Tetrahedron Vol. 37, pp. 715 to 719
Pergamon Press Ltd., 1981. Printed in Great Britain

0040-4020/81/0215-0715/$02.00/0

STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DCCLXII

ALTERNATIVE SYNTHESIS OF *TRANS*-3-(1'R*-HYDROXYETHYL)-4-(2',2'-DIMETHOXYETHYL)-2-AZETIDINONE, A SYNTHETIC INTERMEDIATE OF THIENAMYCIN

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(*Received in Japan* 28 *May* 1980)

Abstract—Synthesis of *trans*-3-(1'R*-hydroxyethyl)-4-(2',2'-dimethoxyethyl)-2-azetidinone (5), an important intermediate for the synthesis of thienamycin (1), was investigated starting from the isoxazoline derivatives 3 and 9. The most effective method was catalytic hydrogenation of *trans*-4-t-butoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methyl-isoxazoline (9) with Adams catalyst in acetic acid, followed by trimethylsilylation of the resulting epimeric aminoesters 11A and B, cyclization with EtMgBr, and deblocking. Novel reductions of the isoxazolines with sodium borohydride and nickel chloride or with diborane followed by catalytic hydrogenation were also reported.

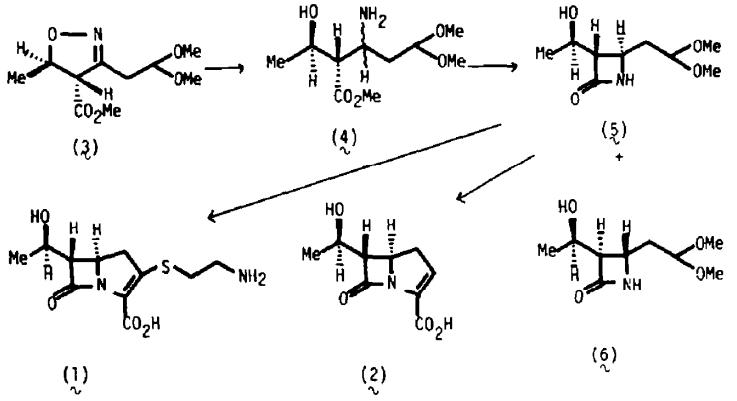
Thienamycin (1) is a highly potent and broad spectrum β-lactam antibiotic,[2,3] having a novel 6α-hydroxyethyl group on the β-lactam ring.[4] The unusual and desirable antibacterial activity has promoted a number of synthetic studies which have resulted in total synthesis of thienamycin[5] and simpler carbapenem analogs.[6-10] Recently, we reported a formal total synthesis of (±)-thienamycin and (±)-8R*-decysteaminylthienamycin (2) through the isoxazoline derivative 3.[11] This synthetic approach is expected to have some advantages over other synthetic methods[5-10,12] because the isoxazoline intermediate contains the hydroxyethyl moiety of thienamycin with the correct stereochemistry as the *erythro* form. However, since the main reduction product of 3 was the undesired stereoisomer, the required *trans*-azetidinone 5, synthesized from the resultant amino ester mixture 4 by formation of the lactam derived amino acid using N,N'-dicyclohexylcarbodiimide, was contaminated with its epimer 6, which was inseparable from 5. On the other hand, treatment of 4 with Grignard reagent selectively produced 5 in about 10% yield.[11] We therefore looked for a more effective synthesis of 5 and here report the improved results, including novel reduction of the isoxazoline and β-lactam formation.[13]

