

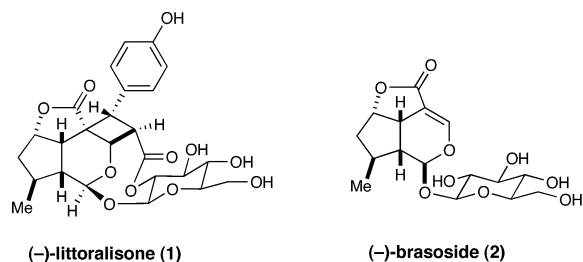
Total Synthesis of Brasoside and Littoralisone

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Extracts of *Verbena littoralis*, a plant used widely in traditional folk remedies, possess intriguing activity as enhancers for the neurotrophic properties of nerve growth factor (NGF).¹ Littoralisone (**1**), isolated in 2001, was demonstrated to be the active agent for increased NGF-induced neurite outgrowth in PC12D cells.^{2,3} While littoralisone is presumed² to be biochemically derived from brasoside (**2**),⁴ no relevant intermediates to support this pathway have been found to date. A uniquely complex member of the iridoid class,⁵ littoralisone presents a variety of challenges for chemical synthesis including the assembly of a stereochemically elaborate cyclobutane ring, an adjacent nine-membered lactone, and 14 stereocenters within a 24-carbon framework. In this communication, we report the first total syntheses of littoralisone and brasoside in 13 overall steps. These syntheses confirm the absolute and relative stereochemistries of isolates **1** and **2** and provide chemical support for a biosynthetic pathway between the two. More importantly, these syntheses demonstrate the capacity of proline catalysis to (i) override the inherent stereochemical bias of iridoid formation and (ii) selectively control aldol additions and C–O bond formation in a complex target setting.



Given the presumed biochemical origins of littoralisone, we envisioned the late-stage construction of both the nine- and four-membered rings via an intramolecular photolytic [2+2] cycloaddition. This strategy would require an unsaturated iridoid and a cinnamoyl olefin held in proximity by an appropriately functionalized glucoside tether **3** that, in turn, would arise from the glycosidic coupling of iridolactone **4** and the 2-cinnamoyl saccharide **5** (Figure 1). As the pivotal step in our synthesis, we hoped the iridoid stereochemical core might be accessed via a catalyst-controlled intramolecular Michael addition with the formyl-enal **6**. While the elegant work of Schreiber⁶ has demonstrated that iridoid systems can be generated under thermodynamic control via stoichiometric enamine Michael additions, we recognized that the resident (3*S*,5*S*) stereogenicity of enal **6** would lead to the undesired *trans*-(1*S*,2*S*) cyclopentyl product **10** (see Table 1). As such, a central goal of this study was to determine if proline might be employed as an external source of stereoinduction to override substrate-directed selectivities in iridoid synthesis. With respect to the glycosidic coupling partner, we identified the glucose system **5** as an ideal target for our recently developed two-step approach to differentially protected carbohydrates.⁷

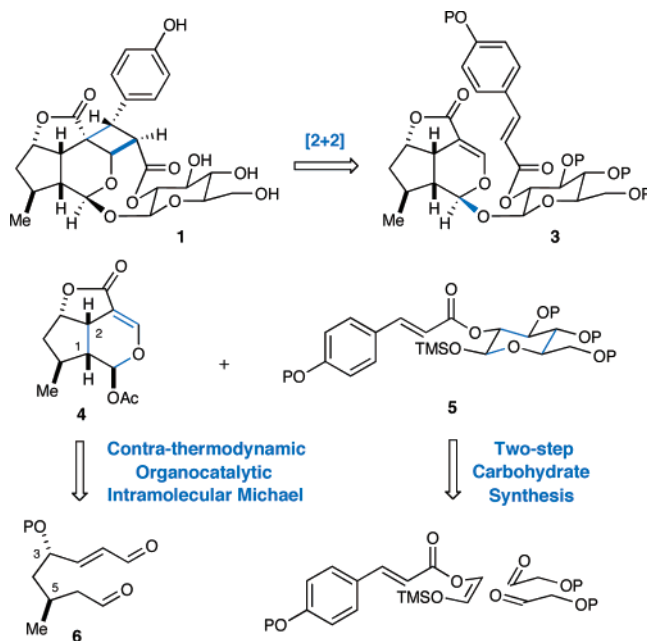
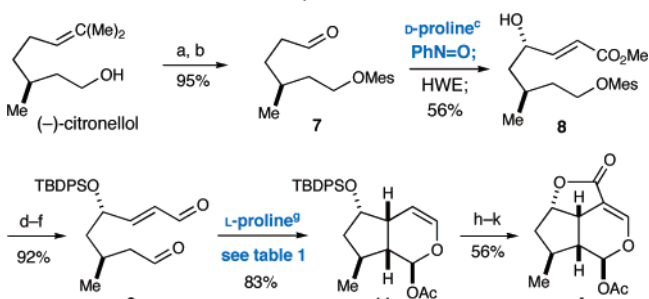


