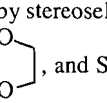
Syntheses of chiral intermediates of 1-β-methylcarbapenems: (3*S*,4*R*)-3-[1(*R*)-*tert*-butyldimethylsilyloxyethyl]-4-chloroazetidin-2-one and (3*S*,4*S*)-3-[1(*R*)-*tert*-butyldimethylsilyloxyethyl]-4-[1(*R*)-*tert*-butylthiocarbonylethyl]azetidin-2-one

MASAKI ENDO

Chemical Process Development, Bristol-Myers Pharmaceutical Research and Development Division, 100 Industrial Blvd., Candiac, P.Q., Canada J5R 1J1

Received March 30, 1987

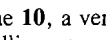
MASAKI ENDO. Can. J. Chem. **65**, 2140 (1987).

The 4-chloroazetidinone **10**, a very reactive chiral intermediate for 1-β-methylcarbapenems (**1***b*), was easily prepared and isolated as a solid crystalline compound from the corresponding sulfide **5**. Another chiral intermediate (**16***d*) bearing the 1-β-methyl moiety was prepared by stereoselective aldol type condensation of either azetidinone **4** or **10** with metal enolates **14** (R = S—Bu^t, M = $ZrCp_2Cl$,  , and SnBr). The β/α ratios were 9:1, 3:1, and 2:1 respectively.

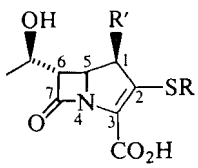
MASAKI ENDO. Can. J. Chem. **65**, 2140 (1987).

On a préparé facilement la chloro-4 azétidinone (**10**), un intermédiaire chiral très réactif dans la synthèse des méthyl-1β carbapénèmes (**1***b*); on l'a isolé sous la forme d'un composé cristallin solide à partir du sulfure **5** correspondant. On a aussi préparé un autre intermédiaire chiral (**16***d*) qui porte une portion méthyle-1β; pour ce faire, on a utilisé une condensation de type aldolique stéréosélective des azétidinones **4** ou **10** avec les énolates métalliques **14** (R = S—*tert*-Bu, M = $ZrCp_2Cl$, $B(OCH_2)_2$ ou SnBr). Les rapports β/α sont respectivement de 9:1, de 3:1 et de 2:1.

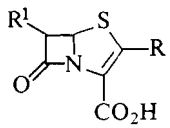
[Traduit par la revue]

Since the discoveries of the highly active β-lactam antibiotics, carbapenem (**1***a*) (R =  , thienamycin) (1) and 1-β-methylcarbapenem (**1***b*) (2), and the synthesis of penems (**2**) by Woodward (3), much attention has been directed toward the syntheses of these compounds and their analogs (4).

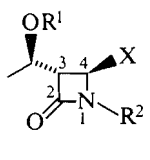
The most commonly used chiral intermediates for both penem and carbapenem syntheses are azetidinones **3**, where



1 *a*: R′ = H
b: R′ = CH_3



2

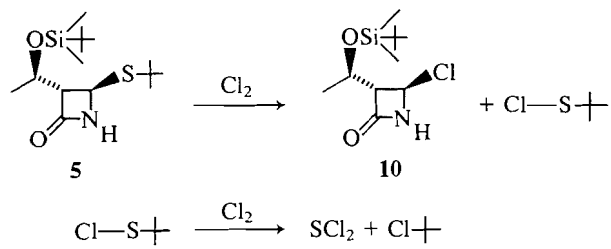


3

particularly 4-acetoxyazetidinone **4** has been widely used as an important intermediate (6). Although compound **4** is a stable solid easily available both from well-described procedures (5, 7) and from a commercial source,[1] its reactivity is limited, particularly at low temperature. It is such low temperature reaction conditions that are required for kinetic control, for example to control the stereochemistry in the syntheses of 1-β-methylcarbapenems (**1***b*). Thus, the more reactive 4-chloroazetidinone **10** might better serve as the substrate for such kinetically controlled reactions.

Karady *et al.* (8) reported the *N*-protected 4-chloroazetidinone **3** ($R^1 = R^2$ = Si  ; X = Cl), and demonstrated it to be a useful intermediate. However, because the nitrogen was protected with a *tert*-butyldimethylsilyl group, the reactivity of **3** ($R^1 = R^2$ = Si; X = Cl) at the C-4 position is dramatically

[1]Kanegafuchi Chemical Industry Company, Osaka, Japan.

