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# Synthetic Approach directed at 1-Carbapenems and 1-Carbapenams

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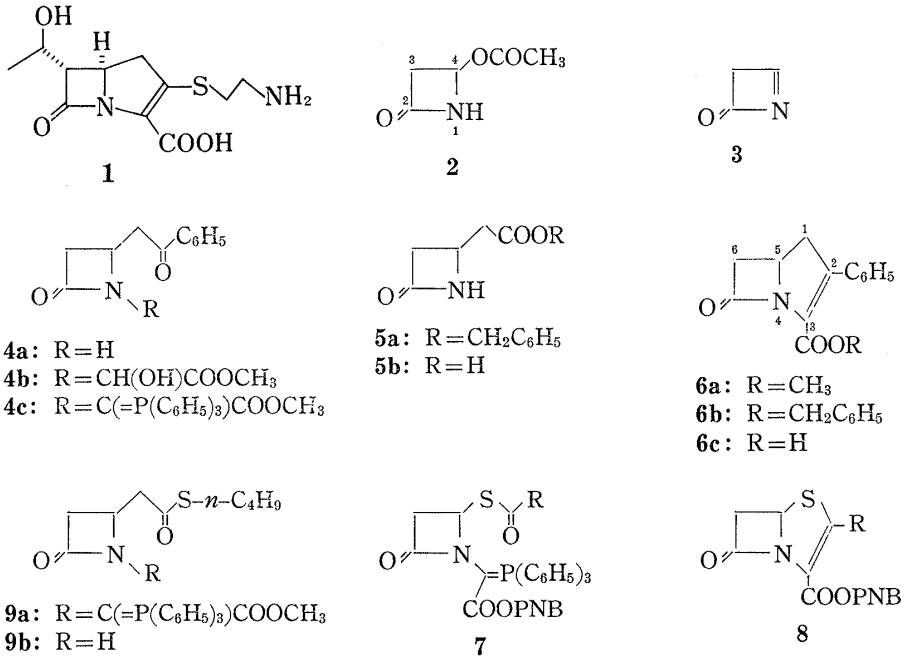
Displacement reactions of the acetoxy group in 4-acetoxy-2-azetidinone (**2**) with aluminum enolates afforded 4-alkylazetidinones **4a**, **5a**, **10** and **11**. The conversion of these azetidinones into 1-carba-penem or -penam compounds was studied.

**Keywords**——$\beta$-lactam C(4) alkylation; aluminum enolate; thienamycin analog; carbapenam; carbapenem; antibiotics; intramolecular Wittig reaction; $\beta$-lactam

Recently, intense interest has been focused on novel 1-carbapenem antibiotics, derived from several strains of *Streptomyces*, which show high antibacterial potency and a wide antibacterial spectrum. Of particular interest is thienamycin[2] (**1**) which has already been the subject of a successful total synthesis,[3] but still provides a special challenge. 4-Acetoxy-2-azetidinone[4] (**2**) is commercially available and is one of the most useful starting materials for synthetic work in $\beta$-lactam chemistry, because its acetoxy group can be easily replaced by a variety of nucleophiles *via* the imine intermediate **3** to give 4-substituted azetidinones.[4] However, there has been no study on the reaction of **2** with any carbon nucleophile to achieve carbon-carbon bond formation.[5] This paper deals with C-4 alkylation of **2** to provide 4-alkylazetidinones, which are key intermediates in synthesizing new $\beta$-lactam antibiotics related to thienamycin.

In 1977, Nozaki and his co-workers[6] developed a new aldol condensation reaction of $\alpha$-halo-ketones or -esters with a variety of carbonyl compounds through reactive aluminum enolates by utilizing diethylaluminum chloride and zinc. Taking advantage of the affinity of the aluminum ion for oxygen, this new method is very efficient and superior to other available procedures. Therefore, assuming that the imine intermediate **3** would also be reactive with the aluminum enolates, we applied this method to **2** in the following way. According to the reported procedure,[6] a solution of the azetidinone **2** (1 equivalent) and bromoacetophenone (2 equivalents) in tetrahydrofuran was gradually added to a mixture of zinc dust (2.3 equivalents) and diethylaluminum chloride (2 equivalents) in tetrahydrofuran at $-10$——$-5°$. Aqueous work-up of the reaction mixture gave a 33% yield of 4-phenylcarbonylmethyl-2-azetidinone (**4a**). Similar reaction of the azetidinone **2** with benzyl bromoacetate resulted in a 43% yield of 4-benzyloxycarbonylmethyl-2-azetidinone (**5a**).

1) Location: *Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
2) G. Albers-Schönberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkle, R.B. Morin, and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).
3) D.B.R. Johnston, S.M. Schmitt, F.A. Bouffard, and B.G. Christensen, *J. Am. Chem. Soc.*, **101**, 315 (1979).
4) K. Clauss, D. Grimm, and G. Prossel, *Liebigs Ann. Chem.*, **1974**, 539.
5) During this study, some other studies along this line were published. T. Kametani, S. Hirata, H. Nemoto, M. Ihara, and K. Fukumoto, *Heterocycles*, **12**, 523 (1979); M. Shibuya and S. Kubota, *ibid.*, **12**, 1315 (1979); T. Kobayashi, N. Ishida, and T. Hiraoka, *J.C.S. Chem. Commun.*, **1980**, 736. Also see H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.*, **1979**, 3867; M.D. Bachi, O. Goldberg, and A. Gross, *ibid.*, **1978**, 4167; I. Ernest, *Tetrahedron*, **33**, 547 (1977).
6) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977).