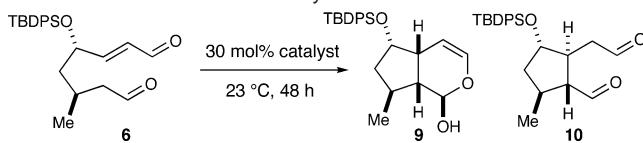
Figure 1. An organocatalytic approach toward (-)-littoralisone.

Scheme 1. Enantioselective Synthesis of the Iridolactone Core^a



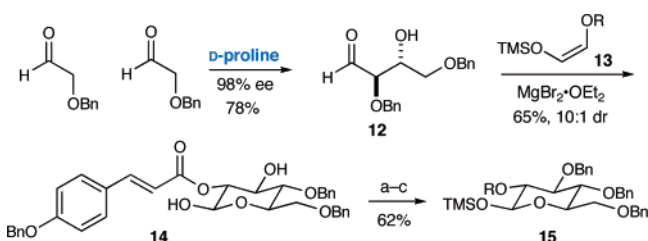
^a Reagents and conditions: (a) MesCl, DMAP, pyridine, CH₂Cl₂. (b) O₃, MeOH, CH₂Cl₂, -78 °C. (c) PhNO, D-proline (40 mol %), DMSO; (EtO)₂P(O)CH₂CO₂Me, LiCl, DBU; NH₄Cl, MeOH. (d) TBDPSCl, imidazole, DMF. (e) DIBAL, Et₂O, -78 °C. (f) DMP, CH₂Cl₂. (g) Table 1, entry 5; Ac₂O, DMAP, pyridine, 0 °C. (h) POCl₃, DMF, 40 °C. (i) NaClO₂, NaH₂PO₄, *t*-BuOH. (j) HF-pyridine, THF. (k) DCC, CH₂Cl₂.

Synthesis of the iridolactone core **4** began with protection of (-)-citronellol as its mesitoate ester followed by ozonolysis of the resident olefin (Scheme 1). Exposure of the resulting aldehyde **7** to the proline-catalyzed α -formyl oxidation protocol using nitrosobenzene furnished the corresponding α -oxoaldehyde with high levels of catalyst-enforced induction.^{8,9} Conveniently, olefination of the resultant aldehyde using Horner–Wadsworth–Emmons conditions and cleavage of the aminoxy bond (upon standing in MeOH) could be accomplished in the same protocol to provide γ -chiral α,β -unsaturated ester **8** in a single operation from **7**.¹⁰ Protection of the resulting alcohol as its TBDPS-ether followed by treatment with DIBAL and then the Dess–Martin oxidant, provided the requisite formyl-enal Michael substrate **6** in six steps.

Table 1. Examination of the Key Intramolecular Michael Addition


entry	catalyst	solvent	yield ^a (%)	9:10
1 ^b	L-proline	CHCl ₃	61	3:1
2	L-proline	CHCl ₃	54	1:19
3	PhNH(Me)	CHCl ₃	87	1:19
4	L-proline	MeOH	26	7:1
5 ^c	L-proline	DMSO	91	10:1
6 ^c	(±)-proline	DMSO	86	2:1
7 ^c	D-proline	DMSO	83	1:2

^a Combined yield of isomers **9**, **10**. ^b After 12 h. ^c Performed at 40 °C.

