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TETRAHEDRON: *ASYMMETRY*

# Enantiopure 1-phosphanorbornadiene-2-carboxaldehydes

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**Abstract**

The reaction of phenylpropargyl aldehyde diethyl acetal with 1-phenyl-3,4-dimethylphosphole at 140°C or 1,2,5-triphenylphosphole at 170°C leads, after deprotection, to the corresponding 1-phosphanorbornadiene-2-carboxaldehydes **3** and **4** in 88 and 45% yields, respectively. The resolution of **3** and **4** was carried out by chromatography or fractional crystallization of the acetals derived from (*S*,*S*)-1,2-diphenylethane-1,2-diol. The absolute configurations were established by X-ray analysis of one of these acetals or of a 2-bromomethyl derivative. 

## 1. Introduction

The ready availability of 1-phosphanorbornadienes from 2*H*-phospholes and alkynes,[1] combined with their unusual geometry which incorporates a non-racemizable phosphorus at the bridgehead of a strained bicyclic structure has led to an extensive investigation into their potential as ligands in homogeneous catalysis. They have proven their worth in the rhodium(I)-catalyzed hydrogenation of alkenes,[2] hydroformylation of alkenes,[3] asymmetric hydrogenation of functional alkenes,[4] and asymmetric isomerization of cyclic dienes.[5] The bis(phosphine) BIPNOR[4,5] is currently under development by Rhodia SA, for use in asymmetric catalysis. Furthermore, sulfonated (NORBOS)[6] and phosphonated[7] water-soluble 1-phosphanorbornadienes have been synthesized and NORBOS has displayed exceptional activity in the biphasic rhodium-catalyzed hydroformylation of propene.[6] Even more recently, the use of oxazoline derivatives in palladium-catalyzed asymmetric allylation and Heck reaction has been described.[8] As a further development of this family of promising catalytic ligands, the investigation of chelating species comprising a 1-phosphanorbornadiene unit and a coordinating side arm at the α-position of the ring appeared as particularly desirable. In practice, a convenient access to these mixed ligands required a straightforward synthesis of 1-phosphanorbornadiene-2-carboxaldehydes both as racemic and enantiopure species and this is the subject of this report.

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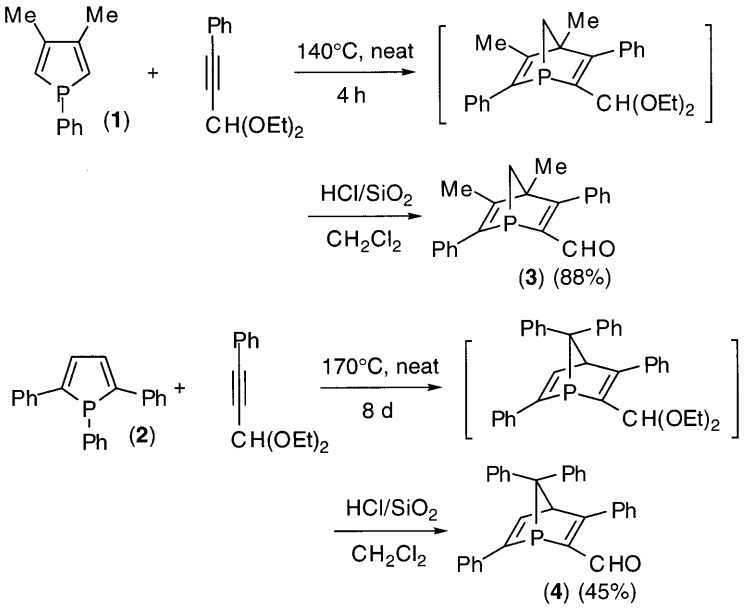
## 2. Results and discussion

All our experiments have been performed with phospholes **1** and **2**. These phospholes equilibrate with the corresponding 2*H*-species around 140 and 170°C, respectively.[1] At these temperatures, a propargyl aldehyde unit has a limited lifetime. In addition, tertiary phosphines are known to react via their lone pairs with activated alkynes.[9] It was thus necessary to protect and deactivate the aldehyde functionality by acetal formation (Scheme 1).