RESULTS AND DISCUSSION

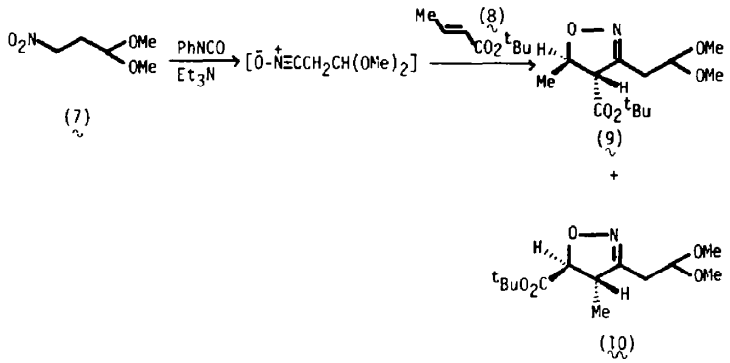
The reduction of the isoxazoline and β-lactam formation were studied in the methyl and t-butyl ester derivatives since a more favorable steric effect was anticipated in the latter case. The isoxazoline t-butyl ester was synthesized by a method similar to that used for the methyl ester 3.[11] Thus, the 1,3-dipolar cycloaddition of the nitrile oxide, formed *in situ* by the reaction of 3-nitropropanal dimethyl acetal[14] (7) and phenyl isocyanate in the presence of a catalytic amount of triethylamine,[15] with t-butyl crotonate[16] (8) was carried out at room temperature in benzene. The required adduct 9 was isolated as the main product along with a small of the regioisomer 10. After a short column chromatography on silica gel, 9 was obtained in 58% yield while 10 was gained in 14% yield.

Reduction of the isoxazolines

Initially catalytic hydrogenation of the isoxazolines using Pd, Pt, Rh and Ru catalyst were examined. Among them, only Adams catalyst gave clean reduced products when the reduction was carried out in glacial acetic acid under a medium pressure of hydrogen. As reported earlier,[11] the reduction of methyl ester 3 with Adams cata-



Scheme 1.



Scheme 2.

lyst under 6 atm of hydrogen yielded quantitatively a stereoisomeric mixture of the two aminoesters **4A** and **B** in a ratio of 2:5. The ratio of the two products was not affected by the hydrogen pressure. On the other hand the hydrogenation of t-butyl ester **9** under the same condition as above gave quantitatively the mixture of aminoesters **11A** and **B** in a ratio of 1:1. The former isomers **4A** and **11A** were the desired stereoisomers and showed lower *Rf* values than that of the epimers **4B** and **11B** on silica gel tlc.

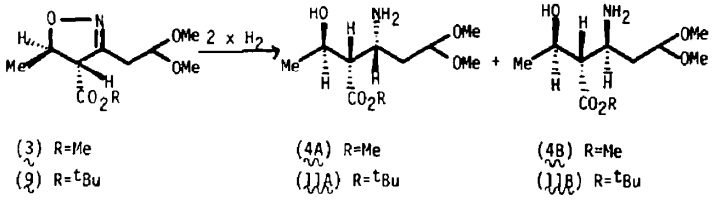
The isoxazolines **3** and **9** were reduced with sodium borohydride in the presence of transition metal salts. Treatments of **3** or **9** with sodium borohydride and nickel chloride or cobalt chloride[17] produced the aminoester **4A** or **11A** in poor yield but the stereoisomer **4B** or **11B** formed in trace yield. The methyl ester was stirred with sodium borohydride and nickel chloride hexahydrate in methanol at room temperature to afford the pure **4A** in 13% yield after chromatographic purification.

Reduction of the isoxazolines with sodium cyanoborohydride or diisobutylaluminum hydride were also tried, but aminoesters were not observed. A treatment of the t-butyl ester **9** with excess diborane at room temperature gave an adduct, the structure of which was obscure. Reduction of the resulting adduct with Adams catalyst under hydrogen atmosphere formed the aminoesters **11A** and **B** in 13 and 72% yields, respectively.

