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Total synthesis of cleomiscosin C via a regioselective cycloaddition reaction of *o*-quinone

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ABSTRACT

We have achieved total synthesis of cleomiscosin C (aquillochin) through regioselective cycloaddition of *o*-quinone and protected sinapyl alcohol as a key step. During preparation of *o*-quinone from phenol by IBX oxidation, silyl substituents adjacent to the phenolic hydroxyl group afforded effective inhibition of an undesired oxidative elimination.

Recently we developed a novel procedure for regioselective cycloaddition of *o*-quinone **1** and a sinapyl alcohol unit **2** to construct 1,4-benzodioxanes **3** (from **1a**,**b**) and **3′** (from **1′a**,**b**).[1,2] The position of the alkoxy substituent on the *o*-quinone ring could effectively control the regioselectivity of the cycloaddition (Fig. 1).

The results prompted us to apply this cycloaddition to the synthesis of natural products. Here, we describe total synthesis of cleomiscosin C (aquillochin, **4**, Fig. 2), a coumarinolignan isolated from many groups of plants.[3–8] It exhibits a vasorelaxant effect[5] and inhibitory activity against tyrosinase,[6] monoamine oxidase,[7] lipid peroxidation,[7] and LDL oxidation.[8] The synthesis of **4** has been accomplished by oxidative coupling between catechol and sinapyl alcohol using silver oxide[9] or diphenyl selonoxide[10] in low yield, accompanied by its regioisomer, cleomiscosin D. In the case of horseradish peroxidase or tyrosinase, the cyclization proceeded selectively but slowly in low yield.[9,11] As an alternative route,

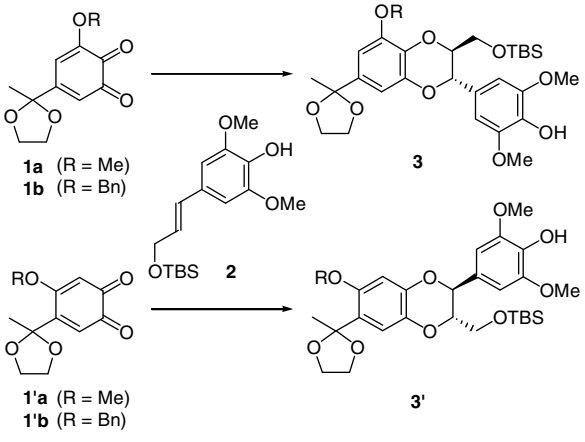

Figure 1. Regioselective cycloaddition of *o*-quinone **1** (**1′**) and sinapyl alcohol unit **2** to afford 1,4-benzodioxane **3** (**3′**).

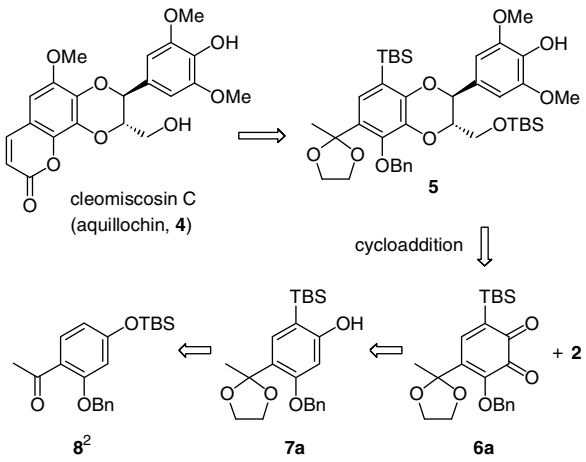

Figure 2. Retrosynthetic strategy for cleomiscosin C (**4**).

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successive nucleophilic substitution and dehydrated condensation have been used to form the 1,4-benzodioxane skeleton.[12]

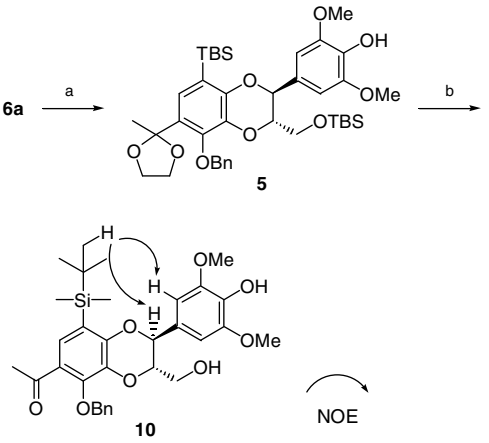
Our approach to the synthesis of **4** is summarized in Figure 2. The coumarin moiety of **4** should be formed from the cyclic acetal part of **5**. The 1,4-benzodioxane framework of **5** could be afforded by cycloaddition of *o*-quinone **6a** and **2**.[13] Preparation of **6a** would be carried out from **7a** by regioselective oxidation with IBX.[14,15] The TBS group was used as the methoxy group precursor[16] after a considerable investigation. Phenol **7a** could be obtained from known **8**.[2]

Preparation of the *o*-quinone precursor **7a** commenced with bromination of **8** using NBS (97% yield), followed by protection of the carbonyl moiety as a cyclic acetal to give **9** in 96% yield (Scheme 1). The resulting **9** was converted to arylsilane **7a** in 79% yield by intramolecular transposition of the TBS group with *n*BuLi.

