# STEREOSELECTIVE SYNTHESIS OF (±)-5-(1-BENZYLOXYETHYL)-6-(2-*tert*-BUTYLDIPHENYLOXYETHYL)-2-PIPERIDINONE: A FORMAL TOTAL SYNTHESIS OF THIENAMYCIN

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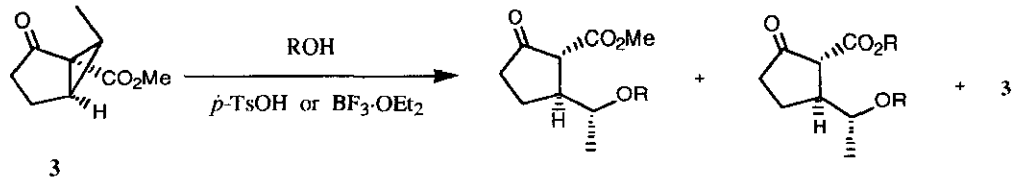
Abstract---(±)-5-(1-Benzyloxyethyl)-6-(2-*tert*-butyldiphenyllsilyloxyethyl)-2-piperidinone (2), a synthetic intermediate for thienamycin (1), has been synthesized stereoselectively in nine steps from methyl 2-oxo-6-*endo*-methylbicyclo[3.1.0]hexane-1-carboxylate (3) using Lewis acid catalyzed homoconjugate addition of benzyl alcohol to 3 as a key step.

Thienamycin (1) possesses potent antibacterial activities as well as broad spectra of action, [1] therefore much attention has been focused on synthetic studies of this compound.[2] Control of the stereochemistry at the three contiguous chiral centers located at C(5), C(6) and C(8) is a difficult task in the synthesis of thienamycin (1). In our previous report, [3] we described one of the solutions to this problem based on the acid catalyzed stereoselective homoconjugate addition of methanol to methyl 2-oxo-6-*exo* -methylbicyclo[3.1.0]hexane -1-carboxylate. In this paper we report the stereoselective synthesis of (±)-5-(1-benzyloxyethyl)-6-(2-*tert*-butyldiphenylsilyloxyethyl)-2-piperidinone (2),[4] the Grieco's intermediate for the synthesis of thienamycin (1), by using Lewis acid catalyzed homoconjugate 1,5-addition of benzyl alcohol to methyl 2-oxo-6-*endo*-methylbicyclo[3.1.0]hexane-1-carboxylate (3) in more short step sequence.

At first, we investigated homoconjugate 1,5-addition of several alcohols[5] to cyclopropane (3), which was prepared from methyl acetoacetate in three steps by the method of Nozaki, [6] in the presence of *p*-toluenesulfonic acid or boron trifluoride etherate as catalyst. The selected results are summarized in Table 1. The stereochemistry

of 1,5-adduct (**A**) and ester-exchanged one (**B**) was tentatively assigned at this stage on the basis of our previous results[5] and afterward confirmed by X-ray crystallographic analysis (*vide infra*). It was found that secondary alcohols were less reactive than primary alcohols and tertiary alcohols were unreactive. Generally, boron trifluoride etherate was more effective catalyst than *p*-toluenesulfonic acid. The target piperidinone (**2**) was synthesized using the 1,5-addition of benzyl alcohol (entry 4) as following reaction sequence (Scheme 1).

