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2-CHLORO-1,3-BUTADIENE AS AN EFFICIENT ENOPHILE IN THE DIELS-ALDER REACTION WITH ANTHRACENE-1,4,9,10-TETRAONE. A SIMPLE SYNTHESIS OF THE 4-DEMETHOXYANTHRACYCLINONE INTERMEDIATE

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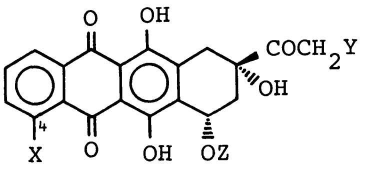
Diels-Alder reaction of 2-chloro-1,3-butadiene with anthracene-1,4,9,10-tetraone was found to occur exclusively at the external($C_{2,3}$) double bond, giving the adduct in an excellent yield. The adduct was readily converted to the 4-demethoxyanthracyclinone intermediate, (±)-7-deoxy-4-demethoxydaunomycinone, by way of 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione.

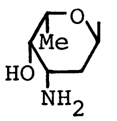
In connection with our synthetic studies on optically active 4-demethoxyanthracyclinones(**1**d,e),[1,2] the aglycones of 4-demethoxyanthracyclines(**2**d,e) which have been expected to show more improved therapeutic indices than natural antibiotics(**2**a,b),[3] an efficient method has been sought to produce a large quantity of (±)-7-deoxy-4-demethoxydaunomycinone((±)-**3**). Since optical resolution of (±)-**3** can be effectively achieved by forming a mixture of the diastereomeric acetals[2] and the C_7-hydroxy group can be highly stereoselectively intro-

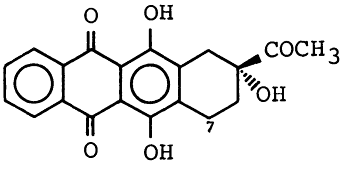


	X	Y
a:	OMe	OH
b:	OMe	H
c:	OH	H
d:	H	OH
e:	H	H

1: Z = H

2: Z =





(±)- or (-)-**3**

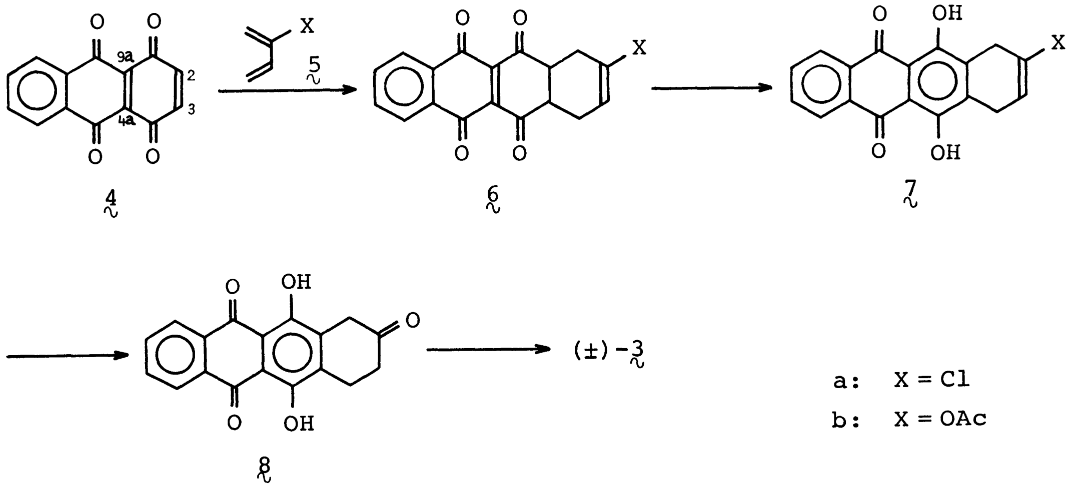
duced into optically pure (-)-**3**,$^{4)}$ (±)-**3** is anticipated to hold a pivotal position in the synthesis of optically active **1**d,e.

We wish here to report a simple and efficient method for the preparation of (±)-**3** by featuring the Diels-Alder reaction of anthracene-1,4,9,10-tetraone (quinizarin quinone)(**4**) with 2-chloro-1,3-butadiene(chloroprene monomer)(**5**a) as a key step. While the synthetic scheme quite similar to ours had already been explored as one of the best methods for synthesizing natural anthracyclinones(**1**b,c) by employing 2-acetoxy-1,3-butadiene(**5**b) as an enophile,$^{5)}$ it was found that **5**b, being not commercially available, could only be prepared in less than 10% yield by our hands according to the reported procedure.$^{6,7)}$ Although a number of the enophiles which can exclusively attack the external($C_{2,3}$) double bond of **4** is of quite limited,$^{5,8,9,10)}$ we have found that **5**a can be employed as an efficient substitute for **5**b in the Diels-Alder reaction with **4**.

Thus, the Diels-Alder reaction(benzene-xylene(5/1), reflux, 4 h) of **4**, prepared from 1,4-dihydroxyanthracene-9,10-dione(qunizarin) in 58% yield by the oxidation with lead tetraacetate,$^{11)}$ with **5**a(2.2 equiv.), regiospecifically occurred at the external double bond, giving a 79% of 2-chloro-1,4,4a,12a-tetrahydronaphthacene-5,6,11,12-tetraone(**6**a), mp 232-234 °C(decomp). When the Diels-Alder reaction(xylene-AcOH, rt, 61 h) was performed using **5**b(5 equiv.) in place of **5**a according to the reported method,$^{5)}$ the adduct(**6**b) could be obtained only in 16% yield. The undesired adduct, which might be produced by the addition of **5**a to the internal($C_{4a,9a}$) double bond, was not detected by TLC and NMR analyses of the crude product. Since **6**a was found to be fairly labile, it was immediately aromatized(NaOAc-AcOH, reflux, 0.5 h), affording the dihydroxyanthraquinone(**7**a), mp 285.5-286.5 °C(from toluene), in 91% yield. Hydrolysis(conc. H_2SO_4, rt, 1 h) of **7**a gave 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione(**8**) as a red powder in 98% yield, mp >250 °C(decomp)(from AcOH)(lit., mp 313-315 °C,$^{12a)}$ 296-298 °C,$^{12b)}$ >300 °C$^{12c)}$).

Reaction of **8**(THF, rt, 41 h) with ethynylmagnesium bromide(25 equiv.), followed by hydration(HgO, 1.5 mol dm^{-3} H_2SO_4, THF, rt, 15 h), according to the reported method$^{5,12c)}$ readily furnished (±)-**3** as a red powder, mp 214-216 °C (lit.,$^{2)}$ 214-216 °C) in 40% overall yield.

Considering operational simplicity and use of readily available cheap **5**a as an enophile, the explored overall process should hold promise for the industrial



a: X = Cl
b: X = OAc

scale preparation of (±)-3.

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