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Supporting Information

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Thermally Induced Cyclobutenone Rearrangements and Domino Reactions

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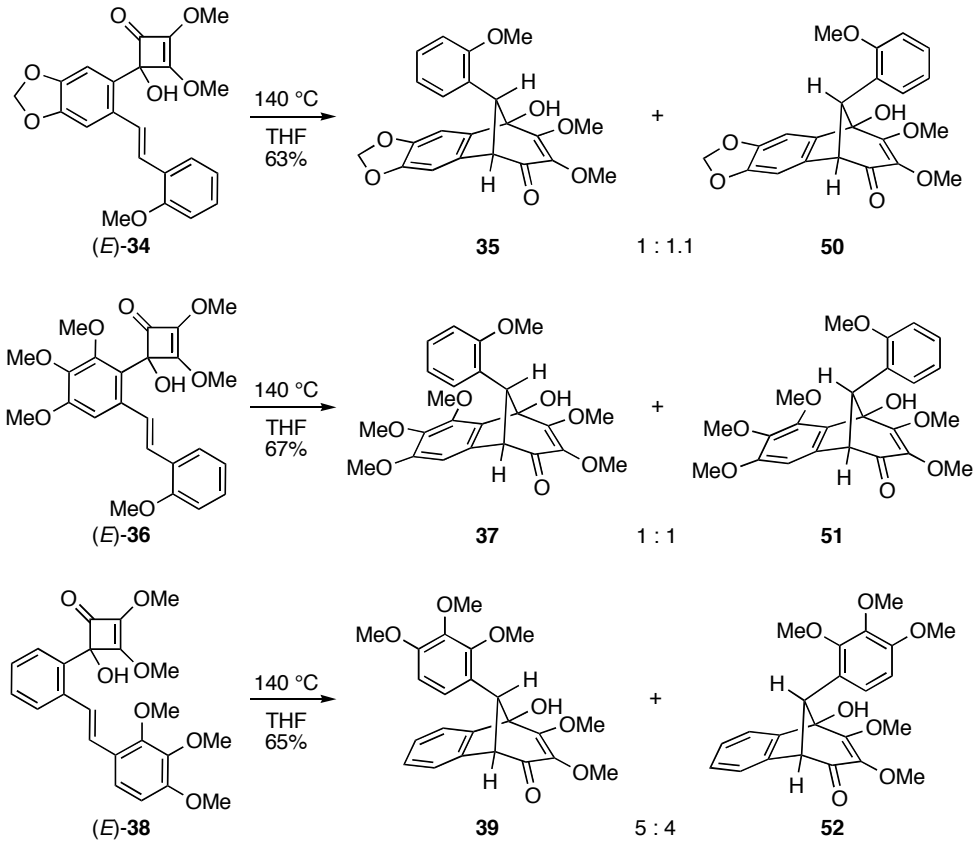
Supporting Information

FURTHER EXAMPLES

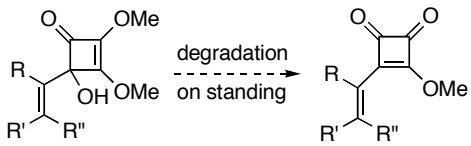
As noted, while thermolysis of (*Z*)-2-(*o*-styryl)-cyclobutenones gave benzobicyclo[3.2.1]octenones as single diastereoisomers (Scheme 6), analogous treatment of the isomeric (*E*)-2-(*o*-styryl)cyclobutenones gave rise to diastereomeric mixtures. These results are summarised in the Scheme below.



Scheme. Rearrangements of (*E*)-2-(*o*-styryl)-cyclobutenones to benzobicyclo[3.2.1]octenones.

NOTES

- Our use of a microwave instrument for the thermolysis reactions was driven by convenience and practicability. On the few occasions where thermolyses were duplicated using a sealed tube immersed in an oil bath (and behind a blast screen), outcomes were broadly comparable. All such experiments were conducted in a CEM Discover microwave reactor operating at a power of 150 W.
- Many of the vinyl- and aryl-cyclobutenones proved highly sensitive and readily degraded to a cyclobutendione on standing.[1] Consequently, it usually proved beneficial to take these materials through the thermolysis stage as crude product mixtures. For a specific example of the degradation see the following experimental account for the preparation of **13**.

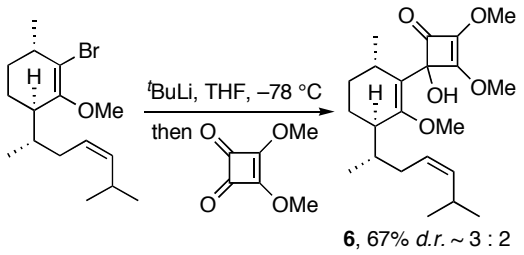


- Diastereomer ratios were determined by integration of ^{1}H NMR signals in spectra attained from crude product mixtures.

EXPERIMENTAL PROCEDURES AND COMPOUND CHARACTERIZATION.

Dimethyl squarate,[2] 3-*tert*-butoxy-4-methyl-cyclobut-3-ene-1,2-dione,[3] 2-bromocyclohexanone,[4] (bromomethyl)triphenyl-phosphonium bromide,[5] 2-bromocyclopent-1-ene-1-carboxaldehyde,[6] 3-phenoxy-cyclohex-2-en-1-one,[7] 2-bromo-1-phenylsulfanyl-cyclohex-1-en-3-ol,[8] (2-methoxybenzyl)triphenylphosphonium bromide,[9] (*Z*)-1-bromo-2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]benzene,[9] (2-bromobenzyl)triphenylphosphonium bromide,[9] and 2-bromo-3,4,5-trimethoxystyrene,[10] were prepared using the referenced literature procedures. *rel*-(2'*S*,3*R*,4'*Z*,6*S*)-1-Bromo-2-methoxy-6-methyl-3-(6'-methyl-hept-4'-en-2'-yl)-cyclohexene was prepared during studies directed towards the total synthesis of elisabethin A. Full details of that synthesis will be reported in due course.

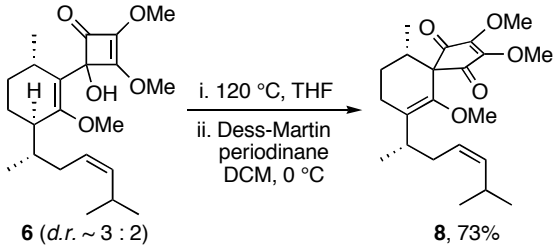
rel-(2"*S*,3'*R*,4*RS*,4"*Z*,6'*S*)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(6"-methyl-hept-4"-en-2"-yl)-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 6



6, 67% *d.r.* ~ 3 : 2

To a solution of ^{t}BuLi (1.27M in pentane, 0.67 mL, 0.856 mmol) in THF (2.5 mL) at –78 °C was added a solution of *rel*-(2'*S*,3*R*,4'*Z*,6*S*)-1-bromo-2-methoxy-6-methyl-3-(6'-methyl-hept-4'-en-2'-yl)-cyclohexene (135 mg, 0.428 mmol) in THF (2.5 mL) over 2 min. After 30 min a solution of dimethyl squarate (61 mg, 0.43 mmol) in THF (2 mL) was added over 2 min, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between water (5 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (30 mL) then the combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc/petrol) gave a yellow oil, vinylcyclobutenones **6** (*d.r.* ~ 3 : 2, 108 mg, 0.285 mmol, 67%), that was used immediately in the following reaction due to instability.

rel-(2'*S*,4'*Z*,10*R*)-7-(6-Methyl-hept-4'-en-2'-yl)-2,3,6-trimethoxy-10-methyl-spiro[4.5]deca-2,6-diene-1,4-dione, 8



6 (*d.r.* ~ 3 : 2) **8**, 73%

A solution of vinylcyclobutenones **6** (108 mg, 0.285 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (181 mg, 0.428 mmol). After 30 min 1M NaOH (3 mL) was added and the temperature raised to RT. The aqueous phase was separated and extracted with ether (2 x 20 mL) then the combined organic phases was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc/petrol) gave spirocycle **8** (78 mg, 0.207 mmol, 73%) as a yellow oil.

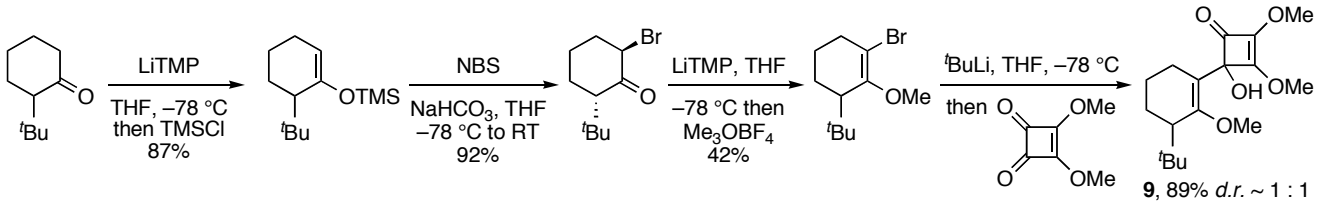
IR ν_{max} (neat, cm^{-1}) 2957 m, 2868 w, 1685 s, 1626 s, 1459 s, 1320 s, 1208 m, 1133 m, 1111 m, 1039 m, 1012 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.25-5.15 (2H, m), 4.23 (3H, s), 4.22 (3H, s), 3.40 (3H, s), 2.84 (1H, sextet, *J* 6.8 Hz), 2.57 (1H, septet of d, *J* 6.8, 1.8 Hz), 2.18-2.00 (5H, m), 1.92-1.83 (1H, m), 1.59-1.53 (1H, m), 1.01 (3H, d, *J* 6.8 Hz), 0.95 (3H, d, *J* 6.8 Hz), 0.94 (3H, d, *J* 6.8 Hz), 0.81 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 197.6 (*C*), 196.9 (*C*), 153.3 (*C*), 152.7 (*C*), 144.8 (*C*), 138.5 (*C*H), 133.2 (*C*), 125.6 (*C*H), 62.4 (*C*H$_3$), 60.8 (*C*), 59.9 (*C*H$_3$), 59.8 (*C*H$_3$), 35.1 (*C*H), 33.0 (*C*H), 32.8 (*C*H$_2$), 26.8 (*C*H$_2$), 26.8 (*C*H), 23.3 (2 x *C*H$_3$), 22.2 (*C*H$_2$), 18.5 (*C*H$_3$), 16.4 (*C*H$_3$).

Mass $^m/_z$ (ES$^+$) 775 ([2M + Na]$^+$, 20%), 399 ([M + Na]$^+$, 100).

4-Hydroxy-4-(3'-(*tert*-butyl)-2'-methoxy-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 9



9, 89% *d.r.* ~ 1 : 1

To a solution of 2,2,6,6-tetramethylpiperidine (1.42 mL, 8.43 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (1.91 M in hexanes, 4.4 mL, 8.4 mmol). After 1 h the reaction mixture was cooled to –78 °C and a solution of 2-*tert*-butylcyclohexanone (1.00 g, 6.48 mmol) in THF (10 mL) was added followed after 1 h by trimethylsilyl chloride (1.1 mL, 8.5 mmol). The reaction mixture was allowed to warm to RT over 30 min then partitioned between sat. $NaHCO_3$ (30 mL) and ether (40 mL). The aqueous phase was separated and extracted with ether (2 x 40 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave 6-(*tert*-butyl)-1-trimethylsilyloxy-cyclohexene as a colourless oil (1.28 g, 5.66 mmol, 87%).

IR ν_{max} (neat, cm^{-1}) 2950 m, 2925 m, 2860 w, 2840 w, 1650 w, 1360 m, 1246 s, 1217 m, 1164 s, 907 s, 833 s, 743 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.90 (1H, t, *J* 3.6 Hz), 1.99-1.92 (3H, m), 1.80-1.62 (2H, m), 1.50-1.28 (2H, m), 0.99 (9H, s), 0.20 (9H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 153.5 (*C*), 106.4 (*C*H), 48.4 (*C*H), 33.8 (*C*), 29.4 (3 x *C*H$_3$), 27.1 (*C*H$_2$), 24.6 (*C*H$_2$), 22.4 (*C*H$_2$), 0.6 (3 x *C*H$_3$).

Mass $^m/_z$ (EI) 226 (M$^+$, 24%), 211 ([M – CH$_3$]$^+$, 22), 170 ([M – C$_4$H$_8$]$^+$, 100), 155 (51), 142 (28), 127 (22), 96 (12), 73 (64).

To a solution of 6-(*tert*-butyl)-1-trimethylsilyloxy-cyclohexene (1.14 g, 5.03 mmol) in THF (30 mL) at –78 °C was added powdered $NaHCO_3$ (507 mg, 6.03 mmol) followed by *N*-bromosuccinimide (941 mg, 5.29 mmol). After 1 h the reaction mixture was warmed to RT and partitioned between sat. $NaHCO_3$ (30 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) yielded 2-bromo-6-(*tert*-butyl)-cyclohexanone (1.07 g, 4.61 mmol, 92%).

IR ν_{max} (neat, cm^{-1}) 2954 m, 2864 w, 1712 vs, 1483 w, 1446 w, 1360 m, 1311 w, 1246 w, 1144 m, 1091 m, 858 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.29 (1H, t, *J* 2.8 Hz), 3.10 (1H, dd, *J* 13.3, 4.7 Hz), 2.30-2.03 (4H, m), 1.83-1.74 (1H, m), 1.44 (1H, qd, *J* 12.8, 3.4 Hz), 1.01 (9H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 206.0 (*C*), 54.6 (*C*H), 53.8 (*C*H), 36.5 (*C*H$_2$), 31.8 (*C*), 29.6 (*C*H$_2$), 27.5 (3 x *C*H$_3$), 21.2 (*C*H$_2$).

Mass $^m/_z$ (EI) 234/232 (M$^+$, 15%), 219/217 ([M – CH$_3$]$^+$, 80), 178/176 ([M – C$_4$H$_8$]$^+$, 30), 139 (21), 109 (33), 98 (83), 83 (91), 67 (83), 55 (100).

To a solution of 2,2,6,6-tetramethylpiperidine (0.73 mL, 4.3 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi (1.91 M in hexanes, 2.25 mL, 4.3 mmol). After 1 h the reaction mixture was cooled to –78 °C and a solution of 2-bromo-6-(*tert*-butyl)-cyclohexanone (500 mg, 2.14 mmol) in THF (10 mL) added followed after 2 h by trimethyloxonium tetrafluoroborate (635 mg, 4.29 mmol). The reaction mixture was warmed to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (10 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (30 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave 1-bromo-3-(*tert*-butyl)-2-methoxy-cyclohexene as a colourless oil (246 mg, 1.00 mmol, 42%).

IR ν_{max} (neat, cm^{-1}) 2950 s, 2925 s, 2864 m, 1642 w, 1360 m, 1221 m, 1201 m, 1123 s, 1001 s, 984 m, 805 m.

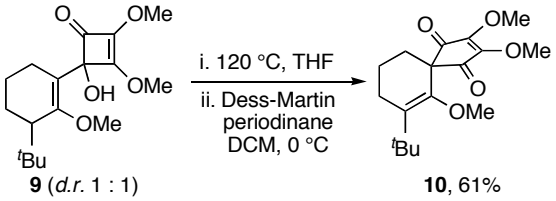
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.52 (3H, s), 2.55-2.39 (2H, m), 2.33-2.28 (1H, m), 1.82-1.71 (2H, m), 1.63-1.47 (2H, m), 0.99 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 155.5 (*C*), 111.6 (*C*), 57.2 (*C*H_3), 45.5 (*C*H), 35.3 (*C*H_2), 34.6 (*C*), 29.1 (3 x *C*H_3), 26.5 (*C*H_2), 23.4 (*C*H_2).

Mass $^m/_z$ (EI) 248/246 (M^+, 7%), 192/190 ($[M - C_4H_8]^+$, 55), 111 (51), 79 (23), 57 (100).
$^m/_z$ (EI) found 246.0616, M^+. $C_{11}H_{19}{}^{79}BrO$ requires 246.0619.

To a solution of ^{t}BuLi (1.24 M in pentane, 0.71 mL, 0.87 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1-bromo-3-(*tert*-butyl)-2-methoxy-cyclohexene (108 mg, 0.437 mmol) in THF (2.5 mL) over 2 min. After 15 min a solution of dimethyl squarate (124 mg, 0.874 mmol) in THF (2 mL) was added over 2 min, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between ether (20 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (2 x 10 mL) then the combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) gave an inseparable 1 : 1 mixture of vinylcyclobutenones **9** (121 mg, 0.390 mmol, 89%) as a yellow oil. These were used immediately in the following reaction due to instability.

7-*tert*-Butyl-2,3,6-trimethoxyspiro[4.5]deca-2,6-diene-1,4-dione, 10



9 (*d.r.* 1 : 1) **10**, 61%

Vinylcyclobutenones **9** (121 mg, 0.390 mmol) in THF (3 mL) were heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (199 mg, 0.468 mmol). After 30 min 2M NaOH (2 mL) was added and the temperature raised to RT. Following dilution with ether (30 mL), the organic phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc/petrol) gave spirocycle **10** as a yellow oil (74 mg, 0.24 mmol, 61%).

