

## CONVENIENT SYNTHESIS OF FRAGMENT E OF ANTIBIOTIC, NOSIHEPTIDE

Chung-gi Shin,\* Yasuhiro Yamada, Keiichiro Hayashi, Yasuchika Yonezawa, Kazuyuki Umemura,<sup>†</sup> Tsuyoshi Tanji,<sup>†</sup> and Juji Yoshimura<sup>†</sup>

Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221, Japan

<sup>\*</sup>College of Science and Engineering, Iwaki Meisei University, Chuodai, Iwaki 970, Japan

**Abstract**—A convenient synthesis of Fragment E, 4-hydroxymethyl-3-methylindole-2-carboxylic acid (1), from 2-methyl-3-nitrobenzyl alcohol through six steps conversion in 32 % overall yield is described.

Antibiotic nosiheptide,<sup>1</sup> obtained from the culture of *Streptomyces actuosus*, is a macrobicyclic polythiazole-dehydropeptide composed from several fragments as shown in Figure 1. Among which, syntheses of a dipeptide, Fragment B-C,<sup>2</sup> chiral Fragment D<sup>3</sup> and their coupling<sup>3</sup> have been successfully accomplished. A synthesis of Fragment E, 4-hydroxymethyl-3-methylindole-2-carboxylic acid (1) *via* an intramolecular Heck reaction was recently reported.<sup>4</sup> Herein we would like to report a more convenient synthesis *via* Reissert reaction.<sup>5</sup>

At first, the hydroxyl group of 2-methyl-3-nitrobenzyl alcohol (2) was protected with

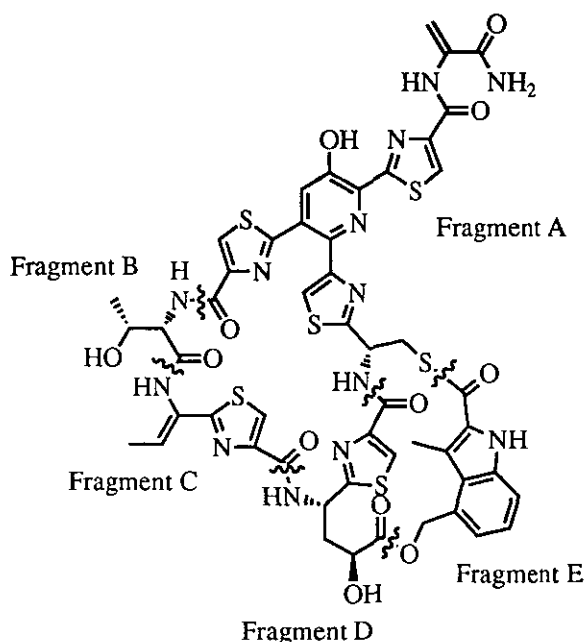


Figure 1. Nosiheptide

methoxymethyl (MOM) or methoxyethoxymethyl (MEM) chloride in the presence of *N,N*-diisopropylethylamine (DIEA), or 3,4-dihydro-4*H*-pyrane (DHP) with *p*-toluenesulfonic acid hydrate to give 2-(*O*-protected hydroxymethyl)-6-nitrotoluene derivatives (3a-c) almost quantitatively. According to the Reissert method,<sup>5</sup> the reactions of 3a-c with diethyl oxalate in the presence of NaH in dimethylformamide (DMF) gave ethyl 6-nitro-2-(*O*-protected hydroxymethyl)phenylpyruvate derivatives (4a-c) in 82-90% yields. Attempted *C*-methylation of the pyruvate moiety in 4b and its trimethylsilyl (TMS) enol ether<sup>6</sup> under various conditions gave only *O*-methyl enol ether,<sup>7</sup> and therefore, the introduction of 3-methyl group in 1 was accomplished after the indole-ring formation. Catalytic hydrogenation of the nitro group in 4a-c on 5% Pd-C in EtOH gave ethyl 4-(*O*-protected hydroxymethyl)indole-2-carboxylates (5a-c) in 80-90% yields. After the ester hydrolysis of 5a-c with 1M-LiOH, the obtained free acid derivatives (6a-c) were treated with MeMgI in the presence of MeI in ether.<sup>8</sup> As a result, the expected 3-methyl-4-(*O*-protected hydroxymethyl)indole-2-carboxylic acid derivatives (7a-c) were obtained in 50-53% yields. Finally, the deprotection of MEM group of 7a,b with KI-TMSCl or 70% AcOH proceeded ultimately to give 1, but the yield was very low. However, in the deprotection of DHP group of 7c with 70% AcOH, the yield of 1 was found to be almost quantitative.

