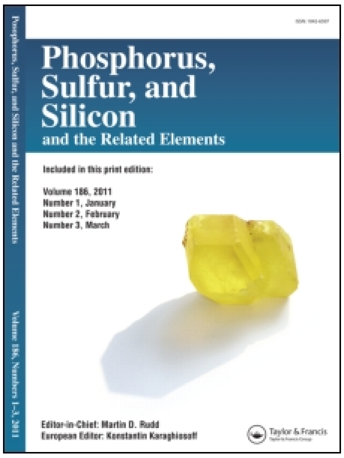

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Synthesis of Phosphine Oxide-Carboxylic Acid Esters Bearing 9,10-Dihydro-9,10-ethanoanthracene Moiety

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SYNTHESIS OF PHOSPHINE OXIDE-CARBOXYLIC ACID ESTERS BEARING 9,10-DIHYDRO-9,10-ETHANOANTHRACENE MOIETY

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A bulky type of phosphine oxide-carboxylic acid bearing 9,10-dihydro-9,10-ethanoanthracene moiety was synthesized by the Diels-Alder reaction of 2-anthryldiphenylphosphine oxide and methyl acrylate, for which the structure was confirmed on the basis of ^1H *NMR spectral data to be dimethyl 2-diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-11,11- and 12,12-dicarboxylates.*

Keywords: 9,10-Dihydro-9,10-ethanoanthracene; Diels-Alder reaction; methyl acrylate; phosphine-carboxylic acid

In the transition metal complex catalyzed asymmetric synthesis, one of the most important needs is the development of effective chiral phosphine ligands. Previously, we have succeeded in the development of chiral phosphine ligands with the carboxyl group, and achieved the high optical yield in the asymmetric allylic alkylation. In addition, it has been clarified that the carboxyl group of the ligands plays an important role for the asymmetric induction.[1] We also found that these phosphine-carboxylic acid ligands had substrate specificity in this alkylation.[1d] Therefore, we planned the synthesis of more effective chiral phosphine-carboxylic acid ligands, which could induce higher enantioselectivity in asymmetric allylic alkylation of a variety of allylic substrates. Here

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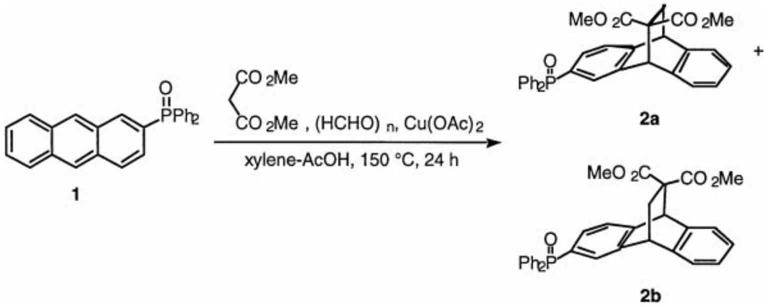
we describe the synthesis of a bulky type of 2-diphenylphosphino-9,10-dihydro-9,10-ethanoanthracene-12-carboxylic acid.

In order to know the spectral feature of the desired phosphine-carboxylic acid, the reaction of 2-anthryldiphenylphosphine oxide (**1**) with dimethyl methylenemalonate was first carried out. In the presence of copper(II) acetate, reaction of **1** with dimethyl malonate and paraformaldehyde afforded a mixture of two regioisomers, dimethyl 2-diphenylphos-phinoyl-9,10-dihydro-9,10-ethanoanthracene-12,12-dicarboxylate (**2a**), and 11,11-dicarboxylate (**2b**) in 89% yield (Eq. 1).[2] Recrystallization of the mixture from ethyl acetate-hexane resulted in separation of **2a** and **2b**. The stereochemical assignment of **2a** and **2b** was made on the basis of ^{1}H NMR and x-ray analysis.



