Tetrahedron Vol. 41, No. 2, pp. 387 to 392, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

A NOVEL SYNTHESIS OF (±)-3-AMINONOCARDICINIC ACID[1]

K. CHIBA, M. MORI and Y. BAN*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

(*Received in Japan* 19 *April* 1984)

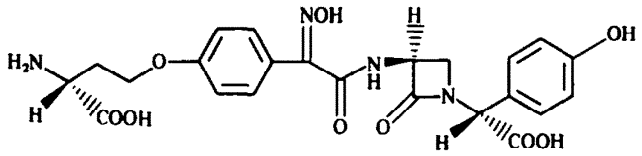
Abstract—(±)-3-Aminonocardicinic acid (3-ANA, **2**), which is an important material for the synthesis of nocardicin A (**1**) and other biologically active analogues, has been synthesized by the application of a new method for the synthesis of α-methylene-β-lactams.

Nocardicin A (**1**) was isolated as the major product from the fermentation broth of *Nocardia uniform* subsp. *tsuyamanesis* ATTS 21806 by Imanaka *et al.*,[2] whose structure was elucidated by Kamiya *et al.*,[3] providing the first example of the new type of monocyclic β-lactam antibiotics. Much attention has been paid to these new antibiotics, since they have been found to be active against a broad spectrum of Gram-negative bacteria.

As 3-aminonocardicinic acid (3-ANA, **2**) is an important starting material for the synthesis of biologically active nocardicin derivatives, this compound had been synthesized independently by several groups[4] by different synthetic methods of β-lactam skeleton before our work. We also developed a general method for the synthesis of β-lactam **4** from 2-bromoallylamine derivative **3** using palladium catalyzed carbonylation,[5] which method was extended to the new synthesis of 3-ANA. The details of this approach are described in this paper.

For the formation of β-lactam skeleton of 3-ANA, the insertion of carbon monoxide into 2-bromoallylamine derivative **3** could be effected, which was prepared from *p*-hydroxyphenylglycine and 2,3-dibromopropene. Protection of amino group of (±)-*p*-hydroxyphenylglycine (**5**) with *t*-butoxycarbonyl azide gave **6** in good yield. Dibenzylation of **6** with benzyl bromide in the presence of potassium carbonate, followed by selective removal of the protecting group with hydrogen chloride in methylene chloride afforded the primary amine hydrochloride **7**. Compound **7** was then condensed with 2,3-dibromopropene in the presence of potassium carbonate in methylene chloride to give the 2-bromoallylamine derivative **8** in good yield. Insertion of carbon monoxide into **8** was effected in the presence of 2 mol% of $Pd(OAc)_2$, 8 mol% of PPh_3 and 1.2 mol eq. of n-Bu_3N in hexamethylphosphoroamide (HMPA) at 100° for 3 hr to afford the desired α-methylene-β-lactam **9b** in 37% yield. The yield was raised to 63% when the reaction was conducted under 4 atm of carbon monoxide at 80° for 38 hr, but the desired product was not obtained at room temp under the same conditions (Table 1).

As a model method for the conversion of α-methylene



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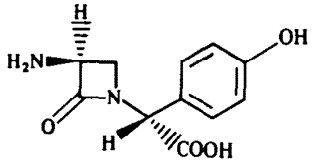
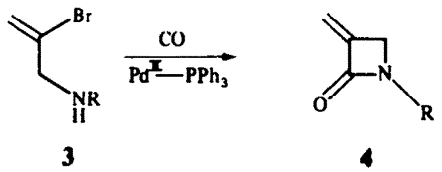
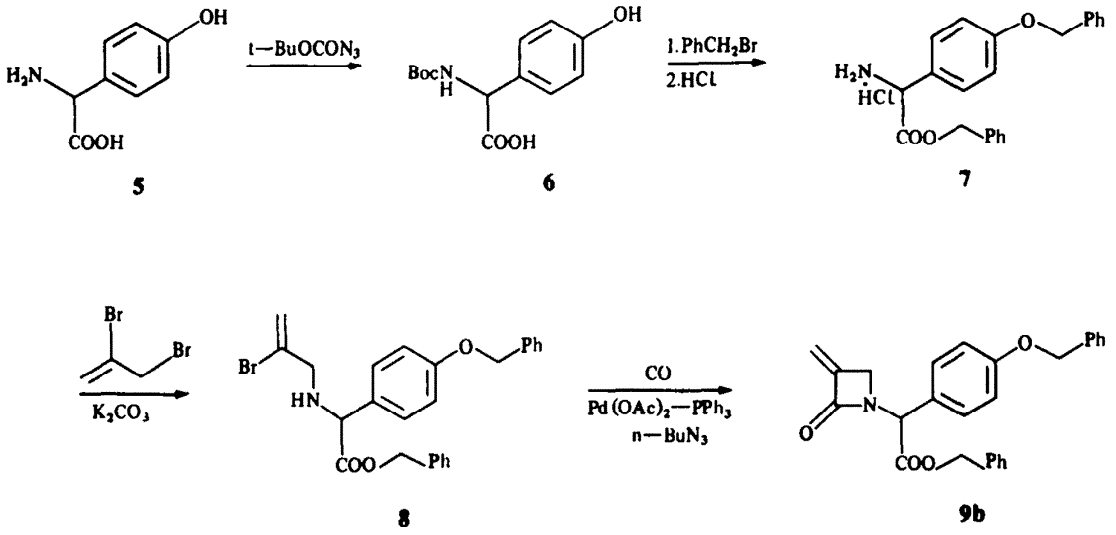


