A concise, convergent total synthesis of monocerin

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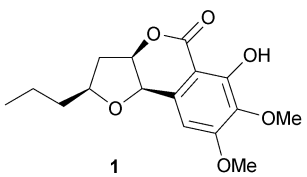
A concise and convergent eight-step synthesis of the antifungal metabolite monocerin **1** is reported. The key step involves an allylsilane metathesis/aldehyde condensation sequence to establish the core 2,3,5-trisubstituted tetrahydrofuran. End-game approaches based around intramolecular Heck chemistry revealed an interesting example of formal 6-*endo* cyclisation, the origin of which was probed using model substrates. The synthesis was ultimately completed by a strategy involving stepwise oxidative cleavage of the C3-ethenyl substituent.

Introduction

Monocerin (**1**) is an anti-fungal and insecticidal natural product that has been isolated from several fungal sources.[1–4] A 15-step total synthesis of racemic monocerin was reported in 1989 by Mori, alongside a 19-step asymmetric variant.[5] Biosynthetically, monocerin has been found to be of heptaketide origin, and ^{13}C labelling studies suggest the tetrahydrofuran ring arises by intramolecular nucleophilic trapping of a quinonemethide intermediate by a pendant alcohol.[2,6] This thesis was explored in an elegant and successful biomimetic synthesis of monocerin by Simpson in 1992,[7] in which radical benzylic bromination was used to initiate quinonemethide formation and cyclisation.



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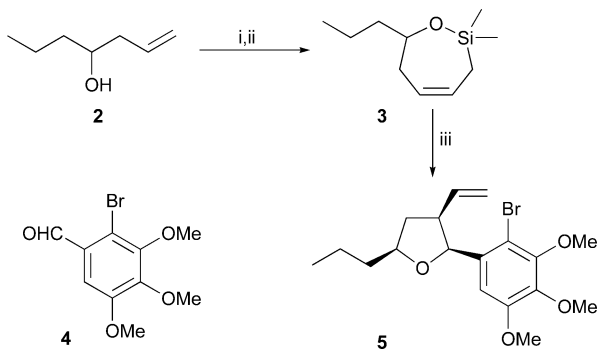
We have developed a stereoselective method for the convergent assembly of tetrahydrofurans based upon the Lewis acid-mediated condensation of cyclic allylsiloxanes (derived by ring-closing metathesis) with aldehydes.[8–12] Using this method, we have prepared 2,3,5-[8] and 2,3,4-trisubstituted[10] as well as 2,3,4,5-tetrasubstituted tetrohydrofurans[11] with various stereochemical motifs in a controlled manner, and have applied them in the synthesis of the diaryllignan virgatusin[11] and the octahydroisobenzofuran core of the eunicellins.[12] With regard to monocerin, we noted that the all-*cis* stereochemistry observed in the formation of 2,3,5-trisubstituted tetrahydrofurans[8] mirrors that observed in the natural product. If we were able to employ the pendant 3-vinyl substituent of such a tetrahydrofuran as a precursor to the oxygen functionality at C3 of monocerin, with retention of stereochemistry, this would allow a concise approach to the total synthesis; further, the convergent nature of the tetrahydrofuran assembly would lend itself well to the further synthesis of analogues[13] as potential antifungals. Herein we describe the successful completion of the target synthesis.

Results and discussion

The requisite coupling partners for the assembly of the target tetrahydrofuran were the allylsiloxane **3** (synthesised from known 4-hydroxyhept-1-ene **2** in two steps by our standard methodology) and the known aldehyde **4**,[14] prepared by bromination of commercial trimethoxybenzaldehyde (Scheme 1).



2 **3** **4** **5**

Scheme 1 *Reagents and conditions*: (i) (allyl)Me_2SiCl, Et_3N, CH_2Cl_2, 0 °C (82%); (ii) 1% $(PCy_3)_2RuCl_2$=CHPh, CH_2Cl_2, rt (95%); (iii) **4**, 1 eq. $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C (86%).

Condensation of **3** and **4** under the previously identified conditions (exposure to boron trifluoride etherate at −78 °C followed by slow warming to room temperature) yielded the desired tetrahydrofuran **5** in 86% yield as a 9 : 1 mixture of diastereoisomers. The all-*cis* relative stereochemistry of the major diastereomer shown was the previously observed stereochemical outcome for 2,3,5-trisubstituted tetrahydrofurans. We have, however, observed in tetrahydrofurans with alternative substitution patterns that the use of boron trifluoride in conjunction with electron-rich aldehydes can lead to predominant formation of 2,3-*trans* isomers by C2-epimerisation of an initially formed *cis*-adduct *via* a stabilised benzylic cation,[10,11] and hence sought confirmation of the assigned stereochemistry. Comparison of diagnostic chemical shift data for both the benzylic proton and the internal vinylic proton for the

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cis and *trans* isomers in each series supports the assignment of **5** as having the stereochemistry shown.† This assignment was eventually confirmed by the successful total synthesis.

Our initial approach to installation of the tricyclic lactone present in monocerin focused on the formation of ketone **6**, which would be accessed by oxidative cleavage of alkene **7**, the product of a 5-*exo* Heck cyclisation of **5** (Fig. 1). We planned that stereoselective insertion of an oxygen between C3 of the tetrahydrofuran and the carbonyl would be possible, either directly by Baeyer–Villiger oxidation, or more likely in a stepwise protocol *via* an enol derivative of **6**. We therefore commenced studies into the Heck reaction.

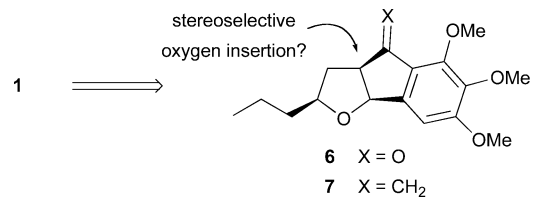
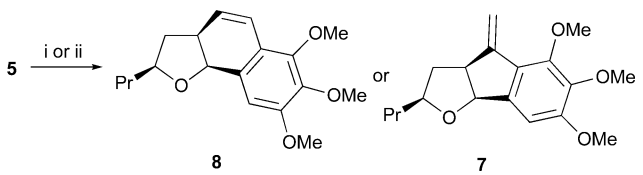


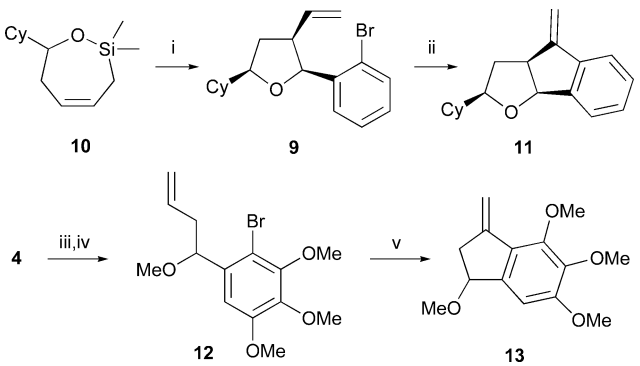
Fig. 1 Proposed approach to monocerin **1** *via* stereoselective oxygen insertion to ketone **6**.

Upon exposure of **5** to standard Heck coupling conditions (palladium(II) acetate, triphenylphosphine and triethylamine), we were surprised to observe that the only identifiable product of the reaction was the undesired 6-*endo* isomer **8**, formed in 67% yield (Scheme 2). Intramolecular Heck reactions of electronically unbiased olefins leading to 6-*endo* products are extremely rare,[15–17] and are usually indicative of some rearrangement of an initially formed 5-*exo* adduct.[15,16] We therefore hoped that the regiochemical outcome might be altered by tuning the reaction conditions. The use of electron-rich alkylphosphines led either to debromination of **5** or simply returned starting material. However, the use of the bidentate ligand bis(diphenylphosphinyl)ferrocene gave an 85% yield of the desired 5-*exo* adduct **7**.



Scheme 2 *Reagents and conditions*: (i) 3% $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, heat (67%, **8**); (ii) 3% $Pd(OAc)_2$, dppf, Et_3N, MeCN, heat (85%, **7**).

