Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 3, pp. 435–445, 1997
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Printed in Great Britain
PII: S0957-4166(97)00003-7
0957-4166/97 $17.00 + 0.00

Synthesis of chiral functionalized phosphine ligands based on camphor skeleton

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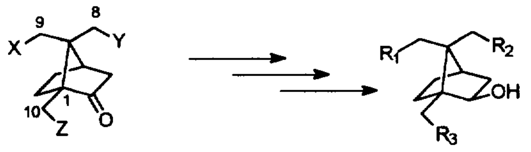
Abstract: Reactions of some nucleophiles with (+)-8- and (+)-9-bromocamphors have been studied. It has been demonstrated that these reactions offer an attractive route for chiral compounds with the rigid camphor skeleton possessing both soft diphenylphosphanyl and hydroxyl or carbonyl groups. The compounds could be used as ligands for asymmetric catalysts realizing a secondary interaction with substrates in the substrate–catalyst complex. Different synthetic strategies have been developed for 8- and 9-substituted camphor derivatives. Reactions of (+)-8-bromocamphor with some nucleophilic reagents give compounds having a 4-oxatricyclo[4.3.0.0^{3,7}]nonane skeleton. Analogously, reaction of 8,10-dibromocamphor with Ph_2PLi can lead to a functionalized tricyclic diphosphine which is more attractive as a ligand for asymmetric catalysts than monophosphines. It is noteworthy, that the formation of the tricyclic structure prevents the known ring cleavage at the C(1)–C(2) bond of 10-bromosubstituted camphor derivatives. © 1997 Published by Elsevier Science Ltd. All rights reserved.

The most impressive catalytic asymmetric syntheses were performed with the catalysts which were able to realize a secondary interaction, when the coordination with a catalyst involves not only the groups undergoing chemical transformations, but other functional groups of the substrate as well. These groups are usually coordinated to the central metal ion of a catalyst[1]. Recently, another possibility of secondary interaction has claimed attention: substrate coordination to the ligands, directly[2] or through a second metal ion in bimetallic catalysts[3]. The ligands in these cases must be properly functionalized to hold the central metal ion – catalytic center – and to interact at the same time with a substrate. In the present work we have examined the possibility of synthesizing the functionalized ligands which are capable of realizing the secondary interaction starting from camphor, available in both enantiomeric forms.

It is well known that camphor can be stereospecifically transformed into a wide variety of its derivatives. Mono- and dibromocamphors **1a–e** are especially attractive for our purpose. Most of them can be obtained by elegant techniques developed by Money *et al.*[4]. We have chosen **1a–e** as key intermediates to synthesize ligands **2a–e** bearing a hydroxyl group for the secondary interaction with substrates and diphenylphosphanyl substituents which can be employed to coordinate a transition metal catalytic center (Scheme 1).

1a, X=Br, Y=Z=H
1b, X=Z=H, Y=Br
1c, Z=Br, X=Y=H
1d, X=H, Y=Z=Br
1e, X=Z=Br, Y=H



2a, R1=PPh2, R2=R3=H
2b, R1=R3=H, R2=PPh2
2c, R3=PPh2, R1=R2=H
2d, R1=H, R2=R3=PPh2
2e, R1=R3=PPh2, R2=H

Scheme 1.

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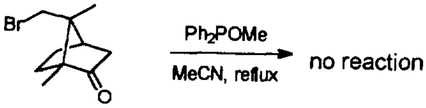
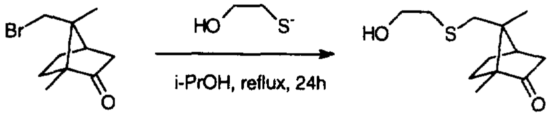


Scheme 2.



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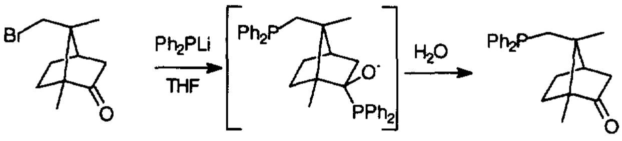
Scheme 3.



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Scheme 4.

To elaborate synthetic approaches to **2a–e**, or to related structures, we studied first the bromine nucleophilic displacement in the mono-bromoderivatives **1a–c**. It was of interest to compare reactions of (+)-8-, (+)-9-, and (+)-10-bromocamphors with phosphorus-containing nucleophiles.

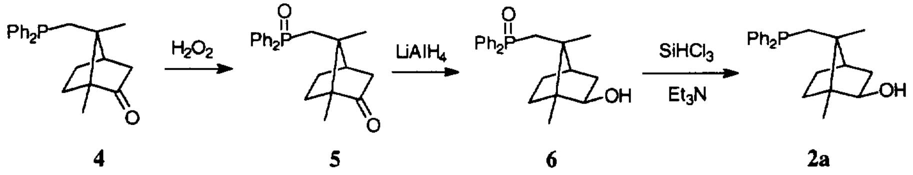
There are several obstacles to be expected on the way to **2a–c**. First, S_N2 displacement at the neopentyl-like 8-, 9-, or 10- positions of camphor skeleton may require forcing conditions leading to by-products. Thus, substitution of –I or –CN for bromine in 9-bromocamphor was reported to proceed with difficulty and moderate yields[5]. Second, phosphorus-containing nucleophiles can, in principle, add to the carbonyl group of **1a–c**. In most cases, however, the products of this reaction are easily transformed back to starting compounds because the reaction is reversible[6]. Finally, the camphor derivatives possessing a 10-halo substituent are known to undergo ring cleavage under treatment of nucleophilic reagents[7].