3-ANA **2**



3 **4**

Scheme 1.



Scheme 2.

Table 1. Various conditions for the synthesis of **9b**

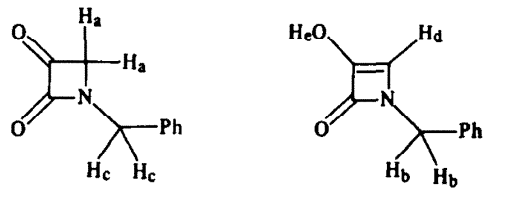
CO pressure (atm)	Reaction temp (°)	Reaction time (hr)	Yield of **9b** (%)
1	100	3	36.5
4	25	6	0
4	80	38	62.7

group into a 3-amino group, 1-benzyl-3-methylene-β-lactam (**9a**), which was easily prepared by the insertion of carbon monoxide into N-benzyl-2-bromoallylamine (**3**, R = CH_2Ph),[5] was oxidized with a catalytic amount of osmium tetroxide in the presence of N-methyl morpholine N-oxide[6] to furnish the diol **10a** in the yield of 94%. This diol was cleaved with sodium metaperiodate in aqueous tetrahydrofuran to give the ketolactam **11a** in a quantitative yield. The NMR spectrum of this ketolactam **11a** in carbon tetrachloride showed five singlet peaks except the peaks of the aromatic protons, but its spectrum in CD_3OD—CD_3COCD_3 showed only two peaks. Since it was known that the enol conformer was predominant in non-polar solvent,[7] the peaks at δ 4.72 and 6.25 in carbon tetrachloride were assigned to H_d and H_e of the enol form of **12a**, respectively. These results suggest that this compound exists in carbon tetrachloride as a mixture of keto and enol tautomers in a ratio of 1 : 1 (Table 2).

The ketolactam was immediately converted into the oxime **13a** with hydroxylamine, which was treated with acetic anhydride in the presence of sodium acetate in ethyl acetate and then hydrogenated with platinum oxide under several atoms of hydrogen to give 3-acetylamino-1-benzyl-β-lactam (**14a**).

It seemed significant that the α-methylene group of **9a** could be converted into 3-acetylamino group in good yield, because monocyclic β-lactams, namely the so-called "monobactams", which exhibit the activities against Gram-negative organisms,[8] might be synthesized by the present palladium catalyzed carbonylation. Subsequently, we attempted to convert the α-methylene group of **9b** to amino group in the same manner for the synthesis of 3-ANA. Treatment of **10b** with osmium tetroxide and N-methyl morpholine N-oxide followed by oxidation with sodium metaperiodate afforded the desired ketolactam **11b** in good yield. The NMR spectrum of **11b** showed that this compound exists as the keto-form even in carbon tetrachloride. The ketolactam was treated with hydroxylamine to afford the oxime **13b**, which was converted into a diastereomeric mixture of the desired 3-acetylamino-β-lactams **14b** and **14b'** of unknown stereochemistry. Various attempts to remove the N-acetyl group of **14a** or **14b** were unsuccessful. Therefore, hydrogenation of the oxime **13b** with rhodium on alumina under several atm pressure of hydrogen afforded a mixture of diastereomers, which was separated by preparative thin layer chromatography on silica gel into **15b** and **15b'** in a ratio of 1.2 : 1. Each isomer was treated with acetic anhydride in the presence of pyridine to afford **14b** and **14b'**, respectively. The compound **15b** was treated with *p*-toluenesulfonic

Table 2. NMR spectrum of compounds **11a** and **12a** in CCl_4 and CD_3OD—CD_3COCD_3—$CDCl_3$



11a	**12a**
CD_3OD—CD_3COCD_3—$CDCl_3$	CCl_4
δ 3.30 (s, 2H, H_a) 4.45 (s, 2H, H_c)	δ 3.24 (s, H_a) 3.71 (s, H_b) 4.40 (s, H_c) 4.72 (s, H_d) 6.25 (br s, H_e)