Scheme 1.

Fortunately, the [4+2] cycloaddition between the 2*H*-phospholes and the alkyne is completely regioselective. The protecting group is removed by acidic treatment of the crude adducts. The final yields are satisfactory in spite of the extreme reaction conditions. In their $^{1}H$ and $^{13}C$ NMR spectra, the formyl groups appear as follows: **3** ($CDCl_3$): $\delta_H$ 9.7, $^{3}J_{HP}=11.6$ Hz; $\delta_C$ 191.0, $^{2}J_{CP}=16.7$ Hz; **4** ($CDCl_3$): $\delta_H$ 9.7, $^{3}J_{HP}=9.2$ Hz; $\delta_C$ 190.3, $^{2}J_{CP}=16.5$ Hz; The $^{31}P$ couplings confirm the α-substitution. The X-ray crystal structure analysis of **3** (Fig. 1) shows that the carbonyl group is coplanar with the $C_5$=$C_6$ double bond and lies in the same direction as the P-lone pair. Otherwise, all the geometrical parameters of **3** are very close to those already reported for the non-functional species (CHO replaced by Ph).[1] The resolution of aldehydes **3** and **4** has been successfully carried out through acetalisation with (*S*,*S*)-1,2-diphenylethane-1,2-diol.[10] The resulting diastereomeric acetals **5a**,**b** and **6a**,**b** are easily separated, either by chromatography on silica gel (for **5a** and **5b**) or by fractional crystallization (for **6a** and **6b**). The deprotection is achieved as previously by acidic workup on silica gel in the presence of acetone as solvent (Scheme 2).

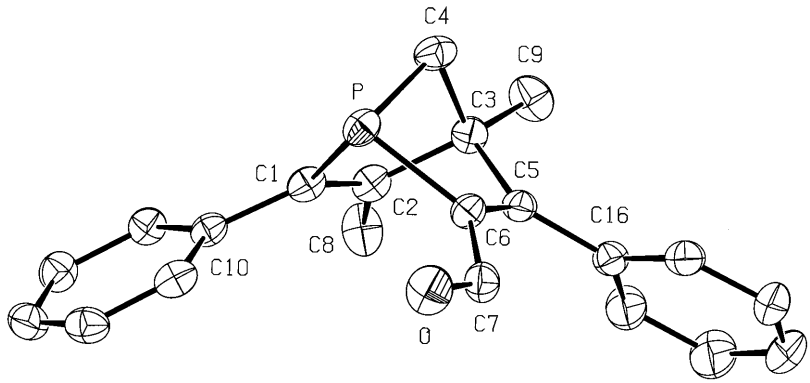
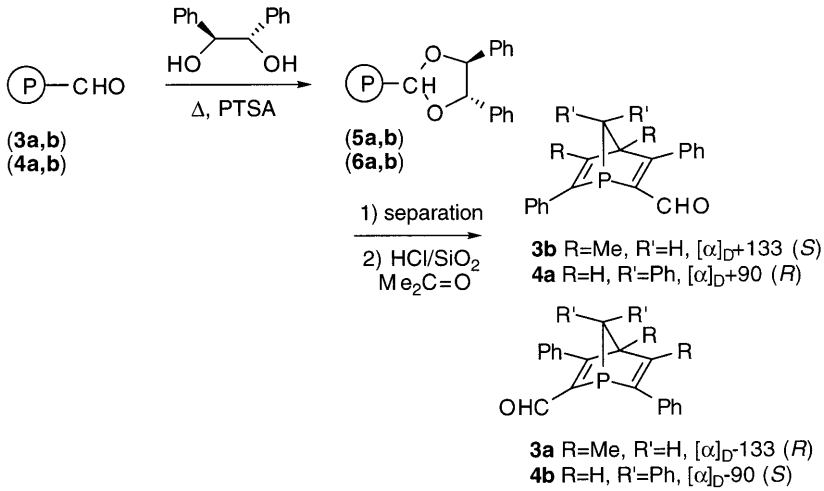



