Enantiospecific synthesis of functionalised bicyclo[3.3.1]nonanes from 10-bromocarvones via tandem intermolecular alkylation-intramolecular Michael addition sequence[1]

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Dedicated to Professor Sukh Dev

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Abstract

A simple and convenient tandem methodology for the enantiospecific generation of functionalised bicyclo[3.3.1]nonanes **9**,**14-18**, via intermolecular alkylation of Michael donors with 10-bromocarvones **7**, **10** and **11**, followed by intramolecular Michael addition, is achieved. An unsuccessful attempt for the extension of the methodology for a possible short enantiospecific approach to AB-ring system **22** of taxanes via the allyl bromide **21**, is also described.

Keywords: Enantiospecific synthesis, bicyclo[3.3.1]nonanes, 10-bromocarvones, tandem alkylation Michael addition, intramolecular addition

Introduction

Tandem reactions are among the most powerful building tools available in organic synthesis, since they rapidly increase the complexity of a substrate starting from simple precursors.[2] Stereocontrolled construction of various molecular frameworks with a high level of regio-, stereo- and enantioselectivity is one of the most challenging aspects in organic synthesis. Ready access to enantiomerically pure multifunctional compounds is highly desirable, as they can serve as chirons in the synthesis of complex products of biological significance. The bicyclo[3.3.1]nonane (**1**) system[3] is present in several natural products such as hyperforin, aristophenone A, guttiferone B, garsubellin A, papuaforin A, upial, trifarienols, etc. (Chart 1).[4] Biosynthetic pathway of many sesquiterpenoids and other naturally occurring materials involve formation and transformation of bicyclo[3.3.1]nonanes.[5] In addition, bicyclo[3.3.1]nonanes have been utilised as synthons for the construction of various complex ring systems, enroute to natural products.[3,6] This system has also received theoretical interest from the conformation point of

view.[7] In continuation of our interest in the enantiospecific synthesis of functionalised bi- and tricyclic carbocyclic systems from the readily and abundantly available monoterpene, (*R*)-carvone,[8] we have developed a simple and convenient methodology for the construction of bicyclo[3.3.1]nonanes employing a tandem intermolecular alkylation-intramolecular Michael addition reaction sequence.[9]

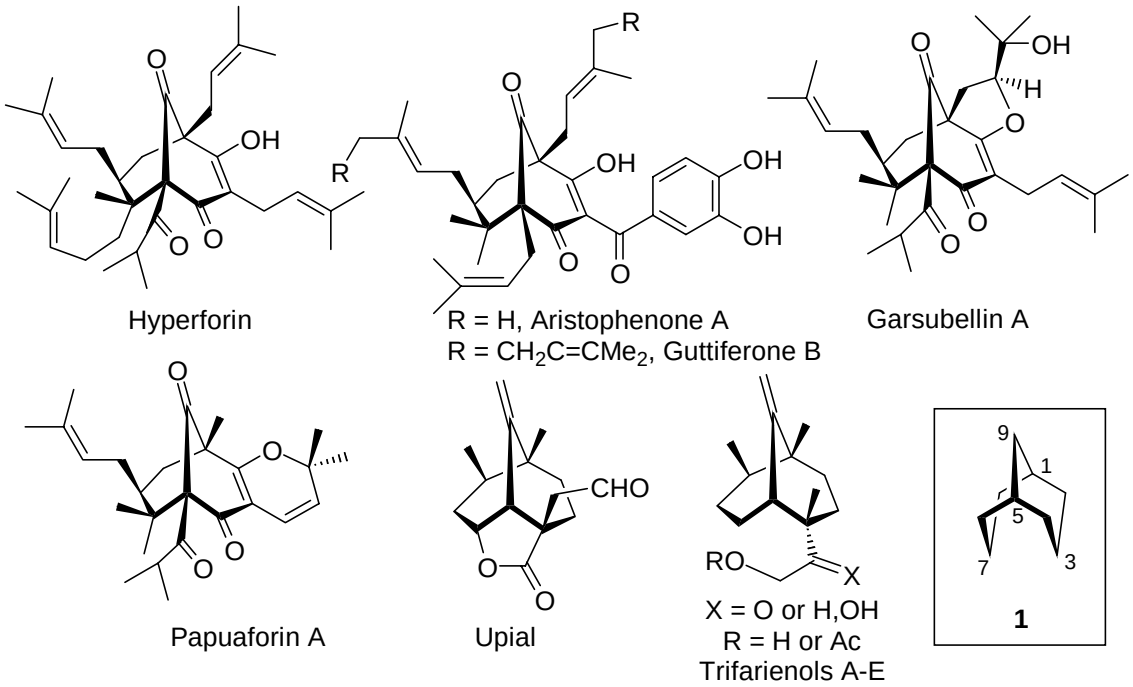
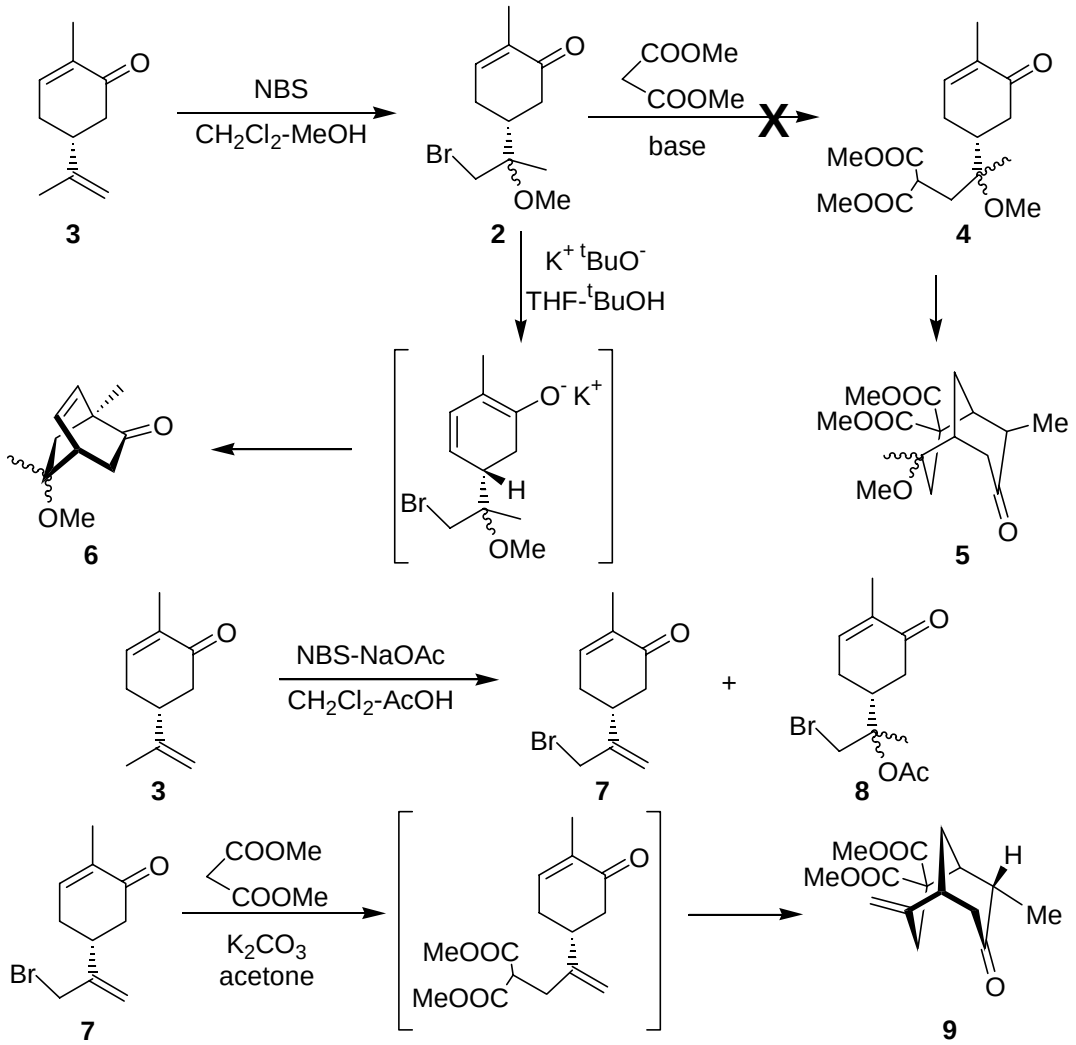