PNB: *p*-nitrobenzyl

Chart 1

We considered that these 4-alkylazetidinones **4a** and **5a**, with a carbonyl function in the side chain, might serve as key intermediates for 1-carbapenem synthesis; and we carried out reactions as described below, following the method which Woodward and his co-workers developed as a general method to approach penem compounds.[7] Reflux of 4-phenylcarbonylmethyl-2-azetidinone (**4a**) with methyl glyoxylate in benzene gave the hemiaminal **4b**, whose treatment with thionyl chloride followed by triphenylphosphine and 2,6-lutidine afforded the phosphorane **4c**. An intramolecular Wittig reaction of **4c** was carried out by refluxing in xylene to give the 1-carbapenem-3-carboxylate (**6a**) in 33% yield. Based on these preliminary experiments, we also synthesized the corresponding carbapenem benzylester (**6b**). Debenzylation of **6b** by hydrogenolysis with palladium–charcoal was attempted in order to obtain its free acid **6c**, but it resulted in extensive decomposition. This result suggests that the desired free acid **6c** may be hard to handle due to instability.[8]

Recently, Woodward and his co-workers[7] reported that the azetidinonephosphoranes **7** bearing 4-acylthio substituents were amenable to intramolecular Wittig reactions to give penem-3-carboxylates **8**. This led us to test the assumption that the thienamymin nucleus having a 2-alkylthio group would be accessible by cyclization of the azetidinonephosphorane **9a** bearing an (alkylthio)carbonylmethyl substituent at the 4-position of the azetidinone. Hydrogenolysis of the azetidinone **5a** with palladium–charcoal gave the acid **5b** whose treatment with butylmercaptan in the presence of diphenylphosphoryl azide and triethylamine[9]

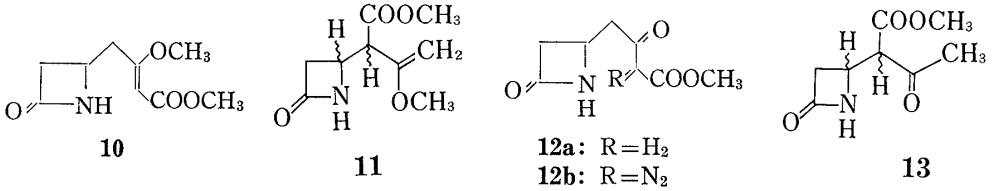
7) I. Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978); M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest, and R.B. Woodward, *ibid.*, **101**, 6296 (1979); I. Ernest, J. Gosteli, and R.B. Woodward,. *ibid.*, **101**, 6301 (1979); H.R. Pfaendler, J. Gosteli, and R.B. Woodward, *ibid.*, **101**, 6306 (1979).

8) Syntheses of 2-unsubstituted 1-carbapenems by the analogous intramolecular Wittig reaction of azetidinonephosphoranes bearing an acetaldehyde function at C-4 were reported during this work. See L.D. Cama and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978); A.J.G. Baxter, K.H. Dickinson, P.M. Roberts, T.C. Smale, and R. Southgate, *J.C.S. Chem. Commun.*, **1979**, 236; H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.*, **1979**, 3857; T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, *J. Am. Chem. Soc.*, **102**, 2060 (1980).

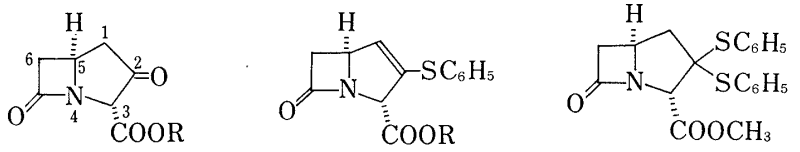
9) S. Yamada, Y. Yokoyama, and T. Shioiri, *J. Org. Chem.*, **39**, 3302 (1974).

afforded the butylthioester **9b**. Similarly, the ester **9b** was converted into the corresponding phosphorane **9a**. Attempted cyclization of **9a** into a 1-carbapenem was investigated under various conditions; however, it was found that **9a** was rather stable and it was recovered together with a small amount of decomposed material even after prolonged reaction under severe conditions.

Thus, the possibility of practical 1-carbapenem synthesis *via* bond formation between C-2 and C-3 by the intramolecular Wittig reaction of phosphoranes such as **9a**[10] seemed remote. Consequently, we studied another possible approach to 1-carbapenems *via* the formation of azetidinones with an extended side chain ($C_4$ unit) at the 4-position and their cyclization between the $\beta$-lactam nitrogen and the $\gamma$-carbon of the side chain to form the N–C bond. An approach along this line is shown below.



