Synthesis and Biological Evaluation of the Analogs of Bioxanthracenes ES-242s, *N*-Methyl-D-aspartate Antagonists

Sir:

Bioxanthracenes ES-242s were isolated from the culture broth of *Verticillium* sp. in 1992 to inhibit the binding of [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine) or [^{3}H]MK-801 (5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate) to the *N*-methyl-D-aspartate (NMDA) receptor complex[1,2]. These were expected to show neuroprotective properties useful in the treatment of neurodegenerative diseases[3].

Very recently, we have synthesized natural ES-242-4 (**1a**) and its atropisomer (**1b**) from the α,β-unsaturated lactone **5** through dimerization of a monomeric naphthopyran (oxanthracene[2]) **9** as shown in Scheme 1[4].

The C-4 hydroxy group of the unsaturated lactone **5** was isomerized to give **6**, which reacted with **7** in tandem Michael-Dieckmann reaction type to afford a single product **8**. Aromatization of **8** with DDQ, followed by deoxygenation, gave a monomer **9**, which was submitted to oxidative dimerization[4,5]. ES-242-4 (**1a**) and its atropisomer (**1b**) were obtained in 37% and 38% yields, respectively.

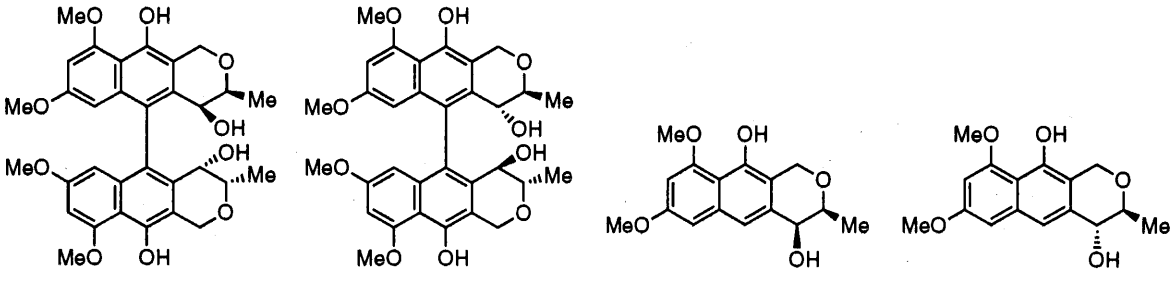
Now, we describe herein the synthesis and preliminary biological evaluation of the diastereomeric analogs of ES-242-4 (**2a** and **2b**) and monomers **3** and **4** to understand the structure-activity relationships (Fig. 1). The analogs **2a** and **2b** were synthesized from **5** by the similar synthetic strategies but without isomerization of the C4 hydroxy group (Scheme 2 and Table 1).

The *O*-methoxymethyl derivative **10**, however, reacted with **7** to give a diastereomeric mixture **11**, which was aromatized by treatment with cyclohexene and Pd-C to produce a single product **12**. Hydride reduction of the corresponding *O*-benzyl ether **13** were followed by deoxygenation with triethylsilane and TFA to give **14**. The *O*-benzyl group was effectively removed by cyclohexadiene and Pd-C to give a monomeric naphthopyran **15**. Oxidative dimerization of **15** afforded a diastereomeric mixture **16** [FAB-MS *m/z* 667 $(M+H)^+$], which was aromatized by NaOH and deprotected with HCl produced from AcCl in MeOH. Finally, two desired atropisomers **2a** [FAB-MS *m/z* 578 (M^+)] and **2b** [FAB-MS *m/z* 578 (M^+)] were obtained in 72% and 17% yields, respectively, by silica gel column chromatography with PhH - MeCN (5 : 1) [Rf values on TLC with PhH - MeCN (10 : 3); 0.35 (**2a**) and 0.07 (**2b**)], although their absolute structures on axial chiralities remained undetermined.