Figure 1. Crystal structure of **3**. Significant bond distances (Å) and angles (°): P–C(1) 1.859(3), P–C(4) 1.843(3), P–C(6) 1.852(3), C(1)–C(2) 1.339(3), C(2)–C(3) 1.542(4), C(3)–C(4) 1.548(4), C(3)–C(5) 1.555(4), C(5)–C(6) 1.352(3), C(6)–C(7) 1.446(4), C(7)–O 1.216(3); C(1)–P–C(4) 86.6(1), C(1)–P–C(6) 94.0(1), C(4)–P–C(6) 85.9(1), P–C(4)–C(3) 98.7(2), P–C(6)–C(7) 122.3(2), C(6)–C(7)–O 124.4(2)




Scheme 2.

Two methods have been used for establishing the absolute configuration of these enantiomers. The most straightforward involves the X-ray crystal structure analysis of **6a** [Flack enantiopole = 0.10 (18)] (Fig. 2). This shows that **4a** has the (*R*)-configuration at phosphorus. Alternatively, **3a** was first reduced by $LiAlH_4$ at low temperature, in order to avoid a reduction of the conjugated C=C double bond, and the resulting alcohol **7a** was reacted with bromine to give the 1-phosphanorbornadiene oxide **8a** (Scheme 3).

The initial bromination takes place at the phosphorus of **7a**; the resulting bromophosphonium bromide shows a $^{31}P$ resonance at +54 ppm. Then, the $[P\text{-}Br]^+Br^-$ unit brominates the alcohol function and is transformed into a P=O group. The absolute configuration of the final 2-bromomethyl-1-phosphanorbornadiene-1-oxide **8a** is shown in Fig. 3. Hence **3a** has the (*R*)-configuration at phosphorus.