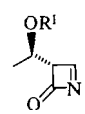


SCHEME 1

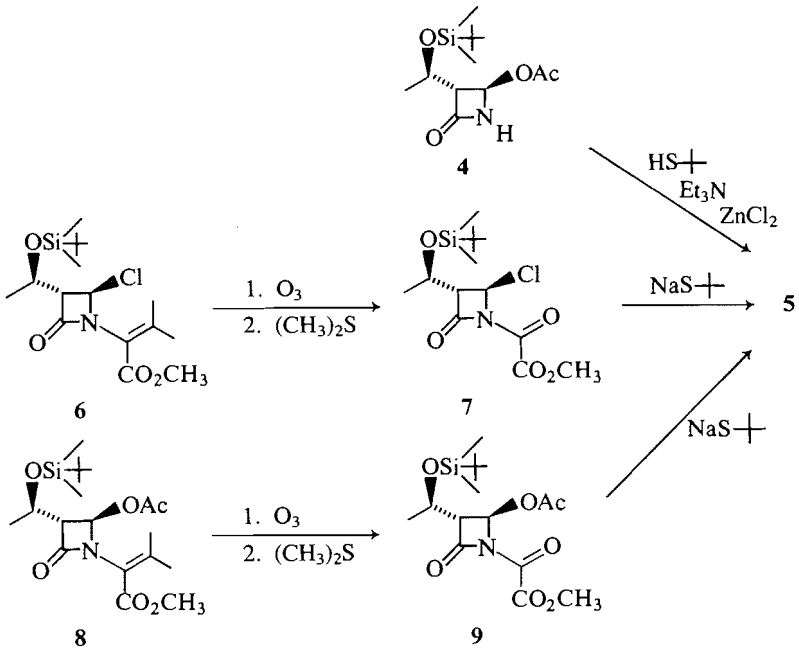
reduced compared to that of **10** without nitrogen protection.[2] Synthesis of the 4-chloroazetidinone **10** has been briefly reported by Perrone and co-workers (9), but these workers do not describe its isolation.

Herein is reported an easy preparation of the title compound **10**. Compound **10** was prepared by chlorinolysis of sulfide **5** with two equivalents of chlorine at −15°C (Scheme 1). Although one equivalent of chlorine is theoretically enough to produce **10**, a nonvolatile by-product produced with one equivalent of chlorine contaminates the product. The by-product, *tert*-butylsulfenyl chloride, reacts with an additional equivalent of chlorine to give volatile products. The crude

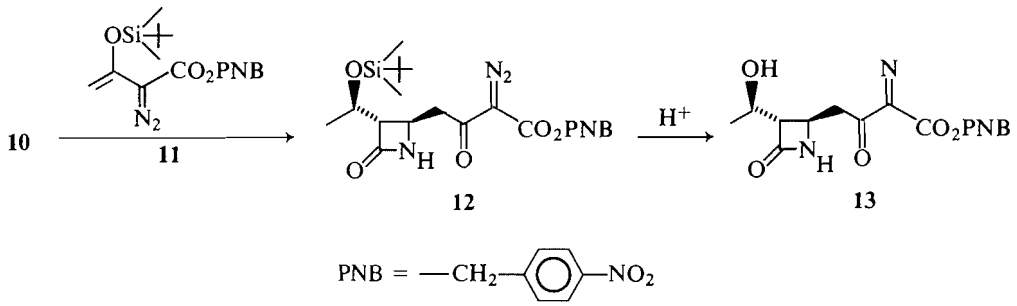
[2]It has been proven that the displacement reactions of 2-azetidinone **3** (R^1 = Si; R^2 = H; X = OAc) at the C-4 position go via a reactive intermediate



(10). It is more difficult to form the corresponding iminium salt of the *N*-protected azetidinone.



SCHEME 2



SCHEME 3

product was easily recrystallized from cold pentane, affording white crystalline solid **10** in 76% yield (Scheme 1). This product is rather unstable at room temperature but reasonably stable at −20°C. Compound **5**, the precursor of **10**, may be prepared from three different starting materials (Scheme 2). Treatment of 4-acetoxyazetidinone **4** (5) with *tert*-butylmercaptan, triethylamine, and zinc chloride gave compound **5** in 70% yield. The other two starting materials **7** (11) and **9** (11) (prepared quantitatively from the corresponding secopenams **6** (11) and **8** (11) by ozonolysis) reacted with sodium *tert*-butylmercaptide in ethanol, affording the sulfide **5** in good yields.

Chiral 4-chloroazetidinone **10** was converted to a known intermediate **13** (6*c*) for carbapenem syntheses (Scheme 3). Compound **10**, as expected, demonstrated its high reactivity, undergoing reaction with the *tert*-butyldimethylsilylenol ether **11** (6*c*) at low temperature to afford azetidinone **12** (6*c*). Deprotection of the hydroxy moiety (6*c*) was carried out by treating **12** with 1 *M* aqueous hydrochloric acid in methanol to give **13** in 64% overall yield.

Compound **10** also showed its usefulness for kinetically controlled reactions in 1-β-methylcarbapenem synthesis by reacting with metal enolates **14** at −78°C to give compound **16** (described below).

1-β-Methylcarbapenems (**1***b*) have been shown to be chemically and metabolically more stable than 1-unsubstituted carbapenems (**1***a*), and also to retain high antimicrobial activity (2). However, a stereoselective introduction of the β-methyl group into the carbapenem precursors has been a major problem (2, 12). Recently, several research groups have discovered means to overcome the problem. Fuentes *et al.* (13) reported that Evans type enolates **14***a* (14) undergo stereoselective aldol type condensation with 4-acetoxyazetidinone **4** in the presence of Lewis acid to afford **16***a* in good yields with predominantly the β-isomer. Similar results on **16***b*, using tin(II) enolates of thiazolidine-2-thiones and oxazolidine-2-thiones, have been reported by other groups (15, 16). As well, Iimori and Shibasaki (17) reported a stereoselective introduction of the β-methyl group by reducing an olefinic ester **15***a* with L-Selectride (β/α 8:1, 77% yield). Kim *et al.* (18) similarly achieved a stereoselective hydrogenation of **15***b* to give **16** (R = OCH_3, β/α 3:1) (Scheme 4).