Our experiments with (+)-9-bromocamphor **1a** have demonstrated that the bromine substituent is quite inert to most nucleophilic reagents. For example, our attempts at the Arbusov–Michaelis reaction failed (Scheme 2).

Even a relatively strong nucleophile – thiolate ion – reacted with **1a** only under the quite severe conditions (Scheme 3).

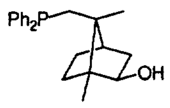
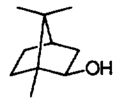
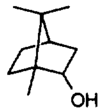
Fortunately, the reaction between **1a** and Ph_2PLi proceeded under milder conditions leading to the desired bromide displacement. ^{31}P-NMR monitoring of the reaction mixture revealed, as expected, the addition of Ph_2PLi to the carbonyl group. Two ^{31}P-NMR signals were observed: at -23 ppm and -30 ppm (aqueous H_3PO_4 as an external standard). Thus, at least 2-fold excess of Ph_2PLi is required for the complete bromine displacement. The product **4** isolated from the reaction mixture (Scheme 4) gave only one peak in the ^{31}P-NMR spectrum at -23 ppm.

At this stage, the seemingly simplest way to the target hydroxyphosphine **2a** – reduction of **4** by $LiAlH_4$ – turned out to be impractical because of high susceptibility of **4** to oxidation in solution. Therefore we have chosen a longer but more efficient route to **2a** (Scheme 5) where the trivalent



Scheme 5.

Table 1. *Relative*[a] ^{1}H-NMR Eu(fod)$_3$-induced shift values for **2a**, isoborneol and borneol

Functional Group	**2a** 	Isoborneol 	Borneol 
$1\text{-C}\underline{\text{H}}_3$	10	10	10
$7\text{-C}\underline{\text{H}}_3$	10.13	11.06	4.20
$\text{C}\underline{\text{H}}\text{-OH}$	21.52	20.73	24.73
$\text{exo-3}\underline{\text{Í}}$	15.82	15.85	9.38

[a] Induced shifts for 1-CH$_3$ group for all the compounds are taken as 10.

phosphorus grouping appears at the last stage and the intermediate phosphine oxides **5** and **6** were purified by recrystallization.

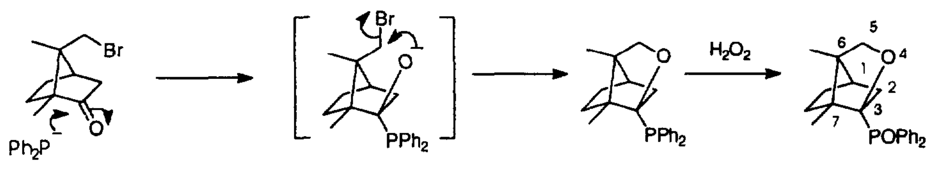
Reduction of **5** by LiAlH$_4$ is stereoselective, the final product **2a** has the 2-exo configuration. This conclusion was drawn based upon examination of Eu(fod)$_3$-induced ^{1}H-NMR shift data for **2a**. Unfortunately, the phosphine oxides **5** and **6** cannot be studied with the europium shift reagent. Addition of Eu(fod)$_3$ to **5** and **6** in CDCl$_3$ caused severe ^{1}H-NMR signals broadening, most likely because of adverse rates of exchange between the phosphine oxides and their adducts with the shift reagent.

As tertiary phosphines exhibit negligible association constants with shift reagents[8], the preferred Eu(fod)$_3$ complexation site in **2a** was postulated to be the hydroxyl group. *Relative* europium-induced shifts values measured for **2a** are given in Table 1 alongside the corresponding Eu(fod)$_3$-induced shifts for borneol and isoborneol reported by Hawkes *et al.*[9]. It can be seen that the shift values in ^{1}H-NMR spectra of **2a** correspond most closely to those of isoborneol, strong evidence in favor of the 2-exo configuration of the hydroxyphosphine.

Reaction of (+)-8-bromocamphor with Ph$_2$PLi followed by oxidation gave with high yield the product which contained no carbonyl groups, judging from its IR spectrum. Further structure elucidation allowed us to assign the product as a tricyclic structure **7** which was obtained by a 'domino' reaction[10] of a simple type (Scheme 6).

The most convincing NMR proof of the five-membered ring formation is the spin coupling $^3J_{P\text{–}C(5)}$ (10.3 Hz) which is about three time as large as $^3J_{P\text{–}C(6)}$ (3.2 Hz, for the numeration of the carbon atoms see Scheme 6). The value 10.3 Hz is in a good agreement with the reported values for $^3J_{P\text{–}C\text{–}O\text{–}C}$[11]. An interesting feature of the ^{13}C-NMR spectra of **7** is the presence of double set of the diastereotopic aromatic carbon signals.

