REGIOSELECTIVE SYNTHESIS OF MATURONE VIA LEWIS ACID CATALYZED DIELS-ALDER REACTION

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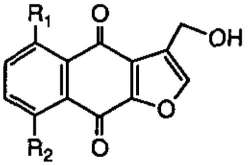
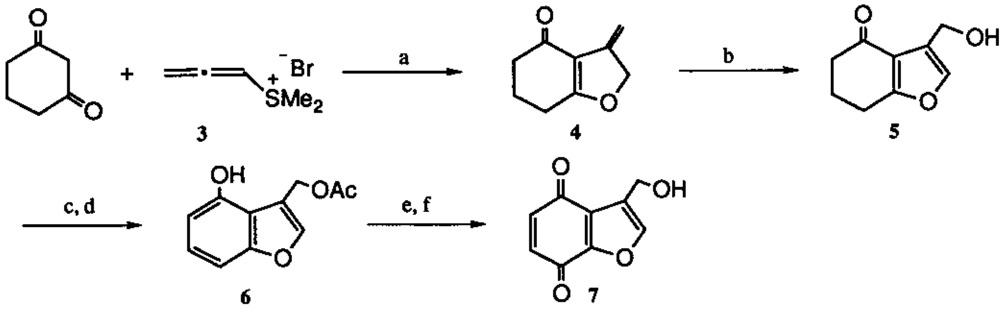
Abstract—Total synthesis of maturone (**1**) by the regioselective Dials-Alder reaction of benzofuranquinone (**7**) is described. Compound (**7**) was easily obtained by an application of the fused furan constructing method using allenic sulfonium salt (**3**) and cyclic 1,3-dicarbonyl compound.

Diels-Alder reaction of quinones has been used frequently for the construction of fundamental skeleton of many natural products. In furanosesquiterpene synthesis, the cycloaddition reaction strategy between benzofuranquinone and appropriate diene is also one of the most useful and direct synthetic approaches[1] but its regiochemical control is a crucial problem when using unsymmetrical diene and dienophile. As part of our research program,[2] we now wish to report the short step synthesis of maturone [3,4] *via* regioselective Diels-Alder reaction.



1; R_1=Me , R_2=H
2; R_1=H , R_2=Me

Maturone (**1**) is a sesquiterpenoid, isolated from *Cacalia decomposita*, the root extract of which has been used for the treatment of diabetes and other diseases. The synthesis of maturone has been already attained by Ghera *et al.* and they constructed lineally tricyclic skeleton of maturone by regioselective annulating method between benzobromosulfone and γ-lactone.[5] In our retrosynthetic analysis, the linear tricyclic furan structure of maturone (**1**) is considered to be formed by the Diels-Alder reaction of diene and 3-hydroxymethylbenzofuranquinone (**7**) as a suitable dienophile. Thus, the desired key compound (7) was readily obtained by furannulation strategy using the reaction of cyclic 1,3-dicarbonyl compound and allenic sulfonium salt (3)[2] as shown in Scheme I. The reaction of 3 with enolate anion of 1,3-cyclohexanedione at room temperature afforded 4 in 50% yield.[6] Compound (4) was treated with monoperoxyphthalic acid magnesium salt (MMPP) to give 3-hydroxymethylfuran (5). Acetylation of 5 followed by aromatization *via* silyl enol ether afforded the phenol (6), which was oxidized to benzofuranquinone (7) by Fremy's salt after hydrolysis.

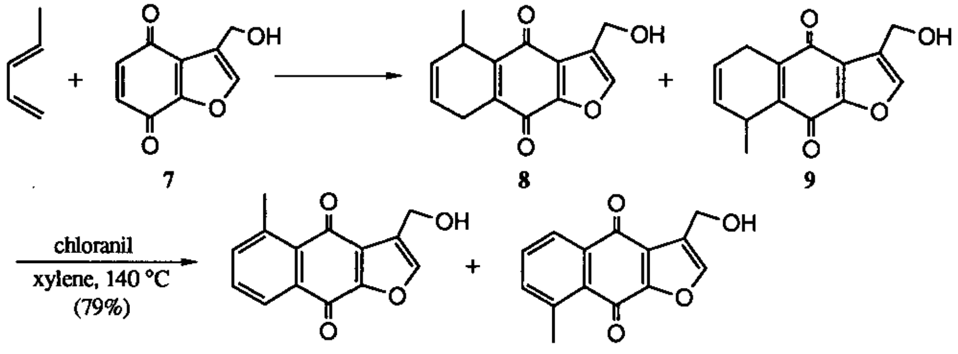


Scheme I. Reagents and Conditions ; (a) NaOEt, EtOH, room temperature, 50%. (b) MMPP, Bu_4NI, CH_2Cl_2 / H_2O, 0 °C, 78%. (c) Ac_2O, Pyridine, DMAP, 0 °C, 99%. (d) TBDMSOTf, NEt_3, 0 °C, then $Pd(OAc)_2$, 48%. (e) K_2CO_3, MeOH, 0 °C, 92%. (f) Fremy's salt, H_2O-KH_2PO_4 buffer, 0 °C, 69%.