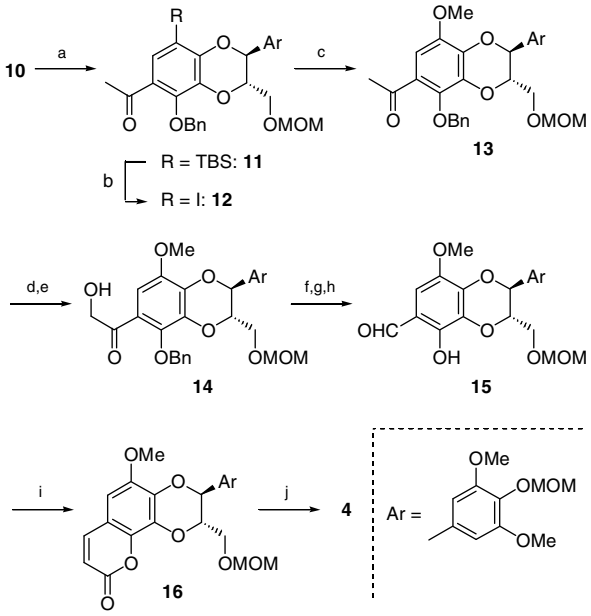
Oxidation of **7a** with IBX afforded the target *o*-quinone **6a** in 59% yield, together with the undesired **1′b** in 29% yield, which was generated by oxidative elimination. *o*-Quinone **6a** and **1′b** could be separated readily by silica gel column chromatography. The selectivity for **6a**/**1′b** was 2.0 (Table 1, entry 1). The selectivity was influenced by the bulkiness of the silyl groups. Thus, the selectivity was increased to 5.2 using the more bulky TIPS group[17] (entry c), and decreased to 1.0 in the case of the less bulky TES group (entry b). Preliminary experiments on the IBX oxidation step revealed that each phenol **7d**,[18] **7e**, and **7f** produces only **1′b**.

Cycloaddition of **6a** and **2** proceeded regioselectively and smoothly in the presence of triethylamine to provide the expected adduct **5** in 51% yield (Scheme 2). The structure of the adduct was confirmed by NOE experiments on **10**, which was obtained after deprotection of **5** under acidic conditions in 82% yield. NOEs were observed for the *tert*-butyl proton of the TBS group to both protons of the upper part of structure **10**.

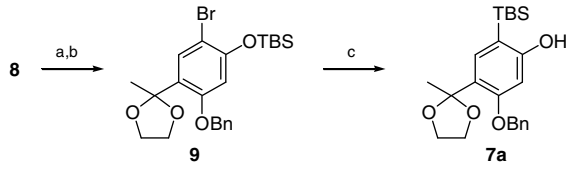
Protection of the hydroxyl and phenol groups of **10** as the MOM ether gave **11** in 88% yield (Scheme 3). The TBS group of **11** was replaced by iodide temporarily with NIS to afford **12** in 66% yield, and introduction of a methoxy substituent by the Ulmann reaction provided **13** in quantitative yield. The methyl ketone **13** was converted to **14** in 60% yield by formation of the silyl enol ether with TBSCl, followed by osmium-mediated dihydroxylation. The resulting α-hydroxy ketone **14** was reduced to the diol in 51% yield, which was subjected to successive oxidative cleavage and hydrogenolysis to give **15** in quantitative yield. To form the coumarin structure from salicylaldehyde, we applied a procedure reported by Harayama and co-workers.[19] Thus, salicylaldehyde **15** was treated with methyl (triphenylphosphoranylidene)acetate in *N*,*N*-diethylaniline at 220 °C to afford protected cleomiscosin C **16** in 82% yield in a one-pot reaction. The MOM groups were removed under acidic conditions to give **4** in 71% yield. Spectroscopic data



Scheme 2. Reagents and conditions: (a) **2**, Et_3N, THF, rt, 8 h (51%); (b) AcCl, MeOH–CH_2Cl_2 (1/1), rt, 1 h (82%).

