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SYNTHESIS OF (–)-TALAUMIDIN, A NEUROTROPHIC 2,5-BIARYL-3,4-DIMETHYLTETRAHYDROFURAN LIGANAN, AND ITS STEREOISOMERS[1]

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Abstract – The enantioselective total synthesis of a neurotrophic (–)-talaumidin (**1**) was achieved in 16 steps from 4-benzyloxy-3-methoxybenzaldehyde in ca. 10.7% overall yield. 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. Its stereoisomers (2*S*,3*S*,4*S*,5*R*)-**1a** and (2*S*,3*S*,4*R*,5*S*)-**1b** were also synthesized from a key intermediate **10** with the 2*S* and 3*S* configurations.

INTRODUCTION

The lignan class of natural products are biosynthesized from the achiral phenylpropanes (C6-C3 units) by oxidaitive coupling and various cyclization sequences.[2] Although their structure frameworks are made up of two simple phenylpropane units, lignans not only consist of a remarkable structural diversity but also possess a wide variety of biological activities such as trypanocidal,[3] antifungal,[4] anti-PAF,[5] cytotoxic,[6] immunomodulatory, antioxidant, and antiviral activities.[7] In the course of our search for neurotrophic natural products, we found that (–)-talaumidin (**1**), a 2,5-diaryl-3,4-dimethyltetrahydrofuran lignan, isolated from Brazilian *Aristolochia arcuata* Masters, showed significant neurite outgrowth

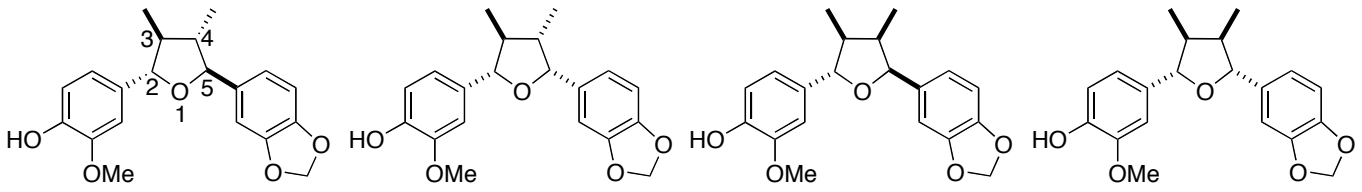


Figure 1. Talaumidin (**1**) and its stereoisomers **1a** - **1c**

promoting and neuroprotective activites in the primary cultured rat cortical and hippocampal neurons.[8] Among a number of lignans, 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans have attracted considerable attention from synthetic chemists and biochemists recently due to their structural diversity and biological activity.[9] While talaumidin (**1**) possesses the four continuous stereogenic centers existing on a tetrahydrofuran ring, there are the possible eight diastereoisomers regarding the four stereogenetic centers of **1**, among which three diastereoisomers **1a** – **1c** on C-4 and C-5 are shown in **Figure 1**. The absolute configurations of **1** have been unambiguously determined to be 2*S*,3*S*,4*S*,5*S* by us.[10] From a synthetic point of view, it is attractive not only to stereoselectively construct the four consecutive chiral centers, but also to prepare stereoisomer libraries which would provide useful information on the structure-activity relationship of **1**. Herein, we report the full detail of the first enatioselective synthesis of (–)-talumidin (**1**)[10] and its stereoisomers **1a** and **1b** (**Figure 1**), in which we applies 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.

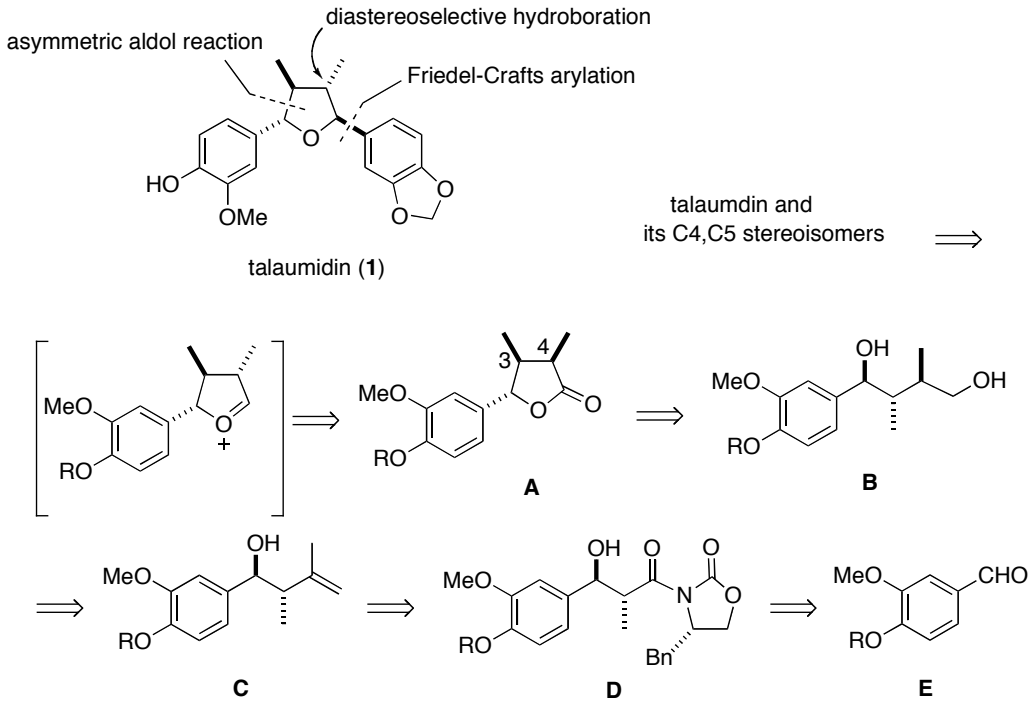


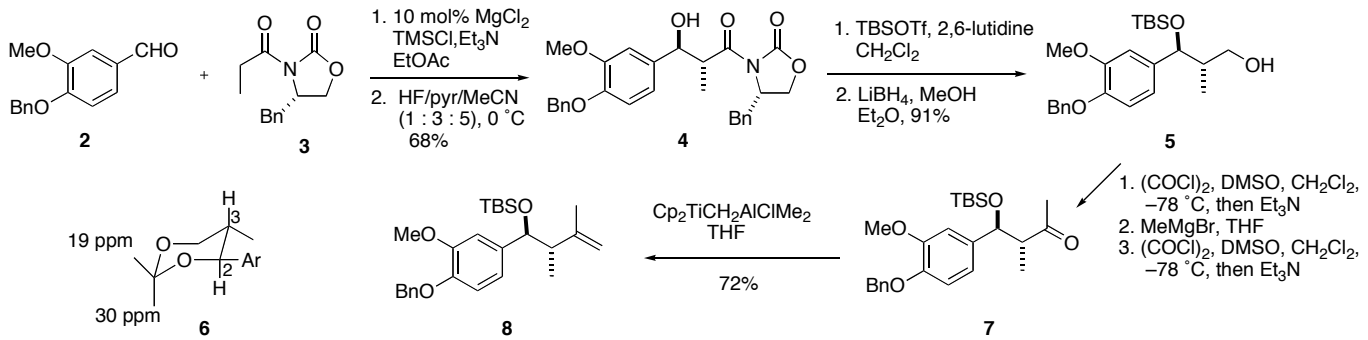
Figure 2. Disconnective analysis for talaumidin (**1**) and its stereoisomers.

