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Total synthesis and morphogenesis-inducing activity of (±)-thallusin and its analogues

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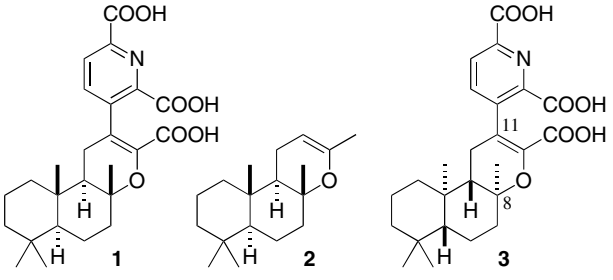
Abstract—Total synthesis of (±)-thallusin was achieved using $Hg(OTf)_2$·$PhNMe_2$-induced olefin cyclization, and Suzuki coupling with a pyridylboronic acid derivative. $Hg(OTf)_2$ also acted as a catalyst to isomerize the double bond into the more thermodynamically stable isomer when treated in toluene. Synthetic (±)-thallusin as well as an analogue showed morphogenesis-inducing activity.

Produced by a marine bacterium, thallusin is an algal morphogenesis inducer, that is, indispensable for the foliaceous morphology of macroalgae. Thallusin, which was isolated in 2005 after pursuing for more than 50 years, showed foliaceous morphology-inducing activity at the exceptionally low concentration of 1 ag/mL at the first stage. Structure **1** (Scheme 1) was established via a spectral study as well as via the single-crystal X-ray diffraction study of a thallusin derivative.[1] In 2006, Snider and co-workers achieved the total synthesis of compound **1** from sclareol oxide **2**.[2] Because compound **1** did not show the foliaceous morphogenesis-inducing activity, the absolute structure of thallusin was determined to be antipodal **3**. Thallusin can be obtained in very limited amounts from cultivation. Thus, in the present study, the total syntheses of (±)-thallusin and analogues were undertaken to allow a detailed examination of thallusin's biological activity.



Scheme 1.

In 1983, we developed $Hg(OTf)_2$ as a highly efficient olefin cyclization agent.[3] In the present study, olefin cyclization in CH_3NO_2 was the fundamental strategy to construct the carbon framework of **3**. Due to its significant π-philicity, $Hg(OTf)_2$ in toluene also acts as a catalyst to isomerize the double bond into the thermodynamically more stable isomer.[4] Suzuki coupling using a pyridylboronic acid derivative was employed for the introduction of an aromatic residue.[5] Herein, we report a total synthesis of (±)-thallusin using homofarnesyl acetate (**4**, Scheme 2) as the starting material, and the morphogenesis-inducing activities of the synthetic (±)-thallusin, its synthetic analogues, and some natural product derivatives.

Homofarnesyl acetate (**4**) was prepared in a total 91% yield from *E*,*E*-farnesol in four steps (a) bromination with PBr_3, (b) coupling of the Grignard reagent derived from chloromethyldimethylisopropoxysilane in the presence of CuI, (c) oxidative cleavage by the Tamao protocol using KH_2F, H_2O_2, and Na_2CO_3,[6] and (d) acetylation with Ac_2O in pyridine. The reaction of **4**

