PERKIN 1

Synthesis of chiral bicyclo[2.2.2]oct-5-en-2-ones *via* an intramolecular alkylation reaction

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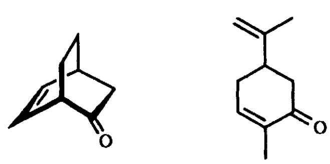
Generation of the thermodynamic dienolate of 9-bromocarvone derivatives 5, 7 and 11 furnished the chiral bicyclo[2.2.2]octenones 6, 8 and 9 and 12 and 13 containing a bridgehead methyl group *via* an intramolecular alkylation reaction. In an analogous manner intramolecular alkylation reaction of the bromo enones 15a–e, obtained from carvone 2 by 1,3-alkylative enone transposition (→14) followed by a regiospecific bromoetherification reaction, furnished the bicyclo[2.2.2]oct-5-en-2-ones 16a–e and 17a–e.

Introduction

Monoterpenes are being widely used as chiral auxiliaries but their potential as chiral starting materials has not been properly exploited. The overwhelming emphasis on carbohydrates as *chirons* in natural product synthesis,[2] during the last decade, has sidelined the importance of monoterpenes as chiral building blocks for the synthesis of natural products in their chiral form. This has come about despite the fact that many terpenes are cheap, readily available (in some cases, in both the enantiomeric forms unlike carbohydrates and amino acids) and endowed with only one or two chiral centres and modest functionality, and thus do not require recourse to destruction of excess chirality or the functionality present in them.[3] More importantly terpenes can be readily restructured into cyclic and acyclic fragments that can be directly incorporated into carbocyclic frameworks and structural moieties of complex target molecules. Diverse terpenoids by virtue of their common biogenesis embody common carbocyclic structural moieties. Therefore, an operationally versatile strategy emerges, in which such structural moieties extracted from a monoterpene can be evolved into a vast array of complex structural frameworks. In continuation of our interest in the use of carvone as a chiral starting material for the construction of a variety of mono- to tetra-cyclic, chiral, bridged carbon frameworks,[4,5] herein we describe an efficient synthesis of chiral bicyclo[2.2.2]oct-5-en-2-ones containing a methyl substituent at the bridgehead carbon atom.

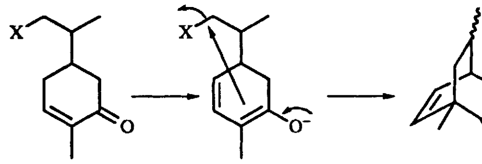
Results and discussion

The bicyclo[2.2.2]octane moiety forms an integral part of a variety of natural products, such as seychellene, patchouli alcohol, eremolactone, 2- and 9-isocyanopupukeananes, *etc.* Bicyclo[2.2.2]oct-5-en-2-one 1 moieties, comprising a β,γ-



1 2

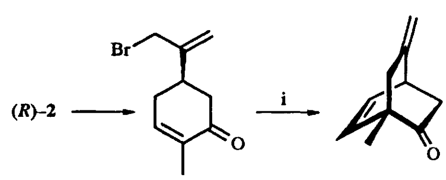
unsaturated ketone functionality, are very interesting synthons and are efficiently used in organic synthesis.[6,7] Diels–Alder reaction of cyclohexadienes using a ketene equivalent[8] is most commonly used for the generation of the enone 1. Recently a Michael–Michael sequence[9] as well as the inverse-electron-demand Diels–Alder reaction of cyclohexadienones[10] and olefins for the generation of bicyclo[2.2.2]octanone moieties present in complex molecules were also developed. In contrast we have resorted to an intramolecular alkylation methodology for the generation of chiral bicyclo[2.2.2]oct-5-en-2-ones starting from the readily available (in both the enantiomeric forms) monoterpene carvone 2. It was anticipated that the presence of a good leaving group at C-9 of carvone framework 3 and generation of a thermodynamic dienolate of 3 could bring about an intramolecular alkylation reaction leading to the formation of the bicyclic enone 4 (Scheme 1). To test the



3 4

Scheme 1

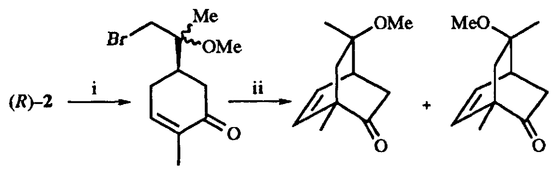
feasibility of this strategy, first 10-bromocarvone 5, a by-product obtained (40% yield)[11] in the reaction of carvone with *N*-bromosuccinimide (NBS) and sodium acetate in dichloromethane–acetic acid medium, was chosen as the starting material. Treatment of the allyl bromide 5 with potassium *tert*-butoxide in 1:1 mixture of *tert*-butyl alcohol and tetrahydrofuran (THF) furnished the dienone 6 in a highly regioselective manner (Scheme 2). The shift in the carbonyl



5 6

Scheme 2 *Reagents:* i, KOBu^t, Bu^{t}OH–THF

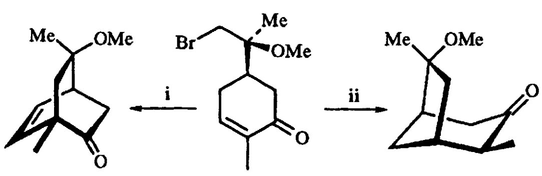
absorption band (1720 cm^{-1}) in the IR spectrum, the presence of two olefinic dd signals at δ 6.5 and 5.88 (typical for the 5-H and 6-H protons of bicyclo[2.2.2]oct-5-en-2-ones)[8b] and the upfield shift of the methyl group (1.26 ppm) in the ^{1}H NMR spectrum established the structure of the dienone 6, which was confirmed by the ^{13}C NMR spectrum[8c] (see Experimental section). To establish this generality, the readily available[11] bromoenones 7 and 11, obtained by reaction of carvone and 6-methylcarvones with NBS in dichloromethane methanol medium, were subjected to intramolecular alkylation reaction. Thus treatment of the epimeric mixture of the bromoenone **7** with potassium *tert*-butoxide in *tert*-butyl alcohol–THF furnished the bicyclic enones **8** and **9** (Scheme 3), whose



7 **8** **9**

Scheme 3 *Reagents:* i, NBS, MeOH–CH_2Cl_2; ii, KOBu^t, Bu^{t}OH–THF

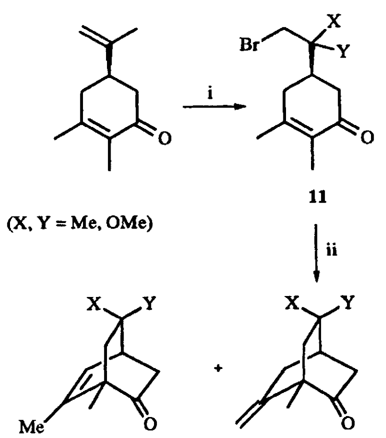
structures were established from their spectral data. The stereochemistry at C-8 was deduced based on the ^1H NMR signals of the $CH_2C{=}O$ moiety. The two protons resonated almost at the same place in the case of the enone **9**, whereas in the case of the enone **8** they appear as a well separated AB quartet because of the presence of *endo* methoxy group (with reference to the carbonyl group), the proton located *syn* to methoxy group is deshielded. The final confirmation of the stereochemistry was achieved as follows: Cooling of a hexane solution of the epimeric mixture of the bromo enone **7** resulted in the partial crystallisation of one of the isomers **7a** (see Experimental section). The intramolecular alkylation reaction of this epimer **7a** furnished the bicyclic enone **8**. On the other hand, the 5-*exo*-trig radical cyclisation reaction of this bromo enone **7a** by employing tributyltin hydride in the presence of a catalytic amount of azo isobutyronitrile (AIBN) generated the bicyclo[3.2.1]octanone **10** in 80% yield (Scheme 4), whose