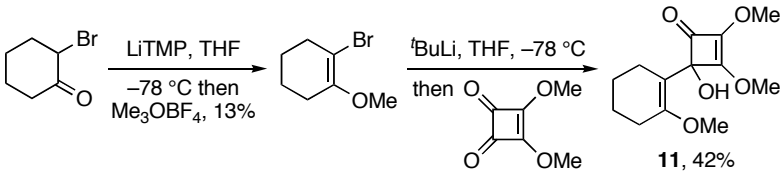
IR ν_{max} (neat, cm^{-1}) 2950 m, 2860 w, 1683 s, 1626 s, 1458 s, 1319 vs, 1193 s, 1140 s, 1107 s, 1025 s, 907 m, 723 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.23 (6H, s), 3.33 (3H, s), 2.15 (2H, t, *J* 6.0 Hz), 1.81-1.69 (4H, m), 1.16 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 197.7 (2 x *C*), 150.6 (2 x *C*), 144.5 (*C*), 137.0 (*C*), 61.8 (*C*H_3), 59.8 (2 x *C*H_3), 57.3 (*C*), 35.8 (*C*), 31.6 (*C*H_2), 30.1 (3 x *C*H_3), 27.0 (*C*H_2), 19.5 (*C*H_2).

Mass $^m/_z$ (EI) 308 (M^+, 39%), 293 ($[M - CH_3]^+$, 55), 243 (35), 205 (20), 169 (41), 105 (28), 91 (74), 79 (42), 43 (100).
$^m/_z$ (EI) found 308.1620, M^+. $C_{17}H_{24}O_5$ requires 308.1624.

4-Hydroxy-4-(2-methoxy-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 11



11, 42%

To a solution of 2,2,6,6-tetramethylpiperidine (0.95 mL, 5.7 mmol) in THF (10 mL) at 0 °C was added ^{n}BuLi (1.92 M in hexanes, 2.90 mL, 5.65 mmol). After 30 min the reaction mixture was cooled to –78 °C and a solution of 2-bromocyclohexanone (500 mg, 2.82 mmol) in THF (10 mL) added followed after 90 min by trimethyloxonium tetrafluoroborate (635 mg, 4.29 mmol). The

reaction mixture was warmed to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (10 mL) and ether (40 mL). The aqueous phase was separated and extracted with ether (2 x 40 mL) then the combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1-3% ether/petrol) gave 1-bromo-2-methoxy-cyclohexene as a colourless oil (69 mg, 0.36 mmol, 13%).

IR ν_{max} (neat, cm^{-1}) 2929 s, 2860 w, 2835 w, 1663 s, 1446 m, 1328 m, 1262 m, 1221 s, 1152 s, 1009 s, 968 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.62 (3H, s), 2.47 (2H, tt, *J* 6.2, 2.2 Hz), 2.25 (2H, tt, *J* 6.1, 2.2 Hz), 1.79-1.62 (4H, m).

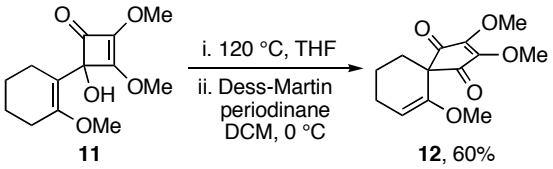
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 150.4 (*C*), 101.8 (*C*), 55.7 (*C*H_3), 34.5 (*C*H_2), 26.3 (*C*H_2), 24.5 (*C*H_2), 22.9 (*C*H_2).

Mass $^m/_z$ (EI) 192/190 (M^+, 78), 164/162 (61), 111 ($[M - Br]^+$, 100), 95 (26), 79 (57), 67 (51).

$^m/_z$ (EI) found 189.9986, M^+. $C_7H_{11}{}^{79}BrO$ requires 189.9993.

To a solution of ^{t}BuLi (1.15 M in pentane, 0.85 mL, 0.97 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1-bromo-2-methoxy-cyclohexene (93 mg, 0.49 mmol) in THF (2.5 mL) over 2 min. After 30 min a solution of dimethyl squarate (69 mg, 0.49 mmol) in THF (2 mL) was added over 2 min, followed after 45 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and the aqueous phase separated and extracted with ether (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-40% EtOAc/petrol) gave a yellow oil, vinylcyclobutenones **11** (52 mg, 0.21 mmol, 42%), that was used immediately in the following reaction due to instability.

2,3,6-Trimethoxyspiro[4.5]deca-2,6-diene-1,4-dione, 12



11 **12**, 60%

A solution of vinylcyclobutenone **11** (52 mg, 0.205 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (207 mg, 0.487 mmol). After 30 min 1M NaOH (3 mL) was added and the temperature raised to RT. The aqueous phase was separated and extracted with ether (2 x 20 mL) then the combined organic phases was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc/petrol) gave spirocycle **12** (31 mg, 0.123 mmol, 60%) as a yellow oil.

IR ν_{max} (neat, cm^{-1}) 3003 w, 2942 m, 2844 w, 1683 s, 1618 s, 1458 s, 1315 s, 1242 m, 1209 s, 1144 s, 997 s.

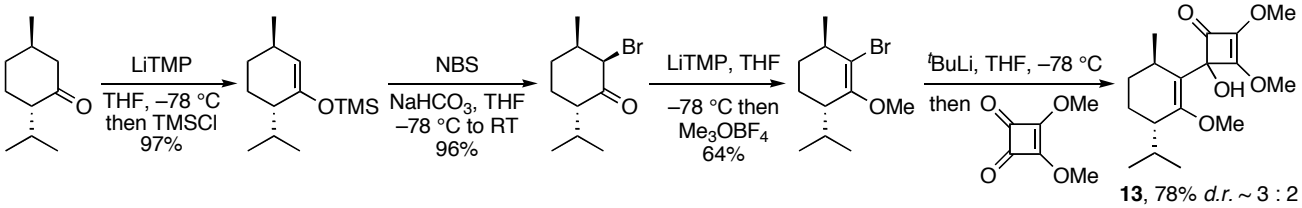
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.08 (1H, t, *J* 4.1 Hz), 4.22 (6H, s), 3.43 (3H, s), 2.21-2.16 (2H, m), 1.84-1.80 (4H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 196.7 (2 x *C*), 151.2 (2 x *C*), 150.0 (*C*), 100.5 (*C*H), 59.8 (2 x *C*H_3), 54.9 (*C*), 54.8 (*C*H_3), 30.2 (*C*H_2), 23.2 (*C*H_2), 19.2 (*C*H_2).

Mass $^m/_z$ (EI) 252 (M^+, 100%), 237 ($[M - CH_3]^+$, 40), 221 ($[M - OCH_3]^+$, 76), 209 (34), 169 (31), 135 (35), 121 (25).

$^m/_z$ (EI) found 252.0988, M^+. $C_{13}H_{16}O_5$ requires 252.0998.

(3'*S*,4*RS*,6'*R*)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 13 and enantiomer.



13, 78% *d.r.* ~ 3 : 2

To a solution of 2,2,6,6-tetramethylpiperidine (2.85 mL, 16.9 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (1.92 M in hexanes, 8.8 mL, 16.9 mmol). After 30 min the reaction mixture was cooled to –78 °C and a solution of L-menthone (1.96 g, 12.7 mmol) in THF (20 mL) was added followed after 2 h by trimethylsilyl chloride (2.14 mL, 16.9 mmol). After a further 45 min the reaction mixture was warmed to RT and partitioned between sat. $NaHCO_3$ (40 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave (3*R*,6*S*)-3-methyl-6-(prop-2-yl)-1-trimethylsilyloxy-cyclohexene as a colourless oil (2.80 g, 12.4 mmol, 97%). Data in agreement with literature values,[11] α_D – 3.5° (c = 0.515, $CHCl_3$).

Note: The enantiomer was prepared analogously in 86% yield and exhibited α_D +3.9° (c = 0.625, $CHCl_3$).

To a solution of (3*R*,6*S*)-3-methyl-6-(prop-2-yl)-1-trimethylsilyloxy-cyclohexene (1.09 g, 4.81 mmol) in THF (35 mL) at –78 °C was added powdered $NaHCO_3$ (485 mg, 5.77 mmol) followed by *N*-bromosuccinimide (899 mg, 5.05 mmol). After 1 h, the reaction mixture was warmed to RT and partitioned between sat. $NaHCO_3$ (20 mL) and ether (25 mL). The aqueous phase was separated and extracted with ether (2 x 25 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) yielded (2*R*,3*R*,6*S*)-2-bromo-3-methyl-6-(prop-2-yl)-cyclohexanone (1.08 g, 4.62 mmol, 96%).

IR ν_{max} (neat, cm^{-1}) 2960 m, 2932 m, 1710 vs, 1454 m, 1378 m, 1207 m, 1161 m, 1088 m, 778 m, 660 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.24 (1H, d, *J* 3.0 Hz), 3.00 (1H, dt, *J* 13.1, 5.8 Hz), 2.11 (1H, app. octet, *J* 6.9 Hz), 2.02 (1H, ddt, *J* 13.1, 5.6, 3.5 Hz), 1.89-1.82 (1H, m), 1.75 (1H, qd, *J* 13.1, 3.5 Hz), 1.67-1.58 (1H, m), 1.34 (1H, qd, *J* 13.1, 3.8 Hz), 1.09 (3H, d, *J* 6.3 Hz), 0.94 (3H, d, *J* 6.8 Hz), 0.87 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 206.3 (*C*), 62.3 (*C*H), 49.2 (*C*H), 38.8 (*C*H), 28.2 (CH_2), 27.9 (CH_2), 26.1 (*C*H), 21.1 (CH_3), 19.7 (CH_3), 18.8 (CH_3).

Mass $^m/_z$ (EI) 234/232 (M^+, 12), 219/217 ($[M - CH_3]^+$, 22), 192/190 ($[M - C_3H_6]^+$, 38), 153 ($[M - Br]^+$, 91), 111 (90), 97 (81), 83 (61), 69 (100), 55 (89).

$^m/_z$ (EI) found 232.0462, M^+. $C_{10}H_{17}{}^{79}BrO$ requires 232.0463.

α_D –219.5° (c = 0.655, $CHCl_3$).

Note: The enantiomer was prepared analogously in 94% yield and exhibited α_D +210.3° (c = 0.510, $CHCl_3$).

To a solution of 2,2,6,6-tetramethylpiperidine (1.46 mL, 8.58 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (2.25 M in hexanes, 3.80 mL, 8.58 mmol). After 30 min the reaction mixture was cooled to –78 °C and a solution of (2*R*,3*R*,6*S*)-2-bromo-3-methyl-6-(prop-2-yl)-cyclohexanone (1.00 g, 4.29 mmol) in THF (10 mL) added followed after 2 h by trimethyloxonium tetrafluoroborate (1.27 g, 8.58 mmol). The reaction mixture was warmed to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (40 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, 0 - 2% ether/petrol) gave (3*S*,6*R*)-1-bromo-2-methoxy-3-(prop-2-yl)-6-methylcyclohexene as a colourless oil (682 mg, 2.76 mmol, 64%).

IR ν_{max} (neat, cm^{-1}) 2957 s, 2932 s, 2870 w, 1640 w, 1452 m, 1385 w, 1368 w, 1307 w, 1221 m, 1021 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.56 (3H, s), 2.56-2.46 (1H, m), 2.39-2.33 (1H, m), 2.18-2.06 (1H, m), 1.97-1.89 (1H, m), 1.75-1.67 (1H, m), 1.53-1.45 (1H, m), 1.35-1.27 (1H, m), 1.17 (3H, d, *J* 7.0 Hz), 0.95 (3H, d, *J* 7.0 Hz), 0.82 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 154.4 (*C*), 116.6 (*C*), 57.8 (CH_3), 42.4 (*C*H), 37.2 (*C*H), 31.4 (CH_2), 28.6 (*C*H), 22.0 (CH_3), 20.9 (CH_2), 20.7 (CH_3), 18.0 (CH_3).

Mass $^m/_z$ (EI) 248/246 (M^+, 22%), 233/231 ($[M - CH_3]^+$, 18), 203 (11), 167 ($[M - Br]^+$, 17), 123 (100), 109 (24), 91 (28).

$^m/_z$ (EI) found 246.0613, M^+. $C_{11}H_{19}{}^{79}BrO$ requires 246.0619.

α_D +75.6° (c = 0.665, $CHCl_3$).

Note: The enantiomer was prepared analogously in 55% yield and exhibited α_D –73.9° (c = 0.450, $CHCl_3$).

To a solution of ^{t}BuLi (1.31 M in pentane, 0.49 mL, 0.643 mmol) in THF (2.5 mL) at –78 °C was added a solution of (3*S*,6*R*)-1-bromo-2-methoxy-3-(prop-2-yl)-6-methylcyclohexene (159 mg, 0.643 mmol) in THF (2.5 mL) over 2 min. After 10 min a solution of dimethyl squarate (87 mg, 0.611 mmol) in THF (2 mL) was added over 2 min, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and diluted with ether (20 mL). The organic phase was separated, washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* giving a yellow oil, crude **13** (188 mg).

*Note: **13** could be purified at this juncture by column chromatography (SiO_2, 20-30% EtOAc/petrol, 78% yield, d.r. ~ 3 : 2). However, on standing the product steadily decomposed to (3'S,6'R)-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-3-methoxy-cyclobuten-1,2-dione. Consequently, higher overall yields were attained when the crude isolate was carried through the subsequent stages, as here.*

IR ν_{max} (neat, cm^{-1}) 3395 bw, 2952 m, 2868 w, 1773 m, 1632 s, 1464 m, 1330 s, 1212 w, 1107 w, 1032 m, 988 w..

^{1}H NMR δ_H (400 MHz, $CDCl_3$) Major isomer: 6.04 (1H, br s), 4.11 (3H, s), 3.98 (3H, s), 3.67 (3H, s), 2.34-2.26 (2H, m), 2.11-2.00 (1H, m), 1.76-1.59 (3H, m), 1.36-1.24 (1H, m), 1.07 (3H, d, *J* 6.8 Hz), 1.02 (3H, d, *J* 6.8 Hz), 0.83 (3H, d, *J* 6.8 Hz). Additional signals attributed to the minor isomer: 4.94 (1H, br s), 4.12 (3H, s), 3.99 (3H, s), 3.50 (3H, s), 2.56-2.49 (1H, m), 0.98 (6H, d, *J* 7.0 Hz), 0.84 (3H, d, *J* 6.8 Hz).

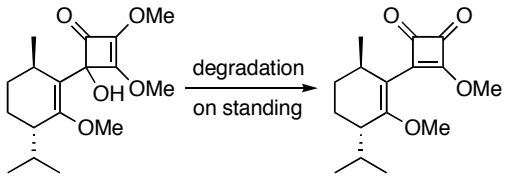
^{13}C NMR δ_C (100 MHz, $CDCl_3$) Major isomer: 185.9 (*C*), 165.3 (*C*), 156.3 (*C*), 135.3 (*C*), 123.7 (*C*), 89.9 (*C*), 60.0 (*C*H_3), 59.2 (*C*H_3), 58.6 (*C*H_3), 38.1 (*C*H), 30.3 (*C*H), 29.2 (*C*H), 28.7 (*C*H_2), 21.4 (*C*H_3), 21.3 (*C*H_3), 18.8 (*C*H_3), 18.4 (*C*H_2). Minor isomer: 184.6 (*C*), 168.8 (*C*), 155.7 (*C*), 134.8 (*C*), 123.2 (*C*), 88.2 (*C*), 60.2 (*C*H_3), 58.6 (*C*H_3), 57.5 (*C*H_3), 38.3 (*C*H), 30.5 (*C*H), 29.5 (*C*H), 28.8 (*C*H_2), 21.3 (2 x *C*H_3) 18.7 (*C*H_3), 18.6 (*C*H_2).

Mass $^{m}/_{z}$ (ES^{+}) 643 ([2M + Na]$^{+}$, 21%), 333 ([M + Na]$^{+}$, 100).

$^{m}/_{z}$ (ES^{+}) found 333.1673, [M + Na]$^{+}$. $C_{17}H_{26}NaO_5$ requires 333.1672.

Note: In the enantiomeric series the analogous reaction proceeded in 75% yield.

Data for degradation product (3'*S*,6'*R*)-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-3-methoxy-cyclobuten-1,2-dione.



13 (*d.r.* 3 : 2)

IR ν_{max} (neat, cm^{-1}) 2957 m, 2929 m, 1783 s, 1746 s, 1575 s, 1449 s, 1373 s, 1341 m, 1326 m, 1130 m, 1036 m.

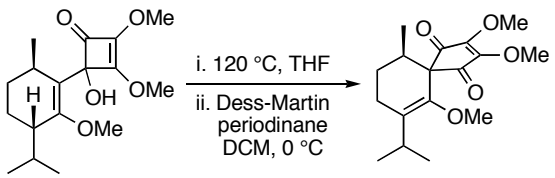
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.47 (3H, s), 3.66 (3H, s), 2.99-2.91 (1H, m), 2.51-2.46 (1H, m), 2.10 (1H, octet, *J* 7.0 Hz), 1.89-1.80 (1H, m), 1.75 (tdd, *J* 10.5, 7.3, 3.3 Hz), 1.68-1.60 (1H, m), 1.36-1.23 (1H, m), 1.02 (3H, d, *J* 7.0 Hz), 0.96 (3H, d, *J* 7.0 Hz), 0.85 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.4 (*C*), 193.6 (*C*), 193.4 (*C*), 178.4 (*C*), 163.2 (*C*), 116.5 (*C*), 61.1 (*C*H_3), 57.8 (*C*H_3), 39.6 (*C*H), 29.3 (*C*H), 29.0 (*C*H), 28.1 (*C*H_2), 21.6 (*C*H_3), 21.1 (*C*H_3), 19.5 (*C*H_2), 18.7 (*C*H_3).

Mass $^{m}/_{z}$ (ES^{+}) 611 ([2M + Na + MeOH]$^{+}$, 5%), 579 (2M + Na]$^{+}$, 13), 333 ([M + Na + MeOH]$^{+}$, 15%), 301 ([M + Na]$^{+}$, 28), 279 (MH^{+}, 100).

