

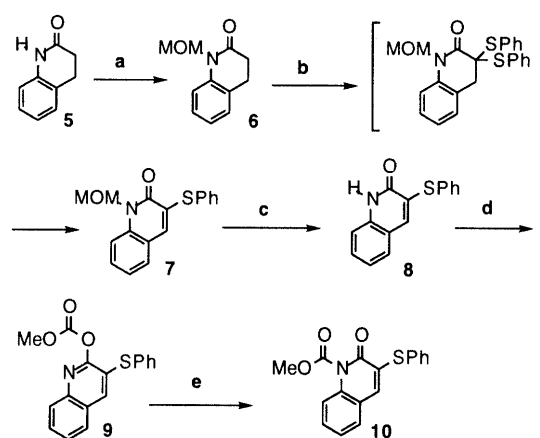
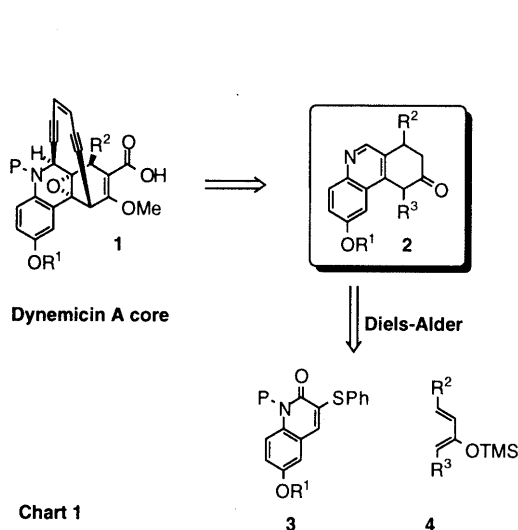
LEWIS ACID CATALYZED DIELS-ALDER REACTION OF 3-PHENYLTHIO-2-QUINOLINONES WITH SILOXYDIENE. SYNTHESIS OF THE INTERMEDIATE FOR DYNEMICIN A CORE

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Preparation of the 1-methoxycarbonyl-3-phenylthio-2-quinolinone (**10**) from dihydro-2-quinolinone (**5**) and its Diels-Alder reaction with 2-trimethylsilyloxy-1, 3-butadiene under Lewis acid catalyst is described. Conversion of the D-A adduct (**11**) to 9-phenanthridinone ketal (**16**) will open a new synthetic route to a dynemicin A core structure.

KEY WORDS Diels-Alder reaction; 2-quinolinone; Lewis acid; phenanthridine

Much attention has been paid to the synthesis¹⁾ of dynemicin A because of its unique structure and remarkable antitumor activity.²⁾ We have already demonstrated the synthetic utility of the Diels-Alder (D-A) reaction of 3-alkyl-dihydropyridinones³⁾ and 3-phenylthio-dihydropyridinones,⁴⁾ the former being successfully applied to the marine alkaloid manzamine A core synthesis. Further extension of these D-A tactics has now led us to investigate the related D-A process, in which 2-quinolinone derivatives (e.g. **3**) are employed as a novel dienophile, with the aim of a synthetic approach to the dynemicin A core structure (e.g. **1**), as summarized in **Chart 1**.



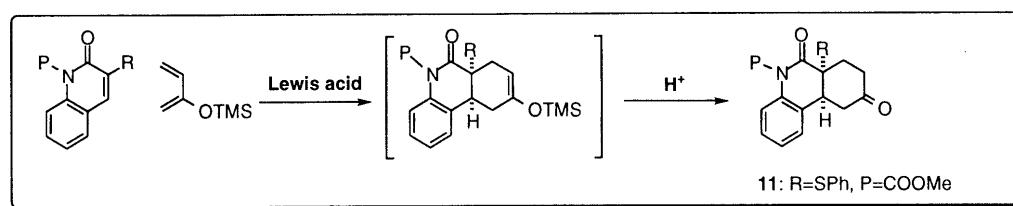
Conditions: a) *n*-BuLi, MOMCl, THF, -78 °C, 94.5 %; b) KN(TMS)₂ (4 eq), PhSSPh (3 eq), THF, -78 °C, 96.0 %; c) TMSI, CH₂Cl₂, or cHCl, MeOH; d) NaH, MeOCOCI, THF, rt, 93.0 %, 2 steps; e) toluene, 120 °C, 86.8 %