Our synthetic plan for **1** is outlined in **Figure 2**.[11] Considering all the possible stereoisomers of **1**, we envisioned that the synthesis would start with the Evans asymmetric *anti*-aldol reaction[12, 13] between 3,4-dialkyloxybenzaldehyde **E** and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone to give (2*S*,3*S*)-aldol adduct **D,** which would be converted to olefin **C**. Next hydroboration/oxidation of **C** would provide 3,4 *cis*-lactone **A**, which could be readily epimerized to more stable 3,4-*trans*-lactone. In the final stage, the diastereoselective Friedel-Crafts-type arylation toward 5-membered oxocarbenium cation intermediate generated from a 3,4-*trans*-lactone would be employed for the installation of (*S*)-configuration on the C-5 position.[14, 15]

RESULTS AND DISCUSSION

The two chiral centers C-2 (*S*) and C-3 (*S*) of (–)-talaumidin (**1**) with the (2*S*,3*S*,4*S*,5*S*)-configuration could be generated by the recently improved Evans asymmetric *anti*-aldol reaction catalyzed by $MgCl_2$[12] (**Scheme 1**). 4-Benzyloxy-3-methoxybenzaldehyde **2** 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 the aldol adduct **4** in modest yield with high diastereoselectivity (98% de). Protection of the hydroxy group as TBS ether with TBSOTf, followed by reductive removal of the oxazolidinone using $LiBH_4$,[16] gave the primary alcohol **5** in high yield. The 2,3-*anti* relative stereochemistry for **5** was confirmed by applying the Rychnovsky-Evans rule[17, 18] to the acetonide **6** that was derived from **5** by deprotection of the TBS group and then acetonide formation. Namely, a vicinal *J* value between H-2 and H-3 was observed to be 10.4 Hz in the ^{1}H NMR spectrum of **6**, whereas two methyl signals were resonated at 19 and 30 ppm in the ^{13}C NMR spectrum. The methyl ketone **7** was obtained from **5** in three steps by Swern oxidation, reaction of the formed aldehyde with MeMgBr, and then repeating Swern oxidation. To avoid the epimerization at the C-3 position, **7** was subjected to the Tebbe olefination[19] without purification of **7** giving rise to the methylene compound **8** in good yield.

Scheme 1



The absolute configuration of the C-2 stereocenter was defined as *S* by applying modified Mosher method[20] to (+) and (–)-MTPA esters that were prepared from the secondary alcohol obtained by removal of the TBS group of **8** (**Figure 3**).

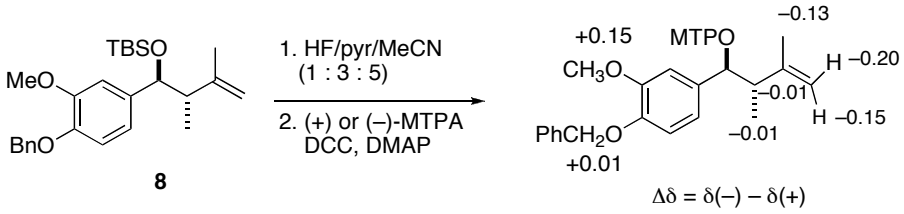
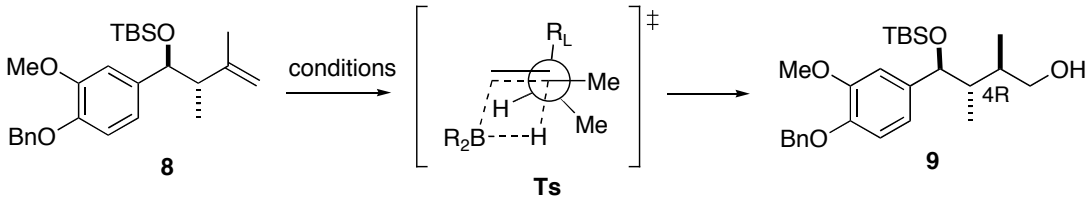


Figure 3. Determination of the absolute configuration of the C-2 chiral center

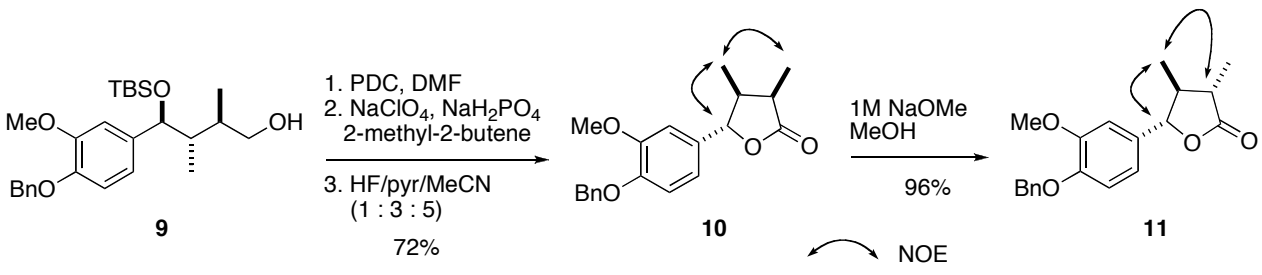
As the attempted stereoselective hydroborations of **8** were summarized in **Table**, BH_3•SMe_2 gave the desired primary alcohol **9** in 64% yield with low diastereoselectivity (entry 1), whereas a relatively bulky disiamylborane improved diastereoselectivity up to 97% but the conversion yield was still unacceptable (entry 2). The best result was brought out by using 9-BBN-H (entry 3), thereby giving rise to **9** with high diastereoselectivity (>99% de) in 74% yield. This high stereoselectivity can be explained by adopting a transition state **Ts** based on a Cram rule.[21] The primary alcohol of **9** was oxidized with PDC and then $NaClO_2$/NaH_2PO_4 to yield carboxylic acid, which was converted to the γ-lactone **10** by deprotection of

Table



entry	conditions	yield (%)	de (%)
1	BH_3•SMe_2, THF, 0 ˚C, 5 h, then 30% H_2O_2, 3 M NaOH, rt.	64	53
2	Sia_2BH, THF, 0 ˚C to rt., 3 h, then 30% H_2O_2, 3 M NaOH, rt.	60	97
3	9-BBN-H, THF, 0 ˚C to rt., 16 h then 30% H_2O_2, 3 M NaOH, rt.	74	>99

