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Organocatalytic asymmetric synthesis of cornolactones A and B, and formal synthesis of brasoside and littoralisone†

Hui Hou,^{a,b} Qi Gu,^a Xuan Wang,^a De-Qun Sun^b and Bing-Feng Sun^{ID}*^a

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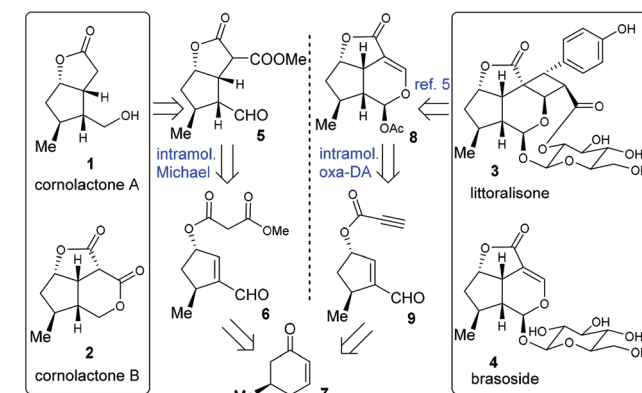
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The asymmetric total synthesis of cornolactones A and B as well as the formal asymmetric synthesis of brasoside and littoralisone were accomplished in short steps, from simple starting materials. The key features of the synthesis include an efficient organocatalytic access to cyclopentenol **15**, an intramolecular Michael addition reaction and an intramolecular oxa-Diels–Alder reaction.

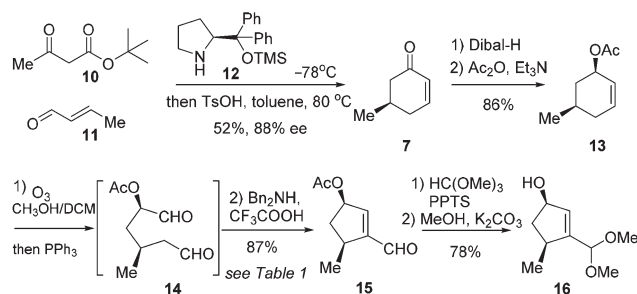
The chemical synthesis of iridoids has attracted much attention from the scientific community owing to the biological and ecological significance of iridoids.¹ Cornolactone A (**1**) and cornolactone B (**2**) were isolated in 2014 by West and co-workers from *Cornus florida*, a tree native to eastern North America that has been traditionally used for the treatment of malaria.² The synthesis of cornolactone A was documented as an synthetic intermediate in the total synthesis of semperoside A,³ but to date no total synthesis of cornolactone B has been reported. Littoralisone (**3**), an iridoid isolated from the traditional medicinal plant *Verbena littoralis* in 2001 by Ohizumi, exhibited enhanced activity of NGF-mediated neurite outgrowth from PC12D cells.⁴ Littoralisone possesses an unprecedented heptacyclic molecular architecture and is biogenetically related to brasoside (**4**).⁵ The first total synthesis of littoralisone and brasoside was achieved elegantly from a common synthetic precursor by MacMillan's group in 2005.^{6a} In this paper, we report the asymmetric total synthesis of cornolactones A and B and the formal synthesis of littoralisone and brasoside by employing a novel synthetic strategy.

A divergent synthetic plan for target molecules **1–4** was envisaged, as illustrated in Scheme 1. Cornolactone A (**1**) and cornolactone B (**2**) were anticipated to be derived from compound **5** which in turn was to be constructed *via* the intramolecular Michael addition reaction of **6**. By employing a ring-contraction strategy, **6** was traced back to the known chiral compound **7**. On the other hand, in MacMillan's pioneering work, compound **8** served as the key common synthetic precursor to littoralisone (**3**) and brasoside (**4**).^{6a} The tricyclic framework of **8** was envisioned to stem from the critical intramolecular oxa-Diels–Alder reaction of the key precursor **9**. Compound **9** may similarly stem from **7**.