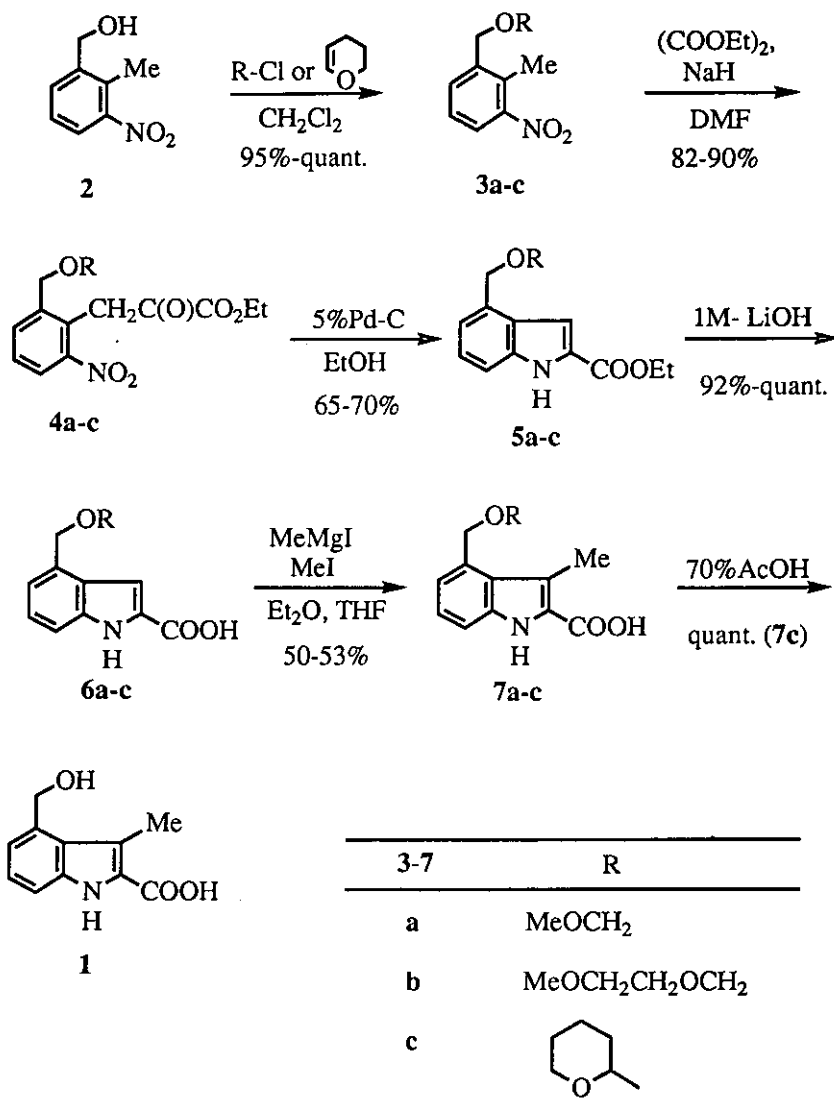
In conclusion, we have disclosed the facile synthesis of Fragment E from 2-methyl-3-nitrobenzyl alcohol in short 6 steps in an overall yield of 32%.

## EXPERIMENTAL

Melting points were determined with Yamato Mp 21 micro melting points apparatus, and are uncorrected. The Ir spectra were recorded on a Hitachi 270-30 spectrophotometer in KBr. The <sup>1</sup>H nmr spectra were measured with JEOL EX 90 spectrometer in CDCl<sub>3</sub> solution with TMS as the internal standard.

**Starting Material:** 2-Methyl-3-nitrobenzyl alcohol (2) was purchased from Aldrich Chemical Co., Inc.

**2-(Methoxymethoxy)methyl-6-nitrotoluene (3a):** To a solution of 2 (2.0 g, 11.96 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) was added with stirring DIEA (6.1 ml, 35.89 mmol) and MOMCl (2.7 ml, 35.89 mmol) at 0 °C for 10 min. After stirring at room temperature for 7 h, Et<sub>2</sub>O (15 ml) was added to the mixture and the resulting solution was washed three times with 10% citric acid (20 ml x 3) and brine (20 ml x 3). Then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration of extracts *in vacuo* gave a crude syrup, which was purified on a silica gel column using hexane and EtOAc (3 : 1 v/v) to give 3a as a yellowish syrup. Yield 2.34 g (quant.). Ir: 2944, 2890, 1530, 1470, 1536 cm<sup>-1</sup>. <sup>1</sup>H Nmr: δ 2.36 (s, 3H, CH<sub>3</sub>), 3.36 (s, 3H, OCH<sub>3</sub>), 4.60 and 4.68 (s x



Scheme 1.