Chart 1

Results and Discussion

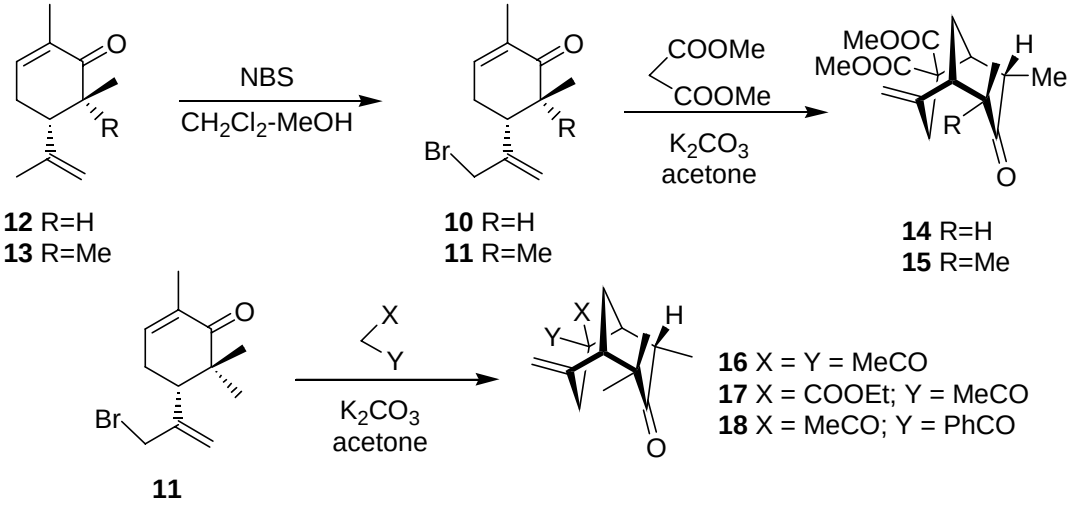
It was anticipated that alkylation of a Michael donor such as dimethyl malonate with a 9-bromocarvone derivative such as the bromoenone **2**,[8b] obtained by bromomethoxylation[10] of (*R*)-carvone **3** [*N*-bromosuccinimide (NBS) in CH_3OH-CH_2Cl_2], would generate **4**, which could undergo an intramolecular Michael addition leading to chiral bicyclo[3.3.1]nonane **5**. Even though the bromoenone **2** was known to participate in the intramolecular alkylation reaction with potassium tertiary butoxide in tertiary butyl alcohol-THF leading to bicyclo[2.2.2]octenone **6**,[8h] contrary to our anticipation, it failed to undergo intermolecular alkylation with dimethyl malonate under a variety of basic conditions, and neither the alkylated product **4** nor the bicyclic product **5** were formed, perhaps due to the neopentylic nature of the electrophilic center. To overcome the steric crowding, the reaction was investigated with the allyl bromide **7**.[8h] Addition of NBS to a solution of carvone (**3**) and sodium acetate in methylene chloride and acetic acid at room temperature furnished a 3:2 mixture of 10-bromocarvone **7** and the bromoacetoxylation product **8**, which were separated by silica gel column chromatography. Reaction of 10-

