Base-induced Cyclization of *N*-[Bis(ethoxycarbonyl)methyl]-2-bromo-3-hydroxybutyramide Derivatives

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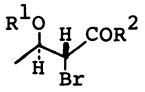
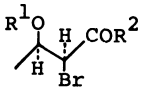
Treatment of (2*R*,3*R*)-*N*-(2,4-dimethoxybenzyl)-*N*-[bis(ethoxycarbonyl)methyl]-2-bromo-3-hydroxybutyramide (**5**) with DBU yielded the bicyclic β-lactam **13** by a direct cyclization, and its diastereoisomer **14** and the γ-lactam **15** *via* the *trans*-epoxide **6**. The same treatment of (2*S*,3*R*)-isomer (**11**) gave the direct cyclization product **14** in 93% yield. On the other hand, reaction of **5** and **11** with sodium hydride afforded the 2-azetidinone derivatives (mainly **14** (23%) from **5**, and **19** (75%) from **11**, respectively) *via* the corresponding epoxides **6** and **12**.

The first report on the discovery of thienamycin (isolation, structure, and biological activity) by the groups of Merck Sharp and Dohme Research Laboratories in 1976 produced a broad impact on organic chemists as well as medicinal chemists. This was because of the unique structure of thienamycin, different from that of traditional β-lactam antibiotics, and because of its powerful biological activity. Since its discovery, many congeners of thienamycin have been isolated as natural products and, at the same time, many attempts at syntheses of these carbapenems have been carried out by many groups. As one of such groups, we have reported on the stereocontrolled syntheses of monocyclic intermediates to carbapenems possessing a (1-hydroxy)ethyl side chain at the C-3 position.[1] Ahead of the cyclization of *N*-(2,4-dimethoxybenzyl)-*N*-(*t*-butoxycarbonylmethyl)-2-bromo-3-hydroxybutyramide[1b] obtained from L-threonine, the cyclization of 2-bromo-3-hydroxybutyramide derivatives (**5** and **11**) by means of bases was investigated in order to use the results in carbapenem synthesis.[2] As a result, it was confirmed that whether passing through the 2,3-epoxy derivatives (**6** or **12**) or not, base-induced intramolecular S_N2 cyclization occurred to give β-lactam derivatives as main products, together with the starting threonines (L-, L-*allo*, D-, and D-*allo*-). Thus we might be able to obtain the desired stereoisomer at the C-3 position and a hydroxyethyl side chain of β-lactam congeners.



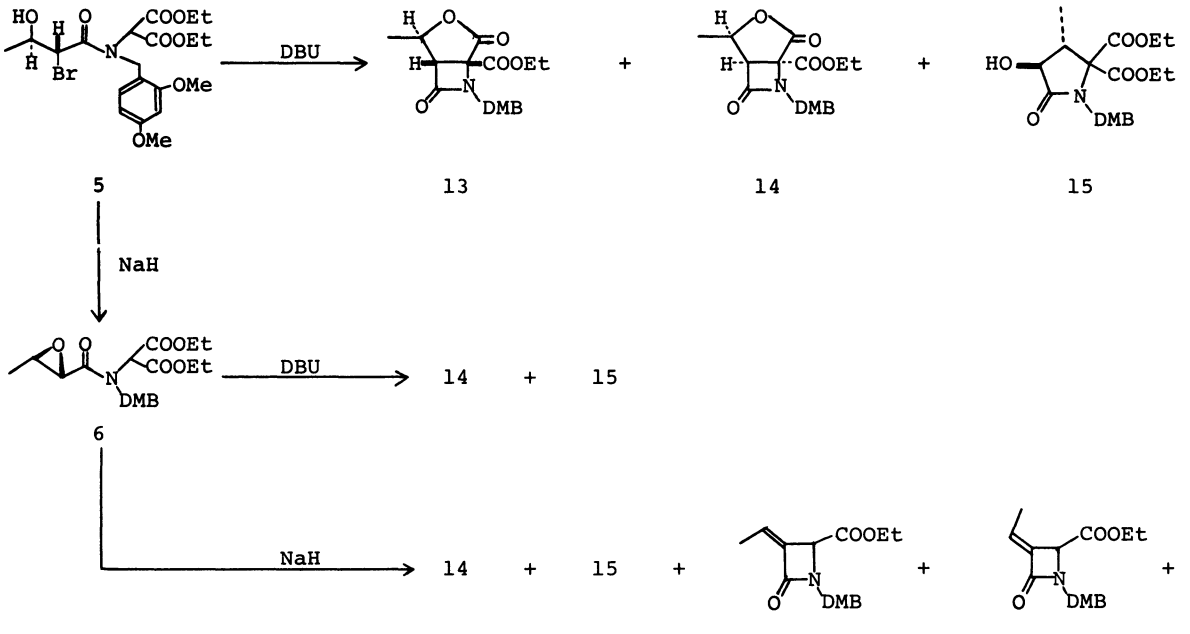
1 R^1 = H, R^2 = OH
2 R^1 = $SiMe_2Bu^t$, R^2 = OH
3 R^1 = $SiMe_2Bu^t$, R^2 = Cl
4 R^1 = $SiMe_2Bu^t$, R^2 = N(DMB)CH(COOEt)$_2$
5 R^1 = H, R^2 = N(DMB)CH(COOEt)$_2$



7 R^1 = H, R^2 = OH
8 R^1 = $SiMe_2Bu^t$, R^2 = OH
9 R^1 = $SiMe_2Bu^t$, R^2 = Cl
10 R^1 = $SiMe_2Bu^t$, R^2 = N(DMB)CH(COOEt)$_2$
11 R^1 = H, R^2 = N(DMB)CH(COOEt)$_2$

DMB = 2,4-dimethoxybenzyl

Scheme 1.