Scheme 1 Cornolactones A (**1**) and B (**2**), littoralisone (**3**), and brasoside (**4**), and the collective retrosynthetic analysis.

The synthetic journey commenced with the preparation of **7** (Scheme 2). According to Jørgensen's one-pot procedure,



Scheme 2 Synthesis of **16**.

^aCAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China. E-mail: bjsun@sioac.ac.cn

^bMarine College, Shandong University at Weihai, 180 Wenhua West Road, Weihai 264209, China

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acetoacetate **10** reacted with crotonaldehyde (**11**) in the presence of the chiral amine **12** (10 mol%) at -78°C before exposure to TsOH in toluene at 80°C to furnish **7** in 52% yield with 83% ee.⁷ Compound **7** was subjected to a diastereoselective reduction with Dibal-H at -78°C before acetylation to give **13** in 86% yield over two steps. Notably, use of Ac as the protecting group for the hydroxyl group was found beneficial for success in the subsequent synthetic sequence. Our initial endeavors with Bn as the masking group met with difficulties. Alkene **13** was then exposed to ozonolysis to give the crude dial **14** after reductive workup (Scheme 2).

This crucial intramolecular aldol condensation of **14** to cyclopentenol **15** was investigated by subjecting the crude mixture containing **14** to various conditions. As summarised in Table 1, the reaction with TsOH in heated toluene gave **15** in 15% yield (entry 1).⁸ Tertiary amines in the presence of AcOH provided the product in slightly higher yields (entries 2 and 3). The catalytic activities of secondary amines were next examined. While piperidine/AcOH in ether only generated **15** in a meager yield,⁹ L-proline in DMSO gave a significantly higher yield of 45% (entries 4 and 5). To our delight, the combination of Bn_2NH and CF_3COOH in DCM could deliver the desired product in a yield of 87% (entry 6).¹⁰ Considering that this is the overall yield covering two steps from **13**, this cleavage/condensation protocol is highly efficient. Compound **15** was converted to **16** via sequential acetalization and deacetylation in a good yield of 78% (Scheme 2).

With the key intermediate **16** in hand, we first set out to explore the total synthesis of **1** and **2** (Scheme 3). To set up the C6 stereocenter, the Mitsunobu reaction of **16** with monomethyl malonate gave **17** which, after hydrolysis of the acetal group, provided the key precursor enal **6**. The critical intramolecular Michael addition reaction was studied (Table 2). When DBU or piperidine was employed as the base, **5** was isolated as an inseparable 1.5/1 diastereomeric mixture in trace amount (entries 1 and 2). Using Et_3N , $t\text{-BuOK}$, or NaH as the base, modest yields were obtained (entries 3–5). The optimal result was achieved with TBAF, offering **5** as an inconsequential diastereomeric mixture in a satisfactory yield of 78% (entry 6). Three stereogenic centres were created in this single step, including C4, C5 and C9. Among these, the stereochemistries at C5 and C9 are critical for the subsequent success of the total synthesis. To our delight, although the diastereoselectivity at C4 was found to be variably poor (*ca.* 1/1), the selectivity was favorably good at C9 (*ca.* 10/1) and excellent at

Table 1 Annulation of **14** to **15**

Entry	Conditions	Yield ^a (%)
1	TsOH, toluene, r.t.~ 80°C	15
2	Pyridine, AcOH, toluene, r.t.	20
3	Et_3N , AcOH, toluene, r.t.	28
4	Piperidine, AcOH, Et_2O , r.t.	10
5	L-Proline, DMSO, r.t.	45
6	Bn_2NH , CF_3COOH , DCM, r.t.	87

^aYield covering two steps from **13**.



