by column chromatography (method A, Table I), while fractional distillation was used to separate **3a** from **3b** and **4a** from **4b** (method B, Table I).

The dehydrodimerization of phenylacetone (200 mmol) was effected with $PbO_2$ (100 mmol) in benzene (100 mL) with mechanical stirring for 1 h at reflux temperature. The filtered mixture was then concentrated by rotary evaporation and the residue crystallized fractionally (method C, Table I) by stirring with 100 mL of ethyl ether–*n*-pentane (1:1) at 30 °C. On cooling in a dry ice bath, **5b** separated as white crystals and was recrystallized from benzene. The **5a** diastereomer was distilled from the filtrate of **5b** between 147 °C and 167 °C at 0.5 to 1.0 mm, yielding a dense oil which readily crystallized. It was recrystallized from benzene. The $^1H$ NMR and mass spectra for each are available as supplementary material.[11] The $^{13}C$ NMR data are in Table II.

**Paal–Knorr Synthesis of Pyrroles.**[13] The γ-diketones (20 mmol), either pure 1 or mixtures of *d,l* and meso diastereomers of **2**, **3**, **4**, and **5**, were stirred with 200 mmol of benzylamine at 50–60 °C for 24 h under Ar atmosphere. Then the excess benzylamine was distilled at 0.5 mm and the residue stirred with 5–10 mL of 95% ethanol at room temperature under Ar and cooled in a dry ice bath to crystallize the pyrroles. The pyrroles were recrystallized from 95% ethanol; mmol, yield, mp for each are given below. The $^{13}C$ NMR, $^1H$ NMR, and mass spectral data are given as supplementary material.[11]

**1-Benzyl-2,5-dimethylpyrrole (6)**: 9.6 mmol; 48%; mp 43–44 °C [lit.[13] mp 45–45.3 °C, lit.[15] mp 43 °C].

**1-Benzyl-2,3,4,5-tetramethylpyrrole (7)**: 12 mmol; 60%; mp 23–24 °C (lit.[16] mp 21–21.5 °C).

**1-Benzyl-3,4-diethyl-2,5-dimethylpyrrole (8)**: 13 mmol; 65%; mp 48–49 °C.

**1-Benzyl-3,4-diisopropyl-2,5-dimethylpyrrole (9)**: 9.8 mmol; 49%; mp 70–71 °C.

**1-Benzyl-3,4-diphenyl-2,5-dimethylpyrrole (10)**: 15 mmol, 75%, mp 145–146 °C [lit.[17] mp 147–149 °C].

**Kinetics of Pyrrole Formation.** The Paal–Knorr[4] reactions were carried out in an Ar atmosphere in cyclohexane at a molar rate of 1:20 (γ-diketone to benzylamine) and a γ-diketone concentration of 10 mM. The reaction mixtures were stirred magnetically at 30 ± 0.05 °C with a Haake Series F constant temperature circulator. At timed intervals aliquots were withdrawn for HPLC analysis. Pseudo-first-order rate constants were calculated from the slope of $\ln [A_0]/([A_0] - [X])$ vs time where $[A_0]$ = initial concentration of diketone (10 mM) and [X] = concentration of the pyrrole at each time point.

**Single-Crystal X-ray Structure Determination of 4b.** $C_{12}H_{22}O_2$ (**4b**), mol wt 198.31, triclinic, $a = 7.230$ (1) Å, $b = 8.282$ (1) Å, $c = 5.724$ (1) Å, $\alpha = 103.69$ (1)°, $\beta = 90.03$ (1)°, $\gamma = 111.88$ (1)°, $V = 307.5$ Å$^3$, $Z = 1$, $D_{calcd} = 1.071$ g cm$^{-3}$, $\mu$(Cu Kα radiation, $\lambda = 1.5418$ Å) = 5.2 cm$^{-1}$. Space group $P1(C^1_1)$ or $P\bar{1}(C^1_i)$ from Laue symmetry; shown to be the latter by structure solution and refinement.

A crystal of dimensions ca. 0.20 × 0.40 × 0.64 mm was sealed inside a thin-walled glass capillary. Oscillation, Weissenberg, and precession photographs yielded preliminary unit-cell parameters and space group information. Intensity data were recorded on an Enraf-Nonius CAD-4 automated diffractometer (Cu Kα radiation, incident-beam graphite monochromator; $\omega$-$2\theta$ scans, $\theta_{max}$ 67°). From a total of 1090 independent measurements, those 958 reflections with $I > 3.0\sigma(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 high-order ($56° < \theta < 67°$) reflections widely separated in reciprocal space.

The crystal structure was solved by direct methods.[9] Approximate non-hydrogen atom coordinates were obtained from an *E* map. Full-matrix least-squares adjustment of atomic positional and anisotropic thermal parameters reduced *R* to 0.120.[10] Hydrogen atoms were then located in a different Fourier synthesis, and their positional and isotropic thermal parameters were included as variables in all subsequent full-matrix least-squares iterations which converged to $R = 0.055$.[10]

Final atomic positional parameters are in Table III. Anisotropic temperature factor parameters are available in the supplementary material.[11]

Neutral atom scattering factors used in the structure-factor calculations were taken from ref 20. In the least-squares iterations, $\Sigma w\Delta^2$ ($\Delta = ||F_o| - |F_c||$) was minimized with weights, *w*, assigned according to the scheme: $w^{1/2} = 1$ for $|F_o| < 2.6$, and $w^{1/2} = 2.6/|F_o|$ for $|F_o| > 2.6$ to ensure no systematic dependence of $\langle w\Delta^2 \rangle$ when analyzed in ranges of $|F_o|$.

