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New route to herbertanes via a Suzuki cross-coupling reaction: synthesis of herbertenediol

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Abstract—The synthesis of herbertenediol, a relevant member of the herbertane-type sesquiterpene family, is described. The synthesis is based on a new general approach to this group of sesquiterpenes where the herbertane skeleton is constructed using a Suzuki cross-coupling reaction and a [2,3]-sigmatropic Still–Wittig rearrangement as key synthetic steps. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

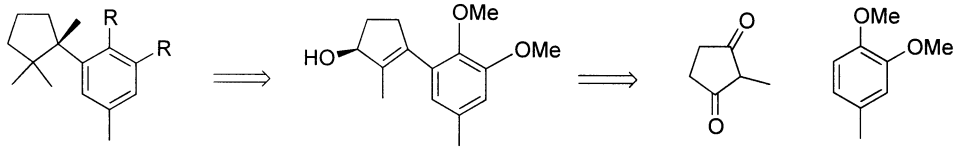
A family of sesquiterpenes sharing the hypothetical herbertane skeleton (**1**) has been isolated from several *Herbertus* species and other liverworts.[1,2] The synthesis of these compounds has attracted the attention of numerous research groups due to the significant biological properties shown by most of them and the difficulties associated with the construction of the vicinal quaternary centres on the five-membered ring.[3] Surely, herbertenediol (**2**), isolated from the liverwort *Herbertus adunca*,[4] is the most relevant member of this group of natural products. Herbertenediol possesses significant anti-fungal properties and exhibits a potent anti-lipid peroxidation activity[5] and may be considered as both the biosynthetic and chemical monomer precursor of the also natural dimeric sesquiterpenes known as mastigophorenes, a small group of compounds that show interesting neurotrofic properties.[6]

In connection with our studies on the synthesis of herbertanes, we have explored a new approach towards these sesquiterpenes based on a Suzuki reaction for the coupling of the aryl and cyclopentane moieties. In this paper, we describe the application of this approach to the synthesis of herbertenediol (**2**).[7]

2. Results and discussion

As shown in Scheme 1, the synthesis of the herbertane framework is based on the preparation of key intermediate allylic alcohol **3**, which is obtained from readily available materials using an intermolecular Suzuki cross-coupling reaction.[8] The allylic hydroxyl group of **3** is used to direct the construction of the benzylic chiral carbon centre, thus facilitating the stereoselective elaboration of the trimethylcyclopentane nucleus of the target herbertane system.

The synthesis of intermediate **3** is outlined in Scheme 2. The required arylboronic acid **6** was conveniently synthesised from commercially available 1,2-dimethoxy-4-methylbenzene (**5**). Thus, **5** was subjected to regioselective



1: R = H
2: R = OH

3 **4** **5**

Scheme 1.

Keywords: terpenes; Suzuki reactions; rearrangements; cyclopropanes.
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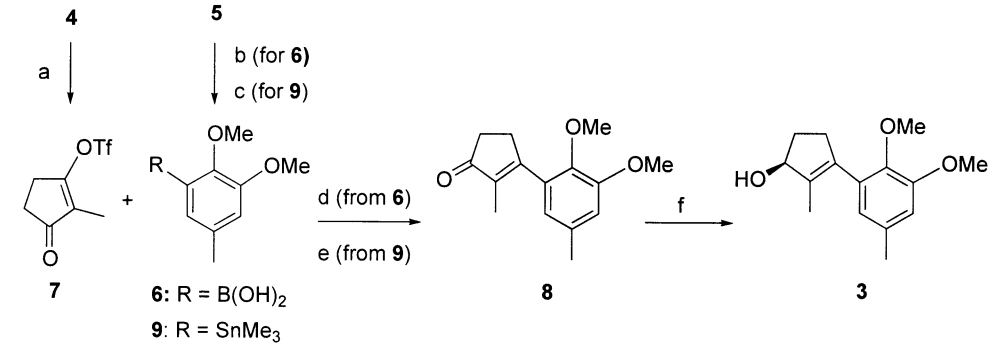
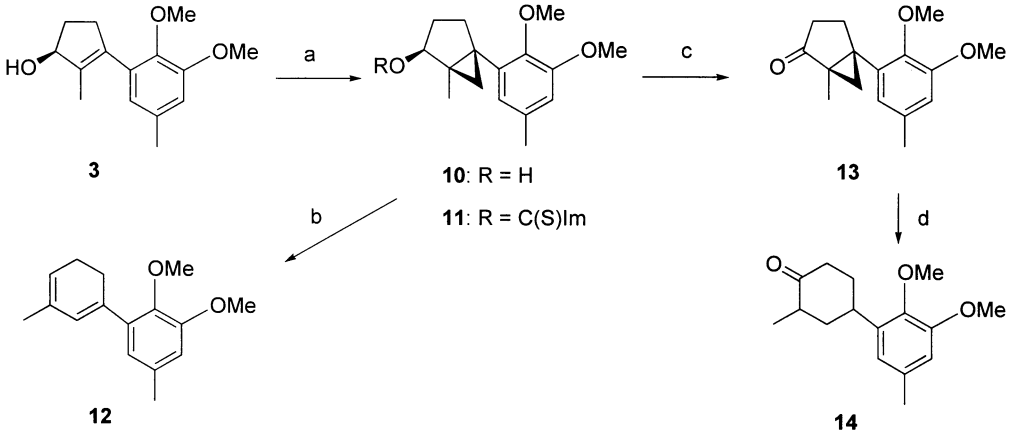


Scheme 2. *Reagents and conditions*: (a) $^{i}Pr_2EtN$, Tf_2O, CH_2Cl_2, −78 to −40°C, 95%; (b) BuLi, THF rt, then $B(OMe)_3$, then 5% aq HCl, 67%; (c) BuLi, THF, rt, then Me_3SnCl, 0°C, 65%; (d) $Pd(PPh_3)_4$, aq. Na_2CO_3, dioxane, reflux, 98%; (e) $Pd_2(dba)_3{\cdot}CHCl_3$, NMP, rt, 60%; (f) DIBAL-H, CH_2Cl_2, −78°C, 98%.