**Table 1.** Acid catalyzed homoconjugate addition of alcohols to cyclopropane (**3**)




| entry | ROH | catalyst | conditions | yield (%, **A** : **B** : **3**) |
|---|---|---|---|---|
| 1 | MeOH (excess) | *p*-TsOH (50 mol%) | reflux 3 h | 76 : - : 0 |
| 2 | EtOH (excess) | *p*-TsOH (50 mol%) | reflux 3 h | 46 : 15 : 12 |
| 3 | BnOH (1.5 eq.) | *p*-TsOH (50 mol%) | 60°C 3 h | 40 : 10 : 5 |
| 4 | BnOH (1.2 eq.) | $BF_3$·$OEt_2$ (10 mol%) | 60°C 30 min | 45 : 0 : 0 |
| 5 | *i*-PrOH (excess) | *p*-TsOH (50 mol%) | reflux 6 h | 27 : 20 : 32 |
| 6 | *i*-PrOH (1.2 eq.) | $BF_3$·$OEt_2$ (10 mol%) | 60°C 1 h | 55 : 0 : 13 |
| 7 | *t*-BuOH (excess) | *p*-TsOH (50 mol%) | reflux 10 h | 0 : 0 : 100 |
| 8 | *t*-BuOH (excess) | $BF_3$·$OEt_2$ (10 mol%) | 60°C 3 h | 0 : 0 : 100 |

The cyclopropane (**3**) was treated with benzyl alcohol in the presence of boron trifluorifde etherate at 60 °C for 30 min to give 1,5-adducts (**4**) in a 45% yield. Though the yield was somewhat low, a suitably protected oxygen functional group was introduced stereoselectively in one operation. Then, **4** was treated with methyl bromoacetate in the presence of potassium carbonate in acetone to afford crystalline diester (**5**) in a 62% yield. The structure of **5** was confirmed by single crystal X-ray analysis (Figure 1).

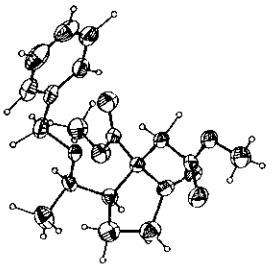
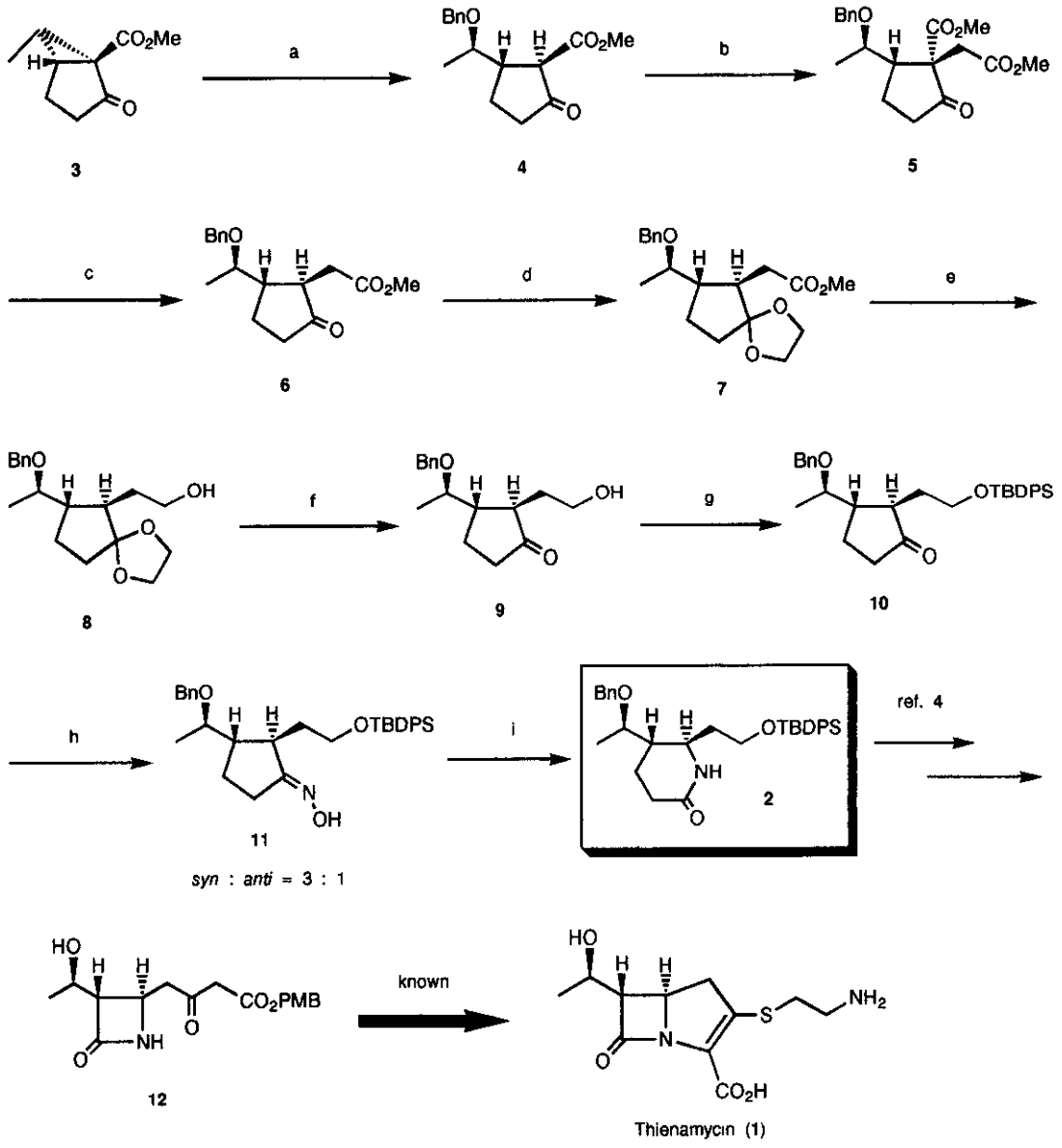