A ring-current effect is clearly responsible for the high-field chemical shift of the 7-CH$_3$ ^{1}H-NMR signal (0.5 ppm, 0.89 ppm for 1-CH$_3$ group in camphor). This shift is temperature-dependent: 0.5 ppm at 293K, 0.62 ppm at 423K (solvent (CD$_3$)$_2$SO); severe broadening of the signal at 213K (solvent CDCl$_3$) is an evidence for the hindered rotation around the P–C(3) bond.



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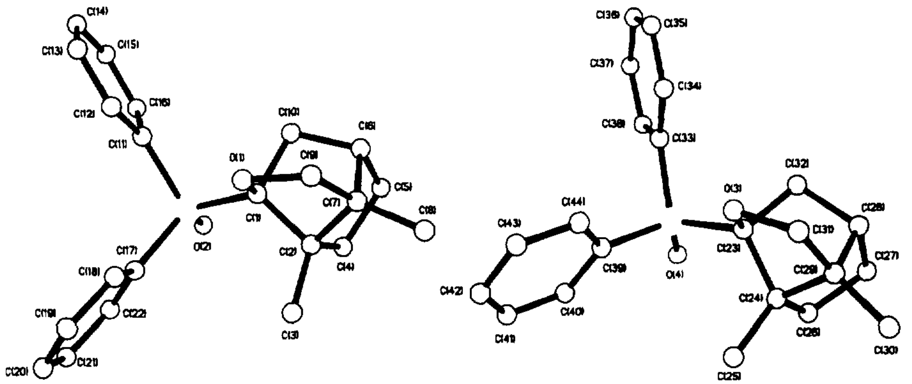
Scheme 6.



a **b**

Figure 1. X-Ray structure of (-)-7

In order to identify unambiguously the structure and conformation of **7** an X-ray structure determination has been performed. The enantiomer of **7** ((−)-**7**) obtained from (−)-8-bromocamphor by the reaction with Ph_2PLi has been subjected to X-ray analysis.

The solid state structure determination (Figure 1) confirms all the spectroscopic expectations. It is noteworthy that the unit cell contains two crystallographically independent molecules (space group $P2_1$, Z=4) of different conformation (Figure 1a and 1b, the structures are shown separately).

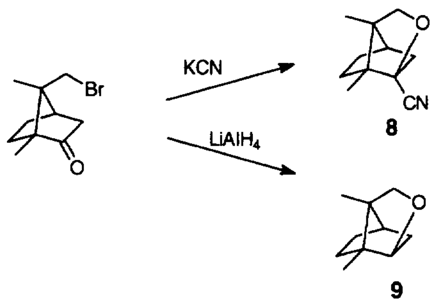
The main difference between the structures **a** and **b** is the conformation about the P–C bonds. For example, the torsion angle O(2)–P(1)–C(1)–O(1) is −175.0(5)°, while the angle O(4)–P(2)–C(23)–O(3) is −163.1(6)°. Judging from the X-ray analysis data one can suggest the ring-current effect caused by the phenyl groups that leads to the unusual 7-CH_3 ^{1}H-NMR chemical shift mentioned above.

Not much can be found in the literature on reactions of other nucleophilic reagents with (+)-8-bromocamphor. As was suggested by Corey *et al.*[12], reaction of (+)-8-bromocamphor **1b** with KCN gave compound **8** with the 4-oxatricyclo[4.3.0.0^{3,7}]nonane skeleton. We have also obtained a tricyclic molecule **9** using $LiAlH_4$ reduction of **1b** (Scheme 7).

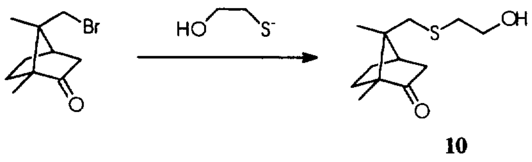
However, reaction of a thiolate ion with **1b** proceeded, as with (+)-9-bromocamphor **1a** through the simple bromine displacement (Scheme 8).

To synthesize 8-diphenylphosphanylcamphor we have protected the carbonyl group obtaining the ethylene ketal **11**. Again, the phosphine **12** formed after the phosphorylation of **11** by Ph_2PLi was oxidized to phosphine oxide **13** which can be easily purified by column chromatography (Scheme 9).

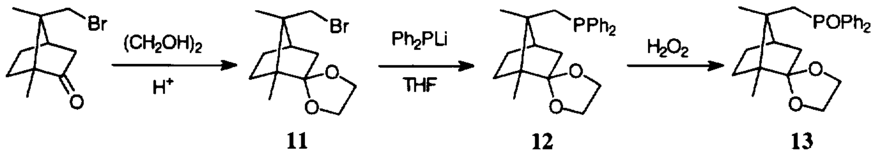
Reduction of the P=O group in **13** followed by hydrolysis yielded chiral 8-diphenylphosphanylcamphor **14** (Scheme 10). This ligand contains a carbonyl group which similarly to –OH group in hydroxyphosphines can be used for the secondary interaction with substrates.



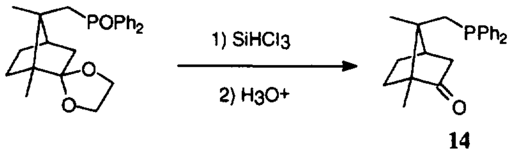
Scheme 7.



Scheme 8.



Scheme 9.