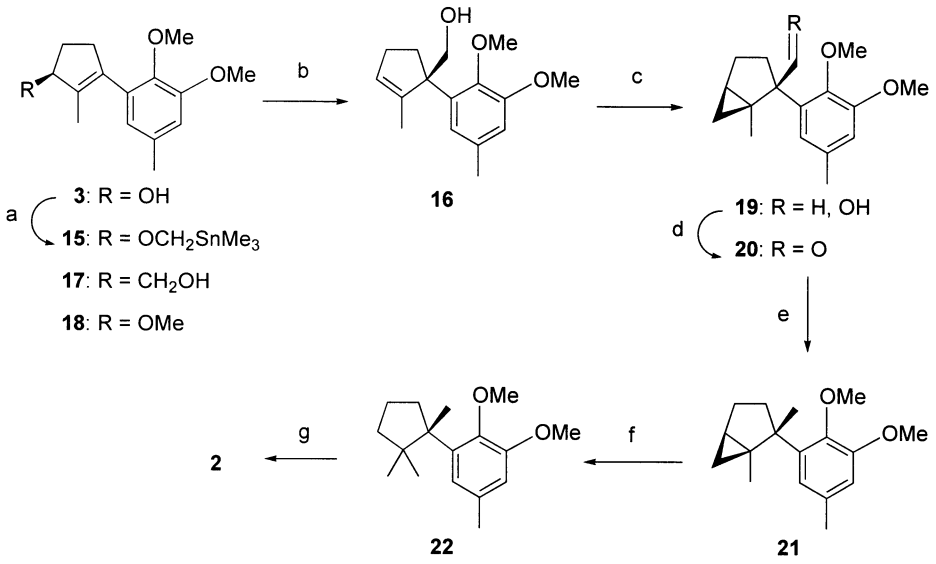
Scheme 3. *Reagents and conditions*: (a) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 93%; (b) Et_3N, MsCl, CH_2Cl_2, 0°C, 56%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −60°C then Et_3N, 90%; (d) Li, NH_3–THF, −78°C, 80%.

metallation with BuLi and was then quenched with $B(OMe)_3$ and finally hydrolysed with aqueous HCl to afford **6** in 67% yield. The Suzuki cross-coupling of the arylboronic acid **6** with the enol triflate **7**, prepared in 95% yield from 2-methylcyclopentane-1,3-dione (**4**) and triflic anhydride-*N*,*N*-diisopropylethylamine,[9] in the presence of the $Pd(PPh_3)_4$/aqueous Na_2CO_3 catalyst system[10] in dioxane at reflux afforded the enone **8** in very high yield. Previously to the above described Suzuki reaction, we also examined the preparation of **8** via the palladium(0)-catalysed reaction of vinyl triflate **7** with aryl trimethylstannane **9**,[11] prepared from **5** in 65% yield by transmetallation of the organolithium derived from **5** with trimethyltin chloride. Although we investigated the optimisation of reaction conditions by varying catalyst, solvent, reaction temperature, running time and additives, the coupling between **7** and **9** was not completely satisfactory. The best conditions [5% $Pd_2(dba)_3{\cdot}CHCl_3$, *N*-methyl-2-pyrrolidinone (NMP), rt][12] provided a moderate 60–65% yield of **8**, always accompanied by varying amounts of methyl transfer and stannane homocoupling products (2,3-dimethylcyclopent-2-enone and 2,3,2′,3′-tetramethoxy-5,5′-dimethylbiphenyl, respectively).

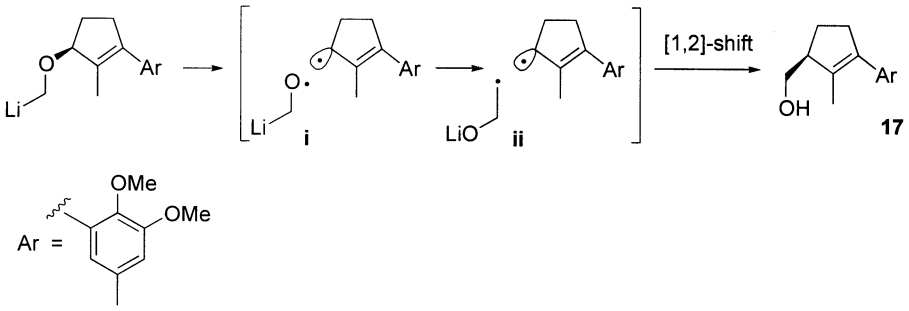
Completion of the synthesis of allylic alcohol **3** was effected in 98% yield by reduction of cyclopentenone **5** with diisobutyl aluminium hydride (DIBAL-H) in CH_2Cl_2 at −78°C.[†]

Having completed the synthesis of alcohol **3**, our attention was turned towards the elaboration of the vicinal quaternary centres on the five-membered ring. Our initial synthetic strategy for the construction of the first quaternary carbon atom was based on the cyclopropanation of the double bond of **3** followed by regioselective exocyclic cleavage of a cyclopropyl carbinyl radical.[13] Towards this end, we set out to transform **3** into thiocarbamate **11** (Scheme 3). Although the double bond of **3** was stereoselectively cyclopropanated in high yield through a hydroxyl directed Simmons–Smith cyclopropanation reaction,[14] all attempts to transform the resulting cyclopropyl alcohol **10** into the thiocarbonyl imidazolide derivative **11** resulted in extensive

[†] The complete sequence described here has been realized with racemic alcohol **3** and, although only one enantiomer is represented, all the chiral compounds that appear in the schemes are in fact racemic mixtures. The application of this approach to the preparation of herbertenediol in optically active form should require enantiopure (*S*)-**3**. This indeed was prepared in 92% yield and 85–88% ee by the chiral-oxazaborolidine-catalyzed borane reduction of ketone **8** (see Section 3). The enantioselective synthesis of (*S*)-**3** and the successful conversion of (±)-**3** into (±)-**2** described here, together establish a route for the enantioselective total synthesis of herbertenediol in natural form.



Scheme 4. *Reagents and conditions*: (a) KH, THF, 0°C then Me_3SnCH_2I, rt, 95%; (b) BuLi, hexane, −78°C to −10°C, 55% of **16**, 14% of **17**, 21% of **3** and 4% of **18**; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 76%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −60°C then Et_3N, 85%; (e) NH_2NH_2, $O(CH_2CH_2OH)_2$, NaOH, 160°C, 75%; (f) H_2, PtO_2, AcOH–NaOAc, 80%; (g) BBr_3, CH_2Cl_2, 0°C, 82%.



Scheme 5.

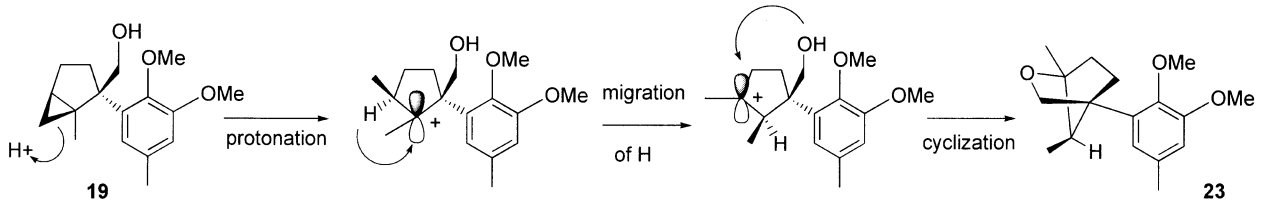
formation of the olefin **12**. Thus, only a 27% of thiocarbamate **11** was obtained by reaction of cyclopropyl alcohol **10** and $(Im)_2C{=}S$ under standard conditions.[15] Similar results were obtained when the formation of other derivatives of the hydroxyl group of **10** was attempted (e.g. the olefin **12** was the only compound identified in the reaction of **10** with mesyl chloride and triethylamine at 0°C). The easy formation of **12** in these reactions is probably the result of the very high stability of the benzylic tertiary cation originated upon endocyclic opening of the cyclopropane ring and loss of the leaving group.