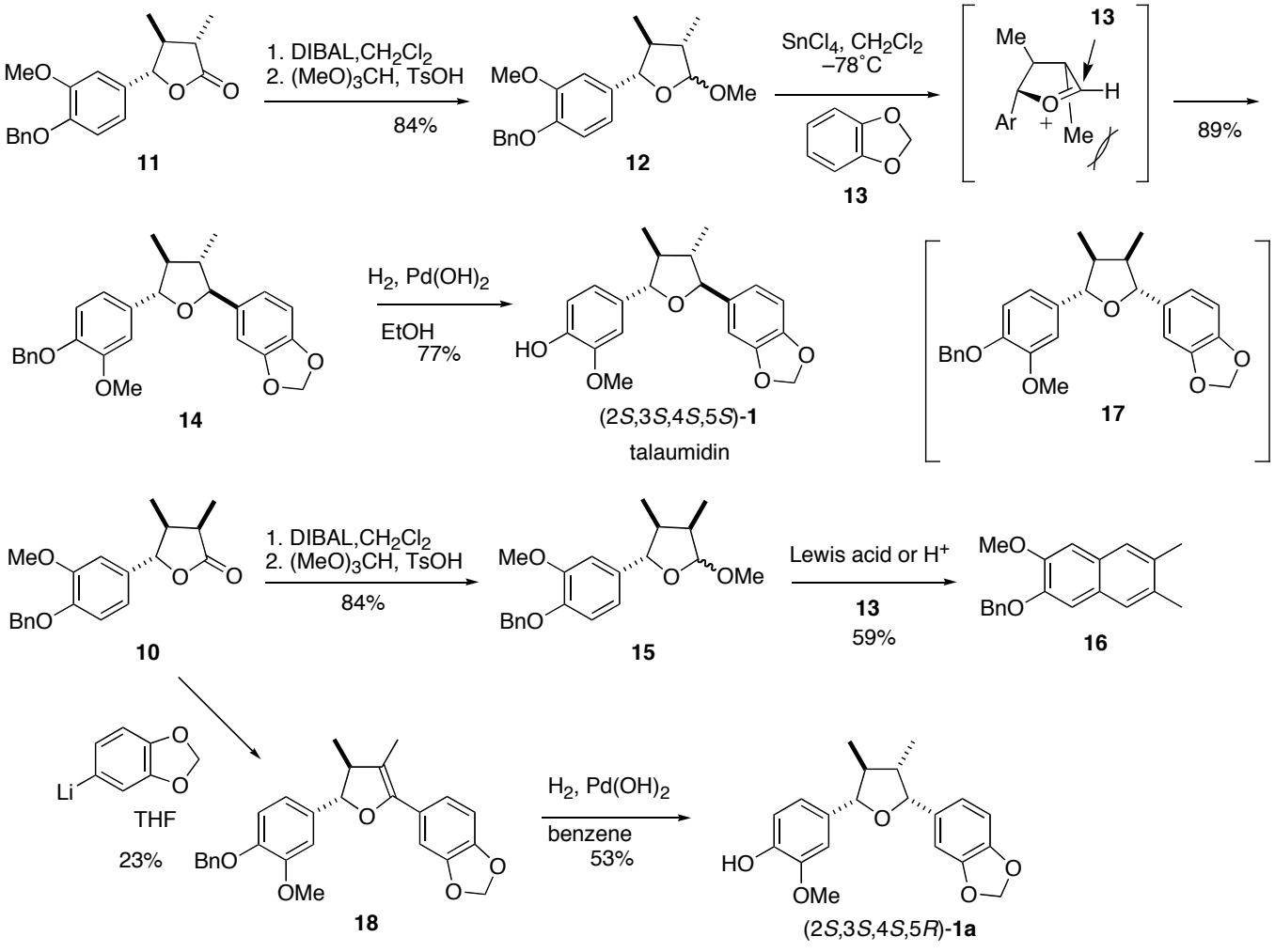
Scheme 2



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 **10** with MeONa in MeOH to (4*S*)-γ-lactone **11**. The relative relationship of the C2 and C3 dimethyl groups in **10** and **11** was confirmed to be *cis* and *trans*, respectively, on the basis of NOEs (**Scheme 2**).

The subsequent DIBAL reduction of **11**, followed by treatment of methyl orthoformate and *p*-toluenesulfonic acid in MeOH, yielded 5-membered acetal **12** as an anomeric mixture in 84% yield. With acetal **12** set up for the crucial Friedel-Crafts type arylation to construct the remaining chiral center C-5, we examined a few acidic conditions. As results, we found that upon treatment of **12** with 1,2-methylenedioxybenzene **13** (7 equiv) and $SnCl_4$ (1 equiv) in CH_2Cl_2 at –78 ˚C for 13 h the reaction smoothly proceeded to give only the desired (5*S*)-**14** in 89% yield accompanied 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 rationalized due to a steric interaction between the C-4 methyl group on the oxocarbenium ion intermediate and approaching nucleophile **13**. Finally debenzylation of **14** 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

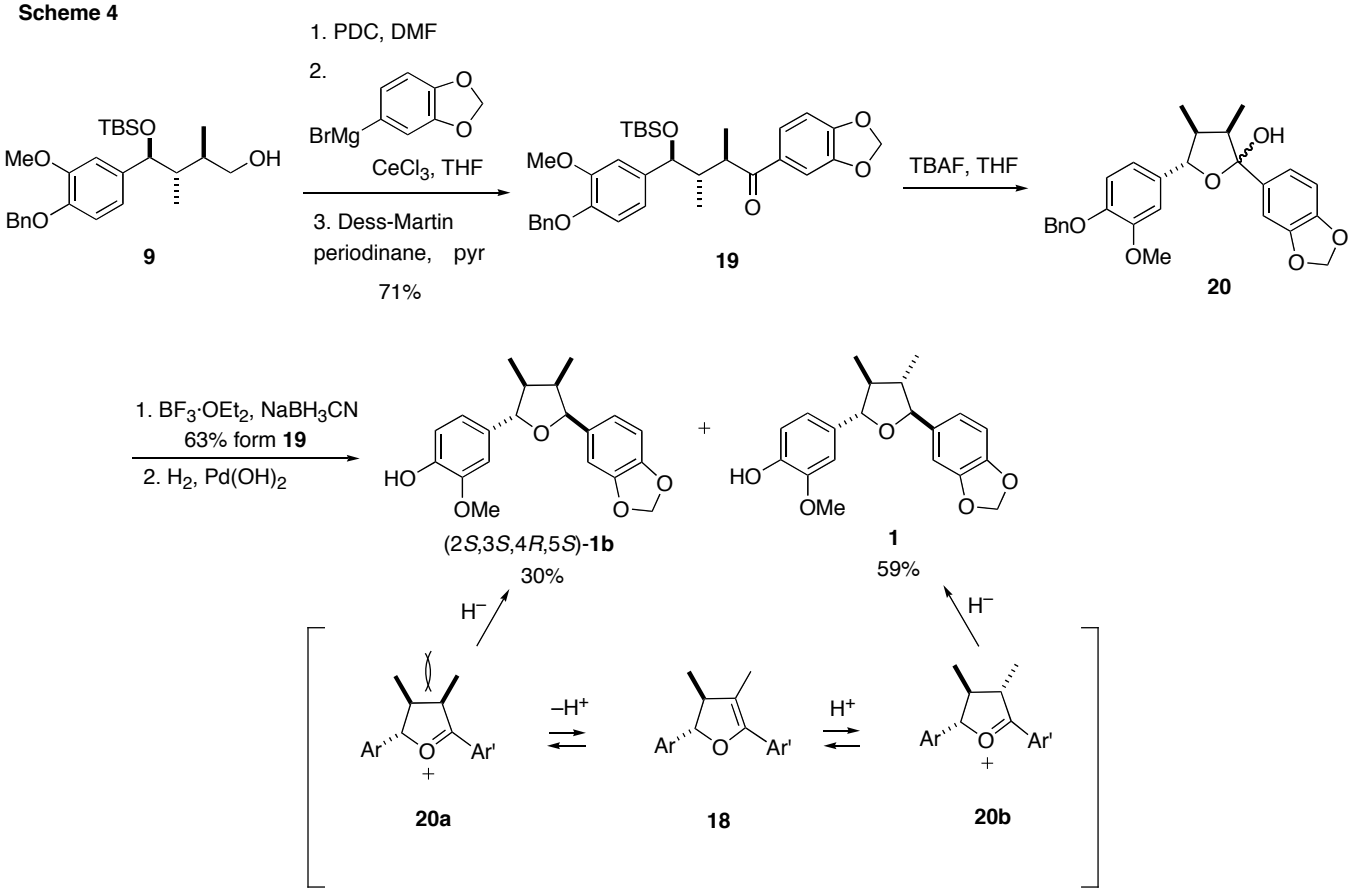
Scheme 3



NHR, IR, HRMS, $[\alpha]_D$, CD) of the synthetic **1** were identical with those of natural talaumidin.[8, 22] Herein, we have achieved the first enantioselective total synthesis of (–)-talaumidin **1** and thereby its absolute configuration has been unambiguously determined to be 2*S*, 3*S*, 4*S*, and 5*S* (**Scheme 3**).

