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Synthesis of the Thienamycin Nucleus: A Synthesis of (±)-Diethyl 3-Benzylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2,2-bis(carboxylate)

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A synthesis of (±)-diethyl 3-benzylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2,2-bis-(carboxylate) (**15**) was accomplished.

Keywords——thienamycin nucleus; cyclization to 2-azetidinone; vinyl sulfide; vinyl sulfoxide; saponificatin; decarboxylation

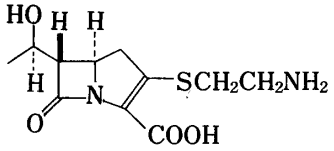
To date, many kinds of β-lactam antibiotics starting with the penicillins[1] have been found as natural products. Among them, thienamycin, isolated[2] from *Streptomyces cattleya*, exhibits broad antibiotic activity against both gram-positive and gram-negative bacteria, and also has activity against *Pseudomonas* spp. and resistance to bacterial β-lactamases.[3] In addition, thienamycin has a unique structure,[4] with the 1-carbapen-2-em nucleus and the 6-hydroxyethyl substituent in place of the more common amide functionality. This led many organic chemists to attempt the total synthesis of thienamycin.[5] We wish to describe an easy synthetic method for vinyl sulfide (**14**), which is a versatile intermediate for the synthesis of the thienamycin nucleus, and a synthesis of (±)-diethyl 3-benzylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2,2-bis(carboxylate) *via* **14b**.

The secondary amine (**1**), obtained from the alkylation of diethyl aminomalonate with ethyl bromoacetate in tetrahydrofuran (THF) using triethylamine as a base, was acylated with bromoacetyl chloride and triethyl amine in THF to give an amide (**2**) which was further cyclized to azetidin-2-one (**3**) in 99% yield by treatment with triethylamine in benzene. This type of cyclization was described by Sheehan and Bose in 1950.[6] The features of this reaction are easy manipulation, high yield of azetidin-2-one, and the possibility of utilizing both one carbon of the malonic diester part and the N-protecting carbon. Thus, it may be one of the most efficient of the thienamycin nucleus formation reactions.

One of the malonic diesters in the azetidin-2-one (**3**) was accessible to saponification to give the mono carboxylic acid (**4**) in 77% yield. The malonic half ester (**4**) was further decarboxylated by thermolysis in pyridine to give a diethyl ester (**5**) in 55% yield. The two esters of **5** were distinguishable, because the azetidin-2-one ring activated the ethyl ester connected directly to the C-4 position of the ring more than the other ethyl ester of the *N*-substituent. This was confirmed by both sodium borohydride reduction of **5** to yield the alcohol (**19**) and saponification of the diester (**16**, mp 40—41°C), which was also prepared from diethyl *N*-benzyl-aminomalonate and bromoacetyl chloride through the same route as for the preparation of compound **6**. Saponification of **16** with 1 eq of 1 N NaOH–pyridine (1 : 5) at room temperature gave the acid (**17**, 34% yield) and **16** (36% recovery). On the other hand, if this reaction were carried out in ethanol, it would be anticipated that the ethyl ester group of **16** would survive, and the benzyl ester would be saponified. In fact, saponification of **16** with 1 eq of 1 N KOH in ethanol at room temperature gave the carboxylic acid (**18**) in 66% yield.

Saponification of **5** with 1 eq of 1 N NaOH–pyridine (2 : 1) gave the carboxylic acid (**6**, 57% yield) as a main product. In addition, a small amount of the acid (**18**) was present as a minor (**18**) was present as a minor by-product which was inseparable this stage. The carboxylic acid (**6**) was converted to the acid chloride with oxalyl chloride in THF and successive treat-

ment of the acid chloride with ethereal diazomethane and then hydrogen chloride gave the chloromethyl ketone (**7**) in 43% yield. The chloride (**7**) was treated with thiophenol or benzylmercaptan to give **8a** or **8b** in 78% or 75% yield, respectively, and **7** could also be reacted with various other kinds of mercaptans. Sodium borohydride reduction of **7**, **8a**, and **8b** in ethanol gave **9a**, **9b**, and **9c** as a mixture of two racemic diastereomers in 93%, 97% and 91% yields, respectively. Acetylation of **9a**, **9b**, and **9c** with acetic anhydride–pyridine (1 : 2) at room temperature gave the acetoxy compounds, **10a**, **10b** and **10c** in 87%, 78% and 85% yields, respectively. The ratio of the two racemic diastereomers of **10a** was elucidated as 1 : 3 from ^{1}H nuclear magnetic resonance (NMR) measurement. This mixture, **10a**, had a sharp melting point (mp 125—126°C) contrary to expectation, and **10b**, and **10c** were oily materials. Treatment of the diastereomeric mixture of **10c** with thiophenol and diazabicyclo[5.4.0]undecene (DBU) in THF at room temperature gave **10a** with almost the same diastereomer ratio as that obtained from the route *via* **9a**. Oxidation of **10b** with *m*-chloroperbenzoic acid in chloroform at 0—5°C gave quantitatively a mixture of four racemic diastereomers, which was inseparable chromatographically. Elimination of acetic acid from **11b** with DBU in toluene at reflux temperature gave the vinyl sulfoxide (**12b**) in 49% yield as an oily mixture of two racemic diastereomers. The acetoxy compound, **10a**, was also converted to **12a** in 51% yield *via* **11a**. Treatment of the vinyl sulfoxides **12b** and **12a** with potassium iodide and acetyl chloride gave vinyl sulfides **13b** and **13a** in 96% and 55% yields, respectively. Treatment of both **13b** and **13a** with four equivalents of lithium hexamethyldisilazide, and successive treatment with ethyl chloroformate at −78°C, gave the diethyl aminomalonate derivatives **14b** and **14a** in 51



