Ring-opening reaction of Bus- and SES-protected aziridines using lithiated dithianes†

Ken Sakakibara and Kyoko Nozaki*

Received 19th August 2008, Accepted 14th October 2008
First published as an Advance Article on the web 25th November 2008
DOI: 10.1039/b814413c

The scope and limitation of the ring-opening reaction of sulfonyl-activated aziridines using lithiated dithianes was investigated. Nucleophilic attack of lithiated dithianes on aziridines containing *tert*-butylsulfonyl (Bus) and 2-(trimethylsilyl)ethylsulfonyl (SES) demonstrated efficient ring cleavage to yield β-amino carbonyl equivalents, γ-lactam and *syn*- and *anti*-1,5-aminoalcohols. The first example of a ring-opening reaction of di-substituted aziridine using dithiane is also reported. Finally, the Bus and SES-possessing dithianes obtained were deprotected to demonstrate their synthetic usefulness.

Introduction

Optically active β-amino carbonyl compounds are common intermediates for various kinds of biologically active compounds. One of the common synthetic approaches to this type of compound is the asymmetric Mannich reaction.[1–3] As an alternative method, nucleophilic ring opening of *N*-*p*-toluenesufonyl (=Ts) aziridine using lithiated dithianes has been reported.[4–12]

The latter methodology is advantageous for several reasons: (1) because the carbonyl group is masked in the product, undesirable side reactions such as self-aldol condensation are suppressed. (2) The amino group in the product is protected by a *p*-tosyl group. (3) The reaction is not reversible, therefore, the products are obtained in high yields. (4) Enantiomerically pure aziridines[13–17] are easily available and the configuration is maintained throughout the reaction. However, the substrates for the ring-opening reaction using lithiated dithianes were limited to *N*-tosylaziridines. Although *N*-tosylaziridines are commonly employed because of their easy preparation, a major drawback is the difficulty in their deprotection.[9] Other sulfonyl-protecting groups such as *tert*-butylsulfonyl (Bus),[18–21] 2-trimethylsilylethylsulfonyl (SES),[22,23] and *p*-nitrophenylsulfonyl (Ns),[24,25] are known to undergo deprotection under much milder reaction conditions (Fig. 1).

In this paper, we report the scope and limitation of *N*-sulfonylaziridines employable as electrophiles in the reaction with lithiated dithianes. Depending on the kind of dithianes, β-amino carbonyl equivalents, a γ-lactam and 1,5-aminoalcohols were obtained in good yields with a Bus- and SES-protecting group on the nitrogen. We also report the first example of a ring-opening reaction of di-substituted aziridine by dithiane. Deprotection of Bus and SES is also described.

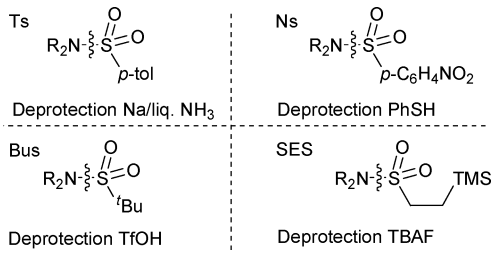
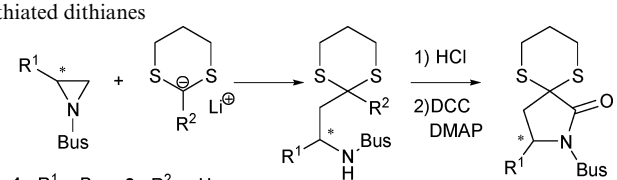


Fig. 1 Possible sulfonyl protecting groups for aziridines.

Results and discussion

Bus-activated aziridines **1** and various dithiane anions **2–5** were chosen as substrates (Table 1). Aziridine *rac*-**1** was allowed to react with lithiated 1,3-dithiane **2** to yield *rac*-**6** (Table 1, run 1). Enantiopure aziridine (*S*)-**1** was converted to (*S*)-**6** by **2** without any racemization (Table 1, run 2). Lithiated carboxyl-1,3-dithiane **3** opened *rac*-**1** in the presence of TMEDA (Table 1, run 3). The crude product could not be purified because of its high

Table 1 Ring-opening reaction of Bus-activated aziridine **1** using lithiated dithianes



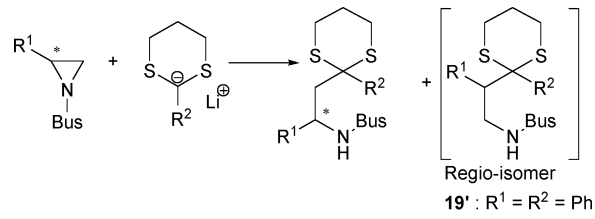
Run	Aziridine	Dithiane anion	Product	Yield (%)
1[a]	*rac*-**1**	**2**	*rac*-**6**	90
2[a]	(*S*)-**1**	**2**	(*S*)-**6**	91
3[b]	*rac*-**1**	**3**	*rac*-**7**	76
4[b]	(*S*)-**1**	**3**	(*S*)-**7**	78
5[c]	*rac*-**1**	**4**	*rac*-**8**	90
6[a]	*rac*-**1**	**5**	*rac*-**9**	92

[a] Experimental procedure A. [b] Experimental procedure B. [c] Experimental procedure C.

