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Reactions of Iminophosphoranes of α-Amino Acid Derivatives with Dimethyl Acetylenedicarboxylate. An Application to a Synthesis of 7α-Methoxycephalosporins

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Thermolysis of phosphorus ylides (III and XIV), obtained by the reactions of the iminophosphoranes (II and XIII) with dimethyl acetylenedicarboxylate, afforded the imino derivatives (IV and XV) with elimination of triphenylphosphine. These imino compounds, IV and XV were methoxylated with lithium methoxide to yield the α-methoxy-amino-acid (X) and 7α-methoxy-cephalosporin (XVI), respectively.

Keywords——amino acid; cephalosporin; dimethyl acetylenedicarboxylate; iminophosphorane; α-methoxy-amino-acid; 7α-methoxy-cephalosporin; methoxylation; phosphorus ylide; pyrrole derivative; triphenylphosphine dibromide

In the preceding paper[2] new methods for the 7α-methoxylation of cephalosporins were disclosed in view of recent finding of natural 7α-methoxycephalosporins.[3] Now we wish to report another new method for methoxylation using phosphorus ylide. Our methodology comprises an intramolecular abstraction of an active hydrogen with a carbanion of C–P ylide with elimination of triphenylphosphine to afford an imino compound (IV) (Chart 1 and Chart 2), which is a key intermediate for methoxylation.

At first ethyl phenylglycinate (I) was chosen as a model compound. The iminophosphorane (II) was prepared by treating the primary amine (I) with triphenylphosphine dibromide in the presence of triethylamine at reflux temperature in carbontetrachloride in almost quantitative yield according to a similar procedure of known method.[4] Brown, *et al.* reported the reaction of an iminophosphorane bearing no active hydrogen at the carbon adjacent to the nitrogen atom with dimethyl acetylenedicarboxylate to give carbon-phosphorus ylide *via*

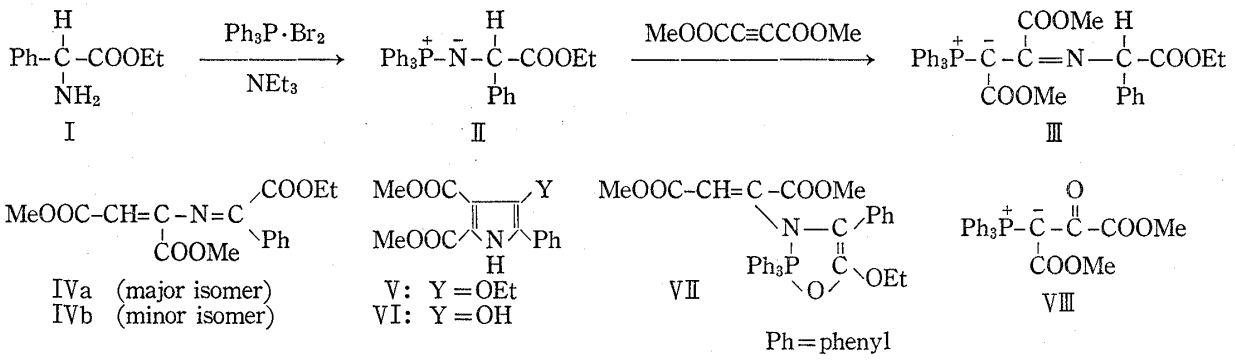


Chart 1

1) Location: *2–58, Hiromachi 1-chome, Shinagawa-ku, Tokyo, 140, Japan.*
2) *a*) T. Saito and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **25**, 784 (1977), see references cited therein for methods of preparation of 7α-methoxycephalosporins; *b*) Y. Sugimura, K. Iino, Y. Iwano, T. Saito, and T. Hiraoka, *Tetrahedron Letters*, **1976**, 1307; *c*) T. Saito, Y. Sugimura, Y. Iwano, K. Iino, and T. Hiraoka, *Chem. Commun.*, **1976**, 516.
3) See references cited in 2*b*); quite recently another 7α-methoxycephalosporin having an additional hydroxyl group to Cephamycin B has been isolated: H. Fukase and H. Iwasaki, *Bull. Chem. Soc. Japan*, **49**, 767 (1976).
4) L. Horner and H. Oediger, *Ann.*, **627**, 142 (1959).