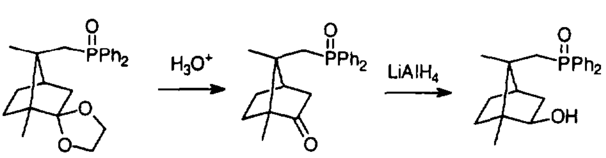
Scheme 10.

The hydroxyphosphine precursor **16**, an isomer of **6**, was obtained after hydrolysis of the ketal **13** (Scheme 11).

^{1}H-NMR chemical shifts and coupling constants for the 2-H proton of **16** are practically identical to those for the isomeric compound **6** described above. This allowed us to postulate that the configuration at 2-C in **16** is 2-exo, as in **6** (Scheme 11).

Serious synthetic problems arose with (+)-10-bromocamphor **1c**: as noted above, nucleophilic reagents usually cause ring cleavage at the C(1)–C(2) bond[7]. The ketal protection would hardly prevent the cleavage[7] which is believed to proceed through nucleophilic attack at the carbonyl or at a carbon atom of the protecting group (Scheme 12).

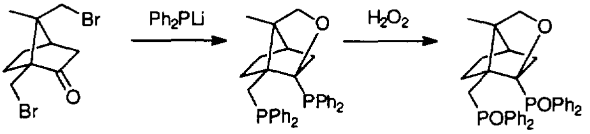
Actually, the reaction of (+)-10-bromocamphor **1c**, as well as commercially available (+)-9,10-dibromocamphor **1e** with Ph_2PLi was accompanied by the ring cleavage. This is very disappointing,



13 15 16

Scheme 11.

Scheme 12.



17

Scheme 13.

because the simple direct synthesis of the diphosphines **2c**, **2e** turned out to be impossible. The diphosphines are supposedly much more effective as ligands for the catalysts employed in asymmetric synthesis.

It would be desirable to preclude the nucleophilic attacks shown in Scheme 12 by modifying the carbonyl group or using other, not ketal, protection.

Another way around the problem exists, in principle, when starting from (+)-8,10-dibromocamphor **1d**. The formation of the 4-oxatricyclo[4.3.0.0^{3,7}]nonane skeleton, similarly to that observed for (+)-8-bromocamphor (Schemes 6 and 7), could 'lock' the structure, were it faster than the ring cleavage. We have found that it is the case: reaction of **1d** with Ph_2PLi followed by oxidation gave the tricyclic derivative **17** which is very perspective as a diphosphine ligand precursor (Scheme 13).

Experimental

General

Most of the NMR spectra were recorded on a Bruker WP-100SY spectrometer (100.13 MHz for protons), some of the ^{13}C-NMR spectra were obtained using a Varian VX-300 instrument (75.44 MHz). TMS was used as an internal standard for ^{1}H and ^{13}C-NMR spectra, 10% H_3PO_4 in D_2O was an external standard for ^{31}P-NMR measurements. IR spectra were measured on SP3-300 Pye Unicam infrared spectrophotometer. Melting points were measured on a hot stage and are uncorrected. Optical rotations were measured at 20°C using a micropolarimeter. Microanalyses were performed at Microanalytical Laboratory of Institute of Organic Chemistry of National Academy of Sciences of Ukraine. Eu(fod)$_3$-induced shifts were obtained using the 'LSR-titration technique'[8]. The standard syringe technique has been used when working in an inert atmosphere. Ph_2PLi was prepared from lithium chips and Ph_2PCl in THF. Tetrahydrofuran was distilled over benzophenoneketyl. $SiHCl_3$

was distilled over quinoline before use. Column chromatography was done using Merck silica gel 60 (230–400 mesh) and thin-layer chromatography (tlc) utilizing silica gel sheets (Silufol UV254).

X-Ray determinations

Crystal data for (−)-**7**: $C_{11}H_{15}NO$, M=177.25, monoclinic, a=9.516(2), b=11.213(3), c=18.200(2) A, β=98.980(10)°, V=1918.2(7) A^3, z=4 (two independent molecules), d_{calc}=1.22 g/cm^3, space group $P2_1$ (N4), absorption coefficient 1.352 mm^{-1}, F(000)=752, temperature 293(2) K.

Crystals of (−)-**7** suitable for X-ray analysis were obtained by slow benzene evaporation from the saturated solution of (−)-**7** in an octane–benzene mixture. A transparent colorless crystal of dimension 0.56×0.38×0.22 mm was glued on top of a glass fiber and transferred to goniometer of an Enraf-Nonius CAD-4 diffractometer operating in the ω-2θ scan mode (the ratio of the scanning rates ω/2θ=1.2). The intensity data were collected within the range $4<\theta<60°$ using graphite monochromated Cu-K_α radiation (λ=1.54178 A); 4174 reflections were collected, 3074 independent. The structure was solved by direct methods and refined by full-matrix least-squares. In the refinement, 2852 reflections with $I>2\sigma$ were used. The position of the hydrogen atoms were calculated. All the hydrogen atoms were included in the final refinement with the fixed positional and thermal (U_{iso}=0.08 A^2) parameters. Convergence was obtained at R1=0.0376 and $R_W(F^2)$=0.1067, GOF=1.024. The calculations were performed using the SHELXS and SHELX-93 programs[13]. The absolute configuration was determined using the Friedel pairs, absolute structure parameter 0.02(2)[14]. The atomic coordinates and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Center.