8 **7a** **10**

Scheme 4 *Reagents:* i, KOBu^t, Bu^{t}OH–THF; ii, Bu_3SnH, AIBN, C_6H_6

structure was unambiguously established.[11] The formation of the bicyclic ketone **10** unambiguously established the structure of the bromo enone as **7a** which in turn, by analogy, established the stereostructure of the bicyclic enone **8** and hence that of the enone **9**. Interestingly, intramolecular alkylation, employing potassium *tert*-butoxide in *tert*-butyl alcohol and THF, of the bromo enone **11** furnished a 1 : 1 mixture of regioisomer the enones **12** and **13** (Scheme 5). In contrast, reaction of the bromo

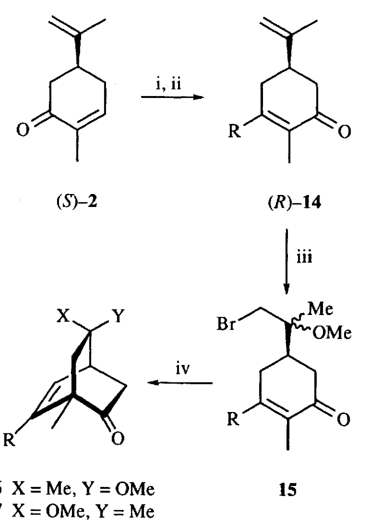


13 **12**

Scheme 5 *Reagents:* i, NBS, MeOH–CH_2Cl_2; ii, KOBu^t, Bu^{t}OH–THF

enone **11** with sodium hydride in refluxing THF furnished only the epimeric mixture of the *exo*-methylene compound **12**.

After succesfully demonstrating the feasibility of the intramolecular alkylation methodology, we extended the sequence to the synthesis of various 6-substituted bicyclo[2.2.2]oct-5-en-2-ones by starting with 6-substituted carvones. For the synthesis of 6-substituted carvones **14** an alkylative 1,3-enone transposition methodology was adopted.[12] Thus reaction of (*S*)-carvone [(*S*)-**2**] with 4-methylphenylmagnesium bromide at ice temperature furnished the 1,2-addition product, which on direct oxidation with pyridinium chlorochromate (PCC) and silica gel[13] in dichloromethane furnished the (*R*)-6-(4-methylphenyl)carvone **14a** in 70% yield. In an analogous manner, 4-methoxyphenyl, 2-methoxyphenyl and 2-phenylethynyl derivatives **14b–d** of carvone were obtained from the appropriate starting materials (see Experimental section). A regiospecific bromoetherification was employed for the generation of 9-bromocarvones. Thus reaction of carvones **14a–d** with NBS in dichloromethane–methanol medium generated 1 : 1 epimeric mixtures of the bromo enones **15a–d** in a regiospecific-manner. Finally, intramolecular alkylation with potassium *tert*-butoxide in *tert*-butyl alcohol–THF at room temperature transformed the bromo enones **15a–d** into bicyclo[2.2.2]oct-5-en-2-ones **16a–d** and **17a–d** (Scheme 6). In

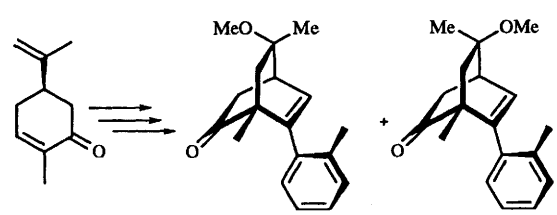


16 X = Me, Y = OMe **15**
17 X = OMe, Y = Me

for **14–17** **a**; R = 4-MeC_6H_4 **b**; R = 4-$MeOC_6H_4$
c; R = 2-$MeOC_6H_4$ **d**; R = PhC≡C

Scheme 6 *Reagents:* i, RMgBr or RLi, THF; ii, PCC–silica gel, CH_2Cl_2; iii, NBS, MeOH–CH_2Cl_2; iv, KOBu^t, Bu^{t}OH–THF

an identical manner starting from (*R*)-carvone [(*R*)-**2**] and 2-bromotoluene, the bicyclooctenones **16e** and **17e** were obtained *via* the corresponding carvones **14e** and the bromoenone **15e**. It is worth mentioning that the enones **14e** and **15e** were found to be a ~ 1 : 1 mixture of the rotational isomers at the aryl–vinyl bond (due to the orthogonal arrangement of aryl and olefin moieties) from the NMR spectrum. Interestingly even in the case of the bicyclic compounds **16e** and **17e** the



(*R*)-2 **16e** **17e**

aryl group is orthogonal to the olefin moiety and there is considerable restricted rotation of the aryl moiety as evidenced by the variable-temperature ^1H NMR spectra, *e.g.* only one set of signals is noticed at higher temperature whereas signals due to both the rotational isomers (~3:2) were observed at −20 °C, and at room temperature broadening of signals due to aromatic methyl and one of the protons at C-7 was observed.

In conclusion, we have achieved the synthesis of chiral bicyclo[2.2.2]oct-5-en-2-ones *via* an intramolecular alkylation of 9-bromo derivatives of carvone, and have extended the methodology to various 6-substituted derivatives *via* the synthesis of the corresponding 6-substituted carvones and their C-9 bromo derivatives. The presence of a methyl group at the bridgehead position (C-1) enhances the importance of this methodology as most of the natural products containing the bicyclo[2.2.2]octane moiety (as part structure) contain a methyl group (or ring residue) at one of the bridgehead carbons.

Experimental

Mps were measured in capillaries on a TEMPO melting point apparatus and are uncorrected. IR spectra (for thin films) were recorded on Perkin-Elmer 781 and Hitachi 270–50 spectrophotometers. UV spectra were recorded on a Shimadzu UV-190 spectrophotometer. ^1H (60, 90, 200 and 270 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on Varian T-60, JEOL FX-90Q, Bruker ACF-200 and Bruker WH-270 spectrometers. The chemical shifts (δ ppm) and the coupling constants (J/Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (δ_C 77.1) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, off-resonance multiplicities, when recorded, are given in parentheses. Low- and high-resolution mass measurements were carried out with a JEOL JMS-DX 303 GC-MS instrument using a direct-inlet mode. Elemental analyses were carried out using a Carlo-Erba 1106 CHN analyser. Relative intensities of the ions are given in parentheses. Optical rotations were measured using a JASCO DIP-303 polarimeter; $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. Acme's silica gel (100–200 mesh) was used for column chromatography. Low-temperature reactions were conducted in a bath made of alcohol and liquid nitrogen. Dry diethyl ether was obtained by distillation over sodium and stored over sodium wire. Dichloromethane was distilled from P_2O_5. Potassium was obtained from Riedel. PCC was prepared according to the literature procedure.[13a] (*R*)-Carvone, NBS, 2- and 4-bromotoluene, and 4-bromoanisole were obtained from Fluka and were used as such. (*S*)-Carvone was obtained as a gift from Professor G. S. Krishna Rao. Phosphate buffer was prepared from equimolar amounts of KH_2PO_4 and Na_2HPO_4.