**Figure 1.** A perspective view of keto diester (**5**)

Demethoxycarbonylation of **5** with lithium chloride and hexamethylphosphoric triamide gave keto ester (**6**) in a 78% yield. Keto ester (**6**) was heated at reflux with ethylene glycol and *p* -toluenesulfonic acid in benzene to give ethylene ketal (**7**) in a 92% yield. Reduction of **7** with lithium aluminium hydride in ether gave alcohol (**8**), which was deketalyzed with 10% hydrochloric acid in tetrahydrofuran to afford keto alcohol (**9**) in a 98% yield from ethylene acetal (**7**). The primary hydroxyl group of **9** was protected as its silyl ether by treating with *tert*-butylchlorodiphenylsilane and imidazole in dimethylformamide to give the known silyl ether (**10**) [4] in an 81% yield. The epimerization of enolizable α-position of carbonyl group in compound (**6**, **9**, and **10**) has not occurred under these conditions. We prepared **10** in fewer steps (10 steps from methyl acetoacetate) in comparison with Grieco's scheme (17 steps from norbornadiene).[4] Then, according to Grieco's procedure, the cyclopentanone (**10**) was converted into δ-lactam (**2**) *via* oxime (**11**) by two step operation. Thus, cyclopentanone (**10**) was converted into oxime (**11**) by treatment with hydroxylamine hydrochloride and sodium acetate in ethanol to give *anti*-oxime (**11**) and *syn*-oxime in a ratio of *ca.* 3:1 in a 95% yield. The mixture was easily separated by silica gel chromatography. The *anti*-oxime (**11**) (less polar) was subjected to Beckmann rearrangement using *p*-toluenesulfonyl chloride and a catalytic amount of dimethylaminopyridine in pyridine to give desired δ-lactam (**2**) in a 54% yield. The spectral data (ir, nmr, ms) of **2** were identical with those recorded in the literature.[4] Since δ-lactam (**2**) has already been transformed into azetidinone (**12**), a known precursor for thienamycin (**1**), by Grieco *et al.*, [4] the preparation of **2** constitutes a formal total synthesis of thienamycin (**1**).

In summary, the usefulness of homoconjugate addition of alcohols to double activated cyclopropane has been shown in the form of the stereoselective synthesis of key intermediate for antibiotic thienamycin (**1**). Because enantiomeric isomers of cyclopropane (**3**) were obtained by Taber,[7] the optically active δ-lactam (**2**) would be obtained by the above process. The synthetic approaches to other biologically active compounds using the homoconjugate addition of various alcohols to activated cyclopropane derivatives are now in progress.




