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Radical Cyclisation Strategies to Bridged Systems. Regioselective Construction of Chiral Bicyclo [2.2.2] and [3.2.1] octanes via 6-*exo* trig and 5-*exo* trig Radical Cyclisation Reactions[1]

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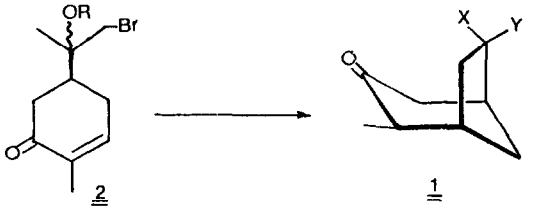
ABSTRACT: *Radical cyclisation reaction of the bromoenones* ***6*** *and* ***7****, obtained from (R)-phenylcarvone* ***3****, gave a mixture of bicyclo [2.2.2] and [3.2.1] octanones via competitive 6-exo trig and 5-exo trig modes. On the other hand, radical cyclisation reaction of the alcohol* ***12*** *furnished the bicyclo[3.2.1]-octanol* ***15*** *as the major cyclised product, where as the alcohol* ***13*** *furnished the bicyclo[2.2.2]octanol* ***18*** *as the major cyclised product. An explanation based on conformational rigidity due to the intramolecular hydrogen bonding between the hydroxy and methoxy groups is proposed, and proved by the formation of bicyclo[2.2.2]octanes as major cyclised products with the corresponding acetates* ***19*** *and* ***20****.*

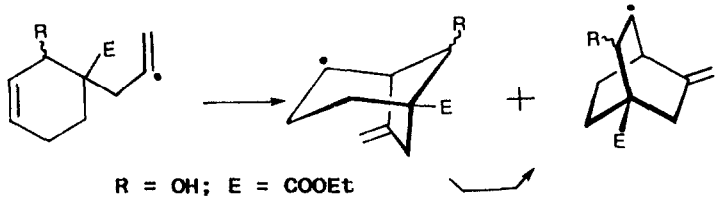
Since Gomberg's discovery of the triphenylmethyl radical in 1900,[2] there has been a steady increase in the interest on free radicals. At the beginning of the 1980's, the place of radical reactions was limited to a few important functional group transformations. However, during the last decade the radical carbon-carbon bond forming reactions, particularly radical cyclisations, have grown in importance to the present status, where they are now routinely considered in strategy level planning of complex target molecules.[3]

Earlier, we have reported[4] a regiospecific construction of chiral bicyclo[3.2.1]octan-3-ones **1**, *via* the 5-*exo* trig radical cyclisation[5] of the bromoenone **2**. This cyclisation is clearly facilitated by electrophilic



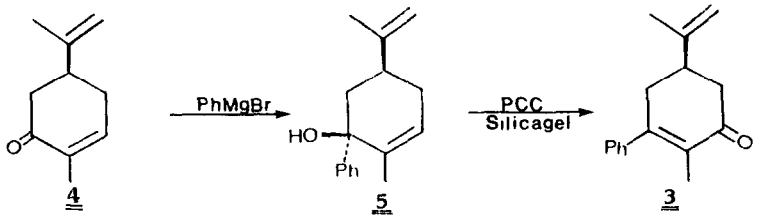
2 **1** X,Y = OR,Me

nature of the receptor olefin, an α,β-unsaturated enone, in combination with the fact that the radical is adding at the less substituted end of the olefin. Hence, we anticipated that the presence of a radical stabilising group, e.g. an aryl group, at the β-position of the enone, which also makes the olefin fully substituted, might change the course of the radical cyclisation reaction. Because now, due to the styrenic nature of the olefin, the 6-*exo* trig mode will compete with the 5-*exo* trig mode, leading to the formation of bicyclo[2.2.2]octanes also along with bicyclo[3.2.1]octanes. Even though, it is well established that the 6-*exo* trig cyclisation takes place slower than the 5-*exo* trig mode by an order of magnitude in acyclic and fused systems,[3] we believe that they occur in a competetive manner when they result in bridged systems. In this account, we now report regiocontrolled construction of both bicyclo [2.2.2] and [3.2.1] octanes via 6-*exo* trig and 5-*exo* trig radical cyclisation reaction, starting from (R)-(−) 6-phenylcarvone (3). Incidentally, there is only one report on radical mediated construction of bicyclo[2.2.2]octanes,[6] using a vinyl radical cyclisation, probably *via* the rearrangement of the initial 5-*exo* trig cyclised bicyclo-[3.2.1]octyl homoallyl radical (eq.1).



(eq. 1)

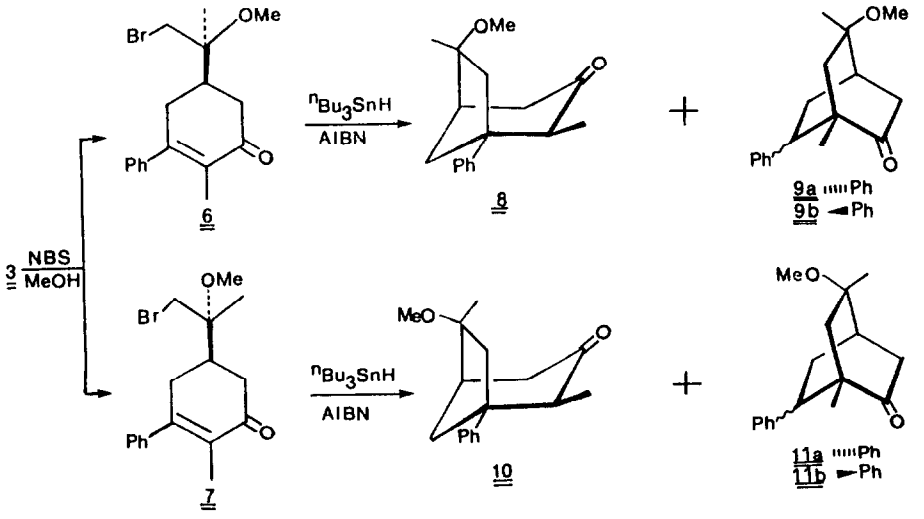
The (R)-(−)-6-phenylcarvone (3)[7] was prepared from (S)-(+)-carvone (4) *via* an arylative 1,3-enone transposition sequence.[8] Thus, Grignard reaction of 4 with phenylmagnesium bromide followed by oxidation of the resultant allylic tertiary alcohol 5 with PCC-silica gel[9] furnished the (R)-6-phenylcarvone (3) in 85% overall yield. Presence of the molecular ion peak at m/e 226 in the mass spectrum, an absorption at λ_{max} 261 nm (ε=10,424) in the UV spectrum, absence of the β-olefinic proton and the presence of a multiplet at δ 7.16-7.6 ppm (aromatic)in the ^{1}H NMR spectrum confirmed the structure



of 3. The regiospecific bromoetherification reaction of 3 with N-bromosuccinimide (NBS) in methylene chloride-methanol furnished the epimeric methoxy bromides 6 and 7 (1:1) in 75% yield. The structures of the bromoenones 6 and 7 were delineated from their spectral data, and the configuration at the new centre was arrived at based on chemical transformations.

Refluxing a 0.02 M benzene solution of the bromoenone 6 with 1.1 eq. of tri-n-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 3 hr furnished an inseparable 1:1 mixture of bicyclo[3.2.1]octan-3-one 8 and bicyclo[2.2.2]octan-2-ones 9. The ratio changed to ≈1:1.5 in favour of bicyclo[2.2.2]octanone 9, when the reaction was carried out in refluxing toluene. The ^{1}H NMR spectrum clearly revealed the presence of two major and one minor sets of signals (4:5:1); one set [δ 0.78 (d, J = 7 Hz, secondary methyl group), 1.32 (s, CH_3–C–OMe), 3.24 (s, OCH_3)] for the bicyclo[3.2.1]octanone 8, another set [0.64 (s, bridgehead methyl group), 1.46 (s, CH_3–C–OMe), 3.21 (s, OCH_3)] for the bicyclo[2.2.2]-octanone 9a and the minor set [0.52 (s, bridgehead methyl group), 1.54 (s, CH_3–C–OMe), 3.17 ppm (s, OCH_3)] for the epimeric bicyclo[2.2.2]octanone 9b. Similarly, radical cyclisation of the bromoenone 7 under standard conditions in refluxing toluene furnished an inseparable mixture (≈1:1.5) of bicyclo [3.2.1] and [2.2.2] octanones 10 and 11. The ^{1}H NMR spectrum of the product mixture also exhibited two major and one minor sets of signals (4:5:1); [δ 0.70 (d, J = 7 Hz, secondary methyl group), 1.28 (s, CH_3C–OMe), 3.18 (s, OCH_3)] for the bicyclo[3.2.1]octanone 10, [0.64 (s, bridgehead methyl group), 1.32 (s, CH_3–C–OMe), 3.28 (s, OCH_3)] for the bicyclo[2.2.2]-octanone 11a and the minor set [0.54 (s, bridgehead methyl group), 1.28 (s,