Next, we focused on the preparation of three diastereoisomers **1a**, **1b**, and **1c** of (–)-talaumidin. The 2,3-*cis*-dimethyl-γ-lactone **10** was converted to the acetal **15** according to the same procedure as used for the preparation of **12**. We expected that compound **17** with the (2*S*,3*S*,4*R*,4*R*)-configuration would preferentially be obtained through the addition of **13** from the inside face of the envelop conformer of oxocarbenium intermediate due to steric hindrance of the neighboring β-methyl group. However, the reaction conditions for acid-catalyzed addition of **13** ($SnCl_4$, $BF_3{\cdot}OEt_2$, TsOH, –78˚C to room temperature) gave a complex mixture containing **16**. On the other hand, reaction of **10** with 3,4-methylenedioxyphenyllithium provided no desired hemiacetal **20** but solely the dihydrofuran **18**, which was anyhow led to a diastereomer **1a** with the (2*S*,3*S*,4*S*,5*R*)-configuration in 53% yield by catalytic hydrogenation of the formed double bond with $Pd(OH)_2$ in benzene (**Scheme 3**).

Scheme 4



For preparation of **1b** and **1c** having the 4*R*-configuration, we have changed our attention to an alternative way in which a 3,4-methylenedioxyphenyl unit is introduced at the early stage of the reactions to gain the desired acetal **20** as shown in **Scheme 4**. Oxidation of **9** with PDC gave the aldehyde, which was

reacted with 3,4-methylenedioxyphenyl magnesium bromide in the presence of $CeCl_3$ and then the formed alcohol was oxidized with Dess-Martin periodinane, giving rise to **19** in 71% yield over three steps. Deprotection of the TBS group of **19** with TBAF provided the acteal **20**, which was readily converted to **18** on being exposed to acidic conditions. When **20** was treated with $BF_3 \cdot OEt_2$ in the presence of $NaBH_3CN$,[23] the expected deoxygenation reaction proceeded to give a 1:2 diastereomeric mixture of **1b** with the (2*S*,3*S*,4*R*,3*S*)-configuration and talaumidin (**1**) in 56% yield after the benzyl group being deprotected. The observed isomerization of the C4 methyl group in **20** can be explained based on the reason that the 2,3-*cis*-methyl groups on the oxocarbenium ion intermediate **20a** was interconverted to another oxocarbenium ion intermediate **20b** *via* a dehydrofuarn **18** because of reducing steric hindrance between both the 2,3-*cis*-methyl groups on the tetrahydrofuran ring. Since the isomerization of the C4 methyl substituent competes with reduction of the oxocarbenium ion intermediate **20b** by hydride reducing agents, more effective reduction conditions are required to overcome this issue. Thus, it becomes a challenging work to develop methodology to stereoselectively synthesize all the seven diastereomers of **1**.

CONCLUSION

In conclusion, we have achieved the first enantioselective total synthesis of (–)-talaumidin (**1**) in a highly efficient and stereocontrolled fashion requiring linear 16 steps in 10.7% overall yield, and also **1a** and **1b** among three diastereomers have been prepared from the same intermediate **9**. This synthetic methodology can apply to prepare other stereoisomers of talaumidin, which will allow us to study structure-activity relationship of **1** in detail. Further synthetic and biological studies on stereoisomers of **1** are now in progress.

EXPERIMENTAL

General

Melting points were determined on a Yanagimoto MPJ-2 melting-point apparatus and were uncorrected. IR spectra were measured on a JASCO FT-IR 5300 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mecury-300 or a Merucry-400 instrument in $CDCl_3$ solution with TMS as an internal standard. MS spectra were measured on a JMS-AX 500 or a Mstation JIM-700. Optical rotations were determined with a JASCO DIP-1000 polarimeter and are referenced to the D-line of sodium. CD spectra were measured on a JASCO J-500 instrument.

(2*R*,3*S*,4*S*)-4-Benzyl-3-[3-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylpropionyl]oxazolidin-2-one (4). To a solution of (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone (1.01 g, 4.33 mmol) in EtOAc

(8.6 mL) was successively added 4-benzyloxy-3-methoxybenzaldehyde (1.23 g, 5.45 mmol), magnesium chloride (84.2 mg, 0.866 mmol), triethylamine (800 μL, 8.66 mmol), and trimethylsilyl chloride (830 μL, 6.50 mmol). The resulting mixture was stirred at rt for 14 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was stirred for 10 min. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. To the residue was added HF-pyridine-MeCN (1 : 3 : 5; 70 mL) at 0 ˚C and the mixture was stirred overnight. To a saturated aqueous $NaHCO_3$ was added the reaction mixture. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford **4** (1.39 g, 68%) as colorless solids (mp 86 ˚C): ^{1}H NMR (300 MHz) δ 1.10 (d, *J*=6.9 Hz, 3H), 2.68 (dd, *J*=13.7, 9.3 Hz, 1H), 3.00 (d, *J*=7.1 Hz, 1H), 3.21 (dd, *J*=13.7, 3.3 Hz, 1H), 3.93 (s, 3H), 4.14 (dd, *J*=9.1, 3.2 Hz, 1H), 4.21 (d, *J*=9.1 Hz, 1H), 4.34 (dq, *J*=6.9, 7.4 Hz, 1H), 4.71 (ddd, *J*=9.3, 3.3, 3.2 Hz, 1H), 4.76 (dd, *J*=7.4, 7.1 Hz, 1H), 5.14 (s, 2H), 6.87 (dd, *J*=8.1, 1.6 Hz, 1H), 7.02 (d, *J*=1.6 Hz, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 7.28-7.43 (m, 10H); ^{13}C NMR (75 MHz) δ 176.7, 153.6, 149.9, 147.9, 137.1, 135.3, 135.2, 129.5, 129.0, 128.6, 127.8, 127.4, 127.3, 118.9, 113.7, 110.0, 76.6, 71.1, 66.0, 56.0, 55.5, 44.2, 37.6, 14.9; IR (ATR) 3482, 1771, 1695 cm^{-1}; EIMS *m/z* (rel. int.) 475 (1) $[M]^+$, 91 (100); HR EIMS calcd 475.1994 for $C_{28}H_{29}O_6N$; found 475.2000; $[\alpha]^{20}_D$ –118.9° (*c* 1.09, $CHCl_3$).

(3*S*,4*S*)-3-(4-Benzyloxy-3-methoxyphenyl)-3-(*tert*-butyldimethylsilanyloxy)-2-methylpropan-1-ol (5). To a solution of **4** (1.13 g, 2.39 mmol) and 2,6-lutidine (560 μL, 4.78 mmol) in CH_2Cl_2 (2.4 mL) was added *t*-butyldimethylsilyl trifluorometanesulfonate (830 μL, 3.59 mmol). After being stirred for 5 min, the reaction mixture was cooled to 0 ˚C followed by quenched with water. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 5:1 to 3:1) to yield TBS-protected compound (1.40 g, 99%) as a yellow oil. To a solution of this compound (101 mg, 4.64 mmol) in MeOH (7.60 μL, 188 μmol) and Et_2O (3.2 mL) was added lithium borohydride (4.31 mg, 188 μmol) and THF (86.0 μL) at 0 ˚C. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was added to 3 M aqueous NaOH (150 μL) and the aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 8:1 to 4:1) to yield **5** (65.4 mg, 92%) as a colorless oil: ^{1}H NMR (300 MHz) δ –0.24 (s, 3H), 0.04 (s, 3H), 0.81 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 1.91 (dddq, *J*=6.9, 6.0, 3.6, 6.9 Hz, 1H), 3.59 (dd, *J*=11.0, 6.0 Hz, 1H), 3.61 (dd, *J*=11.0, 3.6 Hz, 1H), 3.88 (s, 3H), 4.48 (d, *J*=6.9 Hz, 1H), 5.13 (s, 2H), 6.70 (dd, *J*=8.2, 1.6 Hz, 1H), 6.80 (d, *J*=8.2 Hz, 1H), 6.90 (d, *J*=1.6 Hz, 1H), 7.28-7.45 (m, 5H); ^{13}C NMR (75 MHz) δ 149.5,

147.4, 137.2, 136.9, 128.5, 127.8, 127.4, 119.0, 113.4, 110.1, 80.9, 71.1, 66.5, 55.9, 43.1, 25.8, 18.0, 14.3, 4.50, 5.18; IR (neat) 3437 cm^{-1}; EIMS *m/z* (rel. int.) 416 (1) $[M]^+$, 357 (100); HR EIMS calcd 416.2383 for $C_{24}H_{36}O_4Si$; found 416.2393; Anal. Cacld for $C_{24}H_{36}O_4Si$: C, 68.19; H, 8.71. Found: C, 68.74; H, 8.58. $[\alpha]^{26}_D$ –83.8° (*c* 1.00, $CHCl_3$).