a four membered ring intermediate.[5] This reaction was applied to the iminophosphorane (II), which was reacted with dimethyl acetylenedicarboxylate in methylene chloride at room temperature for 5 hr to furnish ethyl α-[N-(2′-triphenylphosphoranyl-1′,2′-dimethoxycarbonyl-ethyliden)]amino-phenylacetate (III) in 44% yield together with several byproducts, IVa (5%), V (8%), VI (8%), VII (1%), and VIII (2%). Isolation of the desired imino compound (IVa) encouraged us to examine the reaction conditions for obtaining IVa in higher yield. Thus, thermolysis in toluene or xylene was found to be most effective for conversion of III into IVa. This reaction gave two geometrical isomers (IVa and IVb) whose assignment was made on the basis of the next methoxylation reaction described later. Thus, the major isomer (IVa) should be *cis* with respect to two ester groups, and the minor one (IVb) should be *trans*. This assignment was supported by a literature[6] which showed a lower field peak of the olefinic hydrogen of dimethyl aziridino-fumarate in nuclear magnetic resonance (NMR) as compared with that of dimethyl aziridino-maleate. A possible mechanism leading to IV from III is shown in Chart 2. Abstraction of the active hydrogen located at the α-position to the carboethoxy group by the carbanion of the C–P ylide (III) would give the imino compound (IV) (path a), whereas attack of the carbanion on the ester carbonyl would afford the pyrrole derivative (V) (path b).

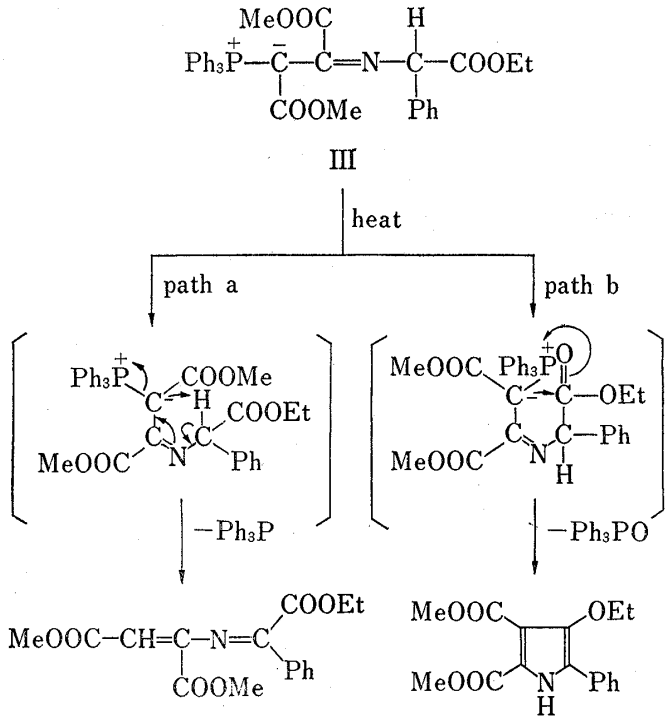


Chart 2

The major isomer (IVa) was easily methoxylated with lithium methoxide in tetrahydrofuran at −78° to yield methoxy phenyl acetate derivative (IX), which was gradually converted to the isomer (X) (higher *Rf* value in thin-layer chromatography (TLC) as compared

