SYNTHESIS OF 9-ETHOXYCARBONYL-10(10a*H*)-OXO-5,6,7,8,8a,9-HEXAHYDRO-9,10a-ANTHRACENECARBOLACTONE AND RELATED COMPOUNDS BY MANGANESE(Ⅲ) MEDIATED CYCLIZATION

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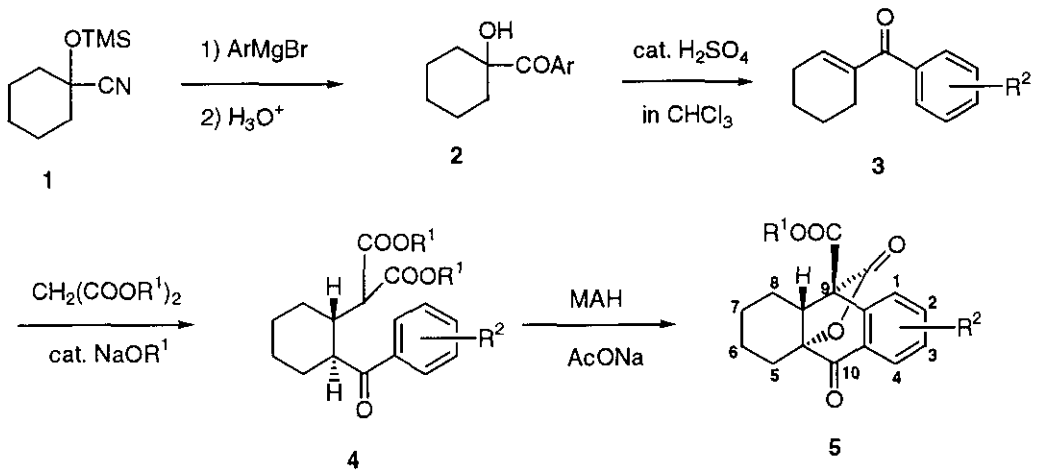
Abstract — Novel tetracyclic lactone (**5a**), 9-ethoxycarbonyl-10(10a*H*)-oxo-5,6,-7,8,8a,9-hexahydro-9,10a-anthracenecarbolactone, was obtained in 34.8% yield by oxidative cyclization of diethyl *trans*-2-benzoylcyclohexylmalonate (**4a**) with manganese(Ⅲ) acetate dihydrate in the presence of sodium acetate in acetic acid.

Manganese(Ⅲ) acetate dihydrate (MAH)[1,2] has been known as a unique reagent for homolysis of active C-H bond such as acetyl, malonic, and β-diketonic C-H, and the reagent has been applied to preparation of various carbocyclic and heterocyclic compounds under intramolecular C-C bond formation.[3~5] In this communication, we would like to report an interesting intramolecular double cyclization by treatment of diethyl *trans*-(2-benzoylcyclohexyl)malonate[6] (**4a**) with MAH to novel tetracyclic 9-ethoxycarbonyl-10(10a*H*)-oxo-5,6,7,8,8a,9-hexahydro-9,10a-anthracenecarbolactone (**5a**).



Scheme 1

Several *trans*-2-(substituted aroyl)cyclohexylmalonates (**4a-e**), substrates for the MAH cyclization, were

prepared by Michael addition of dialkyl malonate to 1-benzoylcyclohexene, which was readily obtained from cyclohexanone trimethylsilylcyanohydrin (**1**),[7] according to the procedure of our previous report.[6] (Scheme 1) The *trans* stereochemistry of **4** is obvious because of the thermodynamically controlled reaction conditions[8] and was also supported by $J_{C1\text{-}H-C2\text{-}H}$ value, 7.5 – 7.7 Hz. Treatment of **4a** at 70℃ with two equivalents of MAH in acetic acid gave a crystalline product in 16.1 % yield. Structure of the product was estimated as **5a** on the basis of its spectral (IR, ^{1}H-NMR, MS) and analytical data, and finally determined on the basis of X-Ray analysis as shown in Figure 1.[9] Yield of **5a** was somewhat improved by addition of sodium acetate and increase of MAH as shown in Table 1.