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**Registry No.** **1**, 110-13-4; **2a**, 28895-03-6; **2b**, 28895-02-5; **3a**, 34506-20-2; **3b**, 34506-19-9; **4a**, 99902-11-1; **4b**, 99902-10-0; **5a**, 69373-32-6; **5b**, 69373-33-7; **6**, 5044-20-2; **7**, 3469-21-4; **8**, 99902-12-2; **9**, 99902-13-3; **10**, 79823-43-1; $C_6H_5CH_2NH_2$, 100-46-9; $CH_3COCH_2CH_3$, 78-93-3; $CH_3COCH_2CH_2CH_3$, 107-87-9; $CH_3COCH_2CH(CH_3)_2$, 108-10-1; $CH_3COCH_2Ph$, 103-79-7.

**Supplementary Material Available:** Table V, proton NMR and mass spectral data for diketones and pyrroles; Table VI, $^{13}C$ NMR shifts of substituted pyrroles; Table VII, anisotropic temperature factor parameters for **4b**; Table VIII, interatomic distances and angles in **4b**; Table IX, torsion angles in **4b** (8 pages). Ordering information is given on any current masthead page.

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# Novel Construction of Penem Ring System from Penicillin Derivatives. Synthesis of 2-Carboxylpenem Derivative[1]

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6-Aminopenicillanic acid derivative 1 was successfully transformed into 2-carboxylpenem derivative 15 by employing a carbene reaction of α-diazoacetate as a key step.

It is now well established that penem derivatives are endowed with potent antibacterial activity. Development of methodology for the construction of a penem ring system is therefore an important objective.[2] During the

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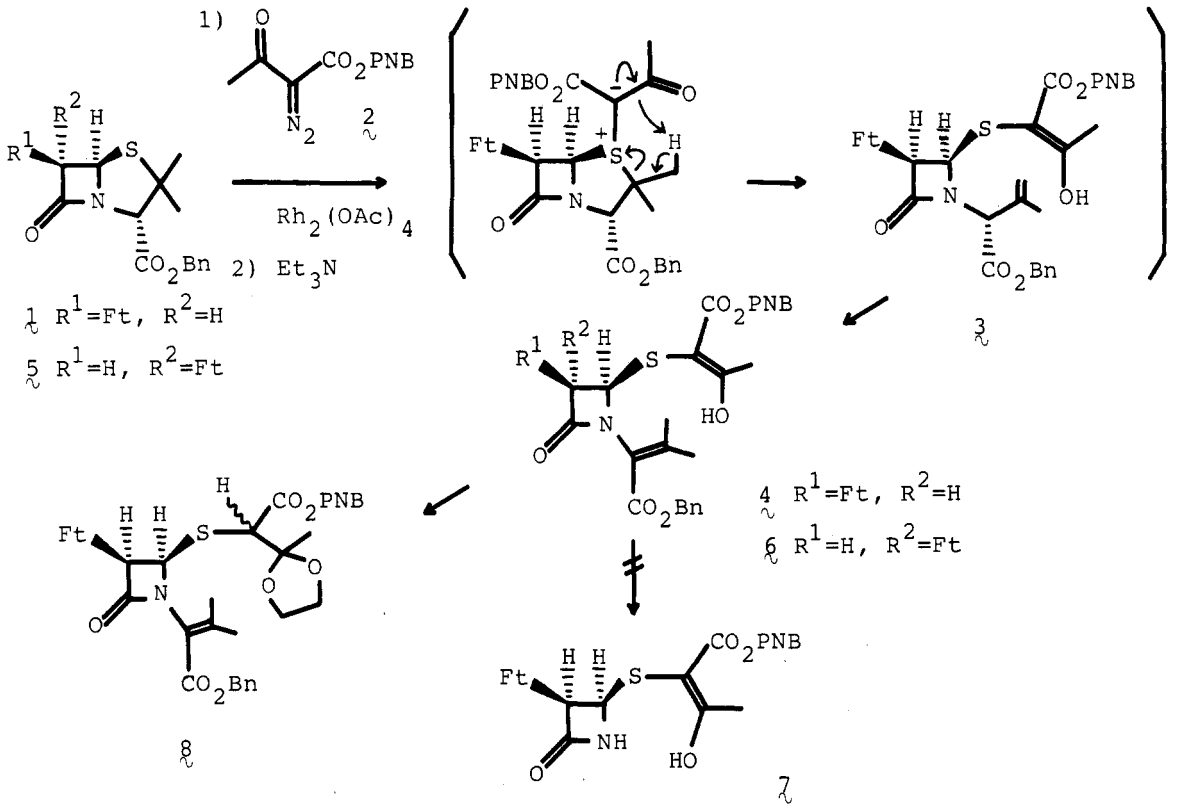
**Scheme I**



course of our studies directed toward the synthesis of nonclassical β-lactam antibiotics, we have been interested in developing an efficient conversion of the penicillin nucleus into penem derivatives, because 6-aminopenicillanic acid (6-APA) is readily available in optically active form as a starting material. It has already been suggested by us[3] and others[4,5] that a carbene reaction might be very useful for preparing a functionalized 1,2-secopenicillin from penicillin. We have recently succeeded in converting 6-APA to a ceph-3-em derivative by using a carbene reaction of α-diazomalonate.[6] We here wish to report a novel transformation of 6-APA into a penem derivative as an extension of our work. Our design for the above purpose involves a carbene reaction of α-diazoacetate with 6-APA derivative as a key reaction.

