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ASYMMETRIC SYNTHESIS OF (+)-MACHILIN F BY UNUSUAL STEREOSELECTIVE MITSUNOBU REACTION

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Abstract – First synthesis of (+)-machilin F (**1c**) has been achieved in 16 steps as part of systematic synthetic studies on (–)-talaumidin (**1**) and its stereoisomers. The 2,3,4,5-tetrasubstituted tetrahydrofuran with the (2*S*,3*S*,4*R*,5*R*)-configuration has been constructed stereoselectively from diol **14** by Mitsunobu reaction.

Talaumidin (**1**),¹ a 2,5-biaryl-3,4-dimethyltetrahydrofuran neolignan with successive four stereogenic centers, was isolated from Brazilian plant *Aristolochia arcuata* Masters along with a series of 2,5-biaryl-3,4-dimethyltetrahydrofuran type lignans. In addition to this structural feature, **1** not only significantly promotes neurite-outgrowth but also exhibits neuroprotective activity in the primary cultured rat cortical neurons and NGF-differentiated PC12 cells.^{2,3} Thus, **1** is expected to be a lead compound for the treatment of neurodegenerative diseases such as Alzheimer's disease. While **1** possesses the four stereogenic centers on a tetrahydrofuran ring, there are the eight diastereomers without their enantiomers.

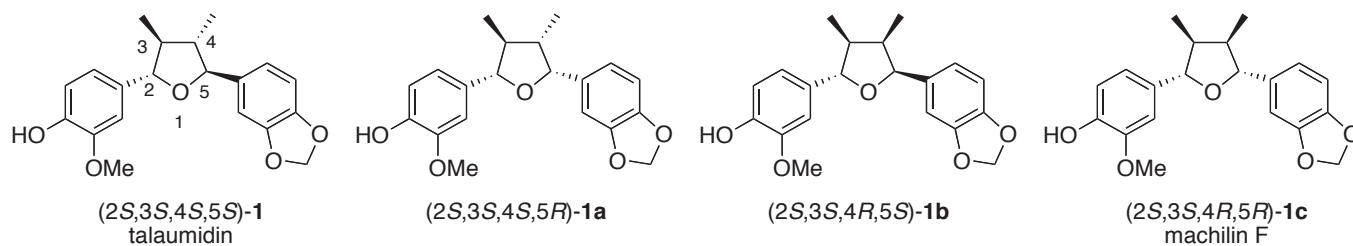
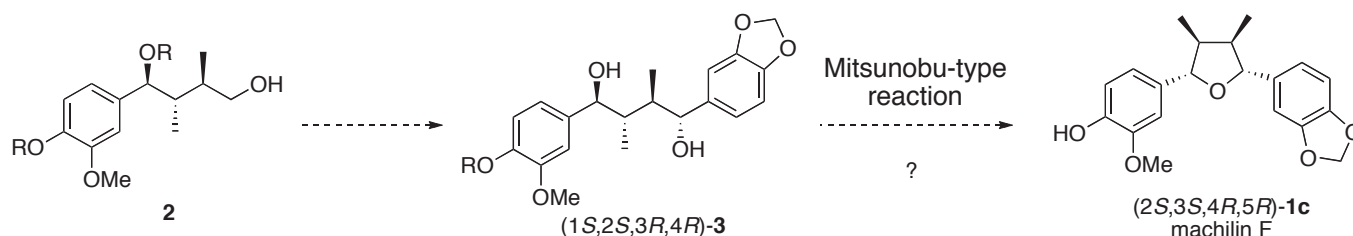