2, 4H, PhCH<sub>2</sub>O, OCH<sub>2</sub>O), 7.10-7.71 (m, 3H, Ph). *Anal.* Calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.90; H, 6.42; N, 6.48.

**2-(2-Methoxyethoxymethoxy)methyl-6-nitrotoluene (3b):** Similarly to the case of 3a, the reaction of 2 (2.0 g, 11.96 mmol) with MEMCl (2.24 g, 17.95 mmol) in the presence of DIEA (3.05 ml, 26.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) gave 3b as a yellowish syrup. Yield 3.65 g (quant.). *Ir:* 2932, 2884, 1530, 1456 cm<sup>-1</sup>. <sup>1</sup>H Nmr: δ 2.45 (s, 3H, CH<sub>3</sub>), 3.40 (s, 3H, OCH<sub>3</sub>), 3.50-3.81 (m, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 4.69 and 4.83 (s x 2, 4H, CH<sub>2</sub>OCH<sub>2</sub>O), 7.21-7.76 (m, 3H, Ph). *Anal.* Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>5</sub>: C, 56.46; H, 6.71; N, 5.49. Found: C,

56.18; H, 6.75; N, 5.44.

**6-Nitro-2-(2-tetrahydropyranyloxy)methyltoluene (3c):** Similarly to the case of **3a**, the reaction of **2** (1.50 g, 8.97 mmol) with THP (1.6 ml, 0.18 mmol) in the presence of *p*-toluenesulfonic acid hydrate (0.17 g, 0.89 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 ml) gave **3c** as a yellowish syrup. Yield 2.1 g (95%). Ir: 2932, 2884, 1530, 1456  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ :  $\delta$  1.54-1.87 (m, 6H, THP's-H), 2.44 (s, 3H,  $\text{CH}_3$ ), 3.44-4.02 (m, 2H, THP's-H), 4.53 and 4.86 (q, 2H,  $J_{\text{AB}}=12.7$  Hz,  $\text{PhCH}_2\text{O}$ ), 4.73 (s, 1H, THP's-H), 7.21-7.76 (m, 3H, Ph). Anal. Calcd for  $\text{C}_{13}\text{H}_{17}\text{NO}_4$ : C, 62.14; H, 6.82; N, 5.57. Found: C, 62.30; H, 7.05; N, 5.69

**Ethyl 2-(2-Methoxymethyloxy)methyl-6-nitrophenylpyruvate (4a):** To a solution of **3a** (2.34 g, 11.96 mmol) in DMF (15 ml) was added, with stirring, 60% NaH (2.39 g, 59.8 mmol) in DMF (15 ml) at 0 °C for 20 min. After further addition of diethyl oxalate (12.95 ml, 95.68 mmol) in DMF (20 ml), the reaction mixture was stirred at room temperature for 18 h and then added to saturated aqueous  $\text{NH}_4\text{Cl}$  (50 ml) and water (100 ml). The resulting solution was extracted three times with ether (30 ml x 3). The combined extract was washed with brine (30 ml x 3) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration of extracts *in vacuo* gave a crude syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **4a** as a yellowish syrup. Yield 2.9 g (82%). Ir: 2944, 1734, 1533  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ :  $\delta$  1.40 (t, 3H,  $J=7.3$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.35 (s, 3H,  $\text{OCH}_3$ ), 4.39 (q, 2H,  $J=7.3$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.56, 4.58 and 4.63 (s x 3, 6H,  $\text{PhCH}_2\text{O}$ ,  $\text{PhCH}_2\text{CO}$ ,  $\text{OCH}_2\text{O}$ ), 7.46 (t, 1H,  $J=7.8$  Hz, H-4), 7.68 (d, 1H,  $J=7.3$  Hz, H-3 or H-5), 8.02 (dd, 1H,  $J=8.3$  Hz,  $J=1.0$  Hz, H-3 or H-5). Anal. Calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_7$ : C, 54.02; H, 5.50; N, 4.50. Found: C, 54.17; H, 5.36; N, 4.32%.