SCHEME 1



CH_3–C–OMe), 3.32 ppm (s, OCH_3)] for the epimeric bicyclo[2.2.2]octanone **11b**. Preparation of individual compounds (discussed later) finally confirmed the structures of the products **8**–**11**. The stereochemistry of the phenyl group was tentatively assigned based on the thermodynamic considerations. The *endo* stereochemistry was assigned to the phenyl group in the ketones **9a** and **11a**, as it was observed in other cases, abstraction of hydrogen from tin hydride by a stable radical resulted in the formation of the thermodynamic products.[4,7,10] Assuming that the effect of carbonyl and phenyl groups on the olefin are comparable, formation of both bicyclo [2.2.2] and [3.2.1] octanes indicates the competitiveness of 6-*exo* and 5-*exo* trig modes of radical cyclisation in the formation of bridged systems.

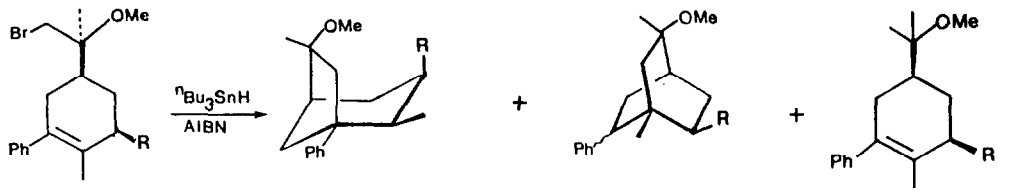
In an attempt to subside the formation of the bicyclo[3.2.1]octanes and direct the course of the cyclisation to bicyclo[2.2.2]octanes *via* 6-*exo* trig mode, by removing the carbonyl activation, radical cyclisations were carried out with the corresponding allylic alcohols **12** and **13**. Thus, LAH reduction[4,11] of a diastereoisomeric mixture (1:1) of the bromoenones **6** & **7** in ether at –60°C furnished *via* the preferred axial attack of the hydride,[12] the two syn allylic alcohols **12** & **13** (1:1) in 85% yield. Radical reaction

$$\underline{6\&7} \xrightarrow{LAH/Et_2O} \underline{12} + \underline{13}$$

of the bromo alcohols **12** and **13** with $^nBu_3SnH$ (1.1 eq.) and AIBN (catalytic) in refluxing benzene at either 0.02M or 0.01M concentrations resulted only in the formation of the reduction product **14**. However, when the reactions were carried out at more dilute (0.005M) conditions, cyclised products were formed (scheme 2).

Thus, refluxing a 0.005M toluene solution of the allylic alcohol **12** with $^nBu_3SnH$ and AIBN for 4 hr, contrary to the anticipation, furnished the bicyclo[3.2.1]octan-3-ol **15** (47%) as the major product along with bicyclo-[2.2.2]octan-2-ols **16** (25%) and the reduced product **14** (12%). In the IR spectrum of the alcohol **15**, the presence of a broad band, which is independent of concentration, at 3424 cm^{-1} due to OH, confirmed the existence of intramolecular hydrogen bonding and hence syn stereochemical relationship of methoxy and hydroxy groups. The structure of the alcohol **16** was delineated from the ^1H and ^{13}C NMR spectral data, in particular the presence of a methyl singlet at δ 0.72 for the bridgehead methyl group and a doublet of a doublet at 2.66 ppm for the benzylic proton (CH–Ph). The syn orientation of the hydroxy and methoxy groups was extended from the structure of **15** and was confirmed by the IR dilution experiments. Oxidation of the alcohol **15** with PCC–silica gel in methylene chloride afforded the ketone **8**. Similarly,

SCHEME 2

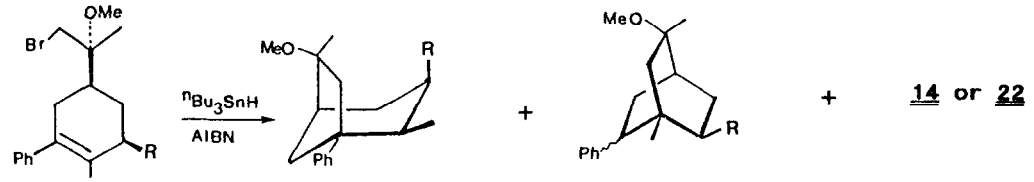


12. R=OH 15. R=OH 16. R=OH, ⟋Ph 14. R=OH

24. R=OH, ◄Ph

19. R=OAc 23. R=OAc 21a. R=OAc, ⟋ Ph 22. R=OAc

21b. R=OAc, ◄ Ph



13. R=OH 17. R=OH 18a. R=OH, ⟋Ph

18b. R=OH, ◄Ph

20. R=OAc 26. R=OAc 25a. R=OAc, ⟋Ph

25b. R=OAc, ◄Ph

PCC oxidation of the alcohol 16 furnished the ketone 9a. The ^{1}H NMR spectra of the two ketones 8 & 9a were found to be identical with the two major sets of signals present in the ^{1}H NMR spectrum of the product mixture obtained *via* the radical cyclisation of the bromoenone 6 (Scheme 1).

$$15 \xrightarrow[\text{Silica gel}]{\text{PCC}} 8$$

$$16 \xrightarrow[\text{Silica gel}]{\text{PCC}} 9a$$

On the other hand, in line with the anticipation, the radical cyclisation of the bromo alcohol 13 in reluxing toluene (0.005M) afforded the bicyclo[3.2.1]octan-3-ol 17, bicyclo[2.2.2]octan-2-ols (18a & 18b; 2.5:1) and the reduction product 14 in a 1:3:2 ratio. In the IR spectra of 18 in $CHCl_3$, bands due to OH appeared at 3622 and 3466; & 3622 and 3472 cm^{-1} respectively, with the disappearance of bands at 3466 and 3472 cm^{-1} (intermolecularly hydrogen bonded) on dilution, established the anti orientation of the methoxy and hydroxy groups. The ^{1}H NMR spectra of 18a & 18b exhibited

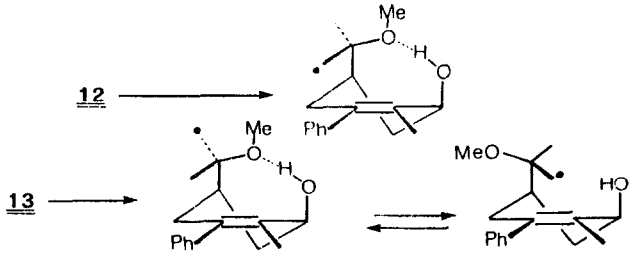
doublet of doublet resonances at δ 2.87 and 2.38 for the benzylic proton (C<u>H</u>–Ph), singlets at 0.58 & 0.46 ppm for the bridgehead methyl group, respectively. The ^{13}C NMR spectra confirmed the assignments. Oxidation of the bicyclooctanols <u>17</u>, <u>18a</u> & <u>18b</u> with PCC-silica gel in methylene chloride furnished the corresponding ketones <u>10</u>, <u>11a</u> & <u>11b</u>, and exhibited the ^1H NMR spectra identical with the two major and one minor set of signals that appeared in the ^1H NMR spectrum of the product mixture obtained *via* the radical cyclisation of the bromoenone <u>7</u> (Scheme 1).