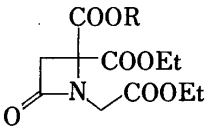
thienamycin

$EtOOCCH_2NHCH(COOEt)_2$

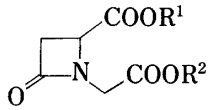
1

$BrCH_2CONCH(COOEt)_2$ with CH_2COOEt

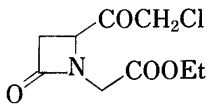
2



3 : R=Et
4 : R=H



5 : $R^1=R^2=Et$
6 : $R^1=H$, $R^2=Et$
16 : $R^1=Et$, $R^2=CH_2Ph$
17 : $R^1=H$, $R^2=CH_2Ph$
18 : $R^1=Et$, $R^2=H$



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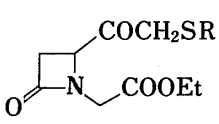
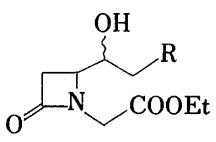
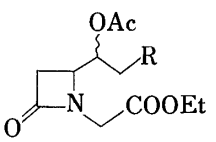


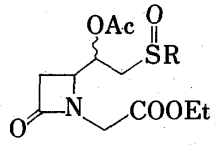
8a : R=Ph
8b : $R=CH_2Ph$



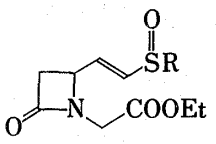
9a : R=SPh
9b : $R=SCH_2Ph$
9c : R=Cl



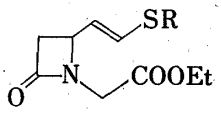
10a : R=SPh
10b : $R=SCH_2Ph$
10c : R=Cl



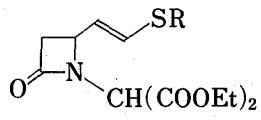
11a : R=Ph
11b : R=CH_2Ph



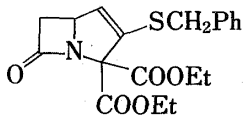
12a : R=Ph
12b : R=CH_2Ph



13a : R=Ph
13b : R=CH_2Ph



14a : R=Ph
14b : R=CH_2Ph



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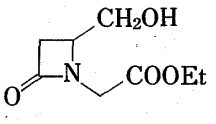

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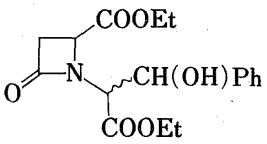

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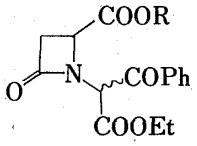
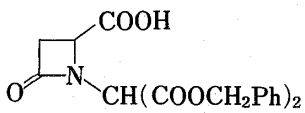
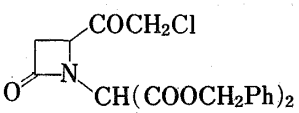


21 : R=Et
22 : R=H



23



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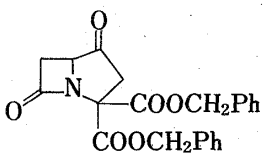

25

Chart 1

and 52% yields, respectively. In this reaction, the C-3 carboethoxylated product was not detected, and the use of almost the same amount of lithium hexamethyldisilazide resulted in recovery of a considerable amount of the starting material. The methylene carbon in the N-branched moiety of compounds **5**, **6**, **16** and **17** as well as **14** readily generated the corresponding carbanion with lithium hexamethyldisilazide for various types of reactions, such as alkylation, aldol condensation, acylation, carboxylation, selenylation and sulfide formation at that position. Therefore, reaction of **5** with benzaldehyde or benzoyl chloride gave **20** or **21** in 49 or 75% yield, respectively. Also, compound **23** was obtained from **17** in 44% yield. Saponification of **21**, which could also be obtained by Jones oxidation of **20**, gave the monoacid (**22**) in 73.5% yield. Successive treatment of the acid (**23**) with oxalyl chloride, diazomethane, and hydrogen chloride gave the chloromethyl ketone (**24**). Cyclization of **24** with various kinds of bases failed to afford the azabicyclo compound (**25**). On the other hand, successive treatment of **14b** with bromine, sodium hydride, and DBU according to the method of a Merck research group[5c] gave (±)-diethyl 3-benzylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2,2-bis(carboxylate) (**15**, mp 125°C) in 57% yield. Thus, the synthesis of the title compound was accomplished.

Experimental

All melting points are uncorrected. Nuclear magnetic resonance spectra were obtained on a Hitachi R-24, Varian A-60 or HA-100 spectrometer using tetramethylsilane as an internal standard, infrared spectra (IR) on a Jasco IR A-2 spectrometer, and mass spectra on a JMS-01SG mass spectrometer. Preparative thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} plates.

