Photolysis of 2-Iodo-1,1-diphenylpropene (1a, X = I) in Cyclohexane. A solution of the vinyl iodide **1a** (X = I, 1 mmol) in cyclohexane (100 mL) was irradiated in the presence of zinc powder (10 mmol) under a nitrogen atmosphere at 10 °C by using a high-pressure mercury lamp (100 W) for 70 min. The solvent was removed under reduced pressure, and the residue was chromatographed over alumina. The only product was the propene **2a**, which was identified by comparison with an authentic sample.[25] Its yield was 53%, as determined by NMR with *p-tert*-butylbenzoic acid as an internal standard.

Photolysis of 2-Bromo-1,1-bis(*p*-methoxyphenyl)propene (1b, X = Br) in THF. A solution of the vinyl bromide **1b** (X = Br, 2 mmol) in THF (200 mL) containing pyridine (0.2 mL) was irradiated in a manner similar to that described for **1a** for 4 h. The solvent was removed under reduced pressure, and the residue was chromatographed over alumina. Elution with 40% benzene–hexane gave the starting material (**1b**, X = Br), the propene **2b**, and the allene **3b**. Elution with benzene gave 1,2-bis(*p*-methoxyphenyl)propene (**12**): mp 124 °C; NMR ($CDCl_3$) δ 2.23 (d, J = 1.2 Hz, 3 H, CH_3), 3.80 (s, 6 H, OCH_3), 6.67–7.50 (m, 9 H, CH and Ar H); UV (EtOH) λ_{max} 287 nm (log ϵ 4.01); mass spectrum, m/e 254 (M^+).[28]

Photolysis of 1,1-Diphenyl-2-halopropenes (1a, X = Br and I) in Ethylene Glycol. A solution of the vinyl halide **1a** (1 mmol) in ethylene glycol (100 mL) containing pyridine (0.1 mL) was irradiated in a similar manner. The reaction mixture was poured into water (500 mL) and extracted with ether. The ethereal solution was washed with water and saturated sodium chloride and dried over anhydrous sodium sulfate. The crude photoproducts were obtained by the removal of the ether and chromatographed over alumina. Elution with 40–80% benzene–hexane gave the starting material **1a**, the propene **2a**, and the allene **3a**. Elution with 50% ether–benzene gave 9-(2-hydroxyethoxy)-10-methylphenanthrene (**13**) which was isolated as the picrate: mp 106–107 °C; NMR ($CDCl_3$) δ 2.59 (s, 3 H, CH_3), 2.58 (br s, 1 H, OH), 3.98 (s, 4 H, CH_2CH_2), 6.96–8.58 (m, 8 H, Ar H); mass spectrum, 252 (M^+). Anal. Calcd for $C_{23}H_{19}O_9N_3$ (picrate): C, 57.38; H, 3.98; N, 8.73. Found (picrate): C, 57.14; H, 4.00; N, 8.77.

Photolysis of 2-Bromo-1,1-diphenylpropene (1a, X = Br) in Methanol at −70 °C. A solution of the vinyl bromide **1a** (X = Br, 141 mg) in methanol (25 mL) containing pyridine (0.05 mL) was placed in a quartz tube and irradiated for 4.5 h under a nitrogen atmosphere at −70 °C by using a high-pressure mercury lamp (100 W). The solvent was removed under reduced pressure, and the residue was chromatographed over alumina in order to remove the pyridinium salt. The photoproducts which were eluted with benzene were analyzed by recording their NMR spectra. The identified products were the propene **2a**, the allene **3a**, the phenanthrene **4a**, and (*E*)- and (*Z*)-1-methoxy-1,2-diphenylpropenes (**8a**).

