STEREOSELECTIVE CONVERSIONS OF cis-4-(2',2'-DIMETHOXYETHYL)-3-[(1'S*)-1'-HYDROXYETHYL]-2-AZETIDINONE INTO THE CORRESPONDING trans-(1'R*)- AND (1'S*)-AZETIDINONES

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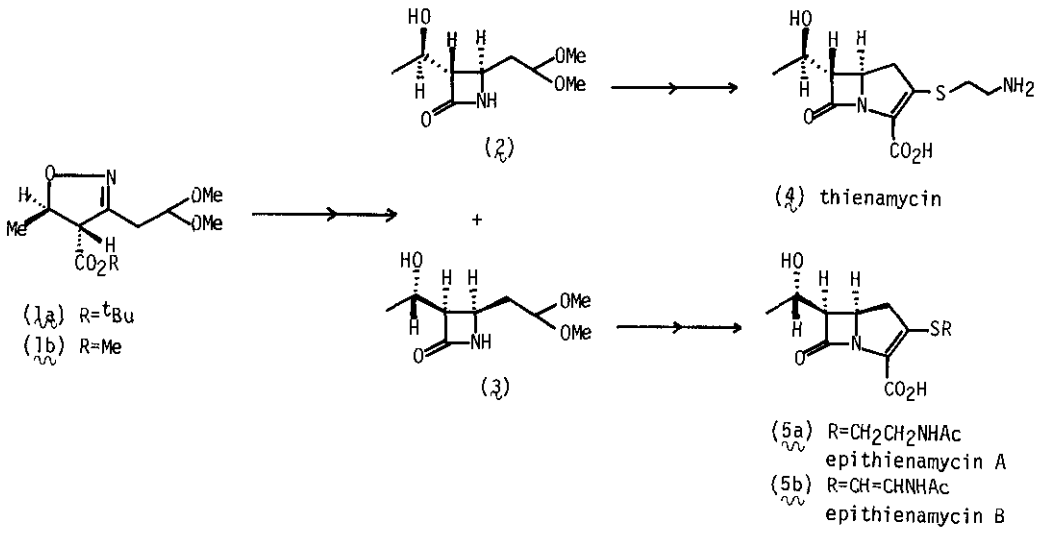
Abstract —— Stereoselective conversions of cis-4-(2',2'-dimethoxyethyl)-3-[(1'S*)-1'-hydroxyethyl]-2-azetidinone into the corresponding trans-(1'R*)- and (1'S*)-azetidinones were achieved by the modification of the Merck's method. Furthermore, selective protection of the secondary amide group of the β-lactam ring and the hydroxyl group on the same molecule with dimethyl-tert.-butylsilyl group is also described.

Recently we have accomplished an efficient synthesis[1-3] of thienamycin, a potent and broad spectral antibiotic,[4-7] via isoxazoline derivatives. Hydrogenation of the isoxazoline tert.-butyl ester (1a) in the presence of Adams catalyst followed by trimethylsilylation of the resulting amino-alcohol, β-lactam formation using Grignard reagent and deprotection,[2] had selectively produced, in 42 % yield from 1a, the trans-(1'R*)-azetidinone (2), which had been converted into (±)-thienamycin (4).[3] On the other hand, by the same reaction procedure as above, the isoxazoline methyl ester (1b) had been transformed into the trans-β-lactam (2) in 21 % yield along with the cis-(1'S*)-one (3) in 38 % yield,[2] which had been correlated to epithienamycins A (5a) and B (5b).[8] We further investigated the conversion of the cis-azetidinone (3) into the stereoisomers. Merck's research groups had reported the transformation of trans-(1'S*)-azetidinone derivatives into (1'R*)-isomers by two different methods.[6,7] On modification of one of their methods,[6] we have succeeded in the stereoselective conversion of our cis-compound (3) into the corresponding two trans-ones (2) and (12) and also found the following interesting results.

