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A total synthesis of (+)-brazilin

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ABSTRACT

Described herein is a concise total synthesis of (+)-brazilin from readily available 4-bromo-1,2-dimethoxybenzene. In this synthetic route, a Sharpless asymmetric dihydroxylation was employed to introduce the chiral hydroxyl group, and trifluoroacetic acid (TFA) catalyzed one-pot intramolecular tandem Prins/Friedel-Crafts reaction was also involved as the key transformation in the construction of the hybrid chromane and indane framework.

Introduction

Homoisoflavones skeleton structures are widely existed in biologically active natural products, which exhibit intriguing biological properties [1]. In recent years, studies on the construction of homoisoflavones framework have attracted extensive attention in structure modification of pharmaceutical molecules and development of new drugs.

Brazilin and its family natural products, including brazilane, brazilein, brazilide A, haematoxylin, and haematoxylane (Figure 1), representing important tetracyclic homoisoflavanoid fundamental units, are isolated from the alcoholic extracts of the heartwood of *Caesalpinia sappan* L. (Leguminosae) [2]. Among them, brazilin is structurally composed of a chroman skeleton *cis*-fused with a 2,3-dihydro-1*H*-indene moiety. Early literatures have indicated that brazilin possesses a series of outstanding bioactivities, including anti-inflammatory [3], hepatoprotective [4], vasorelaxant [5], antibacterial [2e], anticancer [6] and antitumor [7] activities. Additionally, brazilin also exhibits other biological properties, such as hypoglycemic [8] and DNA nicking activity [9].

Such unique structure and its variety biological properties have drawn considerable attention in the synthesis of brazilin and its related family natural products. In recent years, several synthetic studies have been realized to afford brazilin (Scheme 1a). Dann in 1963 reported the first synthesis of brasilin from 7-methoxychroman-4-one in 8 steps [10a]. Then, Pettus et al. in 2005 accomplished a synthetic route to (±)-brazilin by employing a regioselective dirhodium-catalyzed aryl C—H insertion approach [10b]. After that, Zhang and co-workers achieved an enantioselective total synthesis of (+)-brazilin as well as (+)-brazilide A and (−)-brazilein through a Lewis acid mediated lactonization to establish the bis-lactone core [10c]. Subsequently, Yadav and co-workers disclosed a formal synthesis of (±)-brazilin and total synthesis of (±)-brazilane via palladium (II)-catalyzed intramolecular Friedel-Crafts reaction [10d]. In the same time, Jahng et al. realized a synthetic route to (+)- and (−)-brazilin through AD-mix-α and AD-mix-β directed enantioselective dihydroxylation [10e]. In 2015, Kim and co-workers described a total synthetic approach to brazilin utilizing Mitsunobu coupling followed by indium(III)-catalyzed alkyne-aldehyde metathesis allowed for rapid construction of brazilin core skeleton [10f]. Then, Kim and co-workers continuously accomplished a concise synthesis of brazilin through palladium (II)-catalyzed allylic arylation [10g]. Recently, Vranken's group completed a racemic total synthetic route to (±)-brazilin via palladium-catalyzed [4+1] annulation [10h]. Although notable methodologies have been achieved in the synthesis of brazilin, most of the synthetic routes were over 7 steps, and some of the aforementioned synthetic strategies were proceeded in a pitiful

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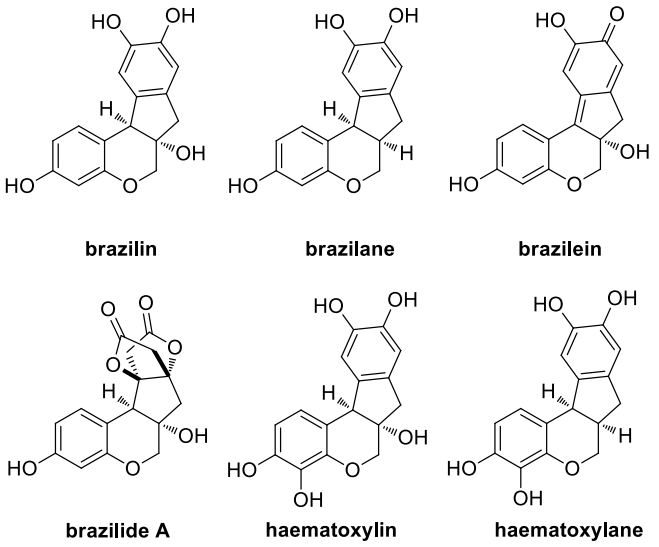
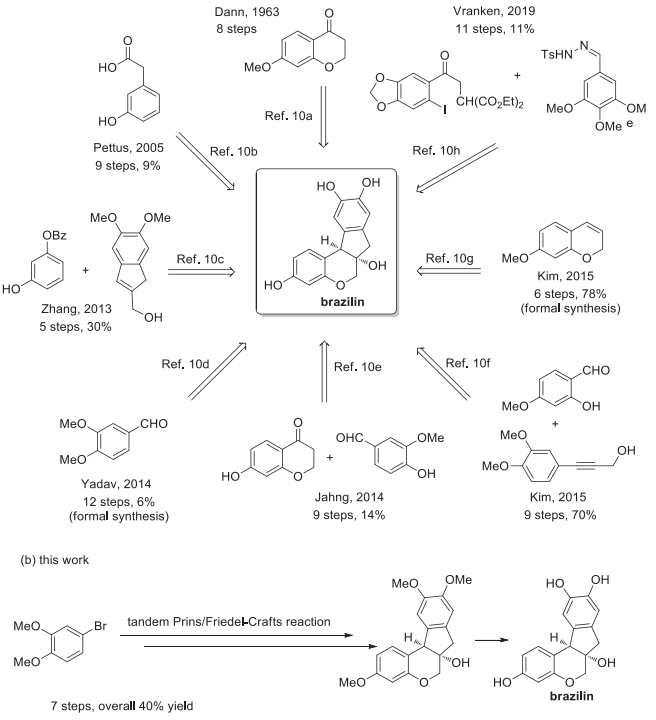


