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Pure Enantiomers of Bicyclo[3.2.0]hept-3-en-6-ones and Bicyclo[3.2.0]hept-3-en-6-*endo*-ols: Resolution, Absolute Configuration and Optical Properties

Emanuela Marotta, Ilaria Pagani, Paolo Righi, Goffredo Rosini*

Dipartimento di Chimica Organica "A. Mangini" dell'Università
Viale Risorgimento, 4 - I-40136 Bologna (Italy)

Valerio Bertolasi,[1] Alessandro Medici

Dipartimento di Chimica dell'Università
Via L. Borsari, 46 - I-44100 Ferrara (Italy)

Abstract: Single crystal X-ray diffraction analysis of compounds **A**, **B** and, **C** helped us to assign the absolute configurations of the enantiomers of the bicyclo[3.2.0]hept-3-en-6-*endo*-ols **4-6**. These bicyclic alcohols were easily obtained by: (i) stereoselective reductions of the bicyclo[3.2.0]hept-3-en-6-ones **1-3**, (ii) conversion into diastereoisomeric pairs using (−)-(1*S*,4*R*)-camphanic acid chloride as resolving agent, (iii) an efficient separation of diastereoisomers by flash-chromatography and, finally, (iv) a mild alkaline hydrolysis. The oxidation of pure enantiomers of the bicyclo[3.2.0]hept-3-en-6-*endo*-ols **4-6** with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant furnished enantiomerically pure bicyclo[3.2.0]hept-3-en-6-ones **1-3**. The different mutual disposition of carbonyl groups in the structure **A** and **B** justifies the different IR (KBr) signals for the carbonyls of each diastereoisomer.

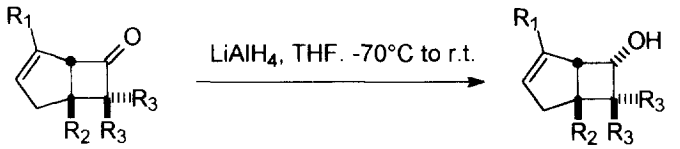
The efficient conversion of 3-hydroxy-6-alkenoic acids into bicyclo[3.2.0]hept-3-en-6-ones by treatment with potassium acetate in acetic anhydride makes these β,γ-unsaturated bicyclic ketones easy available to be employed as useful starting materials or intermediates in synthesis of complex molecules.[2]

Bicyclo[3.2.0]hept-3-en-6-ones possess an appealing structure with two fused rings of different size, each functionalized in a different manner, thus allowing for chemio-, regio- and stereoselective transformations. Recently we found useful applications of these interesting building blocks in the synthesis of different natural products such as grandisol,[2] lineatin,[2] filifolone[3] and some important lactone intermediates for the synthesis of triquinane sesquiterpenes.[3]

The synthetic potential and usefulness of bicyclo[3.2.0]hept-3-en-6-ones will be greatly enhanced if a procedure to have them enantiomerically pure would be developed. Recently, we have reported that the mechanism of the bicyclization precludes the EPC synthesis of bicyclo[3.2.0]hept-3-en-6-ones starting from enantiomerically pure 3-hydroxy-6-alkenoic acids.[4]

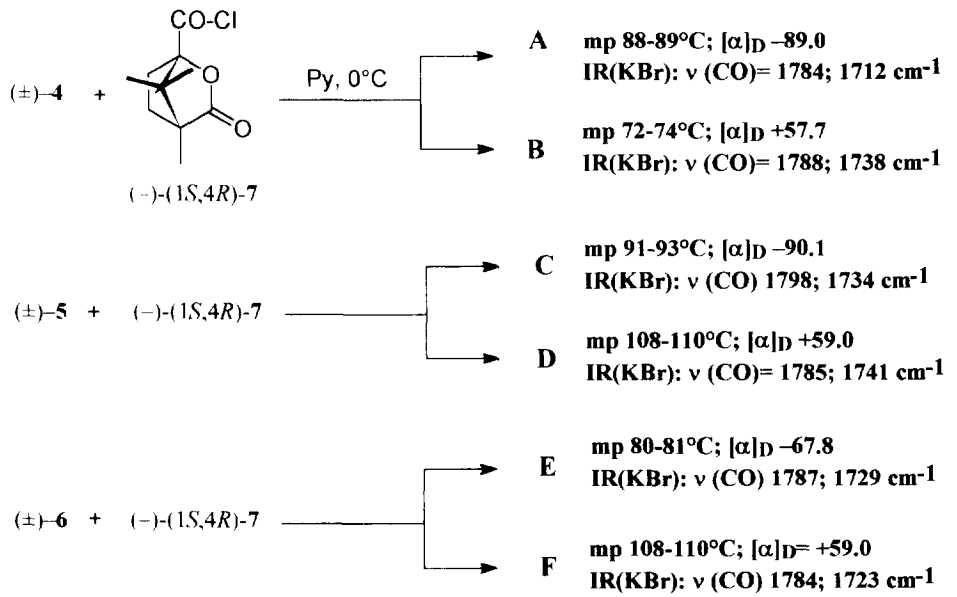
This paper reports the results of our efforts to prepare pure enantiomers of bicyclo[3.2.0]hept-3-en-6-ones **1-3** and bicyclo[3.2.0]hept-3-en-6-*endo*-ols **4-6**, their optical properties, and the assignment of absolute

configurations. Our attention has been focused on those unsaturated bicyclic ketones and *endo*-alcohols we have previously used in the stereoselective total synthesis of racemic grandisol, lineatin and filifolone.



