

THE FIRST TOTAL SYNTHESIS OF (*R*)-(-)-PYRIDINDOLOL K2 AND ITS ENANTIOMER

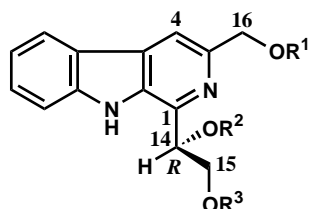
Naoko Kanekiyo,^a Tominari Choshi,^a Takeshi Kuwada,^b Eiichi Sugino,^{† a} and Satoshi Hibino*^a

^a Graduate School of Pharmacy and Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan

^b Process Chemistry Laboratory, Pharmaceutical Research Laboratory, Taisho Pharmaceutical Co. Ltd., 1-403 Yoshino-cho, Ohmiya, Saitama 330-8530, Japan

Abstract The enantioselective first total synthesis of (*R*)-(-)-pyridindolol K2 (**2**) together with its enantiomer (**2a**) has been achieved in nine steps.

Pyridindolol K2 (**2**) was isolated from the culture broth of *Streptomyces* sp. K93-0711 together with pyridindolol K1 (**1**) and pyridindolol (**3**) in 1997 by Omura and co-workers.¹ Pyridindolol (**3**) is already known to be a β -galactosidase inhibitor,² and pyridindolol glucosides have also been isolated from *Streptomyces parvulus*.³ The structures of these compounds (**1-3**) have been elucidated by spectroscopic and X-Ray crystallographic analyses.^{1,2} The absolute stereochemistry of three pyridindolols (**1-3**) has been determined to be an *R*-configuration.¹



1 : $R^1=R^3=\text{COMe}$, $R^2=\text{H}$ (pyridindolol K1)

2 : $R^1=\text{COMe}$, $R^2=R^3=\text{H}$ (pyridindolol K2)

3 : $R^1=R^2=R^3=\text{H}$ (pyridindolol)

We here describe the first total synthesis of (*R*)-(-)-pyridindolol K2 (**2**). *N*-Methoxymethyl-(MOM)-3-iodoindole-2-carbaldehyde (**4**)⁴ was used as a starting material for the synthesis of 1,3-disubstituted β -carboline nucleus. 3-Iodoindole (**4**) was subjected to the palladium catalyzed cross-coupling reaction with [(methoxymethoxy)propynyl]tributyltin in the presence of tetraethylammonium chloride in DMF to

[†] Death: May 29, 2000

yield the 3-(methoxymethoxy)propynylindole (**5**) (95%).⁵ The treatment of the indole-2-carbaldehyde (**5**) with hydroxylamine gave the oxime (**6a**) (90%). Thermal cyclization of **5** was carried out at 180°C in *o*-dichlorobenzene to produce the β -carboline *N*-oxide (**7a**) in 80% yield. This type of cyclization reaction for the synthesis of β - and γ -carbolines has recently been reported by the Sakamoto group.⁶ In order to examine the reaction mechanism of this cyclization, the oxime (**6a**) was treated with deuterated water-deuterated acetone (1:2) to give the deuterated oxime (**6b**). After the removal of solvent, the deuterated oxime (**6b**) was heated at 180°C in *o*-dichlorobenzene to give the 4-deuterated β -carboline *N*-oxide (**7b**). In the ¹H-NMR spectra, a singlet signal at δ 8.12 due to the proton at the 4-position of β -carboline (**7a**) was observed, but a singlet signal attributable to the 4-position of **7b** was not. Based on this fact, it was confirmed that D atom was incorporated at the 4-position of **7b**. The incorporation of D atom of **7b** was also supported by observations of the molecular ion peaks in the mass spectra, **7a**: *m/z* 302 and **7b**: *m/z* 303, respectively. These results indicated that the reaction proceeded through an ionic process similar to that described by Sakamoto.⁷