In view of the difficulties we found in the preparation from **3** of a suitable precursor of the cyclopropyl carbinyl radical, we examined the cyclopropane ring cleavage of the cyclopropyl ketone **13**. Oxidation of **10** with oxalyl chloride and DMSO afforded the ketone **13** in 90% yield together with minor amounts (up to 5%) of the cyclohexadiene **12**. Unfortunately, reductive cleavage of the cyclopropyl ketone moiety of **13** with lithium in liquid NH_3 afforded exclusively the product of the endocyclic cyclopropane ring opening, the α-methyl cyclohexenone **14** as a 2:1 mixture of epimers in 80% yield. It is obvious from the above result that the usually favoured kinetic exocyclic bond cleavage of cyclopropanes fused to another ring, which has been attributed to the better overlap of this bond with the adjacent singly occupied orbital,[16] is completely altered in the case of the cyclopropyl ketone **13** probably due to the presence of the 2,3-dimethoxy-5-methylphenyl substituent. Such thermodynamic fragmentation has been previously reported for other substituted cyclopropyl carbinyl radicals.[17]

In view of the above results, an alternative approach for the construction of the quaternary benzylic carbon atom based on a [2,3]-sigmatropic Still–Wittig rearrangement was explored.[18] Towards this end, the alcohol **3** was transformed into the allyl stannylmethyl ether **15** by deprotonation with potassium hydride followed by alkylation with iodomethyltrimethyltin (Scheme 4).[19]

Treatment of **15** with BuLi in hexane at −78°C generated the α-lithioether that underwent a smooth [2,3]-sigmatropic rearrangement upon warming to −10°C overnight to deliver the homoallylic alcohol **16** in 55% overall yield after column chromatography, together with a 3:2 mixture of allylic alcohol **3** and the product of [1,2]-rearrangement **17** in 35% yield, and a small amount of the methyl ether **18** (up to 5%).[20‡] It should be mentioned that the formation of the [1,2]-rearrangement product in this reaction was not

‡ The result of this reaction was very little different when the reaction was done with the (tributylstannanyl)methyl allyl ether (**15**, R=OCH_2SnBu_3).



Scheme 6. Formation of **23**.

unexpected in view of the results which are often observed in the rearrangement of related β-substituted cyclic allylic systems[18a,21] and the presumably stability of the radical intermediate through which this rearrangement takes places (e.g. radical **i**–**ii** in Scheme 5).[22]

In any case, completion of the synthesis of the herbertane system was effected as follows. First **16** was submitted to Simmons–Smith cyclopropanation conditions to cyclopropanate the double bond, an indirect way of introducing the geminal dimethyl group at C-2 of the herbertane system. Thus, treatment of **16** with diiodomethane and diethyl zinc under the same conditions used previously for the conversion of **3** into **10** afforded the cyclopropane **19** in 76% yield. Although irrelevant from the synthetic point of view, the cyclopropanation reaction of **16** also took place stereoselectively, *syn* to the homoallylic hydroxyl group, as shown by the NOE observed between the hydrogen of the cyclopropane ring at δ 0.50 ppm and the hydroxymethyl group at 3.93 ppm.

Swern oxidation of **19** under standard conditions[23] provided the aldehyde **20**, which upon Huang–Minlon reduction[24] of the formyl group to methyl afforded the cycloherbertane **21** in ca. 64% overall yield. The following step, the opening of the cyclopropane ring into a *gem*-dimethyl group, proved to be more problematic than initially expected, and appropriate conditions had to be found. The best results were obtained by stirring a solution of **21** in AcOH–NaOAc and 3 equiv. of PtO_2 under an atmosphere of H_2 (1.6 atm.) at room temperature for several days. Under these conditions, the cyclopropane hydrogenation proceeded very smoothly, less than 10% of products originated from reduction of the aromatic moiety were formed and the compound **22** was obtained in 80% yield after chromatographic purification. The use of the acetate buffer was crucial for the success of the above hydrogenolysis, since in the absence of NaOAc it was not possible to avoid the over-reduction of the aromatic ring and the formation of complex diastereoisomeric mixtures of products.[25§]

Final conversion of dimethyl ether **22** into herbertenediol was easily effected by removal of the methyl groups with BBr_3 as described in previous syntheses.[7]

§ We also attempted the hydrogenolysis of the cyclopropane ring of **19** to form the *gem*-dimethyl group before the conversion of the hydroxymethyl group into the methyl group. The hydrogenation of **19** with PtO_2 as catalyst and AcOH as solvent afforded a mixture of products from which the bridged ether **23** (see Scheme 6) was identified as the main product formed (48% yield). The structural assignment of **23** was based on a detailed spectroscopic study that included NOE experiments. Spectroscopic data and experimental details for the preparation of **23** are given in Section 3.

In conclusion, we have developed a new approach to the construction of the bicyclic herbertane system, based on a Suzuki cross-coupling reaction and a [2,3]-sigmatropic Still–Wittig rearrangement, which has culminated in the synthesis of herbertenediol (**2**) and may be easily adapted for the synthesis of other natural herbertanes and related sesquiterpenes.

3. Experimental

3.1. General experimental details

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. All ^{1}H spectra were recorded in $CDCl_3$ at 300 or 400 MHz, and all ^{13}C at 75 MHz. Complete assignment for compounds **10**, **19** and **23** was made on the basis of a combination of HMQC, HMBC and NOE experiments. Mass spectra were obtained by electron impact (EI) at 70 eV. IR spectra were measured as KBr pellets or liquid films. All reactions were carried out under an inert atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh.

3.1.1. Trifluoromethanesulfonic acid 2-methyl-3-oxocyclopent-1-enyl ester (7). *N*,*N*-Diisopropylethylamine (0.356 mL, 2.051 mmol) was added to a suspension of diketone **4** (100 mg, 0.892 mmol) in anhydrous CH_2Cl_2 (6 mL). The resulting pale orange solution was cooled to −78°C and treated dropwise with triflic anhydride. (0.175 mL, 1.043 mmol). The mixture was allowed to warm to −40°C over 1 h before being quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and then evaporated in vacuo. Chromatography of the residue on silica gel using hexane–CH_2Cl_2 (1:1) as eluent gave the triflate **7** (208 mg, 95%) as a pale brown oil: IR ν_{max} (film) 1725, 1682, 1429, 1384, 1245, 1216 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.9–2.8 (2H, m, H_2-5), 2.7–2.6 (2H, m, H_2-4), 1.77 (3H, dd, J=2.4, 1.8 Hz, Me-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 203.1 (C3), 172.1 (C1), 130.0 (C2), 118.3 (q, J=319 Hz, CF_3), 34.8 (C4), 26.9 (C5), 6.6 (Me-2); MS (EI) (relative intensity): 244 (M^+, 100), 175 (19), 111 (27) and 69 (61); HRMS, calcd for $C_7H_7O_4F_3S$ 244.0017, found 244.0015.