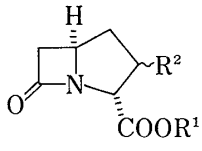
**10** **11** **12a**: R=$H_2$, **12b**: R=$N_2$ **13**



**14a** : R=$CH_3$
**14b** : R=$CH_2C_6H_5$

**15a** : R=$CH_3$
**15b** : R=H

**16**



**17a** : $R^1$=$CH_3$, $R^2$=OH
**17b** : $R^1$=$CH_3$, $R^2$=$OSO_2CH_3$
**17c** : $R^1$=$CH_3$, $R^2$=S-*n*-$C_4H_9$
**17d** : $R^1$=$CH_3$, $R^2$=$SCH_2CH_2NHCOCH_3$
**17e** : $R^1$=H, $R^2$=$SCH_2CH_2NHCOCH_3$

Chart 2

Reaction of 4-acetoxy-2-azetidinone (**2**) with methyl $\gamma$-bromo-$\beta$-methoxycrotonate[11] in the presence of zinc and diethylaluminum chloride resulted in the formation of three azetidinones in the ratio of 2:1:1 (56% yield). The major product was the $\gamma$-substituted butyric ester **10** and the others were diastereomers of the $\alpha$-substituted ester **11**. Acid hydrolysis of **10** and **11** gave $\beta$-ketoesters, **12a** and **13**, respectively. Diazo transfer reaction[12] to the $\gamma$-substituted $\beta$-ketoester **12a** with *p*-toluenesulfonyl azide afforded a diazoketoester **12b**. Treatment of **12b** with rhodium (II) acetate[13] resulted in cyclization into a single isomer of the 2-oxo-1-carbapenam-3-carboxylate **14a** in 71% yield. It is likely that the 3,5-stereoche-

10) It was recently reported that the phenylthioester of an azetidinonephosphorane such as **9a** could be converted into the 2-phenylthio-1-carbapenem-3-carboxylate by intramolecular Wittig reaction. See R.J. Ponsford, P.M. Roberts, and R. Southgate, *J.C.S. Chem. Commun.*, **1979**, 847.
11) R.B. Reid and W.B. Ruby, *J. Am. Chem. Soc.*, **73**, 1054 (1951).
12) M. Regitz, *Synthesis*, **1972**, 351.
13) R. Paulissen, H. Reimlinger, E. Hayez, A.J. Hubert, and P. Teyssié, *Tetrahedron Lett.*, **1973**, 2233. Also see L.D. Cama and B.G. Christensen, *ibid.*, **1978**, 4233.

mical relationship in **14a** is the same stable one as in penicillins, although no physical evidence was available. It was also found that **14a** was rather unstable to acids,[14] but treatment of **14a** with diphenyl disulfide in the presence of tributylphosphine according to Tazaki *et al.*[15] afforded 2-phenylthio-1-carba-1-penem-3-carboxylate (**15a**) along with a dithioketal (**16**). Surprisingly, the 1-carba-1-penem (**15a**) thus obtained was rather stable to bases, and gave a sodium salt of the free acid **15b** on treatment with 0.1 N aqueous sodium hydroxide (1 equivalent). Sodium borohydride reduction of the 2-oxo-1-carbapenam (**14a**) occurred stereospecifically to give a single alcohol **17a** which was converted into a methanesulfonate **17b** in the usual manner. Displacement reaction of **17b** with butylmercaptan or N-acetylcysteamine in the presence of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) at $-50°$ resulted in the formation of a diastereomeric mixture of the corresponding 2-alkylthio-1-carbapenam-3-carboxylates **17c** and **17d**, respectively, which indicates that this reaction may proceed through the intermediacy of a 1-carbapenem compound.[16] Alkaline hydrolysis of the 2-acetamidoethylthio derivative **17d** gave the sodium salt of the acid **17e**. These carbapenam-3-carboxylic acids, **15b** and **17e**, did not show any significant antibacterial activity or $\beta$-lactamase inhibitory activity.

During this study, several other studies on 1-carbapenem synthesis were independently carried out and recently disclosed.[8,10,16] Ratcliffe *et al.*[17] independently announced the synthesis of benzyl 2-oxo-1-carbapenam-3-carboxylate **14b** by the above-mentioned metal-catalyzed decomposition of the $\alpha$-diazo-$\beta$-ketoester and further successfully converted **14b** into the 2-alkylthio-1-carbapenem-3-carboxylate, also developing a new method for the synthesis of thienamycin and its analogs.

## Experimental

Melting points are not corrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and proton magnetic resonance spectra (NMR) on a Varian A-60 or a Hitachi–Perkin–Elmer R-24 spectrometer, using, unless otherwise specified, tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel $F_{254}$ precoated, layer thickness 0.25 mm (E. Merck) and spots were made visible by UV-irradiation or by spraying with vanadic acid-sulfuric acid followed by heating, or by iodine treatment. Chromatography columns were prepared with Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) and preparative TLC plates were provided with Silica gel $60F_{254}$ (E. Merck). The amount of silica gel used and the developing solvents are shown in parenthesis. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; q, quartet; m, multiplet; br., broad.

**4-Phenylcarbonylmethyl-2-azetidinone** (**4a**)——To a stirred mixture of activated zinc dust[18] (1.91 g, 29.4 mmol) and $Et_2AlCl$ (2.83 g, 23.5 mmol) in THF (60 ml) was added dropwise a solution of **2** (1.62 g, 12.6 mmol) and bromoacetophenone (4.65 g, 23.4 mmol) in THF (45 ml) at $-10°$ over a period of 30 min, and stirring was continued for 30 min at $-10°$——$-5°$. After addition of pyridine (6 ml), the cooled mixture was successively diluted with water (20 ml), EtOAc (50 ml), and 1 N HCl (20 ml), then filtered. The organic layer was collected, washed with dil. HCl, then with dil. $NaHCO_3$, dried and evaporated *in vacuo* to leave a syrup (*ca.* 4 g). Silica gel chromatography (50 g, benzene: AcOEt=1: 1, v/v) followed by recrystallization from benzene gave **4a** (785 mg, 33%, prisms, mp 141—143°). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3420, 1760, 1685. NMR ($CDCl_3+D_2O$, 60 MHz) $\delta$: 2.69 (1H, dd, $J$=15.5, 3 Hz), 3.26 (1H, dd, $J$=15.5, 5 Hz), 3.21 (1H, dd, $J$=18,

