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Enantioselective total synthesis of (+)-galbulin *via* organocatalytic domino Michael–Michael–aldol condensation†‡

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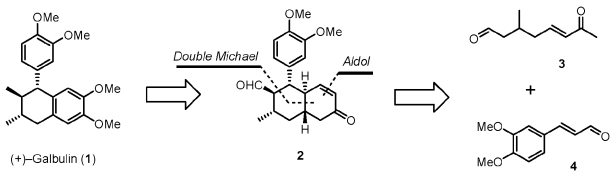
A concise and practical enantioselective synthesis of (+)-galbulin has been achieved using organocatalytic domino Michael–Michael–aldol condensation and organocatalytic kinetic resolution as the key steps.

The tetrahydronaphthalene carbon skeleton is prevalent in many lignans, a class of secondary metabolites widely found in plants which are derived biosynthetically from the oxidative dimerization of two phenylpropanoid (cinnamic acid) units. The lignans possess a vast array of biological activities and have been used as folk remedies in treating an assortment of maladies. Contemporarily, the significant pharmacological activities of lignans include anti-inflammatory, antioxidant, anti-tumor, antiviral, cardiovascular, anti-HIV, and immunosuppression properties, and are of immense interest to scientists.[1] The significant bioactivities and structural diversity of lignans have driven many efforts for the total synthesis of lignans,[2] especially the tetrahydronaphthalenes (THN)[3] and the dihydronaphthalenes (DHN).[4] The most prominent examples of these compounds include the anti-cancer drugs: podophyllotoxin,[5] etoposide,[6] and conidendrin.[7] Despite these synthetic advances, enantioselective total synthesis of the THN lignans by organocatalysis has not been reported. Nevertheless, inspired by the burgeoning number of organocatalytic and cascade reactions,[8] elegant applications of organocatalysis in natural product syntheses have recently been demonstrated.[9] In continuing our efforts in exploring new organocatalytic annulations,[10,11] we envisioned an approach to this system *via* a domino Michael–Michael–aldol condensation (Scheme 1) that targeted galbulin, a natural lignan first isolated from *Himantandra baccata* and *Himantandra belgraveana*.[12] Although syntheses of galbulin have been reported, most of them start from other known lignans of similar structure and proceed by stepwise interconversion reactions.[13]



Scheme 1 Retrosynthetic analysis of galbulin (**1**).

Whitby[14] and Charlton[15] described the stereoselective synthesis of (±)-galbulin using a metal-mediated cyclization of a 1,7-diene and acid-catalyzed cyclizations of *E*,*E*-dibenzylidenesuccinate esters, respectively. However, the enantioselective total synthesis of galbulin has not yet been realized. Herein, we describe the application of organocatalysis in the first enantioselective total synthesis of (+)-galbulin.

At the outset, a suspension of 3,4-dihydro-2-methoxy-4-methyl-2*H*-pyran (**5**) in H_2O was treated with concentrated aqueous HCl solution and stirred for 2 h until the solution turned clear. The solution was then neutralized by slow addition of $NaHCO_3$ powder until the pH value reached 7. To the solution of crude 3-methylpentanedial[16,17] was slowly added a solution of 1-triphenylphosphoranylidene-2-propanone in CH_2Cl_2 over 1.5 h and the mixture was stirred for an additional 14 h at ambient temperature to give (*E*)-3-methyl-7-oxooct-5-enal (**3**) in 54% overall yields for the two consecutive reactions (Scheme 2). At the outset of the study of the key reaction of the synthesis, *i.e.*, the organocatalytic double Michael reaction, a nearly 1 : 1 ratio of ketoaldehyde **3** and aldehyde **4**[18] was reacted with Jørgensen–Hayashi catalyst **I** (20 mol%) and acetic acid in CH_3CN. After many days of reaction, the reaction reached only ~50% conversion without further progress. Thus, ketoaldehyde **3** and aldehyde **4** were then reacted in a ratio of 2.4 : 1 under the same reaction conditions for 3 days until the complete consumption of aldehyde **4**, followed by the addition of *p*-TsOH with stirring for an additional 5 h to give the adduct (+)-**2** as the only observable stereoisomer in 82% yield.[19] This result supports the idea that a kinetic asymmetric transformation (KAT) of racemic **3** took place, and the proposed mechanism is depicted in Scheme 3 to account for the resulting stereoselectivity in KAT. The initial Michael addition of (*S*)-**3** to aldehyde **4**-iminium activated from the *Re* face under the control of catalyst, *via* the transition state TS A, gives intermediate **I-1**, which cyclizes by the second Michael reaction to afford **I-2**.