In the search for a new way to introduce the β-methyl group, we conducted a series of coupling reactions of azetidinones **4** or **10** with the metal enolates **14** (R = OBz and S—Bu^t).

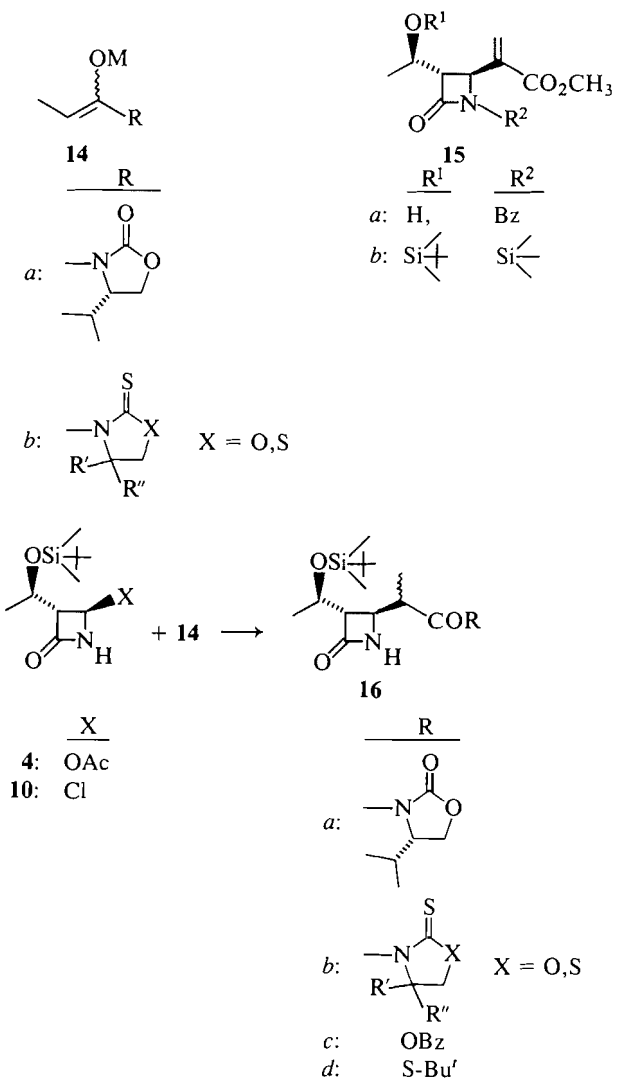
The enolates **14** were prepared by three known methods (19–21) depending on the reagent used (Scheme 5).

As mentioned earlier, 4-chloroazetidinone **10** has an advantage over 4-acetoxyazetidinone **4** in dealing with unstable metal enolates **14** that require low reaction temperature. The required low reaction temperature, as well, fulfils the kinetic condition to

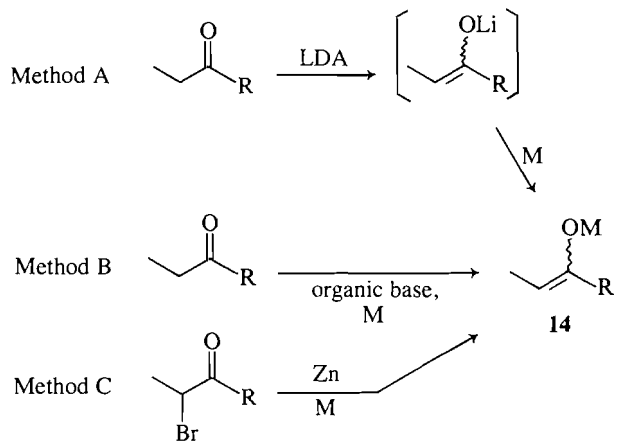
TABLE 1. Results of coupling reaction

	R	Parameters	$AlEt_2$	$Sn\phi_3$	SnBr	$ZrCp_2Cl$		$B(n\text{-}Bu)_2$	$TiCp_2Cl$
16*c*	OBz	β/α[a]	52:48	42:58		33:67	45:55	38:62	33:67
		Yield (%)	73	37	—	20	20	29	71
		Method[b]	C	C		A	C	C	C
		Amount used (equiv.)	1.9	3.1		2.5	2.0	2.0	2.0
		Reaction temperature (°C)	−10	23		0	0	23	0
		Reaction time (h)	1	1		1	3	1	1
16*d*	S-Bu^t	β/α	25:75	20:80	69:31	94:6	77:23	20:80	16:84
		Yield (%)	68	24	66	15	30	57	51
		Method	C	C	C[c]	A[d]	B	C	C
		Amount used (equiv.)	1.9	2.0	3.0	2.5	2.0	2.0	2.0
		Reaction temperature (°C)	0	−5 to 0	23	−78	23	−5 to 0	−10 to −5
		Reaction time (h)	1/3	2	72	2	48	2/3	5/6

[a]The ratio was determined by hplc (column: Hypersil, column length: 200 × 2.1 mm, solvent: 10–20% EtOAc/hexane, detection: uv 260 nm).
[b]**4** was used for all cases except the one indicated.
[c]Tin powder (3 equiv.) was used instead of zinc dust and $AgBF_4$ (10 mol%) was added to activate metal tin.
[d]**10** was used. This gives slightly better yield than **4**.