Photolysis of 2-Bromo-1,1-diphenylpropene (1a, X = Br) in Methanol-*O-d*. A solution of the vinyl bromide **1a** (X = Br, 144 mg) in methanol-*O-d* (10 mL) containing pyridine (0.05 mL) was placed in a quartz tube and irradiated for 5.5 h under conditions similar to those for the photolysis in methanol at 5 °C. After workup of the reaction mixture, the NMR spectrum showed the same products: the propene **2a**, the allene **3a**, and the phenanthrene **4a**. The mass spectral analysis of the propene **2a**, which was separated by column chromatography on alumina, indicated only 2% of incorporation of deuterium.

Sensitized Irradiation of 1,1-Diaryl-2-bromopropene (1a or 1b, X = Br) in Methanol. A solution of the vinyl bromide **1a** (X = Br, 1 mmol) in methanol (100 mL) containing pyridine (0.1 mL) was similarly irradiated in the presence of benzophenone (10 mmol) with a Pyrex filter for 3 h. After the workup of the reaction mixture, the vinyl bromide **1a** (X = Br) was recovered unchanged. Similar irradiation of the vinyl bromide **1a** (X = Br) with acetophenone and the vinyl bromide **1b** (X = Br) with benzophenone and a Pyrex filter, respectively, gave no products, and the starting material was recovered unchanged.

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Registry No. 1a (X = Cl), 781-34-0; **1a** (X = Br), 781-32-8; **1a** (X = I), 81360-97-6; **1b** (X = Cl), 81360-98-7; **1b** (X = Br), 39179-87-8; **1b** (X = I), 81360-99-8; **2a**, 778-66-5; **2b**, 4663-13-2.

Further Studies on the Synthesis of Thienamycin: a Facile and Stereoselective Synthesis of a Bicyclic β-Keto Ester by 1,3-Dipolar Cycloaddition

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Received December 30, 1981

A potential compound, ethyl 6-[(1R*)-1-hydroxyethyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (**18**), for the synthesis of thienamycin (**1**), was stereoselectively prepared by 1,3-dipolar cycloaddition of the nitrone (**12**) and benzyl crotonate as a key reaction.

The carbapenem antibiotics have become an increasingly interesting class of naturally occurring substances with regards to both biology and synthesis. Thienamycin (**1**) is a novel member of this family of compounds, isolated from *Streptomyces cattleya*[1] and fully characterized by spectroscopic and X-ray technique.[2] The first synthesis of **1** has been reported by Merck group,[3] and modified syntheses have also been published by them.[4-8] Recently we have developed[9-11] a stereoselective synthesis of **1** by

(1) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.

(2) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratchiffe, R. W.; Walton, E.; Ruswinkle, L. J.f Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

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(4) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

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(7) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913.

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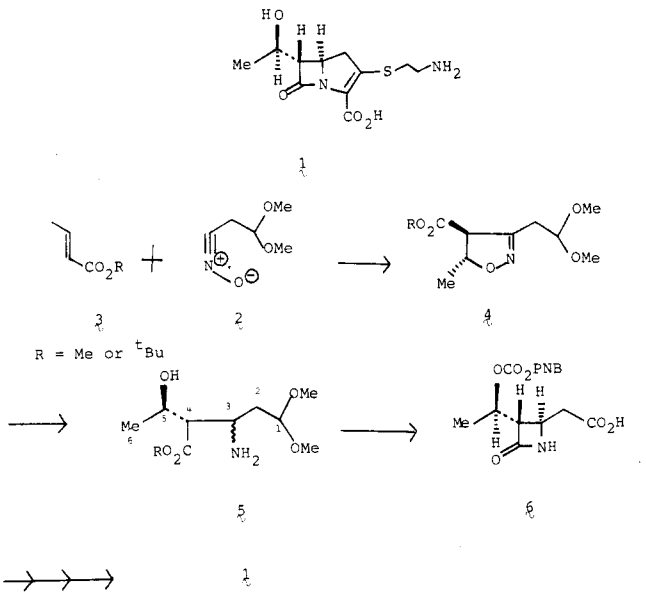
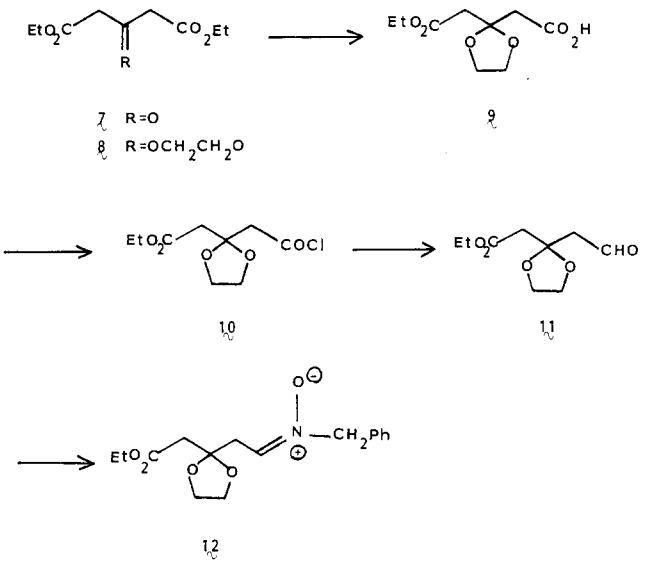
0022-3263/82/1947-2328$01.25/0