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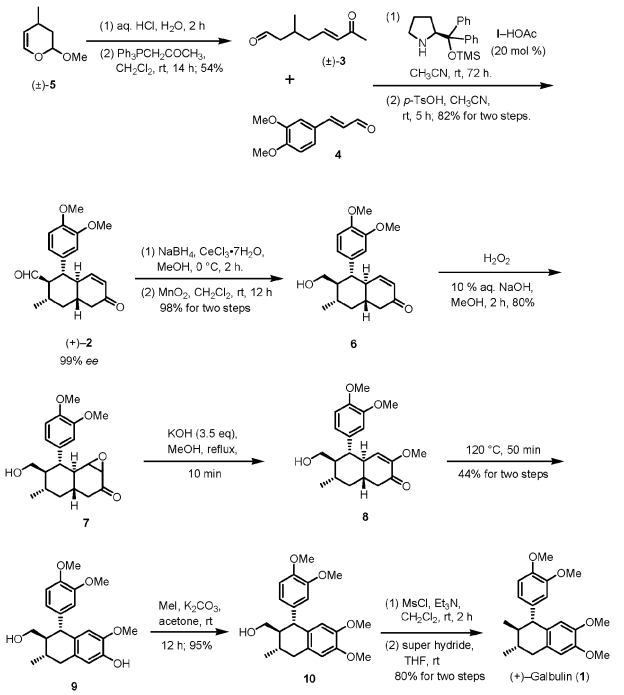
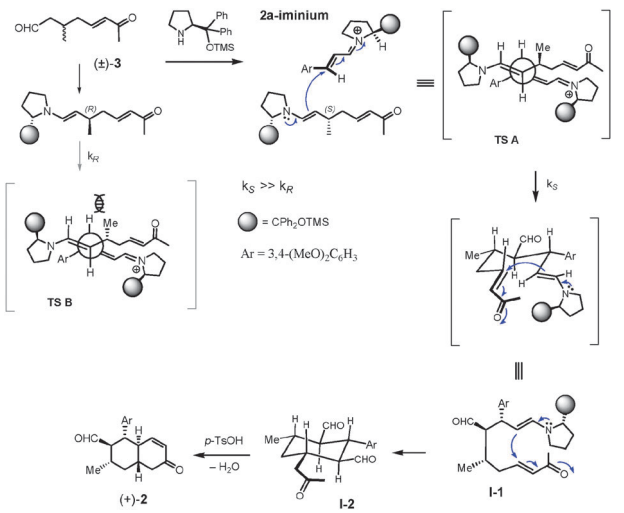


Scheme 2 Total synthesis of galbulin (**1**).



Scheme 3 Proposed mechanisms for the organocatalytic domino Michael–Michael–aldol condensation.

After the addition of *p*-TsOH, aldol reaction of **I-2** followed by dehydration to provide the hexahydronaphthalenone (+)-**2** took place. Alternatively, Michael addition of (*R*)-**3** to aldehyde **4**-iminium *via* the transition state TS B suffers a severe steric hindrance and hampers the subsequent reactions, and results in the observation of kinetic resolution of (±)-**3**. The structure of (+)-**2** was assigned unambiguously by the X-ray analysis (Fig. 1). Thus, the origin of the stereoselectivity in this Michael–Michael reaction of **3** to **4** by the Jørgensen–Hayashi catalyst was identical to that observed in the similar examples of our earlier study in the organocatalytic domino Michael–Michael–aldol condensation.[20]

