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First enantioselective synthesis of (−)-talaumidin, a neurotrophic diaryltetrahydrofuran-type lignan

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Abstract—The first enantioselective total synthesis of a neurotrophic (−)-talaumidin (**1**) is described in 16 steps from 4-benzyloxy-3-methoxybenzaldehyde in ca. 10.7% overall yield, and thus has established the absolute configurations of the four stereogenic centers C-2 ~ C-5 of **1**. The synthesis features the construction of the two successive chiral centers C-2 and C-3 by Evans asymmetric *anti*-aldol protocol as well as of the two chiral centers C-4 and C-5 in a highly stereocontrolled fashion by hydroboration/oxidation and epimerization, followed by Friedel–Crafts arylation.

With the increase in the advanced age population, neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, have been emerging as a major social issue, thus resulting in a great demand of new therapeutic drugs to prevent these diseases.[1] In this context, neurotrophins (e.g., NGF and BDNF), which play key roles in the prevention of neuronal death as well as in the maintenance and growth of neurons, make hopeful agents for the treatment of neurodegenerative disorders. However, neurotrophins are not effective in clinical trails, mostly because they are not able to pass through the blood–brain barrier due to the peptidyl properties. Our continuing efforts on exploring for small-molecule-based natural products with neurotrophic properties led to the discovery of (−)-talaumidin (**1**) from Brazilian *Aristolochia arcuata* Masters.[2] Talaumidin and its analogues exhibit significant neurite outgrowth-promoting and neuroprotective activities in the primary cultured rat cortical[2] and additionally in the hippocampal neurons, as shown in Figure 1. Compound **1**, belonging to a diaryltetrahydrofuran-type lignan, possesses the four continuous stereogenic centers existing on a tetrahydrofuran ring. The relative configurations of **1** have been defined as (2*S**,3*S**,4*S**,5*S**) on the basis of NOESY spectrum,[3] but its absolute configuration has not been determined. These promising biological activities and selective preparation of the possible stereoisomers with regard to the four stereogenic centers of **1** make it an attractive synthetic target. Although a few elegant enantioselective syntheses of 2,3-diaryl-3,4-dialkyltetrahydrofuran lignans, such as (+)- and/or (−)-virgatusin, were already reported,[4–6] general methodology for synthesizing their possible stereoisomers has remained unexplored. Herein, we report the first enantioselective total synthesis of (2*S*,3*S*,4*S*,5*S*)-**1**, in which we apply a flexible and reliable synthetic way involving Evans asymmetric aldol reaction as well as stereocontrolled hydroboration and Friedel–Crafts arylation to construct the four continuous chiral centers on the tetrahydrofuran ring.

Our synthetic plan is outlined in Scheme 1. Considering all the possible stereoisomers of **1**, we envisioned that the synthesis would start with the Evans asymmetric aldol reaction[7,8] between 3,4-dialkyloxybenzaldehyde **2** and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone **3** to give (2*S*,3*S*)-aldol adduct **4**, which would be converted to olefin **5**. Although the next hydroboration/oxidation of **5** would be anticipated to give rise to the undesirable (4*R*)-isomer **6**, more stable (4*S*)-lactone **7b** would be obtained by the epimerization of C-4 in **7a**, which is readily derived from **6**. In the final stage, the diastereoselective Friedel–Crafts-type arylation toward the five-membered oxocarbenium cation intermediate **9** generated from acetal **8** would be employed for the installation of (*S*)-configuration on the C-5 position.[9,10]