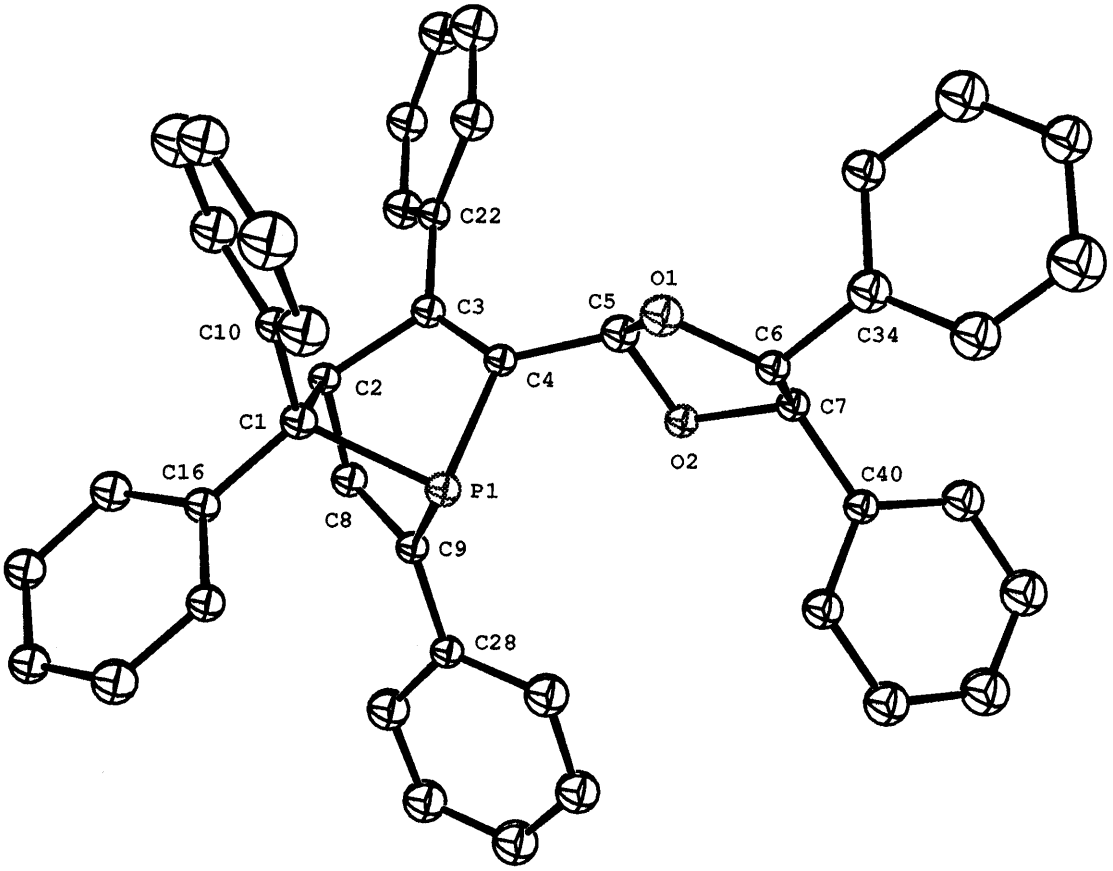
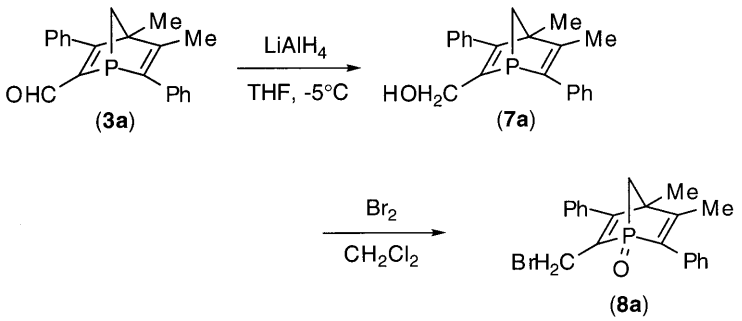



Figure 2. Absolute configuration of **6a**




Scheme 3.

The ready availability of the enantiopure 1-phosphanorbornadiene-2-carboxaldehydes **3a**, **4a**, **3b** and **4b** opens a pathway to a wide range of mixed chelating ligands containing an enantiomerically pure 1-phosphanorbornadiene unit. This possibility is currently being investigated.

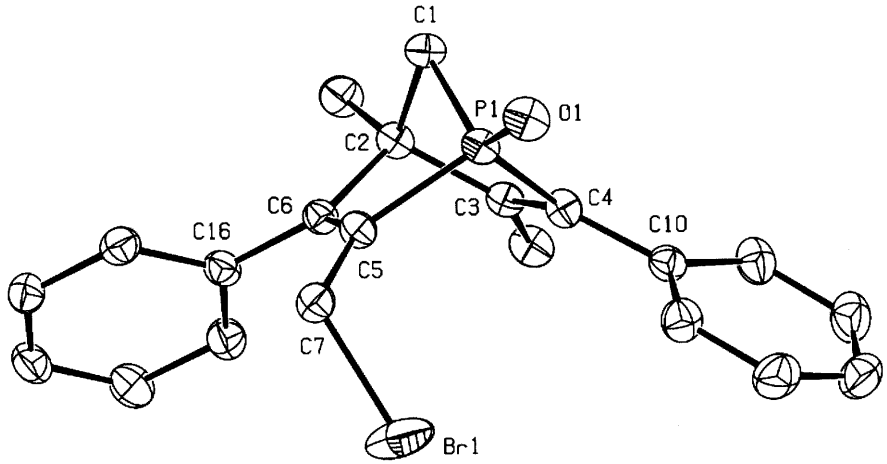



Figure 3. Absolute configuration of **8a**

## 3. Experimental

### 3.1. General

All reactions were carried out under argon by using standard techniques. Solvents were dried under nitrogen by standard procedures, distilled before use and stored under argon. The elemental analyses were performed by the Service microanalyse de Gif/Yvette, France. NMR spectra were recorded on a Bruker AC 200 SY spectrometer operating at 200.13 MHz for $^{1}H$, 50.32 MHz for $^{13}C$ and 81.01 MHz for $^{31}P$. Chemical shifts are expressed in parts per million (ppm) downfield from external tetramethylsilane ($^{1}H$ and $^{13}C$) and 85% aqueous $H_3PO_4$ ($^{31}P$).