We envisaged that the 9-phenanthridinone (**2**), in which the alignment of the carbonyl functionality is totally different from the previously reported intermediates,⁵⁾ could be a versatile intermediate for the dynemicin A core (**1**). (**Chart 1**) A closely related compound is described in the recent approach to the optically active dynemicin A by Myers' group,^{1b)} which prompted us to describe here our own research in this area.

For a successful Diels-Alder reaction, the dienophile had to be carefully designed.^{3, 4)} Thus, *N*-MOM-dihydro-2-quinolinone (**6**), easily prepared from **5**, was treated with a base [KN(TMS)₂ or *t*-BuOK, ~4 equiv.] in the presence of PhSSPh (3 equiv.) to afford the *N*-MOM-3-phenylthio-2-quinolinone (**7**) in 96 % yield. Deprotection of the *N*-MOM group in the usual manner gave an *N*-H derivative (**8**), to which an electron-withdrawing group should be added to gain higher reactivity as a dienophile.

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Table 1. Diels-Alder Reaction of 2-Quinolinones



Run	P	R	Lewis acid (2eq)	Solvent	Temp.	Result	Calculation (PM3) Dienophiles	
							HOMO	LUMO
1	CO ₂ Me	SPh	—	Toluene	Reflux	NR		
2	CO ₂ Me	SPh	EtAlCl ₂	Toluene	rt	11 60–70%	-8.6021	-1.0070
3	CO ₂ Me	SPh	Et ₂ AlCl	Toluene	rt	11 11%		
4	CO ₂ Me	H	EtAlCl ₂	Toluene	rt	NR	-9.1604	-0.9234
5	MOM	SPh	EtAlCl ₂	Toluene	rt	NR	-8.4333	-0.9096
6	MOM	SPh	EtAlCl ₂	CH ₂ Cl ₂	rt	NR		
7	MOM	SOPh	EtAlCl ₂	Toluene	rt	NR	R- -8.9305 S- -8.8960	-1.0760 -1.0357
8	H	SPh	EtAlCl ₂	Toluene	rt	NR		

Preliminary MO(Molecular Orbital) calculation⁴⁾ (see **Table 1**) revealed that the alkoxycarbonyl group could be a choice for activation of **8**. The methoxycarbonylation of **8** afforded stable *O*-protected compound (**9**) in high yield. Thermal rearrangement (Chapmann rearrangement) of **9** into the *N*-COOMe derivative (**10**) was effectively carried out by heating (toluene, or dioxane, 120°C) to furnish the desired dienophile (**10**)⁶⁾. (**Chart 2**)

The stage has now been set for the D-A reaction of (**10**). Although attempted thermal reactions of **10** with 2-trimethylsilyloxy-1,3-butadiene or more reactive Danishefsky diene were unsuccessful, Lewis acid-mediated reactions were found to be promising, as observed in the previous case.⁴⁾ Results are summarized in **Table 1**, in which EtAlCl₂ was a more effective reagent for this transformation than Et₂AlCl or ZnBr₂.⁷⁾

Other more modern catalysts such as methylaluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide) (MAD), Sm(OTf)₂, SmI₂, Yb(OTf)₃, Sc(OTf)₃, and 5M-LiClO₄-ether were tested with more stable 2-trimethylsilyloxy-1,3-butadiene, with no fruitful results leading to a decomposition of the diene along with recovery of the dienophile.

Efforts were still continuing for the discovery of the more efficient catalyst for this process, because the best conditions (run 2) suffered tedious purification steps from unreacted dienophile and reprotection of the *N*-H adduct formed by the deprotection of *N*-COOMe group by Lewis acid catalyst.