Scheme 1



Studies on the blocking of the hydroxyl β-lactams with various protecting groups led us to discover a selective blocking of the secondary amide group of the azetidinone and the hydroxyl group on the same molecule with dimethyl-tert.-butylsilyl group. Namely, the reaction of (3) with excess dimethyl-tert.-butylchlorosilane in the presence of imidazole in dimethylformamide[9] for 24 hr gave the O-mono-silylated product (6) in 93.5 % yield but no nitrogen protected compound formed. On the other hand, after treatment of 3 with excess n-butyllithium in tetrahydrofuran at -78 ∿ -10°C, the resulting anion was reacted with the excess of the chlorosilane at -50 ∿ -5°C to produce the N-mono-silylated compound (7) in 65.5 % yield. No formation of 6 was observed after reaction for 1 hr under the above conditions.

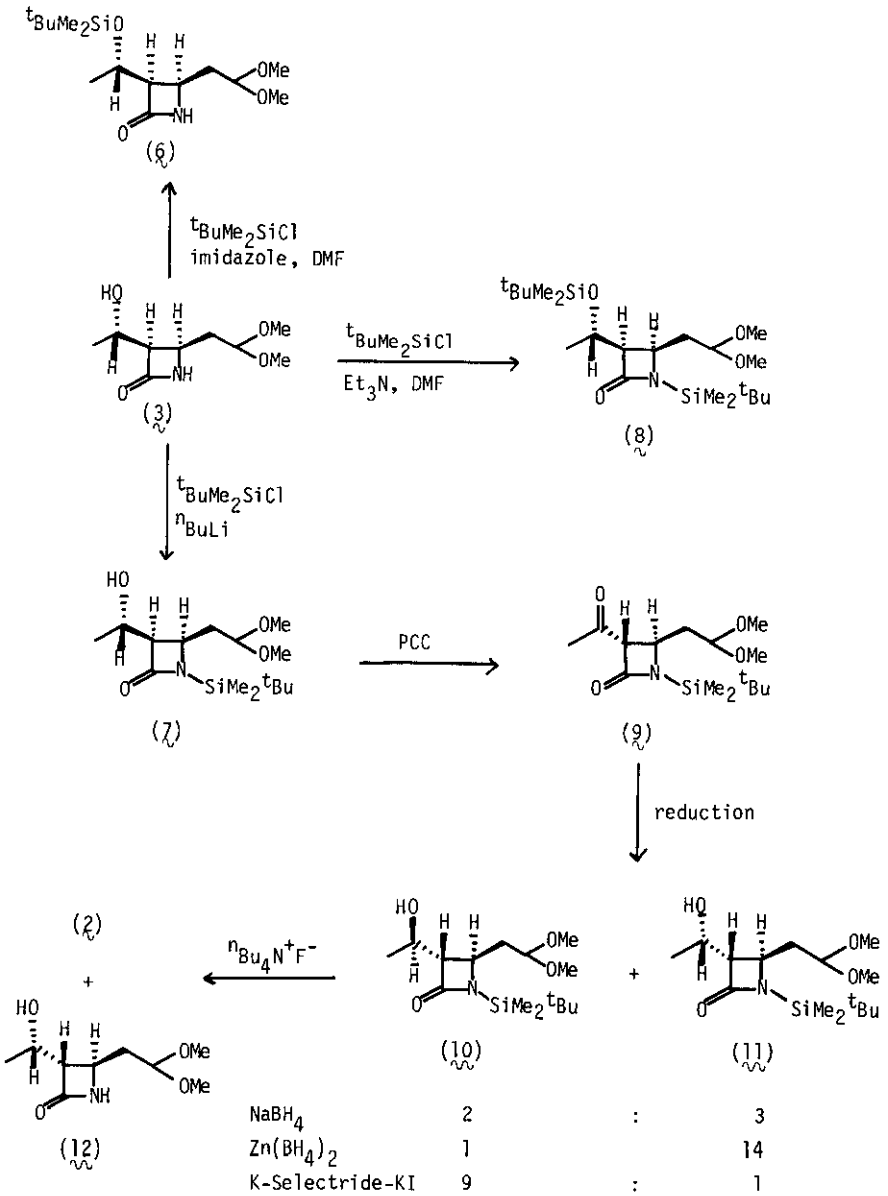
Treatment of (3) with the silyl chloride and triethylamine in dimethylformamide[6] at room temperature produced a mixture of the N- and O-protected compounds eventually leading to the N,O-bis-silylated product (8). Although theoretical reason is obscure, the selectivities observed would be mainly due to the different acidity between the hydroxyl group and the secondary β-lactam group.