(±)-**1**	$R_1 = R_2 = CH_3$; $R_3 = H$	(±)-**4**
(±)-**2**	$R_1 = CH_3$; $R_2 = R_3 = H$	(±)-**5**
(±)-**3**	$R_1 = R_3 = CH_3$; $R_2 = H$	(±)-**6**

Lithium aluminium hydride reduction of the racemic starting ketones **1-3** performed in tetrahydrofuran (THF) at low temperature afforded racemic *endo*-alcohols **4-6** with very high stereoselectivities and yields. The reaction of the racemic *endo*-alcohols **4-6** with (−)-(1*S*,4*R*)-camphanic acid chloride[5] (**7**) in pyridine at 0° C, gave the diastereoisomeric mixtures of esters with excellent yields (Scheme 1). In every case the separation of diastereoisomers was performed by an efficient flash-chromatography[6] (400 g of silica gel every 2.0 g of the mixture) eluting with dichloromethane. The efficiency of these chromatographic separations include the utilisation of the same silica gel column for at least three consecutive separations of portions of the same mixture of diastereoisomers and the use of dichloromethane alone as eluent, with consequent recovery and reutilisation of materials.



Scheme 1.

Scheme 1 summarises the results of the separations for, respectively, the *endo*-alcohols **4-6** esterified by (−)-(1*S*,4*R*)-camphanic acid chloride (**7**), and collects the spectroscopic and physico-chemical data of each

diastereoisomer obtained. It must be pointed out that is always the levorotating diastereoisomer (**A**, **C**, and **E**) the first compound to be eluted.

The known chirality of (−)-(1*S*,4*R*)-camphanic acid chloride (**7**) used as resolving agent and the very nice crystals of the (1*S*,4*R*)-camphanate ester diastereoisomers (the pairs **A-B**, **C-D**, and **E-F**, respectively) obtained by a single crystallisation from *n*-hexane after the chromatographic separation, allowed us to assign the absolute configuration (−)-(1*R*,5*S*,6*S*,1'*S*,4'*R*)-**8** to compound **A** (Fig. 1), and the absolute configuration (−)-(1*R*,5*S*,6*S*,1'*S*,4'*R*)-**10** to compound **C** (Fig. 2) by single crystal X-ray diffraction analysis. The diffraction data for the destrorotating diastereoisomer **B** revealed the structure to be (+)-(1*S*,5*R*,6*R*,1'*S*,4'*R*)-**9** (Fig. 3) .

