Concentration of the hexane extracts gave 2.9 g (79%) of slightly yellow 4-fluorotriphenylmethane (**7a**). One recrystallization from methanol gave colorless crystals, mp 62–63 °C (lit.[9] mp 40–42 °C). Because the melting point difference was great, the sample was analyzed and its NMR spectrum recorded: NMR δ 5.50 (s, 1 H, CH), 6.7–7.3 (m, 14 H, aromatic H).[10]

Anal. Calcd for $C_{19}H_{15}F$: C, 87.00; H, 5.76; F, 7.24. Found: C, 86.83; H, 5.86; F, 7.13.

Similar results were obtained when the formic acid contained 0.1 M sodium formate.

Acknowledgment. The author is indebted to Mr. David Clare for the ^1H NMR measurements and to Mr. Marc Agnew for the ^{13}C NMR measurement and interpretation of **7a** and **7b**. Thanks are also due Mrs. Kathleen Huppert for assistance in preparation of this manuscript.

Registry No.—**1b**, 54595-78-7; **1c**, 60582-06-1; **1d**, 60582-07-2; **2b**, 59142-51-7; **2c**, 59143-29-2; **2d**, 60081-30-3; **2e**, 59143-25-8; **2f**, 59142-50-6; **2g**, 60582-08-3; **3**, 60582-09-4; **4**, 60081-31-4; **6**, 427-39-4; **7a**, 437-23-0; **7b**, 791-92-4; **8**, 54595-73-2; phenyl bromide, 108-86-1; 4-fluorophenyl bromide, 460-00-4.

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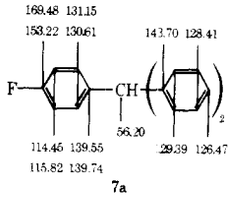
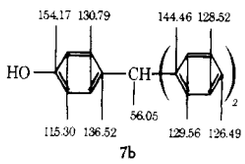
(10) The structures of **7a** and **7b** were confirmed by ^{13}C NMR. The carbon shifts are delineated below.



7a



7b

Enolate Amination with *O*-Mesitylenesulfonylhydroxylamine[1]

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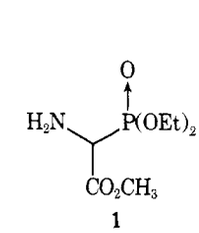
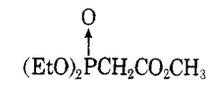
We wish to report the use of enolate amination to achieve a short, simple preparation of a key intermediate for cephalosporin synthesis, methyl α-aminodiethylphosphonoacetate (**1**).[3] Reaction of methyl diethylphosphonoacetate with sodium hydride, followed by the addition of *O*-mesitylenesulfonylhydroxylamine,[4] afforded **1** in 39–47% yield. The major impurity was the neutral **2**, which was conveniently removed by extraction of **1** into aqueous *p*-toluenesulfonic acid. By way of contrast, the previous synthesis of **1** goes in 18–21% yield, and it involves five steps and a chromatography.[3] This method of enolate amination is similar to an approach which has been described by Yamada for the synthesis of α-amino acids.[5]

We have extended the utility of the intermediate **1** to the preparation of a cephem with a methylthio substituent in the 6 position. Condensation of **1** with carbon disulfide in aqueous K_2HPO_4, followed by the addition of methyl iodide, gave the dithiocarbamate **4** in 25% yield. By analogy to the Merck report,[6] the reaction of **4** with chloroacetone in acetone containing K_2CO_3 gave the expected thiazine **5** in 81% yield. When a mixture of **5** and diphenylketene was heated under N_2 at 110 °C for a total of 4 h, there was obtained after preparative TLC workup the β-lactam **6**.