bromocarvone **7** with dimethyl malonate and potassium carbonate in refluxing acetone for 12 hours cleanly furnished the bicyclo[3.3.1]nonane **9** in 86% yield.

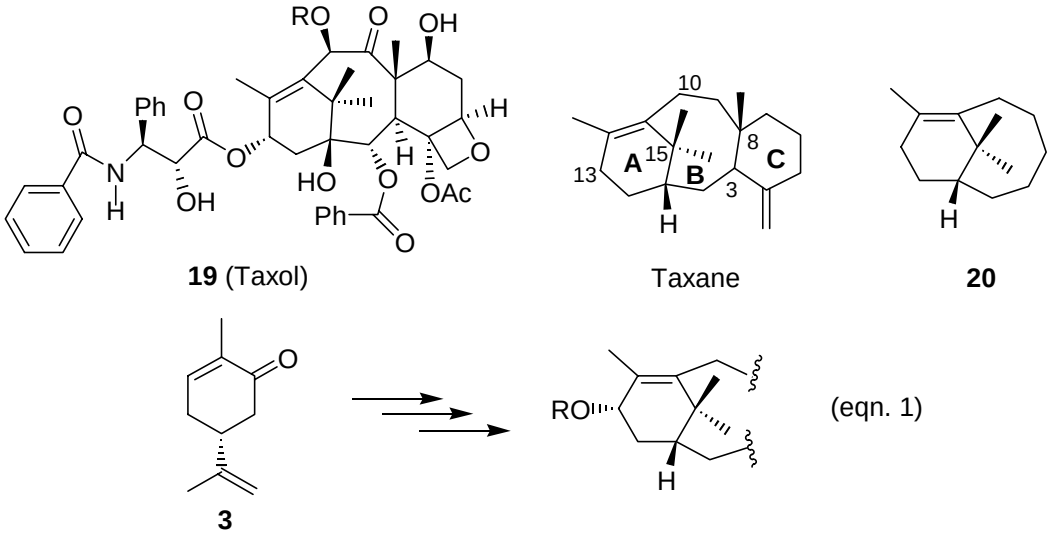


Presence of a strong absorption band at 1715 cm^{-1} due to the ester carbonyl group and shift in the absorption band due to the ketone carbonyl group to 1700 cm^{-1} suggested the formation of the bicyclic product **9**. The ^{1}H NMR spectrum exhibited characteristic resonances, in particular, two singlets at δ 4.79 and 4.72 due to the exomethylene protons, a singlet at 3.69 due to the two ester methyl groups, and a doublet at 1.02 ppm due to the secondary methyl group establishing the structure of the bicyclic ketone **9**, which was further confirmed by the 15 lines ^{13}C NMR spectrum (see experimental section). The conformation and stereochemistry of **9** were deduced from the spectral data, in particular the various H-H coupling constants in the 400 MHz ^{1}H NMR spectrum. The twin chair conformation was assigned based on the ^{13}C NMR spectrum, as it was well established[11] that the resonance due to C-9 appear at δ 34.4, 28.6, and 23.7 ppm for the twin chair, boat chair and twin boat conformations of the bicyclo[3.3.1]nonanes. The equitorial

orientation of the methyl group at C-8 in **9** was assigned based on the quintet resonance for the C-8 axial proton at δ 2.73 (*J* 7.0 Hz), as the $J_{1,8eq}$ is known to be less than 3 Hz.[12] To establish the generality of this methodology, the reaction was also carried out with the allyl bromides **10** and **11** derived from 6-methylcarvone **12** and 6,6-dimethylcarvone **13**,[13] respectively. Interestingly, treatment of 6,6-dimethylcarvone **13** with NBS in methylene chloride and methanol furnished, exclusively, the allyl bromide **11**, in 84% yield, unlike the reaction with carvone, no product derived from bromomethoxylation reaction was observed probably due to the steric crowding. In a similar manner, reaction of *trans*-6-methylcarvone **12** with NBS in methanol and methylene chloride furnished the allyl bromide **10**.[8l] Treatment of the allyl bromide **10** with dimethyl malonate and potassium carbonate in refluxing acetone furnished the bicyclo[3.3.1]nonane **14** in 82% yield. Reaction of the allyl bromide **11** with dimethyl malonate furnished the bicyclo[3.3.1]nonane **15**, and with other Michael donors acetylacetone, ethyl acetoacetate and benzoylacetone furnished the bicyclic compounds **16, 17** and **18**, respectively. Structures of the products **14-18** were established from their interrelated spectral data. Presence of an upfield shifted resonance due to the C-4 secondary methyl group at δ 0.66 ppm (shielded due to the equatorial aroyl group at the C-6 position) in the bicyclic compound **18** established the equatorial orientation of the benzoyl group.

