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Synthesis of *ent*-Thallusin

Xiaolei Gao,[†] Yoshihide Matsuo,[‡] and Barry B. Snider*,[†]

Department of Chemistry MS 015, Brandeis University, Waltham, Massachusetts 02454-9110, and Marine Biotechnology Institute Company Ltd., 3-75-1 Heita, Hamaishi-shi, Iwate 026-0001, Japan

snider@brandeis.edu

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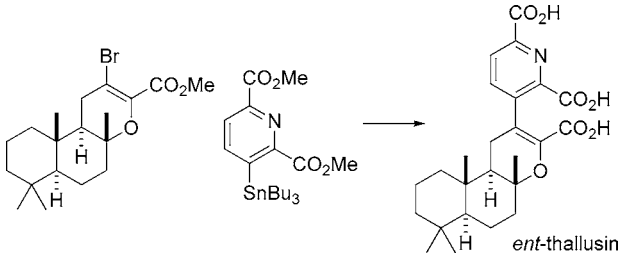
ABSTRACT



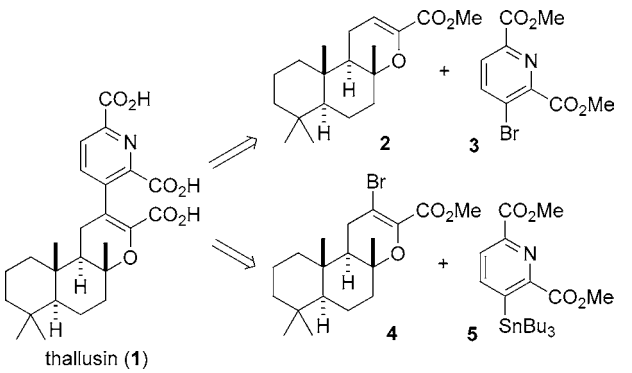
A three-step route from sclareol oxide (6) to bromo ester 4 in 53% overall yield was achieved using the efficient oxidation of an allylic bromide to an enal with bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate in DMSO. Stille coupling of bromo ester 4 with stannylpyridine 5 gave the trimethyl ester of *ent*-thallusin in 54–92% yield by the stoichiometric conversion of 4 to a vinyl palladium intermediate prior to the addition of 5 to the reaction.

Matsuo and co-workers recently reported the isolation of thallusin (**1**) from the epiphytic marine bacterium strain YM2-23 belonging to the Cytophaga−Flavobacterium−Bacteroides group that was isolated from a green alga *Monostroma* sp.[1] Pure thallusin strongly induced the differentiation of *Monostroma oxyspermum* with a minimum effective concentration between 1 fg/mL and 1 ag/mL. The structure of **1** was established by X-ray crystal structure determination of a derivative Me1H1W4 (**16**); the absolute stereochemistry was not assigned.

Thallusin (**1**) contains a terpenoid lower half attached to a 2,6-pyridinedicarboxylic acid. We thought that it should be possible to prepare **1** by either a Heck reaction of bromopyridine **3**[2] with unsaturated ester **2** or a Stille coupling of bromo ester **4** with stannylpyridine **5**, which should be readily available from **3** (see Scheme 1). Esters **2** and **4** should be readily available from sclareol oxide **6**, which can be prepared by oxidation of sclareol with $KMnO_4$ and $MgSO_4$ in acetone to give a hydroxy ketone,[3] followed by cyclization to the dihydropyran by heating in benzene at reflux.[4]

Treatment of sclareol oxide (**6**)[3,4] with 2 equiv of NBS and 2.2 equiv of $CaCO_3$ in CCl_4 or CH_2Cl_2 at 25 °C for 1 h afforded dibromide **7** in 61% yield as previously described (see Scheme 2).[5] Reaction of **7** with CsOAc (3 equiv) in DMF at 70 °C for 4 h provided allylic acetate **8** in 96% yield. Saponification of **8** with K_2CO_3 in MeOH afforded

Scheme 1. Retrosynthesis of Thallusin (**1**)



[†] Brandeis University.
[‡] Marine Biotechnology Institute.