SCHEME 4



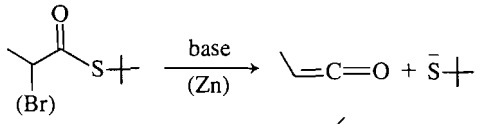
SCHEME 5

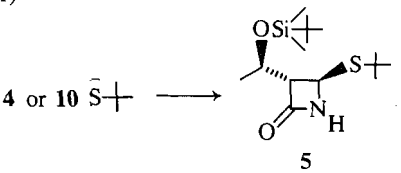
control the stereochemistry. The 4-chloroazetidinone **10** reacts at temperatures as low as −78°C, while 4-acetoxyazetidinone **4** does not react at a significant rate below −10°C.

The results are shown in Table 1. When R = OBz, product **16***c* was obtained, for which there was little stereoselectivity observed favoring the β-isomer regardless of the metal enolate used. The β/α ratio was more or less in a range of 1:1, or weighted towards the α-isomer. On the other hand, *tert*-butyl thiopropionate (R = S—Bu^t), giving product **16***d*, showed greater stereoselectivity, either favoring the α-isomer or the β-isomer. Thus, zirconium, boronyl, and tin(II) enolates were found to be good reagents to introduce the β-methyl group stereoselectivity.

It is not yet known which factors determine the stereochemical outcome in the coupling reaction with azetidinones **4** or **10**. Therefore it is rather difficult to predict the result, while the stereochemistry of analogous aldol condensations is generally well predicted (22).

One of the causes of the low yields in the series of *tert*-butyl thio(bromo)propionate reactions seems to be ketene formation,

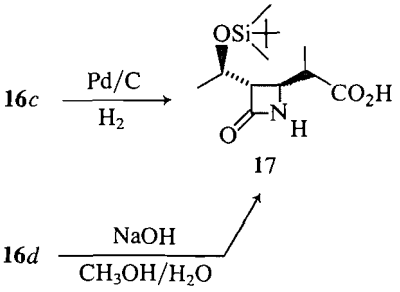




5

particularly under strongly basic conditions where more by-product **5** was isolated.

The structures **16***c* and **16***d* were confirmed by converting them to the known acid **17** (2*a*). Thus, the benzyl ester **16***c* was subjected to hydrogenolysis to give crystalline **17** as a β/α mixture in 76% yield. The α-isomer crystallized out from an ethyl acetate solution and was isolated pure. The thioester **16***d*



(β/α 94:6) was hydrolyzed under basic conditions to **17** (90%). However, the ^{1}H nmr spectrum indicated partial epimerization of the β-methyl group (β/α 70:30). Intermediate **17** has been converted to 1-β-methylcarbapenems (2*a*).

Experimental

*(3S,4R)-3-[1(R)-*tert*-Butyldimethylsilyloxyethyl]-4-chloro-1-(1-methoxycarbonyl-2-methyl-1-propenyl)azetidin-2-one (6)*

Compound **6** was prepared as described in ref. 11 except that the *tert*-butyldimethylsilyl function served to protect the hydroxy group instead of the trichloroethyl carbonate group. The crude solid (100% yield) was used without further purification; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 0.03 (s, 6H, CH_3), 0.83 (s, 9H, CH_3CSi), 1.23 (d, J = 6 Hz, 3H, CH_3CHO), 1.93, 2.22 (2s, 6H, $=C(CH_3)_2$), 3.32 (dd, J = 1.5 Hz, 1H, H-3), 3.71 (s, 3H, CO_2CH_3), 4.18 (m, 1H, CH_3CHO), 5.86 (d, J = 1.5 Hz, H-4).

*(3S,4R)-4-Acetoxy-3-[1(R)-*tert*-butyldimethylsilyloxyethyl]-1-(2-methoxy-1,2-dioxyethyl)azetidine-2-one (9)*

A solution of compound **8** (5) (7.98 g, 0.02 mol) in dichloromethane (80 mL) was cooled to −78°C and ozone gas was bubbled in until a blue color persisted. The cooling bath was removed and the excess ozone was expelled by bubbling nitrogen gas. The ozonide solution was treated at room temperature with dimethyl sulfide (3 mL) for 1.5 h. The clear, colorless solution was washed with water (3×), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give the white crystalline title compound (7.7 g, 98%), which was recrystallized from ether/petroleum ether (1:1), mp 54–55°C; ir (Nujol): 1700, 1760, 1828 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.01, 0.06 (2s, 6H, CH_3Si), 0.81 (s, 9H, CH_3CSi), 1.29 (d, J = 6.4 Hz, 3H, CH_3CHO), 2.11 (s, 3H, $OCOCH_3$), 3.26 (dd, J = 1.9 and 2.0 Hz, 1H, H-3), 3.90 (s, 3H, CO_2CH_3), 4.31 (m, 1H, CH_3CHO), 6.73 (d, J = 2.0 Hz, 1H, H-4). *Anal.* calcd. for $C_{16}H_{27}NO_7Si$ (373.447): C 51.46, H 7.29, N 3.75; found: C 51.44, H 7.37, N 3.71.