Scheme I



Scheme II



employing 1,3-dipolar cycloaddition of the nitrile oxide (2) and crotonates (3) to the isoxazoline (4) as a key reaction. In this synthesis, however, the reduction of 4 with platinum oxide in acetic acid afforded the mixture of diastereomers at the C-3 position of the amino alcohol (5), and the introduction of an acetic acid unit into 6 to construct a [3.2.0] bicyclic ring system was required in a later stage.

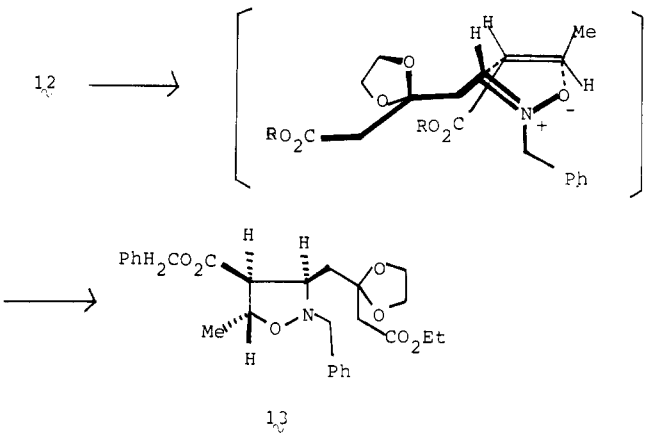
We here publish a versatile and entirely stereoselective synthesis of a [3.2.0] bicyclic compound employing 1,3-dipolar cycloaddition of the nitrone[12,13] and benzyl crotonate. Our synthetic strategy using 1,3-dipolar cycloaddition for a construction of a carbapenem ring system is based on the following considerations: (1) *trans*-crotonate could be the appropriate dipolarophile to control the stereochemistry at the C-6 and C-8 positions of thienamycin; (2) a nitrone, which should have all the functional groups to construct a [3.2.0] bicyclic ring system, would be a better 1,3 dipolar than a nitrile oxide for the purpose of restricting the stereochemistry at the C-5 position; (3) a chiral product would be expected by using a chiral nitrone (see Scheme I).

Results and Discussion

The requisite nitrone was synthesized in the following manner. Diethyl 1,3-acetonedicarboxylate (7) (Scheme II) was treated with ethylene glycol to give the diester (8), whose selective hydrolysis with 0.25 N sodium hydroxide afforded the monoacid (9). The aldehyde (11) was prepared from the corresponding acid chloride (10) according to Fleet's procedure[14] in overall 85.6% yield from 7.