Reduction of (+)-**2** with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in methanol at 0 °C for 2 h gave the corresponding diol, without further purification, which was subjected to selective allylic oxidation

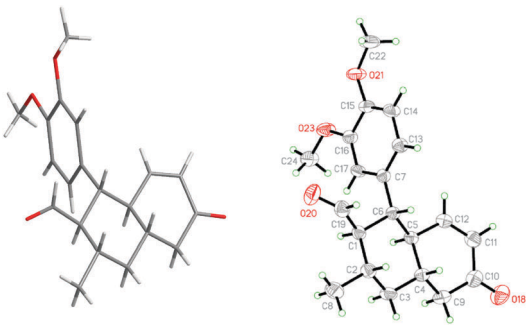


Fig. 1 Stereo plot of the X-ray crystal structure of (+)-**2**: C, gray; O, red, and the ORTEP diagram (thermal ellipsoids drawn at the 30% probability level).

(MnO_2, CH_2Cl_2, rt, 12 h) to give alcohol **6** in 98% overall yield for the two consecutive reactions (Scheme 2). The subsequent attempts at the introduction of the hydroxy group on the ring system and aromatization were tricky and many efforts to complete the transformation were futile. Finally, the transformation was achieved *via* a reaction sequence of epoxidation, oxidation, and aromatization. Specifically, epoxidation of **6** with H_2O_2 in aqueous methanolic NaOH solution for 2 h gave 80% yield of the epoxide **7**. We purified a small amount of epoxide **7** for analysis, but in general, the product was unstable upon silica gel chromatography. In the routine process, epoxide **7** was obtained but not purified and was used as the crude product for the next reaction step. Aromatization of **7** to **9** required a special reaction condition and was achieved in a two-step reaction sequence. A solution of **7** in MeOH and KOH (3.5 equiv.) was heated to reflux for 10 min to afford enone **8**, followed by evaporation of the major part of MeOH to give a sticky residue[21] and the mixture was then heated to 120 °C for 50 min to provide the methoxyphenol **9** in 44% yield. Methylation of alcohol **9** with methyl iodide and K_2CO_3 in acetone at room temperature for 12 h produced 95% yield of dimethoxytetrahydronaphthalene **10**. Finally, treatment of alcohol **10** with MsCl in Et_3N and CH_2Cl_2 gave the corresponding mesylate which was reduced by superhydride, lithium triethylborohydride, in THF to afford the (+)-galbulin (**1**) in 80% yield.[22]

In summary, we have achieved the first enantioselective synthesis of (+)-galbulin in 11% overall yield through 12 reaction steps with 7 isolations and purifications of the intermediates. Noteworthy features of the synthesis include: (1) the highly stereoselective organocatalyzed domino Michael–Michael–aldol condensation, which was effective for constructing the skeleton, (2) an unusual kinetic resolution of (±)-**3** with a remote stereocenter, (3) special operation and mild conditions in the oxidation and aromatization of the cyclohexenone system. The synthesis demonstrated a successful strategy and provides a venue for the application of organocatalyzed domino Michael–Michael–aldol condensations to a natural product synthesis. Further applications of this protocol in the synthesis of other elaborate natural products are currently underway.

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of the organocatalytic domino Michael–Michael–aldol condensation by Dr Roshan Y. Nimje, help in the HPLC analysis by Mr Nitin S. Dange, and the help from Miss Wan-Chen Chang are all acknowledged.

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20 See ref. 10*g*; in the previous study, the absolute configurations of the products were assigned based on the X-ray analysis of the adducts; with the subtle differences in the substituents on **3** and **4**, (+)-**2** should have the same enantioselectivity as the previous examples. In fact, the subsequent transformation of (+)-**2** to (+)-galbulin further supports the conclusion, *vide infra*.

21 A small amount, but not too much, of MeOH is necessary in the beginning of the reaction to dissolve KOH and **8**.

22 The synthetic material was identical in all respects (^{1}H, ^{13}C NMR) to the literature data, see ESI‡ for details.