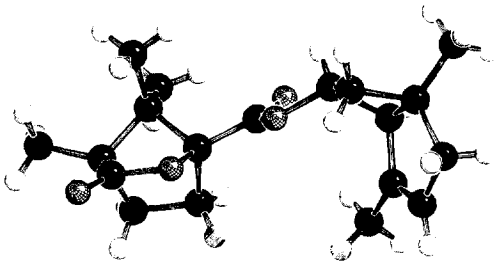


Fig. 1. Perspective view of **A**:
(−)-(1*R*,5*S*,6*S*,1'*S*,4'*R*)-**8**

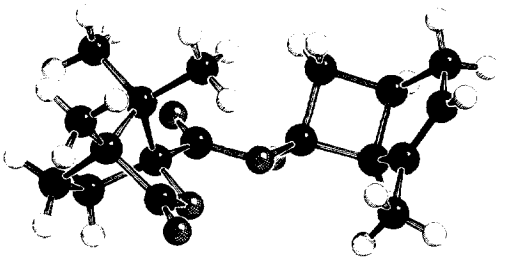


Fig. 2. Perspective view of **C**:
(−)-(1*R*,5*S*,6*S*,1'*S*,4'*R*)-**10**

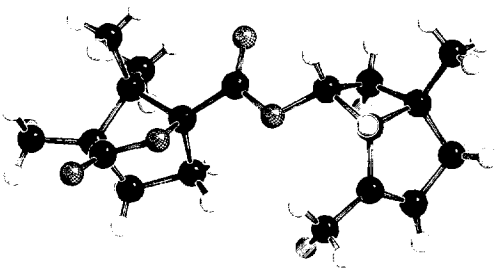


Fig. 3. Perspective view of **B**:
(+)-(1*S*,5*R*,6*R*,1'*S*,4'*R*)-**9**

As depicted in Scheme 1 the IR spectrum (KBr pellets) of each of diastereoisomeric (1*S*,4*R*)-camphanic acid esters **A** and **B**, **C** and **D**, has two distinct sharp signals for carbonyl groups. In the IR spectra of compounds **A** and **C** the carbonyl signals are closer with respect to those observed in the IR spectra of corresponding diastereoisomeric compounds **B** and **D**. The same difference in the carbonyl signals of the diastereoisomeric esters of (1*S*,4*R*)-camphanic acid was already observed in the case of 2,6,6-trimethyl- and of 2,5-dimethylbicyclo[3.2.0]heptan-2-*endo*-ol.[7]

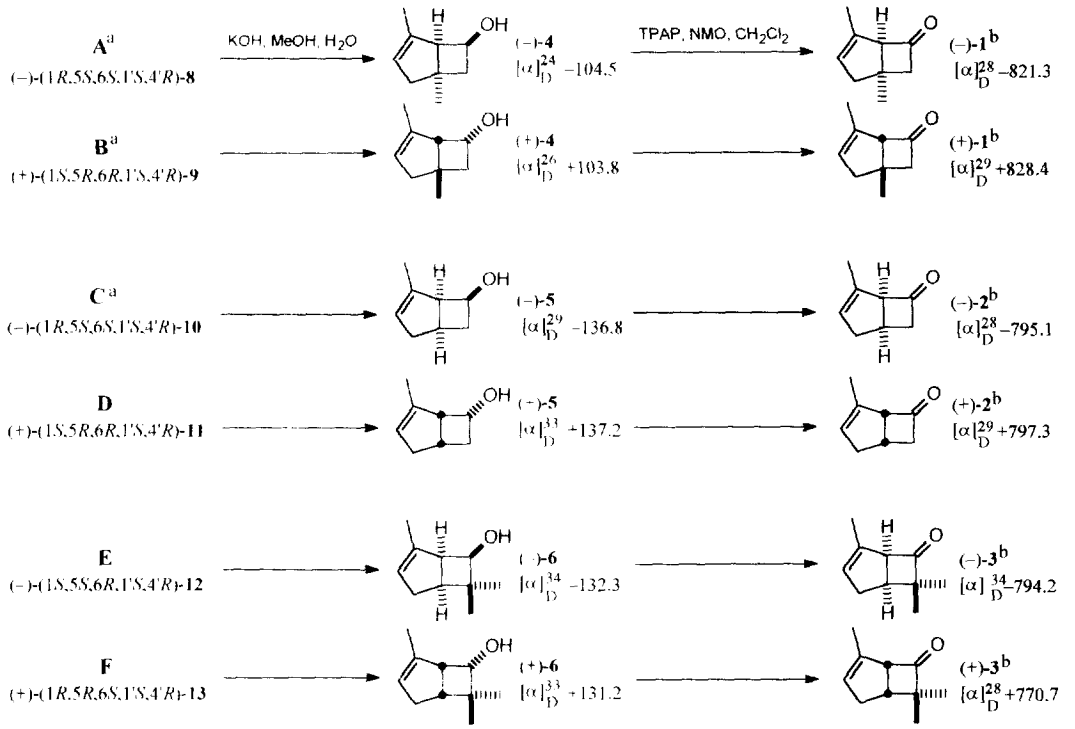
These new examples induced us to verify if some structural difference in solid phase can be considered as responsible of the different signals.

It is significant that in both the structures of compounds **A** and **C**, the two carbonyls of the lactone and ester groups are almost exactly lying down a single plane. In contrast in the structure of compound **B** is possible to observe a dihedral angle (120°) of the plane containing the rigid lactone moiety of camphanic acid with the plane containing the estereal group. This difference, well reflected in the IR spectra (KBr) pellets of

diastereoisomers, could be present in every diastereoisomeric camphanic acid derivatives in which the assembling of two rigid and hindered moieties, one of which having an enantiomeric relationship with the counterpart of the other, forces the groups of one diastereoisomer to deflect from the coplanar disposition of the lactone-ester assembly.

However, the almost identical IR (KBr) data for carbonyl signals recorded on each diastereoisomers obtained from racemic **6** (compounds **E** and **F**) contradicts the previous hypothesis and seems to indicate a better ability of the lactone and ester groups to retain the same disposition in a rigid crystalline lattice when the cyclobutanone part of the structure is 7,7-dimethylsubstituted.

Upon alkaline hydrolysis the pure compounds **A-F** gave, in high yields, the corresponding enantiomerically pure bicyclo[3.2.0]hept-3-en-6-*endo*-ols **4-6** that were converted into the enantiomerically pure bicyclo[3.2.0]hept-3-en-6-ones **1-3**, by tetra-*n*-propylammonium perruthenate (TPAP) oxidation using *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant[8] (Scheme 2).



a - Absolute configuration assigned by X-ray crystallography.

b - Absolute configuration verified by Cotton effect and octant rule.