1



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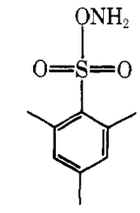

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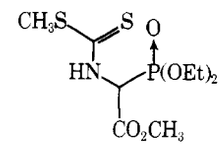

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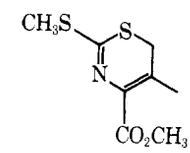

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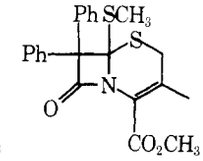

6

We were unsuccessful in our attempts to add azidoketene to the thiazine **5** under conditions which we had used for other imines.[7] The unreactivity of **5** toward azidoketene is consistent with the results from our model studies, and it probably stems in large part from the conjugation of the dithioimine unit with a double bond.

Experimental Section

IR spectra are in $CHCl_3$ and NMR spectra are in $CDCl_3$.

Methyl α-Aminodiethylphosphonoacetate (1). To a suspension of 210 mg of sodium hydride (57% mineral oil dispersion) in 15 ml of dimethoxyethane (DME) was added dropwise 1.07 g (5 mmol) of methyl diethylphosphonoacetate (**2**). After cessation of gas evolution there was added dropwise over a 15-min period a solution of ca. 1.05 g (4.9 mmol) of *O*-mesitylenesulfonylhydroxylamine (**3**)[4,8] (see *Caution*) in 5 ml of DME (temperature held below 30 °C). After stirring for 30 min the mixture was filtered and the filtrate was evaporated in vacuo to give a crude product whose main contaminant was **2**. The crude product was dissolved in $CHCl_3$ and was extracted twice with aqueous *p*-toluenesulfonic acid. The aqueous phase was extracted with $CHCl_3$, basified with K_2HPO_4, and thoroughly extracted with $CHCl_3$. After drying over Na_2SO_4 and removal of solvent there was obtained 530 mg (47%) of TLC pure **1**, whose IR and NMR spectra were in accord with the published values.[3]

Caution: We experienced a mild explosion in attempting to dry 4.5 g of **3** *at room temperature under vacuum.*[8] *Subsequent to this explosion we dispensed with the vacuum drying step of ref 8 and in its place we substituted a routine in which the wet* **3** *obtained according to ref 8 was dissolved in DME and the solution was dried over 4A molecular sieves for ca. 1 h.*

Methyl α-(*S*-Methyldithiocarbonyl)aminodiethylphosphonoacetate (4). A mixture of 225 mg (1 mmol) of **1** 100 mg of carbon disulfide (excess), 87 mg (1 mmol) of dipotassium hydrogen phosphate, and 7 ml of water was stirred at room temperature for 6 h. Methyl iodide (142 mg, 1 mmol) was added and the mixture was stirred for an additional 2 h. The mixture was extracted with an equal volume of diethyl ether. The aqueous layer was treated with 100 mg of carbon disulfide and 40 mg of K_2HPO_4, stirred for 5 h, treated with 142 mg of methyl iodide, stirred for 2 h, and extracted with an equal volume of diethyl ether. The combined ether extract was dried (Na_2SO_4) and concentrated to a gum. A crystalline product, mp 91–92 °C, was obtained from diethyl ether–hexane (80 mg, 25%): IR 1746 cm^{-1}; NMR δ 1.34 (t, J = 7 Hz, CH_2CH_3), 2.64 (s, SCH_3), 3.82 (s, OCH_3), 4.22 (m, $POCH_2CH_3$), 6 (d of d, J_{HP} = 21.5, $J_{NH} \sim$ 7.5 Hz, NHCHP), 7.95 (broad, NH); *m/e* (70 eV) 315 (M^+). Anal. Calcd for $C_9H_{18}NPO_5S_2$: C, 34.28; H, 5.75; N, 4.44. Found: C, 34.41; H, 5.85; N, 4.35.

