Communication

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Supporting Information Placeholder

ABSTRACT: The enantioselective synthesis of (–)-pavidolide B (**1**) was achieved in a linear sequence of 10 steps. The key steps are a) an enantioselective organocatalytic cyclopropanation; b) a radical-based cascade annulation for the regio- and diastereoselective synthesis of the highly functionalized lactone **3** bearing the characteristic tricyclic core and seven contiguous stereocenters; c) a sequential ring-closing metathesis reaction and a $RhCl_3$-catalyzed double bond isomerization to form the seven-membered D ring of (–)-pavidolide B.

(–)-Pavidolide B (**1**, Figure 1), a tetracyclic diterpenoid, was isolated in a small quantity from the marine soft coral *Sinularia pavida* by Lin and co-workers in 2012.[1] This molecule shows high selective inhibitory activity against a number of human promyelocytic leukemia cell lines.[1]

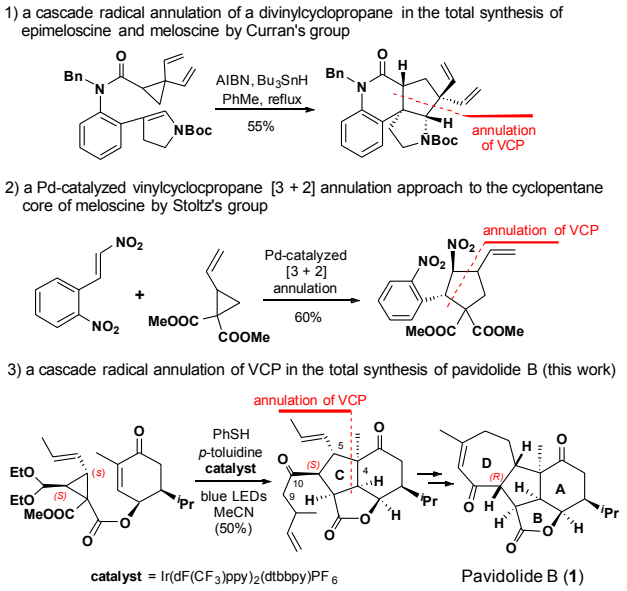


Figure 1. Application of Annulation of Vinylcyclopropane in the Total Synthesis of Complex Natural Products

The efficient synthesis of the dome-shaped 5/5/6 fused-ring system and fully functionalized C ring of pavidolide B, with seven contiguous stereocenters (one of which is quaternary), poses huge challenges, and efficient strategies for successful execution need to be designed.

Strain-release annulations of vinylcyclopropane (VCP) with alkenes (or alkynes) is a concise method for the synthesis of cyclopentanoids.[2] In 2011, Curran and coworkers[3] reported the total synthesis of meloscine and epimeloscine, featuring an intramolecular radical-based annulation reaction of VCP (Figure 1, eq 1). In the same year, Stoltz's group[4] reported the use of a palladium-catalyzed intermolecular annulation of VCP to construct the cyclopentane core of meloscine (Figure 1, eq 2). Here, we report our recent development of an asymmetric total synthesis of (–)-pavidolide B (**1**) with a cascade radical annulation of VCP[5] as the key step (Figure 1, eq 3).

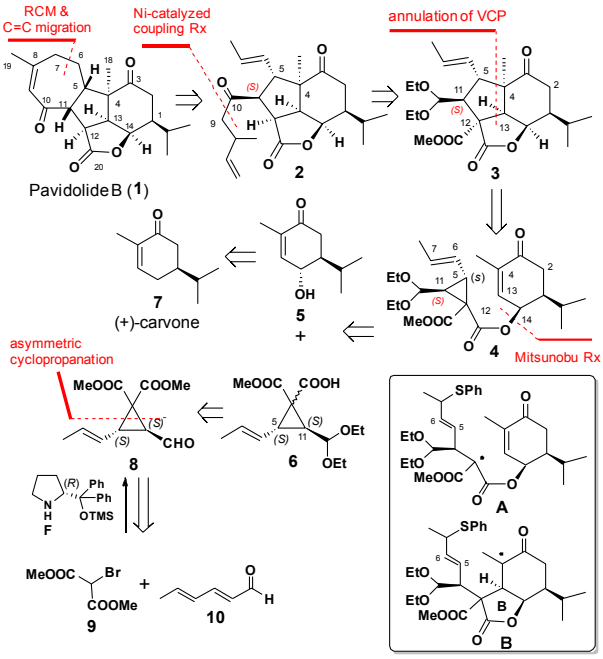
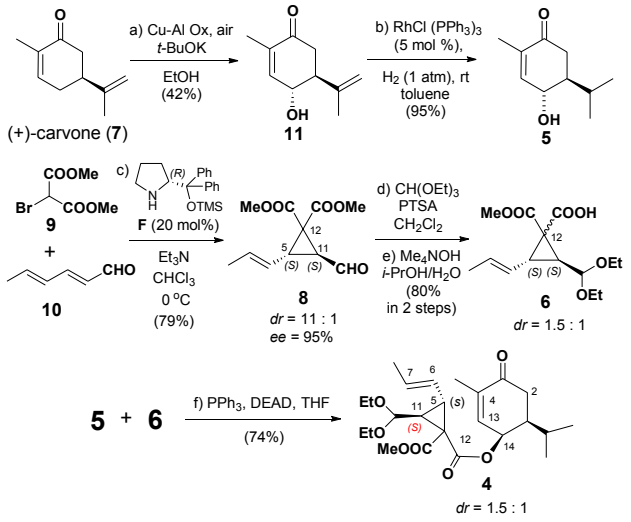