## Results and Discussion

Heating of benzyl 6-phthalimidylpenicillanate (1) with *p*-nitrobenzyl α-diazoacetoacetate (2) in benzene–methylene chloride (1:1 v/v) in the presence of a catalytic amount of rhodium acetate for 16 h afforded the 1,2-secopenicillin (3), whose treatment with triethylamine in methylene chloride brought about isomerization of the double bond to give the α,β-unsaturated ester 4, in 79% yield from 1. The $^1$H NMR spectrum of 4 exhibits three olefinic methyl singlets at δ 2.05, 2.22, and 2.33 and a pair of doublets at δ 4.94 and 5.53 due to $C_3H$ and $C_4H$ with $J$ = 5 Hz which indicate that the cis stereochemistry of 4 between the $C_3$ and $C_4$ positions remains unchanged during the above conversion and that the β-keto ester moiety exists completely in the enol form. In order to confirm the stereochemistry of 4, the trans isomer 5 was subjected to the carbene reaction using *p*-nitrobenzyl α-diazoacetoacetate (2) under the same reaction conditions to yield the *trans*-azetidinone (6) in 55.4% yield, whose $^1$H NMR spectrum showed a pair of doublets ($J$ = 2.0 Hz) at δ 5.30 and 5.49 due to $C_3H$ and $C_4H$ in a trans relationship. Similarly, the reaction of 1 and 5 with methyl α-diazoacetoacetate afforded 7 and 8 in 72.9% and 56.6% yields, respectively.

As a definitive proof of structure for 4, we next studied the removal of the substituent at the $N_1$ position. Ozonolysis of 4 in methylene chloride–methanol (1:1 v/v) at −78 °C to give the azetidinone 7 was not reproducible, hence ester 4 was converted to the ethylene ketal 8 (Scheme I).

Removal of the substituent at the 1-position of 8 was achieved by treatment[7] with potassium permanganate in

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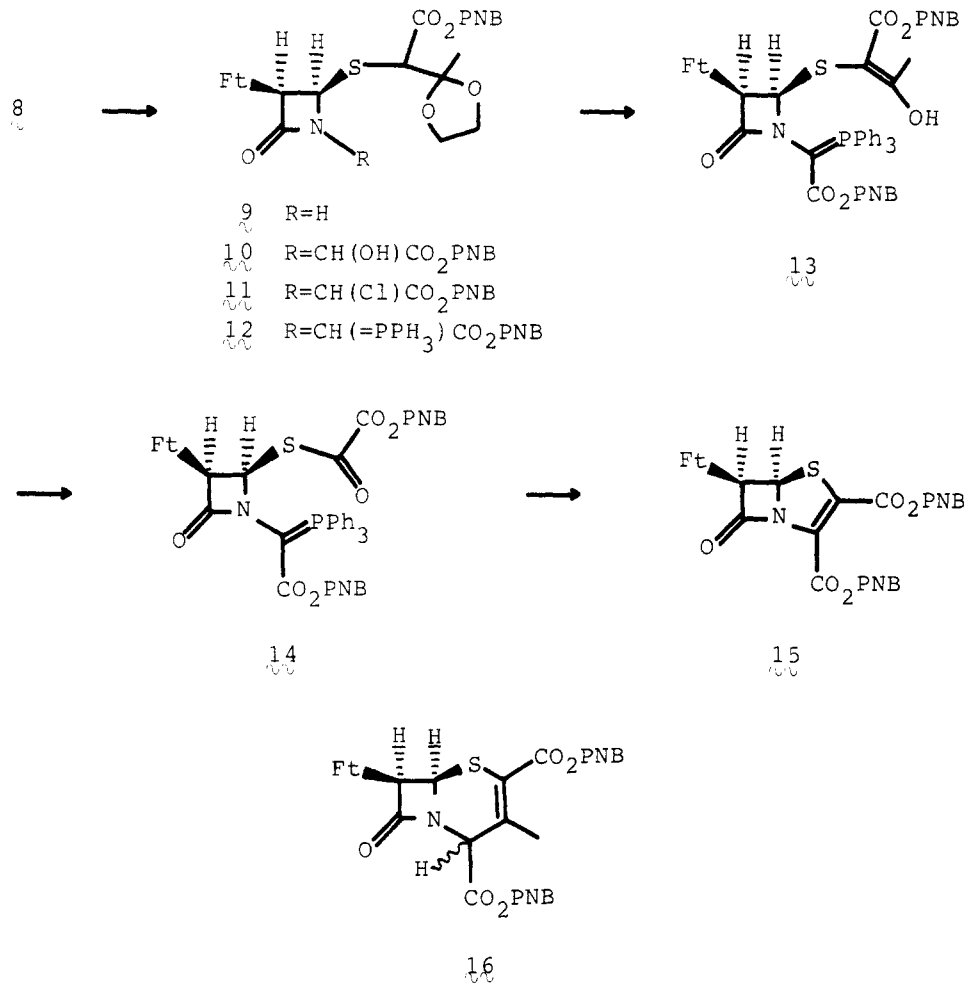
**Scheme II**




a mixed solvent system [dimethylformamide–pyridine–water (5:5:1 v/v)] at 0 °C to afford the azetidinone **9** in 68% yield. Introduction of the $C_2$ unit at the 1-position of **9** was carried out by adopting Woodward's procedure[8] to give phosphorane **12** via alcohol **10** and chloride **11**. After deprotection of ethylene ketal group of **12**, the β-keto ester **13** was ozonized in methylene chloride in the presence of trifluoroacetic acid at −78 °C to afford phosphorane **14**. Heating **14** at 80 °C in benzene brought about the intramolecular Wittig cyclization to provide the desired penem **15** in 42.2% yield from **13**. Thus, the transformation of 6-APA into a penem derivative that bears a functional group at the $C_2$ position was achieved.

Intramolecular Wittig cyclization of **13** would be expected to give a ceph-3-em derivative, however, heating of **13** in toluene for 2 h furnished ceph-2-em derivative **16** in 21.4% yield (Scheme II).

The deprotection of the PNB group of **15** and the biological evaluation of the compound synthesized are under investigation.

We next turned our attention to forming the $C_3$–$N_4$ bond for construction of the penem ring skeleton. Only one successful result in this direction has been reported recently by Wasserman.[2o] We planned an alternative approach which involved an intramolecular Michael addition of a β-lactam nitrogen onto an α,β-unsaturated ester.

