction of this compound under our hydrogenation conditions gave the desired compound **24**, but only in 30% yield. This disappointing yield is an indication as to the degree of steric hindrance around the hydroxy group from the adjacent quaternary centre and the two *ortho*-methoxy groups of the aromatic ring. The remainder of the material (60%) was the ketone formed from deprotection of the cyclic ketal of **23**, which, despite resubmission to the hydrogenation conditions, could not be reduced to **24**. This step is at a convergent point in the synthesis and we are currently investigating other methods of removing the hydroxy function from **23**. Treatment with Nysted's reagent furnished the exocyclic methylene compound **25** in an unoptimised 58% yield.

Preliminary results for the biaryl coupling reaction look fruitful on our model system (Scheme 6). Treatment of **16**



Scheme 6 *Reagents and conditions*: i, $Tl(OAc)_3$, BF_3·OEt_2, MeCN, −40 °C to rt

(X = OMe) with thallium acetate and boron trifluoride–diethyl ether resulted in the formation of biaryl **26** in 54% isolated yield,[19] the structure of which has been confirmed by single crystal X-ray analysis. Similar systems have been oxidised with ceric ammonium nitrate[7] and subsequently treated with acid or ultra-violet irradiation to effect rearrangement to the benzofuran quinone skeleton.[7,8]

We have outlined a potential synthetic route to popolohuanone E **1**. The relative stereochemistry of the *cis*-decalin system was derived from Tokoroyama's[9] Hosomi–Sakurai cyclisation of **13**. The problems associated with the introduction of the hindered benzylic system were addressed and an efficient protocol was illustrated by the formal synthesis of (±)-arenarol **3**. It is noteworthy that the yield of this crucial coupling step was diminished, due to severe steric hindrance, in our desired total synthesis of popolohuanone E **1**. Further work is in progress and will be reported in due course.

Experimental

General details

Our general experimental details have been reported.[20]

2-Bromocyclohex-2-en-1-one

Bromine (32 g, 0.200 mol, 1 equiv.) was added dropwise to cyclohexenone **9** (19.2 g, 0.200 mol) in trichloromethane (400 ml) at 0 °C. After 10 min, triethylamine (30.3 g, 0.300 mol, 1.5 equiv.) was added slowly and the reaction was stirred for a further 45 min. Water (300 ml) was added and the organic phase separated and then washed with 1 M HCl (200 ml), brine (200 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was recrystallised from light petroleum to yield the bromoenone (25.67 g, 73%) as a clear crystalline solid mp 76–78 °C (lit.,[21] 75–76 °C) (Found: C, 41.32; H, 3.97; Br, 45.97. C_6H_7OBr requires C, 41.17; H, 4.03; Br, 45.65%); ν_{max}(thin film)/cm^{-1} 1686, 1590; δ_H(250 MHz; $CDCl_3$) 2.13–2.01 (2H, m, CH_2), 2.45 (2H, q, *J* 6.0, CHCH_2), 2.63 (2H, dd, *J* 7.5, 7.0, CH_2CO), 7.42 (1H, t, *J* 5.0, C3*H*); δ_C(62.9 MHz; $CDCl_3$) 22.7, 28.4, 38.3, 123.8, 151.3, 191.3; *m*/*z* (EI^+) 176 and 174 (95, M^+), 148 and 146 (88, $M^+ - CO$), 135 and 133 (20), 118 and 120 (30), 67 (100).

6-Bromo-1,4-dioxaspiro[4,5]dec-6-ene 10

The bromoenone (10.00 g, 57.1 mmol), 1,2-dihydroxyethane (14.13 g, 0.228 mol, 4 equiv.) and camphorsulfonic acid (662 mg, 2.85 mmol, 0.05 equiv.) in benzene (570 ml) were brought to reflux in a Dean–Stark apparatus and refluxed overnight. The reaction was cooled and then poured carefully into saturated aqueous sodium hydrogen carbonate (500 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (2 × 200 ml). The combined organic phases were dried over a mixture of magnesium sulfate and potassium carbonate (1 : 1), filtered and concentrated *in vacuo* to give a crude oil which was purified by flash chromatography (5% ethyl acetate–light petroleum) to give **10** (10.81 g, 86%) as a clear pale yellow oil bp 74 °C/0.05 mmHg (Found: C, 43.64; H, 4.92; Br, 36.65. $C_8H_{11}O_2Br$ requires C, 43.86; H, 5.06; Br, 36.47%); ν_{max}(thin film)/cm^{-1} 2949, 1695, 1176, 1157, 739; δ_H(250 MHz; $CDCl_3$) 1.84–1.73 (2H, m, CH_2), 1.95–1.87 (2H, m, CHCH_2), 2.13–2.05 (2H, m, CH_2CO), 4.04–3.92 (2H, m, OC*H*HC*H*H), 4.25–4.12 (2H, m, OCH*H*CH*H*), 6.34 (1H, t, *J* 5.0, C7*H*); δ_C(62.9 MHz; $CDCl_3$) 20.3, 27.5, 35.6, 65.8, 105.8, 124.6, 136.0; *m*/*z* (EI^+) 219.9912 (19% M^+. $C_8H_{11}O_2{}^{81}Br$ requires M^+, 219.9921), 218 (M^+), 192 and 190 (100, $M^+ - CH_2CH_2$), 148 and 146 (33, $M^+ - CH_2CH_2OC$), 139 (38), 99 (85).

(*E*)-3-Methyl-1-trimethylsilylpent-3-en-2-ol

Dry magnesium (3.70 g, 0.15 mol, 1.25 equiv.) was stirred vigorously overnight before diethyl ether (10 ml) was added followed by a solution of chloromethyltrimethylsilane (20.00 g, 0.16 mol, 1.33 equiv.) in Et_2O (190 ml) at such a rate to maintain gentle reflux. The resulting black solution was refluxed for a further 1 h then cooled to 0 °C. (*Z*)-2-Methylbut-2-enal **12** (10.00 g, 0.12 mol) in diethyl ether (35 ml) was added dropwise and the reaction was stirred at 0 °C for 0.5 h, then warmed to room temperature for a further 0.5 h. The reaction was cooled to 0 °C and carefully quenched by the cautious addition of saturated aqueous ammonium chloride (200 ml). The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 200 ml). The combined organic extracts were washed with brine (200 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by distillation at reduced pressure to yield the allylic alcohol (19.75 g, 95%) as a clear mobile oil bp 50 °C/0.12 mmHg (Found: C, 62.35; H, 12.08. $C_9H_{20}SiO$ requires C, 62.72; H, 11.7%); ν_{max}(thin film)/cm^{-1} 1670; δ_H(250 MHz; $CDCl_3$) −0.02 (9H, s, SiMe_3), 0.95 (2H, d, *J* 7.5, CH_2SiMe$_3$), 1.57 (3H, d, *J* 7.0, CH_3), 1.58 (3H, s, CH_3), 4.21 (1H, t, *J* 7.5, C*H*OH), 5.44 (1H, q, *J* 7.0, C4*H*); δ_C(62.9 MHz; $CDCl_3$) −1.2, 10.3, 13.0, 23.9, 76.2, 120.1, 139.5; *m*/*z* (EI^+) 171 (34, $M^+ - H$), 155 (55, $M^+ - OH$), 82 (100, $M^+ - H_2O - TMS$), 73 (45, $SiMe_3{}^+$).