Scheme 2. Two Step Assembly of Selectively Substituted Glucose^a

differentiated glucose 98% ee

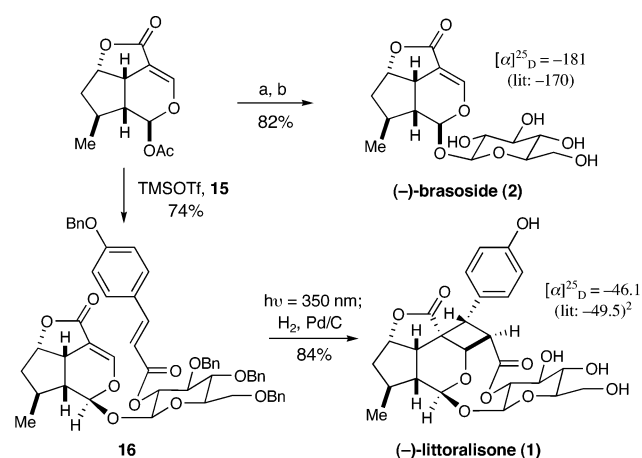
R = *p*-benzyloxy cinnamoyl

^a Reagents and conditions: (a) Ag₂O, BnBr. (b) Pd/Al₂O₃, HCO₂NH₄. (c) TMSOTf, Et₃N, 80 °C.

At this point, we sought to test the feasibility of the proposed contra-thermodynamic intramolecular Michael addition. To our delight treatment of **6** with L-proline in CHCl₃ provided the desired lactol **9** in good yield, albeit as a 3:1 mixture with its monocyclic isomer **10** (Table 1, entry 1). Unfortunately, prolonged exposure of **9** to catalytic conditions (entry 2) resulted in its complete conversion to **10**, revealing that the *trans* isomer is thermodynamically favored. Exposure of enal **6** to Schreiber's protocol^{6a} also results in *trans*-cyclopentyl formation (entry 3). However, proline catalysis can be employed in high dielectric media to provide the desired kinetic outcome,¹¹ in accord with our retrosynthetic hypothesis. Indeed, exposure of **6** to L-proline in DMSO provides the lactol **9** in 91% yield and with 10:1 *cis*-selectivity (entry 5). Interestingly, catalyst turnover appears to be rate limiting, a process that can be accelerated by heat or by the addition of water.¹² The former was found to be amenable to in situ acetylation of **9**, leading directly to **11** in 83% yield in a single operation. Conversion of the iridoid **11** to the lactone moiety **4** was then accomplished in four steps and 56% yield using standard methods (Scheme 1).

Synthesis of the requisite glycosidic coupling partner began with proline-catalyzed dimerization of benzyloxyacetaldehyde to provide **12**,¹³ which upon treatment with enolsilane **13**¹³ led to trisbenzyl-2-cinnamoyl glucose **14** (Scheme 2). Benzylation of this carbohydrate was then followed by regio- and diastereoselective functionalization of the anomeric alcohol to provide exclusively the TMS-ether β -anomer **15**.

The glycosidic union of **11** and **15** was accomplished in a facile process using TMSOTf¹⁴ to provide the desired glucose-tethered diene **16** in 74% yield (Scheme 3). In a similar fashion, iridoid **11** was coupled with 1-*O*-(TMS)- β -D-glucose tetracetate, which upon deacetylation, furnished (*-*)-brasoside in 13 overall steps. To complete the synthesis of littoralisone, we next turned our attention to the proposed intramolecular [2+2] photocycloaddition. To our delight, exposure of **16** to UV light (350 nm) for 2 h followed by in situ hydrogenolysis furnished synthetic (*-*)-littoralisone as a single isomer in 84% yield, a substance that was identical in all

Scheme 3. Completion of the Synthesis of Brasoside and Littoralisone^a

^a Reagents and conditions: (a) 1-*O*-(TMS)- β -D-glucose tetraacetate, TMSOTf (0.4 equiv), CH₃CN, -30 °C. (b) Et₃N, H₂O, MeOH, CH₂Cl₂, -15 °C.

respects to the natural isolate. It should be noted that the [2+2] cycloaddition was also observed to occur slowly in ambient light, a result that lends support to the proposed biochemical formation of littoralisone from brasoside.²

In summary, the first total synthesis of littoralisone has been achieved in 13 steps and in 13% overall yield. Prominent features of this synthesis include the use of proline to (i) overcome the inherent stereoselection of enamine-Michael reactions and (ii) enable the two-step asymmetric construction of a polyol differentiated glucose coupling partner.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Exposure of **9** to D-proline in DMSO for 48 h does not lead to formation of **10**. This reveals that the outcomes of entries 5, 6, and 7 are kinetic.
- H₂O (2% v/v) enables full conversion to **9** in 48 h at 23 °C in DMSO.
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- See Supporting Information for details.

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