Scheme 2.

Each enantiomer of *endo*-alcohols **4-6** and ketones **1-3** has been confirmed to be chemically and enantiomerically pure by GLC analysis performed on a capillary column with cyclodestrine as the chiral stationary phase.[9]

In 1967, Bates et al.,[10] assigned the absolute configuration (1*S*,5*S*)-**3** to a scalemic levorotating sample ([α] –270) of filifolone obtained from *Artemisia filifolia* Torrey, and the absolute configuration (1*R*,5*R*)-**3** to the destrorotating scalemic enantiomer ([α] +307) obtained from *Zieria smithii* Andrews. The assignment was based on circular dichroism spectra and chemical conversion into optically active α-fenchonic acid. Registering the circular dichroism spectra of optically pure enantiomers of **1-3**, we have confirmed these assignments for the enantiomers of compound **3** and we have established the absolute configurations for the enantiomers of compounds **1**, and **2** as reported in Scheme 2.

The negative Cotton effect curve and the utilisation of the octant rule implicates the absolute configuration (1*S*,5*S*) for the levorotating enantiomer of filifolone (**3**) and the absolute configuration (1*R*,5*R*) for its destrorotating enantiomer. For both compounds **1** and **2** the absolute configurations were (1*R*,5*S*) and (1*S*,5*R*) for the levorotating and destrorotating enantiomers respectively. The difference for absolute configuration at C1 between **3** and the pair **1** and **2** is only due to the Cahn-Ingold-Prelog rules.

The magnitudes of the rotational strengths of the optically pure bicyclo[3.2.0]hept-3-en-6-ones **1-3** are consistent with the geometric structures of this unsaturated ketone chromophore type, in which the overlap of the olefinic π and π* orbitals create the intense charge-transfer band and the overlap of non bonded p and olefinic π orbitals causes coupling of the transitions. Erman et al.[11] pointed out the attention on this favourable geometry for satisfying both overlap requirements in sharp contrast with the unsaturated chromophore typical of bicyclo[3.2.0]hept-2-en-6-ones, poor in both these requirements. For the first time, the optical rotations we have recorded using enantiomerically pure samples of compounds **1-3** give the true dimension of the rotational strengths of these bicyclic β,γ-unsaturated bicycloketones and marks the difference with the data of isomeric bicyclo[3.2.0]hept-2-en-6-ones reported in the literature.[12]

The achievements here reported pave the route to a systematic study concerning the utilisation of micro-organism for effective and practical enantioselective conversions of bicyclo[3.2.0]hept-3-en-6-*endo*-ols and bicyclo[3.2.0]hept-3-en-6-ones opening up new horizons for their utilisations in synthesis.

EXPERIMENTAL SECTION

General. Melting points were obtained with a Büchi apparatus and are uncorrected. Yields are referred to isolated products. If not otherwise stated proton and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solvent. If not already stated, chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in Hertz. Signal multiplicities were established by DEPT experiments. Flash chromatographic separations were performed using Merck Silica Gel 60 (70-230 mesh ASTM). For thin layer chromatography (tlc) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. Tetrahydrofuran (THF) was freshly distilled from sodium metal using benzophenone ketyl as indicator. Dichloromethane was distilled from P_2O_5, and stored over 4Å molecular sieves. Pyridine was freshly distilled before use from potassium hydroxide. All air-sensitive reactions were run under nitrogen. Optical rotations were measured on a JASCO DIP–360 polarimeter equipped with a sodium lamp. Bulb-to-bulb distillations were performed using a Büchi Kugelrohr apparatus, and the oven temperature is recorded as the boiling point. X-ray diffraction analysis data were collected on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated $Mo_{K\alpha}$ radiation, $\omega/2\theta$ scan technique. Cell parameters were determined and refined from 25 reflections in the range $10<\theta<15°$; three standard reflections monitored

every 2 h showed no significant variation during data collection. All data were corrected for Lorentz and polarization effects. The structures were solved by direct methods with the SIR88 system of programs.[13] All other calculations were accomplished by the MolEN system of programs.[14] Atomic coordinates, thermal parameters, bond lengths and angles are available from the Cambridge Crystallographic Data Centre.

Materials. Racemic ketones **1**–**3** were prepared in a multi-gram scale according to Ref. 1. Lithium aluminium hydride, (–)-(1*S*,4*R*)-camphanic acid chloride, potassium hydroxide, tetra-n-propylammonium perruthenate (TPAP), and *N*-methylmorpholine *N*-oxide (NMO) are commercially available and were used as purchased.

