Highly asymmetric Pummerer-type cyclization of chiral, non-racemic β-amido sulfoxides

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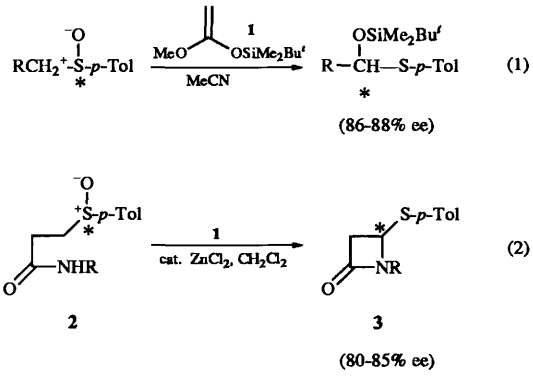
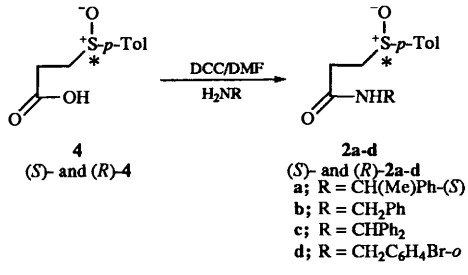
The first highly asymmetric Pummerer-type cyclization of chiral, non-racemic β-amido sulfoxides to enantiomerically enriched β-lactams (80–85% ee) is described. *S*- and *R*-Sulfoxides (*S*-**2a–d** and *R*-**2a–c**) were treated with *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal **1** in the presence of a catalytic amount of zinc chloride in methylene dichloride to give predominantly the corresponding 4*R*- and 4*S*-β-lactams (*R*-**3a–d** and *S*-**3a–c**) in more than 80% ee. These results show that the stereoinduction is governed by the absolute configuration of the sulfoxides. Optically pure *R*- and *S*-**3c** were readily obtained by simple recrystallization in about 60% yield. The usefulness of the chiral, non-racemic 4-tolylsulfanyl-β-lactams **3a–d** has been shown by their conversion into the key intermediate **11** for the optically pure carbapenem antibiotic, (+)-PS-5.

The asymmetric Pummerer reaction of chiral, non-racemic sulfoxides,[1] a self-immolative-type asymmetric induction, is of significant interest, since it allows the synthesis of enantiomerically pure α-substituted sulfides.[2] The intramolecular version of the asymmetric Pummerer-type reaction is especially useful for the synthesis of optically active heterocyclic compounds.[3,4] Few examples of these types of reactions have been reported, the enantiomeric excess (ee) yields of which were low.[3,4] Several years ago, we reported a novel silicon-induced Pummerer-type reaction of sulfoxides using *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal **1**, which gave α-siloxy sulfides under mild conditions.[5] This we applied to the intramolecular cyclization of ω-amido sulfoxides to give α-thio-*N*-heterocycles involving 4- to 7-membered α-thiolactams,[4,6] and the first highly asymmetric Pummerer-type reaction of chiral, non-racemic acyclic sulfoxides which gave enantiomerically enriched α-siloxy sulfides in high yields[7] [eqn. (1)]. Very recently, we briefly communicated[8] the first highly asymmetric intramolecular cyclization of chiral, non-racemic β-amido sulfoxides **2a–d** leading to enantiomerically enriched β-lactams (80–85% ee) in good yields using our silicon-induced Pummerer-type cyclization[4,6] [eqn. (2)]. Here we report a full account of our studies on the highly asymmetric Pummerer-type cyclization of chiral, non-racemic β-amido sulfoxides **2a–d** leading to the enantiomerically enriched β-lactams **3a–d**.



Scheme 1



Scheme 2

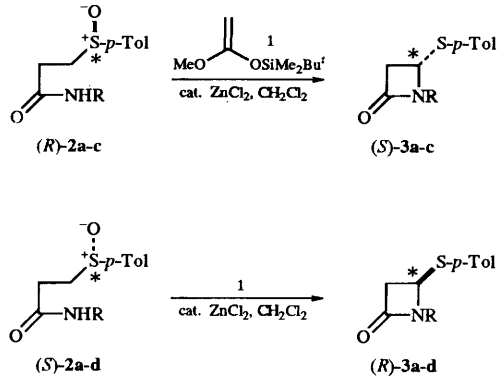
Asymmetric Pummerer-type cyclization induced by *O*-silylated ketene acetal

The starting chiral, non-racemic sulfoxides **2a–d** were prepared in good yield from the known chiral, non-racemic carboxylic acid **4**[9] by condensation with the corresponding amine in the presence of 1,3-dicyclohexylcarbodiimide (DCC) in dimethylformamide (DMF) (Scheme 2).

Treatment of the optically pure *S*-sulfoxide **2a**, which has a chiral amido group, under the standard silicon-induced Pummerer conditions[4,6] (**1**, cat. zinc iodide, acetonitrile) gave *R*-β-lactam **3a** in 60% ee (72% chemical yield) stereoselectively. A change in the reaction conditions from catalytic zinc iodide–acetonitrile to zinc chloride–methylene dichloride improved the ee. The use of these conditions was found to give the best results. Thus, *S*- and *R*-sulfoxides (*S*)-**2a–d** and (*R*)-**2a–c** were treated with **1** in the presence of a catalytic amount of zinc chloride in methylene dichloride to give predominantly the corresponding 4*R*- and 4*S*-β-lactams, (*R*)-**3a–d** and (*S*)-**3a–c**, in more than 80% ee. The *N*-silylated 4-thio-β-lactam was converted into the known β-lactam antibiotics.[10] These results show that the stereoinduction is influenced by the absolute configuration of the sulfoxides (Table 1). Optically pure (*R*)- and (*S*)-**3c** were readily obtained by simple recrystallization in about 60% chemical yield. The present Pummerer cyclization shows higher optical induction than the earlier described method.[3,4]

The absolute stereochemistry at the newly generated chiral centre of the β-lactams **3a–d** was established on the basis of CD results (Table 2), which showed a strong positive or negative Cotton effect at 210–220 nm (Octant rule). This agreed with the value for monocyclic β-lactams reported by Reling and

Table 1 Asymmetric Pummerer-type cyclization of chiral, non-racemic sulfoxides (**2**) with **1**