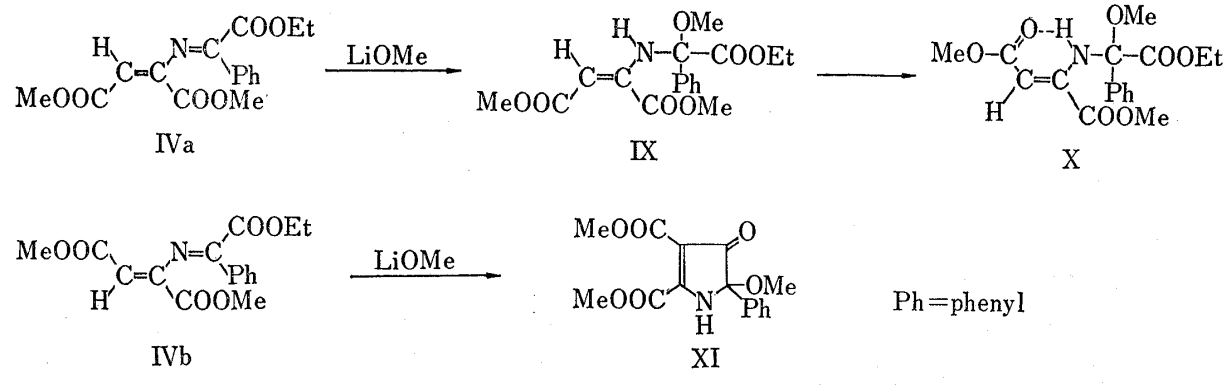
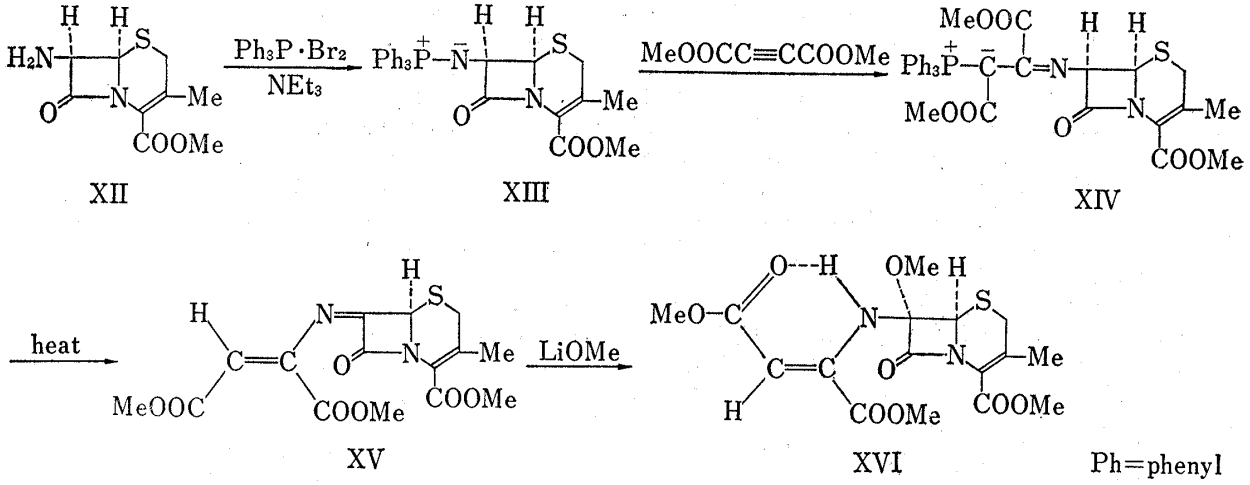


