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Enantioselective total synthesis of (+)-brazilin, (−)-brazilein and (+)-brazilide A†

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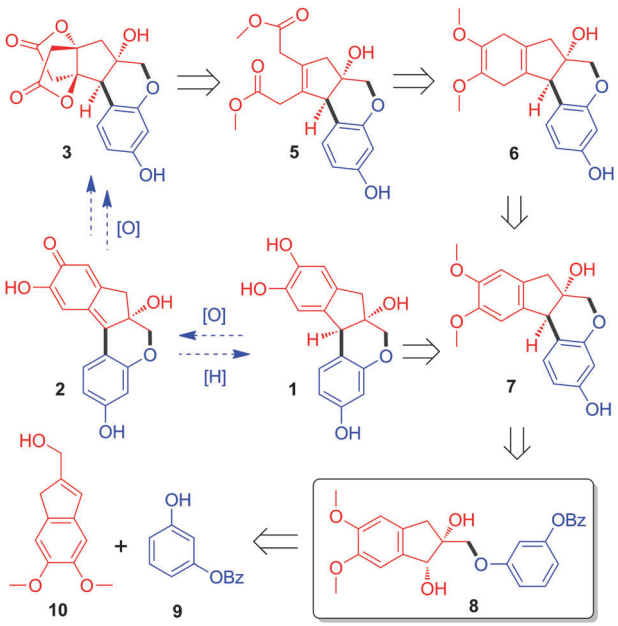
An enantioselective strategy for the synthesis of (+)-brazilin, (−)-brazilein and (+)-brazilide A has been developed. A Lewis acid mediated lactonization established the novel fused bis-lactone core of brazilide A and finalized the first total synthesis of (+)-brazilide A.

Brazilin (**1**), brazilein (**2**), brazilide A (**3**) and haematoxylin (**4**) were isolated from the heartwood of *Caesalpinia sappan*, a famous traditional Chinese medicine used for the treatment of emmeniopathy, convulsion, straumatic disease and menstrual disorders.[1] Recent reports have demonstrated that brazilin (**1**) possesses antitumor activity and acts as a micromolar telomerase inhibitor and produces DNA nicks.[2] Haematoxylin (**4**) was recently proven to be a potent inhibitor of protein tyrosine kinase.[3] These natural products belong to homoisoflavonoids and are structurally related. Brazilein has been proven to be the oxidized form of brazilin,[4a] while brazilide A might be the A-ring further oxidative product of brazilein (Scheme 1, dashed-line arrows).[4b]

The structures and the diverse biological activities of brazilin and its related compounds (Fig. 1) have attracted considerable attention towards their synthesis. There are two accomplished total synthesis procedures of (±)-brazilin in the literature; these involve the elegant total synthesis demonstrated by Pettus *et al.*[5a] and the synthesis conducted by Lee *et al.*[2c] An elegant enantioselective synthesis of *O*-trimethylbrazilin was also reported by Davis and Chen in 1993.[5b] To date, the structurally more challenging and interesting brazilide A (**3**), with a novel fused bis-lactone ring system, has remained untouched. As part of our ongoing program in seeking more efficient and flexible synthetic strategies towards synthesis of bioactive natural products and their analogues,[6] we recently initiated a program towards the syntheses of natural products isolated from *Caesalpinia sappan*.



Scheme 1 Retrosynthetic analysis of (**1**), (**2**) and (**3**).

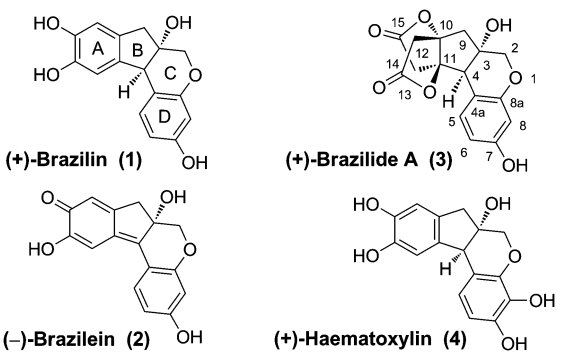


Fig. 1 Natural products isolated from *Caesalpinia sappan*.