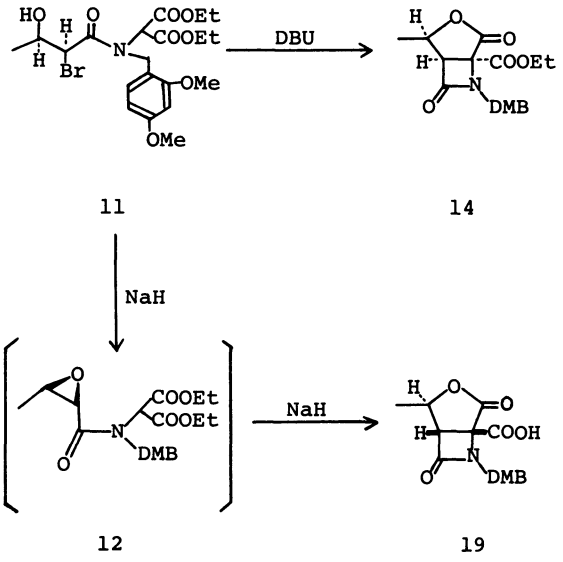
DMB = 2,4-dimethoxybenzyl

Scheme 2.

We wish here to report the results.

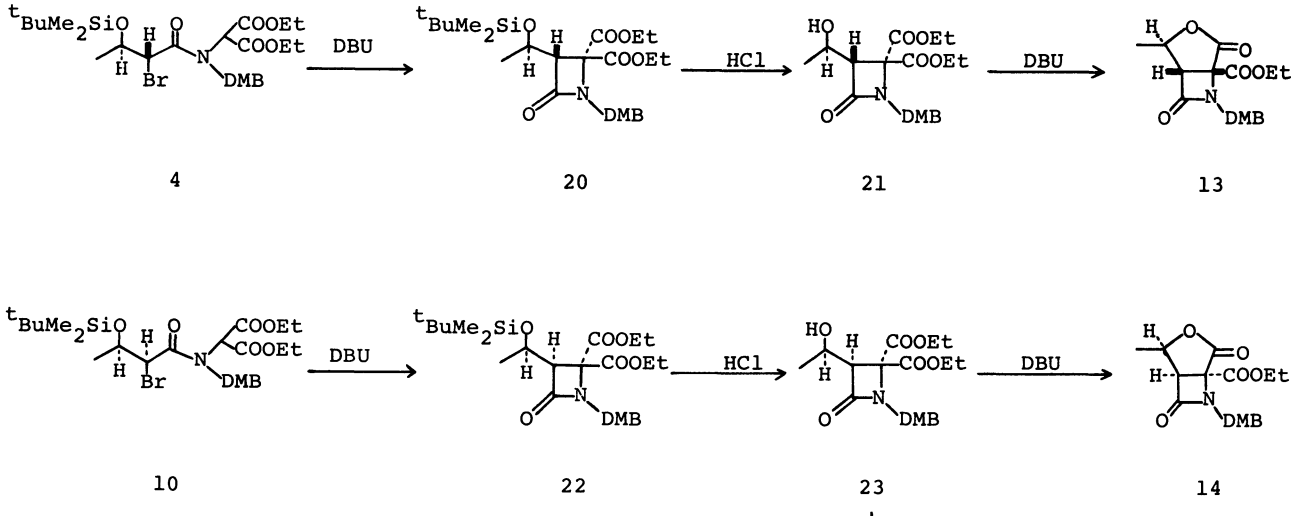
The starting **5** and **11** were synthesized as follows (Scheme 1). (2*R*,3*R*)-2-Bromo-3-hydroxybutyric acid (**1**) obtained from (2*R*,3*R*)-threonine (D-*allo*-threonine) was converted to the corresponding *t*-butyldimethylsilyl ether **2**, which was further treated with oxalyl dichloride in tetrahydrofuran (THF) at 20 °C for 3—16 h to give the acid chloride **3**. Treatment of **3** with diethyl (2,4-dimethoxybenzylamino)malonate in THF in the presence of Et_3N gave the *t*-butyldimethylsilyl ether **4**: Mp 90—91 °C: $[\alpha]_D^{25}$ −18.5° (*c*=2.00, $CHCl_3$). Desilylation of **4** with EtOH–H_2O–conc. HCl (9:2:1) gave **5**: Mp 74.5—75.5 °C: $[\alpha]_D^{24}$ −18.0° (*c*=2.00, $CHCl_3$). In addition, (2*S*,3*R*)-2-bromo-3-hydroxybutyric acid (**7**) obtained from (2*S*,3*R*)-threonine (L-threonine) was converted to **11** *via* **8**, **9**, and **10** according to the procedures described above. In the proton NMR of these *N*,*N*-disubstituted amides which contain a chiral part on the molecule, each of the methylene protons neighboring the nitrogen becomes non-equivalent. As a result, the methylene protons often show an AB-type coupling, and each part of the malonyl esters occasionally shows a different chemical shift.

