CONVENIENT SYNTHESIS OF FRAGMENT E OF ANTIBIOTIC, NOSIHEPTIDE

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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,[1] 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,[2] chiral Fragment D[3] and their coupling[3] 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.[4] Herein we would like to report a more convenient synthesis *via* Reissert reaction.[5]

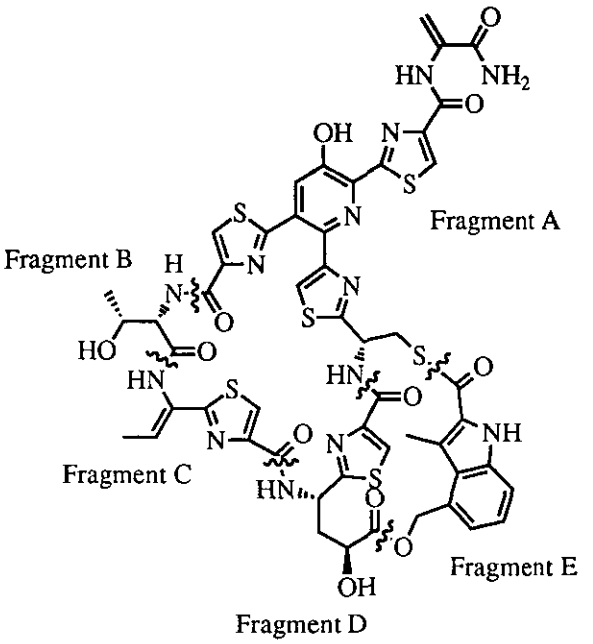


Figure 1. Nosiheptide

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

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,[5] 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[6] under various conditions gave only *O*-methyl enol ether,[7] 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.[8] 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.

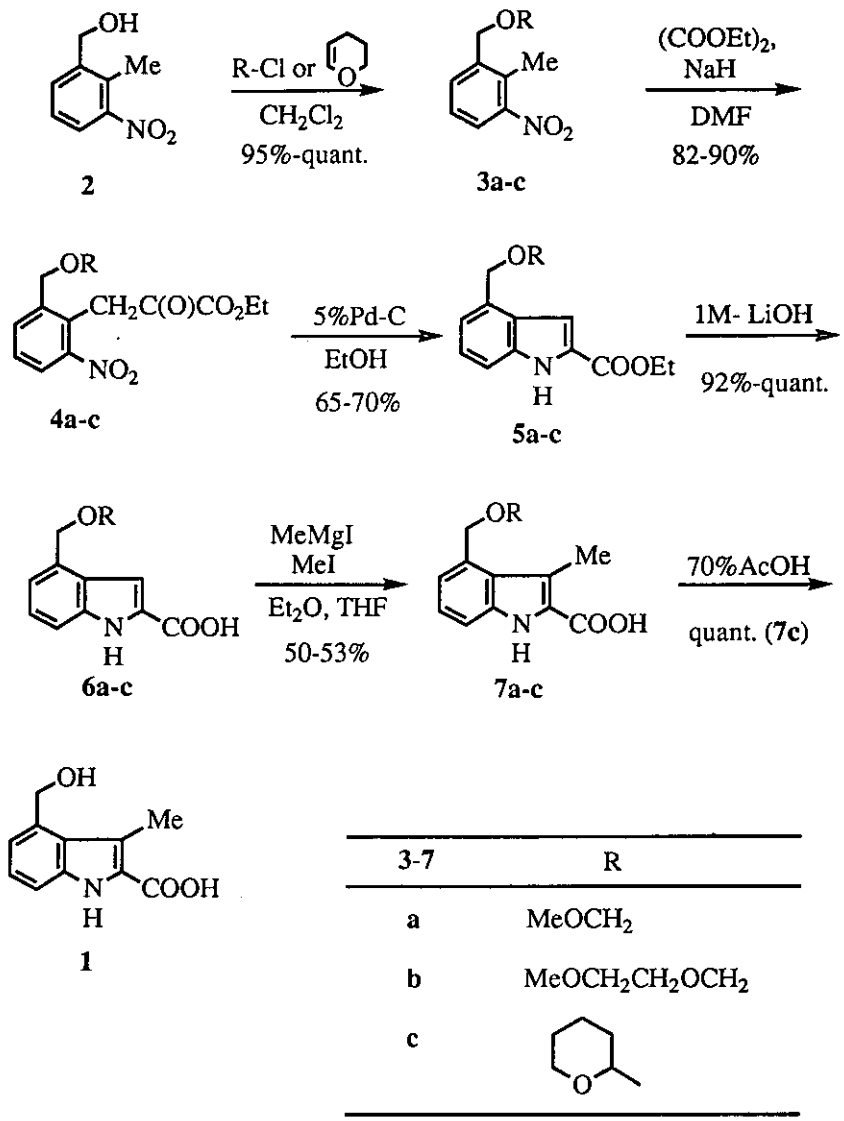
In conclusion, we have disclosed the facile synthesis of Fragment E from 2-methyl-3-nitrobenzyl alcohol in short 6 steps in an overall yield of 32%.