Herein we report the first asymmetric total synthesis of (+)-brazilin, (−)-brazilein and (+)-brazilide A based on the same intermediate (**8**) as outlined in Scheme 1.

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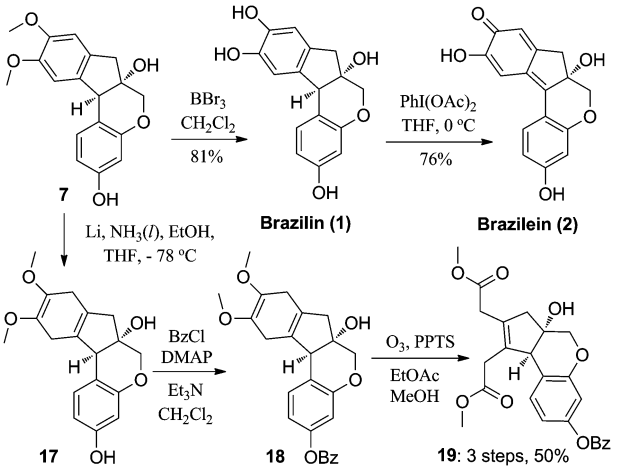
The ring system of brazilide A is quite unique, with a bis-lactone ring system fused to a cyclopentane (the red color part in compound **3**). The synthetic challenge associated with brazilide A is the formation of the fused bis-lactone ring system. To the best of our knowledge, no methodology has been documented previously in the literature for the synthesis of this bis-lactone unit bearing two fully substituted carbon centers. Therefore, developing a synthetic strategy for the synthesis of brazilide A (**3**) might also provide an access to this fused bis-lactone ring system. We anticipated that epoxidation of **5** followed by lactonization might give brazilide A (**3**). Selective Birch reduction of **7** followed by oxidative cleavage of the electron rich double bond in **6** would result in intermediate **5**. Compound **7** could be obtained by a Friedel–Crafts reaction of diol **8**. Diol **8**, with the key structural unit for the construction of the tetracyclic core for brazilin and its related natural products isolated from *Caesalpinia sappan*, could be prepared from compounds **9** and **10**.

We started our journey by synthesizing indene **10**, which was obtained in 4 steps in 61% yield by following our previous procedure.[6c] After treatment of indene **10** with 3-hydroxyphenol benzoate (**9**) under Mitsunobu conditions (Scheme 2),[7] the ether (**15**) was obtained in 60% yield. Next, a Sharpless asymmetric dihydroxylation with AD-mix-β[8] was conducted and diol **8** was obtained. We found that addition of phenol **9** (1.0 eq.) in this reaction could improve the enantioselectivity and accelerate the reaction rate.[9] Next, the Friedel–Crafts reaction of diol **8** gave the desired annulation product (**16**) in 80% yield. Hydrolysis of benzoylate **16** afforded the key intermediate **7** in 92% yield. After recrystallization, HPLC analysis established that the isomeric purity of compound **7** was >99%.

Next we came to the final stage for the synthesis of brazilin and brazilein. Treatment of **7** with boron tribromide in dichloromethane furnished the enantioselective synthesis of (+)-brazilin (Scheme 3, **1**, 9 steps, 14% overall yield). Oxidation of **1** with (diacetoxyiodo)benzene in THF provided (−)-brazilein (**2**) in 76% yield. The NMR spectra of our synthetic samples were in complete agreement with the reported data.[1c,e]

After having accomplished the syntheses of brazilin and brazilein, we decided to continue our journey towards brazilde A.