**Scheme 1.** Reagents and Conditions:
(a) BnOH, $BF_3{\cdot}OEt_2$, 60°C, 30 min, 45%; (b) $BrCH_2CO_2Me$, $K_2CO_3$, $Me_2CO$, reflux, 3 h, 62%; (c) LiCl, HMPA, 130°C, 4 h, 78%; (d) $(CH_2OH)_2$, *p*-TsOH, $C_6H_6$, reflux, 3 h, 92%; (e) $LiAlH_4$, $Et_2O$, 0°C, overnight; (f) 10% aq.HCl, THF, room temperature, 1 h, 98% (from 7); (g) TBDPSCl, imidazole, DMF, room temperature, 70 h, 81%; (h) $H_2NOH{\cdot}HCl$, NaOAc, EtOH, room temperature, 50 h, 70%; (i) *p*-TsCl, DMAP, pyridine, room temperature 30 min to 60°C 3 h, 54%.

## EXPERIMENTAL

Melting points (mp) are uncorrected. Infrared (IR) spectra were measured with a Hitachi 260-10 IR spectrophotometer. Nmr spectra were obtained with a JEOL JNM-GX 270 NMR spectrometer, using tetramethylsilane as an internal standard, and mass spectra were taken by a JEOL JMS-AX 500 mass spectrometer.

**2-Methoxycarbonyl-3-(1-benzyloxyethyl)cyclopentanone (4).** A solution of cyclopropane derivative (**3**) (6.0 g, 35.7 mmol), boron trifluoride etherate (0.51g, 3.57 mmol) in benzyl alcohol (4.2 g, 39.3 mmol) was stirred at 60 °C for 30 min. The mixture was diluted with ethyl acetate and washed with saturated aqueous solution of sodium hydrogen carbonate, water and brine. The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give the crude product, which was purified by chromaography on silica gel (elution with chloroform) to afford keto ester (**4**) (4.4 g, 45%) as an oil. Ir $\nu_{max}$ $cm^{-1}$: 2990, 1770, 1735, 1125, 705; $^1$H-nmr δ ($CDCl_3$): 1.23(3H, d, *J*=6.1 Hz), 1.50-2.83(5H, m), 3.12(1H, d, *J*=10.6 Hz), 3.45(1H, m), 3.61(3H, s), 4.48(2H, ABq, *J*=11.6 Hz, ΔνAB=73.9 Hz), 7.20-7.40(5H, m); ms *m/z* (%): 276($M^+$, 0.4), 217(0.6), 200(0.8), 181(1), 169(2), 141(7), 109(9), 91(100), 79(3), 65(5), 53(3), 41(3); HR-ms: found, *m/z* 276.1371($M^+$); calcd for $C_{16}H_{20}O_4$, 276.1361.

**2-Methoxycarbonyl-2-methoxycarbonylmethyl-3-(1-benzyloxyethyl)cyclopentanone (5).** A mixture of keto ester (**4**) (1.47 g, 5.3 mmol), methyl bromoacetate (1.22 g, 8.0 mmol) and anhydrous potassium carbonate (1.47 g, 10.6 mmol) in acetone (30 ml) was heated at reflux for 3 h. After cooling, the reaction mixture was filtered and concentrated *in vacuo* to give a crude keto diester. Chromatography on slica gel (eluting with 20% ethyl acetate in hexane) provided 1.15 g (62%) of keto diester (**5**). mp 82.5-83 °C; ir $\nu_{max}$ $cm^{-1}$: 2965, 1765, 1745, 1720, 705; $^1$H-nmr δ ($CDCl_3$): 1.24(3H, d, *J*=5.8 Hz), 1.79-2.15(2H, m), 2.49-2.78(3H, m), 3.32(2H, s), 3.40-3.60(1H, m), 3.54(3H, s), 3.60(3H, s), 4.36(2H, ABq, *J*=10.7 Hz, ΔνAB=73.7 Hz), 7.20-7.40(5H, m); ms *m/z* (%): 348($M^+$, 0.4), 330(0.8), 257(0.5), 242(2), 224(2), 210(2), 195(2), 185(6), 171(4), 150(3), 138(9), 122(19), 105(68), 91(100), 83(22), 77(48), 43(68); HR-ms: found, m/z 348.1572($M^+$); calcd for $C_{19}H_{24}O_6$, 348.1573; Anal. Calcd for $C_{19}H_{24}O_6$; C, 65.50; H, 6.94. Found for C, 65.45; H, 6.80.