Fig. 1. Pharmaceutical molecules containing tetracyclic homoisoflavonoids skeleton.

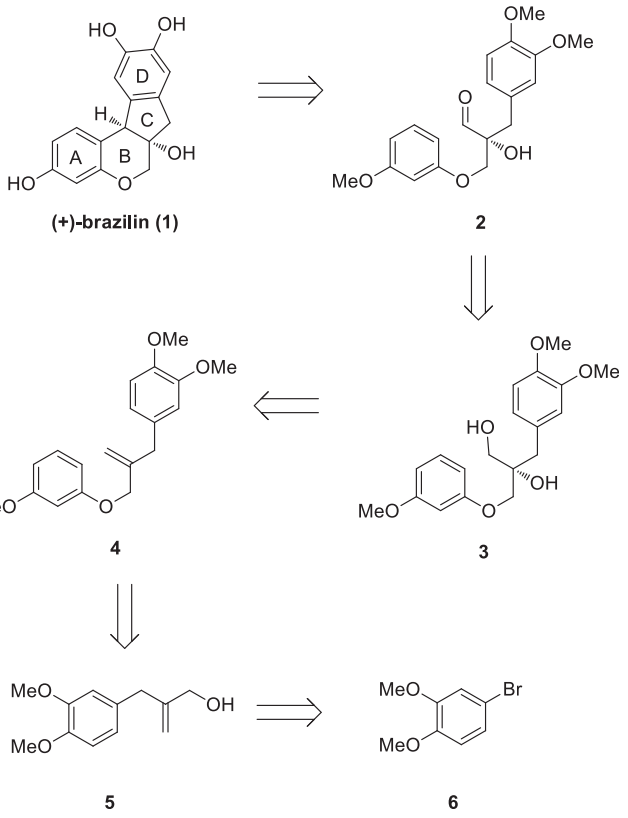


Scheme 1. Different strategies for the synthesis of brazilin.

overall yield. Thus, a short and efficient synthetic approach is still of great interest. Herein, we disclose a concise total synthesis of (+)-brazilin from commercially available material within 7 steps (Scheme 1b).

Results and discussion

As outlined in Scheme 2 of our retrosynthetic approach, the key synthetic challenge associated with (+)-brazilin (**1**) was the construction of *cis*-fused chromane and indane framework of the B and C rings, which could be achieved from precursor **2** through an intramolecular tandem Prins/Friedel-Crafts reaction. The intermediate **2** would be obtained via Parikh-Doering oxidation from

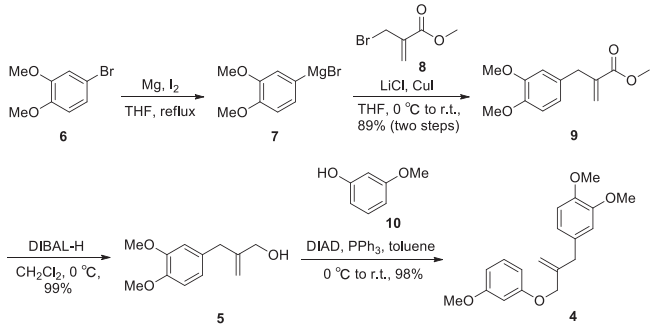


Scheme 2. Retrosynthetic approach to (+)-brazilin (**1**).

3, which in turn could be generated from **4** by employing a classic Sharpless asymmetric dihydroxylation. We envisaged that the intermediate **4** could be obtained through Mitsunobu etherification reaction from terminal hydroxyl compound **5** and commercially available 3-methoxyphenol (**10**). Synthesis of the intermediate **5** could be realized from another commercially available 4-bromo-1,2-dimethoxybenzene (**6**) via three sequential procedures, including preparation of the Grignard reagent, lithium and copper co-catalyzed coupling reaction and diisobutylaluminium hydride (DIBAL-H) reduction.