<u>17</u> —PCC, Silica gel→ <u>10</u>

<u>18a</u> —PCC, Silica gel→ <u>11a</u>

<u>18b</u> —PCC, Silica gel→ <u>11b</u>

Contrary to the expectation, the formation of bicyclo[3.2.1]octan-3-ol <u>15</u> as the major product (47%) in the radical cyclisation of the bromo alcohol <u>12</u> can be rationalised as follows: the presence of a strong intramolecular hydrogen bonding between the OH and OCH_3 groups in the alcohol <u>12</u>, conformationally inhibited the approach of the radical to C–2 carbon and hence the bicyclo[3.2.1]octanol <u>15</u> *via* the 5–*exo* trig mode of cyclisation was formed as the major cyclised product. On the other hand, in the case of

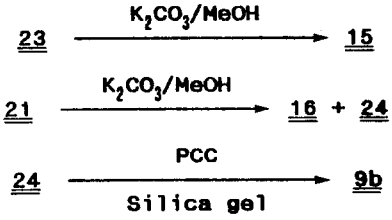


the allylic alcohol <u>13</u>, the hydrogen bonding is not possible in the transition state that leads to cyclisation, whereas in the hydrogen bonded conformation the cyclisation is not possible, and hence alcohols <u>18</u> *via* 6–*exo* trig mode of cyclisation and the reduced product <u>14</u> were formed as major products. To test this hypothesis, the radical cyclisations were attempted on the corresponding acetates, where no hydrogen bonding is possible.

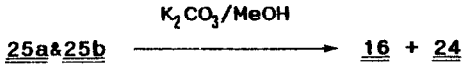
Treatment of the diastereoisomeric mixture (1:1) of the allylic alcohols <u>12</u> and <u>13</u> with acetic anhydride and DMAP (catalytic) in pyridine-

<u>12&13</u> —Ac_2O/Py/DMAP→ <u>19</u> + <u>20</u>

methylene chloride furnished the acetates 19 and 20. As predicted, radical cyclisation of the acetate 19 in refluxing toluene (scheme 2) furnished epimeric mixture (1:1) of the bicyclo[2.2.2]octyl acetate 21 as the major product (35%) accompanied by the reduced product 22 (20%) and the bicyclo-[3.2.1]octyl acetate 23 (14%). The structures of the cyclised products 21 & 23 were deduced from their spectral data and confirmed by hydrolysis to corresponding alcohols. Hydrolysis of the acetate 23 with potassium carbonate in methanol furnished the bicyclic alcohol 15. Similarly, hydrolysis of the mixture of acetates 21a & 21b with potassium carbonate in methanol afforded alcohols 16 and 24. PCC oxidation of the alcohol 24 furnished the



bicyclo[2.2.2]octanone 9b, which exhibited the ^1H NMR resonances coinciding with the minor set of signals present in the ^1H NMR spectrum of product mixture (8 & 9) obtained *via* the radical cyclisation of the bromoenone 6 (scheme 1). Similarly, radical cyclisation of acetate 20 afforded the epimeric mixture of bicyclo[2.2.2]octyl acetate 25 (50%) as the major product accompanied by the bicyclo[3.2.1]octyl acetate 26 (15%) and the reduction product 22 (15%). Hydrolysis of the mixture of 25a & 25b with potassium carbonate in methanol afforded the bicyclic alcohols 18a & 18b. Formation of the bicyclo[2.2.2]octane as the major product in the radical cyclisation



of the acetate 19 clearly established the strong influence of the intramolecular hydrogen bonding on the course of the cyclisation *via* a rigid conformation, whereas enhanced formation of the reduction product may be a result of the extra steric crowding generated due to the acetate group.

In conclusion, radical cyclisation strategies have been developed for the construction of chiral bicyclo [2.2.2] and [3.2.1] octanes starting from carvone in a regiocontrolled manner.

EXPERIMENTAL SECTION:

UV and IR spectra were recorded on a Shimadzu UV-190 and Hitachi 270-50 spectrophotometers respectively. ^1H (90, 200, 270 MHz) and ^{13}C NMR (22.5

MHz) spectra were recorded on Jeol FX-90Q, Varian ACF-200 and WH-270 spectrometers, and the chemical shift (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal Me_4Si (for ^1H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, off-resonance multiplicities, when recorded are given in parentheses. High and low resolution mass measurements were carried out with a JEOL JMS-DX 303 GC-MS instrument using a direct inlet mode. Relative intensities of the ions are given in parentheses. Optical rotations were measured with a Jasco DIP-303 polarimeter. Acme's silica gel (100-200 mesh) was used for column chromatography. All chromatographic fractions were monitored by analytical TLC before mixing. Solvent evaporations were done with a Buchi rotary evaporator. Dry benzene and toluene were obtained by washing with H_2SO_4, followed by distillation over sodium and stored over pressed sodium wire. CH_2Cl_2 was distilled from P_2O_5. LAH, $^nBu_3SnH$, NBS were obtained from Fluka, and were used without further purication. AIBN was recrystallised from methanol and stored in dark.

(−)-(R)-2-Methyl-5-isopropenyl-3-phenylcyclohex-2-en-1-one (3): To a freshly prepared, magnetically stirred, ice-cold suspension of phenylmagnesium bromide [prepared from magnesium (1.92 g, 0.08 g atom) and bromobenzene (8.4 ml, 80 mmol) in dry ether (80 ml)] was added a ether (20 ml) solution of (S)-carvone (4, 6 g, 40 mmol) over a period of 60 min. The reaction mixture was stirred at room temperature (RT) for 6 hr and then poured into an ice-cold phosphate buffer solution (pH 7, 80 ml). The ether layer was separated and the aqueous phase was extracted with more ether (3 x 30 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the alcohol 5 as a pale yellow oil and was used as such in the oxidation reaction.

To a magnetically stirred suspension of PCC (12.8 g, 60 mmol) and silica gel (12.8 g) in dry CH_2Cl_2 (50 ml) was added a solution of the tertiary alcohol 5 (8.21 g) in dry CH_2Cl_2 (50 ml) in one portion. The reaction mixture was stirred at room temperature for 6 hr. The entire reaction mixture was then loaded on a silica gel (100 g) column and eluted with more CH_2Cl_2. The solvent was evaporated and the residue was further purified over a silica gel (30 g) column with benzene as eluent to furnish phenylcarvone (3, 7.7 g, 85%) as a yellow oil. $[\alpha]_D^{26}$: −102.6° ($CHCl_3$, c 1.14). UV (MeOH): λ_{max} 261nm (ε=10,420) IR (neat): ν_{max} 3100, 3050, 1670, 1630, 1495, 1390, 1360, 1330, 1110, 900, 770, 710 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.1–7.6 (5 H, m, aromatic), 4.82 (2 H, br s, olefinic), 2.4-3.0 (5 H, m), 1.76 ppm (6 H, br s, 2 x olefinic Me). Mass: m/e 226 (M^+, 50%), 198 (35), 184 (94), 183 (40), 169 (98), 158 (15), 130 (60), 129 (65), 128 (40), 116 (30), 115 (100), 116 (30), 91 (35). HRMS: m/e Calcd. for $C_{16}H_{18}O$,

226.1358; Found, 226.1343.

(−)-(5R)-5-[(S)-1-Bromo-2-methoxyprop-2-yl]-2-methyl-3-phenylcyclohex-2-en-1-one (6) and (−)-(5R)-5-[(R)-1-bromo-2-methoxyprop-2-yl]-2-methyl-3-phenylcyclohex-2-en-1-one (7): To a cold (-10°C, freezing bath), magnetically stirred solution of 3 (6.78 g, 30 mmol) in a 3:2 mixture of CH_2Cl_2–MeOH (50 ml) was added NBS (6.4 g, 36 mmol) in small portions over a period of 90 min. The reaction mixture was stirred for 18 hr at RT, and then diluted with more CH_2Cl_2 (50 ml), washed with 10% aq. NaOH solution (3 x 30 ml), and brine and dried (Na_2SO_4). Solvent was evaporated and the residue was purified over a silica gel (100 g) column with ethyl acetate-benzene (1:49) as eluent. Careful pooling (monitored by TLC) of fractions furnished the bromides 6 & 7 (1:1, 7.6 g, 75%).

Compound 6: $[\alpha]_D^{26}$: −118.9° ($CHCl_3$, c 1.59). UV (MeOH): λ_{max} 265 nm (ε=15,200). IR (neat): ν_{max} 1671, 1629, 1494, 1380, 1080, 762, 705 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.1-7.5 (5 H, m, aromatic), 3.48 (2 H, s, $C\underline{H}_2Br$), 3.26 (3 H, s, OCH_3), 2.64 (3 H, br s), 2.4 and 2.6 (2 H, ABq, J = 15 Hz), 1.72 (3 H, s, C_2–Me), 1.31 ppm (3 H, s, CH_3C–O). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 199.1 (C=O), 156.0 (C-3), 141.1 (C-2), 131.0, 128.2 (2 C), 127.8 (d) and 126.9 (2 C) (aromatic), 75.9 (C–OMe), 49.5 (OMe), 40.1 (C-5), 38.4 ($C\underline{H}_2Br$), 36.6, 33.0, 17.7 ($C\underline{H}_3C$–O), 12.6 ppm (C_2–Me). Mass: m/e 336 (M^+, 40%), 338 (M^++2, 38), 186 (40), 185 (100), 184 (60), 183 (60), 153 (75), 151 (77), 129 (30), 115 (52). HRMS: m/e Calcd. for $C_{17}H_{21}BrO_2$, 336.0725; Found, 336.0737.

