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ASYMMETRIC DIELS-ALDER REACTION DIRECTED TOWARD CHIRAL ANTHRACYCLINE INTERMEDIATES

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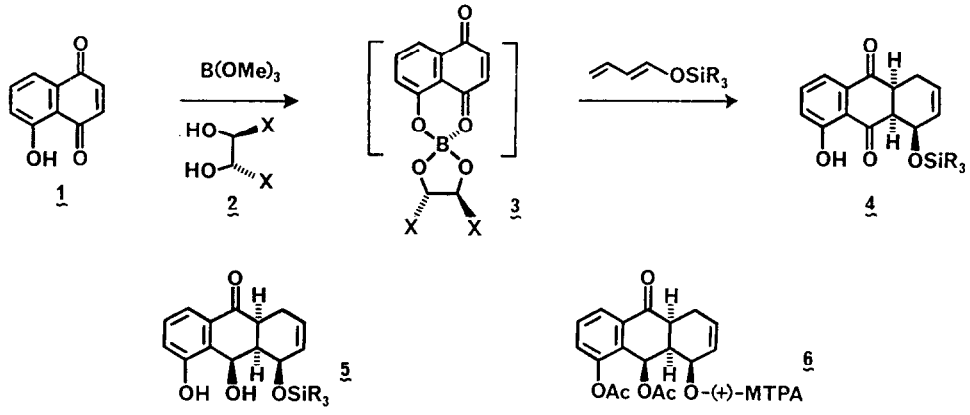
Abstract: The asymmetric Diels-Alder reaction of naphthoquinone derivative and diene in the presence of chiral boron reagent derived from $B(OMe)_3$ and (R,R)-(+)-tartaric acid diamide has been described as a model for the enantioselective preparation of important tetracycline natural products.

A recent communication by Kelly et al.[1] has prompted the publication of our independent results on the similar reaction sequence:[2]



The synthesis of naturally occurring anthracyclines and related analogue structures has been the central subject of intense study since 1970.[3] Among various strategies for these aglycone (anthracyclinone) synthesis, the asymmetric Diels-Alder approach using chiral metal catalyst appears to be one of the most desirable in view of the efficiency, selectivity, and synthetic flexibility.[4] Accordingly, we have initiated to study an asymmetric Diels-Alder reaction of naphthoquinone derivative and diene in the presence of chiral Lewis acid as a model for the enantioselective preparation of important tetracycline natural products. The method depends on the combining use of boron reagents and tartaric acid derivatives recently reported in our laboratory[5] and others.[6]

Reaction of juglone (**1**)[7] with trimethyl borate and (R,R)-(+)-diisopropyl tartrate (**2**) (X = $COOPr^i$) in CH_2Cl_2 gave rise to an intermediate **3** which was directly treated with 1-trimethylsiloxy-1,3-diene[8] at room temperature for 54 h affording the chiral adduct **4** (R = Me; 74% yield: $[\alpha]^{24}_D$ -27° (c 1.5, $CHCl_3$)) with rigorous regio- and stereochemistry. Because of its instability for oxygen, the adduct **4** was transformed to the more stable derivative **5** (R = Me; $[\alpha]^{21}_D$ -16.7° (c 1.5, $CHCl_3$)) with $NaBH_4$ in THF.[4a,9] The optical purity was substantiated by HPLC analysis to be 9% ee after converting to the (+)-MTPA

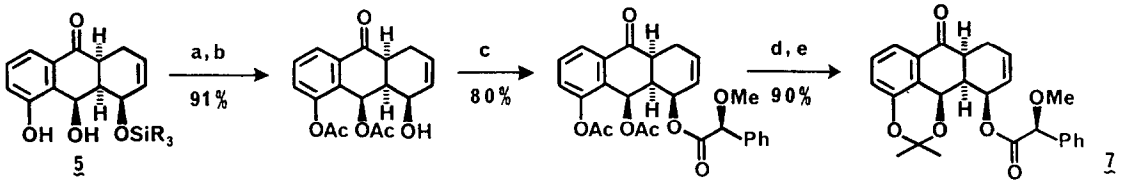
Table I. Asymmetric Diels-Alder Reaction of Juglone and Dienes[a]