(1*S*,4*S*)-1-Methyl-8-methylenebicyclo[2.2.2]oct-5-en-2-one 6

A solution of the allyl bromide **5**[11] (458 mg, 2 mmol) in dry THF (3 cm^3) was added rapidly to an ice-cold, magnetically stirred solution of KOBu^t in *tert*-butyl alcohol (0.5 mol dm^{-3}; 5 cm^3, 2.5 mmol) in dry THF (2 cm^3). The reaction mixture was stirred at room temperature for 6 h, diluted with diethyl ether (20 cm^3), and washed successively with 0.5 mol dm^{-3} aq. HCl (10 cm^3) and brine and dried (Na_2SO_4). Evaporation off of the solvent and purification of the residue over a silica gel (10 g) column with ethyl acetate–hexane (1:9) as eluent furnished the *dienone* **6** (133 mg, 45%) as a pale yellow oil, $[\alpha]_D^{26}$ −578 (*c* 2.15; $CHCl_3$); ν_{max}/cm^{-1} 3080, 1720 (C=O), 1080, 890 (C=CH_2), 770 and 680; δ_H(90 MHz; $CDCl_3$) 6.5 (1 H, dd, *J* 8 and 6.5, 5-H), 5.88 (1 H, dd, *J* 8 and 2, 6-H), 4.92 (1 H, br s) and 4.74 (1 H, br s) (C=CH_2), 3.34 (1 H, m, 4-H), 2.32 (2 H, m, CH_2C=O), 2.18 (2 H, br s, 7-H) and 1.26 (3 H, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$) 212.3 (s, C=O), 146.7 (s, *C*=CH_2), 135.6 (d) and 134.1 (d) (CH=CH), 106.5 (t, C=*C*H_2), 50.7 (s, C-1), 42.9 (d, C-4), 40.3 (t, C-3), 38.3 (t, C-7) and 17.2 (q, 1-CH_3); *m/z* 148 (M^+, 2%), 106 (98) and 91 (100) (Found: M^+, 148.0887. $C_{10}H_{12}O$ requires M, 148.0888). Further elution of the column with the same solvent furnished unchanged substrate **5** (70 mg, 15% recovery).

(5*R*)-5-[(2*S*)-1-Bromo-2-methoxypropan-2-yl]-2-methylcyclohex-2-enone 7a

To a cold (0 °C) magnetically stirred solution of (*R*)-carvone (4.5 g, 30 mmol) in a 2:3 mixture of methanol and dichloromethane (45 cm^3) was added NBS (6.4 g, 36 mmol) in portions over a period of 1.5 h. The reaction mixture was stirred for 16 h at room temperature, diluted with dichloromethane (50 cm^3) washed successively with 2% aq. sodium hydroxide and brine and dried (Na_2SO_4). Evaporation off of the solvent and purification of the residue over a silica gel (50 g) column with ethyl acetate–hexane (1:10) as eluent furnished a 1:1 epimeric mixture of the *bromo enone* **7** (6.4 g, 82%) as an oil.[11] Cooling of a hexane solution of the epimeric mixture **7** resulted in the crystallisation of the title epimer **7a**, mp 65–66 °C; $[\alpha]_D^{27}$ 7 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 1665 (C=O), 1370, 1105 and 1075; δ_H(200 MHz; $CDCl_3$) 6.7 (1 H, br s, olefinic), 3.45 (2 H, AB q, *J* 11.2, $\Delta\nu$ 6.2 Hz, CH_2Br), 3.24 (3 H, s, OCH_3), 2.1–2.65 (5 H, m), 1.78 (3 H, s, 2-CH_3) and 1.26 (3 H, s, *tert*-CH_3).

(1*S*,4*S*,8*R*)- and (1*S*,4*S*,8*S*)-8-Methoxy-1,8-dimethylbicyclo-[2.2.2]oct-5-en-2-one 8 and 9

Intramolecular alkylation of the bromo enone **7** (1:1 mixture of epimers; 2.61 g, 10 mmol) in dry THF (15 cm^3) with KOBu^t (1 mol dm^{-3} in Bu^{t}OH; 15 cm^3, 15 mmol) for 8 h as described earlier, followed by purification over a silica gel (20 g) column with ethyl acetate–hexane (1:4) as eluent, furnished the *bicyclic octenones* **8** and **9** (1:1; 1.08 g, 60%) as pale yellow oils. *Compound* **8** (reaction using the crystalline bromo enone **7a** resulted in the formation of this bicyclic enone **8** as the sole product): $[\alpha]_D^{26}$ −408 (*c* 1.8, $CHCl_3$); ν_{max}/cm^{-1} 3046, 1720 (C=O), 1460, 1188, 1134, 1116, 1080 and 680; δ_H(200 MHz; $CDCl_3$) 6.45 (1 H, t, *J* 6.9, 5-H), 5.86 (1 H, d, *J* 7.2, 6-H), 3.20 (3 H, s, OCH_3), 2.95 (1 H, m, 4-H), 2.56 (1 H, dd, *J* 18.1 and 2) and 1.89 (1 H, dd, *J* 18.1 and 3.1) (CH_2C=O), 1.79 and 1.47 (2 H, AB q, *J* 13.6, 7-H_2), 1.28 (3 H, s, 8-CH_3) and 1.17 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$) 211.7 (s, C=O), 135.5 (d) and 134.1 (d) (CH=CH), 78.3 (s, *C*OCH_3), 49.8 (s, C-1), 49.1 (q, OCH_3), 45.8 (t, *C*H_2C=O), 41.1 (d, C-4), 34.2 (t, C-7), 24.4 (q, 8-CH_3) and 16.8 (q, 1-CH_3).

Compound **9**: $[\alpha]_D^{26}$ −443 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3046, 1728 (C=O), 1131, 1077, 750 and 684; δ_H(200 MHz; $CDCl_3$) 6.475 (1 H, dd, *J* 8 and 6.3, 5-H), 5.94 (1 H, d, *J* 8, 6-H), 3.18 (3 H, s, OCH_3), 3.0 (1 H, m, 4-H), 2.11 (2 H, m, CH_2C=O), 1.76 and 1.54 (2 H, AB q, *J* 14, 7-H), 1.38 (3 H, s, 8-CH_3) and 1.19 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$) 211.8 (s, C=O), 135.4 (d) and 134.3 (d) (CH=CH), 79.0 (s, *C*OMe), 49.9 (s, C-1), 49.2 (q, OCH_3), 46.2 (t, *C*H_2C=O), 41.1 (d, C-4), 36.0 (t, C-7), 22.2 (q, 8-CH_3) and 17.2 (q, 1-CH_3). For a mixture of isomers **8** and **9**: *m/z* 165 (M^+ − 15, 100%), 135 (15), 123 (18) and 107 (20) (Found: M^+, 180.1131. $C_{11}H_{16}O_2$ requires M, 180.1150).

(1*S*,4*R*,8*S*)- and (1*S*,4*R*,8*R*)-8-Methoxy-1,8-dimethyl-6-methylenebicyclo[2.2.2]octan-2-one 12

A solution of the bromo enone **11** (1:1 mixture of epimers; 825 mg 3 mmol) in dry THF (6 cm^3) was added to a magnetically stirred suspension of sodium hydride (50% in oil; 220 mg, 4.5 mmol, washed with dry hexane) in dry THF (2 cm^3). The reaction mixture was refluxed for 10 h, cooled, diluted with diethyl ether (20 cm^3), washed successively with 0.5 mol dm^{-3} aq. HCl and brine and dried (Na_2SO_4). Evaporation off of the solvent and purification of the residue over a silica gel (10 g) column with ethyl acetate–hexane (1:4) as eluent furnished a 1:1 epimeric mixture of the *enones* **12** (410 mg, 70%) as an oil, $[\alpha]_D^{26}$ −87.7 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1} 3100, 1730 (C=O), 1650, 1380, 1130, 1080, 1075, 885 (C=CH_2) and 750; δ_H(90 MHz; $CDCl_3$) 4.92 (1 H, br s) and 4.88 (1 H, br s) (C=CH_2), 3.18 and

3.2 (3 H, s, OCH_3), 1.4–3.0 (7 H, m), 1.32 and 1.24 (3 H, s, 8-CH_3) and 1.08 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$) 211.1 (s, C=O), 145.1 and 144.7 (s, *C*=CH_2), 108.7 (t, C=*C*H_2), 74.6 and 74.3 (s, C-8), 51.3 (s, C-1), 49.1 and 48.6 (q, OCH_3), 47.6 and 47.0 (t, *C*H_2C=O), 40.1 and 38.9 (t, C-7), 35.8 and 35.6 (d, C-4), 31.6 and 29.8 (t, C-5), 22.7 and 22.4 (q, 8-CH_3) and 15.7 (1-CH_3); *m/z* 195 (M^+, 1.5%), 179 (2), 121 (45), 120 (100), 119 (25), 105 (62) and 85 (53) [Found: *m/z*, 179.1082. $C_{11}H_{15}O_2$ (M^+ − 15) requires *m/z*, 179.1072].