Acetonide 6. Diol (30 mg, 99.2 μmol) obtained from **5** by removal of TBS was stirred in dimethoxypropane (1 mL) containing TsOH (0.6 mg) at rt overnight. The reaction mixture was added to 3 M NaOH and the aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 2:1) to give acetonide **6** (29 mg, 87%) as a colorless oil: ^1H NMR (300 MHz) δ 0.60 (d, *J*=6.9 Hz, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 1.90 (ddqd, *J*=11.5, 10.4, 6.9, 5.2 Hz, 1H), 3.67 (dd, *J*=11.5, 11.5 Hz, 1H), 3.82 (dd, *J*=11.5, 5.2 Hz, 1H), 3.91 (s, 3H), 4.35 (d, *J*=10.4 Hz, 1H), 5.12 (s, 2H), 6.80 (d, *J*=1.8 Hz, 1H), 6.90 (dd, *J*=8.0, 1.8 Hz, 1H), 6.90 (d, *J*=8.0 Hz, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 12.6, 19.0, 30.0, 36.0, 55.9, 66.4, 70.9, 98.7, 110.7, 119.9, 133.4, 137.1, 147.9, 149.6.

(3*R*,4*S*)-4-(4-Benzyloxy-3-methoxyphenyl)-4-(*tert*-butyldimethylsilanyloxy)-3-methylbutan-2-one (7). To a solution of oxalyl chloride (90.0 μL, 1.05 mmol) in CH_2Cl_2 (14 mL) was added dimethyl sulfoxide (150 μL, 2.10 mmol) at –78 ˚C. The mixture was stirred for 10 min at the same temperature, and an alcohol **5** (292 mg, 701 μmol) was added. After being stirred at the same temperature for 10 min, triethylamine (592 μL, 4.20 mmol) was added, and the mixture was allowed to warm up to 0 ˚C. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue (307 mg) was treated with methyl magnesium bromide (370 μL, 1.11 mmol) in THF (3.7 mL) at 0 ˚C. The mixture was stirred for 4 h. Saturated aqueous NH_4Cl was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 8:1 to 6:1) to yield methyl alcohol as a diastereomeric mixture (291 mg): IR (neat) 3458 cm^{-1}; EIMS *m/z* (rel. int.) 430 (1) $[M]^+$, 91 (100). To a solution of oxalyl chloride (87.0 μL, 1.02 mmol) in CH_2Cl_2 (15 mL) was added dimethyl sulfoxide (144 μL, 2.03 mmol) at –78 ˚C. The mixture was stirred for 10 min at same temperature, and the resulting methyl alcohol (291 mg, 670 μmol) was added. After being stirred at the same temperature for 10 min, triethylamine (580 μL, 4.06 mmol) was added, and the mixture was allowed to warm up to 0 ˚C. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give **7** (249 mg) as a colorless oil: ^1H NMR

(300 MHz) δ -0.30 (s, 3H), -0.05 (s, 3H), 0.73 (d, *J*=7.1 Hz, 3H), 0.80 (s, 9H), 2.25 (s, 3H), 2.86 (dq, *J*= 9.3, 7.1 Hz, 1H), 3.88 (s, 3H), 4.59 (d, *J*=9.3 Hz, 1H), 5.13 (s, 3H), 6.71 (dd, *J*=8.2, 1.6 Hz, 1H), 6.81 (d, *J*= 8.2 Hz, 1H), 6.88 (d, *J*=1.6 Hz, 1H), 7.28-7.46 (m 5H).

(1*S*,2*S*)-[1-(4-Benzyloxy-3-methoxyphenyl)-2,3-dimethylbut-3-enyloxy]-*tert*-butyldimethylsilane (8). To a solution of **7** (249 mg) in THF (3.7 mL) was added 0.5 M Tebbe reagent (1.28 mL, 640 μmol) at -40 ˚C. The mixture was stirred at –40 ˚C for 30 min and then at rt for 15 min. Saturated aqueous $NaHCO_3$ was added dropwise, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 60:1) to yield **8** (208 mg, 72% in four steps) as a pale green solid (mp 137 ˚C): ^{1}H NMR (300 MHz) δ 0.01 (s, 3H), 0.28 (s, 3H), 0.78 (d, *J*=6.9 Hz, 3H), 0.84 (s, 9H), 1.72 (brs, 3H), 2.39 (dq, *J*=7.4, 6.9 Hz, 1H), 3.87 (s, 3H), 4.41 (d, *J*=7.4 Hz, 1H), 4.68 (d, *J*=1.6 Hz, 1H), 4.76 (d, *J*=1.6 Hz, 1H), 5.12 (s, 2H), 6.68 (dd, *J*=8.2, 1.6 Hz, 1H), 6.79 (d, *J*=8.2 Hz, 1H), 6.87 (d, *J*=1.6 Hz, 1H), 7.30-7.46 (m, 5H); ^{13}C NMR (75 MHz) δ149.3, 147.6, 147.2, 137.5, 137.4, 128.5, 127.8, 127.4, 119.3, 113.2, 111.6, 110.5, 78.1, 71.2, 55.9, 49.7, 25.7, 20.7, 18.2, 16.1, 4.6, 5.3; IR (ATR) 1515 cm^{-1}; EIMS *m/z* (rel. int.) 426 (1) $[M]^+$, 411 (2), 357 (100); HR EIMS: calcd 426.2590 for $C_{26}H_{38}O_3Si$; found 426.2545; $[\alpha]^{22}_D$ –46.5˚ (*c* 0.54, $CHCl_3$).

(2*R*,3*S*,4*S*)-4-(4-Benzyloxy-3-methoxyphenyl)-4-(*tert*-butyldimethylsilanyloxy)-2,3-dimethylbutan-1-ol (9). To a solution of **8** (456 mg, 1.07 mmol) in THF (7.1 mL) was added 0.5 M 9-BBN-H (8.60 mL, 4.28 mmol) at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 1 h, and then at rt for 20 h. The reaction mixture was treated with 3 M aqueous NaOH (1.95 mL) and 30% H_2O_2 (1.95 mL, 4.28 mmol) for 1 h. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc 20:1 to 6:1) to yield **9** (356 mg, 74%, >99% de) as a colorless oil: ^{1}H NMR (300 MHz) δ 0.07 (s, 3H), 0.17 (s, 3H), 0.78 (d, *J*=7.0 Hz, 3H), 0.91 (s, 9H), 0.91 (d, *J*=6.9 Hz, 3H), 1.77-1.84 (m, 1H), 1.91-1.99 (m, 1H), 3.30 (dd, *J*=11.0, 4.8 Hz, 1H), 3.52 (dd, *J*=11.0, 8.9 Hz, 1H), 3.88 (s, 3H), 4.65 (d, *J*=4.8 Hz, 1H), 5.13 (s, 2H), 6.72 (dd, *J*=8.2, 1.9 Hz, 1H), 6.83 (d, *J*=8.2 Hz, 1H), 6.91 (d, *J*=1.9 Hz, 1H), 7.29-7.46 (m, 5H); ^{13}C NMR (75 MHz) δ 149.2, 147.0, 137.2, 136.7, 128.5, 127.8, 127.4, 118.8, 113.5, 110.5, 78.8, 71.1, 63.9, 55.9, 45.7, 33.9, 25.8, 18.2, 17.2, 12.2, 4.6, 5.1; IR (neat) 3416 cm^{-1}; EIMS *m/z* (rel. int.) 444 (1) $[M]^+$, 91 (100); HR EIMS calcd 444.2696 for $C_{26}H_{40}O_4Si$; found 444.2698; $[\alpha]^{19}_D$ –39.4˚ (*c* 1.00, $CHCl_3$).

