Tetrahedron Letters, Vol. 33, No. 32, pp. 4603-4604, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

A Simple and Efficient Synthesis of the Naphthoate Moiety of Neocarzinostatin Chromophore

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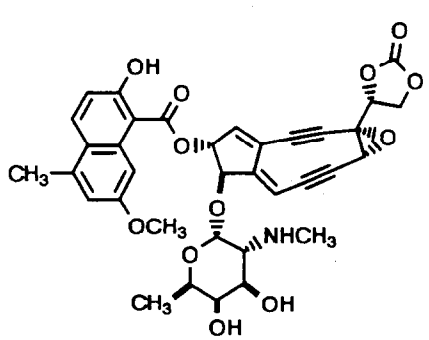
Key Words: Neocarzinostatin; Chromophore; Synthesis; 2-Hydroxy-7-methoxy-5-methylnaphthalene-1-carboxylic acid

Abstract: *A six-step synthesis of 2-hydroxy-7-methoxy-5-methylnaphthalene-1-carboxylic acid (2), the naphthoate moiety of neocarzinostatin chromophore (1), has been achieved.*

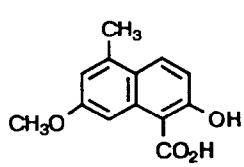
The naphthoate moiety of neocarzinostatin (NCS) chromophore (**1**)[1] has been proposed to play an important role for the specific binding both to NCS apoprotein[2,3] and to target DNAs.[4] Preparation of the naphthoate derivatives and their binding studies[5] are requisite for clarifying the precise mechanism of those interactions. Synthetic routes reported thus far to the essential acid, 2-hydroxy-7-methoxy-5-methyl-naphthalene-1-carboxylic acid (**2**), are elegant but quite laborious.[6] Accordingly the model studies have been hindered. We report herein an expeditious synthesis of **2**.

Commercially available 5-methylcyclohexane-1,3-dione (**3**) was enolized to methyl ether (**4**) and Robinson annulation of **4** through regioselective deprotonation by using LDA followed by alkaline treatment gave dienone methyl ether (**6**) in 63% overall yield. Dehydrogenative aromatization of **6** with 5% palladium on activated carbon (water content 1.8%, Kawaken Fine Chemicals Co., Ltd.)[7] in 1-methylnaphthalene under reflux for a short time under nitrogen atomosphere afforded the properly substituted naphthalene (**7**) (53% yield). Thus, the selective preparation of C3 monomethyl ether (**7**) of diol was accomplished in four steps from **3**. Final regioselective bromination[8] to **8** (79%)[9] followed by metalation and carboxylation with CO_2 gas provided **2**[10] in 70% overall yield. The physical data of its methyl ester (**9**) were identical with those of authentic **9**.[6a]

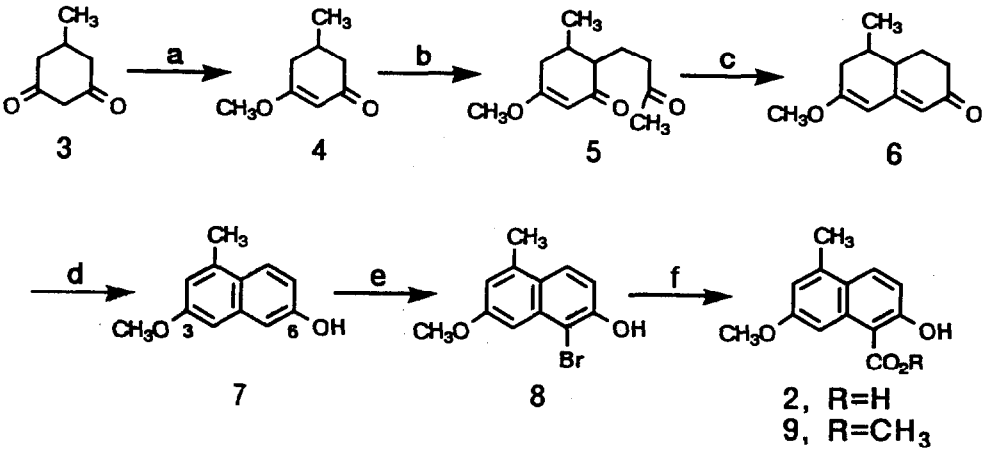
Our synthesis of **2**[10] is concise (6 steps) and efficient (23% overall yield) enough to encourage not only the binding studies of chromophore model compounds[5] but also synthetic studies toward **1**.



1



2



Reagents and conditions: a) $HC(OMe)_3$ (1.0 eq.), cat. TsOH, MeOH, rt, 20 h (95%); b) LDA (1.1 eq.), -78°C, then 3-Buten-2-one (1.0 eq.), THF, -78°C, 40 min (80%); c) NaOMe (2.5 eq.), MeOH, 60°C, 1 h (83%); d) 5% Pd/C, 1-Methylnaphthalene, reflux, 30 min (53%); e) n-Bu_4NBr_3 (1.0 eq.), CH_2Cl_2 / MeOH (1:2), 0°C, 2 h (79%); f) n-BuLi (2.4 eq.), THF, -50°C to -30°C, 1 h, then CO_2, -30°C (88%).

Acknowledgements: This work was supported by the Ministry of Education, Science and Culture, Japan, and the Mitsubishi, CIBA-GEIGY, Shorai, and TERUMO Science Foundations.

References and Notes:

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7. Ratio of 5% palladium on activated carbon to the substrate (6) was 0.5 (w/w).
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9. A small amount of 4-bromo isomer (16%) was produced and separated by silica gel chromatography (hexane / AcOEt = 5:1) and/or recrystallization from CH_2Cl_2.
10. Physical data of **2** (pale yellow crystals): mp 136-138°C ($CHCl_3$); IR (KBr) 3440, 1632, 1247, 1232cm^{-1}; ^{1}H-NMR (200MHz, $CDCl_3$) δ 2.65 (br s, 3H), 3.95 (s, 3H), 6.93 (br d, J=2.8Hz, 1H), 7.06 (d, J=9.2Hz, 1H), 8.11 (d, J=9.2Hz, 1H), 8.23 (d, J=2.8Hz, 1H), 12.10 (s, 1H); UV (EtOH) λ_{max} 332nm (ε 5.9 × 10^3); HRMS calcd for $C_{13}H_{12}O_4$: 232.0736 Found 232.0732.

(Received in Japan 8 April 1992)