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

Toshiaki NAGATA,[a] Yuuki KOIDE,[a] Kazumasa NARA,[a] Etsuko ITOH,[a] Mitsuhiro ARISAWA,[a] Shunji NARUTO,[b] Yasuhiro TORISAWA,[a] Tohru HINO,[a] and Masako NAKAGAWA*,[a]
Faculty of Pharmaceutical Sciences, Chiba University,[a] 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan, Neuroscience Research Laboratories, Sankyo Co.LTD.,[b] 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140, Japan

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 synthesis[1] 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-dihydropyridinones[3] 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**.

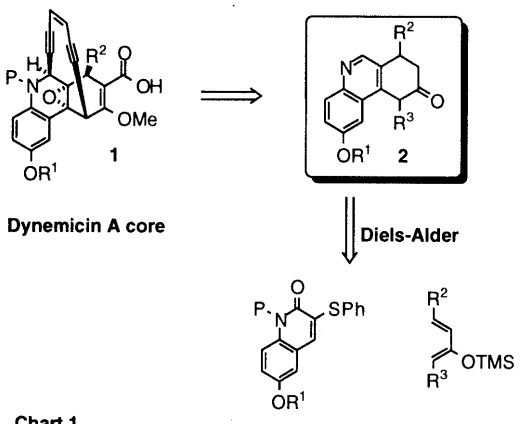


Chart 1

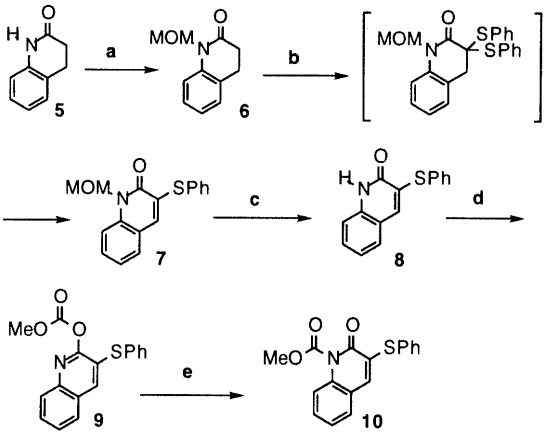


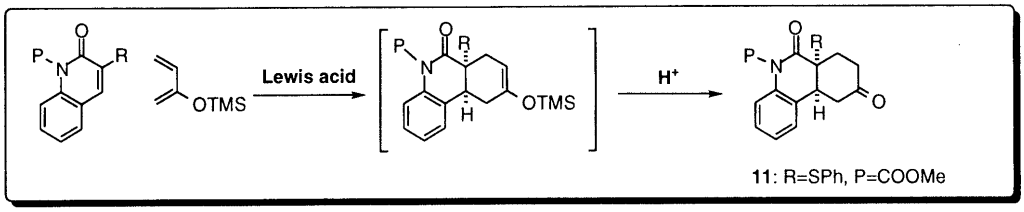
Chart 2
Conditions: a) *n*-BuLi, MOMCl, THF , - 78 °C, 94.5 %; b) $KN(TMS)_2$ (4 eq), PhSSPh (3 eq), THF, - 78 °C, 96.0 %; c) TMSI, CH_2Cl_2, or cHCl, MeOH; d) NaH, MeOCOCl, THF, rt, 93.0 %, 2 steps ; e) toluene, 120 °C, 86.8 %

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.

* To whom correspondence should be addressed.

Table 1. Diels-Alder Reaction of 2-Quinolinones



Run	P	R	Lewis acid (2eq)	Solvent	Temp.	Result	Calculation (PM3) Dienophiles HOMO	LUMO
1	CO_2Me	SPh	—	Toluene	Reflux	NR		
2	CO_2Me	SPh	$EtAlCl_2$	Toluene	rt	**11** 60~70%	-8.6021	-1.0070
3	CO_2Me	SPh	Et_2AlCl	Toluene	rt	**11** 11%		
4	CO_2Me	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_2Cl_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) calculation[4] (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 $EtAlCl_2$ was a more effective reagent for this transformation than Et_2AlCl or $ZnBr_2$.[7]

Other more modern catalysts such as methylaluminium bis(4-methyl-2,6-di-tert-butylphenoxide) (MAD), $Sm(OTf)_2$, SmI_2, $Yb(OTf)_3$, $Sc(OTf)_3$, and 5M-$LiClO_4$-ether were tested with more stable 2-triethylsilyloxy-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.