*(3S,4R)-3-[1(R)-*tert*-Butyldimethylsilyloxyethyl]-4-chloro-1-(2-methoxy-1,2-dioxyethyl)azetidin-2-one (7)*

Compound **7** was prepared in 97% yield as described in ref. 11 except that the *tert*-butyldimethylsilyl group served as protection for the hydroxy group instead of the trichloroethyl carbonate group. The crystalline solid was pure enough to be used in the next step without further purification; mp 69–71°C (recrystallized from petroleum ether); ir (Nujol): 1715, 1760, 1825 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.01, 0.06 (2s, 6H, CH_3Si), 0.81 (s, 9H, CH_3CSi), 1.28 (d, J = 6.3 Hz, 3H, CH_3CHO), 3.53 (overlapping dd, 1H, H-3), 3.92 (s, 3H, CO_2CH_3), 4.32 (m, 1H, CH_3CHO), 6.01 (d, J = 1.9 Hz, 1H, H-4). *Anal.* calcd. for $C_{14}H_{24}ClNO_5Si$ (349.856): C 48.06, H 6.91, N 4.00, Cl 10.13; found: C 47.94, H 7.03, N 3.95, Cl 9.89.

*(3S,4R)-3-[1(R)-*tert*-Butyldimethylsilyloxyethyl]-4-*tert*-butylthioazetidin-2-one (5)*

Method A: via 4-acetoxyazetidinone 4

To a solution of compound **4** (57.4 g, 0.2 mol) in dichloromethane (600 mL) under nitrogen atmosphere was added *tert*-butylmercaptan (24.6 mL, 0.22 mol) followed by addition of triethylamine (30.6 mL, 0.2 mol). The solution was cooled to 0°C and zinc chloride (27.2 g, 0.2 mol) was added. The resulting milky solution was stirred at room temperature for 2 days. The reaction mixture was successively washed with 1 *M* aqueous hydrochloric acid (500 mL), saturated sodium bicarbonate (500 mL), and water (500 mL), dried over anhydrous magnesium sulfate, and concentrated to give a wet crystalline solid (70 g). The crude product was triturated in isopropyl alcohol (150 mL) and then diluted with water (150 mL). The slurry was cooled to 5°C and the solid was collected by filtration. The cake was washed with cold (5°C) isopropyl alcohol – water (1:2, 100 mL) and dried *in vacuo* to give the title compound **5**. Yield 44.3 g (70%); mp 152–154°C; $[\alpha]_D^{23}$ +85.0° (*c* 0.57, $CHCl_3$); ir (Nujol): 1715, 1762 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.06, 0.07 (2s, 6H, CH_3Si), 0.87 (s, 9H, CH_3CSi), 1.20 (d, J = 6.3 Hz, 3H, CH_3CHO), 1.36 (s, 9H, $S(CH_3)_3$), 3.03 (m, 1H, H-3), 4.25 (m, 1H, CH_3CHO), 5.00 (d, J = 2.6 Hz, 1H, H-4), 6.06 (br s, 1H, NH). *Anal.* calcd. for $C_{15}H_{31}NO_2SSi$ (317.563): C 56.73, H 9.84, N 4.41, S 10.10; found: C 56.74, H 9.91, N 4.37, S 10.09.

Method B: via 4-chlorooxamate (7)

To an ice-cooled solution of compound **7** (0.349 g, 1 mmol) in ethanol (5 mL) under nitrogen atmosphere was added dropwise sodium *tert*-butylmercaptide (1.1 mL of 1 *M* solution in ethanol–water 6:1). The resulting solution was stirred at 5–10°C for 15 min. The reaction mixture was diluted with diethyl ether (70 mL), washed with brine (4×), dried over anhydrous magnesium sulfate, and concentrated to give crystalline **5** (0.31 g, 98%).

Method C: via 4-acetoxyoxamate (9)

To a solution of compound **9** (0.389 g, 1.04 mmol) in ethanol (6 mL) under nitrogen atmosphere was added sodium *tert*-butylmercaptide (1.1 mL of 1 *M* solution in ethanol–water 6:1). The hazy solution was stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether (70 mL), washed with brine (4×), dried over anhydrous magnesium sulfate, and concentrated to dryness, affording the white crystalline product **5** (0.32 g, 96%).

Compound **5** produced by methods B and C showed identical spectral values to compound **5** produced by method A.

*(3S,4R)-3-[1(R)-*tert*-Butyldimethylsilyloxyethyl]-4-chloroazetidin-2-one (10)*

Chlorine gas (2.24 g, 31.54 mmol) was gently bubbled into a solution of compound **5** (5.0 g, 15.77 mmol) in dichloromethane (50 mL) while maintaining the temperature at −5 to −15°C. The yellow solution was concentrated (*in vacuo*, <20°C) to give a crystalline solid, which was recrystallized from cold (−70°C) pentane to give the title compound **10**. Yield 3.12 g (76%), white crystals; mp 84–85°C; $[\alpha]_D^{23}$ +23.5° (*c* 0.49, $CHCl_3$); ir (Nujol): 1736, 1775 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.03, 0.05 (2s, 6H, CH_3Si), 0.84 (s, 9H, CH_3CSi), 1.26 (d, J = 6.4 Hz, 3H, CH_3CHO), 3.41 (m, 1H, H-3), 4.21 (m, 1H, CH_3CHO), 5.67 (d, J = 1.3 Hz, 1H, H-4), 6.25 (br s, 1H, NH). *Anal.* calcd. for $C_{11}H_{22}ClNO_2Si$ (263.810): C 50.08, H 8.41, N 5.30, Cl 13.43; found: C 50.11, H 8.50, N 5.22, Cl 13.24.