(1R,4R,7R)-7-(2-hydroxyethylsulphanylmethyl)-1,7-dimethylbicyclo[2.2.1]heptan-2-one 3

Sodium (0.5 g, 21.7 mmol) was carefully dissolved in i-PrOH (40 ml). 2-Mercaptoethanol (1.6 ml, 22.8 mmol) and (+)-9-bromocamphor (4.7 g, 20.3 mmol) were added to the solution under stirring. The mixture was brought to reflux for 24 h, cooled, filtered; the solvent was removed using rotary evaporator. The remained oil was dissolved in $CHCl_3$ (100 ml), the chloroform solution was washed with 10% KOH, water, and dried (Na_2SO_4). Evaporation of the solvent and distillation (98°C/0.15 mm) gave **3** as a colorless viscous oil, 4.1 g (88.5% yield). ^{1}H-NMR ($CDCl_3$): δ 0.93 (s, 3H), 0.97 (s, 3H), 1.15–2 (m, 6H), 2,28 (s, broad, 1H, removed after addition of D_2O), 2.32 (t, 1H), 2.43 (s, 2H), 2.77 (t, 2H), 3.75 (t, 2H). Anal. calcd. for $C_{12}H_{20}O_2S$: C 63.12, H 8.83; found: C 63.05, H 8.85.

((1R,4R,7R)-1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-ylmethyl) diphenylphosphine oxide 5

A solution of Ph_2PLi in THF (20 ml, containing ~10.9 mmol of Ph_2PLi) was added dropwise to a stirred solution of (+)-9-bromocamphor[4] (1.2 g, 5.19 mmol) in THF (5 ml) at −50°C during 15′ under argon atmosphere. The reaction mixture was left overnight at ambient temperature, and then was heated to reflux for 0.5 h. Water (20 ml) was carefully added into the reaction flask cooled by an ice bath and the remained mixture was treated with 10% H_2O_2 until the iodine–starch test was positive. The resulting mixture was diluted with $CHCl_3$ (200ml), the chloroform solution was washed (water, 10% KOH, water again), and dried (Na_2SO_4). The solvent was removed, and the remained solid was crystallized from heptane. White needles, 1.43 g (78.2% yield), m.p. 122°C, $[\alpha]^{20}_D$ +72.3 (c 6.84, MeOH); tlc (eluent EtOAc): R_f=0.52. ^{1}H-NMR ($CDCl_3$): δ 0.88 (s, 3H), 0.93 (s, 3H), 1.15–2.65 (m, 8H), 2.79 (t, 1H), 7.45–7.6 (m, 6H), 7.7–7.95 (m, 4H); ^{31}P-NMR ($CDCl_3$): δ +29.0; ^{13}C-NMR ($CDCl_3$): δ 13.2 (CH_3), 22.6 (CH_3), 30.7 (CH_2), 33.1(CH_2), 35.8 ($POCH_2$, $^1J_{CP}$=70 Hz), 44.8 (4-CH), 46.5 (3-CH_2), 53.2 (1-C), 64.0 (7-C, $^2J_{CP}$=22.5 Hz); 132.5, 134.2, 135.3, 140.5 (aromatic carbons), 221.6 (C=O); IR (KBr, cm^{-1}): 1735 (C=O), 1195 (P=O). Anal. calcd. for $C_{22}H_{25}O_2P$: C 74.98, H 7.15; found: C 75.08, H 7.11.

((1R,2R,4R,7R)-2-Hydroxy-1,7-dimethylbicyclo[2.2.1]hept-7-ylmethyl) diphenyl phosphine oxide 6

Lithium aluminum hydride (53.1 mg, 1.4 mmol) was added by small portions to a stirred solution of the phosphine oxide **5** (1 g, 2.8 mmol) in dry THF (30 ml). The mixture was stirred for about 0.5 h, then quenched carefully by water (70 ml), and evaporated by half under vacuum. The remainder was neutralized to pH$\sim$7, and the product was extracted with chloroform. The extract was dried (Na_2SO_4), the solvent was evaporated, and **6** obtained was recrystallized from diethyl ether. White crystals, 0.91 g (91.7% yield), m.p. 189°C, $[\alpha]^{20}_D$ +26.5 (c 1.39, MeOH); tlc (eluent EtOAc): R_f=0.42. ^{1}H-NMR ($CDCl_3$): δ 0.94 (s, 3H), 1.13 (s, 3H), 0.9–1.8 (m, 6H), 2.0–2.4 (m, 4H), 3.57 ('t', ^{3}J=6.8 Hz, 1H (2-H)), 7.35–7.65 (m, 6H), 7.65–8.0 (m 4H); ^{31}P-NMR ($CDCl_3$): δ +28.0; IR (KBr, cm^{-1}): 3350 (OH), 2880, 2940 (CH), 1435 (Ph), 1180 (P=O). Anal. calcd. for $C_{22}H_{27}O_2P$: C 74.55, H 7.68; found: C 74.68, H 7.59.