Figure 1. Talaumidin and its (2*S*,3*S*)-stereoisomers **1a-1c**

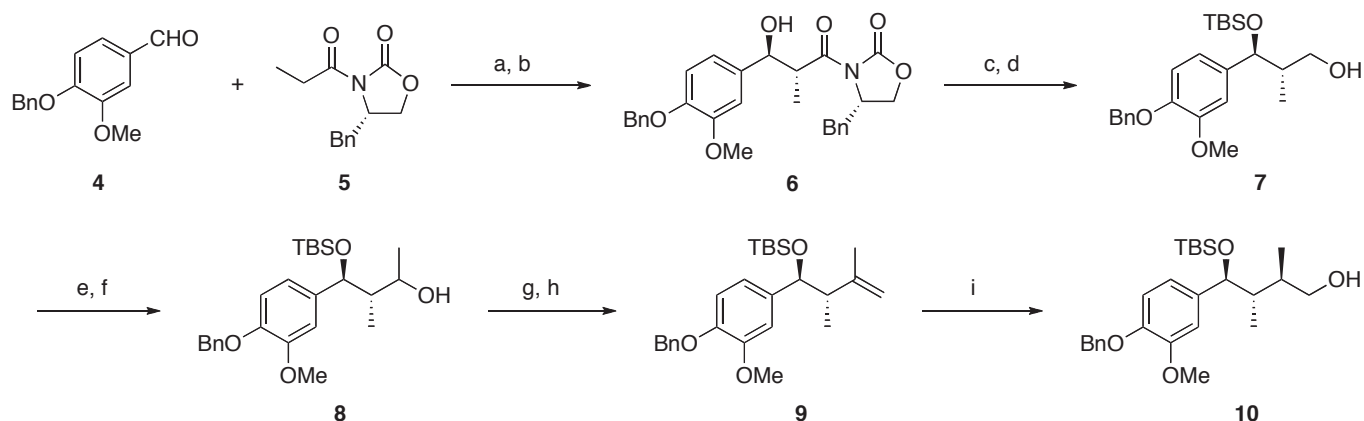
From synthetic and biological points of view, it is desirable to develop a stereoselective approach toward each synthesis of the seven diastereomers, which are specifically intended to compare the neurotrophic activity of **1** and its stereoisomers. In the preceding papers,^{4,5} we reported the stereo-controlled syntheses of (–)-talaumidin (**1**) and its stereoisomers (2*S*,3*S*,4*S*,5*R*)-**1a** and (2*S*,3*S*,4*R*,5*S*)-**1b**, but the synthesis of (2*S*,3*S*,4*R*,5*R*)-**1c**, which is the sole remaining (2*S*,3*S*)-series, has not been achieved (Figure 1). As part of our studies on the systematic synthesis of all the stereoisomers of talaumidin, we herein report the efficient synthesis of (2*S*,3*S*,4*R*,5*R*)-**1c** by applying unusual stereoselective Mitsunobu reaction to construct a tetrahydrofuran ring bearing (2*S*,5*R*)-configuration. It should be noted that the stereoisomer **1c** is a natural product, named machilin F⁶ and also 7-*epi*-austrobailignan,⁷ isolated from *Machilus thunbergii* and *Aristolochia Chilensis*, respectively and no asymmetric synthesis of (2*S*,3*S*,4*R*,5*R*)-series such as **1c** has been reported though a number of syntheses of 2,5-biaryl-3,4-dimethyl tetrahydrofuran lignans were reported.⁸⁻¹⁴

Our synthetic strategy for machilin F (**1c**) is outlined in Scheme 1. An optically active compound **2** is prepared by *anti*-selective Evans aldol reaction and diastereoselective hydroboration according to the synthetic route of **1**.^{4,5} (1*S*,2*S*,3*R*,4*R*)-Diol **3** would be derived from **2** by oxidation and Grignard reaction. We envisioned the construction of the tetrahydrofuran ring of the target molecule **1c** from diol **3** through an intramolecular Mitsunobu reaction. This strategy introduces an intriguing question concerning the stereochemical course of its reaction toward benzylic alcohols in **3**.