Diethyl *N*-(Ethoxycarbonylmethyl)aminomalonate (1)——Ethyl bromoacetate (167 g, 1.0 mol) and Et_3N (111 g, 1.1 mol) were added to a suspension of diethyl aminomalonate HCl salt (105.9 g, 0.50 mol) in THF (1.2 l), and the mixture was refluxed for 4 h, then cooled. The resulting precipitate was removed by suction filtration, and the remaining THF solution was concentrated *in vacuo*. The product was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oily residue. Column chromatography of the oily residue on silica gel (1 kg; eluent, PhH–EtOAc (4: 1)) gave **1** (75 g, 57.6%) as an oil; NMR ($CDCl_3$) δ: 1.27 (3H×3, t, J=7.5 Hz), 2.55 (1H, br s, NH), 3.51 (2H, s), 4.15 (1H, s), 4.21 (2H, q, J=7.5 Hz), 4.27 (2H×2, q, J=7.5 Hz); IR ν_{max} (film): 3360 (w), 1750 (sh), 1740 cm^{-1}.

***N*-Bis(ethoxycarbonyl)methyl-*N*-ethoxycarbonylmethyl-2-bromoacetamide (2)**——Et_3N (7.5 g, 74.5 mmol) was added to a solution of **1** (17.8 g, 68 mmol) and bromoacetyl chloride (11.8 g, 75 mmol) in THF (250 ml) at 0°C with stirring. The reaction mixture was stirred for 30 min, then diluted with EtOAc, washed with 10% HCl aq., sat $NaHCO_3$ and brine, dried over $MgSO_4$, decolorized with activated charcoal, and concentrated *in vacuo* to give an oily residue. Column chromatography on silica gel gave **2** (22.9 g, 88.5%) as an oil; NMR ($CDCl_3$) δ: 1.28 (9H, t, J=7 Hz), 3.85—4.50 (10H, m), 6.06 (1H, s); IR ν_{max} (film): 1745, 1670 cm^{-1}.

1-Ethoxycarbonylmethyl-4,4-bis(ethoxycarbonyl)-2-azetidinone (3)——Et_3N (6.65 g, 66 mmol) was added to a solution of **2** (22.9 g, 60 mmol) in PhH (200 ml), and the mixture was heated for 5 min in a hot water bath (80°C), then allowed to stand for 15 h at room temp. The reaction mixture was washed with 10% HCl aq., sat $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of PhH gave an oily residue, which was purified by column chromatography on silica gel (600 g; eluent, PhH–EtOAc (4: 1)) to give **3** (17.9 g, 99%) as an oil; NMR (CDCl) δ: 1.24 (3H, t, J=6.5 Hz), 1.26 (6H, t, J=6.5 Hz), 3.44 (2H, s, C_3–$\underline{H}_2$), 4.0—4.5 (8H, m); IR ν_{max} (film): 1785, 1745 cm^{-1}; MS *m/e*: 301 (M^+), 228, 200, 173, 172, 149.

(±)-1-Ethoxycarbonylmethyl-4-ethoxycarbonyl-2-azetidinone-4-carboxylic Acid (4)——A solution of KOH (16 g, 85% purity) in 99% EtOH (150 ml) was added to a solution of **3** (86 g, 0.286 mol) in 99% EtOH (100 ml) at 0°C over 1 h with stirring. The mixture was stirred for another 1 h at ice-bath temp. and then for 2 h at room temperature. The ethanol was removed using a rotary evaporator. EtOAc and dil. $NaHCO_3$ were added to the residue, and the whole was then stirred vigorously to remove non-acidic material. The aqueous layer was acidified by addition of conc.HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **4** (56.5 g, 77%); NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 1.23 (3H, t, J=7 Hz), 3.46 (2H, s), 4.0—4.5 (6H, m), 8.00 (1H, br s, COO$\underline{H}$); IR ν_{max} (film): 3600—2400 (br), 1790 (shoulder), 1755 cm^{-1}.

(±)-Ethyl 1-Ethoxycarbonylmethyl-2-azetidinone-4-carboxylate (5)——A mixture of **4** (27.5 g, 1.0 mol) and pyridine (0.8 ml) was heated at 150—155°C for 50 min with gentle stirring. After cooling, the reaction mixture was diluted with EtOAc. The solution was washed with sat.$NaHCO_3$ to recover unchanged **4** (4.1 g recovery). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give an oily residue, which was distilled under reduced pressure, bp 125—130°C (1.5 mmHg). The yield of **5** was 11.5 g (55%). IR ν_{max} (film): 1780, 1750 cm^{-1}; MS *m/e*: 229 (M^+), 201, 183, 156, 128; NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz), 1.30 (3H, t, J=7 Hz), 3.02 (1H, dd, J=3, 14 Hz), 3.37 (1H, dd, J=5, 14 Hz), 3.79, 4.44 (2H, AB-q, J=18 Hz), 4.23 (2H, q, J=7 Hz), 4.25 (2H, q, J=7 Hz), 4.48 (1H, dd, J=3, 5 Hz, C_4–$\underline{H}$).

(±)-1-Ethoxycarbonylmethyl-2-azetidinone-4-carboxylic Acid (6)——A 1 N NaOH solution (10 ml) was added dropwise to a solution of the diester (**5**, 2.29 g, 10 mmol) in pyridine (5 ml) at −5°C with stirring over a period of 10 min. The reaction mixture was allowed to stand for 16 h at 0°C, then poured into sat.$NaHCO_3$ (40 ml), and washed with EtOAc. The aqueous layer was acidified with conc.HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **6** (1.15 g, 57%); IR ν_{max} (film): 3600—2400, 1750 cm^{-1}; NMR (CD_3COCD_3) δ: 1.17 (3H, t, J=7 Hz), 2.95 (1H, dd, J=3, 14.5 Hz), 3.34 (1H, dd, J=5, 14.5 Hz), 3.82, 4.31 (2H, AB-q, J=19 Hz), 4.13 (2H, q, J=7 Hz), 4.41 (1H, dd, J=3, 5 Hz).