MTPA esters of 8. (+)- and (–)-MTPA esters were prepared from **8** after removal of TBS group

according to the literature.[20] (+)-MTPA ester: ^{1}H NMR (300 MHz) δ 0.80 (d, *J*=7.0 Hz, 3H), 1.76 (s, 3H), 2.70 (dq, *J*=10.4, 7.0 Hz, 1H), 3.49 (s, 3H), 3.71 (s, 3H), 4.86 (s, 1H), 4.90 (s, 1H), 5.16 (s, 2H), 5.72 (d, *J*=10.4 Hz, 1H), 6.66 (d, *J*=1.8 Hz, 1H), 6.73 (d, *J*=8.2, 1.8 Hz, 1H), 6.79 (d, *J*=8.2 Hz, 1H), 7.17-7.47 (m, 10H). (–)-MTPA ester: ^{1}H NMR (300 MHz) δ 0.79 (d, *J*=7.1 Hz, 3H), 1.64 (s, 3H), 2.70 (dq, *J*=10.2, 7.1 Hz), 3.37 (s, 3H), 3.86 (s, 3H), 4.66 (s, 1H), 4.75 (s, 1H), 5.16 (s, 2H), 5.80 (d, *J*=10.2 Hz, 1H), 6.86 (brs, 2H), 6.89 (brs, 1H), 7.22-7.46 (m, 10H).

(3*R*,4*S*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-3,4-dimethyldihydrofuran-2-one (10). To a solution of **9** (391 mg, 881 μmol) in DMF (8.8 mL) was added pyridinium dichromate (1.18 g, 3.08 mmol). The mixture was stirred at rt for 2 h. The reaction was terminated with 2 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue (402 mg) was dissolved in *t*-BuOH (1.1 mL), followed by addition of 2-methyl-2-butene (430 μL, 4.00 mmol), a solution of sodium phosphate monobasic (112 mg, 910 μmol) in *t*-BuOH/water (3.6:1, 8.3 mL) and sodium chlorite (332 mg, 3.63 mmol). After being stirred for 1 h, the solution was acidified with 2 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue (397 mg) was added to HF-pyridine-MeCN (1 : 3 : 5; 11.8 mL, 1.30 mmol) at 0 ˚C, and stirred for 41 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 6:1 to 3:1) to yield **7** (205 mg, 72% in three steps) as a yellow oil: ^{1}H NMR (300 MHz) δ 1.08 (d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=7.7 Hz, 3H), 2.53 (ddq, *J*=7.4, 6.9, 6.9 Hz, 1H), 2.78 (dq, *J*=7.4, 7.7 Hz, 1H), 3.90 (s, 3H), 4.96 (d, *J*=6.9 Hz, 1H), 5.15 (s, 2H), 6.78 (dd, *J*=8.1, 1.9 Hz, 1H), 6.85 (d, *J*=1.9 Hz, 1H), 6.86 (d, *J*=8.1 Hz, 1H), 7.29-7.44 (m, 5H); ^{13}C NMR (75 MHz) δ 179.8, 149.9, 148.3, 136.9, 131.1, 128.6, 127.9, 127.2, 118.2, 113.6, 109.0, 85.7, 71.0, 56.1, 42.1, 38.4, 12.5, 10.3; IR (ATR) 1770 cm^{-1}; EIMS *m/z* (rel. int.) 326 (24) $[M]^+$, 91 (100); HR EIMS calcd 326.1518 for $C_{20}H_{22}O_4$; found 326.1516; $[\alpha]^{19}_D$ +16.1˚ (*c* 0.41, $CHCl_3$).

(3*S*,4*S*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-3,4-dimethyldihydrofuran-2-one (11). To a solution of **10** (16.3 mg, 50.0 μmol) in MeOH (0.20 ml) was added sodium methoxide (1 M solution in MeOH, 100 μl, 123 μmol). After being stirred at rt for 14 h, the reaction mixture was diluted with CH_2Cl_2 and water. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 6:1 to 3:1) to yield **11** (15.6 mg, 96%, 4*S* : 4*R* = 94 : 6) as a yellow oil:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, *J*=6.3 Hz, 3H), 1.30 (d, *J*=7.1 Hz, 3H), 1.99 (ddq, *J*=12.1, 10.2, 6.3 Hz, 1H), 2.34 (dq, *J*=12.1, 7.1 Hz, 1H), 3.91 (s, 3H), 4.75 (d, *J*=10.2 Hz, 1H), 5.16 (s, 2H), 6.80 (dd, *J*=8.2, 1.9 Hz, 1H), 6.87 (d, *J*=2.2 Hz, 1H), 6.87 (d, *J*=8.0 Hz, 1H), 7.30-7.44 (m, 5H); ^{13}C NMR (75 MHz) δ 178.6, 149.8, 148.5, 136.8, 130.1, 128.6, 127.9, 127.2, 119.0, 113.4, 109.4, 86.3, 70.9, 56.1, 47.7, 43.4, 14.4, 12.9; IR (ATR) 1768 cm^{-1}; EIMS *m/z* (rel. int.) 326 (67) $[M]^+$, 91 (100); HR EIMS calcd 326.1519 for $C_{20}H_{22}O_4$; found 326.1523; $[\alpha]^{19}{}_D$ –9.6° (*c* 0.92, $CHCl_3$).

(2*S*,3*S*,4*S*)-2-(4-Benzyloxy-3-methoxyphenyl)-5-methoxy-3,4-dimethyltetrahydrofuran (12). A solution of **12** (38.0 mg, 117 μmol) in CH_2Cl_2 (0.9 mL) was added DIBAL-H (1 M solution in hexane, 280 μL, 268 μmol) at –78 ˚C. After being stirred for 1 h, MeOH (560 μL), trimethyl orthoformate (47.0 μL, 431 μmol) and *p*-toluenesulfonic acid (75.6 mg, 0.397 mmol) were added. The mixture was warmed up to rt, and stirred for 10 h. The reaction mixture was diluted with EtOAc followed by washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 12:1 to 8:1) to yield a diastereomer mixture **12** (33.5 mg, 84% in two steps) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.0 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.53-1.66 (m, 2H), 1.79-1.91 (m, 2H), 3.43 (s, 3H), 3.49 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.38 (d, *J* = 9.1 Hz, 1H), 4.46 (d, *J* = 9.6 Hz, 1H), 4.78 (d, *J* = 4.1 Hz, 1H), 4.85 (d, *J* = 3.8 Hz, 1H), 5.15 (s, 4H), 6.76-6.86 (m, 4H), 6.92 (d, *J* = 1.4 Hz, 1H), 6.99 (d, *J* = 1.6 Hz, 1H), 7.29-7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8 (x2), 147.9, 147.7, 137.3, 137.2, 135.6, 133.3, 128.5 (x2), 127.8 (x2), 127.2 (x2), 119.4, 119.3, 113.7, 113.4, 111.3, 110.3, 110.1, 106.5, 89.5, 86.5, 71.0 (x2), 56.0, 55.9, 55.8, 55.0, 49.9, 48.8, 46.5, 46.3, 16.0, 14.1, 14.0, 11.0; EIMS *m/z* (rel. int.) 342 (81) $[M]^+$, 91 (100); HR EIMS calcd 342.1831 for $C_{21}H_{26}O_4$; found 342.1838.

