JOC*Note*

Synthesis of Novel Antitumor Agent 1-Methoxy-5,10- dioxo-5,10-dihydro-1*H*-benzo[*g*]isochromene Carboxylic Acid (3-Dimethylylaminopropyl)amide with a Dual Role Pd(II) Catalyst

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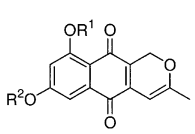
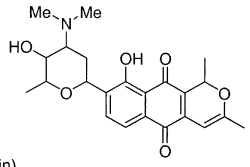
Abstract: A convenient and simple method for the synthesis of 1-methoxy-5,10-dioxo-5,10-dihydro-1*H*-benzo[*g*]isochromene-3-carboxylic acid (3-(dimethylamino)propyl)amide **4c** was developed. The key step involves the easy formation of 1,3-disubstituted cyclic alkenyl ether, an important framework of isochromene natural products, with a dual role Pd-(II) catalyst.

Naphtho[2,3-*c*]pyran-5,10-diones exhibit a broad range of biological activities[1−4] and therefore much attention has been paid to the synthesis of these compounds. Pentalongin **1**, dehydroherbarin **2a**, and its analogues **2b**,**c**, and compound **3** (**3543R1**) are these classes.[5−7] On the other hand, 1,3-disubstituted-3,4-dehydropyranonaphthoquinones **4a**−**c** have been found as very effective antitumor chemotherapeutics.[2] The anthracycline analogues daxorubicin **5a** and daunomycin **5b** have been used in the clinic to treat various cancers but they have limited activity for solid tumors[8] and these agents also induce serious side effect such as bone marrow depression and cardio toxicity.[9a−c] It was found by Wang et al. that the carboxamide side chain of (**4b**, **4c**) is potentially important in the interaction with DNA.[2] Among them (**4b** and **4c**), **4c** (**BCH-2051**) was the most potent analogue identified, showing better activity in resistant cell lines. It is active against the human varian cancer cell line SKOV3, its P-170 glycoprotein mediated multi-drug-resistant variant SKVLB, and the colon carcinoma cell line HT-29.[2] The activity was expressed by IC_{50} ratio of SKVLB over SKOV3 and the value was 9.3 for compound **4c** (**BCH-2051**). The value of IC_{50} of compound **4c** was 0.07 μM for HT-29. These results indicate that the compound **BCH-2051** is the most potent analogue.

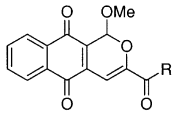
1 (pentalongin)



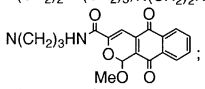
2a R^1 = Me, R^2 = Me (dehydroherbarin)
2b R^1 = H, R^2 = H
2c R^1 = H, R^2 = Me



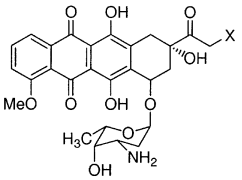
3 (3543R1)



4a R = OMe
4b R = NR^1R^2 [R^1 = H, R^2 = $N(CH_2)_4N(CH_3)_2$, $N(CH_2)_3OH$, $N(CH_2)_3Br$, $N(CH_2)_3S^+(CH_2)_2$, $N(CH_2)_2N^+(CH_2)_3$, $N(CH_2)_2N$,



; R^1 = CH_3, R^2 = $N(CH_2)_2N(CH_3)_2$]
4c R = $NH(CH_2)_3N(CH_3)_2$ (**BCH-2051**)



5a doxorubicin (adriamycin), X = OH
5b daunomycin, X = H

Hence, we were interested in the synthesis of the potential antitumor agent **BCH-2051**. For this, we needed to construct the 1,3-disubstituted cyclic alkenyl ether moiety of the isochromene system. There are only a limited number of examples of the one-pot synthesis of the 1,3-disubstituted cyclic alkenyl ether moiety of isochromene derivatives.[4b,10,11] The procedure used by Wang et al. for the synthesis of **BCH-2051**[2] and construction of the 1,3-disubstituted cyclic alkenyl ether derivative[2,12] involved a difficult multistep conversion, including oxidation with DDQ, Diels−Alder cyclocondensation, and careful hydrolysis. Furthermore, in this case, synthesis of the starting material was also a lengthy and difficult procedure.[13]

