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AN EFFICIENT SYNTHESIS OF THE NAPHTHALENE MOIETY OF NEOCARZINOSTATIN CHROMOPHORE

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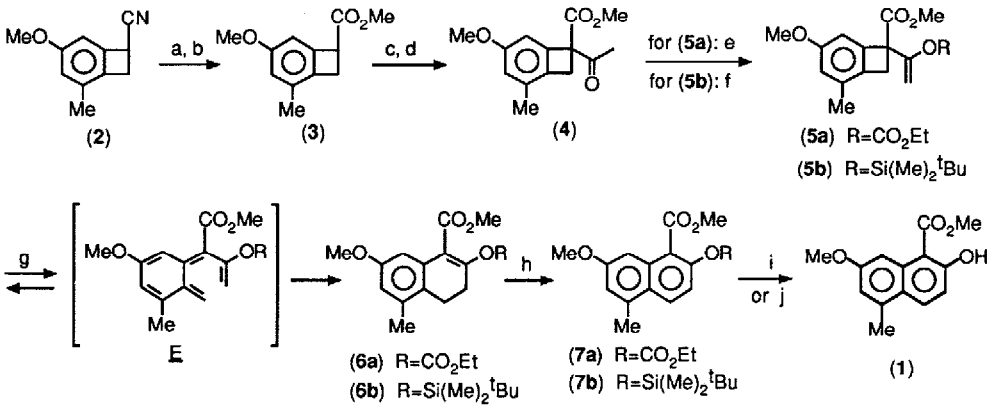
Abstract: Methyl 2-hydroxy-7-methoxy-5-methyl-1-naphthalenecarboxylate, the methanolysis product of neocarzinostatin chromophore, was efficiently synthesized from 1-cyano-5-methoxy-3-methylbenzocyclobutene employing an electrocyclic reaction of E-o-quinodimethane as the key step.

Neocarzinostatin chromophore (NCS-chr.), non-protein component of the antitumor antibiotic neocarzinostatin isolated from the culture filtrate of Streptomyces carzinostaticus var. *F-41* by Ishida[1], has attracted considerable interest among synthetic organic chemists due to its intriguing structural features.[2] Our efforts in this area have focussed on construction of the naphthalene moiety (**1**)[3], which was obtained by methanolysis of NCS-chr., possessing four different kinds of functionalities on the naphthalene ring. The chemical objectives of this total synthesis endeavor were not only to establish a novel and practical synthetic route for (**1**) but also to examine whether the highly selective electrocyclic reaction via E-o-quinodimethane, generated in situ by the thermolysis of 1-alkenyl-1-carbomethoxybenzocyclobutene[4], for constructing the naphthalene ring system would succeed with fully functionalized benzocyclobutenes, i.e. (**5**)⟶(**6**).

The syntheses of (**5a,b**), the key intermediates in the experimental verification of this approach, start with 1-cyano-5-methoxy-3-methylbenzocyclobutene (**2**)[5], which is readily prepared from 4-methoxy-2-methylbenzaldehyde[6] by a standard five step sequence in 62 % overall yield. Hydrolysis of (**2**) and esterification of the resulting carboxylic acid provided the methyl ester (**3**) in 93 % yield. Treatment of (**3**) with lithium diisopropylamide (LDA) and acetaldehyde followed by oxidation with the conditions of Swern provided (**4**) in 86 % yield. Conversion of (**4**) into the key intermediate (**5a**) was achieved by treatment with LDA and ethyl chloroformate in 80 % yield. Heating of the enol carbonate (**5a**) at 180°C for 5 min in o-dichlorobenzene yielded the expected dihydronaphthalene (**6a**), as a sole product, in 79 % yield. Subsequent treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene caused a rapid and clean dehydrogenation to provide the

naphthalene (**7a**) in quantitative yield. Finally, (**7a**) was converted by alkaline hydrolysis into the desired crystalline (**1**), mp 109-110°C (lit.[3], mp 104-105°C), in 97 % yield. Alternatively, treatment of (**4**) with ^{t}butyldimethylsilyl trifluoromethanesulfonate and triethylamine[7] provided the silyl enol ether (**5b**), which was immediately heated at 180°C in o-dichlorobenzene for 1 h followed by oxidation of the resulting (**6b**) with DDQ in a one-pot operation to give the corresponding naphthalene (**7b**). Desilylation of the crude (**7b**) with tetrabutylammonium fluoride proceeded smoothly to afford (**1**) in 46 % overall yield from (**4**). The material thus obtained was identical both chromatographically and spectroscopically (^{1}H nmr, ir, mass) with an authentic sample of (**1**).



Reagents a, KOH, aq.EtOH; b, AcCl, MeOH; **c**, LDA, CH_3CHO; d, $(COCl)_2$, DMSO, NEt_3; e, LDA, $ClCO_2Et$; f, $^{t}Bu(Me)_2SiOTf$, NEt_3; g, 180°C, *o*-dichlorobenzene; h, DDQ; i, K_2CO_3, aq.MeOH; j, Bu_4NF

The synthesis reported here is a practical method for the preparation of naphthalene moiety of NCS-chr. since it requires eight steps from the literature known benzocyclobutene (**2**) and proceeds in 51 % (via enol carbonate) overall yield. Of equal importance, this synthesis demonstrates that the electrocyclic process via E-o-quinodimethane is also predominant during the thermolyses of highly functionalized benzocyclobutenes.

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References and Notes

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