Treatment of 11 with benzylhydroxylamine in dry benzene gave rise to the desired nitrone (12), which without isolation was heated at reflux with benzyl crotonate to furnish the cycloaddition product (13) with a desired stereochemistry in 83.7% yield from 11. The stereochemical assignment for 13 was confirmed based on its NMR

Chart I



data.[15] This observation would lead to the conclusion that the cycloaddition has proceeded via the endo-crotonate–(*E*)-nitrone transition state, shown in Chart I, selectively. Although the use of a nitrone–crotonate cycloaddition to establish the relative C_5, C_6, C_8 stereochemistry of a 6-(hydroxyethyl)carbapenam system has been previously shown by Tufariello,[16,17] they failed to generate a molecule having the correct functionality for conversion to thienamycin-type antibiotics.

Since the required adduct (13) was synthesized stereoselectively, we next studied its conversion to an azetidin-2-one. First, the catalytic hydrogenation on palladium–carbon for 13 was carried out in ethanol under medium hydrogen pressure (~4–5 atm) of hydrogen to give rise to an amino acid, whose cyclization with *N*,*N*-dicyclohexylcarbodiimide (DCC) in acetonitrile to azetidin-2-one afforded two compounds (14 and 15) in 54% yield (see Scheme III). The major product (14) was assigned to be the *N*-ethyl derivative, arising from the condensation of the amino acid with ethanol under the reduction conditions.[18,19] In order to inhibit the formation of 14, the

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(14) Fleet, G. W. J.; Harding, P. J. C. *Tetrahedron Lett.* **1979**, 975. Fleet, G. W. J.; Fuller, C. J.; Harding, P. J. C. *Ibid.* **1978**, 1437.
(15) The other possible stereo- and regioisomers could not be isolated.
(16) Tufariello, J. J.; Lee, G. E.; Senaratne, P. A.; Al-Nuri, M. *Tetrahedron Lett.* **1979**, 4359.
(17) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373.
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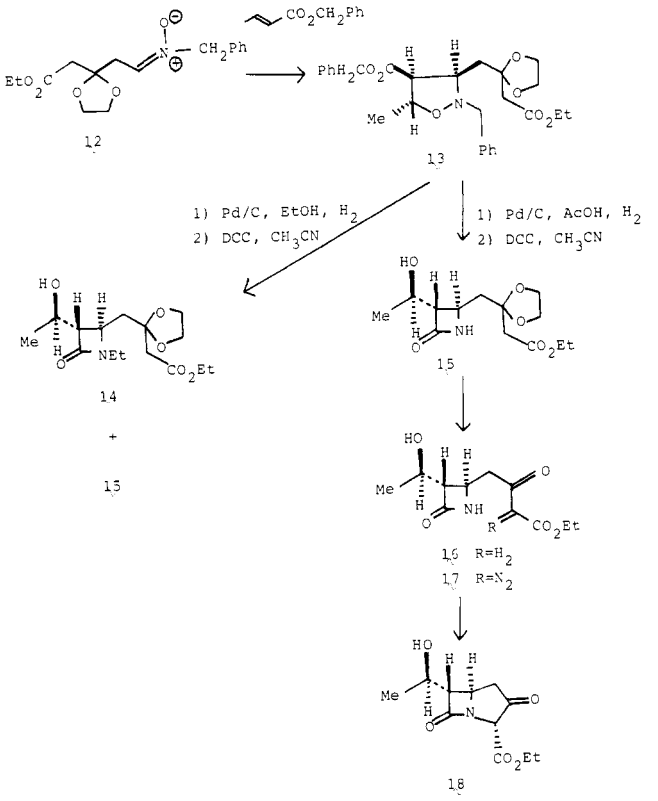
(19) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229.