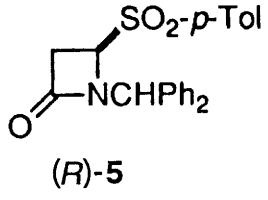
2a–d	R	Conditions	3	Product[a] % Ee[d] (% Yield)	Product[a] $[\alpha]_D(c, CHCl_3)$
(*S*)-**2a**	CH(Me)Ph[b]	0 °C, 1 d[c]	(*R*)-**3a**	60[e] (72)	−98.8 (1.96)[f]
(*S*)-**2a**	CH(Me)Ph[b]	0 °C, 3 d	(*R*)-**3a**	82[e] (96)	−98.8 (1.96)[f]
(*R*)-**2a**	CH(Me)Ph[b]	0 °C, 3 d	(*S*)-**3a**	85[e] (89)	+116 (0.954)[f]
(*S*)-**2b**	CH_2Ph	5 °C, 6 d	(*R*)-**3b**	80 (54)	−73.2 (1.01)
(*R*)-**2b**	CH_2Ph	5 °C, 6 d	(*S*)-**3b**	82 (54)	+75.2 (0.934)
(*S*)-**2c**	$CHPh_2$	15 °C, 2 d	(*R*)-**3c**	80 (84)	−37.0 (0.303)
(*R*)-**2c**	$CHPh_2$	15 °C, 2 d	(*S*)-**3c**	83 (90)	+38.4 (0.522)
(*S*)-**2d**	CH_2-*o*-BrPh	5 °C, 7 d	(*R*)-**3d**	83 (59)	−59.2 (1.49)

[a] Small amounts of α-siloxy-β-amido sulfides were obtained as side-products in all reactions. [b] (*S*)-Phenethylamine was used. [c] ZnI_2 was used as a catalyst in MeCN. [d] Ee value was determined by ^1H NMR (C_6D_6) with Eu(hfc)$_3$. [e] % De. [f] $[\alpha]_D$ Value was determined from a diastereoisomerically pure sample.

Table 2 CD spectrum of chiral compound **3**

3	CD (MeOH) λ ext (Δε)
(*R*)-**3a**	253 (+2.9), 242 (0), 222 (−20.4)[a]
(*R*)-**3a**	253 (+2.9), 242 (0), 222 (−20.4)[a]
(*S*)-**3a**	254 (−5.7), 240 (0), 221 (+24.5)[a]
(*R*)-**3b**	252 (+3.1), 239 (0), 220 (−16.6)
(*S*)-**3b**	252 (−2.6), 240 (0), 220 (+19.2)
(*R*)-**3c**	253 (+5.1), 243 (0), 221 (−21.5)[b]
(*S*)-**3c**	255 (−4.3), 243 (0), 221 (+21.4)[b]
(*R*)-**3d**	253 (+1.5), 240 (0), 221 (−14.4)

[a] CD spectrum was obtained from a diasteroisomerically pure sample. [b] CD spectrum was obtained from an enantiomerically pure sample.



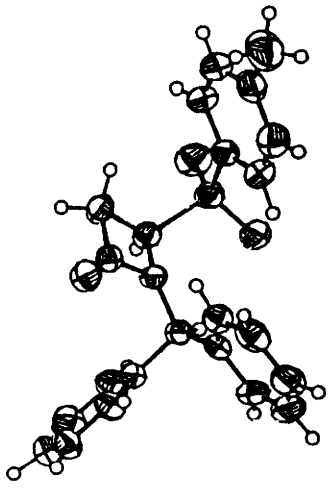


Fig. 1 X-Ray crystallographic structure of (*R*)-**5**

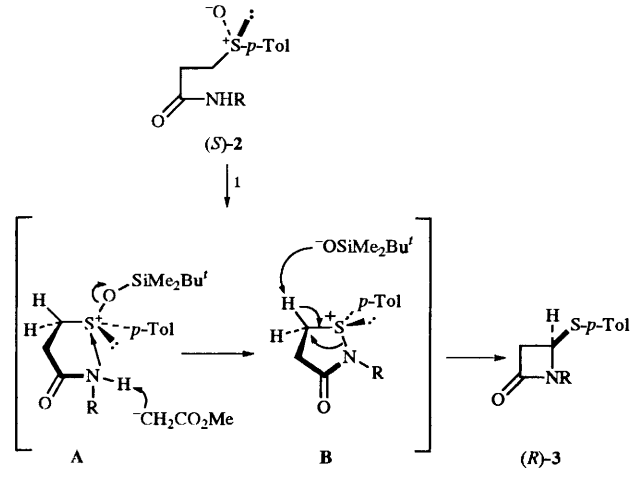
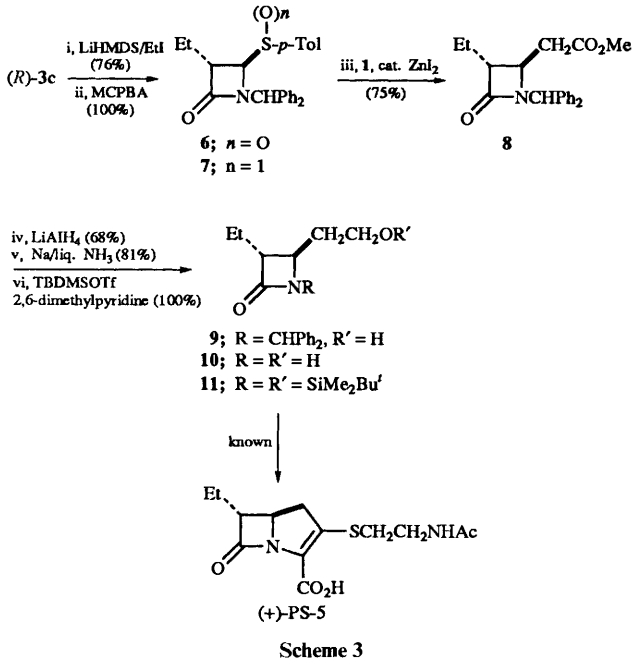


Fig. 2

Jensen.[11] The absolute stereochemistry was finally confirmed by an X-ray crystallographic determination of the oxidized derivative (*R*)-**5** of (*R*)-**3c**. (Fig. 1)

The following mechanism is proposed to explain the results and for which the transition state is analysed for the reaction of (*S*)-**2** with **1** (Fig. 2). Silylation of (*S*)-**2** with **1** affords an intermediate **A** which may then yield a chiral pseudo isothiazolone derivative **B**[12] through axial attack of the amido anion generated by abstraction with the ester anion and elimination of the siloxy ligand. The hydrogen neighbouring the sulfur atom is then removed by the siloxy anion and the amido ligand then undergoes 1,2 rearrangement from the α-face to give the β-lactam (*R*)-**3**. Of course, an alternative mechanism involving deprotonation of the α-*S*-hydrogen of **A** followed by asymmetric nucleophilic ring closure cannot be ruled out completely.