Racemic bicyclo[3.2.0]hept-3-en-6-*endo*-ols (4–6). General preparation. A suspension of $LiAlH_4$ (42 mmol) in dry THF (75 mL) is placed, under an inert atmosphere, in a three-necked 250 mL round bottomed flask, equipped with a dropping funnel, a thermometer, and a mechanical stirrer. The stirred mixture is cooled down to –70 °C with a dry-ice/acetone bath and then a solution of the starting racemic ketone (30 mmol) in dry THF (25 mL) is slowly added dropwise; during this process the temperature should not rise above –65 °C. The reaction is monitored by tlc and GC and is complete within an hour. The mixture is quenched at 0 °C by the sequential careful addition of 50 mL of wet diethyl ether, and a few millilitres of a saturated solution of NH_4Cl. The mixture is filtered and the two clear phases obtained are separated. The aqueous layer is extracted with 3 × 15 mL portions of diethyl ether. The organic phase are reunited, dried over $MgSO_4$, filtrated, and concentrated at ambient pressure. The crude product (22.5 – 27.6 mmol; 75–92 %) is obtained as a pale yellow oil and is used in the following steps without further purifications.

(±)-1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(±)-4]. IR (film) ν 3347, 2947, 1447 cm^{-1}. ^1H NMR (200 MHz) δ 5.45 (m, 1H), 4.50 (m, 1H), 2.90 (bd, 1H), 2.40–2.20 (m, 4H), 1.82 (s, 3H), 1.72 (m, 1H), 1.18 (s, 3H). ^{13}C NMR (50 MHz) δ 140.1, 127.9, 68.32, 61.48, 49.07, 45.42, 37.20, 25.52, 17.91. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.18; H, 10.25.

(±)-4-Methylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(±)-5]. IR (film) ν 3344, 2909, 1446, 1102 cm^{-1}. ^1H NMR (200 MHz) δ 5.50 (m, 1H), 4.44 (m, 1H), 3.38 (bs, 1H), 2.70–2.42 (m, 2H), 2.35 (m, 1H), 2.20–2.02 (m, 2H), 1.85 (s, 3H), 1.56 (m, 1H). ^{13}C NMR (50 MHz) δ 139.7, 128.2, 69.61, 68.63, 57.71, 41.37, 40.17, 28.82, 17.82. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.43; H, 9.76.

(±)-4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(±)-6]. IR (film) ν 3428, 2944, 1449, 1091 cm^{-1}. ^1H NMR (200 MHz) δ 5.50 (m, 1H), 3.90 (t, 1H, J = 6), 3.34 (bs, 1H), 2.32 (m, 3H), 1.82 (s, 3H), 1.75 (m, 1H), 1.12 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (50 MHz) δ 140.3, 130.3, 77.18, 52.97, 43.00, 42.60, 34.95, 31.43, 18.14, 17.93. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.97; H, 10.62.

Optical resolution of racemic bicyclo[3.2.0]hept-3-en-6-*endo*-ols.

*Reaction of racemic alcohols **4–6** with (–)-(1S,4R)-camphanic acid chloride and separation of the diastereoisomeric esters derivatives **A–B**; **C–D**; **E–F**. General Procedure.* In a three-necked round-bottomed 100-mL flask, equipped with a thermometer, magnetical stirring, and under an inert atmosphere, is placed a solution of the racemic alcohol (20 mmol) in pyridine (60 mL). The mixture is cooled down to 0 °C by means of an ice-water bath and (–)-(1*S*,4*R*)-camphanic acid chloride (20 mmol) is added in small portions over a period of 10 min. At the end the cooling bath is removed and the solution is stirred at room temperature. The reaction is monitored by tlc and GC and is usually complete within three hours. The mixture is then taken up

with CH_2Cl_2 (200 mL) and is sequentially washed with water (3 × 90 mL), 2N HCl (30 mL portions) until pH 2 (paper indicator), 1M $NaHCO_3$ (40 mL), sat. $CuSO_4 \cdot 5H_2O$ (2 × 20 mL), and sat. NaCl (3 × 30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The crude mixture of diastereoisomeric esters (18–19 mmol; 90–95% yield) is obtained as a pale yellow solid and is separated by flash chromatography (400 g of silica gel; i.d. 7.5 cm; eluent CH_2Cl_2 only) in 2.0 g portions at a time. The silica gel and the eluent are recycled for at least three portions of the crude mixture of esters. Crystallisation from *n*–hexane for each of the two separated esters afforded white crystals.