EXPERIMENTAL

Melting points were determined with Yamato Mp 21 micro melting points apparatus, and are uncorrected. The Ir spetcra were recorded on a Hitachi 270-30 spectrophotometer in KBr. The ^{1}H nmr spectra were measured with JEOL EX 90 spectrometer in $CDCl_3$ solution with TMS as the internal standard.

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

2-(Methoxymethyloxy)methyl-6-nitrotoluene (3a): To a solution of **2** (2.0 g, 11.96 mmol) in CH_2Cl_2 (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_2O (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_2SO_4. 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^{-1}. ^{1}H Nmr: δ 2.36 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 4.60 and 4.68 (s x



3-7	R
a	$MeOCH_2$
b	$MeOCH_2CH_2OCH_2$
c	

Scheme 1.

2, 4H, $PhCH_2O$, OCH_2O), 7.10-7.71 (m, 3H, Ph). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.90; H, 6.42; N, 6.48.

2-(2-Methoxyethoxymethyloxy)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_2Cl_2 (15 ml) gave **3b** as a yellowish syrup. Yield 3.65 g (quant.). Ir: 2932, 2884, 1530, 1456 cm^{-1}. ^1H Nmr: δ 2.45 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 3.50-3.81 (m, 4H, OCH_2CH_2O), 4.69 and 4.83 (s x 2, 4H, CH_2OCH_2O), 7.21-7.76 (m, 3H, Ph). *Anal.* Calcd for $C_{12}H_{17}NO_5$: 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 CH_2Cl_2 (20 ml) gave **3c** as a yellowish syrup. Yield 2.1 g (95%). Ir: 2932, 2884, 1530, 1456 cm^{-1}. ^1H Nmr: δ 1.54-1.87 (m, 6H, THP's-H), 2.44 (s, 3H, CH_3), 3.44-4.02 (m, 2H, THP's-H), 4.53 and 4.86 (q, 2H, J_{AB}=12.7 Hz, $PhCH_2O$), 4.73 (s, 1H, THP's-H), 7.21-7.76 (m, 3H, Ph). *Anal.* Calcd for $C_{13}H_{17}NO_4$: 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 NH_4Cl(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 Na_2SO_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 cm^{-1}. ^1H Nmr: δ 1.40 (t, 3H, *J*=7.3 Hz, CH_2CH_3), 3.35 (s, 3H, OCH_3), 4.39 (q, 2H, *J*=7.3 Hz, CH_2CH_3), 4.56, 4.58 and 4.63 (s x 3, 6H, $PhCH_2O$, $PhCH_2CO$, OCH_2O), 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 $C_{14}H_{17}NO_7$: 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 cm^{-1}. ^1H Nmr: δ 1.41 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 3.38 (s, 3H, OCH_3), 3.51-3.78 (m, 4H, OCH_2CH_2O), 4.39 (q, 2H, *J*=7.0 Hz, CH_2CH_3), 4.58, 4.66 and 4.68 (s x 3, 6H, $PhCH_2O$, $PhCH_2CO$, OCH_2O), 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 $C_{16}H_{21}NO_8$: 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 cm^{-1}. ^1H Nmr: δ 1.40 (t, 3H, *J*=7.0 Hz, CH_2CH_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, CH_2CH_3), 4.54 and 4.81 (2 x d, 2H, J_{AB}=12.3 Hz, $PhCH_2O$), 4.61 (s, 3H, $PhCH_2O$, 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 $C_{17}H_{21}NO_7$: C, 58.12; H, 6.02; N, 3.99. Found: C, 58.60; H, 6.10; N, 3.54.