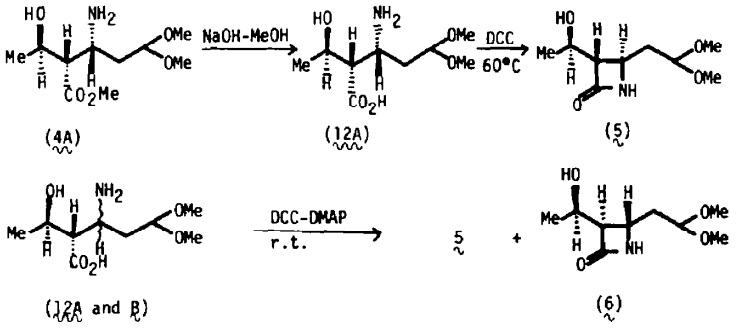
β-Lactam formation

After conversion of the pure aminoester **4A**, obtained by the reduction with sodium borohydride and nickel chloride, into the corresponding amino acid **12A**, heating **12A** with N,N'-dicyclohexylcarbodiimide in aqueous dioxane at 60° produced the desired β-lactam **5** as a single stereoisomer in 59% overall yield. It is clear from this experiment that the formation of the C_1-epimer **6** from the mixture of aminoesters **4A** and **B** by the same reaction conditions[11] was due to the epimerization of **4B**. The cyclization using N,N'-dicyclohexylcarbodiimide proceeded at lower temperature by addition of 4-dimethylaminopyridine[18] but the epimerization still occurred. Namely, after hydrolysis of the epimeric mixture of the aminoester **4A** and **B**,[11] prepared by reduction with Adams catalyst in acetic acid, the resulting amino acids **12A** and **B** were stirred with N,N'-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in a mixture of methylene chloride and acetonitrile at room temperature to give the mixture of **5** and **6** in a ratio of 1:2.5.

In order to prevent the undesired epimerization, direct ring closure of the aminoesters was investigated. Ac-



Scheme 3.



Scheme 4.

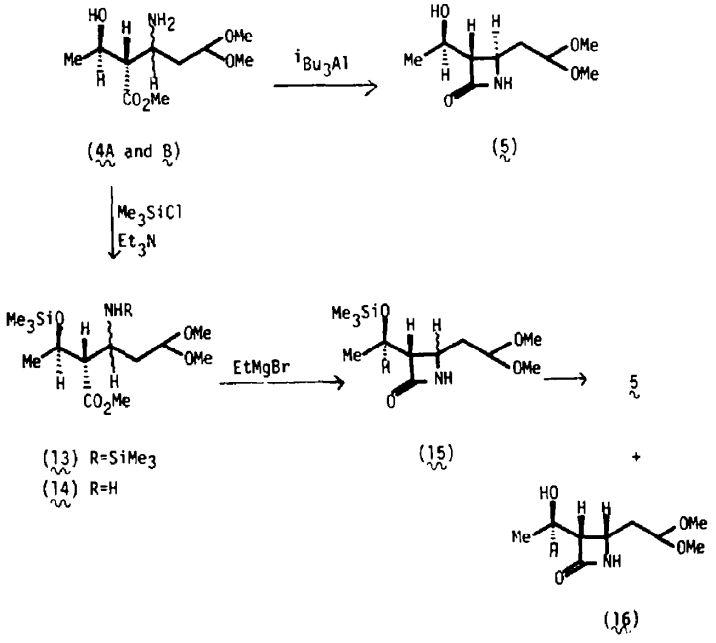
cording to Woodward's method,[19] the epimeric mixture of the aminoesters **4A** and **B** was treated with triisobutylaluminum to give only the desired azetidinone **5** in 11% yield. Consequently it was decided to determine whether protection of the OH group in the aminoesters would enable a more efficient conversion to **5**. Thus, treatment of the mixture of **4A** and **B** with excess trimethylsilyl chloride in the presence of triethylamine in benzene at room temperature, afforded the mixture of N,O-disilylated product **13**. When the reaction was carried out for a shorter period, using a limited amount of the reagents, stable trimethylsilyl ethers **14** were obtained. On treatment with excess EtMgBr[20] in THF at room temperature, both products **13** and **14** were effectively converted into a mixture of *trans*- and *cis*-azetidinones **15**, *m/e* 276($M^+ + 1$), in 63~78.3% yield. The IR spectrum ($CHCl_3$) of this product showed NH group absorption at 3425 cm^{-1} and CO group absorption at 1758 cm^{-1}. The trimethylsilyl group was observed as a singlet (9H) at 0.1 ppm in the NMR spectrum (CCl_4). Deprotection using aqueous ammonium chloride gave the *trans*- and *cis*-β-lactam **5** and **16**, which were separable by silica gel column chromatography. By this method the *trans*-β-lactam **5** was synthesized in 21% yield from the isoxazoline **3**, while **16** was produced in 38% overall yield.