(*R*)-5-Isopropenyl-2-methyl-3-(4-methylphenyl)cyclohex-2-enone 14a

To a magnetically stirred suspension of magnesium (480 mg, 20 mmol) and iodine (few crystals) in dry diethyl ether (15 cm^3), placed in a two-necked 100 cm^3 flask equipped with a condenser and a pressure-equalising funnel, was added dropwise a solution of 4-bromotoluene (3.42 g, 20 mmol) in dry diethyl ether (25 cm^3) over a period of 1 h. The reaction mixture was cooled in an ice-bath soon after the initiation. To the 4-methylphenylmagnesium bromide thus formed was added dropwise a solution of (*S*)-carvone (*S*)-**2** (2.25 g, 15 mmol) of dry diethyl ether (10 cm^3). The reaction mixture was stirred for 1.5 h at room temperature, slowly poured into a cold pH 7 phosphate buffer (20 cm^3), and extracted with diethyl ether (3 × 20 cm^3). The combined extract was washed successively with water and brine, and dried (Na_2SO_4). Evaporation off of the solvent furnished the tertiary alcohol (3.6 g), which was oxidised without further purification.

A solution of the above crude alcohol in dichloromethane (10 cm^3) was added to a magnetically stirred suspension of a finely ground mixture of PCC (6.48 g, 30 mmol) and silica gel (6.48 g) in dichloromethane (40 cm^3). The reaction mixture was stirred for 2 h at room temperature and filtered through a silica gel (50 g) column with dichloromethane as eluent. Evaporation off of the solvent and purification of the residue over a silica gel (80 g) column with ethyl acetate–hexane (3:100) as eluent furnished the *tolylcarvone* **14a** (2.52 g, 70%) as a liquid, $[\alpha]_D^{25}$ −100.6 (*c* 0.8, $CHCl_3$); λ_{max}(CH_3OH)/nm 273 (ε 13 380 dm^3 mol^{-1} cm^{-1}) and 232 (10 200); ν_{max}/cm^{-1} 3080, 3020, 1665 (C=O), 1620 (C=C), 1505, 1435, 1380, 1360, 1345, 1265, 1100, 890 (C=CH_2), 810 and 795; δ_H(60 MHz; CCl_4) 7.0 (4 H, s, ArH), 4.75 (2 H, br s, olefinic), 2.4–2.7 (5 H, m), 2.35 (3 H, s, ArC*H*$_3$), 1.75 (3 H, br s, CH_3 of isopropenyl group) and 1.66 (3 H, br s, 2-CH_3); δ_C(22.5 MHz; $CDCl_3$) 198.9 (s, C=O), 155.0 (s, *C*=C–C=O), 146.2 (s, *C*=CH_2), 137.9 (s), 137.4 (s, C=*C*–C=O), 131.0 (s), 128.7 (2 C, d) and 126.8 (2 C, d) (arom), 110.2 (t, C=*C*H_2), 42.3 (t), 41.5 (d, C-5), 37.8 (t), 20.8 (q, Ar-*C*H_3), 20.2 (q, CH_3 of isopropenyl) and 12.5 (q, 2-CH_3); *m/z* 240 (M^+, 62%), 225 (35), 212 (80), 198 (87), 197 (50), 183 (100), 144 (40), 129 (95), 128 (70), 115 (45), 105 (40) and 91 (35) (Found: M^+, 240.1523. $C_{17}H_{20}O$ requires M, 240.1514).

(5*R*)-5-[(2*R*)- and (2*S*)-1-Bromo-2-methoxypropan-2-yl]-2-methyl-3-(4-methylphenyl)cyclohex-2-enone 15a

Bromoetherification of tolylcarvone **14a** (2.4 g, 10 mmol) in a 2:3 mixture of methanol and dichloromethane (25 cm^3) with NBS (2.14 g, 12 mmol) for 16 h at room temperature as described for compound **7**, followed by purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (1:10) as eluent, furnished a 1:1 epimeric mixture of the *bromoenones* **15a** (2.4 g, 68%) as an oil, ν_{max}/cm^{-1} 3040, 1675 (C=O), 1630 (C=C), 1515, 1460, 1385, 1340, 1115, 1085 and 820; δ_H(60 MHz; CCl_4) 7.07 (4 H, s, ArH), 3.4 (2 H, s, CH_2Br), 3.22 (3 H, s, OCH_3), 2.3–2.7 (5 H, m), 2.33 (3 H, s, ArC*H*$_3$), 1.66 (3 H, br s, 2-CH_3) and 1.26 (3 H, s, *tert*-CH_3); δ_C(22.5 MHz; $CDCl_3$; 1:1 mixture of epimers) 199.5 and 199.2 (s, C=O), 156.2 and 155.3 (s, *C*=C–C=O), 138.1(s), 137.7 (s), 131.2 (s), 128.9 (2 C, d), 127.0 (2 C, d), 75.9 (s, *C*OCH_3), 49.4 (q, OCH_3), 40.1 (d, C-5), 38.5 and 37.6 (t), 36.6 (t), 33.8 and 33.0 (t), 21.2 (q, Ar*C*H_3), 17.9 (q, *tert*-CH_3) and 12.6 (q, 2-CH_3); *m/z* 350 and 352 (M^+ and M^+ + 2, 75%), 199 (100), 198 (50), 197 (52), 153 (55), 151 (55) and 129 (35) (Found: M^+ 352.0884, $C_{18}H_{23}BrO_2$ requires M, 352.0863).

(1*S*,4*S*,8*R*)- and (1*S*,4*S*,8*S*)-8-Methoxy-1,8-dimethyl-6-(4-methylphenyl)bicyclo[2.2.2]oct-5-en-2-one 16a and 17a

Intramolecular alkylation of the bromo enone **15a** (2.1 g, 6 mmol) with $KOBu^t$ (1 mol dm^{-3} in Bu^tOH; 9 cm^3, 9 mmol) and dry THF (9 cm^3) for 16 h as described for compound **6** and purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (1:20) as eluent, furnished a 1:1 mixture of the *bicyclic enones* **16a** and **17a** (1.46 g, 90%) as an oil, λ_{max}(CH_3OH)/nm 245 (ε 9030); ν_{max}/cm^{-1} 3040, 1725 (C=O), 1510, 1455, 1380, 1325, 1280, 1185, 1130, 1080, 850, 820 and 680; δ_H(90 MHz; $CDCl_3$, for **16a**) 7.12 and 6.92 (4 H, AB q, *J* 7, ArH), 6.1 (1 H, d, *J* 7, olefinic), 3.27 (3 H, s, OCH_3), 3.0 (1 H, t of d, *J* 7 and 3, 4-H), 2.7 and 2.06 (2 H, d of AB q, *J* 18 and 3, CH_2C=O), 2.36 (3 H, s, ArCH_3), 1.9 and 1.64 (2 H, AB q, *J* 14, 7-H_2), 1.38 (3 H, s, 8-CH_3) and 1.04 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$, mixture of **16a** and **17a**) 212.2 and 212.0 (s, C=O), 145.4 (s), 143.4 (s), 136.9 (s), 135.7 (s), 135.5 (s), 134.5 (s), 132.5 (d), 128.6 (2 C, d) and 128.1 (2 C, d), 78.5 and 79.0 (s, C-8), 52.8 (s, C-1), 49.7 (q, OCH_3), 47.3 and 46.1 (t, *C*H_2C=O), 41.1 (d, C-4), 34.7 and 36.3 (t, C-7), 25.1 (q, 8-CH_3), 21.1 (q, Ar*C*H_3) and 16.5 (q, 1-CH_3); *m/z* 270 (M^+, 30%), 198 (100), 196 (70) and 183 (95) (Found: M^+, 270.1605; C, 80.1; H, 8.5%. $C_{18}H_{22}O_2$ requires M, 270.1620; C, 79.96; H, 8.20%).