(1)

In the ^{1}H NMR spectrum of **2a**, characteristic resonances of methyl and H11 protons were observed at δ 3.45 (s, 3H, OCH_3) and 3.57 (s, 3H, OCH_3), and 2.46 (dd, $J = 2.9$ and 13.1 Hz, 1H, CH_2) and 2.54 (dd, $J = 2.9$ and 13.1 Hz, 1H, CH_2) ppm respectively. In contrast, in that of **2b**, characteristic resonances of methyl and H12 protons were observed at δ 3.58 (s, 3H, OCH_3) and 3.59 (s, 3H, OCH_3), and 2.35 (dd, $J = 2.6$ and 13.1 Hz, 1H, CH_2) and 2.62 (dd, $J = 2.9$ and 13.1 Hz, 1H, CH_2) ppm respectively. On the other hand, the corresponding methyl signals in dimethyl 9,10-dihydro-9,10-ethanoanthracene-11,11-dicarboxylate and the mixture of dimethyl 2-methyl-9,10-dihydro-9,10-ethanoanthracene-11,11- and 12,12-dicarboxylates were observed at δ 3.58 (s, 6H, OCH_3) [2], and 3.53 (s, 3H, OCH_3), and 3.55 (s, 3H, OCH_3) ppm respectively.* Owing to the ring current of the phenyl group of

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*A mixture of two regioisomers, dimethyl 2-methyl-9,10-dihydro-9,10-ethanoanthracene-11,11- and 12,12-dicarboxylates prepared by the reaction of 2-methylanthracene, dimethyl malonate, and paraformaldehyde in the presence of copper(II) acetate in 92% yield, ^{1}H NMR ($CDCl_3$) δ 2.25 and 2.26 (s, 3H CH_3), 2.47 and 2.48 (br s, 2H, CH_2), 3.53 and 3.55 (s, 6H, OCH_3), 4.26 and 4.27 (br t, 1H, CH), 4.92 and 4.94 (s, 1H, CH), 6.85–7.31 (m, 7H, ArH).

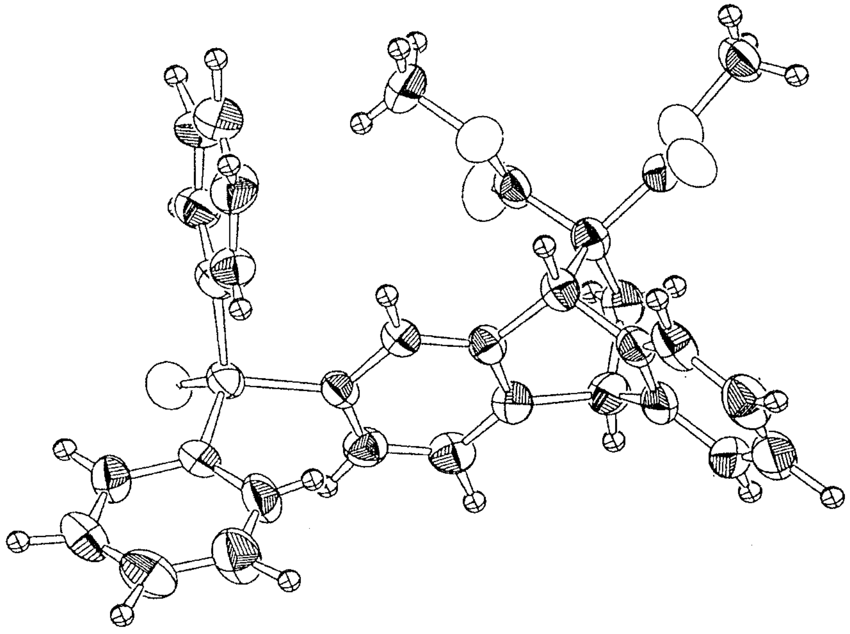
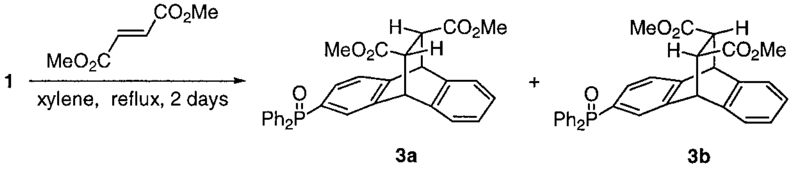


FIGURE 1 ORTEP diagram of **2a**.

the phosphorus functional group, one methyl signal in **2a** and one proton signal of H12 in **2b**, which were close to the phosphorus functional group, were shifted to the higher field. The signals of the two methyl groups in **2b** and methylene protons in **2a** were observed comparatively close to each other. The stereochemistry of **2a** was also confirmed by x-ray crystallographic analysis (Figure 1).