**Ethyl 2-(2-Methoxyethoxymethyloxymethyl)-6-nitrophenylpyruvate (4b):** Similarly to the case of **4a**, the reaction of **3b** (3.05 g, 11.95 mmol) with 60% NaH (2.39 g, 59.8 mmol) and diethyl oxalate (16.19 ml, 11.95 mmol) gave **4b** as a yellowish syrup. Yield 3.32 g (90%). Ir: 2940, 2888, 1732, 1530, 1470  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ :  $\delta$  1.41 (t, 3H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.38 (s, 3H,  $\text{OCH}_3$ ), 3.51-3.78 (m, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.39 (q, 2H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.58, 4.66 and 4.68 (s x 3, 6H,  $\text{PhCH}_2\text{O}$ ,  $\text{PhCH}_2\text{CO}$ ,  $\text{OCH}_2\text{O}$ ), 7.45 (t, 1H,  $J=7.9$  Hz, H-4), 7.68 (dd, 1H,  $J=8.1$  Hz,  $J=1.5$  Hz, H-3 or H-5), 8.01 (dd, 1H,  $J=7.9$  Hz, H-3 or 5). Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}_8$ : C, 54.08; H, 5.96; N, 3.94. Found: C, 54.12; H, 6.12; N, 4.03.

**Ethyl 2-Nitro-6-(2-tetrahydropyranyloxymethyl)phenylpyruvate (4c):** Similarly to the case of **4a**, the reaction of **3c** (1.9 g, 7.56 mmol) with 60% NaH (0.90 g, 22.5 mmol) and diethyl oxalate (6.1 ml, 45.1 mmol) gave **4c** as a yellowish syrup. Yield 2.26 g (85%). Ir: 2944, 1614, 1530, 1461  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ :  $\delta$  1.40 (t, 3H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.43-1.76 (m, 6H, THP's-H), 3.44-3.94 (m, 2H, THP's-H), 4.39 (q, 2H,  $J=7.0$

Hz,  $\text{CH}_2\text{CH}_3$ ), 4.54 and 4.81 (2 x d, 2H,  $J_{\text{AB}}=12.3$  Hz,  $\text{PhCH}_2\text{O}$ ), 4.61 (s, 3H,  $\text{PhCH}_2\text{O}$ , THP's-H), 7.44 (t, 1H,  $J=7.8$  Hz, H-4), 7.69 (dd, 1H,  $J=7.7$  Hz,  $J=1.5$  Hz, H-3 or H-5), 8.01 (dd, 1H,  $J=8.1$  Hz,  $J=1.7$  Hz, H-3 or H-5). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_7$ : C, 58.12; H, 6.02; N, 3.99. Found: C, 58.60; H, 6.10; N, 3.54.

**Ethyl 4-(Methoxymethoxy)methylindole-2-carboxylate (5a):** A solution of **4a** (2.35 g, 7.55 mmol) in EtOH (25 ml) was hydrogenated catalytically on 5% Pd-C (240 mg). After Pd-C was filtered off, the filtrate was concentrated *in vacuo* to give crude crystals. Recrystallization from hexane-EtOAc gave **5a** as colorless needles. Yield 1.33 g (80%). mp 78-79°C. Ir: 3490, 3352, 1692, 1530  $\text{cm}^{-1}$ .  $^1\text{H}$  Nmr:  $\delta$  1.42 (t, 3H,  $J=7.3$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.45 (s, 3H,  $\text{OCH}_3$ ), 4.43 (q, 2H,  $J=7.3$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.76 and 4.90 (s x 2, 4H,  $\text{PhCH}_2\text{O}$ ,  $\text{OCH}_2\text{O}$ ), 7.13-7.43 (m, 4H, Ph), 9.24 (br s, 1H, NH). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_4$ : C, 63.87; H, 6.51; N, 5.32. Found: C, 63.72; H, 6.40; N, 5.15.