(*R*)-5-Isopropenyl-3-(4-methoxyphenyl)-2-methylcyclohex-2-enone 14b

To a cold (−78 °C) magnetically stirred solution of *p*-bromoanisole (3.74 g, 20 mmol) in dry THF (25 cm^3) under nitrogen was added a hexane solution of butyllithium (1.6 mol dm^{-3}; 12.5 cm^3, 20 mmol) and the mixture was stirred at the same temperature for 0.5 h. To the 4-methoxyphenyllithium thus formed was added a solution of (*S*)-carvone (*S*)-**2** (2.25 g, 15 mmol) in dry THF (10 cm^3) at −78 °C. The reaction mixture was stirred for 12 h at room temperature, quenched with aq. ammonium chloride (10 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined extract was washed with brine and dried (Na_2SO_4). Evaporation off of the solvent furnished the tertiary alcohol (3.87 g), which was directly oxidised with PCC (6.48 g, 30 mmol) and silica gel (6.48 g) in dichloromethane (40 cm^3) for 2 h as described for compound **14a**; purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (3:100) as eluent furnished the *methoxyphenylcarvone* **14b** (2.1 g, 55%) as an oil, $[\alpha]_D^{25}$ −71.8 (*c* 3, $CHCl_3$); λ_{max}(CH_3OH)/nm 289 (ε 11 500) and 243 (ε 8200); ν_{max}/cm^{-1} 3050, 1665 (C=O), 1620 (C=C), 1510, 1435, 1380, 1285, 1255, 1165, 1100, 1025, 890 (C=CH_2), 815 and 760; δ_H(90 MHz; $CDCl_3$) 7.18 (2 H, d, *J* 8.2, 2′- and 6′-H ArH), 6.92 (2 H, d, *J* 8.2, 3′- and 5′-H ArH), 4.8 (2 H, br s, C=CH_2), 3.82 (3 H, s, ArOC*H*$_3$), 2.3–2.9 (5 H, m) and 1.76 (6 H, s, 2 × olefinic CH_3); δ_C(22.5 MHz; $CDCl_3$) 199.6 (s, C=O), 159.3 (s, *C*OCH_3), 155.1 (s, *C*=C–C=O), 146.5 (s, *C*=CH_2), 133.3 (s, C-1′ arom), 131.0 (s, C=*C*–C=O), 128.7 (2 C, d, C-2′ and 6′ arom), 113.6 (2 C, d, C-3′ and-5′ arom, 110.5 (t, C=*C*H_3), 55.1 (q, OCH_3), 42.5 (t), 41.6 (d, C-5), 37.9 (t), 20.5 (q, CH_3 of isopropenyl group) and 12.8 (q, 2-CH_3); *m/z* 256 (M^+, 100%), 228 (80), 214 (60), 213 (50), 199 (60), 150 (65), 135 (50) and 121 (50) (Found: M^+, 256.1465. $C_{17}H_{20}O_2$ requires M, 256.1463).

(5*R*)-5-[(2*S*)- and (2*R*)-1-Bromo-2-methoxypropan-2-yl]-3-(4-methoxyphenyl)-2-methylcyclohex-2-enone 15b

Bromoetherification of the *p*-methoxyphenylcarvone **14b** (2.56 g, 10 mmol) in a 3:2 mixture of dichloromethane–methanol (20 cm^3) with NBS (2.14 g, 12 mmol) for 12 h as described for compound **7** and purification of the product over a silica gel (60 g) column with ethyl acetate–hexane (1:10) as eluent, furnished a 1 : 1 epimeric mixture of the *bromo enones* **15b** (3.17 g, 87%) as a viscous liquid, $[\alpha]_D^{25}$ −81 (*c* 3.9, $CHCl_3$); ν_{max}/cm^{-1} 1670 (C=O), 1615 (aromatic), 1515, 1390, 1340, 1290, 1250, 1180, 1109, 1080, 910, 835 and 735; δ_H(90 MHz; $CDCl_3$; 1 : 1 mixture of epimers) 7.2 (2 H, d, *J* 9, 2′- and 6′-H ArH), 6.92 (2 H, d, *J* 9, 3′- and 5′-H ArH), 3.86 (3 H, s, $ArOCH_3$), 3.5 (2 H, s, CH_2Br), 3.28 (3 H, s, OCH_3), 2.2–2.8 (5 H, m), 1.76 (3 H, s, 2-CH_3) and 1.32 (3 H, s, *tert*-CH_3); δ_C(22.5 MHz; $CDCl_3$; 1 : 1 mixture of epimers) 199.8 and 199.5 (s, C=O), 159.4 (s, C-4′ arom), 156.0 and 155.0 (s, *C*=C–C=O), 133.4 (s, C-1′ arom), 131.3 and 131.0 (s, C=*C*–C=O), 128.8 (2 C, d, C-2′ and 6′-arom), 113.8 (2 C, d, C-3′ and 5′ arom), 76.0 (s, *C*OCH_3), 55.4 (q, ArO*C*H_3), 49.6 (q, CH_3COCH_3), 40.3 (d, C-5), 38.7 and 37.9 (t), 36.8 (t), 34.0 and 33.2 (t), 18.2 and 17.9 (q, *tert*-CH_3) and 13.0 (q, 2-CH_3); *m/z* 366 and 368 (M^+ and $M^+ + 2$, 20%), 215 (100), 213 (45), 153 (50) and 151 (50) (Found: M^+, 366.0840. $C_{18}H_{23}BrO_3$ requires M, 366.0831).

(1*S*,4*S*,8*R*)- and (1*S*,4*S*,8*S*)-8-Methoxy-6-(4-methoxyphenyl)-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-one 16b and 17b

Intramolecular alkylation of the bromo enone **15b** (1 : 1 mixture of epimers; 2.2 g, 6 mmol) with $KOBu^t$ (1 mol dm^{-3} in Bu^tOH; 9 cm^3, 9 mmol) in dry THF (9 cm^3) for 12 h as described for compound **6** and purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (1 : 20) as eluent, furnished a 1 : 1 mixture of the *bicyclooctenones* **16b** and **17b** (1.225 g, 70%) as an oil, $[\alpha]_D^{25}$ −155.67 (*c* 6.17, $CHCl_3$); ν_{max}/cm^{-1} 3040, 1725 (C=O), 1610, 1575, 1510, 1460, 1410, 1380, 1370, 1285, 1240, 1175, 1075, 1030 and 825; δ_H(90 MHz; $CDCl_3$, for **16b**) 6.98 (2 H, d, *J* 7.2, 2′- and 6′-H ArH), 6.82 (2 H, d, *J* 7.2, 3′- and 5′-H ArH), 6.3 (1 H, d, *J* 7.2, olefinic), 3.82 (3 H, s, ArOC*H*$_3$), 3.26 (3 H, s, 8-OCH_3), 3.0 (1 H, m, 4-H), 2.71 (1 H, d of $\frac{1}{2}$ AB q, *J* 18 and 2) and 2.08 (1 H, d of $\frac{1}{2}$ AB q, *J* 18 and 3.5) (together CH_2C=O), 1.92 and 1.66 (2 H, AB q, *J* 14.4, 7-H_2), 1.39 (3 H, s, 8-CH_3) and 1.06 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$; 1 : 1 mixture of **16b** and **17b**) 212.2 and 211.8 (s, C=O), 145.0 and 142.9 (s, Ar*C*=CH), 132.3 (d, ArC=*C*H), 158.8 (s, C-4′ arom), 130.9 and 130.7 (s, C-1′, arom), 129.6 and 129.2 (2 C, d, C-2′ and 6′-arom), 113.2 (2 C, d, C-2′ and 6′-arom), 78.9 and 78.4 (s, *C*OCH_3), 55.1 (q, ArO*C*H_3), 52.6 (s, C-1), 49.6 (q, 8-OCH_3), 47.1 (t, CO*C*H_2), 40.9 (d, C-4), 36.2 and 34.5 (t, C-7), 24.9 and 22.3 (q, 8-CH_3) and 16.5 (q, 1-CH_3); *m/z* 286 (M^+, 30%), 271 (10), 215 (30), 214 (100), 213 (30) and 183 (40) (Found: M^+, 286.1573. $C_{18}H_{22}O_3$ requires M, 286.1569).