*(3S,4R)-3-[1(R)-*tert*-Butyldimethylsilyloxyethyl]-4-(3-*p*-nitrobenzyloxycarbonyl-2-oxo-3-diazopropan-1-yl]-azetidin-2-one (**12**) and (3S,4R)-3-[1(R)-hydroxyethyl]-4-(3-*p*-nitrobenzyloxycarbonyl-2-oxo-3-diazopropan-1-yl]-azetidin-2-one (**13**)*

To a solution of compound **10** (0.264 g, 1 mmol) in dichloromethane (6 mL) at −40°C under nitrogen atmosphere was added silver tetrafluoroborate (0.195 g, 1 mmol), followed by addition of a solution of enol ether **11** (0.57 g, 1.5 mmol) (6*c*) in dichloromethane (6 mL) over 20 min. The resulting solution was stirred at −30 to −40°C for 2 h. The reaction mixture was diluted with ethyl acetate (40 mL), then washed successively with saturated sodium bicarbonate (30 mL) and brine (2 × 40 mL). Concentration of the organic phase gave a mixture of oil and solid that was dissolved in methanol (10 mL). Insoluble solids were filtered off and washed with methanol (5 mL). The combined filtrate (containing compound **12**) was treated at room temperature with 1 *M* aqueous hydrochloric acid (2.5 mL) for 18 h. The reaction mixture was diluted with water (30 mL), then extracted with ethyl acetate (60 mL and 40 mL respectively). The organic phase was washed successively with saturated sodium bicarbonate (40 mL) and brine (2 × 50 mL), dried over anhydrous magnesium sulfate, and concentrated to give a wet solid. The product (**13**) was isolated by triturating in ether (10 mL). Yield 0.24 g (64%), mp 149–150°C (lit. (6*c*) mp 151–152°C). The ^{1}H nmr spectrum was identical to that reported (6*c*).

Metal enolate/azetidinone coupling reactions

A typical procedure for each method is described.

Method A (ref. 19)

To a lithium diisopropylamine (2.5 mmol) solution in dry tetrahydrofuran (6 mL) at −78°C was added a solution of *tert*-butyl thiopropionate (0.365 g, 2.5 mmol) in tetrahydrofuran (2 mL) over 10 min. The resulting lithium enolate solution was stirred at −78°C for 0.5 h. Then, a solution of zirconocene dichloride (0.73 g, 2.5 mmol) in tetrahydrofuran (10 mL) was added dropwise over 15 min and the mixture was stirred for 0.5 h. To this was added all at once 4-chloroazetidinone **10** (0.264 g, 1 mmol). The resulting solution was stirred at −78°C for 2 h. The reaction mixture was diluted with ether (60 mL), washed successively with 1 *M* hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and brine (2 × 30 mL), dried over anhydrous magnesium sulfate, and concentrated to give an oil (0.248 g), which was chromatographed on silica gel (ether – petroleum ether 1:1), yielding 56 mg (15%) of **16***d* with a β/α ratio of 94:6; mp 109–113°C (recrystallized from petroleum ether); ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.04, 0.05 (2s, CH_3—Si, αβ), 0.84, 0.85 (2s, CH_3—C—Si, αβ), 1.14, 1.24 (2d, J = 6.4 and 7.0 Hz, CH_3—CH—OSi and CH_3—CH—C=O, β), 1.20 (2 overlapping d, J = 6.2 and 7.2 Hz, CH_3—CH—OSi and CH_3—CH—C=O, α), 1.43 (s, *t*-BuS, β), 1.44 (s, *t*-BuS, α), 2.61 (m, CH_3—*CH*—C=O, α), 2.73 (m, overlapping, H-3, α, and CH_3—*CH*—C=O, β), 2.94 (dd, J = 2.2 and 3.5 Hz, H-3, β), 3.68 (dd, J = 2.1 and 9.5 Hz, H-4, α), 3.82 (dd, J = 2.2 and 6.2 Hz, H-4, β), 4.15 (m, CH_3—*CH*—OSi, αβ), 5.86 (br s, NH, β), 5.93 (br s, NH, α). *Anal.* calcd. for $C_{18}H_{35}NO_3SSi$ (373.601): C 57.87, H 9.44, N 3.75, S 8.58; found: C 58.11, H 9.50, N 3.70, S 8.42.

Method B (ref. 20)

To an ice-cooled solution of *tert*-butylthiopropionate (0.584 g, 4 mmol) in dry methylene chloride (10 mL) was added diisopropylethylamine (0.75 mL, 4.3 mmol), followed by dropwise addition of a solution of ethylenechloroboronate (4 mmol) in methylene chloride (3 mL). The resulting solution was stirred at room temperature for 3.5 h. To this solution was added **4** (5) (0.574 g, 2 mmol) and it was stirred at room temperature for 2 days. The reaction mixture was washed successively with 1 *M* hydrochloric acid, saturated sodium bicarbonate, and water, dried over anhydrous magnesium sulfate, concentrated, and chromatographed on silica gel (ether – petroleum ether 1:1), giving 0.23 g of **16***d* (30%, β/α 77:23). The ^{1}H nmr spectrum was identical to that of compound **16***d* produced by method A.