In order to obtain the ^{1}H NMR spectral data to elucidate the structure of the target monophosphine oxide-monocarboxylic acid with 9,10-dihydro-9,10-ethanoanthracene skeleton, **1** was reacted with dimethyl fumarate at reflux for 2 days in xylene to afford a mixture of dimethyl 2-diphenyl-phosphinoyl-9,10-dihydro-9,10-ethanoanthracene-11(anti),12(syn)- and 11(syn),12(anti)-dicarboxylates (**3a** and **3b**) in a quantitative yield (Eq 2).



(2)

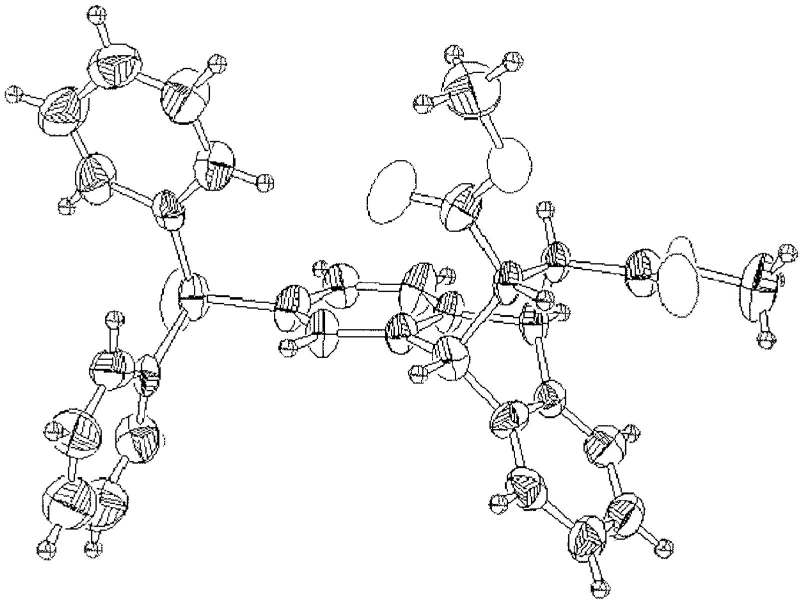
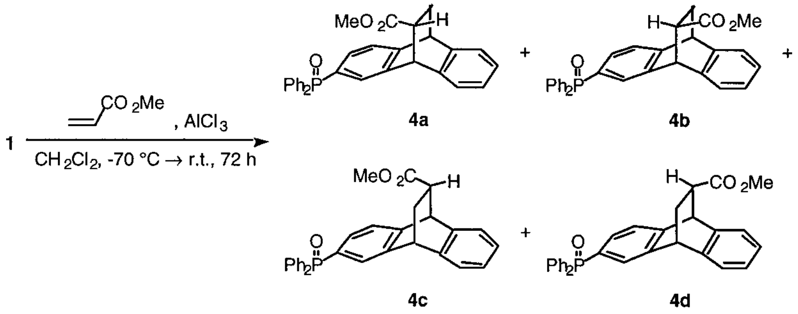


FIGURE 2 ORTEP diagram of **3a**.

Recrystallization of the mixture from ethyl acetate-hexane succeeded to separate **3b** as the first crystal and **3a** as the second crystal. The structures of **3a** and **3b** were assigned on the basis of their ^{1}H NMR spectrum. That is, the ^{1}H NMR spectrum of **3a** shows a signal for one methyl (s, 3H) at δ 3.52, and the other methyl signal (s, 3H) at δ 3.63, while that of **3b** exhibits the corresponding peaks at δ 3.62 (s, 3H) and 3.63 (s, 3H). One methyl group of **3a** is shifted to higher field, suggesting that the methyl group is closed to the phosphorus functional group. The stereochemistry of **3a** was also confirmed by x-ray crystallographic analysis (Figure 2).

