# Absolute and Atropisomeric Structure of ES-242s, *N*-Methyl-D-aspartate Receptor Antagonists

Sir:

ES-242s were isolated from the culture broth of *Verticillium* sp. in 1992 as *N*-methyl-D-aspartate (NMDA) antagonists. Structurally, ES-242s belong to bioxanthracene groups corresponding to a dimer of naphthopyran[1].

Recently, we have synthesized natural ES-242-4 (**1a**) and its atropisomer **1b**[2], which are chromatographically less-polar and polar, respectively, from the $\alpha,\beta$-unsaturated lactone **3** through dimerization of a monomeric naphthopyran **4** and deprotection of **5a** and **5b**, respectively, as shown in Fig. 1 and Scheme 1. Similarly, their *trans* analogs **2a** and its atropisomer **2b** have been synthesized from **8a** and **8b**, respectively, which were prepared from **6** through **7**[3].

However, their absolute structures including atropisomerism remained undetermined.

Herein, we describe the determination of their absolute configurations mainly on the basis of X-ray crystallographic analysis and chemical derivation to more understand the structure-activity relationships.

First of all, many kinds of derivatives were synthesized from previously reported atropisomeric intermediates **5a**, **5b**, **8a** and **8b**[2,3] (Scheme 2). For examples, **8a** was *O*-benzylated with NaH and BnBr in DMF at 20°C for 1 hour, followed by treatment with AcCl in MeOH-dioxane at 20°C for 1.5 hours to give **9a** [FAB-MS *m/z* 758 ($M^+$)] (Table 1). Similarly, **9b**, **12a** and **12b** were obtained from **8b**, **5a** and **5b**, respectively. We found **9a** to be recrystallized from MeOH-$H_2O$ (10:1) to give rods (mp 160~161°C), which proved conductive to the X-ray crystallographic analysis.

A pale yellow crystal of **9a** having approximate dimensions of $0.40\times0.30\times0.35$ mm was chosen for the analysis. The crystal data are as follows: Orthorhombic, $P2_12_12_1$, a=11.475(2), b=42.315(4), c=8.648(2)Å, V=4199(1)Å$^3$, Z=4. The structure was solved by direct methods(SIR92). The final cycle of full-matrix least-squares refinement was based on 2825 observed reflections ($I>1.5\ \sigma\ [I]$) and 440 variable parameters and converged with the agreement factor of R=0.080.

Consequently, **9a** was confirmed to exist only as one atropisomer of (a*S*)-configuration as shown in Fig. 2, although the flipping of its pyran ring and *O*-benzyl groups was observed in the crystal structure. The dihedral angle between two naphthalene planes is 82.3°.

The absolute structure including the atropisomerism of **9a** was determined as depicted in Scheme 2 and, consequently, the atropisomer was as **9b**.

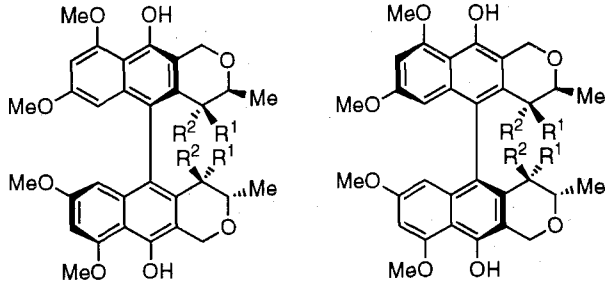
Both compounds **9a** and **9b** were oxidized under Swern's conditions to give the diketones **10** and **11**, respectively, which were also obtained from oxidation of **12b** and **12a**, respectively. Both products **10** and **11** showed *m/z* 755 ($[M+H]^+$) in their FAB-MS. These results indicated that **9a** and **12b** have the same (a*S*)-configurational atropisomerism, and their diastereomers **9b** and **12a** have the (a*R*)-configurational one (Scheme 2).

