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A Regioselective Synthesis of 6-Deoxyanthracyclinone Intermediate

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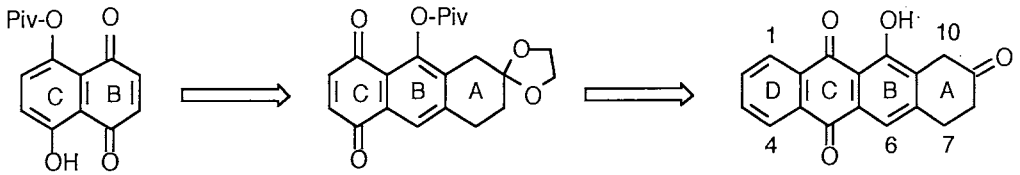
A new route for synthesis of 6-deoxyanthracyclinone has been developed. Preparation of the key intermediate 2-ethylenedioxy-9-pivaloyloxy-1,2,3,4-tetrahydro-anthracene-5,8-dione was achieved by chemoselective reduction of the adduct of naphthazarin monopivalate with 1-methoxy-3-trimethylsiloxybutadiene, and successive dehydration of the resulting alcohol.

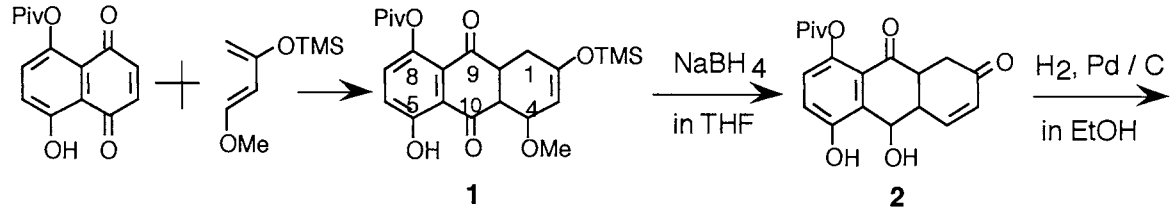
Recently, potent antitumor antibiotics yellamycins and alldimycins, which are 6-deoxyanthracyclines, have been isolated in our laboratories.[1] On the other hand, current attentions to the anthracycline chemistry are directed toward a synthesis of less oxygenated anthracyclines. Although several total syntheses of 6-deoxyanthracyclines such as α-citoromycinone[2] and 4-demethoxy-6-deoxydaunomycinone[3] have been reported, the synthesis using Diels-Alder reaction has never been presented. Our interest was therefore focused on the regioselective synthesis of 6-deoxyanthracyclinones by sequential Diels-Alder reactions. In the total synthesis of daunomycinone employing Diels-Alder reaction, naphthazarin was conveniently used as the BC-ring.[4] We have also demonstrated the alternative utility of naphthazarin as their BC-ring of 11-deoxy-anthracyclines, aklavinone,[5] 2-hydroxyaklavinone,[6] and 11-deoxyrhodomycinone analogue.[7] Furthermore, naphthazarin was effectively used as a starting material in this study. We report here the regioselective synthesis of a tricyclic quinone (**6**), a useful 6-deoxyanthracyclinone precursor, and the results of a model synthesis of 6-deoxyanthracyclinone intermediates.