entry	siloxy-diene[b]	diol, **2** (X)	time[c] (h)	chem. yield[d] (%)	$[\alpha]_D$ (c 1.5, $CHCl_3$)	opt. yield[e] (% ee)
1	R = Me	Me	69	89	-1.5	
2		$COOPr^i$	54	74	-27.0	9
3		$COOCH_2Ph$	48	95	-68.0	
4		$CONMe_2$	50	95	+31.8	
5		$CON(CH_2)_4$	48	83	+6.9	
6		CONHMe	21	96	-292.6	81
7		CONHPr	23	90	-304.6	84
8			98[g]	88	-250.4	
9		$CONHCH_2Ph$	24	96	-247.2	77
10		$CONHPr^i$	23	95	-279.8	81
11		$CONHCHEt_2$	7	78	-273.4	81
12		$CONHCH(CH_2)_4$	20	85	-268.8	80
13		$CONHCH(CH_2)_5$	16	84	-264.1	80
14		[f]	16	82[i]	+266.2	80
15		$CONHCH(CH_2)_{11}$	22	84	-185.4	7
16		$CONHBu^t$	13	77	-295.4	82
17		$CONHCEt_3$	10	73	-281.1	81
18		CONH(m-Tolyl)	3	78	-289.2	83
19			9[g]	79	-295.2	84
20			70[h]	78	-216.4	75
21	R = Et	$CONHCHEt_2$	29	82	-260.1	83
22		CONH(m-Tolyl)	6	73	-280.7	87
23			12[g]	73	-296.9	92
24	R_3 = t-$BuMe_2$	CONH(m-Tolyl)	5	82	-284.4	79[j]

[a] Reaction was carried out as described in note 11 to give the Diels-Alder product **4**. [b] A mixture of cis and trans isomers (~4:6) was utilized. [c] Reaction time at room temperature, unless otherwise noted. [d] Isolated yield of **4**. [e] Determined by HPLC analysis after converting to the (+)-MTPA ester **6**. [f] Use of the enantiomer of **2** (X = $CONHCH(CH_2)_5$). [g] At 0°C. [h] At -20°C. [i] The enantiomer of **4** (R = Me) was obtained. [j] The optical yield was determined by the optical rotation value after converting **5** to the desilylated triol with HF·Py; $[\alpha]^{26}_D$ -163.9° (c 0.5, $CHCl_3$). The optical rotation value of the triol derived from **5** (entry 21) follows: $[\alpha]^{24}_D$ -171.7° (c 0.5, $CHCl_3$).

ester **6**.[10] With the boron-mediated asymmetric Diels-Alder process and the optical purity determination in hand, we next examined various optically active 1,2-diols possessing the C_2-chirality as the chiral auxiliary, and the selected data are presented in Table I.[11] Apparently, (R,R)-(+)-tartaric acid diamide of type **2** (X = CONHR') has proved to be quite effective (entries 6-20) compared with dialkyl tartrate (entries 2 and 3) and the diamide **2** (X = $CONR'_2$) (entries 4 and 5), and in the particular case of the arylamide **2** (X = CONH(m-Tolyl)) by combining use of 1-triethylsiloxy-1,3-butadiene the chiral adduct **4** (R = Et) was obtained in 92% ee (entry 23). Use of bulky t-butyldimethylsiloxydiene

exhibited somewhat low enantioselectivities (entry 24). The absolute configuration of the adduct **5** (R = Me: $[\alpha]^{24}_{D}$-143.2° (c 1.5, $CHCl_3$))[12] was deduced from the optical rotation of the known compound **7**[13] as outlined below.