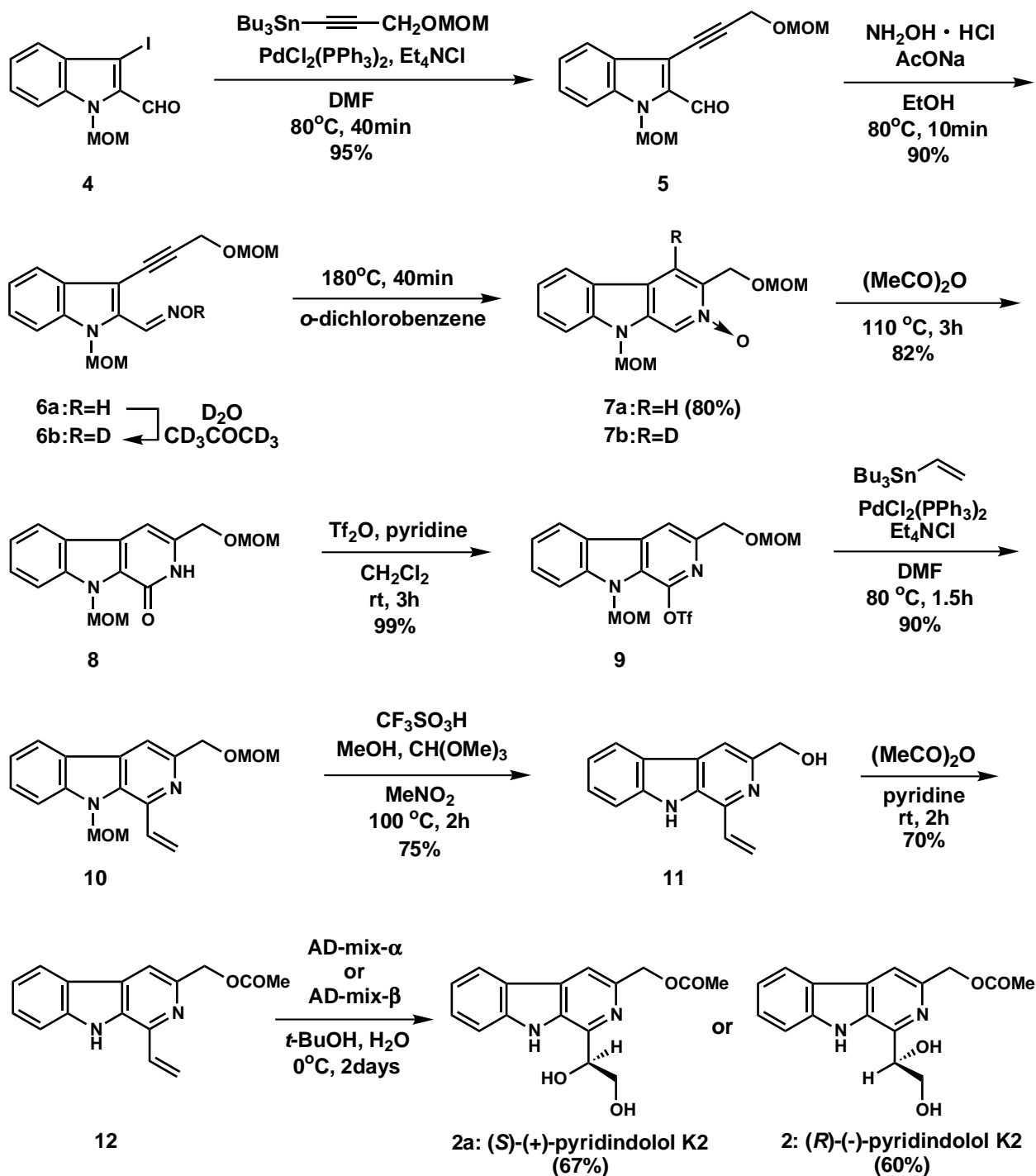
Next, the *N*-oxide (**7a**) was heated at 110°C in acetic anhydride to give the *N*-MOM-1-hydroxy-3-(methoxymethoxy)methyl- β -carboline (**8**) (82%). Treatment of **8** with trifluoromethanesulfonic acid and pyridine afforded the triflate (**9**) (99%), which was subjected to the palladium catalyzed cross-coupling reaction with ethenyltributyltin in the presence of tetraethylammonium chloride in DMF to give the 1-vinyl- β -carboline (**10**) (90%). Deprotection of the *N,O*-bis-MOM group of **10** with trimethyl orthoformate, trifluoromethanesulfonic acid, and methanol in nitromethane⁸ afforded the 1,3-disubstituted β -carboline (**11**) (75%).