**2-Methoxycarbonylmethyl-3-(1-benzyloxyethyl)cyclopentanone (6).** Lithium chloride (210 mg, 4.94 mmol) was dissolved in dry hexamethylphosphoric triamide (7 ml) at 130 °C under nitrogen atmosphere. Keto diester (**5**) (550 mg, 1.58 mmol) in hexamethyphosphoric triamide (2 ml) was added dropwise to the reaction solution, and the mixture was stirred for 4 h. After cooling, it was poured into 5% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The

residue was purified by chromatography on silica gel (eluting with 20% ethyl acetate in hexane) to give keto ester (**6**)(360mg, 78%) as an oil. Ir $\nu_{max}$ $cm^{-1}$: 2980, 1740, 700; $^1$H-nmr δ ($CDCl_3$): 1.25(3H, d, *J*=6.1 Hz), 1.40-2.45(6H, m), 2.84(2H, s), 3.50(1H, m), 3.57(3H, s), 4.51(2H, ABq, *J*=11.6 Hz, ΔνAB=67.1 Hz), 7.23-7.40(5H, m); ms *m/z* (%): 290($M^+$, 0.5), 272(0.8), 259(2), 231(0.6), 214(1), 198(6), 182(9), 167(9), 155(70), 138(5), 123(21), 105(28), 91(100), 79(7), 65(9), 51(9), 43(12); HR-ms: found, *m/z* 290.1490($M^+$); calcd for $C_{17}H_{22}O_4$, 290.1518.

**2-Methoxycarbonylmethyl-1-oxo-ethylene acetal-3-(1-benzyloxyethyl)cyclopentanone (7).** A solution of keto ester (**6**) (300 mg, 1.03 mmol), *p*-toluenesulfonic acid (3 mg) and ethylene glycol (513 mg, 8.28 mmol) in benzene (12 ml) was heated at reflux for 3 h with a Dean-Stark water separator. The solution was cooled, solid potassium carbonate was added, and the mixture was filtered and concentrated *in vacuo*. The residual oil was purified by chromatography on silica gel (eluting with 20% ethyl acetate in hexane) to give ethylene acetal (**7**) (316 mg, 92%) as an oil. Ir $\nu_{max}$ $cm^{-1}$: 2975, 1740, 1110, 700; $^1$H-nmr δ ($CDCl_3$): 1.16(3H, d, *J*=6.1 Hz), 1.20-2.60(8H, m), 3.39-3.50(1H, m), 3.59(3H, s), 3.70-3.96(4H, m), 4.50(2H, ABq, *J*=11.9 Hz, ΔνAB=44.4 Hz), 7.21-7.42(5H, m); ms *m/z* (%): 334($M^+$, 1), 303(2), 243(14), 228(6), 199(31), 182(2), 155(4), 139(7), 123(9), 99(93), 91(100), 86(13), 79(8), 67(9), 55(11), 43(13); HR-ms: found, *m/z* 334,1785($M^+$); calcd for $C_{19}H_{26}O_5$, 334.1781.

**2-(2-Hydroxyethyl)-3-(1-benzyloxyethyl)cyclopentanone (9).** A solution of acetal (**8**)(460 mg, 1.38 mmol) in dry ether (5 ml) was added to a suspension of lithium aluminium hydride (52 mg, 1.38 mmol) in dry ether (20 ml) at 20 °C. After stirring overnight at room temperature, the excess reagent was quenched by the dropwise addition of water. Finally, saturated aqueous solution of ammonium chloride (15 ml) was added, and two layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give crude alcohol (**8**), which was used without purification in the next reaction.