Chart 3

5) G.W. Brown, R.C. Cookson, and I.D.R. Stevens, *Tetrahedron Letters*, **1964**, 1263.
6) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

to IX) with hydrogen bonding on standing in chloroform solution or during purification by TLC. The assignment of *cis-trans* configuration in IX and X was confirmed by NMR spectra, in which NH peak of *cis* isomer (IX) appeared in higher field as compared with that of *trans* isomer (X) having a hydrogen bonding with the ester carbonyl. On the other hand the minor isomer (IVb) could not be methoxylated under the same conditions, but methoxylation was achieved under more forced reaction conditions such as treatment of IVb with lithium methoxide in methanol at room temperature to yield the cyclized product (XI). In consideration of these observations we tentatively assigned the major isomer (IVa) for *cis* configuration (*E*-isomer) and the minor one (IVb) for *trans* isomer (*Z*-isomer)as shown in Chart 3. The reason why the imine (IVa) was more easily methoxylated than IVb is not clear at the present time. Methoxylation of IVa at room temperature under the same reaction conditions as in the case of IVb was not carried out, however, under those conditions IVa will give the cyclized product (XI).

Then these model reactions were applied to methyl 7-amino-3-methyl-3-cephem-4-carboxylate (XII). Heating the amine (XII) with triphenylphosphine dibromide in the presence of triethylamine in carbontetrachloride produced the ylide (XIII) in good yield. Purification of XIII by silica gel preparative TLC could be possible with slight decomposition, however, next reaction proceeded well without purification. The reaction of the ylide (XIII) with dimethyl acetylenedicarboxylate was carried out in methylene chloride at room temperature for 20 hr to afford the phosphorus ylide (XIV) in good yield. Refluxing of XIV in xylene for 1 hr produced 7-imino-cephalosporin (XV) with elimination of triphenylphosphine in 30% yield. Methoxylation of XV took place easily at −78° with lithium methoxide



XII XIII XIV XV XVI

Chart 4

as in the case of IVa. Only one isomer of XVI was obtained by this methoxylation reaction. Configuration of two carbomethoxy groups in the 7β-side chain would be trans since NMR spectrum of NH hydrogen showed a peak at lower field (δ 8.81) due to a hydrogen bonding with the carbonyl of ester group located in the *cis* position. Acylation of XVI with phenylacetyl chloride gave a poor result and only less than one percent of the phenylacetamido-cephalosporin derivative was obtained. In the case of 7α-H-7β-enamino-cephalosporins, acylation with an acyl chloride gives the desired acylamino-cephalosporins in moderate yield.[7] This difference between 7α-methoxy and 7α-H derivatives in acylation reaction would arise from a steric hindrance and lower basicity of 7β-amino group having methoxy function at the 7α-position.[8]

7) Japanese patent application, 48–19864, laid open to public, October 14, 1974, No. 49–108091.
8) This difference will be discussed in more detail in forthcoming paper in near future.

Thus these reactions have a limited utility in the synthesis of 7α-methoxycephalosporin derivatives, however, they present a new method for oxidation of α-amino acid derivatives at the α-position, although the yields were not optmized.

Experimental

All melting points are not corrected. Infrared (IR) spectra were recorded on a JASCO A-2 spectrometer, ultraviolet (UV) spectra on a Cary 14 CM-50 (Serial 1258) and mass (MS) spectra on a JEOL JMS-01SG mass spectrometer. NMR spectra were taken on a Hitachi-Perkin Elmer R-24 and Varian T-60 spectrometer using tetramethylsilane as an internal standard. The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and b (broad). TLC was performed on TLC plates, Silica Gel F_{254} precoated, layer thickness 0.25 mm (E. Merck) and spots were visualized by UV-irradiation. Plates used for preparative TLC were Silica Gel $60F_{254}$ (E. Merck). Evaporation was carried out under reduced pressure with rotatory evaporator at room temperature.