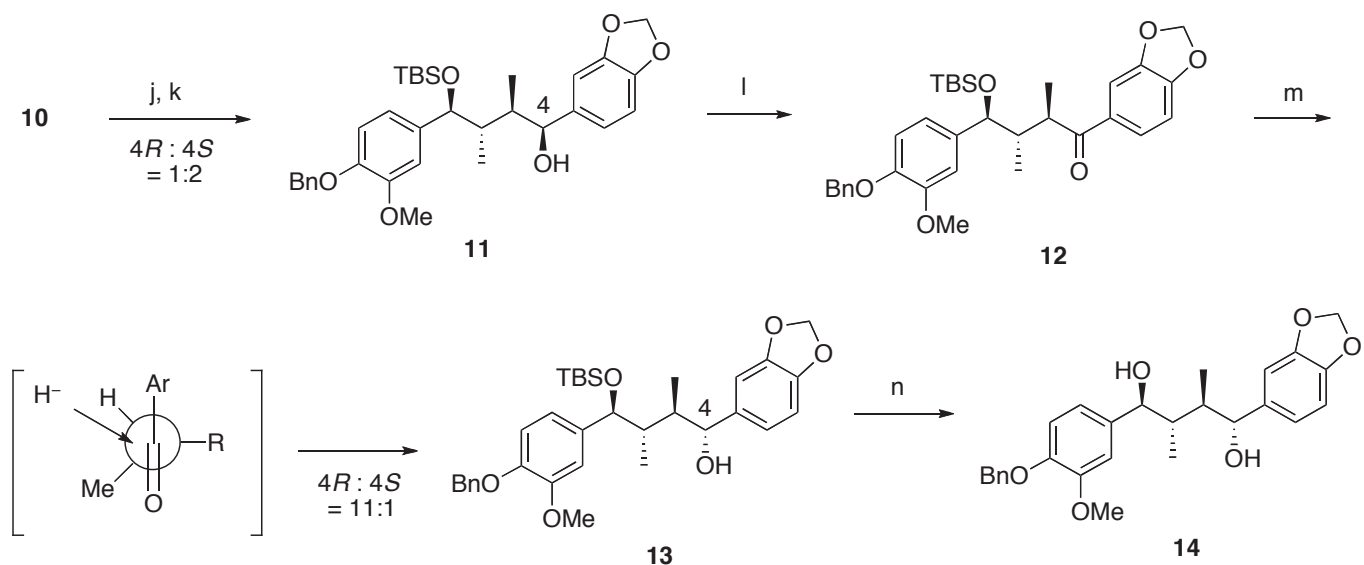
Scheme 1. Synthetic strategy for machilin F

The synthesis of machilin F began with the *anti*-selective Evans aldol reaction¹⁵⁻¹⁸ (Scheme 2). Reaction of 4-benzyloxy-3-methoxybenzaldehyde (**4**) with (+)-4-benzyl-3-propionyloxazolidinone (**5**) catalyzed by 10 mol% MgCl₂ in the presence of TMSCl and Et₃N gave the (2*S*,3*S*)-aldol **6** in 86% yield with 98% *de*. The alcohol **7** was obtained from **6** in 91% yield by TBS protection of secondary alcohol followed by reductive removal of the oxazolidinone auxiliary. Swern oxidation of **7** followed by treatment with CH₃MgBr provided secondary alcohol **8** in 89% yield. Swern oxidation of **8** gave the ketone, which was converted to the exo-methylene **9** by Tebbe olefination in 77% yield. The subsequent hydroboration of **9** with 9-BBN generated a new chiral center C-3, giving rise to the alcohol **10** in 71% yield with 99% *de*.^{5,19,20}