Scheme 3

Formal synthesis of the antibiotic (+)-PS-5

The usefulness of the chiral, non-racemic 4-tolylsulfanyl-β-lactams **3a–d** was shown by the conversion of *R*-**3c** into the optically active carbapenem antibiotic (+)-PS-5. Thus, ethylation at the C-3 position of pure *R*-**3c** gave the *trans*-azetidin-2-one **6**, which was oxidized with MCPBA to give the sulfoxide **7**. Treatment of **7** with **1** in the presence of a catalytic amount of zinc iodide in acetonitrile gave the *trans*-azetidin-2-one **8** selectively.[6b] Reduction of **8** with $LiAlH_4$, reductive debenzylation under Birch conditions, and silylation with TBDMSOTf gave the *trans*-3-ethylazetidin-2-one **11**, which is the known key intermediate to (+)-PS-5.[13,14]

Experimental

All mps were determined on a Yanaco micro melting point apparatus and are uncorrected. IR absorption spectra were recorded on JASCO HPIR-102 and Shimadzu FTIR-8100 spectrophotometers with $CHCl_3$ as a solvent. ^1H NMR spectra were measured on JEOL JNM-FX90Q (90 MHz), JEOL JNM-EX270 (270 MHz) and JEOL JNM-GX500 (500 MHz) spectrometers with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard unless otherwise noted. Mass spectra (MS) and high-resolution MS were obtained by ESCO EMD-05A and JEOL JMS-D300 mass spectrometers. Optical rotations were measured in 1-dm cells of 1 cm^3 capacity with a Perkin-Elmer 241 instrument and are recorded in units of 10^{-1} deg cm^2 g^{-1}. E. Merck silica gel 60 (70–230 mesh ASTM) for column chromatography and E. Merck pre-coated TLC plates with silica gel F_{254} for preparative TLC (PLC) were used. Organic layers were dried with anhydrous Na_2SO_4.

General procedure for the synthesis of optically pure ω-amido sulfoxides 2a–d

DCC (1.10 mmol), a solution of 1-hydroxybenzotriazole (HOBT) (1.10 mmol) in DMF (3 cm^3), RNH_2 (1.20 mmol) and triethylamine (2.40 mmol) were added to a solution of optically pure compound **4** (1.00 mmol) in DMF (8 cm^3) at 0 °C and the mixture stirred at room temperature for 1–5 d. The white precipitate was filtered off and the filtrate was concentrated on a rotary evaporator to give a crude oil, which was purified by column chromatography on silica gel eluting with AcOEt in hexane to give the corresponding optically pure ω-amido sulfoxide **2** in yields in the range 57–95%.

(*S*)-*N*-[(*S*)-Phenethyl]-*p*-tolylsulfinylpropionamide (*S*)-2a. Compound (*S*)-**4** {$[\alpha]_D^{15}$ −172 (*c* 0.793, MeOH), 150 mg, 0.708 mmol}, DCC (160 mg, 0.779 mmol), HOBT (105 mg, 0.779 mmol), (*S*)-phenethylamine (103 mg, 0.850 mmol), triethylamine (172 mg, 1.70 mmol) and DMF (3 cm^3) gave *compound* (*S*)-**2a** (133 mg, 60%) as colourless crystals; $[\alpha]_D^{26}$ −217 (*c* 0.158, $CHCl_3$); mp 135.7–137 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3280, 1650, 1545, 1080, 1040 and 1020; δ_H 1.48 (3 H, d, *J* 7.3, NCH*Me*), 2.40 (3 H, s, Me), 2.45 (1 H, ddd, *J* 5.5, 7.3 and 13.4, C*H*^{a}H^{b}CO), 2.72 (1 H, dt, *J* 13.4 and 7.3, CH^a*H*^{b}CO), 2.92 [1 H, ddd, *J* 5.5, 7.3 and 13.4, C*H*^{a}H^{b}S(O)], 3.26 [1 H, dt, *J* 13.4 and 7.3, CH^a*H*^{b}S(O)], 5.08 (1 H, quint, *J* 7.3, NC*H*Me), 6.52 (1 H, d, *J* 7.3, NH) and 7.23–7.47 (9 H, m, ArH); *m/z* 315 (M^+) (Found: M^+, 315.1321. $C_{18}H_{21}NO_2S$ requires *M*, 315.1293).

(*R*)-*N*-[(*S*)-Phenethyl]-*p*-tolylsulfinylpropionamide (*R*)-2a. Compound (*R*)-**4** {$[\alpha]_D^{15}$ +171 (*c* 0.703, MeOH), (lit.,[9] $[\alpha]_D^{15}$ +188 (*c* 0.7, MeOH), 300 mg, 1.42 mmol}, DCC (321 mg, 1.56 mmol), HOBT (211 mg, 1.56 mmol), (*S*)-phenethylamine (206 mg, 1.70 mmol), triethylamine (344 mg, 3.41 mmol) and DMF (4 cm^3) gave *compound* (*R*)-**2a** (297 mg, 66%) as colourless crystals; $[\alpha]_D^{26}$ +110 (*c* 0.542, $CHCl_3$); mp 119–122.5 °C (hexane–CH_2Cl_2); *m/z* 315 (M^+) (Found: C, 68.25; H, 6.8; N, 4.75%; M^+, 315.1295. $C_{18}H_{21}NO_2S$ requires C, 68.55; H, 6.70; N, 4.45%; *M*, 315.1293).

(*S*)-*N*-Benzyl-*p*-tolylsulfinylpropionamide (*S*)-2b. Compound (*S*)-**4** (150 mg, 0.708 mmol), DCC (160 mg, 0.779 mmol), HOBT (105 mg, 0.779 mmol), benzylamine (90.8 mg, 0.850 mmol), triethylamine (172 mg, 1.70 mmol) and DMF (8 cm^3) gave *compound* (*S*)-**2b** (200 mg, 95%) as colourless crystals; $[\alpha]_D^{25}$ −196 (*c* 0.408, $CHCl_3$); mp 85.2–86.5 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3441, 1672, 1086, 1036 and 1015; δ_H 2.42 (3 H, s, Me), 2.48 (1 H, ddd, *J* 6.0, 7.6 and 15.5, C*H*^{a}H^{b}CO), 2.74 (1 H, dt, *J* 15.5 and 7.6, CH^a*H*^{b}CO), 2.97 [1 H, ddd, *J* 6.0, 7.6 and 13.5, C*H*^{a}H^{b}S(O)], 3.29 [1 H, dt, *J* 13.5 and 7.6, CH^a*H*^{b}S(O)], 4.41 (2 H, d, *J* 5.6, NCH_2Ph), 6.23 (br s, 1 H, NH) and 7.20–7.50 (m, 9 H, ArH); *m/z* 301 (M^+) (Found: C, 67.55; H, 6.35; N, 4.65; S, 10.60%; M^+, 301.1117. $C_{17}H_{19}NO_2S$ requires C, 67.75; H, 6.35; N, 4.65; S, 10.65%; *M*, 301.1136).

