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

Tomoyuki Esumi, Daisuke Hojyo, Haifeng Zhai and Yoshiyasu Fukuyama*

Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

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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.

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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 trials, 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 arculata Masters.2 Talaumidin and its analogues exhibit significant neurite outgrowth-promoting and neuroprotective activities in the primary cultured rat cortical2 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 (2S,3S,4S,5S) 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 (2S,3S,4S,5S)-1, in which we apply a flexible and reliable synthetic way involving Evans asymmetric aldol reaction as well as sterecontrolled 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 reaction7,8 between 3,4-dialkylbenzaldehyde 2 and (S)-4-benzyl-3-propionyl-2-oxazolidinone 3 to give (2S,3S)-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 (4R)-isomer 6, more stable (4S)-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
According to the plan illustrated in Scheme 1, the synthesis of \((-\text{C}0\)\)-(2\(S\),3\(S\),4\(S\),5\(S\))-talaumidin (1) began with the recently improved Evans asymmetric \textit{anti}\-aldol reaction catalyzed by MgCl\(_2\) (Scheme 2). 4-Benzylxylo-3-methoxybenzaldehyde 2a was reacted with (S)-4-benzyl-3-propionyl-2-oxazolidinone 3 in the presence of TMSCl, Et\(_3\)N, 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\(_4\), gave the primary alcohol 12 in high yield. The 2,3-\textit{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\(_3\)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\(_2\)PO\(_4\) yielded carboxylic acid, which was converted to the \(\text{\textit{\textgamma}}\)-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 inverted upon treatment of 16a with MeONa in MeOH to (4\(S\))-\(\text{\textgamma}\)-lactone 16b.\(^{17}\) The subsequent DIBAL reduction of 16b, followed by treatment of methylthorotormate and \(p\)-toluenesulfonic acid in MeOH, yielded five-membered acetal 17 as an anomic 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\(_2\)Cl\(_2\) at –78 °C for 13 h, the reaction
smoothly proceeded to give only the desired (5S)-18 in 89% yield along with 2% of talamidin (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.
structure–activity relationship of \(1\)mers of talaumidin, which will allow us to study the linear 16 steps in 10.7% overall yield. This synthetic neurotrophic 2,5-diaryl-3,4-dimethyltetrahydrofuran, in progress.

Synthesis studies on stereoisomers of total synthesis of \((\pm S, 3,4,5,5)\)-I. Herein, we have achieved the first enantioselective total synthesis of \((\pm S, 3,4,5,5)\)-I and have determined the absolute configuration of \((\pm\)talaumidin \((\pm S)\) as \((2S, 3S, 4S, 5S)\) (Scheme 3).

In conclusion, we have achieved the first enantioselective total synthesis of \((\pm)-(2S, 3S, 4S, 5S)\)-talaumidin. \(1\) Herein, we have achieved the first enantioselective total synthesis of \((\pm)-\) and have determined the absolute configuration of \((\pm)\)-talaumidin \((\pm)\) as \((2S, 3S, 4S, 5S)\) (Scheme 3).

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

In conclusion, we have achieved the first enantioselective total synthesis of \((\pm)-(2S, 3S, 4S, 5S)\)-talaumidin \((\pm)\), a neurotrophic 2,5-diaryl-3,4-dimethyltetrahydrofuran, in a highly efficient and stereocompeted 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 \(I\) in detail. Further synthetic studies on stereoisomers of \(I\) are now in progress.

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References and notes

17. Although 16a and 16b were inseparable, all minor components could be removed by silica gel column chromatography after the arylation.
18. \((\pm)-(2S, 3S, 4S, 5S)\)-I: \([\delta]_{D}^{19}=–58.2\) (c 0.43, CHCl\(_3\)); CD (CHCl\(_3\)) \(\Delta_e=–128.0\) (238 nm), \(-25.4\) (287 nm); HR EIMS calcd 342.1467 for \(C_{20}H_{22}O_5\); found 342.1471. \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta 1.02\) (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, 3H), 7.02–7.08 (m, 3H), 7.26–7.35 (m, 3H), 7.60–7.67 (m, 3H), 7.73 (s, 1H)}
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 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 (−)-I: $[\alpha]_D^{16} = -81.8$ (c 0.43, CHCl$_3$); CD (CHCl$_3$) $\Delta e = -36.2$ (238 nm), $\Delta e = -7.2$ (287 nm); HR EIMS calcd 342.1467 for C$_{20}$H$_{22}$O$_5$; found 342.1472; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 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.