To a solution of above alcohol (**8**) in tetrahydrofuran (2 ml) was added 10% hydrochloric acid (2 ml). The mixture was stirred for 1 h at room temperature, diluted with ethyl acetate, and washed with saturated aqueous solution of sodium hydrogen carbonate. The resulting solution was dried over magnesium sulfate and concetrated *in vacuo*. The residue was purified by chromatography on silica gel (eluting with hexane-ethyl acetate=3:1) to give keto alcohol (**9**) (351 mg, 98%, from **7**) as an oil. Ir $\nu_{max}$ $cm^{-1}$: 3650-3200, 2985, 1740, 1080, 705; $^1$H-nmr δ ($CDCl_3$): 1.23(3H, d, *J*=6.1 Hz), 1.40-2.40(8H, m), 3.40-4.00(4H, m), 4.50(2H, ABq, *J*=10.9 Hz, ΔνAB=62.3Hz), 7.20-7.40(5H, m); ms *m/z* (%): 263($MH^+$, 1), 245(2), 199(2), 181(2), 165(2), 155(5),

137(12), 127(5), 111(16), 105(17), 91(100), 83(29), 77(10), 67(9), 55(24), 41(16); HR-ms: found, *m/z* 262.1564($M^+$); calcd for $C_{16}H_{22}O_3$, 262.1569.

**2-(2-*tert*-Butyldiphenylsilyloxyethyl)-3-(1-benzyloxyethyl)cyclopentanone (10).** Keto alcohol (**9**) (350 mg, 1.34 mmol) was dissolved in dimethylformamide (7 ml) and treated with *tert*-butylchlorodiphenylsilane (404 mg, 1.47 mmol) and imidazole (200 mg, 2.94 mmol) for 70 h at room temperature. The reaction mixture was diluted with ether, and successively washed with saturated aqueous solution of sodium hydrogen carbonate, water and brine. The residue was purified by chromatography on silica gel (eluting with hexane-ethyl acetate=10:1) to give silyl ether (**10**) (544 mg, 81%) as an oil. Ir $\nu_{max}$ $cm^{-1}$: 2925, 1735, 1425, 1110, 700; $^1$H-nmr δ ($CDCl_3$): 1.02(9H, s), 1.19(3H, d, *J*=6.4 Hz), 1.50-2.38(8H, m), 3.41-3.58(1H, m), 3.70-3.82(2H, m), 4.48(2H, ABq, *J*=11.5 Hz, ΔνAB=47.4 Hz), 7.20-7.68(15H, m); ms *m/z* (%): 443(M-*tert*-Bu, 2), 397(21), 335(20), 319(20), 275(9), 245(9), 217(7), 199(43), 181(8), 155(17), 137(24), 127(13), 109(81), 91(100), 77(35), 67(23), 55(24), 43(27); HR-ms: found, *m/z* 443.1945(M-*tert*-Bu); calcd for $C_{28}H_{31}O_3Si$, 443.2042. Anal. Calcd for $C_{32}H_{40}O_3Si$: C, 76.75; H, 8.05. Found: C, 76.55; H, 8.00.