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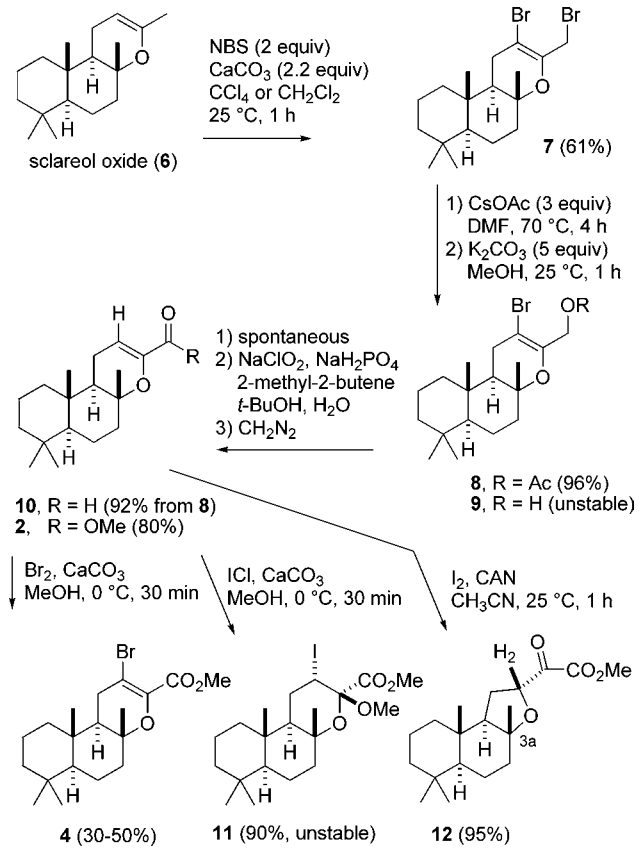
Scheme 2. Preparation of **2** and **4**



allylic alcohol **9** as a colorless oil that rapidly decomposed to a thick dark green oil. To our surprise, the NMR spectrum of this oil indicated the presence of almost pure desbromo aldehyde **10**, which was obtained in 92% yield from **8**. Presumably, protonation of the double bond of **9** followed by loss of a proton from the CH_2OH group affords a bromo enol, which loses HBr to give **10**. Oxidation of **10** with $NaClO_2$, NaH_2PO_4, and 2-methyl-2-butene afforded the carboxylic acid which was treated with CH_2N_2 to give methyl ester **2** in 80% yield.

Unfortunately, attempted Heck coupling of bromopyridine **3**[2] with ester **2** under a variety of conditions gave mainly recovered starting materials. However, reaction of **3**, methyl acrylate, Et_3N, tri-*o*-tolylphosphine, and $Pd(OAc)_2$ in CH_3CN at 90 °C for 10 h gave the Heck product methyl 3-(2,6-dicarbomethoxy-3-pyridinyl)-2-propenoate in 95% yield. This indicates that the problem in the desired Heck reaction involves ester **2**, which may be too hindered to react with the pyridylpalladium intermediate derived from **3**. Alternately, it is possible that addition of the pyridylpalladium intermediate to **2** occurs with the desired regioselectivity but that β-hydride elimination cannot occur because the hydrogen is not syn to the palladium. We therefore halogenated **2** to prepare a precursor for a Stille coupling.

Bromination of **2** with Br_2 and $CaCO_3$ in MeOH at 0 °C for 30 min afforded bromo ester **4**, which was hard to purify, in variable yield (30−50%). Reaction of **2** with ICl under similar conditions gave the unstable iodo methoxy ester **11** in 90% yield.[6] Reaction of **2** with I_2 and ceric ammonium nitrate in CH_3CN[7] provided the rearranged tetrahydrofuran α-keto ester **12** in 95% yield. Presumably, the first step involves the formation of an iodo nitrate analogous to **11**. Hydrolysis followed by intramolecular S_N2 reaction of the ϵ-hydroxy-β-iodo-α-keto ester affords **12**. The stereochemistry of **12** was established by an NOE between H_2 and the C_{3a}-methyl group.

The five-step sequence that converts dibromide **7** to bromo ester **4** was unsatisfying because of its length and the difficulty of obtaining pure **4**. Moreover, the necessity for introducing the vinylic bromide twice was aesthetically unappealing. We therefore set out to convert dibromide **7** to bromo ester **4** without proceeding through the unstable allylic alcohol **9**.

The silver-assisted oxidation of allylic bromides to aldehydes in DMSO using silver salts with nonnucleophilic counterions is well-known.[8] An oxysulfonium salt forms slowly over 1−18 h and is converted to the aldehyde by addition of Et_3N. Unfortunately, $AgBF_4$ and other silver salts with nonnucleophilic counterions are hygroscopic and hard to handle. Bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate,[9] which is easily prepared and isolated by precipitation from water, is not hygroscopic and can be easily stored and handled. We were delighted to find that reaction of dibromide **7** with 1.5 equiv of bis(2,4,6-trimethylpyridine)-silver(I) hexafluorophosphate in DMSO at 25 °C for 5 h without added base afforded β-bromo enal **13** in 87% yield (see Scheme 3). The 2,4,6-trimethylpyridine liberated in the formation of AgBr converts the oxysulfonium salt to the aldehyde and Me_2S.