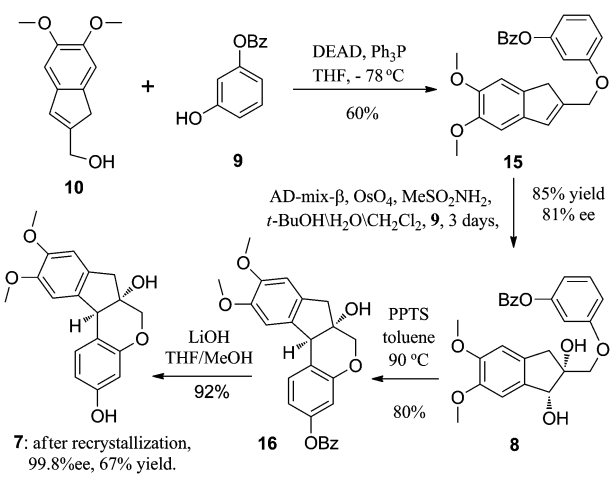


Scheme 3 Synthesis of (+)-brazilin (**1**) and (−)-brazilein (**2**).

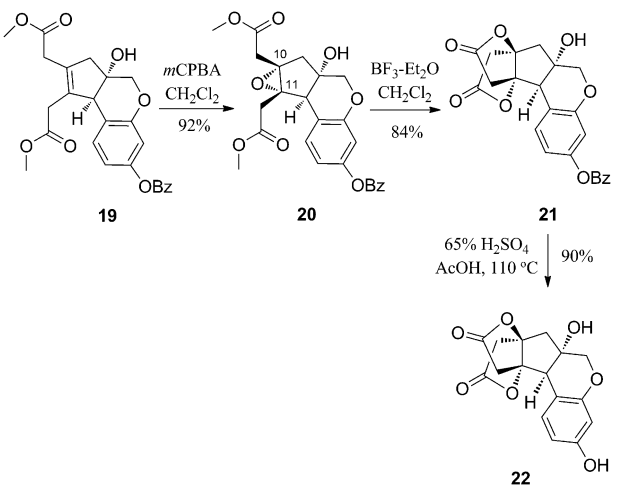
Treatment of compound **7** under Birch reduction conditions[10] selectively reduced the aromatic ring bearing two methoxyl groups and afforded the desired diene compound (**17**). The unstable diene (**17**) was then subjected to ozone oxidation, which unfortunately gave a complex mixture. After some experimentation, the diene (**17**) was converted to a benzoate (**18**) before oxidative cleavage of the electron rich double bond. Finally the desired intermediate **19** was obtained in 50% isolated yield over three consecutive steps (Scheme 3).

With the key intermediate **19** in hand, we came to the key bis-lactonization to finalize the synthesis of brazilide A. Epoxidation of **19** directed by the neighboring hydroxyl group provided **20** in high yield (92%) as a single diastereomer. To our disappointment, Lewis acid or proton acid mediated lactonization did not yield the natural product. Instead of brazilide A, the lactonization afforded a bis-lactone (**21**) with wrong stereochemistry at the lactone ring system (Scheme 4). After debenzoylate,[11] the C-10,11 epimer of brazilide A (**22**) was obtained in 90% yield.

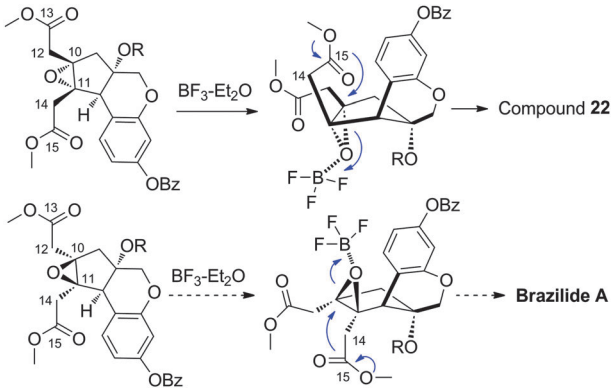
In principle, the Lewis acid mediated oxirane ring opening from both sides (C10 and C11) should result in compound **22**