**2-(2-*tert*-Butyldiphenylsilyloxyethyl)-3-(1-benzyloxyethyl)cyclopentanone oxime (11).** Cyclopentanone (**10**) (500 mg, 1.00 mmol) was dissolved in dry ethanol (10 ml) and treated with sodium acetate (98.4 mg, 1.20 mmol) and hydroxylamine hydrochloride (83.4 mg, 1.20 mmol) for 50 h at room temperature. The reaction mixture was diluted with ethyl acetate, water and brine. The resulting solution was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluting with hexane-ethyl acetate=10:1) to give desired *anti*-oxime (**11**) (317 mg, 70%, less polar) and *syn*-oxime (113 mg, 25%, more polar) as an oil. *Anti*-oxime (**11**): Ir $\nu_{max}$ $cm^{-1}$: 3500-3150, 2940, 1115, 705; $^1$H-nmr δ ($CDCl_3$): 1.03(9H, s), 1.13(3H, d, *J*=6.1 Hz), 1.40-2.70(8H, m), 3.40-3.48(1H, m), 3.80(2H, t, *J*=6.7 Hz), 4.45(2H, ABq, *J*=11.9 Hz, ΔνAB=36.1 Hz), 7.20-7.74(15H, m), 8.80(1H, br s). *Syn*-oxime: Ir $\nu_{max}$ $cm^{-1}$: 3500-3150, 2935, 1430, 1115, 705; $^1$H-nmr δ (CDCl3): 1.03(9H, s), 1.12(3H, d, J=6.1 Hz), 1.30-2.40(8H, m), 3.00-3.09(1H, m), 3.30-3.39(1H, m), 3.75(2H, t, J=6.7 Hz), 4.45(2H, ABq, J=11.9 Hz, ΔνAB=43.6 Hz), 7.20-7.74(15H, m); ms *m/z* (%): 458(M-*tert*-Bu, 11), 442(2), 396(6), 364(9), 335(5), 306(4), 199(69), 181(7), 171(6), 135(9), 105(11), 99(13), 91(100), 77(22), 67(9), 58(16); HR-ms: found, *m/z* 458.2173(M-*tert*-Bu); calcd for $C_{28}H_{32}NO_3Si$, 458.2152.

**5-(1-Benzyloxyethyl)-6-(2-*tert*-butyldiphenylsilyloxyethyl)-2-piperidinone (2).** To a stirred solution of *anti*-oxime(**11**)(50 mg, 0.1 mmol) in dry pyridine (1.6 ml) was added *p*-toluenesulfonyl chloride (46

mg, 0.24 mmol) and 4-(dimethylamino)pyridine (3 mg). The reaction was stirred for 30 min at room temperature, followed by heating at 65 °C for 3 h. The resulting dark brown solution was cooled to room temperature, and the pyridine was removed *in vacuo*. The residual oil was diluted with ethyl acetate, and washed with 10% hydrochloric acid, saturated aqueous solution of sodium hydrogen carbonate and brine. The resulting solution was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluting with ether-ethyl acetate=3:2) to give δ-lactam (**2**) (27 mg, 54%) as an oil. Ir $\nu_{max}$ $cm^{-1}$: 3450-3250, 2925, 1650, 1110, 695; $^1$H-nmr δ ($CDCl_3$): 1.05(9H, s), 1.18(3H, d, J=6.1 Hz), 1.55-1.79(4H, m), 1.91-2.05(11H, m), 2.18-2.39(2H, m), 3.55-3.79(4H, m), 4.50(2H, ABq, *J*=11.6 Hz, ΔνAB=42.1 Hz), 6.16(1H, br s), 7.25-7.75(15H, m); ms *m/z* (%): 458(M-*tert*-Bu, 25), 380(20), 290(21), 224(5), 199(39), 183(8), 135(8), 105(13), 91(100), 77(17), 57(16); HR-ms: found, *m/z* 458.2201(M-*tert*-Bu); calcd for $C_{28}H_{32}NO_3Si$, 458.2152.

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## REFERENCES

1. J. S. Kahan, F. Kahn, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, 1979, **32**, 1.
2. C. Palomo, in "Recent Progress in the Chemical Synthesis of Antibiotics" ed. by G. Lukacus and M. Ohno, Springer-Verlag, Berlin, Heidelberg, 1990, pp. 565-612.
3. S. Tanimori and M. Nakayama, *Agric. Biol. Chem.*, 1989, **53**, 2531.
4. P. A. Grieco, D. L. Flynn, and R. E. Zelle, *J. Am. Chem. Soc.*, 1984, **106**, 6414.
5. Recentry, we reported the same reaction using long-chain primary alcohol and its application for the synthesis of 22-oxa-vitamin $D_3$ derivatives; S. Tanimori, M. He, and M. Nakayama, *Synth. Commun.*, 1993, **23**, 2861.
6. Y. Morizawa, T. Hiyama, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 1123.
7. D. F. Taber, J. C. Amedio, Jr., and K. Raman, *J. Org. Chem.*, 1988, **53**, 2984.

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