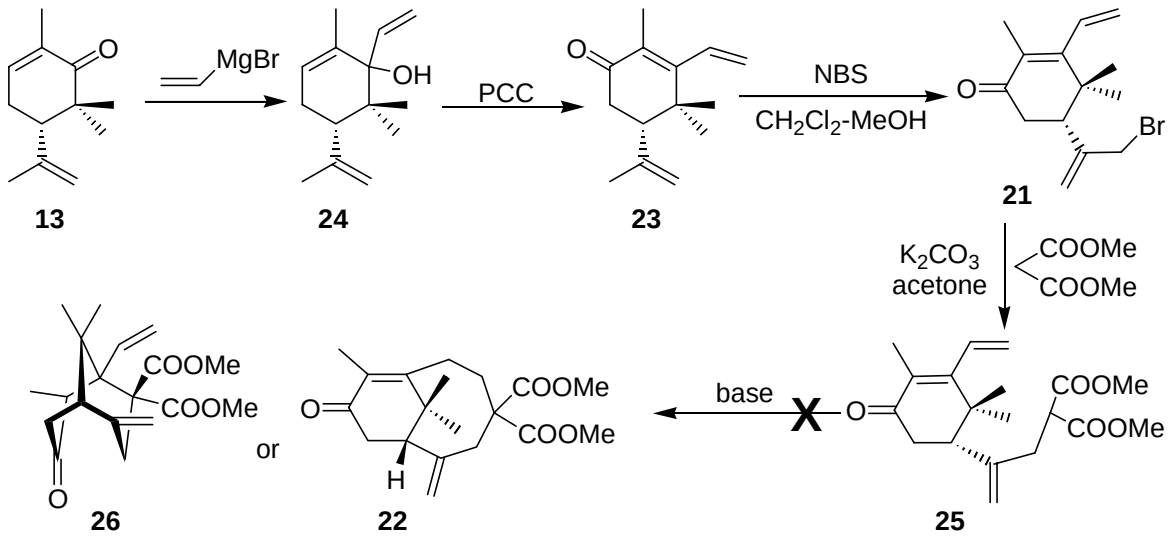


Paclitaxel (**19**, Taxol),[14] by virtue of its complex and densely functionalised structure, coupled with its novel mechanism of action, potent antitumor activity and its clinical use as a powerful anti-cancer drug has attracted the attention of many synthetic chemists.[15] Indeed, only very few molecules in the last two decades have stirred as much imagination and activity among synthetic chemists as taxanes. While a few paid attentions to the total synthesis of taxol, a large number of research groups confined themselves to the development of methodologies toward



various segments of taxol as well as analogues of taxanes.[16] Assembling of the AB ring system of taxane, containing a bicyclo[5.3.1]undecane (**20**) framework and a bridgehead olefin, is proved to be one of the most difficult tasks in the construction of taxanes. Earlier,[17] we have developed an approach to functionalised A-ring of taxanes starting from (*R*)-carvone, wherein the C-5 and C-3 carbons of carvone were transformed into the C-1 and C-13 of taxanes (eqn. 1). In this context, after successful enantiospecific synthesis of the functionalised bicyclo[3.3.1]nonanes **9**, **14-18**, it was contemplated to explore the tandem intermolecular alkylation followed by intramolecular Michael addition methodology for a very short enantiospecific approach to the AB-ring system of the taxanes starting from 6,6-dimethylcarvone **13**. In analogy to the synthesis of bicyclo[3.3.1]nonanes, it was anticipated that generation of the bromide **21** followed by tandem intermolecular alkylation with dimethyl malonate and intramolecular 1,6-conjugate addition leads to the AB-ring system of taxanes **22**. A 1,3-enone-transposition methodology[18] was opted for the synthesis of the requisite vinyl enone **23**. Thus, Grignard reaction of 6,6-dimethylcarvone **13** with vinylmagnesium bromide followed by oxidation of the resultant biallylic tertiary alcohol **24** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished 4,4-dimethyl-3-vinylcarvone **23**. Treatment of the vinyl enone **23** with one equivalent of NBS in a 3:2 mixture of methylene chloride and methanol furnished, exclusively, the bromoenone **21** in 85% yield, analogous to the reaction of dimethylcarvone, whose structure was established from its spectral data. However, contrary to our anticipation, treatment of the allyl bromide **21** with dimethyl malonate and potassium carbonate in refluxing acetone furnished only the alkylated product **25** in 85% yield. Presence of the molecular ion peak at m/z 334 ($C_{19}H_{26}O_5$) in the mass spectrum, presence of a strong absorption band at 1730 cm^{-1} due to ester carbonyl in the IR spectrum and absence of resonances due to bromomethyl group in the ^1H NMR spectrum indicated the formation of the compound **25**. In the ^1H NMR spectrum presence of typical ABX pattern resonances for the vinyl group, a six protons singlet at δ 3.73 and a doublet of a doublet at 3.61 ppm due to the C*H*$(COOMe)_2$

group established the structure of the compound **25**, which was further confirmed by the 17 lines ^{13}C NMR spectrum. The diester **25** was treated with base once again. However, a variety of basic conditions failed to induce either the intramolecular 1,6-conjugate addition to generate AB ring system of the taxanes **22**, or the intramolecular Michael addition to produce the bicyclo[3.3.1]nonane **26**, perhaps due to the steric crowding generated because of the gem-dimethyl group.