Next we attempted the synthesis of a phosphine oxide monocarboxylic acid bearing the 9,10-dihydro-9,10-ethanoanthracene moiety. Reaction of **1** with methyl acrylate in the presence of anhydrous $AlCl_3$ as a Lewis acid catalyst[3] gave an isomer mixture of methyl 2-diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-12- and -11-carboxylates (**4a**, **4b**, **4c**, and **4d**) in 95% yield (Eq. 3). Recrystallization of the mixture from ethyl acetate-hexane succeeded to give pure **4b** as the first crystal. On the basis of the mentioned ^{1}H NMR spectrum of **2a,b** and **3a,b**, the structure of **4b** was assigned as methyl 2-diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylate. That is, characteristic resonances of methyl, methylene H11, and methine H12 protons in **4b** were observed at δ 3.58 (s, 3H,

OCH_3), 2.16–2.22 (m, 1H, CH_2) and 2.84–2.88 (m, 1H, CH_2), and 1.95–2.00 (m, 1H, CH) ppm, respectively. Since the methyl signal is not shifted to higher field, the methyl group is not situated close to the phosphorus functional group.

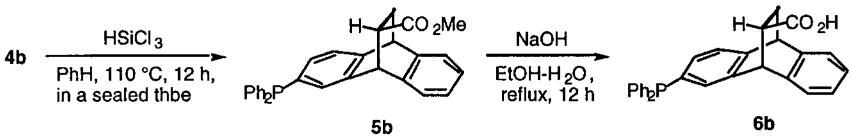


(3)

And the methine proton, H12, is on the syn side to the phosphorus functional group, so its signal shifts to the higher field.

Unfortunately, isolation of stereoisomers **4a**, **4c**, and **4d** has not succeeded yet.

Reduction of the isolated **4b** with trichlorosilane afforded methyl 2-diphenylphosphino-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylate (**5b**) in 79% yield. Subsequent hydrolysis of **5b** with NaOH gave racemic (±)-2-diphenylphosphino-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylic acid (**6b**) in 55% yield.



SCHEME 1

Thus, methyl 2-diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylate (**4b**) was easily isolated by recrystallization of the mixture of Diels-Alder adducts **4a–d** from ethyl acetate-hexane to derive the phosphine-carboxylic acid **6b**. The structure of **4b** was confirmed on the basis of ^1H NMR spectral data of **2a**,**b** and **3a**,**b**.

EXPERIMENTAL

General Procedures

^1H NMR and ^{31}P NMR spectra were obtained on a JEOL JNM-EX400 spectrometer in $CDCl_3$ operating at 400 Mz and 160 Mz respectively, with Me_4Si and H_3PO_4 as internal standard. IR spectra were recorded with a Shimadzu FTIR-8100A instrument. X-Ray analysis was made on a Rigaku AFC7R and AFC6S diffractometers with graphite monochromated Mo-Kα radiation (0.71069). Melting points were measured in open capillary tubes and are uncorrected. All reactions were carried out using degassed solvents under an argon atmosphere.

Materials

Tetrahydrofuran (THF) was purified by distillation from benzophenone ketyl under an argon atmosphere before use. Dichloromethane was distilled from P_2O_5. 2-Bromoanthracene was synthesized by the successive reduction of 2-bromoanthraquinone with stannous(II) chloride dihydrate in hydrochloric acid-acetic acid and with zinc powder in sodium hydroxide aqueous solution containing catalytic amount of copper(II) sulfonate, which was prepared by the reaction of 4-bromophthalic anhydride with benzene in the presence of anhydrous $AlCl_3$ and subsequent ring closure with concentrated sulfuric acid.

Synthesis of 2-Anthryldiphenylphosphine oxide (1)

To a suspension of magnesium (0.29 g, 12 mmol) and a piece of iodine in dry THF (2 ml) was added dropwise a solution of 2-bromoanthracene (3.54 g, 10 mmol) in dry THF (15 ml) under an argon atmosphere. After the mixture was stirred at room temperature for 14 h, chlorodiphenylphosphine (1.98 ml, 11 mmol) was added dropwise to the mixture. After being stirred for 2 h at reflux, the reaction mixture was quenched by the addition of 2M HCl. The mixture was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel using $CHCl_3$ to give crude phosphine product. To an acetone solution of the crude phosphine was added dropwise 30% hydrogen peroxide solution (2 ml). After the mixture had been stirred at room temperature for 12 h, the reaction mixture was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel using $CHCl_3$/AcOEt (1/1, v/v) to give **1** (2.83 g, 8 mmol) in 89% yield, m.p. 205°C (AcOEt-hexane) (lit. 206–207°C [5]); IR (KBr) cm^{-1} 1117, 1179; ^1H NMR δ 7.26–8.47 (m, 19H, ArH); ^{31}P NMR δ 29.83 (s).

