Total Synthesis of Acetylcholinesterase Inhibitor Macakurzin C

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Received: 29.08.2014; Accepted after Revision: 02.10.2014

Abstract: A concise total synthesis of macakurzin C has been accomplished in nine steps (21% overall yield) from commercially available phloroglucinol, featuring a sequential aromatic Claisen rearrangement–cyclization.

Key words: total synthesis, natural products, aromatic Claisen rearrangement, acetylcholinesterase inhibitors, flavonoids

Natural products exhibiting acetylcholinesterase (AChE) inhibition are considered as promising new entities for the treatment of Alzheimer's disease (AD), because most promising drugs for symptomatic of AD are AChE inhibitors. Thus, flavonoids with AChE inhibitory activity are of interest for the medicinal chemistry community.[1]

Recently, macakurzins A–C (**1**–**3**, Figure 1) were isolated from the leaves of *Macaranga kurzii* (Euphorbiaceae) collected from Yen-Bai, Vietnam by Mai and Pham in 2012.[2] Their structures were determined by extensive NMR spectroscopic analysis, and the absolute stereochemistry of macakurzins A and B were both identified as racemic mixture by their esterification with Mosher's reagent.[2]

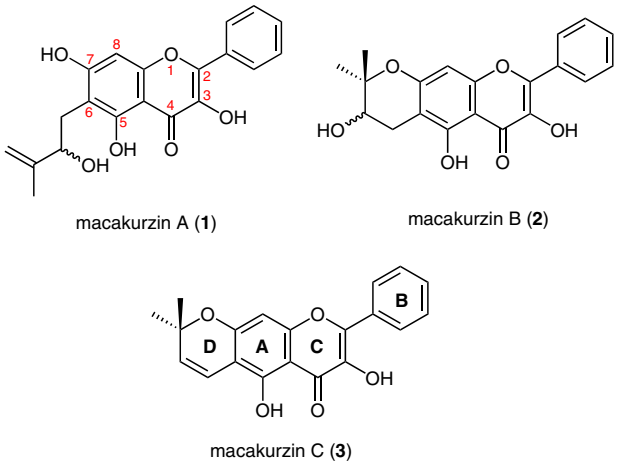
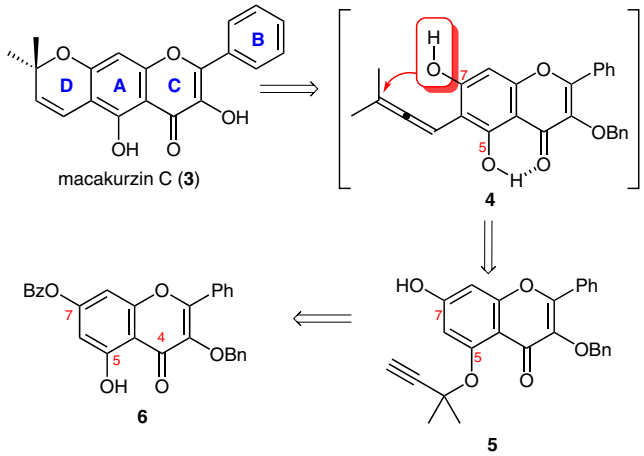


Figure 1 Macakurzin A, B, and C

Interestingly, macakurzin C (**3**) showed potent AChE inhibitory activity (IC_{50} = 20 μM), while closely related macakurzin B (**2**) displayed no activity against AChE (no inhibition at 50 μM against AChE). Based on the initial results, Mai and Pham demonstrated that the lack of a hydroxyl group in the pyran ring of **3** increased the activity in comparison with **2**. Due to the interesting biological properties of **3**, further studies on the structure–activity relationship of **3** may be crucial for developing more potent drug candidates. However, its natural source is too scarce (0.006% isolated yield from crude EtOAc extracts). Macakurzin C was previously synthesized in very poor overall yield (<3%) by prenylation at C(6) in glalangin and DDQ-mediated oxidative cyclization of the resultant C(6)-prenylated galangin.[3] Therefore, we sought to develop an efficient and scalable synthetic route that would provide a sufficient quantity of **3** and its analogues for extensive in vitro/in vivo biological studies to develop more potent AChE inhibitors. Herein, we report a concise and efficient synthetic route to **3** through a sequential aromatic Claisen rearrangement and cyclization.[4,5]