Interestingly, the epimeric mixture of the t-butyl esters **11A** and **B**, obtained by hydrogenation using Adams catalyst, afforded only the *trans*-azetidinone **5** by the aforementioned reaction sequence; silylation, cyclization with EtMgBr, and deprotection. The undesired isomer **11B** in the aminoesters reacted with EtMgBr to give ether-soluble unidentified products. Therefore purification of the β-lactam **5** was readily achieved by utilizing its high water-solubility. According to this method, reduction with Adams catalyst followed by cyclization of the protecting aminoester, the thienamycin synthetic intermediate **5** was obtained in 41% overall yield from the isoxazoline **9**.

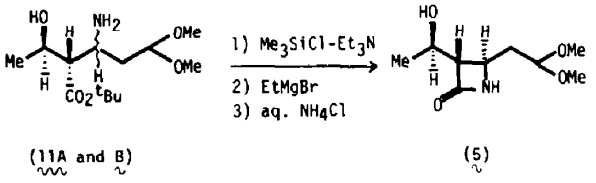
EXPERIMENTAL

General. IR spectra were obtained with a Hitachi 215 spectrometer, NMR spectra with a JNM-PM-60 instrument (TMS as an internal reference), and mass spectra with Hitachi M-52G and JMS-01SG-2 spectrometers.

trans - 4 - *t* - *Butoxycarbonyl* - 3 - (2',2' - *dimethoxyethyl*) - 5 - *methylisoxazoline* (**9**) *and* trans - 5 - *t* - *butoxycarbonyl* - 3 - (2',2' - *dimethoxyethyl*) - 4 - *methylisoxazoline* (**10**). Several drops of Et_3N were added to a mixture of **7**[14] (15.7 g), **8**[16] (15.0 g), and phenyl isocyanate (25 g) in dry benzene (200 ml). The resulting mixture was stirred for 16 hr at room temp under a current of N_2. After filtration of the mixture, the fitrate was washed with water,



Scheme 5.



Scheme 6.

dried over Na_2SO_4 and evaporated to give a viscous syrup. Distillation of the residue afforded a yellowish liquid (b.p. 115~125° at 0.3 mmHg), which was further pruified by silica gel column chromatography. Evaporation of the ether - n - hexane (1:4 v/v) eluate gave **9** (16.5 g, 58%) as a yellowish oil; IR ν_{max} ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.33 (3H, d, J = 6 Hz, C_5–Me), 1.46 (9H, s, 3 × Me), 2.66 [2H, m, $CH_2CH(OMe)_2$], 3.26 and 3.30 (each 3H, each s, 2 × OMe), 3.43 (1H, d, J = 9 Hz, C_4–H), 4.56 [1H, t, J = 6 Hz, $CH(OMe)_2$], 4.63 (1H, m, C_5–H); MS *m/e* 274 (M^+ + 1), 273 (M^+); *m/e* 273.1585 (Calc. for $C_{13}H_{23}NO_5$: M^+ *m/e* 273.1575).

Evaporation of the CH_2Cl_2 eluate gave the isomer **10** (4 g, 14%) as a yellowish oil, IR ν_{max} ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.27 (3H, d, J = 7 Hz, C_4–Me), 1.47 (9H, s, 3 × Me), 2.53 [2H, t, J = 6 Hz, $CH_2CH(OMe)_2$], 3.30 (6H, s, 2 × OMe), 4.23 (1H, d, J = 6 Hz, C_5–H), 4.50 (1H, t, J = 6 Hz, $CH(OMe)_2$]; MS *m/e* 274 (M^+ + 1), 273 (M^+); *m/e* 273.1555 (Calc. for $C_{13}H_{23}NO_5$: M^+ *m/e* 273.1575).