### 3.2. Synthesis of 2,5-diphenyl-3,4-dimethyl-6-formyl-1-phosphanorborna-2,5-diene **3**

A mixture of 9.4 g (50 mmol) of 3,4-dimethyl-1-phenylphosphole **1**[11] and 10.2 g (50 mmol) of phenylpropargyl aldehyde diethyl acetal was heated at 140°C for 4 h. After cooling to room temperature, 40 ml of $CH_2Cl_2$, 12 g of silica gel and 4 ml of HCl (11N) were added to the brown oil. The mixture was stirred for 15 min at room temperature. It was then filtered and the solvent was evaporated in vacuo. The oily product was chromatographed on silica gel with $CH_2Cl_2$ as the eluent. Crystals suitable for a crystal stucture determination were obtained from hexane. Mp = 112°C; 14.8 g; 87% yield. Anal. calcd for $C_{21}H_{19}OP$: C, 79.25; H, 6.01; P, 9.70. Found: C, 78.62; H, 6.14; P, 9.62. Mass spectrum: $M^+$ (318, 10%); $M^+-C_9H_6O$ (188, 100%). $^{1}H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.4 (s, 3H), 2.1 (s, 3H), 2.2 (m, 2H), 6.8–7.3 (m, 10H), 9.7 (d, $J$ = 9.2 Hz, 1H).$^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 16.5, 20.4, 65.1, 73.6 (d, $J$ = 5.9 Hz), 191.0 (d, $J$ = 16.7 Hz).$^{31}P$ ($CDCl_3$) $\delta$ (ppm) = −31.2.

### 3.3. Synthesis of 2,5,7,7'-tetraphenyl-6-formyl-1-phosphanorborna-2,5-diene **4**

A mixture of 6.2 g (20 mmol) of 1,2,5-triphenylphosphole **2** and 4.1 g (20 mmol) of phenylpropargyl aldehyde diethyl acetal was heated at 170°C for 8 days. After cooling to room temperature, 20 ml of $CH_2Cl_2$, 6 g of silica gel and 2 ml of HCl (11N) were added to the brown

oil. The mixture was stirred for 15 min at room temperature then filtered and evaporated to dryness in vacuo. The crude product was obtained as a white powder which was further purified by chromatography on silica with $CH_2Cl_2$ as eluent. Crystals were obtained from hexane–toluene. Mp = 234°C; 5.0 g; 45% yield. Mass spectrum $m/z$: $M^+$ (442, 40%); $M^+-C_{18}H_{14}OP$ (165, 100%). $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 5.4 (m, 1H), 7.6 (m, 21H), 9.7 (d, $J$ = 9.2 Hz, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 71.6 (d, $J$ = 5.6 Hz), 88.2, 190.3 (d, $J$ = 16.5 Hz).$^{31}P$ ($CDCl_3$) $\delta$ (ppm) = −0.3.

### 3.4. Synthesis and separation of the two diastereoisomers **5a** and **5b**

To a solution of 6.4 g (20 mmol) of **3** in 50 ml of toluene were added 4.3 g (20 mmol) of (*S*,*S*)-1,2-diphenyl-1,2-ethanediol and 0.04 g of *p*-toluenesulfonic acid. The solution was then refluxed for 3 h. Complete formation of the two diastereoisomers can be monitored by $^{31}P$ NMR. The solvent was removed in vacuo and the oily product was chromatographed through silica gel (500 g) with hexane–$CH_2Cl_2$ (80:20) as solvent. **5a** was eluted first and crystallized from hexane. Mp = 181°C; 4.5 g; 87% yield. $[\alpha]_D^{25} = -69.3$ ($c$ = 0.4 $CHCl_3$). **5b** was then eluted and crystallized from pentane. Mp = 116°C; 4.2 g; 80% yield. $[\alpha]_D^{25} = -19$ ($c$ = 1.0 $CHCl_3$).