Reaction of 4-acetoxy-3-ethyl-2-azetidinone (**17**)[9] with the sodium salt of ethyl 2-mercaptoacetate yielded **18**, which was converted to the N-silylated azetidinone **19** in 78% yield from **17**. Condensation of **18** with dibenzyl oxalate afforded keto ester **20** in 64.5% yield. Removal of the silyl group of **20** gave **21** which was further converted into the mesylate **22** or the phosphate **23** in 69.6% and 69.7% yields, respectively. Attempted intramolecular Michael additions of **22** and **23** failed to produce the desired product under various reaction conditions. As noted earlier,[2p] the formation of the $C_3$–$N_4$ bond seems to be difficult. However, the following interesting observation was made. Treatment of the silyl compound **24**, prepared from **19** and acetyl chloride, with tetrabutylammonium fluoride in tetrahydrofuran brought about transposition of the acetyl function to give *N*-acetyl compound **25** in 99.3% yield. This result indicated that transacetylation might have occurred via a penem derivative formed through 3–4 bond formation, followed by a retro-aldol reaction as shown in Scheme III and suggests an alternative to penem construction. The structure of **25** was confirmed by direct comparison with an authentic sample prepared by acetylation of **18**.

## Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are not corrected. NMR spectra were obtained in $CDCl_3$ solution with tetramethylsilane as an internal standard.

**Reaction of Benzyl 6-Phthalimidylpenicillanate (1 and 5) with *p*-Nitrobenzyl or Methyl α-Diazoacetoacetate.** A solution of benzyl 5,6-*cis*-6-phthalimidylpenicillanate (**1**) (18.9 g, 44 mmol) and *p*-nitrobenzyl α-diazoacetoacetate (**2**) (14.74 g, 56 mmol) in benzene–methylene chloride (200 mL, 1:1 v/v) in

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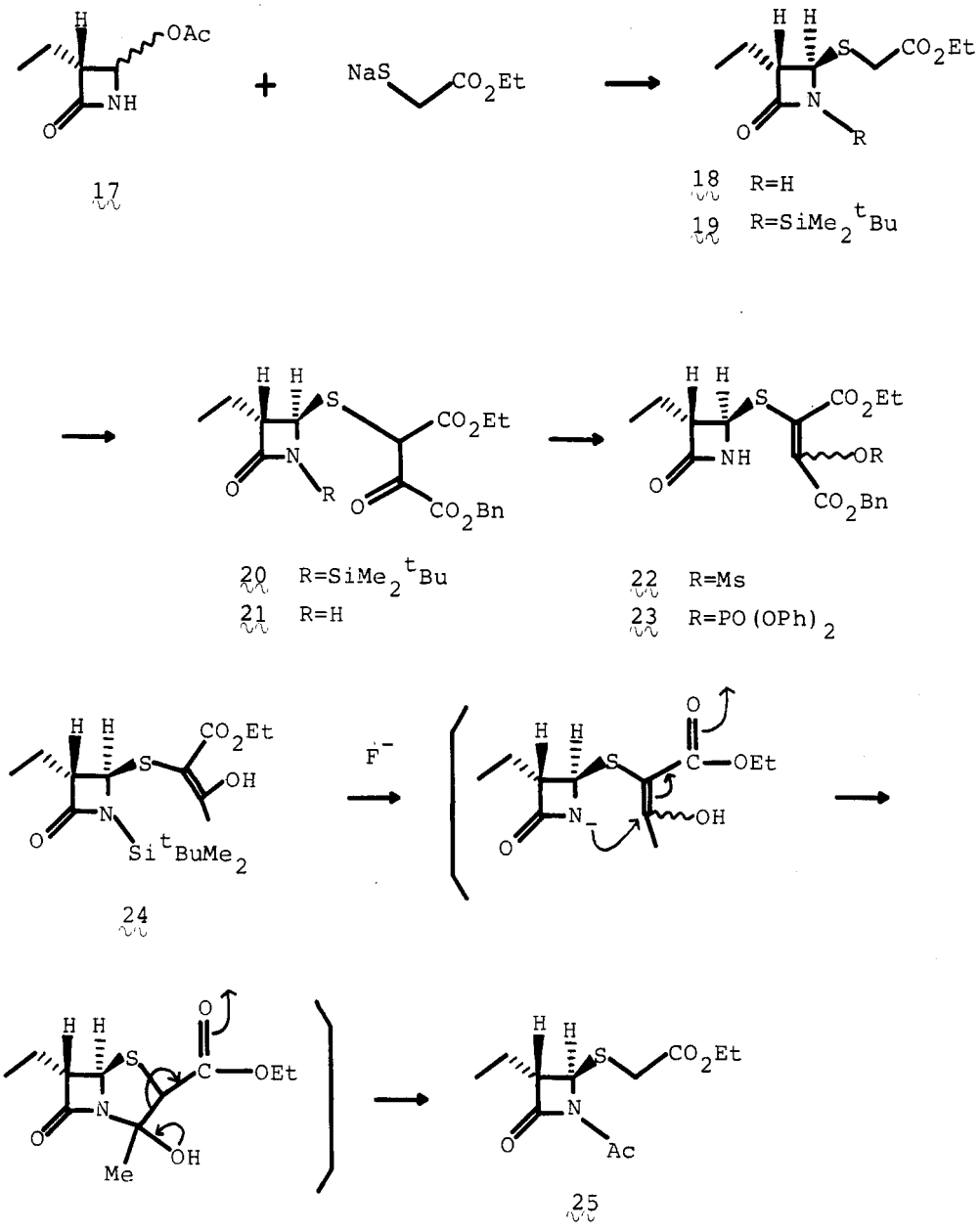
**Scheme III**