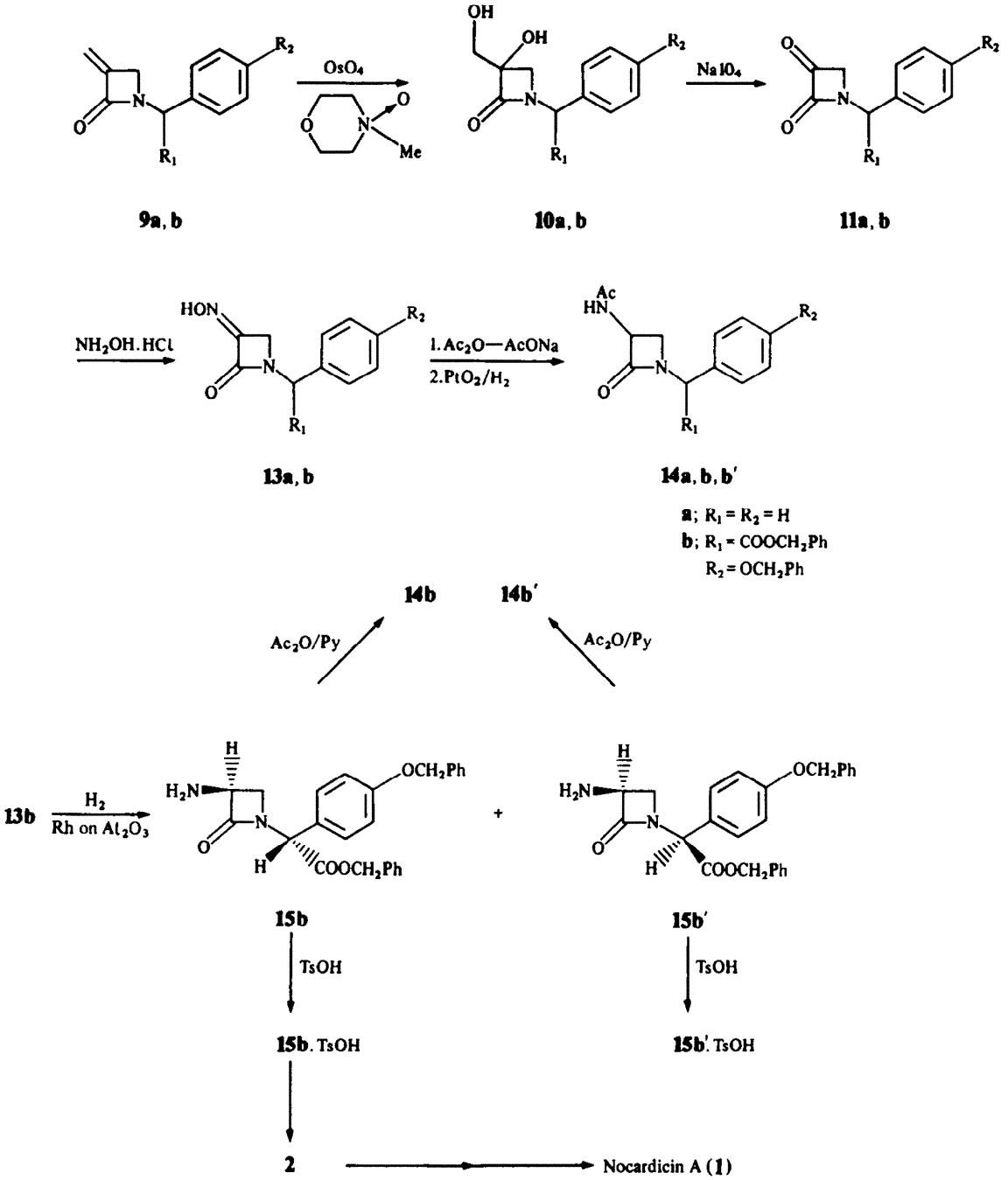
acid in ethyl acetate to give **15b**·TsOH, which was identical (NMR, IR and mass spectra and mixed m.p.) with an authentic sample kindly provided by Professor Wasserman. The hydrotosylate of the other stereoisomer **15b'** was also prepared to give **15b'**·TsOH in the same manner and its structure was confirmed mainly by spectral data.

Compound **15b**·TsOH is readily converted into **2**,[4b] thus the present synthesis of dibenzyl 3-ANA hydrotosylate (**15b**·TsOH) constitutes a formal synthesis of nocardicin A.

EXPERIMENTAL

M.ps were measured with a hot stage microscope (Yanaco MP-J2) and with an m.p. apparatus (Yamato MP-1) and are uncorrected. ^{1}H-NMR spectra were reported in the indicated solvent on a Hitachi R-20B (60 MHz), a JEOL JNM-FX 100 (100 MHz) and JEOL JNM-FX 200 (200 MHz) spectrometers with Me_4Si as an internal standard. A Jasco IRA-2 diffraction grating infrared spectrophotometer and a Hitachi RMU-7M double focussing mass spectrometer were used, respectively, to determine IR and mass spectra.