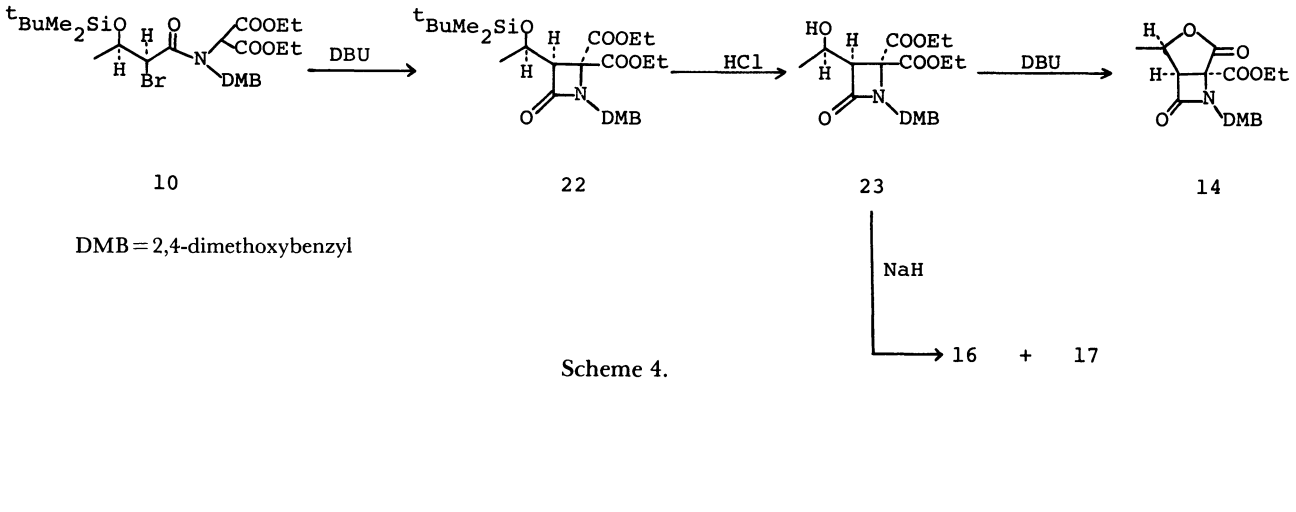
Treatment of **5** with 2 equivalents of NaH in THF at 0 °C for 30 min gave the *trans*-epoxide **6** in 86% yield (Scheme 2). However, treatment of **5** with 1 equivalent of NaH resulted only in the recovery of the starting **5**. On the other hand, treatment of **5** with 2 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at 25 °C for 4 h gave mainly three products, a 6:1 mixture of bicyclic lactone azetidinones (**13** and **14**) in 75% yield (both were inseparable chromatographically and the ratio of **13** and **14** (6:1) was estimated by comparison with the authentic ^{1}H-NMR data of **13** and **14** obtained from **21** and **23**, respectively), and the hydroxy γ-lactam **15** in 7% yield. This result reveals that treatment of **5** with DBU incurs both direct 2-azetidinone formation to give **13** and epoxidation to give the intermediate **6**, and then successive ring closure of **6** branches off two pathways to give a normal ring closure product with a 4-membered ring and a 5-membered ring product, which results in a violation of Baldwin's ring closure rules.[3] As a matter of course, treatment of the epoxide **6** with DBU yielded two products, **14** and **15**, in 60% and 30% yields, respectively. On the other hand, treatment of **6** with 1.2 equivalents of NaH at 25 °C for 2 h gave **14** (23%) as a major product, and **15** (7.5%), **16** (6%), **17** (2%), and an unknown product (**18**) (mp 148—153 °C) as minor products. In this experiment, **14** was obtained *via* lactonization of the corresponding hydroxy carboxylic acid. The absolute configuration and the rate of racemization of **16** and **17** were not clear; however, the value of $[\alpha]_D^{25}$ of **16** was −2.7° in EtOH. The tendency for ring closure of the epoxide **6** by treatment with DBU or NaH was a little different, that is, the yields of **14** and **15** were 60% and 30% for use of DBU,



DMB = 2,4-dimethoxybenzyl

Scheme 3.





DMB = 2,4-dimethoxybenzyl

Scheme 4.

but 23% and 7% for use of NaH. In addition, it was obvious that the common intermediate to form **14**, **16**, and **17** was the compound **23**, as mentioned later.

We tried the cyclization of **11** with DBU and NaH (Scheme 3). Treatment of **11** with 2 equivalents of DBU in THF at 25 °C for 3 h gave **14** (93%), *via* a corresponding hydroxy carboxylic acid and by direct cyclization without passing through the epoxide **12**, as a single product. However, treatment of **11** with 3.7 equivalents of NaH in THF at 15 °C for 16 h gave a carboxylic acid **21** (76%) as a crystalline solid: Mp 180—184 °C; $[\alpha]_D^{25}$ −77.9° (*c*=2.00, THF), *via* the *cis*-epoxide **12**.

Alternatively, the compounds **13**, **14**, **15**, and **17** were synthesized from the O-protected compounds, **4** and **10** (Scheme 4). Treatment of **4** with DBU gave **20** (93%) as an oil: $[\alpha]_D^{25}$+28.5° (*c*=2.55, $CHCl_3$). Desilylation of **20** with EtOH–H_2O conc. HCl (9:2:1) at 20 °C for 16 h gave **21** (92%). Lactonization of **21** with DBU gave **13** (89%). In the same way, cyclization of **10** with DBU gave **22** (86%). Desilylation of **22** with EtOH–H_2O-conc. HCl (9:2:1) at 25 °C for 3 h gave **23** (60%) as a crystyalline solid: Mp 91—92 °C; $[\alpha]_D^{24}$ −75.6° (*c*=0.44, $CHCl_3$). Lactonization of **23** with DBU gave **14** in good yield. On the other hand, treatment of **23** with 1.56 equiv of NaH at 15 °C for 16 h gave **16** (13.9%), whose $[\alpha]_D^{24}$ value was −2.8° (*c*=0.47, EtOH), and **17** (7.5%).

Thus, we can obtain the required stereoisomers by use of the reaction of the O-protected or nonprotected 2-bromo-3-hydroxybutyramide derivatives or their corresponding epoxides[4] with alkaline metal or amine base.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. Optical rotations were obtained by the use of a Perkin-Elmer 241 polarimeter. ^{1}H-NMR spectra were recorded at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The IR absorption spectra were determined on a Jasco IR A-2 spectrophotometer. Mass spectra were obtained on a JMS-OlSG mass spectrometer. Preparative TLC was performed on silica gel plates (Merck 60 PF_{245}), and column chromatography was carried out on columns packed with Merck silica gel 60 using slightly increased pressure (1.5 atm) for elution. Elemental analyses were performed by the Analytical Centre of Analytical and Metabolic Research Laboratories, Sankyo Company, Limited.