the presence of rhodium(II) acetate (50 mg) was heated under reflux for 16 h. After evaporation of the solvent, the residue was subjected to a short-column chromatography. Elution with benzene–acetone (97:3 v/v) gave the secopenicillin **3**, which was then dissolved into methylene chloride (200 mL). To the above solution was added triethylamine (5.5 mL) at 0 °C, and the resulting mixture was further stirred at 0 °C for 2 h. Evaporation of the solvent afforded the residue, which was subjected to column chromatography on silica gel. Elution with methylene chloride–acetone (98:2 v/v) gave **4** (22.98 g, 79%) as a powder: IR ($CHCl_3$) 1780, 1765, 1720, 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.05 (s, 3 H, $CH_3$), 2.22 (s, 3 H, $CH_3$), 2.33 (s, 3 H, $CH_3$), 4.94 (d, $J$ = 5.4 Hz, 1 H, $C_3H$), 5.53 (d, $J$ = 5.4 Hz, 1 H, $C_4H$), 8.0 (d, $J$ = 8 Hz, 2 H, Ar H), 13.20 (s, 1 H, OH); $[\alpha]^{25}_D$ +15.84° ($c$ 0.084, $CHCl_3$). Anal. Calcd for $C_{34}H_{29}N_3O_{10}S$: C, 60.80; H, 4.35; N, 6.26. Found: C, 61.39; H, 4.30; N, 6.11.

Compound **6** was obtained from the reaction of **5** with **2** by the similar procedure as described above, in 55.4% yield: IR ($CHCl_3$) 1775, 1765, 1720, 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.02 (s, 3 H, $CH_3$), 2.19 (s, 3 H, $CH_3$), 2.25 (s, 3 H, $CH_3$), 5.30 (d, $J$ = 2.0 Hz, 1 H, $C_3H$), 5.49 (d, $J$ = 2.0 Hz, 1 H, $C_4H$); $[\alpha]^{25}_D$ +87.9° ($c$ 0.06, $CHCl_3$). Anal. Calcd for $C_{34}H_{29}N_3O_{10}S\cdot H_2O$: C, 59.21; H, 4.53; N, 6.09. Found: C, 59.35; H, 4.21; N, 6.13.

**7**: 72.9% yield; IR ($CHCl_3$) 1780, 1765, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.15 (s, 3 H, $CH_3$), 2.48 (s, 6 H, 2 × $CH_3$), 3.63 (s, 3 H, $OCH_3$), 5.00 (d, $J$ = 5.0 Hz, 1 H, $C_3H$), 5.10 (dd, $J$ = 12, 18 Hz, 1 H, C*H*HAr), 5.40 (dd, $J$ = 12, 18 Hz, 1 H, CH*H*Ar), 5.63 (d, $J$ = 5.0 Hz, $C_4H$); $[\alpha]^{25}_D$ +23.15° ($c$ 0.58, $CHCl_3$). Anal. Calcd for $C_{28}H_{26}N_2O_8S\cdot H_2O$: C, 59.15; H, 4.96; N, 4.93. Found: C, 59.32; H, 4.61; N, 4.58.

**8**: 56.6% yield; IR ($CHCl_3$) 1775, 1765, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.00 (s, 3 H, $CH_3$), 2.15 (s, 3 H, $CH_3$), 2.26 (s, 3 H, $CH_3$), 3.60 (s, 3 H, $OCH_3$); $[\alpha]^{25}_D$ +61.13° ($c$ 1.4, $CHCl_3$). Anal. Calcd for $C_{28}H_{26}N_2O_8S\cdot 0.5H_2O$: C, 60.10; H, 4.86; N, 5.01. Found: C, 60.31; H, 4.71; N, 4.49.

**Ketalization of β-Keto Ester 4.** A solution of β-keto ester **4** (5 g, 13.4 mmol), ethylene glycol (150 mL), and *p*-toluenesulfonic acid (200 mg) in benzene (200 mL) was heated under reflux with azeotropic removal of water for 48 h. The solution was basified with saturated aqueous sodium hydrogen carbonate, washed with water, and dried over sodium sulfate. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with benzene–acetone (95:5 v/v) afforded the ketal compound **8** (1.6 g, 30%) as a mixture of its diastereomers as a powder: IR ($CHCl_3$) 1770, 1725, 1345 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (s, 1.5 H, $CH_3$), 1.28 (s, 1.5 H, $CH_3$), 2.29 (s, 6 H, 2 × $CH_3$), 3.29 (s, 0.5 H, SCHCO), 3.35 (s, 0.5 H, SCHCO), 3.75 (s, 2 H, $OCH_2CH_2O$), 3.81 (s, 2 H, $OCH_2CH_2O$), 5.59 (d, $J$ = 5.7 Hz, 0.5 H, $C_4H$), 5.60 (d, $J$ = 5.7 Hz, 0.5 H, $C_4H$), 5.74 (d, $J$ = 5.7 Hz, 0.5 H, $C_3H$), 5.89 (d, $J$ = 5.7 Hz, 0.5 H, $C_3H$); $[\alpha]^{25}_D$ −19.23°

(c 0.091, $CHCl_3$). Anal. Calcd for $C_{36}H_{33}N_3O_{11}S$: C, 60.42; H, 4.65. Found: C, 60.29; H, 4.83.

**Removal of the Substituent at the 1-Position of 8.** To a stirred solution of the ketal compound **8** (500 mg, 0.7 mmol) in dimethylformamide (5 mL), pyridine (5 mL), and water (1 mL) was added potassium permanganate (140 mg) at 0 °C, and the resulting mixture was further stirred at 0 °C for 5 h. After acidification with 10% hydrochloric acid, the mixture was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated to give the residue, which was chromatographed on silica gel. Elution with methylene chloride–acetone (94:6 v/v) provided **9** (230 mg, 68%) as a powder: IR ($CHCl_3$) 3425, 1795, 1775, 1740, 1730, 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.38 (s, 1.5 H, $CH_3$), 1.42 (s, 1.5 H, $CH_3$) 6.76 (s, 1 H, NH); $[\alpha]^{25}_D$ −18.77° (c 1.141, $CHCl_3$). Anal. Calcd for $C_{23}H_{21}N_3O_9S\cdot 0.5\ H_2O$: C, 53.73; H, 4.13, N, 7.83. Found: C, 53.66; H, 4.09; N, 7.83.