α_D +837.2° (c = 0.750, $CHCl_3$).

(*R*)-7-Isopropyl-2,3,6-trimethoxy-10-methyl-spiro[4.5]deca-2,6-diene-1,4-dione, 14 and enantiomer.



13 (*d.r.* 3 : 2) **14**, 69%[†]
(54% from dimethyl squarate)

A solution of the crude cyclobutenones **13** (188 mg) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (389 mg, 0.917 mmol). After 1 h 1M NaOH (3 mL) was added and the temperature raised to RT. Following dilution with ether (40 mL), the organic phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-15% EtOAc/petrol) gave spirocycle **14** as a yellow oil (101 mg, 0.328 mmol, 69% (54% from dimethyl squarate)).†

IR ν_{max} (neat, cm^{-1}) 2958 w, 2868 w, 1683 s, 1622 s, 1458 m, 1315 s, 1209 m, 1136 m, 1107 m, 1042 m, 1009 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.22 (3H, s), 4.21 (3H, s), 3.39 (3H, s), 3.01 (1H, septet, *J* 6.9 Hz), 2.13-1.99 (3H, m), 1.83 (1H, tdd, *J* 12.8, 10.5, 6.0 Hz), 1.55 (1H, dq, *J* 12.8, 2.5 Hz), 1.00 (3H, d, *J* 6.8 Hz), 0.97 (3H, d, *J* 7.0 Hz), 0.79 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 197.5 (*C*), 197.2 (*C*), 153.3 (*C*), 152.6 (*C*), 144.0 (*C*), 134.4 (*C*), 62.4 (CH_3), 60.7 (*C*), 59.9 (CH_3), 59.8 (CH_3), 35.0 (*C*H), 27.0 (CH_2), 26.9 (*C*H), 21.7 (CH_2), 21.1 (CH_3), 20.7 (CH_3), 16.4 (CH_3).

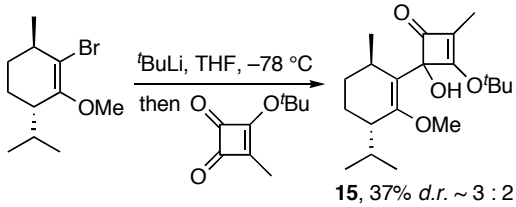
Mass $^m/_z$ (EI) 308 (M^+, 100%), 293 ($[M - CH_3]^+$, 93), 277 (32), 265 ($[M - C_3H_6]^+$, 70), 233 (68), 183 (83), 91 (58).
$^m/_z$ (EI) found 308.1616, M^+. $C_{17}H_{24}O_5$ requires 308.1624.

α_D +92.9° (c = 0.660, $CHCl_3$).

Note: The enantiomer was prepared analogously in 72% yield and exhibited α_D –90.6° (c = 0.475, $CHCl_3$).

*†The quoted yield of 69% assumes a 78% yield for the formation of **13** from dimethyl squarate (vide infra). The yield for the two-step sequence from dimethyl squarate is 54%.*

(3'*R*,4*RS*,6'*S*)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-2-methyl-3-(*tert*-butoxy)-cyclobut-2-enone, 15 and enantiomer.



15, 37% *d.r.* ~ 3 : 2

To a solution of ^{t}BuLi (1.31 M in pentane, 0.37 mL, 0.482 mmol) in THF (2.5 mL) at –78 °C was added a solution of (3*S*,6*R*)-1-bromo-2-methoxy-3-(prop-2-yl)-6-methylcyclohexene (60 mg, 0.241 mmol) in THF (2.5 mL) over 2 min. After 15 min a solution of 3-(*tert*-butoxy)-4-methyl-cyclobut-3-en-1,2-dione (41 mg, 0.241 mmol) in THF (2 mL) was added over 2 min, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between ether (15 mL) and water (5 mL). The organic phase was separated, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-60% ether/petrol) yielded firstly the major diastereoisomer of vinylcyclobutenone **15** as a white solid (18 mg, 54 μmol, 22%) followed by the minor diastereoisomer of vinylcyclobutenone **15** as a colourless oil (12 mg, 36 μmol, 15%).

Data for the major diastereoisomer:

IR ν_{max} (neat, cm^{-1}) 3384 bw, 2951 m, 2930 m, 1757 m, 1602 s, 1379 s, 1324 s, 1225 w, 1153 s, 1117 s, 1009 m.

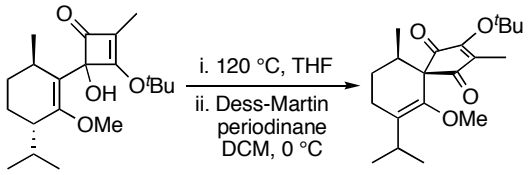
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.16 (1H, s), 3.67 (3H, s), 2.37-2.27 (2H, m), 2.07 (1H, d of septets, *J* 4.0, 7.0 Hz), 1.77 (3H, s), 1.75-1.59 (3H, m), 1.53 (9H, s), 1.31-1.26 (1H, m), 0.98 (3H, d, *J* 7.0 Hz), 0.93 (3H, d, *J* 6.8 Hz), 0.84 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 193.7 (*C*), 178.8 (*C*), 155.7 (*C*), 124.8 (*C*), 124.1 (*C*), 95.7 (*C*), 83.6 (*C*), 59.1 (CH_3), 38.0 (*C*H), 29.8 (*C*H), 29.1 (*C*H), 28.8 (3 x CH_3), 28.5 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 18.7 (CH_3), 18.2 (CH_2), 8.5 (CH_3).

Mass $^m/_z$ (ES^+) 695 ($[2M + Na]^+$, 25%], 359 ($[M + Na]^+$, 100).
$^m/_z$ (ES^+) found 359.2193 $(M + Na)^+$. $C_{20}H_{32}NaO_4$ requires 359.2193.

Note: The minor diastereoisomer deteriorated more rapidly on standing and was best used immediately in the thermolysis reaction. In the enantiomeric series the analogous reaction proceeded in 33% yield, d.r. ~ 3:2.

(5*R*,10*S*)-2-(*tert*-Butoxy)-3,10-dimethyl-6-methoxy-7-(prop-2-yl)-spiro[4.5]deca-2,6-diene-1,4-dione, 16 and enantiomer.



15 (*d.r.* ~ 3 : 2) **16**, 75%

A solution of the major diastereoisomer of cyclobutenone **15** (16 mg, 48 μmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (31 mg, 72 μmol). After 30 min 1M NaOH (1.5 mL) was added and the temperature raised to RT. Following dilution with ether (30 mL), the organic phase was separated, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) yielded spirocycle **16** as a pale yellow oil that crystallised on standing (12 mg, 36 μmol, 75%).

mp 89-91 °C (EtOH/H_2O).

IR ν_{max} (neat, cm^{-1}) 2958 m, 2929 m, 2868 w, 2831 w, 1740 w, 1683 vs, 1622 m, 1377 m, 1319 m, 1152 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s), 3.02 (1H, septet, *J* 6.8 Hz), 2.15-2.01 (3H, m), 1.97-1.89 (1H, m), 1.96 (3H, s), 1.57-1.51 (1H, m), 1.52 (9H, s), 1.03 (3H, d, *J* 6.8 Hz), 0.99 (3H, d, *J* 6.8 Hz), 0.71 (3H, d, *J* 6.8 Hz).

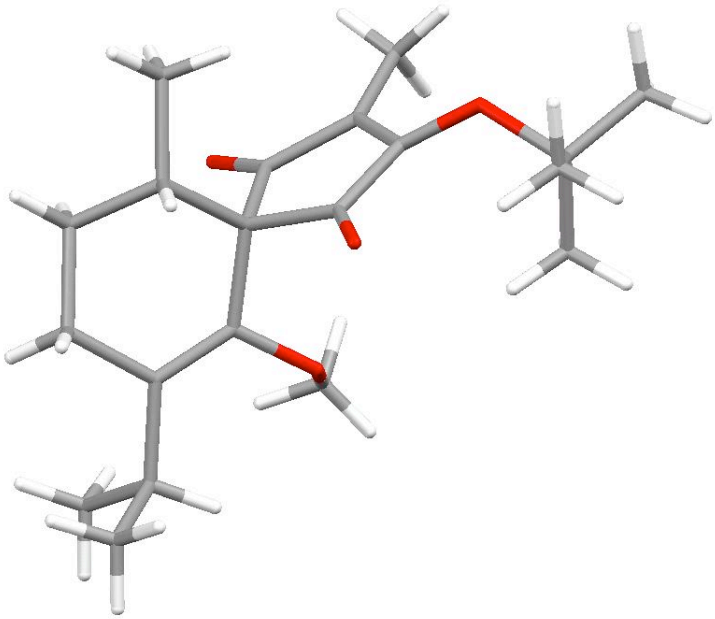
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 203.4 (*C*), 201.9 (*C*), 169.3 (*C*), 145.9 (*C*), 144.7 (*C*), 133.6 (*C*), 85.3 (*C*), 61.9 (CH_3), 61.2 (*C*), 35.4 (*C*H), 29.7 (3 x CH_3), 27.0 (CH_2), 26.9 (*C*H), 21.9 (CH_2), 21.3 (CH_3), 20.8 (CH_3), 16.3 (CH_3), 7.9 (CH_3).

Mass $^m/_z$ (ES^+) 691 ([2M + Na]$^+$, 84%), 357 ([M + Na]$^+$, 100).

$^m/_z$ (ES^+) found 357.2039, [M + Na]$^+$. $C_{20}H_{30}NaO_4$ requires 357.2036.

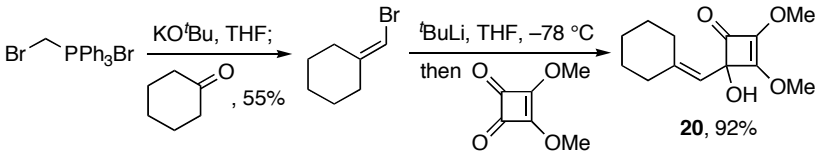
α_D +61.3° (c = 0.550, $CHCl_3$).

X-ray of ent-16



*Note: Both diastereoisomers of **15** gave **16** following thermolysis and oxidation. The enantiomer was prepared analogously in 72% yield and exhibited α_D –62.9° (c = 0.680, $CHCl_3$), mp 89-91 °C (EtOH/H_2O).*

4-Cyclohexylidenemethyl-4-hydroxy-2,3-dimethoxy-cyclobut-2-enone, 20



To a suspension of (bromomethyl)triphenylphosphonium bromide (3.00 g, 6.88 mmol) in THF (30 mL) at –78 °C was added potassium *tert*-butoxide (772 mg, 6.88 mmol). After warming to RT over 30 min, a solution of cyclohexanone (519 mg, 5.29 mmol) in THF (10 mL) was added. After 16 h the reaction mixture was partitioned between water (60 mL) and ether (60 mL). The aqueous phase was separated and extracted with ether (2 x 60 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave bromomethylene-cyclohexane as a colourless oil (508 mg, 2.90 mmol, 55%).

IR ν_{max} (neat, cm^{-1}) 3064 w, 2929 s, 2856 m, 1630 w, 1446 s, 1332 m, 1279 s, 1225 m, 980 m, 854 m, 768 s, 695 s.

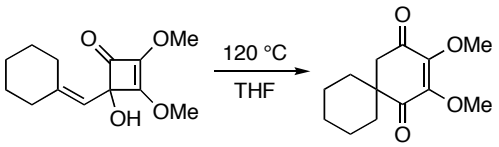
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.85 (1H, t, *J* 1.0 Hz), 2.36-2.29 (2H, m), 2.22-2.15 (2H, m), 1.61-1.52 (6H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 145.3 (*C*), 97.7 (*C*H), 35.8 (*C*H_2), 31.3 (*C*H_2), 28.1 (*C*H_2), 26.9 (*C*H_2), 26.4 (*C*H_2).

Mass $^m/_z$ (EI) 176/174 (M^+, 45), 134 (16), 132 (17), 95 ([M – Br]$^+$, 100), 67 (78), 53 (74).

To a solution of ^{t}BuLi (1.31 M in pentane, 1.10 mL, 1.44 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromomethylene-cyclohexane (126 mg, 0.719 mmol) in THF (2.5 mL) over 2 min. The reaction mixture was warmed to 0 °C over 30 min then cooled to –78 °C. Dimethyl squarate (92 mg, 0.65 mmol) in THF (2 mL) was then added over 2 min, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between ether (15 mL) and brine (20 mL). The aqueous phase was separated and extracted with ether (2 x 15 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil, crude cyclobutenone **20** (142 mg, 0.596 mmol, 92%), was used directly in the next reaction due to its instability.

2,3-Dimethoxyspiro[5.5]undec-2-ene-1,4-dione, 21



A solution of the crude cyclobutenone **20** (142 mg, 0.596 mmol, 92%) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% EtOAc/petrol) gave spirocycle **21** as a yellow oil (88 mg, 0.369 mmol, 62%).

IR ν_{max} (neat, cm^{-1}) 2925 m, 2852 w, 1671 vs, 1591 s, 1450 m, 1307 m, 1266 s, 1189 m, 1095 s, 1058 s, 972 m.

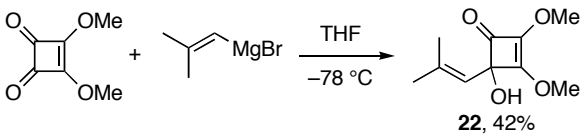
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s), 3.94 (3H, s), 2.73 (2H, s), 1.90-1.79 (2H, m), 1.68-1.59 (2H, m), 1.57-1.31 (6H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 199.4 (*C*), 193.6 (*C*), 148.7 (*C*), 148.0 (*C*), 60.7 (*C*H_3), 60.6 (*C*H_3), 48.0 (*C*), 46.5 (*C*H_2), 34.1 (2 x *C*H_2), 25.5 (*C*H_2), 21.6 (2 x *C*H_2).

Mass $^m/_z$ (EI) 238 (M^+, 22%), 210 ([M – CO]$^+$, 72), 196 (43), 183 (100), 155 (73).

$^m/_z$ (EI) found 238.1206, M^+. $C_{13}H_{18}O_4$ requires 238.1205.

4-Hydroxy-4-(2-methylpropenyl)-2,3-dimethoxy-cyclobut-2-enone, 22



To a solution of dimethyl squarate (200 mg, 1.41 mmol) in THF (5 mL) at –78 °C was added over 3 min 2-methyl-1-propenyl-magnesium bromide (0.5M in THF, 3.4 mL, 1.69 mmol). After 1 h sat. $NaHCO_3$ (3 mL) was added. The reaction mixture was

warmed to RT and extracted with ether (3 x 15 mL). The combined organic phases were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, 20-30% EtOAc/petrol) yielded vinylcyclobutenone **22** as a pale yellow oil (118 mg, 0.595 mmol, 42%).

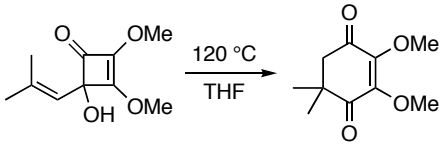
IR ν_{max} (neat, cm^{-1}) 3391 bm, 2950 w, 2913 w, 2852 w, 1769 m, 1622 vs, 1467 s, 1332 vs, 1213 w, 1025 s, 988 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.41 (1H, app. septet, *J* 1.2 Hz), 4.12 (3H, s), 3.95 (3H, s), 2.58 (1H, br s), 1.89 (3H, d, *J* 1.1 Hz), 1.77 (3H, d, *J* 1.3 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 185.3 (*C*), 167.4 (*C*), 141.2 (*C*), 134.7 (*C*), 120.0 (*C*H), 85.3 (*C*), 60.2 (CH_3), 58.6 (CH_3), 26.7 (CH_3), 19.8 (CH_3).

Mass $^m/_z$ (ES^+) 419 ($[2M + Na]^+$, 8%), 221 ($[M + Na]^+$, 100).

2,3-Dimethoxy-5,5-dimethylcyclohex-2-ene-1,4-dione, 23



22 **23**, 73%

A solution of cyclobutenone **22** (94 mg, 0.474 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) gave cyclohexenedione **23** as a colourless oil (69 mg, 0.348 mmol, 73%).

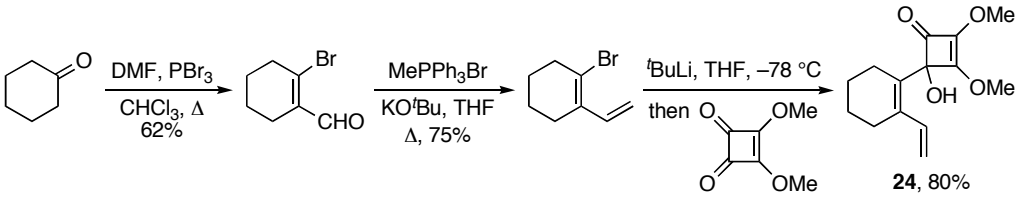
IR ν_{max} (neat, cm^{-1}) 2946 w, 2868 w, 1671 s, 1589 s, 1446 m, 1328 m, 1274 s, 1246 m, 1209 m, 1070 s, 993 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.97 (3H, s), 3.95 (3H, s), 2.65 (2H, s), 1.24 (6H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 198.9 (*C*), 193.5 (*C*), 148.8 (*C*), 148.3 (*C*), 60.7 (2 × CH_3), 50.7 (CH_2), 44.4 (*C*), 26.3 (2 × CH_3).