Method C (ref. 21)

To a slurry of activated zinc dust (0.5 g, 7.7 mmol) in dry tetrahydrofuran (10 mL) at −10°C was added diethylaluminum chloride (3.8 mmol, in hexane). A solution of **4** (0.574 g, 2 mmol) and benzyl 2-bromopropionate (1.46 g, 6 mmol) in tetrahydrofuran (10 mL) was added dropwise over 0.5 h. The resulting slurry was stirred at −10°C for 1 h. The reaction mixture was filtered on Celite and the filtrate was diluted with ether (70 mL), washed successively with 1 *M* hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), and brine (2 × 30 mL), dried over anhydrous magnesium sulfate, and concentrated to give an oil, which was chromatographed on silica gel (ether – petroleum ether 1:1), yielding 0.57 g of **16***c* (73%, β/α 52:48); mp 61–62°C (recrystallized from petroleum ether); ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.04, 0.06 (2s, CH_3—Si, αβ), 0.84, 0.85 (2s, CH_3—C—Si, αβ), 1.12, 1.23 (2d, J = 6.3 and 7.0 Hz, CH_3—CH—OSi and CH_3—CHC=O, β), 1.22 (2 overlapping d, J = 6.2 and 7.2 Hz, CH_3—CH—OSi and CH_3—CH—C=O, α), 2.55 (m, CH_3—*CH*—C=O, α), 2.71 (m, overlapping H-3, α, and CH_3—*CH*—C=O, β), 2.96 (dd, J = 2.2 and 4.3 Hz, H-3, β), 3.69 (dd, J = 2.0 and 9.4 Hz, H-4, α), 3.90 (dd, J = 2.2 and 5.4 Hz, H-4, β), 4.42 (m, CH_3—*CH*—OSi, αβ), 5.11 (CH_2Ph, β), 5.13 (s, CH_2Ph, α), 5.82 (br s, NH, β), 5.92 (br s, NH, α), 7.33 (s, Ph, αβ). *Anal.* calcd. for $C_{21}H_{33}NO_4Si$ (391.553): C 64.42, H 8.50, N 3.58; found: C 64.65, H 8.83, N 3.54.

*Hydrogenolysis of **16**c*

Compound **16***c* (β/α 52:48, 0.41 g, 1.05 mmol) was dissolved in methanol (30 mL). To this were added 10% Pd/C (200 mg), water (1.5 mL), and pH 7 phosphate buffer (3 mL). This mixture was placed in an hydrogenation bottle that was shaken at room temperature under 7 psi/H_2 (1 psi = 6.9 kPa) for 1.5 h. The reaction mixture was filtered on Celite and the Celite was washed with methanol (10 mL). The filtrate was concentrated to give a white solid (0.33 g), which was dissolved in a mixture of saturated sodium bicarbonate (8 mL) and water (8 mL), and washed with ether (2 × 10 mL). The aqueous phase was acidified with 2 *M* hydrochloric acid and extracted with ether (2 × 15 mL). The ether extract was washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated to give crystalline **17** as a β/α mixture (0.24 g, 76%, β/α 1:1, mp 130–134°C). The pure α-isomer was isolated by crystallization from ethyl acetate; mp 160–162°C, $[\alpha]_D^{23}$ −2.7° (*c* 0.11, CH_3OH); ir (Nujol): 2190, 2800–2400 (br), and 1712 (br) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.06, 0.07 (2s, 6H, CH_3—Si), 0.87 (s, 9H, CH_3—C—Si), 1.24, 1.27 (2 overlapping d, J = 5.7 and 7.0 Hz, 6H, CH_3—CH—OSi and CH_3—CH—C=O), 2.55 (m, 1H, CH_3—CH—C=O), 2.78 (dd, J = 1.0 and 5.2 Hz, 1H, H-3), 3.68 (dd, J = 1.9 and 9.8 Hz, 1H, H-4), 4.18 (m, 1H, CH_3—CH—OSi), 6.59 (br s, NH). *Anal.* calcd. for $C_{14}H_{27}NO_4Si$ (301.428): C 55.78, H 9.03, N 4.65; found: C 55.63, H 9.20, N 4.61. The reported ^{1}H nmr spectrum of the β-isomer (2*a*) supports the structure as well.

*Hydrolysis of **16**d*

Compound **16***d* (β/α 94:6, 31 mg, 0.083 mmol) was dissolved in methanol (1.7 mL). To this were added water (0.25 mL) and 2.5 *M* sodium hydroxide (0.1 mL). The resulting solution was stirred at room temperature for 2 days. The reaction mixture was diluted with water (20 mL) and washed with ether (2 × 20 mL). The aqueous phase was then acidified with concentrated hydrochloric acid (0.5 mL) and extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with brine (2 × 25 mL), dried over anhydrous magnesium sulfate, and concentrated to give crystalline **17** as a white solid (23 mg, 90%). Although the ^{1}H nmr spectrum showed the expected product, it indicated partial epimerization of the methyl group (β/α 70:30).

Acknowledgement

The author would like to thank Drs. J. L. Douglas and Y. G. Perron for advice during the course of this work.