Compound **5a**: $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.4 (s, 3H), 2.0 (s, 3H), 2.3 (m, 2H), 4.7 (d, $J$ = 8.0 Hz, 1H), 5.1 (d, $J$ = 8.0 Hz, 1H), 5.9 (d, $J$ = 8.7 Hz, 1H), 6.9–7.5 (m, 20H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 16.4, 21.0, 66.9, 71.8 (d, $J$ = 6.0 Hz), 86.1 (d, $J$ = 2.8 Hz), 87.6, 103.0 (d, $J$ = 15.3 Hz).$^{31}P$ ($CDCl_3$) $\delta$ (ppm) = −22.9.

Compound **5b**: $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.5 (s, 3H), 2.2 (s, 3H), 2.3 (m, 2H), 5.0 (d, $J$ = 8.0 Hz, 1H), 5.2 (d, $J$ = 8.0 Hz, 1H), 6.0 (d, $J$ = 9.0 Hz, 1H), 6.9–7.5 (m, 20H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 16.2, 20.9, 66.4, 71.8 (d, $J$ = 6.0 Hz), 83.8, 87.6, 102.6 (d, $J$ = 15.4 Hz).$^{31}P$ ($CDCl_3$) $\delta$ (ppm) = −22.1.

### 3.5. Synthesis and separation of the two diastereoisomers **6a** and **6b**

To a solution of 4.4 g (10 mmol) of **4** in 50 ml of toluene were added 2.15 g (10 mmol) of (*S*,*S*)-1,2-diphenylethanediol, 0.02 g of *p*-toluenesulfonic acid and the solution was heated at 50°C for 5 h. The solvent was removed in vacuo. Crystals of diastereoisomer **6a** suitable for a crystal stucture determination were obtained from hexane–toluene; 3.0 g; 45% yield. $[\alpha]_D^{25} = -119.6$ ($c$ = 2.7 $CDCl_3$). The diastereoisomer **6b** was crystallized in hexane–$CH_2Cl_2$; 2.6 g; 40% yield. $[\alpha]_D^{25} = +241$ ($c$ = 2.5 $CDCl_3$).

Compound **6a**: Anal. calcd for $C_{45}H_{35}O_2P$: C, 84.61; H, 5.52; P, 4.85. Found: C, 84.41; H, 5.55; P, 5.1.$^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 4.6 (d, $J$ = 8.1 Hz, 1H), 5.0 (d, $J$ = 8.1 Hz, 1H), 5.2 (m, 1H), 6.0 (d, $J$ = 9.7 Hz, 1H), 7–7.6 (m, 21H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 70.1 (d, $J$ = 5.3 Hz), 86.0, 87.3, 87.8, 102.1 (d, $J$ = 15.6 Hz). $^{31}P$ ($CDCl_3$) $\delta$ (ppm) = 7.8

Compound **6b**: $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 4.6 (d, $J$ = 8.0 Hz, 1H), 5.1 (d, $J$ = 8.0 Hz, 1H), 5.2 (m, 1H), 6.0 (d, $J$ = 9.8 Hz, 1H), 7–7.6 (m, 21H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 71.0 (d, $J$ = 5.7 Hz), 86.8 (d, $J$ = 2.4 Hz), 88.1, 88.6, 102.7 (d, $J$ = 15.3 Hz). $^{31}P$ ($CDCl_3$) $\delta$ (ppm) = 6.7