**Preparation of the Penem Derivative 15.** A solution of **9** (500 mg, 0.97 mmol) and *p*-nitrobenzyl glyoxylate (550 mg) in dry dimethylformamide (4 mL) and toluene (16 mL) in the presence of 3-Å 1/16 molecular sieves was stirred at ambient temperature for 24 h under a current of nitrogen. The mixture was diluted with benzene (30 mL), washed with water, and dried over sodium sulfate. Removal of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with benzene–ethyl acetate (9:3 v/v) afforded the alcohol **10** (560 mg, 79.5%) as an amorphous solid: IR ($CHCl_3$) 1790, 1780, 1730, 1360 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26 (s, 3 H, $CH_3$), 1.86 (s, 1 H, OH), 3.38 (s, 1 H, SCHCO), 3.88 (s, 4 H, $OCH_2CH_2O$), 5.65 (d, $J$ = 5.5 Hz, 1 H, $C_4H$), 5.82 (d, $J$ = 5.5 Hz, 1 H, $C_3H$).

To a stirred solution of the alcohol **10** (560 mg, 0.77 mmol) in dry tetrahydrofuran (20 mL) containing 2,6-lutidine (244 mg) was added a solution of thionyl chloride (270 mg) in tetrahydrofuran (5 mL) at ambient temperature, and the resulting mixture was further stirred for 20 min. Evaporation of the solvent gave the chloro compound **11**, which without purification was used in the next reaction. To a stirred solution of the chloro compound **11** obtained above in dry dioxane (20 mL) were added 2,6-lutidine (240 mg) and triphenylphosphine (300 mg, 1.15 mmol), and the resulting mixture was stirred at ambient temperature for 36 h. After separation of the insoluble material by filtration, the filtrate was concentrated to leave the residue, which was subjected to column chromatography on silica gel. Elution with benzene–ethyl acetate (8:2 v/v) furnished the phosphorane **12** (670 mg, 89.5%) as an amorphous solid: IR ($CHCl_3$) 1780, 1765, 1740, 1725, 1340 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 (s, 1.5 H, $CH_3$), 1.39 (s, 1.5 H, $CH_3$), 3.21 (s, 0.5 H, SCHCO), 3.26 (s, 0.5 H, SCHCO), 3.64 (s, 2 H, $OCH_2CH_2O$), 3.90 (s, 2 H, $OCH_2CH_2O$).

To a stirred solution of **12** (100 mg, 0.103 mmol) in methylene chloride (15 mL) was added 60% perchloric acid (2 drops) at 0 °C. After being stirred for 40 min at ambient temperature, the mixture was neutralized with aqueous sodium hydrogen carbonate, and the organic layer separated was dried over sodium sulfate. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with methylene chloride–acetone (98:2 v/v) afforded **13** (76 mg, 79.6%) as an amorphous solid: IR ($CHCl_3$) 1790, 1770, 1735, 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.26 (s, 3 H, $CH_3$), 13.16 (s, 1 H, OH).

To a stirred solution of **13** (160 mg, 0.17 mmol) in methylene chloride (30 mL) was added trifluoroacetic acid (0.5 mL) at −30 °C, and the solution was stirred for 10 min at the same temperature. A stream of ozone was bubbled through the above solution at −78 °C until a persistent blue color was observed (1.5 h). The reaction mixture was flushed with nitrogen and treated with dimethyl sulfide (20 mL) at −78 °C. The resulting mixture was allowed to warm to room temperature over 3 h. After neutralization with saturated sodium hydrogen carbonate, the mixture was extracted with methylene chloride, and the organic extract was washed with water, dried over sodium sulfate, and concentrated to leave **14**: IR ($CHCl_3$) 1785, 1765, 1730, 1350 $cm^{-1}$.

A solution of **14** in dry benzene (40 mL) was warmed at reflux under a current of nitrogen for 1 h. Evaporation of the solvent gave the residue, which was chromatographed on silica gel with methylene chloride–acetone (98:2 v/v) to afford the penem **15** (46 mg, 42.2%) as an amorphous solid: IR ($CHCl_3$) 1820, 1780, 1735, 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.33 (s, 2 H, $CH_2Ar$), 5.40 (s, 2 H, $CH_2Ar$), 6.10 (d, $J$ = 4.2 Hz, 1 H, $C_5H$), 6.16 (d, $J$ = 4.2 Hz, 1 H, $C_6H$); FDMS, $m/z$ 630 ($M^+$); $[\alpha]^{25}_D$ −11.79° (c 0.0184, $CHCl_3$).

**Preparation of Ceph-2-em Derivative 16.** A solution of **13** (190 mg, 0.206 mmol) in dry toluene (50 mL) was heated at reflux under a current of nitrogen for 2 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with benzene–acetone (96:4 v/v) afforded the cephem **16** (29 mg, 21.4%) as an amorphous solid: IR ($CHCl_3$) 1800, 1780, 1735, 1355 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.29 (s, 1.5 H, $CH_3$), 2.41 (s, 1.5 H, $CH_3$), 4.37 (s, 0.5 H, $C_4H$), 5.05 (d, $J$ = 4 Hz, 1 H, $C_6H$), 5.74 (d, $J$ = 4 Hz, 0.5 H, $C_7H$), 5.84 (d, $J$ = 4 Hz, 0.5 H, $C_7H$); FDMS, $m/z$ 658 ($M^+$).