(*R*)-*N*-Benzyl-*p*-tolylsulfinylpropionamide (*R*)-2b. Compound (*R*)-**4** (267 mg, 1.26 mmol), DCC (272 mg, 1.32 mmol), HOBT (186 mg, 1.38 mmol), benzylamine (161 mg, 1.51 mmol), triethylamine (152 mg, 1.51 mmol) and DMF (5 cm^3) gave *compound* (*R*)-**2b** (351 mg, 93%) as colourless crystals; $[\alpha]_D^{25}$ +194 (*c* 0.241, $CHCl_3$); mp 83.5–84.7 °C (hexane–CH_2Cl_2); *m/z* 301 (M^+) (Found: C, 67.45; H, 6.35; N, 4.65; S, 10.55%; M^+, 301.1137. $C_{17}H_{19}NO_2S$ requires C, 67.75; H, 6.35; N, 4.65; S, 10.65%; *M*, 301.1137).

(*S*)-*N*-Diphenylmethyl-*p*-tolylsulfinylpropionamide (*S*)-2c. Compound (*S*)-**4** (165 mg, 0.778 mmol), DCC (176 mg, 0.856 mmol), HOBT (116 mg, 0.856 mmol), diphenylmethylamine (171 mg, 0.934 mmol), triethylamine (189 mg, 1.87 mmol) and DMF (3 cm^3) gave *compound* (*S*)-**2c** (167 mg, 57%) as colourless crystals; $[\alpha]_D^{25}$ −108 (*c* 2.17, $CHCl_3$); mp 141.5–143 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3450, 3000, 1660, 1085, 1020 and 1015; δ_H 2.41 (3 H, s, Me), 2.54 (1 H, ddd, *J* 5.9, 7.5 and 14.5, C*H*^{a}H^{b}CO), 2.84 (1 H, dt, *J* 14.5 and 7.5, CH^a*H*^{b}CO), 2.92 [1 H, ddd, *J* 5.9, 7.5 and 13.5, C*H*^{a}H^{b}S(O)], 3.25 [1 H, dt, *J* 13.5 and 7.5, CH^a*H*^{b}S(O)], 6.20 (1 H, d, *J* 7.9, $CHPh_2$), 7.14 (1 H, d, *J* 7.9, NH) and 7.20–7.46 (m, 14 H, ArH); *m/z* 377 (M^+) (Found: C, 72.8; H, 6.25; N, 4.05%; M^+, 377.1437. $C_{23}H_{23}NO_2S$ requires C, 73.15; H, 6.15; N, 3.70%; *M*, 377.1449).

(*R*)-*N*-Diphenylmethyl-*p*-tolylsulfinylpropionamide (*R*)-2c. Compound (*R*)-**4** (497 mg, 2.34 mmol), DCC (531 mg, 2.58 mmol), HOBT (348 mg, 2.58 mmol), diphenylmethylamine (515

mg, 2.81 mmol), triethylamine (568 mg, 5.63 mmol) and DMF (5 cm^3) gave *compound* (*R*)-**2c** (515 mg, 58%) as colourless crystals; $[\alpha]_D^{20}$ +171 (*c* 1.13, $CHCl_3$); mp 143.5–144.2 °C (hexane–CH_2Cl_2); *m/z* 377 (M^+) (Found: M^+, 377.1470. $C_{23}H_{23}NO_2S$ requires *M*, 377.1450).

(*S*)-*N*-(*o*-Bromobenzyl)-*p*-tolylsulfinylpropionamide (*S*)-2d. Compound (*S*)-**4** (501 mg, 2.36 mmol), DCC (584 mg, 2.84 mmol), HOBT (383 mg, 2.84 mmol), *o*-bromobenzylamine hydrochloride (631 mg, 2.84 mmol), triethylamine (573 mg, 5.67 mmol) and DMF (10 cm^3) gave *compound* (*S*)-**2d** (855 mg, 95%) as colourless crystals; $[\alpha]_D^{25}$ −149.5 (*c* 0.612, $CHCl_3$); mp 109–111 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3440, 3290, 3010, 2930, 1670, 1240, 1090, 1030 and 1010; δ_H 2.41 (3 H, s, Me), 2.49 (1 H, ddd, *J* 6, 7.5 and 14, C*H*^{a}H^{b}CO), 2.75 (1 H, dt, *J* 14 and 7.5, CH^a*H*^{b}CO), 2.95 [1 H, ddd, *J* 6, 7.5 and 13.5, C*H*^{a}H^{b}S(O)], 3.26 [1 H, dt, *J* 13.5 and 7.5, CH^a*H*^{b}S(O)], 4.48 (2 H, d, *J* 5.6, CH_2Ar), 6.56 (1 H, br s, NH) and 7.11–7.56 (8 H, m, ArH); *m/z* 379 (M^+) (Found: C, 53.5; H, 4.75; N, 3.65%; M^+, 379.0251. $C_{17}H_{18}BrNO_2S$ requires C, 53.70; H, 4.80; N, 3.70%; *M*, 379.0242).

General procedure for the Pummerer-type reaction of *O*-silylated ketene acetal 1 with sulfoxides 2a–d

To a stirred solution of the sulfoxide **2** (0.100 mmol), $ZnCl_2$ or ZnI_2 (0.01–0.05 mmol) in dry CH_2Cl_2 or MeCN (3 cm^3) was added dropwise ketene *tert*-butyldimethylsilyl methyl acetal **1** (0.500 mmol) under the conditions indicated in Table 1 for 1–5 d under nitrogen. The mixture was then poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The organic extract was washed with brine, dried, and evaporated. The residue was purified by PLC to give the corresponding enantiomerically enriched β-lactams **3a-d** in yields in the range 54–96%.