The Diels-Alder reaction of 7 with piperylene was conducted in dichloromethane at appropriate temperature to give the cycloadducts, which were oxidized by air to a mixture of regioisomers (8) and (9). These isomers without isolation were aromatized to give a mixture of maturone (1) and isomaturone(2) (Scheme II). Separation of 1 and 2 by column chromatography was unsuccessful, however, the ratio of isomers could be determined by the ^1H nmr spectroscopy. The signals of aromatic methyl group of 1 and 2 were observed at δ 2.81 and 2.83 ppm and the ratio was determined by comparison of integrations of these peaks. Unfortunately, under uncatalyzed reaction, the regioselectivity of cycloaddition was low and the ratio of 1 and 2 was almost same (δ 2.81 / 2.83 ppm = 1.2 : 1).

For regiospecific maturone synthesis, Diels-Alder reaction was examined under Lewis acid catalyzed reaction. The results of the cycloaddition reaction in the presence and absence of Lewis acid were summarized in Table I. In the presence of $BF_3 \cdot Et_2O$, the reaction proceeded with higher regioselectivity compared with the uncatalyzed reaction. Furthermore, using $TiCl_2(Oi\text{-}Pr)_2$[7] as a catalyst, which was freshly prepared from an equimolar amount of $TiCl_4$ and $Ti(Oi\text{-}Pr)_4$, higher regioselectivity was observed compared with $BF_3 \cdot Et_2O$ catalyst. The major isomers were isolated by recrystallization from acetone-*n*-hexane, and the physical and spectral data of which were identical with these of maturone.[8,9]

Scheme II



maturone (1) isomaturone (2)

The short step synthesis of maturone was thus accomplished *via* regioselective Diels-Alder reaction of benzofuranquinone (7). At present, it is difficult to provide a suitable rationale for enhancement of the regioselectivity of Diels-Alder reactions by Lewis acid catalysts. To elucidate these phenomena from the standpoint of frontier molecular orbital theory (FMO theory), we are now performing semi-empirical molecular orbital calculations, and will be published in near future.[10]

Table I. Diels-Alder reaction of **7** with piperylene under Lewis acid catalyzed conditions

Lewis acid (eq.)	temperature (°C)	time *	yield (%)	ratio **1 : 2**
none [in CH_2Cl_2]	r.t.	4 d	96	1.2 : 1
none [in toluene]	110	3 d	78	1.3 : 1
none [in EtOH]	r.t.	4 d	79	1 : 2
$BF_3{\bullet}Et_2O$ (0.5)	- 40	6 h	61	3.3 : 1
(1.0)	- 40	4 h	85	2 : 1
(3.0)	- 40	3 h	96	1 : 1.6
Ti(O*i*-Pr)$_4$ (1.0)	0	1 d	27	1 : 1.2
$TiCl_2$(O*i*-Pr)$_2$ (0.5)	- 50	17 h	66	20 : 1
(1.0)	- 40	3 h	60	12.5 : 1

* d : day, h : hour

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6. When the same reaction was conducted under reflux condition, 3-methylfuran derivative was obtained in 75% yield *via* isomerization of **4**. Compound (**4**) was somewhat unstable and isomerized to 3-methylfuran derivative slowly at room temperature.
7. To a dichloromethane suspension (9 ml) of MS 4A (400 mg) and **7** (60 mg, 0.34 mmol) was added a dichloromethane solution (0.8 ml) of $TiCl_2(Oi\text{-}Pr)_2$ (0.5 eq.) which was freshly prepared from $TiCl_4$ and $Ti(Oi\text{-}Pr)_4$ at low temperature, and the mixture was stirred at - 50 °C. After 1 h, piperylene (0.34 ml, 0.34 mmol) was added to the mixture and stirred for 17 h at -50 °C.
8. ^1H Nmr ($CDCl_3$) δ 2.81 (s, 3H), 3.82 (br s, 1H), 4.77 (s, 2H), 7.53-7.67 (m, 2H), 7.69 (s, 1H), 8.17 (d, J=7.8Hz, 1H), ir ($CHCl_3$) 1680, 1660 cm^{-1}, mp 167-168°C (lit.,[3] 169-170 °C)
9. We thank Professor E. Ghera, the Weizmann Institute of Science, for ^1H nmr spectrum data of maturone.
10. Private communication from Professor E. Osawa.

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