**(±)-4-[((Ethoxycarbonyl)methyl)thio]-3-ethyl-2-azetidinone (18).** To a stirred solution of potassium hydroxide (1.64 g, 25 mmol) and ethyl thioglycolate (3.12 g, 28 mmol) in ethanol–water (2:1 v/v, 50 mL) was added a solution of 4-acetoxy-3-ethyl-2-azetidinone (**17**) (3.4 g, 22 mmol) in ethanol (20 mL) at 0 °C, and the resulting mixture was stirred for 0.5 h. After evaporation of the solvent, the residue was chromatographed on silica gel with benzene–ethyl acetate (4:1 v/v) as eluant to give the azetidinone **18** (4.3 g, 92%) as a syrup: IR ($CHCl_3$) 3420, 1770, 1740 $cm^{-1}$, $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.25 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.68 (g, $J$ = 7 Hz, 2 H, $C_3CH_2CH_3$), 3.16 (dt, $J$ = 2, 7 Hz, 1 H, $C_3H$), 3.19 (s, 2 H, $SCH_2CO$), 4.10 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.35 (d, $J$ = 2 Hz, 1 H, $C_4H$), 6.90 (s, 1 H, NH); exact mass for $M^+$ peak, calcd $m/z$ 217.0594, found $m/z$ 217.0710.

**(±)-1-(*tert*-Butyldimethylsilyl)-4-[((ethoxycarbonyl)methyl)thio]-3-ethyl-2-azetidinone (19).** To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (2.9 mL, 13.8 mmol) and 15% solution of *n*-butyllithium in *n*-hexane (5.4 mL, 13.6 mmol)] in dry tetrahydrofuran (40 mL) was added a solution of **18** (2.28 g, 11 mmol) in dry tetrahydrofuran (15 mL) at −78 °C under a current of nitrogen. After the mixture was stirred for 5 min at −78 °C, a solution of *tert*-butyldimethylchlorosilane (1.74 g, 11.6 mmol) in dry tetrahydrofuran (5 mL) was added, and the resulting mixture was stirred for 0.5 h at −78 °C and then for 1 h at 0 °C. The solution was treated with water and extracted with methylene chloride. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to leave the residue, which was subjected to column chromatography on silica gel. Elution with benzene–ethyl acetate (95:5 v/v) afforded the silylated azetidinone **19** (2.95 g, 84.8%) as a gum: IR ($CHCl_3$) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.24 (s, 3 H, $CH_3$), 0.27 (s, 3 H, $CH_3$), 0.92 (s, 9 H, *t*-Bu), 0.98 (t, $J$ = 7 Hz, 3 H, $CH_3$), 1.13 (t, $J$ = 7 Hz, 3 H, $CH_3$), 1.68 (q, $J$ = 7 Hz, 2 H, $C_3CH_2CH_3$), 3.17 (s, 2 H, $SCH_2CO$), 4.10 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.32 (d, $J$ = 2 Hz, 1 H, $C_4H$); exact mass for $M^+$ − 57 peak, calcd $m/z$ 274.0810, found $m/z$ 274.0920.

**Reaction of 19 with Dibenzyl Oxalate.** To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (2.6 mL, 12 mmol) and 15% solution of *n*-butyllithium in *n*-hexane (4.93 mL, 11.6 mmol)] in dry tetrahydrofuran (50 mL) was added a solution of the above azetidinone **19** (2.55 g, 7.7 mmol) in dry tetrahydrofuran (10 mL) at −78 °C under a current of nitrogen. After the mixture was stirred for 0.1 h at −78 °C, a solution of dibenzyl oxalate (2.29 g, 8.5 mmol) in dry tetrahydrofuran (10 mL) was added, and the resulting mixture was further stirred for 2 h at ambient temperature. The mixture was treated with 10% ammonium chloride solution and extracted with methylene chloride. The organic extract was washed with brine, dried over sodium sulfate, and evaporated to leave the residue, which was chromatographed on silica gel with benzene–ethyl acetate (8:1 v/v) as eluant to give **20** (2.45 g, 64.5%) as a gum: IR ($CHCl_3$) 1750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.25 (s, 3 H, $CH_3$), 0.28 (s, 3 H, $CH_3$), 0.92 (s, 9 H, *t*-Bu), 3.92 (dt, $J$ = 2, 7 Hz, 1 H, $C_3H$), 5.28 (s, 2 H, $CH_2Ph$), 7.32 (s, 5 H, Ar H); mass spectrum, $m/z$ 493 ($M^+$).

**Desilylation of 20.** To a stirred solution of the above azetidinone **20** (400 mg, 0.81 mmol) in tetrahydrofuran (10 mL) was added tetrabutylammonium fluoride (1 mmol solution in tetrahydrofuran, 0.81 mL) at ambient temperature. After the mixture was stirred for 10 min, the solvent was evaporated to leave the residue, which was chromatographed on silica gel with chloroform–methanol (10:1 v/v) as eluant to afford the azetidinone **21**

(220 mg, 72%) as a gum: IR ($CHCl_3$) 3400, 1742, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.10 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.35 (d, $J$ = 2 Hz, 1 H, $C_4$-H), 5.20 (s, 2 H, $CH_2Ph$), 7.40 (s, 5 H, Ar H).

**Mesylate 22.** A solution of the azetidinone **21** (50 mg, 0.13 mmol), triethylamine (0.02 mL, 0.14 mmol), and methanesulfonyl chloride (0.1 mL, 0.13 mmol) in methylene chloride (5 mL) was stirred at ambient temperature for 2 h under a current of nitrogen. After the mixture had been diluted with methylene chloride (50 mL), the organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated to leave the residue, which was subjected to column chromatography on silica gel. Elution with benzene–ethyl acetate (95:5 v/v) provided the mesylate **22** (42 mg, 69.6%) as a gum: IR ($CHCl_3$) 3400, 1773, 1726 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.15 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.72 (q, $J$ = 7 Hz, 2 H, $C_3CH_2CH_3$), 3.20 (s, 3 H, $SO_2CH_3$), 4.00 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.22 (d, $J$ = 2 Hz, 1 H, $C_4H$), 5.10 (s, 2 H, $CH_2Ph$), 7.24 (s, 5 H, Ar H).