Compound 7: m.p.: 90-91°C; $[\alpha]_D^{26}$: −131.8° ($CHCl_3$, c 1.84). UV (MeOH): λ_{max} 264 nm (ε=10,140). IR (CCl_4): ν_{max} 1674, 1629, 1380, 1332, 1200, 1083 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.1-7.6 (5 H, m, aromatic), 3.52 and 3.36 (2 H, ABq, J = 10.8 Hz, CH_2Br), 3.26 (3 H, s, OMe), 2.3-2.85 (5 H, m), 1.7 (3 H, s, C_2–Me), 1.30 ppm (3 H, s, CH_3C–O). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 199.4 (s, C=O), 155.1 (s, C-3), 131.1 (s, C-2), 140.9 (s), 128.1 (2 C, d), 127.7 (d) & 126.8 (2 C, d) (aromatic), 75.7 (s, C–OMe), 49.2 (q, OMe), 40.0 (d, C-5), 37.5 (t, CH_2Br), 36.6 (t, C-6), 33.6 (t, C-4), 17.7 (q, $C\underline{H}_3C$–O), 12.5 ppm (q, C_2–Me). Anal. Calcd. for $C_{17}H_{21}BrO_2$, C:60.54; H:6.28. Found, C:60.53; H:6.23%.

Radical cyclisation of the bromoenone 6: A solution of the bromoenone 6 (202 mg, 0.6 mmol), $^nBu_3SnH$ (0.175 ml, 0.66 mmol) and AIBN (catalytic) in toluene (32 ml) was refluxed for 3 hr. The reaction mixture was cooled, washed with 1% aq. NH_4OH (3 x 20 ml) followed by brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified over silica gel (10 g) column. The tin byproducts were removed by elution with hexane. Elution of the column with ethyl acetate-hexane (1:3) furnished a 1:1.5 mixture (by ^1H NMR) of the cyclised products 8 & 9 (110 mg, 80%) as an oil.

Radical cyclisation of the bromoenone 7: Radical cyclisation of the bromoenone 7 (170 mg, 0.5 mmol) with $^{n}Bu_3SnH$ (0.15 ml, 0.55 mmol) and AIBN (catalytic) in toluene (28 ml) for 3 hr as described above and purification of the crude product over a silica gel (10 g) column with ethyl acetate-hexane (1:3) as eluent furnished the 1:1.5 mixture (by ^1H NMR) of the cyclised products 10 & 11 as an oil.

(−)-(1R,5R)-5-[(S)-1-Bromo-2-methoxyprop-2-yl]-2-methyl-3-phenylcyclohex-2-en-1-ol (12) and (−)-(1R,5R)-5-[(R)-1-bromo-2-methoxyprop-2-yl]-2-methyl-3-phenylcyclohex-2-en-1-ol (13): To a cold (-78°C, ethanol–liq N_2 bath), magnetically stirred solution of a 1:1 mixture of bromoenones 6 & 7 (3.37 g, 10 mmol) in dry ether (30 ml) was added LAH (190 mg, 5 mmol) in one portion. The reaction mixture was stirred at −60°C for 2 hr and allowed to warm upto -10°C over a period of 15 min. Ethyl acetate (2 ml) was added dropwise to consume the excess LAH, and the reaction was quenched with ice-cold water (10 ml) and 10% dilute H_2SO_4 (30 ml), and stirred at RT for 10 min. The ether layer was separated and the aqueous layer was extracted with ether (3 x 30 ml). The ether extract was washed with saturated aq. $NaHCO_3$ solution (3 x 20 ml) followed by brine and dried (Na_2SO_4). Solvent was evaporated and the residue was purified over a silica gel (80 g) column with ethyl acetate-benzene (1:49) as eluent. Careful pooling of fractions furnished the alcohols 12 & 13 (1:1, 2.88 g, 85%) as viscous liquids.

Compound 12: $[\alpha]_D^{26}$: −80.3° ($CHCl_3$, c 2.99). **IR (neat):** ν_{max} 3442 (broad, OH), 1668, 1575, 1494, 1377, 1080, 765 cm^{-1}. **^1H NMR (90 MHz, $CDCl_3$):** δ 7.0-7.5 (5 H, m, aromatic), 4.2-4.5 (1 H, m, CHOH), 3.56 (2 H, s, CH_2Br), 3.24 (3 H, s, OCH_3), 1.95-2.5 (5 H, m), 1.88 (1 H, br s, OH), 1.68 (3 H, s, C_2–Me), 1.28 ppm (3 H, s, CH_3C–O). **^{13}C NMR (22.5 MHz, $CDCl_3$):** δ 143.0 (s, C–3), 134.9 (s, C–2), 131.5 (s), 128.1 (4 C, d) and 126.4 (d) (aromatic), 76.4 (s, C–OMe), 71.8 (d, CHOH), 49.2 (q, OCH_3), 38.5 (d, C–5), 37.8 (t, CH_2Br), 34.3 (t), 32.9 (t), 17.8 (q, CH_3C–O), 15.7 ppm (q, C_2–Me). **Mass: m/e** 338 (M^+, 5%), 340 (M^++2, 5), 227 (38), 169 (100), 168 (100), 153 (47), 151 (46), 91 (25). HRMS: m/e Calcd. for $C_{17}H_{23}BrO_2$, 338.0882; Found, 338.0872.

Compound 13: $[\alpha]_D^{26}$: −113° ($CHCl_3$, c 2.5). **IR (neat):** ν_{max} 3394 (OH), 3052, 1665, 1602, 1575, 1494, 1377, 1264, 1230, 1200, 1080, 1041, 978, 765, 738, 702 cm^{-1}. **^1H NMR (90 MHz, $CDCl_3$):** δ 7.0-7.5 (5 H, m, aromatic), 4.2-4.46 (1 H, m, CHOH), 3.58 and 3.34 (2 H, ABq, J = 11 Hz, CH_2Br), 3.26 (3 H, s, OCH_3), 1.95-2.5 (5 H, m), 2.16 (1 H, br s, OH), 1.64 (3 H, s, C_2–Me), 1.2 ppm (3 H, s, CH_3C–O). **^{13}C NMR (22.5 MHz, $CDCl_3$):** δ 143.0 (s, C–3), 134.0 (s, C–2), 132.3 (s), 128.1 (4 C, d) and 126.4 (d) (aromatic), 76.3 (s, C–OMe), 71.6 (d, CHOH), 49.1 (q, OCH_3), 38.5 (d, C–5), 37.5 (t, CH_2Br), 33.8 (t), 33.2 (t), 17.1 (q, CH_3C–O), 15.6 ppm (q, C_2–Me). **Mass: m/e** 338 (M^+, 12%), 340 (M^++2, 10), 227 (100), 185 (64), 169 (67), 168 (60), 153 (65), 151 (65), 131

(40), 91 (25). HRMS: m/e Calcd. for $C_{17}H_{23}BrO_2$, 338.0881; Found, 338.0887.