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-8656, Tokyo, Japan. E-mail: nozaki@chembio.t.u-tokyo.ac.jp; Fax: +81-3-5841-7263; Tel: +81-3-5841-7261

† Electronic supplementary information (ESI) available: Full identification data, ^{1}H NMR spectra and ^{13}C NMR spectra of newly synthesized compounds. See DOI: 10.1039/b814413c

Table 2 Ring-opening reaction of various Bus-activated aziridines



10 : R^1 = **2** : R^2 = H
11 : R^1 = $^nC_{10}H_{21}$ **5** : R^2 = Ph
12 : R^1 = $BnOCH_2$
13 : R^1 = $TrOCH_2$
14 : R^1 = Ph

15 : R^1 = R^2 = Ph
16 : R^1 = $^nC_{10}H_{21}$ R^2 = Ph
17 : R^1 = $BnOCH_2$ R^2 = Ph
18 : R^1 = $TrOCH_2$ R^2 = Ph
19 : R^1 = Ph R^2 = Ph

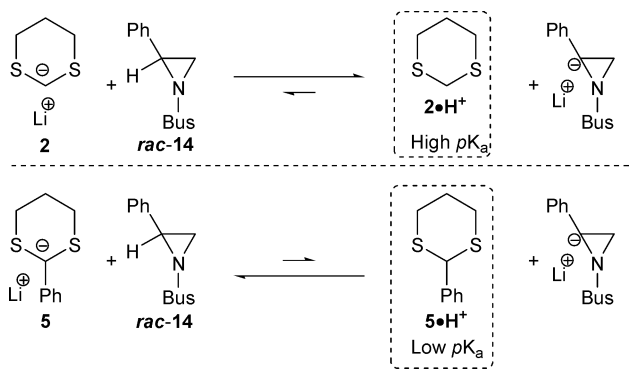
Run	Aziridine	Dithiane anion	Product	Yield (%)
1[a]	*rac*-**10**	**5**	*rac*-**15**	83
2[a]	*rac*-**11**	**5**	*rac*-**16**	94
3[a]	*rac*-**12**	**5**	*rac*-**17**	90
4[a]	(*R*)-**13**	**5**	(*R*)-**18**	85
5[a]	*rac*-**14**	**5**	*rac*-**19**[b]	95[b]
6[a]	*rac*-**14**	**2**	—[c]	–[c]

[a] Experimental procedure A. [b] Regioisomer *rac*-**19′** was obtained in addition to **19**. [c] Complex mixture was obtained.

polarity. After neutralization by HCl–MeOH, the crude material was treated with DCC–DMAP and γ-lactam **7** was isolated. Ring opening of enantiopure aziridine (*S*)-**1** by **3** yielded (*S*)-**7** without racemization (Table 1, run 4). Aziridine *rac*-**1** yielded *rac*-**8** and *rac*-**9** by the reactions with lithiated dithianes **4** and **5** (Table 1, runs 5–6).

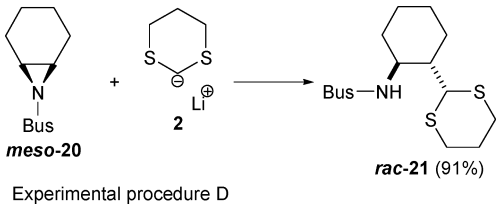
We next examined the scope of Bus-aziridines bearing various substituents **10–13** by lithiated dithiane **5** (Table 2, runs 1–4). All of them easily provided the ring-opening products **15–18**. The product *rac*-**19** was obtained from *rac*-**14** as a mixture with its regio-isomer **19′** (**19** : **19′** = ~3 : 1 or ~1 : 3) (Table 2, run 5). On the other hand, ring-opening product was not obtained from *rac*-**14** and **2** to detect a complex mixture (Table 2, run 6).[10]

The different reactivity between dithiane anions **2** and **5** may be explained as follows. Considering the big difference of pK_a values between dithiane **2**·H^+ (pK_a 39) and **5**·H^+ (pK_a 30.7),[26] dithiane anion **2** would cause deprotonation of aziridine *rac*-**14** to give a complex mixture, while lithiated dithiane **5** triggers smooth ring-opening due to the low pK_a value of **5**·H^+ (Scheme 1). The order of pK_a can roughly be estimated to rationalize our hypothesis: **5**·H^+ (pK_a 30.7) < α-proton to N atom and Ph group < **2**·H^+ (pK_a 39).



Scheme 1 Ring-opening reaction of Bus-activated Ph-aziridine.