Ethyl α-(N-Triphenylphosphoranyl)amino-phenylacetate (II)——To a solution of triphenyl phosphine (6.55 g, 25 mmol) in CCl_4 (70 ml) was added dropwise a solution of bromine (40 g, 25 mmol) in CCl_4 (10 ml) under stirring at −10°. To the resulting yellow mixture was added successively NEt_3 (5.06 g, 50 mmol) and a solution of ethyl phenylglicinate (4.48 g, 25 mmol) in CCl_4 (10 ml). After stirring at −10° for 30 min, the reaction mixture was refluxed for 30 min with vigorous stirring. The cooled reaction mixture was filtered to remove precipitates of triethylamine hydrochloride. The filtrate was evaporated *in vacuo* to give ethyl α-(N-triphenylphosphoranyl)amino-phenylacetate (II) as a red colored oil (1.10 g, quantitative yield). MS *m/e*: 439 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 1740, 1715, 1600. NMR ($CDCl_3$) δ ppm: 1.00 (3H, t, J=7 Hz), 3.85 (2H, q, J=7 Hz), 4.86 (1H, d, J=21 Hz), 7.8—8.0 (20H, m).

Ethyl α-[N-(2′-Triphenylphosphoranyl-1′,2′-dimethoxycarbonylethyliden)]amino-phenylacetate (III)——To a solution of the iminophosphorane (II) (1.318 g, 3.0 mmol) obtained above in absolute $CHCl_3$ (10 ml) was added dimethyl acetylenedicarboxylate (850 mg, 5.98 mmol) and the resulting solution was stirred for 5 hr at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was purified by preparative TLC to yield III (768 mg, 44% yield) as pale yellow foam: *Anal.* Calcd. for $C_{34}H_{32}NO_6P$: C, 70.22; H, 5.55; N, 2.41; P, 5.33. Found: C, 70.43; H, 5.24; N, 2.48; P, 5.36. MS *m/e*: 581 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1650, 1560. NMR ($CDCl_3$) δ ppm: 1.04 (3H, t, J=7 Hz), 3.17 (3H, s), 3.84 (2H, q, J=7 Hz), 3.85 (3H, s), 4.72 (1H, s), 6.5—8.0 (20H, m). The following by-products were also separated by this TLC: IVa (48 mg, 5% yield), V (73 mg, 8% yield), VI (66 mg, 8% yield), VII (17 mg, 1% yield) and VIII (25 mg, 2% yield). Physical data of by-products are as follows.

2,3-Dimethoxycarbonyl-4-ethoxy-5-phenyl-pyrrole (V): White powder (from *n*-hexane). mp 103—104°. *Anal.* Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 62.81; H, 5.54; N, 4.53. MS *m/e*: 303 (M^+). UV λ_{max}^{EtOH} nm (ε): 251 (11390), 313 (18310). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1740, 1725, 1695, 1610, 1590, 1575. NMR ($CDCl_3$) δ ppm: 1.27 (3H, t, J=7 Hz), 3.87 (3H, s), 3.92 (3H, s), 3.96 (2H, q, J=7 Hz), 7.2—7.9 (5H, m), 9.25 (1H, b).

2,3-Dimethoxycarbonyl-4-hydroxy-5-phenyl-pyrrole (VI): White needles (from *n*-hexane). mp 145—146°. *Anal.* Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.66; H, 4.71; N, 5.13. MS *m/e*: 275 (M^+). UV λ_{max}^{EtOH} nm (ε): 219 (17060), 261 (17300), 347 (13790). IR ν_{max}^{Nujol} cm^{-1}: 3310, 3270, 2460, 1675, 1655, 1605, 1590, 1575. NMR ($CDCl_3$) δ ppm: 3.77 (3H, s), 3.84 (3H, s), 7.0—7.85 (5H, m), 8.88 (1H, s), 9.63 (1H, b).

N-(1′,2′-Dimethoxycarbonylvinyl)-4-ethoxy-5-phenyl-P-(triphenyl)-3-oxa-2-phosphora-pyrrole (VII): Pale yellow oil. MS *m/e*: 581 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 1730, 1645, 1600, 1595, 1575. NMR ($CDCl_3$) δ ppm: 1.08 (3H, t, J=7 Hz), 3.65 (6H, s), 3.87 (2H, dq, J=2.5 and 7 Hz), 5.96 (1H, s), 6.8—7.8 (20H, m).