14) The following attempts on **14a** were unsuccessful: enol ether formation by treatment with diazomethane, and thioketal formation with ethylthiotrimethylsilane-zinc iodide [D.A. Evans, K.G. Grimm, and L.K. Truesdale, *J. Am. Chem. Soc.*, **97**, 3229 (1975)] and reaction with Wittig reagents such as $(C_6H_5)_3P=CHCOOCH_2C_6H_5$ or $(C_6H_5)_3P=CHCH_3$.

15) M. Tazaki, M. Takagi, T. Matsuda, and K. Ueno, Abstract Papers of the 37th Spring Meeting of the Japan Chemical Society, 1978, p. 898. Also see M. Tazaki, and M. Takagi, *Chemistry Letters*, **1979**, 767.

16) Very recently, it was reported that base-catalyzed addition of N-acetylcysteamine to 1-carbapenem-3-carboxylate produced a diastereomeric mixture of **17d** ($R^1=CH_2C_6H_5$ instead of $CH_3$), which was oxidized to $\alpha$-chlorosulfoxide derivatives and then dehydrochlorinated to form the 2-(2-acetamidoethylsulfinyl)-1-carbapenem-3-carboxylate. L.H. Bateson, P.M. Roberts, T.C. Smale, and R. Southgate, *J.C.S. Chem. Commun.*, **1980**, 185.

17) R.W. Ratcliffe, T.N. Salzmann, and B.G. Christensen, *Tetrahedron Lett.*, **1980**, 31.

18) Refer to C.R. Hauser and D.S. Breslow, "Organic Synthesis," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 408.

8 Hz), 3.50 (1H, dd, $J$=18, 5 Hz), 4.13 (1H, m), 7.4—8.1 (5H, m). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.75; H, 5.96; N, 7.32.

**Methyl 2-(4-Phenylcarbonylmethyl-2-oxo-1-azetidinyl)-2-hydroxyacetate (4b) and Its Benzyl Ester**——A solution of **4a** (131 mg) and methyl glyoxylate (130 mg) in benzene (4 ml) was refluxed for 1.5 hr. After cooling, the mixture was evaporated *in vacuo* to leave a syrup. Preparative TLC (AcOEt: benzene=1: 2, v/v) afforded **4b** (138 mg, 72%) as a syrup. IR $\nu_{max}^{liq.}$ cm$^{-1}$: 3350, 1750, 1680. NMR ($CDCl_3+D_2O$, 60 MHz) $\delta$: 2.75 and 2.79 (1H, dd, $J$=15.5, 2.5 Hz, 1: 1), 3.35 and 3.39 (1H, dd, $J$=15.5, 5 Hz, 1: 1), 3.4—4.0 (2H, m), 3.71 and 3.90 (3H, s, 1: 1), 4.40 (1H, m), 5.49 and 5.60 (1H, s, 1: 1), 7.1—8.1 (5H, m). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.79; H, 5.22; N, 4.77.

Similar treatment of **4a** (192 mg) with benzyl glyoxylate (251 mg) in benzene (5 ml) gave a benzyl ester (370 mg, 100%). IR $\nu_{max}^{liq.}$ cm$^{-1}$: 3400, 1750, 1680. NMR ($CDCl_3+D_2O$, 60 MHz) $\delta$: 2.65 and 2.69 (1H, dd, $J$=15, 2.5 Hz, 1: 1), 3.23 and 3.30 (1H, dd, $J$=15, 5 Hz, 1: 1), 3.2—3.7 (2H, m), 4.35 (1H, m), 5.15 and 5.34 (2H, s, 1: 1), 5.63 and 5.68 (1H, s, 1: 1), 7.3—8.1 (10H, m). *Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.47; H, 5.28; N, 3.65.

**Methyl 2-(4-Phenylcarbonylmethyl-2-oxo-1-azetidinyl)-2-(triphenylphosphoranylidene)acetate (4c) and Its Benzyl Ester**——To a solution of **4b** (138 mg, 0.50 mmol) and 2,6-lutidine (161 mg, 3 eq.) in THF (10 ml) was added $SOCl_2$ (179 mg, 3 eq.) with cooling at −15° and stirring. After being stirred for a further 15 min, the mixture was evaporated to dryness *in vacuo*. The residue was added to a solution of triphenylphosphine (262 mg, 2 eq.) and 2,6-lutidine (107 mg, 2 eq.) in THF (7 ml). The resulting mixture was kept at 60° for 8 hr with stirring under an $N_2$ atmosphere and, after cooling, was diluted with AcOEt, washed with water, dried and evaporated *in vacuo*. The product was purified by preparative TLC (AcOEt: benzene=1: 1, v/v), giving **4c** (167 mg, 64%). IR $\nu_{max}^{liq.}$ cm$^{-1}$: 1745, 1680, 1620. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.4 (2H, br.), 3.15 and 3.45 (3H, br. s, 2: 3).