Our synthesis commenced with the preparation of the Grignard reagent **7** from readily available **6** in the presence of magnesium ribbon and iodine (Scheme 3). With fresh Grignard reagent **7** in hand, α,β-unsaturated keto ester **9** could be easily achieved from methyl 2-(bromomethyl)acrylate (**8**) through lithium chloride and copper iodide co-catalyzed coupling reaction [11]. In the presence of DIBAL-H, compound **9** was converted into the corresponding terminal hydroxyl compound **5** in an excellent yield. Under the promotion of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine [12], the benzyl ether bond in the intermediate **4** was smoothly constructed in 98% yield from compound **5**.

To establish the dihydroxyl groups, a classic Sharpless asymmetric dihydroxylation conditions [13], including potassium osmate(VI) dihydrate, red prussiate ($K_3Fe(CN)_6$) and $(DHQD)_2PHAL$ (Hydroquinidine 1,4-phthalazinediyl diether), were introduced into those reaction system, and the desired product **3** was provided in 86% yield with 98% ee value. However, when 4-methylmorpholine *N*-oxide (NMO) instead of $K_3Fe(CN)_6$ was adopted as the pro-oxidant, the enantioselectivity of dihydroxyl product **3** was dropped to 90% ee value. In the process of Parikh-Doering oxidation, the hydroxyl-aldehyde **2** was generated in 85% yield when sulfur trioxide-pyridine was employed [14]. It should be noticed that, when *N*,*N*-diisopropylethylamine (DIPEA) was replaced with



Scheme 3. Preparation of the intermediate **4**.

triethylamine, compound **2** was obtained in only 31% yield under Parikh-Doering oxidation condition. Besides, the yield of **2** decreased to 60% when Swern oxidation condition was introduced into this transformation. Furthermore, the oxidation reaction was failed to proceed in the presence of Dess-Martin periodinane (DMP) or 2-iodoxybenzoic acid (IBX). These above-mentioned comparison results indicated that sulfur trioxide-pyridine combined with DIPEA were the optimal oxidation condition. With the key intermediate **2** in hand, we subsequently focused our attention on the construction of *cis*-fused chromane and indane framework of the B and C rings. In the presence of TFA, the desired product **13** was smoothly obtained in 80% yield in one-step via an intramolecular tandem Prins/Friedel-Crafts reaction [15], in which the C ring may be first formed (**11**) [10c,16]. Subsequently, under the control of the quaternary carbon center, the B ring was then constructed with the desired *cis*-fused rings. Finally, the methoxy groups were successfully removed to deliver the desired natural product (+)-brazilin (**1**). Under the treatment of boron tribromide [17], precursor **13** was transformed into the target molecular **1** in 79% yield (Scheme 4). Additionally, the NMR data of compound **1** was consistent with previous report [10b], which helps us to further confirm the absolute configuration of (+)-brazilin (**1**) in our synthetic works.

Conclusion

In summary, we described a concise and practical strategy for the synthesis of (+)-brazilin in overall 40% yield within 7 steps, and our synthetic approach was easily scaled up to a gram level with high yield. The synthetic route involved bimetallic catalyzed coupling reaction in the preparation of α,β-unsaturated keto ester group, Mitsunobu etherification in the formation of benzyl ether bond, Sharpless asymmetric dihydroxylation in the establishment of dihydroxyl groups, and one-pot intramolecular tandem Prins/Friedel-Crafts reaction in the construction of the hybrid chromane and indane framework. Further synthetic works on other related brazilin family natural products and their analogues are currently in progress in our lab.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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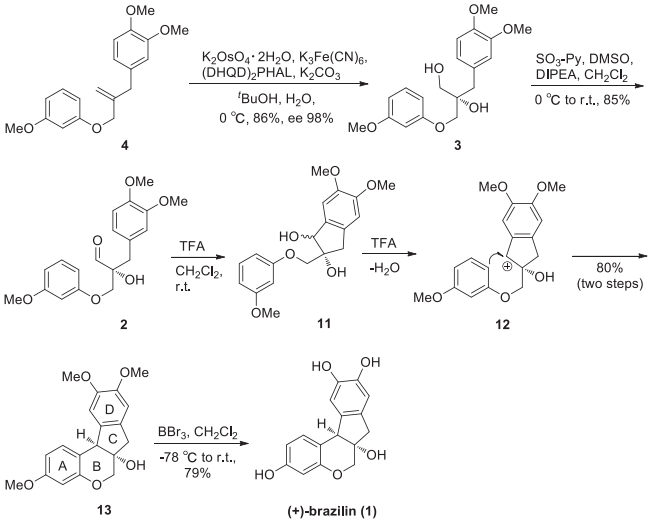

Scheme 4. Synthesis of the target molecular (+)-brazilin (**1**).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152052.

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