N-t-Butoxycarbonyl-p-hydroxyphenylglycine (**6**). To a soln



Scheme 3.

of t-BuOCON$_2$H$_3$ (10 g, 75.8 mmol) in AcOH (9 ml) and water (12 ml) was added a soln of $NaNO_2$ (6.26 g, 90.9 mmol) in water (8 ml) and a soln was stirred at room temp for 1 hr. The oily product was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with 4% $NaHCO_3$ aq and water, dried over Na_2SO_4 and evaporated. To a soln of the residue dissolved in THF–dioxane–water (9:9:2, 400 ml) was added *p*-hydroxyphenylglycine (**5**, 8.35 g, 50 mmol) and $NaHCO_3$ (10.6 g, 126 mmol) and a mixture was warmed at 40–50° for 69 hr. Solvent was evaporated under reduced pressure and water was added to the residue. The aqueous layer was washed with EtOAc, acidified with 0.5 M citric acid soln, satd with NaCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give brown solids of **6** (10.91 g, 81.7%). IR ν ($CHCl_3$) cm^{-1}: 3425 (NH), 1700 (C=O).

Benzyl p-*benzyloxyphenylglycinate hydrochloride* (**7**). To a soln of **6** (8.94 g, 33.5 mmol) and K_2CO_3 (13.8 g, 100 mmol) in DMF (60 ml) was added a soln of benzyl bromide (11.7 g, 68.7 mmol) in DMF (30 ml) and a mixture was stirred at room temp for 50 hr. Water was added to the soln and the aqueous layer was dried over $MgSO_4$ and evaporated. The residual oil was purified by chromatography on silica gel eluted with n-hexane–Et_2O (2:1) to give colorless solids of benzyl N-t-butoxycarbonyl-*p*-benzyloxyphenylglycinate (12.19 g, 81.5%). IR ν (neat) cm^{-1}: 3370 (NH), 1730 (C=O), 1710 (C=O). To a soln of the above product (5.25 g, 11.7 mmol) in CH_2Cl_2 (35 ml) was passed dry hydrogen chloride in an ice bath for 20 min. After standing at room temp overnight, white ppts were filtered off and washed with CH_2Cl_2 to give **7** (4.1 g, 91.3%), which was recrystalized from EtOH—Et_2O, m.p. 160–164° (colorless plates). IR ν (Nujol) cm^{-1}: 2720, 2670, 2580 (NH), 1735 (C=O). (Found: C, 69.13; H, 5.78; N, 3.44; Cl, 9.18. Calc for $C_{22}H_{22}ClNO_3$: C, 68.83; H, 5.78; N, 3.65; Cl, 9.24%.)

Benzyl N - (2 - *bromo* - 2 - *propenyl*) - p - *benzyloxyphenylglycinate* (**8**). A mixture of 2,3-dibromopropene (5.67 g, 28.3 mmol), **7** (7.245 g, 18.9 mmol), K_2CO_3 (5.22 g, 37.8 mmol) and KI (314 mg, 1.89 mmol) in CH_3CN (55 ml) was stirred at room temp for 3 days. Solvent was removed under reduced pressure and water was added to the residue. The aqueous layer was extracted with ether and the organic layer was dried over $MgSO_4$ and evaporated. The residual oil was purified by chromatography on silica gel eluted with n-hexane–ether (4:1) to give a pale yellow oil of **8** (7.177 g, 81.6%), which was crystallized in an ice-box, m.p. 42–44° (from ether). IR ν (neat) cm^{-1}: 3340 (NH), 1730 (C=O), 1625 (C=C). NMR ($CDCl_3$): δ 2.23 (s, 1H, NH), 3.37 (s, 2H, NCH_2), 4.37 (s, 1H, NCH), 5.01 (s, 2H, $PhCH_2O$), 5.09 (s, 2H, $PhCH_2OCO$), 5.51 (d, 1H, J = 1.5 Hz, vinyl), 5.67 (d, 1H, J = 1.5 Hz, vinyl), 6.88 (d, 2H, J = 9 Hz, aromatic), 7.15–7.50 (m, 12H, aromatic). MS *m/e* 333, 331, 332, 330, 250, 241, 239, 91. (Found: C, 64.22; H, 5.17; N, 2.75; Br, 17.23. Calc for $C_{25}H_{24}BrNO_3$: C, 64.39; H, 5.19; N, 3.00; Br, 17.13%.)