Scheme III



hydrogenation for **13** was carried out in acetic acid as solvent, and subsequent DCC treatment gave the desired azetidinone (**15**) as the sole cyclized product in 40% yield. Deketalization of **15** with perchloric acid furnished the β-keto ester (**16**), which was converted to the bicyclic compound **18** via the diazo ketone (**17**), adopting Merck's procedure.[4-7]

The bicyclic β-keto ester ring system has been proved to be an appropriate precursor for the synthesis of carbapenem antibiotics such as thienamycin and PS-5 by Merck group[4-7] and by us.[9-11,20] We have now achieved a short and stereoselective synthesis of the bicyclic ring system, and its chiral synthesis is under investigation in our laboratory.

Experimental Section

Infrared spectra were run on a Hitachi 215 spectrophotometer in $CHCl_3$ solution. NMR spectra were determined with JEOL-PMX-60 and JNM-FX-100 spectrometers in $CDCl_3$ solution, and chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained with a JEOL-JMS-D300 spectrometer.

Ethyl 3,3-(Ethylenedioxy)-4-formylbutyrate (11). To a solution of the acid **9** (2.18 g, 0.01 mol) in 20 mL of dry benzene was added oxalyl chloride (3.8 g, 0.03 mol), and the resulting mixture was stirred for 3 h at room temperature under nitrogen. The solvent was evaporated to afford the acid chloride (**10**) as a yellowish oil: IR ($CHCl_3$) 1800, 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz, CH_2**Me**), 2.82 (s, 2 H, 2 H_2), 3.59 (s, 2 H, 4 H_2), 4.04 (s, 4 H, OCH_2CH_2O), 4.17 (q, 2 H, J = 7 Hz, CH_2Me).

A mixture of the above acid chloride (**10**) in 15 mL of acetone was added to a solution of triphenylphosphine (5.24 g, 0.02 mol) and bis(triphenylphosphine)copper(I) tetrahydroborate (6.03 g, 0.01 mol) in 30 mL of acetone. The resulting mixture was stirred for 0.5 h at room temperature. After filtration, the solvent was evaporated to give a syrup which was subjected to chromatography on silica gel. Elution with benzene–ether (9:1) afforded the aldehyde (**11**) (1.73 g, 85.6%) as a colorless syrup: IR ($CHCl_3$) 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, CH_2**Me**), 2.75 (s, 2 H, 2 H_2), 2.99 (d, 2 H, J = 2.7 Hz, 4 H_2), 4.05 (s, 4 H, OCH_2CH_2O), 4.17 (q, 2 H, J = 7 Hz, CH_2Me), 9.76 (t, 1 H, J = 2.7 Hz, CHO); mass spectrum, m/e 202 (M^+), 201 ($M^+ - 1$).

Benzyl (3,4-*cis*:4,5-*trans*)-2-Benzyl-3-[3-(ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-5-methylisoxazolidine-4-carboxylate (13). A mixture of the aldehyde (**11**) (2 g, 0.01 mol) and benzylhydroxylamine (1.2 g, 0.01 mol) in 20 mL of dry benzene was refluxed for 1 h under nitrogen. The solvent was evaporated to give the nitrone (**12**) as a pale yellowish liquid: NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, CH_2**Me**), 2.67 (s, 2 H, CH_2CO_2), 3.09 (d, 2 H, J = 5.5 Hz, CH_2C=N), 3.87–4.24 (m, 6 H, OCH_2CH_2O and CH_2Me), 4.91 (s, 2 H, NCH_2Ar), 6.72 (t, 1 H, J = 5.5 Hz, CH=N), 7.38, (br s, 5 H, Ar H).