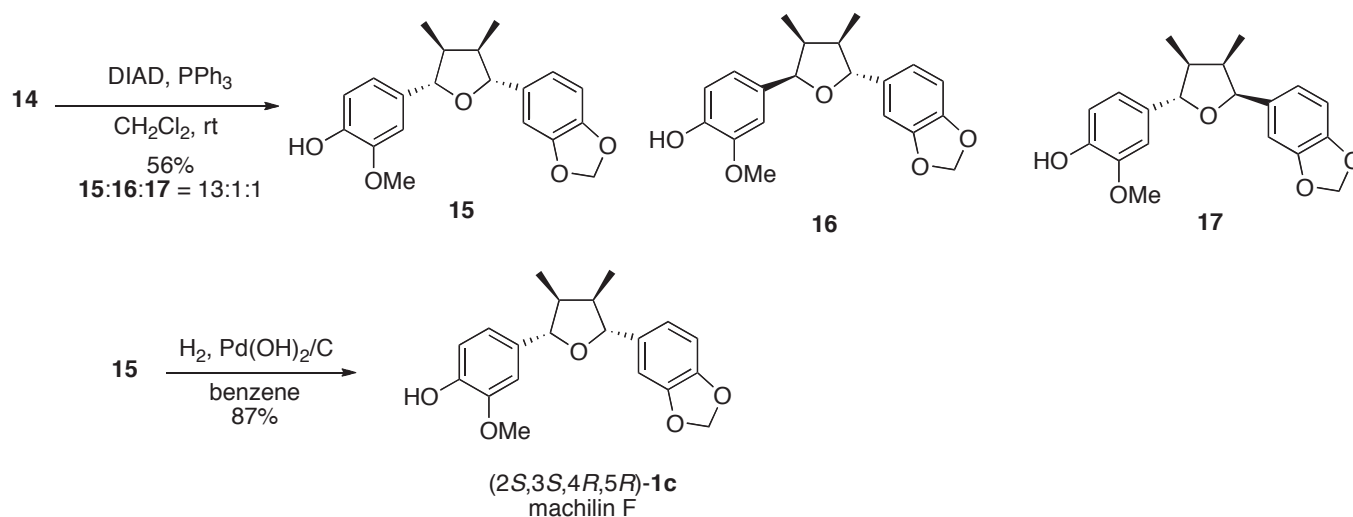


Scheme 2. Reagents and Conditions: (a) 10 mol% MgCl_2 , TMSCl , Et_3N , EtOAc , rt; (b) HF , pyridine, MeCN , rt, 86% in 2 steps, 98% *de*; (c) TBSCl , imidazole, DMF , rt; (d) LiBH_4 , MeOH , ether, rt, 91% in 2 steps; (e) $(\text{COCl})_2$, DMSO , CH_2Cl_2 , -78°C , then Et_3N , -10°C ; (f) MeMgBr , THF , 0°C , 89% in 2 steps; (g) $(\text{COCl})_2$, DMSO , CH_2Cl_2 , -78°C , then Et_3N , -10°C ; (h) Tebbe reagent, THF , -40°C , 77% in 2 steps; (i) 9-BBN, THF , 0°C , then H_2O_2 , NaOH , 0°C , 71%, 99% *de*.

Our next attention was directed toward preparation of (1*S*,4*R*)-diol and the subsequent intramolecular Mitsunobu-type cyclization. Dess-Martin oxidation of **10** gave an aldehyde, which was reacted with 3,4-methylenedioxyphenyl magnesium bromide, giving rise to the undesired diastereomer as the main product (desired 4*R*:undesired 4*S* = 1:2) (Scheme 3). The 4*S* isomer, however, could be readily converted to the necessary 4*R*-configuration with a high selectivity by Dess-Martin oxidation and the subsequent Luche reduction.⁹ This stereochemical inversion is rationalized as proceeding through Felkin-Anh fashion.



Scheme 3. Reagents and Conditions: (j) Dess-Martin periodinane, CH_2Cl_2 , rt; (k) 3,4-methylenedioxyphenyl magnesium bromide, THF , 0°C , ratio of 4*R*:4*S* = 1:2; (l) Dess-Martin periodinane, CH_2Cl_2 , rt, 71% in 3 steps; (m) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH , 0°C , 72%, ratio of 4*R*:4*S* = 11:1; (n) TBAF, THF , 0°C , 85%.



