A Novel Synthesis of (±)-3-Aminonocardicinic Acid

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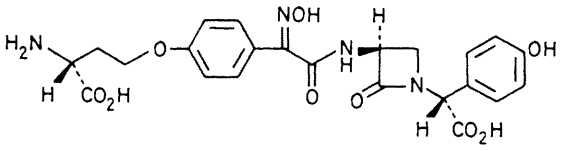
Summary (±)-3-Aminonocardicinic acid, which is an important starting material for the synthesis of nocardicin A and other biologically active analogues, has been synthesized by application of a new method for synthesis of α-methylene-β-lactams.

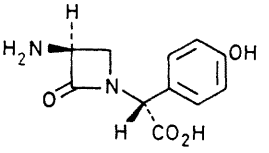
NOCARDICIN A (**1**) has been isolated as the major product from the fermentation broth of *Nocardia uniforms* subsp. *tsuyamanensis* ATTC 21806 by Imanaka *et al.*;[1] its structure was elucidated by Kamiya *et al.*,[2] providing the first example of this new type of monocyclic β-lactam antibiotic. Much attention has been paid to these new anti-

biotics, since they have been found to be active against a broad spectrum of Gram-negative bacteria.

As (±)-3-aminonocardicinic acid (3-ANA, **2**) is potentially an important starting material for the synthesis of biologically active nocardicin derivatives, this compound has been synthesized independently by Kamiya,[3] Koppel,[4] and Wasserman[5] by different methods. We describe here a novel synthesis of 3-ANA using an extension of our method for the synthesis of β-lactams.[6]

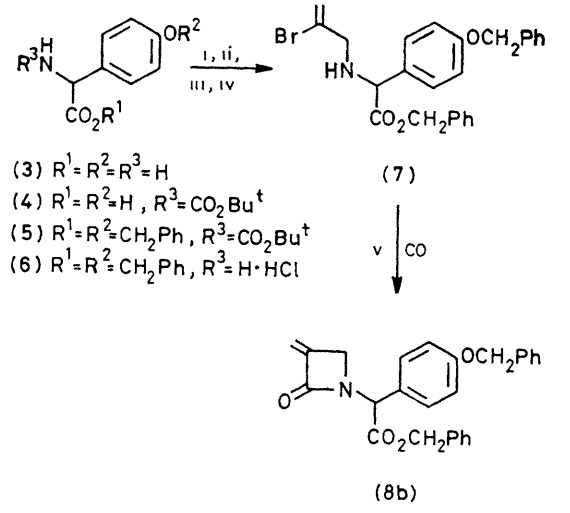


(1)



3-ANA (2)

Protection of the amino group of (±)-*p*-hydroxyphenylglycine (**3**) gave (**4**) in 81·7% yield (Scheme 1). Dibenzylation of (**4**) gave (**5**) (81·5%) and the protecting group was selectively removed by treatment with hydrogen chloride in CH_2Cl_2 to give (**6**) (m.p. 160—164 °C, 91·3%). Compound (**6**) was then condensed with 2,3-dibromopropene to give the amine (**7**) (m.p. 42—44 °C, 81·6%). Insertion of carbon monoxide into (**7**) was effected in the presence of 2 mol % of $Pd(OAc)_2$, 8 mol% of PPh_3, and 1·2 mol. equiv. of Bu^n_3N in hexamethylphosphoramide at 100 °C for 3 h to afford the desired α-methylene-β-lactam (**8b**, m.p. 89·5—90·5 °C) in 36·5% yield. The yield was increased to 62·7% when the reaction was conducted under 4 atm of carbon monoxide at 80 °C for 38 h.