(2R,3R)-2-Bromo-3-(t-butyldimethylsilyloxy)butyric Acid (2). To a solution of (2*R*,3*R*)-2-Bromo-3-hydroxybutyric acid[1c] (**1**, 18.3 g, 0.10 mol) in DMF (50 ml) was added *t*-butyldimethylsilyl chloride (45 g, 0.30 mol), Et_3N (30 g) and 4-dimethylaminopyridine (1.0 g). The mixture was stirred for 16 h at room temperature, then poured into water (300 ml), adjusted to pH 2 with dil HCl and then pH 8 with powdery $NaHCO_3$, and washed twice with Et_2O (each 200 ml). The aqueous layer was saturated with NaCl, and reacidified to pH 2 with dil HCl, and extracted with Et_2O (200 ml×3). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 6.4 g (21.5%) of **2**, which was employed for the next reaction without further purificaiton. ^{1}H NMR ($CDCl_3$) δ=0.12 (6H, s), 0.90 (9H, s), 1.38 (3H, d, *J*=6 Hz), 4.01 (1H, d, *J*=8 Hz), 4.20 (1H, qd, *J*=6, 8 Hz), 9.62 (1H, bs, COOH). IR ν_{max} (film) 3600—2400, 1720 cm^{-1}. MS *m/z* 241 (M^+–Bu^t, ^{81}Br), 239.

(2S,3R)-2-Bromo-3-(t-butyldimethylsilyloxy)butyric Acid (8). (2*S*,3*R*)-2-Bromo-3-hydroxybutyric acid (**7**) was treated as described above to give **8** (30%) as an oil. IR ν_{max} (film) 3600—2400, 1723 cm^{-1}. NMR ($CDCl_3$) δ=0.12 (6H, s), 0.93 (9H, s), 1.21 (3H, d, *J*=6 Hz), 4.0—4.4 (2H, m), 9.51 (1H, bs, COOH). MS *m/z* 241 (M^+–Bu^t, ^{81}Br), 239.

(2R,3R)-2-Bromo-3-(t-butyldimethylsilyloxy)butyryl Chloride (3). To a solution of **2** (6.0 g, 20.2 mmol) in THF (30 ml) was added oxalyl dichloride (5.0 ml, 59 mmol) at 25 °C. After 3 h stirring, the reaction mixture was concentrated *in vacuo* to give 6.3 g (99%) of **3** as an oil, which was employed for the next reaction without purification. NMR ($CDCl_3$) δ=0.10 (6H, s), 0.88 (9H, s), 1.40 (3H, d, *J*=6 Hz), 4.1—4.5 (2H, m). IR ν_{max} (film) 1810 cm^{-1}.

(2S,3R)-2-Bromo-3-(t-butyldimethylsilyloxy)butyryl Chloride (9). The acid **8** was treated as described above to give an acid chloride **9** (quantitative), which was employed for the next reaction without purification. IR ν_{max} (film) 1815 cm^{-1}.

(2R,3R)-N-(2,4-Dimethoxybenzyl)-N-[bis(ethoxycarbonyl)methyl]-2-bromo-3-(t-butyldimethylsilyloxy)butyramide (4). To a solution of **3** (5.25 g, 16.6 mmol) and diethyl (2,4-dimethoxybenzylamino)malonate[1b] (5.40 g, 16.6 mmol) in THF (50 ml) was added a solution of Et_3N (1.70 g, 16.6 mmol) in THF (20 ml) at 5 °C with stirring over a period of 10 min. After the stirring was continued for 30 min at room temperature, the reaction mixture was extracted with EtOAc. The organic layer was washed with dil HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica-gel (200 g) column. Elution with cyclohexane–EtOAc (4:1) gave 0.25 g of an unknown material at lower R_f value and 5.32 g (54%) of **4** as a crystalline solid: Mp 90—91 °C (from hexane). $[\alpha]_D^{25}$ −18.5° (*c*=2.0, $CHCl_3$). IR ν_{max} ($CHCl_3$) 1750 (shoulder), 1740, 1665, 1613, 1590 cm^{-1}. NMR ($CDCl_3$) δ=0.12 (6H, s), 0.90 (9H, s), 1.05 (3H, t, *J*=7 Hz), 1.26 (3H, t, *J*=7 Hz), 1.31 (3H, d, *J*=6 Hz), 3.4—4.6 [12H, m, (containing 3H singlet at δ=3.80 and 3H singlet at δ=3.83)], 4.70 (2H, s), 5.58 (1H, s), 6.28—6.48 (2H, m), 7.22 (1H, d, *J*=9 Hz).

Found: C, 51.97; H, 7.11; N, 2.27; Br, 13.17%. Calcd for $C_{26}H_{42}NO_8SiBr$: C, 51.60; H, 6.95; N, 2.32; Br, 13.21%.

(2S,3R)-N-(2,4-Dimethoxybenzyl)-N-[bis(ethoxycarbonyl)methyl]-2-bromo-3-(t-butyldimethylsilyloxy)butyramide (10). The acid chloride (**9**, 3.25 g) was treated as described above to give 1.62 g (26%) of **10**, 2.18 g of unknown material and 0.88 g of *N*-(2, 4-dimethoxybenzyl)-*N*-[bis(ethoxycarbonyl)methyl]-2-bromocrotonamide, which was due to the contamination of the corresponding acid chloride in the starting **9**. MS *m/z* 548 (M^+–Bu^t, ^{81}Br), 546. IR ν_{max} (film) 1750, 1662, 1612, 1588 cm^{-1}. NMR ($CDCl_3$) δ= 0.10 (3H, s), 0.14 (3H, S), 0.90 (9H, s), 1.20 (3H, t, *J*=7 Hz), 1.22 (3H, t, *J*=7 Hz), 1.25 (3H, d, *J*=6 Hz), 3.78 (3H, s), 3.80 (3H, s), 3.9—4.9 (9H, m), 6.40 (1H, d, *J*=2 Hz), 6.40 (1H, dd, *J*=2, 9 Hz), 7.16 (1H, d, *J*=9 Hz).