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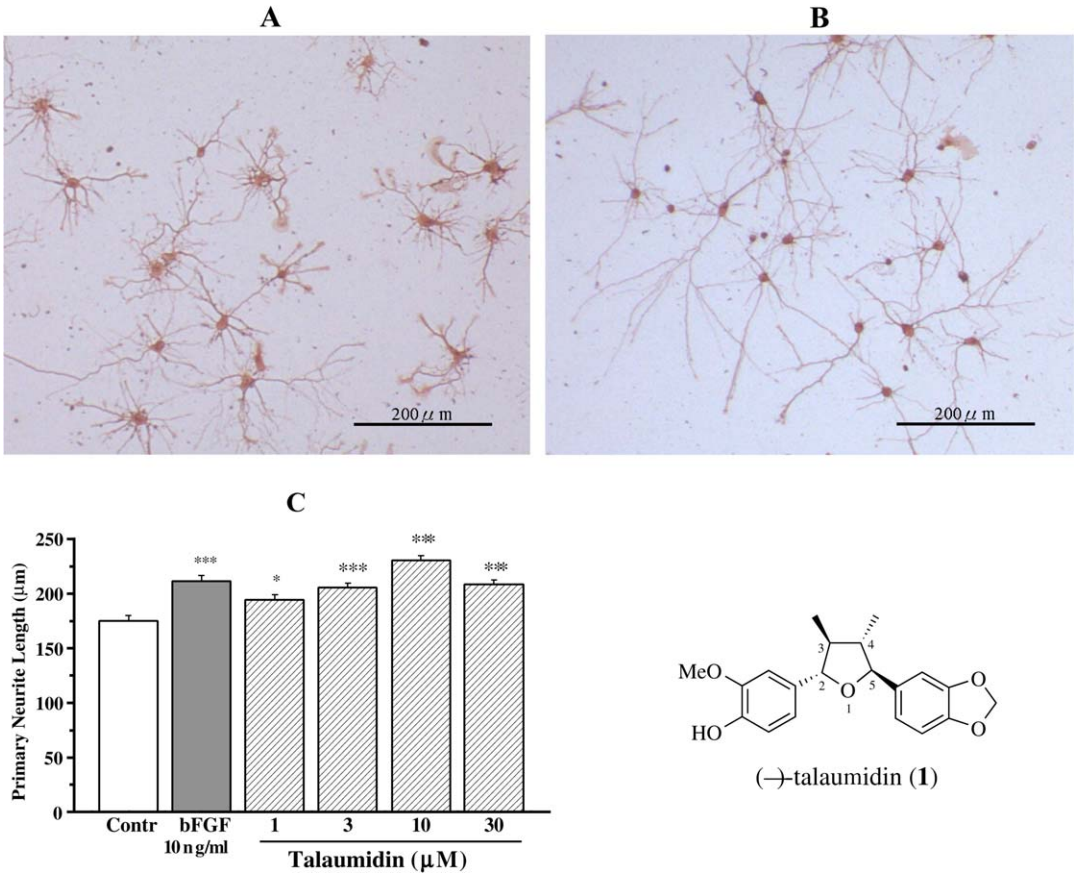
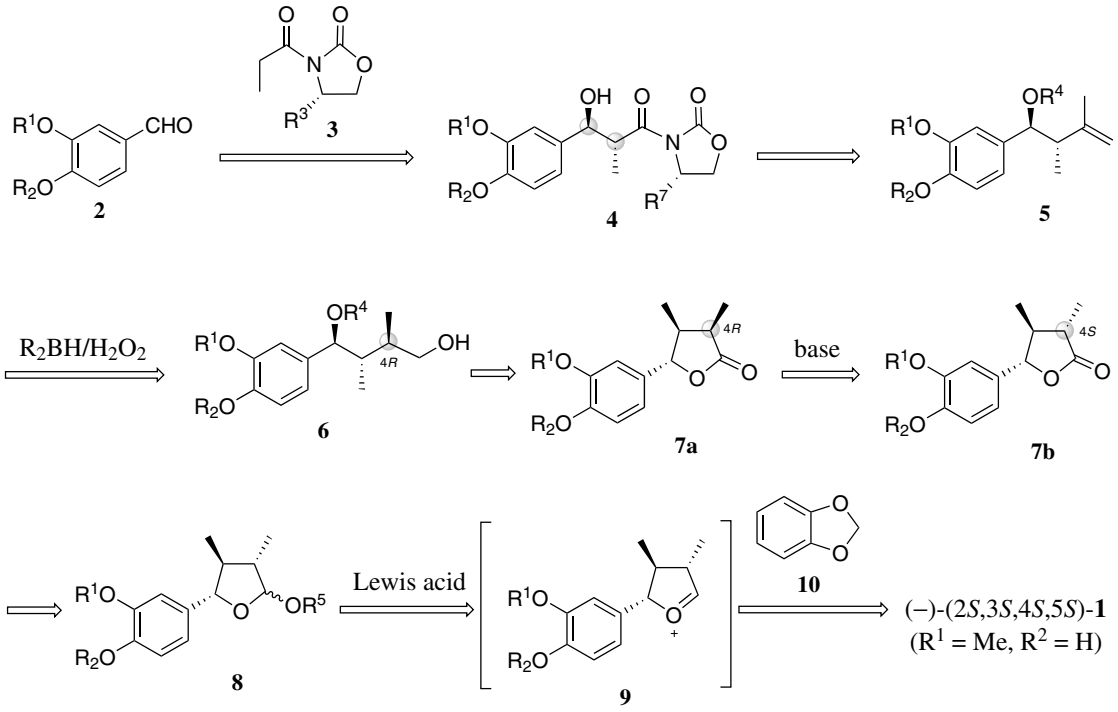