(5*R*)-5-Isopropenyl-3-(2-methoxyphenyl)-2-methylcyclohex-2-enone 14c

To a cold (−78 °C) magnetically stirred solution of anisole (2.16 g, 20 mmol) in dry THF (25 cm^3) and tetramethylethylenediamine (TMEDA) (2 cm^3), under nitrogen was added a hexane solution of butyllithium (1.6 mol dm^{-3}; 12.5 cm^3, 20 mmol) and the mixture was stirred for 0.5 h. To the *o*-methoxyphenyllithium thus formed was added a solution of (*S*)-carvone (S)-**2** (2.25 g, 15 mmol) in dry THF (10 cm^3). The reaction mixture was stirred at room temperature for 10 h, slowly poured into a cold pH 7 phosphate buffer (20 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined extract was washed successively with water and brine and dried (Na_2SO_4). Evaporation off of the solvent followed by oxidation of the resultant tertiary alcohol (3.87 g) with PCC (6.48 g, 30 mmol) and silica gel (6.48 g) in dichloromethane (40 cm^3) for 2 h as described for compound **14a** and purification of the product over a silica gel (100 g) column with ethyl acetate–hexane (1 : 50) as eluent furnished the o-*methoxyphenylcarvone* **14c** (2.3 g, 60%) as an oil, $[\alpha]_D^{25}$ −69.4 (*c* 0.86, $CHCl_3$); λ_{max}(CH_3OH)/nm 247.5 (ε 9250); ν_{max}/cm^{-1} 3064, 1671 (C=O), 1599, 1491, 1461, 1437, 1380, 1344, 1290, 1248, 1104, 1023, 891 (C=CH_2) and 753; δ_H(60 MHz; CCl_4) 6.6–7.3 (4 H, m, ArH), 4.7 (2 H, br s, olefinic), 3.77 (3 H, s, OCH_3), 2.3–2.8 (5 H, m), 1.73 (3 H, br s, CH_3 of isopropenyl and 1.5 (3 H, br s, 2CH_3); δ_C(22.5 MHz; $CDCl_3$) 199.8 (C=O), 155.5, 146.9, 132.5, 130.1, 129.2, 128.3, 120.6, 114.5 (C-1′ arom), 111.1 (C-3′ arom), 110.4 (C=*C*H_2), 55.5 (ArO*C*H_3), 43.0, 42.0 (C-5), 37.3, 20.6 (CH_3 of isopropenyl and 12.6 (2-CH_3); *m/z* 256 (M^+, 40%), 214 (100), 199 (60), 150 (40), 145 (80), 135 (40), 121 (60), 115 (50) and 91 (60) (Found: M^+, 256.1479. $C_{17}H_{20}O_2$ requires M, 256.1463).

(5*R*)-[(2*S*)- and (2*R*)-1-Bromo-2-methoxypropan-2-yl]-3-(2-methoxyphenyl)-2-methylcyclohex-2-enone 15c

Bromoetherification of the *o*-methoxyphenylcarvone **14c** (2.56 g, 10 mmol) in a 3 : 2 mixture of dichloromethane–methanol (25 cm^3) with NBS (2.14 g, 12 mmol) for 12 h as described for compound **7** and purification of the product over a silica gel (60 g) column with ethyl acetate–hexane (1 : 10) as eluent furnished a 1 : 1 epimeric mixture of the *bromo enones* **15c** (2.55 g, 70%) as a syrupy liquid, $[\alpha]_D^{25}$ −76.4 (*c* 5.57, $CHCl_3$); λ_{max}(CH_3OH)/nm 247 (ε 16 950); ν_{max}/cm^{-2} 1668 (C=O), 1599, 1581, 1488, 1461, 1437, 1380, 1338, 1248, 1218, 1182, 1104 and 750; δ_H(60 MHz; CCl_4) 6.6–7.4 (4 H, m, ArH), 3.7 (3 H, s, ArOC*H*$_3$), 3.4 (2 H, s, CH_2Br), 3.17 (3 H, s, CH_3COCH_3), 2.3–2.7 (5 H, m), 1.56 (3 H, br s, olefinic CH_3) and 1.23 (3 H, s, *tert*-CH_3); δ_C(22.5 MHz; $CDCl_3$; mixture of epimers) 199.2 (s, C=O), 155.4 (s), 132.3 (s), 129.9 (s), 129.2 (d), 128.2 (d) and 120.5 (d), 112.8 (s, C-1′ arom), 111.0 (d, C-3′ arom), 76.0 (s, *C*OCH_3), 55.4 (q, ArO*C*H_3) 49.5 (q, CH_3COCH_3), 40.3 (d, C-5), 38.8 and 38.2 (t), 36.9 (t), 32.2 and 33.0 (t), 18.0 (q, *tert*-CH_3) and 12.4 (q, 2-CH_3); *m/z* 366 and 368 (M^+ and $M^+ + 2$, 10%), 255 (15), 216 (25), 215 (100), 214 (40), 153 (60) and 151 (60) (Found: M^+, 366.0931. $C_{18}H_{23}BrO_3$ requires M, 366.0831).

(1*S*,4*S*,8*R*)- and (1*S*,4*S*,8*S*)-8-Methoxy-6-(2-methoxyphenyl)-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-one 16c and 17c

Intramolecular alkylation of the bromo enone **15c** (1 : 1 mixture of epimers; 2.2 g, 6 mmol) with $KOBu^t$ (1 mol dm^{-3} in Bu^tOH; 9 cm^3, 9 mmol) in dry THF (9 cm^3) for 12 h as described for compound **6** and purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (1 : 20) as eluent, furnished a 1 : 1 mixture of the *bicyclooctenones* **16c** and **17c** (1.06 g, 60%) as a liquid, $[\alpha]_D^{25}$ −82.1 (*c* 0.76, $CHCl_3$); ν_{max}/cm^{-1} 1728 (C=O), 1599, 1491, 1461, 1437, 1272, 1245, 1113, 1080, 1026 and 750; δ_H(60 MHz; CCl_4; for one isomer) 6.5–7.4 (4 H, m, ArH), 6.13 (1 H, d, *J* 6, olefinic), 3.7 (3 H, s, ArOC*H*$_3$), 3.17 (3 H, s, 8-OCH_3), 2.7–3.1 (1 H, m, 4-H), 1.4–2.7 (4 H, m, 3- and 7-Hz), 1.33 (3 H, s, 8-CH_3) and 0.8 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$; one of the isomers) 212.2 (s, C=O), 143.7 (s, Ar*C*=CH), 132.3 (d, ArC=*C*H), 156.8 (s, C-2′ arom), 130.0 (d), 128.8 and 120.2 (C-4′, 5′ and 6′ arom), 127.9 (C-1′ arom), 110.0 (d, C-3′ arom), 78.6 (s, C-8), 55.0 (q, ArOCH_3), 53.0 (s, C-1), 49.6 (q, OCH_3), 46.4 (t, CO*C*H_2), 41.0 (d, C-4), 34.8 (t, C-7), 24.9 (q, 8-CH_3) and 15.0 (q, 1-CH_3); *m/z* 286 (M^+, 20%), 215 (40), 214 (100), 213 (40), 212 (75) and 183 (40) (Found: M^+, 286.1582. $C_{18}H_{22}O_3$ requires M, 286.1569).