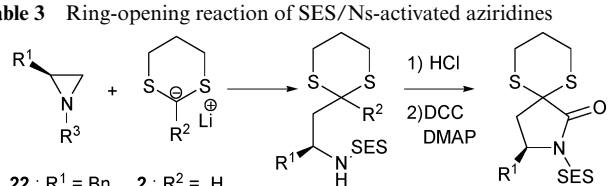
Furthermore, di-substituted aziridine *meso*-**20** yielded the *trans*-substituted product *rac*-**21** (Scheme 2). Although several examples of ring opening using dithiane have been reported for 2,3-di-substituted oxiranes,[27–30] this is the first example of a ring-opening reaction of di-substituted aziridine using dithiane.



Scheme 2 Ring-opening reaction of 2,3-di-substituted-aziridine.

SES- and Ns-activated aziridines **22** and **23** were reacted with lithiated dithianes (Table 3, runs 1–5). Treatment of azridine (*S*)-**22** with anion **2** resulted in quantitative recovery of dithiane, and a complex mixture derived from aziridine was obtained (Table 3, run 1). (*S*)-**22** was treated with **3** to yield (*S*)-**24** *via* cyclization (Table 3, run 2). In contrast, reaction of (*S*)-**22** with **4** resulted in quantitative recovery of dithiane and a complex mixture derived from aziridine (Table 3, run 3). Lithiated dithiane **5** smoothly opened aziridine (*S*)-**22** to (*S*)-**25** (Table 3, run 4). The following may be an explanation for the quantitative recovery of dithiane and the complex mixture derived from aziridine (Table 3, runs 1 and 3). In the case of lithiated dithianes **2** and **4**, equilibrium between an α-carbanion on the sulfonyl group of SES and the anion of dithiane would lie to the right because of the higher pK_a of dithianes **2**·H^+ and **4**·H^+ (Scheme 3). Deprotonated aziridines would lead to a complex mixture and recovery of protonated dithiane. In contrast, lithiated dithanes **3** and **5** would retain the carbanion character to open the aziridines because of the lower pK_a of dithianes **3**·H^+ and **5**·H^+ (Scheme 3). The order of pK_a can roughly be estimated to rationalize our hypothesis: **3**·H^+, **5**·H^+ (pK_a 30.7) < α-proton neighboring SES sulfonyl group < **2**·H^+ (pK_a 39), **4**·H^+.[26,31] Given that 2-CO_2Me-1,3-dithiane (pK_a 20.9) and $MeSO_2Me$ (pK_a 31.1) have similar pK_a values of dithiane **3**·H^+ and α-proton neighboring SES sulfonyl group, our roughly estimated order of pK_a would

Table 3 Ring-opening reaction of SES/Ns-activated aziridines



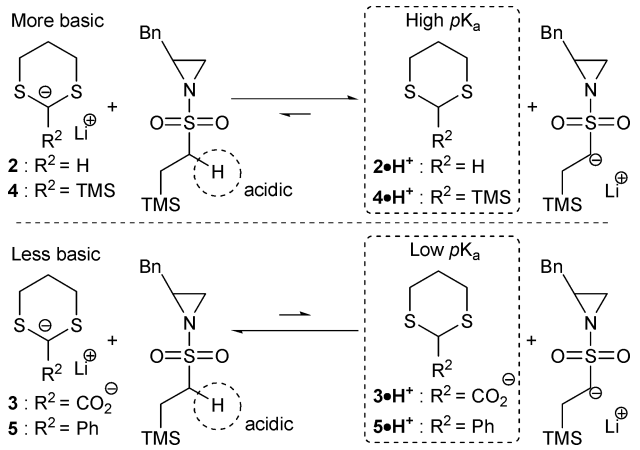
22 : R^1 = Bn **2** : R^2 = H
R^3 = SES **3** : R^2 = CO_2^-
23 : R^1 = Bn **4** : R^2 = TMS
R^3 = Ns **5** : R^2 = Ph

25 : R^1 = Bn, R^2 = Ph

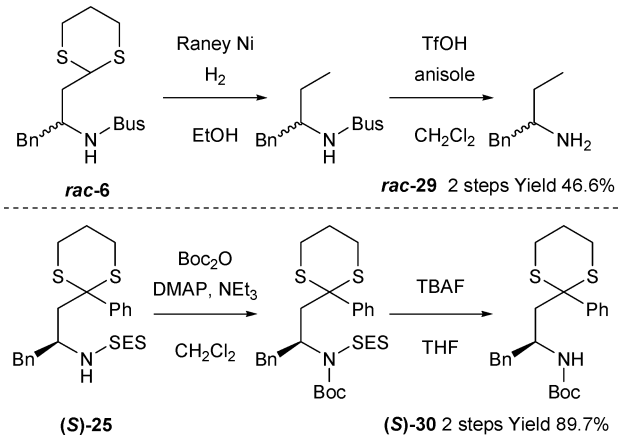
24 : R^1 = Bn

Run	Aziridine	Dithiane anion	Product	Yield (%)
1[a]	(*S*)-**22**	**2**	—	—[d]
2[b]	(*S*)-**22**	**3**	(*S*)-**24**	45
3[c]	(*S*)-**22**	**4**	—	—[d]
4[a]	(*S*)-**22**	**5**	(*S*)-**25**	86
5[a]	(*S*)-**23**	**5**	—	—[e]

[a] Experimental procedure A. [b] Experimental procedure B. [c] Experimental procedure C. [d] Recovery of dithiane and a complex mixture from aziridine were detected. [e] A complex mixture was given.