Hydrogenolysis of **9a**, **9b**, **12a** and **12b** afforded quantitatively the corresponding **2a**, **2b**, **1a** (ES-242-4) and **1b**, respectively. Therefore, these structural features were defined unambiguously as shown in Fig 1.

Two hydroxy groups at C-4 and C-4′ in **1a** and **2a** are observed to be far apart, while two hydroxy groups in **1b** and **2b** are close together. The shorter distance between these two hydroxy groups may be responsible for the stronger inhibitory activities against [$^3$H]MK-801 binding to the NMDA receptor (Table 2)[3]. Namely, **1b** and **2b** showed stronger activities than **1a** and **2a**, suggesting that the appearance of their activities may be attributed to the intramolecular metal chelation formation between their two hydroxy groups[4].

Furthermore, the information gained by transforming **12a** into the 4-deoxy derivative (ES-242-5)[1] of **1a** was adequate to permit definition of other ES-242s in absolute stereochemical terms as well[5].

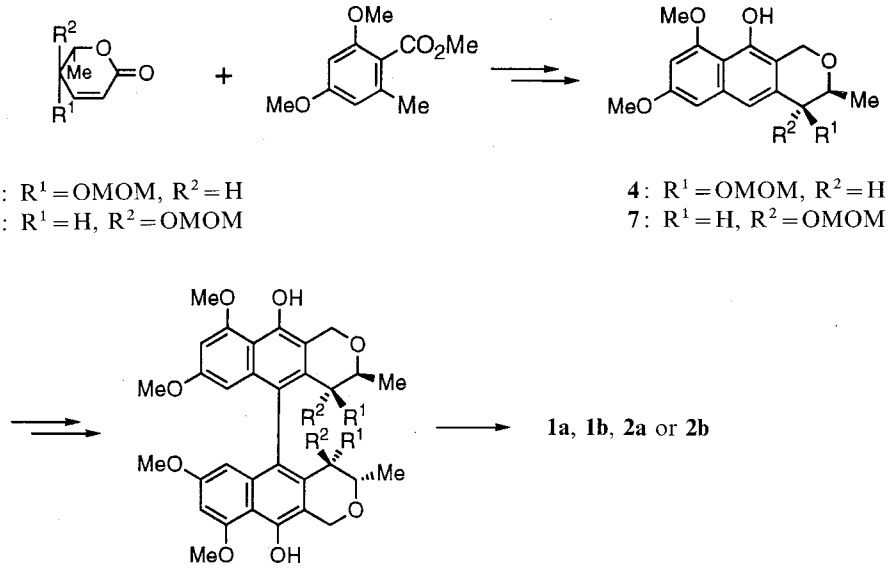
Fig. 1



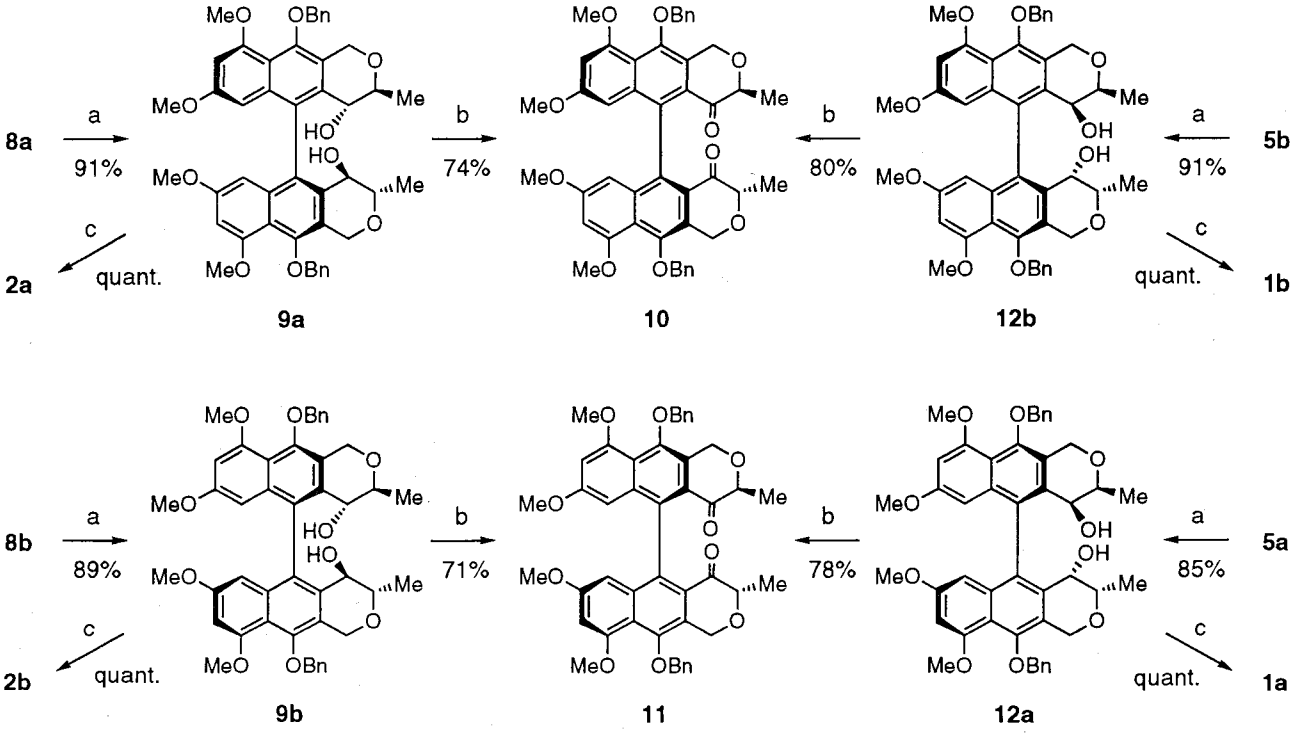

**1a** (ES242-4): $R^1$=OH, $R^2$=H
**2b**: $R^1$=H, $R^2$=OH

**1b**: $R^1$=OH, $R^2$=H
**2a**: $R^1$=H, $R^2$=OH

Scheme 1




Scheme 2



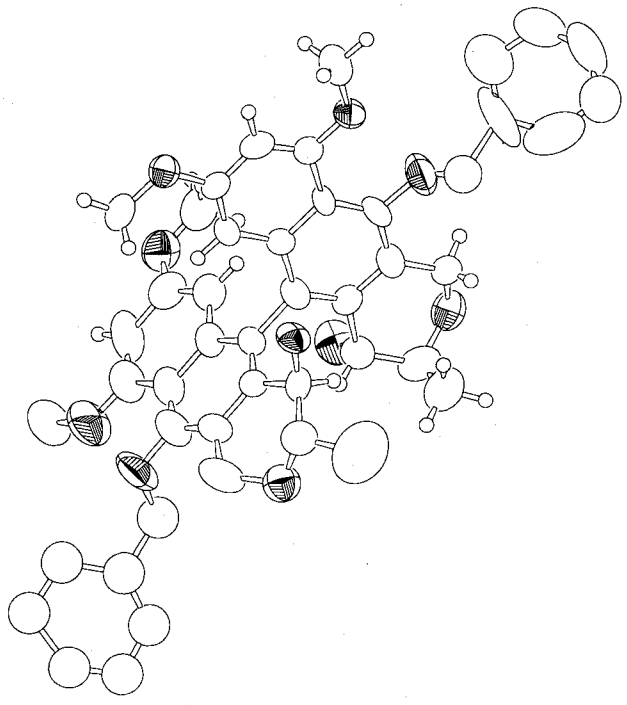

a) 1) BnBr, NaH/DMF, rt, 1 hour. 2) AcCl/MeOH, rt, 1.5 hours.
b) $(COCl)_2$, DMSO, $Et_3N/CH_2Cl_2$, $-78°C$ $-$rt, 30 minutes
c) $H_2$, Pd-C/EtOH-THF, rt.