Oxidation of the above N-silylated compound with pyridinium chlorochromate[10] in the presence of sodium acetate in dichloromethane gave a single ketone in 62.9 % yield,

the structure of which was assigned as the trans-azetidinone (9) because of the small coupling constant of 2.3 Hz due to two hydrogens on the β-lactam ring. Epimerisation occurred at the C-3 position under the above conditions producing the more stable trans-isomer.

Reduction of the ketone (9) with sodium borohydride in methanol afforded a mixture of the trans-(1'R*)- and (1'S*)-stereoisomers (10 and 11) in a ratio of 2 : 3 in 90 % yield. When 9 was reduced with zinc borohydride[11] in ether, the (1'S*)-compound (11) formed exclusively in 86 % yield along with a small amount of the (1'R*)-one (10), the ratio of (1'R*)- and (1'S*)-ones was about 1 : 14. On the other hand, on the reaction of 9 with potassium tri-sec.-butylborohydride (K-Selectride) in the presence of potassium iodide[6] in a mixture of ether and tetrahydrofuran, the (1'R*)-alcohol (10) was selectively obtained in 80 % yield together with the isomer (11); the ratio of 10 and 11 was about 9 : 1. The ratios of two reduced products were determined by nmr spectroscopy. Signals due to the methyl group at C-1' position and the methine hydrogens at C-3,4, 1' and 2" positions of both compounds (10 and 11) were observed at well distinguished chemical shifts; those hydrogens of 10 were resonated at 1.30, 2.89, 3.57, 4.03 and 4.48 ppm, respectively while those signals were shown at 1.28, 2.99, 3.51, 4.02 and 4.41 ppm, respectively. The authentic (1'R*)-compound (10) was prepared by the silylation of the β-lactam (2). Deprotections of dimethyl-tert.-butylsilyl group of the above products were carried out by treatments with tetra-n-butylammonium fluoride[9] in aqueous tetrahydrofuran at room temperature to give quantitatively the corresponding β-lactams (2) and (12), respectively. Thus stereoselective conversions of the cis-β-lactam (3) into the trans-(1'R*) and (1'S*)-compounds (2) and (12) were achieved with more 90 % stereocontrol. Furthermore both trans-isomers (2) and (12) were convertible each other by the same procedure as above.

Scheme 2


tBuMe2SiO
OMe
OMe
NH
(6)
tBuMe2SiCl
imidazole, DMF
HO
(3)
tBuMe2SiCl
Et3N, DMF
SiMe2tBu
(8)
tBuMe2SiCl
nBuLi
(7)
PCC
(9)
reduction
(2)
+
(12)
nBu4N+F-
(10)
(11)
NaBH4 2 : 3
Zn(BH4)2 1 14
K-Selectride-KI 9 : 1

EXPERIMENTAL

Ir spectra were taken with a Hitachi 260-10 spectrophotometer, nmr spectra with JEOL PMX-60 and JEOL-PS-100 spectrometers (tetramethylsilane as internal reference) and mass spectra with Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers.