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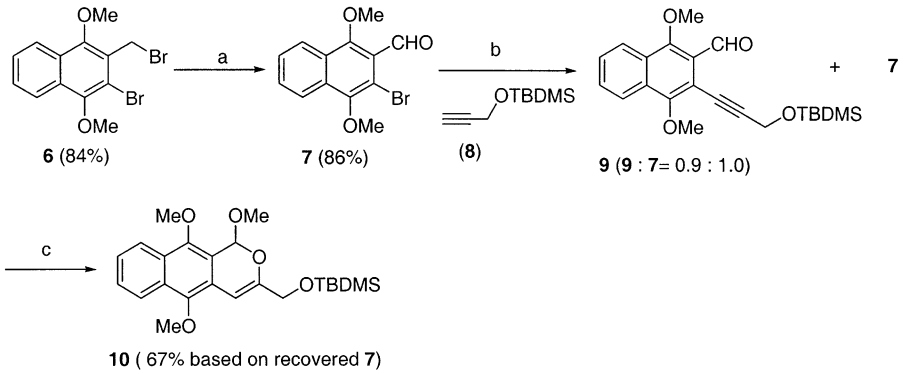
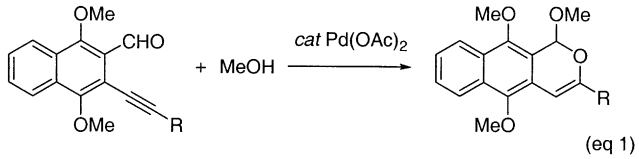
SCHEME 1[a]



[a] Reagents and conditions: (a) 1 equiv of $PhSeO_2K$, 0.97 equiv of K_2HPO_4, 0.1 equiv of TBAB, acetonitrile. (b) 10 mol % of CuI, 10 mol % of PPh_3, 5 mol % of $PdCl_2$, Et_3N (solvent), 70−80 °C, 8 h. (c) 5 mol % of $Pd(OAc)_2$, 1 equiv of benzoquinone, 2 equiv of MeOH, 1,4-dioxane, rt, 3 h.

Herein, we report an easy and convenient procedure for the construction of the 1,3-disubstituted cyclic alkenyl ether framework of the isochromene system and its application to the synthesis of the potent antitumor agent **BCH-2051**. The key step of this synthesis is the use of a dual role catalyst, in which Pd(II) exhibits a Lewis acidic activity for enhancing the electrophilicity of aldehyde and exhibits the activity of a transition metal catalyst for enhancing the electrophilicity of the alkyne bond, for constracting the α-methoxycyclic alkenyl ether from the *o*-alkynylaryl aldehyde (eq 1).[14]



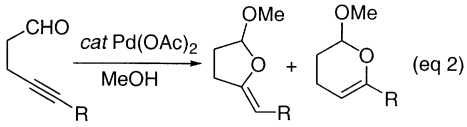
(eq 1)

For the synthesis of **BCH-2051**, we first construct the 1,3-disubstituted cyclic alkenyl ether moiety of the isochromene system. The construction of the 1,3-disubstituted cyclic alkenyl ether moiety of the isochromene system is outlined in Scheme 1.

Compound **6** was prepared according to the reported procedure.[15] Oxidation of **6** with potassium benzoselenide and potassium hydrogen phosphate in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB) in acetonitrile under refluxing conditions for 30 h with vigorous stirring gave aldehyde **7** in 86% yield.[16,17] The modified sonogashira reaction[18] of **7** with suitable acetylenic silane **8** in the presence of a catalytic amount of copper(I) iodide, triphenylphosphine, and palladium chloride in triethylamine at 70−80 °C for 8 h gave the acetylinic aldehyde **9**, mixed with starting material **7**. The reaction was not heated further as decomposition started and the yield of **9** decreased.

The mixture could not be separated due to the same R_f value. We then decided to use the mixture for the next step. The NMR ratio of the product (**9**) to the starting material (**7**) was found to be 0.9:1.0. From the NMR ratio, we calculated the amount of product **9** present in the mixture and hence the reagents necessary for the next step. A mixture of 5 mol % of $Pd(OAc)_2$, 1 equiv of benzoquinone, 2 equiv of methanol, and compound **9** (mixed with **7**) in 1,4-dioxane under argon atmosphere was stirred for 3 h at room temperature. The desired 1,3-disubstituted cyclic alkenyl ether **10** was obtained in 67% yield (based on recovered **7**).