Ethyl 4-(Methoxymethyloxy)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 cm^{-1}. ^1H Nmr: δ 1.42 (t, 3H, *J*=7.3 Hz, CH_2CH_3), 3.45 (s, 3H, OCH_3), 4.43 (q, 2H, *J*=7.3 Hz, CH_2CH_3), 4.76 and 4.90 (s x 2, 4H, $PhCH_2O$, OCH_2O), 7.13-743 (m, 4H, Ph), 9.24 (br s, 1H, NH). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.72; H, 6.40; N, 5.15.

Ethyl 4-(2-Methoxyethoxymethyloxy)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 cm^{-1}. ^1H Nmr: δ 1.42 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 3.42 (s, 3H, OCH_3), 3.53-3.85 (m, 4H, OCH_2CH_2O), 4.43 (q, 2H, *J*=7.0 Hz, CH_2CH_3), 4.58 and 4.94 (s x 2, 4H, $PhCH_2O$, OCH_2O), 7.11-7.42 (m, 4H, Ph), 9.34 (br s, 1H, NH). *Anal.* Calcd for $C_{16}H_{21}NO_5$: 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 cm^{-1}. ^1H Nmr: δ 1.41 (t, 3H, *J*=7.0 Hz, CH_2CH_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, CH_2CH_3), 4.73 (s, 1H, THP's-H), 4.81 and 5.10 (q, 2H, J_{AB}=12.3 Hz, $PhCH_2O$), 7.14-7.42 (m, 4H, Ph), 8.94 (br s, 1H, NH). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.05; H, 6.82; N, 4.72.

4-(2-Methoxymethyloxy)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 Na_2SO_4. Concentration of extracts *in vacuo* gave crude crystals, which were recrystallized from $CHCl_3$-hexane to give **6a** as a colorless powder. Yield 313

mg (92 %). mp 131-132°C. Ir: 3348, 1698, 1516 cm^{-1}. ^1H Nmr: δ 3.47 (s, 3H, OCH_3), 4.78 and 4.93 (s x 2, 4H, $PhCH_2O$, OCH_2O), 7.12-7.53 (m, 4H, Ph), 8.73 (br s, 1H, COOH), 9.13 (br s, 1H, NH). *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.08; H, 5.45; N, 5.91.

4-(2-Methoxyethoxymethyloxy)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 cm^{-1}. ^1H Nmr: (DMSO-d_6): δ 3.26 (s, 3H, OCH_3), 3.42-3.72 (m, 4H, OCH_2CH_2O), 4.74 and 4.80 (s x 2, 4H, $PhCH_2O$, OCH_2O), 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 $C_{14}H_{17}NO_5$: 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 cm^{-1}. ^1H Nmr (DMSO-d_6): δ 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, $PhCH_2O$), 7.00-7.43 (m, 4H, Ph), 11.79 and 12.85 (br s x 2, 2H, NH, COOH). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.53; H, 6.33; N, 4.81.

4-(2-Methoxymethyloxy)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 NH_4Cl 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 $CHCl_3$. The extract was washed with brine (30 ml x 2) and dried over anhydrous Na_2SO_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 cm^{-1}. ^1H Nmr: δ 2.86 (s, 3H, CH_3), 3.44 (s, 3H, OCH_3), 4.76 and 4.99 (s x 2, 4H, $PhCH_2O$, OCH_2O), 7.06-7.32 (m, 3H, Ph), 8.90 (br s, 1H, NH), 9.66 (br s, 1H, COOH). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.42; H, 6.13; N, 5.73.

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

7a, the methylation of **6b** (800 mg, 2.86mmol) 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 $CHCl_3$, 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^{-1}. ^1H Nmr: δ 2.86 (s, 3H, CH_3), 3.42 (s, 3H, OCH_3), 3.53-3.85 (m, 4H, OCH_2CH_2O), 4.86 and 5.03 (s x 2, 4H, $PhCH_3O$, OCH_2O), 7.10-7.32 (m, 3H, Ph), 8.90 (br s, 1H, NH), 9.44 (br s, 1H, COOH). *Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.44; H, 7.08; N, 4.84.