(±)-4β-(2",2"-Dimethoxyethyl)-3β-[(1'S*)-1'-dimethyl-tert.-butylsilyloxyethyl]-2-azetidinone (6).— A mixture of the acetal (3)[2] (98 mg), dimethyl-tert.-butylchlorosilane (109 mg), imidazole (97 mg) and dry dimethylformamide (10 ml) was stirred at room temperature for 24 hr under nitrogen. The mixture was partitioned between benzene and water. The organic layer was dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene-acetone (19 : 1 v/v) gave the O-silylated cis-β-lactam (6) (143 mg, 93.5 %) as a syrup (Found: N, 4.32. $C_{15}H_{31}NO_4Si$ requires N, 4.41), ν max.($CHCl_3$) 3420 (NH), 1755 cm^{-1} (C = O); δ ($CDCl_3$) 0.07 (6H, s, 2 x SiMe), 0.89 (9H, s, $SiCMe_3$), 1.33 (3H, d, J 6.3 Hz, 1"-Me), 1.91 ∿ 2.29 (2H, m, 1"-H_2), 3.17 (1H, ddd, J 7.6, 5.2 and 1.2 Hz, 3-H), 3.32 and 3.33 (each 3H, each s, 2 x OMe), 3.63 ∿ 3.94 (1H, m, 4-H), 4.24 (1H, dq, J 7.6 and 6.3 Hz, 1'-H), 4.44 (1H, t, J 5.5 Hz, 2"-H), 6.14 (1H, s, NH).

(±)-4β-(2",2"-Dimethoxyethyl)-3β-[(1'S*)-1'-hydroxyethyl]-1-dimethyl-tert.-butylsilyl-2-azetidinone (7).— To a stirred solution of the acetal (3) (2.97 g) in dry tetrahydrofuran (15 ml) was added n-butyllithium in n-hexane (15 % w/w; 11.8 ml) at - 78°C under nitrogen. After stirring for 1 hr at - 10°C, dimethyl-tert.-butylchlorosilane (2.31 g) in dry tetrahydrofuran (5 ml) was added to the above mixture at - 50°C, and the resulting mixture was then stirred for 1 hr at - 5°C. The mixture was poured into ice and extracted with ether-dichloromethane (5 : 1 v/v). The extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel and elution with benzene-acetone (19 : 1 v/v) gave a N-silylated cis-β-lactam (7) (3.07 g, 65.5 %) as a syrup (Found: C, 56.91; H, 10.09; N, 4.22. $C_{15}H_{31}NO_4Si$ requires C, 56.75; H, 9.84; N, 4.41), ν max.($CHCl_3$) 3430 (OH), 1735 cm^{-1} (C = O); δ ($CDCl_3$) 0.24 (6H, s, 2 x SiMe), 0.96 (9H, s, $SiCMe_3$), 1.37 (3H, d, J 6.3 Hz, 1'-Me), 1.95 (1H, ddd, J 14.3, 4.3 and 2.3 Hz, 1"-H), 2.21 (1H, ddd, J 14.3, 9.4 and 5.7 Hz, 1"-H), 3.20 (1H, dd, J 10.5 and 5.7 Hz, 3-H), 3.36 and 3.41 (each 3H, each s, 2 x OMe), 3.81 (1H, ddd, J 9.4, 5.7 and 2.3 Hz, 4-H), 3.91 ∿ 4.25 (1H, m, 1'-H), 4.51 (1H, dd, J 5.7 and 4.3 Hz, 2"-H); m/e 318 (M^++1),

(±)-4β-(2",2"-Dimethoxyethyl)-3α-[(1'R*)-1'-hydroxyethyl]-1-dimethyl-tert.-butylsilyl-2-azetidinone (10).— To a stirred solution of the acetal (2) (260 mg)