(4*R*)-1-[(*S*)-Phenethyl]-4-*p*-tolylsulfanylazetidin-2-one(*R*)-3a. (i) Compound (*S*)-**2a** (15.4 mg, 0.049 mmol), the acetal **1** (46.0 mg, 0.244 mmol), ZnI_2 (1.6 mg, 0.005 mmol) and MeCN (2 cm^3) gave *compound* (*R*)-**3a** (10.4 mg, 72%, 60% de) as a pale yellow oil. Pure (*R*)-**3a** was isolated in a pure state by column chromatography; $[\alpha]_D^{19}$ −98.8 (*c* 1.96, $CHCl_3$); ν_{max}/cm^{-1} 3020 and 1750; δ_H 1.79 (3 H, d, *J* 7.3, NCH*Me*), 2.35 (3 H, s, Me), 2.77 (1 H, dd, *J* 2.3 and 14.9, 3-H^a), 3.16 (1 H, dd, *J* 5.0 and 14.9, 3-H^b), 4.55 (1 H, q, *J* 7.3, NC*H*Me), 4.58 (1 H, dd, *J* 2.3 and 5.0, 4-H) and 7.10–7.36 (m, 9 H, ArH); *m/z* 297 (M^+) (Found: M^+, 297.1176. $C_{18}H_{19}NOS$ requires *M*, 297.1188).

(ii) Compound (*S*)-**2a** (22.5 mg, 0.071 mmol), the acetal **1** (67.1 mg, 0.357 mmol), $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.016 cm^3, 0.036 mmol) and CH_2Cl_2 (2 cm^3) gave compound (*R*)-**3a** (20.4 mg, 96%, 82% de) as an oil.

(4*S*)-1-[(*S*)-Phenethyl-4-*p*-tolylsulfanylazetidin-2-one (*S*)-3a. Compound (*R*)-**2a** (30.6 mg, 0.097 mmol), the acetal **1** (91.4 mg, 0.486 mmol), $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.022 cm^3, 0.049 mmol) and CH_2Cl_2 (3 cm^3) gave *compound* (*S*)-**3a** (25.8 mg, 89%, 85% de) as a pale yellow oil. Pure (*S*)-**3a** was isolated in a pure state by column chromatography; $[\alpha]_D^{19}$ +116 (*c* 0.954, $CHCl_3$); ν_{max}/cm^{-1} 3000 and 1745; δ_H 1.72 (3 H, d, *J* 7.3, NCH*Me*), 2.33 (3 H, s, Me), 2.81 (1 H, dd, *J* 2.3 and 14.8, 3-H^a), 3.18 (1 H, dd, *J* 5.0 and 14.8, 3-H^b), 4.67 (1 H, dd, *J* 2.3 and 5.0, 4-H), 4.90 (1 H, q, *J* 7.3, NC*H*Me) and 7.10–7.36 (m, 9 H, ArH); *m/z* 297 (M^+) (Found: M^+, 297.1186. $C_{18}H_{19}NOS$ requires *M*, 297.1188).

(4*R*)-1-Benzyl-4-*p*-tolylsulfanylazetidin-2-one (*R*)-3b. Compound (*S*)-**2b** (40.0 mg, 0.133 mmol), the acetal **1** (125 mg, 0.665 mmol), $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.03 cm^3, 0.067 mmol) and CH_2Cl_2 (4 cm^3) gave *compound* (*R*)-**3b** (21.1 mg, 54%, 80% ee) as a colourless oil; $[\alpha]_D^{21}$ −73.2 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} 2922 and 1760; δ_H 2.35 (3 H, s, Me), 2.79 (1 H, dd, *J* 2.0 and 15, 3-H^a), 3.22 (1 H, dd, *J* 5.0 and 15, 3-H^b), 4.08 and 4.73 (2 H, ABq, *J* 15.5, CH_2Ph), 4.69 (1 H, dd, *J* 2.0 and 5.0, 4-H) and 7.11–7.32 (m, 9 H, ArH); *m/z* 283 (M^+) (Found: M^+, 283.1022. $C_{17}H_{17}NOS$ requires *M*, 283.1031).

(4*S*)-1-Benzyl-4-*p*-tolylsulfanylazetidin-2-one (*S*)-3b. Compound (*R*)-**2b** (39.6 mg, 0.132 mmol), the acetal **1** (124 mg, 0.660 mmol), $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.03 cm^3, 0.066 mmol) and CH_2Cl_2 (4 cm^3) gave *compound* (*S*)-**3b** (20.0 mg, 54%, 82% ee) as a colourless oil; $[\alpha]_D^{21}$ +75.2 (*c* 0.934, $CHCl_3$); *m/z* 283 (M^+) (Found: C, 71.75; H, 6.2; N, 4.85; S, 11.25%; M^+, 283.1015. $C_{17}H_{17}NOS$ requires C, 72.05; H, 6.05; N, 4.95; S, 11.30%; *M*, 283.1031).

(4*R*)-1-Diphenylmethyl-4-*p*-tolylsulfanylazetidin-2-one (*R*)-3c. Compound (*S*)-**2c** (30.4 mg, 0.081 mmol), the acetal **1** (75.8 mg, 0.403 mmol), $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.018 cm^3, 0.040 mmol) and CH_2Cl_2 (3 cm^3) gave *compound* (*R*)-**3c** (24.3 mg, 84%, 80% ee) as colourless crystals; $[\alpha]_D^{21}$ −37.0 (*c* 0.303, $CHCl_3$). Optically pure (*R*)-**3c** was isolated easily by recrystallization with hexane–CH_2Cl_2 as colourless crystals; $[\alpha]_D^{21}$ −51.1 (*c* 0.742, $CHCl_3$); mp 120–122.5 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3000 and 1750; δ_H 2.33 (3 H, s, Me), 2.95 (1 H, dd, *J* 2.5 and 15, 3-H^a), 3.28 (1 H, dd, *J* 4.8 and 15, 3-H^b), 4.78 (1 H, dd, *J* 2.5 and 4.8, 4-H), 5.75 (1 H, s, C*H*Ph_2) and 7.03–7.37 (14 H, m, ArH); *m/z* 359 (M^+) (Found: C, 76.65; H, 5.9; N, 3.9; S, 8.75%; M^+, 359.1322. $C_{23}H_{21}NOS$ requires C, 76.85; H, 5.90; N, 3.90; S, 8.90%; *M*, 359.1344).