(*E*,*Z*)-3,4-Dimethyl-6-trimethylsilylhex-4-enal

A solution of (*E*)-3-methyl-1-trimethylsilylpent-3-en-2-ol (17 g, 98.8 mmol) in ethyl vinyl ether (170 ml) was treated with $Hg(OAc)_2$ (850 mg, 2.74 mmol, 0.028 equiv.) and the reaction

‖ Compound **18** is also identical to the intermediate synthesised by Terashima *et al.* in their synthesis of (+)-arenarol,[4] but in racemic form.

refluxed for 2 days. The reaction mixture was cooled to room temperature, diluted with Et_2O (200 ml) and washed with 1 M NaOH (2 × 100 ml), brine (100 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude allyl vinyl ether wan then taken up in toluene (200 ml) and refluxed for 2 h. The reaction was then cooled and concentrated *in vacuo*. Not all of the toluene was removed from the aldehyde due to its volatility, consequently no yield or characterisation were recorded. This material was used crude in the next step.

(*E*,*Z*)-3,4-Dimethyl-6-trimethylsilylhex-4-en-1-ol

To a solution of the crude (*E*,*Z*)-3,4-dimethyl-6-trimethylsilylhex-4-enal, which still contained toluene, in ethanol (170 ml) was added $NaBH_4$ (1.87 g, 49.2 mmol, 0.5 equiv.) in small portions over 5 min at room temperature. The cloudy metallic grey coloured reaction was stirred for 1 h before saturated aqueous ammonium chloride (150 ml) was carefully added and the mixture concentrated *in vacuo* to a volume of approximately 200 ml. Water (100 ml) was added to dissolve any inorganic salts and the solution was extracted with ethyl acetate (2 × 200 ml). The combined organic extracts were washed with brine (200 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield the alcohol (17.01 g, 87% from **12**) as a clear colourless oil. The product was generally used crude but a sample for analysis was obtained by flash chromatography (10% ethyl acetate–light petroleum); ν_{max}(thin film)/cm^{-1} 1654, 1410, 855; δ_H(250 MHz; $CDCl_3$) −0.02 (9H, s, SiMe_3), 1.00 (2H, d, *J* 8.0, CH_2SiMe$_3$), 1.39 (3H, d, *J* 8.0, C8H_3), 1.48 (3H, s, C8*Me*), 1.7–1.5 (2H, m, CH_2), 2.34–2.21 (1H, m, C*H*Me), 3.58 (2H, t, *J* 6.5, CH_2OH), 5.25 (1H, t, *J* 8.0, C2*H*); δ_C(62.9 MHz; $CDCl_3$) −1.7, 11.9, 18.4, 20.3, 37.6, 40.1, 61.9, 120.3, 136.2; *m*/*z* (EI$^+$) 200.1590 (22% M$^+$. $C_{11}H_{24}OSi$ requires M$^+$, 200.1596), 155 (5, M$^+$ − 3Me), 95 (37), 82 (31), 73 (100, $SiMe_3^+$).

(*E*,*Z*)-3,4-Dimethyl-1-iodo-6-trimethylsilylhex-4-ene 11

Imidazole (6.11 g, 89.8 mmol, 1.3 equiv.) and triphenylphosphine (23.6 g, 89.8 mmol, 1.3 equiv.) were added to a solution of (*E*,*Z*)-3,4-dimethyl-6-trimethylsilylhex-4-en-1-ol (13.8 g, 69.1 mmol) in acetonitrile (690 ml) at room temperature. Iodine (21.0 g, 82.9 mmol, 1.2 equiv.) was added in small portions over 30 min and the reaction stirred for 3 h before being poured into 0.5 M HCl (500 ml) and extracted with ethyl acetate (2 × 500 ml). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (100 ml), brine (500 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting solid was preadsorbed onto silica gel and the product purified by flash chromatography (light petroleum) to yield the iodide **11** (16.2 g, 59% from **12**) as a clear colourless oil bp 125 °C/0.1 mmHg; ν_{max}(thin film)/cm^{-1} 1654, 853; δ_H(250 MHz; $CDCl_3$) −0.02 (9H, s, SiMe_3), 0.99 (3H, d, *J* 7.0, CH*Me*), 1.4 (2H, dd, *J* 5.0, 3.0, CH_2SiMe$_3$), 1.45 (3H, s, *Me*), 1.92–1.69 (2H, m, ICH$_2$CH_2), 2.26 (1H, m, C*H*Me), 3.05–2.93 (1H, m, CH*H*I), 3.2–3.06 (1H, m, C*H*HI), 5.28 (1H, t, *J* 8.0, C5*H*); δ_C(62.9 MHz; $CDCl_3$) −1.6, 6.0, 11.6, 18.6, 19.6, 38.4, 43.6, 121.6, 158.3; *m*/*z* (EI$^+$) 310.0615 (55% M$^+$. $C_{11}H_{23}SiI$ requires M$^+$, 310.0613), 82 (65, M$^+$ − TMS–CH$_2$CH$_2$–I), 73 (100, $SiMe_3^+$).