Similarly, the benzyl glyoxylate adduct of **4a**, described above, was transformed to the corresponding phosphorane benzyl ester in 64% yield. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1740, 1685, 1615. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.4 (2H, br.), 4.73 and 5.13 (2H, br. s, 1: 1).

**Methyl and Benzyl 3-Phenyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6a and 6b)**——A solution of **2c** (130 mg) in xylene (10 ml) was kept at 135° (bath temp.) for 45 min with stirring under an $N_2$ atmosphere. After cooling, the mixture was evaporated to dryness *in vacuo* and the residue was purified by preparative TLC (AcOEt: benzene=1: 2, v/v) to give 20 mg (33%) of **6a**, prisms, mp 118—120° (from AcOEt–hexane). UV $\lambda_{max}^{EtOH}$ nm: 222 ($\varepsilon$ 7900), 303 ($\varepsilon$ 9050). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1785, 1730. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.97 (1H, dd, $J$=16, 3 Hz), 3.51 (1H, dd, $J$=16, 5.5 Hz), 3.20 (2H, d-like, $J$=9 Hz), 3.75 (3H, s), 4.30 (1H, m), 7.43 (5H, s). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.99; H, 5.39; N, 5.69. MS $m/e$: 243 ($M^+$, $C_{14}H_{13}NO_3$), 212 ($M^+-CH_3O$), 201 (base peak, $M^+-CH_2CO$), 170 ($M^+-CH_2CO-CH_3O$), 169 ($M^+-CH_2CO-CH_3OH$), 115 ($C_6H_5C_3H_2^+$).

Similar treatment of the corresponding benzyl ester (190 mg) in xylene (15 ml) at 135° for 40 min followed by work-up and preparative TLC (acetone: hexane=2: 3, v/v) gave **6b** (62 mg, 61%) as a syrup. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1790, 1725. UV $\lambda_{max}^{EtOH}$ 295 nm: ($\varepsilon$ 9000). NMR ($CDCl_3$, 60 MHz) $\delta$: 2.98 (1H, dd, $J$=16, 3 Hz), 3.49 (1H, dd, $J$=16, 5.5 Hz), 3.20 (2H, d-like, $J$=8.5 Hz), 4.31 (1H, m), 5.25 (2H, s), 7.37 (5H, s), 7.40 (5H, s). MS $m/e$: 319 ($M^+$, $C_{20}H_{17}NO_3$).

The sample of **6b** was found to be unstable on prolonged storage, even at low temperatures. Hydrogenation of **6b** (55 mg) in MeOH (2 ml) was carried out with 10% palladium–charcoal (25 mg). After filtration, the mixture was evaporated *in vacuo* to give a syrup. This was dissolved in AcOEt and the solution was filtered. Removal of the solvent gave an unidentified product (38 mg), and TLC indicated the existence of degradation products. Further treatment of the product with ethereal diazomethane did not afford **6a**, as judged by TLC analysis.

**4-Benzyloxycarbonylmethyl-2-azetidinone (5a)**——A cooled solution of **2** (0.5 g, 3.9 mmol) and benzyl bromoacetate (2.64 g, 11.5 mmol) in THF (10 ml) was added slowly to a stirred mixture of $Et_2AlCl$ (0.93 g, 7.7 mmol), activated zinc dust[18] (1.0 g, 15 mmol) and THF (15 ml) over a period of 40 min at 0°. The mixture was stirred for 1 hr at the same temperature, then pyridine (2 ml) was added. The mixture was diluted with AcOEt and filtered. The organic layer was washed with water, dried and evaporated to dryness *in vacuo*, then the residue was chromatographed on silica gel (10 g, benzene: AcOEt=2: 1, v/v). The crude **5a** thus obtained was recrystallized from benzene, giving **5a** (363 mg, 43%, fine needles, mp 95—95.5°). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3230, 1739, 1729, 1720. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.58 (1H, ddd, $J$=15, 3, 1.5 Hz), 2.65 (2H, d-like), 3.12 (1H, ddd, $J$=15, 5, 2 Hz), 3.95 (1H, m), 5.16 (2H, s), 6.65 (1H, br.), 7.40 (5H, s). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.81; H, 6.03; N, 6.76.

**4-Carboxymethyl-2-azetidinone (5b)**——Hydrogenation of a solution of **5a** (1.044 g) in MeOH (20 ml) over 10% palladium-charcoal (100 mg) was carried out for 40 min, then the reaction mixture was filtered and evaporated *in vacuo* to dryness, giving 616 mg (100%) of **5b**. An analytical sample (prisms, mp 116—117°) was obtained by recrystallization from AcOEt–EtOH. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3230, ~2700, 1752, 1695. *Anal.* Calcd for $C_5H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.42; H, 5.45; N, 10.74.

**4-[(Butylthio)carbonylmethyl]-2-azetidinone (9b)**——A solution of **5b** (100 mg), BuSH (87 mg), $Et_3N$ (159 mg), and diphenylphosphoryl azide (426 mg) in DMF (2 ml) was allowed to stand overnight at room

temperature and then evaporated to dryness *in vacuo*. The residue was purified by preparative TLC (AcOEt: benzene=1: 2, v/v) to give **9b** (146 mg, 94%) as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3240, 1765, 1580. NMR ($CDCl_3$, 60 MHz) $\delta$: 0.92 (3H, t, $J$=7 Hz), 1.5 (4H, m), 2.66 (1H, ddd, $J$=15, 3, 1.5 Hz), 3.17 (1H, ddd, $J$=15, 5, 2.5 Hz), 2.88 (2H, d-like), 2.93 (2H, t, $J$=7 Hz), 3.99 (1H, m), 6.52 (1H, m). *Anal.* Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96; S, 15.93. Found: C, 53.51; H, 7.38; N, 6.69; S, 15.77.

