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SYNTHESIS OF 11-DEOXYANTHRACYCLINONE PRECURSOR. A NEW STRATEGY TOWARD TETRACYCLIC SYSTEM VIA TANDEM 1,4/[4+2] ADDITION[1)]

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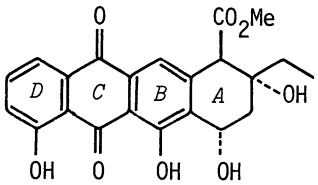
Direct and regioselective reaction of 2,4-pentadienyltrimethylstannane with 3-acryloyl-5-methoxy-1,4-naphthoqinone afforded a tetracyclic compound, a key precursor for synthesizing 11-deoxyanthracycline antibiotics, by single step.

Since the discovery of daunorubicin in 1963, the anthracycline antibiotics have continuously attracted the attention of many chemists because of their remarkable clinical efficacy against human cancers.[2)] However, severe dose limiting side effects have stimulated the search for improved anthracycline antibiotics.[3)] Recently, aclacinomycin A[4)] and 11-deoxydaunomycin[5)] were established as a new group of anthracycline antibiotics, which have a low incidence of cumulative cardiomyophathy. Although several synthetic efforts toward these "second generation" anthracycline antibiotics, especially their aglycons (11-deoxydaunomycinone (1)[6)] and aklavinone (2)[7)]), have been done, they were based on the longitudinal and stepwise construction of the demanded tetracyclic skeletons. We report herein a general synthetic route to 11-deoxy-type tetracyclic intermediate by one step construction of AB rings via tandem 1,4/[4+2] addition of conjugated diene and activated double bond (Scheme 1).



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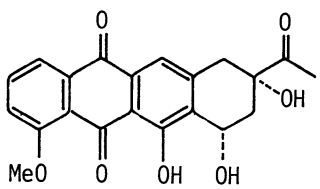

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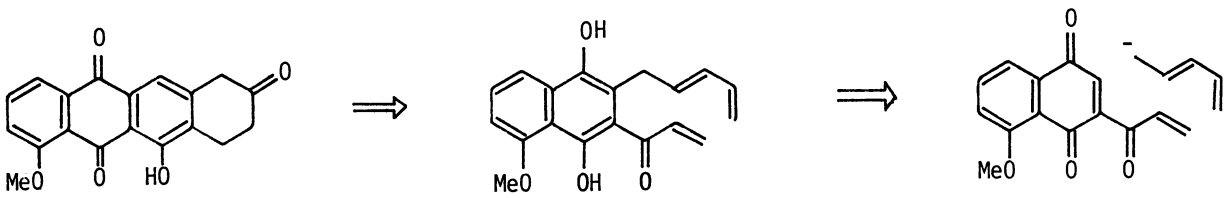
Scheme 1.

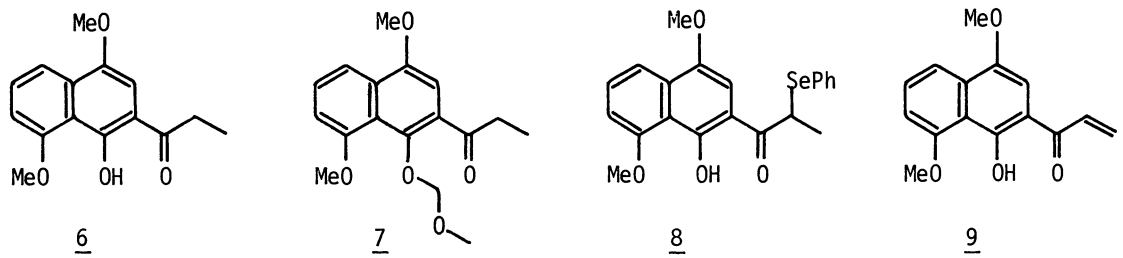


3 4 5

Our retrosynthetic scheme (Scheme 1) is based on formation of intermediate 4. Once compound 4 was generated, it might spontaneously induce the intramolecular Diels-Alder reaction to give a desired tetracyclic compound, which would be suitably functionalized as a key precursor for synthesizing the anthracyclinones. Central to this strategy is the requirement that the *selective* introduction of 2,4-pentadienyl side chain to 3 position of 2-alkenoyl-1,4-naphthoquinone (5), which possesses many reactive sites. Choice of an appropriate reagent is an important problem. In the preceding paper,[8] we described that 2,4-pentadienyltrimethylstannane (10) performed the selective pentadienylation toward quinones and acyclic α,β-unsaturated carbonyl compounds without accompanying any Diels-Alder adducts. This methodology provides us a promising route to the present synthesis.