Scheme 3 Equilibrium between lithiated dithiane and α-sulfonyl proton.



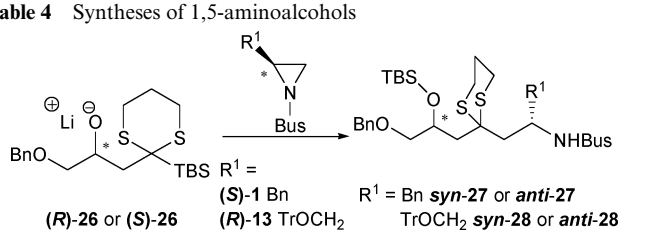
Scheme 4 Deprotection of Bus and SES.

be supported. Finally, Ns-aziridine (*S*)-**23** provided an insoluble complex mixture due to competing deprotection (Table 3, run 5).[32]

We have further extended the ring opening of Bus-activated aziridines to the syntheses of 1,5-amino alcohols *via* 1,4-Brook rearrangement (Table 4, runs 1–4). Lithiated carbinol **26** induced the 1,4-Brook rearrangement in the presence of HMPA, yielding 1,5-amino alcohols *via* the ring-opening reaction of aziridines.[4] 1,5-Amino alcohol *syn*-**27** can be obtained from aziridine (*S*)-**1** and lithiated dithiane (*R*)-**26** (Table 4, run 1). *Anti*-**27** can be exclusively obtained using the opposite enantiomer of **26** (Table 4, run 2). In addition, *syn* and *anti*-**28** were obtained by using aziridine (*R*)-**13** and both enantiomers of lithiated dithiane **26** (Table 4, runs 3 and 4).

Finally, the Bus and SES groups of the dithianes obtained were removed to demonstrate their synthetic usefulness (Scheme 4). First of all, Bus-bearing dithiane *rac*-**6** was chosen as a substrate. Unfortunately, use of the normal conditions (TfOH–anisole[21]) or use of the Ts-removing conditions (Na–naphtalenide–DME[9]) led to decomposition of the dithiane ring. Thus, after the dithiane moiety was removed by Raney Ni, the deprotected compound *rac*-**29** was obatined using TfOH and anisole (Scheme 4). Next, SES-possessing dithiane (*S*)-**25** was efficiently deprotected *via* Boc-introduction to yield (*S*)-**30**. It is well known that *N*-acyl-SES is much more easily deprotected than monoprotected SES-amine.[23]

Table 4 Syntheses of 1,5-aminoalcohols



Run	Aziridine	Dithiane	Product	Yield (%)
1[a]	(*S*)-**1**	(*R*)-**26**	*syn*-**27**	69
2[a]	(*S*)-**1**	(*S*)-**26**	*anti*-**27**	61
3[a]	(*R*)-**13**	(*R*)-**26**	*syn*-**28**	58
4[a]	(*R*)-**13**	(*S*)-**26**	*anti*-**28**	78

[a] Experimental procedure E.

Conclusions

Bus- and SES-activated aziridines undergo an efficient ring-opening reaction with various lithiated dithiane anions to yield various β-amino carbonyl equivalents, γ-lactam and *syn*- and *anti*-1,5-aminoalcohols. The successful employment of aziridines containing Bus and SES will enhance the synthetic value of the ring-opening reaction between aziridines and dithianes. The scope of substrates was elucidated from a pK_a viewpoint. Furthermore, we report the first example of a ring-opening reaction of di-substituted aziridine using dithiane. The Bus and SES groups of the dithianes obtained were deprotected to demonstrate their synthetic usefulness.

Experimental procedures and analytical data

General information

All manipulations involving air- and/or moisture-sensitive compounds were carried out in a glove box under an argon atmosphere or with the standard Schlenk technique under argon purified by passing through a hot column packed with BASF catalyst R3–11. All the solvents used for the reactions were distilled under argon after drying over an appropriate drying reagent or passed through solvent purification columns. Most reagents were used without further purification, unless otherwise specified. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). For silica gel column chromatography, Silica gel 60 N (spherical, neutral, particle size 63–210 μm, Kanto Kagaku Co., Ltd.) was used. NMR spectra were recorded in $CDCl_3$ using a 500 MHz spectrometer (^{1}H 500 MHz; ^{13}C 125 MHz). Chemical shifts are reported in ppm relative to the residual protiated solvent peak (7.26 ppm for $CHCl_3$) for ^{1}H and $CDCl_3$ (77.16 ppm) for ^{13}C. Otherwise, TMS (0.00 ppm) was used as an internal standard for ^{1}H. Data are presented below: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiplet resonances, br = broad), coupling constants in hertz (Hz), and signal area integration in natural numbers. Melting points of general organic compounds were determined using a Yanaco MP-500D melting point apparatus. Optical rotations were measured on a JASCO P-1010 spectrometer