(4*S*)-1-Diphenylmethyl-4-*p*-tolylsulfanylazetidin-2-one (*S*)-3c. Compound (*R*)-**2c** (60.2 mg, 0.160 mmol), the acetal **1** (150 mg, 0.800 mmol) $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.036 cm^3, 0.080 mmol) and CH_2Cl_2 (6 cm^3) gave *compound* (*S*)-**3c** (51.5 mg, 90%, 83% ee) as colourless crystals; $[\alpha]_D^{22}$ +38.4 (*c* 0.522, $CHCl_3$). Optically pure *S*-**3c** was isolated easily by recrystallization with hexane–CH_2Cl_2 as colourless crystals; $[\alpha]_D^{20}$ +49.4 (*c* 0.599, $CHCl_3$); mp 121.5–123 °C (hexane–CH_2Cl_2); *m/z* 359 (M^+) (Found: C, 76.85; H, 5.95; N, 3.9; S, 8.9%; M^+, 359.1356. $C_{23}H_{21}NOS$ requires C, 76.85; H, 5.90; N, 3.90; S, 8.90%; *M*, 359.1344).

(4*R*)-1-(*o*-Bromobenzyl)-4-*p*-tolylsulfanylazetidin-2-one (*R*)-3d. Compound (*S*)-**2d** (62.0 mg, 0.163 mmol), the acetal **1** (153 mg, 0.815 mmol), $ZnCl_2$–Et_2O complex (2.20 mol dm^{-3} solution in CH_2Cl_2; 0.037 cm^3, 0.082 mmol) and CH_2Cl_2 (6 cm^3) gave *compound* (*R*)-**3d** (34.8 mg, 59%, 83% ee) as a pale yellow oil; $[\alpha]_D^{25}$ −59.2 (*c* 1.49, $CHCl_3$); ν_{max}/cm^{-1} 3020, 2930 and 1760; $\delta_H(C_6D_6)$ 2.00 (3 H, s, Me), 2.60 (1 H, dd, *J* 1.8 and 15, 3-H^a), 2.71 (1 H, dd, *J* 4.8 and 15, 3-H^b), 4.30 and 4.63 (2 H, ABq, *J* 15.5, CH_2Ar), 4.32 (1 H, dd, *J* 1.8 and 4.8, 4-H) and 6.66–7.49 (m, 8 H, ArH); *m/z* 361 (M^+) (Found: C, 56.15; H, 4.5; N, 3.8%; M^+, 361.0159. $C_{17}H_{16}BrNOS$ requires C, 56.35; H, 4.45; N, 3.85%; *M*, 361.0136).

(4*R*)-1-Diphenylmethyl-4-*p*-tolylsulfonylazetidin-2-one (*R*)-5

MCPBA (80%; 55.7 mg, 0.323 mmol) was added to a stirred solution of compound (*R*)-**3c** (52.8 mg, 0.147 mmol) in CH_2Cl_2 (4 cm^3) at 0 °C for 30 min. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2 to give *compound* (*R*)-**5** (45.0 mg, 78%) as colourless crystals; $[\alpha]_D^{22}$ −86.0 (*c* 1.14, $CHCl_3$); mp 179.5–181 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3030, 3010, 1770, 1320, 1300, 1150, 1140 and 1070; δ_H 2.45 (3 H, s, Me), 3.06 (1 H, dd, *J* 2.8 and 15, 3-H^a), 3.15 (1 H, dd, *J* 5 and 15, 3-H^b), 4.63 (1 H, dd, *J* 2.8 and 5, 4-H), 5.68 (1 H, s, C*H*Ph_2) and 7.19–7.60 (14 H, m, ArH); *m/z* 391 (M^+) (Found: C, 70.45; H, 5.5; N, 3.6; S, 8.05%; M^+, 391.1216. $C_{23}H_{21}NO_3S$ requires C, 70.55; H, 5.40; N, 3.60; S, 8.20%; *M*, 391.1243).

(3*S*,4*R*)-1-Diphenylmethyl-3-ethyl-4-*p*-tolylsulfanylazetidin-2-one 6

A solution of LiHMDS [prepared from BuLi (1.60 mol dm^{-3} solution in hexane; 7.31 cm^3, 11.7 mmol) and HMDS (2.44 cm^3, 11.7 mmol)] in THF (50 cm^3) was cooled at −45 °C under a N_2 atmosphere. After being stirred for 30 min, the mixture was treated with EtI (15.6 cm^3, 195 mmol) followed immediately by a solution of compound (*R*)-**3c** (3.5 g, 9.75 mmol) and HMPA (1.9 cm^3) in THF (50 cm^3). The mixture was stirred for 1 h after which it was diluted with 50% AcOEt in hexane, washed with water and brine, dried and evaporated under reduced pressure. The residue was chromatographed with CH_2Cl_2 in hexane to give *compound* **6** (2.87 g, 76%) as colourless crystals; $[\alpha]_D^{24}$ +3.78 (*c* 0.925, $CHCl_3$); mp 138.2–139 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3030, 3010, 2970 and 1750; δ_H 0.91 (3 H, t, *J* 7.4, *Me*CH_2), 1.55–1.83 (2 H, m, MeCH_2), 2.33 (3 H, s, Me), 3.07 (1 H, ddd, *J* 2.0, 6.1 and 8.3, 3-H), 4.43 (1 H, d, *J* 2.0, CHS), 5.74 (1 H, s, C*H*Ph_2) and 7.03–7.39 (14 H, m, ArH); *m*/*z* 387 (M^+) (Found: C, 77.25; H, 6.55; N, 3.6; S, 8.2%; M^+, 387.1634. $C_{25}H_{25}NOS$ requires C, 77.50; H, 6.50; N, 3.60; S, 8.30%; *M*, 387.1657).

(3*S*,4*R*)-1-Diphenylmethyl-3-ethyl-4-*p*-tolylsulfinylazetidin-2-one 7

MCPBA (749 mg, 4.34 mmol) was added to a stirred solution of compound **6** (1.60 g, 4.13 mmol) in CH_2Cl_2 (100 cm^3) at 0 °C for 10 min. The reaction mixture was then poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The combined extracts were washed with brine, dried and evaporated. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2 to give *compound* **7** (1.75 g, quant.) as colourless crystals; $[\alpha]_D^{20}$ −110 (*c* 0.763, $CHCl_3$); mp 142.5–144 °C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3010, 2970, 1760, 1330, 1090, 1050 and 1020; δ_H 0.46 (3 H, t, *J* 7.4, *Me*CH_2), 1.15–1.46 (2 H, m, MeCH_2), 2.37 (3 H, s, Me), 3.67–3.72 (2 H, br m, 3-H and 4-H), 6.15 (1 H, s, C*H*Ph_2) and 7.15–7.48 (14 H, m, ArH); *m*/*z* 403 (M^+) (Found: M^+, 403.1614. $C_{25}H_{25}NO_2S$ requires *M*, 403.1606).

