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

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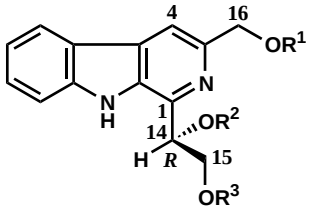
Abstract — The enantioselective first total synthesis of (*R*)-(-)-pyridindolol K2 (**2**) together with its enantiomer (**2a**) has been achieved in nine steps.

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=COMe, R^2=H (pyridindolol K1)
2 :R^1=COMe, R^2=R^3=H (pyridindolol K2)
3 :R^1=R^2=R^3=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 [(methoxymethyloxy)propynyl]tributyltin in the presence of tetraethylammonium chloride in DMF to

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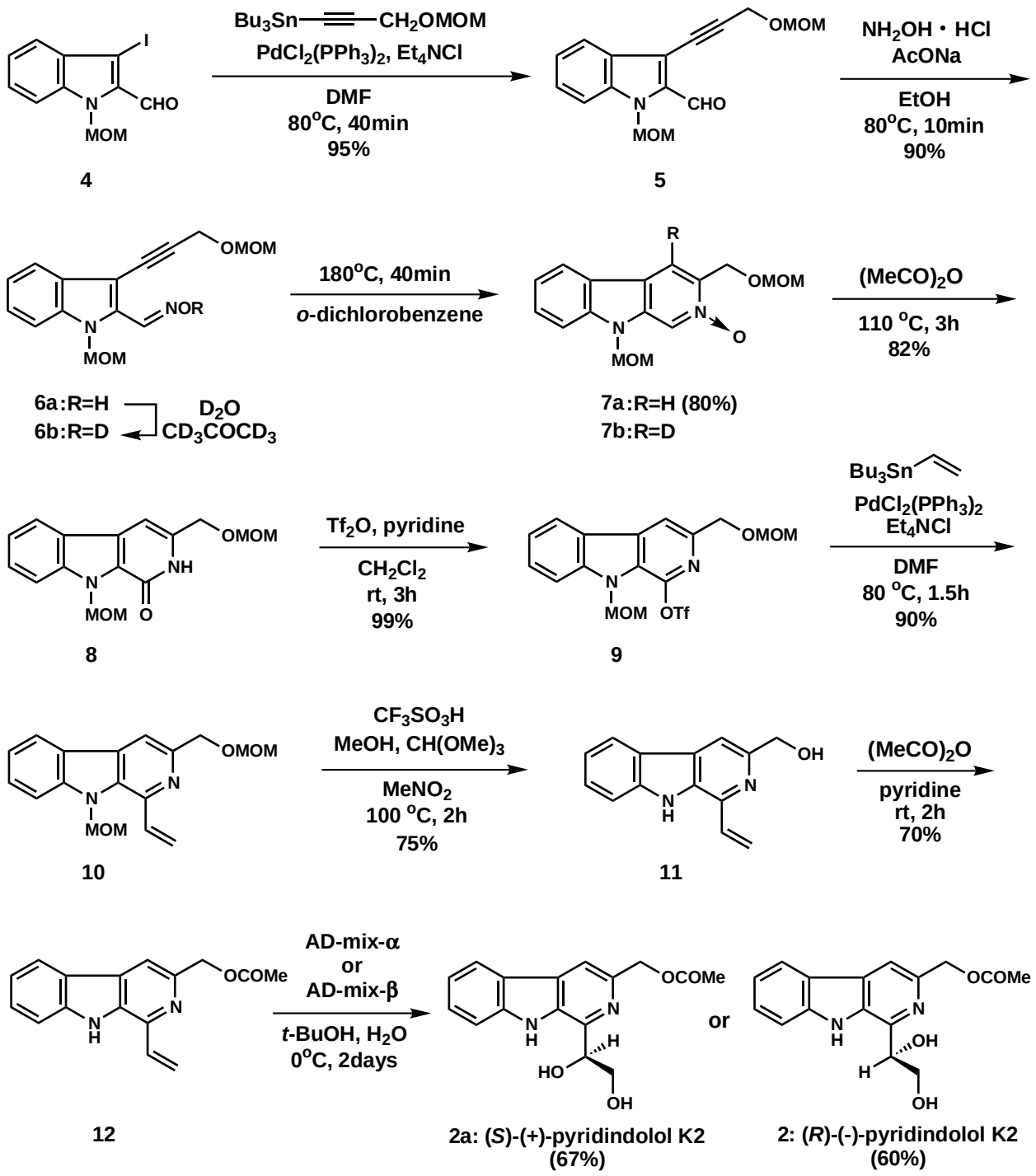
yield the 3-(methoxymethyloxy)propynylindole (**5**) (95%).[5] The treatment of the indole-2-carbaldehyde (**5**) with hydroxylamine gave the oxime (**6a**) (90%). Thermal cyclization of **5** was carried out at 180°C in *o*-dichlorobenzene to produce the β-carboline *N*-oxide (**7a**) in 80% yield. 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 ^{1}H-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-(methoxymethyloxy)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 nitromethane[8] 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 procedure[9] 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, $[\alpha]_D^{23}$ +33.0° (*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, $[\alpha]_D^{23}$ –33.8° (*c*=0.195, MeOH)}. The specific rotation of the latter (-)-pyridindolol K2 (**2**) approximately corresponded to that reported for natural pyridindolol K2 (**2**) {$[\alpha]_D^{20}$ -35°(*c*=0.40 in MeOH)}. The spectral data[10] of **2a** and **2** were identical in all respects to data[1] 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-dihyhydroxylation. 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-$CHCl_3$); ^{1}H-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); ^{13}C-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-$CHCl_3$); ^{1}H-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); ^{13}C-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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