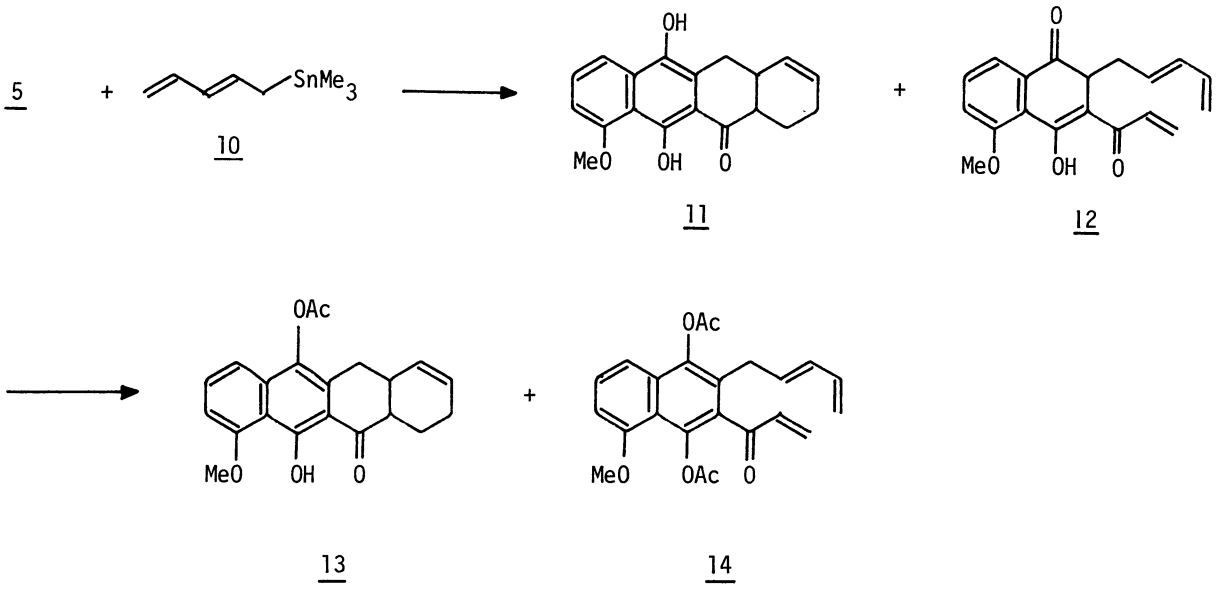
First, 5-methoxy-3-acryloyl-1,4-naphthoquinone (5) was prepared in five steps from 6, as follows. Naphthol 6[9] was converted to the corresponding methoxymethyl (MOM) ether 7 in a 95% yield (NaH/THF/0 °C then $ClCH_2OCH_3$). The lithium enolate of the MOM ether 7 ($LiN(i\text{-}Pr)_2$/THF/-78 °C to 0 °C/2 h) was added to the solution of PhSeCl.[10] After purification by column chromatography on silica gel (CH_2Cl_2) and deprotection of MOM ether (pyridinium p-toluenesulfonate/aq-acetone), selenide 8 was obtained in a 45% yield. Oxidative elimination of a selenyl group from 8 (MCPBA/CH_2Cl_2/-78 °C, 40 min then r.t., 3 h) and successive oxidation of the corresponding phenol 9 (CAN/aq-CH_3CN) afforded the desired quinone 5[11] in a 76% yield.

Pentadienylation of the quinone 5 and simultaneous bicyclization were performed as follows (Scheme 2). To the dichloromethane solution of the quinone 5,



6 7 8 9

Scheme 2.



2,4-pentadienyltrimethylstannane (10; 1.2 equiv. to 5) was added at -78 °C followed by addition of $SnCl_4$ (2.0 equiv. to 5). After 10 min, the reaction mixture was poured into brine and extracted with CH_2Cl_2. After evaporating the solvent, the remains consisted of a mixture of cyclic product 11 (45%) and Michael-type adduct 12 (55%) (^{1}H-NMR analysis). Fortunately, no other possible adducts were observed, and the addition of stannane 10 to quinone 5 proceeded regiospecifically. Since adduct 12 was unstable, the mixture was acetylated with Ac_2O-pyridine (r.t., 4 h) without separation of them. The acetylated mixture was separated by column chromatography on silica gel (ether/hexane). The major product was 12-acetoxy-5-hydroxy-4-mehtoxy-6-oxo-6,6a,7,8,10a,11-hexahydronaphthacene (13; 55%); yellow fluorescent oil; ^{1}H-NMR ($CDCl_3$) δ 2.14(4H, bm), 2.43(3H, s), 2.84(4H, bm), 3.98(3H, s), 5.63 (2H, m), 6.80(1H, d, J=8 Hz), 7.13(1H, d, J=8 Hz), 7.45(1H, t, J=8 Hz); IR (KBr) 1760, 1610, 1575, 1390 and 1370, 1250 cm^{-1}; MS (20 eV) m/e 352(M^+,65%), 309(M^+-CH_3CO, 100%). The minor one was 1,4-diacetoxy-3-acryloyl-5-methoxy-2-(2',4'-pentadienyl) naphthalene (14; 31%); pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 2.12(3H, s), 2.14(3H, s), 3.45(2H, d, J=7 Hz), 3.87(3H, s) ,4.9-5.5(3H, m), 5.8-6.2(3H, m), 6.52(1H, d, J=9 Hz), 6.7(1H, m), 7.1-7.5(3H, m); IR (KBr) 1760, 1660, 1570, 1370, 1190 cm^{-1}; MS (20 eV) m/e 394(M^+, trace), 351(M^+-CH_3CO, 100%), 309(M^+-$2CH_3CO$, 89%). Tetracyclic compound 13 has suitable functions to be converted to 11-deoxydaunomycinone (1).