Benzyl α - (2 - *oxo* - 3 - *methylene* - 1 - *azetidinyl*) - p - *benzyloxyphenylacetate* (**9b**). A soln of **8** (2.797 g, 6.0 mmol), $Pd(OAc)_2$ (27 mg, 0.12 mmol), PPh_3 (126 mg, 0.48 mmol) and n-Bu_3N (1.33 g, 7.20 mmol) in HMPA (12 ml) was warmed at 75–80° under 4 kg/cm^2 pressure of CO for 38 hr. After cooling, ether was added to the mixture and the organic layer was washed with 0.2 N HCl soln and water, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on silica gel eluted with n-hexane–ether (1:1) to give colorless crystals of **9b** (1.554 g, 62.7%) and the starting material **8** (134 mg, 4.8%), m.p. 89.5–90.5° (from ether–petroleum ether); IR ν (Nujol) cm^{-1}: 1745 (C=O), 1730 (C=O). NMR (CCl_4): δ 3.45 (d, 1H, J = 7 Hz, H-4), 4.00 (d, 1H, J = 7 Hz, H-4), 4.98 (s, 2H, $PhCH_2OAr$), 5.00 (m, 1H, vinyl), 5.10 (s, 2H, $PhCH_2OCO$), 5.55 (s, 1H, NCH), 5.60 (m, 1H, vinyl), 6.70–7.35 (m, 14H, aromatic). MS *m/e* 413 (M^+), 278, 211, 91. (Found: C, 75.43; H, 5.83; N, 3.47. Calc for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39%.)

1 - *Benzyl* - 3 - *hydroxy* - 3 - *hydroxymethyl azetidin* - 2 - *one* (**10a**). To a soln of N-methyl morphorine N-oxide (1.75 g, 11.4 mmol) and OsO_4 (1% t-BuOH soln, 1.09 ml, 0.043 mmol) in water–acetone (3:1, 8 ml) was added a soln of **9a** (1.857 g, 10.7 mmol) in acetone (2 ml) under N_2 in a water bath. After stirring for one week, a mixture of sodium hydrogensulfite (0.125 g) and magnesium silicate (1.5 g) in water (10 ml) was added to the soln and the mixture was stirred for 15 min. Undissolved material was filtered off and the filtrate was acidified with 5% H_2SO_4 and saturated with NaCl. The aqueous layer was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Solvent was removed to give colorless crystals of **10a** (2.077 g, 93.7%), m.p. 104–105° (from $CHCl_3$). IR ν ($CHCl_3$) cm^{-1}: 3350 (OH), 1730. NMR ($CDCl_3$): δ 3.13 (d, 1H, J = 5 Hz, H-4), 3.40 (d, 1H, J = 5 Hz, H-4), 3.76 (s, 2H, CH_2OH), 4.35 (br s, 1H, OH), 4.41 (s, 2H, NCH_2Ph), 5.84 (br s, 1H, OH), 7.25–7.45 (m, 5H, aromatic). MS *m/e* 133, 132, 105, 104, 91. (Found: C, 63.62; H, 6.30; N, 6.69. Calc for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%.)

1-*Benzyl azetidine*-2,3-*dione* (**11a**). To a soln of **9a** (255 mg, 1.23 mmol) in THF (3 ml) and water (1 ml) was added sodium metaperiodate (395 mg, 1.84 mmol) at room temp for 2 hr. Ether was added to the mixture and the organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel eluted with CH_2Cl_2—MeOH (20:1) to give a colorless solid, **11a** (208 mg, 96.7%). IR ν (neat) cm^{-1}: 3300 (OH), 1830 (C=O), 1750 (C=O). NMR (CCl_4): δ 3.24 (s), 4.40 (s), 4.72 (s), 6.25 (br s), 7.26 (s), 7.32 (s); (CD_3OD—CD_3COCD—$CDCl_3$): δ 3.30 (s, 2H, H-4), 4.45 (s, 2H, NCH_2Ph), 7.25–7.40 (m, 5H, aromatic). MS *m/e* 133, 119, 105, 104, 91.

1-*Benzyl azetidine*-2,3-*dion*-3-*oxime* (**13a**). To a soln of **9a** (1.035 g, 5.00 mmol) in THF (3.6 ml) and water (1.2 ml) was added sodium metaperiodate (1.605 g, 7.50 mmol) at room temp for 70 min and the mixture was stirred for 2 hr. Ether was added to the mixture and the organic layer was dried over $MgSO_4$ and concentrated. To the residual oil **11a**, dissolved in dry pyridine (5 ml), was added $NH_2OH \cdot HCl$ (0.695 g, 10.0 mmol) and the solution was stirred at room temp for 24 hr. Water was added and the aqueous layer was extracted with EtOAc. The residue was purified by chromatography on silica gel eluted with CH_2Cl_2—MeOH (20:1) to give colorless prisms of **13a** (618 mg, 65.2%), m.p. 140–144° (from n-hexane–EtOAc). IR ν ($CHCl_3$) cm^{-1}: 3250 (OH), 1755 (C=O). NMR ($CDCl_3$): δ 3.79 (s, 2H, H-4), 4.49 (s, 2H, NCH_2Ph), 7.10–7.40 (m, 5H, aromatic), 8.86 (br s, 1H, OH); MS *m/e* 190 (M^+), 173, 91. (Found: C, 63.36; H, 5.36; N, 14.75. Calc for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30, N, 14.73%.)