After acetylation (70%) of the alcohol (**11**), the enantioselective oxidation of 1-vinyl- β -carboline (**12**) by the Sharpless procedure⁹ was attempted. The reaction of **12** with AD-mix- α provided the 1,2-diol (**2a**)¹⁰ in 67% yield {99.2% ee by HPLC, $[\alpha]_{\text{D}}^{23} +33.0^\circ$ ($c=0.212$, MeOH)}. By contrast, the reaction of **12** with AD-mix- β provided the 1,2-diol (**2**)¹⁰ in 60% yield {99.6% ee by HPLC, $[\alpha]_{\text{D}}^{23} -33.8^\circ$ ($c=0.195$, MeOH)}. The specific rotation of the latter (-)-pyridindolol K2 (**2**) approximately corresponded to that reported for natural pyridindolol K2 (**2**) $\{[\alpha]_{\text{D}}^{20} -35^\circ$ ($c=0.40$ in MeOH)}. The spectral data¹⁰ of **2a** and **2** were identical in all respects to data¹ reported for the natural product.

Thus, the first total synthesis of (*R*)-(-)-pyridindolol K2 (**2**) together with its enantiomer (**2a**) was established in a nine-step sequence through the thermal cyclization of 3-ethynylindole-2-carbaldehyde oxime (**6**), followed by enantioselective 1,2-dihydroxylation. The conversion of pyridindolol K2 (**2**) to pyridindolol (**3**) has previously been carried out with sodium methoxide in methanol by the Omura

group.¹ Consequently, formal total synthesis of pyridindolol (**3**) was also completed. We are now in the process of constructing of the β -carboline nucleus (**7a**) based on the thermal electrocyclic reaction of 1-azahexatriene system^{8,11} involving the indole 2,3-bond, along with the total synthesis of pyridindolol K1

(1).



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- 10 (*S*)-(+)-Pyridindolol K2 (**2a**): mp 124-125°C (MeOH-CHCl₃); ¹H-NMR (300 MHz, MeOH-*d*₄) δ 2.13 (3H, s), 3.97 (2H, br s), 5.20 (1H, br s), 5.32 (2H, s), 7.22 (1H, t, *J*=7.7 Hz), 7.53 (1H, dd, *J*=7.0, 1.1 Hz), 7.60 (1H, d, *J*=8.0 Hz), 8.05 (1H, s), 8.15 (1H, d, *J*=8.0 Hz); ¹³C-NMR (75 MHz, MeOH-*d*₄) δ 20.9, 67.0, 68.4, 76.0, 113.0, 114.3, 120.7, 122.0, 122.5, 129.6, 131.6, 134.7, 142.8, 144.1, 145.7, 172.7; MS *m/z*: 300 (M⁺). (*R*)-(-)-Pyridindolol K2 (**2**): mp 123-124°C (MeOH-CHCl₃); ¹H-NMR (300 MHz, MeOH-*d*₄) δ 2.13 (3H, s), 3.97 (2H, br s), 5.20 (1H, br s), 5.32 (2H, s), 7.22 (1H, t, *J*=7.0 Hz), 7.54 (1H, dd, *J*=8.0, 1.1 Hz), 7.60 (1H, d, *J*=8.0 Hz), 8.05 (1H, s), 8.15 (1H, d, *J*=8.0 Hz); ¹³C-NMR (75 MHz, MeOH-*d*₄) δ 20.9, 67.0, 68.4, 76.1, 113.0, 114.3, 120.7, 122.0, 122.5, 129.6, 131.6, 134.7, 142.8, 144.2, 145.7, 172.7; MS *m/z*: 300 (M⁺).
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