In conclusion, we have developed a simple and convenient enantiospecific procedure for the construction of functionalised bicylo[3.3.1]nonanes employing a tandem intermolecular alkylation of Michael donors with 10-bromocarvone derivatives followed by an intramolecular Michael addition reaction.

Experimental Section

General Procedures. Melting points are recorded using Tempo melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Perkin Elmer 781 spectrophotometer. ^{1}H (200, 300 and 400 MHz) and ^{13}C (22.5 and 75 MHz) NMR spectra were recorded on Brucker ACF-200 and AMX-400, and Jeol FX 90Q and JNM λ-300 spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons was determined by recording the off-resonance spectra. Low and high-resolution mass measurements were carried out using Jeol JMS-DX 303 GCMS instrument using direct inlet mode. Relative intensities are given in parentheses. Elemental analyses were carried out using Carlo Erba 1106 CHN analyser. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Acme's silica gel (100-200 mesh) was used for column chromatography

(approximately 15-20 g per 1 g of the crude product). Acetone was purified by distilling over potassium permanganate and storing over molecular sieves. 6,6-Dimethylcarvone **13**,[13] and the allyl bromides **7**[8h] and **10**[8l] were prepared as reported earlier.

(-)-(R)-5-(3-Bromopropen-2-yl)-2,6,6-trimethylcyclohex-2-enone (11). To a magnetically stirred solution of the dimethylcarvone **13** (178 mg, 1.0 mmol) in a 3:2 mixture of CH_2Cl_2 and methanol (3.1 ml) was slowly added NBS (216 mg, 1.2 mmol) over a period of 40 min and the reaction mixture was stirred for 8 h. It was then diluted with water and extracted with CH_2Cl_2 (2 x 4 ml). The combined CH_2Cl_2 extract was washed with 5% aq. NaOH and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the allyl bromide **11** (215 mg, 84%) as oil. $[\alpha]_D^{26}$: -28.4 (c 4.5, $CHCl_3$). IR (neat): ν_{max} 1670, 915 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.63 (1 H, br s, H-3), 5.41 (1 H, s) and 5.07 (1 H, s) [$C=CH_2$], 3.97 and 3.90 (2 H, AB quartet, *J* 9.9 Hz, CH_2Br), 2.75 (1 H, t, *J* 7.5 Hz, H-5), 2.50-2.45 (2 H, m, H-6), 1.79 (3 H, olefinic CH_3), 1.10 (3 H, s) and 1.03 (3 H, s) [CH_3-C-CH_3]. ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 203.6 (C=O), 145.5 (*C*=CH_2), 142.5 (C-3), 133.5 (C-2), 118.0 (C=*C*H_2), 47.2, 45.0 (C-6), 39.4, 30.3, 23.5, 19.6, 16.5. Mass: m/z 256 (M^+, 10%), 258 (M+2, 10), 177 (30), 135 (14), 95 (16), 82 (100).

Typical Procedure for the Tandem Sequence

(-)-Dimethyl (1S,5R,8S)-4-methylene-8-methyl-7-oxobicyclo[3.3.1]nonane-2,2-dicarboxylate. A magnetically stirred mixture of 10-bromocarvone **7** (200 mg, 1.33 mmol), dimethyl malonate (116 mg, 0.88 mmol) and potassium carbonate (242 mg, 1.75 mmol) in dry acetone (4 ml) was refluxed for 12 h (monitored by TLC). After the completion of the reaction, the solvent was evaporated, water (2 ml) was added to the residue and extracted with ether (5 x 5 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20 to 1:10) as eluent furnished the diester **9** (210 mg, 86%) as solid which was recrystallised from a mixture of hexane and methylene chloride. m.p. 106 °C. $[\alpha]_D^{25}$: -16.0 (c 2.0, $CHCl_3$). IR (nujol): ν_{max} 1740, 1715, 1700, 915 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.79 (1 H, s) and 4.72 (1 H, s) [$C=CH_2$], 3.69 (6 H, s, 2 x $COOCH_3$), 3.26 (1 H, br s), 2.88 (1 H, d, *J* 15.4 Hz, H-3a), 2.98 (1 H, br s), 2.73 (1 H, quintet, *J* 7.0 Hz, H-8), 2.55 (1 H, dd, *J* 16.0 and 5.8 Hz, H-6ax), 2.48 (1 H, d, 16.0 Hz, H-3b), 2.40 (1 H, d, 16.0 Hz, H-6eq), 2.29 (1 H, q of d, *J* 13.8 and 3.0 Hz, H-9a), 2.08 (1 H, t of d, *J* 13.8 and 3.0 Hz, H-9b), 1.02 (3 H, d, *J* 7.1 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 210.7 (s, C=O), 170.2 (s) and 169.6 (s) [2 x *C*OOMe], 146.3 (s, *C*=CH_2), 110.0 (t, C=*C*H_2), 58.0 (s, C-2), 52.3 (q) and 52.0 (q) [2 x COO*C*H_3], 48.7 (d, C-8), 46.5 (t, C-6), 41.5 (d), 39.8 (d), 34.3 (t, C-9), 32.5 (t, C-3), 11.3 (q, *sec*-CH_3). Mass: m/z 281 (M^++1, 80%), 248 (55), 220 (40), 189 (100), 91 (45). Anal.: For $C_{15}H_{20}O_5$ Calcd.: C, 64.3; H, 7.19, Found: C, 64.1; H, 7.18%.