3.1.2. (2,3-Dimethoxy-5-methylphenyl)boronic acid (6). Butyl lithium (1.6 M in hexane, 17.2 mL, 27.59 mmol) was added to a solution of 1,2-dimethoxi-4-methylbenzene

(**5**) (3.0 g, 19.71 mmol) in THF (18 mL) at 0°C. The mixture was stirred for 1 h at room temperature. The white slurry was slowly transferred into a solution of $B(OMe)_3$ (4.4 mL, 39.42 mmol) in THF (9 mL) at −78°C. The resulting mixture was allowed to warm to room temperature and stirred overnight and then HCl (5%, 22 mL) was added to the mixture and stirred for 15 min. It was then poured into H_2O and extracted with CH_2Cl_2. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished a solid residue which was chromatographed using hexane–ethyl acetate (8:2) as eluent to give arylboronic acid **6** (2.58 g, 67%) as colourless crystals; mp 123.5–124.8°C (from hexane–ethyl acetate); IR ν_{max} (KBr) 3429, 3344, 1583, 1475, 1432, 1405, 1349, 1271, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.21 and 6.86 (1H each, each s, H-4 and H-6), 6.77 (2H, brs, 2×OH), 3.91 and 3.87 (3H each, s each, 2×OMe), 2.33 (3H, s, Me-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.1 and 151.1 (C2 and C3), 134.4×2 (C1 and C5), 127.4 (C6), 116.6 (C4), 61.4 (MeO-C2), 55.6 (MeO-C3), 21.1 (Me-5); MS (EI) *m/z* (relative intensity) 196 (M^+, 100), 195 (26), 181 (48), 153 (38), 149 (50); HRMS, calcd for $C_9H_{13}BO_4$ 196.0907, found 196.0906.

3.1.3. (2,3-Dimethoxy-5-methylphenyl)trimethylstannane (9). A solution of **5** (500 mg, 3.28 mmol) in THF (3.5 mL) was treated with BuLi (1.6 M in hexane, 2.66 mL, 4.26 mmol) as above. The resulting suspension was cooled to 0°C and treated with a solution of Me_3SnCl (1.05 g, 5.25 mmol) in THF (1.9 mL). The mixture was left stirring at ambient temperature for 2 h, poured into saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by flash chromatography, using 95:5 hexane–ethyl acetate containing 1% Et_3N, gave the stannane **9** (671 mg, 65%) as a colourless oil; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.75 and 6.73 (1H each, each s, H-4 and H-6), 3.85 and 3.81 (3H each, s, 2×MeO), 2.33 (3H, s, Me-5), 0.29 (9H, s, Me_3Sn); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.3 and 151.0 (C2 and C3), 135.3 and 134.2 (C1 and C5), 127.7 (C6), 114.2 (C4), 60.8 (MeO-2), 55.3 (MeO-3), 21.1 (Me-5), 8.9 (Me_3Sn); MS (FAB) *m/z* (relative intensity) 316 (M^+, 33), 301 (100), 286 (12), 271 (4), 256 (2); HRMS, calcd for $C_{12}H_{20}O_2Sn$ 316.0485, found 316.0476.

3.1.4. 3-(2′,3′-Dimethoxy-5′-methylphenyl)-2-methylcyclopent-2-enone (8). From **6** and **7**. To a mixture of boronic acid **6** (964 mg, 4.92 mmol) and $Pd(PPh_3)_4$ (106 mg, 0.092 mmol) in degassed dioxane (30 mL), an aqueous solution of Na_2CO_3 (2 M, 4.5 mL, 9.02 mmol), which has been previously purged with nitrogen, and the triflate **7** (1.32 g, 5.41 mmol) were added. The resulting mixture was rigorously degassed by the freeze–thaw process and then heated at reflux for 3 h. The reaction mixture was cooled down to 10°C, and 35% H_2O_2 (12 drops) was added carefully. When the gas evolution ceased, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed successively with water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column, using CH_2Cl_2–ether (9:1) as eluent, furnished the enone **8** (1.185 g, 98%) as a white solid; mp 109.2–110.3°C (from hexane–ether); IR ν_{max} (KBr) 3072, 2997, 2966, 2938, 2841, 1692, 1644, 1584, 1481, 1352, 1120, 1062, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.75 (1H, brs, H-6′), 6.53 (1H, brs, H-4′), 3.87 and 3.67 (3H each, each s, 2×MeO), 2.89–2.82 (2H, m, H_2-4), 2.53–2.48 (2H, m, H_2-5), 2.33 (3H, s, Me-5′), 1.71 (3H, t, J=2.1 Hz, Me-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 210 (C1), 167.5 (C3), 152.7 (C2′), 144.0 (C3′), 138.4 (C2), 134.0 (C5′), 131.0 (C1′), 120.4 (C6′), 113.6 (C4′), 61.2 (MeO-2′), 55.8 (MeO-3′), 34.4 (C5), 30.8 (C4), 21.3 (Me-5′), 9.4 (Me-2); MS (EI) *m/z* (relative intensity) 246 (M^+, 100), 231 (8), 203 (20), 189 (66), 175 (6); HRMS, calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1251.

From **7** and **9**. Triflate **7** (603 mg, 2.47 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (116 mg, 0.112 mmol) were dissolved in anhydrous degassed NMP (10 mL). After 10 min, a degassed solution of stannane **9** (705 mg, 2.24 mmol) in NMP (4 mL) was added and the mixture was stirred at room temperature for 3 h. The resulting brownish reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with water then brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure and the residue obtained purified by flash chromatography using hexane–ether (7:3) as eluent to afford, in order of elution, 40.5 mg (6%) of the homocoupling product 2,3,2′,3′-tetramethoxy-5,5′-dimethylbiphenyl and 454.8 mg of a 5:1 mixture of **8** and 2,3-dimethylcyclopent-2-enone as a semisolid. This mixture was suspended in cold pentane and filtered off to afford nearly pure **8** (329.7 mg, 60%) as a white solid.

3.1.5. 3-(2′,3′-Dimethoxy-5′-methylphenyl)-2-methylcyclopent-2-enol (3). Preparation of (±)-**3**. To a solution of enone **8** (104 mg, 0.423 mmol) in CH_2Cl_2 (2 mL), cooled to −78°C, DIBAL-H (0.634 mL, 0.634 mmol of 1 M in cyclohexane) was added. The solution was stirred at −78°C for 1 h and then water was added and the mixture was extracted with CH_2Cl_2. Workup and flash chromatography (1:1 hexane–ether) afforded the alcohol **3** (102.5 mg, 98%) as a colourless oil; IR ν_{max} (film) 3407, 2934, 2855, 1583, 1481, 1464, 1425, 1349, 1230, 1127, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.66 (1H, brs, H-6′) 6.53 (1H, brs, H-4′), 4.74 (1H, m, H-1), 3.85 (3H, s, MeO-2′), 3.68 (3H, s, MeO-3′), 2.31 (3H, s, Me-4′), 1.71 (3H, t, J=2.1 Hz, Me-2); ^{13}C NMR (75 MHz, C_6D_6)] δ_C 153.1 (C2′), 145.7 (C3′), 138.0 (C3), 136.8 (C2), 132.9 (C5′), 132.8 (C1′), 122.6 (C6′), 112.7 (C4′), 80.9 (C1), 60.4 (MeO-2′), 55.3 (MeO-3′), 35.1 (C4), 33.6 (C5), 21.1 (Me-5′), 12.5 (Me-2); MS (EI) *m/z* (relative intensity) 248 (M^+, 68), 230 (100), 233 (80), 215 (38); HRMS, calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1403.