We were intrigued by this unusual regiochemical outcome and undertook some model studies to clarify the origin of the selectivity. We suspected that the highly electron-rich nature of the aryl bromide was at least partly responsible, and we therefore examined the behaviour of the simplified model **9**, readily prepared from siloxane **10** (Scheme 3). Upon exposure to the same standard Heck conditions which had given the 6-*endo* adduct with **5**, we instead found that **9** underwent a clean and high-yielding (84%) cyclisation to give the 5-*exo* isomer **11**. This result confirmed that the highly electron-rich arene was playing some part in the formation of the 6-*endo* product, and we therefore prepared the acyclic substrate **12** in two steps from aldehyde **4**. Treatment of **12** with palladium(II) acetate and triphenylphosphine (with potassium carbonate as base) gave an 80% yield of the 5-*exo* adduct **13**, which confirmed that the highly hindered nature of the tricyclic carbopalladation adduct(s) formed from **5** was also responsible for the anomalous regiochemical outcome.



Scheme 3 *Reagents and conditions*: (i) (*o*-Br)PhCHO, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to rt (81%); (ii) 3% $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, heat (84%); (iii) allylMgBr, Et_2O, −15 °C to rt (93%); (iv) NaH, MeI, THF, 0 °C to rt (89%); (v) 10% $Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, heat (80%).

A possible explanation for the observed behaviour is that all of the substrates undergo an initial 5-*exo* cyclisation, which for substrates **5**/**9** generates tricyclic intermediates of type **14**/**15** (Fig. 2). If β-hydride elimination to the *exo*-methylene products **7**/**11** is slow in these highly hindered intermediates, the opportunity for the intervention of the electron-rich arene arises. This would presumably be triggered by π,η^1 complexation of the arene to the palladium, following dissociation of one of the phosphine ligands, in a complex such as **16**. Complexes of the type **16** have previously been observed and characterised by X-ray crystallography.[18] The precise mechanism for the conversion of **16** to the 6-*endo* adduct **8** is not known, but a potential pathway is indicated. Nucleophilic substitution at palladium by electron-rich π-systems is well documented,[19,20] and would in this case lead to a palladacyclobutane. Reductive elimination of palladium generates a phenonium ion, which could then undergo fragmentation and loss of a proton to generate **8**. Skeletal migrations of aryl groups in formal E1 processes, likely proceeding *via* phenonium ions, are known.[21] Regardless of the actual mechanism for the formation of **8**, the intermediacy of complex **16** *en route* to the 6-*endo* product does, however, help to explain the experimental observations. Using substrate **9**, the less electron-rich phenyl substituent would be less likely to form a complex of type **16** and would therefore undergo slow β-hydride elimination to the observed 5-*exo* product **11**. Likewise, although substrate **12** contains the same highly electron-rich arene as **5**, the reduced steric constraints in the initially formed 5-*exo* carbopalladation product means that

† We have previously observed in the 2,3,4-trisubstituted series that the benzylic tetrahydrofuran proton in the 2,3-*cis* diastereomer appears between 5.18 and 5.08 ppm (*cf.* 4.64–4.52 ppm for the *trans*-diastereomer),[10] a trend mirrored in previously synthesised 2,3,5-trisubstituted tetrahydrofurans (5.20–5.01 ppm for *cis*-diastereomer).[8] The benzylic proton of **5** appears at 5.20 ppm. Additionally, for 2-aryl-2,3,5-trisubstituted tetrahydrofurans, the internal vinylic proton for the major *cis*-diastereomer routinely occurs at *ca.* 5.2 ppm (*cf.* 5.7–6.0 ppm for the minor *trans*-isomer):[8] the signals for this proton in **5** occur at 5.18 and 5.94 ppm for major and minor isomers respectively.

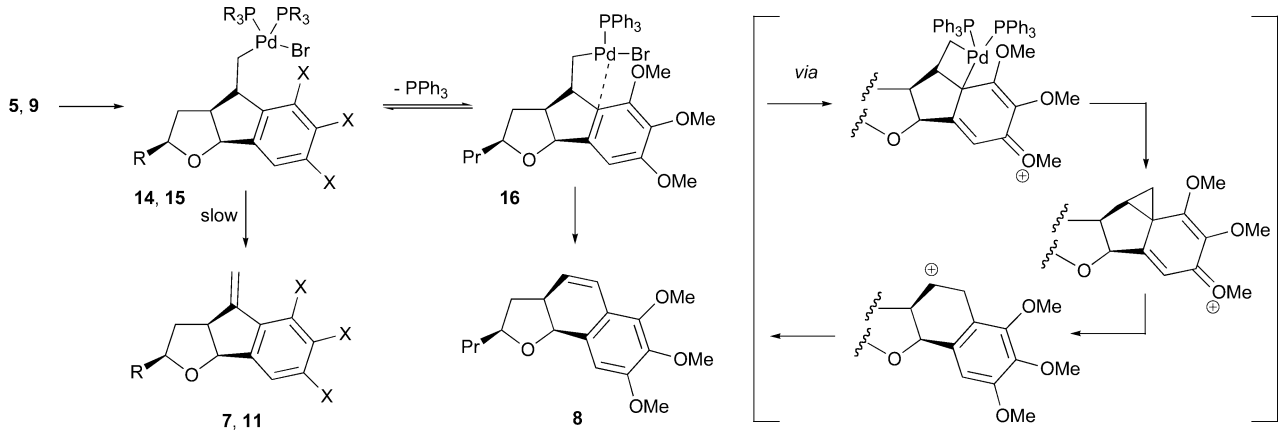
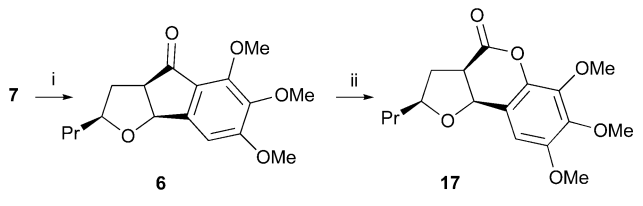


Fig. 2 Diversion of 5-*exo* pathway to formal 6-*endo* product for substrate **5**. (**5**, **14**, **7**: R = Pr, X = OMe; **9**, **15**, **11**: R = Cy, X = H).

β-hydride elimination will be too fast to compete with formation of a π,η[1] complex, and again the 5-*exo* product is observed. Finally, the observation that the 5-*exo* product **7** is observed when bidentate phosphines are used as ligands is also explained by this model: the reluctance of the bidentate phosphine to undergo decomplexation due to the chelate effect would disfavour formation of complex **16**, and hence the 'normal' product **7** is observed.

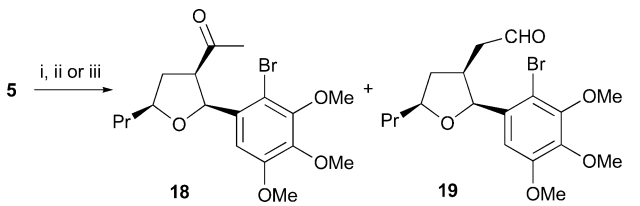
With the alkene **7** in hand, oxidative cleavage to ketone **6** was easily achieved using osmium tetroxide followed by periodate (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) OsO_4, NMO, ^tBuOH–acetone–H_2O, then KIO_4 (67%); (ii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C (76%).

Attempts to install the C3 oxygen directly by Baeyer–Villiger oxidation were unsuccessful, with the sole product of the reaction being the isomeric lactone **17** formed by migration of the electron-rich aryl substituent in preference to the inductively-destabilised secondary alkyl group. Although the migratory tendencies of aryl and secondary alkyl groups are similar,[22] the electronic imbalances caused by the substituents in this case bias the migration exclusively in the undesired direction. We therefore attempted to form silyl enol ethers of ketone **6** as a prelude to oxidative olefin cleavage, but were unable to effect enolate formation using lithium amide bases, with starting material being returned in most cases. We therefore elected to return to the monocyclic series and attempt to effect installation of the C3-oxygenation at this stage.