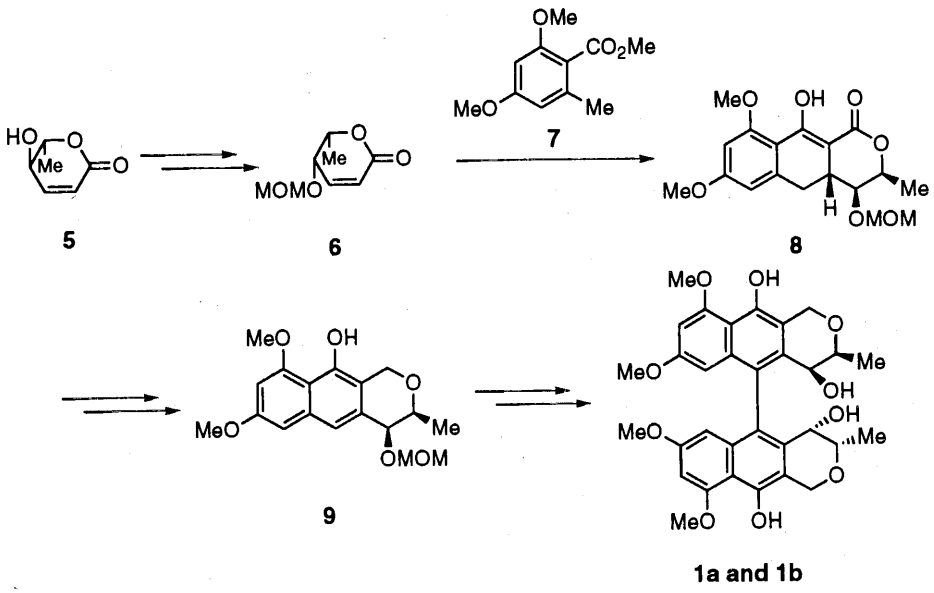
In order to discuss the structure-activity relationships, the monomers **3** and **4** were also prepared by deprotection of **9** and **15** with AcCl in MeOH, respectively.

The inhibitory activities against [^{3}H]MK-801 binding to the NMDA receptor were assayed according to the methods reported by TOKI[3] as summarized in Table 2. Both the synthetic ES-242-4 (**1a**) and its atropisomer (**1b**) showed significant inhibiting activities in a similar concentration range. However, their diastereomeric isomers **2a** and **2b** showed remarkable differences: namely, the one isomer **2b** was the most potent among the tested compounds, inhibiting [^{3}H]MK-801 binding with an IC_{50} value of 0.4 μM, while the other **2a** showed almost no activities. Furthermore, the monomers **3** and **4** also exhibited no activities, suggesting that the dimerization of a naphthopyran (or oxanthracene) is essential for the appearance of such inhibitory activities.

Fig. 1.



Scheme 1.



Scheme 2.

