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The First Total Synthesis of a Bioxanthracene (-)-ES-242-4, an *N*-Methyl-D-aspartate Receptor Antagonist

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Abstaract: Bioxanthracene (-)-ES-242-4 has been synthesized from oxidative dimerization of a naphthopyran which was derived from an α,β-unsaturated lactone and methyl 2,4-dimethoxy-6-methylbenzoate through tandem Michael-Dieckmann reactions.

Bioxanthracene (-)-ES-242-4 (**1**) was isolated from the culture broth of *Verticillium* sp. in 1992 as one of eight antagonists for the *N*-methyl-D-aspartate receptor.[1-3] These novel natural products are reported to inhibit the [^{3}H]thienyl cyclohexylpiperidine binding to rat crude synaptic membranes, and therefore, are of potential therapeutic interest for the treatment of neurodegenerative diseases. (-)-ES-242-4 (**1**) is structurally remarkable having an axially chiral binaphthalene core that is adorned with two pyrans of the same absolute chirality. Our interest in the construction of densely functionalized naphthopyran ring systems,[4,5] *via* tandem Michael-Dieckmann reactions, promoted us to attempt the first stereocontrolled total synthesis of (-)-ES-242-4 (**1**).

To this end, we naturally selected the naphthopyran derivative **7** as our first target, which could be derived from the α,β-unsaturated lactone **4** and methyl 2,4-dimethoxy-6-methylbenzoate (**5**) through Michael and Dieckmann reactions. We conjectured that the pivotal conversion of a monomer **10** to a dimer **1** could be accomplished by oxidative coupling.[6]

The α,β-unsaturated lactone **2**[7], which was derived from di-*O*-acetyl-L-rhamnal according to reported procedures, was submitted to Mitsunobu inversion with HCO_2H, followed by hydrolysis to give **3** and methoxymethylation to afford **4** (mp 31°C, $[\alpha]_D$ +275°). On the other hand, methyl 2,4-dimethoxy-6-methylbenzoate (**5**) was obtained from 3,5-dihydroxytoluene under the protocols described by Solladié.[8]

Addition of lithiated **5** to **4** was followed by Dieckmann reaction to provide a single product **6** as expected from *trans* addition to the C-4 *O*-MOM group. Aromatization of **6** gave **7**[9][mp 148°C, $[\alpha]_D$ -336°(MeOH)], which was converted to the *O*-benzyl derivative **8** (syrup, $[\alpha]_D$ +64°). Hydride reduction of **8** to the lactol was followed by treatment with Et_3SiH and TFA. This reaction gave the pyran **9** (mp 98°C, $[\alpha]_D$ +38°), which, upon mild hydrogenolysis, was converted to **10** (mp 133°C, $[\alpha]_D$ +58°). Oxidative dimerization of **10** was assayed under several conditions[6] with a variety of metals such as Fe(II), Mn(II), and Cu(II). The best result was realized by the protocols reported by Noji, Nakajima, and Koga using CuCl(OH)·TMEDA, which was prepared from CuCl and TMEDA under oxygen.[6] The diastereomeric mixture of **11** was obtained as a stable intermediate (IR [KBr] 1648 cm^{-1}). Finally, **11** was aromatized with aq. NaOH followed by acid hydrolysis to remove the *O*-MOM group. Expectedly, two atropisomers were produced and isolated by silica gel column chromatography with PhH - MeCN (4 : 1) to give **1a** and **1b** in 37% and 38% overall yields, respectively: **1a**: Rf 0.36 [TLC: PhH - MeCN (4 : 1)]; mp 185°C, $[\alpha]_D$ -58°; **1b**: Rf 0.14, mp 280°C (dec.), $[\alpha]_D$ -86°. The former **1a** was identical in all respects with an authentic sample of the natural (-)-ES-242-4.[10]