(−)-(1S,2S,3R,5R,6R)-2,6-Dimethyl-6-methoxy-1-phenylbicyclo[3.2.1]octan-3-ol (15) and (−)-(1S,2R,4R,5R,7S)-1,5-dimethyl-5-methoxy-7-phenylbicyclo-[2.2.2]octan-2-ol (16): Radical cyclisation of the bromo alcohol 12 (170 mg, 0.5 mmol) with $^nBu_3SnH$ (0.15 ml, 0.55 mmol) and AIBN (8 mg in 4 ml of dry toluene was added in batches for every 30 min) in 110 ml of toluene for 4 hr, and purification of product mixture over a silica gel (15 g) column with ethyl acetate-benzene (1:9) furnished first the bicyclo[3.2.1]octanol 15 (61 mg, 47%) as a pale yellow viscous liquid. $[\alpha]_D^{26}$: −4.33° ($CHCl_3$, c 4.09). IR (neat): ν_{max} 3424 (broad, OH), 3058, 3028, 1599, 1494, 1377, 1209, 1152, 1134, 1113, 1056, 882, 858, 696 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.1-7.4 (5 H, m, aromatic), 3.6-3.9 (1 H, m, CHOH), 3.36 (3 H, s, OCH_3), 2.72 (1 H, ½ ABq, J = 14 Hz), 1.65-2.4 (7 H, m), 1.36 (3 H, s, CH_3C–O), 0.68 ppm (3 H, d, J = 7.2 Hz, C_2–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 148.6 (s), 127.8 (2 C, d), 126.7 (2 C, d) and 125.5 (d) (aromatic), 85.1 (s, C–OMe), 69.1 (d, CHOH), 51.3 (q, OCH_3), 49.5 (s, C–1), 48.1 (d, C–5), 44.7 (t, C–7), 43.8 (d, C–2), 42.3 (t, C–8), 36.2 (t, C–4), 26.3 (q, CH_3C–O), 13.7 ppm (q, C_2–Me). Mass: m/e 260 (M^+, 25%), 228 (72), 227 (55), 185 (70), 184 (40), 183 (35), 170 (40), 169 (100), 168 (58), 161 (40), 156 (38), 153 (38), 151 (36), 131 (40), 91 (50). HRMS: m/e Calcd. for $C_{17}H_{24}O_2$, 260.1776; Found, 260.1793.

Further elution of the column with the same solvent furnished the bicyclo[2.2.2] octanol 16 (33 mg, 25%) as a colourless solid which was recrystallised from hexane. m.p.: 86-88°C; $[\alpha]_D^{26}$: −2.02° ($CHCl_3$, c 1.29). IR (CCl_4): ν_{max} 3514 (OH), 3028, 1494, 1374, 1140, 1071, 1035 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.1-7.4 (5 H, m, aromatic), 3.53 (1 H, br s, CHOH), 3.23 (3 H, s, OCH_3), 2.66 (1 H, dd, J = 12, 5.6 Hz, CHPh), 2.42 (1 H, br s, H–4), 2.20 (1 H, ddd, J = 15, 12, 2.1 Hz, H–3b), 2.0-2.15 (1 H, m, H–8b), 1.94 (1 H, d, J = 14.7 Hz, H–6b), 1.76-1.96 (2 H, m, H–3a & H–8a), 1.68 (1 H, br s, OH), 1.31 (3 H, s, CH_3C–O), 1.19 (1 H, dd, J = 14.7, 1.3 Hz, H–6a), 0.72 ppm (3 H, s, C_1–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 143.0 (s), 129.2 (2 C, d), 128.0 (2 C, d) and 126.2 (d) (aromatic), 76.3 (s, C–OMe), 67.7 (d, CHOH), 49.1 (q, OCH_3), 48.6 (d, C–4), 45.5 (t, C–6), 38.1 (s, C–1), 34.3 (2 C, t & d, C–3 & C–7), 31.2 (t), 23.1 (q, CH_3C–O), 22.2 ppm (q, C_1–Me). Anal. Calcd. for $C_{17}H_{24}O_2$, C:78.42; H:9.29. Found, C:78.88; H:9.41%.

Continued elution with the same solvent gave the reduced product 14 (16 mg, 12%) as a yellow liquid. ^1H NMR (90 MHz, $CDCl_3$): δ 7.0-7.44 (5 H, m, aromatic), 4.1-4.45 (1 H, m, CHOH), 3.2 (3 H, s, OCH_3), 1.4-2.4 (5 H, m), 1.62 (3 H, br s, olefinic Me), 1.12 ppm (6 H, s, Me_2C-O).

(+)-(1S,2S,5R,6R)-2,6-Dimethyl-6-methoxy-1-phenylbicyclo[3.2.1]octan-3-one (8): To a magnetically stirred suspension of PCC (215 mg, 1 mmol), sodium acetate (82 mg, 1 mmol) and silica gel (215 mg) in dry CH_2Cl_2 (5 ml) was

added a solution of the bicyclic alcohol **15** (130 mg, 0.5 mmol) in dry CH_2Cl_2 (3 ml) and the reaction mixture was stirred at RT for 3 hr. The reaction mixture was passed through a silica gel (10 g) column and eluted with more CH_2Cl_2. Evaporation of the solvent furnished the bicyclic ketone **8** (120 mg, 93%) as a yellow viscous liquid. $[\alpha]_D^{26}$: +30° ($CHCl_3$, c 2.86). IR (neat): ν_{max} 3532, 1713, 1602, 1497, 1374, 1098, 1065, 894, 768, 741, 702 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.1-7.45 (5 H, m, aromatic), 3.24 (3 H, s, OCH_3), 1.8-2.92 (6 H, m), 2.22 and 1.92 (2 H, d of ABq J = 15, 2.5 Hz, H-8), 1.32 (3 H, s, CH_3C-O), 0.78 ppm (3 H, d, J = 7 Hz, C_2-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 209.3 (s, C=O), 146.3 (s), 127.9 (2 C, d), 126.4 (2 C, d) and 125.8 (d) (aromatic), 83.4 (s, C-OMe), 57.0 (d, C-2), 50.9 (2 C, q & s, OCH_3 & C-1), 44.5 (d, C-5), 43.6 (2 C, t, C-4 & C-7), 42.6 (t, C-8), 25.6 (q, CH_3C-O), 9.5 ppm (q, C_2-Me). Mass: m/e 258 (M^+, 51%), 227 (44), 184 (100), 170 (35), 169 (64), 155 (30), 154 (32), 129 (25), 115 (22). HRMS: m/e Calcd. for $C_{17}H_{22}O_2$, 258.1620; Found, 258.1625.

*(-)-(1S,4R,5R,7S)-1,5-Dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octan-2-one (**9a**):* Oxidation of the alcohol **16** (85 mg, 0.33 mmol) with PCC (142 mg, 0.66 mmol), sodium acetate (54 mg, 0.66 mmol) and silica gel (145 mg) in dry CH_2Cl_2 (10 ml) for 3 hr and purification over silica gel (5 g) column as described earlier furnished the bicyclic ketone **9a** (78 mg, 93%) as a white solid and was recrystallised from hexane. m.p.: 102-104°C; $[\alpha]_D^{26}$: -39.6° ($CHCl_3$, c 1.05). IR (CCl_4): ν_{max} 3028, 1722, 1671, 1605, 1497, 1350, 1158, 1122, 1071, 885, 759, 702 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.15-7.35 (3 H, m) and 6.96 (2 H, dd, J = 8.3, 1.7 Hz) (aromatic), 3.21 (3 H, s, OCH_3), 2.89 (1 H, td, J = 19, 2.7 Hz, H-3b), 2.86 (1 H, dd, J = 10.3, 7.5 Hz, CHPh), 2.2-2.5 (2 H, m, H-4, H-8b), 2.26 (1 H, d of ½ ABq, J = 19, 3 Hz, H-3a), 1.87 and 1.71 (2 H, ABq, J = 14.4 Hz, H-6), 1.79 (1 H, ddd, J = 10, 8, 2.3 Hz, H-8a), 1.47 (3 H, s, CH_3C-O), 0.64 ppm (3 H, s, C_1-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 215.3 (s, C=O), 143.5 (s), 128.3 (2 C, d), 128.0 (2 C, d) and 126.6 (d) (aromatic), 75.2 (s, C-OMe), 49.2 (s, C-1), 48.8 (2 C, t & q, CH_2CO & OCH_3), 48.3 (d, C-4), 40.6 (t, C-6), 36.2 (d, CHPh), 33.0 (t, C-8), 23.8 (q, C_5-Me), 18.4 ppm (q, C_1-Me). Anal. Calcd. for $C_{17}H_{22}O_2$, C:79.03; H:8.58. Found C:79.0; H:8.75%.