(–)–[(1*S*,4*R*)–Camphanic acid (1*R*,5*S*,6*S*)–1,4–dimethylbicyclo[3.2.0]hept–3–en–6–*endo*–yl ester] (A, 8). R_f 0.20 (CH_2Cl_2); mp 87–89 °C; $[\alpha]^{31}_D$ –89.05 (*c* 0.968, $CHCl_3$). IR (KBr) ν 2974, 2917, 1784, 1712, 1276, 1101 cm^{-1}. ^1H NMR δ 5.43 (m, 1H), 5.31 (q, 1H, *J* = 7.8), 3.05 (m, 1H), 2.30–2.49 (m, 2H), 2.22 (m, 2H), 1.82–2.03 (m, 3H), 1.79 (s, 3H), 1.63 (m, 1H), 1.26 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H). ^{13}C NMR δ 178.7, 167.6, 139.6, 127.7, 91.35, 71.78, 59.04, 55.20, 54.54, 48.41, 41.88, 39.24, 30.88, 29.24, 24.79, 17.22, 17.10, 17.04, 10.12. Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.66; H, 8.24. Found: C, 71.66; H, 8.28. X-ray diffraction analysis: $C_{19}H_{26}O_4$, orthorhombic, $P2_12_12_1$ (N.19), *a* = 6.804(2), *b* = 11.919(2), *c* = 22.029(3) Å; V = 1786.4(7) $Å^3$; Z = 4, ρ_{calcd} = 1.183 g cm^{-3}, μ = 0.076 mm^{-1}. Of the 2234 independent reflections, 1346 with $I \geq 3\sigma(I)$ were used in the refinement. Full matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens atoms in fixed calculated positions. R(on F) = 0.046, R_w = 0.056.

(+)–[(1*S*,4*R*)–Camphanic acid (1*S*,5*R*,6*R*)–1,4–dimethylbicyclo[3.2.0]hept–3–en–6–*endo*–yl ester] (B, 9). R_f 0.15 (CH_2Cl_2); mp 72–74°C; $[\alpha]^{24}_D$ +57.66 (*c* 0.978, $CHCl_3$). IR (KBr) ν 2973, 2911, 1788, 1738, 1263, 1099 cm^{-1}. ^1H NMR δ 5.45 (m, 1H), 5.38 (q, 1H, 7.2), 3.06 (m, 1H), 2.48–2.32 (m, 2H), 2.25 (m, 2H), 2.09–1.83 (m, 3H), 1.78 (s, 3H), 1.67 (m, 1H), 1.28 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.95 (s, 3H). ^{13}C NMR δ 178.5, 167.3, 139.5, 127.8, 91.36, 71.58, 59.07, 55.16, 54.47, 48.57, 42.15, 39.18, 30.98, 29.45, 24.88, 17.31, 17.15, 10.18. Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.66; H, 8.24. Found: C, 71.69; H, 8.24. X ray diffraction analysis: $C_{19}H_{26}O_4$; orthorhombic; $P2_12_12_1$, (N. 19) *a* = 11.358(5), *b* = 11.457(2), *c* = 13.579(2) Å; V = 1766.9(8) $Å^3$; Z = 4; ρ_{calcd} = 1.197 g cm^{-3}; μ = 0.077 mm^{-1}. Of the 2406 unique measured reflections 1777 with $I \geq 3\sigma(I)$ were used in the refinement. Full matrix least squares refinement with all non hydrogen atoms anisotropic and hydrogen atoms in fixed calculated positions. R(on F) = 0.049; R_w = 0.065.

(–)–[(1*S*,4*R*)–Camphanic acid (1*R*,5*S*,6*S*)–4–methylbicyclo[3.2.0]hept–3–en–6–*endo*–yl ester] (C, 10). R_f 0.31 (CH_2Cl_2); mp 91–93 °C; $[\alpha]^{26}_D$ –90.10 (*c* 1.068, $CHCl_3$). IR (KBr) ν 2983, 2928, 1798, 1734, 1280, 1103 cm^{-1}. ^1H NMR δ 5.47 (m, 1H), 5.23 (q, 1H, *J* = 7.5), 3.50 (m, 1H), 2.67 (m, 1H), 2.60–2.36 (m, 4H), 2.18–2.07 (m, 1H), 2.05–1.73 (m, 2H), 1.81 (s, 3H), 1.64 (m, 1H); 1.12 (s, 3H); 1.02 (s, 3H), 0.95 (s, 3H). ^{13}C NMR δ 178.9, 167.7, 139.4, 127.9, 91.51, 72.19, 55.40, 55.30, 54.72, 40.70, 36.60, 31.08, 30.67, 29.44, 17.29, 17.23, 17.19, 10.30. Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found: C, 70.96; H, 7.91. X ray diffraction analysis: $C_{18}H_{24}O_4$; orthorhombic; $P2_12_12_1$ (N.19); *a* = 10.797(3), *b* = 12.374(6), *c* = 12.554(3) Å; V = 1677(1) $Å^3$; Z = 4; ρ_{calcd} = 1.205 g cm^{-3}; μ = 0.078 mm^{-1}. Of the 2301 independent reflections, 1455 with $I \geq 3\sigma(I)$ were used in the refinement. Full matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogen atoms in fixed calculated positions. R(on F) = 0.052, R_w = 0.068.