Figure 1. Neurite outgrowth-promoting activity of talaumidin (**1**) in the primary cultured rat hippocampal neurons and structure of **1**. After 24 h preculture in NB/B27 medium, rat hippocampal neurons (18 days) were treated with talaumidin and basic fibroblast growth factor (bFGF) for 72 h, and then fixed for anti-tau immunochemical staining. **A**, **B** are representative morphological changes, respectively, in control (0.5% EtOH) and 10 μM talaumidin. **C** is the quantitative analysis of the primary neurite outgrowth, and the primary neurite was defined as the longest process. Data were expressed as means ± SEM, $^{*}P < 0.05$; $^{***}P < 0.001$, and compared with control.

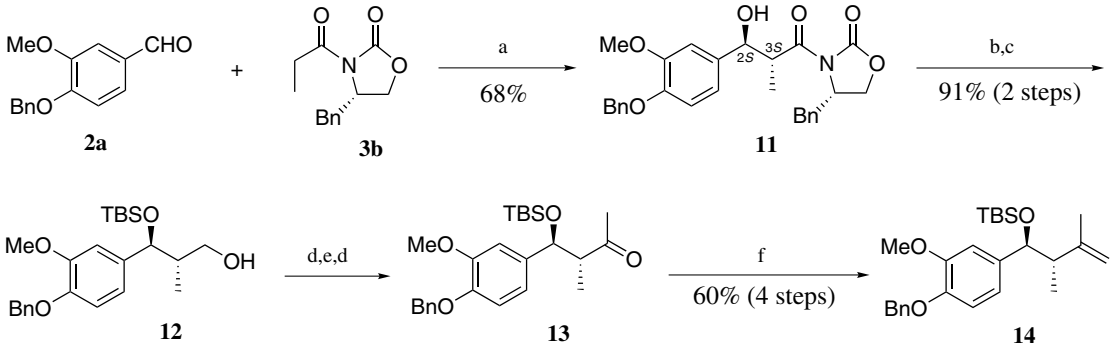
According to the plan illustrated in Scheme 1, the synthesis of (−)-(2*S*,3*S*,4*S*,5*S*)-talaumidin (**1**) began with the recently improved Evans asymmetric *anti*-aldol reaction catalyzed by $MgCl_2$[8] (Scheme 2). 4-Benzyloxy-3-methoxybenzaldehyde **2a** was reacted with (*S*)-4-benzyl-3-propionyl-2-oxazolidinone **3** in the presence of TMSCl, Et_3N, and 10 mol % of $MgCl_2$ to provide (2*S*,3*S*)-aldol adduct **11** in modest yield with high diastereoselectivity (de = 98%). Then, protection of the hydroxy group as TBS ether with TBSOTf, followed by reductive removal of the oxazolidinone using $LiBH_4$,[11] gave the primary alcohol **12** in high yield. The 2,3-*anti* relative stereochemistry for **12** was confirmed by applying the Rychnovsky–Evans rule[12,13] to the acetonide of **12**. Methyl ketone **13** was derived from **12** in three steps: by Swern oxidation, reaction of the formed aldehyde with MeMgBr, and then by repeating Swern oxidation. To avoid the epimerization at the C-3 position, **13** was subjected to the Tebbe olefination[14] without purification, giving rise to the methylene compound **14** in good yield. The absolute configuration of the C-2 position was defined as 2*S* by applying modified Mosher method[15] to (+) and (−)-MTPA esters prepared from the secondary alcohol obtained by the removal of the TBS group of **14**.