(5*R*)-5-Isopropenyl-2-methyl-3-(2-phenylethynyl)cyclohex-2-enone 14d

Reaction of 1-lithio-2-phenylacetylene [obtained from phenylacetylene (2.04 g, 20 mmol) and butyllithium (1.6 mol dm^{-3} in hexanes; 12.5 cm^3, 20 mmol) in dry THF (25 cm^3)] with (*S*)-carvone (*S*)-**2** (2.25 g, 15 mmol) in dry THF (35 cm^3), followed by oxidation of the resultant tertiary alcohol (3.78 g) with PCC (6.48 g, 30 mmol) and silica gel (6.48 g) in dichloromethane (40 cm^3) as described for compound **14a**, and purification of the product over a silica gel (80 g) column with ethyl acetate–hexane (3 : 100) as eluent, furnished the (R)-6-(2-*phenylethynyl*)-2-*carvone* **14d** (1.87 g, 50%) as a liquid, $[\alpha]_D^{25}$ −110 (*c* 3.33, $CHCl_3$); λ_{max}(CH_3OH)/nm 318.5 (ε 13 270), 289 (13 180) and 234 (11 500); ν_{max}/cm^{-1} 3050, 2200 (C≡C), 1670 (C=O), 1605, 1495, 1385, 1340, 1310, 1265, 1200, 1060, 910 (C=CH_2), 755 and 685; δ_H(90 MHz, $CDCl_3$) 7.2–7.7 (5 H, m, ArH), 4.7–4.95 (2 H, m, olefinic), 2.0–3.0 (5 H, m) and 2.1 (3 H, s) and 1.82 (3 H, s) (2 × olefinic CH_3); δ_C(22.5 MHz; $CDCl_3$) 197.8 (s, C=O), 145.9 (s); 138.2 (s), 136.4 (s), 131.4 (2 C, d), 129.0 (d), 128.3 (2 C, d) and 122.2 (s) (arom), 110.6 (t, C=*C*H_2), 103.1 (s, Ph*C*≡C), 88.0 (s, PhC≡*C*), 42.3 (t), 41.3 (d, C-5), 35.7 (t), 20.2 (q, CH_3 of isopropenyl group) and 13.6 (q, 2-CH_3); *m/z* 250 (M^+, 50%), 222 (70), 208 (100), 207 (50), 193 (80), 178 (40), 165 (40), 153 (50), 139 (45) and 115 (40) (Found: M^+, 250.1355. $C_{18}H_{18}O$ requires M, 250.1358).

(5*R*)-[(2*S*)- and (2*R*)-1-Bromo-2-methoxypropan-2-yl]-2-methyl-3-(2-phenylethynyl)cyclohex-2-enone 15d

Bromoetherification of the 6-(2-phenylethynyl)carvone **14d** (2.5 g, 10 mmol) in 2:3 mixture of methanol–dichloromethane (25 cm^3) with NBS (2.14 g, 12 mmol) for 12 h as described for compound **7** and purification of the product over a silica gel (60 g) column with ethyl acetate–hexane (1:10) as eluent, furnished a 1:1 epimeric mixture of the *bromo enones* **15d** (2.53 g, 70%) as a syrupy liquid; $[\alpha]_D^{25}$ −92.2 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 3050, 2200 (C≡C), 1670 (C=O), 1605, 1490, 1440, 1380, 1340, 1200, 1100, 1080, 1070, 760 and 695; δ_H(90 MHz; $CDCl_3$; 1:1 mixture of epimers) 7.2–7.6 (5 H, m, ArH), 3.46 (2 H, s, CH_2Br), 3.28 and 3.26 (3 H, s, OCH_3), 2.2–2.8 (5 H, m), 2.06 (3 H, br s, 2-CH_3) and 1.3 and 1.32 (3 H, s, *tert*-CH_3); δ_C(22.5 MHz; $CDCl_3$; 1:1 mixture of epimers) 198.0 and 197.6 (s, C=O), 138.5 and 138.4 (s), 137.0 and 136.1 (s), 131.6 (2 C, d), 129.2 (d), 128.4 (2 C, d), 122.3 (s), 103.2 (s, Ph*C*≡C), 88.3 (s, PhC≡*C*), 75.8 (s, *C*OCH_3), 49.5 (q, OCH_3), 40.1 (d, C-5), 38.7 and 37.9 (t), 36.5 (t), 31.8 and 31.2 (t), 18.0 (q, *tert*-CH_3) and 13.8 (q, 2-CH_3); *m/z* 360 and 362 (M^+ and M + 2, 25%), 209 (100), 153 (70) and 151 (70) (Found: M^+, 360.0713. $C_{19}H_{21}BrO_2$ requires M, 360.0725).

(1*S*,4*S*,8*R*)- and (1*S*,4*S*,8*S*)-8-Methoxy-1,8-Dimethyl-6-(2-phenylethynyl)bicyclo[2.2.2]oct-5-en-2-one (16d and 17d)

Intramolecular alkylation of the bromo enone **15d** (1:1 mixture of epimers; 2.16 g, 6 mmol) with $KOBu^t$ (1 mol dm^{-3} in Bu^tOH; 9 cm^3, 9 mmol) in dry THF (9 cm^3) for 12 h as described for compound **6**, and purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (1:20) as eluent, furnished a 1:1 mixture of the *bicyclooctenones* **16d** and **17d** (1.01 g, 68%) as an oil, $[\alpha]_D^{25}$ −111.8 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3050, 1725 (C=O), 1490, 1450, 1380, 1140, 1080, 1070, 920, 840, 760 and 695; δ_H(90 MHz; $CDCl_3$; 1:1 mixture of isomers **16d** and **17d**) 7.2–7.6 (5 H, m, ArH), 6.84 and 6.87 (1 H, d, *J* 7.2, olefinic), 3.22 and 3.2 (3 H, s, OCH_3), 2.9–3.3 (1 H, m, 4-H), 1.4–2.8 (4 H, m, 2 × CH_2) and 1.4 and 1.38 (3 H, s) and 1.36 and 1.34 (3 H, s) (2 × *tert*-CH_3); δ_C(22.5 MHz; $CDCl_3$; 1:1 mixture of isomers **16d** and **17d**) 211.0 and 210.5 (s, C=O), 140.8 and 140.4 (d, C=*C*H), 131.4 (2 C, d), 128.3 (3 C, d), 127.6 (s), 122.9 (s, *C*=CH), 93.6 and 93.1 (s, Ph*C*≡C), 85.1 and 84.9 (s, PhC≡*C*), 78.4 (s, C-8), 52.0 (s, C-1), 49.6 (q, OCH_3), 46.1 (t, CO*C*H_2), 41.6 (d, C-4), 35.8 and 34.3 (t, C-7), 25.0 and 22.3 (q, 8-CH_3) and 16.1 (q, 1-CH_3); *m/z* 280 (M^+, 15%), 208 (100), 179 (25) and 165 (50) (Found: M^+, 280.1475. $C_{19}H_{20}O_2$ requires M, 280.1463).