Table 1. Physico-chemical properties of compounds.

| No. | Rf[a] (Solvents) | MP (°C) | $[\alpha]_D$ ($CHCl_3$) | $^1H$ NMR (270, 300 or 500 MHz; $CDCl_3$; $\delta$ ppm; $J$ Hz) |
|---|---|---|---|---|
| **1a** | 0.55 (A) | 185~186 | −58° (*c* 0.18) | These $^1H$ NMR spectra have been already reported in our previous papers[2,3]. |
| **1b** | 0.29 (A) | 280~281 (dec.) | −86° (*c* 0.18) | |
| **2a** | 0.48 (A) | 268~269 | +129° (*c* 0.18) | |
| **2b** | 0.16 (A) | 208~209 | +171° (*c* 0.18) | |
| **5a** | 0.33 (B) | 105~106 | −38° (*c* 1.1) | $\delta$ 1.13 (3H, d, $J$=6), 3.05 (3H, s), 3.12 (1H, d, $J$=7), 3.39 (3H, s), 3.49 (1H, d, $J$=7), 3.75 (1H, dq, $J$=6 and 1.6), 3.82 (1H, q, $J$=1.6), 4.05 (3H, s), 4.89 (1H, d, $J$=16), 5.27 (1H, d, $J$=16), 6.01 (1H, d, $J$=2), 6.43 (1H, d, $J$=2), 9.51 (1H, s). |
| **5b** | 0.24 (B) | 115~116 | −64° (*c* 0.75) | $\delta$ 1.25 (3H, d, $J$=6), 3.21 (3H, s), 3.22 (1H, d, $J$=7), 3.46 (3H, s), 3.63 (1H, dq, $J$=6 and 1.6), 3.89 (1H, d, $J$=1.6), 4.07 (3H, s), 4.28 (1H, d, $J$=7), 4.90 (1H, d, $J$=16), 5.25 (1H, d, $J$=16), 6.01 (1H, d, $J$=2), 6.45 (1H, d, $J$=2), 9.53 (1H, s). |
| **8a** | 0.32 (B) | 202~303 | −46° (*c* 1.1) | $\delta$ 1.26 (3H, d, $J$=6), 3.06 (1H, d, $J$=7), 3.12 (3H, s), 3.42 (3H, s), 3.55 (1H, d, $J$=7), 3.67 (1H, d, $J$=3), 4.05 (3H, s), 4.26 (1H, dq, $J$=6 and 3), 4.86 (1H, d, $J$=16), 5.09 (1H, d, $J$=16), 6.01 (1H, d, $J$=2), 6.42 (1H, d, $J$=2), 9.50 (1H, s). |
| **8b** | 0.18 (B) | 115~116 | +26° (*c* 1.2) | $\delta$ 1.13 (3H, d, $J$=6), 3.23 (3H, s), 3.47 (3H, s), 3.47 (1H, d, $J$=7), 3.72 (1H, d, $J$=2), 4.07 (3H, s), 4.18 (1H, dq, $J$=6 and 2), 4.31 (1H, q, $J$=7), 4.89 (1H, d, $J$=16), 5.08 (1H, d, $J$=16), 6.03 (1H, d, $J$=2), 6.45 (1H, d, $J$=2), 9.53 (1H, s), |
| **9a** | 0.48 (C) | 160~161 | +81° (*c* 1.6) | $\delta$ 1.15 (3H, d, $J$=6), 1.69 (1H, d, $J$=3), 3.44 (3H, s), 3.91 (3H, s), 3.97 (2H, m), 4.90 (1H, d, $J$=16), 5.02 (1H, d, $J$=10), 5.03 (1H, d, $J$=16), 5.13 (1H, d, $J$=10), 6.01 (1H, d, $J$=3), 6.54 (1H, d, $J$=3), 7.32~7.50 (5H, m). |