(+)–[(1*S*,4*R*)–Camphanic acid (1*S*,5*R*,6*R*)–4–methylbicyclo[3.2.0]hept–3–en–6–*endo*–yl ester] (D, 11). R_f 0.21 (CH_2Cl_2); mp 108–110 °C; $[\alpha]^{28}_D$ +58.96 (*c* 1.004, $CHCl_3$). IR (film) ν 2999, 2910, 1785, 1741,

1229, 1111 cm^{-1}. ^1H NMR δ 5.50 (m, 1H), 5.31 (q, 1H, J = 7.4), 3.47 (m, 1H), 2.70 (m, 1H), 3.61–3.35 (m, 3H), 2.20–2.09 (m, 1H), 2.06–1.86 (m, 2H), 1.75 (s, 3H), 1.73–1.61 (m, 1H), 1.10 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR δ 178.6, 167.3, 139.2, 128.0, 91.51, 71.99, 55.27, 54.62, 40.84, 36.81, 31.15, 30.56, 29.61, 17.31, 17.25, 10.26. Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found: C, 71.06; H, 7.93.

(–)-[(1*S*,4*R*)-Camphanic acid (1*S*,5*S*,6*R*)-4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-*endo*-yl ester] (E, 12). R_f 0.39 (CH_2Cl_2); mp 78–81 °C; $[\alpha]^{30}_D$ –67.76 (*c* 1.037; $CHCl_3$). IR (KBr) ν 2963, 1787, 1729, 1268, 1103 cm^{-1}. ^1H NMR (200 MHz) δ 5.42 (m, 1H), 4.92 (d, 1H, J = 8.0), 3.39 (m, 1H), 2.50–2.30 (m, 2H), 2.35 (m, 2H), 1.96 (m, 2H), 1.78 (s, 3H), 1.67 (m, 1H), 1.22 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (50 MHz) δ 178.7, 167.9, 140.1, 129.0, 91.70, 79.74, 55.30, 54.33, 49.93, 42.58, 42.48, 34.33, 31.11, 30.58, 29.27, 18.23, 17.23, 17.17, 17.13, 10.18. Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.29; H, 8.54.

(+)-[(1*S*,4*R*)-Camphanic acid (1*R*,5*R*,6*S*)-4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-*endo*-yl ester] (F, 13). R_f 0.29 (CH_2Cl_2); mp 112–114 °C; $[\alpha]^{31}_D$ +52.87 (*c* 1.034; $CHCl_3$). IR (KBr) ν 2949, 1784, 1723, 1272, 1108 cm^{-1}. ^1H NMR (200 MHz) δ 5.49 (m, 1H), 4.96 (d, 1H, J = 8.0), 3.38 (m, 1H), 2.49–2.29 (m, 2H), 2.35 (m, 2H), 2.09–1.84 (m, 2H), 1.78 (s, 3H), 1.66 (m, 2H), 1.22 (s, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (50 MHz) δ 178.6, 167.7, 140.0, 129.1, 91.57, 79.54, 55.27, 54.35, 49.38, 42.48, 34.37, 31.38, 30.58, 29.44, 18.27, 17.15, 10.11. Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.31; H, 8.54.

Hydrolysis of camphanic acid esters. General Procedure. To the stirred solution of 87% KOH pellets (30 mmol) in water (10 mL), at room temperature, are added the ester (6 mmol), and methanol (10 mL). The mixture is then stirred at room temperature for 16 h. In the case of ester **F** a further 12 h stirring at 45 °C was necessary to complete the hydrolysis. The mixture is concentrated at ambient pressure and the residue is taken up with 10 mL of diethyl ether. The aqueous layer is separated and extracted with 3 × 10 mL of diethyl ether. The reunited organic phases are dried on $MgSO_4$, filtered, and concentrated at ambient pressure. The crude material is purified by vacuum bulb-to-bulb distillation.

(–)-(1*R*,5*S*,6*S*)-1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(–)-4]. A colourless clear oil is obtained (3.66 mmol, 61% yield); bp 150 °C/30 mbar; $[\alpha]^{24}_D$ –104.5 (*c* 1.055, $CHCl_3$). The IR, ^1H and ^{13}C NMR are identical as those of (±)-**4**. GLC analysis:[9] 10.43 min. Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.30; H, 10.29.

(+)-(1*S*,5*R*,6*R*)-1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(+)-4]. A colourless clear oil is obtained (4.68 mmol, 78% yield); bp 150 °C/30 mbar; $[\alpha]^{26}_D$ +103.8 (*c* 1.040, $CHCl_3$). The IR, ^1H and ^{13}C NMR are identical as those of (±)-**4**. GLC analysis:[9] 10.78 min. Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.32; H, 10.27.