Found: C, 51.83; H, 7.20; N, 2.30; Br, 13.14%. Calcd for $C_{26}H_{42}O_8NBrSi$: C, 51.60; H, 6.95; N, 2.32; Br, 13.21%.

(2R,3R)-N-(2,4-Dimethoxybenzyl)-N-[bis(ethoxycarbonyl)methyl]-2-bromo-3-hydroxybutyramide (5). A solution of **4** (4.26 g, 7.0 mmol) in EtOH (180 ml) and dil HCl (H_2O/conc. HCl=2/1, 60 ml) was stirred for 8 h at 20 °C, concentrated to a volume of 100 ml, and extracted with EtOAc (300 ml). The organic layer was washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give an oily residue which was chromatographed on a silica-gel (100 g) column. Elution with cyclohexane–EtOAc (1:1) gave 3.45 g (quantitative) of **5** as a crystalline solid: Mp 74.5—75.5 °C (from EtOH). $[\alpha]_D^{24}$ −18.0° (*c*=2.00, $CHCl_3$). IR ν_{max} ($CHCl_3$) 3560, 1760—1740, 1650, 1613, 1590 cm^{-1}. NMR ($CDCl_3$) δ=1.17 (3H, t, *J*=7 Hz), 1.22 (3H, t, *J*=7 Hz), 1.40 (3H, d, *J*=6 Hz), 3.52 (1H, d, *J*=4 Hz, OH), 3.78 (3H, s), 3.81 (3H, s), 4.08 (2H, q, *J*=7 Hz), 4.11 (2H, q, *J*=7 Hz), 4.40 (1H, d, *J*=3.5 Hz, C_2–H), 4.48, 4.85 (2H,

AB-q, J=16 Hz), 4.63 (1H, s), 6.28—6.47 (2H, m, olefinic), 7.02—7.17 (1H, m, olefinic).

Found: C, 48.88; H, 5.70; N, 2.77; Br, 16.12%. Calcd for $C_{20}H_{28}O_8NBr$: C, 48.95; H, 5.71; N, 2.85; Br, 16.30%.

(2S,3R)-N-(2,4-Dimethoxybenzyl)-N-[bis(ethoxycarbonyl)methyl]-2-bromo-3-hydroxybutyramide (11). The silyl ether **10** was treated with EtOH–H_2O-conc. HCl (9:2:1) for 1 h at 20 °C as described above to give **11** (81.5%) as a viscous oil. IR ν_{max} (film) 3475, 1750, 1739, 1655, 1610, 1587 cm^{-1}. NMR ($CDCl_3$) δ=1.20 (3H, t, J=7 Hz), 1.22 (3H, t, J=7 Hz), 1.26 (3H, d, J=7 Hz), 3.84 (6H, s), 3.97—5.05 (10H, m), 6.48 (1H, d, J=2 Hz), 6.48 (1H, dd, J=2, 9 Hz), 7.15 (1H, J=9 Hz).

Found: C, 48.76; H, 5.80; N, 2.81; Br, 16.17%. Calcd for $C_{20}H_{28}O_8NBr$: C, 48.95; H, 5.71; N, 2.85; Br, 16.30%.

(2S,3R)-N-(2,4-Dimethoxybenzyl)-N-[bis(ethoxycarbonyl)methyl]-2,3-epoxybutyramide (6). To a solution of **5** (490.3 mg, 1.0 mmol) in THF (4 ml) was added NaH (55% dispersion in mineral oil, 83 mg, 2.0 mmol) at 0 °C. After 30 min stirring, the starting **5** had disappeared completely. The reaction mixture was diluted with EtOAc, washed with 5% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on preparative silica-gel TLC plates. Development with cyclohexane–EtOAc (1:1) gave 352 mg (86%) of **6** as a viscous oil. NMR ($CDCl_3$) δ=1.20 (6H, t, J=7 Hz), 1.22 (3H, d, J=5 Hz), 3.65 (1H, dq, J=2, 5 Hz), 3.38 (1H, d, J=2 Hz), 3.80 (3H, s), 3.81 (3H, s), 4.10 (2H, q, J=7 Hz), 4.13 (2H, q, J=7 Hz), 4.71 (2H, s), 5.29 (1H, s), 6.43 (2H, m), 7.17 (1H, d, J=9 Hz). IR ν_{max} (film) 1750—1730, 1672, 1612, 1590 cm^{-1}.

Found: C, 58.30; H, 6.51; N, 3.29%. Calcd for $C_{20}H_{27}O_8N$: C, 58.67; H, 6.65; N, 3.42%.