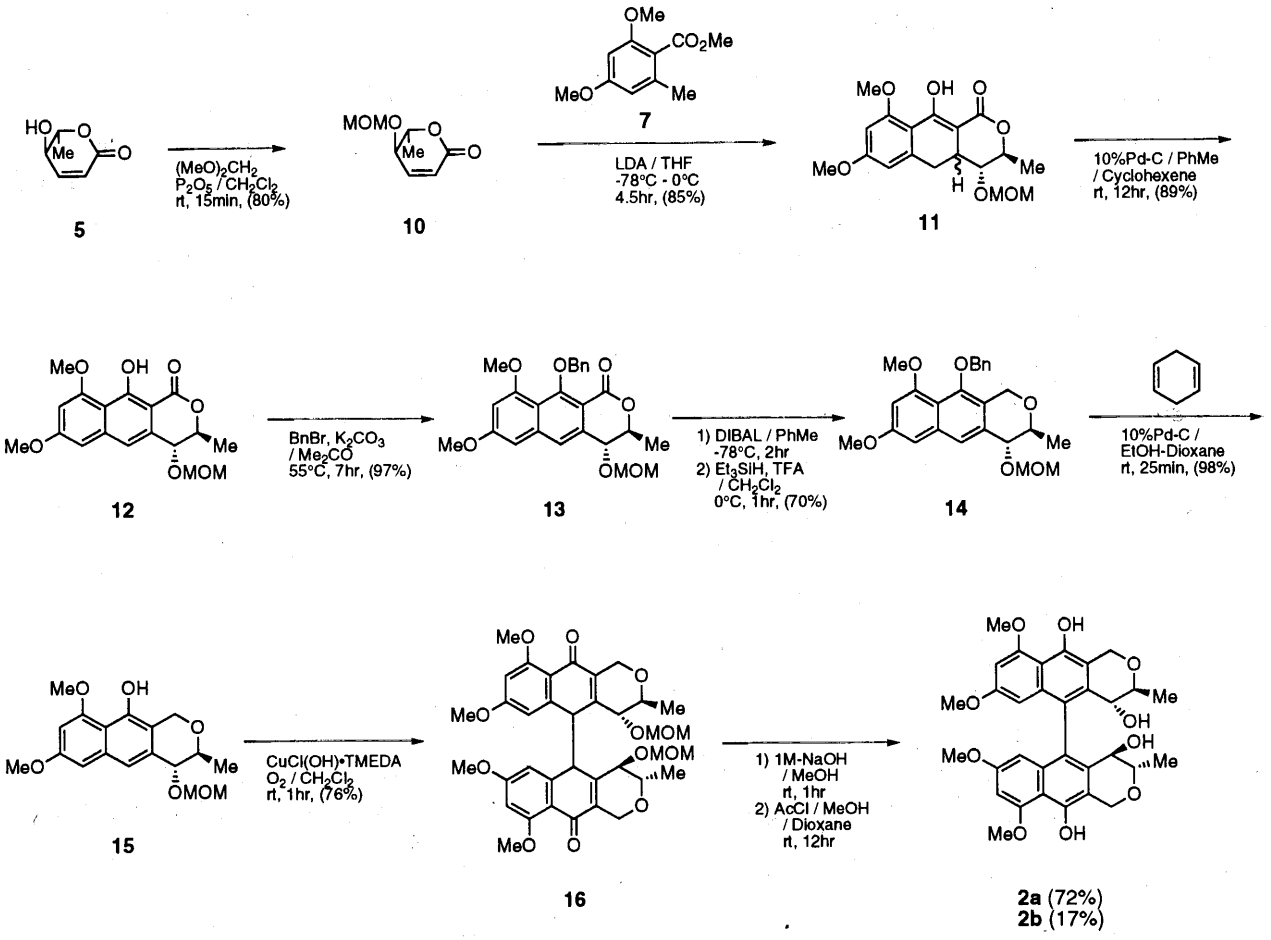


Table 1. Physico-chemical properties of compounds.