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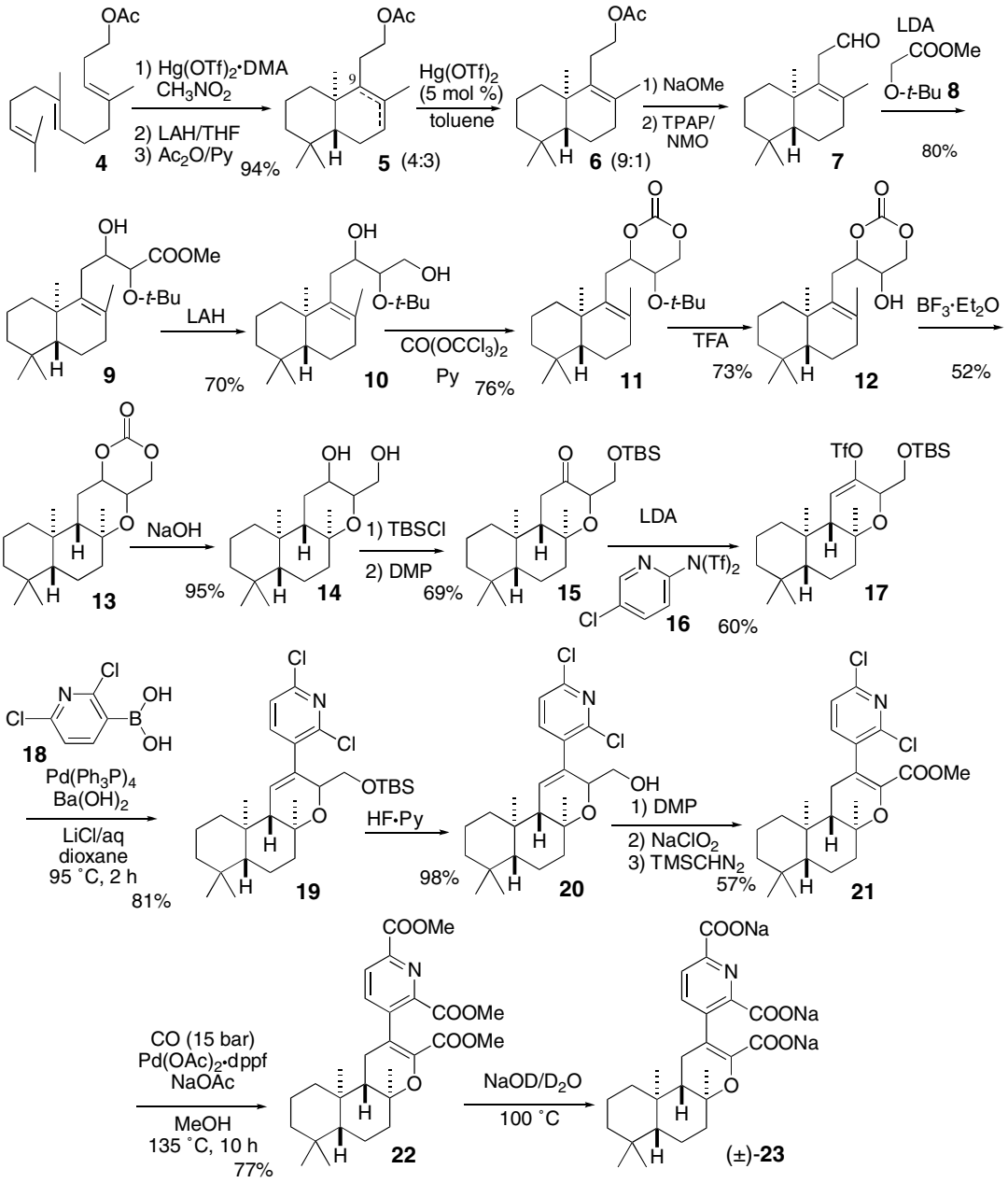


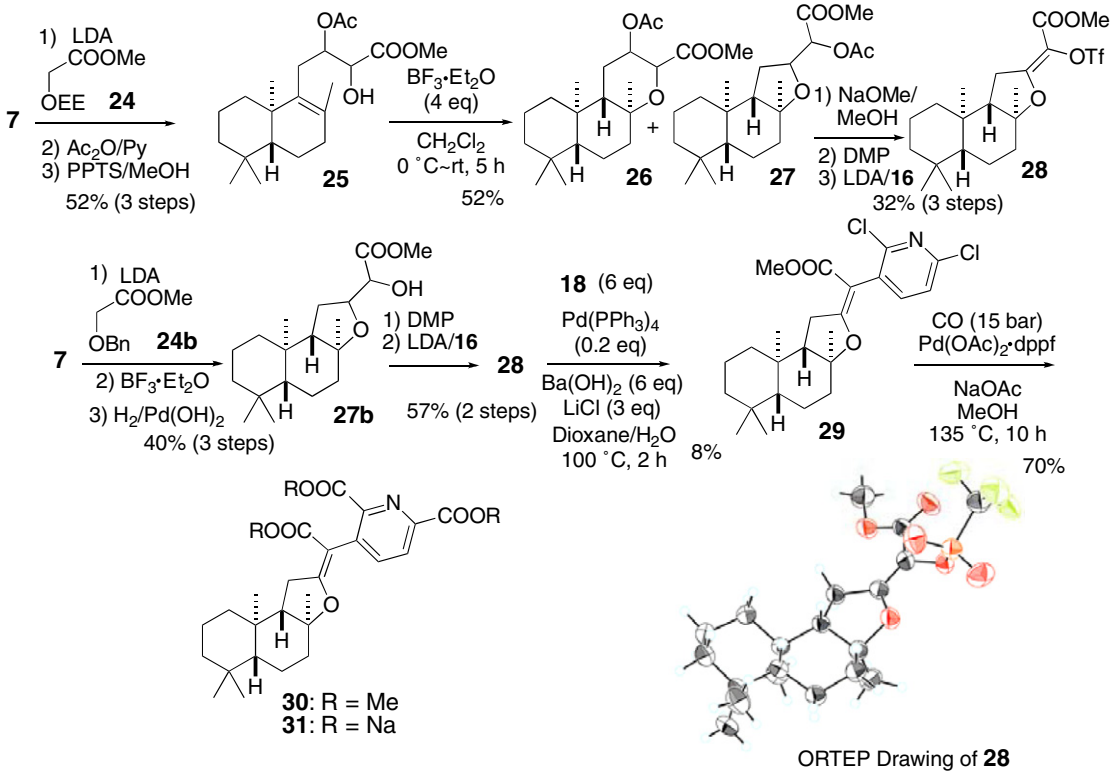
Scheme 2.