Reaciton of 5 with DBU. To a solution of **5** (245 mg, 0.5 mmol) in THF (4 ml) was added DBU (152 mg, 1 mmol) at 25 °C with stirring. After 4 h, the reaction mixture was diluted with EtOAc, then washed with 10% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture. The mixture was chromatographed on preparative silica-gel TLC plates. Development with EtOAc–cyclohexane (1:1) gave 136 mg (75%) of a 6:1 mixture of **13** and **14** which could not be separated because the R_f values of 0.40 were almost the same (The ratio of **13**:**14** was estimated by comparison with authentic ^{1}H-NMR data of **13** and **14** obtained from **21** and **22**, respectively.), and 14 mg (7%) of **15** (R_f=0.25). MS m/z 409 (M^+), 223, 167, 151. IR ν_{max} (film) 3360, 1750 (shoulder), 1730, 1695, 1612, 1590 cm^{-1}. NMR ($CDCl_3$) δ=1.07 (3H, t, J=7 Hz), 1.19 (3H, t, J=7 Hz), 1.25 (3H, d, J=7 Hz), 2.55—3.12 (1H, m), 3.6—4.3 [12H, m, (containing 6H singlet at δ=3.77)], 4.49, 4.78 (2H, AB-q, J=16 Hz), 6.35 (1H, d, J=2 Hz), 6.35 (1H, dd, J=2, 9 Hz), 6.90 (1H, d, J=9 Hz).

Found: C, 58.22; H, 6.99; N, 3.37%. Calcd for $C_{20}H_{27}O_8N$: C, 58.67; H, 6.65; N, 3.42%.

Reaction of 6 with DBU. A soluiton of 6 (205 mg, 0.5 mmol) and DBU (80 mg, 0.53 mmol) in THF (5 ml) was stirred for 6 h at 25 °C and concentrated *in vacuo* to give an oily mixture, which was chromatographed on preparative silica-gel TLC plates. Development with cyclohexane–EtOAc (1:1) gave 61 mg (29.8%) of **15** on R_f=0.25 as a viscous oil, and an acidic product on R_f=0, which was eluted off from the silica gel with MeOH. The MeOH solution was concentrated *in vacuo* to give an oily residue which was diluted with EtOAc. The EtOAc solution was washed with 5% HCl, H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 108 mg (59.5%) of the lactonized product **14** as a viscous oil. MS m/z 363 (M^+). IR ν_{max} (film) 1770, 1750 (shoulder), 1735 (shoulder), 1613, 1590 cm^{-1}. NMR ($CDCl_3$) δ=1.26 (3H, t, J=7 Hz), 1.55 (3H, d, J=6 Hz), 3.90 (1H, d, J=7 Hz, C_1-H), 4.22 (2H, q, J=7 Hz), 4.38, 4.63 (2H, AB-q, J=15 Hz), 4.76 (1H, quintaplet, J=7 Hz, C_2-H), 6.2—6.5 (2H, m), 7.12 (1H, d, J=9 Hz).

Found: C, 59.47; H, 5.86; N, 3.73%. Calcd for $C_{18}H_{21}O_7N$: C, 59.49; H, 5.83; N, 3.86%.

Raction of 6 with NaH. To a solution of **6** (150 mg, 0.367 mmol) in THF (2 ml) was added NaH (55% dispersion in mineral oil, 20 mg, 0.458 mmol) at 25 °C with strirring. After 2 h, the reaction mixture was diluted with EtOAc, washed with 5% HCl, H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a preparative silica-gel TLC plate. Development with cyclohexane–EtOAc (1:1) gave 7 mg (6%) of **16** (R_f=0.683); $[\alpha]_D^{25}$ −2.7 ° (c=0.77, EtOH), 15 mg of a mixture of **17** and unknown **18** (R_f=0.583, Fractional crystallization of this mixture from *i*-Pr_2O gave 11 mg of **18** as a crystalline solid; mp 148—153 °C. The remaining mother liquor contained 4 mg of a 1:1 mixture of **17** and **18**. This was estimated by the comparison with the ^{1}H NMR of each authentic sample of **17**, obtained from **23**, and **18**.), 17 mg (7.5%) of **15** (R_f=0.283), and an acidic product (R_f=0) which was eluted off from the silica-gel with MeOH, and concentrated *in vacuo* to give an oily residue which was diluted with EtOAc (50 ml). The solution was washed with 10% HCl, H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 31 mg (23.3%) of **14**.

Reaction of 11 with DBU. A solution of **11** (120 mg, 0.245 mmol) and DBU (76 mg, 0.500 mmol) in THF (2 ml) was stirred for 1 h at 25 °C. The precipitated DBU-HBr salt was filtrated, and the filtrate was concentrated *in vacuo* to give an oily residue which was chromatographed on a preparative silica gel TLC plate. Development with cyclohexane–EtOAc (1:1) gave an acidic material of R_f=0. The silica gel layer of this part was eluted with MeOH which was concentrated *in vacuo* to give a residue. The residue was diluted with EtOAc which was washed with 10% HCl, H_2O and brine, and dried over $MgSO_4$, and then concentrated *in vacuo* to give 83 mg (93.4%) of **14** as a viscous oil.

Reaction of 11 with NaH. To a solution of **11** (120 mg, 0.245 mmol) in THF (2 ml) was added NaH (55% dispersion in mineral oil, 40 mg, 0.917 mmol) under cooling with ice bath.

The mixture was kept for 16 h at 15 °C, then diluted with EtOAc, washed with 10% HCl, H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude crystalline acid. The acid was suspended in a small amount of EtOAc, triturated in large excess of hexane, and then collected by suction filtration to give 62 mg (75.6%) of **19** as a crystalline solid: Mp 180—184 °C (from EtOAc). $[\alpha]_D^{23}$ −77.9 °C (c=2.00, THF). IR ν_{max} (Nujol) 3500—2400, 1780, 1740, 1730 (shoulder), 1613, 1588 cm^{-1}. NMR (DMF-d_7) δ=1.40 (3H, d, J=6 Hz), 3.78 (6H, s), 4.10 (1H, d, J=1 Hz), 4.47 (2H, s), 4.93 (1H, dq, J=1, 6 Hz), 6.55 (1H, dd, J=2, 9 Hz), 6.58 (1H, d, J=2 Hz), 7.18 (1H, d, J=9 Hz), 10.50 (1H, bs, COOH).