Mass $^m/_z$ (EI) 198 (M^+, 100%), 183 ($[M - CH_3]^+$, 94), 153 (55), 141 (28), 123 (54), 99 (55), 86 (83), 67 (49), 55 (71).
$^m/_z$ (EI) found 198.0894, M^+. $C_{10}H_{14}O_4$ requires 198.0892.

4-Hydroxy-4-(2-vinylcyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 24



24, 80%

To a solution of *N,N*-dimethylformamide (2.40 mL, 30.6 mmol) in chloroform (20 mL) at 0 °C was added phosphorus tribromide (2.60 mL, 27.5 mmol). After 30 min the reaction mixture was warmed to RT and a solution of cyclohexanone (1.00 g, 10.2 mmol) in chloroform (10 mL) added. The reaction mixture was heated at reflux for 3 h then cooled to RT and poured onto ice water (50 mL). Solid sodium bicarbonate was added to neutralise the aqueous phase, which was then separated and extracted with ether (3 x 75 mL). The combined organic phases were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) yielded 2-bromocyclohexenecarboxaldehyde as a pale yellow oil (1.20 g, 6.35 mmol, 62%).

IR ν_{max} (neat, cm^{-1}) 3334 w, 2933 m, 2860 w, 2733 w, 1671 s, 1610 s, 1340 m, 1262 m, 1201 s, 968 s, 796 m, 702 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 10.02 (1H, s), 2.77-2.73 (2H, m), 2.30-2.25 (2H, m), 1.80-1.64 (4H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 193.9 (*C*H), 143.7 (*C*), 135.5 (*C*), 39.0 (CH_2), 25.2 (CH_2), 24.4 (CH_2), 21.3 (CH_2).

Mass $^m/_z$ (EI) 190/188 (M^+, 36%), 174/172 (34), 160/158 (36), 109 ($[M - Br]^+$, 52), 91 (27), 79 (100).

To a suspension of methyltriphenylphosphonium bromide (1.92 g, 5.39 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (605 mg, 5.39 mmol). After warming to RT over 30 min, a solution of 1-bromocyclohexenecarboxaldehyde (679 mg, 3.59 mmol) in THF (10 mL) was added. The reaction mixture was heated at reflux for 14 h then cooled to RT and partitioned

between water (50 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave 1-bromo-2-vinylcyclohexene as a colourless oil (502 mg, 2.68 mmol, 75%).

IR ν_{max} (neat, cm^{-1}) 3085 w, 2929 s, 2856 m, 2835 m, 1626 s, 1446 m, 1409 m, 1021 s, 984 s, 964 s, 903 s, 792 s.

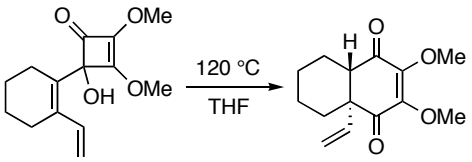
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.92 (1H, dd, *J* 17.5, 10.9 Hz), 5.27 (1H, d, *J* 17.5 Hz), 5.14 (1H, d, *J* 10.9 Hz), 2.63 (2H, br s), 2.28 (2H, br s), 1.73 (4H, br s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 137.3 (*C*H), 132.5 (*C*), 125.3 (*C*), 114.5 (*C*H_2), 37.7 (*C*H_2), 27.0 (*C*H_2), 24.9 (*C*H_2), 22.3 (*C*H_2).

Mass $^m/_z$ (EI) 188/186 (M^+, 18), 107 ($[M - Br]^+$, 51), 91 (44), 79 (100), 65 (19), 51 (22).

To a solution of ^{t}BuLi (1.31 M in pentane, 1.03 mL, 1.35 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1-bromo-2-vinylcyclohexene (126 mg, 0.674 mmol) in THF (2.5 mL) over 2 min. The reaction mixture was warmed to RT over 20 min then cooled to –78 °C. Dimethyl squarate (91 mg, 0.64 mmol) in THF (2 mL) was then added over 2 min, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between ether (20 mL) and brine (20 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield crude cyclobutenone **24** as a yellow oil (134 mg, 0.536 mmol, 80%), which was used directly in the next reaction due to its instability.

***rel*-(4a*R*,8a*S*)-2,3-Dimethoxy-4a-vinyl-4a,5,6,7,8,8a-hexahydro[1,4]naphthoquinone, 25**



24 **25**, 50% *d.r.* ~ 9 : 1

A solution of the crude cyclobutenone **24** (134 mg, 0.536 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc/petrol) gave an inseparable 9 : 1 mixture of *trans*- and *cis*-hexahydronaphthoquinones **25** as a pale yellow oil (67 mg, 0.268 mmol, 50%).

IR ν_{max} (neat, cm^{-1}) 2995 w, 2929 m, 2856 w, 1671 s, 1589 s, 1446 m, 1274 s, 1095 s, 1066 m, 980 m, 911 m.

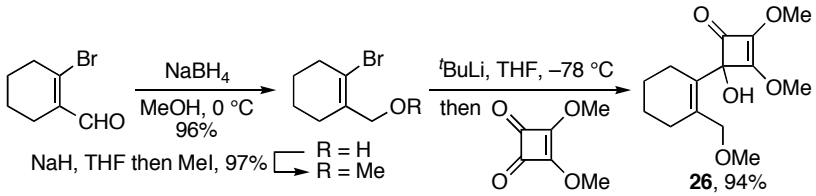
^{1}H NMR δ_H (300 MHz, $CDCl_3$) *trans*-isomer 5.63 (1H, dd, *J* 17.3, 10.5 Hz), 5.32 (1H, d, *J* 10.5 Hz), 5.18 (1H, d, *J* 17.3 Hz), 3.95 (3H, s), 3.90 (3H, s), 2.62 (1H, dd, *J* 11.8, 3.3 Hz), 2.27 (1H, d with fine splitting, *J* 13.3 Hz), 2.12-2.04 (1H, m), 1.83 (1H, d with fine splitting, *J* 13.3 Hz), 1.64-1.54 (3H, m), 1.37 (1H, qt, *J* 13.3, 3.5 Hz), 1.19 (1H, qt, *J* 13.3, 3.8 Hz). Less intense signals attributed to the *cis*-isomer: 5.71 (1H, dd, *J* 17.6, 10.6 Hz), 5.11 (1H, d, *J* 10.6 Hz), 5.05 (1H, d, *J* 17.6 Hz), 2.78 (1H, dd, *J* 12.3, 4.3 Hz), 2.46 (1H, d with fine splitting, *J* 13.9 Hz), 1.96 (1H, d with fine splitting, *J* 13.3 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) *trans*-isomer: 195.3 (*C*), 195.2 (*C*), 149.2 (*C*), 149.0 (*C*), 135.9 (*C*H), 120.0 (*C*H_2), 60.7 (*C*H_3), 60.2 (*C*H_3), 54.8 (*C*), 53.2 (*C*H), 32.3 (*C*H_2), 24.8 (*C*H_2), 21.3 (*C*H_2), 21.0 (*C*H_2). Less intense signals attributed to the *cis*-isomer: 195.1 (*C*), 141.7 (*C*H), 116.4 (*C*H_2), 60.7 (*C*H_3), 60.6 (*C*H_3), 55.2 (*C*H), 30.6 (*C*H_2), 24.3 (*C*H_2), 22.7 (*C*H_2).

Mass $^m/_z$ (EI) 250 (M^+, 66%), 235 ($[M - CH_3]^+$, 14), 222 (83), 207 (59), 190 (23), 174 (34), 165 (53), 91 (81), 79 (100).
$^m/_z$ (EI) found 250.1205, M^+. $C_{14}H_{18}O_4$ requires 250.1205.

*Note: cis- and trans-**25** were assigned on the basis of a close correlation of signals in the ^{1}H NMR spectra with analogous data attained for cis- and trans-**27**.*

4-Hydroxy-4-(2-methoxymethyl-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 26



To a cooled (0 °C) solution of 2-bromocyclohexenecarboxaldehyde (1.15 g, 6.08 mmol) in methanol (10 mL) was added sodium borohydride (242 mg, 6.39 mmol), portionwise over 10 min. The reaction mixture was warmed to RT and after 1 h water (20 mL) and ether (50 mL) were added. The aqueous phase was separated and extracted with ether (2 x 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated to yield 2-bromocyclohexenemethanol as a colourless oil (1.12 g, 5.86 mmol, 96%).

IR ν_{max} (neat, cm^{-1}) 3297 bm, 2925 s, 2856 m, 1654 w, 1434 m, 1328 m, 1103 m, 1062 m, 1005 s, 972 s, 792 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.15 (2H, s), 2.53-2.45 (2H, m), 2.26-2.19 (2H, m), 1.75-1.59 (5H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 135.5 (*C*), 121.6 (*C*), 66.5 (*C*H_2), 36.8 (*C*H_2), 29.3 (*C*H_2), 24.8 (*C*H_2), 22.4 (*C*H_2).

Mass $^m/_z$ (EI) 192/190 (M^+, 10), 111 ($[M - Br]^+$, 67), 93 (82), 77 (53), 67 (100), 55 (56).

To a solution of 2-bromocyclohexenemethanol (1.06 g, 5.57 mmol) in THF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 668 mg, 16.7 mmol) portionwise over 5 min. After 15 min methyl iodide (1.73 mL, 27.9 mmol) was added. After a further 2 h the reaction mixture was partitioned between ether (50 mL) and sat. NH_4Cl (50 mL). The organic phase was separated, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% ether/petrol) gave 1-bromo-2-methoxymethyl-cyclohexene as a colourless oil (1.11 g, 5.41 mmol, 97%).

IR ν_{max} (neat, cm^{-1}) 2978 w, 2925 m, 2860 w, 2819 w, 1654 w, 1442 w, 1176 m, 1111 s, 1082 s, 968 s, 796 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.07 (2H, s), 3.32 (3H, s), 2.55-2.48 (2H, m), 2.24-2.16 (2H, m), 1.72-1.66 (4H, m).

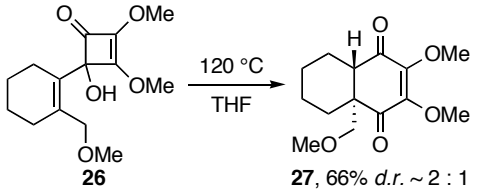
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 133.2 (*C*), 122.3 (*C*), 75.4 (*C*H_2), 58.0 (*C*H_3), 37.0 (*C*H_2), 28.9 (*C*H_2), 24.9 (*C*H_2), 22.4 (*C*H_2).

Mass $^m/_z$ (EI) 206/204 (M^+, 12), 174/172 ($[M - MeOH]^+$, 31), 125 ($[M - Br]^+$, 99), 93 (100), 77 (52).

$^m/_z$ (EI) found 204.0151, M^+. $C_8H_{13}{}^{79}BrO$ requires 204.0150.

To a solution of ^{t}BuLi (1.31 M in pentane, 0.85 mL, 1.12 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1-bromo-2-methoxymethyl-cyclohexene (107 mg, 0.56 mmol) in THF (2.5 mL) over 2 min. After 10 min dimethyl squarate (81 mg, 0.56 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT, partitioned between ether (15 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (10 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting pale yellow oil, crude cyclobutenone **26** (144 mg, 0.537 mmol, 94%), was used directly in the next reaction due to instability.

***rel*-(4a*S*,8a*S*)-2,3-Dimethoxy-4a-methoxymethyl-4a,5,6,7,8,8a-hexahydro[1,4]naphthoquinone, 27**



A solution of the crude cyclobutenone **26** (144 mg, 0.54 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-25% EtOAc/petrol) gave an inseparable 2 : 1 mixture of *trans*- and *cis*-hexahydronaphthoquinones **27** as a pale yellow oil (95 mg, 0.36 mmol, 66%).

IR ν_{max} (neat, cm^{-1}) 2933 m, 2860 w, 1671 s, 1589 s, 1450 m, 1279 m, 1205 m, 1189 m, 1107 s, 993 w.

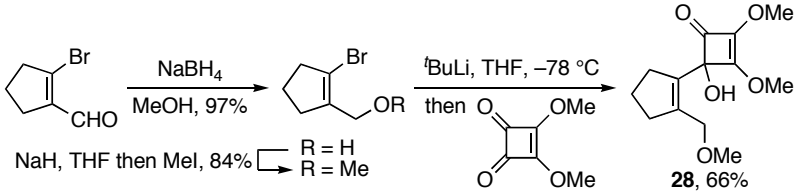
^{1}H NMR δ_H (400 MHz, $CDCl_3$) *trans*-isomer 3.98 (3H, s), 3.90 (3H, s), 3.55 (1H, d, *J* 9.4 Hz), 3.45 (1H, d, *J* 9.4 Hz), 3.21 (3H, s), 2.49 (1H, dd, *J* 12.0, 3.5 Hz), 2.08 (1H, m), 1.86 (1H, m), 1.69 (1H, m), 1.52-1.36 (3H, m), 1.29-1.13 (2H, m). Less intense signals attributed to the *cis*-isomer 3.97 (3H, s), 3.93 (3H, s), 3.41 (1H, d, *J* 8.9 Hz), 3.28 (1H, d, *J* 8.9 Hz), 3.22 (3H, s), 2.70 (1H, dd, *J* 11.2, 4.4 Hz), 2.34-2.27 (1H, m).

nOe For the major diastereoisomer irradiation of the signal at δ_H 3.55 (1H, d, *J* 9.4 Hz, C*H*HOMe) caused nOe enhancement at δ_H 3.45 (1H, d, *J* 9.4 Hz, CH*H*OMe) and 3.21 (3H, s, OMe); irradiation of the signal at δ_H 3.45 (1H, d, *J* 9.4 Hz, CH*H*OMe) caused nOe enhancement at δ_H 3.55 (1H, d, *J* 9.4 Hz, C*H*HOMe) and 3.21 (3H, s, OMe); irradiation of the signal at δ_H 2.49 (1H, dd, *J* 12.0, 3.5 Hz, C*H*C=O) caused nOe enhancement at δ_H 2.08 (1H, m, CHC*H*H). For the minor diastereoisomer irradiation of the signal at δ_H 3.41 (1H, d, *J* 8.9 Hz, C*H*HOMe) caused nOe enhancement at δ_H 3.28 (1H, d, *J* 8.9 Hz, CH*H*OMe) and 3.22 (3H, s, OMe); irradiation of the signal at δ_H 3.28 (1H, d, *J* 8.9 Hz, CH*H*OMe), caused nOe enhancement at δ_H 3.41 (1H, d, *J* 8.9 Hz, C*H*HOMe), 3.22 (3H, s, OMe) and 2.70 (1H, dd, *J* 11.2, 4.4 Hz, C*H*C=O); irradiation of the signal at δ_H 2.70 (1H, dd, *J* 11.2, 4.4 Hz, C*H*C=O) caused nOe enhancement at δ_H 3.28 (1H, d, *J* 8.9 Hz, CH*H*OMe). The aforementioned assignments were aided by a **^{1}H-^{1}H COSY** experiment.

^{13}C NMR δ_C (100 MHz, $CDCl_3$) *trans*-isomer 198.2 (*C*), 194.3 (*C*), 150.3 (*C*), 148.9 (*C*), 73.5 (*C*H_2), 60.7 (*C*H_3), 60.5 (*C*H_3), 59.6 (*C*H_3), 53.1 (*C*), 52.0 (*C*H), 29.4 (*C*H_2), 24.7 (*C*H_2), 21.1 (*C*H_2), 20.7 (*C*H_2). Less intense signals attributed to the *cis*-isomer 197.2 (*C*), 196.8 (*C*), 149.1 (*C*), 149.0 (*C*), 80.1 (*C*H_2), 60.8 (*C*H_3), 60.5 (*C*H_3), 59.6 (*C*H_3), 53.0 (*C*), 52.5 (*C*H), 29.9 (*C*H_2), 29.7 (*C*H_2), 24.2 (*C*H_2), 22.0 (*C*H_2).

Mass $^m/_z$ (EI) 268 (M^+, 30%), 223 ([M – $CH_2OMe]^+$, 46), 209 (64), 191 (12), 177 (19), 157 (15), 79 (22), 45 (100).
$^m/_z$ (EI) found 268.1311, M^+. $C_{14}H_{20}O_5$ requires 268.1311.

4-Hydroxy-4-(2-methoxymethyl-cyclopentenyl)-2,3-dimethoxy-cyclobut-2-enone, 28



To a cooled (0 °C) solution of 2-bromocyclopentenecarboxaldehyde (941 mg, 5.38 mmol) in methanol (10 mL) was added sodium borohydride (214 mg, 5.65 mmol), portionwise over 10 min. The reaction mixture was warmed to RT and after 1 h water (20 mL) and ether (50 mL) were added. The aqueous phase was separated and extracted with ether (2 x 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated to yield 2-bromocyclopentenemethanol as a pale yellow oil (925 mg, 5.22 mmol, 97%).

IR ν_{max} (neat, cm^{-1}) 3297 bm, 2958 m, 2921 m, 2852 m, 1438 m, 1307 m, 1091 s, 1021 s, 997 s, 952 s, 903 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.27 (2H, d, *J* 5.3 Hz), 2.66 (2H, t with fine splitting, *J* 7.3 Hz), 2.48 (2H, t with fine splitting, *J* 7.5 Hz), 1.98 (2H, quin, *J* 7.4 Hz), 1.49 (1H, t, *J* 5.3 Hz, O*H*).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 139.9 (*C*), 118.2 (*C*), 60.7 (*C*H_2), 40.5 (*C*H_2), 32.7 (*C*H_2), 21.9 (*C*H_2).

Mass $^m/_z$ (EI) 178/176 (M^+, 15%), 97 ([M – Br]$^+$, 100), 79 (81), 67 (81).