Preparation of (−)-(*S*)-**3**. A solution of $BH_3{\cdot}THF$ in THF (1 M, 0.113 mL, 0.113 mmol) was added to a solution of (*R*)-2-methyl-CBS-oxazaborolidine in toluene (1 M, 0.225 mL, 0.225 mmol) at 0°C.[26] After stirring at room temperature for 20 min, the mixture was cooled again to 0°C and a solution of the enone **8** (27.7 mg, 0.113 mmol) in THF (1.2 mL) was added over 2.30 h. After 30 min of additional stirring at the same temperature, the reaction mixture was quenched with MeOH (0.2 mL). The solvents were evaporated under reduced pressure and the residue was

chromatographed on silica gel with hexane–ether (1:1) as eluent to give (*S*)-**3** (25.1 mg, 90%) as a colourless oil, $[\alpha]_D^{25}=-1.5°$ (*c* 1.6, $CHCl_3$). The enantiomeric excess (ee) was determined by ^1H and ^{19}F NMR analysis in C_6D_6 of the (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid ester of (*S*)-**3**.[27] Thus, when the ^1H NMR was recorded on a racemic mixture of **3**, two peaks corresponding to the two methyl groups at C-2 of both diastereomers were observed at δ 1.57 and 1.68 ppm, allowing an easy measurement of the diastereomeric excess (de). This NMR analysis gave a de of 85–88% for the (*R*)-MTPA-ester of (*S*)-**3** and so an 85–88% ee for (*S*)-**3**. A similar ee was also determined from the analysis of the ^{19}F NMR, in which the peaks corresponding to the CF_3 group at C-2 of both enantiomers are also well differentiated.

3.1.6. 5-(2′,3′-Dimethoxy-5′-methylphenyl)-1-methylbicyclo[3.1.0]hexan-2-ol (10). To a cooled (0°C) solution of diethylzinc (1.0 M solution in hexane, 1.64 mL, 1.64 mmol) in CH_2Cl_2 (2 mL), diiodomethane (0.132 mL, 1.64 mmol) was added. After stirring for 30 min at the same temperature, a solution of the alcohol **3** (81.4 mg, 0.328 mmol) in CH_2Cl_2 (2 ml) was added. The mixture was allowed to warm to room temperature over 2 h, before being quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The organic extracts were washed with saturated aqueous Na_2SO_3 solution, water and brine, dried, and concentrated to give an oil. Flash chromatography, using hexane–ethyl acetate (1:1) as eluent, yielded alcohol **10** (80.0 mg, 93%) as a solid; mp 76.2–76.8°C (from hexane–ether); IR ν_{max} (KBr) 3392, 3058, 2956, 2926, 2866, 1585, 1485, 1464, 1462, 1308, 1142, 1095, 1040, 1014 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ_H 6.63 (1H, brs, H-6′), 6.40 (1H, brs, H-4′), 4.34 (1H, m, CH-2), 3.75 (3H, s, MeO-2′), 3.30 (3H, s, MeO-3′), 2.12 (3H, s, Me-5′), 2.07 (1H, m, H-4), 1.85 (2H, m, H-3, H-4), 1.11 (3H, s, Me-1), 1.1 (1H, m, H-3), 1.00 and 0.51 (1H each, each d, *J*=5.1 Hz, H_2-6); ^{13}C NMR (75 MHz, C_6D_6) δ_C 152.7 (C3′), 147.7 (C2′), 135.3 and 132.3 (C1′ and C5′), 124.3 (C6′), 112.7 (C4′), 79.1 (C2), 60.5 (MeO-2′), 55.2 (MeO-3′), 34.9 and 34.2 (C5 and C1), 32.4 (C4), 30.5 (C3), 21.1 (Me-5′), 17.1 (Me-1), 15.9 (C6); MS (EI) *m/z* (relative intensity) 262 (M^+, 77), 244 (100), 229 (40), 203 (52), 178 (36); HRMS, calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1563.

3.1.7. 1,2-Dimethoxy-5-methyl-3-(3′-methylcyclohexa-1′,3′-dienyl)benzene (12). Triethylamine (0.11 mL, 0.72 mmol) and methanesulfonyl chloride (30 μL, 0.4 mmol) were added to a solution of **10** (30 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) at 0°C. The mixture was stirred at the same temperature for 40 min, and water was added. After extraction with CH_2Cl_2, the organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Flash chromatography, using hexane–ethyl acetate (3:2) as eluent, yielded diene **12** (15.6 mg, 56%) as a colourless liquid; IR ν_{max} (film) 2926, 2854, 2823, 1584, 1482, 1464, 1425, 1341, 1329, 1248, 1231, 1148, 1014, 833 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ_H 6.65 (1H, brs, H-4), 6.60 (1H, brs, H-6), 5.78 (1H, brs, H-2′), 5.45 (1H, m, H-4′), 3.85 and 3.73 (3H each, each s, 2×MeO), 2.89 (4H, m, H_2-5′ and H_2-6′), 2.30 (3H, s, Me-5), 1.72 (3H, s, Me-3′); ^{13}C NMR (75 MHz, C_6D_6) δ_C 152.8 (C2), 144.8 (C1), 137.8 (C1′), 134.3 (C3′), 133.9 and 132.3 (C3 and C5), 123.7 (C4′), 122.3 (C4), 118.0 (C2′),112.4 (C6), 61.2 (MeO-2), 56.2 (MeO-1), 34.8 (C6′), 28.4 (C5′), 23.6 (Me-3′), 21.7 (Me-5); MS (EI) *m/z* (relative intensity) 244 (M^+, 42), 242 (100), 227 (62), 212 (41), 179 (50), 91 (7); HRMS, calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1462.