in dry tetrahydrofuran (5 ml) was added n-butyllithium in n-hexane (15 % w/w; 1.59 ml) at - 78°C under nitrogen. After stirring for 1 hr at - 10°C, dimethyl-tert.-butylchlorosilane (386 mg) in dry tetrahydrofuran (5 ml) was added to the above mixture at - 50°C, and the resulting mixture was then stirred for 1 hr at - 5°C. Work-up as above gave the N-silylated trans-β-lactam (10) (280 mg, 69.0 %) as a syrup, ν max.($CHCl_3$) 3430 (OH), 1730 cm^{-1} (C = O); δ ($CDCl_3$) 0.23 and 0.26 (each 3H, each s, 2 x SiMe), 0.97 (9H, s, $SiCMe_3$), 1.30 (3H, d, J 6.3 Hz, 1'-Me), 1.76 (1H, ddd, J 14.0, 11.3 and 4.3 Hz, 1"-H), 2.20 (1H, ddd, J 14.0, 6.6 and 3.0 Hz, 1"-H), 2.89 (1H, dd, J 7.9 and 2.4 Hz, 3-H), 3.32 and 3.34 (each 3H, each s, 2 x OMe), 3.57 (1H, ddd, J 11.3, 3.0 and 2.4 Hz, 4-H), 4.03 (1H, dq, J 7.9 and 6.3 Hz, 1'-H), 4.48 (1H, dd, J 6.6 and 4.3 Hz, 2"-H); m/e 318 (M^++1).

(±)-3α-Acetyl-4β-(2",2"-dimethoxyethyl)-1-dimethyl-tert.-butylsilyl-2-azetidinone (9).—— To a suspension of pyridinium chlorochromate (1.50 g) and sodium acetate (1.14 g) in dry dichloromethane (30 ml) was quickly added the cis-N-silylated β-lactam (7) (1.44 g) in dry dichloromethane (10 ml) at 0°C under nitrogen. After stirring for 6 hr at room temperature, the mixture was partitioned between 10 % ammonia and dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel and elution with benzene-acetone (49 : 1 v/v) gave the keto β-lactam (9) (900 mg, 62.9 %) (Found:C, 57.37; H, 9.46; N, 4.28. $C_{15}H_{29}NO_4Si$ requires C, 57.11; H, 9.27; N, 4.44), ν max. ($CHCl_3$) 1740 and 1710 cm^{-1} (C = O); δ ($CDCl_3$) 0.23 and 0.26 (each 3H, each s, 2 x SiMe), 0.96 (9H, s, $SiCMe_3$), 1.59 ∿ 2.26 (2H, m, 1"-H_2), 2.29 (3H, s, 1'-Me) 3.30 and 3.33 (each 3H, each s, 2 x OMe), 4.00 (1H, ddd, J 10.0, 2.6 and 2.3 Hz, 4-H), 4.06 (1H, d, J 2.3 Hz, 3-H), 4.36 (1H, dd, J 5.4 and 4.9 Hz, 2"-H); m/e 316 (M^++1), and further elution with benzene-acetone (19 : 1 v/v) recovered the starting material (7) (411 mg).

Reduction of (9) with Sodium Borohydride.—— To a stirred solution of the keto β-lactam (9) (35 mg) in methanol (5 ml) was added sodium borohydride (4 mg) at 0°C. After stirring for 30 min at room temperature, the excess reagent was decomposed with acetic acid under cooling with ice and the solvent was evaporated. The residue was chromatographed on silica gel and elution with benzene-acetone (19 : 1 v/v) gave a mixture (32 mg, 90 %) of 10 and 11 in a ratio of 2: 3, ν max.($CHCl_3$); 3430 (OH), 1730 cm^{-1} (C = O); ($CDCl_3$) 0.23 and 0.26 (each 3H, each s, 2 x SiMe), 0.97 (9H, s, $SiCMe_3$), 1.28 (1.8 H, d, J 6.3 Hz, 1'-Me), 1.30 (1.2 H, d, J 6.3 Hz, 1'-Me),