**Ethyl 4-(2-Methoxyethoxymethoxy)methylindole-2-carboxylate (5b):** Similarly to the case of **5a**, the hydrogenation of **4b** (100 mg, 0.281 mmol) on 5% Pd-C (11 mg) gave a crude syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give **5b** as a yellowish syrup. Yield 86 mg (90%). Ir: 3340, 2980, 2932, 2884, 1707, 1530  $\text{cm}^{-1}$ .  $^1\text{H}$  Nmr:  $\delta$  1.42 (t, 3H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.42 (s, 3H,  $\text{OCH}_3$ ), 3.53-3.85 (m, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.43 (q, 2H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.58 and 4.94 (s x 2, 4H,  $\text{PhCH}_2\text{O}$ ,  $\text{OCH}_2\text{O}$ ), 7.11-7.42 (m, 4H, Ph), 9.34 (br s, 1H, NH). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}_5$ : C, 62.53; H, 6.89; N, 4.56. Found: C, 62.73; H, 7.03; N, 4.32.

**Ethyl 4-(2-Tetrahydropyranyloxy)methylindole-2-carboxylate (5c):** Similarly to the case of **5a**, the hydrogenation of **4c** (4.27 g, 12.21 mmol) on 5% Pd-C (400 mg) gave crude crystals, which were recrystallized from hexane-EtOAc to give **5c** as colorless needles. Yield: 3.04 g (82%). mp 114-115°C. Ir: 3324, 2940, 2872, 1694, 1526  $\text{cm}^{-1}$ .  $^1\text{H}$  Nmr:  $\delta$  1.41 (t, 3H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.34-1.91 (m, 6H, THP's-H), 3.49-3.99 (m, 2H, THP's-H), 4.42 (q, 2H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.73 (s, 1H, THP's-H), 4.81 and 5.10 (q, 2H,  $J_{\text{AB}}=12.3$  Hz,  $\text{PhCH}_2\text{O}$ ), 7.14-7.42 (m, 4H, Ph), 8.94 (br s, 1H, NH). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_4$ : C, 67.31; H, 6.98; N, 4.62. Found: C, 67.05; H, 6.82; N, 4.72.

**4-(2-Methoxymethoxy)methylindole-2-carboxylic Acid (6a):** A solution of **5a** (383 mg, 1.45 mmol) in MeOH (6 ml) and 1M-LiOH (2.9 ml, 2.9 mmol) was stirred at room temperature for 30 min. The reaction mixture was added to water (10 ml) and washed with ether (5 ml). The aqueous layer was acidified to pH 3-4 with 10% citric acid (3.5 ml) and then extracted with EtOAc (29 ml x 3). The combined extract was washed with brine (20 ml x 3) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration of extracts *in vacuo* gave crude crystals, which were recrystallized from  $\text{CHCl}_3$ -hexane to give **6a** as a colorless powder. Yield 313

mg (92 %). mp 131-132°C. Ir: 3348, 1698, 1516  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ :  $\delta$  3.47 (s, 3H,  $\text{OCH}_3$ ), 4.78 and 4.93 (s x 2, 4H,  $\text{PhCH}_2\text{O}$ ,  $\text{OCH}_2\text{O}$ ), 7.12-7.53 (m, 4H, Ph), 8.73 (br s, 1H, COOH), 9.13 (br s, 1H, NH). *Anal.* Calcd for  $\text{C}_{12}\text{H}_{13}\text{NO}_4$ : C, 61.27; H, 5.57; N, 5.95. Found: C, 61.08; H, 5.45; N, 5.91.

**4-(2-Methoxyethoxymethoxy)methylindole-2-carboxylic Acid (6b)**: Similarly to the case of **6a**, the hydrolysis of **5b** (1.29 g, 4.19 mmol) with 1M-LiOH (8.38 ml) gave **6b** as a colorless powder. Yield 1.17 g (quant.). mp 147-148°C. Ir: 3316, 2896, 1671, 1536  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ : ( $\text{DMSO}-d_6$ ):  $\delta$  3.26 (s, 3H,  $\text{OCH}_3$ ), 3.42-3.72 (m, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.74 and 4.80 (s x 2, 4H,  $\text{PhCH}_2\text{O}$ ,  $\text{OCH}_2\text{O}$ ), 7.03 (d, 1H,  $J=5.9$  Hz, H-5 or H-7), 7.17 (s, 1H, H-3), 7.21 (t, 1H,  $J=7.9$  Hz, H-6), 7.40 (d, 1H,  $J=7.7$  Hz, H-5 or H-7), 11.79 and 12.89 (br s x 2, 2H, NH, COOH). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_5$ : 60.21; H, 6.14; N, 5.02. Found: C, 60.30; H, 6.30; N, 4.87.