Dimethyl 1-Triphenylphosphoranyl-2-oxo-succinate (VIII): White crystal (from *n*-hexane). mp 166—167°. *Anal.* Calcd. for $C_{24}H_{21}O_5P$: C, 68.57; H, 5.04; P, 7.37. Found: C, 68.74; H, 4.97; P, 7.22. MS *m/e*: 420 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1675, 1570. NMR ($CDCl_3$) δ ppm: 3.28 (3H, s), 3.83 (3H, s), 7.2—8.0 (15H, m).

Ethyl α-[N-(1′,2′-Dimethoxycarbonylvinyl)]imino-phenylacetate (IVa: Major Isomer; IVb: Minor Isomer)——A) Reflux in Toluene: A solution of III (582 mg, 1.0 mmol) in toluene (10 ml) was refluxed for 7 hr. After cooling to room temperature, toluene was evaporated *in vacuo*. The residue was purified by silica gel preparative chromatography to afford IVa (64 mg, 20%; lower R_f-value) and IVb (23 mg, 7%; higher R_f-value), together with V (31 mg, 10%), VIII (12 mg, 3%) and unidentified compound ($C_{32}H_{30}O_5NP$, 81 mg, (15%). Physical data of these products are shown below.

Ethyl α-[N-(1′,2′-*cis*-Dimethoxycarbonylvinyl)]iminophenylacetate (IVa): Pale yellow oil. *Anal.* Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.78; H, 5.38; N, 4.39. MS *m/e*: 319 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 1735, 1635, 1600, 1585. NMR ($CDCl_3$) δ ppm: 1.33 (3H, t, J=7 Hz), 3.68 (3H, s), 3.83 (3H, s), 4.38 (2H, q, J=7 Hz), 5.37 (1H, s), 7.2—8.0 (5H, m).

Ethyl α-[N-(1′,2′-*trans*-Dimethoxycarbonylvinyl)]imino-phenylacetate (IVb): Pale yellow oil. MS *m/e*: 319 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 1735, 1650, 1620, 1600, 1585. NMR ($CDCl_3$) δ ppm: 1.28 (3H, t, J=7 Hz), 3.64 (3H, s), 3.80 (3H, s), 4.31 (2H, q, J=7 Hz), 6.12 (1H, s), 7.2—8.2 (5H, m).

Unidentified Compound: Colorless foam. *Anal.* Calcd. for $C_{32}H_{30}NO_5P$: C, 71.23; H, 5.60; N, 2.60; P, 5.74. Found: C, 71.37; H, 5.14; N, 2.46; P, 5.70. MS *m/e*: 539 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1740, 1630, 1585. NMR ($CDCl_3$) δ ppm: 1.16 (3H, t, J=7 Hz), 2.13 (3H, s), 4.12 (2H, q, J=7 Hz), 5.53 (1H, d, J=8 Hz), 7.2—8.0 (20H, m), 9.63 (1H, b). This compound was tentatively assigned as ethyl α-[N-(2′-triphenylphosphoranyl-2′-methoxycarbonyl)acetyl]amino-phenylacetate.

B) Reflux in Xylene: A solution of III (500 mg, 0.86 mmol) in dry xylene (40 ml) was refluxed for 2.5 hr. Then the solvent was removed *in vacuo*. The residue was purified by TLC to give a mixture of IVa and IVb (53 mg) (5: 1 by NMR), V (115 mg, 44%), and VIII (24 mg, 7%). Unreacted starting material (III) was also recovered (92 mg, 18%).