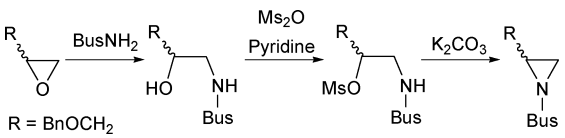
using a 10 cm cell. The recycling preparative GPC was performed with JAI GEL-1H and JAI GEL-2H columns ($CHCl_3$ as an eluent). Confirmation of enantiopurity was obtained by chiral HPLC. HPLC analyses were carried out using a JASCO LC-2000Plus system (HPLC pump: PU-2080; gradient unit: LG-2080-02; degasser: DG-2080-53, column oven: CO-2060; UV detector: MD-2010) equipped with a DAICEL CHIRALPAK IA or IB column (4.6 mm × 250 mm). Elemental analyses were performed at the University of Tokyo. High resolution mass spectra were recorded by the FAB method using a JEOL JMS-700 mass spectrometer.

Literature methods were used for known compounds $^tBuSO_2NH_2$,[20] 2-CO_2H-1,3-dithiane (precursor of **3**),[33] carbinol (precursor of **26**),[34] (*R*)-(2,3-epoxypropyl)benzene,[35] SESNHBoc[36] and most of aziridines.[20,25,37,38] Other aziridines *rac*-**12** and (*S*)-**22** were synthesized as follows.

Synthetic procedure for aziridine *rac*-12

rac-1-(*tert*-Butylsulfonyl)-2-(benzyloxymethyl)aziridine

Aziridine *rac*-**12** was synthesized *via* the literature method with a slight modification (Scheme 5).[37] $BnNEt_3^+Cl^-$ (91.2 mg, 0.400 mmol) was added to a stirred suspension of benzyl glycidyl ether (657 mg, 4.00 mmol), $^tBuSO_2NH_2$ (823 mg, 6.00 mmol) and K_2CO_3 (55.3 mg, 0.400 mmol) in 1,4-dioxane (1.80 mL). The suspension was heated at 90 °C for 48 h, then cooled, and subsequently, the solvent was removed by rotary evaporation. Purification of the residue by column chromatography (hexane–Et_2O = 1 : 2, v/v) yielded β-hydroxysulfonamide, which was used directly in the next step.



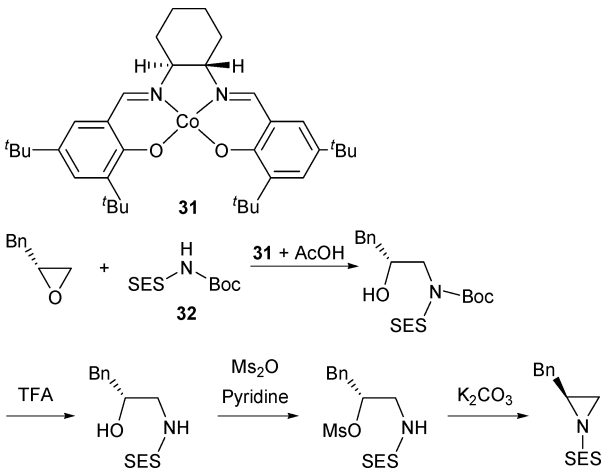
Scheme 5 Synthetic procedure for aziridine *rac*-**12**.

The β-hydroxysulfonamide obtained was dissolved in CH_2Cl_2 (20.0 mL) and pyridine (0.650 mL, 8.00 mmol). DMAP (49.0 mg, 0.400 mmol) and Ms_2O (1.04 g, 6.00 mmol) were added to the resulting solution and stirred for 2 h. Saturated aqueous K_2CO_3 solution was added to the suspension until bubbles were no longer produced, and then reduced pressure was applied. The material obtained was dissolved in CH_2Cl_2, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The crude material was used directly in the next step.

The crude mesylate was dissolved in THF (30.0 mL) and H_2O (15.0 mL), and K_2CO_3 (2.20 g, 16.0 mmol) was added. Following stirring at 70 °C for 17 h, the reaction mixture was cooled and the solvents were removed under reduced pressure. Purification of the residue by column chromatography (hexane–AcOEt = 5 : 1, v/v) yielded a brown liquid. Complete purification was achieved by the recycling preparative SEC to obtain a colourless liquid (650 mg, 2.50 mmol, 63% yield). The characteristics of the colourless liquid were as follows: R_f = 0.25 (hexane–EtOAc = 5 : 1, v/v); ^1H NMR ($CDCl_3$): δ 1.51 (s, 9H), 2.18 (d, J = 4.4 Hz, 1H), 2.62 (d, J = 7.1 Hz, 1H), 2.94–3.04 (m, 1H), 3.54 (dd, J = 6.1, 11.1 Hz, 1H), 4.53–4.62 (m, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 24.33, 30.28, 38.14, 59.75, 69.48, 73.28, 127.81, 127.96, 128.58, 137.81; IR (KBr disc): 1113, 1130, 1229, 1306, 1366, 1454, 1481, 2870, 2986 cm^{-1}. HRMS-FAB$^+$ (m/z + H^+) calcd for $C_{14}H_{22}NO_3S_1$ 284.1320, found 284.1329.