1.74 (0.6 H, ddd, J 13.8, 10.8 and 4.7 Hz, 1"-H), 1.76 (0.4 H, ddd, J 14.0, 11.3 and 4.3 Hz, 1"-H), 2.18 (0.6 H, ddd, J 13.8, 6.4 and 3.3 Hz, 1"-H), 2.20 (0.4 H, ddd, J 14.0, 6.6 and 3.0 Hz, 1"-H), 2.89 (0.4 H, dd, J 7.9 and 2.4 Hz, 3-H), 2.99 (0.6 H, dd, J 6.5 and 2.4 Hz, 3-H), 3.30 and 3.33 (each 3.6 H, each s, OMe), 3.32 and 3.34 (each 2.4 H, each s, OMe), 3.51 (0.6 H, ddd, J 10.8, 3.3 and 2.4 Hz, 4-H), 3.57 (0.4 H, ddd, J 11.3, 3.0 and 2.4 Hz, 4-H), 4.02 (0.6 Hz, dq, J 6.5 and 6.3 Hz, 1'-H), 4.03 (0.4 H, dq, J 7.9 and 6.3 Hz, 1'-H), 4.41 (0.6 H, dd, J 6.4 and 4.7 Hz, 2"-H), 4.48 (0.4 H, dd, J 6.6 and 4.3 Hz, 2"-H): m/e 318 (M^++1).

Reduction of (9) with Potassium tri-sec.-Butylborohydride.—— To a stirred solution of the keto β-lactam (9) (65 mg) and potassium iodide (34.3 mg) in dry ether (5 ml) was added potassium tri-sec.-butylborohydride in tetrahydrofuran (0.5 M solution, 0.62 ml) at 0°C under nitrogen. After stirring for 30 min at room temperature, the excess reagent was quenched with water under cooling with ice and the solvents were evaporated. The residue was chromatographed on silica gel and elution with benzene-acetone (49 : 1 v/v) recovered the starting keto β-lactam (7 mg). Further elution with benzene-acetone (19 : 1 v/v) gave a mixture (52 mg, 80 %) of 10 and 11 in a ratio of 9 : 1 as a syrup (Found: N, 4.22. $C_{15}H_{31}NO_4Si$ requires N, 4.41), ν max. ($CHCl_3$) 3430 (OH), 1730 cm^{-1} (C = O); δ ($CDCl_3$) 0.23 and 0.26 (each 3H, each s, 2 x SiMe), 0.97 (9 H, s, $SCMe_3$), 1.28 (0.3 H, d, J 6.3 Hz, 1'-Me), 1.30 (2.7 H, d, J 6.3 Hz, 1'-Me), 1.74 (0.1 H, ddd, J 13.8, 10.8 and 4.7 Hz, 1"-H), 1.76 (0.9 H, ddd, J 14.0, 11.3 and 4.3 Hz, 1"-H), 2.18 (0.1 H, ddd, J 13.8, 6.4 and 3.3 Hz, 1"-H), 2.20 (0.9 H, ddd, J 14.0, 6.6 and 3.0 Hz, 1"-H), 2.89 (0.9 H, dd, J 7.9 and 2.4 Hz, 3-H), 2.99 (0.1 H, dd, J 6.5 and 2.4 Hz, 3-H), 3.30 and 3.33 (each 0.3 H, each s, OMe), 3.32 and 3.34 (each 2.7 H, each s, OMe), 3.51 (0.1 H, ddd, J 10.8, 3.3 and 2.4 Hz, 4-H), 3.57 (0.9 H, ddd, J 11.3, 3.0 and 2.4 Hz, 4-H). 4.02 (0.1H, dq, J 6.5 and 6.3 Hz, 1'-H), 4.03 (0.9 H, dq, J 7.9 and 6.3 Hz, 1'-H), 4.41 (0.1 H, dd, J 6.4 and 4.7 Hz, 2"-H), 4.48 (0.9 H, dd, J 6.6 and 4.3 Hz, 2"-H); m/e 318 (M^+ +1).

Reduction of (9) with Zinc Borohydride.—— To a stirred solution of the keto β-lactam (9) in dry ether (3 ml) was added zinc borohydride (60 mg) in ether (3 ml) at 0°C under nitrogen. After stirring for 30 min at room temperature, the excess reagent was quenched with water under cooling with ice and the solvent was evaporated. The same work-up as above gave a mixture (25 mg, 86 %) of 10 and 11 in a ratio of 1: 14 as a syrup, ν max.($CHCl_3$) 3430 (OH), 1730 cm^{-1} (C = O); δ ($CDCl_3$) 0.23 and 0.26 (each 3H, each s, 2 x SiMe), 0.97 (9H, s, $SiCMe_3$), 1.28 (2.8 H, d, J 6.3 Hz,