2-[(*E*,*Z*)-3′,4′-Dimethyl-6′-trimethylsilylhex-4′-enyl]cyclohex-2-en-1-one 13

To a solution of the 6-bromo-1,4-dioxaspiro[4,5]dec-6-ene **10** (9.44 g, 43.1 mmol, 2.2 equiv.) in tetrahydrofuran (200 ml) at −78 °C was added *sec*-butyllithium (67 ml of 1.3 M solution in hexane, 87.0 mmol, 4.4 equiv.) dropwise and the reaction stirred for 5 min. Hexamethylphosphoramide (21.5 ml) was added rapidly and the reaction stirred for a further 20 min. A solution of (*E*,*Z*)-3,4-dimethyl-1-iodo-6-trimethylsilylhex-4-ene **11** (6.07 g, 19.6 mmol) in tetrahydrofuran (10 ml + 5 ml wash) was added slowly *via* cannula. The reaction was stirred at −78 °C for 20 h before water (200 ml) was carefully added. The solution was then extracted with ethyl acetate (3 × 200 ml). The combined organic extracts were washed sequentially with water (4 × 100 ml), brine (100 ml), dried over sodium sulfate and potassium carbonate (1:1), filtered and concentrated *in vacuo*. The resultant oil was purified by flash chromatography (gradient elution light petroleum to 5% ethyl acetate–light petroleum) to yield the coupled ketal as a clear colourless oil (5.25 g). The ketal was dissolved in tetrahydrofuran (82 ml) and 1 M HCl (82 ml) was added. The reaction was stirred vigorously and after 4.5 h extracted with ethyl acetate (3 × 80 ml). The combined organic extracts were washed with brine (80 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resultant oil was purified by flash chromatography, to yield the product **13** (4.50 g, 83% from **11**) as a clear colourless oil bp 150 °C/0.05 mmHg (Found: C, 73.47; H, 10.89. $C_{17}H_{30}OSi$ requires C, 73.31; H, 10.86%); ν_{max}(thin film)/cm^{-1} 1676, 855; δ_H(400 MHz; $CDCl_3$) −0.03 (9H, s, SiMe_3), 0.95 (3H, d, *J* 7.0, C3′CH_3), 1.43–1.25 (4H, m, C2′H_2 and C6′H_2), 1.46–1.44 (3H, m, C4′CH_3), 1.99–1.93 (2H, m, C5H_2), 2.09–2.01 (3H, m, C1′H_2 and C3′*H*), 2.31 (2H, qt, *J* 5.0, 1.0, C4H_2), 2.39 (2H, t, *J* 6.0, C6H_2), 5.17 (1H, tqd, *J* 7.0, 1.0, 0.5, C5′*H*), 6.66 (1H, tt, *J* 5.0, 1.0, C3*H*); δ_C(100.6 MHz; $CDCl_3$) −1.7, 11.9, 18.3, 20.2, 23.2, 26.1, 28.0, 33.9, 38.6, 43.0, 119.9, 135.1, 140.2, 144.7, 199.6; *m*/*z* (EI$^+$) 278.2072 (20% M$^+$. $C_{17}H_{30}OSi$ requires M$^+$, 278.2065), 183 (78, M$^+$ − C_6H_7O), 73 (100, $SiMe_3^+$).

(4a*R,5*S**,6*R**,8a*R**)-5,6-Dimethyl-8a-methylthiomethyl-5-vinyloctahydronaphthalen-1(2*H*)-one 8**

A solution of the enone allylsilane **13** (55.8 mg, 0.20 mmol) and chloromethyl methyl sulfide (21.2 mg, 0.22 mmol, 1.1 equiv.) in dichloromethane (1 ml + 0.5 ml wash) was added dropwise *via* cannula to a solution of $TiCl_4$ (75.8 mg, 0.40 mmol, 2 equiv.) in dichloromethane (2 ml) at 0 °C. The reaction was stirred at 0 °C for 1 h then poured into water (10 ml) and extracted with dichloromethane (3 × 10 ml). The combined organic extracts were washed with brine (15 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (gradient elution 5–10% ethyl acetate–light petroleum) to give the proton trapped by-product (3.4 mg, 8%) as a clear pale yellow oil (Found: C, 81.50; H, 10.88. $C_{14}H_{22}O$ requires C, 81.49; H, 10.75%); ν_{max}(thin film)/cm^{-1} 1709, 1635; δ_H(400 MHz; $CDCl_3$) 0.84 (3H, s, C5*Me*), 0.99 (3H, d, *J* 4.0, C6*Me*), 1.38–1.11 (5H, m), 1.55–1.40 (2H, m), 1.74 (1H, dt, *J* 7.0, 1.0), 1.88 (1H, dq, *J* 7.0, 2.0), 2.03–1.94 (1H, m), 2.15 (1H, tdd, *J* 6.0, 2.0, 1.0), 2.27 (1H, ddd, *J* 8.0, 3.0, 1.0), 2.35–2.29 (1H, m), 4.90 (1H, dd, *J* 17.0, 2.0, =CH*H*), 5.05 (1H, dd, *J* 10.0, 2.0, =C*H*H), 5.42 (1H, dd, *J* 17.0, 10.0, C*H*=); δ_C(100.6 MHz; $CDCl_3$) 8.8, 16.5, 25.4, 26.0, 26.2, 28.5, 39.7, 41.8, 44.1, 49.2, 51.6, 113.1, 147.7, 213.5; *m*/*z* (EI$^+$) 206.1671 (48% M$^+$. $C_{14}H_{22}O$ requires M$^+$, 206.1670), 191 (5, M$^+$ − CH_3), 179 (9, M$^+$ − $CHCH_2$), 122 (100); followed by the methylene methyl sulfide trapped product **8** (40 mg, 77%) as a clear pale yellow oil that slowly solidified on standing mp 61–63 °C (lit.,[9] 60–62 °C) (Found: C, 72.37; H, 10.14; S, 12.04. $C_{16}H_{26}OS$ requires C, 72.13; H, 9.84; S, 12.03%); ν_{max}(thin film)/cm^{-1} 1705, 1635; δ_H(400 MHz; $CDCl_3$) 0.65 (3H, d, *J* 7.0, C6*Me*), 0.76 (3H, s, C5*Me*), 1.13–1.02 (1H, m), 1.22–1.14 (1H, m), 1.33 (1H, dd, *J* 8.0, 4.0), 1.74–1.68 (1H, m), 1.84 (1H, d, *J* 8.0), 2.50–1.88 (1H, m), 2.08 (3H, s, S*Me*), 2.54–2.22 (1H, m), 2.43 (1H, dt, *J* 14.0, 4.0), 2.61–2.52 (1H, m), 2.74 (1H, d, *J* 12.0, C15*H*), 3.03 (1H, d, *J* 12.0, C15*H*), 4.87 (1H, dd, *J* 18.0, 2.0, =CH*H*), 5.06 (1H, dd, *J* 9.0, 2.0, =C*H*H), 5.36 (1H, dd, *J* 18.0, 9.0, C*H*=); δ_C(100.6 MHz; $CDCl_3$) 12.4, 16.5, 17.6, 20.2, 24.1, 26.5, 31.5, 36.72, 40.4, 45.6, 47.3, 51.4, 51.7, 113.3, 148.8, 214.5; *m*/*z* (EI$^+$) 266.1697 (35% M$^+$. $C_{16}H_{26}OS$ requires M$^+$, 266.1704), 251 (14, M$^+$ − CH_3), 219 (31, M$^+$ − SMe), 206 (57, M$^+$ − CHSMe), 122 (100).