*(-)-(1S,2S,3R,5R,6S)-2,6-Dimethyl-6-methoxy-1-phenylbicyclo[3.2.1]octan-3-ol (**17**) and (-)-(1S,2R,4R,5S,7S) & (+)-(1S,2R,4R,5S,7R)-1,5-dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octan-2-ols (**18a** & **18b**):* Radical cyclisation of the bromo alcohol **13** (170 mg, 0.5 mmol) with $^nBu_3SnH$ (0.15 ml, 0.55 mmol) and AIBN (8 mg in 4 ml of dry toluene) in dry toluene (110 ml) for 4 hr, and purification of the product mixture over a silica gel (15 g) column with ethyl acetate-benzene (1:9) as eluent furnished the bicyclo[3.2.1]-octanol **17** (20 mg, 15%) as a colourless solid, then the bicyclo[2.2.2]octa-

nols 18b (18 mg, 13%) and 18a (42 mg, 32%) as colourless solids and the reduced product 14 (39 mg, 30%) as a yellow oil. The alcohols 18a & 18b were recrystallised from hexane.

Compound 17: m.p.: 108-110°C; $[\alpha]_D^{26}$: -30° ($CHCl_3$, c 0.15). IR (CCl_4): ν_{max} 3608 (sharp) and 3368 (broad) (OH) 1660, 1374, 1122, 1066, 968 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.0-7.45 (5 H, m, aromatic), 3.88-4.2 (1 H, m, CHOH), 3.1 (3 H, s, OCH_3), 2.54 (1 H, d of ½ ABq, J = 15, 2 Hz), 1.64-2.4 (7 H, m), 1.56 (3 H, s, CH_3C–O), 1.44 (1 H, s, OH), 0.62 ppm (3 H, d, J = 7 Hz, C_2–Me). Anal. Calcd. for $C_{17}H_{24}O_2$, C:78.42; H:9.29. Found: C:78.09; H:9.05%.

Compound 18a: m.p.: 100-101°C; $[\alpha]_D^{26}$: -89.0° ($CHCl_3$, c 1.32). IR (CCl_4): ν_{max} 3622 (sharp) and 3466 (broad) (OH), 1599, 1491, 1374, 1233, 1188, 1137, 1074, 1032, 924 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.1-7.35 (5 H, m, aromatic), 3.92 (1 H, br d, J = 7.6 Hz, CHOH), 3.22 (3 H, s, OCH_3), 2.87 (1 H, dd, J = 10.7, 7.5 Hz, CHPh), 2.2-2.4 (2 H, m, H–3b & 8b), 1.99 (1 H, br s, H–4), 1.87 (1 H, d, J = 14.2 Hz, H–6b), 1.55 (2 H, m, H–3a & 8a), 1.35 (3 H, s, CH_3C–O), 1.28 (1 H, dd, J = 14, 1.5 Hz, H–6a), 1.24 (1 H, br s, OH), 0.58 ppm (3 H, s, C_1–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 143.3 (s), 129.4 (2 C, d), 127.8 (2 C, d) and 126.0 (d) (aromatic), 76.1 (s, C–5), 67.6 (d, CHOH), 48.9 (q, OCH_3), 46.6 (d, C–4), 43.5 (t, C–6), 37.8 (s, C–1), 35.3 (t, C–3), 34.8 (d, CHPh), 29.6 (t, C–8), 22.8 (q, CH_3C–O), 21.5 ppm (q, C_1–Me). Anal. Calcd. for $C_{17}H_{24}O_2$, C:78.42; H:9.29. Found, C:78.22; H:9.43%.

Compound 18b: m.p.: 105-106°C; $[\alpha]_D^{26}$: +5.7° ($CHCl_3$, c 0.965). IR (CCl_4): ν_{max} 3622 (sharp) & 3472 (broad) (OH), 3058, 3028, 1674, 1599, 1494, 1374, 1155, 1122, 1107, 1071, 1032, 696 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.41 (2 H, d, J = 7.2 Hz), 7.29 (2 H, t, J = 7.2 Hz) and 7.2 (1 H, t, J = 7.2 Hz) (aromatic), 3.60 (1 H, d, J = 9.4 Hz, CHOH), 3.28 (3 H, s, OCH_3), 2.38 (1 H, dd, J = 10.8, 7 Hz, CHPh), 2.22 (1 H, tdd, J = 15.7, 9.8, 2.5 Hz, H–8b), 2.10 (1 H, ddd, J = 15, 9.6, 2.8 Hz, H–3b), 1.91 (1 H, m, H–4), 1.6-1.8 (4 H, m, H–8a, H–3a, H–6b and OH), 1.49 (1 H, d of ½ ABq, J = 14.5, 1.7 Hz, H–6a), 1.39 (3 H, s, CH_3C–O), 0.46 ppm (3 H, s, C_1–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 143.9, 130.0 (2 C), 127.9 (2 C) and 126.1 (aromatic), 75.6 (COMe), 74.4 (CHOH), 48.7 (OMe), 45.2, 38.3 (C–1), 36.3, 34.6, 34.2, 29.6 (C–8), 23.5 (CH_3C–O), 21.8 ppm (C_1–Me). Anal. Calcd. for $C_{17}H_{24}O_2$, C:78.42; H:9.29. Found, C:78.21; H:9.30%.

(1S,2S,5R,6S)-2,6-Dimethyl-6-methoxy-1-phenylbicyclo[3.2.1]octan-3-one (10): Oxidation of the alcohol 17 (15 mg, 0.06 mmol) with PCC (26 mg, 0.12 mmol), sodium acetate (10 mg, 0.12 mmol) and silica gel (26 mg) in dry CH_2Cl_2 (2 ml) for 3 hr and purification over a silica gel (2 g) column furnished the ketone 10 (10 mg, 67%) as a pale yellow oil. IR (neat): ν_{max} 3022, 2932, 1710, 1602, 1497, 1380, 1347, 1149, 1074, 942, 747, 702 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.1-7.4 (5 H, m), 3.12 (3 H, s, OCH_3), 1.4-2.6 (8

H, m), 1.24 (3 H, s, CH_3C–O), 0.7 ppm (3 H, d, J = 7 Hz, C_2–Me).

(–)-(1S,4R,5S,7S)-1,5-Dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octan-2-one (11a): Oxidation of the alcohol 18a (130 mg, 0.5 mmol) with PCC (215 mg, 1 mmol), sodium acetate (82 mg, 1 mmol) and silica gel (215 mg) in dry CH_2Cl_2 (10 ml) for 3 hr and purification over a silica gel (10 g) column furnished the bicyclic ketone 11a (125 mg, 97%) as a colourless solid and was recrystallised from hexane. m.p.: 111–112°C; $[\alpha]_D^{26}$: –74.8° ($CHCl_3$, c 1.31). IR (CCl_4): ν_{max} 3028, 1725, 1494, 1377, 1344, 1191, 1131, 930, 696 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.15–7.35 (3 H, m) and 6.98 (2 H, d, J = 6.7 Hz) (aromatic), 3.29 (3 H, s, OCH_3), 3.12 (1 H, dd, J = 10.8, 7.8 Hz, CHPh), 2.7 (1 H, br t, J = 10 Hz, H–3b), 2.46 (1 H, br s, H–8b), 2.37 (1 H, m, H–4), 1.94 and 1.58 (2 H, ABq, J = 14.7 Hz, H–6), 1.48–1.64 (2 H, m, H–3a & 8a), 1.32 (3 H, s, CH_3C–O), 0.63 ppm (3 H, s, C_1–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 215.0 (s, C=O), 143.9 (s), 128.0 (4 C, d) and 126.3 (d) (aromatic), 75.1 (s, C–OMe), 49.5 (q, OCH_3), 48.5 (s, C–1), 47.7 (t, C–3), 47.3 (d, C–4), 41.7 (t, C–6), 36.0 (d, CHPh), 32.0 (t, C–8), 22.9 (q, CH_3C–O), 18.1 ppm (q, C_1–Me). Anal. Calcd. for $C_{17}H_{22}O_2$, C:79.03; H:8.58. Found, C:79.22; H:8.69%.

