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Total syntheses of norartocarpin and artocarpin

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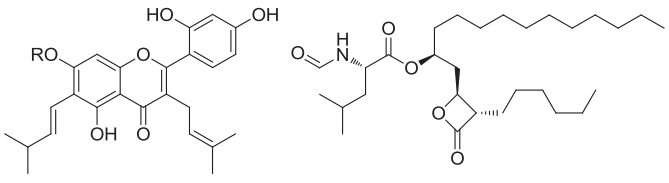
ABSTRACT

The total syntheses of norartocarpin and artocarpin, two biologically interesting natural flavonoids with two regioisomeric isoprenyl side chains, were achieved for the first time via a linear reaction sequence of 9 and 12 steps with the overall yields of 14% and 3.5%, respectively, starting from commercially available 1,3,5-trimethoxybenzene.

1. Introduction

Norartocarpin (**1**) and artocarpin (**2**) are natural isoprenylated flavonoids isolated from the genus *Artocarpus* (Fig. 1),[1] which were reported to possess a variety of interesting biological activities including inhibitory effects on melanin biosynthesis and 5α-reductase, antibacterial activity, and cytotoxicity.[2] Recently, **1** was found to inhibit the activity of pancreatic lipase (PL) by our group[1a] with an IC_{50} value close to that of orlistat, a clinical PL inhibitor used as an anti-obesity drug.



Norartocarpin (**1**): R = H
Artocarpin (**2**): R = CH_3

Orlistat

Fig. 1. Structures of norartocarpin (**1**), artocarpin (**2**), and orlistat.

On the other hand, natural resources of **1** and **2** are limited due to the low contents in *Artocarpus* plants, which negatively influenced their further bioactivity evaluation. Therefore, chemical syntheses of **1** and **2** will be an important alternative approach for addressing the problem of their availability. As the continuation of our study on the chemistry and biology of isoprenylated flavonoids,[1a,3] we herein report the first total syntheses of **1** and **2** via a linear reaction sequence of 9 and 12 steps with the overall yields of 14% and 3.5%, respectively, starting from commercially available 1,3,5-trimethoxybenzene.

2. Results and discussion

Retrosynthetic analysis is shown in Scheme 1. These two flavones carry two different isoprenyl side chains, and our key synthetic strategy involves the introduction of isopentanoyl group into ring A and isoprenyl group into ring C of the flavone scaffold, respectively. The former relies on Friedel–Crafts acylation of 1,3,5-trimethoxybenzene (**7**) and the latter could be achieved by the enolate acylation[4] of 2-hydroxyl acetophenone **6** followed by alkylation with 1-bromo-3-methyl-2-butene at the α-position of two carbonyl groups of β-diketo **5** and the subsequent cyclization to obtain the key intermediate **3** with flavone scaffold. The key intermediate **3** could be converted into the target molecules **1** and **2** via the reduction of benzylic carbonyl group, dehydration and selective demethylation, respectively.

As shown in Scheme 2, the synthesis of key intermediate **3** is quite straightforward. Although the structure of **6** seems simple, its synthesis still remains unreported in the literature. Starting from 1,3,5-trimethoxybenzene (**7**), twice sequential Friedel–Crafts acylation of **7** in dichloromethane in the presence of $AlCl_3$ using acetyl chloride and 3-methylbutanoyl chloride as the acylated reagents,

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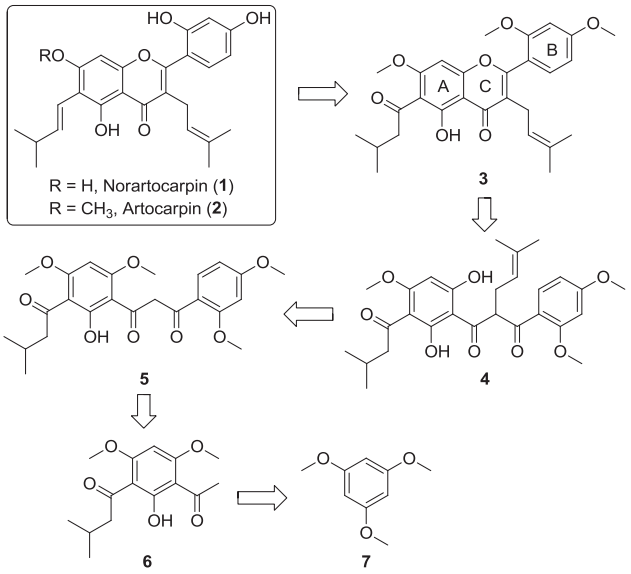
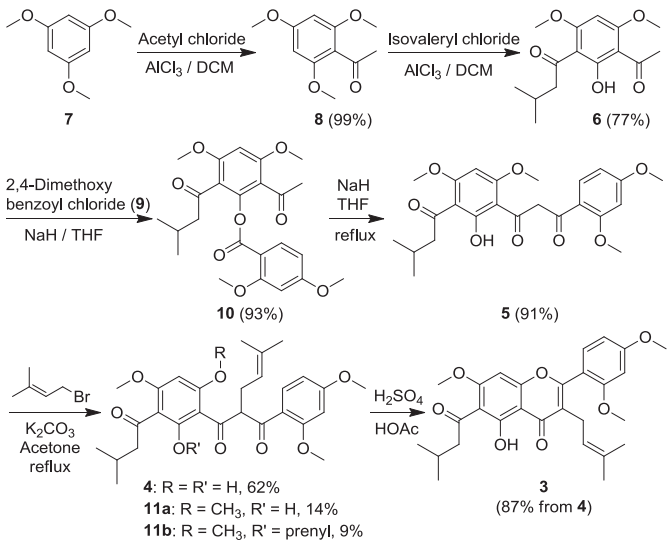