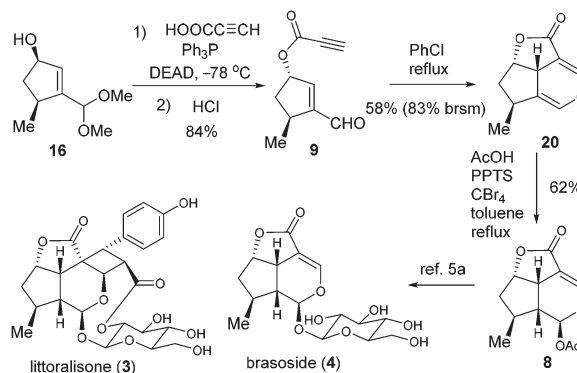
Scheme 3 Total synthesis of cornolactone A (**3**) and cornolactone B (**4**).

Table 2 Intramolecular Michael addition reaction of **6**

Entry	Conditions	Yield (%)
1	DBU, THF, r.t.	5
2	Piperidine, THF, r.t.	10
3	Et_3N , THF, r.t.	25
4	$t\text{-BuOK}$, THF, r.t.	20
5	NaH, THF, 0°C -r.t.	38
6	TBAF, THF, 0°C -r.t.	78

C5 (>20/1). The selectivity at C5 could be ascribed to the high propensity to form the *cis*-[3.3.0] bicyclic ring system. The selectivity at C9 was deemed a kinetically controlled result and probably arose from the preferred protonation from the more accessible convex face of the bicyclic system.

With the key intermediate **5** in hand, we moved on to finish the total synthesis of **1** and **2** (Scheme 4). First, a decarboxylation reaction was realized by exposing **5** to NaCl in refluxing DMSO/ H_2O , furnishing **18** (29%) and *epi*-**18** (43%). Reduction



Scheme 4 Formal synthesis of littoralisone (**3**) and brasoside (**4**).

of **18** with NaBH₄ gave cornolactone A (**1**) in 89% yield. And *epi*-**1** was obtained in 83% yield with the same procedure. On the other hand, compound **5** was reduced to give a 1/1.5 mixture of **19** and *epi*-**19** in a combined yield of 87%. Treatment of the mixture with Amberlyst-15 in refluxing toluene furnished cornolactone B (**2**) in a yield of 87%.

Encouraged by the success of the total synthesis of cornolactones, we moved on to the formal synthesis of **3** and **4** (Scheme 4). The Mitsunobu reaction of **16** was effected with propiolic acid before being further converted to **9** in 84% yield over two steps. The key intramolecular oxa-Diels–Alder reaction of **9** was then explored.¹¹ Fortunately, when the solution of **9** in toluene was refluxed for 8 hours, the desired cycloaddition product **20** was isolated. Although the yield of **20** based on recovered **9** was as high as 91%, the conversion was only 18%. To our delight, the conversion could be dramatically enhanced to 70% when refluxing chlorobenzene was employed, with **20** being isolated in 58% yield (83% brsm). To the best of our knowledge, this represents the first example of an oxa-Diels–Alder reaction between enal and propiolate. The last challenge was to convert **20** to MacMillan's intermediate **8** by selective acetoxylation. After examination of various conditions, **20** was treated with AcOH in the presence of PPTS/CBr₄ in refluxing toluene to successfully engender **8** in 62% yield, thus forming the formal synthesis of littoralisone (**1**) and brasoside (**2**).

Conclusions

In summary, the asymmetric total synthesis of cornolactone A and cornolactone B as well as the formal asymmetric synthesis of brasoside and littoralisone were accomplished in a collective and concise fashion from simple starting materials. Salient transformations include the efficient organocatalytic access to the key cyclopentenol **15**, the intramolecular Michael addition of **6** that set up the critical C5 and C9 stereocenters, and the unprecedented intramolecular oxa-Diels–Alder reaction of **9**. Some analogues, including *epi*-**1**, cornusoside A aglycone (**19**) and *epi*-**19**, were achieved as well. The newly demonstrated synthetic strategy may readily lend itself to the total synthesis of a broad scope of iridoid natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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