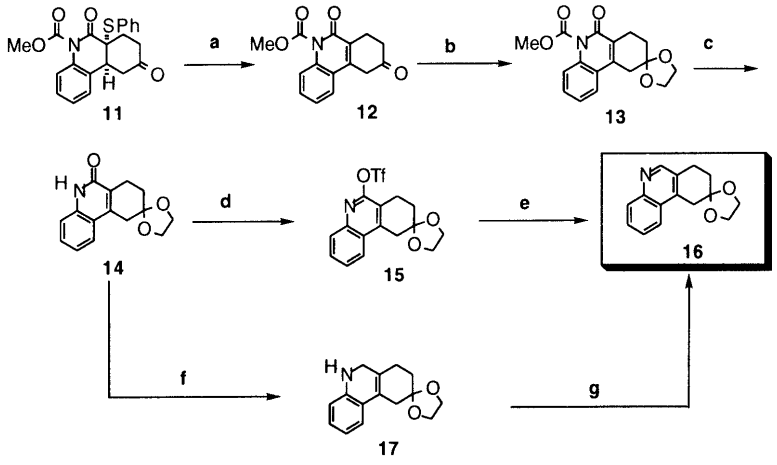


Chart 3

a) i. *m*CPBA, CH_2Cl_2, 0°C, 15min; ii. benzene, reflux, 3h, 92%; b) $HOCH_2CH_2OH$, *p*-TsOH , toluene, reflux, 3h, 100%; c) 10%NaOH, MeOH-CH_2Cl_2, rt, 1h, ~100%; d) 2,6-di(*t*-Bu)-pyridine, Tf_2O (1.5eq), CH_3CN, 0°C, 30min, 90%; e) $Pd(PPh_3)_4$, Et_3N, HCO_2H, DMF, 60°C, 15min, ~100%; f) DIBAH (1eq.), LAH (2eq.), THF, reflux, 1h; g) O_2, SiO_2, CH_2Cl_2, rt, 72h, 31% (2 steps)

We next turned our attention to the conversion of the adduct (**11**)[8] into the requisite intermediate for dynemicin A substructure. 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).

REFERENCES AND NOTES

1) a) Taunton J., Wood J. L., Schreiber S. L., *J. Am. Chem. Soc.*, **115**, 10378 (1993); b) Myers A. G., Fraley M. E., Tom N. J., Cohen S. B., Mader D. J., *Chemistry & biology*, **2**, 33 (1995); c) Shair M.D., Yoon T., Danishefsky S. J., *Angew. Chem. Int. Ed. Engl..*, **34**, 1721 (1995).

2) Kamei H., Nishiyama Y., Takahashi A., Obi Y., Oki T., *J. Antibiot*, **44**, 1306 (1991). Nicolaou K. C., Dai W. M., *Angew. Chem. Int. Ed. Engl.*, **30**, 1387, (1991). Suigiura Y., Shiraki. T., Konishi M., Oki T., *Proc. Natl. Acad. Sci. USA*, **87**, 3831 (1990)

3) Nakagawa M., Lai Z., Torisawa Y., Hino T., *Heterocycles*, **31**, 999 (1990). Torisawa Y., Nakagawa M., Arai H., Lai Z., Hino T., Nakata T., Oishi T, *Tetrahedron Lett.*, **31**, 3195 (1990). Torisawa Y., Nakagawa M., Hosaka T., Tanabe K., Lai Z., Ogata K., Nakata T., Hino T., *J. Org. Chem.*, **57** , 5741 (1992). Nakagawa M., Torisawa Y., Hosaka T., Tanabe K., Da-te T., Okamura K., Hino T., *Tetrahedron Lett.*, **34** , 4543 (1993).

4) Torisawa Y., Nakagawa M., Takami H., Nagata T., Ali A., Hino T., Naruto S., *Heterocycles*, **39**, 277 (1994); see also Ma J., Nakagawa M., Torisawa Y., Hino T., *Heterocycles*, **38**, 1609 (1994).

5) a) Nicolaou K. C., Hwang C.-K., Smith A. L., Wenderborn S. V., *J. Am. Chem. Soc.*, **112**, 7416 (1990); b) Nicolaou K. C., Smith A. L., Wenderborn S. V., Hwang C.-K., *J. Am. Chem. Soc.*, **113**, 3106 (1991); c) Wender P. A., Zercher C. K., *J. Am. Chem. Soc.*, **113**, 2311 (1991); d)Nishikawa T., Isobe M., Goto T., *Synlett.*, **1991**, 393. Nishikawa T., Ino A., Isobe M., Goto T., *Chem. Lett.*, **1991**, 1271; e) Magnus P., Fortt S. M., *J. Chem. Soc., Chem. Commun.*, **1991**, 544

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; **^{1}H-NMR** (500 MHz, $CDCl_3$) 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 $C_{17}H_{14}NO_3S$ (MH^+): 312.0690, found:312.0694.

7) References of effective catalysts in this Diels-Alder reaction are as follows: $EtAlCl_2$ *Fieser*, **6**, 261. **7**, 146. **10**, 177. **13**, 5. **16**, 2. Et_2AlCl *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; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 1.98 (1H, ddd, J=4.03, 13.19, 13.56 Hz, H-7β), 2.34 (1H, ddd, J=4.03, 6.41, 14.17 Hz, H-8α), 2.47 (1H, m, H-8β), 2.53 (1H, m, H-10α), 2.58 (1H, m, H-10β), 2.60 (1H, ddd, J=6.42, 7.14, 13.56 Hz, H-7α), 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); **^{13}C-NMR** (100 MHz, $CDCl_3$) 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 $C_{21}H_{20}NO_4S$ (MH^+): 382.1113, found: 382.1110. The relative configuration was clarified by differential NOE experiments; for example, the irradiation of the C-7β 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; **^{1}H-NMR** (500 MHz, $CDCl_3$) 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 $C_{15}H_{16}NO_2$ (MH^+): 242.1181, found: 242.1188.

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