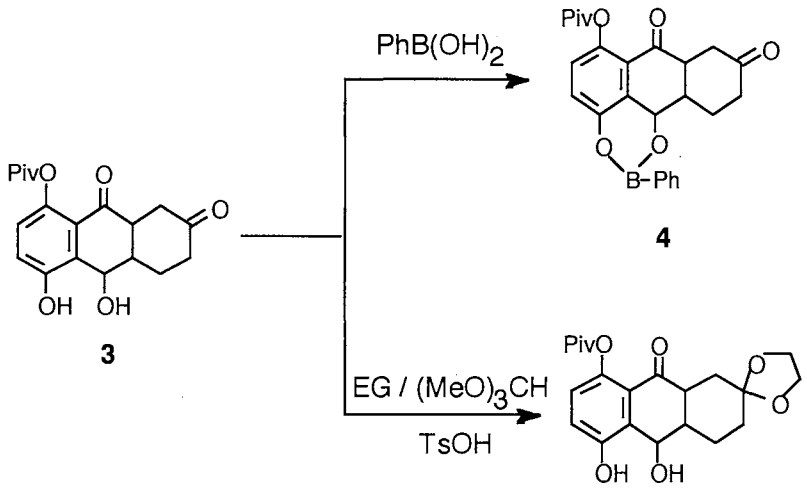
piv ; Pivaloyl

Diels-Alder reaction of naphthazarin monopivalate[4a] and 1-methoxy-3-trimethylsiloxybutadiene in chloroform gave a desired adduct **1** (mp 144-146 ℃) in 86% yield. The adduct **1** was reduced with one equivalent of sodium borohydride in THF (0 ℃, N_2 atmosphere) to afford exclusively the enone alchohol **2** (mp 99-101 ℃) in 93% yield. This reaction involved simultaneously the reduction of the C-10 carbonyl and an enone formation. It was considered that the reaction was caused by hydride-induced cleavage of the siloxy

bond in a similar manner as a reaction using lithium alminium hydride reported by Fraser-Reid et al.[8] The olefinic bond of **2** was hydrogenated over palladium carbon to give the keto alcohol **3**[9] (mp 66 ℃) in quantitative yield. Evidence of chemoselective reduction of the C-10 carbonyl of **1** was supported by the the formation of 5,10-phenylboronate **4**[10] (mp 87-89 ℃) derived from **3**. In ^{1}H-NMR, the hydroxyl protons at the C-5 and C-10 positions of **3** were observed at δ 8.72 (singlet) and 4.27 (doublet, J=5.4 Hz) respectively, however, these signals disappeared in compound **4** by the phenyboronation. The compound **3** was converted to ethylene ketal **5** (mp 167-169 ℃) with ethyleneglycol and trimethyl orthoformate in the presence of *p*-toluenesulfonic acid.