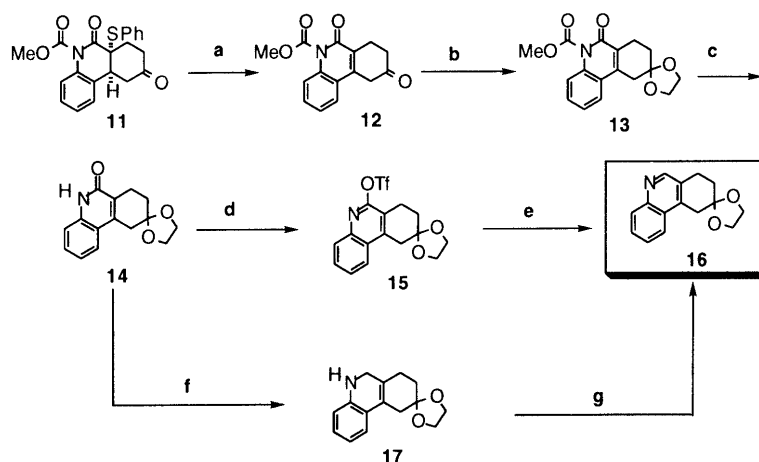


Chart 3

a) i. *m*CPBA, CH₂Cl₂, 0°C, 15min; ii. benzene, reflux, 3h, 92%; b) HOCH₂CH₂OH, *p*-TsOH, toluene, reflux, 3h, 100%; c) 10%NaOH, MeOH-CH₂Cl₂, rt, 1h, ~100%; d) 2,6-di(*t*-Bu)-pyridine, Tf₂O (1.5eq), CH₃CN, 0°C, 30min, 90%; e) Pd(PPh₃)₄, Et₃N, HCO₂H, DMF, 60°C, 15min, ~100%; f) DIBALH (1eq.), LAH (2eq.), THF, reflux, 1h; g) O₂, SiO₂, CH₂Cl₂, rt, 72h, 31% (2 steps)

We next turned our attention to the conversion of the adduct (**11**)⁸ into the requisite intermediate for dynamic NMR. Elimination of the SPh group *via* oxidation (*m*CPBA) and thermal elimination afforded the olefin (**12**). Ketalization of the carbonyl followed by deprotection in the usual manner gave **14**.

Two different routes were devised for the lactam ring aromatization of **14**: the first one was based on the conventional protocol, which involved a reduction-reoxidation sequence, as shown in steps f and g in **Chart 3**. This process suffered a low overall yield, especially in a large-scale operation. The second one utilized an efficient Pd-mediated reductive elimination^{1b,9} of the triflate (**15**), which was proven to be a useful process (steps d and e, **Chart 3**) to give **16**¹⁰ in 90% yield from **14**. Further conversion of **16** to the enediyne derivative is now in progress and will be reported in due course.

ACKNOWLEDGMENT

Financial support of this work by the Ministry of Education, Science and Culture, in the form of a Grant-in-Aid for Scientific Research, and by the Naito Foundation is gratefully acknowledged. Thanks are also due to the Fujisawa Foundation and to Japan Tobacco Inc. We also thank Dr. K. Yamaguchi, Dr. H. Seki, Ms. R. Hara, Mr. T. Kuramochi at the Chemical Analysis Center of Chiba University for measurement of spectroscopic data (NMR and mass).

