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Total synthesis of (±)-brazilin and formal synthesis of (±)-brazilein, (±)-brazilide A using *m*-CPBA

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ABSTRACT

Total synthesis of (±)-brazilin has been accomplished. *m*-CPBA epoxidation of allyl alcohol **10** and epoxy opening reaction mediated by *m*-chlorobenzoic acid, formed in situ as a byproduct, gave advanced intermediate diol **14**. O-alkylation and cyclization gave phenol **6** which enabled the formal synthesis of (±)-brazilein and (±)-brazilide A.

Introduction

Five phenolic compounds from MeOH extracts of heartwood of *Caesalpinia sappan* L. in Figure 1 showed broad bioactivities.[1–4] Among them, brazilin and brazilein are most investigated in terms of oncology.[1b,2] Their antitumor mechanisms were also extensively studied,[2b,3] which will accelerate the research of Sappan Lignum constituents for medical purpose. During our hunt for efficient antitumor lead compounds originally from bioactive natural products,[5] brazilin and brazilein attracted our attention due to their ability to suppress migration and invasion of breast cancer cells.[2b] Several syntheses of brazilin were reported: apart from two reports[2a,6] through chromone intermediates, Pettus group[7] devised an underutilized strategy including aryl cyclization with a *p*-quinone methide to complete total synthesis in 9 steps, 8.5% overall yield. Recently, Professor Zhang's group[8] reported an elegant enantioselective total synthesis via a Sharpless asymmetric dihydroxylation in 9 steps, 14% overall yield. Herein, we will disclose a more flexible strategy with features that divergent derivatives synthesis can be realized at a late stage in high yield.

Our retrosynthetic analysis is depicted in Scheme 1. According to Professor Zhang's report[8], brazilin, brazilein, and brazilide A could be synthesized through a common intermediate **6**. The tetracyclic skeleton could be constructed through intramolecular Friedel–Crafts cyclization of indanol **7**, which could be obtained by nucleophilic attack of phenol salt to key Tosylate ester **9**. Compound **9** is available from selective protection of diol formed by single treatment of known allyl alcohol **10** with *m*-CPBA.

Allyl alcohol **10** was synthesized from indanone **11** (Scheme 2).[9] Sequential methoxycarbonyl group introduction, $NaBH_4$ reduction,

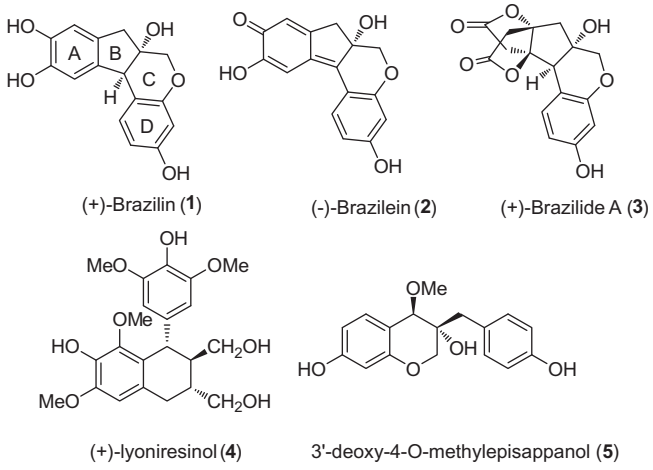

Figure 1. Phenol compounds isolated from *Caesalpinia sappan*.