(–)-(1S,4R,5S,7R)-1,5-Dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octan-2-one (11b): Oxidation of the alcohol 18b (65 mg, 0.25 mmol) with PCC (108 mg, 0.5 mmol), sodium acetate (41 mg, 0.5 mmol) and silica gel (108 mg) in dry CH_2Cl_2 (4 ml) for 3 hr and purification over a silica gel column, furnished the ketone 11b (58 mg, 90%) as a colourless solid and was recrystallised from hexane. m.p.: 96–97°C; $[\alpha]_D^{26}$: –33.77° ($CHCl_3$, c 0.965). IR ($CHCl_3$): ν_{max} 1716, 1602, 1584, 1377, 1332, 1131, 1071, 1020 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.43 (2 H, d, J = 7.0 Hz), 7.33 (2 H, t, J = 6.7 Hz) and 7.26 (1 H, m) (aromatic), 3.33 (3 H, s, OCH_3), 2.83 (1 H, dd, J = 10, 7.5 Hz, PhCH), 2.4–2.6 (3 H, m, H–3 & 8b), 2.37 (1 H, br s, H–4), 2.21 and 1.24 (2 H, ABq, J = 15 Hz, H–6), 2.02 (1 H, ddd, J = 14, 11.3, 3.5 Hz, H–8a), 1.28 (3 H, s, CH_3C–O), 0.54 ppm (3 H, s, C_1–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 215.6 (s, C=O), 141.3 (s), 129.6 (2 C, d), 128.1 (2 C, d) and 126.7 (d) (aromatic), 74.9 (s, C–OMe), 49.4 (q, OCH_3), 47.4 (s, C–1), 42.3 (d, C–4), 41.0 (t, C–3), 39.7 (t, C–6), 36.2 (d, CHPh), 28.5 (t, C–8), 23.6 (q, CH_3–C–O), 17.9 ppm (q, C_1–Me). Anal. Calcd. for $C_{17}H_{22}O_2$, C:79.03; H:8.58. Found, C:79.32; H:8.71%.

(–)-(1R,5R)-5-[(S)-1-bromo-2-methoxyprop-2-yl]-2-methyl-3-phenylcyclohex-2-en-1-yl acetate (19) and (–)-(1R,5R)-5-[(R)-1-bromo-2-methoxyprop-2-yl]-2-methyl-3-phenylcyclohex-2-en-1-yl acetate (20): To an ice-cold, magnetically stirred solution of the bromo alcohols 12 and 13 (1:1 mixture, 1.7 g, 5 mmol), DMAP (catalytic) and dry pyridine (5 ml) in dry CH_2Cl_2 (20 ml) was added acetic anhydride (1.2 ml, 12.5 mmol) and stirred at RT for 2 hr. The

reaction mixture was diluted with CH_2Cl_2 (10 ml) and the organic layer was washed with water (3 x 20 ml), 0.5N aq. HCl (3 x 20 ml), aq. sat. $NaHCO_3$ solution (3 x 20 ml) followed by brine and dried (Na_2SO_4). Solvent was evaporated and the residue was purified over a silica gel (25 g) column with ethyl acetate-benzene (1:49) as eluent. Careful mixing (TLC) of the fractions furnished the bromoacetates 19 & 20 (1:1, 1.82 g, 95%) as pale yellow viscous liquids.

Compound 19: $[\alpha]_D^{26}$: −44° ($CHCl_3$, c 4.18). IR (neat): ν_{max} 3052, 1731, 1602, 1494, 1374, 1239, 1122, 1080, 765, 702 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.08-7.44 (5 H, m, aromatic), 5.4-5.72 (1 H, m, CHOAc), 3.5 (2 H, s, CH_2Br), 3.24 (3 H, s, OCH_3), 2.2-2.44 (5 H, m), 2.12 (3 H, s, $COCH_3$), 1.52 (3 H, s, C_2–Me), 1.26 ppm (3 H, s, CH_3C–O). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 170.7 (s, O–C=O), 142.6 (s, C–3), 137.1 (s, C–2), 128.1 (5 C, d & s) and 126.7 (d) (aromatic), 76.4 (d, CHOAc), 74.3 (s, C–OMe), 49.5 (q, OCH_3), 38.4 (d, C–5), 37.5 (t, CH_2Br), 32.8 (t, C–6), 30.3 (t, C–4), 21.2 (q, $COCH_3$), 18.0 (q, CH_3C–O), 15.6 ppm (q, C_2–Me). Mass: m/e 380 (M^+, 2%), 382 (M^++2, 2), 269 (36), 227 (84), 209 (63), 195 (32), 169 (100), 168 (40), 153 (48), 151 (48), 91 (25). HRMS: m/e Calcd. for $C_{19}H_{25}BrO_3$, 380.0987; Found, 380.1024.

Compound 20: $[\alpha]_D^{26}$: −45.2° ($CHCl_3$, c 1.58). IR (neat): ν_{max} 3052, 1731, 1602, 1494, 1374, 1317, 1239, 1107, 1083, 969, 765, 735, 702 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.0-7.5 (5 H, m, aromatic), 5.4-5.76 (1 H, m, CHOAc), 3.34 and 3.56 (2 H, ABq, J = 10.8 Hz, CH_2Br), 3.2 (3 H, s, OMe), 2.0-2.5 (5 H, m), 2.12 (3 H, s, $COCH_3$), 1.5 (3 H, s, C_2–Me), 1.22 ppm (3 H, s, CH_3C–O). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 170.5 (COO), 142.4 (C–3), 136.1 (C–2), 128.8, 128.1 (4 C) and 126.6 (aromatic), 76.0 (C–1), 74.0 (C–8), 49.1 (OCH_3), 38.2 (C–5), 37.1 (CH_2Br), 33.4 (C–6), 29.3 (C–4), 21.1 ($OCOCH_3$), 17.2 (CH_3–C–O), 15.4 ppm (C_2–Me). Mass: m/e 380 (M^+, 1%), 382 (M^++2, 1), 269 (47), 227 (100), 209 (51), 195 (25), 169 (68), 168 (60), 153 (55), 151 (55), 91 (18). HRMS: m/e Calcd. for $C_{17}H_{21}BrO$, (M^+–AcOH), 320.0776; Found, 320.0754.

(−)-(1S,2R,4R,5R,7S) & (1S,2R,4R,5R,7R)-2-Acetoxy-1,5-dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octanes [21a & 21b] and (−)-(1S,2S,3R,5R,6R)-3-acetoxy-2,6-dimethyl-1-phenylbicyclo[3.2.1]octane (23): Radical cyclisation of the bromo acetate 19 (191 mg, 0.5 mmol) with $^nBu_3SnH$ (0.15 ml, 0.55 mmol) and AIBN (15 mg in 7 ml of dry tolune) in dry toluene (110 ml) for 4 hr, and purification of the product mixture over a silica gel (15 g) column with ethyl acetate-benzene (1:19) as eluent first furnished the reduced product 22 (30 mg, 20%) as a yellow oil. ^1H NMR (90 MHz, $CDCl_3$): δ 7.0-7.44 (5 H, m, Ph), 5.4-5.72 (1 H, m, CHOAc), 3.2 (3 H, s, OCH_3), 2.12 (3 H, s, $COCH_3$), 1.6-2.4 (5 H, m), 1.72 (3 H, br s, olefinic Me), 1.12 ppm (6 H, s, Me_2C–O).

Further elution of the column with the same solvent furnished a 1:1 epimeric mixture of bicyclic acetate 21 (53 mg, 35%) as a pale yellow oil.

$[\alpha]_D$: −11.41° ($CHCl_3$, c 0.885). IR (neat): ν_{max} 1731, 1605, 1497, 1374, 1251, 1152, 1074, 1032, 768, 705 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.24 (5 H, br s, aromatic), 4.48-5.0 (1 H, m, CHOAc), 3.2 (3 H, s, OCH_3), 2.36-2.72 (1 H, m, CHPh), 2.08 & 2.0 (3 H, s, $COCH_3$), 1.0-2.3 (7 H, m), 1.46 & 1.32 (3 H, s, CH_3C–O), 0.52 & 0.40 ppm (3 H, s, C_1–Me). Mass: m/e 302 (M^+, 27%), 260 (42), 227 (25), 211 (26), 210 (25), 138 (50), 123 (62), 107 (25), 99 (40), 91 (45), 85 (65). HRMS: m/e Calcd. for $C_{19}H_{26}O_3$, 302.1882; Found, 302.1886.

Continued elution with the same solvent furnished the bicyclic acetate 23 (24 mg, 16%) as a pale yellow oil. $[\alpha]_D^{26}$: −23.6° ($CHCl_3$, c 3.68). IR (neat): ν_{max} 3052, 3022, 1731, 1602, 1545, 1497, 1374, 1317, 1248, 1215, 1176, 1131, 1077, 1020, 759, 702 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.0-7.5 (5 H, m, aromatic), 4.96 (1 H, t, J = 6.5 Hz, CHOAc), 3.3 (3 H, s, OCH_3), 2.84 (1 H, ½ ABq, J = 10.5 Hz), 1.64-2.5 (7 H, m), 2.08 (3 H, s, $COCH_3$), 1.3 (3 H, s, CH_3C–O), 0.52 ppm (3 H, d, J = 7 Hz, C_2–Me). Mass: m/e 302 (M^+, 47%), 211 (50), 210 (76), 170 (43), 169 (30), 156 (30), 155 (40), 91 (44). HRMS: m/e Calcd. for $C_{19}H_{26}O_3$, 302.1882; Found, 302.1885.