Table 1. Influence of Amount of the Reagents

Entry	MAH (equiv.)	AcONa (equiv.)	Isolated Yield (%) of **5a**
1	4	0	16.1
2	1	2	5.6
3	2	2	13.3
4	4	2	34.8
5	4	4	33.9
6	8	2	35.1

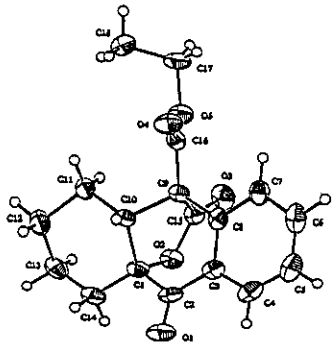


Figure 1 ORTEP View of **5a**

Influences of introduction of an appropriate substituent into the benzene ring and change of alkyl group in the malonic ester portion were examined by using the best conditions of Entry 4 in Table 1, and the results were summarized in Table 2. Although the yield of dimethyl malonate derivative (**4b**; Entry 2) gave almost same results as that of the diethyl derivative (**4a**; Entry 1), dibenzyl derivative (**4c**; Entry 3) gave only a complex mixture. Introduction of electron donating 4-methoxy group into the bezene ring (Entries 5 and 6) somewhat improved yield of the cyclized product, but electron withdrawing 4-chloro group (Entry 7) decreased the yield. Introduction of a methoxy group into 2-position of the benzene ring (Entry 4) gave a complex mixture probably due to its interference for cyclization.[10]

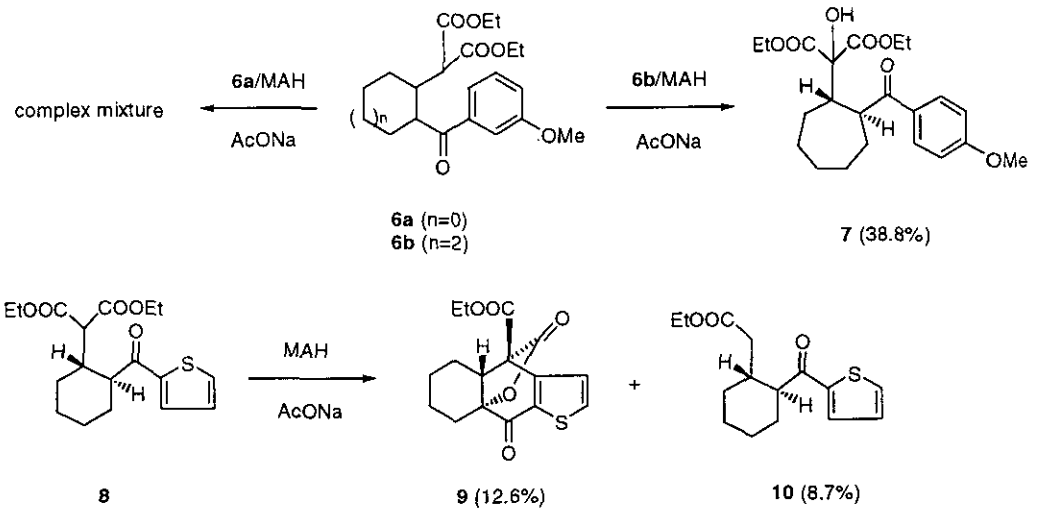
Table 2. Influence of Alkoxy Group in the Ester and Substituent on the Benzene Ring of 4[a]

Entry	Substrate	R^1	R^2	Product	Isolated Yield (%)
1	**4a**	Et	H	**5a**	34.8
2	**4b**	Me	H	**5b**	30.5
3	**4c**	Bn	H	**5c**	complex mixture
4	**4d**	Et	2-MeO	**5d**	complex mixture[b]
5	**4e**	Et	4-MeO	**5e**	42.1
6	**4f**	Me	4-MeO	**5f**	39.8
7	**4g**	Et	4-Cl	**5g**	26.0

a: Four equiv. of MAH and two equiv. of AcONa were used at 70 ℃.

b: Considerable amount of *o*-Anisic acid was detected on TLC in the reaction product mixture.