3-*Acetylamino*-1-*benzyl azetidin*-2-*one* (**14a**). A soln of **13a** (10.8 mg, 0.057 mmol), AcONa (8.2 mg, 0.10 mmol) and Ac_2O (0.03 ml) in EtOAc (0.2 ml) was stirred at room temp for 14 hr. An additional EtOAc (4 ml) and PtO_2 (2 mg) was added to the soln, and the mixture was stirred under 4 kg/cm^2 of H_2 for 23 hr. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluted with CH_2Cl_2—MeOH (20:1) to give colorless needles of **14a** (7.2 mg, 58.2%), m.p. 101–104° (from EtOAc–n-hexane). IR ν ($CHCl_3$) cm^{-1}: 3430 (NH), 1750 (C=O), 1680 (C=O). NMR ($CDCl_3$): δ 2.01 (s, 3H, $COCH_3$), 3.15 (dd, 1H, J = 5, 2 Hz, H-4), 3.49 (t, 1H, J = 5 Hz, H-4), 4.20, 4.40 (ss, 2H, NCH_2Ph), 4.94 (m, 1H, H-3), 6.21 (br s, 1H, NH), 7.20–7.40 (m, 5H, aromatic). MS *m/e* 175 ($M^+ - COCH_3$), 120, 106, 91, 85, 43. (Found: C, 66.10; H, 6.57; N, 12.96. Calc for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84%.)

Benzyl α - (3 - *hydroxy* - 3 - *hydroxymethyl* - 2 - *oxo* - 1 - *azetidinyl*) - p - *benzyloxyphenylacetate* (**10b**). To a soln of N-methyl morpholine N-oxide (1.59 g, 10.4 mmol) and OsO_4 (1% t-BuOH soln, 1 ml, 0.039 mmol) in acetone–water (2.5:1, 7 ml) was added **9b** (4.044 g, 9.78 mmol) in acetone (8 ml) and CH_2Cl_2 (3 ml) under an atmosphere of N_2 in a water bath and a mixture was stirred for one week. A mixture of sodium hydrogensulfite (0.1 g) and magnesium silicate (1.2 g) in water (8 ml) was added to the soln and a mixture was stirred for 30 min. Undissolved material was filtered off and the filtrate was acidified with 5% H_2SO_4 and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The

residue was purified by chromatography on silica gel eluted with CH_2Cl_2—MeOH (20:1) to give colorless hard crystalline material of **10b** (3.487 g, 83.0%); IR ν ($CHCl_3$) cm^{-1}: 3400 (OH), 1740 (C=O); NMR ($CDCl_3$): δ 3.12, 3.17 (2d, 1H, J = 10 Hz, H-4), 3.50–3.94 (m, 5H, OH, CH_2OH, H-4), 5.02 (s, 2H, $PhCH_2OAr$), 5.16 (s, 2H, $PhCH_2OCO$), 5.58 (s, 1H, NCH), 6.90 (d, 2H, J = 9 Hz, aromatic); MS *m/e* 373, 284, 212, 91.

Benzyl α - (2,3 - dioxo - 1 - azetidinyl) - p - benzyloxyphenylacetate (**11b**). To a soln of **10b** (18 mg, 0.043 mmol) in THF–water (3:1, 0.2 ml) was added sodium metaperiodate (17 mg, 0.086 mmol) in a ice bath and a mixture was stirred for 2 hr. Ether was added and the organic layer was dried over $MgSO_4$ and evaporated. The residual oil was purified by chromatography on silica gel eluted with CH_2Cl_2—MeOH (40:1) to give a colorless oil of **11b** (13.0 mg, 72.8%) and the starting material (**10b**, 4.9 mg, 27.2%); IR ν ($CHCl_3$) cm^{-1}: 3350 (OH), 1830 (C=O), 1765 (C=O), 1740 (C=O); NMR (CCl_4): δ 3.55 (d, 1H, J = 10 Hz, H-4), 4.15 (d, 1H, J = 10 Hz, H-4), 5.00 (s, 2H, $PhCH_2OAr$), 5.15 (s, 2H, $PhCH_2OCO$), 5.80 (s, 1H, NCH), 6.80 (d, 2H, J = 9 Hz, aromatic), 6.95–7.40 (m, 12H, aromatic). MS *m/e* 415 (M^+), 387, 373, 331, 224, 91.