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- 6) **10**: IR (KBr) cm^{-1} : 3160, 3000, 2950, 2920, 2860, 1770, 1730, 1690, 1620, 1580, 1570, 1490, 1470, 1440, 1370, 1350, 1320, 1300, 1270, 1190, 1150, 1130, 1070, 1010, 940, 910, 860, 820, 770, 750, 690; ¹H-NMR (500 MHz, CDCl₃) δ : 3.93 (3H, s), 7.38-7.39 (3H, m), 7.49-7.51 (3H, m), 7.64-7.68 (2H, m), 7.87 (1H, s), 7.98 (1H, d, J=8.00 Hz); LREIMS *m/z*: 311 (*M*⁺, 100 %); HRFABMS calcd for C₁₇H₁₄NO₃S (*MH*⁺): 312.0690, found: 312.0694.
- 7) References of effective catalysts in this Diels-Alder reaction are as follows: EtAlCl₂ *Fieser*, **6**, 261. **7**, 146. **10**, 177. **13**, 5. **16**, 2. Et₂AlCl *Fieser*, **4**, 144.
- 8) **11**: IR (neat) cm^{-1} : 3050, 2950, 1770, 1720, 1690, 1610, 1495, 1460, 1440, 1360, 1325, 1310, 1290, 1250, 1240, 1225, 1200, 1140, 1120, 1020, 925, 755, 740, 705, 695; ¹H-NMR (400 MHz, CDCl₃) δ : 1.98 (1H, ddd, J=4.03, 13.19, 13.56 Hz, H-7 β), 2.34 (1H, ddd, J=4.03, 6.41, 14.17 Hz, H-8 α), 2.47 (1H, m, H-8 β), 2.53 (1H, m, H-10 α), 2.58 (1H, m, H-10 β), 2.60 (1H, ddd, J=6.42, 7.14, 13.56 Hz, H-7 α), 3.36 (1H, dd, J=5.32, 13.19 Hz, H-10a), 4.08 (3H, s, MeO), 6.98 (1H, d, J=8.24 Hz, H-4), 7.17 (1H, d, J=4.22 Hz, H-1), 7.18 (1H, t like, J=8.24 Hz, H-2), 7.30-7.36 (1H, m, H-3), 7.32-7.34 (2H, d like, SPh), 7.37-7.42 (1H, t like, SPh), 7.43-7.46 (2H, d like, SPh); ¹³C-NMR (100 MHz, CDCl₃) δ : 33.2 (C-7), 38.7 (C-8), 45.3 (C-10), 45.9 (C-10a), 52.9 (C-6a), 55.4 (C-12), 117.0 (C-4), 125.2 (C-2), 125.3 (C-1a), 127.8 (C-1), 128.3 (C-1'), 128.7 (C-3), 128.9 (C-3', 5'), 130.1 (C-4'), 135.0 (C-4a), 137.3 (C-2', 6'), 153.9 (C-11), 166.2 (C-6), 207.4 (C-9); LREIMS *m/z*: 381 (*M*⁺, 100 %); HRFABMS calcd for C₂₁H₂₀NO₄S (*MH*⁺): 382.1113, found: 382.1110. The relative configuration was clarified by differential NOE experiments; for example, the irradiation of the C-7 β proton (1.98 ppm) clearly indicates responses from SPh protons (7.43-7.46) and the 10-a proton (3.36).
- 9) Dai W. M., *J. Org. Chem.*, **58**, 7581 (1993).
- 10) **16**: IR (neat) cm^{-1} : 3050, 2950, 2925, 2875, 1660, 1590, 1575, 1500, 1460, 1430, 1410, 1390, 1360, 1340, 1320, 1280, 1260, 1230, 1210, 1140, 1110, 1085, 1060, 1005, 940, 880, 830, 780, 760, 680; ¹H-NMR (500 MHz, CDCl₃) δ : 2.06 (2H, t, J=6.60 Hz), 3.15 (2H, t, J=6.60 Hz), 3.33 (2H, s), 4.00-4.13 (4H, m), 7.53-7.56 (1H, m), 7.63-7.67 (1H, m), 7.85 (1H, dd, J=0.70, 7.80 Hz), 8.07 (1H, dd, J=0.5, 8.30 Hz), 8.07 (1H, s); LREIMS *m/z*: 242 (*M*⁺, 100 %); HRFABMS calcd for C₁₅H₁₆NO₂ (*MH*⁺): 242.1181, found: 242.1188.

(Received November 15, 1995; accepted December 20, 1995)