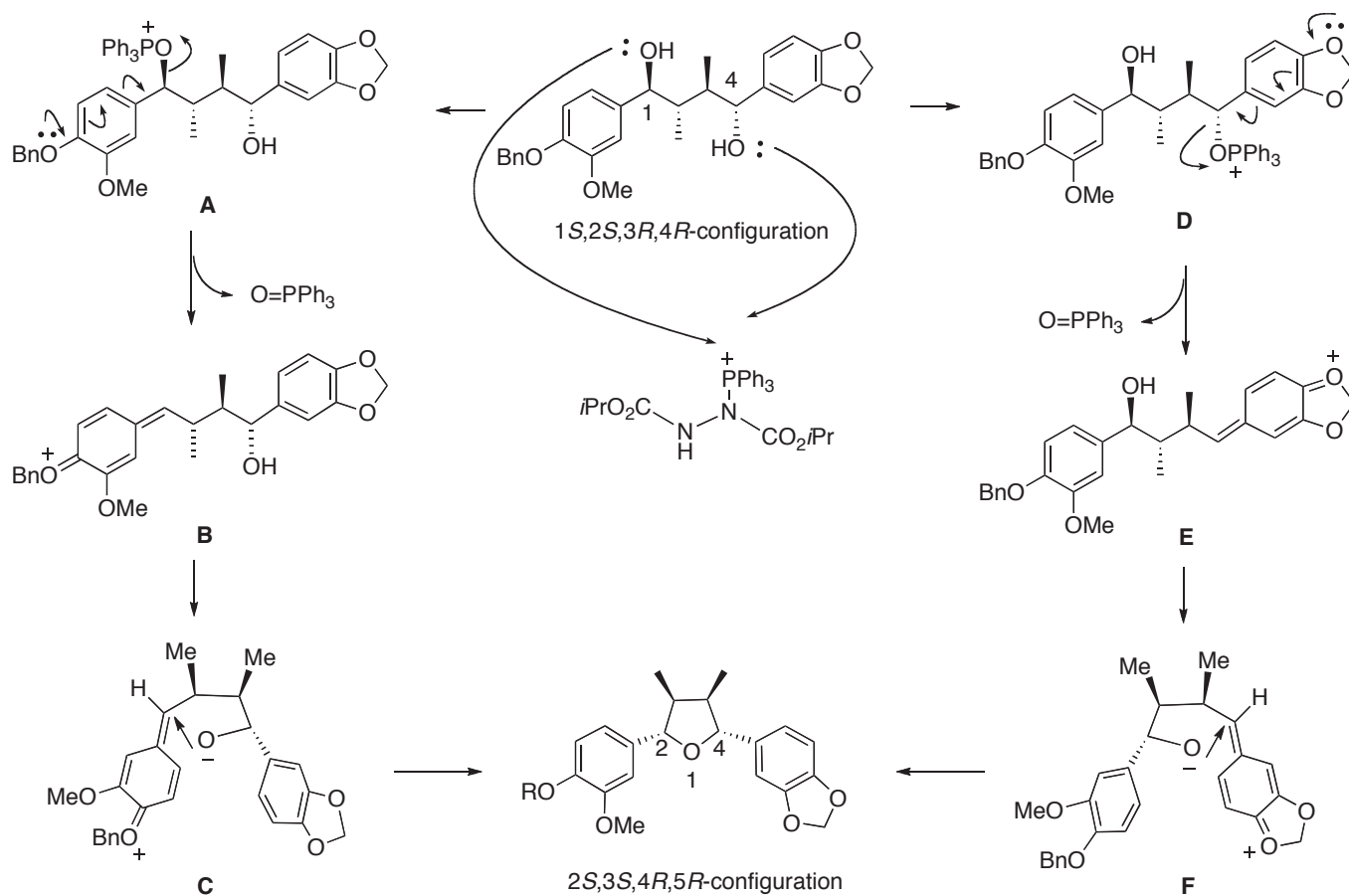
Scheme 4. Mitsunobu reaction of diol **14** and total synthesis of machilin F

The diol **14** was obtained by deprotecting the TBS group in **13** with TBAF in 85% yield. This diol **14**²¹ had all configurations necessary for the crucial Mitsunobu-type reaction to construct the tetrahydrofuran ring of **1c** (Scheme 4). Mitsunobu-type cyclization of **14** was carried out under normal conditions, with DIAD and PPh₃ in CH₂Cl₂ at room temperature. *It should be emphasized that our desired product 15 was predominantly produced along with small amounts of diastereomers 16 and 17 (15:16:17=13:1:1) in 56% yield.* It is important to note that major product **15** is the result of a net retention stereochemical process. Finally, removal of the benzyl group with Pd(OH)₂/C in benzene furnished (+)-machilin F, (2*S*,3*S*,4*R*,5*R*)-**1c**, in 87% yield. All the spectroscopic data²² (¹H NMR, ¹³C NMR, and mass spectra) of the synthetic **1c** were identical with those of natural machilin F.