Next, stereoselective hydroboration of **14** was attempted. As shown in Table 1, $BH_3{\cdot}SMe_2$ gave **15** in 65% yield with low diastereoselectivity (entry 1), whereas a relatively bulky disiamylborane improved the diastereoselectivity up to 97%, but the conversion yield was still unsatisfactory (entry 2). The best result was accomplished by using 9-BBN-*H* (entry 3), thereby giving rise to the primary alcohol **15** with high diastereoselectivity (de >99%) in 74% yield. This high stereoselectivity can be rationalized by transition state Ts matched to a Cram rule.[16] Oxidation of the primary alcohol **15** with PDC and then $NaClO_4/NaH_2PO_4$ yielded carboxylic acid, which was converted to the γ-lactone **16a** by deprotection of the TBS group in 72% yield over three steps.

Although the newly generated chiral center C-4 was opposite to the desired natural 4*S*, the C-4 chirality could be readily inversed upon treatment of **16a** with MeONa in MeOH to (4*S*)-γ-lactone **16b**.[17] The subsequent DIBAL reduction of **16b**, followed by treatment of methylorthoformate and *p*-toluenesulfonic acid in MeOH, yielded five-membered acetal **17** as an anomeric mixture in 84%. With acetal **17** set up for the crucial Friedel–Crafts type arylation to construct the remaining chiral center C-5, we examined a few acidic conditions. In consequence, we found that upon treatment of **17** with 1,2-methylenedioxybenzene **10** (7 equiv) and $SnCl_4$ (1 equiv) in CH_2Cl_2 at −78 °C for 13 h, the reaction

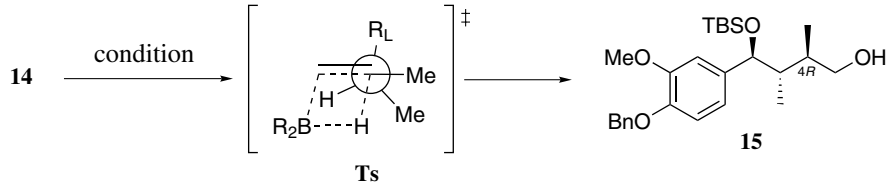


Scheme 1. Synthetic plan of (−)-**1**.



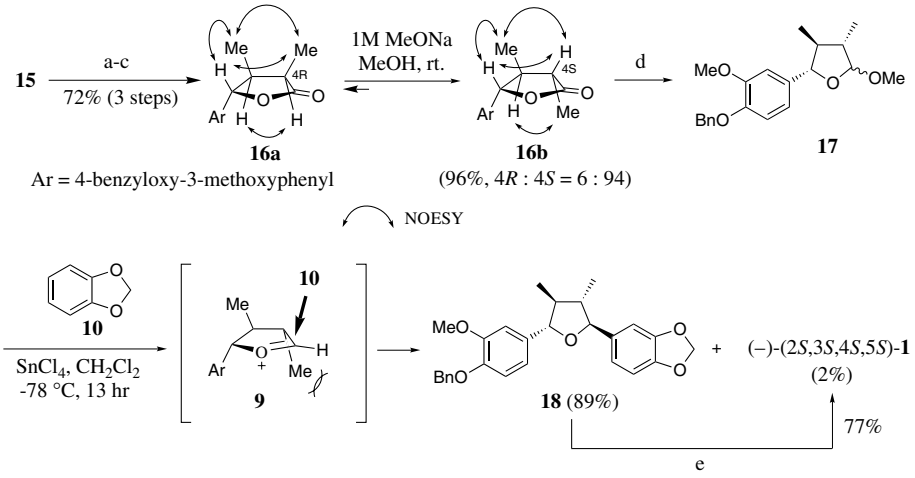
Scheme 2. Synthesis of **14**. Reagents and conditions: (a) **3**, 10 mol % $MgCl_2$, TMSCl, Et_3N, EtOAc, rt, 16 h; ii. HF/py/MeCN (1:3:5), 0 °C, overnight; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 5 min; (c) $LiBH_4$, MeOH, Et_2O, rt, 1 h; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C; (e) CH_3MgBr, THF, 0 °C, 11 h; (f) $Cp_2TiCH_2AlClMe_2$, THF, −40 °C → rt, 4.5 h.