This route including tandem 1,4/[4+2] addition reaction is clearly one of the

most promising one to anthracyclinones. Further study on the synthesis of anthracyclinones via this route is under progress.

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References

1) Synthesis of Naturally Occurring Quinones Part 14; Part 13: Y.Naruta, N.Nagai, and K.Maruyama, Chem. Lett., 1983, 1383.
2) a) R.H.Blum and S.K.Carter, *Ann. Intern. Med.*, 80, 249 (1974); b) D.W.Henry, "Cancer Chemotherapy," ed by A.C.Sartorelli, American Chemical Society, Washington D.C. (1976), Chap. 2; c) F.Arcamone, "Topics in Antibiotics Chemistry," ed by P.G.Sammes, Halstead Press, New York (1978), Vol. 2; d) J.R.Brown, *Prog. Med. Chem.*, 15, 125 (1978); e) "Anthracyclines: Current Status and New Developments," ed by S.T.Crooke and S.D.Reich, Academic Press, New York (1980).
3) For recent reviews: W.A.Remers, "The Chemistry of Antitumor Antibiotics," Wiley, New York (1979), Vol. 1, pp. 63-132; F.Arcamone, "Anticancer Agents Based on Natural Product Models," ed by J.M.Cassady and J.D.Douros, Academic Press, New York (1981); "Anthracycline Antibiotics," ed by H.S.E.Kahadem, Academic Press, New York (1982).
4) T.Oki, in Ref. 2e, pp. 323-342.
5) F.Arcamone, G.Cassinelli, F.DiMatteo, S.Forenza, M.C.Ripamonti, G.Rivola, A. Vigevani, J.Clardy, and T.McCabe, *J. Am. Chem. Soc.*, 102, 1462 (1980).
6) S.D.Kimball, D.R.Walt, and F.Johnson, *J. Am. Chem. Soc.*, 103, 1561 (1981); J.-P. Gesson and M.Mondon, *J. Chem. Soc., Chem. Commun.*, 1982, 421; A.V.R.Rao, V.H. Deshpande, and N.L.Reddy, *Tetrahedron Lett.*, 23, 775 (1982); F.M.Hauser, S. Prasanna, and D.W.Combs, *J. Org. Chem.*, 48, 1328 (1983); A.V.R.Rao, K.Bal, N.L. Reddy, and A.R.Mehendale, *J. Chem. Soc, Chem. Commun.*, 1983, 564.
7) A.B.Pearlman, J.M.McNamara, I.Hasan, S.Hatakeyama, H.Suzuki, and Y.Kishi, *J. Am. Chem. Soc.*, 103, 4248 (1981); A.S.Kende and J.P.Rizzi, *ibid.*, 103, 4247 (1981); P.N.Confalone and G.Pizzolato, *ibid.*, 103, 4251 (1981); T.-T.Li and Y.L.Wu, *ibid.*, 103, 7007 (1981); J.M.McNamara, and Y.Kishi, *ibid.*, 104, 7371 (1982); H.Sekizaki, M.Jung, J.M.McNamara, and Y.Kishi, *ibid.*, 104, 7372 (1982).
8) Y.Naruta, N.Nagai, Y.Arita, and K.Maruyama, *Chem. Lett.*, the preceding paper.
9) 1,5-Dimethoxy-3-propionyl-4-naphthol (mp 129-130 °C) was prepared by the similar method of an acetyl derivative, see Y.Naruta, H.Uno, and K.Maruyama, *J. Chem. Soc., Chem. Commun.*, 1981, 1277.
10) H.J.Reich, J.M.Renga, and I.L.Reich, *J. Am. Chem. Soc.*, 97, 5435 (1975).
11) For instability of quinone 5 under chromatographic conditions, it was directly used without further purification after oxidation. The obtained quinone possessed sufficient purity by means of TLC and NMR. 5: orange yellow crystals, mp 133-134 °C; ^{1}H-NMR ($CDCl_3$) δ 4.00(3H, s), 5.98(1H, d, J=10 Hz), 6.26(1H, d, J=17 Hz), 6.74(1H, dd, J=17, 10 Hz), 6.90(1H, s), 7.31(1H, t, J=5 Hz), 7.67(2H, d, J=5 Hz).

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