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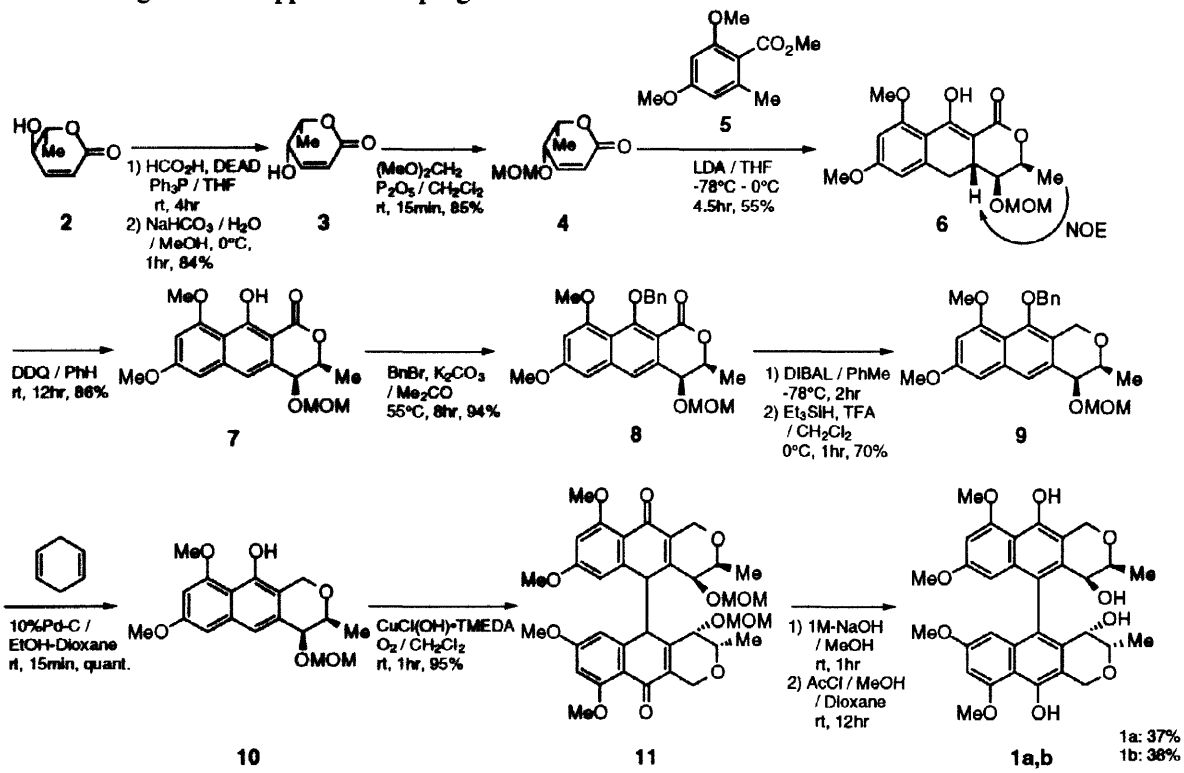

REFERENCES AND NOTES

1. Toki, S.; Ando, K.; Yoshida, M.; Kawamoto, I.; Sano, H.; Matsuda, Y. *J. Antibiot.*, **45**, 88-93 (1992).
2. Toki, S.; Ando, K.; Kawamoto, I.; Sano, H.; Yoshida, M.; Matsuda, Y. *J. Antibiot.*, **45**, 1047-1054 (1992).
3. Toki, S.; Tsukuda, E.; Nazawa, M.; Nonaka, H.; Yoshida, M.; Matsuda, Y. *J. Biolog. Chem.*, **267**, 14884-14892 (1992).
4. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.*, **58**, 1699-1706 (1985).
5. Tatsuta, K.; Yoshimoto, T.; Gunji, H. *J. Antibiot.*, **50**, 289-290 (1997).
6. Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.*, **35**, 7983-7984 (1994).
7. Jarglis, P.; Lichtenthaler, F. W. *Tetrahedron Lett.*, **23**, 3781-3784 (1982).
8. Solladié, G.; Rubio, A.; Carreño, M. C.; Ruano, J. L. G. *Tetrahedron Assym.*, **1**, 187-198 (1990).
9. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Optical rotations were measured in $CHCl_3$, except for **7** in MeOH, using a 0.5 dm tube at 22°C. Significant ^{1}H-NMR spectral data (270, 400, and 500 MHz, δ; TMS=0) are the following.
   1a($CDCl_3$): 1.27(3H, d, *J*=6.0Hz), 1.45(1H, d, *J*=5.0Hz), 3.44(3H, s), 3.66(1H, qd, *J*=6.0, 1.6Hz), 3.81(1H, dd, *J*=5.0, 1.6Hz), 4.06(3H, s), 4.82(1H, d, *J*=16.0Hz), 5.25 (1H, d, *J*=16.0Hz), 5.99(1H, d, *J*=2.0Hz), 6.46,(1H, d, *J*=2.0Hz), 9.54(1H, s). **1b**($CDCl_3$): 1.23(3H, d, *J*=6.0Hz), 1.28(1H, br s), 3.46(3H, s), 3.66(1H, qd, *J*=6.0, 1.6Hz), 3.89(1H, d, *J*=1.6Hz), 4.06(3H, s), 4.91(1H, d, *J*=16.0Hz), 5.23 (1H, d, *J*=16.0Hz), 5.91(1H, d, *J*=2.0Hz), 6.46,(1H, d, *J*=2.0Hz), 9.51(1H, s). **4**($CDCl_3$): 3.99(1H, dd, *J*= 5.0, 3.0Hz), 4.58(1H, qd, *J*= 6.9, 3.0Hz). **6**($CDCl_3$): 2.54(1H, t, *J*=14.0 Hz), 2.80(1H, ddd, *J*=14.0, 10.0, 5.0Hz), 2.95(1H, dd, *J*=14.0, 5.0Hz), 14.36(1H, s). **7**(Me_2CO-d_6): 4.63(1H, d, *J*=2.0Hz), 7.10(1H, s), 12.96(1H, s). **8**(Me_2CO-d_6): 4.97(1H, d, *J*=10.0Hz), 5.22(1H, d, *J*=10.0Hz), 7.25-7.40(3H, m), 7.53(1H, s), 7.55-7.65, (2H, m). **9**($CDCl_3$): 4.82(1H, d, *J*=16.0Hz), 5.25 (1H, d, *J*=16.0Hz), 7.50(1H, s). **10**($CDCl_3$): 7.20(1H, s), 9.25(1H, s).
10. An authentic sample of (-)-ES-242-4 was kindly provided by Dr. S. Toki, Kyowa Hakko Kogyo Co., Ltd.