Corey−Gilman−Ganem oxidation[10] of enal **13** with MnO_2, NaCN, and HOAc in MeOH afforded the desired bromo ester **4** in 99% yield. Using this sequence, bromo ester **4** is available in 53% overall yield from sclareol oxide (**6**) in only three steps.

Coupling[11] of bromopyridine **3**[2] and excess hexabutylditin catalyzed by 2 mol % $(Ph_3P)_2PdCl_2$ in toluene at reflux for 3 h afforded the requisite stannylpyridine **5** in an unoptimized 41% yield. With both bromo ester **4** and stannylpyridine **5** in hand, we turned to the crucial Stille coupling.

Initial attempts at Stille coupling of **4** and **5** were not promising. For instance, reaction of **4**, 2 equiv of **5**, 10 mol % $(Ph_3P)_4Pd$, and 1.1 equiv of CuI in DMF at 50 °C for 12

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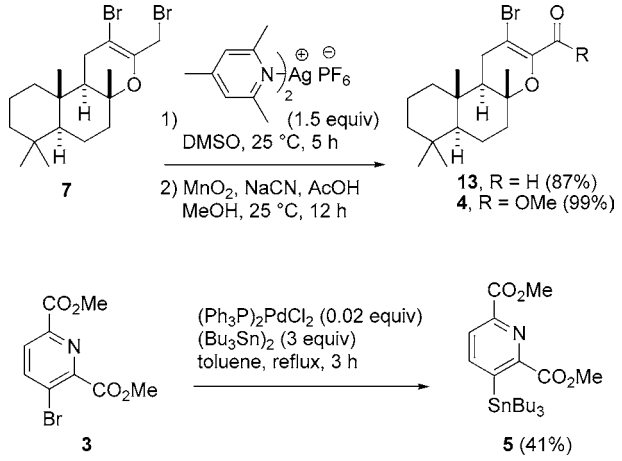
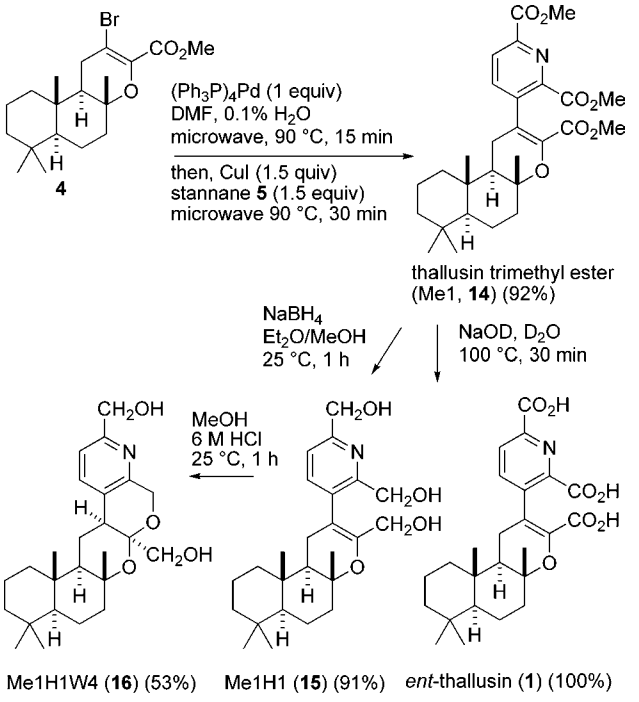
Scheme 3. Preparation of **4** and **5**



h provided only 10% of the desired Stille coupling product **14**. The major products were recovered **4** (86%) and tetramethyl 3,3′-bipyridine-2,2′,6,6′-tetracarboxylate formed by homocoupling of stannylpyridine **5**. The Pd-catalyzed formation of biaryls from stannylbenzenes has been described.[12] The formation of the bipyridine suggests that adventitious Pd(II) transmetalates with the aryl tin bond of **5** more readily than Pd(0) inserts in the vinyl bromide bond of **4**. It should be possible to prevent this by reaction of bromo ester **4** with a stoichiometric amount of Pd(0) to form the vinylpalladium intermediate before the addition of stannylpyridine **5**.

