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A novel synthetic approach to benzo[*h*]chromones via sequential intramolecular alkynoyl transfer followed by 6-*endo* ring closure

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Abstract

An intramolecular acyl transfer reaction took place on treatment of 1-methoxymethoxy-3-(2-alkynoyloxy)methyl-2-iodonaphthalenes with *n*-BuLi at −78°C to give 1-methoxymethoxy-2-alkynoyl-3-hydroxymethylnaphthalenes in high yields. After protection of the hydroxymethyl group as benzoates, formation of a γ-pyrone ring was easily achieved by deprotection of the MOM group followed by spontaneous 6-*endo*-digonal ring closure under mild acidic conditions.

Keywords: intramolecular acyl transfer; 6-*endo* ring closure; benzo[*h*]chromones; espicufolin; naphtho[2,3-*h*]chromone quinones.

There has been considerable interest in pyran-fused quinones due to their important bioactivity, and many methods for construction of the pyranoquinones have been reported.[1] Although the traditional synthesis of chromones and chromenes represented by the Kostaneki–Robinson and Simonis reactions[2] is still useful, a strategy involving an intramolecular Michael addition of a phenoxide anion to an α,β-unsaturated ketone moiety seems to be the method of choice especially in the synthesis of highly substituted pyranoquinones. The success of this approach depends largely upon preparation of the α-alkenoyl or alkynoylphenols and control of the cyclization mode: 5-*exo* versus 6-*endo*. There is no problem in the control of cyclization of *o*-alkenoylphenols; a 6-*endo*-trigonal cyclization predominates over a 5-*exo*-trigonal ring closure.[3] However, a subsequent oxidation of the resulting dihydropyrans is, somehow, problematic.[4] Contrary to the case of *o*-alkenoylphenols, both 6-*endo*-digonal and 5-*exo*-digonal processes were reported to occur in the base-catalyzed cyclization of *o*-alkynoylphenols.[5] The precise study of Saito's group revealed that the 5-*exo*-digonal closure was fairly favored under the kinetic conditions, while the 6-*endo*-digonal products were preferably obtained via an equilibrium between the anionic intermediates in the absence of a proton donor.[6] We have devised a novel approach to the pyranoquinones based on an intramolecular alkynoyl transfer followed by the 6-*endo*-digonal closure

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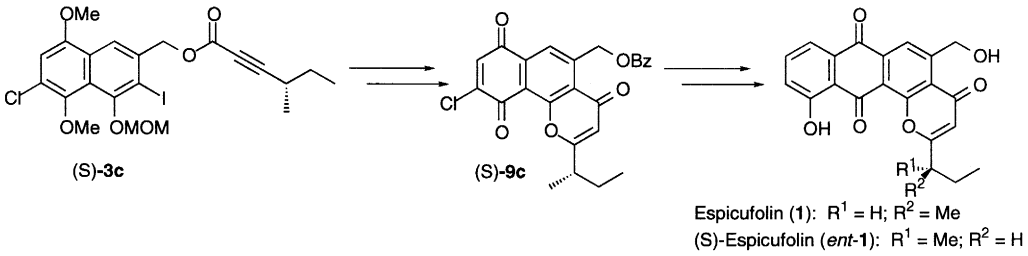
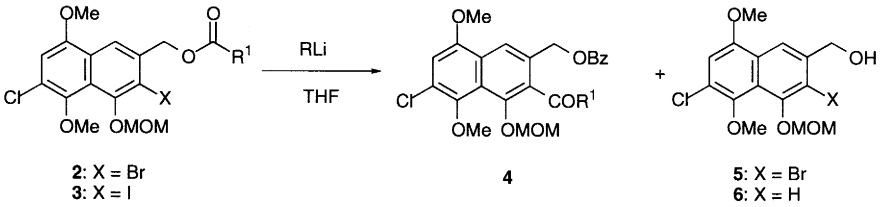
under acidic conditions, and succeeded in preparing (*S*)-espicufolin (*ent*-**1**),[7] which is an enantiomer of espicufolin **1** bearing a neuronal cell-protecting activity (Scheme 1). In this paper, we describe the utility and limitations of our approach.



Scheme 1.

The starting 3-(acyloxymethyl)naphthalenes **2** and **3**[7] were obtained in good overall yields (>50%) from the known 7-chloro-3-hydroxymethyl-5,8-dimethoxynaphthol.[8] An acyl-transfer reaction (Eq. (1)) was examined by generation of an anion at the 2-position of the naphthalenes under various conditions depicted in Table 1 . First, a bromine–lithium exchange reaction of **2a** was carried out by using *n*-BuLi at −78°C to give an almost equal amount of the aimed product **4a** as a mixture of its hemiacetal form (ca. 7:1 in $CDCl_3$ at ambient temperature) and a simply deacylated alcohol **5a**. In order to avoid the undesired nucleophilic attack, *t*-BuLi was employed instead of *n*-BuLi. The transacylation compound **4a** was obtained in good yield as well as a small amount of **6** (run 2). Under similar conditions, however, the acyl-transfer reaction of **2b** was partially hampered by the nucleophilic attack to give a mixture of **4b** and **6**, probably due to the sterically less hindered nature of the alkynoyl ester moiety. The side reaction could not be suppressed by reduction of the reaction temperature to −100°C (run 4). This problem was finally solved by changing the starting bromide **2b** to iodide **3b**, and the desired **4b** was obtained in good yield (run 5). The other alkynoyloxy derivatives **3c**–**f** were also converted to **4c**–**f** in good yields as shown in Table 1.