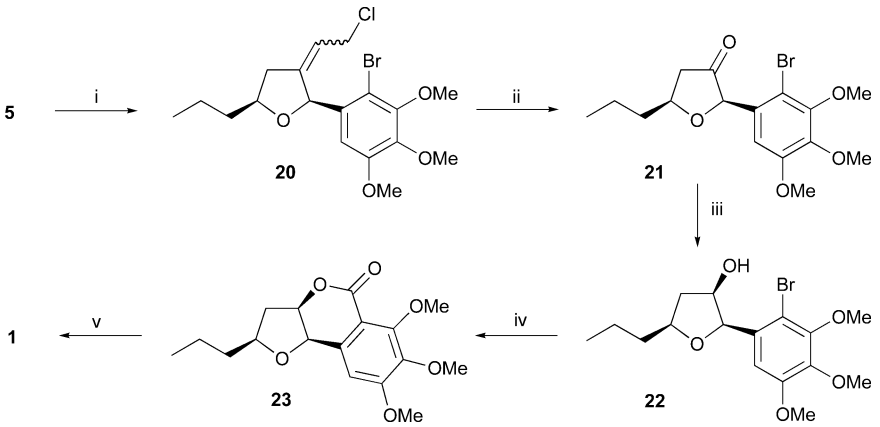
Our first attempts focused again on Baeyer–Villiger oxidation, this time on ketone **18** – here the reluctance of methyl groups to undergo migration ought to bias the regiochemistry in the desired sense.[22] Initial attempts to form **18** by Wacker oxidation of the ethenyl substituent of **5** were complicated by the competing formation of the regioisomeric aldehyde product **19**, using either oxygen or benzoquinone as co-oxidant. Ultimately we were able to direct the regiochemistry by performing sequential oxymercuration/palladium-catalysed oxidation,[23] although high catalyst loadings of palladium and superstoichiometric copper(II) chloride were required to attain high conversions. Under these conditions, a 70% yield of the ketone **18** was obtained, along with 7% of aldehyde **19** (Scheme 5). Disappointingly, however, the ketone **18** proved stubbornly resistant to Baeyer–Villiger oxidation: the use of mCPBA returned starting material, whereas peracetic or pertrifluoroacetic acid led to decomposition of the ketone to unidentified by-products.



Scheme 5 *Reagents and conditions*: (i) 10% $PdCl_2$, O_2, DMF–H_2O (73%, **18** : **19** = 1 : 1); (ii) 10% $PdCl_2$, benzoquinone, perchloric acid, MeCN–H_2O (80%, **18** : **19** = 3 : 2); (iii) $Hg(OAc)_2$, THF–H_2O, then 65 mol% $PdCl_2$, $CuCl_2$ (77%, **18** : **19** = 10 : 1).

Our final approach to monocerin **1** was therefore to install the C3-oxygenation by olefin migration and oxidative cleavage to yield a ketone, which ought to be subject to stereoselective hydride addition from the less hindered face to deliver the desired C3-stereochemistry. Attempts to isomerise the vinyl group to the exocyclic trisubstituted olefin under rhodium catalysis were unsuccessful, but application of Sharpless' allylic chlorination technology using phenylselenenyl chloride gave a 50% yield of allylic chloride **20** as a 5 : 1 mixture of olefin isomers (Scheme 6).[24] Ozonolytic cleavage of the olefin gave ketone **21** in 48% yield. Finally, stereoselective reduction of the ketone with sodium borohydride afforded **22** as a single diastereoisomer in 88% yield.

The final ring closure to the tetrahydrofuro[3,2-*c*][2]benzopyran-5-one ring system was achieved by sequential treatment of the alcohol with one equivalent each of lithium hexamethyldisilazide then butyllithium, quenching the resulting dianion with methyl chloroformate. This gave an 80% yield of the known monocerin methyl ether **23**, which exhibited identical spectroscopic data



Scheme 6 *Reagents and conditions*: (i) PhSeCl, H_2O_2, pyridine, CCl_4, −30 °C (50%); (ii) O_3, CH_2Cl_2, −78 °C, then PPh_3, −78 to 0 °C (48%); (iii) $NaBH_4$, MeOH, 0 °C (88%); (iv) LiHMDS, THF, −40 °C, then BuLi, −60 °C, then MeO_2CCl, −60 °C to rt (80%); (v) BBr_3, CH_2Cl_2, −30 °C (57%).

to that reported in the literature.[5] Application of Mori's conditions for regioselective demethylation of monocerin methyl ether gave a 57% yield of monocerin **1**, whose ^{1}H NMR data was also in agreement with the reported values.[5]

Conclusions

We have completed a concise, 8-step synthesis of monocerin **1** from known alcohol **2** in 6.5% overall yield. The core trisubstituted tetrahydrofuran **5** was assembled using our previously disclosed allylsiloxane/aldehyde condensation chemistry. In the course of attempts to construct the tricyclic ring system by Heck annulation, an unusual dependence of regiochemical outcome upon ligand type was observed. Model experiments show that the observation of formal 6-*endo* products is due to a combination of the hindered nature of the tricyclic system and the highly electron-rich character of the aryl bromide, and suggest possible pathways proceeding *via* initial 5-*exo* ring-closure followed by rearrangement to the 6-*endo* product mediated by the electron-rich arene. Successful conclusion of the total synthesis was instead achieved by oxidative removal of the ethenyl side-chain of **5**, followed by stereoselective reduction of the resulting ketone and cyclocarbonylation of the hydroxy aryl bromide. The current work provides further evidence of the synthetic utility of allylsiloxane/aldehyde condensation chemistry for the rapid elaboration of tetrahydrofuran-containing natural products.[25]

Experimental

All dry glassware was oven-dried at 150 °C overnight or flame-dried prior to use. All reactions in anhydrous solvent were carried out under a dry nitrogen atmosphere. Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}). Visualisation was accomplished with UV light (254 nm), acidic ammonium molybdate(IV) or potassium permanganate. Flash column chromatography was performed on Merck Kieselgel 60 (200–300 mesh) under gentle pressure from hand bellows.

^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX250, JEOL-GSL270, Bruker DRX300 and DPX300 and Bruker Avance 500 spectrometers. Chemical shifts are expressed in part per million (δ) relative to tetramethylsilane, and are referenced to (residual protic) solvent; coupling constants (J) are expressed in Hertz. Infrared spectra were recorded on a Perkin Elmer 683 Infrared Spectrometer. Mass spectra were recorded on a VG Autospec Q or Micromass Platform II spectrometer under chemical ionisation (CI) with ammonia, or under electrospray ionisation (ES) on a Bruker micrOTOF instrument. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected.

Tetrahydrofuran and dichloromethane for use as reaction solvents were dried by prolonged heating under reflux over, and distillation from, sodium/benzophenone ketyl and calcium hydride respectively.

4-Allyldimethylsilyloxy-1-pentene

To a solution of allylchlorodimethylsilane (1.46 ml, 10.0 mmol), in DCM (60 ml) at 0 °C was added dropwise *via* cannula a solution of triethylamine (1.54 ml, 11.0 mmol) and alcohol **2** (1.26 g, 11.0 mmol) in DCM (40 ml). The mixture was stirred at 0 °C for 90 min and the reaction then quenched by the addition of a saturated solution of $NaHCO_3$ (50 ml). The mixture was separated and the aqueous layer washed with DCM (3 × 15 ml). The combined organic extracts were washed with brine (50 ml), water (50 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on basic alumina (eluent petrol) to yield the title compound as a clear oil (1.73 g, 82%): ν_{max}/cm^{-1} 3015, 1632, 1255, 1158, 1027, 1042, 837. ^{1}H NMR ($CDCl_3$; 250 MHz) δ 5.77 (2H, m, 2 × CH=CH_2), 5.01 (4H, m, 2 × CH=CH_2), 3.69 (1H, app. p, J 5.7, OCH), 2.20 (2H, app. t, J 6.6, CH_2–C=C), 1.62 (2H, d, J 7.9, Si–CH_2), 1.46–1.26 (4H, m, -$(CH_2)_2$), 0.93 (3H, t, J 6.8, Me), 0.11 (6H, s, $SiMe_2$). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 135.3, 134.3, 116.7, 113.5, 72.2, 42.1, 39.2, 25.2, 18.8, 14.1, −1.8. m/z (CI^+/NH_3) 230 (M + NH_4), 188, 171, 116, 74. HRMS (CI^+/NH_3) calc. for $[M + NH_4]^+$: $C_{12}H_{28}NOSi$ = 230.1940. Found 230.1952.