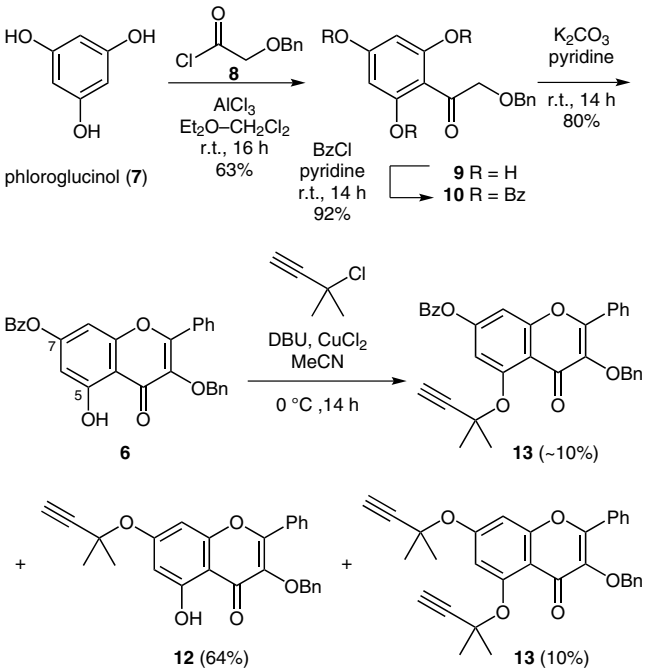


Scheme 1 Retrosynthetic plan

Our retrosynthetic plan for macakurzin C (**3**) is outlined in Scheme 1. We envisioned that the synthesis of macakurzin C (**3**) could be accomplished from aryl propargyl ether **5** by a tandem aromatic Claisen rearrangement–cyclization for the D ring in the natural product. We expected that the chemoselective cyclization of the C(7) phenolic hydroxyl over the C(5) hydroxyl in allenyl bisphenol **4**

SYNLETT 2014, 25, 2794–2796
Advanced online publication: 29.10.2014
DOI: 10.1055/s-0034-1378904; Art ID: ss-2014-u0726-l

should be dictated by the intrinsic reactivity of C(5) and C(7) hydroxyl groups. Preparation of aryl propargyl ether **5** would be challenging because of the low reactivity of the C(5) hydroxyl group in flavonol **6**.

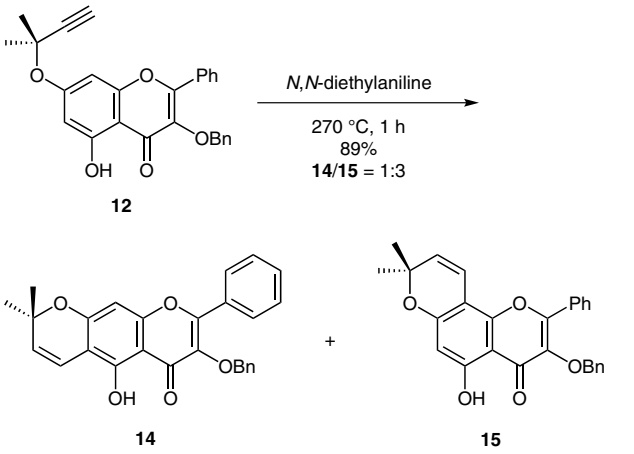


Scheme 2 Attempted preparation of the substrate for the aromatic Claisen rearrangement

Our synthesis of macakurzin C commenced with commercially available phloroglucinol (**7**), which was transformed to the known tribenzoate **10**[6] by Friedel–Crafts acylation[7] followed by benzoylation of the resulting trihydroxyphenol **9** in 58% overall yield (Scheme 2). Exposure of tribenzoate **10** to K_2CO_3 in hot pyridine (140–150 °C) gave rise to flavonol monobenzoate **6** in 80% yield through Baker–Venkataraman rearrangement and dehydration followed by concomitant deprotection of the C(5) benzoyl group.

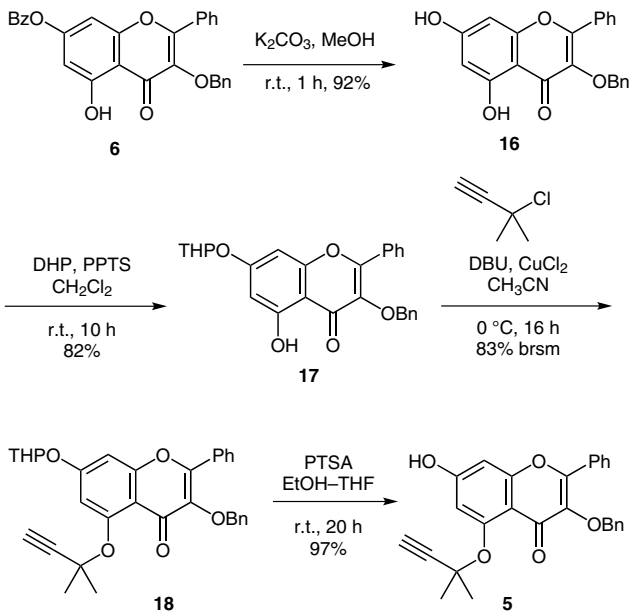
With monobenzoate **6** in hand, we attempted propargylation at the C(5) hydroxyl group. However, attempts to propargylate the C(5) hydroxyl group were proven to be problematic due to the low reactivity of the C(5) hydroxyl group and instability of the C(7) benzoyl protection group. Indeed, all our attempts using conventional conditions [methyl- or trifluoro-(2-methylbut-3-yn-2-yl] carbonate, DBU, $CuCl_2$, MeCN) failed to give **11**. In addition, exposure of monobenzoate **6** to more reactive conditions (3-chloro-3-methylbut-1-yne, DBU, $CuCl_2$, MeCN) gave rise to the C(5) propargyl ether **11** in very poor yield (<10%), but the C(7) propargyl ether **12** (64%) as a major product along with C(5)/C(7) bispropargyl ether **13** (<10%).[8]

The aromatic Claisen rearrangement of the C(7) propargyl ether **12** provided **15** as a major product (**14**/**15** = 1:3, Scheme 3).[9] To overcome this problem, the C(5) propargylation should be crucial. Thus, we investigated the C(7) hydroxyl protecting groups, which should be tolerant to the reaction conditions of propargylation.