Ethyl α-Methoxy-α-[N-(1′,2′-*trans*-dimethoxycarbonylvinyl)]-amino-phenylacetate (X)——To a stirred solution of IVa (64 mg, 0.20 mmol) in tetrahydrofran (THF) (10 ml) was added dropwise a solution of lithium (7 mg) in methanol (5 ml) at −78°. The reaction mixture was stirred at the same temperature for 30 min, during which time complete disappearance of the starting material (IVa) was observed by TLC. Then 0.1 ml of acetic acid was added to the solution to cease the reaction. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water and dried over $MgSO_4$. The solvents were removed under reduced pressure to give a residue, which was purified by preparative TLC (silica gel, benzene–AcOEt=9: 1) to afford X (33 mg, 46%; Rf=0.68) as a pale yellow oil: *Anal.* Calcd. for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.16; H, 5.80; N, 4.01. MS *m/e*: 278 (M^+−COOEt). UV λ_{max}^{EtOH} nm (ε): 282 (13360). IR ν_{max}^{Liquid} cm^{-1}: 3270, 1740, 1675, 1605. NMR ($CDCl_3$) δ ppm: 1.09 (3H, t, J=7 Hz), 3.19 (3H, s), 3.31 (3H, s), 3.63 (3H, s), 4.07 (2H, q, J=7 Hz), 4.99 (1H, s), 7.1—8.0 (5H, m), 9.73 (1H, b). From lower band (Rf=0.39) a mixture of IX and X was obtained (15 mg, 21%, a pale yellow oil, ratio of IX: X=2: 1 by NMR). NMR spectrum of *cis*-dimethoxycarbonyl isomer (IX): ($CDCl_3$) δ ppm: 1.09 (3H, t, J=7 Hz), 3.22 (3H, s), 3.40 (3H, s), 3.78 (3H, s), 4.07 (2H, q, J=7 Hz), 4.73 (1H, s), 6.06 (1H, b), 7.1—7.8 (5H, m). After standing at room temperature for 30 min in NMR tube, the ratio of IX to X changed from 2: 1 to 1: 3.

2,3-Dimethoxycarbonyl-4-oxo-5-methoxy-5-phenyl-pyrroline (XI)——A methanolic solution of LiOMe prepared from metallic lithium (21 mg) and MeOH (10 ml) was added to IVb (19.1 mg, 0.0598 mmol). The reaction mixture was stirred for 30 min at room temperature and quenched with acetic acid (0.3 ml). The solution was poured into water and extracted with AcOEt. The extract was washed with water thoroughly to remove acetic acid and methanol. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford crude XI (16 mg, 87%) as a pale yellow oil: MS *m/e*: 305 (M^+). UV λ_{max}^{EtOH} nm (ε): 238 (11800), 319 (5000). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3430, 3230, 1740, 1700. NMR ($CDCl_3$) δ ppm: 3.31 (3H, s), 3.63 (3 H, s), 3.92 (3H, s), 7.1—7.7 (5H, m).

Methyl 3-Methyl-7β-(N-triphenylphosphoranyl)amino-3-cephem-4-carboxylate (XIII)——To a solution of triphenylphosphine (2.62 g, 10 mmol) in CCl_4 (30 ml) was added a solution of bromine (1.6 g, 10 mmol) in CCl_4 (10 ml) at −10—0° in an atmosphere of nitrogen. After 30 min stirring NEt_3 (2.1 g, 20 mmol) was added, followed by the addition of methyl 7β-amino-3-methyl-3-cephem-4-carboxylate (XII) (2.28 g, 10 mmol) at −10°. The reaction mixture was stirred at that temperature for 30 min and then the temperature was allowed to rise gradually to reflux. After refluxing for 30 min, NEt_3·HCl was filtered off and washed with a small amount of CCl_4. The filtrate was evaporated under diminished pressure to afford XIII (5.5 g) as a foam. This compound was dissolved in dry THF, insoluble substance was removed by filtration and the filtrate was again evaporated to give practically pure XIII (5 g) as a foam, which could be used in the next reaction without further purification. MS *m/e*: 488 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1770, 1725, 1640, 1595. NMR ($CDCl_3$) δ ppm: 2.30 (3H, s), 3.10 and 3.40 (2H, AB-q, J=18 Hz), 3.71 (3H, s), 4.5—5.2 (2H, m, these hydrogens couple with phosphorus), 7.0—8.2 (15H, m).