2,2-Dimethyl-7-propyl-1-oxa-2-sila-4-cycloheptene 3

To a thoroughly degassed solution of the above siloxane (300 mg, 1.4 mmol) in DCM (70 ml) was added $[Cl_2(PCy_3)_2Ru$=CHPh] (11 mg, 1 mol%) in one portion. The mixture was stirred at room temperature for 4 h, then evaporated *in vacuo* and purified

through a short pad of silica (eluent 15% EtOAc–hexane) to yield **3** as a clear oil (295 mg, 95%). Found C 65.06, H 10.97; calc. for $C_{10}H_{20}OSi$ C 65.21, H 11.00%. ν_{max}/cm^{-1} 3021, 2959, 1641, 1455, 1421, 1266, 1081, 1040, 896, 838 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 5.77 (1H, dt, *J* 10.4, 6.8, C=CH), 5.54 (1H, dt, *J* 10.4, 6.3, C=CH), 4.85 (1H, app. p, *J* 7.5, OCH), 2.26–2.24 (2H, m, $C{=}CCH_2$), 1.52 (2H, d, *J* 7.0 $SiCH_2$), 1.51–1.26 (4H, m, $-(CH_2)_2$), 0.89 (3H, t, *J* 6.9, Me), 0.11 (3H, s, SiMe), 0.10 (3H, s, SiMe). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 127.6, 124.2, 72.4, 40.4, 37.0, 19.1, 18.8, 14.1, −1.6, −1.8. *m/z* (CI^+/NH_3) 202 (M + NH_4), 185 (M + H), 137, 92,81, 74. HRMS (CI^+/NH_3): *m/z* calc. for $[M + H]^+$: $C_{10}H_{21}OSi$ = 185.1361. Found 185.1360.

(2*SR*,3*SR*,5*SR*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-3-ethenyl-5-propyltetrahydrofuran 5

To a solution of siloxane **3** (1.50 g, 8.2 mmol) in dry DCM (41 ml) at −78 °C, was added $BF_3{\cdot}OEt_2$ (1.01 ml, 8.2 mmol) and the solution stirred for 5 min prior to the addition of aldehyde **4** (2.24 g, 8.2 mmol). The mixture was stirred at −78 °C for 2 h and then allowed to warm to room temperature over 18 h. The reaction was quenched by the addition of brine (50 ml) and the mixture extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with water (50 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography on silica gel (eluent 10% ether–petrol) to yield **5** as an inseparable 90 : 10 mixture of diastereomers (2.71 g, 86%). Anal. calc. for $C_{18}H_{25}BrO_4$: C 55.93, H 6.48%. Found: C 56.14, H 6.49. ν_{max}/cm^{-1} 2959, 2936, 1569, 1484, 1427, 1328, 1108, 852. ^1H NMR ($CDCl_3$, 250 MHz) (major diastereomer) δ 6.91 (1H, s, Ar-H), 5.20 (1H, d, *J* 7.5, Ar–CHO), 5.19–5.15 (1H, ddd, *J* 17.0, 10.0, 9.2, C*H*=CH_2), 4.88 (1H, app. dt, *J* 17.0, 0.9, CH=C*H*H′), 4.67 (1H, app. dt, *J* 10.0, 0.9, CH=CH*H*′), 3.99–3.92 (1H, m, C_3H_7CHO), 3.85 (6H, app. s, 2 × OMe), 3.86 (3H, s, OMe), 3.25 (1H, app. p, *J* 8.1, CH–C=C), 2.29 (1H, dt, *J* 12.7, 6.3, C*H*H′–CC=C), 1.79 (1H, ddd, *J* 12.7, 9.4, 6.8, CH*H*′–CC=C), 1.76–1.40 (4H, m, $-(CH_2)_2$), 0.99 (3H, t, *J* 7.3, Me); signals for the minor diastereomer are visible at: 5.94 (1H, app. dt, *J* 16.8, 10.0, 1.0, C*H*=CH_2), 4.05 (1H, m, C_3H_7CHO), 1.93 (1H, ddd, *J* 12.1, 6.6, 5.4, C*H*H′CC=C). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (major diastereomer) 141.8, 138.4, 138.1, 137.2, 136.0, 135.2, 115.2, 107.0, 84.0, 78.9, 61.0, 56.0, 51.6, 46.3, 45.9, 38.5, 37.4, 19.5. *mlz* (CI^+/NH_3) 404/402 (M + NH_4, $^{81}Br/^{79}Br$), 386/384, (M + H, $^{81}Br/^{79}Br$), 305, 276, 274, 233. HRMS (CI^+/NH_3): *m/z* calc. for $[M + H]^+$: $C_{18}H_{26}{}^{81}BrO_4$ 387.0994. Found 387.0999.

(2a*SR*,3a*SR*,9*SR*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydronaptho[1,2-*b*]furan 8

To a solution of olefin **5** (39 mg, 0.10 mmol) in acetonitrile (2 ml) was added triphenylphosphine (52 mg, 0.20 mmol), triethylamine (50 µl, 0.36 mmol) and palladium acetate (0.7 mg, 3 mol%). The resulting dark solution was heated under reflux for 16 h, allowed to cool to room temperature and quenched by the addition of a saturated $NaHCO_3$ solution (5 ml). This solution was extracted with EtOAc (5 × 5 ml), and the combined organic extracts were washed with brine (5 ml), water (5 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 10% ether–petrol) to yield **8** (20 mg, 67%) as a yellow oil. ν_{max}/cm^{-1} 2957, 2932, 1643, 1569, 1108, 832. ^1H NMR ($CDCl_3$, 250 MHz) δ 6.97 (1H, s, Ar-H), 6.26 (1H, d, *J* 9.5, Ar–CH=C), 5.50 (1H, dd, *J* 5.6, 9.5, CH=CAr), 5.31 (1H, d, *J* 7.8, Ar–CHO), 4.06–3.98 (1H, m, C_3H_7CHO), 3.85 (3H, s, OMe), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.55–3.46 (1H, m, CH–C=C), 2.38 (1H, ddd, 11.2, 5.9, 4.3, C*H*H′CC=C), 1.52–1.12 (5H, m, CH*H*′CC=C and $-(CH_2)_2$), 1.04–0.99 (3H, t, *J* 7.1, Me). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 132.5, 130.5, 130.1, 128.2, 126.9, 126.0, 125.0, 107.0, 82.3, 79.1, 61.0, 60.9, 56.1, 45.9, 38.9, 39.0, 37.6, 19.5. *m/z* (CI^+/NH_3) 305 (M + H), 291, 233. HRMS (CI^+/NH_3): *m/z* calc. for $[M + H]^+$: $C_{18}H_{25}O_4$ requires 305.1753. Found 305.1755.

(2*SR*,3a*SR*,8b*SR*)-4,5,6-Trimethoxy-4-methylene-2-propyl-3,3a,4,8b-tetrahydro-2*H*-indene[1,2-*b*]furan 7

To a solution of olefin **5** (l50 mg, 0.38 mmol) in acetonitrile (8 ml) was added dppf (399 mg, 0.72 mmol), triethylamine (0.10 ml, 0.72 mmol) and palladium acetate (2.5 mg, 3 mol%). The resulting dark solution was heated under reflux for 16 h, allowed to cool to room temperature and quenched by the addition of a saturated $NaHCO_3$ solution (5 ml). This solution was extracted with EtOAc (5 × 10 ml) and the combined organic extracts were washed with brine (15 ml), water (15 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 10% ether–petrol) to yield **7** (95 mg, 85%) as a yellow oil. ν_{max}/cm^{-1} 2959, 2934, 1636, 1596, 1471, 1418, 1338, 1132, 1029, 743. ^1H NMR ($CDCl_3$, 250 MHz) δ 6.80 (1H, s, Ar-H), 5.80 (1H, d, *J* 1.2, Ar–C=C*H*H′), 5.21 (1H, d, *J* 7.4, ArCHO), 5.06 (1H, d, *J* 1.2, Ar–C=CH*H*′), 3.91–3.86 (1H, m, C_3H_7CHO), 3.92 (3H, s, OMe), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 3.57–3.50 (1H, m, CHC=C), 2.43 (1H, m, C*H*H′CC=C) 1.49–1.38 (5H, m, CH*H*′CC=C and $-(CH_2)_2$), 0.91–0.87 (3H, t, *J* 7.2, Me). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 150.4, 128.5, 128.3, 126.3; 126.0, 125.0, 122.9, 106.8, 84.1, 81.7, 62.0, 60.1, 56.0, 49.2, 48.6, 39.5, 37.2, 19.6. *m/z* 305 (M + H), 205, 196, 77. HRMS *m/z* calc. for $[M + H]^+$: $C_{18}H_{25}O_4$ requires 305.1753. Found 305.1761.