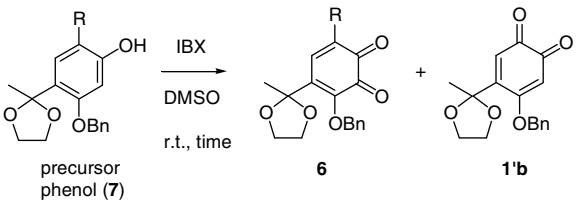


Scheme 3. Reagents and conditions: (a) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 0 °C to rt, 3 h (88%); (b) NIS, CH_3CN, 80 °C, 3 h (66%); (c) NaOMe, CuCl, MeOH, DMF, 80 °C, 3 h (quant.); (d) TBSCl, Et_3N, NaI, CH_3CN, 80 °C, 1 h; (e) OsO_4, NMO, acetone–H_2O (2/1), rt, 2 h (60% in two steps); (f) $NaBH_4$, EtOH–THF (1/1), rt, 5 h (51%); (g) $NaIO_4$, THF–H_2O (2/1), rt, 1 h; (h) Pd/C, H_2, EtOAc, rt, 0.5 h (quant. in two steps); (i) $Ph_3P{=}CH$-CO_2Me, Et_2NPh, 220 °C, 5 h (82%); (j) AcCl, MeOH, 0 °C to rt, 0.5 h (71%).



Scheme 1. Reagents and conditions: (a) NBS, CH_3CN, rt, 3 h (97%); (b) ethylene glycol, *p*TsOH, benzene, reflux, 3 h (96%); (c) *n*BuLi, THF, −78 °C, 3 h (79%).

Table 1
Synthesis of **6** from precursor phenols (**7**)



Entry	R	Time (h)	**6** (%)	**1′b**	**6**/**1′b**
a	TBS	3	59	29	2.0
b	TES	3	50	50	1.0
c	TIPS	3	52	10	5.2
d	Br	1	0	69	0
e	CHO	0.5	0	60	0
f	$CH(SCH_2)_2$	0.5	0	65	0

(^{1}H, ^{13}C NMR) for synthetic **4**[20] were identical to those for natural cleomiscosin C.[4]

In summary, a total synthesis of cleomiscosin C (15 steps from **8**, 1.9% overall yield) has been achieved as an application of the regioselective cycloaddition of *o*-quinone and **2**. It is noteworthy that silyl substituents were useful in avoiding the oxidative elimination in the IBX-mediated oxidation of phenol for selective formation of the target *o*-quinone **6**. Further application of the cycloaddition is currently under way.

Acknowledgment

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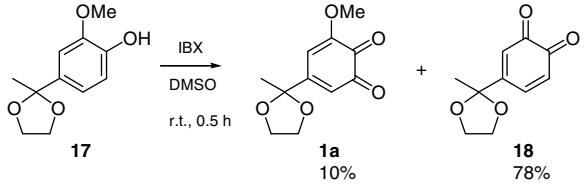
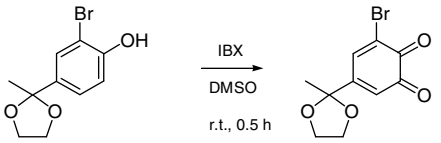
References and notes