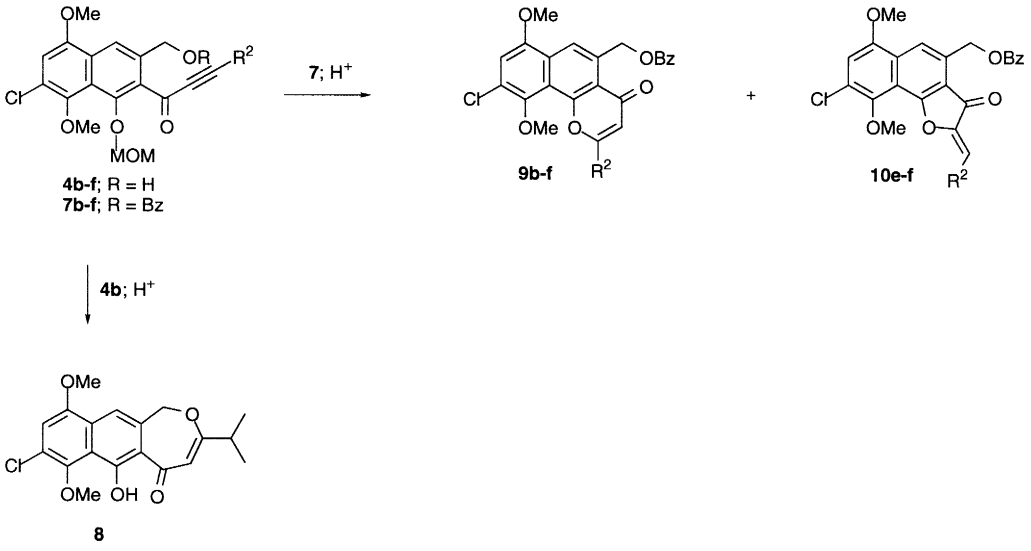
(1)

Next, the pyran ring formation was examined, and the MOM group of **4b** was intended to be removed under acidic conditions (3.0 M HCl:THF:*i*-PrOH=1:2:7; reflux) (Scheme 2). However, an oxepin derivative **8** derived via favorable 7-*endo*-digonal ring closure[9] was obtained in 62% yield instead of a simply MOM-deprotected compound. Thus, prior to the acidic deprotection, the primary hydroxyl group of **4** was protected as a benzoate by treatment with BzCl in pyridine to give **7** in good to excellent yields. Removal of the MOM group of **7b** under the acidic conditions (3.0 M HCl:THF:*i*-PrOH=1:2:7; reflux) was carried out and the progress was monitored by TLC. A thin yellow spot near **7b** appeared at the very first stage and a polar spot increased as time passed. After leaving overnight, all of **7b** had disappeared. Two spots were identified and separated by chromatography. The polar spot was proved to be benzo[*h*]chromone **9b** derived from the deprotection of the MOM group followed by a simultaneous ring closure forming a pyran ring. From the NMR and MS analyses, the other material was assigned as a mixture of several compounds, some of which were dimeric compounds bearing at least a phenolic hydroxyl group. In order to prevent the dimerization, the reaction was carried out under an argon

Table 1
Acyl transfer reaction of **2** and **3**

Run	Substrate			Conditions		Yield/%		
		X	R^1	RLi (equiv)	Temp/°C	**4**	**5**	**6**
1	**2a**	Br	Me	*n*-BuLi (1.0)	-78	33	28	—
2	**2a**	Br	Me	*t*-BuLi (2.1)	-78	75	—	8
3	**2b**	Br	-C≡C-*i*-Pr	*t*-BuLi (2.2)	-78	40	—	52
4	**2b**	Br	-C≡C-*i*-Pr	*t*-BuLi (2.2)	-100	59	—	41
5	**3b**	I	-C≡C-*i*-Pr	*n*-BuLi (1.2)	-78	80	—	5
6	**3c**	I	-C≡C-*s*-Bu	*n*-BuLi (1.2)	-78	95	—	trace
7	**3d**	I	-C≡CMe	*n*-BuLi (1.2)	-78	65	—	trace
8	**3e**	I	-C≡CPh	*n*-BuLi (1.2)	-78	73	—	trace
9	**3f**	I	-C≡CC_6H_4-*p*-OMe	*n*-BuLi (1.2)	-78	95	—	trace