(±)-1-Ethoxycarbonylmethyl-4-(1-oxo-2-chloro)ethyl-2-azetidinone (7)——Oxalyl chloride (1.5 ml) was added to a solution of the acid **6** (2.01 g, 10 mmol) in THF (40 ml) at 24°C with stirring. After a reaction time of 2.5 h, the mixture was concentrated *in vacuo*, and dried with a pump to give an acid chloride as a crystalline solid. A solution of the obtained acid chloride in THF (20 ml) was added to a magnetically stirred solution of excess ethereal CH_2N_2 at 20°C. After 30 min, the solution was concentrated *in vacuo* to give a diazoketone as an oil; IR ν_{max} (film): 2120, 1770, 1740, 1640 cm^{-1}. Excess HCl gas was introduced into a solution of this diazoketone in THF (20 ml) at 0°C, and the resulting acidic solution was allowed to stand for 1 h, then diluted with EtOAc, washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. Column chromatography on silica gel (50 g) gave a chloromethyl ketone, **7**, (1.01 g, 43%) as a viscous oil, IR ν_{max} (film): 1770, 1745 cm^{-1}; NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 2.8—4.6

(8H, m), 4.85 (1H, dd, J=3, 6 Hz, C_4–H).

(±)-1-Ethoxycarbonylmethyl-4-(1-oxo-2-phenylthio)ethyl-2-azetidinone (8a)——Et_3N (1.1 g, 11 mmol) was added to a solution of **7** (2.34 g, 10 mmol) and PhSH (1.21 g, 11 mmol) in THF (20 ml) with stirring at 25°C. A precipitate of $Et_3N \cdot HCl$ salt appeared immediately. After 10 min, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. Column chromatography on silica gel (60 g; eluent, PhH–EtOAc (3: 1)) gave **8a** (2.40 g, 78%) as a viscous oil; IR ν_{max} (film): 1770, 1740, 1585 cm^{-1}: MS *m/e*: 307 (M^+), 265 (M^+-42); NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.76 (1H, ddd, J=14.5, 3, 0.5 Hz, C_3–H), 3.24 (1H, dd, J=14.5, 6 Hz, C_3–H), 3.71 (1H, dd, J=18, 0.5 Hz), 3.74 (2H, s), 4.16 (2H, q, J=7 Hz), 4.33 (1H, d, J=18 Hz), 4.81 (1H, dd, J=3, 6 Hz, C_4–H), 7.29 (5H, s).

(±)-1-Ethoxycarbonylmethyl-4-(1-oxo-2-benzylthio)ethyl-2-azetidinone (8b)——Et_3N (1.1 g, 11 mmol) was added to a solution of **7** (2.34 g, 10 mmol) and $PhCH_2SH$ (1.36 g, 11 mmol) in THF (20 ml) with stirring at 25°C. After 10 min, the reaction mixture was treated as described above for the formation of **8a** from **7** and PhSH, to give **8b**: (2.42 g, 75%) as a foam; IR ν_{max} (film): 1770, 1745 cm^{-1}; MS *m/e*: 321 (M^+); NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.83 (1H, dd, J=3.2, 15 Hz), 3.15 (2H, s), 3.30 (1H, dd, J=5.5, 15 Hz), 3.70 (2H, s), 3.75 (1H, d, J=18.5 Hz), 4.20 (2H, q, J=7 Hz), 4.38 (1H, d, J=18.5 Hz), 4.68 (1H, dd, J=3.2, 5.5 Hz), 7.34 (5H, s).

A Mixture of (±)-(*R,*R**)- and (±)-(*R**,*S**)-1-Ethoxycarbonylmethyl-4-(1-hydroxy-2-phenylthio)ethyl-2-azetidinone (9a)**——$NaBH_4$ (20 mg, 0.53 mmol) was added to a solution of **8a** (563 mg, 1.80 mmol) in 99.5% EtOH (20 ml) at −20°C with stirring. After a reaction time of 10 min at −20°C, the reaction mixture was acidified with dil.HCl, and extracted with EtOAc. The extract was washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **9a** (530 mg, 93%) as a gummy mixture of diastereomers. This mixture was employed for the next reaction without further purification.

A Mixture of (±)-(*R,*R**)- and (±)-(*R**,*S**)-1-Ethoxycarbonylmethyl-4-(1-hydroxy-2-benzylthio)ethyl-2-azetidinone (9b)**——$NaBH_4$ (100 mg, 2.36 mmol) was added to a solution of **8b** (2.25 g, 7 mmol) in 99.5% EtOH (80 ml) at −20°C with stirring. After 20 min at −20°C, the reaction mixture was treated as described above for the formation of **9a** by the reduction of **8a**, to give **9b** (2.20 g, 97%) as an oily mixture of diastereomers, which was employed for the next reaction without further purification.

A Mixture of (±)-(*R,*R**)- and (±)-(*R**,*S**)-1-Ethoxycarbonylmethyl-4-(1-hydroxy-2-chloro)ethyl-2-azetidinone (9c)**——The chloromethylketone **7** was reduced with $NaBH_4$ in EtOH, according to the procedure described for the formation of **9a** from **8a**, to give **9c** (91%) as a mixture of diastereomers, which was employed for the next reaction without further purification.