Table 1. Diastereoselectivity for hydroboration/oxidation of **14**



Entry	Condition	Yield (%)	de (%)
1	$BH_3{\cdot}SMe_2$, THF, 0 °C, 5 h, then 30% H_2O_2, 3 M NaOH, rt	64	53
2	Sia_2BH, THF, 0 °C, rt, 3 h, then 30% H_2O_2, 3 M NaOH, rt	60	97
3	9BBN-*H*, THF, 0 °C, rt, 16 h, then 30% H_2O_2, 3 M NaOH, rt	74	>99

smoothly proceeded to give only the desired (5*S*)-**18** in 89% yield along with 2% of talaumidin (**1**). The relative stereochemistry with regard to C-2 ~ C-5 was established by NOESY correlation. This perfect β-facial selectivity is due to a steric interaction between the C-4 methyl group and the approaching nucleophile **10**.



Scheme 3. Completion of the total synthesis of (−)-(2*S*,3*S*,4*S*,5*S*)-**1**: (a) PDC, DMF, rt, 2 h; (b) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}C(H)CH_3$, *t*-BuOH/H_2O, rt, 1 h; (c) HF/py/MeCN (1:3:5), 0 °C, overnight; (d) DIBAL, CH_2Cl_2, −78 °C, 1 h, then $(CH_3O)_3CH$, TsOH·H_2O, MeOH, rt, 10 h; (e) H_2/$Pd(OH)_2$, EtOH, rt, 10 min.

Finally, debenzylation of **18** with $Pd(OH)_2$ in EtOH furnished (−)-(2*S*,3*S*,4*S*,5*S*)-**1** in 77% yield. All the spectroscopic data (^{1}H NMR, ^{13}C NHR, IR, HRMS, $[\alpha]_D$, CD) of the synthetic **1** were identical with those of natural talaumidin.[18] Herein, we have achieved the first enantioselective total synthesis of (−)-**1** and have determined the absolute configuration of (−)-talaumidin (**1**) as (2*S*,3*S*,4*S*,5*S*) (Scheme 3).

In conclusion, we have achieved the first enantioselective total synthesis of (−)-(2*S*,3*S*,4*S*,5*S*)-talaumidin (**1**), a neurotrophic 2,5-diaryl-3,4-dimethyltetrahydrofuran, in a highly efficient and stereocontrolled fashion requiring linear 16 steps in 10.7% overall yield. This synthetic methodology opens the way to prepare other stereoisomers of talaumidin, which will allow us to study the structure–activity relationship of **1** in detail. Further synthetic studies on stereoisomers of **1** are now in progress.

Acknowledgements

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17. Although **16a** and **16b** were inseparable, all minor components could be removed by silica gel column chromatography after the arylation.
18. (−)-(2*S*,3*S*,4*S*,5*S*)-**1**: $[\alpha]_D^{16}$ −85.2 (*c* 0.43, $CHCl_3$); CD ($CHCl_3$) $\Delta\varepsilon$ −128.0 (238 nm), −25.4 (287 nm); HR EIMS calcd 342.1467 for $C_{20}H_{22}O_5$; found 342.1471; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, $J = 5.8$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.73–1.78 (m, 2H), 3.92 (s, 3H), 4.61 (d, $J = 9.1$ Hz, 2H), 5.57 (s, 1H), 5.95 (s, 2H), 6.76–6.94 (m,

6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.0, 136.6, 134.1, 119.7, 119.4, 114.0, 108.5, 107.9, 106.6, 101.0, 88.4, 88.2, 56.0, 51.2, 50.9, 13.8. Natural (−)-**1**: $[\alpha]_D^{16}$ −81.8 (*c* 0.43, $CHCl_3$); CD ($CHCl_3$) $\Delta\varepsilon$ −36.2 (238 nm), −7.2 (287 nm); HR EIMS calcd 342.1467 for $C_{20}H_{22}O_5$; found 342.1472; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, $J = 5.8$ Hz, 3H), 1.06 (d, $J = 5.8$ Hz, 3H), 1.73–1.78 (m, 2H), 3.93 (s, 3H), 4.63 (d, $J = 9.1$ Hz, 2H), 5.57 (s, 1H), 5.96 (s, 2H), 6.76–6.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.0, 136.6, 134.1, 119.7, 119.4, 114.0, 108.5, 107.9, 106.6, 101.0, 88.4, 88.2, 56.0, 51.2, 50.9, 13.8.[2a]