(3*R*,4*R*)-1-Diphenylmethyl-3-ethyl-4-methoxycarbonylmethylazetidin-2-one 8

To a stirred solution of compound **7** (800 mg, 1.99 mmol) and ZnI_2 (31 mg, 0.100 mmol) in dry MeCN (35 cm^3) under nitrogen at 0 °C was added dropwise over 20 min the acetal **1** (562 mg, 2.99 mmol). The mixture was poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The extract was washed with brine, dried and evaporated. The residue was purified by column chromatography on silica gel eluting with 20% AcOEt in hexane to give *compound* **8** (448 mg, 75%) as a pale yellow oil; $[\alpha]_D^{23}$ −22.5 (*c* 0.775, $CHCl_3$); ν_{max}/cm^{-1} 3030, 3010 and 1740; δ_H 0.96 (3 H, t, *J* 7.4, *Me*CH_2), 1.64–1.82 (2 H, m, MeCH_2), 2.39 (1 H, d, *J* 8.0, C*H*^{a}H^bCO_2), 2.41 (1 H, d, *J* 5.8, CH^a*H*^{b}), 2.84 (1 H, dt, *J* 2.0 and 7.5, 3-H), 3.57 (3 H, s, MeO), 3.65 (1 H, ddd, *J* 2.0, 5.8 and 8.0, 4-H), 5.95 (1 H, s, C*H*Ph_2) and 7.23–7.39 (10 H, m, ArH); *m*/*z* 337 (M^+) (Found: C, 74.35; H, 6.95; N, 4.1%; M^+, 337.1687. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.85; N, 4.15%; *M*, 337.1678).

(3*R*,4*R*)-1-Diphenylmethyl-3-ethyl-4-hydroxyethylazetidin-2-one 9

A solution of compound **8** (250 mg, 0.742 mmol) in dry THF (10 cm^3) was added to a stirred suspension of $LiAlH_4$ (56.4 mg, 1.48 mmol) at 0 °C under nitrogen. After 20 min, AcOEt (5 cm^3) and aq. NH_4Cl (0.5 cm^3) were added to the mixture which was then passed through a Celite pad to remove the precipitate. Concentration and purification of the filtrate by PLC eluting with 60% AcOEt in hexane gave *compound* **9** (156 mg, 68%) as a yellow oil; $[\alpha]_D^{21}$ +1.06 (*c* 1.41, $CHCl_3$); ν_{max}/cm^{-1} 3620, 3440, 3010, 2970, 2940 and 1740; δ_H 0.97 (3 H, t, *J* 7.4, *Me*CH_2), 1.43–1.86 (4 H, m, MeCH_2 and C$H_2$$CH_2$OH), 2.80 (1 H, ddd, *J* 2.0, 6.1 and 8.1, 3-H), 3.36 (1 H, ddd, *J* 2.0, 5.9 and 9.6, 4-H), 3.53 (2 H, t, *J* 6.1, CH_2OH), 5.96 (1 H, s, C*H*Ph_2) and 7.24–7.40 (10 H, m, ArH); *m*/*z* 309 (M^+) (Found: M^+, 309.1700. $C_{20}H_{23}NO_2$ requires *M*, 309.1729).

(3*R*,4*R*)-3-Ethyl-4-hydroxyethylazetidin-2-one 10[10]

A solution of Na (44.9 mg, 1.95 mmol) in liq. NH_3–THF was added to a solution of compound **9** (100 mg, 0.324 mmol) in THF (3 cm^3) at −78 °C under nitrogen. The resulting blue solution was stirred at that temperature for 1 h after which solid NH_4Cl was added to it and the resulting colourless solution was warmed to room temperature to distil off NH_3. Ether was added to the residue to give an insoluble white precipitate which was filtered off. Concentration of the filtrate and purification of the residue by PLC eluting with 10% MeOH in CH_2Cl_2 gave *compound* **10** (37.6 mg, 81%) as a colourless oil; $[\alpha]_D^{21}$ +21.6 (*c* 0.353, $CHCl_3$); ν_{max}/cm^{-1} 3630, 3410, 3020, 2970, 2940 and 1750; δ_H 1.02 (3 H, t, *J* 7.4, *Me*CH_2), 1.59–1.97 (4 H, m, MeCH_2 and C$H_2$$CH_2$OH), 2.74–2.79 (2 H, br m, 3-H and OH), 3.47 (1 H, ddd, *J* 2.2, 5.0 and 8.1, 4-H), 3.68–3.83 (2 H, m, CH_2OH) and 6.60 (1 H, br s, NH); *m*/*z* 143 (M^+) (Found: M^+, 143.0961. $C_7H_{13}NO_2$ requires *M*, 143.0947).

(3*R*,4*R*)-1-*tert*-Butyldimethylsilyl-4-*tert*-butyldimethylsilyloxyethyl-3-ethylazetidin-2-one 11[10,11]

A solution of compound **10** (8.3 mg, 0.058 mmol) in CH_2Cl_2 was treated with 2,6-dimethylpyridine (65.8 mg, 0.615 mmol) and then with TBDMSOTf (61.2 mg, 0.232 mmol) at 0 °C under nitrogen, with stirring. After 1 h, the reaction was quenched with MeOH (0.17 cm^3) and the mixture was evaporated. Purification by PLC eluting with 20% AcOEt in hexane gave *compound* **11** (21.7 mg, quant.) as a colourless oil; $[\alpha]_D^{22}$ −40.9 (*c* 1.02, $CHCl_3$), lit.,[13] $[\alpha]_D^{25}$ −39.6 (*c* 2.92, $CHCl_3$); ν_{max}/cm^{-1} 2960, 2930, 2860 and 1720; δ_H 0.0368, 0.0404, 0.199 and 0.233 (total 12 H, each s, $SiMe_2$ × 2), 0.88 and 0.95 (total 18 H, each s, Bu^t × 2), 1.00 (3 H, t, *J* 7.4, *Me*CH_2), 1.51–1.81 (3 H, m, MeCH_2Me, C*H*^{a}H^bCH_2O), 2.01–2.13 (1 H, m, CH^a*H*^{b}CH_2O), 2.79 (1 H, ddd, *J* 2.3, 6.3 and 7.9, 3-H), 3.37 (1 H, td, *J* 2.6 and 10.6, 4-H) and 3.56–3.72 (2 H, m, CH_2OH); *m*/*z* 314 (M^+ − Bu^t) [Found: C, 61.4; H, 10.95; N, 3.75%; (M^+ − Bu^t), 314.1948. $C_{19}H_{41}NO_2Si_2$ requires C, 61.40; H, 11.10; N, 3.75%; $C_{15}H_{32}NO_2Si_2$ requires *m*/*z* 314.1972].