with a complex of $Hg(OTf)_2$ and *N*,*N*-dimethylaniline (1.2 equiv) was achieved in CH_3NO_2 at −20 °C for 3 h (Scheme 2). The crude extract was directly reacted with LAH in THF at 0 °C for 1 h and the resulting alcohol was acetylated with acetic anhydride and pyridine to give rise to a mixture (double bond regio-isomers as well as stereoisomers at C-9) of acetates **5** in 94% yield. To reduce the number of isomers of **5**, we first examined isomerization according to the Grieco and Nishizawa protocol using 5 mol % of $RhCl_3{\cdot}3H_2O$ in EtOH at 100 °C for 10 h.[7] However, a complex mixture was formed. Then, we examined the reaction of **5** with catalytic amount of $Hg(OTf)_2$, which has significant π-philicity.[4] The original 4:3 mixture of Δ^8-**5** and Δ^7-**5** had converted into a 9:1 mixture on treatment with 5 mol % of $Hg(OTf)_2$ in toluene at room temperature for 2 h. The 9:1 ratio seemed to be the final equilibrium composition because this ratio did not change after 24 h. The acetyl group of **6** was cleaved by the treatment with NaOMe in MeOH and the subsequent oxidation with TPAP afforded an aldehyde **7** in quantitative yield. The enolate prepared from **8**[8] with LDA in THF was treated with aldehyde **7** to give alcohol **9** as a complicated diastereomeric mixture in 80% yield. LAH reduction of **9** in THF at 0 °C afforded diol **10**, also as a complex mixture of stereoisomers, in 70% yield. Treatment of **10** with triphosgene (2 equiv) in CH_2Cl_2 in the presence of pyridine (5 equiv) at 0 °C for 2 h afforded carbonate **11** in 76% yield. The *t*-butyl group was cleaved by using 20 equiv of TFA in CH_2Cl_2 at 0 °C for 2 h to give alcohol **12** in 73% yield. Reaction of **12** with 6 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C to room

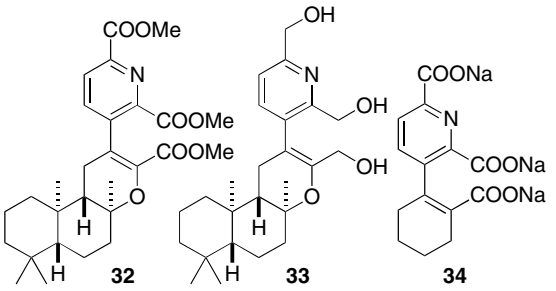
temperature for 12 h selectively afforded the expected *trans*-cyclization product **13** selectively in 52% yield.[9] Upon exposure of **13** to aqueous NaOH in dioxane at room temperature for 5 min, diol **14** was provided in 95% yield. The primary alcohol of **14** was selectively protected with a TBS group by reaction with TBSCl, DMAP, and Et_3N in CH_2Cl_2 at 0 °C for 4 h. Subsequent oxidation with Dess–Martin periodinate in CH_2Cl_2 at 0 °C to room temperature for 12 h afforded ketone **15** as a mixture of two stereoisomers in 69% yield. After the treatment of **15** with LDA at −78 °C, the resulting lithium enolate was treated with Comins reagent **16** at −78 °C to room temperature for 4 h, giving rise to the kinetically controlled enol triflate **17** in 60% yield.[10] The unstable enol triflate **17** was mixed with pyridylboronic acid **18**,[11] $Pd(Ph_3P)_4$, $Ba(OH)_2$, and LiCl in aqueous dioxane and heated to 95 °C for 2 h, giving rise to coupling product **19** in 81% yield.[5,12] The TBS group of **19** was cleaved by treatment with HF–pyridine in THF at 0 °C for 2 h to give the primary alcohol **20** in 98% yield. Compound **20** was subjected to Dess–Martin oxidation in CH_2Cl_2 at 0 °C to room temperature for 2 h, followed by $NaClO_2$ oxidation in the presence of NaH_2PO_4, and 2-methyl-2-butene in aqueous *t*-BuOH. Subsequent reaction with TMS diazomethane afforded the α,β-unsaturated ester **21** in 57% yield (total of three steps). The double bond of **20** had migrated to the conjugated position during these oxidation steps. Reaction of **21** with $Pd(OAc)_2$·dppf and NaOAc in MeOH under CO atmosphere (15 bar) at 135 °C for 10 h afforded trimethyl ester **22** in 77% yield.[13] The ^1H NMR spectrum of **22** was indistinguishable from that of the natural thallusin trimethyl ester. Finally, the methyl groups on **22** were cleaved by treatment with NaOD in D_2O at 100 °C with NMR monitoring. After 2 h, trisodium tricarboxylates of (±)-thallusin [(±)-**23**] were obtained in quantitative yield.