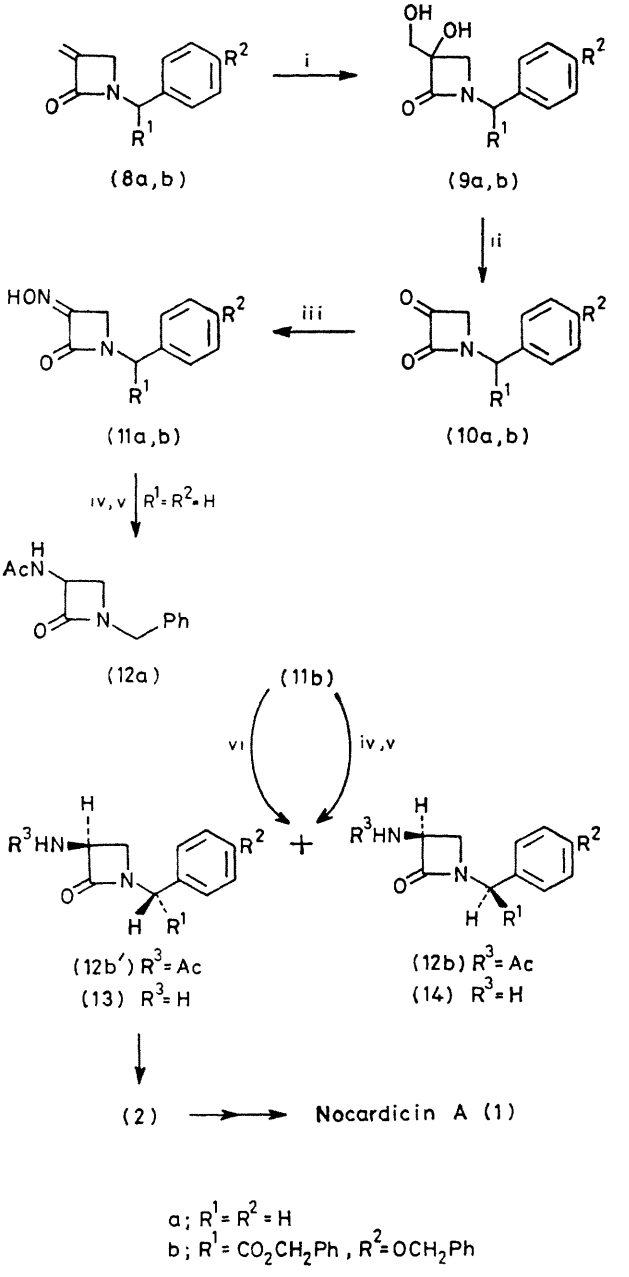
(3) $R^1=R^2=R^3=H$
(4) $R^1=R^2=H$, $R^3=CO_2Bu^t$
(5) $R^1=R^2=CH_2Ph$, $R^3=CO_2Bu^t$
(6) $R^1=R^2=CH_2Ph$, $R^3=H\cdot HCl$

(7)

(8b)

SCHEME 1 *Reagents*, i, $Bu^tCO_2N_3$, ii, $PhCH_2Br, K_2CO_3$, iii, HCl(g) CH_2Cl_2, iv, 2,3-dibromopropene, K_2CO_3, v, $Pd(OAc)_2$, PPh_3, Bu^n_3N.

As a trial method for the conversion of the α-methylene group into a 3-amino group, the 1-benzyl-3-methylene-β-lactam (**8a**), which was easily prepared by the insertion of carbon monoxide into *N*-benzyl-2-bromoallylamine,[1] was oxidized with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide[7] to furnish the diol (**9a**, m.p. 104—105 °C, 93·7%). This diol was cleaved with $NaIO_4$ in aq. tetrahydrofuran to give the ketolactam (**10a**, 96·7%), whose n.m.r. spectrum in CCl_4 showed it to be in a 1 : 1 equilibrium with the enol form. The ketolactam (**10a**) was immediately converted into the



(8a,b) (9a,b) (10a,b) (11a,b) (12a) (11b) (12b′) R^3=Ac (13) R^3=H (12b) R^3=Ac (14) R^3=H (2) Nocardicin A (1)

a; $R^1=R^2=H$
b; $R^1=CO_2CH_2Ph$, $R^2=OCH_2Ph$

SCHEME 2. *Reagents*, i, OsO_4, ii, $NaIO_4$, iii, $NH_2OH\cdot HCl$, pyridine, iv, Ac_2O, AcONa, v, PtO_2, H_2, vi, $Rh-Al_2O_3-H_2$.

oxime (**11a**, m.p. 140—144 °C, 65.2%), which was treated with acetic anhydride in the presence of NaOAc in ethyl acetate and then hydrogenated with PtO_2 under several atm. of hydrogen to give the 1-benzyl-3-acetylamino-β-lactam (**12a**, m.p. 101—104°, 58.2%).

Since the α-methylene group could be converted into 3-acetamino group, the desired α-methylene-β-lactam (**8b**) was converted into the diol (**9b**, 83.0%) which was oxidized to the ketolactam (**10b** 72.8%) and then treated with NH_2OH·HCl to afford (**11b**, m.p. 99—102 °C, 65.4%), in the same manner. The oxime (**11b**) was converted into a diastereomeric mixture of the desired 3-acetamino-β-lactam which could be separated by preparative thin layer chromatography on silica gel into (**12b**) and (**12b'**) (24.5% and 28.0%, respectively) but it was not possible to cleave the *N*-acetyl group of (**12**). However, hydrogenation of the oxime (**11b**) with rhodium on alumina under several atm. pressure of hydrogen afforded a mixture of diastereomers which was separated by preparative t.l.c. on silica gel into (**13**) and (**14**). Each isomer was treated with acetic anhydride in the presence of pyridine to give (**12b'**) and (**12b**). The compound (**13**) was treated with toluene-*p*-sulphonic acid in ethyl acetate to give (**13**·TsOH, m.p. 163—166 °C), which was identical (n.m.r. and i.r. spectrum, mixed m.p.) to an authentic sample. The hydrotosylate of the other diastereoisomer (**14**) was also prepared (**14**·TsOH, m.p. 179—183 °C) and its structure was confirmed mainly by spectral data.

Compound (**13**) is readily converted into (**2**),[4] thus the present synthesis of dibenzyl 3-ANA hydrotosylate (**13**·TsOH) constitutes a formal synthesis of nocardicin A (**1**).

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