(2*SR*,3*SR*,5*RS*)-2-(2′-Bromophenyl)-5-cyclohexyl-3-ethenyltetrahydrofuran 9

To a solution of siloxane **10** (45 mg, 0.20 mmol), in dry DCM (1 ml) at −78 °C, was added $BF_3{\cdot}OEt_2$ (20 µl, 0.20 mmol) and the solution stirred for 5 min prior to the addition of 2-bromobenzaldehyde (25 mg, 0.20 mmol). The mixture was stirred at −78 °C for 2 h and then allowed to warm to room temperature over 18 h. The reaction was quenched by the addition of brine (10 ml) and the mixture extracted with EtOAc (3 × 10 ml). The combined organic layers were washed with water (10 ml), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo.* The residue was purified by chromatography on silica gel (eluent 5% ether–petrol) to yield **9** as an inseparable 96 : 4 mixture of diastereomers (54 mg, 81%). ν_{max}/cm^{-1} 2924, 1612, 1069, 1022, 993, 843. ^1H NMR ($CDCl_3$, 250 MHz) (major diastereomer) δ 7.50 (1H, dd, *J* 7.6, 1.7, Ar-H), 7.47 (1H, dd, *J* 7.9, 1.1, Ar-H), 7.29 (1H, td, *J* 7.5, 1.2, Ar-H), 7.12 (1H, td, *J* 7.9, 1.7. Ar-H), 5.21 (1H, d, *J* 7.4, OCHAr), 5.26–5.19 (1H, m, C*H*=CH_2), 4.91 (1H, ddd, *J* 17.0, 2.0, 0.8, CH=C*H*H′), 4.68 (1H, ddd, *J* 10.1, 2.0, 0.8, CH=CH*H*′), 3.69 (1H, ddd, *J* 9.4, 7.4, 6.2, CyC*H*O), 3.33 (1H, app. q, *J* 7.9,

CHC=C), 2.24 (1H, ddd, *J* 12.5, 8.3, 6.2, C*H*H′C=C), 2.05 (1H, m, CH of Cy), 1.91–1.60 (7H, m, 3 × (CH_2) and CH*H*′CC=C), 1.49–1.20 (4H, m, 2 × CH_2); signals for minor diastereomer visible at 6.03 (1H, m, C*H*=CH_2), 5.02 (1H, m, CH=C*H*H′), 3.86 (1H, m, CyC*H*O) : ^{13}C NMR ($CDCl_3$, 62.5 MHz) (major diastereomer) δ 139.6, 138.5, 132.1, 128.3, 126.9, 121.9, 114.5, 83.4, 81.9, 46.1, 43.0, 30.0, 29.2, 26.6, 26.1, 25.9; *m*/*z* (CI^+/NH_3) 354/352 (M + NH_4, $^{81}Br/^{79}Br$), 337/335 (M + H, $^{81}Br/^{79}Br$), 317, 239, 150, 108. HRMS (CI^+/NH_3): *m*/*z* calc. for $[M + H]^+$: $C_{18}H_{24}{}^{79}BrO$ requires 335.1012. Found 335.1011.

(2*SR*,3a*SR*,8b*SR*)-2-Cyclohexyl-4-methylene-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan 11

To a solution of **9** (50 mg, 0.15 mmol) in acetonitrile (1.5 ml) was added triphenylphosphine (79 mg, 0.30 mmol), triethylamine (0.04 ml, 0.30 mmol) and palladium acetate (l mg, 3 mol%). The resulting dark solution was refluxed for 16 h, allowed to cool to room temperature and the reaction quenched with a saturated solution of $NaHCO_3$ (5 ml). This solution was extracted with EtOAc (5 × 5 ml) and the combined organic extracts washed with brine (15 ml), water (l5 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 1% ether–petrol) to yield **11** (32 mg, 84%) as a clear oil. ν_{max}/cm^{-1} 2962, 1642, 1266, 1071, 740. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.51–7.45 (2H, m, ArH), 7.35–7.21 (2H, m, ArH), 5.52 (1H, d, *J* 1.9, Ar–C=C*H*H′), 5.05 (1H, d, *J* 7.6, ArCHO), 5.05 (1H, d, *J* 1.9, Ar–C=CH*H*′), 3.68 (1H, ddd, *J* 10.1, 7.8, 5.0, CH–C=C), 3.60 (1H, app. p, *J* 7.6, CyCHO), 2.36 (1H, ddd, *J* 12.4, 9.4, 5.0, C*H*H′CCC=C), 1.94–1.89 (1H, m, CH of Cy), 1.67–1.40 (7H, m, 3 × CH_2 and CH*H*′CC=C), 1.41–1.21 (4H, m, 2 × CH_2). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 141.2, 138.6, 129.0, 128.7, 127.3, 126.1, 122.5, 104.3, 87.0, 84.1, 42.5, 37.4, 30.3, 29.1, 26.5, 25.9. *m*/*z* (CI^+/NH_3) 272 (M + NH_4), 255 (M + H), 237, 171, 143, 129. HRMS (CI^+/NH_3): *m*/*z* calc. for $[MH]^+$: $C_{18}H_{23}O$ requires 255.1749. Found 255.1759.

1-(2-Bromo-3,4,5-trimethoxyphenyl)but-3-en-1-ol

To a solution of 2-bromo-3,4,5-trimethoxybenzaldehyde (935 mg, 3.40 mmol) in Et_2O (35 ml) at −15 °C was added a 1.0 M solution of allylmagnesium bromide in Et_2O (5.10 ml, 5.10 mmol) slowly. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was cooled to 0 °C, a saturated solution of NH_4Cl (22 ml) slowly added and the flask warmed to room temperature. This solution was extracted with Et_2O (2 × 60 ml) and the combined organic extracts dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 40% EtOAc–petrol) to yield the title compound as a colourless oil (997 mg, 93%): ν_{max}/cm^{-1} 3435, 2938, 1569, 1481, 1426, 1394, 1324, 1195, 1162, 1105, 1009. ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.97 (1H, s, Ar H), 5.95–5.86 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, C*H*=CH_2), 5.24–5.19 (2H, m, CH_2=CH), 5.10 (1H, dt, *J* = 8.6, 3.0 Hz, CHO), 3.89 (6H, s, 2 × CH_3O), 3.88 (3H, s, CH_3O), 2.66–2.62 (1H, m, 1H of CH_2CHO), 2.34–2.27 (1H, m, 1H of CH_2CHO), 2.19 (1H, d, *J* = 3.0 Hz, OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.0, 150.4, 142.1, 138.5, 134.5, 118.9, 107.8, 105.8, 71.8, 61.1, 61.0, 56.1, 42.2. HRMS (ES): *m*/*z* calc. for $[M + Na]^+$: $C_{13}H_{17}{}^{79}BrNaO_4$ requires 339.0202. Found 339.0191.

2-Bromo-3,4,5-trimethoxy-1-(1-methoxybut-3-enyl)benzene 12

To a solution of the above alcohol (997 mg, 3.15 mmol) in THF (32 ml) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 631 mg, 15.77 mmol) and iodomethane (0.98 ml, 15.77 mmol) and the resulting solution stirred for 5 min at 0 °C and a further 18 h at room temperature. The reaction mixture was cooled to 0 °C and H_2O (15 ml) added dropwise. Et_2O (35 ml) was added and the biphasic solution partitioned. The aqueous layer was washed with Et_2O (3 × 40 ml) and the combined organic extracts dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 25% ether–petrol) to yield the title compound as a colourless oil (928 mg, 89%): ν_{max}/cm^{-1} 2978, 2936, 2825, 1568, 1480, 1426, 1394, 1350, 1323, 1235, 1195, 1163, 1105, 1010, 921. ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 6.83 (1H, s, Ar H), 5.88 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, C*H*=CH_2), 5.13–5.05 (2H, m, CH_2=CH), 4.65 (1H, dd, *J* = 8.3, 4.0 Hz, CHO), 3.90, 3.89, 3.87, 3.27 (4 × 3H, s, CH_3O), 2.49–2.44 (1H, m, 1H of CH_2CHO), 2.39–2.33 (1H, m, 1H of CH_2CHO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 150.5, 142.2, 136.5, 134.6, 117.0, 109.1, 105.6, 81.9, 61.1, 61.0, 57.2, 56.2, 41.1. HRMS (ES): *m*/*z* calc. for $[M + Na]^+$: $C_{14}H_{19}{}^{79}BrNaO_4$ requires 353.0359. Found 353.0362.