**Methyl 2-[4-[(Butylthio)carbonylmethyl]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetate (9a)**——A solution of **9b** (170 mg) and methyl glyoxylate (110 mg) in benzene (4 ml) was refluxed for 1.5 hr. The solvent was evaporated off *in vacuo* and the residue was subjected to preparative TLC (AcOEt: benzene=1: 2), giving methyl 2-[4-[(butylthio)carbonylmethyl]-2-oxo-1-azetidinyl]-2-hydroxyacetate (146 mg, 60%) as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3360, 1755, 1680. NMR ($CDCl_3+D_2O$, 60 MHz) $\delta$: 0.95 (3H, t, $J$=7 Hz), 3.85 and 3.87 (3H, s, 2:3), 4.25 (1H, m), 5.61 and 5.70 (1H, s, 2:3). MS *m/e*: 230 [$M^+-CO_2CH_3$], 185, 112.

A mixture of the hydroxyacetate (142 mg) obtained as described above, 2,6-lutidine (161 mg), $SOCl_2$ (179 mg) and THF (12 ml) was stirred at −15° for 20 min and then the solvent was evaporated off *in vacuo*. The residue was added to a solution of triphenylphosphine (262 mg) and 2,6-lutidine (107 mg) in THF (7.5 ml). The mixture was kept at 60° for 7.5 hr under an $N_2$ atmosphere, then work-up as usual and preparative TLC of the product (acetone: hexane=1: 2.5, v/v) gave **9a** (182 mg, 69% from the hydroxyacetate) as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1748, 1680, 1620. NMR ($CDCl_3$, 60 MHz) $\delta$: 0.90 (3H, t, $J$=6 Hz), 3.60 (3H, s), 7.0—8.0 (15H, m).

**4-(2-Methoxy-3-methoxycarbonyl-2-propenyl)-2-azetidinone (10) and 4-(2-Methoxy-1-methoxycarbonyl-2-propenyl)-2-azetidinone (11)**——A mixture of $Et_2AlCl$ (3.50 g, 29 mmol), activated zinc dust[18] (3.27 g, 50 mmol) and THF (53 ml) was stirred for 15 min at room temperature and cooled at 0°. Next, a solution of **2** (1.85 g, 14.3 mmol) and methyl $\gamma$-bromo-$\beta$-methoxycrotonate[11] (8.12 g, 38.8 mmol) in THF (30 ml) was added over a period of 30 min with stirring. The mixture was stirred for 2.5 hr with cooling and worked-up as described above, giving a crystalline product which was washed with benzene-isopropyl ether to leave a diastereomer of **11** (**11-A**) as crystals (317 mg). The washings were collected and evaporated to dryness *in vacuo*. Repeated chromatography on silica gel of the residue (30 g, benzene: AcOEt=5: 1, v/v) gave 82 mg (total 399 mg, 14%) of **11-A**, 400 mg (14%) of another diastereomer of **11** (**11-B**) as an oil and 802 mg (28%) of **10** as crystals. Analytical samples of **10** (needles, mp 93.5—94.5°) and **11-A** (needles, mp 139.5—140.5°) were obtained by recrystallization from EtOH–isopropyl ether. IR $\nu_{max}^{Nujol}$ $cm^{-1}$ for **10**: 3280, 1760, 1680, 1617; for **11-A**: 1760, 1718, 1663, 1630; $\nu_{max}^{CHCl_3}$ $cm^{-1}$ for **11-B**: 3430, 1760, 1740, 1664, 1626. NMR ($CDCl_3$, 100 MHz) $\delta$ for **10**: 2.76 (1H, ddd, $J$=15, 2.5, 2 Hz), 2.95 (1H, dd, $J$=13, 6.5 Hz), 3.04 (1H, ddd, $J$=15, 5, 2 Hz), 3.28 (1H, dd, $J$=13, 5.5 Hz), 3.64 and 3.66 (3H each, s), 3.87 (1H, m), 6.10 (1H, br. s); for **11-A**: 2.68 (1H, ddd, $J$=15, 3, 1 Hz), 3.01 (1H, ddd, $J$=15, 5, 2 Hz), 3.12 (1H, d, $J$=10 Hz), 3.52 (3H, s), 3.72 (3H, s), 4.03 (1H, ddd, $J$=10, 5, 3 Hz), 4.08 (2H, s); for **11-B**: 2.70 (1H, ddd, $J$=15, 2.5, 1 Hz), 3.15 (1H, ddd, $J$=15, 5, 2 Hz), 3.18 (1H, d, $J$=9 Hz), 3.55 (3H, s), 3.71 (3H, s), 4.02 (1H, ddd, $J$=9, 5, 2.5 Hz), 4.10 and 4.17 (1H each, ABq, $J$=3 Hz). *Anal.* Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found for **10**: C, 54.10; H, 6.56; N, 6.93; for **11-A**: C, 54.21; H, 6.61; N, 7.13. MS *m/e* for **11-B**: 199 ($M^+$, $C_9H_{13}NO_4$).