2,6-Dimethoxyiodobenzene 14

To a solution of 1,3-dimethoxybenzene **15** (690 mg, 5.0 mmol)

in diethyl ether (50 ml) and tetra-*N*-methylethylenediamine (638 mg, 5.5 mmol, 1.1 equiv.) was slowly added butyllithium (2.2 ml of 2.5 M solution in hexanes, 5.5 mmol, 1.1 equiv.). The reaction was refluxed for 24 h and then cooled to room temperature before being added *via* cannula to a solution of iodine (1.28 g, 5.05 mmol, 1.01 equiv.) in diethyl ether (10 ml). The reaction was stirred for 1.5 h and then poured into saturated aqueous ammonium chloride (60 ml). The aqueous phase was separated and extracted with ethyl acetate (2 × 60 ml) and the combined organic extracts washed with saturated aqueous sodium thiosulfate (60 ml), brine (60 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (10% ethyl acetate–light petroleum) to give **14** (726 mg, 55%), as a white solid; mp 104 °C; ν_{max}(thin film)/cm^{-1} 2921, 1095, 768; δ_H(250 MHz; $CDCl_3$) 3.89 (6H, s, OCH_3), 6.5 (2H, d, *J* 8.0, Ar*H*), 7.25 (1H, t, *J* 8.0, Ar*H*); δ_C(62.9 MHz; $CDCl_3$) 56.1, 76.3, 103.6, 129.4, 158.9; *m*/*z* (EI$^+$) 263.9653 (100% M$^+$. $C_8H_9O_2I$ requires M$^+$, 263.9647), 249 (5, M$^+$ − CH_3), 221 (15, M$^+$ − CH_3OC), 107 (28, M$^+$ − CH_3 − CH_3 − I).

1-(2′,6′-Dimethoxyphenyl)-2,2-dimethylpropane 16 X = H *via* palladium catalysed cross coupling

A solution of neopentylmagnesium bromide in diethyl ether (20 ml), prepared from neopentyl bromide (3.02 g, 20 mmol) and magnesium (583 mg, 24 mmol, 1.2 equiv.), was added *via* cannula to a solution of 2,6-dimethoxyiodobenzene **14** (5.28 g, 20 mmol, 1.0 equiv.) and dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) (146 mg, 0.20 mmol, 0.01 equiv.) in diethyl ether (180 ml) at room temperature. The reaction was refluxed for 24 h and then carefully poured into 1 M HCl (200 ml). The phases were separated, the aqueous layer extracted with ethyl acetate (2 × 200 ml) and the combined organic extracts washed with brine (200 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (3% ethyl acetate–light petroleum) to give **16 X = H** (2.03 g, 49%), as a clear colourless oil (Found: C, 74.82; H, 9.63. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%); ν_{max}(thin film)/cm^{-1} 2929, 1105; δ_H(250 MHz; $CDCl_3$) 0.88 (9H, s, *Bu*^{t}), 2.60 (2H, s, ArCH_2), 3.76 (6H, s, OCH_3), 6.53 (2H, d, *J* 8.0, Ar*H*), 7.12 (1H, t, *J* 8.0, Ar*H*); δ_C(62.9 MHz; $CDCl_3$) 29.9, 33.3, 35.2, 55.3, 103.5, 117.1, 126.6, 159.1; *m*/*z* (EI$^+$) 208.1456 (30% M$^+$. $C_{13}H_{20}O_2$ requires M$^+$, 208.1463), 193 (13, M$^+$ − CH_3), 151 (100, M$^+$ − Bu^t).

1-(2′,6′-Dimethoxyphenyl)-2,2-dimethylpropan-1-ol 17 X = H

To a solution of 1,3-dimethoxybenzene **15 X = H** (414 mg, 3 mmol) and tetra-*N*-methylethylenediamine (351 mg, 3.03 mmol, 1.01 equiv.) in diethyl ether (10 ml) was added butyllithium (1.21 ml of a 2.5 M solution in hexanes, 3.03 mmol, 1.01 equiv.) at room temperature. The reaction was refluxed for 24 h then cooled to 0 °C before trimethylacetaldehyde (284 mg, 3.3 mmol, 1.1 equiv.) was added slowly and the reaction stirred for 45 min. The reaction was then carefully poured into 1 M HCl (15 ml), the phases were separated and the aqueous phase extracted with ethyl acetate (2 × 15 ml). The combined organic extracts were washed with brine (15 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (10% ethyl acetate–light petroleum) to give **17 X = H** (508 mg, 80%) as a white solid mp 102 °C (Found: C, 69.26; H, 8.69. $C_{13}H_{20}O_2$ requires C, 69.61; H, 8.99%); ν_{max}(thin film)/cm^{-1} 2969, 2866, 2842, 1590; δ_H(250 MHz; $CDCl_3$) 0.92 (9H, s, *Bu*^{t}), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.33 (1H, d, *J* 11.0, ArCHO*H*), 4.92 (1H, d, *J* 11.0, ArC*H*OH), 6.56 (2H, d, *J* 8.0, Ar*H*), 7.17 (1H, t, *J* 8.0, Ar*H*); δ_C(62.9 MHz; $CDCl_3$) 26.5, 37.9, 55.3, 55.5, 76.0, 104.2, 104.3, 117.7, 128.1, 158.0, 158.6; *m*/*z* (EI$^+$) 224.1403 (17% M$^+$. $C_{13}H_{20}O_3$ requires M$^+$, 224.1412), 209 (58, M$^+$ − CH_3), 206 (19, M$^+$ − H_2O), 191 (92), 167 (100, M$^+$ − Bu^t).

1-(2′,6′-Dimethoxyphenyl)-2,2-dimethylpropane 16 X = H *via* ionic hydrogenation

Trifluoroacetic acid (1.36 ml) was added dropwise to 1-(2′,6′-dimethoxyphenyl)-2,2-dimethylpropan-1-ol **17 X = H** (100 mg, 0.45 mmol) and triethylsilane (156 mg, 1.35 mmol, 3.0 equiv.) dropwise with stirring at room temperature. After the addition was complete the reaction was carefully poured into 1 M NaOH (20 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (3% ethyl acetate–light petroleum) to give **16 X = H** (74 mg, 80%), as a clear colourless oil. Spectral data was in agreement with that prepared above.