To a solution of 2-bromocyclopentenemethanol (901 mg, 5.09 mmol) in THF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 611 mg, 15.3 mmol) portionwise over 5 min. After 5 min methyl iodide (1.6 mL, 25.5 mmol) was added. After a further 2 h the reaction mixture was partitioned between ether (50 mL) and sat. NH_4Cl (40 mL). The organic phase was separated, washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% ether/petrol) gave 1-bromo-2-methoxymethyl-cyclopentene as a pale yellow oil (818 mg, 4.28 mmol, 84%).

IR ν_{max} (neat, cm^{-1}) 2925 m, 2852 m, 2823 m, 1654 w, 1446 w, 1319 w, 1185 m, 1111 s, 1082 s, 964 m, 890 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.05 (2H, s), 3.32 (3H, s), 2.68 (2H, t with fine splitting, *J* 7.5 Hz), 2.42 (2H, t with fine splitting, *J* 7.5 Hz), 1.97 (2H, quin, *J* 7.5 Hz).

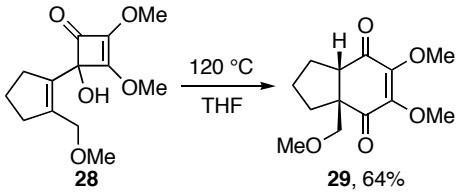
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 137.9 (*C*), 119.6 (*C*), 69.7 (CH_2), 58.2 (CH_3), 40.5 (CH_2), 32.8 (CH_2), 21.9 (CH_2).

Mass $^m/_z$ (EI) 192/190 (M^+, 6%), 111 ($[M - Br]^+$, 100), 79 (84), 65 (26).

$^m/_z$ (EI) found 189.9995, M^+. $C_7H_{11}{}^{79}BrO$ requires 189.9993.

To a solution of ^{t}BuLi (1.24 M in pentane, 0.90 mL, 1.12 mmol) in THF (2.5 mL) at –78 °C under argon was added a solution of 1-bromo-2-methoxymethyl-cyclohexene (107 mg, 0.56 mmol) in THF (2.5 mL) over 2 min. After 10 min dimethyl squarate (80 mg, 0.56 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT, partitioned between ether (25 mL) and water (5 mL) and the aqueous phase extracted with ether (2 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield crude cyclobutenone **28** as a pale yellow oil (94 mg, 0.37 mmol, 66%). The product was used directly in the next reaction due to instability.

***rel*-(3a*R*,7a*S*)-*5*,6-Dimethoxy-3a-methoxymethyl-2,3,3a,7a-tetrahydro-1*H*-indene-4,7-dione, 29**



28 **29**, 64%

A solution of the crude cyclobutenone **28** (94 mg, 0.37 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-25% EtOAc/petrol) gave a single diastereoisomer of dione **29** as a pale yellow oil (60 mg, 0.236 mmol, 64%).

IR ν_{max} (neat, cm^{-1}) 2942 w, 2872 w, 1663 s, 1593 s, 1446 m, 1274 m, 1197 m, 1099 s, 931 m, 903 m.

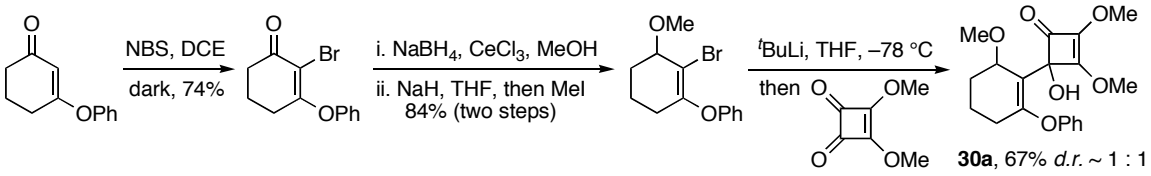
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.99 (3H, s), 3.93 (3H, s), 3.72 (1H, d, *J* 8.4 Hz), 3.24 (3H, s), 3.19 (1H, d, *J* 8.4 Hz), 3.00 (1H, app. t, *J* 8.4 Hz), 2.18-2.06 (2H, m), 1.88 (1H, m), 1.71-1.51 (3H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 197.7 (*C*), 195.7 (*C*), 149.6 (*C*), 149.3 (*C*), 78.9 (CH_2), 60.8 (CH_3), 60.7 (CH_3), 59.5 (CH_3), 59.2 (*C*), 54.3 (*C*H), 34.1 (CH_2), 31.4 (CH_2), 23.9 (CH_2).

Mass $^m/_z$ (ES^+) 531 ($[2M + Na]^+$, 11%), 309 ($[M + Na + MeOH]^+$, 22), 277 ($[M + Na]^+$, 100).

$^m/_z$ (ES^+) found 255.1222, MH^+. $C_{13}H_{19}O_5$ requires 255.1227.

4-Hydroxy-4-(6-hydroxy-2-phenoxy-cyclohex-enyl)-2,3-dimethoxy-cyclobut-2-enone, 30a



30a, 67% *d.r.* ~ 1 : 1

To a solution of 3-phenoxy-cyclohex-2-enone (1.42 g, 7.54 mmol) in DCE (20 mL) at 0 °C in the dark was added *N*-bromosuccinimide (1.75 g, 9.81 mmol) portionwise over 20 min. The reaction mixture was warmed to RT, stirred for 40 h then sat. $NaHCO_3$ (20 mL) was added. The aqueous phase was separated and extracted with DCM (2 x 40 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-30% EtOAc/petrol) gave 2-bromo-3-phenoxy-cyclohex-2-enone as a white crystalline solid (1.50 g, 5.62 mmol, 74%).

MP 90-91 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 3052 w, 2938 w, 1663 s, 1601 s, 1573 s, 1479 s, 1356 s, 1336 s, 1225 s, 1172 s, 1136 s, 984 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.33 (2H, td, *J* 7.5, 1.3 Hz), 7.18 (1H, tt, *J* 7.5, 1.3 Hz), 6.98 (2H, dd, *J* 7.5, 1.3 Hz), 2.52 (2H, t, *J* 6.4 Hz), 2.37 (2H, t, *J* 6.4 Hz), 1.92 (2H, quintet, *J* 6.4 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 191.7 (*C*), 171.3 (*C*), 153.3 (*C*), 130.2 (2 x *C*H), 126.1 (*C*H), 120.8 (2 x *C*H), 106.6 (*C*), 37.3 (CH_2), 29.1 (CH_2), 20.9 (CH_2).

Mass $^m/_z$ (EI) 268/266 (M^+, 44%), 187 ($[M - Br]^+$, 57), 145 (35), 131 (45), 117 (44), 94 (100), 77 (78), 65 (77).

CHN Found C 53.61%, H 4.15%. $C_{12}H_{11}BrO_2$ requires C 53.96%, H 4.15 %.

To a solution of 2-bromo-3-phenoxy-cyclohex-2-enone (750 mg, 2.81 mmol) in MeOH (15 mL) was added cerium trichloride heptahydrate (1.15 g, 3.09 mmol) then sodium borohydride (117 mg, 3.09 mmol) in portions over 8 min. After 30 min the reaction mixture was partitioned between water (20 mL) and EtOAc (30 mL). The aqueous phase was separated and extracted with EtOAc (30 mL) then the combined organic phases were washed with sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield 2-bromo-3-phenoxy-cyclohex-2-enol as a colourless oil (764 mg).

The crude product was immediately dissolved in THF (20 mL) and sodium hydride (60% dispersion in mineral oil, 337 mg, 8.43 mmol) added. After 10 min at RT methyl iodide (0.87 mL, 14.1 mmol) was added, followed after 90 min by sat. NH_4Cl (30 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (2 x 30 mL) then the combined organic phases were washed with water (60 mL) and brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% ether/petrol) gave 2-bromo-3-methoxy-1-phenoxy-cyclohexene as a colourless oil (667 mg, 2.36 mmol, 84% over 2 steps).

IR ν_{max} (neat, cm^{-1}) 2929 m, 2823 w, 1659 m, 1589 s, 1483 s, 1340 m, 1209 s, 1078 s, 984 m, 890 m, 845 m, 748 s.

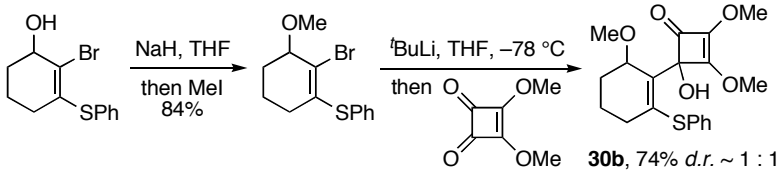
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.31 (2H, dd, *J* 8.0, 7.5 Hz), 7.06 (1H, t, *J* 7.5 Hz), 6.95 (2H, d, *J* 8.0 Hz), 4.03 (1H, br s), 3.50 (3H, s), 2.24-2.03 (3H, m), 1.97-1.86 (1H, m), 1.79-1.68 (2H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 155.1 (*C*), 152.1 (*C*), 129.8 (2 x *C*H), 123.2 (*C*H), 117.6 (2 x *C*H), 109. 3 (*C*), 80.0 (*C*H), 57.8 (CH_3), 28.4 (CH_2), 28.3 (CH_2), 18.1 (CH_2).

Mass $^m/_z$ (EI) 284/282 (M^+, 12%), 252/250 ($[M - MeOH]^+$, 32), 203 ($[M - Br]^+$, 16), 171 (48), 128 (32), 94 (47), 77 (100).
$^m/_z$ (EI) found 284.0238, M^+. $C_{13}H_{15}{}^{81}BrOS$ requires 284.0235.

To a solution of ^{t}BuLi (1.15M in pentane, 0.87 mL, 0.996 mmol) in THF (2.5 mL) at –78 °C was added a solution of 2-bromo-3-methoxy-1-phenoxy-cyclohexene (141 mg, 0.498 mmol) in THF (2.5 mL) over 2 min. After 15 min dimethyl squarate (67 mg, 0.473 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase extracted with ether (20 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone **30a** as a pale yellow oil (*d.r.* ~ 1 : 1, 115 mg, 0.332 mmol, 67%). The product was used directly in the next reaction due to instability.

2,3-Dimethoxy-4-hydroxy-4-(3-methoxy-1-phenylsulfanyl-cyclohex-1-en-2-yl)-cyclobut-2-enone, 30b



30b, 74% *d.r.* ~ 1 : 1

To a solution of 2-bromo-1-phenylsulfanyl-cyclohex-1-en-3-ol (420 mg, 1.47 mmol) in THF (15 mL) was added sodium hydride (60% dispersion in mineral oil, 177 mg, 4.42 mmol). After 10 min methyl iodide (0.46 mL, 7.35 mmol) was added followed after 2 h by sat. NH_4Cl (25 mL). The aqueous phase was separated and extracted with ether (2 x 25 mL) then the combined organic phases were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-10% ether/petrol) gave 2-bromo-3-methoxy-1-phenylsulfanyl-cyclohexene as a colourless oil (372 mg, 1.24 mmol, 84%).

IR ν_{max} (neat, cm^{-1}) 3052 w, 2933 m, 1605 m, 1581 w, 1471 m, 1435 m, 1344 m, 1189 m, 1081 vs, 1009 s, 899 s.

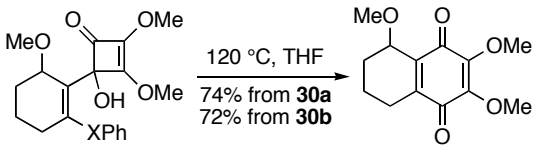
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.48-7.44 (2H, m), 7.36-7.32 (3H, m), 3.89 (1H, br s), 3.47 (3H, s), 2.02-1.54 (6H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 139.0 (*C*), 135.1 (2 x *C*H), 131.4 (*C*), 129.2 (2 x *C*H), 128.8 (*C*H), 118.8 (*C*), 80.4 (*C*H), 57.7 (*C*H_3), 32.2 (*C*H_2), 28.4 (*C*H_2), 18.7 (*C*H_2).

Mass $^m/_z$ (EI) 300/298 M^+, 21), 268/266 ($[M - MeOH]^+$, 40), 219 ($[M - Br]^+$, 82), 187 (60), 154 (33), 109 (100), 77 (86).
$^m/_z$ (EI) found 298.0024, M^+. $C_{13}H_{15}{}^{79}BrOS$ requires 298.0027.

To a solution of ^{t}BuLi (1.15M in pentane, 0.82 mL, 0.94 mmol) in THF (2.5 mL) at –78 °C was added a solution of 2-bromo-3-methoxy-1-phenylsulfanyl-cyclohexene (141 mg, 0.47 mmol) in THF (2.5 mL) over 2 min. After 15 min dimethyl squarate (67 mg, 0.47 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase extracted with ether (20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone **30b** as a pale yellow oil (*d.r.* ~ 1 : 1, 126 mg, 0.348 mmol, 74%). The product was used directly in the next reaction due to instability.

2,3,5-Trimethoxy-5,6,7,8-tetrahydro[1,4]naphthoquinone, 31



30a, X = O
30b, X = S

31

A) Cyclobutenones **30a** (115 mg, 0.322 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% EtOAc/petrol) gave quinone **31** as an orange oil (62 mg, 0.246 mmol, 74%).

B) Cyclobutenones **30b** (56 mg, 0.155 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc/petrol) gave quinone **31** as an orange oil (28 mg, 0.111 mmol, 72%).

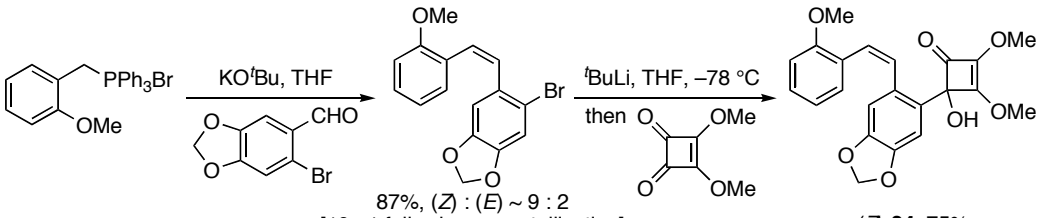
IR ν_{max} (neat, cm^{-1}) 2938 m, 2819 w, 1648 s, 1605 s, 1450 m, 1291 s, 1230 s, 1197 s, 1082 s, 988 s, 841 m, 739 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.30 (1H, br s), 4.01 (3H, s), 3.96 (3H, s), 3.45 (3H, s), 2.64 (1H, dt, *J* 19.6, 3.5 Hz), 2.19-2.09 (2H, m), 1.79-1.71 (2H, m), 1.38-1.29 (1H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 184.8 (*C*), 183.6 (*C*), 145.2 (*C*), 144.9 (*C*), 142.7 (*C*), 137.8 (*C*), 68.6 (*C*H), 61.3 (2 x *C*H_3), 58.0 (*C*H_3), 25.9 (*C*H_2), 22.7 (*C*H_2), 15.9 (*C*H_2).

Mass $^m/_z$ (EI) 252 (M^+, 26%), 237 ($[M - CH_3]^+$, 13), 222 (100), 207 (74), 173 (63), 147 (43), 105 (75), 77 (88).
$^m/_z$ (EI) found 275.0889, $[M + Na]^+$. $C_{13}H_{16}NaO_5$ requires 275.0890.

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{6-[2-(2-methoxyphenyl)vinyl]-benz[1,3]dioxol-5-yl}cyclobut-2-enone, (*Z*)-34



87%, (*Z*) : (*E*) ~ 9 : 2
[10 : 1 following recrystallisation]

(*Z*)-**34**, 75%

To a suspension of (2-methoxybenzyl)triphenylphosphonium bromide (2.20 g, 5.24 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (687 mg, 6.12 mmol). After 30 min a solution of 6-bromopiperonal (1.00 g, 4.37 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to RT, stirred for 16 h then partitioned between water (30 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) yielded a ~9 : 2 mixture of (*Z*)- and (*E*)-5-bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole as a white solid (1.26 g, 3.78 mmol,

87%). Recrystallisation from hexanes afforded a 10 : 1 mixture of the (*Z*)- and (*E*)-isomers as white needles. Data for the (*Z*)-isomer:

MP 116-118 °C (hexanes).

IR ν_{max} (neat, cm^{-1}) 3060 w, 3007 w, 2966 w, 2831 w, 1589 m, 1467 s, 1303 m, 1223 s, 1168 m, 1099 s, 1017 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.20 (1H, td, *J* 7.7, 1.6 Hz), 7.06-7.01 (1H, m), 7.04 (1H, s), 6.88 (1H, d, *J* 8.2 Hz), 6.77 (1H, d, *J* 12.2 Hz), 6.75 (1H, app. t, *J* 7.7 Hz), 6.61 (1H, d, *J* 12.2 Hz), 6.60 (1H, s), 5.90 (2H, s), 3.85 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 157.4 (*C*), 147.7 (*C*), 147.0 (*C*), 131.3 (*C*), 130.3 (*C*H), 129.4 (*C*H), 128.9 (*C*H), 126.5 (*C*H), 125.5 (*C*), 120.5 (*C*H), 115.1 (*C*), 112.6 (*C*H), 110.8 (*C*H), 110.4 (*C*H), 101.7 (CH_2), 55.7 (CH_3).

Mass $^m/_z$ (EI) 334/332 (M^+, 59%), 253 ($[M - Br]^+$, 10), 238 (42), 223 (33), 195 (31), 180 (27), 152 (100), 98 (40).

CHN Found C 57.99%, H 3.93%. $C_{16}H_{13}BrO_3$ requires C 57.68%, H 3.93%.