atmosphere (Table 2). In the cases of aliphatic alkynoyl derivatives **7b–d**, the benzo[*h*]chromones **9b–d** were obtained in good yields (runs 1–3), while the reaction of the phenylpropynoyl derivative **7e** under similar conditions gave an almost equal amount of benzo[*h*]chromone **9e** and a new orange material (run 4). From the NMR, MS, and analytical data, the orange compound was determined to be an isomer of **9e**. The IR spectra (1693 cm^{-1}) suggested that this compound had a benzylidenefuranone skeleton, which was unambiguously determined by the X-ray analysis (Fig. 1).[10] A similar result was obtained in the reaction of **7f** (run 6).



Scheme 2.

We were surprised by the formation of the naphtho[1,2-*b*]furanones **10**, because we thought that the key intermediate of this cyclization was a protonated alkynone such as **12** (Scheme 3). The intermediate should be attacked only at the β-position either by an intramolecular hydroxyl group or by water followed by 6-*exo*-trigonal ring closure[11] to give **9**. Taking into account that the oxidative dimerization was observed in the presence of oxygen (vide ante) and that the furanone formation was observed only in the reactions of the aromatic derivatives **7e–f**, it was presumed that a radical intermediate might participate to

Table 2
Pyrone ring formation

Run	Substrate		Yield/%	
	7	R^2	**9**	**10**
1	**7b**	*i*-Pr	85	—
2	**7c**	*s*-Bu	77	—
3	**7d**	Me	65	—
4	**7e**	Ph	41	41
5[a]	**7e**	Ph	87	—
6	**7f**	C_6H_4-*p*-OMe	48	46
7[a]	**7f**	C_6H_4-*p*-OMe	92	—

[a] The starting alkynone was treated with Et_2NH prior to the acid treatment.

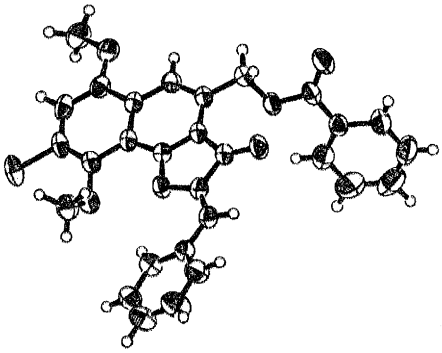
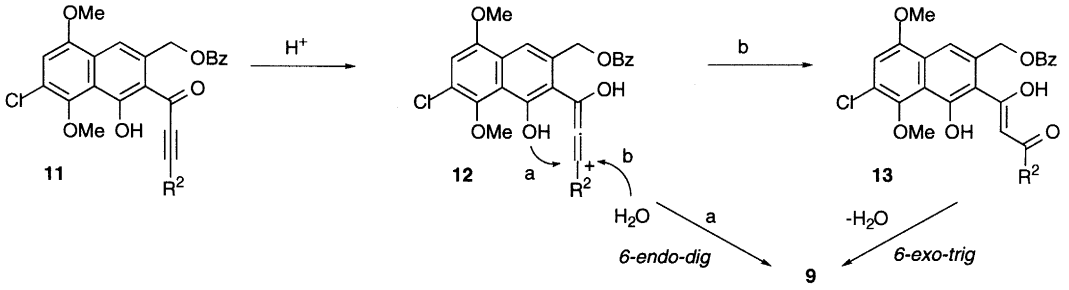


Fig. 1. ORTEP drawing of **10e**

give the undesired furanones **10e–f**.[12] Even in the presence of tocopherol as a radical scavenger, however, the ratio was not changed. The mechanism for formation of the furanones **10e–f** is not clear at this moment.



Scheme 3. Reaction pathways

In order to suppress the undesired furanone formation, a two-step method was examined.[11] Thus, the alkynones **7e–f** were first converted to enaminones by treatment with diethylamine and then refluxed under similar acidic conditions without isolation of the intermediate enaminones. In this procedure, the desired benzo[*h*]chromones **9e–f** were obtained in good yields (Table 2, runs 5 and 7).

In conclusion, we have demonstrated an efficient synthesis of benzo[*h*]chromone derivatives based on

intramolecular alkynoyl transfer followed by the 6-*endo* ring closure. This methodology could provide a new synthetic entry to naphtho[2,3-*h*]chromone quinones including espicufolin and indomycinones.

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10. Compound **10e**: $C_{29}H_{21}ClO_6$; P-1 (#2); of the collected 3875 reflections, 3668 were unique (R_{int}=0.0369). The final cycle of full-matrix least-squares refinement yields R=0.047, R_W=0.059 and goodness-of-fit=1.92 for 3325 observed reflections [I>1.00s(I)] and 409 variable parameters. Atomic coordinates for this structure were deposited with the Cambridge Crystallographic Data Centre (CCDC-138106). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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