The surprising stereoselectivity of this Mitsunobu reaction is rationalized as follows: normal Mitsunobu reaction occurs *via* S_N2 inversion mechanism after activation of hydroxy group.²³ In this case, the activated hydroxy group preferentially eliminates over the normal substitution pathway giving rise to quinone methides **B** and **E**, presumably due to the benzylic nature of the hydroxy group^{9,24} (Scheme 5). The steric repulsion between an aryl substituent and a methyl group results in forcing the active intermediates **B** and **E** to adopt *trans* configurations **C** and **F** to adjacent methyl group.

As results, the cyclization would proceed with net retention of the original configuration at C-1 and C-4. This mechanistic insight can account for the stereoselective formation of the same product **15** with (2*S*,3*S*,4*R*,5*R*)-configuration from **A** and **D** even if either a hydroxy group at C-1 or C-4 is activated by the Mitsunobu reaction conditions.

In conclusion, we have achieved the first asymmetric synthesis of (+)-machilin F, (2*S*,3*S*,4*R*,5*R*)-**1c**, by applying Mitsunobu reaction to the diol **14**, and thus all (2*S*,3*S*)-series of talaumidin are now prepared for assessment of comparable neurotrophic activity. Further synthetic studies on the remaining four stereoisomers with (2*S*,3*R*)-configuration are now in progress and will be reported in due time.



Scheme 5. The unusual stereoselectivity of Mitsunobu reaction

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21. Data of **14**: ^1H NMR (400 MHz, CDCl_3) δ 0.78 (3H, d, $J = 6.0$ Hz), 0.80 (3H, d, $J = 6.0$ Hz), 2.04-2.11 (2H, m), 3.90 (3H, s), 4.52 (2H, d, $J = 7.4$ Hz), 5.14 (2H, s), 5.94 (2H, s), 6.73-6.91 (6H, m), 7.27-7.43 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.9, 15.1, 41.9, 42.2, 56.0, 71.1, 100.9, 102.1, 107.0, 107.9, 110.1, 113.6, 118.9, 120.1, 127.3, 127.8, 128.5, 137.2, 137.7, 138.7, 146.7, 147.4, 147.7, 149.6; IR (ATR) 1037, 1249, 1506, 2961, 3209 cm^{-1} ; EIMS m/z (rel. int.) 450 $[\text{M}]^+$ (10), 190 (50), 149 (20), 91 (100); HREIMS calcd 450.2043 for $\text{C}_{27}\text{H}_{30}\text{O}_6$, found 450.2068; $[\alpha]_D^{20} +14.6$ (c 0.18, CHCl_3).
22. Data of **1c**: ^1H NMR (400 MHz, CDCl_3) δ 1.02 (6H, d, $J = 6.6$ Hz), 2.22-2.34 (2H, m), 3.91 (3H, s), 4.45 (1H, d, $J = 6.4$ Hz), 4.46 (1H, d, $J = 6.7$ Hz), 5.57 (1H, s), 5.96 (2H, s), 6.79 (1H, d, $J = 7.8$ Hz), 6.88 (1H, dd, $J = 7.8, 1.6$ Hz), 6.90 (1H, s), 6.94 (1H, d, $J = 1.6$ Hz), 6.97 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 12.9, 12.9, 44.5, 44.5, 55.9, 87.4, 87.5, 101.0, 106.8, 108.0, 109.0, 114.1, 119.4, 119.9, 134.0, 136.2, 145.0, 146.5, 147.0, 147.8; IR (ATR) 1038, 1247, 1516, 2964, 3481 cm^{-1} ; EIMS m/z (rel. int.) 342 $[\text{M}]^+$ (54), 190 (100), 145 (67); HREIMS calcd 342.1470 for $\text{C}_{20}\text{H}_{22}\text{O}_5$, found 342.1467; $[\alpha]_D^{20} +8.4$ (c 0.65, CHCl_3). Machilin F was reported as optically inactive form.⁶
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