To a solution of ^{t}BuLi (1.22M in pentane, 0.96 mL, 1.18 mmol) in THF (2.5 mL) at –78 °C was added a solution of 5-bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole (*Z* : *E* ~ 10 : 1, 196 mg, 0.588 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate (84 mg, 0.588 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (3 mL). The reaction mixture was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase extracted with ether (20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ether/petrol yielded (*Z*)-**34** (174 mg, 0.439 mmol, 75%) as an off-white powder.

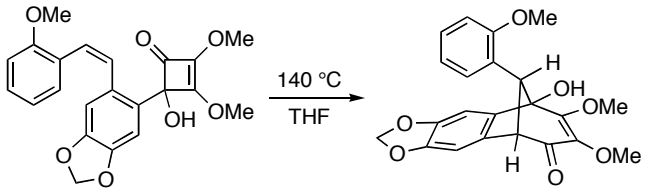
IR ν_{max} (neat, cm^{-1}) 3297 br w, 2950 w, 2837 w, 1773 m, 1642 s, 1610 s, 1475 s, 1462 s, 1332 vs, 1234 vs, 1021 vs.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* 11.8 Hz), 7.17 (1H, app. td, *J* 8.1, 1.5 Hz), 7.10 (1H, dd, *J* 7.5, 1.3 Hz), 6.98 (1H, s), 6.82 (1H, app. t, *J* 7.5 Hz), 6.78 (1H, d, *J* 8.1 Hz), 6.75 (1H, d, *J* 11.8 Hz), 6.43 (1H, s), 5.86 (2H, s), 4.20 (3H, s), 4.01 (3H, s), 3.89 (1H, s), 3.64 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 184.9 (*C*), 166.1 (*C*), 156.4 (*C*), 147.2 (*C*), 146.6 (*C*), 135.1 (*C*), 131.7 (*C*), 131.2 (*C*H), 130.5 (*C*H), 129.5 (*C*), 128.8 (*C*H), 126.9 (*C*H), 125.6 (*C*), 120.7 (*C*H), 111.1 (*C*H), 110.6 (*C*H), 107.2 (*C*H), 101.3 (CH_2), 88.9 (*C*), 60.6 (CH_3), 58.7 (CH_3), 55.3 (CH_3).

Mass $^m/_z$ (ES^+) 815 ($[2M + Na]^+$, 5%), 419 ($[M + Na]^+$, 100).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-7,8-dimethoxy-2,3-methylenedioxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 35**



(*Z*)-**34** **35**, 69%

Cyclobutenone (*Z*)-**34** (109 mg, 0.275 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) gave benzobicyclo[3.2.1]octenone **35** as a yellow oil (75 mg, 0.189 mmol, 69%).

IR ν_{max} (neat, cm^{-1}) 3461 bw, 3003 w, 2954 w, 2925 w, 2835 w, 1659 m, 1467 s, 1283 s, 1234 s, 1091 s, 1033 s.

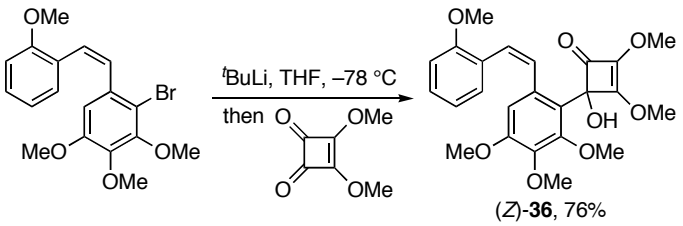
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.19 (1H, app. td, *J* 8.3, 1.7 Hz), 6.87 (1H, dd, *J* 8.3, 0.8 Hz), 6.86 (1H, s), 6.83 (1H, dd, *J* 7.7, 1.7 Hz), 6.81 (1H, s), 6.74 (1H, app. td, *J* 7.7, 0.8 Hz), 5.97 (1H, d, *J* 1.3 Hz), 5.93 (1H, d, *J* 1.3 Hz), 4.57 (1H, s), 4.19 (3H, s), 3.92 (1H, s), 3.87 (3H, s), 3.70 (1H, br s), 3.63 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.8 (*C*), 168.5 (*C*), 157.9 (*C*), 147.4 (*C*), 147.3 (*C*), 140.1 (*C*), 132.2 (*C*), 128.7 (*C*), 128.7 (*C*H), 128.4 (*C*H), 125.4 (*C*), 120.8 (*C*H), 110.6 (*C*H), 106.5 (*C*H), 103.7 (*C*H), 101.6 (CH_2), 83.7 (C), 62.3 (CH_3), 60.7 (*C*H), 60.3 (CH_3), 59.5 (CH_3), 54.9 (*C*H).

Mass $^m/_z$ (ES^+) 815 ($[2M + Na]^+$, 100%), 419 ($[M + Na]^+$, 100), 397 (MH^+, 24).

$^m/_z$ (ES^+) found 419.1100, $[M + Na]^+$. $C_{22}H_{20}NaO_7$ requires 419.1101.

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]phenylcyclobut-2-enone, (*Z*)-36



(*Z*)-**36**, 76%

To a solution of ^{t}BuLi (1.24 M in pentane, 0.57 mL, 0.704 mmol) in THF (2.5 mL) at –78 °C was added a solution of (*Z*)-1-bromo-2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]benzene (133 mg, 0.352 mmol)[9] in THF (2.5 mL) over 2 min. After 10 min dimethyl squarate (100 mg, 0.704 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase re-extracted with ether (20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-40% EtOAc/petrol) yielded cyclobutenone (*Z*)-**36** as a pale yellow oil (119 mg, 0.269 mmol, 76%).

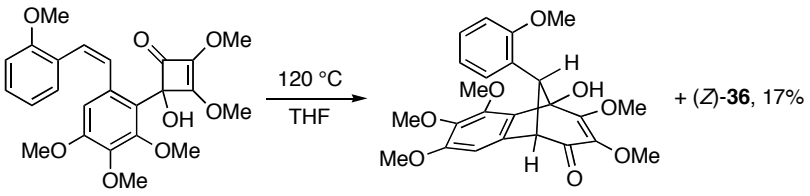
IR ν_{max} (neat, cm^{-1}) 3281 bw, 3003 w, 2946 w, 2827 w, 1757 m, 1630 s, 1462 s, 1389 s, 1332 s, 1242 s, 1119 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.14 (1H, td, *J* 7.8, 1.5 Hz), 7.04 (1H, d, *J* 12.1 Hz), 6.98 (1H, dd, *J* 7.8, 1.3 Hz), 6.80 (1H, d, *J* 12.1 Hz), 6.78 (1H, d, *J* 7.8 Hz), 6.74 (1H, t, *J* 7.8 Hz), 6.29 (1H, s), 5.36 (1H, s, O*H*), 4.11 (3H, s), 3.99 (3H, s), 3.91 (3H, s), 3.82 (3H, s), 3.70 (3H, s), 3.46 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 183.6 (*C*), 165.7 (*C*), 156.7 (*C*), 152.7 (*C*), 152.1 (*C*), 141.4 (*C*), 134.5 (*C*), 133.0 (*C*), 131.2 (*C*H), 130.1 (*C*H), 128.7 (*C*H), 125.7 (*C*H), 125.4 (*C*), 121.2 (*C*), 120.5 (*C*H), 110.7 (*C*H), 110.2 (*C*H), 87.3 (*C*), 62.3 (CH_3), 60.9 (CH_3), 59.9 (CH_3), 58.5 (CH_3), 55.8 (CH_3), 55.3 (CH_3).

Mass $^m/_z$ (ES$^+$) 907 ([2M + Na]$^+$, 52%), 465 ([M + Na]$^+$, 100).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-1,2,3,7,8-pentamethoxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 37**



(*Z*)-**36** **37**, 75%

Cyclobutenone (*Z*)-**36** (47 mg, 0.106 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 2 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded firstly recovered (*Z*)-**36** as a yellow oil (8 mg, 0.018 mmol, 17%), then benzobicyclo[3.2.1]octenone **37** as a cream solid (35 mg, 0.079 mmol, 75%).

MP 179-181 °C (EtOH).

IR ν_{max} (neat, cm^{-1}) 3363 bw, 3003 w, 2950 w, 2929 w, 2831 w, 1659 m, 1458 m, 1328 m, 1266 s, 1103 s, 1042 s.

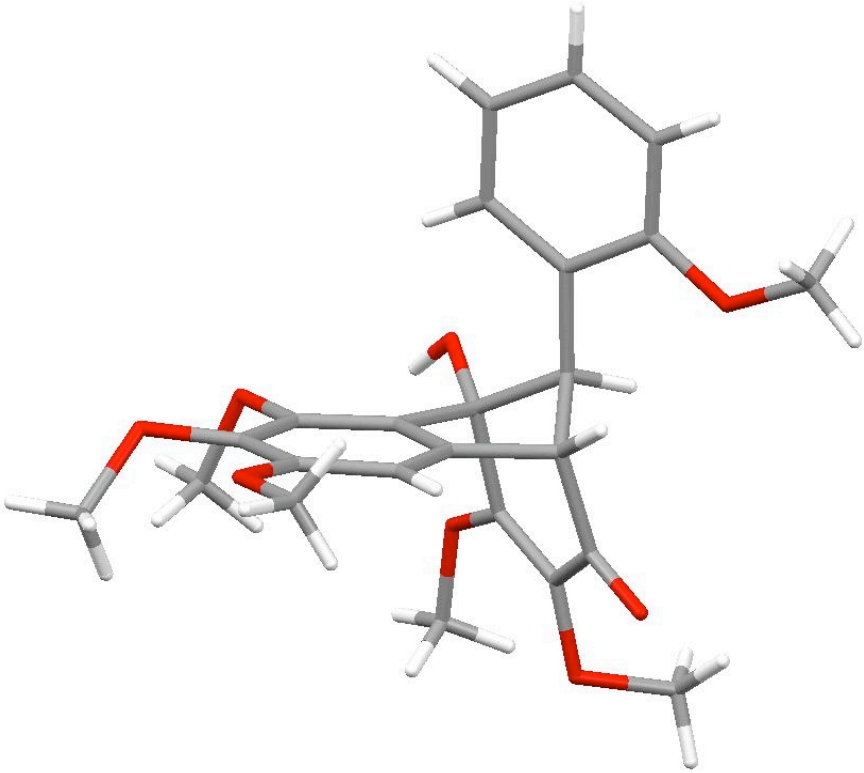
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.18 (1H, t, *J* 7.8 Hz), 6.92-6.85 (2H, m), 6.71 (1H, app. t, *J* 7.3 Hz), 6.71 (1H, s), 4.60 (1H, s), 4.22 (3H, s), 4.02 (1H, s), 3.94 (3H, s), 3.88 (1H, br s), 3.86 (3H, s), 3.85 (3H, s), 3.82 (3H, s), 3.66 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 195.1 (*C*), 169.5 (*C*), 158.1 (*C*), 154.0 (*C*), 150.1 (*C*), 141.4 (*C*), 135.4 (*C*), 129.3 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.4 (*C*), 125.9 (*C*), 120.2 (*C*H), 110.6 (*C*H), 105.8 (*C*H), 84.3 (*C*), 61.7 (*C*H), 61.7 (CH_3), 61.6 (CH_3), 61.3 (CH_3), 61.2 (CH_3), 60.4 (*C*H), 56.4 (CH_3), 55.8 (CH_3).

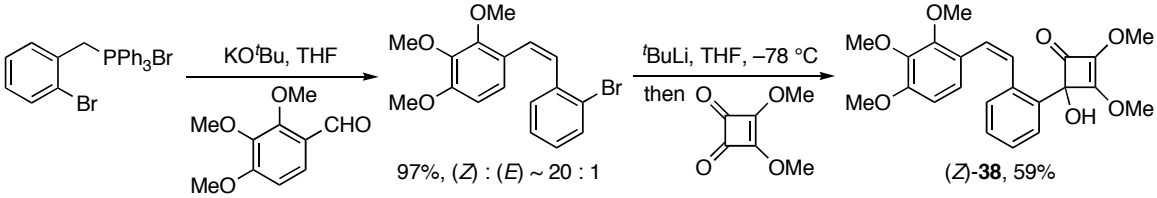
Mass $^m/_z$ (ES$^+$) 907 ([2M + Na]$^+$, 40%), 465 ([M + Na]$^+$, 100), 443 (MH$^+$, 11).

$^m/_z$ (ES$^+$) found 443.1701, MH$^+$. $C_{24}H_{27}O_8$ requires 443.1697.

Xray



(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{2-[2-(2,3,4-trimethoxyphenyl)vinyl]phenylcyclobut-2-enone, (*Z*)-38



To a suspension of (2-bromobenzyl)triphenylphosphonium bromide (2.46 g, 4.80 mmol) in THF (30 mL) at 0 °C was added potassium *tert*-butoxide (628 mg, 5.60 mmol). After 30 min a solution of 2,3,4-trimethoxybenzaldehyde (785 mg, 4.00 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to RT, stirred for 16 h then partitioned between water (30 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) yielded a 20 : 1 mixture of (*Z*)- and (*E*)-1,2,3-trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene as a colourless oil (1.35 g, 3.87 mmol, 97%).

IR ν_{max} (neat, cm^{-1}) 3048 w, 2995 w, 2827 w, 1601 m, 1487 s, 1450 s, 1405 s, 1274 s, 1230 m, 1091 vs, 1017 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.59 (1H, dd, *J* 7.3, 2.2 Hz), 7.19 (1H, dd, *J* 7.3, 2.2 Hz), 7.09 (1H, td, *J* 7.3, 2.2 Hz), 7.05 (1H, td, *J* 7.3, 2.2 Hz), 6.79 (1H, d, *J* 12.1 Hz), 6.67 (1H, d, *J* 8.8 Hz), 6.61 (1H, d, *J* 12.1 Hz), 6.40 (1H, d, *J* 8.8 Hz), 3.91 (3H, s), 3.88 (3H, s), 3.80 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 153.4 (*C*), 152.3 (*C*), 142.3 (*C*), 138.4 (*C*), 132.8 (*C*H), 130.9 (*C*H), 128.9 (*C*H), 128.6 (*C*H), 127.1 (*C*H), 126.4 (*C*H), 124.6 (*C*H), 124.1 (*C*), 123.4 (*C*), 107.2 (*C*H), 61.3 (CH_3), 61.1 (CH_3), 56.1 (CH_3).

Mass $^m/_z$ (EI) 350/348 (M^+, 78%), 254 (26), 238 (100), 211 (36), 195 (33), 168 (58), 152 (46), 140 (79), 127 (40).

CHN Found C 58.88%, H 5.01%; $C_{17}H_{17}BrO_3$ requires C 58.47%, H 4.91%

To a solution of ^{t}BuLi (1.22M in pentane, 0.93 mL, 1.14 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1,2,3-trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene ((*Z*) : (*E*) ~ 20 : 1, 199 mg, 0.570 mmol) in THF (2.5 mL) over 2 min. After 30 min dimethyl squarate (81 mg, 0.570 mmol) in THF (2 mL) was added, followed after a further 30 min by sat. $NaHCO_3$ (3 mL). The

reaction mixture was warmed to RT and diluted with ether (20 mL). The aqueous phase was extracted with ether (20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded cyclobutenone (*Z*)-**38** as a pale yellow oil (138 mg, 0.335 mmol, 59%).

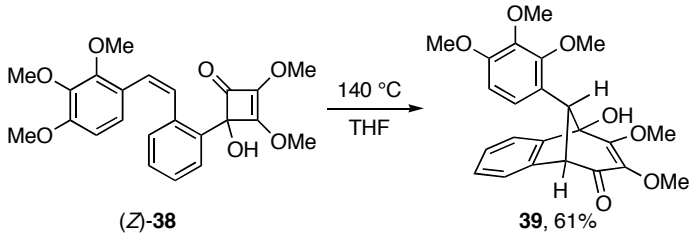
IR ν_{max} (neat, cm^{-1}) 3399 bw, 2974 m, 2856 m, 1769 m, 1634 s, 1589 m, 1491 s, 1458 s, 1332 s, 1091 vs, 1037 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.49 (1H, d, *J* 8.0 Hz), 7.28 (1H, d, *J* 12.1 Hz), 7.24-7.04 (3H, m), 6.81 (1H, d, *J* 12.1 Hz), 6.68 (1H, d, *J* 8.8 Hz), 6.42 (1H, d, *J* 8.8 Hz), 4.19 (3H, s), 4.01 (3H, s), 3.90 (1H, br s), 3.80 (3H, s), 3.79 (3H, s), 3.78 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 184.5 (*C*), 165.8 (*C*), 153.3 (*C*), 151.9 (*C*), 142.3 (*C*), 137.1 (*C*), 136.1 (*C*), 135.1 (*C*), 130.9 (*C*H), 130.1 (*C*H), 128.5 (*C*H), 127.3 (*C*H), 126.9 (*C*H), 126.4 (*C*H), 124.8 (*C*H), 123.3 (*C*), 107.2 (*C*H), 89.2 (*C*), 61.1 (CH_3), 61.0 (CH_3), 60.5 (CH_3), 58.7 (CH_3), 56.1 (CH_3).

Mass $^m/_z$ (ES^+) 847 ($[2M + Na]^+$, 14%), 435 ($[M + Na]^+$, 100).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-7,8-dimethoxy-10-(2,3-dimethoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 39**



(*Z*)-**38** **39**, 61%

Cyclobutenone (*Z*)-**38** (112 mg, 0.272 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded a pale yellow solid which was recrystallised from EtOAc to give benzobicyclo[3.2.1]octenone **39** as a white crystalline solid (68 mg, 0.165 mmol, 61%).

MP 222-224 °C (EtOAc).