Methyl 3 - amino - 5 - hydroxy - 1,1 - dimethoxyhexane - 4 - carboxylate (**4A**). *trans*-3[11] (1 g) and $NiCl_2 \cdot 6H_2O$ (1.25 g) were dissolved in MeOH (50 ml) and $NaBH_4$ (0.82 g) was added to the above mixture under stirring at the rate that the temp was maintained at 15~25°. The resulting mixture was stirred for 1 hr at room temp. After evaporation of the solvent, the residue was partitioned between conc. ammonia and $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to give a residue, which was subjected to silica gel chromatography. Evaporation of the MeOH–CH_2Cl_2 (1:50 v/v) eluate gave **4A** (128 mg, 13%) as a yellowish oil, IR ν_{max} ($CHCl_3$) 1725 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 [3H, d, J = 6.6 Hz, MeCH(OH)], 1.86 (2H, dd, J = 5.6 and 6.6 Hz, C_2–H_2), 3.21 (2H, s, NH_2 disappeared by D_2O), 3.37 (6H, s, 2 × OMe), 3.77 (3H, s, OMe), 4.33 (1H, dq, J = 6 and 6.6 Hz, C_5–H), 4.57 [1H, t, J = 5.6 Hz, $CH(OMe)_2$]; MS *m/e* 236 (M^+ + 1); *m/e* 236.1490 (Calc. for $C_{10}H_{22}NO_5$: M^+ + 1 *m/e* 236.1497).

t - Butyl 3 - amino - 5 - hydroxy - 1,1 - dimethoxyhexane - 4 - carboxylates (**11A** *and* **11B**)

(a) To a soln of **9** (669 mg) in dry THF (10 ml), 1M BH_3. THF (4.95 ml) was added at 0~16°. The mixture was stirred for 16 hr at room temp under a current of N_2. After addition of 10% NaOH, the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The resulting oily residue was dissolved in AcOH (10 ml) and then stirred for 16 hr with PtO_2 (100 mg) under a current of H_2 (1 atm) at room temp. After filtration, the filtrate was concentrated under reduced pressure at 40° to afford a residue, which was partitioned between $CHCl_3$ and 10% NH_4OH. The $CHCl_3$ extract was washed with brine, dried over Na_2SO_4, and evaporated to give a syrup, which was subjected to silica gel chromatography. Evaporation of the MeOH–$CHCl_3$ (1:49 v/v) eluate gave **11B** (488 mg, 72%) as a colorless oil, NMR ($CDCl_3$)δ 1.16 [3H, d, J = 6 Hz, MeCH(OH)], 1.43 (9H, s, 3 × Me), 3.33 (6H, s, 2 × OMe), 3.83~4.26 (1H, m, C_5–H), 4.58 [1H, t, J = 6 Hz, $CH(OMe)_2$]; MS *m/e* 278 (M^+ + 1), 277 (M^+); *m/e* 277.1870 (Calc. for $C_{13}H_{27}NO_5$: M *m/e* 277.1888).

Evaporation of the MeOH-$CHCl_3$ (3:47 v/v) eluate afforded **11A** (88 mg, 13%) as a colorless oil: NMR ($CDCl_3$) δ 1.28 [3H, d, J=6 Hz, MeCH(OH)], 1.50 (9H, s, 3×Me), 3.40 (6H, s, 2× OMe), 4.03~4.43 (1H, m, C_5–H), 4.53 [1H, t, J = 6 Hz, $CH(OMe)_2$]; MS *m/e* 278 (M^+ + 1), 277 (M^+); *m/e* 277.1921 (Calc. for $C_{13}H_{27}NO_5$: M^+ *m/e* 277.1888).