A solution of the above nitrone (**12**) and benzyl crotonate (4.4 g, 0.025 mol) in 20 mL of dry benzene was refluxed for 6 h under nitrogen. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with benzene–ether (49:1–19:1) afforded the isoxazolidine (**13**) (4 g, 83.7%) as a colorless syrup: exact mass for M^+ peak, calcd m/e 483.2253, found 483.2255; IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, CH_2**Me**), 1.32 (d, 3 H, J = 6.5 Hz, 5 Me), 2.15 (dd, 1 H, J = 5.5, 15.5 Hz, 3 CH**H**), 2.21 (dd, 1 H, J = 7, 15.5 Hz, 3 CH**H**), 2.53 (d, 1 H, J = 15.5 Hz, CH_2CO_2), 2.69 (d, 1 H, J = 15.5 Hz, CH_2CO_2), 3.07 (dd, 1 H, J = 8.5, 8.5 Hz, 4 H), 3.24–3.52 (m, 1 H, 3 H), 5.14 (s, 2 H, CO_2CH_2Ar), 7.35 (br s, 10 H, 2 × Ar H). Anal. Calcd for $C_{27}H_{35}NO_7$: C, 67.06; H, 6.88; N, 2.96. Found: C, 66.73; H, 6.72; N, 2.81.

(±)-4β-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-1-ethyl-3α-((1*R)-1-hydroxyethyl)azetidin-2-one (14) (±)-4β-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-3α-((1*R**)-1-hydroxyethyl)azetidin-2-one (15).** A mixture of the isoxazolidine (**13**) (570 mg, 1.18 mmol) and 10% palladium–carbon (500 mg) in 15 mL of ethanol was stirred at room temperature under a current of hydrogen (4.5 atm) for 40 h. After filtration and washing of the solid with ethanol, evaporation of the combined filtrates gave a syrup which was dissolved in 20 mL of acetonitrile, and then *N*,*N*′-dicyclohexylcarbodiimide (297 mg, 1.44 mmol) was added. The reaction mixture was stirred for 3.5 h at 60 °C. After filtration, the solvent was evaporated to give a syrup which was subjected to chromatography on silica gel. Elution with benzene–methanol (49:1) afforded the azetidinone (**14**) (201 mg, 51.2%) as a colorless syrup: exact mass for M^+ peak, calcd m/e 315.1682, found 315.1707; IR ($CHCl_3$) 1740, 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.16 (t, 3 H, J = 7 Hz, NCH_2**Me**), 1.28 (t, 3 H, J = 7 Hz, CH_2**Me**), 1.34 (d, 3 H, J = 6.5 Hz, CH**Me**), 1.88 (br s, 1 H, OH), 2.05 (dd, 1 H, J = 8.5, 15.5 Hz, 4 CH**H**), 2.55 (dd, 1 H, J = 4.5, 15.5 Hz, 4 CH**H**), 2.73 (s, 2 H, CH_2CO_2), 2.90 (dd, 1 H, J = 2, 7 Hz, 3 H), 3.06 (dq, 1 H, J = 7, 7 Hz, NCH**H**Me), 3.42 (dq, 1 H, J = 7, 7 Hz, NCH**H**Me), 3.68 (ddd, 1 H, J = 2, 4.5, 8.5 Hz, 4 H).

Further elution with benzene–methanol (97:3) afforded the azetidinone (**15**) (13.5 mg, 3.4%) as a colorless syrup: mass spectrum, m/e 288 $(M + 1)^+$; IR ($CHCl_3$) 3245 (NH), 1750, 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, CH_2**Me**), 1.32 (d, 3 H, J = 6.5 Hz, CH**Me**), 1.83 (br s, 1 H, OH), 2.14 (dd, 1 H, J = 9.5, 15.5 Hz, 4 CH**H**), 2.39 (dd, 1 H, J = 5, 15.5 Hz, 4 CH**H**), 2.68 (s, 2 H, CH_2CO_2), 2.90 (ddd, 1 H, J = 1.5, 2.5, 6.5 Hz, 3 H), 3.83 (ddd, 1 H, J = 2.5, 5, 9.5 Hz, 4 H), 6.17 (br s, 1 H, NH). Anal. Calcd for $C_{13}H_{21}NO_6 \cdot 0.5\ H_2O$: C, 52.69; H, 7.48; N, 4.73. Found: C, 53.14; H, 7.33; N, 4.74.