3.1.8. 5-(2′,3′-Dimethoxy-5′-methylphenyl)-1-methylbicyclo[3.1.0]hexan-2-one (13). To a stirred, cooled (−60°C) solution of oxalyl chloride (18 μL, 0.21 mmol) in CH_2Cl_2 (0.5 mL), a solution of DMSO (32 μl, 0.45 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise. The mixture was stirred at −60°C for 10 min, followed by dropwise addition of a solution of **10** (49.2 mg, 0.19 mmol) in CH_2Cl_2 (0.2 mL). After the mixture was stirred at the same temperature for 30 min, triethylamine (131 μl, 0.94 mmol) was added and stirring was continued for 5 min. The mixture was then allowed to warm up slowly to room temperature over 2 h. Saturated aqueous $NaHCO_3$ was added to the mixture and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried. Chromatography of the residue left after evaporation of the solvent, using hexane–ethyl acetate (75:25) as eluent, provided the enone **13** (44 mg, 90%) as a white solid; mp 94–95°C (from hexane); IR ν_{max} (KBr) 2966, 2936, 1718, 1585, 1487, 1464, 1427, 1371, 1233, 1143, 1079, 1009, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.69 (1H, brs, H-6′), 6.60 (1H, brs, H-4′), 3.84 (6H, s, 2×MeO), 2.30 (3H, s, Me-5′), 2.27–2.13 (4H, m, H_2-3 and H_2-4), 1.44 and 1.32 (1H each, each d, *J*=4.7 Hz, H_2-6), 1.02 (3H, s, Me-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 216.1 (C1), 152.3 (C3′), 146.6 (C2′), 133.1 and 132.8 (C1′ and C5′), 123.3 (C6′), 112.8 (C4′), 61.0 (MeO-2′), 55.7 (MeO-3′), 40.1 (C5), 38.5 (C1), 32.8 (C4), 29.4 (C3), 25.2 (C6), 21.2 (Me-5′), 12.0 (Me-1); MS (EI) *m/z* (relative intensity) 260 (M^+, 100), 245 (17), 203 (27); HRMS, calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1420.

3.1.9. 4-(2′,3′-Dimethoxy-5′-methylphenyl)-2-methylcyclohexanone (14). To a cooled (−78°C) solution of lithium (10 mg, 1.5 mmol) in liquid NH_3 (5 mL), a solution of **13** (26.6 mg, 0.1 mmol) in THF (1.5 mL) was added over a period of 15 min. After 15 min, NH_4Cl was added to the reaction mixture and the solvent was removed. The residue was dissolved in water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by chromatography, using hexane–ethyl acetate (75:25) as eluent, furnished the ketone **14** (21.2 mg, 80%) as a 3:1 mixture of epimers at C-2; IR ν_{max} (KBr) 2960, 2931, 2861, 1713, 1589, 1489, 1464, 1429, 1377, 1324, 1305, 1228, 1147, 1066, 1011, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H (*major isomer*): 6.61 (1H, brs, H-6′), 6.57 (1H, brs, H-4′), 3.85 and 3.84 (3H each, each s, 2×MeO), 3.55 (1H, m, H-2), 2.29 (3H, s, Me-5′), 1.06 (3H, d, *J*=6.4 Hz, Me-2); ^{13}C NMR (75 MHz, $CDCl_3$) (*major isomer*): δ_C 213.0 (C1), 152.3 (C3′), 144.1 (C2′), 137.8 (C1′), 133.8 (C5′), 118.7 (C6′), 111.2 (C4′), 61.1 (MeO-2′), 55.6 (MeO-3′), 44.9 (C2), 36.0 (C4), 42.8, 41.7 and 34.3 (C3, C5 and C6), 21.5 (Me-5′), 14.5 (Me-2); MS (EI) *m/z* (relative intensity) 262 (M^+, 100), 247 (4), 178 (52); HRMS, calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

3.1.10. [3-(2′,3′-Dimethoxy-5′-methylphenyl)-2-methyl-cyclopent-2-enyloxymethyl] trimethylstannane (15). To a stirred slurry of pre-washed (pentane) potassium hydride (40% dispersion oil; 36.3 mg, 0.90 mmol) in THF (1 mL), a solution of **3** (150 mg, 0.60 mmol) in THF (1 mL) was added. After the hydrogen evolution had ceased, a solution of Me_3SnCH_2I (329 mg, 1.08 mmol) in THF (0.6 mL) was added and the mixture was stirred at room temperature for 1 h. The mixture was cooled to 0°C and carefully treated with saturated aqueous NH_4Cl solution followed by extraction with diethyl ether. The organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated to give an oil. Flash chromatography, using hexane–ether (9:1) as eluent afforded the stannane **15** (244.2 mg, 95%) as a yellowish oil; IR ν_{max} (film) 2955, 2932, 2857, 1698, 1583, 1482, 1464, 1351, 1230, 1128, 1052, 1015, 834, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.65 (1H, d, J=2 Hz, H-6′), 6.53 (1H, d, J=2 Hz, H-4′), 4.38 (1H, brt, H-1), 3.84 (3H, s, MeO-2′), 3.66 (3H, s, MeO-3′), 3.77 and 3.62 (1H each, each d, J=10.4 Hz, OCH_2Sn), 2.7 (1H, m), 2.6 (1H, m), 2.30 (3H, s, Me-5′), 2.2 (1H, m), 1.8 (1H, m), 1.64 (3H, s, Me-2), 0.14 (9H, s, Me_3Sn); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.4 (C3′), 144.6 (C2′), 137.1, 136.0, 133.2 and 132.3 (C3, C2, C5′ and C1′), 122.2 (C6′), 111.8 (C4′), 91.2 (C1), 60.8 (MeO-2′), 58.2 (OCH_2Sn), 55.7 (MeO-3′), 35.1 (C4), 28.0 (C5), 21.3 (Me-5′), 12.8 (Me-2), −10.3 (Me_3Sn); MS (EI) m/z (relative intensity) 425 (M^+, 29), 410 (7), 395 (20), 318 (100); HRMS, calcd for $C_{19}H_{31}O_3Sn$ 425.1289, found 425.1293.

3.1.11. [1-(2′,3′-Dimethoxy-5′-methylphenyl)-2-methyl-cyclopent-2-enyl]methanol (16). A solution of trimethylstannane **15** (145 mg, 0.34 mmol) in hexane (3.3 mL) was treated dropwise with BuLi (1.6 M in hexane, 0.23 mL, 0.37 mmol) at −78°C. After 2 h at the same temperature, the mixture was allowed to warm slowly to −10°C overnight. The reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and then evaporated under reduced pressure. Flash chromatography of the residue, using hexane–ethyl acetate (from 8:2 to 6:4) as eluent, gave, in order of elution, methyl ether **18** (3.6 mg, 4%), the [2,3]-rearrangement product **16** (49.0 mg, 55%) and a 3:2 mixture (^1H NMR analysis) of alcohols **3** and the [1,2]-rearrangement product **17** (31.1 mg, 35%). Compound **17** was separated from the above mixture with **3** by MPLC chromatography, using hexane–ethyl acetate (8:2) as eluent.

