A Novel Synthetic Intermediate in β-Lactam Chemistry: An Efficient Preparation of *cis*-1,3,4-Tris(trimethylsilyl)azetidin-2-one and Its Transformation into 4-Acetoxy-3-alkylideneazetidin-2-ones

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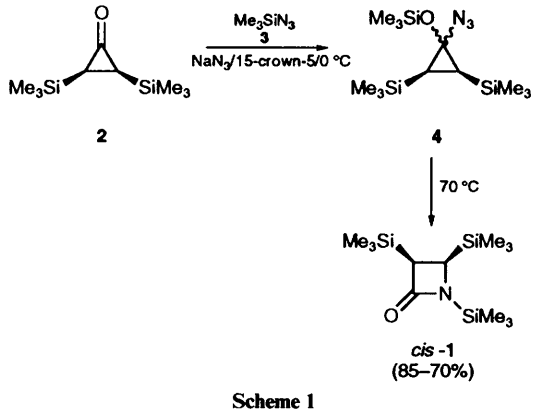
The addition of trimethylsilyl azide to *cis*-2,3-bis(trimethylsilyl)cyclopropan-1-one in the presence of a sodium azide/15-crown-5 catalyst gave *cis*-1,3,4-tris(trimethylsilyl)azetidin-2-one, which could easily be transformed into 4-acetoxy-3-alkylideneazetidin-2-ones by way of Peterson olefination followed by anodic oxidation.

Since the introduction of appropriate substituents into the C-3 and/or C-4 positions of β-lactam rings is a most important synthetic process in β-lactam antibiotic chemistry, many methods have been developed to achieve this.[1] Among the intermediates developed in this work, 3-silylazetidin-2-ones have received considerable attention because they are useful starting materials for the introduction of 3-alkylidene substituents into β-lactam rings.†[,2] Recently, we reported that electrochemical oxidation of 4-trimethylsilylazetidin-2-ones provided 4-alkoxy- and 4-acetoxy-azetidin-2-ones both conveniently and regioselectively.‡[,4] Therefore, we expected that 3,4-disilyl substituted azetidin-2-ones would be further useful intermediates for the synthesis of 3,4-disubstituted β-lactams. To our knowledge, however, the preparation and reactivity of such azetidin-2-ones has not so far been reported. We now describe here a facile and highly stereoselective preparation of *cis*-1,3,4-tris(trimethylsilyl)azetidin-2-one, *cis*-**1**, and its preliminary application as a useful synthetic building block in β-lactam chemistry.

The preparation of *cis*-**1** was achieved by nitrogen-inserting ring-enlargement of *cis*-2,3-bis(trimethylsilyl)cyclopropan-1-one, **2**, with trimethylsilyl azide, **3**, in the presence of a catalytic amount of sodium azide/15-crown-5 at 0 °C (Scheme 1). The



Scheme 1

starting bis(silyl)cyclopropanone **2** was readily accessible from the addition of trimethylsilyl ketene and trimethylsilyldiazomethane.[6] Unlike most cyclopropanones, which are unstable in solutions even at low temperatures, **2** is a distillable and easy-to-handle liquid monomer, and can be stored for a long time without polymerization. Heating of the resulting adduct **4** *in situ* at 70 °C for 2 h gave rise to *cis*-**1** in excellent yield (85–70%). In this reaction, *cis*-**1** was the sole isomer: no corresponding *trans* isomer was observed. Although Zaitseva *et al.* have reported that the reaction of silyl azide **3** with 2-trimethylsilylcyclopropan-1-one proceeds in the absence of catalyst to give a mixture of 1,3- and 1,4-bis(trimethylsilyl)azetidin-2-ones in moderate yields,[7] in our transformation of **2** into *cis*-**1**, the use of the catalyst is necessary. The stereochemistry of *cis*-**1** was established by comparison of its ^{1}H NMR spectral data with those of the corresponding *trans* isomer, *trans*-**1**.§·¶ The vicinal coupling constant between 3-H and 4-H for *cis*-**1** (6.9 Hz) is larger than that for *trans*-**1** (3.6 Hz), which is a typical *cis* and *trans* relationship in β-lactam rings.[8]

Table 1 Peterson olefination reactions of *cis*-**1** with aldehydes **5**

Aldehydes	Products (% yield[a])	
5a	*Z*-**6a** (53)	*E*-**6a** (31)
5b	*Z*-**6b** (45)	*E*-**6b** (27)
5c	*Z*-**6c** (36)	*E*-**6c** (38)
5d	*Z*-**6d** (14)	*E*-**6d** (41)

[a] Isolated yields based on *cis*-**1**.