| **9b** | 0.17 (C) | 120~121 | +146° (*c* 0.66) | $\delta$ 1.05 (3H, d, $J$=7), 3.41 (3H, s), 3.91 (3H, s), 3.97 (1H, d, $J$=3), 4.09 (1H, dq, $J$=7 and 3), 5.02 (1H, d, $J$=10.5), 5.05 (2H, s), 5.17 (1H, d, $J$=10.5), 5.90 (1H, d, $J$=3), 6.52 (1H, d, $J$=3), 7.34~7.60 (5H, m). |
| **10** | 0.48 (D) | Syrup | +60° (*c* 0.17) | $\delta$ 1.28 (3H, d, $J$=7), 3.37 (3H, s), 3.91 (3H, s), 4.04 (1H, q, $J$=7), 4.82 (1H, d, $J$=15), 5.09 (1H, d, $J$=11), 5.18 (1H, d, $J$=11), 5.25 (1H, d, $J$=15), 5.94 (1H, d, $J$=2), 6.59 (1H, d, $J$=2), 7.35~7.55 (5H, m). |
| **11** | 0.56 (D) | Syrup | +2.4° (*c* 0.34) | $\delta$ 1.23 (3H, d, $J$=7), 3.40 (3H, s), 3.90 (3H, s), 4.10 (1H, q, $J$=7), 4.76 (1H, d, $J$=15), 4.98 (1H, d, $J$=11), 5.21 (1H, d, $J$=11), 5.44 (1H, d, $J$=15), 5.98 (1H, d, $J$=2.4), 6.58 (1H, d, $J$=2.4), 7.35~7.55 (5H, m). |
| **12a** | 0.57 (C) | 129~130 | −49° (*c* 0.82) | $\delta$ 1.28 (3H, d, $J$=6), 1.54 (1H, d, $J$=5), 3.42 (3H, s), 3.63 (1H, dq, $J$=6 and 2), 3.84 (1H, dd, $J$=5 and 2), 3.89 (3H, s), 4.78 (1H, d, $J$=17), 5.01 (1H, d, $J$=11), 5.14 (1H, d, $J$=11), 5.38 (1H, d, $J$=17), 5.97 (1H, d, $J$=2), 6.52 (1H, d, $J$=2), 7.33~7.52 (5H, m). |
| **12b** | 0.31 (C) | 158~159 | −132° (*c* 1.1) | $\delta$ 1.23 (3H, d, $J$=6), 3.41 (3H, s), 3.60 (1H, q, $J$=6 and 0), 3.90 (3H, s), 3.94 (1H, s, $J$=0), 4.96 (1H, d, $J$=16), 5.03 (1H, d, $J$=12), 5.16 (1H, d, $J$=12), 5.30 (1H, d, $J$=16), 5.84 (1H, d, $J$=3), 6.52 (1H, d, $J$=3), 7.34~7.56 (5H, m). |

[a] Solvents: (A) PhH : MeCN = 2 : 1 (B) PhMe : MeCN = 3 : 1 (C) PhH : MeCN = 4 : 1 (D) PhH : MeCN = 10 : 1.

Fig. 2. ORTEP drawing of compound **9a**.



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KUNIAKI TATSUTA*
TAKESHI NAGAI
TAKANOBU MASE
TAKUYA TAMURA

Table 2. Inhibitory activities in the binding of [$^3$H]MK-801 [$IC_{50}$ ($\mu$M)].

| Compounds | | | |
|---|---|---|---|
| **1a** | **1b** | **2a** | **2b** |
| 40 | 14 | >200 | 0.4 |

Department of Applied Chemistry,
School of Science and Engineering,
Waseda University
3-4-1 Ohkubo, Shinjuku, Tokyo 169-8555, Japan

HIKARU NAKAMURA

Institute of Microbial Chemistry,
3-14-23 Kamiosaki, Shinagawa,
Tokyo 141-0021, Japan

(Received February 10, 1999)

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