Synthetic procedure for aziridine (*S*)-22

(2*S*)-2-Benzyl-1-[2-(trimethylsilyl)ethanesulfonyl]aziridine. Aziridine (*S*)-**22** was synthesized *via* the literature method with a slight modification (Scheme 6).[13] A 20 mL Schlenk flask equipped with a magnetic stirring bar was charged with (*S*,*S*)-Co-salen complex **31** (202 mg, 0.334 mmol). The catalyst was dissolved in toluene (1.00 mL) and treated with acetic acid (0.200 mL, 210 mg, 3.50 mmol). The solution was stirred at room temperature open to air for 30 min; over this time the colour changed from orange–red to dark brown. The solution was concentrated *in vacuo* to yield a crude dark brown solid. The resulting catalyst residue was dissolved in (*R*)-(2,3-epoxypropyl)benzene (2.24 g, 16.7 mmol) and THF (1.00 mL). BocNHSES **32** was added to the mixture. The reaction mixture was stirred overnight at room temperature. The resulting mixture was dried to obtain the crude material. This material was filtered by flash column chromatography (hexane–AcOEt = 1 : 1, v/v) to obtain a pale brown white solid.



Scheme 6 Synthetic procedure for aziridine (*S*)-**22**.

This residue was dissolved in CH_2Cl_2 (14.0 mL) and cooled to 0 °C. TFA (14.0 mL) was added dropwise, and the reaction mixture was allowed to warm to room temperature with stirring. After 1.5 h the solution was cooled to 0 °C and diluted with Et_2O (350 mL) and saturated aqueous $NaHCO_3$ (150 mL). The organic layer was washed with brine twice, dried over Na_2SO_4, filtered and concentrated.

The β-hydroxysulfonamide obtained was dissolved in CH_2Cl_2 (120 mL) and pyridine (2.82 mL, 35.0 mmol); DMAP (208 mg, 1.70 mmol) and Ms_2O (4.36 g, 25.0 mmol) were added, and the resultant suspension was stirred for 2 h. Saturated aqueous K_2CO_3 solution was added to the suspension until bubbles were no longer produced, and put under reduced pressure. The obtained material was dissolved in CH_2Cl_2, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The crude material was used directly in the next step.

The crude mesylate was dissolved in THF and H_2O (80.0 mL, 9.00 mL), and K_2CO_3 (20.0 g, 145 mmol) was added. Following

stirring at 85 °C for 6 h, the reaction was cooled and the solvents were removed under reduced atmosphere. Purification of the residue by column chromatography (hexane–AcOEt = 5 : 1, v/v) yielded a colourless liquid (2.80 g, 9.40 mmol, 56% yield). Spectral data coincided with the previous data.[13]

General procedure

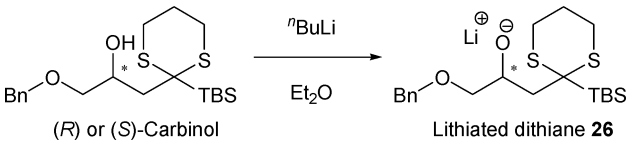
Typical procedure A. A solution of 1,3-dithiane or 2-Ph-1,3-dithiane (0.550 mmol, 1.10 equiv.) in THF (3.00 mL) was cooled to −78 °C and treated with a ~1.6 M hexane solution of ^{n}BuLi (0.550 mmol, 1.10 equiv.) dropwise *via* syringe. After 2 h, a solution of the selected aziridine (0.500 mmol) in THF (2.00 mL) was added dropwise to the reaction mixture at −78 °C *via* syringe. The resultant solution was warmed to 0 °C and stirred for 3 h, and then poured into excess HCl in MeOH and concentrated *in vacuo.* Flash chromatography on silica gel, using AcOEt–hexane as eluant, provided the ring-opening product.

Typical procedure B. A solution of 2-CO_2H-1,3-dithiane (90.4 mg, 0.550 mmol, 1.10 equiv.) in THF (3.50 mL) was cooled to 0 °C and treated with a ~1.6 M hexane solution of ^{n}BuLi (1.10 mmol, 2.20 equiv.) dropwise *via* syringe. After 10 min, a solution of assigned aziridine (0.500 mmol) in THF (2.00 mL) and TMEDA (0.195 mL, 1.30 mmol, 2.60 equiv.) was added dropwise to the reaction mixture at 0 °C *via* syringe. The resultant solution was warmed to 65 °C and stirred for 13 h. The resultant mixture was poured into excess HCl in MeOH and concentrated *in vacuo.* The residue was dissolved in CH_2Cl_2 (~50 mL), filtered and concentrated *in vacuo.* The resulting oil was dissolved in CH_2Cl_2 (5.00 mL), DMAP (7.33 mg, 0.0600 mmol) and DCC (124 mg, 0.600 mmol). The suspension was stirred for 1 h at room temperature. Flash chromatography (AcOEt–hexane = 3 : 1, v/v) provided the γ-lactam.