References

1 Asymmetric Pummerer rearrangement; (*a*) J. E. McCormick and R. S. McElhinney, *Chem. Commun.*, 1969, 171; (*b*) S. Glue, I. T. Kay and M. R. Kipps, *Chem. Commun.*, 1970, 1158; (*c*) T. Numata and S. Oae, *Tetrahedron Lett.*, 1977, 1337; (*d*) T. Numata, O. Itoh and S. Oae, *Chem. Lett.*, 1977, 909; (*e*) M. Mikolajczyk, A. Zatorski, S. Grzejszczak, B. Costisella and W. Midura, *J. Org. Chem.*, 1978, **43**, 2518; (*f*) T. Numata, O. Itoh and S. Oae, *Tetrahedron Lett.*, 1979, 1869; (*g*) T. Masuda, T. Numata, N. Furukawa and S. Oae, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1302; (*h*) T. Numata, O. Itoh, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 257; (*i*) O. Itoh, T. Numata, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 266. Asymmetric additive Pummerer reaction (enantioselective 3,3-sigmatropic rearrangement); J. P. Marino and A. D. Perez, *J. Am. Chem. Soc.*, 1984, **106**, 7643.

2 Reviews, see: (*a*) S. Oae and T. Numata, The Pummerer and Pummerer Type of Reactions, in *Isotopes in Organic Chemistry*, ed. E. Buncel and C. C. Lee, Elsevier, New York, 1980, vol. 5, ch. 2; (*b*) O. D. Lucchi, U. Miotti and G. Modena, *Organic Reac.* (N.Y.) 1990, **40**, 157.

3 (*a*) B. Stridsberg and S. Allenmark, *Acta Chem. Scand., Ser. B*, 1974, **28**, 591; 1976, **30**, 219; (*b*) S. Wolfe, P. M. Kazmaier and H. Auksi, *Can. J. Chem.*, 1979, **57**, 2404; (*c*) T. Kaneko, Y. Okamoto and K. Hatada, *J. Chem. Soc., Chem. Commun.*, 1987, 1511.

4 Y. Kita, O. Tamura, T. Miki, H. Tono, N. Shibata and Y. Tamura, *Tetrahedron Lett.*, 1989, **30**, 729.
5 (*a*) Y. Kita, H. Yasuda, O. Tamura, F. Itoh and Y. Tamura, *Tetrahedron Lett.*, 1984, **25**, 4681; (*b*) Y. Kita, H. Yasuda, O. Tamura, F. Itoh and Y. Tamura, *Chem. Pharm. Bull.*, 1985, **33**, 4235; (*c*) Y. Kita, O. Tamura, F. Itoh, H. Yasuda, T. Miki and Y. Tamura, *Chem. Pharm. Bull.*, 1987, **35**, 562.
6 (*a*) Y. Kita, O. Tamura, T. Miki and Y. Tamura, *Tetrahedron Lett.*, 1987, **28**, 6479; (*b*) Y. Kita, O. Tamura, N. Shibata and T. Miki, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1862; (*c*) Y. Kita, O. Tamura, N. Shibata and T. Miki, *Chem. Pharm. Bull.*, 1990, **38**, 1473; (*d*) Y. Kita, N. Shibata, T. Miki, Y. Takemura and O. Tamura, *J. Chem. Soc., Chem. Commun.*, 1990, 727; (*e*) Y. Kita, N. Shibata, O. Tamura and T. Miki, *Chem. Pharm. Bull.*, 1991, **39**, 2225; (*f*) Y. Kita, N. Shibata, T. Miki, Y. Takemura and O. Tamura, *Chem. Pharm. Bull.*, 1992, **40**, 12.
7 (*a*) Y. Kita, N. Shibata and N. Yoshida, *Tetrahedron Lett.*, 1993, **34**, 4063; (*b*) Y. Kita, N. Shibata, N. Yoshida, S. Fukui and C. Fujimori, *Tetrahedron Lett.*, 1994, **35**, 2569; (*c*) Y. Kita, N. Shibata, N. Yoshida and S. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3335; (*d*) Y. Kita, N. Shibata, S. Fukui and S. Fujita, *Tetrahedron Lett.*, 1994, **35**, 9733.
8 Y. Kita, N. Shibata, N. Kawano, T. Tohjo, C. Fujimori and K. Matsumoto, *Tetrahedron Lett.*, 1995, **36**, 115.
9 A. Albinati, P. Bravo, F. Ganazzoli, G. Resnati and F. Viani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1405.
10 (*a*) A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, *Chem. Pharm. Bull.*, 1981, **29**, 1854 and 2899; (*b*) M. Shibasaki, A. Nishida and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 1982, 1324; (*c*) A. Nishida, M. Shibasaki and S. Ikegami, *Tetrahedron Lett.*, 1984, **25**, 765.
11 H. Rehling and H. Jensen, *Tetrahedron Lett.*, 1972, 2793.
12 The formation of the acylaminosulfonium ion (isothiazolone B) as an intermediate has been widely accepted under Pummerer-type conditions; (*a*) Y. Uchida and S. Kozuka, *J. Chem. Soc., Chem. Commun.*, 1981, 510; (*b*) T. Kaneko, *J. Am. Chem. Soc.*, 1985, **107**, 5490; (*c*) Y. Uchida and S. Oae, *Gazz. Chim. Ital.*, 1987, **117**, 640; (*d*) K. Yamamoto, S. Yamazaki and I. Murata, *J. Org. Chem.*, 1987, **52**, 5239; (*e*) S. W. Wright, M. M. Abelman, L. L. Bostrom and R. C. Corbett, *Tetrahedron Lett.*, 1992, **33**, 153.
13 C. Gennari and P. G. Cozzi, *J. Org. Chem.*, 1988, **53**, 4015; M. Shibasaki, Y. Ishida, G. Iwasaki and T. Iimori, *J. Org. Chem.*, 1987, **52**, 3488.
14 K. Okano, T. Izawa and O. Masaji, *Tetrahedron Lett.*, 1983, **24**, 217.

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