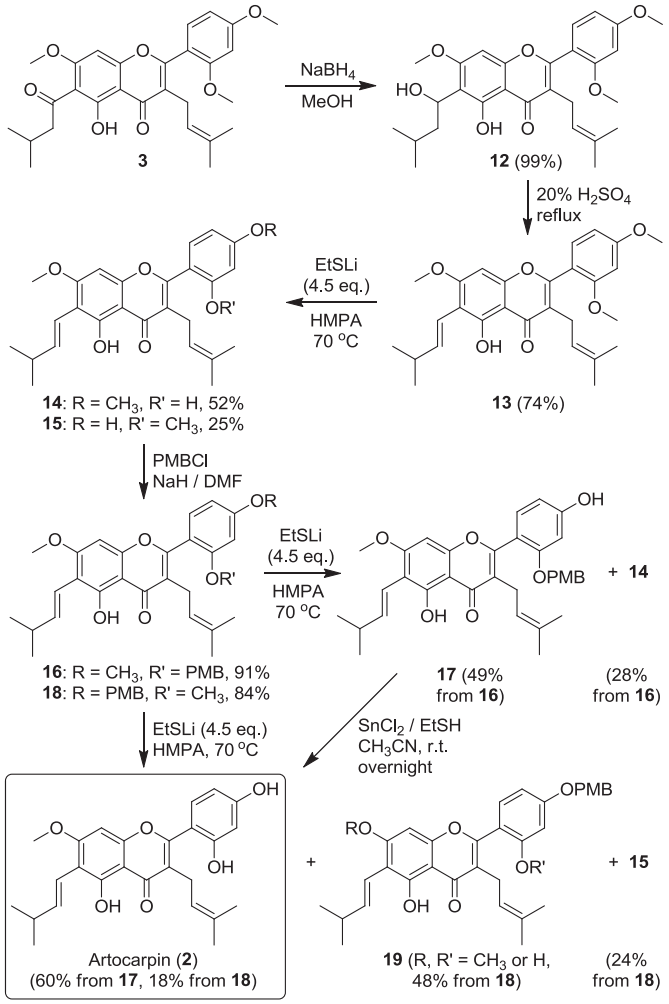
Scheme 1. Retrosynthetic analysis of norartocapin (**1**) and artocarpin (**2**).



Scheme 2. Synthesis of key intermediate **3**.

respectively, afforded the intermediate **6** in good yields (75% for two steps). In the course of Friedel–Crafts acylation, the desired demethylation simultaneously occurred, which may be attributed to the effect of two carbonyl groups at *ortho* positions. On the other hand, if the two F–C reactions were performed in a reversed sequence, 2,4,6-trimethoxyacetylbenzene (**8**) rather than expected target molecule **6** was obtained as the major product, i.e., the isopentanoyl group was cleaved via reverse F–C reaction during the second step. 2,4-Dimethoxybenzoyl chloride (**9**) was readily prepared by reacting the corresponding carboxylic acid with $SOCl_2$ at room temperature. With precursors **6** and **9** in hand, the esterification and Baker–Venkataraman rearrangement were carried out in a stepwise approach under the condition of NaH/THF to give β-diketo **5** in excellent yields (93% and 91%), rather than in one-pot manner to afford **5** in a poor yield. The alkylation of **5** with prenyl bromide in the presence of K_2CO_3 in refluxing acetone provided the prenylated and simultaneously demethylated intermediate **4** as the major product (62% yield), and on the other hand the expected monoprenylated product **11a** and diprenylated product **11b** as the minor (14% and 9% yields, respectively). The demethylation position in product **4** was confirmed by comprehensive spectroscopic methods, especially HMBC to be luckily at 6-position of ring A to give the correct demethylated product for the next step of cyclization. It was found that prolonging the reaction time was beneficial to the formation of the desired product **4** but the formation of **11a**–**b** seemed to be unavoidable. The following regioselective cyclization of **4** in the presence of H_2SO_4/AcOH generated the flavone intermediate **3** in 87% yield (overall yield of 35% from **7**).

With key intermediate **3** in hand, we subsequently proceeded to its reduction with $NaBH_4$ and dehydration of reduced product. As shown in Scheme 3, the reduction product **12** could be obtained in almost quantitative yield. The following dehydration of **12** was carried out in 20% H_2SO_4 to give **13** in 74% isolated yield.



Scheme 3. Synthesis of artocarpin (**2**) by demethylation with EtSLi/HMPA.

At this point, the final step of the synthesis was focused on the demethylation of **13**. Attempts to treat with BBr_3, $AlCl_3$, 48% HBr (aq) or pyridinium hydrohalides to give the target molecules were unsuccessful and in all cases they were proceeded with decomposed or recovered starting material. However, monodemethylated products **14** and **15** were obtained as a mixture (**14**/**15**=2:1) in 77% yield under the conditions of EtSLi (4.5 equiv)/HMPA,[5] which encouraged us to carry this synthetic route through to the end. Prolonging the reaction time, raising temperature and increasing the amount of EtSLi to 30 equiv did not result in the