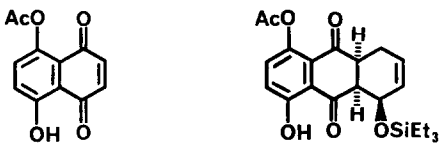


5 7

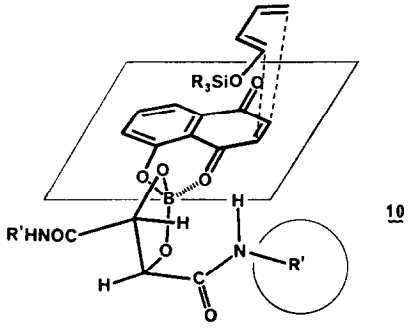
$[\alpha]^{24}_{D}$ -234.9° (c 0.1, $CHCl_3$)

(a) Ac_2O/Py in CH_2Cl_2; (b) HF·Py in THF; (c) (S)-(+)-α-Methoxyphenylacetic acid/DCC/ cat. DMAP in CH_2Cl_2; (d) K_2CO_3 in MeOH; (e) cat. p-TsOH·H_2O/2-Methoxypropene in DMF.

More significant is the asymmetric Diels-Alder reaction with naphthazarin as the dienophile which is already shown to be a versatile starting material for anthracycline synthesis.[14] Thus, reaction of naphthazarin monoacetate **8**[14g] with (R,R)-(+)-tartaric acid diamide **2** (X = CONH(m-Tolyl)) and $B(OMe)_3$ in CH_2Cl_2 followed by treatment with 1-triethylsiloxy-1,3-butadiene at 0°C for 11 h yielded the chiral adduct **9** (93% yield: $[\alpha]^{24}_{D}$ -217.2° (c 1.5, $CHCl_3$)), the optical purity of which was determined to be 88% ee by HPLC analysis in a similar manner as described in **4**.



8 9



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The high enantioselectivity observed for the auxiliary of type **2** (X = CONHR') should be ascribed to the novel intramolecular hydrogen bonding between amide-hydrogen and naphthoquinone carbonyl as depicted in **10**, where the diene would approach preferentially from the upper side of the dienophile, giving the cycloadduct **4** in accord with the observed configuration. The rate enhancement by using the arylamide **2** (X = CONH(m-Tolyl)) (entries 18 and 22) would be interpreted as forming the stronger hydrogen bonding in view of the electron-withdrawing aryl group.

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9. 5 (R = Me): 270-MHz ^{1}H NMR ($CDCl_3$) δ7.96 (s, 1H), 7.35 (d, 1H, J = 7.6 Hz), 7.11 (t, 1H, J = 7.8 Hz), 6.96 (d, 1H, J = 8.1 Hz), 5.78 (m, 1H), 5.59 (m, 1H), 5.36 (m, 1H), 4.47 (s, 1H), 2.62-2.77 (m, 3H), 1.95 (d, 1H, J = 19 Hz), 1.42 (s, 1H), -0.25 (s, 9H); IR ($CHCl_3$) 3344, 1680, 1578, 1456, 1247, 1222, 1205, 1056, 838 cm^{-1}.

10. The (+)-MTPA ester **6** was prepared from **5** by (i) acetylation with Ac_2O and Py in CH_2Cl_2, (ii) desilylation with Py·HF in THF, and (iii) esterification with (+)-MTPA-Cl and NEt_3 in CH_2Cl_2 in the presence of catalytic DMAP.

11. The experimental procedure for the asymmetric Diels-Alder reaction is given here (entry 7): To a solution of juglone (**1**) (52 mg, 0.3 mmol) and amide **2** (X = CONHPr) (84 mg, 0.36 mmol) in CH_2Cl_2 (40 mL) was added $B(OMe)_3$ (0.041 mL, 0.36 mmol) at room temperature. CH_2Cl_2-MeOH azeotrope (20 mL) was distilled off at 60°C over 40-50 min to remove the in situ generated MeOH. The residual yellow solution was cooled to 0°C and treated with 1-trimethylsilyloxy-1,3-butadiene (0.154 mL, 0.9 mmol). The mixture was stirred at room temperature for 23 h and worked up with aqueous $NaHCO_3$. Concentration of the CH_2Cl_2 extracts left the brown oil which was purified by column chromatography on silica gel (ether/hexane = 1:5) to give **4** (R = Me) (87 mg, 90% yield; $[\alpha]^{24}_D$ -304.6° (c 1.5, $CHCl_3$)).

12. Obtained by the reduction of **4** (R = Me) (entry 13) with $NaBH_4$ in THF at 0°C.

13. Authentic **7**: $[\alpha]^{23}_D$ -311° (c 0.013, $CHCl_3$). See ref 2a.

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