IR ν_{max} (neat, cm^{-1}) 3387 bw, 3056 w, 3032 w, 2974 w, 2827 w, 1650s, 1587 s, 1446 s, 1254 s, 1093 vs, 1058 s.

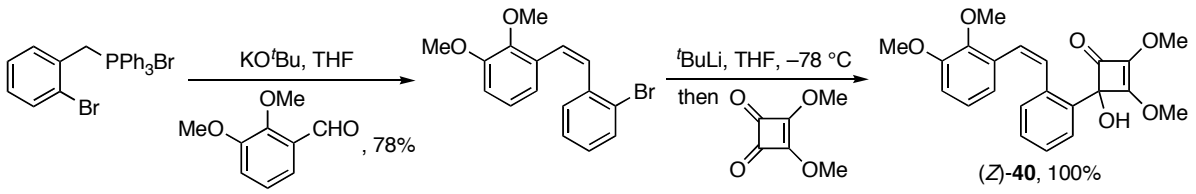
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.40 (1H, m), 7.28 (1H, br dd, *J* 8.2, 6.0 Hz), 7.24-7.18 (2H, m), 6.36 (1H, d, *J* 8.9 Hz), 6.28 (1H, d, *J* 8.9 Hz), 4.45 (1H, s), 4.19 (3H, s), 4.03 (1H, s), 3.96 (3H, s), 3.84 (3H, s), 3.73 (3H, s), 3.61 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.5 (*C*), 168.3 (*C*), 153.3 (*C*), 152.6 (*C*), 146.0 (*C*), 141.9 (*C*), 139.1 (*C*), 128.9 (*C*), 128.1 (*C*H), 127.8 (*C*H), 125.0 (*C*H), 122.6 (*C*), 122.1 (2 x *C*H), 107.2 (*C*H), 84.1 (*C*), 62.3 (*C*H), 61.5 (CH_3), 61.3 (CH_3), 61.2 (CH_3), 61.1 (CH_3), 60.8 (CH_3), 55.9 (*C*H).

Mass $^m/_z$ (ES^+) 847 ($[2M + Na]^+$, 95%), 435 ($[M + Na]^+$, 100), 413 (MH^+, 23).

CHN Found C 66.58%, H 5.79%; $C_{23}H_{24}O_7$ requires C 66.98%, H 5.87%.

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{2-[2-(2,3-dimethoxyphenyl)vinyl]phenylcyclobut-2-enone, (*Z*)-40



(*Z*)-**40**, 100%

To a suspension of (2-bromobenzyl)triphenylphosphonium bromide (2.46 g, 4.80 mmol) in THF (30 mL) at 0 °C was added potassium *tert*-butoxide (628 mg, 5.60 mmol). After 30 min a solution of 2,3-dimethoxybenzaldehyde (665 mg, 4.00 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to RT, stirred for 16 h then partitioned between water (25 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) then the combined organic phases were

washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% ether/petrol) yielded 1,2-dimethoxy-3-[2-(2-bromophenyl)vinyl]benzene as a white crystalline solid (991 mg, 3.10 mmol, 78%).

MP 91-92 °C (hexane), Lit.[9b] m.p. 88-92 °C (hexane).

IR ν_{max} (neat, cm^{-1}) 3064 w, 3007 w, 2962 w, 2831 w, 1475 s, 1458 s, 1426 s, 1254 s, 1213 s, 1172 s, 1070 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.59 (1H, m), 7.17-7.04 (3H, m), 6.90 (1H, d, *J* 12.2 Hz), 6.80-6.75 (2H, m), 6.73 (1H, d, *J* 12.2 Hz), 6.57 (1H, m Hz), 3.89 (3H, s), 3.87 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 152.9 (*C*), 147.6 (*C*), 138.0 (*C*), 132.8 (*C*H), 131.1 (*C*H), 131.0 (*C*), 130.3 (*C*H), 128.7 (*C*H), 127.0 (*C*H), 126.9 (*C*H), 124.1 (*C*), 123.6 (*C*H), 122.2 (*C*H), 111.7 (*C*H), 61.0 (CH_3), 55.9 (CH_3).

Mass $^m/_z$ (EI) 320/318 (M^+, 34%), 239 ($[M - Br]^+$, 33), 224 (89), 208 (62), 196 (38), 181 (61), 165 (54), 152 (100).

To a solution of ^{t}BuLi (1.22 M in pentane, 1.02 mL, 1.25 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1,2-dimethoxy-3-[2-(2-bromophenyl)vinyl]benzene (200 mg, 0.627 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate (89 mg, 0.627 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (3 mL). The reaction mixture was warmed to RT and diluted with ether (20 mL). The aqueous phase was extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield cyclobutenone (*Z*)-**40** (240 mg, 0.627 mmol, 100%). The bulk was used without further purification due to product instability - an analytical sample being purified by recrystallisation from ether/petrol to yield a cream solid.

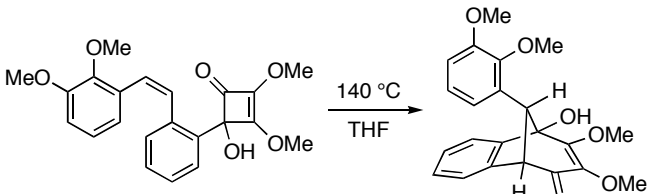
IR ν_{max} (neat, cm^{-1}) 3399 bw, 2946 w, 2835 w, 1769 m, 1630 s, 1573 m, 1462 s, 1336 s, 1070 m, 1042 m, 988 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.48 (1H, d, *J* 7.5 Hz), 7.39 (1H, d, *J* 12.2 Hz), 7.18 (1H, td, *J* 7.5, 1.8 Hz), 7.06 (1H, td, *J* 7.5, 1.0 Hz), 7.05-7.02 (1H, m), 6.89 (1H, d, *J* 12.2 Hz), 6.79 (1H, t, *J* 7.9 Hz), 6.74 (1H, dd, *J* 7.9, 1.5 Hz), 6.60 (1H, dd, *J* 7.9, 1.5 Hz), 4.19 (3H, s), 4.01 (3H, s), 3.82 (3H, s), 3.78 (3H, s), 3.63 (1H, s, OH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 184.5 (*C*), 166.0 (*C*), 152.8 (*C*), 147.2 (*C*), 136.7 (*C*), 136.2 (*C*), 135.1 (*C*), 131.8 (*C*H), 131.1 (*C*H), 131.0 (*C*), 128.4 (*C*H), 127.4 (*C*H), 126.9 (*C*H), 126.5 (*C*H), 123.6 (*C*H), 122.4 (*C*H), 111.7 (*C*H), 89.2 (*C*), 60.8 (CH_3), 60.6 (CH_3), 58.7 (CH_3), 55.9 (CH_3).

Mass $^m/_z$ (ES^+) 787 ($[2M + Na]^+$, 31%), 405 ($[M + Na]^+$, 100).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-7,8-dimethoxy-10-(2,3-dimethoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 41**



(*Z*)-**40** **41**, 68%

Cyclobutenone (*Z*)-**40** (66 mg, 0.173 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 90 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded benzobicyclo[3.2.1]octenone **41** as a pale yellow oil (45 mg, 0.118 mmol, 68%).

IR ν_{max} (neat, cm^{-1}) 3448 bw, 2999 w, 2954 m, 2831 w, 1663 s, 1581 s, 1471 s, 1454 s, 1254 vs, 1074 s, 1045 s.

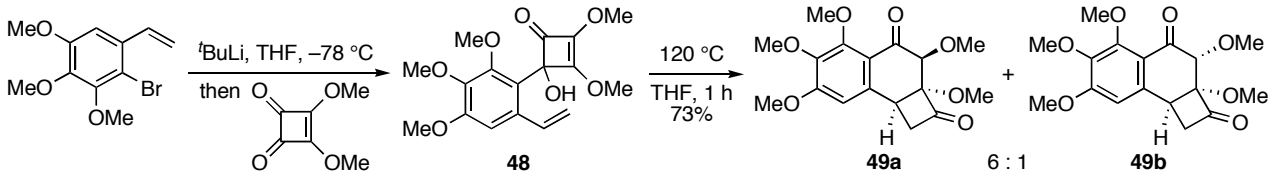
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.44-7.38 (1H, m), 7.32-7.18 (3H, m), 7.21 (1H, dd, *J* 5.3, 3.3 Hz), 6.80-6.74 (2H, m), 6.22 (1H, dd, *J* 6.8, 2.1 Hz), 4.54 (1H, s), 4.19 (3H, s), 4.08 (1H, s), 3.91 (3H, s), 3.88 (1H, br s), 3.83 (3H, s), 3.62 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.5 (*C*), 168.7 (*C*), 152.4 (*C*), 147.9 (*C*), 145.9 (*C*), 139.1 (*C*), 130.4 (*C*), 128.9 (*C*), 128.1 (*C*H), 127.9 (*C*H), 125.0 (*C*H), 124.0 (*C*H), 122.1 (*C*H), 119.7 (*C*H), 112.1 (*C*H), 84.2 (*C*), 62.5 (CH_3), 61.6 (CH_3), 61.1 (2 x CH_3), 60.8 (*C*H), 55.9 (*C*H).

Mass $^m/_z$ (ES^+) 787 ($[2M + Na]^+$, 100%), 421 ($[M + K]^+$, 58), 405 ($[M + Na]^+$, 57), 383 (MH^+, 5).

$^m/_z$ (ES^+) found 405.1303, $[M + Na]^+$. $C_{22}H_{22}NaO_6$ requires 405.1308.

rel-(2a*R*,3*S*,8b*S*)-2a,3,5,6,7-Pentamethoxy-1,2a,3,8b-tetrahydrocyclobuta[*a*]naphthalene-2,4-dione, 49a and the rel-(2a*R*,3*R*,8b*S*)-diastereoisomer, 49b



To a solution of ^{t}BuLi (1.15 M in pentane, 0.63 mL, 0.724 mmol) in THF (2.5 mL) at –78 °C was added a solution of 2-bromo-3,4,5-trimethoxystyrene (99 mg, 0.362 mmol) in THF (2.5 mL) over 2 min. After 1 h dimethyl squarate (52 mg, 0.362 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and diluted with ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil, crude cyclobutenone **48**, was dissolved in THF (3 mL) and heated at 120 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 30-50% EtOAc/petrol) to give firstly cyclobuta[*a*]naphthalene **49a** (76 mg, 0.226 mmol, 62% over 2 steps) then cyclobuta[*a*]naphthalene **49b** (14 mg, 0.0416 mmol, 11%) as pale yellow oils.

Data for **49a**

IR ν_{max} (neat, cm^{-1}) 2933 m, 1784 s, 1696 m, 1588 s, 1489 m, 1456 m, 1347 s, 1253 s, 1196 s, 1100 s, 747 vs.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.54 (1H, s), 4.36 (1H, s), 3.96 (3H, s), 3.92 (3H, s), 3.88 (3H, s), 3.72 (1H, app. t, *J* 10.1 Hz), 3.50 (3H, s), 3.41 (3H, s), 3.26 (1H, dd, *J* 17.4, 10.8 Hz), 2.90 (1H, dd, *J* 17.4, 9.3 Hz).

nOe Irradiation of the signal at δ_H 4.36 (1H, s, C*H*OCH_3) caused nOe enhancement at δ_H 3.50 (3H, s, OC*H*$_3$) and 3.41 (3H, s, OC*H*$_3$); irradiation of the signal at δ_H 3.72 (1H, app. t, *J* 10.1 Hz, C*H*CH_2) caused nOe enhancement at δ_H 3.50 (3H, s, OC*H*$_3$); irradiation of the signal at δ_H 3.50 (3H, s, OC*H*$_3$) caused nOe enhancement at δ_H 4.36 (1H, s, C*H*OCH_3) and 3.72 (1H, app. t, *J* 10.1 Hz, C*H*CH_2); irradiation of the signal at δ_H 3.41 (3H, s, OC*H*$_3$) caused nOe enhancement at δ_H 4.36 (1H, s, C*H*OCH_3). The aforementioned assignments were aided by a **^{1}H-^{1}H COSY** and short and long-ragnge **^{1}H-^{13}C COSY** experiment (HMQC and HMBC respectively).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.1 (*C*), 194.1 (*C*), 158.0 (*C*), 153.9 (*C*), 142.2 (*C*), 138.8 (*C*), 119.3 (*C*), 107.1 (*C*H), 95.8 (*C*), 83.4 (*C*H), 62.5 (CH_3), 61.2 (CH_3), 59.0 (CH_3), 56.3 (CH_3), 53.6 (CH_3), 50.4 (CH_2), 33.1 (*C*H).

Mass $^{m}/_{z}$ (ES^+) 695 ($[2M + Na]^+$, 11%), 391 ($[M + Na + MeOH]^+$, 40), 359 ($[M + Na]^+$, 100), 337 (MH^+, 88).

$^{m}/_{z}$ (ES^+) found 359.1102, $[M + Na]^+$. $C_{17}H_{20}NaO_7$ requires 359.1101.

Data for **49b**

IR ν_{max} (neat, cm^{-1}) 2926 m, 2848 w, 1785 s, 1698 s, 1589 s, 1489 s, 1457 s, 1349 s, 1271 s, 1116 s, 1102 s.

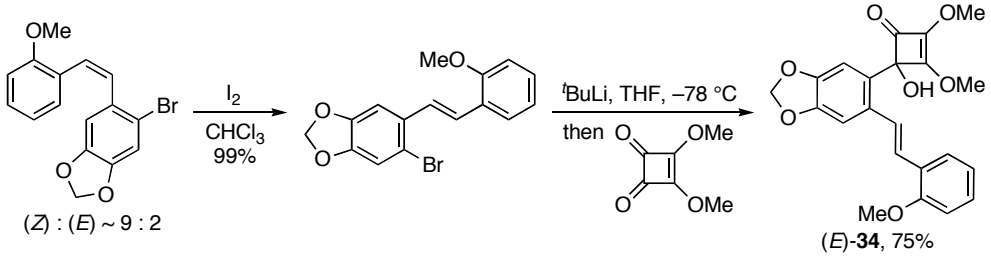
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.54 (1H, s), 3.98 (3H, s), 3.97 (1H, s), 3.94 (3H, s), 3.90 (3H, s), 3.73 (1H, app. t, *J* 10.1 Hz), 3.52 (3H, s), 3.43 (3H, s), 3.27 (1H, dd, *J* 17.6, 10.8 Hz), 2.94 (1H, dd, *J* 17.6, 9.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.2 (*C*), 194.1 (*C*), 158.0 (*C*), 154.0 (*C*), 142.2 (*C*), 138.8 (*C*), 119.4 (*C*), 107.1 (*C*H), 95.9 (*C*), 83.4 (*C*H), 62.5 (CH_3), 61.3 (CH_3), 59.1 (CH_3), 56.4 (CH_3), 53.7 (CH_3), 50.4 (CH_2), 33.2 (*C*H).

Mass $^{m}/_{z}$ (ES^+) 695 ($[2M + Na]^+$, 14%), 391 ($[M + Na + MeOH]^+$, 35), 359 ($[M + Na]^+$, 100), 337 (MH^+, 83).

$^{m}/_{z}$ (ES^+) found 359.1101, $[M + Na]^+$. $C_{17}H_{20}NaO_7$ requires 359.1101.

(*E*)-4-Hydroxy-2,3-dimethoxy-4-{6-[2-(2-methoxyphenyl)vinyl]-benz[1,3]dioxol-5-yl}cyclobut-2-enone, (*E*)-34



To a solution of 5-bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole ((*Z*) : (*E*) ~ 9 : 2, 540 mg, 1.62 mmol) in chloroform (20 mL) was added a solution of iodine (41 mg, 0.16 mmol) in chloroform (5 mL). After 10 days at RT the reaction mixture was diluted with DCM (40 mL), washed with sat. $Na_2S_2O_3$ (30 mL) and water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a white solid. Recrystallisation from hexane gave (*E*)-5-bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole (538 mg, 1.61 mmol, 99%) as off-white needles.

mp 120-122 °C (Hexane).

IR ν_{max} (neat, cm^{-1}) 3064 w, 3007 w, 2905 w, 1593 m, 1463 s, 1307 m, 1232 s, 1036 m, 1022 s, 967 s, 932 m, 741 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.63 (1H, dd, *J* 7.5, 1.5 Hz), 7.43 (1H, d, *J* 16.3 Hz), 7.29 (1H, d, *J* 16.3 Hz), 7.28 (1H, ddd, *J* 8.3, 7.5, 1.5 Hz), 7.23 (1H, s), 7.05 (1H, s), 7.00 (1H, t, *J* 7.5 Hz), 6.93 (1H, d, *J* 8.3 Hz), 6.01 (2H, s), 3.92 (3H, s).

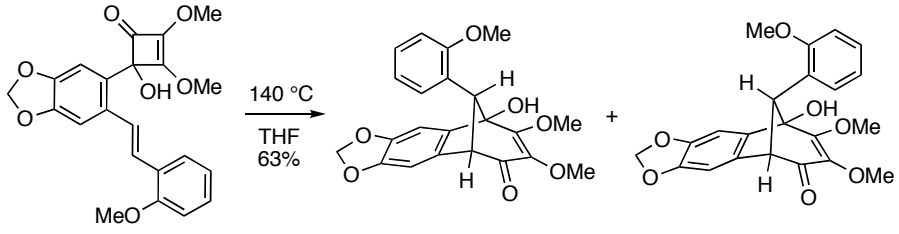
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 157.1 (*C*), 147.9 (*C*), 147.9 (*C*), 131.5 (*C*), 129.1 (*C*H), 127.9 (*C*H), 126.9 (*C*H), 126.4 (*C*), 124.8 (*C*H), 121.0 (*C*H), 115.4 (*C*), 112.9 (*C*H), 111.2 (*C*H), 106.2 (*C*H), 101.9 (CH_2), 55.7 (CH_3).