1-(2′,3′,6′-Trimethoxyphenyl)-2,2-dimethylpropan-1-ol 17 X = OMe

To a solution of 1,2,4-trimethoxybenzene **15 X = OMe** (504 mg, 3.0 mmol) and tetra-*N*-methylethylenediamine (351 mg, 3.03 mmol, 1.01 equiv.) in tetrahydrofuran (9 ml) was added butyllithium (1.21 ml of a 2.5 M solution in hexanes, 3.03 mmol, 1.01 equiv.) at 0 °C. The reaction was stirred for 2 h before trimethylacetaldehyde (775 mg, 9.0 mmol, 3.0 equiv.) was added slowly and the reaction stirred for 1 h at 0 °C. The reaction was then carefully poured into 1 M HCl (20 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (5% ethyl acetate–toluene) to give **17 X = OMe** (645 mg, 85%), as an off white solid mp 60 °C; ν_{max}(thin film)/cm^{-1} 2951, 1590, 842; δ_H(250 MHz; $CDCl_3$) 0.91 (9H, s, *Bu*^{t}), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.35 (1H, d, *J* 10.0, O*H*), 4.76 (1H, d, *J* 10.0, ArC*H*), 6.59 (1H, d, *J* 8.0, Ar*H*), 6.77 (1H, d, *J* 8.0, Ar*H*); δ_C(62.9 MHz; $CDCl_3$) 26.5, 37.9, 55.4, 56.1, 60.5, 105.9, 110.8, 123.5, 147.3, 147.6, 152.2; *m*/*z* (EI$^+$) 254.1511 (47% M$^+$. $C_{14}H_{22}O_4$ requires M$^+$, 254.1518), 236 (18, M$^+$ − H_2O), 221 (21, M$^+$ − H_2O − CH_3), 197 (100, M$^+$ − Bu^t), 182 (19, M$^+$ − Bu^t − CH_3).

1-(2′,3′,6′-Trimethoxyphenyl)-2,2-dimethylpropane 16 X = OMe

Subjection of 1-(2′,3′,6′-trimethoxyphenyl)-2,2-dimethylpropan-1-ol **17 X = OMe** (100 mg, 390 μmol) for 45 min to the ionic hydrogenation procedure described above followed by flash chromatography (10% ethyl acetate–light petroleum) gave **16 X = OMe** (91 mg, 97%) as a white solid mp 30 °C; ν_{max}(thin film)/cm^{-1} 2949, 2832, 1592; δ_H(250 MHz; $CDCl_3$) 0.90 (9H, s, *Bu*^{t}), 2.58 (2H, s, ArCH_2), 3.72 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.54 (1H, d, *J* 10.0, Ar*H*), 6.72 (1H, d, *J* 10.0, Ar*H*); δ_C(62.9 MHz; $CDCl_3$) 30.0, 33.3, 35.3, 55.4, 56.1, 60.1, 104.9, 109.8, 123.2, 147.0, 148.9, 153.0; *m*/*z* (EI$^+$) 238.1554 (75% M$^+$. $C_{14}H_{22}O_3$ requires M$^+$, 238.1568), 223 (13, M$^+$ − CH_3), 181 (100, M$^+$ − Bu^t), 166 (55, M$^+$ − Bu^t − CH_3).

(4a*R**,5*S**,6*R**,8a*S**)-5,6,8a-Trimethyl-5-vinyloctahydronaphthalen-1(2*H*)-one

Raney nickel (2 g) was refluxed in acetone (14 ml) for 1 h. The Raney nickel was then washed with tetrahydrofuran (3 × 20 ml) and suspended in tetrahydrofuran (15 ml) to which **8** (360 mg, 1.35 mmol), as a solution in tetrahydrofuran (3 ml + 2 ml washings), was added *via* cannula. The reaction was then refluxed for 2 h, cooled, filtered through Celite, washing with ethyl acetate and the organics concentrated *in vacuo*. The crude product was purified by flash chromatography (10% ethyl acetate–light petroleum) to give the desulfurised *cis*-decalin (254 mg, 86%) as a clear colourless oil bp 190 °C/0.5 mmHg (Found: C, 81.55; H, 11.14. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%); ν_{max}(thin film)/cm^{-1} 1705, 1635; δ_H(400 MHz; $CDCl_3$) 0.66 (3H, d, *J* 3.0, C6*Me*), 0.75 (3H, s, CH_3), 0.99–0.84 (2H, m), 1.25 (3H, s, CH_3),

1.42–1.07 (3H, m), 1.68 (2H, dd, *J* 9.0, 3.0), 2.09–1.87 (3H, m), 2.18 (1H, dd, *J* 6.0, 3.0), 2.35 (1H, dt, *J* 5.0, 2.0), 2.61 (1H, dt, *J* 7.0, 4.0), 4.87 (1H, dd, *J* 18.0, 2.0, =C*H*H), 5.06 (1H, dd, *J* 9.0, 2.0, =CH*H*), 5.36 (1H, dd, *J* 18.0, 9.0, C*H*=); δ_C(100.6 MHz; $CDCl_3$) 12.2, 16.6, 20.3, 23.8, 26.8, 30.4, 34.6, 36.1, 40.9, 45.6, 47.2, 53.5, 113.1, 149.0, 216.8; *m*/*z* (EI^+) 220.1833 (32% M^+. $C_{15}H_{24}O$ requires M^+, 220.1827), 205 (8, $M^+ - CH_3$), 136 (100).

(4a*R,5*R**,6*R**,8a*S**)-5,6,8a-Trimethyldecahydronaphthalene-1-spiro-2′-(1′,3′-dioxolane) 18**

The desulfurised *cis*-decalin (5.08 g, 23.1 mmol), ethane-1,2-diol (5.73 g, 92.4 mmol, 4 equiv.) and camphorsulfonic acid (267 mg, 1.2 mmol, 0.05 equiv.) in benzene (230 ml) were brought to reflux in a Dean–Stark apparatus and refluxed overnight. The reaction was then cooled and poured into saturated aqueous sodium hydrogen carbonate (250 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (2 × 250 ml). The combined organic extracts were washed with brine (250 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (5% ethyl acetate–light petroleum) to give **18** (5.94 g, 97%) as a clear colourless oil bp 170 °C/0.9 mmHg (Found: C, 77.16; H, 10.90. $C_{17}H_{28}O_2$ requires C, 77.21; H, 10.68%); ν_{max}(thin film)/cm^{-1} 1633; δ_H(400 MHz; $CDCl_3$) 0.72 (3H, d, *J* 7.0, C6*Me*), 0.99 (1H, dt, *J* 14.0, 5.0), 1.12 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.28–1.18 (2H, m), 1.42–1.38 (1H, m), 1.80–1.45 (7H, m), 2.02 (1H, dt, *J* 13.0, 4.0), 3.95–3.87 (4H, m, OCH_2-CH_2O), 4.91 (1H, dd, *J* 18.0, 2.0, =C*H*H), 5.00 (1H, dd, *J* 11.0, 2.0, =CH*H*), 5.42 (1H, dd, *J* 18.0, 11.0, C*H*=); δ_C(100.6 MHz; $CDCl_3$) 17.1, 21.6, 22.2, 28.3, 30.7, 30.9, 33.7, 35.9, 40.1, 40.1, 45.2, 50.5, 64.2, 64.6, 112.1, 113.6, 152.0; *m*/*z* (EI^+) 264.2088 (21% M^+. $C_{17}H_{28}O_2$ requires M^+, 264.2089), 249 (7, $M^+ - CH_3$), 99 [100, $CH_3CC(OCH_2CH_2O)$].