**4-(2-Tetrahydropyranyloxy)methylindole-2-carboxylic Acid (6c)**: Similarly to the case of **6a**, the hydrolysis of **5c** (1.13 g, 3.72 mmol) with 1M-LiOH (8.0 ml) gave crude crystals, which were recrystallized from EtOAc to give **6c** as colorless needles. Yield 963 mg (94 %). mp 164-165°C. Ir: 3316, 2948, 1690, 1532  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$  ( $\text{DMSO}-d_6$ ):  $\delta$  1.30-1.90 (m, 6H, THP's-H), 3.20-3.92 (m, 2H, THP's-H), 4.71 (s, 1H, THP's-H), 4.69 and 4.95 (q, 2H,  $J_{AB}=12.1$  Hz,  $\text{PhCH}_2\text{O}$ ), 7.00-7.43 (m, 4H, Ph), 11.79 and 12.85 (br s x 2, 2H, NH, COOH). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_4$ : C, 65.44; H, 6.22; N, 5.09. Found: C, 65.53; H, 6.33; N, 4.81.

**4-(2-Methoxymethoxy)methyl-3-methylindole-2-carboxylic Acid (7a)**: A solution of **6a** (200 mg, 0.85 mmol) in THF (6 ml) was added, with stirring, to Grignard reagent [made from Mg (165 mg, 6.79 mmol) and MeI (0.42 ml, 6.74 mmol)] in ether (6 ml) under Ar gas. After stirring at room temperature for 1 h, excess MeI (0.53 ml, 8.50 mmol) was added to the resulting mixture, which was refluxed for 48 h. Then small amount of ether and saturated aqueous  $\text{NH}_4\text{Cl}$  solution (3 ml) was added to it. The reaction mixture was acidified with 10% citric acid (1 ml) to pH 4-5 and then extracted with  $\text{CHCl}_3$ . The extract was washed with brine (30 ml x 2) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration of extracts *in vacuo* gave crude crystals, which were recrystallized from MeOH-hexane to give **7a** as colorless needles. Yield 112 mg (53%). mp 150-151°C. Ir: 3340, 2938, 1695, 1575, 1464  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$ :  $\delta$  2.86 (s, 3H,  $\text{CH}_3$ ), 3.44 (s, 3H,  $\text{OCH}_3$ ), 4.76 and 4.99 (s x 2, 4H,  $\text{PhCH}_2\text{O}$ ,  $\text{OCH}_2\text{O}$ ), 7.06-7.32 (m, 3H, Ph), 8.90 (br s, 1H, NH), 9.66 (br s, 1H, COOH). *Anal.* Calcd for  $\text{C}_{13}\text{H}_{15}\text{NO}_4$ : C, 62.64; H, 6.07; N, 5.62. Found: C, 62.42; H, 6.13; N, 5.73.

**4-(2-Methoxyethoxymethoxy)methyl-3-methylindole-2-carboxylic Acid (7b)**: Similarly to the case of

**7a**, the methylation of **6b** (800 mg, 2.86 mmol) in THF (15 ml) with Grignard reagent [made from Mg (690 mg, 28.39 mmol) and MeI (2 ml, 32.13 mmol)] in ether (5 ml) under Ar gas gave a crude syrup, which was purified on a silica gel column using a mixture of CHCl<sub>3</sub>, MeOH, and AcOH (20 : 1 : 1 v/v) to give **7b** as colorless needles. Yield 420 mg (50%). mp 122-123°C. Ir: 3335, 2944, 1680, 1551 cm<sup>-1</sup>. <sup>1</sup>H Nmr: δ 2.86 (s, 3H, CH<sub>3</sub>), 3.42 (s, 3H, OCH<sub>3</sub>), 3.53-3.85 (m, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 4.86 and 5.03 (s x 2, 4H, PhCH<sub>3</sub>O, OCH<sub>2</sub>O), 7.10-7.32 (m, 3H, Ph), 8.90 (br s, 1H, NH), 9.44 (br s, 1H, COOH). *Anal.* Calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.44; H, 7.08; N, 4.84.