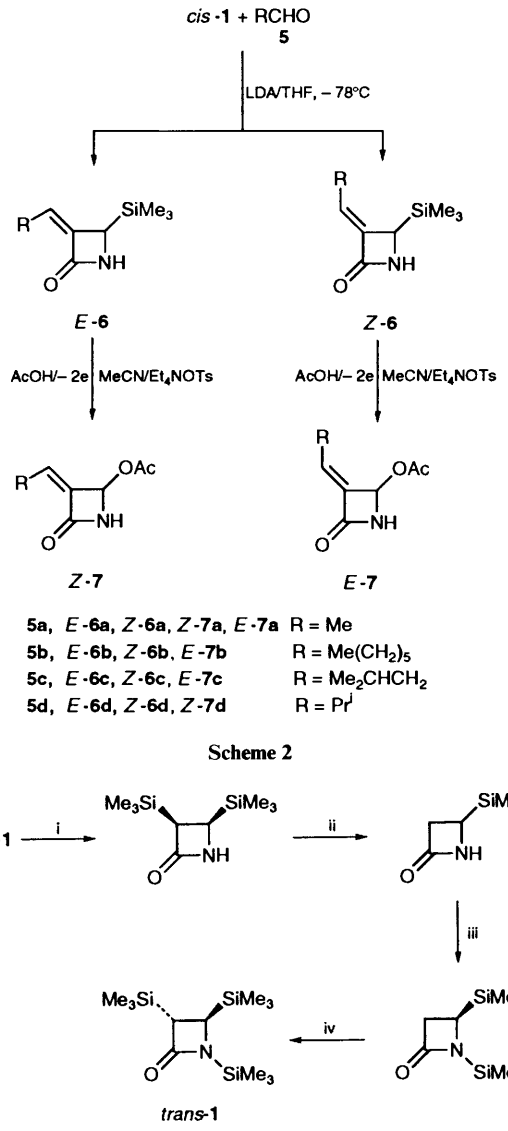
In order to estimate the potential of *cis*-**1** as a valuable building block in β-lactam chemistry, we next examined its stepwise conversion into 4-acetoxy-3-alkylideneazetidin-2-ones, **7**, by way of Peterson olefination followed by anodic oxidation (Scheme 2).

The tris(silyl)azetidin-2-one, *cis*-**1**, was easily deprotonated at C-3 by lithium diisopropylamide (LDA) in tetrahydrofuran (THF), and the resulting anion was allowed to react with the aldehydes **5**. Since the crude products obtained were a mixture of *E*- and *Z*-isomers of 3-alkylidene-4-trimethylsilylazetidin-2-ones, **6**, they were separated by column chromatography on silica gel to give pure *E*-**6** and *Z*-**6** in good total yields (Table 1).

Electrochemical acetoxylation of the alkylidene derivatives **6** with acetic acid took place smoothly with a graphite plate anode–graphite plate cathode in acetonitrile containing tetraethylammonium tosylate as a supporting electrolyte. The carbon–silicon bond was cleaved selectively and the acetoxy group was introduced onto the carbon, giving the correspond-

† 3-Trialkylsilylazetidin-2-ones are also accepted as useful precursors of several optically active mono- and bi-cyclic β-lactams (see ref. 3).
‡ A number of workers have reported that 4-acetoxyazetidin-2-ones can react with a variety of hetero and carbon centred nucleophiles, affording rapid access to C-4 substituted β-lactams (see ref. 1 and 5).

§ The stereoisomer *trans*-**1** was prepared in almost quantitative yield from *cis*-**1** *via* the four-steps sequence shown below.
¶ δ_H(270 MHz, $CDCl_3$) data for *trans*-**1**: δ 0.05 (9 H, s), 0.08 (9 H, s), 0.23 (9 H, s), 2.61 (1 H, d, *J* 3.6) and 2.67 (1 H, d, *J* 3.6).



Scheme 2

Reagents and conditions: i, 0.2% HCl, MeOH, room temp. ii, Bu_4NF, AcOH, THF, room temp. iii, Me_3SiCl, Et_3N, CH_2Cl_2, 0 °C. iv, Me_3SiCl, LDA, THF, –78 °C.

ing 4-acetoxyazetidin-2-ones **7** in high yields (Table 2). It should be noted that the stereochemistry of the alkylidene side chain of **6** is kept during the electrolysis under the present conditions. For example, the electrolysis of (*Z*)-3-ethylidene-4-trimethylsilylazetidin-2-one, *Z*-**6a**, gave 4-acetoxy-(*E*)-3-ethylideneazetidin-2-one, *E*-**7a**, as the sole isomer, none of the corresponding stereoisomer *Z*-**7a** being detected in the ^1H NMR spectrum of the crude products.

3-Alkylideneazetidin-2-ones having a C-4 substituent replaceable with a variety of nucleophiles are well known to be readily accessible, synthetically useful precursors for β-lactam antibiotics such as asparenomycin, carpetimycin, thienamycin, Ro15-1903, and 6-[(*Z*)-methoxymethylene]penicillanic acid.[9,10] Although the addition of chlorosulfonyl isocyanate (CSI) to allenes has been demonstrated as a straightforward procedure for the preparation of C-4-substituted 3- alkylideneazetidin-2-ones, the yields are usually low.[10] Therefore, the present transformation of *cis*-**1** into **7** should also be valuable. Further applications of the novel intermediate, *cis*-**1**, to the synthetic chemistry of β-lactam antibiotics are now in progress.