(4a*R,5*S**,6*R**,8a*S**)-9-Formyl-5,8,9-trimethyldecahydronaphthalene-1-spiro-2′-(1′,3′-dioxolane) 19**

Ozone was bubbled through a solution of **18** (5.94 g, 22.5 mmol) in dichloromethane (168 ml) and methanol (56 ml) at −78 °C at a steady rate for 20 min. Analysis by TLC indicated that no more starting material was present. Nitrogen was bubbled through the reaction for 15 min, triphenylphosphine (7.07 g, 27.0 mmol, 1.2 equiv.) added in one portion and the reaction warmed to room temperature and left to stir overnight. The reaction was then concentrated and the product adsorbed onto silica gel prior to purification by flash chromatography (10% ethyl acetate–light petroleum) to give **19** (4.12 g, 69%) as a white solid mp 68 °C (Found: C, 72.39; H, 9.92. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%); ν_{max}(thin film)/cm^{-1} 1715; δ_H(400 MHz; $CDCl_3$) 0.91 (3H, d, *J* 7.0, C6*Me*), 0.97 (6H, d, *J* 5.0), 1.18–1.10 (2H, m), 1.53–1.30 (3H, m), 1.57 (3H, t, *J* 5.0), 1.73–1.64 (2H, m), 1.88–1.83 (2H, m), 3.95–3.86 (4H, m, OCH_2-CH_2O), 9.28 (1H, s, *H*CO); δ_C(100.6 MHz; $CDCl_3$) 17.6, 22.1, 23.4, 26.2, 30.1, 44.6, 64.5, 64.7, 112.9, 207.1; *m*/*z* (EI^+) 266.1882 (22% M^+. $C_{16}H_{26}O_3$ requires M^+, 266.1881), 238 (37, $M^+ - CO$), 176 (45), 99 [100, $CH_3CC(OCH_2CH_2O)$].

(4a*R,5*S**,6*R**,8a*S**)-5-{(2,5-Dimethoxyphenyl)[(*RS*)-hydroxy]methyl}-5,6,8a-trimethyldecahydronaphthalene-1-spiro-2′-(1′,3′-dioxolane) 20**

To a solution of 1,4-dimethoxybenzene (342 mg, 2.48 mmol) and tetra-*N*-methylethylenediamine (862 mg, 7.44 mmol, 3.0 equiv.) in tetrahydrofuran (5 ml) was added butyllithium (1.15 ml of a 2.5 M solution in hexanes, 2.50 mmol, 1.01 equiv.) at 0 °C. The reaction was stirred for 1.5 h before **19** (200 mg, 0.83 mmol) was added *via* cannula as a solution in tetrahydrofuran (2 ml + 1.5 ml washings). The reaction was stirred for 30 min at 0 °C, then poured into water (20 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (30% ethyl acetate–light petroleum) to give an, unquantifiable by NMR, mixture of inseparable diastereoisomers **20** (297 mg, 89%), as a white solid mp 212 °C; ν_{max}(thin film)/cm^{-1} 2926, 1490, 1465, 880; δ_H(400 MHz; $CDCl_3$) 0.49 (3H, d, *J* 6.0, C6*Me*), 1.27 (3H, s), 0.95 (3H, s), 1.7–1.56 (5H, m), 1.48–1.18 (6H, m), 1.84 (1H, dt, *J* 14.0, 5.0), 2.1–2.04 (1H, m), 2.00–1.91 (1H, m), 3.76 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.94 (4H, br s, OCH_2CH_2O), 6.79–6.73 (2H, m, Ar*H*), 6.99 (1H, d, *J* 2.5, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 13.6, 16.4, 22.6, 25.3, 26.5, 27.7, 28.5, 31.0, 30.1, 42.5, 44.3, 45.7, 55.7, 64.6, 64.7, 111.3, 112.5, 114.3, 115.9, 132.7, 151.6, 153.2; *m*/*z* (EI^+) 404.2559 (35% M^+. $C_{24}H_{36}O_5$ requires M^+, 404.2562), 386 (15, $M^+ - H_2O$), 253 [20, $M^+ - C_6H_3(OCH_3)_2CHOH$], 237 (100).

(4a*R,5*S**,6*R**,8a*S**)-5-[(2,5-Dimethoxyphenyl)methyl]-5,6,8a-trimethyldecahydronaphthalen-1(2*H*)-one 21**

A reaction vessel containing **20** (30 mg, 0.074 mmol) and $Pd(OH)_2$/C (5 mg) in ethyl acetate (10 ml) was purged with hydrogen *via* several vacuum/purge cycles and then vigorously stirred under hydrogen for 3 days. The reaction mixture was filtered through Celite, washed with ethyl acetate and the organics concentrated *in vacuo*. The product was purified by flash chromatography (10% ethyl acetate–light petroleum) to give **21** (18.8 mg, 75%), as a clear colourless oil; ν_{max}(thin film)/cm^{-1} 1695, 1580, 850; δ_H(250 MHz; $CDCl_3$) 0.79 (3H, s, CH_3), 0.96 (3H, d, *J* 5.0, C6*Me*), 1.14 (3H, s, CH_3), 1.40–1.17 (4H, m), 1.68 (1H, d, *J* 5.0), 2.33–1.96 (6H, m), 2.55 (1H, d, *J* 15.0, ArCH*H*), 2.69–2.55 (1H, m), 2.80 (1H, d, *J* 15.0, ArC*H*H), 3.73 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.79–6.73 (3H, m, Ar*H*); *m*/*z* (EI^+) 344.2348 (32% M^+. $C_{22}H_{32}O_3$ requires M^+, 344.2351), 200 (51), 152 (100).