1,4,5,6-Tetramethoxy-3-(methylene)indan 13

To a solution of **12** (60 mg, 0.18 mmol) in MeCN (2.2 ml) was added potassium carbonate (150 mg, 1.09 mmol), triphenylphosphine (19.0 mg, 40 mol%) and palladium acetate (4.1 mg, 10 mol%). The resulting dark solution was heated under reflux for 27 h, allowed to cool to room temperature and the reaction quenched with a saturated solution of $NaHCO_3$ (6 ml). This solution was extracted with Et_2O (3 × 6 ml) and the combined organic extracts washed with brine (15 ml), water (15 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 20% ether–petrol) to yield the title compound as a colourless oil (36 mg, 80%): ν_{max}/cm^{-1} 2936, 2823, 1599, 1470, 1417, 1354, 1328, 1109, 1064, 1029. ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.76 (1H, s, Ar H), 5.75 (1H, app. q, *J* = 2.0 Hz, 1H of CH_2=C), 5.11 (1H, app. q, *J* = 1.5 Hz, 1H of CH_2=C), 4.81 (1H, dd, *J* = 6.9, 3.6 Hz, CHO), 3.92, 3.89, 3.87, 3.40 (4 × 3H, s, CH_3O), 3.02 (1H, ddt, *J* = 16.4, 6.9, 1.9 Hz, 1H of CH_2CHO), 2.72 (1H, ddt, *J* = 16.4, 3.6 and 1.9 Hz, 1H of CH_2CHO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.4, 149.2, 143.4, 141.6, 140.3, 124.9, 105.3, 102.6, 80.2, 59.9, 58.9, 55.0, 54.9, 38.3. HRMS (ES): *m*/*z* calc. for $[M + Na]^+$: $C_{14}H_{18}NaO_4$ requires 273.1097. Found 273.1085.

(2S*R*,3a*SR*,8b*SR*)-4,5,6-Trimethoxy-2-propyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-4-one 6

To a solution of the olefin **7** (91 mg, 0.3 mmol) in acetone–water (8:5, 3 ml) was added *N*-methylmorpholine-*N*-oxide (39 mg, 0.33 mmol) and a 5% solution of OsO_4 in *t*-BuOH (0.05 ml). The resulting solution was stirred for 16 h at room temperature until no more starting material was visible by TLC. At this point KIO_4 (76 mg, 0.33 mol) was added and the solution was stirred for

another 40 min. The reaction was then quenched by the addition of a saturated sodium thiosulfate solution (10 ml) and extracted with EtOAc (4 × 10 ml). The combined organic extracts were washed with brine (20 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was purified by chromatography on silica gel (eluent 50% ether–hexane) to yield **6** as a yellow oil (68 mg, 67%). ν_{max}/cm^{-1} 2916, 2815, 1714, 1596, 1294, 1204, 1006, 840. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.89 (1H, s, Ar-H), 5.30, (1H, d, *J* 6.6, ArCHO), 4.09–4.03 (1H, m, C_3H_7CHO), 4.01 (3H, s, OMe), 3.96 (3H, s, OMe), 3.92 (3H, s, OMe), 3.39 (1H, app. dt, *J* 10.4, 6.7, -CHC=O), 2.41 (1H, ddd, *J* 10.4, 7.6, 5.3, CH*H*′CC=O), 1.83–1.38 (5H, m, CH*H*′CC=C and -$(CH_2)_2$), 0.98 (3H, t, *J* 7.1, Me). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 200.4, 163.4, 150.0, 141.2, 139.6, 130.1, 128.1, 104.1, 83.9, 79.6, 61.4, 56.1, 52.9, 37.3, 36.4, 34.5, 19.4. *mlz* (CI^+/NH_3) 307 (M + H), 235, 61. HRMS (CI^+/NH_3): *m/z* calc. for $[M + H]^+$: $C_{17}H_{23}O_5$ requires 307.1545. Found 307.1551.

(2*SR*,3a*RS*,9b*RS*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]-1-benzopyranone 17

To ketone **6** (20 mg, 0.065 mmol) in DCM (6 ml) at 0 °C was added $NaHCO_3$ (11 mg, 0.13 mmol) and *meta*-chloroperbenzoic acid (87 mg, 0.13 mmol). The solution was stirred at 0 °C for 4 h before being allowed to warm to room temperature overnight. Brine (5 ml) was added and the mixture extracted with DCM (5 × 5 ml). The combined organic fractions were washed with brine (10 ml), water (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was purified by chromatography over silica gel (eluent 40% ether–petrol) to yield **17** as a white solid (16 mg, 76%). Mp 82 °C. ν_{max}/cm^{-1} 2957, 1761, 1651, 1593, 1470, 1143, 754. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.70 (1H, s, Ar-H), 4.78, (1H, d, *J* 6.1, ArCHO), 4.06–3.98 (1H, m, C_3H_7CHO), 3.95 (3H, s, OMe), 3.90 (3H, s, OMe), 3.85 (3H, s, OMe), 3.28 (1H, ddd, *J* 9.2, 6.1, 4.7, -CHC=O), 2.59 (1H, ddd, *J* 13.0, 7.7, 9.0, C*H*H′CC=O), 2.58 (1H, ddd, *J* 13.0, 7.4, 4.7, CH*H*′CC=O), 1.61–1.18 (4H, m, -$(CH_2)_2$), 0.93 (3H, t, *J* 7.2, Me). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 175.8, 159.4, 158.6, 155.6, 152.0, 148.9, 149.8, 75.2, 74.3, 61.3, 55.6, 52.9, 41.3, 35.2, 23.5, 22.4, 14.0. *m/z* (CI^+/NH_3) 323 (M + H), 219, 203, 139, 105. HRMS (CI^+/NH_3): *m/z* calc. for $[M + H]^+$: $C_{17}H_{23}O_6$ requires 323.1495. Found 323.1496.

(2*SR*,3*RS*,5*SR*)-2-(2-Bromo-3,4,5-trimethoxy)phenyl-3-(1-oxoethyl)-5-propyltetrahydrofuran 18 and (2*SR*,3*SR*,5*SR*)-2-(2-bromo-3,4,5-trimethoxy)phenyl-3-(2-oxoethyl)-5-propyltetrahydrofuran 19

To a solution of **5** (152 mg, 0.4 mmol) in THF–water (3 : 1, 3.4 ml) was added mercury(II) acetate (128 mg, 0.4 mmol) in a single portion. The resulting yellow suspension was stirred for 48 h at room temperature until no more starting material was visible by TLC. A mixture of palladium acetate (30 mg, 0.26 mmol) and copper(II) chloride (204 mg, 1.20 mmol) was added and the mixture stirred for a further 12 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (10 ml) and extracted with EtOAc (4 × 10 ml). The combined organic extracts were washed with brine (10 ml), water (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was purified by chromatography on silica gel (eluent 12% EtOAc–petrol) to yield **18** as a white crystalline solid (160 mg, 70%). Mp 89 °C. ν_{max}/cm^{-1} 2958, 2361, 1713, 1569, 1483, 1165, 930. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.99 (1H, s, Ar-H), 5.38 (1H, d, *J* 4.3, ArCHCO), 4.11–4.01 (1H, m, C_3H_7CHO), 3.88 (3H, s, OMe), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 3.12 (1H, ddd, *J* 9.8, 4.3, 2.5, C*H*COMe), 2.26 (3H, s, COMe), 2.10 (1H, ddd, *J* 15.0, 5.3, 2.5, C*H*H′CC=O), 1.82–1.73 (1H, ddd, *J* 15.2, 9.6, 3.0, CH*H*′CC=O), 1.62–1.20 (4H, m, -$(CH_2)_2$), 0.99 (3H, t, 7.3, Me). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 208.0, 152.8, 150.2, 142.2, 137.6, l08.0, 106.4, 81.2, 79.2, 77.6, 76.6, 60.9, 55.9, 54.4, 36.7, 35.1, 30.7, 19.4. *m/z* (CI^+/NH_3) 420/418 (M + NH_4, ^{81}Br/^{79}Br), 402/400 (MH, ^{81}Br/^{79}Br), 343/341, 195, 172, 155. HRMS (CI^+/NH_3): *m/z* calc. for $[M + NH_4]^+$: $C_{18}H_{29}{}^{81}BrNO_5$ requires 420.1208. Found 420.1183. Further elution gave **19** as a white solid (11 mg, 7%). Mp 67 °C. ν_{max}/cm^{-1} 3128, 3067, 1735, 1600, 1584, 1548, 1010. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.04 (1H, dd, *J* 4.2, 5.6 CHO), 6.84 (1H, s, Ar-H), 5.26 (1H, d, *J* 6.7, ArCHCO), 3.92–3.86 (1H, m, C_3H_7CHO), 3.88 (3H, s, OMe), 3.87 (6H, app. s, OMe), 3.26 (1H, ddd, *J* 12.3, 6.3, 4.0, C*H*H′CO), 3.14 (1H, ddd, *J* 12.3, 7.2, 4.6, CH*H*′CO), 2.53 (1H, m, CHCC=O), 2.15 (1H, ddd, *J* 14.8, 8.4, 5.3, C*H*H′CCC=O), 1.87–1.32 (5H, m, CH*H*′CCC=O and -$(CH_2)_2$), 0.96 (3H, t, *J* 6.9, Me). *m/z* (CI^+/NH_3) 420/418 (M + NH_4, ^{81}Br and ^{79}Br), 402/400 (M + H, ^{81}Br and ^{79}Br), 343/341, 300, 172, 155. HRMS (CI^+/NH_3): *m/z* calc. for $[M + NH_4]^+$: $C_{18}H_{29}{}^{81}BrNO_5$ requires 420.1208. Found 420.1198.