(1R,2R,4R,7R)-7-[(Diphenylphosphanyl)-methyl]-1,7-dimethylbicyclo[2.2.1]heptan-2-ol **2a**

All the operations were performed under a dry, inert atmosphere. The hydroxyphosphine oxide **6** (100 mg, 0.28 mmol), benzene (8 ml), triethylamine (0.39 ml, 2.8 mmol), and $SiHCl_3$ (0.28 ml, 2.8 mmol) were placed in a flask equipped with a reflux condenser and magnetic stirring. The mixture was stirred and heated to reflux for 4 h. Degassed water (10 ml) was added to the reaction mixture after cooling to room temperature. The aqueous layer was removed, and the organic layer was washed twice with water, filtered. The solvent was removed in vacuum leaving white amorphous solid (80 mg, 85.7% yield). ^{1}H-NMR ($CDCl_3$): δ 0.95 (s, 3H), 1.1 (s, 3H), 0.9–1.85 (m, 6H), 2.0–2.3 (m, 4H), 3.60 (dd, 1H), 7.25–7.55 (m, 10H); ^{31}P-NMR ($CDCl_3$): δ −22.0; Anal. calcd. for $C_{22}H_{27}OP$: C 78.08, H 8.04; found: C 78.12, H 7.95.

(1R,3S,6S,7R)-(6,7-dimethyl-4-oxatricyclo[4.3.0.$0^{3,7}$]non-3-yl) diphenylphosphine oxide **7**

A solution of Ph_2PLi in THF ($\sim$25 ml, 13 mmol Ph_2PLi) was added dropwise to (+)-8-bromocamphor[4] **1b** (2 g, 8.65 mmol) in THF ($\sim$5 ml) at −50°C under argon. The mixture was left overnight at room temperature, then treated successfully with water ($\sim$5 ml) and 10% H_2O_2 until the iodine–starch test became positive. The product was extracted with $CHCl_3$, washed (water, 10% KOH, water), dried (Na_2SO_4). Evaporation of the solvent yielded crude **7** which was crystallized from hexane. White crystals, 2.9 g (95% yield), m.p. 148–149°C, $[\alpha]^{20}_D$ +45.7 (c 13.8, MeOH). ^{1}H-NMR ($CDCl_3$): δ 0.62 (s, 3H), 0.8 (s, 3H), 1.1–2.0 (m, 6H), 2.50 (m, 1H), 3.55, 3.80 (AB q, 2H) 7.22–7.56 (m, 6H), 7.95–8.45 (m, 4H); ^{31}P-NMR ($CDCl_3$): δ +25.3; ^{13}C-NMR (75.44 MHz, $CDCl_3$): δ 10.86 (CH_3), 13.25 (CH_3), 25.93 (CH_2), 29.77 (CH_2), 38.19 (2-CH_2, $^2J_{CP}$=6.1 Hz), 43.45 (CH, $^3J_{CP}$=8.13 Hz), 54.78 (7-C, $^2J_{CP}$=10.5 Hz), 56.52 (6-C, $^3J_{CP}$=3.2 Hz), 72.07 (O–CH_2, $^3J_{CP}$=10.3 Hz), 87.24 (3-C, $^1J_{CP}$=96,4 Hz), 127.8, 128.01 (o-arom., $^2J_{CP}$=11.5 Hz), 131.07, 131.15 (m-arom., $^4J_{CP}$=4 Hz), 132.17, 132.29 (p-arom.), 132.38, 133.64 (ipso-arom., $^1J_{CP}$=67.5 Hz); IR (KBr, cm^{-1}): 2880, 2912, 2925, 2960 (CH), 1460 (phenyl), 1200 (P=O),1105 (–O–). Anal. calcd. for $C_{22}H_{25}O_2P$: C 74.98, H 7.15; found: C 74.93, H 7.18.

(1R,3R,6S,7R)-6,7-Dimethyl-4-oxatricyclo[4.3.0.$0^{3,7}$]nonane-3-carbonitrile **8**

A stirred solution of (+)-8-bromocamphor (1.5 g, 6.5 mmol), KCN (0.6 g, 9.2 mmol) in DMF (20 ml) was heated at 150°C for 8 h. The reaction mixture was poured into ice water (100 ml), the solid **8** was filtered, washed with water, and dried over P_2O_5. Crude **8** was purified by sublimation at 0.1 mm, 1.12 g (96.8% yield). White crystals, m.p. 135–136°C; $[\alpha]^{20}_D$ +147.2 (c 6.4, MeOH). ^{1}H-NMR ($CDCl_3$): δ 0.91 (s, 3H), 1.07 (s, 3H), 1.0–2.15 (m 7H), 3.55, 3.77 (AB q, 2H); ^{13}C-NMR ($CDCl_3$): δ 9.95 (CH_3), 10.5 (CH_3), 24.5 (CH_2), 28.7 (CH_2), 40.1 (2-CH_2), 42.8 (CH), 52.7 (7-C), 55.9 (6-C), 71.2 (0–CH_2), 80.6 (3-C), 117.2 (CN); IR (KBr, cm^{-1}): 2880, 2950 (CH), 2240 (CN), no carbonyl absorption. Anal. calcd. for $C_{11}H_{15}NO$: C 74.53, H 8.54, N 7.91; found: C 74.54, H 8.53, N 7.90.