During this synthetic program, several problems were encountered. Initially the alkylation of aldehyde **7** was performed with an anion derived from **24** (Scheme 3).[14] After the acetylation, the ethoxyethyl protecting group was cleaved by methanolysis affording **25**. Treatment of hydroxyacetate **25** with a variety of acids afforded a mixture of **26** and **27**. Compound **27** was always the major product formed after acetyl group migration. Acetate **27** was further transformed into stable enol triflate **28** by methanolysis, Dess–Martin oxidation and treatment with LDA and then Comins' reagent **16**.[10] The structure of **28** was confirmed by a single-crystal X-ray diffraction study.[15] Alternatively, the five-membered ring ether **28** was selectively prepared by reacting benzyl ether **24b** with **7** via **27b**. Suzuki coupling of **28** with **18** afforded **29** in poor yield probably due to the electron-deficient conjugated system. In contrast, the reaction of nonconjugated enol triflate **17** with **18** occurred readily, affording **19**. Carbomethoxylation of **29** provided **30**, and alkaline hydrolysis of **30** gave the trisodium salt of thallusin isomer **31**.

Finally, the morphogenesis-inducing activities of the synthetic (±)-thallusin (**23**) and analog (±)-**31** in comparison with natural thallusin (**3**), two natural product derivatives (**32** and **33**)[1] and tricarboxylate **34** (the model compound used to develop the synthetic route,[5] Scheme 4) were investigated in *Monostroma oxyspermum*.[16] As



Scheme 3.



Scheme 4.

Table 1. Morphogenesis-inducing activity against *M. oxyspermum* after 7 days cultivation

Compound	MEC (fmol/mL)[a]
Natural Thallusin (**3**)	3.8
Synthetic (±)-Thallusin (**23**)	7.6
Natural product derivative **32**	3900
Natural product derivative **33**	15,600
31	1630
34	Inactive

[a] MEC was measured as the mean of the three independent tests.

shown in Table 1, natural thallusin (**3**) showed activity even at 3.8 fmol/mL,[1] and synthetic (±)-thallusin also showed comparable activity (at 7.6 fmol/mL). Interestingly, thallusin analog (±)-**31** showed substantial activity (at 1630 fmol/mL) that was more potent than that of trimethyl ester **32** or the reduction product **33**. Model compound **34** did not show any morphogenesis-inducing activity or growth inhibitory activity. These results suggest that the free carboxylic residues and picolinic acid moiety are indispensable for morphogenesis-inducing activity and that the diterpene skeleton also plays an important role.

Thus, we completed the total synthesis of (±)-thallusin based on the $Hg(OTf)_2$–TMU complex induced biomimetic olefin cyclization and Suzuki coupling with pyridylboronic acid derivative as the key steps, and we developed a novel $Hg(OTf)_2$-catalyzed olefin isomerization leading to thermodynamically more stable isomer by using in toluene.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.075.

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15. Crystal data for **27**: A single crystal of **27** was obtained by the recrystallization from hexane/dichloromethane. The crystal was a colorless cube (dimensions $0.20 \times 0.20 \times 0.20$ mm) and was stable at room temperature. Measurements were performed with a Mac Science (Bruker Nonius) dip image plate diffractometer using graphite-monochromated Mo K_a radiation ($l = 0.71073$ Å). Cell parameters were as follows: $a = 6.5980$ (3) Å, $b = 23.6990$ (12) Å, $c = 13.8790$ (8) Å, $b = 92.133$ (2)°, $V = 2168.7$

(2) Å^3, space group $P2_1/c$, $Z = 4$, $D_x = 1.392$ Mg m^{-3}, $m = 0.080$ mm^{-1}, $T = 298$ K. A total of 3834 reflections were collected, of which 3770 were independent. The crystal structure was solved by the direct method with SIR-97. Refinement was performed by a full matrix least-squares method on F^2 with SHELXL-97. Anisotropic refinement was applied for all non-hydrogen atoms. All hydrogens could be located by difference Fourier methods. The final values of R, wR factors and goodness-of-fit (S) were 0.0492, 0.1332, and 1.059, respectively. Crystallographic data for the structure of **27** were deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 635112. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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