(b) PtO_2 (80 mg) was shaken for 15 min under a current of H_2 in AcOH (15 ml) and **9** (500 mg) was added. The mixture was shaken for 2 days under a current of H_2 (4.5~5 atm) at room temp. After filtration, the filtrate was concentrated at 40° under reduced pressure to give a residue, which was dissolved in $CHCl_3$ and washed with 10% NH_4OH and brine. The extract was dried over Na_2SO_4 and evaporated to afford the epimeric mixture of **11A** and **B** (507 mg, 100%) as a colorless oil, NMR spectrum ($CDCl_3$) of which indicated it to be a mixture of **11A** and **B** in the ratio of 1:1.

trans - 3 - (1'R* *and* S* - *Hydroxyethyl*) - 4 - (2',2' - *dimethoxyethyl*) - 2 - *azetidinones* (**5** *and* **6**). A mixture of the methyl esters[11] **4A** and **B** (1.98 g), prepared by the reduction with H_2-Adams Pt in AcOH, Na (0.23 g) and several drops of H_2O in MeOH (10 ml) was stirred for 20 hr at room temp. After evaporation of the solvents, the residue was dissolved in H_2O and adjusted to pH 7.0 with dil. H_2SO_4. The mixture was dried by distillation of H_2O under reduced pressure and the residue was extracted with EtOH. The extract was evaporated to give a yellowish syrup, which was dissolved in CH_2Cl_2–CH_3CN (10:3 v/v) (130 ml). After addition of 4 - dimethylaminopyridine (100 mg) and N,N' - dicyclohexylcarbodiimide (1.74 g), the mixture was stirred for 24 hr at room temp. After filtration, the solvents were removed by distillation under reduced pressure to give a yellowish syrup, which was subjected to silica gel chromatography. Evaporation of the benzene–acetone (3:1 v/v) eluate gave the mixture of **5** and **6** (410 mg, 24%) as a colorless syrup, NMR spectrum ($CDCl_3$) of which indicated it to be a mixture of **5** and **6** in the ratio of 1:2.5.

trans *and* cis - 3 - (1'R* - *Hydroxyethyl*) - 4 - (2',2' - *dimethoxyethyl*) - 2 - *azetidinones* (**5** *and* **16**). To a mixture of **4A** and **B**[11] (1.497 g) and Et_3N (1.60 g) in dry benzene (15 ml), a soln of Me_3SiCl (1.728 g) in dry benzene (5 ml) was slowly added under cooling with ice. The mixture was stirred for 8 hr at room temp under a current of N_2. After filtration, the filtrate was evaporated to give a syrup, which was dissolved in dry THF (25 ml). 3M - EtMgBr·Et_2O (6.3 ml) was slowly added to the mixture under cooling with ice and a current of N_2. The resulting mixture was stirred for 15 hr at room temp under a current of N_2. H_2O (1.5 ml) was added drop by drop under cooling with ice and the mixture was stirred for 30 min at room temp. After addition of CH_2Cl_2 (50 ml), the mixture was well stirred and filtered. The filtrate was evaporated to give a residue, which was subjected to short column chromatography on silica gel. Evaporation of acetone–benzene (1:4 v/v) eluate afforded the epimeric mixture of **15** (1.375 g, 79%) as a yellowish oil; IR ν_{max} ($CHCl_3$) 3425 (NH), 1758 (C=O); NMR (CCl_4) δ 0.1 (9H, s, $OSiMe_3$), 1.15–1.40 (3H, C_1 – Me), 3.3 (6H, s, 2 × OMe), 7.4 br (1H, s, NH); MS *m/e* 276 (M^+ + 1), *m/e* 276.1592 (Calc. for $C_{12}H_{26}NO_4Si$: (M^+ + 1) *m/e* 276.1629). This compound was used for the next reaction without further purification. The mixture of the above **15** (1.375 g), NH_4Cl (0.294 g), H_2O (30 ml) and ether (5 ml) was stirred for 20 hr at room temp. The aqueous layer was evaporated to give a residue which was extracted with CH_2Cl_2. After evaporation of the solvent, the resulting syrup was subjected to silica gel column chromatography. Evaporation of the acetone–benzene (3:17 v/v) eluate afforded the *cis*-**16** (494 mg, 38%) as a colorless syrup, whose spectral data and tlc behaviors were identical with those of the authentic sample.[11]