Typical procedure C. A solution of 2-Me_3Si-1,3-dithiane (106 mg, 0.550 mmol, 1.10 equiv.) in Et_2O (3.00 mL) was cooled to −78 °C and treated with a ~1.5 M pentane solution of ^{t}BuLi (0.550 mmol, 1.10 equiv.) dropwise *via* syringe. The resulting solution was warmed to −45 °C over 1 h and then cooled to −78 °C. A solution of assigned aziridine (0.500 mmol) in Et_2O (2.00 mL) was added dropwise to the reaction mixture at −78 °C *via* syringe. The resultant solution was warmed to −20 °C over 15 min, and stirred for an additional 3 h at 0 °C. The isolation procedure was the same as described in typical procedure A.

Typical procedure D. The molar ratio was the same as described in typical procedure A. The resultant solution was warmed to 30 °C and stirred for 12 h. The isolation procedure was the same as described in typical procedure A.

Typical procedure E. A solution of carbinol (precursor of **26**, 250 mg, 0.627 mmol, 1.25 equiv.) in Et_2O (4.00 mL) was cooled to 0 °C and treated with a ~1.6 M hexane solution of ^{n}BuLi (0.627 mmol, 1.25 equiv.) dropwise *via* syringe (Scheme 7). The resulting solution was cooled to −78 °C. A solution of assigned aziridne (0.500 mmol) and HMPA (0.41 mmol, 0.820 equiv.) in Et_2O (2.00 mL) was added dropwise to the reaction mixture at −78 °C *via* syringe. The resultant solution was warmed to 0 °C, and stirred for an additional 3 h at 0 °C. The resultant mixture was poured into aqueus NH_4Cl and concentrated *in vacuo.* Flash chromatography on silica gel, using AcOEt–hexane as eluant, yielded the ring-opening product.



Scheme 7 Preparation of lithiated dithiane **26**.

Deprotection procedure

Deprotection of *rac*-6 to *rac*-29 2-amino-1-phenylbutane. A suspension of Raney Ni in water (from TCI, ~3 mL) was added to a solution of dithiane *rac*-**6** (187 mg, 0.500 mmol) in EtOH (10.0 mL). The mixture was stirred under H_2 (1 atm) for 20 h at 80 °C. The resulting mixture was diluted with CH_2Cl_2 (~50 mL) and H_2O (~100 mL). The aqueous layer was extracted with CH_2Cl_2 (~50 mL × 2) twice, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (AcOEt–hexane = 5 : 1, v/v, ref 0.25) to isolate dithiane-free material (126 mg, 0.468 mmol, 93.7% yield.

Next, the *tert*-butylsulfamide moiety was deprotected by using the conditions and the isolation procedures developed by Weinreb.[21] Sulfoamide (60.0 mg, 0.227 mmol) in CH_2Cl_2 (10.0mL), anisole (491 mg, 4.54 mmol) and TfOH (2.27 mmol in CH_2Cl_2 10.0 mL) were used. The crude product was purified by flash chromatography (AcOEt–MeOH–NEt_3 = 9 : 1 : 0.05, v/v, ref 0.2) to afford the amine *rac*-**29** (16.8 mg, 0.113 mmol, 49.8% yield). Spectral data coincided with the previous data.[39]

Deprotection of (*S*)-25 to (*S*)-30

(*S*)-1-(2-Phenyl-1,3-dithian-2-yl)-2-(*tert*-butoxycarbonyl)-3-phenylpropane. A 80 mL Schlenk flask equipped with a magnetic stirring bar was charged with (*S*)-**25** (1.30 g, 2.15 mmol) and DMAP (26.3 mg, 0.263 mmol). They were dissolved in CH_2Cl_2 (10.0 mL) and NEt_3 (435 mg, 4.30 mmol). Boc_2O (1.10 g, 5.00 mmol) was dropped in one portion into the resultant solution. The reaction mixture was stirred for 2 h at room temperature and overnight at 40 °C. The solution was concentrated *in vacuo* and the residue was treated with EtOAc and excess 1M HCl. The EtOAc was washed with brine twice, dreid ($NaSO_4$) and concentrated to leave a viscous solid. The material obtained was used without further purification.

The crude material in THF (20 mL) was treated with TBAF in 1M THF solution (10 mL). Following stirring at room temperature for 2 h, the solvents were removed under reduced pressure. Purification of the residue by column chromatography (hexane–AcOEt = 5 : 1, v/v) yielded a colorless liquid (*S*)-**30** (1.01 g, 2.35 mmol, 90% yield). The characteristics of (*S*)-**30** were as follows: R_f = 0.50 (hexane–EtOAc = 5 : 1, v/v); ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H), 2.08–2.30 (m, 2H), 2.45–2.83 (m, 6H), 3.55–4.18 (m, 2H) 6.91–7.07 (m, 2H), 7.13–7.30 (m, 4H), 7.35 (t, J = 8.0 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 24.93, 27.53, 28.42, 42.28, 48.29, 48.70, 57.51, 78.69, 126.19, 127.10, 128.22, 128.62, 128.68, 129.45, 137.98, 141.08, 154.44; IR (KBr disc): 1028, 1051, 1171, 1246, 1275, 1364, 1389, 1499, 1508, 1701, 2907, 2974, 3368 cm^{-1}. Calcd for $C_{24}H_{31}NO_2S_2$: C, 67.09; H, 7.27; N, 3.26. Found: C, 67.01; H, 7.40; N, 3.21. $[\alpha]^{21}_D$ = 0.342 (*c* 9.11 in Et_2O).