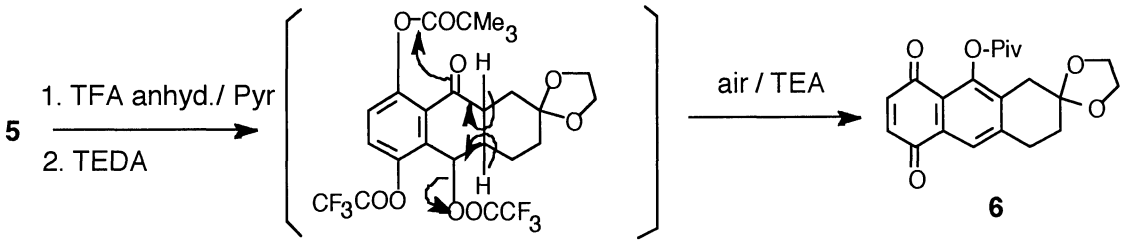
1 **2**



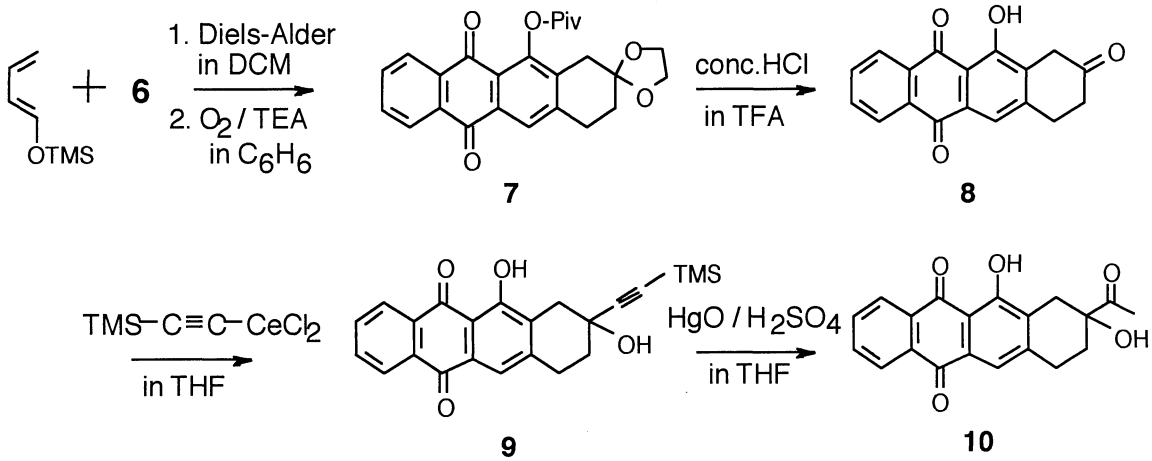
3 **4** **5**

In next step, it was found that the dehydration of the C-10 alcohol group in the compound **5** was promoted by trifluoroacetylation. Namely **5** was trifluoroacetylated with trifluoroacetic anhydride in pyridine at -5 ℃, and the resulting C-10 trifluoroacetoxy group was then eliminated by addition of 1,4-diazabicyclo[2.2.2]octane at 50 ℃. The resulting air-sensitive product was extracted with benzene and oxidized by air-bubbling in the presence of triethylamine, to afford the target tricyclic quinone **6** in 92% yield from **5**[10] (73% overall yield from naphthazarin monopivalate). Sequential reactions from **5** to **6** were accomplished by (i) the β-elimination

of trifluoroacetate, (ii) the transfer of pivaloyl (Piv) group to C-9 hydroxyl group, and (iii) the oxidation to quinone system. The structure of **6** was confirmed by its ^{1}H-NMR and MS, and the absorption of the quinone carbonyl groups of **6** in IR was observed at 1669 cm^{-1}.[11]



Total synthesis of 4-demethoxy-6-deoxydaunomycin, an unnatural anthracycline, has been reported by Penco *et al.* [3] We have also prepared the aglycone by use of the tricyclic quinone **6** as below. Addition reaction of **6** with 1-trimethylsiloxy-1,3-butadiene, followed by aromatization under O_2 atmosphere in the presence of triethylamine gave a naphthacenequinone compound **7** (mp 187-189 ℃). The ketal and pivaloyl groups of **7** were removed in a solution of conc. HCl and trifluoroacetic acid (1 : 10 vol. ratio) to obtain **8** (mp 249-253 ℃) in quantitative yield. Introduction of an ethynyl group into the C-9 carbonyl was carried out using trimethylsilylethynyl cellium (III) chloride (2.5 equiv., -65 ℃, 40 min in THF) providing **9** (mp 160-161 ℃) in 85% yield. Treatment of **9** with mercury (II) oxide and sulfuric acid in THF gave the desired compound **10** in 92% yield. The physico-chemical properties of **10**[12] were identical with those of (±)-4-demethoxy-6,7-dideoxydaunomycinone.[3] This result has demonstrated the advantage of the tricyclic quinone **6** as a 6-deoxyanthracyclinone precursor.



References

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9) **3**: ^{1}H-NMR($CDCl_3$) δ 4.27(1H, d, J=5.4Hz, 10-OH), 5.43(1H, t, J=5.4Hz, 10-H), 6.71(1H, d, J=9.0 Hz, 7-H), 6.91(1H, d, J=9.0Hz, 6-H), 8.72(1H, s, 5-OH).

10) **4**: ^{1}H-NMR($CDCl_3$) δ 5.70(1H, d, J=5.4Hz, 10-H), 6.90(1H, d, J=9.0Hz, 6-H), 7.15-7.53 (4H, m, aromatic-H), 7.92(2H, dd, J=2.0, 7.5Hz, aromatic-H).

11) **6**: mp 145-146 ℃. IR(KBr) 1745, 1669 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 1.98(2H, m, 3a,b-H), 2.68(1H, d, J=18Hz, 1a-H), 3.00(1H, d, J=18Hz, 1b-H), 3.11(2H, m, 4a,b-H), 6.78, 6.81(2H,each d, J=9.0Hz, 6 and7-H), 7.81(1H, s, 10-H), FAB-MS: m/z 371 $(M+H)^+$. Anal. Found: C, 67.96; H, 5.98%. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.98%.

12) **10**: mp 202-203 ℃, IR(KBr) 1705, 1665, 1625 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 1.90(1H, m, 8a-H), 2.09 (1H, m, 8b-H), 2.38(3H, s, COMe), 2.9-3.3(4H, m, 7a,b-H,10a,b-H), 3.82(1H, s, 9-OH), 7.67(1H, s, 6-H), 7.78-7.82(2H, m, 2,3-H), 8.28-8.32(2H, m, 1,4-H). FAB-MS: m/z 337 $(M+H)^+$.

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