For **16**: colourless oil; IR ν_{max} (film) 3457, 3032, 2934, 2851, 1583, 1480, 1464, 1416, 1316, 1233, 1149, 1012, 834, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.63 (1H, brs, H-6′), 6.50 (1H, brs, H-4′), 5.70 (1H, bs, H-3), 3.96 (2H, m, CH_2O), 3.84 (3H, s, MeO-2′), 3.81 (3H, s, MeO-3′), 2.37–2.00 (4H, m), 2.30 (3H, s, Me-5′), 1.65 (3H, m, Me-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.9 (C3′), 145.2 (C2′), 142.6 (C2), 137.4 and 133.1 (C1′ and C5′), 128.8 (C3), 121.2 (C6′), 111.5 (C4′), 66.9 (CH_2O), 60.7 (MeO-2′), 60.0 (C1), 55.6 (MeO-3′), 36.8 and 30.5 (C4 and C5), 21.6 (Me-2), 14.1 (Me-5′); MS (EI) m/z (relative intensity) 262 (M^+, 26), 232 (33), 231 (100), 200 (13), 175 (19); HRMS, calcd for 262.1569 $C_{16}H_{22}O_3$, found 262.1559.

For **17**: IR ν_{max} (film) 3447, 2930, 2853, 1696, 1577, 1480, 1460, 1344, 1001, 908, 777, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.63 (1H, brs, H-6′), 6.51 (1H, brs, H-4′), 3.85 (3H, s, MeO-2′), 3.73 (1H, dd, 11.7, 12.6 Hz, OCH_2), 3.72 (1H, dd, 11.7, 11.7 Hz, OCH'_2), 3.68 (3H, s, MeO-3′), 2.85 (1H, m, CH), 2.56–2.74 (2H, m), 2.1–2.2 (1H, m), 1.82–1.9 (1H, m), 2.30 (3H, brs, Me-5′), 1.60 (3H, dd, 2.4, 1.6 Hz, Me-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.38 (C3′), 144.30 (C2′), 136.33, 134.86, 133.29 and 132.62 (C2, C3, C1′ and C5′), 122.12 (C6′), 111.80 (C4′), 64.84 (CH_2O), 60.62 (MeO-2′), 55.69 (MeO-3′), 52.44 (C1), 36.84 (C4), 26.36 (C5), 21.27 (Me-5′), 13.49 (Me-2); HRMS, calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1558.

For **18**: IR ν_{max} (film) 2933, 2873, 2822, 1730, 1585, 1482, 1464, 1353, 1231, 1129, 1014, 834, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.65 (1H, brs, H-6′), 6.53 (1H, brs, H-4′), 4.40 (1H, brs, H-1), 3.80 (3H, s, MeO-2′), 3.70 (3H, s, MeO-3′), 3.41 (3H, s, MeO-1), 2.8–2.5 (2H, m), 2.31 (3H, s, Me-5′), 2.20 (1H, m), 1.80 (1H, m), 1.70 (3H, brs, Me-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.4 (C3′), 144.6 (C2′), 137.6, 135.7, 133.2 and 132.2 (C2, C3, C1′ and C5′), 122.1 (C6′), 111.9 (C4′), 89.4 (C1), 60.8 (MeO-2′), 55.7 (MeO-3′), 55.2 (MeO-1), 35.0 (C4), 28.5 (C5), 21.2 (Me-5′), 15.3 (Me-2); MS (EI) m/z (relative intensity) 262 (M^+, 52), 247 (100), 231 (56), 230 (50), 77 (7); HRMS, calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1558.

3.1.12. [2-(2′,3′-Dimethoxy-5′-methyl-phenyl)-1-methyl-bicyclo[3.1.0]hex-2-yl]methanol (19). Cyclopropanation of cyclopentene **16** (96.5 mg, 0.38 mmol) in the same way as for **3** afforded, after purification by chromatography using hexane–ethyl acetate (8:2) as eluent, the cyclopropane–alcohol **19** (77.2 mg, 76%) as a white solid; mp 80–81°C (from hexane); IR ν_{max} (film) 3514, 3059, 2997, 2934, 2868, 2833, 1603, 1582, 1478, 1463, 1414, 1324, 1229, 1147, 1006, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.86 (1H, brs, H-6′), 6.64 (1H, brs, H-4′), 4.11 (1H, dd, J=11.6, 7.1 Hz, CH_2O), 3.93 (1H, dd, J=11.6, 8.3 Hz, CH_2O), 3.86 (3H, s, MeO-3′), 3.84 (3H, s, MeO-2′), 3.19 (1H, dd, J=8.3, 7.1 Hz, OH), 2.33 (3H, s, Me-5′), 2.01 and 1.66 (1H each, each m, CH_2), 1.43–1.16 (3H, m, CH_2 and H-5), 1.13 (3H, s, Me-1), 0.50 (1H, t, J=5.0 Hz, H-6), 0.37 (1H, ddd, J=7.9, 5.0, 0.8 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 153.0 (C3′), 143.9 (C2′), 137.3 and 133.2 (C5′ and C1′), 123.2 (C6′), 110.8 (C4′), 68.7 (CH_2O), 61.3 (MeO-2′), 55.6 (MeO-3′), 54.4 (C2), 35.2 (C3), 26.6 (C4), 33.1 (C1), 28.2 (C5), 21.9 (Me-5′), 19.5 (Me-1), 14.3 (C6); MS (EI) m/z (relative intensity) 276 (M^+, 49), 258 (46), 245 (100), 231 (30), 208 (55), 165 (58); HRMS, calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1728.

3.1.13. 4-(2′,3′-Dimethoxy-5′-methyl-phenyl)-1,7-dimethyl-2-oxa-bicyclo[2.2.1]heptane (23). To a solution of cyclopropane–alcohol **19** (9.5 mg, 0.035 mmol) in AcOH (1 mL) was added a catalytic amount of PtO_2 (30 mg), and the resulting suspension was stirred under a hydrogen atmosphere (4 atm.) for 15 h. The catalyst was removed by filtration and the filtrate was concentrated to give the crude product that was purified by flash chromatography, with pentane–ether (7:3) as eluent, to give the compound **23** (4.6 mg, 48%) as a colourless oil; IR ν_{max} (film) 2963, 2931, 2872, 2837, 1586, 1486, 1463, 1419, 1326, 1274, 1240, 1136, 1038, 1010, 988, 864, 832 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ_H 6.63 (1H, brs, H-6′), 6.42 (1H, brs, H-4′), 4.15 (1H, d, J=7.3 Hz, H-3β), 4.05 (1H, dd, J=7.3, 2.4 Hz, H-3α), 3.84 and 3.79 (3H each, each s, 2×MeO), 2.30 (3H, s, Me-5′), 2.23 (1H, q, J=6.6 Hz, H-7), 1.95–1.70 (4H, m, H_2-5 and H_2-6), 1.30 (3H, s, Me-1), 0.85 (3H, d, J=6.6 Hz, Me-7); ^{13}C NMR δ_C (75 MHz, $CDCl_3$) 152.7 (C3′), 145.8 (C2′), 134.2 and 133.3 (C5′ and C1′), 120.8 (C6′), 111.5 (C4′), 84.7 (C1), 74.4 (CH_2O), 60.7 (MeO-2′), 55.6 (MeO-3′), 54.4 (C4), 47.9 (C7), 37.1 and 36.7 (C5 and C6), 21.4 (C5′), 17.4 (Me-1), 8.0 (Me-7); MS (EI) *m/z* (relative intensity) 276 (M^+, 100), 261 (4), 247 (57), 231 (53), 218 (45), 203 (35), 187 (20), 151 (5); HRMS, calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1731.