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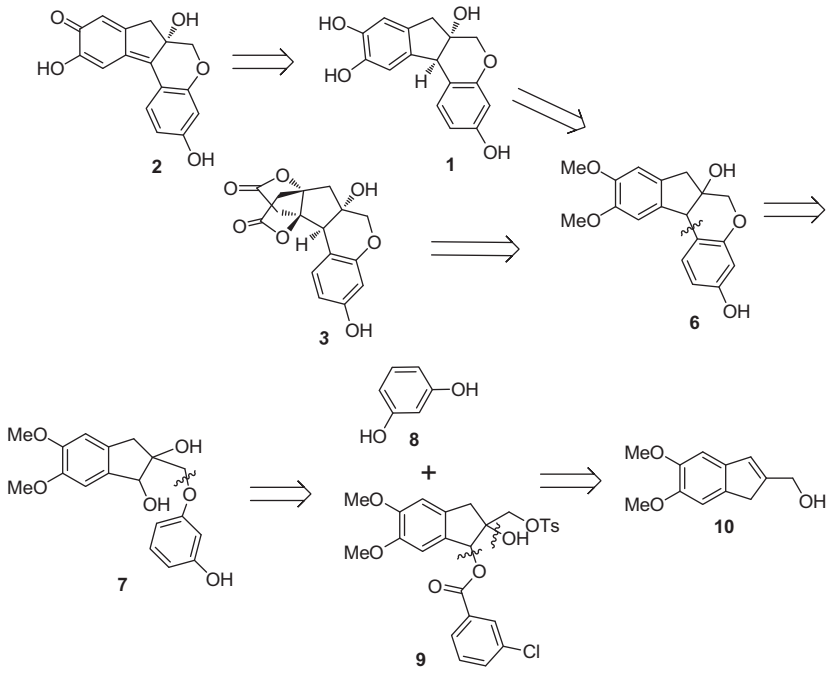
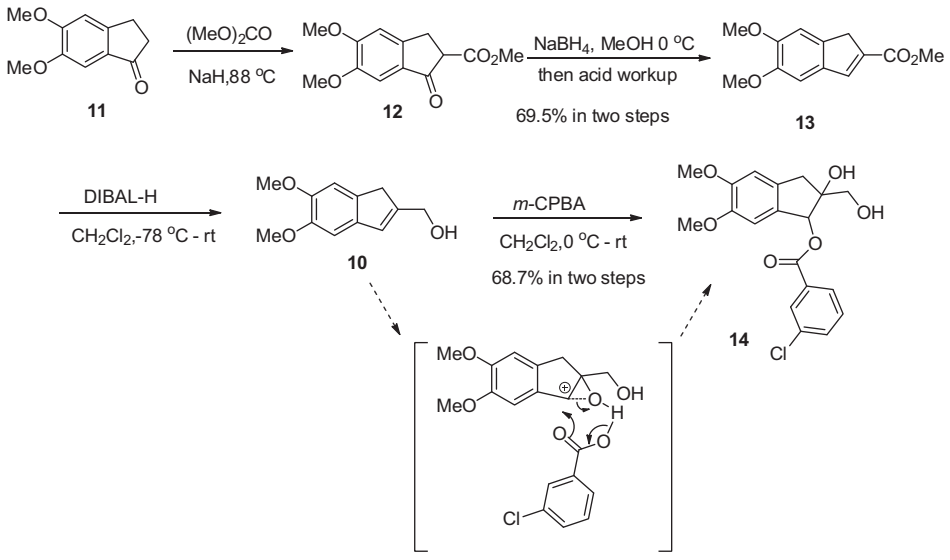


Scheme 1. Retrosynthetic analysis.

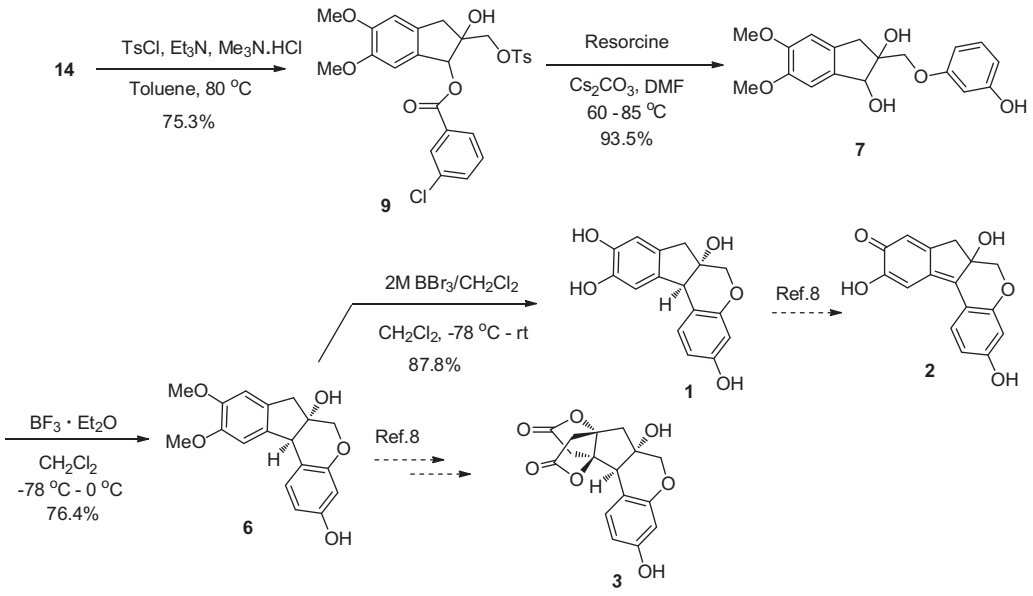


Scheme 2. Synthetic route to diol **14**.