Synthesis of Methyl 5-Methyl-2-methylthio-6*H*-1,3-thiazine-4-carboxylate (5) and Its Conversion to Methyl 3-Methyl-6-methylthio-7,7-diphenylceph-3-em-4-carboxylate (6). Di-

thiocarbamate 4 (260 mg, 0.825 mmol), chloroacetone (85 mg, 0.92 mmol), potassium carbonate (185 mg, 1.34 mmol), and 25 ml of acetone were stirred at room temperature for 18 h. The solids were filtered and the filtrate was evaporated in vacuo. Chromatography of the residue from ca. 30 g of silica gel gave 145 mg (81%) of TLC pure thiazine **5** as an oil: IR 1720 cm^{-1}; NMR δ 2.24 (s, $CH_3C=$), 2.53 (s, SCH_3), 3.26 (s, SCH_2), 3.8 (s, OCH_3); *m/e* (70 eV) 217 (M^+). Thiazine **5** (120 mg, 0.55 mmol) and diphenylketene (50 mg, 0.26 mmol) in 5 ml of benzene were evaporated to a thin film in vacuo. This mixture was heated under N_2 in an oil bath at 110 °C for 2 h. TLC showed the presence of a new component. A further quantity of diphenylketene (50 mg in 5 ml of benzene) was added and the mixture was evaporated to a thin film in vacuo. This mixture was heated at 110 °C under N_2 for 2 h. The product was isolated by preparative TLC using benzene. A quantity of 27 mg of the thiazine **5** was recovered. Cephem **6** was a colorless solid: mp 168.5–170 °C dec (25 mg, 14% yield based on consumed thiazine); IR 1772, 1728 cm^{-1}; NMR δ 1.31 (s, SCH_3), 2.08 (s, $CH_3C=$), 3.09 (d, J_{gem} = 18 Hz, SCH_AH_B), 3.78 (d, J_{gem} = 18 Hz, SCH_AH_B), 3.87 (s, OCH_3), 7.2–7.85 (m, C_6H_5); *m/e* (70 eV) 411 (M^+), 365 ($M - SCH_3$). Anal. Calcd for $C_{22}H_{21}NO_3S_2$: C, 64.21; H, 5.14; N, 3.4. Found: C, 63.9; H, 5.09; N, 3.31.

Registry No.—**1**, 50917-77-6; **2**, 1067-74-9; **3**, 36016-40-7; **4**, 60762-07-4; **5**, 60762-08-5; **6**, 60762-09-6.

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Asymmetric Induction. Enantioselective Alkylation of Cyclohexanone

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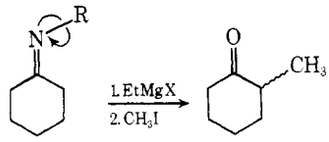
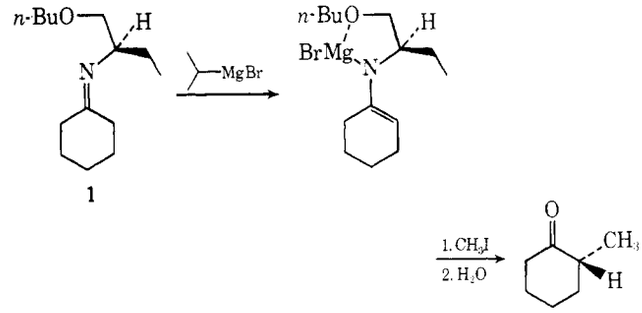
The field of asymmetric induction is one with a plethora of reported efforts but a dearth of actual techniques which lead to a high degree of enantioselectivity in a predictable manner.[1,2] We wish to report a sequence that accomplishes overall the α-alkylation of a ketone, providing a product with a high level of optical purity wherein the absolute configuration can be predicted with some degree of confidence.

The imine anion alkylation sequence of Stork[3] is one of the best techniques for achieving α-alkylation of ketones. The utilization of a chiral amine in forming the imine affords the opportunity for induction of asymmetry in the product, and though this approach has been examined with the cyclohexanone imine derived from isobornylamine, free rotation about the bond indicated would be expected to limit both the



level of and the predictability of the asymmetric induction.[4] We have directly addressed this problem by incorporating into the amine moiety a suitably situated ether oxygen so that *intra*molecular solvation of the metal ion will inhibit rotation. In particular, the *O*-*n*-butyl derivative of (*R*)-2-amino-1-butanol[5] was condensed with cyclohexanone to form the imine **1**. Conversion to the anion with isopropylmagnesium bromide in tetrahydrofuran and then alkylation at −78 °C with methyl



iodide led to (*R*)-2-methylcyclohexanone[6] with an optical purity of 81%. By effecting alkylation at −100 °C, the observed optical purity was increased to 85% while alkylation at reflux afforded the same sense of induction but with an optical purity of only 20%.