In the previous communication,[14] we reported that the reaction of alkenyl aldehydes with methanol in the presence of Pd(II) catalyst gave a mixture of five- and six-membered alkenyl ethers (eq 2). In the present



(eq 2)

transformation starting from **9**, only the six-membered product **10** was obtained. The reason for this different observation is not yet clear. The cyclization of *o*-alkynyl carboxylic acids also gives a mixture of five- and six-membered rings and the isomer ratio is dependent on the reaction conditions and reagent used,[19] and under certain conditions the selective synthesis of six-membered alkenyl ethers is accomplished.

The formation of potent antitumor agent **BCH-2051** is outlined in Scheme 2. The desylation[20] of **10** was carried out in the presence of tetrabutylammonium fluoride in THF at room temperature for 1 h, giving alcohol **11**, which was used without purification for the next step. The oxidation of the crude material **11** with

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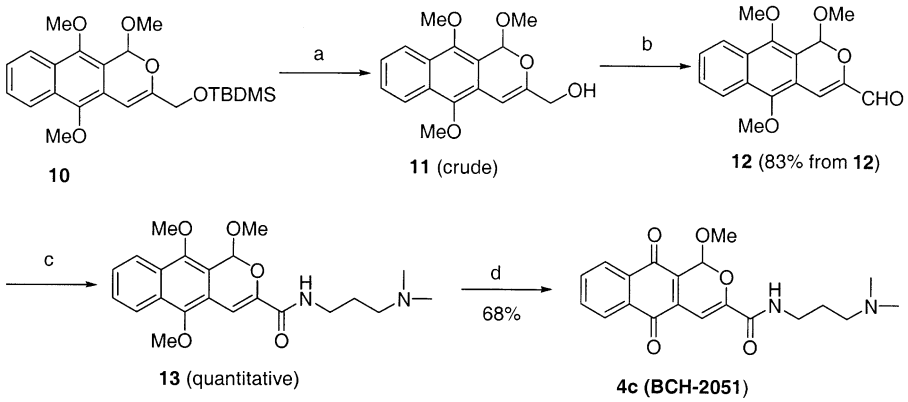
SCHEME 2[a]



[a] Reagents and conditions: (a) 1.1 equiv of TBAF, THF, rt, 1 h. (b) DMSO, Et_3N, CH_2Cl_2, 3 equiv of SO_3·Py complex, 0 °C to room temperature, 3 h. (c) 5 equiv of NaCN, 20 equiv of MnO_2, 5 equiv of *N*,*N*-dimethyl-1,3-propanediamine, isopropyl alcohol, 0 °C, 5 h. (d) 5 equiv of CAN buffering with $NaHCO_3$ (1.8 equiv with respect to CAN), CH_3CN/H_2O, 0 °C, 15 min.

SO_3·Py complex in the presence of DMSO/Et_3N in dichloromethane at 0 °C to room temperature[21] gave aldehyde **12** in excellent 83% yield from **10**.

Aldehyde **12** was then treated with *N*,*N*-dimethyl-1,3-propanediamine in the presence of excess NaCN and manganese dioxide to give amide **13** in almost quantitative yield.[22] Oxidative demethylation[23] of amide **13** with 5 equiv of cerium(IV) ammonium nitrate (CAN) buffered with $NaHCO_3$ (1.8 equiv with respect to CAN) in aqueous acetonitrile at 0 °C gave the biologically active yellow solid compound **4c** (**BCH-2051**) in 68% yield, which matches the given NMR value reported earlier.[23]

In conclusion, we described herein a convenient and simple method for the synthesis of the potent antitumor agent **4c** (**BCH-2051**). Our method has 2-fold utilities. Using this method we can easily construct the 1,3-disubstituted cyclic alkenyl ether moiety of the isochromene system by one-pot reaction and synthesize a wide range of amides and related compounds with different side chains from isochromene aldehyde **12**.

Supporting Information Available: Experimental procedure, characterization data, and spectra for compounds **7**, **9** (mixed with **7**), **10**, **12**, **13**, and **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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