A Mixture of (±)-(*R,*R**)- and (±)-(*R**,*S**)-1-Ethoxycarbonylmethyl-4-(1-acetoxy-2-phenylthio)ethyl-2-azetidinone (10a)**——A solution of a diastereomeric mixture **9a** (1.55 g, 5 mmol) in Ac_2O–pyridine (1: 2, 9 ml) was allowed to stand for 18 h at 24°C. The reaction mixture was concentrated under reduced pressure, and diluted with EtOAc. This solution was washed with dil. HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a mixture of diastereomers **10a** (1.53 g, 87%) as a crystalline solid; mp 125—126°C (from EtOAc–*n*-hexane); MS *m/e*: 351 (M^+), 291 (M^+-AcOH); NMR ($CDCl_3$) δ: 1.91 ($OCOCH_3$ of one of the diastereomers), 1.96 ($OCOCH_3$ of the other diastereomer). The ratio of the former to the latter was 1: 3. *Anal.* Calcd for $C_{17}H_{21}NO_5S$: C, 58.11; H, 6.02; N, 3.99. Found: C, 57.90; H, 6.26; N, 4.12.

A Mixture of (±)-(*R,*R**)- and (±)-(*R**,*S**)-1-Ethoxycarbonylmethyl-4-(1-acetoxy-2-benzylthio)ethyl-2-azetidinone (10b)**——A solution of a diastereomeric mixture **9b** (2.0 g, 6.2 mmol) in Ac_2O–pyridine (1: 2, 18 ml) was allowed to stand for 18 h at 24°C. The reaction mixture was treated as described in the preparation of **10a** by acetylation of **9a**, to give a mixture of epimers **10b** (1.76 g, 78%) as an oil, which was inseparable on a silica gel TLC plate; IR ν_{max} (film): 1760, 1735 cm^{-1}; NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz), 2.01 (3H, s), 2.4—4.5 (11H, m), 4.87—5.36 (1H, m), 7.30 (5H, s); MS *m/e*: 365 (M^+).

A Mixture of (±)-(*R,*R**)- and (±)-(*R**,*S**)-Ethoxycarbonylmethyl-4-(1-acetoxy-2-chloro)ethyl-2-azetidinone (10c)**——The diastereomeric mixture **9c** was acetylated with Ac_2O–pyridine according to the procedure described for the transformation to **10a** from **9a**, to give a mixture of diastereomers **10c** (85%) as an oily mixture, which was employed for the next reaction without further purification.

Preparation of 10a from 10c——A mixture of **10c** (279 mg, 1 mmol), PhSH (132 mg, 1.2 mmol) and DBU (182 mg, 1.2 mmol) in THF (10 ml) was allowed to stand for 18 h at 25°C. The reaction mixture was diluted with EtOAc, washed with 10% HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a mixture of two racemic diastereomers as a crude crystalline solid. This solid was purified by preparative silica gel TLC (developed with PhH–EtOAc (3: 1), Rf=0.36 as a single spot) to give **10a** (250 mg, 71%) as a crystalline solid; mp 125—126°C (needles from EtOAc–*n*-hexane). The ratio of the diastereomers was almost the same as that obtained *via* the route **7**→**8**→**9a**→**10a** (1: 3 from NMR).

A Mixture of Four Racemates of 1-Ethoxycarbonylmethyl-4-(1-acetoxy-2-phenylsulfinyl)ethyl-2-azetidinone (11a)——A solution of **10a** (351 mg, 1 mmol) in CH_2Cl_2 (5 ml) was treated with *m*-chloroperbenzoic acid (80—90% purity, 200 mg) at 0°C with stirring. After 50 min, the reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **11a** (368 mg, quantitatively) as a crystalline solid; mp 130—165°C; IR ν_{max} (nujol): 1765, 1735 cm^{-1}; MS *m/e*: 368 (M^++1), 367 (M^+). *Anal.* Calcd for $C_{17}H_{21}NO_6S$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.85; H, 5.81; N, 3.89.

This mixture of 4 racemates showed two spots on a silica gel TLC plate (developed with EtOAc, Rf=0.303 and 0.393).

A Mixture of Four Racemates of 1-Ethoxycarbonylmethyl-4-(1-acetoxy-2-benzylsulfinyl)ethyl-2-azetidinone (11b)——A solution of **10b** (1.5 g) in $CHCl_3$ (25 ml) was treated with *m*-chloroperbenzoic acid (80—90% purity, 820 mg) at 0—5°C with stirring. After 10 min, the reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a mixture of 4 racemates, **11b** (1.57 g, quantitative), as a gummy residue which was inseparable on a silica gel preparative TLC plate (Rf=0.27, developed with EtOAc). This product was employed for the next reaction without further purification; NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.03—2.08 (3H), 2.7—4.5 (11H), 5.2—5.8 (1H), 7.4 (5H).

A Mixture of (±)-[4*R(*E*,*R**)]- and (±)-[4*R**(*E*,*S**)]-1-Ethoxycarbonylmethyl-4-(2-phenylsulfinyl)-ethenyl-2-azetidinone (12a)**——A solution of **11a** (240 mg, diastereomeric mixture) and DBU (100 mg) in toluene (10 ml) was refluxed for 2 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was chromatographed on a silica gel TLC plate (developed with PhH–EtOAc (1: 4) to give a mixture of diastereomers, **12a** (104 mg, in 51%), as a viscous oil which was employed for the next reaction without further purification. IR ν_{max} (film): 1770, 1750 cm^{-1}; NMR ($CDCl_3$) δ: 6.3—6.7 (2H, olefinic); MS *m/e*: 308 (M^++1), 290.