Acknowledgements

We thank Professor Yoshiaki Nishibayashi and Dr Yoshihiro Miyake (Tokyo University) for HRMS analyses. We also thank Professor Makoto Fujita for measurement of optical rotation. K. S. is grateful for financial support from the Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

References

1 G. K. Friestad and A. K. Mathies, *Tetrahedron*, 2007, **63**, 2541.
2 M. Yus, C. Najera and F. Foubelo, *Tetrahedron*, 2003, **59**, 6147.
3 S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069.
4 A. B. Smith, III and D. S. Kim, *J. Org. Chem.*, 2006, **71**, 2547.
5 H. J. Reich, A. W. Sanders, A. T. Fiedler and M. J. Bevan, *J. Am. Chem. Soc.*, 2002, **124**, 13386.
6 H. Mao, G. J. Joly, K. Peeters, G. J. Hoornaert and F. Compernolle, *Tetrahedron*, 2001, **57**, 6955.
7 G. Harms, E. Schaumann and G. Adiwidjaja, *Synthesis*, 2001, 577.
8 G. J. Joly, K. Peeters, H. Mao, T. Brossette, G. J. Hoornaert and F. Compernolle, *Tetrahedron Lett.*, 2000, **41**, 2223.
9 W. Howson, H. M. I. Osborn and J. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2439.
10 H. M. I. Osborn, J. B. Sweeney and B. Howson, *SYNLETT*, 1993, 675.
11 G. S. Bates and S. Ramaswamy, *Can. J. Chem.*, 1980, **58**, 716.
12 G. S. Bates, *J. Chem. Soc., Perkin Trans. 1*, 1979, 161.
13 S. K. Kim and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2004, **43**, 3952.
14 P. Muller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905.
15 J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247.
16 H. M. I. Osborn and J. Sweeney, *Tetrahedron: Asymmetry*, 1997, **8**, 1693.
17 D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599.
18 J. M. Schomaker, S. Bhattacharjee, J. Yan and B. Borhan, *J. Am. Chem. Soc.*, 2007, **129**, 1996.
19 D. M. Hodgson and S. M. Miles, *Angew. Chem., Int. Ed.*, 2006, **45**, 935.
20 A. V. Gontcharov, H. Liu and K. B. Sharpless, *Org. Lett.*, 1999, **1**, 783.
21 P. Sun, S. M. Weinreb and M. Shang, *J. Org. Chem.*, 1997, **62**, 8604.
22 B. M. Trost and T. Zhang, *Angew. Chem., Int. Ed.*, 2008, **47**, 3759.
23 P. Ribiere, V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev.*, 2006, **106**, 2249.
24 T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353.
25 D. A. Alonso and P. G. Andersson, *J. Org. Chem.*, 1998, **63**, 9455.
26 F. G. Bordwell, G. E. Drucker, N. H. Andersen and A. D. Denniston, *J. Am. Chem. Soc.*, 1986, **108**, 7310.
27 M. Ide and M. Nakata, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 2491.
28 M. Rubiralta, A. Diez, I. Reig, J. Castells, J. L. Bettiol, D. S. Grierson and H. P. Husson, *Heterocycles*, 1990, **31**, 173.
29 M. L. Bennasar, A. Torrens, M. Rubiralta, J. Bosch, D. S. Grierson and H. P. Husson, *Heterocycles*, 1989, **29**, 745.
30 W. Amrein and K. Schaffner, *Helv. Chim. Acta.*, 1975, **58**, 380.
31 F. G. Bordwell, J. A. Harrelson and X. Zhang, *J. Org. Chem.*, 1991, **56**, 4448.
32 P. E. Maligres, M. M. See, D. Askin and P. J. Reider, *Tetrahedron Lett.*, 1997, **38**, 5253.
33 E. Juaristi, J. Tapia and R. Mendez, *Tetrahedron*, 1986, **42**, 1253.
34 A. B. Smith, III and A. M. Boldi, *J. Am. Chem. Soc.*, 1997, **119**, 6925.
35 S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.
36 B. R. Neustadt, *Tetrahedron Lett.*, 1994, **35**, 379.
37 D. M. Hodgson, P. G. Humphreys, S. M. Miles, C. A. J. Brierley and J. G. Ward, *J. Org. Chem.*, 2007, **72**, 10009.
38 D. M. Hodgson, M. J. Fleming and S. J. Stanway, *Org. Lett.*, 2005, **7**, 3295.
39 E. Haak, H. Siebeneicher and S. Doye, *Org. Lett.*, 2000, **2**, 1935.