Table 2 Electrochemical preparation of 4-acetoxy-3-alkylideneazetidin-2-ones **7**

Substrates	Products	Electricity (F mol^{-1})	Yields[a] (%)
Z-**6a**	*E*-**7a**	2.2	80
E-**6a**	*Z*-**7a**	2.5	77
Z-**6b**	*E*-**7b**	2.3	70
Z-**6c**	*E*-**7c**	2.3	67
E-**6d**	*Z*-**7d**	2.6	73

[a] Isolated yields based on **6**.

Experimental

Preparation of cis-1,3,4-*Tris(trimethylsilyl)azetidin-2-one* cis-**1**.—To a mixture of silyl-substituted cyclopropanone **2** (4.0 g, 20 mmol) and the silyl azide **3** (4.64 g, 40 mmol) was added NaN_3 (140 mg, *ca.* 2 mmol) and 15-crown-5 (240 mg, *ca.* 1 mmol) without solvent at 0 °C. After 1 h, the excess of **3** was removed under a reduced pressure, and the residue was heated at 70 °C for 2 h (**CAUTION**: during the heating, vigorous liberation of nitrogen occurred). The mixture was poured into water and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated under a reduced pressure to give *cis*-**1** as a pale yellow oil (4.90 g, 85%). Purification of *cis*-**1** could be accomplished by distillation under a reduced pressure (4.07 g, 71%); b.p. 75–80 °C/1 × 10^{-3} mmHg (bath temp.); ν_{max}(neat)/cm^{-1} 1720; δ_H(270 MHz, $CDCl_3$) 0.13 (9 H, s) 0.16 (9 H, s), 0.25 (9 H, s), 3.21 (1 H, d, *J* 6.9) and 3.24 (1 H, d, *J* 6.9) (Found: 287.1558. $C_{12}H_{29}NOSi_3$ requires 287.1557).

General Procedure for the Preparation of 3-*Alkylidene*-4-*trimethylsilylazetidin-2-ones* **6**.—A solution of LDA was prepared from diisopropylamine (4.4 mmol) and BuLi (1.6 molar hexane solution; 4.2 mmol) in THF (70 cm^3). To the LDA solution was added a solution of *cis*-**1** (4 mmol) in THF (10 cm^3) at –78 °C. After 30 min, the appropriate aldehyde **5** (5–8 mmol) was added to the solution at the same temperature and the mixture stirred at –78 °C for 1 h. It was then poured into ice-cooled water and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated under a reduced pressure and the residue was purified by column chromatography on silica gel with hexane–AcOEt (2 : 1) as eluent to give *E*-**6** and *Z*-**6**, respectively. All the products have been characterized on the basis of IR, NMR, and high resolution mass spectrometry; δ_H(270 MHz, $CDCl_3$) data of *E*-**6a** and *Z*-**6a** are as follows: *E*-**6a** δ 0.04 (9 H, s), 2.01 (3 H, d, *J* 7.3), 3.50 (1 H, s), 5.53 (1 H, q, *J* 7.3, CH=C), 6.35 (1 H, br s, NH); *Z*-**6a** δ 0.09 (9 H, s), 1.71 (3 H, d, *J* 7.1), 3.67 (1 H, s), 6.14 (1 H, br s, NH) and 6.18 (1 H, q, *J* 7.1, CH=C).

General Procedure for the Electrochemical Preparation of 4-*Acetoxy*-3-*alkylideneazetidin-2-ones* **7**.—A solution of **6** (1 mmol) and AcOH (10 mmol) in MeCN (10 cm^3) containing Et_4OTs (0.2 mol dm^{-3}) as an electrolyte was placed in an undivided cell equipped with a graphite anode and a graphite cathode. The system was subjected to constant current electrolysis (40 mA) at ambient temperature. After 2–3 F mol^{-1} of **6** had been passed, the mixture was poured into water and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated under a reduced pressure and the residue was purified by column chromatography on silica gel with hexane–AcOEt (4 : 1) as an eluent to give **7**. All the products gave satisfactory IR, NMR, and high resolution mass spectra; δ_H(270 MHz, $CDCl_3$) data of *Z*-**7a** and *E*-**7a** are as follows: *Z*-**7a** δ 2.06 (3 H, d, *J* 7.3), 2.11 (3 H, s), 6.01 (1 H, q, *J* 7.3, CH=C), 6.09 (1 H, s, N–CH–O), 6.97 (1 H, br s, NH); *E*-**7a** δ 1.85 (1 H, d, *J* 7.3),

2.14 (3 H, s), 6.25 (1 H, s, N–CH–O), 6.30 (3 H, q, *J* 7.3, CH=C) and 7.08 (1 H, br s, NH).

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