Found: C, 57.49; H, 5.22; N, 4.18%. Calcd for $C_{16}H_{17}O_7N$: C, 57.31; H, 5.11; 4.18%.

(3S)-1-(2,4-Dimethoxybenzyl)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4,4-bis(ethoxycarbonyl)-2-azetidinone (20). To a solution of **4** (1.0 g, 1.65 mmol) in THF (20 ml) was added DBU (300 mg, 1.97 mmol) at 20 °C. After 16 h stirring at 20 °C, the reaction mixture was diluted with EtOAc, washed with a cold 5% HCl aqueous solution, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 0.79 g (92.8%) of **20** as an oil. $[\alpha]_D^{25}$ +28.5 ° (c=2.55, $CHCl_3$). NMR ($CDCl_3$) δ=0.08 (6H, s), 0.88 (9H, s), 1.04 (3H, t, J=7 Hz), 1.26 (3H, t, J=7 Hz), 1.33 (3H, d, J=6 Hz), 3.6—4.5 [12H, m, (containing 6H singlet at δ=3.79)], 4.50, 4.79 (2H, AB-q, J=15 Hz), 6.39 (1H, d, J=2 Hz), 6.39 (1H, dd, J=2, 9 Hz), 7.09 (1H, d, J=9 Hz). IR ν_{max} (film) 1770, 1742, 1613, 1590 cm^{-1}. MS m/z 466 (M^+–C_4H_9).

Found: C, 58.84; H, 7.45; N, 2.58%. Calcd for $C_{26}H_{41}O_8NSi$: C, 59.58; H, 7.83; N, 2.67%.

(3S)-1-(2,4-Dimethoxybenzyl)-3-[(R)-1-(hydroxy)ethyl]-4,4-bis(ethoxycarbonyl)-2-azetidinone (21). A solution of **20** (523.7 mg, 1.0 mmol) in EtOH–H_2O–conc HCl (9:2:1, 24 ml) was allowed to stand for 16 h at 20 °C. The reaction mixture was diluted with EtOAc, washed with water, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude mixture which was chromatographed on preparative silica-gel TLC plates. Development with cyclohexane–EtOAc (1:1) gave 376 mg (91.8%) of **21** (R_f=0.52) as a viscous oil. IR ν_{max} (film) 3475, 1765-1730, 1610, 1588 cm^{-1}. NMR ($CDCl_3$) δ=1.10 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.38 (3H, d, J=6 Hz), 3.18 (1H, bs, OH), 3.66 (1H, d, J=9 Hz), 3.78 (6H, s), 3.88 (2H, q, J=7 Hz), 4.27 (2H, q, J=7 Hz), 4.38, 4.72 (2H, AB-q, J=15 Hz), 4.0—4.5 (1H, m), 6.38 (1H, d, J=2 Hz), 6.38 (1H, dd, J=2, 9 Hz), 7.05 (1H, d, J=9 Hz). MS m/z 409 (M^+), 364.

Found: C, 58.61; H, 6.69; N, 3.40%. Calcd for $C_{20}H_{27}O_8N$: C, 58.67; H, 6.65; N, 3.42%.

(1S,2R,5S)-6-(2,4-Dimethoxybenzyl)-5-ethoxycarbonyl-2-methyl-4,7-dioxo-3-oxa-6-azabicyclo[3.2.0]heptane (13). A solution of **21** (107 mg, 0.261 mmol) in THF (2 ml) containing DBU (40 mg, 0.263 mmol) was stirred for 3 h at 24 °C. The reaction mixture was diluted with EtOAc, washed with 5% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a preparative silica-gel TLC plate. Development with cyclohexane–EtOAc (1:1) gave 85 mg (89%) of **13** (R_f=0.46). NMR ($CDCl_3$) δ=1.26 (3H, t, J=7.5 Hz), 1.45 (3H, d, J=6 Hz), 3.66 (1H, d, J=1 Hz), 3.81 (6H, s), 4.26 (2H, q, J=7.5 Hz), 4.51 (2H, s), 4.90 (1H, dq, J=1, 6 Hz), 6.43 (1H, d, J=2 Hz), 6.43 (1H, dd, J=2, 9 Hz), 7.15 (1H, d, J=9 Hz). IR ν_{max} (film) 1770, 1730 (shoulder), 1612, 1590 cm^{-1}. MS m/z 363 (M^+).

Found: C, 59.27; H, 5.94; N, 3.80%. Calcd for $C_{18}H_{21}O_7N$: C, 59.49; H, 5.83; N, 3.86%.

(3R)-1-(2,4-Dimethoxybenzyl)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4,4-bis(ethoxycarbonyl)-2-azetidinone (22). A solution of **10** (485 mg, 0.80 mmol) in THF (5 ml) containing DBU (122 mg, 0.802 mmol) was refluxed for 30 min. After cooling, the reaction mixture was diluted with EtOAc, washed with 1% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil which was chromatographed on silica-gel preparative TLC plates. Development with cyclohexane–EtOAc (3:1) gave 363 mg (86%) of **22** (the same R_f value as that of the starting **10**). NMR ($CDCl_3$) δ=0.05 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.05 (3H, t, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.35 (3H, d, J=6 Hz), 3.62 (1H, d, J=3.5 Hz), 3.78 (6H, s), 3.78 (2H, q, J=7 Hz), 4.20 (2H, q, J=7 Hz), 4.33 (1H, dq, J=3.5, 6 Hz), 4.43, 4.72 (2H, AB-q, J=15 Hz), 6.36 (1H, d, J=2 Hz), 6.36 (1H, dd, J=2, 9 Hz), 7.16 (1H, d, J=9 Hz). IR ν_{max} (film) 1770, 1740, 1613, 1590 cm^{-1}. MS m/z 466 (M^+–Bu^t).