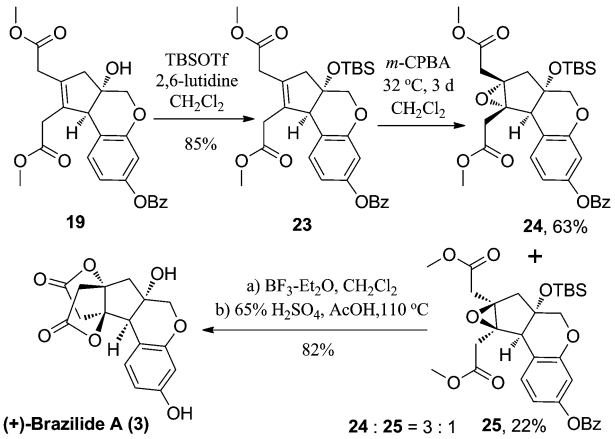
Scheme 2 Synthesis of *O*-dimethylbrazilin **7**.



Scheme 4 Synthesis of **22**, C-10,11-epimer of brazilide A.



Scheme 5 Possible pathway for bis-lactonization.



Scheme 6 Enantioselective synthesis of (+)-brazilide A (**3**).

and brazilide A (**3**). However, after the epoxide moiety is coordinated to boron trifluoride etherate, the methoxycarbonyl group (Scheme 5) attacked exclusively the less hindered side of the epoxide, namely the C10 position, thus resulting in the observed stereochemical outcome for the bis-lactonization. Besides the steric effects, the neighboring groups (OH or OR, benzene ring) might also assist this process by stabilizing the transition states. From the above analysis, we deduced that the orientation of the epoxide unit might control the stereochemistry for the formation of the lactone ring system.

In order to cope with this problem, the hydroxyl group in **19** was then protected by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate. The epoxidation of compound **23** occurred slowly (3 days) and afforded the epoxide **24** (from the less hindered side) and **25** (the desired orientation), respectively, in a ratio of 3 to 1.[12]

Treatment of epoxide **25** with ethereal boron trifluoride in dichloromethane (Scheme 6) followed by hydrolysis of the benzoate (one pot reaction, 82% yield) in the presence of 65% sulfuric acid finalized the first total synthesis of (+)-brazilide A ($[\alpha]_D$ = +3.4, *c* 1.36, acetone, lit.[1f] $[\alpha]_D$ = +3.3, *c* 3.0, acetone). The NMR spectra of our synthetic sample were in complete agreement with the reported spectra.[1f,13] The absolute configuration of brazilide A (**3**) was established by X-ray crystallography (CCDC 923325) using Cu-K_α radiation.[14]

In summary, an enantioselective strategy for the synthesis of (+)-brazilin, (−)-brazilein and (+)-brazilide A has been developed. This new route, which features a stereocontrolled Friedel–Crafts cyclization to establish the tetracyclic ring system of brazilin and a Lewis acid mediated formation of the novel fused bis-lactone core of brazilide A, leads to the first total synthesis of (+)-brazilide A in 16 steps from commercially available starting materials. The absolute configuration of (+)-brazilide A was also confirmed by this total synthesis. Biological studies towards brazilide A and its analogues are currently under investigation in our laboratory.

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9 Although the actual effect of phenol **9** is unclear, it seems to us the additive phenol might form a complex with the substrate (**15**) through hydrogen bonds thus may change the shape of the substrate and also improve the solubility. The ee% value was improved from 60% to 81%, while the reaction time was reduced from 14 days to 3 days. For reaction conditions, see ESI†.

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12 Treatment of epoxide **24** with Lewis acid or proton acid again afforded compound **22** after debenzoylate.

13 Dr Yang Ye in Shanghai Institute of Materia Medica is gratefully acknowledged for providing the spectra of brazilide A (**3**).

14 Dr Xiaonian Li in Kunming Institute of Botany is gratefully acknowledged for X-ray crystallography analysis of compound **21** and brazilide A (**3**). CCDC 923326 (for compound **21**) and CCDC 923325 (for brazilide A).