(5*S*)-5-Isopropenyl-2-methyl-3-(2-methylphenyl)cyclohex-2-enone 14e

Reaction of 2-lithiotoluene [obtained from 2-bromotoluene (1.8 g, 13 mmol) and butyllithium (1.6 mol dm^{-3} in hexanes; 9 cm^3, 14.4 mmol) in dry THF (20 cm^3)] with (*R*)-carvone (*R*)-**2** (1.9 g, 12 mmol) in dry THF (15 cm^3), followed by oxidation of the resultant tertiary alcohol with PCC (3.87 g, 18 mmol) and silica gel (6 g) in dichloromethane (25 cm^3), as described for compound **14a**, and purification of the product over a silica gel (60 g) column with ethyl acetate–hexane (3:100) as eluent, furnished the 6-(*2-methylphenyl*)*carvone* **14e** (2.38 g, 80%) as a solid, which was recrystallised from hexanes, mp 104–105 °C; $[\alpha]_D^{24}$ 88 (*c* 0.14, $CHCl_3$); λ_{max}/nm (CH_3OH) 241 (ε 7750); ν_{max}/cm^{-1} 1670 (C=O), 1380, 1140, 1120, 900 (C=CH_2), 770 and 730; δ_H(200 MHz; $CDCl_3$; mixture of rotational isomers) 6.8–7.3 (4 H, m, ArH), 4.82 (1 H, br s) and 4.78 (1 H, br s) (together C=CH_2), 2.3–3.0 (5 H, m), 2.19 and 2.17 (3 H, s, ArCH_3), 1.77 (3 H, s, 2-CH_3) and 1.54 (3 H, s, isopropenyl CH_3); δ_C(22.5 MHz; $CDCl_3$; mixture of rotational isomers) 199.2 (s, C=O), 156.4 and 155.9 (s), 146.4 (s), 140.8 (s), 133.3 (s), 132.1 (s), 130.3 (d), 127.6 (d), 126.5 (d), 125.9 (d), 110.5 (t, C=*C*H_2), 42.8 (t), 42.1 (d, C-5), 38.0 and 37.7 (t), 20.5 (q), 19.1 (q) and 12.2 (q, 2-CH_3). Only one set of signals was observed at 100 °C; *m/z* 240 (M^+, 25%), 198 (100), 183 (55), 129 (40) and 128 (30) (Found: C, 85.2; H, 8.4. $C_{17}H_{20}O$ requires C, 84.96; H, 8.39%).

(5*S*)-[(2*S*)- and (2*R*)-1-Bromo-2-methoxypropan-2-yl]-2-methyl-3-(2-methylphenyl)cyclohex-2-enone 15e

Bromoetherification of the *o*-tolylcarvone **14e** (3.35 g, 13.3 mmol) in a 2:3 mixture of methanol–dichloromethane (65 cm^3) with NBS (4.5 g, 26 mmol) for 8 h as described for compound **7**, and purification of the product over a silica gel (60 g) column with ethyl acetate–hexane (1:10) as eluent, furnished a 1:1 epimeric mixture of the *bromo enone* **15e** (4.5 g, 91%) as a syrupy liquid. One of the epimers (mp 136 °C) was partially crystallised on cooling of the hexane solution of the mixture, $[\alpha]_D^{26}$ 14.4 (*c* 0.14, $CHCl_3$); λ_{max}/nm (CH_3OH) 241 (ε 1910); ν_{max}/cm^{-1} 1662 (C=O), 1455, 1100, 730 and 675; δ_H(200 MHz; $CDCl_3$; 1:1 mixture of epimers) 6.85–7.3 (4 H, m, ArH), 3.25–3.6 (2 H, m, CH_2Br), 3.24 (3 H, s, OCH_3), 2.2–2.8 (5 H, m), 2.17 and 2.21 (3 H, s, ArCH_3), 1.53 (3 H, s, 2-CH_3) and 1.26 and 1.27 (3 H, s, *tert*-CH_3); δ_C(22.5 MHz; $CDCl_3$; mixture of epimers and rotamers) 199.1 (s, C=O), 157.0, 156.3, 155.9 and 155.3 (s), 140.7 (s), 133.3 and 133.0 (s), 132.0 and 131.7 (d), 130.3 and 129.9 (d), 127.6 and 126.4 (d), 126.1 and 125.8 (d), 75.7 (s, *C*OCH_3), 49.4 (q, OCH_3), 40.6 (d, C-5), 38.5 and 37.9 (t), 36.4 (t), 33.8, 33.6, 33.0 and 32.5 (t), 19.0 (q), 17.9 and 17.5 (q) and 12.1 (q, 2-CH_3) (Found: C, 61.8; H, 6.6. $C_{18}H_{23}BrO_2$ requires C, 61.55; H, 6.60%).

(1*R*,4*R*,8*S*) and (1*R*,4*R*,8*R*)-8-Methoxy-1,8-dimethyl-6-(2-methylphenyl)bicyclo[2.2.2]oct-5-en-2-one 16e and 17e

Intramolecular alkylation of the bromo enone **15e** (1:1 mixture of epimers; 2.43 g, 6.9 mmol) with $KOBu^t$ (1 mol dm^{-3} in Bu^tOH; 9 cm^3, 9 mmol) in dry THF (9 cm^3) for 12 h as described for compound **6** and purification of the product over a silica gel (50 g) column with ethyl acetate–hexane (1:20) as eluent furnished a 1:1 mixture of the *bicyclooctenones* **16e** and **17e** (1.43 g, 76%) as an oil, ν_{max}/cm^{-1} 1715 (C=O), 1450, 1415, 1375 and 1062. For isomer **16e**: mp 78 °C (from hexanes); $[\alpha]_D^{27}$ 224 (*c* 0.94, $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 7.16 (3 H, m) and 6.85 (1 H, br s) (ArH), 6.27 (1 H, d, *J* 6.9, olefinic), 3.25 (3 H, s, OCH_3), 3.03 (1 H, t of d, *J* 6.8 and 2.5, 4-H), 2.69 (1 H, d of $\frac{1}{2}$ AB q, *J* 18.2 and 2) and 2.09 (1 H, d of $\frac{1}{2}$ AB q, *J* 18.2 and 3.2) (together CH_2C=O), 1.8–2.3 (3 H, br, ArCH_3), 1.91 (1 H, $\frac{1}{2}$ AB q, *J* 13.8, 7-H *endo* to C=O), 1.7 (1 H, br, 7-H *exo* to C=O), 1.42 (3 H, s, 8-CH_3), 0.84 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$) 212.8 (s, C=O), 145.0 (s), 138.1 (s), 135.5 (s), 132.2 (d), 129.6 (d), 128.9 (d), 127.3 (d), 125.1 (d), 78.3 (s, C-8), 53.2 (s, C-1), 49.5 (q, OCH_3), 46.9 (t, C-3), 41.1 (d, C-4), 34.6 (t, C-7), 24.9 (q, 8-CH_3) and 15.6 (q, 1-CH_3). For isomer **17e**: $[\alpha]_D^{27}$ 313 (*c* 1, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 6.8–7.2 (4 H, m, ArH), 6.26 (1 H, d, *J* 6.4, olefinic), 3.23 (3 H, OCH_3), 3.09 (1 H, br s, 4-H), 2.28 (2 H, br s, CH_2C=O), 1.8–2.15 (4 H, br, ArCH_3 and 7-H *exo* to C=O), 1.62 (1 H, $\frac{1}{2}$ AB q, *J* 14.1, 7-H *endo* to C=O), 1.43 (3 H, s, 8-CH_3) and 0.86 (3 H, s, 1-CH_3); δ_C(22.5 MHz; $CDCl_3$) 212.0 (s, C=O), 142.5 (s), 138.4 (s), 136.0 (s), 132.3, 129.7 (2 C, d), 127.5 (d), 125.2 (d), 78.9 (s, C-8), 52.8 (s, C-1), 49.3 (q, OCH_3), 47.1 (t, *C*H_2C=O), 41.0 (C-4), 36.2 (t, C-7), 22.2 (q, 8-CH_3), 20.2 (q, ArCH_3) 15.7 (q, 1-CH_3); *m/z* 270 (M^+, 10%), 199 (40), 198 (97), 197 (45), 196 (65), 183 (80), 181 (40), 155 (35) and 73 (100) (Found: M^+, 270.1598. $C_{18}H_{22}O_2$ requires M, 270.1620).

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