(4a*R,5*S**,6*R**,8a*S**)-5-[(2,5-Dimethoxyphenyl)methyl]-1-methylene-5,6,8a-trimethyldecahydronaphthalene 22**

Nysted's reagent (192 mg, 0.42 mmol, 3.5 equiv.) followed by titanium(IV) chloride (68 mg, 0.36 mmol, 3.0 equiv.) were added to a solution of **21** (41.6 mg, 0.12 mmol) in dichloromethane (0.4 ml) at −78 °C. The reaction was allowed to warm to room temperature and stirred for 20 h. Triethylamine (266 mg, 2.64 mmol, 22.0 equiv.) was then added in one portion and the reaction stirred for 10 min, filtered through a short plug of Celite and washed with ethyl acetate. The organics were concentrated and the product purified by flash chromatography (25% benzene–hexane) to give **22** (32 mg, 78%) as a clear colourless oil; ν_{max}(thin film)/cm^{-1} 1498, 1463, 888; δ_H(400 MHz; $CDCl_3$) 0.90 (3H, s, CH_3), 0.97 (3H, d, *J* 6.0, C6*Me*), 1.02 (3H, s, CH_3), 1.41–1.15 (4H, m), 1.73–1.65 (1H, m), 1.61–1.46 (1H, m), 2.00–1.80 (3H, m), 2.25–2.10 (2H, m), 2.53–2.40 (1H, m), 2.56 (1H, d, *J* 14.0, ArCH*H*), 2.76 (1H, d, *J* 14.0, ArC*H*H), 3.72 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.73–4.67 (2H, m, =CH_2), 6.78–6.67 (3H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 18.0, 19.2, 22.3, 25.0, 27.7, 32.1, 32.9, 37.3, 37.4, 37.8, 39.3, 43.6, 46.3, 55.5, 55.7, 105.7, 111.0, 111.2, 118.8, 129.0, 152.7, 153.0, 153.8; *m*/*z* (EI^+) 342.2550 (31% M^+. $C_{23}H_{34}O_2$ requires M^+, 342.2558), 191 [19, $M^+ - C_6H_3(OCH_3)_2 - CH_2$], 152 (100%).

(4a*R,5*S**,6*R**,8a*S**)-5-{(2,3,6-Trimethoxyphenyl)[(*RS*)-hydroxy]methyl}-5,6,8a-trimethyldecahydronaphthalene-1-spiro-2′-(1′,3′-dioxolane) 23**

To a solution of 1,2,4-trimethoxybenzene (1.89 g, 11.3 mmol) and tetra-*N*-methylethylenediamine (3.92 g, 33.8 mmol, 3.0 equiv.) in tetrahydrofuran (28 ml) was added butyllithium (4.56 ml of a 2.5 M solution in hexanes, 11.4 mmol, 1.01 equiv.) at −78 °C. The reaction was stirred for 30 min, warmed to 0 °C and stirred for a further 30 min before the addition of **19** (1 g, 3.76 mmol) *via* cannula as a solution in tetrahydrofuran (8 ml + 2 ml washings). The reaction was stirred for 0.5 min at 0 °C, then carefully poured into water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts

were washed with brine (50 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (30% ethyl acetate–light petroleum) to give **23** (1.28 g, 78%) as a white solid mp 151–153 °C (Found: C, 69.15; H, 9.04. $C_{25}H_{38}O_6$ requires C, 69.08; H, 8.82%); ν_{max}(thin film)/cm^{-1} 2938, 1485, 735; δ_H(400 MHz; $CDCl_3$) 0.28 (3H, d, *J* 7.0, C6*Me*), 0.81 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.70–1.26 (9H, m), 1.80 (1H, dt, *J* 14.0, 5.0), 2.21–2.12 (1H, m), 2.31 (1H, dd, *J* 12.0, 5.0), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.93–3.90 (4H, m, OCH_2CH_2O), 5.40 (1H, s, ArC*H*OH), 6.57 (1H, d, *J* 9.0, Ar*H*), 6.74 (1H, d, *J* 9.0, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 14.5, 18.3, 22.8, 27.3, 27.4, 30.2, 42.8, 43.6, 46.9, 55.4, 56.0, 60.2, 64.7, 74.9, 106.1, 110.5, 114.4, 125.1, 147.4, 147.8, 152.6; *m*/*z* (EI$^+$) 434.2664 (0.5% M$^+$. $C_{23}H_{34}O_2$ requires M$^+$, 434.2668), 416 (0.4, M$^+$ − H_2O), 324 (54), 237 (38, M$^+$ − $C_{10}H_{13}O_4$), 197 (100).

(4a*R,5*S**,6*R**,8a*S**)-5-[(2,3,6-Trimethoxyphenyl)methyl]-5,6,8a-trimethyldecahydronaphthalen-1(2*H*)-one 24**

Subjection of **23** (495 mg, 1.14 mmol) with $Pd(OH)_2$/C (50 mg) under the hydrogenation conditions described for **21** led to a crude product which was purified by flash chromatography (gradient elution 20 to 30% ethyl acetate–light petroleum) to give **24** (127 mg, 30%) as a clear viscous oil; ν_{max}(thin film)/cm^{-1} 1703, 1485, 1463, 722; δ_H(250 MHz; $CDCl_3$) 0.80 (3H, s), 0.86 (3H, d, *J* 6.0), 1.38–1.11 (8H, m), 2.20–1.80 (7H, m), 2.56 (1H, d, *J* 8.0, ArC*H*), 2.81 (1H, d, *J* 8.0, ArC*H*), 3.73 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.51 (1H, d, *J* 9.0, Ar*H*), 6.74 (1H, d, *J* 9.0, Ar*H*); *m*/*z* (EI$^+$) 374.2462 (3% M$^+$. $C_{23}H_{34}O_4$ requires M$^+$, 374.2457), 208 (71, M$^+$ − $C_9H_{11}O_3$), 152 (100). Followed by the cyclic ketal deprotected material of **23** (265 mg, 60%) a white solid mp 93 °C (Found: C, 70.79; H, 8.48. $C_{23}H_{34}O_5$ requires C, 70.74; H, 8.78%); ν_{max}(thin film)/cm^{-1} 2937, 1701, 1589, 1486, 794, 752; δ_H(400 MHz; $CDCl_3$) 0.78 (3H, s, CH_3), 0.85 (3H, d, *J* 7.0, C6*Me*), 1.02 (1H, br s), 1.28 (3H, s, CH_3), 1.34 (2H, td, *J* 10.0, 5.0), 1.70 (1H, br s), 1.56–1.47 (1H, m), 1.88–1.78 (2H, m), 2.04–1.96 (1H, m), 2.13 (2H, dq, *J* 15.0, 3.0), 2.37 (1H, br s), 2.55 (1H, dt, *J* 19.0, 7.0), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.57 (1H, br s, O*H*), 5.10 (1H, br s, ArC*H*OH), 6.55 (1H, d, *J* 9.0, Ar*H*), 6.76 (1H, d, *J* 9.0, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 14.2, 17.7, 22.3, 24.2, 27.8, 29.9, 33.1, 34.9, 36.2, 47.6, 48.3, 48.9, 55.3, 56.0, 60.2, 73.9, 105.3, 110.6, 124.3, 147.3, 147.6, 152.4, 217.7; *m*/*z* (EI$^+$) 390.2398 (3% M$^+$. $C_{23}H_{34}O_4$ requires M$^+$, 390.2406), 372 (26, M$^+$ − H_2O), 197 (100, $C_9H_{11}O_3$-CHOH).