Synthesis of Dimethyl 2-Diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-11,11- (2a) and 12,12-dicarboxylate (2b)

A mixture of **1** (1.51 g, 4.0 mmol), dimethyl malonate (0.91 ml, 8.0 mmol), paraformaldehyde (0.48 g, 16.0 mmol), and copper(II) acetate monohydrate (0.08 g, 0.4 mmol) in acetic acid (1.8 ml) and xylene (1.8 ml) was heated at reflux for 12 h. The mixture was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was passed through a short silica gel column with $CHCl_3$/AcOEt (1/1, v/v) to give the mixture **2a**,**b** (1.86 g, 3.6 mmol) in 89% yield. The mixture was recrystallized from AcOEt-hexane to give pure **2a** and **2b**.

Dimethyl 2-diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-12,12-dicarboxylate (**2a**) had m.p. 181°C; IR (KBr) cm^{-1} 1734; ^1H NMR δ 2.46 (dd, $J = 2.9$ and 13.1 Hz, 1H, CH_2), 2.54 (dd, $J = 2.9$ and 13.1 Hz, 1H, CH_2), 3.45 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 4.41 (t, 1H, CH), 4.97 (s, 1H, CH), 7.12–7.66 (m, 17H, ArH); ^{31}P NMR δ 29.68 (s); Anal. calcd. for $C_{32}H_{27}O_5P$: C, 73.55; H, 5.21. Found: C, 73.47; H, 5.19. Crystal Data: monoclinic, C-centered, a = 13.300(5), b = 27.884(6), c = 8.486(6) Å, $\alpha = 122.88(3)^\circ$, V = 2642(2) Å^3, Mo-Kα (0.71069 Å), Residuals: R = 0.050, Rw = 0.065.

Dimethyl 2-diphenylphosphinyl-9,10-dihydro-9,10-ethanoanthracene-11,11-dicarboxylate (**2b**) had m.p. 215°C; IR (KBr) cm^{-1} 1744; ^1H NMR δ 2.35 (dd, $J = 2.6$ and 13.1 Hz, 1H, CH_2), 2.62 (dd, $J = 2.9$ and 13.1 Hz, 1H, CH_2), 3.58 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 4.36 (t, 1H, CH), 5.04 (s, 1H, CH), 7.11–7.66 (m, 17H, ArH); ^{31}P NMR δ 29.95 (s); Anal. calcd. for $C_{32}H_{27}O_5P$: C, 73.55; H, 5.21. Found: C, 73.35; H, 5.21.

Reaction of 1 with Dimethyl Fumarate

A solution of **1** (0.76 g, 2.0 mmol) and dimethyl fumarate (4.0 mmol) in xylene (6 ml) was refluxed for 2 days. The mixture was chromatographed on silica gel using $CHCl_3$/AcOEt (1/1, v/v) to give a mixture of dimethyl 2-diphenylphosphinyl-9,10-dihydro-9,10-ethanoanthracene-11(anti),12(syn)- and -11(syn),12(anti)-dicarboxylate (**3a** and **3b**) in a quantitative yield. Recrystallization of the mixture from AcOEt-hexane gave pure **3a** and **3b**.

3a: 0.61 g (21%); m.p. 166–167°C; ^1H NMR δ 3.40–3.60 (m, 2H, CH), 3.52 (s, 3H OCH_3), 3.63 (s, 3H, OCH_3), 4.72 (br d, 1H, CH), 4.80 (br d, 1H, CH), 7.14-7.63 (m, 17H, ArH); ^{31}P NMR δ 29.83 (s); Anal. calcd. for $C_{32}H_{27}O_5P$: C, 73.55; H, 5.21. Found: C, 73.53; H, 5.17. Crystal Data: orthorhombic, Primitive, a = 19.232(4), b = 8.887(2), c = 15.323(3) Å, V = 2619.0(9) Å^3, Mo-Kα (0.71069 Å), Residuals: R = 0.077, Rw = 0.055.