Mass $^m/_z$ (EI) 334/332 (M^+, 56%), 253 ([M – Br]$^+$, 8), 238 (38), 223 (31), 195 (36), 180 (25), 165 (34), 152 (100).

CHN Found C 57.27%, H 3.89%. $C_{16}H_{13}BrO_3$ requires C 57.68%, H 3.93%.

To a solution of ^{t}BuLi (1.15 M in pentane, 0.63 mL, 0.724 mmol) in THF (2.5 mL) at –78 °C was added a solution of (*E*)-5-bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole (138 mg, 0.414 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate (59 mg, 0.414 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone (*E*)-**34** as a pale yellow oil (124 mg, 0.312 mmol, 75%), which was used immediately in the next reaction.

***rel*-(5*S*,9*S*,10*R*)- and *rel*-(5*S*,9*S*,10*S*)-9-Hydroxy-7,8-dimethoxy-2,3-methylenedioxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 35 and 50**



(*E*)-**34** **35** ~ 1 : 1.1 **50**

A solution of cyclobutenone (*E*)-**34** (124 mg, 0.312 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purification by column chromatography (SiO_2, 30-45% EtOAc/petrol) to afford firstly benzobicyclo[3.2.1]octenone **50** as a pale yellow oil (41 mg, 0.103 mmol, 33%) then diastereoisomer **35** as a pale yellow oil (37 mg, 0.094 mmol, 30%).

Data for **35** as described previously. Data for **50**:

IR ν_{max} (neat, cm^{-1}) 3236 bw, 2917 m, 2848 w, 1654 s, 1569 s, 1464 s, 1244 s, 1118 s, 1101 s, 1031 s, 937 s, 749 s.

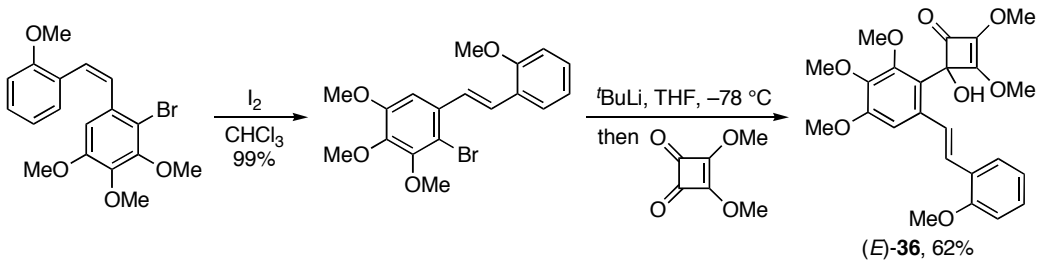
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.31-7.28 (2H, m), 6.99-6.94 (2H, m), 6.96 (1H, s), 6.92 (1H, s), 6.01 (1H, d, *J* 1.4 Hz), 5.97 (1H, d, *J* 1.4 Hz), 4.43 (1H, d, *J* 4.1 Hz), 4.41 (1H, s), 4.31 (1H, d, *J* 4.1 Hz), 4.15 (3H, s), 3.91 (3H, s), 3.40 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.3 (*C*), 162.8 (*C*), 158.1 (*C*), 147.0 (C), 146.9 (*C*), 144.0 (*C*), 132.9 (*C*), 130.1 (*C*H), 129.6 (*C*), 128.6 (*C*H), 124.5 (*C*), 120.9 (*C*H), 111.2 (*C*H), 106.3 (*C*H), 103.0 (*C*H), 101.4 (CH_2), 81.5 (*C*), 64.6 (*C*H), 61.5 (CH_3), 60.7 (CH_3), 58.3 (CH_3), 55.7 (*C*H).

Mass $^m/_z$ (ES^+) 815 ([2M + Na]$^+$, 30%), 793 ([2M + H$^+$], 4), 419 ([M + Na]$^+$, 27), 397 (MH^+, 100).

$^m/_z$ (ES^+) found 419.1103, [M + Na]$^+$. $C_{22}H_{20}NaO_7$ requires 419.1101.

(*E*)-4-Hydroxy-2,3-dimethoxy-4-{2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]phenylcyclobut-2-enone, (*E*)-36



(*E*)-**36**, 62%

To a solution of (*Z*)-1-bromo-2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]benzene (200 mg, 0.527 mmol) in chloroform (10 mL) was added a solution of iodine (13 mg, 0.053 mmol) in chloroform (5 mL). After 16 h at RT the reaction mixture was diluted with DCM (20 mL), washed with sat. $Na_2S_2O_3$ (20 mL) and water (20 mL) and dried ($MgSO_4$). Concentration *in vacuo* gave (*E*)-1-bromo-2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]benzene (199 mg, 0.525 mmol, 99%) as a pale yellow oil.

IR ν_{max} (neat, cm^{-1}) 3053 w, 2935 m, 1554 m, 1471 s, 1388 s, 1345 s, 1314 s, 1239 s, 1104 vs, 1006 s, 962 s, 749 s.

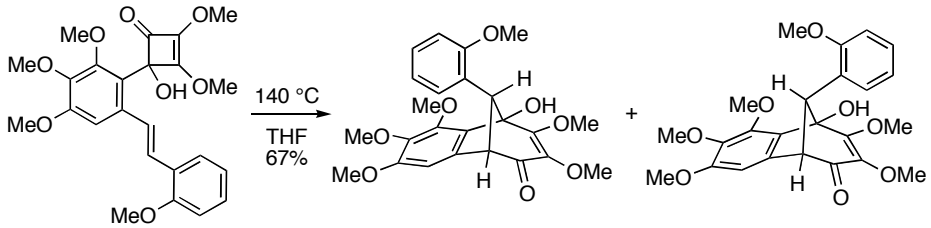
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.64 (1H, dd, *J* 7.5, 1.5 Hz), 7.49 (1H, d, *J* 16.3 Hz), 7.31 (1H, d, *J* 16.3 Hz), 7.29 (1H, td, *J* 7.9, 1.5 Hz), 7.06 (1H, s), 7.00 (1H, t, *J* 7.5 Hz), 6.93 (1H, d, *J* 7.9 Hz), 3.95 (3H, s), 3.93 (6H, s), 3.91 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 157.2 (*C*), 153.0 (*C*), 151.1 (*C*), 142.9 (*C*), 133.7 (*C*), 129.2 (*C*H), 128.3 (*C*H), 127.1 (*C*H), 126.3 (*C*), 125.7 (*C*H), 121.0 (*C*H), 111.3 (*C*), 111.1 (*C*H), 105.6 (*C*H), 61.4 (*C*H_3), 61.1 (*C*H_3), 56.4 (*C*H_3), 55.7 (*C*H_3).

Mass $^m/_z$ (EI) 380/378 (M^+, 84%), 365/363 ($[M - CH_3]^+$, 22), 299 ($[M - Br]^+$, 16), 284 (43), 268 (100), 198 (32), 155 (50).
$^m/_z$ (EI) found 378.0469, M^+. $C_{18}H_{19}BrO_4$ requires 378.0466.

To a solution of ^{t}BuLi (1.24M in pentane, 0.56 mL, 0.691 mmol) in THF (2.5 mL) at –78 °C was added a solution of (*E*)-1-bromo-2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]benzene (131 mg, 0.345 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate (49 mg, 0.345 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone (*E*)-**36** (95 mg, 0.214 mmol, 62%) as a pale yellow oil, which was used immediately in the next reaction.

***rel*-(5*S*,9*S*,10*R*)- and *rel*-(5*S*,9*S*,10*S*)-9-Hydroxy-1,2,3,7,8-pentamethoxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 37 and 51**



(*E*)-**36** **37** ~ 1 : 1 **51**

A solution of cyclobutenone (*E*)-**36** (95 mg, 0.214 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 40-50% EtOAc/petrol) to afford firstly benzobicyclo[3.2.1]octenone **51** as a pale yellow oil (32 mg, 0.072 mmol, 34%) then diastereoisomer **37** as a cream solid (31 mg, 0.070 mmol, 33%).

Data for **37** as described previously. Data for **51**:

IR ν_{max} (neat, cm^{-1}) 3379 bw, 2933 m, 2852 w, 1668 s, 1593 s, 1467 s, 1323 s, 1254 s, 1111 s, 1050 m, 751 w.

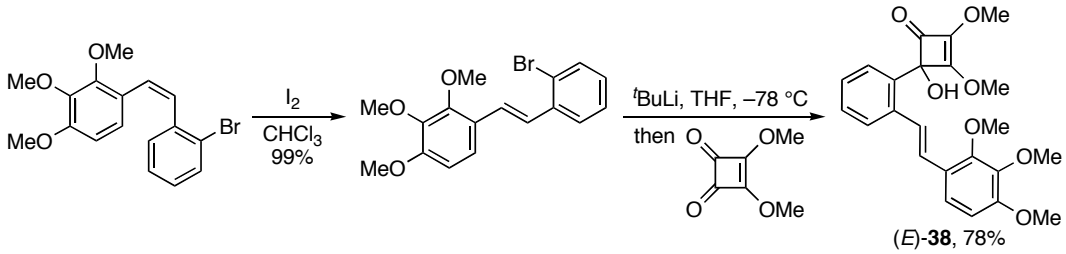
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.35 (1H, d, *J* 7.8 Hz), 7.21 (1H, t, 7.8 Hz), 6.91 (1H, t, *J* 7.8 Hz), 6.86 (1H, d, *J* 7.8 Hz), 6.81 (1H, s), 4.48 (1H, d, *J* 4.2 Hz), 4.45 (1H, br s), 4.37 (1H, d, *J* 4.2 Hz), 4.21 (3H, s), 4.00 (3H, s), 3.86 (3H, s), 3.85 (3H, s), 3.84 (3H, s), 3.31 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 193.9 (*C*), 164.4 (*C*), 158.8 (*C*), 153.6 (*C*), 149.1 (*C*), 140.9 (*C*), 136.3 (*C*), 131.7 (*C*), 130.3 (*C*H), 129.4 (*C*), 128.3 (*C*H), 124.0 (*C*), 120.1 (*C*H), 110.9 (*C*H), 105.6 (*C*H), 81.8 (*C*), 63.8 (*C*H), 61.8 (CH_3), 61.5 (CH_3), 61.2 (CH_3), 60.7 (CH_3), 58.8 (*C*H), 56.5 (CH_3), 55.4 (CH_3).

Mass $^m/_z$ (ES^+) 923 ($[2M + K]^+$, 18%), 907 ($[2M + Na]^+$, 54), 481 ($[M + K]^+$, 47), 465 ($[M + Na]^+$, 100), 443 (MH^+, 14).
$^m/_z$ (ES^+) found 443.1699, MH^+. $C_{24}H_{27}O_8$ requires 443.1697.

Xray

(*E*)-4-Hydroxy-2,3-dimethoxy-4-{2-[2-(2,3,4-trimethoxyphenyl)vinyl]phenylcyclobut-2-enone, (*E*)-38



(*E*)-**38**, 78%

To a solution of (*Z*)-1,2,3-trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene (520 mg, 1.49 mmol) in chloroform (20 mL) was added a solution of iodine (38 mg, 0.149 mmol) in chloroform (5 mL). After 64 h at RT the reaction mixture was diluted with DCM (30 mL), washed with sat. $Na_2S_2O_3$ (30 mL) and water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was recrystallised from hexane to afford (*Z*)-1,2,3-trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene (518 mg, 1.48 mmol, 99%) as a pale yellow crystalline solid.

mp 93-95 °C (hexane).

IR ν_{max} (neat, cm^{-1}) 3032 w, 2964 w, 2840 w, 1593 m, 1492 s, 1464 s, 1412 s, 1226 m, 1091 s, 1014 s, 946 s, 750 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.71 (1H, dd, *J* 8.0, 1.5 Hz), 7.59 (1H, dd, *J* 8.0, 1.0 Hz), 7.42 (1H, d, *J* 16.4 Hz), 7.38 (1H, d, *J* 8.8 Hz), 7.32 (1H, t, *J* 8.0 Hz), 7.27 (1H, d, *J* 16.4 Hz), 7.11 (1H, td, *J* 8.0, 1.5 Hz), 6.74 (1H, d, *J* 8.8 Hz), 3.94 (3H, s), 3.92 (3H, s), 3.91 (3H, s).

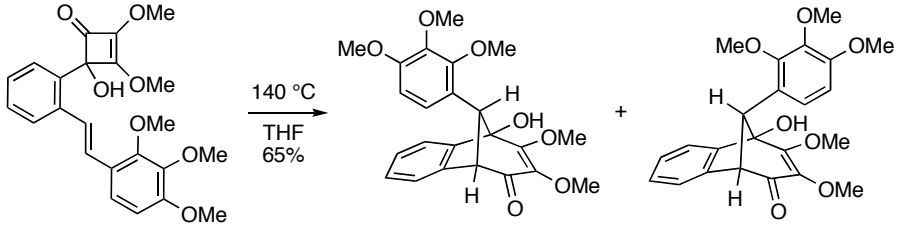
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 153.9 (*C*), 152.2 (*C*), 142.7 (*C*), 137.9 (*C*), 133.2 (*C*H), 128.6 (*C*H), 127.7 (*C*H), 126.9 (*C*H), 126.9 (*C*H), 126.0 (*C*H), 124.4 (*C*), 124.2 (*C*), 121.5 (*C*H), 108.1 (*C*H), 61.6 (CH_3), 61.1 (CH_3), 56.3 (CH_3).

Mass $^{m}/_{z}$ (EI) 350/348 (M^+, 92), 254 (48), 238 (100), 211 (65), 195 (60), 168 (83), 152 (68), 140 (91), 127 (93).

CHN Found C 58.12%, H 4.86%; $C_{17}H_{17}BrO_3$ requires C 58.47%, H 4.91%.

To a solution of ^{t}BuLi (1.15M in pentane, 0.83 mL, 0.950 mmol) in THF (2.5 mL) at –78 °C was added a solution of (*Z*)-1,2,3-trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene (166 mg, 0.475 mmol) in THF (2.5 mL) over 2 min. After 30 min dimethyl squarate (68 mg, 0.475 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone (*E*)-**38** (152 mg, 0.369 mmol, 78%) as a pale yellow oil, which was used immediately in the next reaction.

***rel*-(5*S*,9*S*,10*R*)- and *rel*-(5*S*,9*S*,10*S*)-9-Hydroxy-7,8-dimethoxy-10-(1,2,3-trimethoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 39 and 52**



(*E*)-**38** **39** ~ 5 : 4 **52**

Cyclobutenone (*E*)-**38** (152 mg, 0.369 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 50% EtOAc/petrol) to afford a 5 : 4 mixture of benzobicyclo[3.2.1]octenones **39** and **52** (99 mg, 0.240 mmol, 65%) as a pale yellow oil. Data obtained on the mixture was identical to that described for **39** with the following additional signals attributed to **52**:

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.45-7.38 (2H, m), 7.32-7.21 (2H, m), 6.98 (1H, d, *J* 8.8 Hz), 6.64 (1H, d, *J* 8.8 Hz), 4.97 (1H, s), 4.32 (1H, d, *J* 4.3 Hz), 4.28 (1H, d, *J* 4.3 Hz), 4.07 (3H, s), 3.94 (3H, s), 3.88 (3H, s), 3.85 (3H, s), 3.41 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.2 (*C*), 162.9 (*C*), 153.4 (*C*), 152.5 (*C*), 150.0 (*C*), 142.4 (*C*), 139.4 (*C*), 130.0 (*C*), 127.6 (*C*H), 127.5 (*C*H), 124.7 (*C*H), 124.4 (*C*H), 121.8 (*C*), 121.1 (*C*H), 107.4 (*C*H), 82.1 (*C*), 64.4 (*C*H), 61.4 (CH_3), 61.2 (CH_3), 61.0 (CH_3), 60.7 (CH_3), 59.1 (CH_3), 56.2 (*C*H).

REFERENCES FOR SUPPORTING INFORMATION.

1. S. T. Perri, H. J. Dyke, H. W. Moore *J. Org. Chem.* **1989**, *54*, 2032-2034.
2. H. Liu, C. S. Tomooka, H. W. Moore *Synth. Commun.* **1997**, *27*, 2177-2180.
3. A. Enhsen, K. Karabelas, J. M. Heerding, H. W. Moore *J. Org. Chem.* **1990**, *55*, 1177-1185.
4. K. Tanemura, T. Suzuki, Y. Nishida, K. Satsumabayashi, T. Horaguchi *Chem. Commun.* **2004**, 470-471.
5. J. G. Rodríguez, R. Martín-Villamil, A. Lafuente *Tetrahedron* **2003**, *59*, 1021-1032.
6. T. Rajamannar, K. K. Balasubramanian *Tetrahedron Lett.* **1988**, *29*, 5789-5792.
7. A. McCoubrey *J. Chem. Soc.* **1951**, 2931-2935.
8. M. Koreeda, Y. Wang, L. Zhang *Org. Lett.* **2002**, *4*, 3329-3332.
9. a. D. C. Harrowven, I. L. Guy, L. Nanson *Angew. Chem. Int. Ed.* **2006**, *45*, 2242-2245. b. D. C. Harrowven, I. L. Guy, M. Howell, G. Packham *SynLett* **2006**, in press (s-2006-948200).
10. P. Appukkuttan, W. Dehaen, E. Vander Eycken *Org. Lett.* **2005**, *7*, 2723-2726.
11. B. S. Davidson, K. A. Plavcan, J. Meinwald *J. Org. Chem.* **1990**, *55*, 3912-3917.