(1R,3R,6S,7R)-6,7-Dimethyl-4-oxatricyclo[4.3.0.$0^{3,7}$]nonane **9**

(+)-8-Bromocamphor (1.5 g, 6.5 mmol) was dissolved in ether ($\sim$20 ml); $LiAlH_4$ (247 mg, 6.5 mmol) was added to the solution in small portions under stirring and cooling in an ice bath. The mixture obtained was stirred for 1 h at room temperature. Water (40 ml) was added (carefully first!), and the product was extracted with ether. The extract was dried ($CaCl_2$), and the solvent was evaporated. Crude **9** obtained was sublimed at 20 mm, 0.81 g (79.5% yield).Volatile white crystals, m.p. 109°C;

$[\alpha]^{20}_{D}$ +129.6 (c 4.9, MeOH). ^{1}H-NMR ($CDCl_3$): δ 0.85 (s, CH_3), 0.95 (s, CH_3), 0.9–2.0 (m, 7H), 3.44, 3,77 (AB q, 2H), 3.7 (dd, 1H); ^{13}C-NMR (CD_3OD): δ 11.0 (CH_3), 13.14 (CH_3), 26.3 (CH_2), 30.1 (CH_2), 36.1 (2-CH_2), 44.4 (CH), 52.8 (7-C), 61.6 (6-C), 72.0 (0–CH_2), 85.3 (3-CH); IR (KBr, cm^{-1}): 2875, 2955 (CH), no carbonyl absorption. Anal. calcd. for $C_{10}H_{16}O$: C 78.90, H 10.60; found: C 79.02, H 10.58.

(1R,4R,7S)-7-(2-hydroxyethylsulphanylmethyl)-1,7-dimethylbicyclo[2.2.1]heptan-2-one ***10***

This compound was obtained as its **7R**-isomer **3** (see above) from (+)-8-bromocamphor and 2-mercaptoethanol (82.3% yield), a colorless viscous oil, b.p. 108/0.15 mm, gives 2,4-dinitrophenylhydrazone, m.p. 155°C. ^{1}H-NMR ($CDCl_3$): δ 0.93 (s, 3H), 1.11 (s, 3H), 1.20–2.00 (m, 7H), 2.33 (s, 2H), 2.45 (dd, 1H), 2.70 (t, 2H), 3.71 (t, 2H); ^{13}C-NMR ($CDCl_3$): δ 8.2 (CH_3), 14.9 (CH_3), 25.6 (CH_2), 29.1 (CH_2), 35.2 (CH_2), 37.0 (CH_2), 39.1 (CH), 41.7 (CH_2), 49.5 (C), 57.9 (C), 59.6 (CH_2), 217.8 (C=O). Anal. calcd. for $C_{12}H_{20}O_2S$: C 63.12, H 8.83; found: C 63.08, H 8.75.

(1R,4R,7S)-1,7-Dimethyl-2-oxobicyclo[2.2.1]hept-7-ylmethyl) diphenyl phosphine oxide ethylene ketal ***13***

A THF solution (~20 ml) of Ph_2PLi (9.3 mmol) was added at −30°C to a stirred solution of (+)-8-bromocamphor ethylene ketal **11** (1.7 g, 6.18 mmol) in THF (~5 ml). The ketal was obtained following the literature procedure[7]. The reaction mixture was allowed to stand overnight at room temperature, then was heated to reflux for 0.5 h. The operations above were performed under argon. Followed oxidation and the working-up procedures are identical with those described for **5**. Crude **13** was purified by column chromatography (eluent EtOAc), tlc: R_f=0.64 (eluent EtOAc). Viscous colorless oil, 1.95 g (79.6% yield). ^{1}H-NMR ($CDCl_3$): δ 0.82 (s, 3H), 1.02 (s, 3H), 1.00–2.41 (m, 9H), 3.72–4.00 (m, 4H), 7.38–7.65 (m, 6H), 7.70–8.00 (m, 4H); ^{31}P-NMR ($CDCl_3$): δ +25.3; Anal. calcd. for $C_{24}H_{29}O_3P$: C 72.71, H 7.37; found: C 72.78, H 7.33.

(1R,4R,7S)-7-[(Diphenylphosphanyl)methyl]-1,7-dimethylbicyclo[2.1.1]heptan-2-one ***14***

All the operations were performed under argon. The phosphine oxide **13** (227 mg, 0.57 mmol) was placed in a flask equipped with a reflux condenser and magnetic stirring. Benzene (~10 ml), triethylamine (0.56 ml, 4.01 mmol), and $SiHCl_3$ (0.4 ml, 4.01 mmol) were added successively into the reaction flask under stirring. The mixture was brought to reflux for 5 h under stirring, then cooled. Aqueous HCl was added (15%, ~5 ml), and the mixture was stirred vigorously for 2 h, then treated with 10% KOH to pH~8. The organic layer was separated, the water solution was extracted twice with benzene. The combined benzene extract was washed with water, filtered, and the solvent was evaporated to obtain white amorphous solid, 158 mg (82.4% yield). ^{1}H-NMR ($CDCl_3$): δ 0.82 (s, 3H), 0.93 (s, 3H), 0.9–2.55 (m, 9H), 7.0–7.55 (m, 10H); ^{31}P-NMR ($CDCl_3$): δ −20.0; Anal. calcd. for $C_{22}H_{25}OP$: C 78.55, H 7.49; found: C 78.49, H 7.38.