Experimental Section

(*R*)-2-Amino-1-butanol. This amine, as supplied by Aldrich Chemical Co. with $\alpha^{28}D$ −6.47° (neat, *l* = 1), was further resolved according to the known procedure.[5] One crystallization as the (+)-tartaric acid salt provided recovered amine with $\alpha^{20}D$ −9.38° (neat, *l* = 1) (lit.[5] max $\alpha^{20}D$ 10.1°, optical purity of 93%).

(*R*)-2-Aminobutyl *n*-Butyl Ether. A solution of 21 g (0.50 mol) of 57% sodium hydride in mineral oil in 200 ml of dimethyl sulfoxide was heated at 80 °C with mechanical stirring under an inert atmosphere for 1 h. To this warm solution was added 42.5 g (0.48 mol) of (*R*)-2-amino-1-butanol as purified above, the heating bath was removed, and the solution was cooled to room temperature, with stirring. After 1 h, the solution was cooled in an ice–water bath and 55 ml (0.51 mol) of *n*-butyl bromide was added over 20 min with vigorous stirring. The reaction mixture was stirred with cooling for an additional 1 h and then the semisolid mixture was washed out into a total volume of 1 l. of water. This solution was extracted with four 200-ml portions of ether, the combined organic layers were extracted with 400 ml of 2.0 N aqueous hydrochloric acid, and the aqueous layer was adjusted to pH 10 with solid potassium hydroxide and then extracted with two 200-ml portions of ether. These organic layers were combined, washed with saturated brine, dried with molecular sieves, concentrated, and then distilled in vacuo, affording 20.6 g (31%) of product, bp 102–106 °C (55 mmHg), $\alpha^{28}D$ −8.37° (neat, *l* = 1).

(*R*)-2-Methylcyclohexanone. The imine **1** was prepared by refluxing a solution of 20 mmol each of cyclohexanone and the amine above in benzene under an inert atmosphere for 12 h with azeotropic removal of water. The benzene was removed in vacuo and a solution of **1** in 5 ml of dry tetrahydrofuran was added under an inert atmosphere to a refluxing solution of 22 mmol of isopropylmagnesium bromide in 15 ml of the same solvent. After 2 h at reflux, the solution was cooled with a dry ice–acetone bath, and 27 mmol of methyl iodide was added dropwise over 15 min with vigorous stirring. The color changed from light yellow to off-white soon after the addition was complete. The reaction was held at −78 °C for a further 15 min, then warmed slowly to 0 °C at which point 11 ml of 2.0 N aqueous hydrochloric acid was added with vigorous stirring. After 15 min the mixture was diluted with 25 ml of pentane, and the organic layer was washed with dilute aqueous oxalic acid, 1 N sodium bicarbonate solution, then with two 20-ml portions of saturated brine. The organic layer was dried with molecular sieves, the solvents removed by distillation, and the residue distilled in vacuo, providing 1.17 g of material with $\alpha^{20}D$ −12.19° (neat, *l* = 1), consisting of 2-methylcycloxanone containing 3% of cyclohexanone (VPC, SE-30 column). After correction for both the presence of recovered cyclohexanone and the optical purity of the amine (93%), and using a maximum rotation[4,6] for 2-methylcyclohexanone of 16.75°, the optical purity was calculated as 81%.

Acknowledgment is gratefully made to the Research Corporation for financial support of this research.

Registry No.—**1**, 60662-02-4; (*R*)-2-amino-1-butanol, 5856-63-3; (*R*)-2-aminobutyl butyl ether, 60662-03-5; butyl bromide, 109-65-9; (*R*)-2-methylcyclohexanone, 22554-29-6; methyl iodide, 74-88-4; cyclohexanone, 108-94-1.