Benzyl α - (3 - hydroxyimino - 2 - oxo - 1 - azetidinyl) - p - benzyloxyphenylacetate (**13b**). To a soln of **10b** (3.34 g, 7.47 mmol) in THF–water (3:1, 12 ml) was added sodium metaperiodate (4.00 g, 18.7 mmol) in an ice bath for 16 hr. Ether was added and the ether layer was dried over $MgSO_4$ and evaporated. To the residual oil dissolved in CH_2Cl_2 (10 ml) was added $NH_2OH \cdot HCl$ (1.04 g, 14.9 mmol) in dry pyridine (2 ml) and a mixture was stirred at room temp for 16 hr. Solvent was evaporated and water was added to the residue. The aqueous layer was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on silica gel eluted with CH_2Cl_2—MeOH (25:1) to give colorless prisms of **13b** (2.1 g, 65.4%), m.p. 99–102° (from n-hexane–EtOAc); IR ν ($CHCl_3$) cm^{-1}: 3250 (OH), 1760 (C=O), 1735 (C=O); NMR ($CDCl_3$): δ 3.77 (d, 1H, J = 9 Hz, H-4), 4.33 (d, 1H, J = 9 Hz, H-4), 5.06 (s, 2H, $PhCH_2OAr$), 5.20 (s, 2H, $PhCH_2OCO$), 5.75 (s, 1H, NCH), 6.94 (d, 2H, J = 9 Hz, aromatic), 7.16 (d, 2H, J = 9 Hz, aromatic), 7.10–7.50 (m, 10H, aromatic); MS *m/e* 412 ($M^+ - H_2O$), 295, 251, 91. (Found: C, 69.80; H, 5.31; N, 6.61. Calc for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51%.)

(±)-Benzyl 3-acetylamino-O-benzylnocardicinate (**14b**) *and (±)-epi-benzyl 3-acetylamino-O-benzylnocardicinate* (**14b'**). To a soln of **13b** (54 mg, 0.125 mmol) in EtOAc (1.5 ml) was added Ac_2O (0.2 ml) and AcONa (20 mg, 0.249 mmol) and a mixture was stirred at room temp for 2 hr. Additional EtOAc (4 ml) and PtO_2 (4 mg) was added to the mixture and a soln was stirred under 4 kg/cm^2 of H_2 for 3 days. After filtration of the catalyst, solvent was evaporated and the residue was purified by preparative TLC on silica gel eluted with CH_2Cl_2—MeOH (40:1). The early fraction was viscous oil of **14b** (14 mg, 24.5%); IR ν ($CHCl_3$) cm^{-1}: 3430 (NH), 1755 (C=O), 1740 (C=O), 1675 (C=O); NMR ($CDCl_3$): δ 1.99 (s, 3H, $COCH_3$), 3.42 (m, 2H, H-4), 5.00 (m, 1H, H-3), 5.05 (s, 2H, $PhCH_2OAr$), 5.18 (s, 2H, $PhCH_2OCO$), 5.57 (s, 1H, NCH), 6.36 (d, 1H, J = 8 Hz, NH), 6.93 (d, 2H, J = 9 Hz, aromatic), 7.13 (d, 2H, J = 9 Hz, aromatic), 7.28, 7.39 (2 s, 10H, aromatic); MS *m/e* 373, 323, 238, 212, 91. The later fraction was a viscous oil of **14b'** (16 mg, 28.0%): IR ν ($CHCl_3$) cm^{-1}: 3430 (NH), 1755 (C=O), 1740 (C=O), 1675 (C=O); NMR ($CDCl_3$): δ 1.94 (s, 3H, $COCH_3$), 3.06 (dd, 1H, J = 5.4, 2.4 Hz, H-4), 3.88 (t, 1H, J = 5.4 Hz, H-4), 4.90 (m, 1H, H-3), 5.04 (s, 2H, $PhCH_2OAr$), 5.18 (s, 2H, $PhCH_2OCO$), 5.59 (s, 1H, NCH), 6.93 (d, 2H, J = 9 Hz, aromatic), 7.17 (d, 2H, aromatic), 7.29, 7.39 (ss, 10H, aromatic); MS *m/e* 458 (M^+), 373, 323, 238, 212, 91.