((1R,4R,7S)-1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-ylmethyl) diphenylphosphine oxide ***15***

Ketal **13** (1g, 2.5 mmol) was dissolved in acetone (~20 ml). Hydrochloric acid (37%, 07 ml) was added and the mixture was left overnight, then neutralized by 10% NaOH. The solvents was removed, the product was extracted from the solid residue with $CHCl_3$. The chloroform extract was washed twice with water, dried ($CaCl_2$), evaporated. Crude **15** obtained can be purified either by crystallization from heptane or by column chromatography (eluent EtOAc), 0.78 g, 88.2%; white crystals, m.p. 55°C, $[\alpha]^{20}_{D}$ +15.9 (c 9.27, MeOH); tlc (eluent EtOAc): R_f=0.65. ^{1}H-NMR ($CDCl_3$): δ 0.88 (s, 3H), 0.94 (s, 3H), 0.8–2.65 (m, 8H), 2.74 (dd, 1H), 7.45–7.6 (m, 6H), 7.7–8.0 (m, 4H); ^{31}P-NMR ($CDCl_3$): δ +27.0; ^{13}C-NMR ($CDCl_3$): δ 12.34 (CH_3), 22.7 (CH_3), 30.44 (CH_2), 31.8 (CH_2), 35.4 ($POCH_2$, $^1J_{CP}$=77 Hz), 44.3 (4-CH), 46.2 (3-CH_2), 54.0 (1-C), 61.0 (7-C, $^2J_{CP}$=20.7 Hz); 132.8, 134.6, 135.9, 140.1 (aromatic carbons), 222.9 (C=O); IR (KBr, cm^{-1}): 1730 (C=O), 1180 (P=O). Anal. calcd. for $C_{22}H_{25}O_2P$: C 74.98, H 7.15; found: C 74.95, H 7.13.

((1R,2R,4R,7S)-2-Hydroxy-1,7-dimethylbicyclo[2.2.1]hept-7-ylmethyl) diphenyl phosphine oxide 16

This compound was obtained from **15** following the procedure described above for its **7R** isomer **6** in 90.5% yield. White crystals, m.p. 194–195°C, $[\alpha]^{20}_{D}$ +21.3 (c 0.99, MeOH); tlc (eluent EtOAc): R_f=0.42. ^{1}H-NMR ($CDCl_3$): δ 0.94 (s, 3H), 0.99 (s, 3H), 0.9–1.9 (m, 5H), 2.0–2.4 (m, 4H), 2.49 (dd, 1H), 3.58 ('t', ^3J=6.9 Hz,1H (2-H)), 7.30–7.65 (m, 6H), 7.65–8.0 (m 4H); ^{31}P-NMR ($CDCl_3$): δ +28.6; IR (KBr, cm^{-1}): 3250 (OH), 2885, 2940 (CH), 1435 (Ph), 1170 (P=O). Anal. calcd. for $C_{22}H_{27}O_2P$: C 74.55, H 7.68; found: C 74.59, H 7.70.

(1R,3S,6S,7R)-(7-diphenyloxyphosphanylmethyl-6-methyl-4-oxatricyclo[4.3.0.0^{3,7}]non-3-yl) diphenylphosphine oxide 17

This compound was obtained following the procedure described above for **7**, starting from (+)-8,10-dibromocamphor which we have obtained by an improved procedure[15] (1 g, 3.2 mmol) and Ph_2PLi (6.7 mmol). Crude **17** has been crystallized from a heptane–chloroform mixture. White crystals (1.48 g, 83.7% yield), m.p. 164°C, $[\alpha]^{20}_{D}$ −12.8 (c 8.2, MeOH); ^{1}H-NMR ($CDCl_3$): δ 1.09 (s, 3H), 1.08–2.25 (m, 8H), 2.26 (dd, 1H), 3.64, 3.84 (AB q, 2H), 7.0–8.4 (m, 20H); ^{31}P-NMR ($CDCl_3$): δ +22.7, +26.3; ^{13}C-NMR (75.44 MHz, $CDCl_3$): δ 13.21 (CH_3), 24.31 (CH_2), 27.5 ($POCH_2$, $^1J_{CP}$=77 Hz), 30.52 (CH_2), 38.97 (2-CH_2, $^2J_{CP}$=4.2 Hz), 44.22 (CH, $^3J_{CP}$=6.3 Hz), 56.72 (7-C), 59.17 (6-C), 72.52 (O–CH_2, $^3J_{CP}$=10.4 Hz), 91.5 (3-C, $^1J_{CP}$=97,8 Hz), 125.3–148.5 (arom.); Anal. calcd. for $C_{34}H_{34}O_3P_2$: C 73.89, H 6.21; found: C 73.92, H 6.20.

Acknowledgements

This work was partially supported by INTAS, International Association for Promotion of Cooperation between Scientists from Western Europe and Former Soviet Union, grant INTAS N 93-1588-Ext.

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15. (+)-8,10-Dibromocamphor has been synthesized starting from (+)-3,8-dibromocamphor which, in turn, has been obtained as a main side product during the synthesis of (+)-3,3,8-tribromocamphor by the reaction of (+)-3,3-dibromocamphor with chlorosulphonic acid. (+)-3,8-Dibromocamphor

has been distilled off from the main reaction product – (+)-3,3,8-tribromocamphor. This route to (+)-8,10-dibromocamphor seems to be more convenient than that described earlier[4].

(Received in UK 23 November 1996; accepted 30 December 1996)