(2*S*,3*S*,4*S*,5*S*)-5-[5-(4-Benzyloxy-3-methoxyphenyl)-3,4-dimethyltetrahydrofuran-2-yl]benzo[1,3]-dioxole (14). To a solution of **12** (95.7 mg, 280 μmol) in CH_2Cl_2 (0.56 ml) was added 1,2-methylenedioxybenzene (210 μL, 1.96 mmol), tetrachlorotin (280 μL, 280 μmol, 1M solution in CH_2Cl_2) at –78 ˚C. The reaction mixture was stirred at the same temperature for 13 h. The reaction was quenched with water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with cooled 1 M HCl and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 16:1 to 8:1) to yield **14** (108 mg, 89%) as a yellow oil: ^{1}H NMR (300 MHz) δ 1.02 (d, *J*=5.8 Hz, 3H), 1.03 (d, *J*=5.8 Hz, 3H), 1.71-1.83 (m, 2H), 3.92 (s, 3H), 4.61 (d, *J*=8.0 Hz, 2H), 5.15 (s, 2H), 5.94 (s, 2H), 6.77 (d, *J*=8.0 Hz, 1H), 6.83 (dd, *J*=8.0, 1.1 Hz, 1H), 6.84 (brs, 2H), 6.92 (d, *J*=1.1 Hz, 1H), 6.97 (brs, 1H), 7.28-7.45 (m, 5H); ^{13}C NMR

(75 MHz) δ 149.7, 147.7, 147.6, 146.9, 137.2, 136.5, 135.3, 128.5, 127.7, 127.2, 119.6, 118.6, 113.7, 109.8, 107.9, 106.5, 100.9, 88.3 (x2), 71.0, 56.0, 51.2, 50.8, 13.8 (x2); EIMS *m/z* (rel. int.) 432 (58) $[M]^+$, 91 (100); HR EIMS calcd 432.1937 for $C_{27}H_{28}O_5$; found 432.1942; $[\alpha]^{19}_D$ –78.4° (*c* 0.97, $CHCl_3$).

Synthesis of (–)-talaumidin (1). To a solution of **14** (7.10 mg, 16.4 μmol) in EtOH (1.6 mL) was added 20% $Pd(OH)_2$/C (15.8 mg). This mixture was stirred vigorously under hydrogen atmosphere at rt for 10 min. After being filtered, removal of solvent afforded the residue, which was purified by prep. TLC (hexane:EtOAc, 2:1) to yield (–)-talaumidin (**1**) (4.3 mg, 77%) as a colorless oil: CD ($CHCl_3$) Δε –128.0 (238 nm), –25.4 (287 nm); ^{1}H NMR (300 MHz) 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), 6.77 (d, *J*=8.0 Hz, 1H), 6.84 (dd, *J*=8.0, 1.6 Hz, 1H), 6.84 (dd, *J*=8.0, 1.6 Hz), 6.89 (d, *J*=8.0 Hz, 1H), 6.93 (d, *J*=1.6 Hz, 1H), 6.94 (d, *J*=1.6 Hz, 1H); ^{13}C NMR (75 MHz) 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; IR (ATR) 3459 cm^{-1}; EIMS *m/z* (rel. int.) 342 (55) $[M]^+$, 190 (100); HR EIMS calcd 342.1467 for $C_{20}H_{22}O_5$; found 342.1471; Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 65.81; H, 5.94. $[\alpha]^{16}_D$ –85.2° (*c* 0.43, $CHCl_3$).

(2*S*,3*S*,4*R*)-2-(4-Benzyloxy-3-methoxyphenyl)-5-methoxy-3,4-dimethyltetrahydrofuran (15).
To a solution of **10** (105 mg, 323 μmol) in CH_2Cl_2 (2.5 mL) was added 1 M Dibal-H (hexane solution, 800 μL, 800 μmol) at –78 ˚C. After being stirred for 1 h, MeOH (1.54 mL), trimethyl orthoformate (130 μL, 1.20 μmol) and *p*-toluenesulfonic acid (205 mg, 1.08 mmol) was added. The reaction mixture was allowed to warm up to rt, and then stirred for 10 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 8:1) to yield **15** (92.7 mg, 84% in two steps) as an α- and β-methoxyl mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 7.3 Hz, 3H), 1.00 (d, *J* = 7.4 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 2.09 (ddq, *J* = 9.5, 6.3, 7.1 Hz, 1H), 2.29 (dq, *J* = 6.3, 7.4 Hz, 1H), 2.43 (ddq, *J* = 9.6, 6.3, 6.9 Hz, 1H), 2.46 (ddq, *J* = 9.5, 4.9, 7.3 Hz, 1H), 3.40 (s, 6H), 3.90 (s, 3H), 3.90 (s, 3H), 4.51 (d, *J* = 9.6 Hz, 1H), 4.54 (d, *J* = 6.3 Hz, 1H), 4.70 (s, 1H), 5.06 (d, *J* = 4.9 Hz, 1H), 5.14 (s, 4H), 6.77 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 1.6 Hz, 1H), 7.27-7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7 (x2), 147.6, 147.5, 137.3, 137.2, 135.8, 135.3, 128.5, 128.4, 127.7 (x2), 127.2 (x2), 119.3, 118.2, 113.9, 113.3, 110.9, 110.3, 109.6, 107.3, 87.7, 86.4, 71.1, 71.0, 56.0, 55.7, 55.1, 54.8, 44.1, 43.5, 42.9, 40.2, 14.4, 11.3, 10.8, 8.9; IR (ATR) 1512 cm^{-1}; EIMS *m/z* (rel. int.) 342 (84) $[M]^+$, 91 (100); HR EIMS calcd 342.1833 for $C_{21}H_{26}O_4$; found 342.1836.

2-Benzyloxy-3-methoxy-6,7-dimethylnaphthalene (16). To a solution of **15** (30.1 mg, 88.0 μmol) in CH_2Cl_2 was added methylenedioxybenzene (10.0 mL, 88.0 μmol) and *p*-toluenesulfonic acid (1.67 mg, 8.80 μmol). After be stirred at rt for 6 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 16:1) to yield **16** (15.2 mg, 59%) as a yellow oil: ^{1}H NMR (300 MHz) δ 2.36 (d, *J*=2.1 Hz, 6H), 3.97 (s, 3H), 5.25 (s, 2H), 7.04 (s, 2H), 7.05 (s, 2H), 7.27-7.49 (m, 5H);); ^{13}C NMR (75 MHz) δ 149.3, 147.9, 137.0, 133.7, 133.5, 128.6, 128.0, 127.8, 127.7, 127.3, 126.2, 126.0, 108.0, 105.9, 70.7, 55.9, 20.0, 20.0; IR (ATR) 1507 cm^{-1}; EIMS *m/z* (rel. int.) 292 (100) $[M]^+$, 201 (62), 91 (65); HR EIMS calcd 292.1464 for $C_{20}H_{20}O_2$; found 292.1469.

(2*S*,3*S*)-5-[5-(4-Benzyloxy-3-methoxyphenyl)-3,4-dimethyl-4,5-dihydrofuran-2-yl]benzo[1,3]dioxole (18). To a solution of 4-bromo-1,2-methylenedioxybenzene (27.1 μL, 225 μmol) in THF (1.0 mL) was added *n*-BuLi (141 μL, 1.6 M solution in hexane) at –78 ˚C, and the mixture was stirred for 1 h. A solution of **10** (33.3 mg, 102 μmol) in THF was added to this reaction mixture. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was stirred for 10 min. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 20:1 to 10:1) to yield **18** (11.1 mg, 23%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.0 Hz, 3H), 1.85 (d, *J*=1.4 Hz, 3H), 2.93 (dqq, *J*=8.5, 6.0, 1.4 Hz, 1H), 3.90 (s, 3H), 4.85 (d, *J*=8.5 Hz, 1H), 5.16 (s, 2H), 5.97 (s, 2H), 6.77-7.11 (m, 6H), 7.28-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.7, 147.4, 147.0, 147.0, 137.2, 135.7, 128.5, 127.8, 127.2, 126.2, 121.1, 118.2, 113.8, 109.5, 108.7, 108.1, 107.6, 101.1, 88.0, 71.1, 56.1, 51.7, 18.0, 11.0; IR (ATR) 1505 cm^{-1}; EIMS *m/z* (rel. int.) 430 (67) $[M]^+$, 149 (100); HR EIMS calcd 430.1780 for $C_{27}H_{26}O_5$; found 430.1788.