(±)-4β-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-3α-((1*R)-1-hydroxyethyl)azetidin-2-one (15).** A mixture of the isoxazolidine (**13**) (570 mg, 1.18 mmol) and 10% palladium–carbon (500 mg) in 15 mL of acetic acid was stirred at room temperature under a current of hydrogen (4.5 atm) for 40 h. After filtration followed by evaporation of the filtrate, the residue was dissolved in 20 mL of acetonitrile. After addition of *N*,*N*′-dicyclohexylcarbodiimide (297 mg, 1.44 mmol), the reaction mixture was stirred for 3.5 h at 60 °C. After filtration, the solvent was evaporated to give a syrup which was subjected to chromatography on silica gel. Elution with benzene–methanol (97:3) afforded the azetidinone (**15**) (135.5 mg, 40%) as a colorless syrup, the IR and

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NMR spectra and TLC behavior of which were identical with those of the sample prepared above.

(±)-4β-[3-(Ethoxycarbonyl)-2-oxopropyl]-3α-((1R*)-1-hydroxyethyl)azetidin-2-one (16). To a stirred and ice-cooled solution of the above ketal (**15**) (11.5 mg, 0.04 mmol) in 2 mL of methylene chloride was added 60% perchloric acid (1 drop). The resulting mixture was stirred for 0.5 h at 0 °C and then for 1 h at room temperature. After neutralization with 10% aqueous ammonium hydroxide solution followed by washing with water and drying (Na_2SO_4), the solvent was evaporated off to give a colorless syrup which was subjected to chromatography on silica gel. Elution with benzene–methanol (49:1) afforded the β-keto ester (**16**) (8.3 mg, 85.2%) as a syrup: exact mass for M^+ peak, calcd *m/e* 243.1107, found 243.1120; IR ($CHCl_3$) 3425 (NH), 1755, 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.29 (t, 3 H, *J* = 7 Hz, CH_2**Me**), 1.33 (d, 3 H, *J* = 6.5 Hz, CH**Me**), 2.85 (dd, 1 H, *J* = 2, 7 Hz, 3 H), 2.90 (dd, 1 H, *J* = 8.3, 18.5 Hz, 4-CH**H**), 3.10 (dd, 1 H, *J* = 5.7, 18.5 Hz, 4 CH**H**), 3.48 (s, 2 H, $COCH_2CO_2$), 3.84–4.32 (m, 4 H, CHOH, 4 H, CH_2Me), 6.14 (br s, 1 H, NH).

(±)-Ethyl 6α-((1R*)-1-Hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (18). To an ice-cooled solution of the above β-keto ester (**16**) (24.3 mg, 0.1 mmol) and *p*-toluenesulfonyl azide (21.7 mg, 0.11 mmol) in 2 mL of dry acetonitrile was added a solution of triethylamine (40 mg, 0.4 mmol) in 2 mL of dry acetonitrile under nitrogen. After the resulting mixture was stirred at 0 °C for 30 min, evaporation of the solvent gave a residue which was subjected to chromatography on silica gel. Elution with benzene–acetone (9:1) afforded the diazo compound (**17**) (24 mg, 86%) as a syrup: IR ($CHCl_3$) 3420 (NH), 2140 (diazo), 1758, 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.32 (d, 3 H, *J* = 6.5 Hz, CH**Me**), 1.34 (t, 3 H, *J* = 7 Hz, CH_2**Me**), 2.89 (ddd, 1 H, *J* = 0.8, 2, 7 Hz, 3 H), 3.16 (dd, 1 H, *J* = 7, 18.5 Hz, 4 CH**H**), 3.34 (dd, 1 H, *J* = 6, 18.5 Hz, 4 CH**H**), 3.97 (ddd, 1 H, *J* = 2, 6, 7 Hz, 4 H), 6.06 (br s, 1 H, NH).

