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# CONCISE SYNTHESIS OF BELAMCANDAQUINONES A AND B BY PALLADIUM (0) CATALYZED CROSS-COUPLING REACTION OF BROMOQUINONE WITH ARYLBORONIC ACIDS

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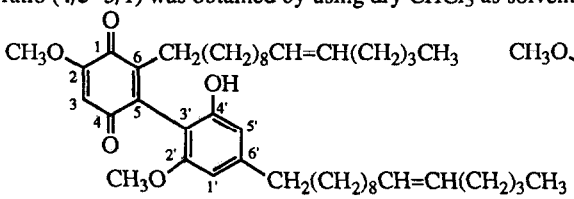
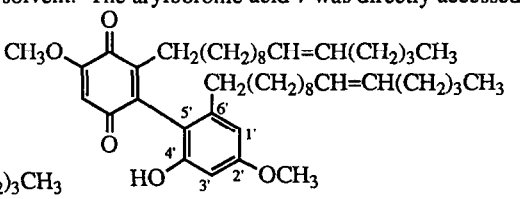
**Abstract**: Belamcandaquinones A (**1**) and B (**2**), new dimeric 1,4-benzoquinone derivatives with cyclooxygenase inhibitory activity have been synthesized by palladium (0) catalyzed cross-coupling reaction between bromoquinone and arylboronic acids readily derived from belamcandol B (**3**), their common biogenetic precursor.

Belamcandaquinones A (**1**) and B (**2**) were isolated as specific cyclooxygenase inhibitor from a medicinal plant, *Belamcanda chinensis* and their structures elucidated on the basis of spectral data and some chemical evidence.[1] Since these compounds were supposed to be biosynthesized via an oxidative coupling of belamcandol B (**3**), a co-metabolite in this plant, the same length and location of the double bond as in **3** were allocated to the two long alkenyl side chains involved in **1** and **2**. In order to confirm the proposed structures of **1** and **2** and to obtain sufficient amount of these compounds for further biological studies, we attempted the synthesis of **1** and **2** starting from **3**, regarded as an important intermediate in their biosyntheses. Here we report facile synthesis of **1** and **2** realized by the successful use of bromobenzoquinone in the palladium catalyzed cross-coupling reaction with arylboronic acids.

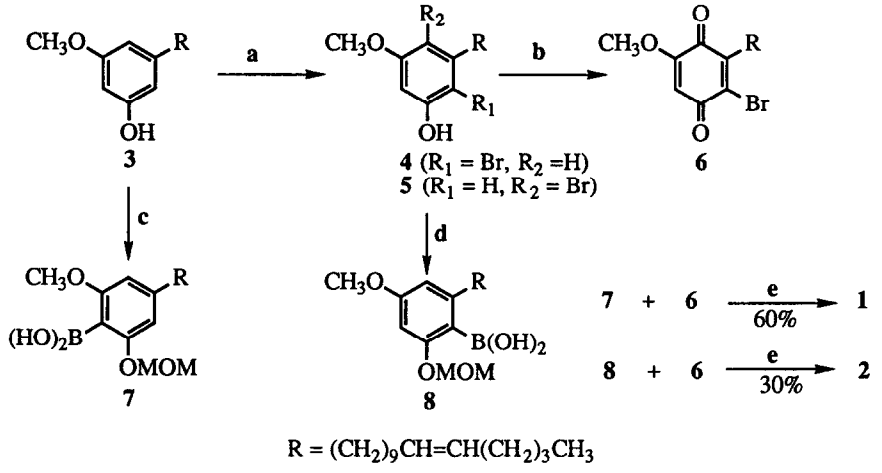
In the retrosynthetic analysis of both **1** and **2** the key carbon-carbon bond between the benzoquinone nucleus and the aryl groups can be derived by a palladium-catalyzed Suzuki reaction[3] from 5-bromo-ardisianone (**6**) and phenylboronic acids **7** or **8**.[4] Three components **6**, **7**, and **8** requisite for the coupling reaction can be readily prepared from belamcandol B (**3**), which is available in a gram-scale by synthesis.[5] The bromoquinone **6** was prepared by selective bromination with NBS followed by air oxidation. The highest ratio (**4**/**5**=5/1) was obtained by using dry $CHCl_3$ as solvent. The arylboronic acid **7** was directly accessed




**1**




**2**




Scheme **a.** NBS, $CHCl_3$, rt (80%); **b.** $O_2$, Salcomine, DMF, rt (75%); **c.** 1. MOMCl, *i*-$Pr_2EtN$, 2. *n*-BuLi, THF, -78°C, then $B(OMe)_3$, 3. $H^+$ (77%); **d.** 1. MOMCl, *i*-$Pr_2EtN$, 2. *n*-BuLi, THF, -78 °C, then $B(OMe)_3$, 3. $H^+$ (63%), **e.** 5 mol% $Pd(PPh_4)_3$, $Na_2CO_3$, THF, reflux, 2. 48% HBr, MeOH

by the addition of trimethyl borate to a THF solution of the lithiated species formed from the MOM-protected **3** and *n*-BuLi *in situ* at -78°C. On the other hand, **8** was derived in high yield from **5** by lithiation with *n*-BuLi followed by the addition of trimethyl borate. The cross-coupling reaction of the boronic acid **7** with the bromobenzoquinone **6** by 5 mol% pd[$PhP_3$]$_4$ in the presence of 2M $Na_2CO_3$ under refluxing THF was smoothly proceeded to give the coupling product in 60% yield. In addition, , applying this protocol to the cross-coupling of the other boronic acid **8** with **6**, the reaction was in competition with protodeboronation of the boronic entity to yield the desired coupling product in poor yield (30%).[6] The coupling products thus obtained were transformed into belamcandaquinones A (**1**) and B(**2**)[7], respectively, by deprotection of the MOM group with 48% HBr.

These results demonstrate a successful use of bromobenzoquinone in the palladium catalyzed cross-coupling reaction with arylboronic acids and have unambiguously established the structures of **1** and **2**.

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**References and Notes**

1. In the preceding paper.
2. Y. Fukuyama, J. Okino, and M. Kodama, *Chem. Pharm. Bull*, **39**, 1877 (1991).
3. N. Miyaura, T. Yanagi, and A, Suzuki, *Synth. Commun.*, **11**, 513 (1981); A. Suzuki, *Pure & Appl.Chem.*, **57**, 1749 (1985).
4. The palladium-catalyzed Still coupling of bromonaphthoquinone with aryl stannes has been reported, but the corresponding reaction with arylboronic acids has been unsuccessful: N. Tamayo, A. M. Echvarrren, and M. C. Paredes, *J. Org. Chem.*, **56**, 6488 (1991). For palladium catalyzed cross-coupling of stannyl benzoquinones with aryl iodides, see: L. S. Liebeskind and S. W. Riesinger, *J. Org. Chem.*, **58**, 408, (1993).
5. Y. Fukuyama, Y. Kiriyama, J. Okino, M. Kodama, H. Iwaki, S. Hosozawa, and K. Matsui, *Chem. Pharm. Bull.*, **41**, 561 (1993).
6. D. Muller and J-P. Fleury, *Tetrahedron Lett.*, **32**, 2229 (1991).
7. All the spectral data of the synthetic **1** and **2** were completely identical with those of natural ones.

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