Found: C, 58.86; H, 7.44; N, 2.70%. Calcd for $C_{26}H_{41}O_8NSi$: C, 59.58; H, 7.83; N, 2.67%.

(3R)-1-(2,4-Dimethoxybenzyl)-3-[(R)-1-(hydroxy)ethyl]-4,4-bis(ethoxycarbonyl)-2-azetidinone (23). A solution of **22** (350 mg, 0.668 mmol) in EtOH–H_2O–conc HCl (9:2:1, 8 ml) was allowed to stand for 3 h at 25 °C. The reaction mixture was diluted with EtOAc, washed with water, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oily mixture which was chromatographed on silica-gel preparative TLC plates. Development with cyclohexane–EtOAc (1:1) gave 164 mg (60%) of **23** (R_f=0.367) as a crystalline solid: Mp 91—92 °C (from EtOAc-hexane). $[\alpha]_D^{24}$ −75.6 (c=0.44, $CHCl_3$). NMR ($CDCl_3$) δ= 1.08 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.43 (3H, d, J=6 Hz), 1.95 (1H, d, J=6 Hz, OH), 3.6—4.2 [8H, m, (containing 6H singlet at δ=3.81)], 4.25 (4H, q, J=7 Hz), 4.48, 4.81 (2H, AB-q, J=15 Hz), 6.39 (1H, d, J=2 Hz), 6.39 (1H, dd, J=2, 9 Hz), 7.13 (1H, d, J=9 Hz). IR ν_{max} (Nujol) 3390, 1760—1730, 1610, 1585 cm^{-1}.

Found: C, 58.70; 6.63; N, 3.44%. Calcd for $C_{20}H_{27}O_8N$: C, 58.67; H, 6.65; N, 3.42%.

(1R,2R,5R)-6-(2,4-Dimethoxybenzyl)-5-ethoxycarbonyl-2-methyl-4,7-dioxo-3-oxa-6-azabicyclo[3.2.0]heptane (14). Treatment of **23** with one equivalent of DBU as described above in the formation of **14** from **11** by DBU gave **14** in 72% yield.

(Z)- and (E)-1-(2,4-Dimethoxybenzyl)-3-ethylidene-4-ethoxycarbonyl-2-azetidinone (16) and (17). To a solution of **23** (120 mg, 0.293 mmol) in THF (2 ml) was added NaH (55% dispersion in mineral oil, 20 mg). The mixture was stirred for 16 h at 15 °C, and diluted with EtOAc. The solution was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica-gel preparative TLC plate. Development with cyclohexane–EtOAc (4:1) gave 13 mg (13.9%) of **16** (R_f=0.17) and 7 mg (7.5%) of **17** (R_f=0.070). **16**: $[\alpha]_D^{25}$ −2.8 ° (c=0.47, EtOH). NMR ($CDCl_3$) δ=1.26 (3H, t, J=7 Hz), 2.00 (3H, d, J=7 Hz), 3.78 (3H, s), 3.81 (3H, s), 4.20 (2H, q, J=7 Hz), 4.21 (1H, d, J=1 Hz), 4.27, 4.72 (2H, AB-q, J=14.5 Hz), 5.66 (1H, dq, J=1, 7 Hz), 6.40 (2H, m), 7.10 (1H, d, J=9 Hz). IR ν_{max} (film) 1750, 1720 (shoulder, w), 1613,1590 cm^{-1}. MS m/z 319 (M^+), 290, 246, 218, 166, 151.

Found: C, 63.39; H, 6.54; N, 4.26%. Calcd for $C_{17}H_{21}O_5N$: C, 63.88; H, 6.57; N, 4.38%. **17**: NMR ($CDCl_3$) δ=1.27 (3H, t, J=7 Hz), 1.76 (3H, d, J=6.5 Hz), 3.80 (3H, s), 3.82 (3H, s), 4.22 (2H, q, J=7 Hz), 4.25, 4.70 (2H, AB-q, J=14 Hz), 4.38 (1H, d, J=1 Hz), 6.15 (1H, dq, J=1, 6.5 Hz), 6.41 (1H, dd, J=2, 9 Hz), 6.41 (1H, d, J=2 Hz), 7.12 (1H, d, J=9 Hz). IR ν_{max} (film) 1760—1740, 1612, 1590 cm^{-1}. MS m/z 319 (M^+), 290, 246, 218, 166, 151, 126, 121.

Found: C, 63.34; H, 6.49; N, 4.27%. Calcd. for $C_{17}H_{21}O_5N$: C, 63.88; H, 6.57; N, 4.38%.

References

1) a) M. Shiozaki and T. Hiraoka, *Tetrahedron*, **38**, 3457 (1982); b) M. Shiozaki, N. Ishida, H. Maruyama, and T. Hiraoka, *ibid.*, **39**, 2399 (1983); c) M. Shiozaki, N. Ishida, T. Hiraoka, and H. Maruyama, *Tetrahedron Lett.*, **22**, 5205 (1981).

2) M. Shiozaki, N. Ishida, T. Hiraoka, and H. Maruyama, *Chem. Lett.*, **1983**, 169.

3) a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976); b) J. E. Baldwin, J. Cutting, W. Dupont, L. I. Kruse, L. Silberman, and R. C. Thomas, *ibid*, 736 (1976); c) J. E. Baldwin, *ibid.*, 738 (1976); d) J. E. Baldwin and J. A. Reiss, *ibid*, 77 (1977); e) J. E. Baldwin and L. I. Kruse, *ibid.*, 233 (1977); f) J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

4) A. K. Bose, B. M. Bhawal, B. B. Shankar, and M. S. Manhas, In 186th ACS Natl Meet., Washington. DC. USA, Aug 28- Sep 2, 1983: Abstr. p. 86.