Evaporation of the acetone–benzene (1:3 v/v) eluate gave the *trans*-**5** (266 mg, 21%) as a colorless syrup, which was identical with the authentic sample[11] on the comparison of IR and NMR spectra and tlc.

trans - 3 - (1'R* - *Hydroxyethyl*) - 4 - (2',2' - *dimethoxyethyl*) - 2 - *azetidinone* (**5**)

(a) A mixture of **4A** (880 mg), prepared by the reduction with $NiCl \cdot 6H_2O$ and $NaBH_4$, NaOH (165 mg) and several drops of H_2O in MeOH (30 ml) was stirred for 48 hr at room temp. After evaporation of the solvent at 30°, the residue was dissolved in H_2O (20 ml) and adjusted to pH 7 with dil. H_2SO_4 under cooling with ice. The mixture was evaporated to dryness and the residue was extracted with $CHCl_3$–EtOH (1:1 v/v). After filtration and evaporation of the solvent, the residue was dissolved in dioxane (18 ml) and H_2O (8 ml). The resulting solution was stirred with N,N' - dicyclohexylcarbodiimide (678 mg) for 10 hr at 60° under a current of N_2. After filtration, the solvents were removed by distillation and the resulting viscous syrup was partitioned between H_2O and ether. The aqueous soln was evaporated to give a syrup, which was subjected to silica gel chromatography. Evaporation of the acetone–benzene (1:3 v/v) eluate afforded **5** (449 mg, 59%) as a colorless syrup, whose spectral data and tlc behaviors were identical with those of the authentic sample.

(b) To a stirred soln of **12A** and **B**[11] (1.83 g), prepared by the reduction with H_2-Adams Pt in AcOH, in dry toluene (70 ml), 15% $^tBu_3Al$–hexane (61.6 ml) was slowly added under cooling

with ice and the mixture was stirred for 6 days at room temp under a current of N_2. Ice (12 g) was added in small portions during 5 hr. The organic layer was separated by decantation and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to give a yellow syrup, which was subjected to silica gel chromatography. Evaporation of the acetone–benzene (1:3 v/v) eluate afforded **5** (174 mg, 11%) as a colorless syrup, which was identified by tlc behavior and spectral comparison.

(c) To a mixture of **11A** and **B** (0.564 g), prepared by the reduction with H_2–Adams Pt in AcOH, and Et_3N (1.1 g) in dry benzene (5 ml), a soln of Me_3SiCl (1.6 g) in dry benzene (5 ml) was slowly added under cooling with ice. After stirring for 8 hr at room temp under a current of N_2 followed by filtration, the filtrate was evaporated. The resulting syrup was dissolved in dry THF (10 ml) and 3M-EtMgBr·Et_2O (3 ml) was slowly added to the stirring mixture under cooling with ice and a current of N_2. The resulting mixture was stirred for 40 hr at room temp under a current of N_2. After evaporation of the solvents, H_2O (1.0 ml) was slowly added to the residue under cooling with ice. After stirring for 30 min at room temp, the product was extracted several times with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated to give a syrup, to which a soln of NH_4Cl (200 ml) in H_2O (10 ml) and ether (5 ml) were added. The resulting mixture was stirred for 16 hr at room temp. After evaporation of the aqueous layer, the residue was subjected to silica gel chromatography. Evaporation of the acetone–benzene (1:3 v/v) eluate afforded the β-lactam **5** (170 mg, 41%) as a colorless syrup, which was identical with the authentic sample by comparison of IR and NMR spectra and tlc behaviors.

Acknowledgements—We thank Prof. H. Vorbrüggen for his kind gift of 4 - dimethylaminopyridine. We are also grateful to Mr. K. Kawamura, Miss Y. Enomoto, Mrs. R. Kobayashi, Miss Y. Kato, Miss K. Kikuchi and Miss K. Ohtomo for spectral measurements and for preparation of the manuscript.

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