1'-Me), 1.30 (0.2 H, d, J 6.3 Hz, 1'-Me), 1.74 (0.93 H, ddd, J 13.8, 10.8 and 4.7 Hz, 1"-H), 1.76 (0.066 H, ddd, J 14.0, 11.3 and 4.3 Hz, 1"-H), 2.18 (0.93 H, ddd, J 13.8, 6.4 and 3.3 Hz, 1"-H), 2.20 (0.066 H, ddd, J 14.0, 6.6 and 3.0 Hz, 1"-H), 2.89 (0.066 H, dd, J 7.9 and 2.4 Hz, 3-H), 2.99 (0.93 H, dd, J 6.5 and 2.4 Hz, 3-H), 3.30 and 3.33 (each 2.8 H, each s, OMe), 3.32 and 3.34 (each 0.2 H, each s, OMe), 3.51 (0.93 H, ddd, J 10.8, 3.3 and 2.4 Hz, 4-H), 3.57 (0.066 H, ddd, J 11.3, 3.0 and 2.4 Hz, 4-H), 4.02 (0.93 H, dq, J 6.5 and 6.3 Hz, 1'-H), 4.03 (0.066 H, dq, J 7.9 and 6.3 Hz, 1'-H), 4.41 (0.93 H, dd, J 6.4 and 4.7 Hz, 2"-H), 4.48 (0.066, dd, J 6.6 and 4.3 Hz, 2"-H).

Deprotection of the Reduction Product with Potassium tri-sec.-Borohydride.—— A mixture of the above product (23 mg) by the reduction with K-Selectride, tetra-n-buthylammonium fluoride (37 mg) and aqueous tetrahydrofuran (5 ml) was stirred for 30 min at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel and elution with benzene-acetone (4 : 1 v/v) gave a mixture of trans-β-lactams (2 and 12)[1] (14.5 mg, 98.5 %) in a ratio of 9 : 1 as a syrup.

Deprotection of Reduction Product with Zinc Borohydride.—— A mixture of the above product (28 mg) by reduction with zinc borohydride, tetra-n-butylammonium fluoride (42 mg) and aqueous tetrahydrofuran (5 ml) was stirred for 30 min at room temperature. The same work-up as above gave a mixture of trans-β-lactams (2 and 12)[1] (17.7 mg, 98 %) in a ratio of 1 : 14 as a syrup.

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REFERENCES

1. T. Kametani, S.-P. Huang, and M. Ihara, Heterocycles, 1979, 12, 1183 and 1189; T. Kametani, S.-P. Huang, Y. Suzuki, S. Yokohama, and M. Ihara, Heterocycles, 1979, 12, 1301; T. Kametani, S-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, J. Amer. Chem. Soc., 1980, 102, 2060.

2. T. Kametani, T. Nagahara, Y. Suzuki, S. Yokohama, S.-P. Huang, and M. Ihara, Heterocycles, 1980, 14, 403; Tetrahedron, in press.

3. T. Kametani, S.-P. Huang, T. Nagahara, and M. Ihara, Heterocycles, 1980, 14,

1305; J. C. S. Perkin I, in press.

4. G. Albers-Schönberg, 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. Amer. Chem. Soc., 1978, 100, 6491.

5. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Amer. Chem. Soc., 1978, 100, 313; S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, J. Org. Chem., 1980, 45, 1142.

6. T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, J. Amer. Chem. Soc., 1980, 102, 6161.

7. D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, Tetrahedron Letters, 1980, 21, 2783.

8. T. Kametani, S.-P. Huang, T. Nagahara, and M. Ihara, Heterocycles, in press.

9. E. J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 1972, 94, 6190.

10. E. J. Corey and J. W. Suggs, Tetrahedron Letters, 1975, 2647.

11. W. J. Gensler, F. Johnson, and A. D. B. Sloan, J. Amer. Chem. Soc., 1960, 82, 6074.

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