### 3.6. Synthesis of the enantiomerically pure aldehydes **3a**, **3b**, **4a** and **4b**

A mixture of 6.0 g of silica gel, 20 ml of acetone and 2 ml of HCl (11N) was stirred at room temperature for 10 min. Then a solution of 2.6 g (5 mmol) of **5a** or **5b** or (4 mmol) of **6a** or **6b**

in 10 ml of acetone was added dropwise and the mixture was stirred for 2 h. Neutralisation was accomplished with NaOH (30%), the solution was filtered and the aldehyde was extracted with $CH_2Cl_2$. The organic phase was dried over magnesium sulfate, filtered and the solvent was removed in vacuo. After crystallization, a pure aldehyde was obtained.

**3a** $[\alpha]_D^{25} = -133$ ($c = 0.55$, $CDCl_3$)
**3b** $[\alpha]_D^{25} = +133$ ($c = 0.5$, $CDCl_3$)
**4a** $[\alpha]_D^{25} = +90$ ($c = 0.4$, $CDCl_3$)
**4b** $[\alpha]_D^{25} = -90$ ($c = 0.4$, $CDCl_3$)

### *3.7. Reduction of 2,5-diphenyl-3,4-dimethyl-6-formyl-1-phosphanorborna-2,5-diene **3a***

To a solution of 1.27 g (4 mmol) of phosphanorbornadiene aldehyde **3a** in 10 ml of THF were added at −20°C 228 mg (6 mmol) of lithium aluminium hydride in one portion. After stirring for 10 min, the reaction mixture was quenched with a small piece of ice. The product was isolated via classical extractive workup which afforded 1.22 g of **7a** (95% yield) as a colourless oil. Mass spectrum $m/z$: $M^+$, (320, 10%); $M^+-C_9H_8O$ (188, 100%). $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.35 (s, 3H), 1.7 (s, 1H), 2.0 (m, 2H), 2.1 (s, 3H), 4.3 (m, 2H), 6.9–7.5 (m, 10H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 16.4, 21.4, 62.0 (d, $J = 19.3$ Hz), 66.9, 71.6 (d, $J = 5.8$ Hz). $^{31}P$ ($CDCl_3$) $\delta$ (ppm) = −19.5.

### *3.8. Synthesis of 2,5-diphenyl-3,4-dimethyl-6-bromomethyl-1-phosphanorborna-2,5-diene 1-oxide **8a***

A solution of 0.16 ml of $Br_2$ (3.1 mmol) in 10 ml of $CH_2Cl_2$ was added dropwise slowly to a solution of 1.0 g of **7a** (3.1 mmol) in 100 ml of $CH_2Cl_2$. The mixture was stirred for 30 min at room temperature. Bromination can be monitored by $^{31}P$ NMR. At the end of the reaction, the excess of $Br_2$ was destroyed with a solution of sodium thiosulfate. The bromophosphine oxide was extracted with $CH_2Cl_2$, dried with magnesium sulfate and the solvent evaporated in vacuo. Crystals of **8a** suitable for a crystal stucture determination were obtained from toluene at −20°C; 830 mg; 67% yield. $[\alpha]_D^{25} = -125$ ($c = 0.95$ AcOEt). Mass spectrum $m/z$: $M^+$ (400, 18%); $M^+-C_9H_7Br$ (204, 100%). $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.4 (s, 3H), 2.1 (d, $J = 2.8$ Hz, 3H), 2.6 (m, 2H), 4.1 (dd, $J = 22.3$ Hz and $J = 12.5$ Hz, 1H), 4.4 (pt, $J = 8.8$ Hz, 1H), 6.9–7.5 (m, 10H). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 15.7 (d, $J = 14.2$ Hz), 19.1 (d, $J = 18.2$ Hz), 25.5 (d, $J = 8.2$ Hz), 49.7 (d, $J = 26.0$ Hz), 68.0 (d, $J = 68.0$ Hz). $^{31}P$ ($CDCl_3$) $\delta$ (ppm) = 45.5.

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