3b: 0.84 g (29%); m.p. 209–210°C; ^1H NMR δ 3.37–3.38 (m, 1H, CH), 3.43–3.44 (m, 1H, CH), 3.62 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 4.72 (d, $J = 2.4$ Hz, 1H, CH), 4.80 (d, $J = 2.4$ Hz, 1H, CH), 7.12–7.68 (m, 17H, ArH); ^{31}P NMR δ 29.83 (s); Anal. calcd. for $C_{32}H_{27}O_5P$: C, 73.55; H, 5.21. Found: C, 73.40; H, 5.20.

Reaction of 1 with Methyl Acrylate

To a cold solution of **1** (0.50 g, 1.41 mmol) and methyl acrylate (0.25 ml, 2.82 mmol) in dry CH_2Cl_2 (15 ml) was added anhydrous aluminum chloride (0.39 g, 2.96 mmol). After the mixture was stirred at room temperature for 3 days, the reaction mixture was poured into 2M HCl. The mixture was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel using $CHCl_3$/AcOEt (1/1, v/v) to give a mixture of **4a–d** in 95% yield. The mixture was recrystallized from AcOEt-hexane to give pure **4b** in 10% yield.

Methyl 2-diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylate (**4b**) had m.p. 203–204°C; ^{1}H NMR δ 1.95–2.00 (m, 1H, CH), 2.16–2.22 (m, 1H, CH_2), 2.84–2.88 (m, 1H, CH_2), 3.58 (s, 3H, OCH_3), 4.40 (t, $J = 2.4$ Hz, 1H, CH), 4.69 (d, $J = 2.4$ Hz, 1H, CH), 7.09–7.68 (m, 17H, ArH); ^{31}P NMR δ 30.06 (s); Anal. calcd. for $C_{30}H_{25}O_3P$: C, 77.57; H, 5.43. Found: C, 77.36; H, 5.42.

Reduction of 4b

To a solution of **4b** (1.3 mmol) in dry benzene (20 ml) in a sealed tube was added trichlorosilane (0.5 ml, 5.2 mmol) at 0°C under argon atmosphere. After the mixture was heated at 65°C for 5 h, the reaction mixture was poured into ice water. The mixture was extracted with $CHCl_3$ and dried over anhydrous Na_2SO_4. This $CHCl_3$ solution was passed through a short silica gel column with $CHCl_3$ to give methyl 2-diphenylphosphino-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylate (**5b**).

5b: 0.46 g (79%); ^{1}H NMR 1.96–1.98 (m, 1H, CH_2), 2.13–2.16 (m, 1H, CH_2), 2.83–2.85 (m, 1H, CH), 3.55 (s, 3H, OCH_3), 4.33 (t, 1H, CH), 4.59 (d, $J = 2.0$ Hz, 1H, CH), 7.06–7.34 (m, 17H, ArH); ^{31}P NMR δ −4.53 (s).

Hydrolysis of 5b

A solution of **5b** (0.67 g, 1.5 mmol) and NaOH (0.30 g, 7.5 mmol) in ethanol-H_2O (1:1, 20 ml) was heated at reflux for 12 h under an argon atmosphere. The reaction mixture was quenched by the addition of 2M HCl, then extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was passed through a short silica gel column with $CHCl_3$/AcOEt (1/1, v/v) to give 2-diphenylphosphino-9,10-dihydro-9,10-ethanoanthracene-12(anti)-carboxylic acid (**6b**) in 55% yield: ^{1}H NMR δ 1.90–1.95 (m, 1H, CH_2), 2.04–2.08 (m, 1H, CH_2), 2.78–2.82 (m, 1H, CH), 4.27 (br t, 1H, CH), 4.56 (d, $J = 2.4$ Hz, 1H, CH), 7.00–7.27 (m, 17H, ArH), 11.56 (br s, 1H, COOH); ^{31}P NMR δ −4.64 (s).

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