We were delighted to find that reaction of bromo ester **4** with $(Ph_3P)_4Pd$ (1 equiv) in wet DMF in a microwave oven at 90 °C for 15 min, followed by addition of CuI (1.5 equiv) and stannylpyridine **5** (1.5 equiv) and heating in a microwave oven at 90 °C for an additional 30 min, provided thallusin trimethyl ester (Me1, **14**) in 92% yield (see Scheme 4). Yields were reproducibly above 90% using 5 mg of **4** in a total of 2 mL of DMF. The use of CuI is critical[13] as is the presence of water (0.1%). Unfortunately, increasing the scale to 25 mg reduced the yield to <20% probably because of problems with effective stirring of a larger-volume heterogeneous reaction in the microwave tube. A scale-independent thermal procedure was therefore developed. Reaction of bromo ester **4** with $(Ph_3P)_4Pd$ (1 equiv) in wet DMF at 60 °C for 6 h, followed by addition of CuI (1.5 equiv) and stannylpyridine **5** (1.5 equiv) and heating at 60 °C for an additional 12 h, provided **14** (45 mg, 54%).[14] The 500 MHz ^{1}H NMR spectra of **14** in both DMSO-d_6 and $CDCl_3$ are identical to those of the natural product. The ^{13}C NMR spectral data differ by 0.2−1.6 ppm from those reported, but the natural product data were determined by analysis of HSQC and HMBC data.

Scheme 4. Synthesis of *ent*-Thallusin (**1**)



Saponification of **14** with excess NaOD in D_2O at 100 °C for 30 min followed by concentration afforded the trisodium salt of thallusin (**1**). The NMR spectral data, which are sensitive to both pH and concentration, correspond well to those previously reported.[1]

Derivatives **15** and **16** were prepared as described by Matsuo and co-workers to assign the absolute stereochemistry of thallusin. Reduction of **14** with $NaBH_4$ in 4:1 Et_2O/MeOH at 25 °C for 1 h provided triol **15** in 91% yield. Treatment of **15** with 6 M HCl in MeOH afforded **16** in 53% yield after recrystallization from ether. The optical rotations of synthetic **15** ($[\alpha]_D$ +77) and **16** ($[\alpha]_D$ +36) correspond closely in magnitude but are of opposite sign to those of natural **15** ($[\alpha]_D$ −73.5) and **16** ($[\alpha]_D$ −41). The absolute configuration of sclareol and sclareol oxide has been established as that shown.[15] Therefore, structure **1** is *ent*-thallusin and the natural product has the opposite absolute stereochemistry to that shown.

Unfortunately, diterpenes that can be converted to sclareol oxide in the opposite enantiomeric series are not readily available in high enantiomeric excess. *ent*-Sclareol has been isolated once from *Conyza trihecatactis*.[16] The related diterpene copalic acid[17] with the same absolute stereochemistry as that of thallusin can be isolated from copaiba oil in up to 46% enantiomeric excess.[18] The widely used natural

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sweetener stevioside contains a tetracyclic diterpene with the same absolute stereochemistry as that of thallusin.[19]

As reported by Matsuo,[1] triester **14** and *ent*-thallusin (**1**) have broad ^{1}H and ^{13}C NMR spectra at 25 °C due to slow rotation about the vinyl pyridine bond. The NMR spectra of **14** in $CDCl_3$ at 55 °C are much sharper, indicating that rotation is fast on the NMR time scale at this temperature. Triol **15** has a broadened ^{1}H NMR spectrum at 25 °C and shows two discrete rotamers in the ^{13}C NMR spectrum as previously reported.[1] The ^{1}H and ^{13}C NMR spectra of diol **16** are sharp because the formation of the additional ring removes conformational freedom.

ent-Thallusin (**1**) shows no morphogenesis inducing activity or growth inhibitory activity against *M. oxyspermum* in the 100 ng/mL to 1 pg/mL range after 10 days cultivation, whereas natural thallusin is active at these concentrations. A mixture of natural thallusin and *ent*-thallusin shows the same activity as thallusin by itself. These results indicate that *ent*-thallusin does not have significant biological activity.

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In conclusion, we have developed a three-step route from sclareol oxide to bromo ester **4** in 53% overall yield using the efficient oxidation of allylic bromide to enal **13** with bis-(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate in DMSO. This reagent is much easier to use than hygroscopic silver salts such as $AgBF_4$. Stille coupling of bromo ester **4** with stannylpyridine **5** gave the trimethyl ester of *ent*-thallusin in 54−92% yield by the stoichiometric conversion of **4** to a vinyl palladium intermediate prior to the addition of **5** to the reaction.

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Supporting Information Available: Full experimental details and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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