and acid workup gave unsaturated ester **13** which was further reduced by DIBAL-H to give **10** smoothly. We found that after $NaBH_4$ reduction of keto ester, dehydration of crude mixture with 3 M HCl, instead of using MsCl, Pyr,[9] gave compound **13** directly in 69.5% yield. This improvement was based on the fact that unsaturated ester **13** was observed from TLC of crude mixture after satd NH_4Cl workup of $NaBH_4$ reduction, which implied that a stronger acid could accelerate dehydration process.

Epoxidation was then performed with *m*-CPBA, which should be followed by the Mitsunobu reaction with resorcin, according to our original synthetic plan.[10] To our surprise, instead of epoxide, diol **14** was isolated in 68.7% yield. The mechanism should be epoxidation and subsequent epoxy opening mediated by in situ formed byproduct *m*-chloro benzoic acid. This result is consistent with some reports[11] in that partly formed benzyl cation, with EDG (electron donating group) in *para* position, was attacked by *m*-chlorobenzoic acid (Scheme 2). Despite that the diol was a single compound, the relative configuration of two newly formed groups was not determined. The relative configuration of compound **14** will not influence the final product because the 5–6 fused ring formation in brazilin could give *cis* product only, to the best of our knowledge.

Successful Tosyl protection of primary alcohol set the stage for quick access of tetracycle skeleton as follows (Scheme 3): substitution occurred when resorcine was heated with Cs_2CO_3 and to our delight, the benzoyl group was also removed at the same time. Indanol **7** smoothly cyclized upon $BF_3{\cdot}OEt_2$ treatment to give key intermediate **6**, which was an advanced intermediate in total synthesis of (±)-brazilide A.[8] Demethylation of **6** with BBr_3 accomplished total synthesis of (±)-brazilin in 87.8% yield. The ^1H and ^{13}C NMR spectra data were totally same when compared with reported data.[12] (±)-Brazilein could be synthesized by IBD (iodobenzene diacetate) oxidation.[8]



Scheme 3. Completion of synthesis of (±)-brazilin, (±)-brazilein, and (±)-brazilide A.

During these transformations, O-protected resorcine, 3-methoxy phenol, was used in our initial trial, but we found that the methoxy group in the D ring could not be selectively removed to get key intermediate **6** of formal total synthesis of brazilide A. However, resorcin worked considerably well during substitution and cyclization to form key intermediate **6**. Therefore, synthesis of brazilin, brazilein, and brazilide A can be accomplished in a linear procedure.

In conclusion, total synthesis of (±)-brazilin and has been accomplished in 8 steps with 22.5% overall yield. Formal synthesis of (±)-brazilein, (±)-brazilide A could be realized by the same strategy. A *m*-CPBA mediated epoxidation and epoxy opening in one step gave advanced intermediate diol **14**. Furthermore, resorcine substitution and benzoic acid ester removal in single step also improved synthetic efficiency. Our strategy is flexible because modification of the D ring can be performed at a late stage. Consequently, quick synthesis of brazilin analogues for further medical screening becomes possible and these studies will be reported in due course.

Acknowledgement

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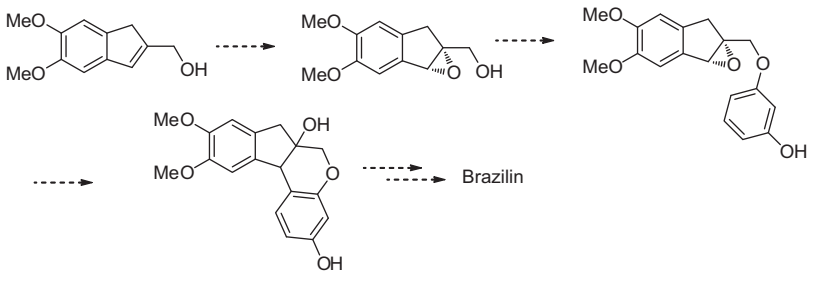

Supplementary data

Supplementary data (experiment details and NMR spectra for compounds **1**, **6**, **7**, **9**, **13** and **14**)associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.081.

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