Synthesis of (2*S*,3*S*,4*S*,5*R*)-1a. To a solution of **18** (4.00 mg, 9.30 μmol) in benzene (1.0 mL) was added 20% $Pd(OH)_2$/C (1.50 mg). This mixture was stirred vigorously under hydrogen atmosphere at rt for 16 h. After being filtered, removal of solvent afforded the residue, which was purified by prep. TLC (hexane:EtOAc, 2:1) to yield **1a** (1.7 mg, 53%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (d, *J*=7.0 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 1.75 (ddq, *J*=9.6, 9.3, 6.6 Hz, 1H), 2.23 (ddq, *J*=9.6, 8.8, 7.0 Hz, 1H), 3.93 (s, 3H), 4.36 (d, *J*=9.3 Hz, 1H), 5.09 (d, *J*=8.8 Hz, 1H), 5.59 (s, 1H), 5.96 (s, 2H), 6.78 (brs, 2H), 6.88 (brs, 1H), 6.92 (d, *J*=8.1 Hz, 1H), 6.97 (d, *J*=8.1, 1.5 Hz, 1H), 7.04 (d, *J*=1.5 Hz);; IR (ATR) 3463 cm^{-1}; EIMS *m/z* (rel. int.) 342 (49) $[M]^+$, 192 (100); HR EIMS calcd 342.1463 for $C_{20}H_{22}O_5$; found 342.1463; $[\alpha]^{26}_D$ +29.0˚ (*c* 0.43, $CHCl_3$).

(2*R*,3*S*,4*S*)-1-Benzo[1,3]dioxol-5-yl-4-(4-benzyloxy-3-methoxyphenyl)-4-(*tert*-butyldimethylsilanyl-oxy)-2,3-dimethylbutan-1-one (19). To a solution of **9** (209 mg, 471 μmol) in DMF (4.7 mL) was added pyridinium dichromate (509 mg, 1.54 mmol). The mixture was stirred at rt for 2 h. The reaction was taken up with water and 2 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give an aldehyde. To a solution of this aldehyde (198 mg, 448 μmol) in THF (4.5 mL) was added anhydrous $CeCl_3$ (276 mg, 1.12 mmol) at 0 ˚C. After the mixture was cooled to –78 ˚C, 3,4-methylenedioxyphenylmagnesium bromide (1.12 mL, 1.0 M solution in THF) was added dropwise and the reaction mixture was further stirred at rt for 2 h and the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue (340 mg) was dissolved in CH_2Cl_2 and to the resulting solution was added pyridine (57.2 μL, 672 μmol) and Dess-Martin periodinane (228 mg, 538 μmol). The reaction mixture was stirred at rt for 1 h. After being taken up with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EOAc, 6:1) to yield **19** (188 mg, 71% in three steps) as a colorless oil: ^{1}H NMR (400 MHz) δ -0.10 (s, 3H), -0.29 (s, 3H), 0.82 (s, 9H), 0.83 (d, *J*=7.2 Hz, 3H), 1.23 (d, *J*=7.0 Hz, 3H), 2.09 (ddq, *J*=6.6, 6.0, 7.2 Hz, 1H), 3.52 (dq, *J*=6.6, 7.0 Hz, 1H), 3.86 (s, 3H), 4.69 (d, *J*=6.0 Hz, 1H), 5.15 (s, 2H), 6.02 (s, 2H), 6.73 (dd, *J*=8.3, 2.0 Hz, 1H), 6.79 (d, *J*= 8.0 Hz, 1H), 6.83 (d, *J*=8.3 Hz, 1H), 6.90 (d, *J*=2.0 Hz, 1H), 7.28-7.47 (m, 7H); ^{13}C NMR (100 MHz) δ 202.3, 151.4, 149.2, 148.1, 147.1, 137.2, 136.8, 132.4, 128.5, 127.8, 127.4, 124.4, 119.1, 113.2, 110.7, 108.2, 107.7, 101.7, 76.2, 71.1, 55.9, 45.8, 40.1, 25.8, 18.1, 17.2, 13.0, -4.6, -5.1; IR (ATR) 1673 cm^{-1}; EIMS *m/z* (rel. int.) 562 (1) $[M]^+$, 357 (100), 149 (77); HR EIMS calcd 562.2751 for $C_{33}H_{42}O_6Si$; found 462.2746.

Synthesis of (2*S*,3*S*,4*R*,5*S*)-1b. To a solution of **19** (9.30 mg, 16.6 μmol) in THF (500 μL) was added TBAF (20 μL, 1.0 M solution in THF). This mixture was stirred for 11 h, and quenched with H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.0 mL) and the resulting solution was cooled to –78 ˚C. To this solution was added $NaBH_3CN$ (1.8 mg, 28.6 μmol) and $BF_3{\cdot}OEt_2$ (2.0 μL, 34.4 μmol). The reaction mixture was stirred at the same temperature for 20 min. After saturated aqueous $NaHCO_3$ was added, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by prep. TLC (hexane:EtOAc, 3:1) to yield a diastereomeric mixture (6.2 mg, 63% in two steps). To a

solution of this mixture (6.20 mg, 14.4 μmol) in benzene (1.0 mL) was added 20% $Pd(OH)_2/C$ (3.10 mg). The reaction mixture was stirred vigorously under hydrogen atmosphere at rt for 10 h. After being filtered, removal of solvent afforded the residue, which was purified by prep. TLC (benzene:Et_2O, 5:1) to yield **1** (2.9 mg, 59%) and **1b** (1.5 mg, 30%). **1b** as a colorless oil: ^{1}H NMR (400 MHz) δ 0.62 (d, *J*=7.3 Hz, 3H), 0.99 (d, *J*=6.2 Hz, 3H), 2.37-2.48 (m, 2H), 3.91 (s, 3H), 4.63 (d, *J*=9.5 Hz, 1H), 5.43 (d, *J*=4.0 Hz, 1H), 5.56 (s, 1H), 5.95 (s, 2H), 6.78 (d, *J*=8.1 Hz, 1H), 6.81 (dd, *J*=8.1, 1.1 Hz, 1H), 6.84 (dd, *J*=8.1, 1.5 Hz, 1H), 6.86 (d, *J*=1.1 Hz, 1H), 6.89 (d, *J*=8.1 Hz, 1H), 6.93 (d, *J*=1.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 147.5, 146.7, 146.3, 145.1, 134.9, 134.7, 119.3, 119.1, 114.1, 108.5, 108.0, 106.9, 100.9, 85.8, 84.8, 56.0, 47.5, 43.5, 11.9, 9.6; IR (ATR) 3493, 1513 cm^{-1}; EIMS *m/z* (rel. int.) 342 (37) $[M]^+$, 192 (100). 145 (42); HR EIMS calcd 342.1467 for $C_{20}H_{22}O_5$; found 342.1476; $[\alpha]^{22}{}_D$ –46.5° (*c* 0.32, $CHCl_3$).

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22. Physical and spectroscopic data for natural (–)-talaumidin (**1**): $[\alpha]^{16}_{D}$ –81.8° (*c* 0.43, $CHCl_3$); CD ($CHCl_3$) Δε –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.
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