(-)-Dimethyl (1S,5R,6S,8S)-6,9-dimethyl-4-methylene-7-oxobicyclo[3.3.1]nonane-2,2-dicarboxylate (14). Yield 82%. $[\alpha]_D^{24}$: -11.4 (c 1.7, $CHCl_3$). IR (neat): ν_{max} 1730, 1700, 900 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.76 (1 H, s) and 4.69 (1 H, s) [$C=CH_2$], 3.70 (3 H, s) and 3.69 (3 H, s) [2 x $COOCH_3$], 3.20 (1 H, br s), 2.87 (1 H, d, *J* 13.5 Hz, H-3a), 2.90-2.80 (1 H, m),

2.55-2.40 (3 H, m), 2.28 (1 H, t of d, *J* 14.1 and 2.8 Hz), 2.09 (1 H, m of d, *J* 17.7 Hz), 1.25 (3 H, d, *J* 7.5 Hz) and 0.99 (3 H, d, *J* 7.1 Hz) [2 x *sec*-CH_3]. ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 215.1 (s, C=O), 170.5 (s) and 170.0 (s) [2 x O-C=O], 147.1 (s, *C*=CH_2), 110.0 (t, C=*C*H_2), 58.0 (s, C-2), 52.6 (q), 52.2 (q), 49.6 (d), 46.4 (d), 45.3 (d), 42.2 (d), 32.8 (t, C-9), 29.6 (t, C-3), 18.8 (q), 11.7 (q). Mass: m/z 294 (M^+, 15%), 262 (50), 234 (25), 203 (100), 202 (45), 162 (40), 119 (40), 101 (50), 91 (50). HRMS: m/z Calcd. for $C_{16}H_{22}O_5$: 294.1467. Found 294.1473.

(-)-Dimethyl (1*S*,5*S*,8*S*)-6,6,8-trimethyl-4-methylene-7-oxobicyclo[3.3.1]nonane-2,2-dicarboxylate (15). Yield: 97%. m.p. 120-122 °C. $[\alpha]_D^{27}$: -1.5 (c 11, $CHCl_3$). IR (neat): ν_{max} 1730, 1700, 900 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (1 H, s) and 4.73 (1 H, s) [C=CH_2], 3.70 (3 H, s) and 3.68 (3 H, s) [2 x $COOCH_3$], 3.22 (1 H, br s), 3.00 (1 H, d of q, *J* 7.0 and 5.0 Hz, H-8), 2.82 (1 H, d, *J* 15.5 Hz, H-3β), 2.44 (1 H, t of d, *J* 14.1 and 2.9 Hz, H-9a), 2.34 (1 H, br s), 2.29 (1 H, d, *J* 15.5 Hz, H-3α), 2.12 (1 H, t of d, *J* 14.1 and 3.2 Hz, H-9b), 1.26 (3 H, s) and 0.99 (3 H, s) [CH_3-C-CH_3], 0.99 (3 H, d, *J* 7.0 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 216.1 (s, C=O), 170.5 (s) and 170.0 (s) [2 x O-C=O], 145.1 (s, *C*=CH_2), 111.9 (t, C=*C*H_2), 58.2 (s, C-2), 52.4 (q, OCH_3), 52.2 (2 C, q and d, OCH_3 and C-8), 46.5 (s, C-6), 44.7 (d), 43.1 (d), 33.0 (t, C-9), 31.4 (t, C-7), 27.7 (q) and 23.0 (q) [*C*H_3-C-*C*H_3], 11.8 (q, *sec*. CH_3). Mass: m/z 308 (M^+, 60%), 276 (80), 248 (60), 220 (70), 217 (100), 151 (60), 119 (70), 99 (70), 91 (95). Anal. For $C_{17}H_{24}O_5$, Calcd: C, 66.2; H, 7.84. Found: C, 66.6; H, 7.95%.

(-)-(1S,4S,5S)-6,6-Diacetyl-8-methylene-2,2,4-trimethylbicyclo[3.3.1]nonan-3-one (16). Yield 80%. $[\alpha]_D^{25}$: -164.0 (c 1.0, $CHCl_3$). IR (neat): ν_{max} 1700, 920 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.82 (1 H, br s) and 4.79 (1 H, br s) [C=CH_2], 3.51 (1 H, br s), 2.98 (1 H, quintet, *J* 7.0 Hz, H-4), 2.85 (1 H, d, *J* 16.0 Hz, H-7a), 2.43 (1 H, t of d, *J* 13.9 and 3.0 Hz, H-9a), 2.33 (1 H, br s), 2.29 (1 H, d, *J* 16.8 Hz, H-7b), 2.12 (3 H, s) and 2.10 (3 H, s) [2 x $COCH_3$], 1.80 (1 H, t of d, *J* 13.9 and 3.1 Hz, H-9b), 1.25 (3 H, s) and 0.99 (3 H, s) [CH_3-C-CH_3], 0.95 (3 H, d, *J* 7.0 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 216.4 (s, C-3), 206.0 (s) and 205.7 (s) [2 x CH_3C=O], 145.4 (s, *C*=CH_2), 112.7 (t, C=*C*H_2), 78.5 (s, C-6), 52.4 (d, C-4), 46.5 (s, C-2), 45.0 (d), 43.3 (d), 32.2 (t) and 31.1 (t) [C-7 and 9], 27.7 (q), 26.8 (q), 26.2 (q), 23.4 (q), 13.4 (q). Mass: m/z 276 (M^+), 233 (45), 192 (30), 135 (65), 99 (35), 43 (100). HRMS: m/z For $C_{17}H_{24}O_3$, Calcd.: 276.1725. Found: 276.1732. Anal.: For $C_{17}H_{24}O_3$, Calcd: C, 73.9; H, 8.75. Found: C, 74.0; H, 8.77%.