Unfortunately, cyclopentyl derivative (**6a**) also gave a complex mixture, and cycloheptyl derivative (**6b**) did not give any cyclized product but only a hydroxymalonate (**7**) in 38.8 % yield. Diethyl (2-thienoyl- cyclohexyl)malonate (**8**) was similarly prepared, and it was subject to the MAH oxidation to give the cyclized tetracycle (**9**) in 12.6 % and uncyclized **10** in 8.7 % yield, respectively.



Scheme 2

By the present reaction sequence, the relatively complex polycyclic and polyfunctiona-lized system could be prepared in short steps starting from cyclohexanone. Elucidation of the reaction mechanisms and improvement of the cyclization yield are in progress, and we are going to prepare various interesting tri- and tetracyclic compounds by the present MAH mediated cyclization for testing their biological activities as an application. We also think it may be applicable to the construction of some antibiotic tetracycline mimics.

Typical Procedure. Synthesis of 5a : MAH (3.22 g, 12 mmol) and AcONa (492 mg, 6 mmol) were added to a solution of **4a** (1.04g, 3 mmol) in AcOH (10 mL), and the mixture was stirred at 70 ℃ for 24 h under N_2 atmosphere. The mixture was filtered to remove inorganic precipitates, and the filtrate was evaporated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with ether (20 mL × 3). The ethereal layer was dried with Na_2SO_4, and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel with AcOEt - hexane (1 : 10) to give colorless needles (328 mg, 34.8 %). mp 131.0 – 132.5 ℃ (AcOEt – hexane). IR ($CHCl_3$): 1796 (lactone), 1724 (ester), 1704 (ketone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 300 MHz) δ : 8.12 (dd, 1H, Ar-H, J = 7.6 and 1.6 Hz), 7.61 (td, 1H, Ar-H, J = 7.6 and 1.6 Hz), 7.52 (td, 1H, Ar-H, J = 7.6 and 1.3 Hz), 7.25 (dd, 1H, Ar-H, J = 7.6 and 1.3 Hz), 4.43 (q, 2H, -OCH_2CH_3, J = 7.2 Hz), 2.96 (dd, 1H, CH of C-8a, J = 11.7 and 6.1 Hz), 2.47 - 2.41 (m, 2H, CH_2 of C-5), 1.39 (t, 3H, -OCH_2CH_3, J = 7.1 Hz), 1.57 - 1.24 (m, 6H, CH_2 of C-6, C-7 and C-8). ^{13}C-NMR ($CDCl_3$; 75 MHz) δ : 190.10, 169.95, 165.96, 138.58, 134.81, 129.66, 129.12,

128.28, 125.65, 83.66, 63.00, 62.12, 52.03, 25.52, 24.72, 22.97, 19.46, 14.21. LRMS (*m/z*): 314 (M^+). *Anal.* Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.77; H, 5.78.

ACKNOWLEDGMENT

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5. For example, treatment of allyl methyl methylmalonate with MAH afforded 2-methyl-γ-lactone derivatives in 73% yield [B. B. Snider, R. Mohan, S. A. Kates, *J. Org. Chem.*, 1985, **50**, 3659].
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8. For example, **4a** was prepared in 73 % yield by treatment of 1-benzoylcyclohexene (**3**) with diethyl malonate in ethanol (80 ℃) in the presence of about 10 mol% of NaOEt.
9. We sent the X-Ray data to Cambridge Crstallograpic Data Center of UK.
10. MAH cleaves active C-H bond in a homolysis manner. The present reaction may be initiated by homolysis of the active C-H bond at the malonate portion of **4**. At a later stage, a carbon radical is generated at the ring juncture (corresponding to C-10a position of **5**) and it probably react with H_2O to introduce OH group at the position.

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