3-Methyl-4-(2-tetrahydropyranyloxy)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^{-1}. ^1H Nmr: δ 1.53-1.74 (m, 6H, THP's-H), 2.87 (s, 3H, CH_3), 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_{AB}=12.1 Hz, $PhCH_2O$), 7.08-7.32 (m, 3H, Ph), 8.88 (br s, 1H, NH), 10.33 (br s, 1H, COOH). *Anal.* Calcd for $C_{16}H_{19}NO_4$: 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_2O with benzene (0.5 mlx 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^{-1}. ^1H Nmr (DMSO-d_6): δ 2.77 (s, 3H, CH_3), 3.40 (s, 1H, OH), 4.89 (s, 2H, $PhCH_2O$), 6.87-7.29 (m, 3H, Ph), 10.12 (br s, 1H, COOH), 10.99 (br s, 1H, NH). *Anal.* Calcd for $C_{11}H_{11}NO_3.0.2H_2O$: C, 63.27; H, 5.50; N, 6.70. Found: C, 63.40; H, 5.53; N, 6.90.

REFERENCES

1. Rhone-Poulenc, S.A. U. S. Patent 3155581 (1962), Fr. Patent 1392453 (1961) (*Chem. Abstr.*, 1963, **58**, 9601).

   H. Depire, J. P. Thomas, and A. Brun, *Tetrahedron Lett.*, 1977, 1397, 1401.

   T. Prange, A. Ducruix, and C. Pascard, *Nature* , 1977, **265**, 189.

   C. Pascard, A. Ducruix, J. Lunel, and T. Prange, *J. Am. Chem. Soc.*, 1977, **99**, 6418.

2. K. Umemura, T. Tate, M. Yamaura, J. Yoshimura, Y. Yonezawa, and C. Shin, *Synthesis* , **1995**, 1423.

3. C. Shin, Y. Nakamura, Y. Yamada, Y. Yonezawa, K. Umemura, and J. Yoshimura, *Bull. Chem. Soc.*

Jpn., 1995, **68**, 3151.

4. K. Koerber-ple and G. Massiot, *Synlett*, **1994**, 759.
5. W. E. Noland, and F. J. Baude, *Org. Syn.*, Coll. Vol., 5, 567, ed. by H. E. Baumgarten, John Wiley and Sons, New York, 1973.
6. *O*-Silylation of **4b** with TMSCl in the presence of DIEA in DMF for 10 h at room temperature gave ethyl α-trimethylsiloxy-2-(2-methoxymethyloxy)methyl-6-nitrocinnamate. Pale yellow syrup, yield 50%. ^{1}H Nmr ($CDCl_3$): δ 0.06 (s, 9H, $SiMe_3$), 1.43 (t, 3H, J = 7.1 Hz, CH_2CH_3), 3.45 (s, 3H, OCH_3), 3.62 (m, 2H, OCH_2), 3.80 (m, 2H, OCH_2), 4.36 (q, 2H, J = 7.1 Hz, CH_2CH_3), 4.70 (s, 2H, $ArCH_2O$), 4.89 (s, 2H, OCH_2O), 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 K_2CO_3 in MeCN for 72 h at room temperature gave ethyl α-methoxy-2-(2-methoxyethoxymethyloxy)methyl-6-nitrocinnamate. Colorless syrup, yield 94%. Ir (KBr): 2940, 2890, 1528, 1350 cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 1.40 (t, 3H, J = 6.9 Hz, CH_2CH_3), 3.39 (s, 3H, OCH_3), 3.52 (s, 3H, α-OCH_3), 3.55 (m, 2H, OCH_2), 3.72 (m, 2H, OCH_2), 4.31 (q, 2H, J = 6.9 Hz, OCH_2CH_3), 4.63 (s, 2H, $ArCH_2O$), 4.83 (s, 2H, OCH_2O), 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).
8. T. Hoshino, *Ann.*, 1932, **35**, 500.

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