No.	Mp (°C)	$[\alpha]_D$ ($CHCl_3$)	^{1}H-NMR (270 or 400MHz; $CDCl_3$; δ ppm; *J* Hz)
2a	268 - 269	+129° (*c* 0.18)	δ 1.25(3H, d, *J*=6.5), 3.45(3H, s), 3.97(1H, d, *J*=4.0), 3.99(1H, qd, *J*=6.5&4.0), 4.07(3H, s), 4.95(1H, d, *J*=16.0), 5.00 (1H, d, *J*=16.0), 6.01(1H, d, *J*=2.0), 6.47,(1H, d, *J*=2.0), 9.54(1H, s).
2b	208 - 209	+171° (*c* 0.18)	δ 1.14(3H, d, *J*=6.0), 3.46(3H, s), 3.91(1H, d, *J*=3.0), 4.08(1H, qd, *J*=6.0&3.0), 4.07(3H, s), 4.95(1H, d, *J*=16.0), 5.03 (1H, d, *J*=16.0), 5.96(1H, d, *J*=2.0), 6.48,(1H, d, *J*=2.0), 9.52(1H, s).
3	186 - 187	-28° (*c* 0.55)	δ 1.44(3H, d, *J*=6.0), 3.83(1H, qd, *J*=6.0&1.6), 3.89(3H, s,), 4.02(3H, s), 4.36(1H, d, *J*=1.6), 4.74(1H, d, *J*=16.0), 5.11 (1H, d, *J*=16.0), 6.45(1H, d, *J*=2.0), 6.71,(1H, d, *J*=2.0), 7.27(1H, s), 9.27(1H, s).
4	207 - 208	+128° (*c* 0.55)	δ 1.44(3H, d, *J*=6.0), 3.64(1H, dq, *J*=8.0&6.0), 3.88(3H, s), 4.02(3H, s), 4.46(1H, d, *J*=8.0), 4.81(1H, d, *J*=16.0), 5.01 (1H, d, *J*=16.0), 6.44(1H, d, *J*=2.0), 6.71,(1H, d, *J*=2.0), 7.40(1H, s), 9.23(1H, s).
10	Oil	-61° (*c* 1.0)	δ 1.47(3H, d, *J*=6.0), 3.42(3H, s), 4.13(1H, ddd, *J*=8.0, 3.0&2.0), 4.34(1H, d, *J*=6.0), 4.48(1H, dq, *J*=8.0&6.0), 4.80(1H, d, *J*=6.0), 6.02(1H, dd, *J*=10.0&2.0), 6.86(1H, dd, *J*=10.0&3.0).
12	128 - 129	-99° (*c* 1.0)	δ 1.37(3H, d, *J*=7.0), 3.44(3H, s), 3.93(3H, s), 4.00(3H, s), 4.54(1H, d, *J*=3.0), 4.64(1H, d, *J*=7.0), 4.73(1H, d, *J*=7.0), 4.94(1H, qd, *J*=7.0&3.0), 6.54(1H, d, *J*=2.0), 6.68,(1H, d, *J*=2.0), 7.06(1H, s), 13.13(1H, s).
13	Syrup	-88° (*c* 1.0)	δ 1.24(3H, d, *J*=6.0), 3.48(3H, s), 3.84(3H, s), 3.93(3H, s), 4.58(1H, d, *J*=4.0), 4.72(1H, d, *J*=7.5), 4.79(1H, qd, *J*=6.0&4.0), 4.85(1H, d, *J*=7.5), 5.06(1H, d, *J*=10.0), 5.31(1H, d, *J*=10.0), 6.56(1H, d, *J*=2.0), 6.75,(1H, d, *J*=2.0), 7.25-7.45(3H, m), 7.44(1H, s), 7.6-7.7, (2H, m).
14	Syrup	+5.8° (*c* 1.0)	δ 1.33(3H, d, *J*=6.0), 3.53(3H, s), 3.89(3H, s), 3.92(3H, s), 3.96(1H, quint, *J*=6.0), 4.49(1H, d, *J*=6.0), 4.81(1H, d, *J*=16.0), 4.88(1H, d, *J*=11.0), 4.89(1H, d, *J*=6.0), 4.93(1H, d, *J*=6.0), 4.95(1H, d, *J*=11.0), 5.01 (1H, d, *J*=16.0), 6.52(1H, d, *J*=2.0), 6.75,(1H, d, *J*=2.0), 7.56(1H, s), 7.30-7.50, (5H, m).
15	117 - 118	+12° (*c* 1.0)	δ 1.36(3H, d, *J*=6.0), 3.52(3H, s), 3.89(3H, s), 4.01(1H, quint, *J*=6.0), 4.02(3H, s), 4.46(1H, d, *J*=6.0), 4.86(1H, d, *J*=7.0), 4.86(1H, d, *J*=16.0), 4.90(1H, d, *J*=7.0), 4.96(1H, d, *J*=16.0), 6.48(1H, d, *J*=2.0), 6.69(1H, d, *J*=2.0), 7.27(1H, s), 9.22(1H, s).

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

Compounds					
1a	**1b**	**2a**	**2b**	**3**	**4**
40	14	>200	0.4	>200	>200

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