Methyl 7β-[N-(2′-Triphenylphosphoranyl-1,′2′-dimethoxycarbonylethylidene)]amino-3-methyl-3-cephem-4-carboxylate (XIV)——The compound (XIII) (5.0 g) obtained above was dissolved in dry CH_2Cl_2 (20 ml), to which was added dimethyl acetylenedicarboxylate (2.84 g, 20 mmol). The reaction mixture was kept at room temperature overnight in an atmosphere of nitrogen. Then the solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography (benzene–AcOEt=1: 1) to give XIV (4.04 g, 64% yield from XII) as a pale yellow foam. MS *m/e*: 368 (M^+−Ph_3P). IR ν_{max}^{Nujol} cm^{-1}: 1780, 1730, 1650, 1540. NMR ($CDCl_3$) δ ppm: 1.97 (3H, s), 2.63 and 3.02 (2H, AB-q, J=18 Hz), 3.20 (3H, s), 3.72 (3H, s), 3.86 (3H, s), 4.60 (1H, d, J=4 Hz), 5.11 (1H, d, J=4 Hz), 7.2—8.0 (15H, m).

Methyl 7-[N-(1′,2′-Dimethoxycarbonylvinyl)]imino-3-methyl-3-cephem-4-carboxylate (XV)——The ylide (XIV) (2.0 g, 3.17 mmol) was dissolved in xylene (150 ml) and refluxed for 1 hr with vigorous stirring. Then the mixture was evaporated under diminished pressure. The residue was purified by preparative TLC (silica gel, benzene–AcOEt=1: 1) to afford XV (350 mg, 30%) as an orange oil. MS *m/e*: 368 (M^+). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1780, 1730, 1630. NMR ($CDCl_3$) δ ppm: 2.19 (3H, s), 3.29 and 3.48 (2H, AB-q, J=18 Hz), 3.71 (3H, s), 3.80 (6H, s), 5.39 (1H, s), 6.29 (1H, s).

Methyl 7α-Methoxy-7β-[N-(1′,2′-*trans*-dimethoxycarbonylvinyl)]-amino-3-methyl-3-cephem-4-carboxylate (XVI)——A) To a stirred solution of XV (200 mg, 0.543 mmol) in dry THF (10 ml) was added a methanolic solution of LiOMe, prepared from metallic lithium (12 mg, 1.7 mmol) and dry MeOH (1 ml), at −78°. Stirring was continued for 30 min at that temperature. Then acetic acid (0.25 ml) was added to the mixture to cease

the reaction. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed successively with water, sat. $-NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated *in vacuo* to give XVI (200 mg, 92% yield) as an orange oil. This product was practically pure for measurement of physical-data. *Anal.* Calcd. for $C_{16}H_{20}O_8N_2S$: C, 48.00; H, 5.04; N, 7.00; S, 8.01. Found: C, 47.58; H, 5.22; N, 6.42; S, 7.96. MS *m/e*: 400 (M^+). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3280, 1780, 1740, 1680, 1620. NMR ($CDCl_3$) δ ppm: 2.05 (3H, s), 3.03 and 3.21 (2H, AB-q, $J=18$ Hz), 3.34 (3H, s), 3.58 (3H, s), 3.68 (6H, s), 4.81 (1H, s), 5.34 (1H, s), 8.81 (1H, b).

B) After a solution of XIV (400 mg, 0.634 mmol) in dry xylene (30 ml) was refluxed for 1 hr, absolute MeOH (15 ml) was added to the solution and the reaction mixture was refluxed for further 7 hr. Solvents were removed under reduced pressure and the residue was purified by preparative TLC (silica gel, benzene–AcOEt=4: 1) to give XVI (25 mg, 10% yield on the basis of XIV) as an oil.

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