(±)-Dibenzyl 3-ANA (**15b**) *and (±)-epi-dibenzyl 3-ANA* (**15b'**). A soln of **13b** (218 mg, 0.507 mmol) in EtOH (7 ml) containing rhodium on alumina (522 mg, 0.523 mmol) was shaken under 70 psi of H_2 for 4 days. After the catalyst was filtered through selite, the filtrate was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluted (twice) with CH_2Cl_2–MeOH (40:1). The early fraction was the starting material (**13b**, 20 mg, 9.2%) and the later fraction was treated again by preparative TLC on silica gel eluted (10 times) with the same solvent systems. The early fraction was a viscous oil of **15b** (27 mg, 12.8%); IR ν ($CHCl_3$) cm^{-1}: 3370 (NH), 1750 (C=O), 1735 (C=O); NMR ($CDCl_3$): δ 1.65 (br s, 2H, NH_2), 2.80 (d, 1H, J = 6 Hz, H-4), 3.86 (t, 1H, J = 6 Hz, H-4), 4.20 (m, 1H, H-3), 5.06 (s, 2H, $PhCH_2Ar$), 5.17 (s, 2H, $PhCH_2OCO$), 5.58 (s, 1H, NCH), 6.94 (d, 2H, J = 9 Hz, aromatic), 7.17 (d, 2H, J = 9 Hz, aromatic), 7.29 (s, 5H, aromatic), 7.39 (s, 5H, aromatic): MS *m/e* 417 ($M^+ + 1$), 379, 373, 248, 238, 212, 148, 91. The later fraction was a viscous oil of **15b'** (22 mg, 11.4%); IR ν ($CHCl_3$) cm^{-1}: 3370 (NH), 1750 (C=O), 1735 (C=O); NMR ($CDCl_3$): δ 1.72 (br s, 2H, NH_2), 3.35 (m, 2H, H-4), 4.03 (m, 1H, H-3), 5.05 (s, 2H, $PhCH_2OAr$), 5.19 (s, 2H, $PhCH_2OCO$), 5.58 (s, 1H, NCH), 6.93 (d, 2H, J = 9 Hz, aromatic), 7.14 (s, 5H, aromatic), 7.30 (s, 5H, aromatic), 7.39 (s, 5H, aromatic); MS *m/e* 417 ($M^+ + 1$), 379, 373, 244, 238, 212, 148, 91.

Acetylation of **15**. To a soln of **15** (6 mg) in pyridine (8 drops) was added Ac_2O (3 drops) and a mixture was stirred for 2 hr. Excess reagents were evaporated under reduced pressure, and the residual oil was purified by chromatography on alumina eluted with n-hexane–EtOAc (1:1) to give **14b** (3 mg) and **14b'** (2.1 mg). The spectral data of these compounds were fully identical with those of the compounds previously obtained, respectively.

(±)-Dibenzyl 3-ANA hydrotosylate (**15b** · TsOH). To a soln of **15b** (42 mg, 0.101 mmol) in EtOAc (0.5 ml) was added a soln of *p*-toluenesulfonic acid hydrate (19 mg, 0.10 mmol) in EtOAc (0.3 ml). Ether was added to a soln until the white solids were precipitated. After standing for several hr, the solids were collected and washed with ether to give colorless prisms of **15b** · TsOH which was recrystalized from MeOH–ether: m.p. 163–166° (authentic sample m.p. 165–168°, mixed m.p. 164–167°); IR ν (KBr) cm^{-1}: 1755 (C=O), 1735 cm^{-1} (C=O); NMR (DMSO-d_6): δ 2.29 (s, 3H, CH_3), 3.08 (m, 1H, H-4), 3.76 (t, 1H, J = 5.5 Hz, H-4), 4.60 (m, 1H, H-3), 5.12 (s, 2H, $PhCH_2OAr$), 5.19 (s, 2H, $PhCH_2OCO$), 5.69 (s, 1H, NCH), 6.99–7.52 (m, 18H, aromatic), 8.63 (br s, 3H, NH_3^+). MS *m/e* 373, 212, 179, 91.

(±)-Epi-dibenzyl 3-ANA hydrotosylate (**15b'** · TsOH). To a soln of **15b'** (35 mg, 0.084 mmol) in EtOAc (0.5 ml) was added to a soln of *p*-toluenesulfonic acid hydrate (16 mg, 0.084 mmol) in EtOAc (0.3 ml). After work up in the same manner, **15b'** · TsOH (35.1 mg, 70.9%) was obtained, which was recrystalized from MeOH–ether as colorless prisms: m.p. 179–183°; IR ν (KBr) cm^{-1}: 1740 (C=O), 1730 (C=O); NMR (Me_2SO-d_6): δ 2.28 (s, 3H, CH_3), 3.50 (m, 2H, H-4), 4.51 (s, 1H, H-3), 5.11 (s, 2H, $PhCH_2OAr$), 5.20 (s, 2H, $PhCH_2OCO$), 5.63 (s, 1H, NCH), 6.96–7.48 (m, 18H, aromatic), 8.70 (br s, 3H, NH_3^+); MS *m/e* 397, 373, 332, 212, 172, 107, 91.

Acknowledgement—We thank Professor Wasserman, Yale University, for supplying an authentic sample of dibenzyl nocardicinic acid hydrotosylate (**15b** · TsOH) and its NMR spectrum. This work was supported by a Grant-in-Aid for Scientific Research A from the Ministry of Education, Sciences and Culture, Japan.

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