**Phosphonate 23.** A solution of the azetidinone **21** (150 mg, 0.4 mmol), diisopropylethylamine (0.075 mL, 0.42 mmol), and diphenylphosphonyl chloride (107 mg, 0.4 mmol) in dry methylene chloride (10 mL) was stirred at 0 °C for 3 h under a current of nitrogen. After the mixture was diluted with methylene chloride (50 mL), the organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated to give the residue, which was chromatographed on silica gel with benzene–ethyl acetate (98:2 v/v) as eluant to afford the phosphonate **23** (168 mg, 69.7%) as a gum: IR ($CHCl_3$) 3410, 1770, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.24 (t, $J$ = 7 Hz, 3 H, $CH_2CH_2$), 4.15 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.45 (d, $J$ = 2 Hz, 1 H, $C_4H$), 5.07 (s, 2 H, $CH_2Ph$), 6.50 (s, 1 H, NH), 7.1–7.5 (m, 15 H, Ar H).

**Reaction of 19 with Acetyl Chloride.** To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (2.5 mL, 11.7 mmol) and 15% solution of *n*-butyllithium in *n*-hexane (4.6 mL, 10.7 mmol)] in dry tetrahydrofuran (30 mL) was added a solution of the azetidinone **19** (1.7 g, 5.1 mmol) in dry tetrahydrofuran (15 mL) at −78 °C under a current of nitrogen. After the mixture was stirred for 0.2 h at −78 °C, acetyl chloride (0.38 mL, 5.1 mmol) was added to the above solution, and the resulting mixture was further stirred for 0.5 h at −78 °C. The mixture was treated with 10% aqueous acetic acid and extracted with methylene chloride. The organic extract was washed with brine and dried over sodium sulfate. Evaporation of the solvent gave the residue, which was chromatographed on silica gel using benzene–ethyl acetate (98:2 v/v) as eluant to furnish **24** (1.2 g, 63.2%) as a gum: IR ($CHCl_3$) 1738 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.32 (s, 3 H, $CH_3$), 0.35 (s, 3 H, $CH_3$), 1.05 (s, 9 H, *t*-Bu), 2.41 (s, 3 H, olefinic $CH_3$), 4.28 (d, $J$ = 2 Hz, 1 H, $C_4H$), 4.30 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$); mass spectrum, $m/z$ 374 ($M^+$ + 1).

**(±)-1-Acetyl-4-[((ethoxycarbonyl)methyl)thio]-3-ethyl-2-azetidinone (25). A.** To a stirred solution of the azetidinone **24** (110 mg, 0.29 mmol) in tetrahydrofuran (10 mL) was added tetrabutylammonium fluoride (1 mmol solution in tetrahydrofuran, 0.29 mL) at ambient temperature. After the mixture was stirred for 0.5 h, the solvent was evaporated to give the residue, which was subjected to column chromatography on silica gel. Elution with benzene–ethyl acetate (95:5 v/v) afforded 25 (76 mg, 99.3%) as a gum: IR ($CHCl_3$) 1795, 1730, 1708 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.26 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$), 1.72 (q, $J$ = 7 Hz, 2 H, $C_3CH_2CH_3$), 2.33 (s, 3 H, $COCH_3$), 2.96 (dt, $J$ = 2, 7 Hz, 1 H, $C_3H$), 3.26 (d, $J$ = 15 Hz, 1 H, $SCHHCO$), 3.91 (d, $J$ = 15 Hz, 1 H, $SCHHCO$), 4.04 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.89 (d, $J$ = 2 Hz, 1 H, $C_4H$); mass spectrum, $m/z$ 259 ($M^+$).

**B.** A mixture of the azetidinone **18** (50 mg, 0.23 mmol), 4-(dimethylamino)pyridine (31 mg, 0.25 mmol), acetic anhydride (25 mg, 0.24 mmol), and methylene chloride (5 mL) was stirred at room temperature of 0.5 h. After evaporation of the solvent, the residue was chromatographed on silica gel with benzene–ethyl acetate (95:5 v/v) as eluant to yield the N-acetylated azetidinone **25**, which was identical with the authentic specimen obtained above in all respects.

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# Practical Synthesis of (*R*)- or (*S*)-2,2′-Bis(diarylphosphino)-1,1′-binaphthyls (BINAPs)

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Practical methods for the synthesis of (*R*)- or (*S*)-2,2′-bis(diarylphosphino)-1,1′-binaphthyls (BINAPs), useful ligands for transition-metal-catalyzed asymmetric reactions, have been developed. (±)-2,2′-Bis(diphenylphosphinyl)-1,1′-binaphthyl [(±)-BINAPO], prepared from 2,2′-dibromo-1,1′-binaphthyl and diphenylphosphinyl chloride, can be resolved into optical antipodes by the use of camphorsulfonic acid or 2,3-di-*O*-benzoyltartaric acid. Reduction of resolved BINAPO with trichlorosilane in the presence of triethylamine affords optically pure 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). In a similar manner, several BINAP analogues have been prepared in optically pure form. The present procedures are suitable for obtaining these axially dissymmetric diphosphines in a large scale. The molecular structure of the 1:1:1 complex of (*S*)-(−)-BINAPO, (1*R*)-(−)-camphorsulfonic acid, and acetic acid has been studied by single-crystal X-ray analysis.

Recently numerous chiral di-*tert*-phosphines have been devised as ligands for transition-metal-catalyzed asymmetric syntheses in the homogeneous phase.[1] Some years ago, we reported (*R*)- or (*S*)-2,2′-bis(diphenyl-

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