(4a*R,5*S**,6*R**,8a*S**)-5-[(2,3,6-Trimethoxyphenyl)methyl]-1-methylene-5,6,8a-trimethyldecahydronaphthalene 25**

Treatment of **24** (117 mg, 0.31 mmol) with Nysted's reagent as for the preparation of **22** led to a crude product which was purified by flash chromatography (10% ethyl acetate–light petroleum) to give **25** (66.5 mg, 58%) as a clear colourless oil. ν_{max}(thin film)/cm^{-1} 1499, 1463, 802; δ_H(400 MHz; $CDCl_3$) 0.85 (3H, d, *J* 6.0, C6*Me*), 0.87 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.30–1.05 (4H, m), 1.47–1.35 (2H, m), 1.65–1.57 (1H, m), 1.95–1.67 (3H, m), 2.11–1.97 (1H, m), 2.40 (1H, tdt, *J* 14.0, 7.0, 2.0), 2.59 (1H, d, *J* 13.0, ArCH*H*), 2.67 (1H, d, *J* 13.0, ArC*H*H), 3.70 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.64 (1H, t, *J* 2.0, =CH*H*), 4.67 (1H, t, *J* 2.0, =C*H*H), 6.50 (1H, d, *J* 9.0, Ar*H*), 6.73 (1H, d, *J* 9.0, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 18.5, 19.1, 23.1, 25.4, 28.2, 32.3, 33.3, 34.9, 37.7, 39.5, 39.7, 44.5, 48.6, 55.2, 56.1, 60.0, 104.5, 105.5, 109.8, 123.6, 147.0, 149.7, 153.5, 154.1; *m*/*z* (EI$^+$) 372.2666 (17% M$^+$. $C_{24}H_{36}O_3$ requires M$^+$, 372.2664), 82 [100, $C_6H_2(OCH_3)_3CH_2$].

2,2′,4,4′,5,5′-Hexamethoxy-3,3′-bis(2,2-dimethylpropyl)-1,1′-biphenyl 26

A solution of **16 X = OMe** (4.10 g, 7.2 mmol) in acetonitrile (5 ml + 4 ml washings) was added *via* cannula to thallium(III) acetate (3.29 g, 8.62 mmol, 0.5 equiv.) in acetonitrile (170 ml) at −40 °C followed immediately by the dropwise addition of BF_3·OEt_2 (9.79 g, 69.0 mmol, 4.0 equiv.). The green reaction was warmed to room temperature and stirred for a further 45 min before being poured into water (100 ml) and extracted with chloroform (3 × 100 ml). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a brown solid. The product biphenyl **26** was obtained by recrystallisation from the minimum amount of hot methanol (~60 ml) to give **26** (2.20 g, 54%) as a white solid, mp 142 °C (Found: C, 70.98; H, 8.91. $C_{28}H_{41}O_6$ requires C, 70.86; H, 8.92%); ν_{max}(thin film)/cm^{-1} 2953, 1593, 1565; δ_H(250 MHz; $CDCl_3$) 0.94 (18H, s, 2 × *Bu*^{t}), 2.60 (4H, s, 2 × ArCH_2), 3.34 (6H, s, 2 × OCH_3), 3.81 (6H, s, 2 × OCH_3), 3.82 (6H, s, 2 × OCH_3), 6.78 (2H, s, 2 × Ar*H*); δ_C(62.9 MHz; $CDCl_3$) 29.8, 33.2, 37.0, 55.5, 59.6, 59.7, 112.6, 126.3, 126.7, 147.5, 148.0, 150.7; *m*/*z* (EI$^+$) 474.2978 (100% M$^+$. $C_{28}H_{42}O_6$ requires M$^+$, 474.2981), 459 (15, M$^+$ − CH_3), 417 (40, M$^+$ − Bu′).

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References

1 J. R. Carney and P. J. Scheuer, *Tetrahedron Lett.*, 1993, **34**, 3727.
2 (*a*) A. D. Rodriguez, W. Y. Yoshida and P. J. Scheur, *Tetrahedron*, 1990, **46**, 8025; (*b*) J. Gripenberg, *Tetrahedron Lett.*, 1974, 619; (*c*) S. Hirsh, A. Rudi, Y. Kashman and Y. Loya, *J. Nat. Prod.*, 1991, **54**, 92; (*d*) P. J. Scheur, Abstracts of papers of the Americal Chemical Society, 1995, **209**, No. Pt 1, p. 2-AGFD.
3 A. T. Watson, K. Park, D. F. Wiemer and W. Scott, *J. Org. Chem.*, 1995, **60**, 5102.
4 H. Kawano, M. Itoh, T. Katoh and S. Terashima, *Tetrahedron Lett.*, 1997, **38**, 7769.
5 J. An and D. F. Wiemer, *J. Org. Chem.*, 1996, **61**, 8775.
6 E. P. Locke and S. M. Hecht, *Chem. Commun.*, 1996, 2717.
7 H. G. H. Erdtman, *Proc. Roy. Soc.*, 1934, **143**, 223.
8 A. J. Shand and R. H. Thomson, *Tetrahedron*, 1963, **19**, 1919.
9 T. Tokoroyama, M. Tsukamoto, T. Asada and H. Iio, *Tetrahedron Lett.*, 1987, **28**, 6645.
10 M. A. Guaciaro, P. O. M. Wovkulich and A. B. Smith, *Tetrahedron Lett.*, 1978, **19**, 4661.
11 K. Tamao, K. Sumitani, Y. Kiso, M. Zembyashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato and M. J. Kumada, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1958.
12 T. Hayashi, M. Konishi, Y. Kobori, M. Kumada and T. Higuchi, *J. Am. Chem. Soc.*, 1984, **106**, 158.
13 R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, 1943, **65**, 1984.
14 A. J. Robichand, G. D. Berger and D. A. Evans, *Tetrahedron Lett.*, 1993, **34**, 8403.
15 D. N. Kursanov, Z. N. Parnes and N. M. Liom, *Synthesis*, 1974, 633.
16 G. Rosenkranz, S. Kaufmann and J. Romo, *J. Am. Chem. Soc.*, 1949, **71**, 3689.
17 For example, see L. F. Tietze, U. Hartfiel, T. Hubsch, E. Voss, K. Bogdanowicz-Szwod and J. Wichmann, *Liebigs Ann.*, 1991, 275.
18 *Aldrichim. Acta*, 1993, **26**, 14.
19 A. McKillop, A. G. Turrell, D. W. Young and E. C. Taylor, *J. Am. Chem. Soc.*, 1980, **102**, 6504.
20 J. C. Anderson, D. C. Siddons, S. C. Smith and M. E. Swarbrick, *J. Org. Chem.*, 1996, **61**, 4820.
21 S. V. Ley and A. J. Whittle, *Tetrahedron Lett.*, 1981, **22**, 3301.
22 S. Kano, T. Ebak and S. Shibuya, *Heterocycles*, 1980, **14**, 43.

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