**3-Methyl-4-(2-tetrahydropyranoyloxy)methylindole-2-carboxylic Acid (7c)**: Similarly to the case of **7a**, the reaction of **6c** (200 mg, 0.72 mmol) with Grignard reagent [made from Mg (173 mg, 7.12 mmol) and MeI (0.5 ml, 8.03 mmol)] gave crude crystals, which were recrystallized from MeOH-hexane to give **7c** as colorless needles. Yield 110 mg (52%). mp 159-160°C. Ir: 3356, 2936, 1676, 1578, 1544 cm<sup>-1</sup>. <sup>1</sup>H Nmr: δ 1.53-1.74 (m, 6H, THP's-H), 2.87 (s, 3H, CH<sub>3</sub>), 3.44-4.14 (m, 2H, THP's-H), 4.79 (s, 1H, THP's-H), 4.90 and 5.19 (d x 2, 2H, J<sub>AB</sub>=12.1 Hz, PhCH<sub>2</sub>O), 7.08-7.32 (m, 3H, Ph), 8.88 (br s, 1H, NH), 10.33 (br s, 1H, COOH). *Anal.* Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.30; H, 6.87; N, 4.54.

**4-Hydroxymethyl-3-methylindole-2-carboxylic Acid (1)**: A solution of **7c** (11 mg, 0.04 mmol) in 70% AcOH (1 ml) was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* to give a residue. The azeotropic distillation of AcOH and H<sub>2</sub>O with benzene (0.5 ml x 3) gave crude crystals, which were recrystallized from MeOH to give **1** as colorless prisms. Yield 8.0 mg (quant.). mp 235-237°C. Ir: 3472, 3244, 2926, 2872, 1635, 1539 cm<sup>-1</sup>. <sup>1</sup>H Nmr (DMSO-*d*<sub>6</sub>): δ 2.77 (s, 3H, CH<sub>3</sub>), 3.40 (s, 1H, OH), 4.89 (s, 2H, PhCH<sub>2</sub>O), 6.87-7.29 (m, 3H, Ph), 10.12 (br s, 1H, COOH), 10.99 (br s, 1H, NH). *Anal.* Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>3</sub>·0.2H<sub>2</sub>O: C, 63.27; H, 5.50; N, 6.70. Found: C, 63.40; H, 5.53; N, 6.90.

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6. *O*-Silylation of **4b** with TMSCl in the presence of DIEA in DMF for 10 h at room temperature gave ethyl  $\alpha$ -trimethylsiloxy-2-(2-methoxymethoxy)methyl-6-nitrocinnamate. Pale yellow syrup, yield 50%.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  0.06 (s, 9H,  $\text{SiMe}_3$ ), 1.43 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.45 (s, 3H,  $\text{OCH}_3$ ), 3.62 (m, 2H,  $\text{OCH}_2$ ), 3.80 (m, 2H,  $\text{OCH}_2$ ), 4.36 (q, 2H,  $J = 7.1$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.70 (s, 2H,  $\text{ArCH}_2\text{O}$ ), 4.89 (s, 2H,  $\text{OCH}_2\text{O}$ ), 7.16 (s, 1H, CH), 7.51 (dd, 1H,  $J_{3,4} = 8.0$  Hz,  $J_{4,5} = 8.1$  Hz, H-4), 7.86 (d, 1H,  $J = 8.1$  Hz, H-3), 7.94 (d, 1H,  $J = 8.1$  Hz, H-5).
7. Methylation of **4b** with MeI in the presence of  $\text{K}_2\text{CO}_3$  in MeCN for 72 h at room temperature gave ethyl  $\alpha$ -methoxy-2-(2-methoxyethoxymethoxy)methyl-6-nitrocinnamate. Colorless syrup, yield 94%. Ir (KBr): 2940, 2890, 1528, 1350  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  1.40 (t, 3H,  $J = 6.9$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.39 (s, 3H,  $\text{OCH}_3$ ), 3.52 (s, 3H,  $\alpha\text{-OCH}_3$ ), 3.55 (m, 2H,  $\text{OCH}_2$ ), 3.72 (m, 2H,  $\text{OCH}_2$ ), 4.31 (q, 2H,  $J = 6.9$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.63 (s, 2H,  $\text{ArCH}_2\text{O}$ ), 4.83 (s, 2H,  $\text{OCH}_2\text{O}$ ), 7.12 (s, 1H, CH), 7.47 (dd, 1H,  $J_{3,4} = 6.8$  Hz,  $J_{4,5} = 7.8$  Hz, H-4), 7.78 (d, 1H,  $J = 6.8$  Hz, H-3), 7.93 (d, 1H,  $J = 7.8$  Hz, H-5).
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