**4-(3-Methoxycarbonyl-2-oxopropyl)-2-azetidinone (12a) and 4-(1-Methoxycarbonyl-2-oxopropyl)-2-azetidinone (13)**——A mixture of **10** (644 mg) and 4% HCl (12 ml) was stirred for 1.5 hr at room temperature, then the mixture was saturated with NaCl and extracted with $CHCl_3$ several times. The collected extracts were washed with brine, dried and evaporated *in vacuo*, leaving **12a** (413 mg, 67%) as an oil which was used directly for the next reaction. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3420, 1752, 1717. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.63 (1H, dd, $J$=15, 2 Hz), 2.95 (1H, d-like, $J$=9 Hz), 2.98 (1H, d-like, $J$=5 Hz), 3.22 (1H, dd, $J$=15, 2 Hz), 3.53 (2H, s), 3.80 (3H, s), 3.98 (1H, m), 6.65 (1H, br. s). MS *m/e*: 185 ($M^+$, $C_8H_{11}NO_4$).

Similar acid treatment of **11A** or **11B** gave **13** in 89% yield. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.29 (3H, s), 2.68 (1H, dt, $J$=15, 3 Hz), 3.19 (1H, ddd, $J$=15, 5, 2.5 Hz), 3.69 and 3.75 (1H, *ca.* 1: 1, d, $J$=9.5 Hz), 3.79 (3H, s), 4.15 (1H, ddd, $J$=9.5, 5, 3 Hz), 6.9 (1H, br. s).

**4-(3-Diazo-3-methoxycarbonyl-2-oxopropyl)-2-azetidinone (12b)**——To a stirred solution of **12a** (334 mg) in $CH_3CN$ (4 ml) was added a solution of $Et_3N$ (201 mg) and $TsN_3$ (536 mg) in $CH_3CN$ (2 ml) and the mixture was allowed to stand overnight at room temperature. The product obtained by evaporation *in vacuo* was chromatographed on silica gel (6 g, benzene: AcOEt=1: 2, v/v) to give **12b** (257 mg, 70%) as an oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3420, 2130, 1760, 1720, 1648. NMR ($CDCl_3$, 60 MHz) $\delta$: 2.70 (1H, ddd, $J$=15, 3, 1 Hz), 2.95 (1H, dd, $J$=18, 5.5 Hz), 3.19 (1H, ddd, $J$=15, 4.5, 1 Hz), 3.37 (1H, dd, $J$=18, 4 Hz), 3.88 (3H, s), 4.0 (1H, m), 6.6 (1H, br. s). MS *m/e*: 183 ($M^+(C_8H_9N_3O_4)-N_2$).

**Methyl 3,7-Dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (14a)**——A solution of **12b** (657 mg) and $Rh_2(OCOCH_3)_4$ (11 mg) in 1,2-dimethoxyethane (14 ml) was stirred overnight at room temperature. The mixture was evaporated to dryness *in vacuo* and the residue was chromatographed on silica gel (6 g, benzene: AcOEt=3: 1) to give **14a** (403 mg, 71%) as an oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1772, 1745. NMR ($CDCl_3$, 100 MHz) $\delta$: 2.43 (1H, dd, $J$=19, 8 Hz), 2.90 (1H, dd, $J$=19, 7 Hz), 2.95 (1H, dd, $J$=16, 2), 3.64 (1H, dd, $J$=16, 5 Hz), 3.79 (3H, s), 4.17 (1H, m), 4.69 (1H, s). MS *m/e*: 183 ($M^+$, $C_8H_9NO_4$).

**Methyl 3-Phenylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylate (15a) and Methyl 3,3-Diphenylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (16)**——A solution of **14a** (102 mg), $Bu_3P$ (337 mg) and

$(C_6H_5S)_2$ (364 mg) in DMF (0.9 ml) was kept at 40—50° for 75 min with stirring and then evaporated to dryness *in vacuo*. Preparative TLC of the residue (benzene: AcOEt=10: 1, v/v) gave **15a** (44 mg, 29%) and **16** (12 mg, 6%) as oils. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$ for **15a**: 1775, 1747; for **16**: 1770, 1748. NMR ($CDCl_3$, 100 MHz) $\delta$ for **15a**: 2.83 (1H, dd, $J$=16, 3 Hz), 3.35 (1H, dd, $J$=16, 6 Hz), 3.70 (3H, s), 4.53 (1H, m), 5.06 (1H, dd, $J$=3, 2 Hz), 5.81 (1H, t, $J$=2 Hz); for **16**: 1.90 (1H, dd, $J$=15, 4 Hz), 2.62 (1H, dd, $J$=15, 8 Hz), 2.96 (1H, dd, $J$=15, 3 Hz), 3.27 (1H, dd, $J$=15, 6 Hz), 3.72 (3H, s), 4.1 (1H, m), 4.66 (1H, s). MS *m/e* for **15a**: 275 ($M^+$, $C_{14}H_{13}NO_3S$); for **16**: 385 ($M^+$, $C_{20}H_{19}NO_3S_2$).