1. Kuboki, A.; Yamamoto, T.; Taira, M.; Arishige, T.; Ohira, S. *Tetrahedron Lett.* **2007**, *48*, 771–774.
2. Kuboki, A.; Yamamoto, T.; Taira, M.; Arishige, T.; Konishi, R.; Hamabata, M.; Shirahama, M.; Hiramatsu, T.; Kuyama, K.; Ohira, S. *Tetrahedron Lett.* **2008**, *49*, 2558–2561.
3. (a) Bhandari, P.; Pant, P.; Rastogi, R. P. *Phytochemistry* **1982**, *21*, 2147–2149; (b) Mizuno, M.; Kojima, H.; Tanaka, T.; Iinuma, M.; Kimura, R.; Min, Z. D.; Murata, H. *Phytochemistry* **1987**, *26*, 2071–2074; (c) Hemlata; Kalidhar, S. B. *J. Indian Chem. Soc.* **1994**, *71*, 213–214; (d) Cheng, X. F.; Chen, Z. L. *Fitoterapia* **2000**, *71*, 341–342; (e) Wu, P.-L.; Chuang, T.-H.; He, C.-X.; Wu, T.-S. *Bioorg. Med. Chem.* **2004**, *12*, 2193–2197; (f) Son, Y. K.; Lee, M. H.; Han, Y. *Arch. Pharm. Res.* **2005**, *28*, 34–38; (g) Wu, P.-L.; Wu, T.-S.; He, C.-X.; Su, C.-H.; Lee, K.-H. *Chem. Pharm. Bull.* **2005**, *53*, 56–59; (h) Jin, W. Y.; Min, B. S.; Lee, J. P.; Thuong, P. T.; Lee, H.-K.; Song, K.; Seong, Y. H.; Bae, K. *Arch. Pharm. Res.* **2007**, *30*, 172–176.
4. Ray, A. B.; Chattopadhyay, S. K.; Kumar, S.; Konno, C.; Kiso, Y.; Hikino, H. *Tetrahedron* **1985**, *41*, 209–214.
5. Iizuka, T.; Nagumo, E.; Yotsumoto, H.; Moriyama, H.; Nagai, M. *Biol. Pharm. Bull.* **2007**, *30*, 1164–1166.
6. Ahmad, V. U.; Ullah, F.; Hussain, J.; Farooq, U.; Zubair, M.; Khan, M. T. H.; Choudhary, M. I. *Chem. Pharm. Bull.* **2004**, *52*, 1458–1461.
7. Yun, B. S.; Lee, I. K.; Ryoo, I. J.; Yoo, I. D. *J. Nat. Prod.* **2001**, *64*, 1238–1240.
8. Jin, W. Y.; Thuong, P. T.; Nguyen, D.; Min, B. S.; Son, K. H.; Chang, H. W.; Kim, H. P.; Kang, S. S.; Sok, D. E.; Bae, K. *Arch. Pharm. Res.* **2007**, *30*, 275–281.
9. (a) Lin, L.-J.; Cordell, G. A. *J. Chem. Soc., Chem. Commun.* **1984**, 160–161; (b) Lin, L.-J.; Cordell, G. A. *J. Chem. Res. (S)* **1988**, 396–397; (c) Lin, L.-J.; Cordell, G. A. *J. Chem. Res. (M)* **1988**, 3052–3080.
10. Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Heterocycles* **1988**, *27*, 2651–2658.
11. Matsumoto, K.; Takahashi, H.; Miyake, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1999**, *40*, 3185–3186.
12. Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Chem. Pharm. Bull.* **1988**, *36*, 3833–3837.
13. Kuboki, A.; Yamamoto, T.; Ohira, S. *Chem. Lett.* **2003**, *32*, 420–421.
14. Magdziak, D.; Rodriguez, A. A.; Water, R. W. V. D.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285–288.
15. Ozanne, A.; Pouysegu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903–2906.
16. From **17** with a methoxy substituent adjacent to the phenolic hydroxyl group, **1′b** was predominantly obtained instead of **1a** in 78% yield by oxidative elimination.[14]



17 **1a** 10% **18** 78%

17. Since cycloaddition of **6c** with **2** did not proceed, the TBS substituent (**6a**) was used in the procedure.
18. In a preliminary investigation, we found that the target *o*-quinone **20** was generated selectively in 59% yield from **19** with no substituent at C-6 of **6d**. On the basis of this result, we initially planned the synthesis using **6d**.



19 **20** 59%

19. Ishi, H.; Kenmotsu, K.; Döpke, W.; Harayama, T. *Chem. Pharm. Bull.* **1992**, *40*, 1770–1772.
20. *Spectral data for* **4**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.30 (ddd, J = 3.4, 4.9, 12.2 Hz, 1H), 3.65 (ddd, J = 2.4, 4.9, 12.2 Hz, 1H), 3.76 (s, 6H), 3.78 (s, 3H), 4.37 (ddd, J = 2.4, 3.4, 7.8 Hz, 1H), 4.95 (d, J = 7.8 Hz, 1H), 5.09 (t, J = 4.9 Hz, 1H), 6.34 (d, J = 9.3 Hz, 1H), 6.73 (s, 2H), 6.91 (s, 1H), 7.96 (d, J = 9.3 Hz, 1H), 8.60 (s, 1H); (400 MHz, $CDCl_3$): δ 2.18 (dd, J = 4.8, 7.8 Hz, 1H), 3.59 (ddd, J = 3.4, 7.8, 12.2 Hz, 1H), 3.90 (s, 3H), 3.92 (s, 6H), 3.95 (ddd, J = 2.9, 4.8, 12.2 Hz, 1H), 4.11 (ddd, J = 2.9, 3.4, 8.3 Hz, 1H), 5.04 (d, J = 8.3 Hz, 1H), 5.62 (s, 1H), 6.34 (d, J = 9.8 Hz, 1H), 6.55 (s, 1H), 6.68 (s, 2H), 7.64 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, pyridine-d_5): δ 56.1, 56.3, 60.8, 77.9, 79.9, 101.0, 106.3, 111.9, 113.8, 126.4, 133.0, 138.4, 139.3, 144.4, 146.3, 149.2, 160.7.