(−)-(1S,2R,4R,5R,7S) and (+)-(1S,2R,4R,5R,7R)-1,5-Dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octan-2-ols (16 and 24): To an ice-cold, magnetically stirred solution of the acetate 21 (1:1 mixture of epimers, 75 mg, 0.25 mmol) in dry MeOH (10 ml) was added anhydrous K_2CO_3 (172 mg, 1.25 mmol) and the reaction mixture was stirred at RT for 10 hr. The solvent was removed under reduced pressure and the residue was dissloved in ether. The ether layer was washed with water (2 x 10 ml) followed by brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified over a silica gel (5 g) column with ethyl acetate-benzene (1:9) as eluent to furnish the alcohols 16 and 24. The bicyclic alcohol 16 was identified by comparison (TLC, IR, ^1H NMR) with the sample obtained earlier.

Compound 24: $[\alpha]_D^{26}$: +49.44° ($CHCl_3$, c 1.43). IR (neat): ν_{max} 3478 (broad, OH), 3058, 3028, 1602, 1584, 1497, 1374, 1356, 1143, 1104, 1086, 1071, 1035, 996, 915, 900, 834, 780, 744, 702 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.1-7.4 (5 H, m, aromatic), 3.61 (1 H, d, J = 6 Hz, OH), 3.44 (1 H, t, J = 9.8 Hz, CHOH), 3.25 (3 H, s, OCH_3), 2.46 (1 H, t, J = 9 Hz, H–7), 2.05 (1 H, br s, H–4), 1.6-2.05 (4 H, m, H–3 & 8), 1.63 and 1.50 (2 H, ABq, J = 16 Hz, H–6), 1.43 (3 H, s, CH_3C–O), 0.50 ppm (3 H, s, C_1–Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 142.5 (s), 129.0 (2 C, d), 127.9 (2 C, d) and 126.3 (d) (aromatic), 76.5 (s, C–OMe), 73.3 (d, CHOH), 49.0 (q, OCH_3), 45.2 (d, C–4), 38.1 (t), 37.8 (t), 34.0 (s, C–1), 33.3 (d, CHPh), 31.3 (t, C–8), 21.8 ppm (2 C, q, CH_3C–O, C_1–Me). Mass: m/e 260 (M^+, 3%), 228 (72), 184 (100), 169 (47), 124 (30), 95 (37). HRMS: m/e Calcd. for $C_{17}H_{24}O_2$, 260.1776; Found, 260.1757.

(+)-(1S,4R,5R,7R)-1,5-Dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octan-2-one (9b): Oxidation of the bicyclic alcohol 24 (65 mg, 0.25 mmol) with PCC (108

mg, 0.5 mmol), sodium acetate (40 mg, 0.5 mmol) and silica gel (108 mg) in dry CH_2Cl_2 (10 ml) for 3 hr as described earlier and purification over a silica gel column (5 g) with ethyl acetate-benzene (1:9) as eluent furnished the ketone **9b** (58 mg, 90%) as a colourless solid and was recrystallised from hexane. m.p.: 90-91°C; $[\alpha]_D^{26}$: +34.2° ($CHCl_3$, c 0.965). IR (CCl_4): ν_{max} 1715, 1602, 1337, 1134, 1071, 1026, 870 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.2-7.4 (3 H, m), 7.19 (2 H, d, J = 7 Hz) (aromatic), 3.17 (3 H, s, OCH_3), 2.88 (1 H, t, J = 9 Hz, CHPh), 2.66 (1 H, t of ½ ABq, J = 18.3, 3.3 Hz, H-3b), 2.4 (1 H, br s, H-4), 2.2-2.4 (2 H, m), 2.0-2.1 (1 H, m), 2.02 (1 H, ABq, J=15 Hz, H-6b), 1.57 (1 H, d, J = 15 Hz, H-6a), 1.54 (3 H, s, CH_3C-O), 0.53 ppm (3 H, s, C_1-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 215.2 (s, C=O), 140.6 (s), 128.9 (2 C, d), 128.2 (2 C, d) and 126.8 (2 C, d) (aromatic), 74.9 (s, C-OMe), 48.7 (q, OCH_3), 46.6 (s, C-1), 43.3 (d, C-4), 41.8 (t, C-3), 37.7 (t, C-6), 36.8 (d, CHPh), 30.1 (t, C-8), 21.5 (q, CH_3C-O), 17.7 ppm (q, C_1-Me). Anal. Calcd. for $C_{17}H_{22}O_2$, C:79.03; H:8.58. Found, C:78.76; H:8.70%.

(-)-(1S,2R,4R,5S,7S) & (1S,2R,4R,5S,7R)-2-Acetoxy-1,5-dimethyl-5-methoxy-7-phenylbicyclo[2.2.2]octane (25) and (-)-(1S,2S,3R,5R,6S)-3-acetoxy-2,6-dimethyl-6-methoxy-1-phenylbicyclo[3.2.1]octane (26): Radical cylclisation of the bromo acetate **20** (191 mg, 0.5 mmol) with $^nBu_3SnH$ (0.15 ml, 0.55 mmol) and AIBN (15 mg in 7 ml of toluene) in dry toluene (110 ml) for 4 hr, and purification of the product mixture over a silica gel (15 g) column with ethyl acetate-benzene (1:19) as eluent furnished the bicyclic acetate **25** (1:1.2 mixture of epimers, 76 mg, 50%) as a pale yellow oil and a mixture (1:1.5) of [3.2.1] acetate **26** and reduced product **22** (45 mg, 30%).

Compound **25**: (mixture of diastereomers) $[\alpha]_D^{26}$: −29.65° ($CHCl_3$, c 0.58). IR (neat): ν_{max} 3058, 3022, 1740, 1602, 1497, 1374, 1155, 1032, 768, cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.0-7.6 (5 H, m, aromatic), 4.6-5.0 (1 H, br d, J = 8 Hz, CH-OAc), 3.28 & 3.22 (3 H, s, OCH_3), 2.86 & 2.48 (1 H, dd, J = 10.8, 7.2 Hz & ddd, J = 10.8, 7.2, 3.6 Hz, CHPh), 2.06 & 1.98 (3 H, s, $COCH_3$), 1.4 − 2.26 (7 H, m), 1.32 (3 H, s, CH_3C-O), 0.52 & 0.40 ppm (3 H, s, C_1-Me). Mass: m/e 302 (M^+, 22%), 270 (43), 269, (30), 260 (42), 228 (48), 227 (100), 211 (42), 210 (76), 209 (40), 169 (73), 168 (55),138 (59), 123 (62), 99 (45),91 (53). HRMS: m/e Calcd. for $C_{19}H_{26}O_3$, 302.1882; Found, 302.1862.

Compound **26**: $[\alpha]_D^{26}$: −8.8° ($CHCl_3$, c 0.91). IR (neat): ν_{max} 3052, 1740, 1602, 1497, 1377, 1239, 1209, 1152, 1128, 1104, 1071, 1017, 960, 903, 759, 702 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.2 (5 H, br s, aromatic), 5.2 (1 H, t, J = 6.5 Hz, CHOAc), 3.16 (3 H, s, OCH_3), 1.6-2.6 (8 H, m), 2.08 (3 H, s, $COCH_3$), 1.44 (3 H, s, CH_3C-O), 0.5 ppm (3 H, d, J = 7 Hz, C_2-Me). Mass: m/e 302 (M^+, 43), 211 (43), 210 (96), 170 (46), 169 (30), 155 (46), 91 (68). HRMS: m/e Calcd. for $C_{19}H_{25}O_3$, 302.1882; Found, 302.1872.

Hydrolysis of acetate 25: Hydrolysis of the acetate **25** (1:1.2 mixture of

epimers, 76 mg, 0.25 mmol) with anhydrous K_2CO_3 (172 mg, 1.25 mmol) in MeOH (10 ml) as described earlier and purification of the product mixture over a silica gel (5 g) column with ethyl acetate-benzene (1:9) as eluent furnished the alcohols 18a & 18b as colourless solids and were identified by comparison (TLC, IR & ^{1}H NMR) with the samples obtained earlier.

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