**Sodium Salt of 3-Phenylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylic Acid (15b)**——To a solution of **15a** (11 mg) in aqueous THF (2 ml, 1: 1, v/v) was added dropwise 0.1 N NaOH (0.4 ml) over a period of 2 days. The mixture was diluted with water, washed with AcOEt and lyophylized, giving the sodium salt of **15b** (7.6 mg, 67%) as a solid. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400 (br.), 1762, 1618 (br.). NMR ($D_2O$, 60 MHz) $\delta$: 2.84 (1H, dd, $J$=17, 3 Hz), 3.34 (1H, dd, $J$=17, 5 Hz), 4.50 (1H, m), 4.81 (1H, dd, $J$=4, 2 Hz), 5.85 (1H, t, $J$=2 Hz), 7.45 (5H, s).

**Methyl 3-Hydroxy-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (17a)**——To a solution of **14a** (114 mg) in MeOH (0.6 ml) was added $NaBH_4$ (8.8 mg) at −50° with stirring under an $N_2$ atmosphere, then the mixture was stirred for 20 min at the same temperature and worked-up in the usual manner. The product was purified by chromatography on silica gel (2 g, benzene: AcOEt=1; 1, v/v) to give **17a** (61 mg, 53%) as an oil. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3430, 1745, 1736. NMR ($CDCl_3$, 100 MHz) $\delta$: 1.86 (1H, dt, $J$=14, 4 Hz), 2.32 (1H, ddd, $J$=14, 7.5, 5 Hz), 2.99 (1H, dd, $J$=16, 3 Hz), 3.34 (1H, dd, $J$=16, 5 Hz), 3.35 (1H, br. s), 3.74 (3H, s), 3.93 (1H, dddd, $J$=7.5, 5, 4, 3 Hz), 4.48 (1H, d, $J$=2.5 Hz), 4.75 (1H, m). MS *m/e*: 185 ($M^+$, $C_8H_{11}NO_4$), 153 ($M^+-CH_3OH$), 126 (base peak, $M^+-COOCH_3$).

**Methyl 3-Methanesulfonyloxy-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (17b)**——A solution of MsCl (40 mg) and $Et_3N$ (53 mg) in $CH_2Cl_2$ was added to a solution of **17a** (61 mg) in $CH_2Cl_2$ (1.5 ml) at −78° and the mixture was stirred for 25 min at the same temperature. Work-up in the usual manner and purification by preparative TLC gave **17b** (65 mg, 75%) as an oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1774, 1740, 1345, 1173. NMR ($CDCl_3$ 60 MHz) $\delta$: 2.15 (1H, dt, $J$=15, 4.5 Hz), 2.65 (1H, ddd, $J$=15, 8, 5 Hz), 3.09 (3H, s), 3.50 (1H, dd, $J$=16, 5 Hz), 3.80 (3H, s), 4.03 (1H, m), 4.80 (1H, d, $J$=2.5 Hz), 5.58 (1H, m).

**Methyl 3-Butylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (17c)**——To a solution of **17b** (51 mg) in THF (1.5 ml) were added BuSH (52 mg) and DBU (152 mg) at −78° with stirring. The temperature was allowed to rise to −50° over 1 hr and the mixture was diluted with AcOEt. The organic layer was collected, washed with brine, dried and evaporated. Preparative TLC of the residue gave **17c** (30 mg, 60%), a 3: 2 diastereomeric mixture as a syrup. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1763, 1747. NMR ($CDCl_3$, 100 MHz) $\delta$: 0.91 (3H, t, $J$=6.5 Hz), 2.60 (2H, t, $J$=7 Hz), 3.57 and 3.77 (1H, 3: 2, m), 3.74 and 3.76 (3H, 3: 2, s), 4.33 (3/5H, d, $J$=6 Hz), 4.73 (2/5H, d, $J$=7.5 Hz). MS *m/e*: 257 ($M^+$, $C_{12}H_{19}NO_3S$), 198 ($M^+-COOCH_3$).

**Methyl 3-(2-Acetamidoethylthio)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (17d)**——Similar treatment of **17b** (60 mg) with 2-acetamidoethanthiol (88 mg) and DBU (69 mg) in THF (1.5 ml) gave **17d** (17 mg, 26%), a 3: 2 diastereomeric mixture, as a syrup. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3460, 1763, 1742, 1668. NMR ($CDCl_3$, 60 MHz) $\delta$: 1.89 and 1.92 (3H, 3: 2, s), 3.74 and 3.83 (3H, 3: 2, s), 4.32 (3/5H, d, $J$=5 Hz), 4.70 (2/5H, d, $J$=7.5 Hz). MS *m/e*: 286 ($M^+$, $C_{12}H_{18}N_2O_4S$), 227 ($M^+-COOCH_3$), 168 (base peak, $M^+-COOCH_3-H_2NCOCH_3$).

**Sodium Salt of 3-(2-Acetamidoethylthio)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid (17e)**——To a solution of **17d** (13 mg) in a mixture of THF (1.0 ml) and $H_2O$ (0.5 ml) was added 0.1 N NaOH (0.45 ml) over a period of 2 days. After being stirred for a further 5 hr, the mixture was diluted with water and washed three times with $CHCl_3$. The aqueous layer was filtered and lyophilized to give the sodium salt of **17e** (13 mg, 97%) as a solid. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3400 (br.), 1753, 1660, 1610, 1560. NMR ($D_2O$, 60 MHz) $\delta$: 1.86 and 1.88 (3H, 4: 3, s), 4.10 (4/7H, d, $J$=5 Hz).