A mixture of the above diazo compound (**17**) (24 mg, 0.086 mmol) and a catalytic amount of rhodium(II) acetate in 3 mL of dry benzene was heated for 1 h at 80 °C under nitrogen. After cooling to room temperature followed by filtration, evaporation of the solvent gave the 3-oxocarbapenam (**18**) (20 mg, 92.6%) as a syrup: exact mass for M^+ peak, calcd *m/e* 241.0949, found 241.0937; IR ($CHCl_3$) 1760, 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.31 (t, 3 H, *J* = 7 Hz, CH_2**Me**), 1.35 (d, 3 H, *J* = 6.5 Hz, CH**Me**), 2.42 (dd, 1 H, *J* = 8, 19 Hz, 4 H), 2.93 (dd, 1 H, *J* = 6.4, 19 Hz, 4 H), 3.18 (dd, 1 H, *J* = 2, 7 Hz, 6 H), 4.67 (s, 1 H, 2 H).

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Registry No. 9, 32296-89-2; **10**, 32367-46-7; **11**, 32296-85-8; **12**, 81477-53-4; **13**, 81477-54-5; **14**, 81477-55-6; **15**, 81477-56-7; **16**, 81477-57-8; **17**, 81477-58-9; **18**, 81477-59-0; benzylhydroxylamine, 622-30-0; benzyl crotonate, 65416-24-2.

Studies on the Syntheses of Heterocyclic and Natural Compounds. 950. Asymmetric Total Synthesis of (+)-Chenodeoxycholic Acid. Stereoselectivity of Intramolecular Cycloaddition of Olefinic *o*-Quinodimethanes†

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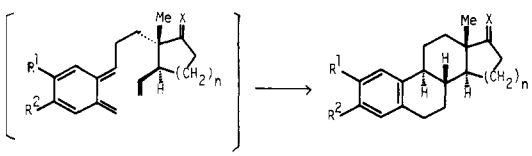
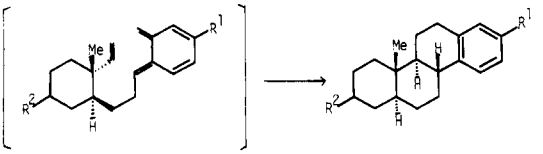
The first asymmetric total synthesis of (+)-chenodeoxycholic acid (**4**) is described. The key step is an intramolecular cycloaddition of the *o*-quinodimethane (**2**), generated in situ from the thermolysis of optically active 4α-acetoxy-1α-ethenyl-2-[2-(4-methoxybenzocyclobutenyl)-2-oxoethyl]-1β-methylcyclohexane (**1**), which gave stereoselectively 3α-acetoxy-17-methoxy-7-oxo-*D*-homo-18-nor-5β-androsta-13,15,17-triene (**3**). The stereoselectivity of this cycloaddition is also discussed.

The versatility of *o*-quinodimethanes in the synthesis of polycyclic ring systems[1] has resulted in a recent focusing of attention on novel methods of generation of such systems.[1,2] The stereochemical course of the synthesis of polycyclic ring system via cycloaddition of olefins and acetylenes to *o*-quinodimethanes has been well studied. Such reactions have been found to proceed with high stereoselectivity, and the stereoselective synthesis of A-ring aromatic steroids, for example, therefore was made possible (eq 1). In connection with our interest in the synthesis of pregnane-type steroids,[3] we have also achieved the stereoselective synthesis of D-ring aromatic steroids (eq 2). The observed stereoselectivity in these syntheses



(1)



(2)

results from the trans relationship of the olefin and

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(1) For a recent review of intramolecular cycloaddition reactions of *o*-quinodimethane, see (a) Oppolzer, W. *Synthesis* **1978**, 793; *Heterocycles* **1980**, *14*, 1615. (b) Kametani, T.; Fukumoto, K. *Kagaku no Ryoiki Zokan* **1980**, 81. (c) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (d) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3.

(2) (a) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863. (b) Djuric, S.; Sarkar, T.; Magnus, P. *Ibid.* **1980**, *102*, 6885.

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