3.1.14. 2-(2′,3′-Dimethoxy-5′-methyl-phenyl)-1-methyl-bicyclo[3.1.0]hexane-2-carbaldehyde (20). Swern oxidation of alcohol **19** (69.6 mg, 0.25 mmol), as described above for compound **13**, and purification of the product on silica gel using hexane–ether (7:3) as eluent, furnished the aldehyde **20** (58.7 mg, 85%) as a crystalline solid; mp 75–76°C (from hexane); IR ν_{max} (film) 3064, 3001, 2962, 2930, 2869, 2831, 2721, 1716, 1586, 1483, 1464, 1325, 1234, 1150, 1117, 1055, 1004, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.81 (1H, s, CHO), 6.76 (1H, brs, H-6′), 6.66 (1H, brs, H-4′), 3.85 (3H, s, MeO-2′), 3.58 (3H, s, MeO-3′), 2.37 (3H, s, Me-5′), 2.30 (1H, m), 2.03 (1H, m), 1.74 (1H, m), 1.40 (1H, m), 1.22 (3H, s, Me-1), 1.15 (1H, m), 0.57 (1H, dd, J=4.5, 4.3 Hz, H-6), 0.28 (1H, dd, J=7.8, 5.3 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 198.8 (CHO), 152.5 (C3′), 143.3 (C2′), 135.7 and 133.6 (C5′ and C1′), 121.3 (C6′), 111.7 (C4′), 60.8 (C2), 59.8 (MeO-2′), 55.6 (MeO-3′), 29.3 (C3), 25.9 (C4), 29.2 (C1), 26.4 (C5), 21.8 (Me-5′), 18.4 (Me-1), 13.6 (C6); MS (EI) *m/z* (relative intensity) 274 (M^+, 100), 245 (89), 165 (56), 93 (34); HRMS, calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1579.

3.1.15. 2-(2′,3′-Dimethoxy-5′-methylphenyl)-1,2-dimethyl-bicyclo[3.1.0]hexane (21). A solution of the aldehyde **20** (49.8 mg, 0.18 mmol) and hydrazine hydrate (0.2 mL, 4.2 mmol) in diethylene glycol (1.5 mL) was heated to 160°C for 4 h. The mixture was cooled to room temperature and treated with powdered sodium hydroxide (210 mg, 4.5 mmol). The reaction mixture was further heated to 180°C overnight. It was then cooled to room temperature, poured into ice-cold water and extracted with hexane. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by chromatography, using hexane–ether (8:2) as eluent, furnished the compound **21** (40.2 mg, 75%) as an oil; IR ν_{max} (film) 3065, 2954, 2868, 1601, 1584, 1477, 1460, 1408, 1310, 1268, 1148, 1063, 1012, 828 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.83 (1H, brs, H-6′), 6.61 (1H, brs, H-4′), 3.84 and 3.79 (3H each, each s, 2×MeO), 2.31 (3H, s, Me-5′), 1.85 (1H, m), 1.61 (3H, s, Me-2), 1.46–1.25 (4H, m), 1.10 (3H, s, Me-1), 0.46 (1H, t, J=4.0 Hz, H-6), 0.16 (1H, dd, J=4.6, 7.8 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 153.3 (C3′), 146.0 (C2′), 140.3 (C5′), 131.6 (C1′), 122.3 (C6′), 110.8 (C4′), 60.3 (MeO-2′), 55.6 (MeO-3′), 48.3 (C1), 38.3 (C3), 26.9 (C4), 29.7 (C2), 27.6 (C6), 23.2 (Me-1), 21.8 (Me-5′), 18.2 (Me-2), 14.0 (C6); MS (EI) *m/z* (relative intensity) 260 (M^+, 100), 245 (68) 231 (36), 192 (65), 177 (35), 91 (38), 77 (31): HRMS, calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1777.

3.1.16. 1,2-Dimethoxy-5-methyl-3-(1′,2′,2′-trimethyl-cyclopentyl)benzene (22). A solution of cyclopropane **21** (18.9 mg, 0.07 mmol) and NaOAc (43 mg) in AcOH (1.5 mL) was hydrogenated at room temperature over PtO_2 (68 mg) and 1.6–1.8 atm. of hydrogen pressure. The reaction was monitored by capillary GC (using a J&R P/N DB®-5 column, 30×0.25 m, He at 30 cm s^{-1}, 100–250°C at 15° min^{-1}; retention time of **21** 11.65 min) and when the reaction was complete (ca. 8 days) it was diluted with CCl_4 and filtered through a short pad of silica gel. Chromatography of the residue left after evaporation of the filtrate, using hexane–ether (8:2) yielded compound **22** (15.2 mg, 80%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.75 (1H, d, J=1.7 Hz, H-6), 6.61 (1H, d, J=1.7 Hz, H-4), 3.83 and 3.77 (3H each, s, 2×MeO), 2.63 (1H, m), 2.29 (3H, s, Me-5), 1.36, 1.12, 0.70 (3H each, each s, Me-1′, Me-2′β and Me-2′α); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 153.2 (C1), 146.8 (C2), 140.2 and 131.7 (C3 and C5), 121.8 (C4), 111.2 (C6), 60.5 (MeO-2), 55.7 (MeO-1), 51.7 (C1′), 45.1 (C2′), 41.1 (C3′), 39.1 (C5′), 27.0 (Me-1′), 25.4 (Me-2′α, 24.3 (Me-2′β, 21.8 (Me-5), 20.5 (C4′).

3.1.17. 1,2-Dimethoxy-5-methyl-3-(1′,2′,2′-trimethyl-cyclopentyl)benzene [Herbertenediol (2)]. A solution of BBr_3 (1 M solution in CH_2Cl_2; 85 μl, 0.085 mmol) was added to a solution of **22** (15 mg, 0.057 mmol) in CH_2Cl_2 (5 mL) at 0°C. After the mixture had been stirred at the same temperature for 3 h, the mixture was treated with MeOH and evaporated under vacuum. The residue was chromatographed on silica gel and eluted with hexane–ether (2:1) to give **2** (11 mg, 82%) as a colourless solid; mp 89–90°C (from hexane) [lit.[4] mp 90–91°C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.68 (1H, brs, H-6), 6.55 (1H, brs, H-4), 5.40 and 5.32 (1H each, each brs, 2×OH), 2.66–2.55 (1H, m), 2.22 (3H, s, Me-5), 1.42, 1.20, 0.77 (3H each, s each, Me-1′, Me-2′β and Me-2′α); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 143.4 (C1), 141.0 (C2), 133.6 and 128.6 (C3 and C5), 122.1 (C4), 113.5 (C6), 51.2 (C1′), 44.9 (C2′), 41.1 (C3′), 39.3 (C5′), 26.9 (Me-1′), 25.5 (Me-2′α, 22.9 (Me-2′β, 21.2 (Me-5), 20.4 (C4′).

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