1. (*a*) H. Kropp, J. S. Kahan, J. Sundelof, G. Darland, and J. Birnbaum. 16th Interscience Conference Antimicrobial Agents and Chemotherapy, Chicago (1976); (*b*) G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen,

E. A. KACZKA, R. E. RHODES, J. S. KAHAN, F. M. KAHAN, R. W. RATCLIFFE, E. WALTON, L. J. RUSWINKLE, R. B. MORIN, and B. G. CHRISTENSEN. J. Am. Chem. Soc. **100**, 6491 (1978).
2. (*a*) D. H. SHIH, L. BAKER, I. CAMA, and B. G. CHRISTENSEN. Heterocycles, 1, 29 (1984); (*b*) D. H. SHIH, J. A. FAYTER, L. D. CAMA, B. G. CHRISTENSEN, and J. HIRSHFIELD. Tetrahedron Lett. **26**, 583 (1985); **26**, 89 (1985).
3. R. B. WOODWARD. *In* Recent advances in the chemistry of β-lactam antibiotics. *Edited by* J. Elks. Chem. Soc. Spec. Publ. No. 28. 1977.
4. (*a*) T. KAMETANI. Heterocycles, **17**, 463 (1982); (*b*) Recent advances in the chemistry of β-lactam antibiotics. *Edited by* A. G. Brown and S. W. Roberts. The Royal Society of Chemistry, London. 1984; (*c*) W. DURCKHEIMER, J. BLUMBACH, R. LATTRELL, and K. H. SCHEUNEMANN. Angew. Chem. Int. Ed. Engl. **24**, 180 (1985).
5. A. YOSHIDA, T. HAYASHI, N. TAKEDA, S. OIDA, and E. OHKI. Chem. Pharm. Bull. **29**, 2899 (1981).
6. (*a*) K. FUJIMOTO, Y. IWANO, and K. HIRAI. Tetrahedron Lett. **26**, 89 (1985); (*b*) W. J. LEANZA, F. DININNO, D. A. MUTHARD, R. R. WILKENING, K. J. WILDONGER, R. W. RATCLIFFE, and B. G. CHRISTENSEN. Tetrahedron, **39**, 2505 (1983); (*c*) Y. UEDA, G. ROBERGE, and V. VINET. Can. J. Chem. **62**, 2936 (1984).
7. (*a*) A. MARTEL and J. P. DARIS. U.S. Patent No. 4,596,677 (1986); (*b*) M. ENDO. Synth. Commun. In press.
8. S. KARADY, J. S. AMATO, R. A. REAMER, and L. M. WEINSTOCK. J. Am. Chem. Soc. **103**, 6765 (1981).
9. A. ALPEGIANI, A. BEDESCHI, M. FOGLIO, F. GIUDICI, and E. PERRONE. Tetrahedron Lett. **24**, 1627 (1983).
10. Y. UEDA and S. C. MAYNARD. Tetrahedron Lett. **26**, 6309 (1985).
11. V. M. GIRIJAVALLABHAN, A. K. GANGULY, S. W. MCCOMBIE, P. PINTO, and R. RIZVI. Tetrahedron Lett. **22**, 3485 (1981).
12. K. FUJIMOTO, Y. IWANO, and K. HIRAI. Tetrahedron Lett. **26**, 89 (1985).
13. L. M. FUENTES, I. SHINKAI, and T. N. SALZMANN. J. Am. Chem. Soc. **108**, 4675 (1986).
14. D. A. EVANS, J. BATTROLI, and T. L. SHIH. J. Am. Chem. Soc. **103**, 2127 (1984).
15. Y. NAGAO, T. KUMAGAI, S. TAMAI, T. ABE, Y. KURAMOTO, T. TAGA, S. AOYAGI, Y. NAGASE, M. OCHIAI, Y. INOUE, and E. FUJITA. J. Am. Chem. Soc. **108**, 4673 (1986).
16. R. DEZIEL and D. FAVREAU. Tetrahedron Lett. **27**, 5687 (1986).
17. T. IIMORI and M. SHIBASAKI. Tetrahedron Lett. **27**, 2149 (1986).
18. C. U. KIM, B. LUH, and R. A. PARTYKA. Tetrahedron Lett. **28**, 507 (1987).
19. (*a*) D. A. EVANS and L. R. MCGEE. Tetrahedron Lett. **21**, 3975 (1980); (*b*) Y. YAMAMOTO and K. MURAYAMA. Tetrahedron Lett. **21**, 4107 (1980); (*c*) T. MUKAIYAMA, H. SUZUKI, and T. YAMADA. Chem. Lett. 915 (1986).
20. (*a*) C. GENNARI, L. COLOMBO, and G. POLI. Tetrahedron Lett. **25**, 2279 (1983); (*b*) **26**, 797 (1985).
21. K. MARUOKA, S. HASHIMOTO, Y. KITAGAWA, H. YAMAMOTO, and H. NOZAKI. J. Am. Chem. Soc. **99**, 7705 (1977).
22. D. A. EVANS, J. V. NELSON, and T. R. TABER. *In* Topics in stereochemistry. Vol. 13. *Edited by* N. L. Allinger, E. L. Eliel, and S. H. Wilen. John Wiley and Sons, New York. 1982. pp. 1–115.