(-)-Ethyl (1*S*,5*S*,6*R*,8*S*)-2-acetyl-6,6,9-trimethyl-4-methylene-7-oxobicyclo[3.3.1]nonane-2-carboxylate (17). Yield: 68%. $[\alpha]_D^{25}$: -58.2 (c 2.1, $CHCl_3$). IR (neat): ν_{max} 1725, 1700, 1645, 895 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.75 (1 H, s) and 4.74 (1 H, s) [C=CH_2], 4.21 and 4.09 (2 H, q of AB q, *J* 10.7 and 7.0 Hz, OC*H*$_2$$CH_3$), 3.35 (1 H, m), 2.99 (1 H, d of q, *J* 7.2 and 5.0 Hz, H-8), 2.77 (1 H, d, *J* 15.4 Hz, H-3β), 2.47 (1 H, t of d, *J* 14.0 and 2.9 Hz, H-9a), 2.35 (1 H, br s), 2.24 (1 H, t of d, *J* 15.4 and 1.8 Hz, H-3α), 2.19 (3 H, s, CH_3CO), 2.09 (1 H, t of d, *J* 14.0 and 3.2 Hz, H-9b), 1.26 (3 H, s) and 1.00 (3 H, s) [CH_3-C-CH_3], 1.23 (3 H, t, *J* 7.0 Hz, OCH_2C*H*$_3$), 0.96 (3 H, d, *J* 7.2 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 215.7 (s, C-7), 203.7 (s, CH_3*C*=O), 169.9 (s, O-C=O), 145.4 (s, *C*=CH_2), 111.6 (t, C=*C*H_2), 65.9 (s, C-2), 61.2 (t, O*C*$H_2$$CH_3$), 52.0 (d, C-8), 46.1 (s, C-6), 44.5 (d), 43.2 (d), 31.9 (t), 31.4 (t), 27.3 (q), 25.1 (q),

22.9 (q), 13.4 (q), 12.6 (q). Mass: m/z 306 (M^+, 5%), 263 (45), 217 (100), 119 (25), 99 (60). HRMS: m/z Calcd. for $C_{18}H_{26}O_4$: 306.1831. Found 306.1822.

(-)-(1S,4S,5S,6S)-6-Acetyl-6-benzoyl-8-methylene-2,2,4-trimethylbicyclo[3.3.1]nonan-3-one (18). Yield: 20%. m.p. 164-166 °C. $[\alpha]_D^{25}$: -143 (c 1.9, $CHCl_3$). IR (neat): ν_{max} 1700, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (2 H, d, *J* 7.7 Hz), 7.51 (1 H, t, *J* 7.35 Hz) and 7.40 (2 H, *J* = 7.7 Hz) [aromatic H], 4.78 (2 H, s, $C=CH_2$), 3.78 (1 H, br s), 2.94 (1 H, d of q, *J* 7.0 and 5.2 Hz, H-4), 2.84 and 2.60 (2 H, 2 x d, *J* 16.2 Hz, H-7), 2.40-2.45 (3 H, m), 2.02 (3 H, s, CH_3CO), 1.25 (3 H, s) and 1.02 (3 H, s) [CH_3-C-CH_3], 0.66 (3 H, d, *J* 7.0 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 216.7 (C-3), 207.3 (CH_3*C*=O), 197.6 (Ph*C*=O), 145.8 (*C*=CH_2), 137.0, 133.0, 129.5 (2 C) and 128.6 (2 C) [aromatic C], 112.0 (C=*C*H_2), 72.3 (C-6), 52.7, 46.7, 45.9, 44.5, 34.5, 31.2, 28.0, 26.6, 23.4, 13.9. Mass: m/z 338 (M^+, 10%), 295 (15), 233 (20), 197 (20), 105 (100), 77 (25). HRMS: m/z Calcd. for $C_{22}H_{26}O_3$: 338.1882. Found 338.1875.

(+)-(5S)-3-Vinyl-5-isopropenyl-2,4,4-trimethylcyclohex-2-enone (23). To a cold (0° C), magnetically stirred solution of vinylmagnesium bromide (3 mmol), prepared from magnesium (72 mg, 3 mmol) and vinyl bromide (535 mg, 0.35 ml, 5 mmol) and a catalytic amount of iodine in 8 ml of dry THF, was added dimethylcarvone **13** (356 mg, 2 mmol) in dry THF over a period of 30 min. The reaction mixture was slowly warmed up to RT and stirred for 8 h. It was then poured into saturated aq. NH_4Cl solution and extracted with ether (2 x 15 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the tertiary alcohol **26**. To a magnetically stirred solution of the tertiary alcohol **24** (400 mg), obtained above, in 5 ml of dry CH_2Cl_2 was added a homogeneous mixture of PCC (645 mg, 3 mmol) and silica gel (645 mg) and stirred vigorously for 6 h at RT. The reaction mixture was then filtered through a small silica gel column and eluted the column with an excess of CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished the vinyl enone **23** (360 mg, 88%) as oil. $[\alpha]_D^{24}$: 48.6 (c 3.6, $CHCl_3$). IR (neat): ν_{max} 1660, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.26 (1 H, dd, *J* 18.1 and 11.7 Hz, C*H*=CH_2), 5.42 (1 H, dd, *J* 11.7 and 2.0 Hz), 5.06 (1 H, dd, *J* 18.1 and 2.0 Hz) [CH=C*H*$_2$], 4.90 (1 H, s) and 4.70 (1 H, s) [C=CH_2], 2.60-2.40 (3 H, m), 1.74 (3 H, s) and 1.65 (3 H, s) [2 x olefinic CH_3], 1.09 (3 H, s) and 1.00 (3 H, s) [CH_3-C-CH_3]. ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 198.9 (s, C=O), 161.5 (s, C-3), 145.1 (s, *C*=CH_2), 133.8 (d, *C*H=CH_2), 129.6 (d, C-2), 120.3 (t, CH=*C*H_2), 114.9 (t, C=*C*H_2), 51.6 (d, C-5), 39.5 (t, C-6), 38.5 (s, C-4), 27.3 (q), 22.8 (q), 22.2 (q), 13.2 (q). Mass: m/z 204 (M^+, 20%), 189 (85), 147 (70), 136 (75), 121 (75), 93 (100).