A Mixture of (±)-[4*R(*E*,*R**)]- and (±)-[4*R**(*E*,*S**)]-1-Ethoxycarbonylmethyl-4-(2-benzylsulfinyl)ethenyl-2-azetidinone (12b)**——A solution of **11b** (1.52 g, 4.0 mmol) and DBU (670 mg, 4.4 mmol) in toluene (25 ml) was refluxed for 2 h. The reaction mixture was treated as described above for the formation of **12a** to give a mixture of two racemates, **12b** (630 mg, 49%), as an oil which was inseparable on a preparative silica gel TLC plate (Rf=0.27, developed with EtOAc). NMR ($CDCl_3$) δ: 6.2—6.7 (2H, olefinic); IR ν_{max} (film): 1765, 1742 cm^{-1}.

(±)-(*E*)-1-Ethoxycarbonylmethyl-4-(2-phenylthio)ethenyl-2-azetidinone (13a)——KI (100 mg, 0.6 mmol) and acetyl chloride (47 mg, 0.6 mmol) were added to a solution of the sulfoxide **12a** (50 mg, 0.163 mmol) in DMF (1.5 ml) at 0°C. After being stirred for 30 min at 0—5°C and for another 30 min at 23°C, the reaction mixture was poured into water, and extracted with EtOAc. The extract was washed with dil. $Na_2S_2O_3$, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil. Purification on a preparative silica gel TLC plate gave **13a** (26 mg, 55%); IR ν_{max} (film): 1770, 1750 (shoulder), 1613 (w), 1588 (w) cm^{-1}; MS *m/e*: 291 (M^+); NMR ($CDCl_3$) δ: 1.25 (3H, t, J=6.5 Hz), 2.71 (1H, dd, J=2.5, 14.5 Hz), 3.28 (1H, dd, J=5, 14.5 Hz), 3.60, 4.17 (2H, AB-q, J=18 Hz), 4.18 (2H, q, J=6.5 Hz), 4.83 (1H, ddd, J=2.5, 5, 9 Hz, C_4–H), 5.64 (1H, dd, J=9, 15 Hz), 6.58 (1H, d, J=15 Hz), 7.37 (5H, s).

(±)-(*E*)-Ethoxycarbonylmethyl-4-(2-benzylthio)ethenyl-2-azetidinone (13b)——KI (664 mg, 4 mmol) and acetyl chloride (314 mg, 4 mmol) were added to a solution of the sulfoxide **12b** (340 mg, 1.06 mmol) in DMF (8 ml) at 0°C. After being stirred for 30 min at 0°C and for another 30 min at 25°C, the reaction mixture was treated as described above for the formation of **13a**, to give **13b** (310 mg, 96%); Rf=0.34, developed with PhH–EtOAc (5: 1) as an oil; IR ν_{max} (film): 1763, 1742 cm^{-1}; MS *m/e*: 305 (M^+); NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7 Hz), 2.60 (1H, dd, J=2.5, 15 Hz), 3.17 (1H, dd, J=5, 15 Hz), 3.45, 4.03 (2H, AB-q, J=18 Hz), 3.87 (2H, s), 4.13 (2H, q, J=7 Hz), 4.22 (1H, ddd, J=2.5, 5, 9 Hz, C_3–H), 5.47 (1H, dd, J=9, 15 Hz), 6.36 (1H, d, J=15 Hz), 7.31 (5H, s).

(±)-(*E*)-1-Bis(ethoxycarbonyl)methyl-4-(2-benzylthio)-ethyl-2-azetidinone (14b)——A solution of *n*-BuLi (15% in *n*-hexane, 2.5 ml, 4 mmol) was added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (646 mg, 4 mmol) in THF (10 ml) under a nitrogen atmosphere at 5°C. To the resulting solution was added a solution of **13b** (305 mg, 1 mmol) in THF (10 ml) at −78°C. After 20 min, a solution of ClCOOEt (434 mg, 4 mmol) in THF (4 ml) was added. After 1 h, the reaction mixture was quenched with AcOH (0.5 ml) in THF (2 ml) at −78°C, diluted with EtOAc, washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. The residue was purified on a preparative silica gel TLC plate to give **14b** (192 mg, 51%) as an oil; MS *m/e*: 377 (M^+); IR ν_{max} (film): 1770, 1745 cm^{-1}; NMR ($CDCl_3$) δ: 1.22 (6H, t, J=7 Hz), 2.66 (1H, dd, J=2.5, 15 Hz), 3.22 (1H, dd, J=5, 15 Hz), 3.84 (2H, s), 4.14 (2H, q, J=7 Hz), 4.22 (2H, q, J=7 Hz), 4.46 (1H, ddd, J=2.5, 5, 9 Hz, C_4–H), 4.97 (1H, s), 5.54 (1H, dd, J=9, 15 Hz, olefinic), 6.35 (1H, d, J=15 Hz, olefinic), 7.30 (5H, s).