(2*SR*,3*E*,5*SR*)- and (2*SR*,3*Z*,5*SR*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-2-chloroethylidene-5-propyltetrahydrofuran 20

A solution of **5** in CCl_4 (8 ml) was cooled to 0 °C, and a solution of phenylselenenyl chloride (240 mg, 1.25 mmol) in CCl_4 (2 ml) added dropwise over 10 min. The reaction mixture was allowed to stir at 0 °C for 30 min, and then cooled to −30 °C. Pyridine (100 µl, 1.32 mmol) was then added, followed by aqueous hydrogen peroxide (27.5%, 1.00 ml). The reaction was stirred vigorously for 2 h while being allowed to warm to room temperature. Water (30 ml) was then added, and the solution extracted with DCM (2 × 30 ml). The combined organic extracts were evaporated *in vacuo*, and purified by flash chromatography over silica gel (eluent ether–petrol 1 : 7) to afford 3 products of elimination of the intermediate chloroselenide. First to be eluted was (2*SR*,3*SR*,5*SR*)-2-(2-bromo-3,4,5-trimethoxyphenyl)-3-(1-chloroethylidene)-5-propyltetrahydrofuran (119 mg, 24%). ν_{max}/cm^{-1} 2960, 2938, 2873, 1569, 1482, 1395, 1363, 1330, 1237, 1198, 1107, 1011. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.72 (1H, s, Ar-H), 5.81 (1H, dd, *J* 13.2, 0.5, CHCl), 5.24 (1H, dd, *J* 13.2, 10.1, CH=CCl), 5.13 (1H, d, *J* 7.6, ArCHO), 3.88 (1H, m, C_3H_7CHO), 3.87 (3H, s, OMe), 3.82 (6H, s, OMe), 3.37 (1H, m, C*H*C=C), 2.27 (1H, ddd, *J* 14.3, 8.3, 6.0, C*H*H′CCC=C), 1.31–1.69 (5H, m, CH*H*′CCC=C and -$(CH_2)_2$), 0.96 (3H, t, *J* 7.2, Me). ^{13}C NMR (62.9 MHz; $CDCl_3$) δ 152.6, 150.6, 142.1, 134.5, 133.4, 107.9, 117.2, 106.7, 81.7, 78.8, 61.1, 56.1, 43.9, 38.6, 37.5, 19.4, 14.2 (two MeO signals overlapped). *m/z* (CI^+/NH_3) 438/436 (M[^{35}Cl$^{81/79}$Br] + NH_4), 421/419 (M[^{35}Cl$^{81/79}$Br] + H), 276/274. HRMS *m/z* (CI^+/NH_3) calc. for $[M + NH_4]^+$: $C_{18}H_{28}NO_4{}^{35}Cl^{81}Br$ requires 438.0870. Found 438.0867. Further elution afforded *E*-**20** (206 mg, 42%) ν_{max}/cm^{-1} 2952, 2938, 2860, 1685, 1587, 1568, 1483, 1392, 1338, 1239, 1196, 1165, 1106. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.74 (1H, s, ArH), 5.65 (1H, br s, ArCHO), 5.35 (1H, m, C=C*H*),

4.06 (1H, m, C_3H_7CHO), 4.02 (2H, br d, *J* 7.9, CH_2Cl), 3.89 (3H, s, OMe), 3.88 (3H, s, OMe), 3.83 (3H, s, OMe), 2.87 (1H, br dd, *J* 5.8, 16.1, $CHH'C{=}C$), 2.36 (1H, m, $CHH'C{=}C$), 1.45–1.78 (4H, m, $-(CH_2)_2-$), 0.98 (3H, t, *J* 7.2, Me). ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 153.0, 150.5, 148.1, 142.9, 135.4, 118.0, 109.8, 107.6, 81.9, 77.7, 61.0, 56.0, 42.0, 37.3, 35.5, 19.1, 14.2 (two MeO signals overlapped). *m/z* (CI^+/NH_3) 438/436 ($M[^{35}Cl^{81/79}Br] + NH_4$), 421/419 ($M[^{35}Cl^{81/79}Br] + H$), 385/383, 340, 305. HRMS (CI^+/NH_3): *m/z* calc. for $[M + H]^+$: $C_{18}H_{25}O_4{}^{35}Cl^{81}Br$ requires 421.0604. Found 421.0604. Eluting last was *Z*-**20** (36 mg, 8%). ν_{max}/cm^{-1} 2962, 2933, 2869, 1679, 1569, 1481, 1459, 1450, 1427, 1394, 1332, 1240, 1195, 1164, 1106, 1012, 975, 925, 842, 738. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.69 (1H, s, Ar-H), 5.80 (1H, br s, CHAr), 5.45 (1H, app. tq, *J* 7.9, 2.4, C=C*H*), 4.37 (1H, m, C_3H_7CHO), 4.06 (2H, br d, *J* 7.9, CH_2Cl), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 2.93 (1H, ddt, *J* 16.2, 7.0, 1.6, $CHH'{=}C$), 2.45 (1H, br d, *J* 17.8, $CHH'{=}C$), 1.35–1.75 (4H, m, $-(CH_2)_2-$), 0.96 (3H, t, *J* 7.1, Me). *m/z* (CI^+/NH_3) 438/436 ($M[^{35}Cl^{81/79}Br] + NH_4$), 421/419 ($M[^{35}Cl^{81/79}Br] + H^+$), 402. HRMS *m/z* ($CI^+/NH_3$) calc. for $[M + NH_4]^+$: $C_{18}H_{28}NO_4{}^{35}Cl^{81}Br$ requires 438.0870. Found: 438.0864.

(2*RS*,5*SR*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-one 21

A solution of **20** (305 mg, 0.73 mmol) in DCM (20 ml) was cooled to −78 °C, and ozone bubbled through until a pale blue colour was clearly visible. The ozoniser was then turned off and oxygen allowed to bubble through the solution for 10 min. Triphenylphosphine (200 mg, 0.76 mmol) was added in a single portion and the solution allowed to warm to room temperature and stir for 16 h. The reaction mixture was then evaporated *in vacuo*, and purified by flash chromatography over silica gel (eluent 25% ether–petrol) to afford **21** (129 mg, 48%) as a colourless oil. ν_{max}/cm^{-1} 2958, 2935, 2871, 1760, 1587, 1569, 1483, 1452, 1394, 1351, 1238, 1197, 1145, 1108, 1008, 975, 831. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.68 (1H, s, Ar-H), 5.15 (1H, br s, ArCHO), 4.33 (1H, app. sextet, *J* 5.7, C_3H_7CHO), 3.89 (3H, s, OMe), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 2.67 (1H, dd, *J* 18.1, 5.6, $CHH'CO$), 2.38 (1H, dd, *J* 18.1, 10.6, $CHH'CO$), 2.01–1.70 & 1.54–1.39 ($2 \times 2H$, m, CH_2CH_2), 1.01 (3H, t, *J* 7.3, Me). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 212.1, 152.9, 151.2, 143.4, 130.7, 110.4, 108.1, 83.3, 75.6, 61.0, 56.1, 42.9, 37.5, 18.7, 14.1 (two aliphatic carbon signals overlapped). *m/z* (CI^+/NH_3) 390/392 ($M + NH_4$), 372/374 (M + H), 262/264, 210. HRMS (CI^+/NH_3): *m/z* calc. for $[M + NH_4]^+$: $C_{16}H_{25}NO_5{}^{81}Br$ requires 392.0896. Found. 392.0897.