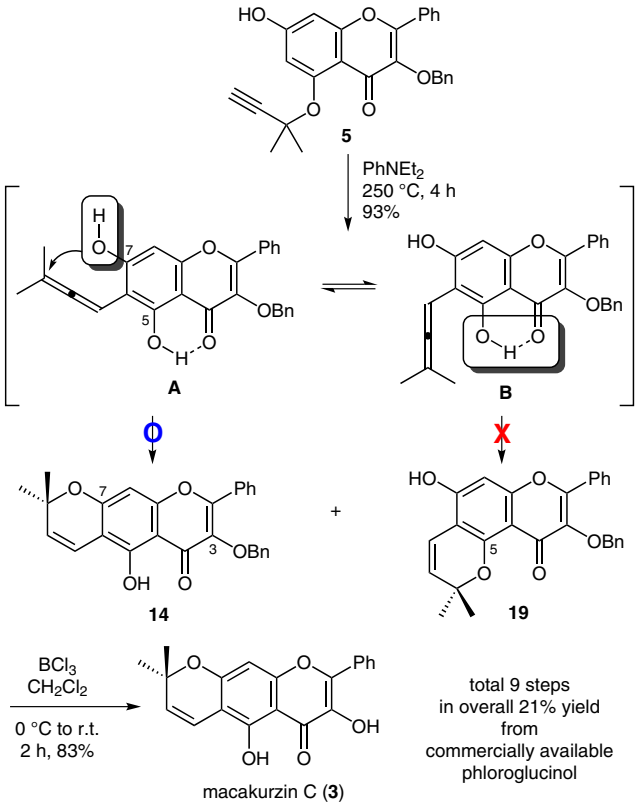


Scheme 3 Attempted aromatic Claisen rearrangement of **12**

After an extensive investigation of the C(7) hydroxyl protecting groups,[10] we were pleased to find that the THP group is tolerant to the reaction conditions and can be easily removed under mild acidic conditions (Scheme 4). Deprotection of the benzoyl group in **6** afforded bisphenol **16**[5] in 92% yield, which was protected by the THP group to provide **17** in 82% yield. Treatment of **17** with 3-chloro-3-methylbut-1-yne and DBU in MeCN in the presence of a catalytic amount of $CuCl_2$ gave rise to C(5) propargyl ether **18** in a good yield (66%, 83% based on the recovered starting material) along with the propargyl ether **12** (5%). Deprotection of the THP group in propargyl ether **18** provided the phenol **5** in 97% yield.



Scheme 4 Preparation of substrate for aromatic Claisen rearrangement



Scheme 5 Total synthesis of macakurzin C (**3**)

Having successfully prepared C(5) propargyl ether **5**, we embarked on the final stage of the synthesis (Scheme 5). As expected, the subjection of **5** to the conventional conditions of the aromatic Claisen rearrangement smoothly provided **14** in 93% as a single isomer.

Finally, the deprotection of the benzyl group with BCl_3 in CH_2Cl_2 completed the synthesis of macakurzin C (**3**) in 83% yield. The spectral data for synthetic **3** were identical with those reported for the natural product (^{1}H NMR, ^{13}C NMR, IR, and HRMS).[2]

In summary, the concise synthesis of macakurzin C (**3**) has been accomplished in nine steps (21% overall yield) from commercially available phloroglucinol, featuring a sequential aromatic Claisen rearrangement and cyclization. We strongly believe that our synthetic routes could provide a sufficient amount of **3**, which would enable us to extensively investigate in vitro/in vivo biological studies to develop lead compounds for AChE inhibitors. The biological evaluation of synthetic macakurzin C (**3**) and its analogues are under way and will be reported in due course.

Acknowledgment

This work was supported by National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (NRF-2012R1A1A1009271).

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(8) Under the reaction conditions, the benzoyl group in **6** was easily cleaved to afford bisphenol **16**, which was rapidly propargylated to afford the C(7) propargyl ether **12**.
(9) For similar results on this type of aromatic Claisen rearrangement of flavone and isoflavone, see: (a) Zheng, S. Y.; Li, X. P.; Tan, H. S.; Yu, C. H.; Zhang, J. H.; Shen, Z. W. *Eur. J. Org. Chem.* **2013**, 1356. (b) Zheng, S. Y.; Shen, Z. W. *Tetrahedron Lett.* **2010**, *51*, 2883.
(10) We also prepared the corresponding MOM-, PMB-, and Bn-protected analogues of **17**, which were tolerant to the reaction conditions. However, the C(5) propargyl ether groups were very susceptible to the various reaction conditions of deprotection, resulting in the decomposition of the starting materials.