(±)-(*E*)-1-Bis(ethoxycarbonyl)methyl-4-(2-phenylthio)-ethyl-2-azetidinone (14a)——**13a** was treated as described above for the formation of **14b** from **13b**, to give **14a** (52%) as a foam; MS *m/e*: 363 (M^+); IR ν_{max} (film): 1775, 1750, 1612 (w), 1585 (w) cm^{-1}: NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 2.78 (1H, dd, J=2.5, 15 Hz), 3.26 (1H, dd, J=5, 15 Hz), 4.20 (2H, q, J=7 Hz), 4.25 (2H, q, J=7 Hz), 4.60 (1H, ddd, J=2.5, 5, 9 Hz, C_4–H), 5.08 (1H, s), 5.68 (1H, dd, J=9, 15 Hz), 6.53 (1H, d, J=15 Hz), 7.33 (5H, s).

(±)-Diethyl 3-Benzylthio-7-oxo-1-azabicyclo[3.2.0]hept-3-ene-2,2-bis(carboxylate) (15)——A stirred solution of **14b** (44 mg) in dry ether (2 ml) was treated with bromine (20 mg) at 0—5°C. The color of the bromine disappeared immediately. After 15 min, NaH (9 mg as a 55% dispersion in mineral oil) and dry DMF (1 ml) was added to this reaction mixture with stirring at 0—5°C. After 1.5 h, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. DBU (20 mg) was added to a solution of this residue in THF (2 ml). After being stirred for 5 h at 24°C, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residual oil. Purification on a preparative TLC plate (developed with

PhH–EtOAc (5: 1)) gave unchanged **14b** (8 mg, 18% recovery) and **15** (20.3 mg, 57%) as a crystalline solid; mp 124—125°C (leaflets, from EtOAc–*n*-hexane); MS *m/e*: 375 (M^+), 333, 260, 91; IR ν_{max} (Nujol): 1770, 1748, 1735 cm^{-1}; NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz), 1.32 (3H, t, J=7 Hz), 2.86 (1H, dd, J=3.2, 16 Hz), 3.33 (1H, dd, J=5.2, 16 Hz), 4.05 (2H, s), 4.26 (2H, q, J=7 Hz), 4.33 (2H, J=7 Hz), 4.53 (1H, ddd, J=1.7, 3.2, 5.2 Hz), 5.80 (1H, d, J=1.7 Hz), 7.33 (5H, singlet-like). *Anal.* Calcd for $C_{19}H_{21}NO_5S$: C, 60.79; H, 5.64; N, 3.73; S, 8.53. Found: C, 60.62; H, 5.62; N, 3.67; S, 8.69.

(±)-Ethyl 1-Benzyloxycarbonylmethyl-2-azetidinone-4-carboxylate (16)——The same successive treatment of bromoacetyl bromide and diethyl (*N*-benzyloxycarbonylmethyl)aminomalonate, as described in the transformation of **1** to **5**, gave **16** (overall 16%) as a crystalline solid; mp 40—41°C; MS *m/e*: 291 (M^+); NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz), 3.04 (1H, dd, J=3, 15 Hz), 3.41 (1H, dd, J=5, 15 Hz), 3.93, 4.51 (2H, AB-q, J=19 Hz), 4.26 (2H, q, J=7 Hz), 4.47 (1H, dd, J=3, 5 Hz), 5.22 (2H, s), 7.47 (5H, s). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.90; H, 5.79; N, 4.79.

(±)-Benzyloxycarbonylmethyl-2-azetidinone-4-carboxylic Acid (17)——A solution of **16** (291 mg, 1 mmol) in pyridine (5 ml) and 1 N NaOH (1 ml) was refluxed for 1 h. The reaction mixture was diluted with sat. $NaHCO_3$ (20 ml), and washed with ether. The starting **16** (104 mg, 36%) was recovered from the organic layer. The aqueous layer was acidified with conc. HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **17** (85 mg) as a viscous oil; NMR ($CDCl_3$) δ: 3.05 (1H, dd, J=3, 15.5 Hz), 3.37 (1H, dd, J=5.5, 15.5 Hz), 3.88, 4.46 (2H, AB-q, J=18 Hz), 4.45 (1H, dd, J=3, 5.5 Hz), 5.14 (2H, s), 7.36 (5H, s); IR ν_{max} (film): 3500—2400 (br), 1750 (br) cm^{-1}.

(±)-Ethyl 1-Carboxymethyl-2-azetidinone-4-carboxylate (18)——A solution of **16** (291 mg, 1 mmol) in EtOH (2 ml) and 1 N KOH (1 ml) was stirred for 5 h at room temperature. The reaction mixture was treated as described above (**16**→**17**) to give **18** (132 mg, 66%) as a viscous oil; NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 3.09 (1H, dd, J=3, 15 Hz), 3.42 (1H, dd, J=5.5, 15 Hz), 3.88, 4.44 (2H, AB-q, J=18 Hz), 4.23 (2H, q, J=7 Hz), 4.52 (1H, dd, J=3, 5.5 Hz).

(±)-1-Ethoxycarbonylmethyl-4-hydroxymethyl-2-azetidinone (19)——$NaBH_4$ (110 mg) was added to an ice-cooled solution of **5** (678 mg, 3 mmol) in THF–H_2O (9: 1, 15 ml). After 15 min, aqueous 10% HCl was added dropwise to the resulting solution, and the whole was extracted with EtOAc. The extract was washed with sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil, which was chromatographed on a silica gel column. Elution with EtOAc–PhH (2: 1) gave **19** (155 mg, 29%) as an oil; MS *m/e*: 188 (M^++1), 187 (M^+), 169 (M^+-H_2O), 144; NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 2.94 (2H, d, J=3.5 Hz), 3.73, 4.27 (2H, AB-q, J=18 Hz), 4.20 (2H, q, J=7 Hz), 3.6—4.0 (4H, m, C_4–H, CH_2OH); IR ν_{max} (film): 3430, 1740 cm^{-1}.