(–)-(1*R*,5*S*,6*S*)-4-Methylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(–)-5]. A colourless clear oil is obtained (4.50 mmol, 75% yield); bp 125 °C/30 mbar; $[\alpha]^{29}_D$ –136.8 (*c* 1.065, $CHCl_3$). The IR, ^1H and ^{13}C NMR are identical as those of (±)-**5**. GLC analysis:[9] 10.97 min. Anal. Calcd. for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.27; H, 9.68.

(+)-(1*S*,5*R*,6*R*)-4-Methylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(+)-5]. A colourless clear oil is obtained (4.44 mmol, 74% yield); bp 125 °C/30 mbar; $[\alpha]^{33}_D$ +137.2 (*c* 1.030, $CHCl_3$). The IR, ^1H and

^{13}C NMR are identical as those of (±)-**5**. GLC analysis:[9] 11.04 min. Anal. Calcd. for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.45; H, 9.80.

(−)-(1*S*,5*S*,6*R*)-4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(−)-6]. A colourless clear oil is obtained (4.35 mmol, 72% yield); bp 140 °C/30 mbar; $[\alpha]^{34}_D$ -132.3 (*c* 0.970, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**6**. GLC analysis:[9] 13.36 min. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.01; H, 10.69.

(+)-(1*R*,5*R*,6*S*)-4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-*endo*-ol [(+)-6]. A colourless clear oil is obtained (3.48 mmol, 58% yield); bp 140 °C/30 mbar; $[\alpha]^{33}_D$ +131.2 (*c* 0.965, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**6**. GLC analysis:[9] 13.70 min. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.85; H, 10.65.

Preparation of optically pure bicyclo[3.2.0]hept-3-en-6-ones. General procedure. A solution of the enantiomerically pure alcohol (3.3 mmol) in dry CH_2Cl_2 (10 mL) is slowly added dropwise to stirred suspension of NMO (6 mmol, activated overnight under vacuum), powdered 4Å molecular sieves (2 g, activated overnight at 120 °C under vacuum), and TPAP (0.17 mmol) in dry CH_2Cl_2 (15 mL). An exothermic reaction soon takes place. The reaction is monitored by tlc and GC and is usually complete within one hour. The mixture is vacuum filtered over a pad of Celite; the solution is then concentrated at ambient pressure. The crude material is filtered over a pad of silica gel, eluting with petrol ether : diethyl ether = 9 : 1. After ambient pressure evaporation the product is purified by in-vacuo bulb-to-bulb distillation.

(−)-(1*R*,5*S*)-1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one [(−)-1]. A colourless clear oil is obtained (2.07 mmol, 63% yield); bp 120 °C/50 mbar; $[\alpha]^{28}_D$ -821.3 (*c* 0.960, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**1**. GLC analysis:[9] 7.08 min. Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.26; H, 8.80.

(+)-(1*S*,5*R*)-1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one [(+)-1]. A colourless clear oil is obtained (2.30 mmol, 70% yield); bp 120 °C/50 mbar; $[\alpha]^{29}_D$ +828.4 (*c* 0.985, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**1**. GLC analysis:[9] 7.39 min. Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.42; H, 8.81.

(−)-(1*R*,5*S*)-4-Methylbicyclo[3.2.0]hept-3-en-6-one [(−)-2]. A colourless clear oil is obtained (2.64 mmol, 80% yield); bp 115 °C/50 mbar; $[\alpha]^{28}_D$ -795.1 (*c* 0.961, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**2**. GLC analysis:[9] 7.78 min. Anal. Calcd. for $C_8H_{10}O$: H 8.25 C 78.65. Found: C, 78.69; H, 8.20.

(+)-(1*S*,5*R*)-4-Methylbicyclo[3.2.0]hept-3-en-6-one [(+)-2]. A colourless clear oil is obtained (2.44 mmol, 74% yield); bp 115 °C/50 mbar; $[\alpha]^{29}_D$ +797.3 (*c* 0.995, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**2**. GLC analysis:[9] 7.97 min. Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.74; H, 8.37.

(−)-(1*S*,5*S*)-4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one [(−)-3]. A colourless clear oil is obtained (2.14 mmol, 65% yield); bp 150 °C/40 mbar; $[\alpha]^{34}_D$ -794.2 (*c* 1.020, $CHCl_3$). The IR, ^{1}H and ^{13}C NMR are identical as those of (±)-**3**. GLC analysis:[9] 9.34 min. Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.09; H, 9.45.

(+)-(1*R*,5*R*)-4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one [(+)-3]. A colourless clear oil is obtained (2.12 mmol, 64% yield); bp 150 °C/40 mbar; $[\alpha]^{28}_D$ +770.7 (*c* 1.100, $CHCl_3$). The IR, ^{1}H and

^{13}C NMR are identical as those of (±)-**3**. GLC analysis:[9] 8.83 min. Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.06; H, 9.31.

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