(+)-(5R)-3-Vinyl-5-(3-bromopropen-2-yl)-2,4,4-trimethylcyclohex-2-enone (21). To a magnetically stirred solution of the enone **23** (40 mg, 0.2 mmol) in a 3:2 mixture of CH_2Cl_2 and methanol (0.6 ml) was slowly added NBS (46 mg, 0.25 mmol) over a period of 40 min and the reaction mixture was stirred for 6 h. It was then diluted with water and extracted with CH_2Cl_2 (3 x 3 ml). The combined organic extract was washed with 5% aq. NaOH and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:50 to 1:20) as eluent furnished the allyl bromide **21** (45 mg, 81%) as oil.

$[\alpha]_D^{24}$: 16.7 (c 2.16, $CHCl_3$). IR (neat): ν_{max} 1660, 920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 6.29 (1 H, dd, *J* 17.4 Hz and 11.7 Hz, C*H*=CH_2), 5.46 (1 H, dd, *J* 11.7 and 2.1 Hz) and 5.12 (1 H, dd, *J* 17.7 Hz and 1.8 Hz) [CH=CH_2], 5.43 (1 H, s) and 5.02 (1 H, s) [C=CH_2], 3.95 and 3.93 (2 H, AB quartet *J* 11.4 Hz, CH_2-Br), 2.77 (1 H, t, *J* 7.5 Hz, H-5), 2.59 (2 H, d, *J* 7.5 Hz, H-6), 1.75 (3 H, s, olefinic CH_3), 1.11 (3 H, s) and 1.08 (3 H, s) [CH_3-C-CH_3]. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$ + CCl_4): δ 197.7 (C, C=O), 160.6 (C, C-3), 145.8 (C, *C*=CH_2), 133.9 (CH, *C*H=CH_2), 130.3 (C, C-2), 120.7 (CH_2, CH=*C*H_2), 119.0 (CH_2, C=*C*H_2), 47.5 (CH, C-5), 40.6 (CH_2, CH_2-Br), 39.1 (C, C-4), 38.6 (CH_2, C-6), 27.4 (CH_3), 21.9 (CH_3), 13.5 (CH_3). Mass: m/z 282 (M^+, 30%), 283 (M^+ + 1, 35%), 203 (60), 189 (30), 159 (50), 135 (52), 123 (100), 107 (83), 91 (90).

(+)-Dimethyl 3-[(1S)-4,6,6-trimethyl-3-oxo-5-vinylcyclohex-4-en-1-yl]but-3-enylmalonate (25). A magnetically stirred mixture of the allyl bromide 21 (35 mg, 0.1 mmol), dimethyl malonate (16.3 mg, 0.124 mmol) and potassium carbonate (34.5 mg, 0.25 mmol) in dry acetone (20 ml) was refluxed for 10 h. The solvent was then evaporated, water (1 ml) was added to the residue and extracted with ether (3 x 3 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:50 to 1:30) as eluent furnished the diester 25 (35 mg, 85%) as oil. $[\alpha]_D^{24}$: 47.0 (c 1.0, $CHCl_3$). IR (neat): ν_{max} 1745, 1730, 1660, 930 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.33 (1 H, dd, *J* 17.7 and 11.7 Hz, C*H*=CH_2), 5.50 (1 H, dd, *J* 11.7 and 2.0 Hz) and 5.14 (1 H, dd, *J* 17.7 and 2.0 Hz) [CH=CH_2], 5.03 (1 H, s) and 4.89 (1 H, s) [C=CH_2], 3.73 (6 H, s, 2 x COOCH_3), 3.61 (1 H, dd, *J* 8.35 and 7.2 Hz, C*H*$(COOMe)_2$), 2.70-2.40 (5 H, m), 1.81 (3 H, s, olefinic CH_3), 1.14 (3 H, s) and 1.09 (3 H, s) [CH_3-C-CH_3]. ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 199.0 (C=O), 169.1 (2 C, 2 x O-C=O), 161.9, 145.8, 133.8, 129.6, 120.5, 114.7 (C=*C*H_2), 52.4 (2 C, 2 x COOMe), 50.6 (*C*H$(COOMe)_2$), 50.0, 40.2, 39.3, 36.8, 27.2, 21.2, 13.2. Mass: m/z 334 (M^+, 20%), 319 (18), 303 (10), 203 (65), 202 (100), 188 (30), 187 (35), 136 (92), 121 (50), 93 (70). HRMS: m/z For $C_{19}H_{26}O_5$, Calcd.: 334.1780. Found: 334.1786.

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