(2*RS*,3*RS*,5*SR*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-3-hydroxy-5-propyltetrahydrofuran 22

To a solution of **21** (52 mg, 0.14 mmol) in methanol (2 ml) at 0 °C was added sodium borohydride (10 mg, 0.26 mmol). After stirring at 0 °C for 30 min, the reaction was quenched by the addition of water (5 ml). The solution was then extracted with DCM (2×10 ml), and the combined organic extracts evaporated *in vacuo*. The crude product was purified by flash chromatography over silica gel (eluent ether–petrol 1 : 2) to afford **22** (46 mg, 88%) as a colourless oil. ν_{max}/cm^{-1} 3480, 2956, 2869, 1569, 1483, 1465, 1450, 1427, 1394, 1344, 1236, 1197, 1164, 1106, 923. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.05 (1H, s, Ar CH), 4.97 (1H, d, *J* 3.7, CHAr), 4.71 (1H, ddt, *J* 2.5, 6.8, 3.7, $CHOH$), 4.00 (1H, app. p, *J* 6.8, CHPr), 3.88 (3H, s, OMe), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 2.48 (1H, app. p, *J* 7.0, ring C*H*H), 1.34–1.81 (5H, m, ring $CHH + CH_2CH_2$), 1.21 (1H, d, *J* 3.7, O*H*), 0.97 (3H, t, *J* 7.2, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 152.8, 150.5, 142.4, 132.1, 107.4, 108.2, 71.8, 77.7, 84.3, 61.0, 56.0, 40.5, 38.3, 19.4, 14.2 (two aliphatic carbon signals overlapped). *m/z* (CI^+/NH_3) 392/394 ($M + NH_4$), 374/376 (M + H), 277, 275, 168. HRMS (CI^+/NH_3): *m/z* calc. for $[M + NH_4]^+$: $C_{16}H_{27}NO_5{}^{79}Br$ requires 392.1073. Found 392.1082.

(2*SR*,3a*RS*,9b*RS*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-*c*]benzopyran-5-one (monocerin methyl ether, 23)

A solution of **22** (4.1 mg, 10.9 mmol) in THF (1 ml) was cooled to −40 °C. A solution of LiHMDS (1 N in THF, 30 µl, 0.030 mmol) was then added dropwise, and the solution allowed to warm to −30 °C over 10 min, before being cooled to −60 °C. n-Butyllithium (20 µl of a 2 N solution in pentane, 0.040 mmol) was then added dropwise, and the solution allowed to stir for 20 min. Methyl chloroformate (50 µl, 60 mg, 0.650 mmol) was then added dropwise, and the solution allowed to warm to room temperature. After 3 h, the reaction was quenched by the addition of water (5 ml) and the solution extracted with DCM (2×10 ml). The combined organic extracts were then evaporated and purified by flash chromatography over silica gel (eluent ether–petrol 3 : 1) to afford **23** (2.8 mg, 80%), whose NMR data matched that reported in the literature.[5]

(±)-Monocerin 1[5]

A solution of **23** (2.4 mg, 7.4 µmol) was dissolved in DCM (1 ml) and cooled to −30 °C. Boron tribromide (80 µl of a 0.92 M solution in DCM, 7.4 µmol) was then added and the solution allowed to warm to −20 °C. After 90 min, TLC indicated complete consumption of starting material, and the reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (2 ml). Water (2 ml) was then added and the mixture extracted with DCM (2×10 ml). The combined organic extracts were combined and evaporated, and the residue purified by flash chromatography over silica gel (eluent EtOAc–petrol 1 : 3) to afford (±)-monocerin **1** (1.3 mg, 57%) as a film, whose NMR data matched that reported in the literature.[5]

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References

1 D. C. Aldridge and W. B. Turner, *J. Chem. Soc. C*, 1970, 2598.
2 J. F. Grive and M. Pople, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2048.

3 D. J. Robeson and G. A. Strobel, *Agric. Biol. Chem.*, 1982, **46**, 2681.
4 F. E. Scott, T. J. Simpson, L. A. Trimble and J. C. Vederas, *J. Chem. Soc., Chem. Commun.*, 1984, 756.
5 K. Mori and H. Takaishi, *Tetrahedron*, 1989, **45**, 1639.
6 L. C. Axford, T. J. Simpson and C. L. Willis, *Angew. Chem., Int. Ed.*, 2004, **43**, 727.
7 M. P. Dillon, T. J. Simpson and J. B. Sweeney, *Tetrahedron Lett.*, 1992, **33**, 7569.
8 J. H. Cassidy, S. P. Marsden and G. Stemp, *Synlett*, 1997, 1411.
9 For an additional report of the same process mediated by TMSOTf, see: C. Meyer and J. Cossy, *Tetrahedron Lett.*, 1997, **38**, 7861.
10 S. M. Miles, S. P. Marsden, R. J. Leatherbarrow and W. J. Coates, *J. Org. Chem.*, 2004, **69**, 6874.
11 T. Akindele, S. P. Marsden and J. Cumming, *Org. Lett.*, 2005, **7**, 3685.
12 T. Akindele, S. P. Marsden and J. Cumming, *Tetrahedron Lett.*, 2005, **46**, 7235.
13 For syntheses of monocerin analogues, see: K. Mallareddy and S. P. Rao, *Tetrahedron*, 1996, **52**, 8535.
14 E. Brown, J. P. Robin and R. Dhal, *Tetrahedron*, 1982, **38**, 2569.
15 For examples proceeding *via* cyclopropylmethyl-type rearrangements, see: R. Grigg, P. Stevenson and T. Worakun, *Tetrahedron*, 1988, **44**, 2033; Z. Owczarczyk, F. Lamaty, E. J. Vawter and E.-i. Negishi, *J. Am. Chem. Soc.*, 1992, **114**, 10091; M. Terakado, M. Miyazawa and K. Yamamoto, *Synlett*, 1994, 134; B. Møller and K. Undheim, *Tetrahedron*, 1998, **54**, 5789; S. Feutren, H. McAlonan, D. Montgomery and P. J. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1129; H. Nüske, M. Noltemeyer and A. de Meijere, *Angew. Chem., Int. Ed.*, 2001, **40**, 3411.
16 Proceeding *via* reversible deacylpalladation: M. O. Terpko and R. F. Heck, *J. Am. Chem. Soc.*, 1979, **101**, 5281.
17 For 6-*endo* products formed in strained ring systems, see: L. S. Hegedus, M. R. Sestrick, E. T. Michaelson and P. J. Harrington, *J. Org. Chem.*, 1989, **54**, 4141; D. St. C. Black, P. A. Keller and N. Kumar, *Tetrahedron*, 1992, **48**, 7601; J. Cossy, C. Poitevin and D. G. Pardo, *Synlett*, 1998, 251.
18 D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 10323.
19 For reviews of attack of carbon and heteroatom nucleophiles on Pd(II)-ligated olefins, with concomitant substitution at palladium, see: T. Lomberget, D. Bouyssi and G. Balme, *Synthesis*, 2005, 311; G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101; G. Balme, D. Bouyssi, T. Lomberget and N. Monteiro, *Synthesis*, 2003, 2115.
20 Attack of an enamine on Pd(II): R. Grigg and V. Savic, *Chem. Commun.*, 2000, 873.
21 See, for example: J. G. Burr and L. S. Ciereszko, *J. Am. Chem. Soc.*, 1952, **74**, 5426.
22 G. R. Krow, *Org. React.*, 1993, **43**, 251.
23 G. T. Rodeheaver and O. T. Hunt, *J. Chem. Soc., Chem. Commun.*, 1971, 818.
24 B. Chabaud and K. B. Sharpless, *J. Org. Chem.*, 1979, **44**, 4204.
25 For other applications of allylsilane metathesis/condensation chemistry in target synthesis, see: S. Garcia Muñoz, L. Jimenez Gonzalez, M. Alvarez Corral, M. Muñoz Dorado and I. Rodriguez Garcia, *Synlett*, 2005, 3011; L. Jimenez Gonzalez, M. Alvarez Corral, M. Muñoz Dorado and I. Rodriguez Garcia, *Chem. Commun.*, 2005, 2689.