A Racemic Mixture of Four Diastereomers of Ethyl 1-(2-Hydroxy-2-phenyl-1-ethoxycarbonyl)ethyl-2-azetidinone-4-carboxylate (20)——An ice-cooled solution of $(Me_3Si)_2NH$ (225 mg, 1.4 mmol) in THF (10 ml) under nitrogen was treated with *n*-BuLi (15% *n*-hexane solution, 0.8 ml, 1.3 mmol). The mixture was stirred for 15 min, then a solution of **5** (229 mg, 1.0 mmol) in THF (10 ml) was added dropwise over 5 min at −78°C. The red color of the carbanion of **5** appeared immediately. After a reaction time of 10 min, a solution of PhCHO (200 mg, 1.88 mmol) in THF (5 ml) was added to this anion solution. After 30 min, the reaction mixture was quenched with dil AcOH in THF, diluted with EtOAc, washed with 10% HCl aq., sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of EtOAc gave an oil, which was purified on a silica gel column (eluted with PhH–EtOAc (3: 1)) to afford **20** (165 mg, 49%); MS *m/e*: 335 (M^+), 229 (M^+−PhCHO), 176, 156, 128, 106, 105; IR ν_{max} (film): 3420, 1770 (shoulder), 1741 cm^{-1}.

A Racemic Mixture of Two Diastereomers of Ethyl 1-(1-Benzoyl-1-ethoxycarbonyl)methyl-2-azetidinone-4-carboxylate (21)——a) Treatment of **5** with PhCOCl in place of PhCHO according to the method described above for the formation of **20** from **5** gave **21** (75%) as a 3: 2 mixture of diastereomers; MS *m/e*: 333 (M^+); NMR ($CDCl_3$) δ: 0.6—1.5 (6H, m), 2.8—5.0 (7H, m), 6.09 (0.4H, s), 6.30 (0.6H, s), 7.4—8.4 (5H, m); IR ν_{max} (film): 1780, 1745, 1690 cm^{-1}.

b) Jones reagent (0.2 ml) was added to an ice-cooled solution of **20** (112 mg) in acetone (5 ml). After being stirred for 30 min, the reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. The residue was purified on a preparative TLC plate (developed with PhH–EtOAc (4: 1), Rf=0.5) to yield **21** (64 mg, 57%).

A Racemic Mixture of Two Diastereomers of 1-(1-Benzoyl-1-ethoxycarbonyl)methyl-2-azetidinone-4-carboxylic Acid (22)——A solution of **21** (500 mg, 1.5 mmol) in pyridine–1 N NaOH (1: 3, 4 ml, 3 mmol) was stirred for 1.5 h at 0°C. The reaction mixture was diluted with sat. $NaHCO_3$ (30 ml) and washed with ether. The aqueous layer was acidified with aq. 10% HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated to give an oily residue. Chromatography on a silica gel column gave **22** (336 mg, 73.5%) as a 2: 1 mixture of diastereomers; NMR ($CDCl_3$) δ: 1.0—1.4 (3H, m), 3.0—3.6 (2H, m), 3.9—4.4 (2H, m), 4.6—5.0 (1H, m), 6.05 (1/3H, s), 6.21 (2/3H, s), 7.3—8.4 (5H, m); IR ν_{max} (film): 3600—2500 (br), 1750, 1695 cm^{-1}.

(±)-1-Bis(benzyloxycarbonyl)methyl-2-azetidinone-4-carboxylic Acid (23)——An ice-cooled solution of $(Me_3Si)_2NH$ (1.61 g, 10 mmol) in THF (10 ml) under nitrogen was treated with *n*-BuLi (15% *n*-hexane solution, 6.1 ml, 10 mmol). The mixture was stirred for 15 min, then a solution of **17** (980 mg, 3.7 mmol) in THF (7 ml) was added at −78°C. After a reaction time of 10 min, a solution of $PhCH_2OOCCl$ (2 g, 11.7 mmol)

in THF (10 ml) was added. The reaction mixture was stirred for 3 h at −78°C, and then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil. Purification by silica gel column chromatography (eluted with PhH–EtOAc (2: 1)) gave **24** (650 mg, 44%) as a viscous oil; NMR ($CDCl_3$) δ: 2.98 (1H, dd, J=3.5, 14 Hz), 3.39 (1H, dd, J=6, 14 Hz), 4.58 (1H, dd, J=3.5, 6 Hz), 5.16 (2H, s), 5.23 (2H, s), 5.26 (1H, s), 7.35 (10H, s).

(±)-1-Bis(benzyloxycarbonyl)methyl-4-(1-oxo-2-chloro)ethyl-2-azetidinone (24)——Treatment of the acid **23** according to the method described for the formation of **7** from **6** gave **24** (29%) as an oil; MS *m/e*: 429 (M^+); NMR ($CDCl_3$) δ: 2.95 (1H, dd, J=3.5, 15 Hz), 3.39 (1H, dd, J=6, 15 Hz), 4.12 (2H, s), 4.99 (1H, dd, J=3.5, 6 Hz), 5.18 (2H, s), 5.34 (1H, s), 7.37 (10H, s); IR ν_{max} (film): 1788, 1755 cm^{-1}.

References and Notes

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