Figure 2. The Retrosynthetic Analysis of Pavidolide B (**1**)

Figure 2 shows our retrosynthetic analysis of pavidolide B (**1**). We envisioned that **1** could be synthesized from diene **2** via a ring-closing metathesis reaction[6] as the key step. Diene **2** could be obtained via a Ni-catalyzed cross-coupling reaction[7] of an aldehyde derived from acetal **3**. Examination of the structure of **3** suggests that its tricyclic core, bearing five contiguous stereogenic centers, could be installed via a VCP-based strain-release annulation of ester **4**, which could complement and reinforce the regio- and stereo-selectivity of the annulation, dictated by the linking ester. The radical cyclization process could involve addition of a thiyl radical to the vinyl group of strained VCP in substrate **4** to generate a homoallylic radical **A**. This radical could approach the enone moiety from its β face via a 5-*exo* radical conjugate addition to give a new alkyl radical **B**, which then might add back to the arylthio allylic moiety to generate product **3** after loss of the thiyl radical, enabling transfer of the C14 chirality to the incipient chiral centers at C13 and C4 (a quaternary carbon). Ester **4** was expected to be easily obtained from alcohol **5** and acid **6** via a Mitsunobu reaction.[8] The chiral alcohol **5** could be generated from (+)-carvone (**7**), with a copper–aluminium mixed oxide (Cu-Al Ox)-mediated oxidation as the key step.[9] Acid **6** could be derived from the corresponding chiral diester **8**, which could be produced from bromide **9** and aldehyde **10** in the presence of chiral amine **F**,[10] providing a concise synthesis of the requisite enantioenriched VCP-based diester **8**.

With this design in mind, we began our synthetic experiments. Scheme 1 shows our preparation of two chiral fragments, **5** and **6**, using the reported protocols. Chiral alcohol **5** was prepared from commercially available (+)-carvone (**7**) by selective Cu–Al Ox-mediated enone allylic hydroxylation[9] in the presence of oxygen in ethanol, followed by selective hydrogenation with Wilkinson's catalyst in a hydrogen atmosphere (1 atm).

Scheme 1. Asymmetric Synthesis of Precursor **4**[a]



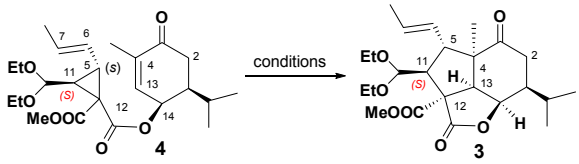
[a]Reagents and conditions: (a) Cu–Al Ox (84 mg per mmol of carvone **7**), air, *t*-BuOK (0.5 equiv), EtOH, rt, 36 h, 42%; (b) $RhCl(PPh_3)_3$ (5 mol %), H_2 (1 atm), toluene, rt, 14 h, 95%; (c) Chiral amine **F** (20 mol %), **10** (1.2 equiv), Et_3N (1.0 equiv), $CHCl_3$, 0 °C, 6 h, 79%; (d) $CH(OEt)_3$ (1.5 equiv), PTSA (0.1 equiv), CH_2Cl_2, rt, 2 h; (e) Me_4NOH (1.1 equiv), *i*-PrOH/H_2O = 10:1, rt, 12 h, 80% in two steps. (f) PPh_3 (2.0 equiv), DEAD (2.0 equiv), **6** (1.1 equiv), THF, 0 °C to 45 °C, overnight, 74%.

We next focused on the enantioselective synthesis of formyl cyclopropane **8**. The reported catalytic domino Michael/α-alkylation reaction[11] between dimethyl 2-bromo-malonate **9** and hexadienalenal **10** in the presence of chiral amine **F**[9] provided a concise and efficient route for the synthesis of **8**. The reaction of **10** with **9** in the presence of a catalytic amount of **F** cleanly provided **8** in 79% yield with 95% *ee*.

Acid **6** was then prepared as follows. Compound **8** was reacted with $CH(OEt)_3$ in the presence of *p*-toluenesulfonic acid (PTSA) in CH_2Cl_2 to afford an acetal, which was then treated with Me_4NOH in a mixed solvent of isopropanol–H_2O to give acid **6** in 80% overall yield as a pair of diastereoisomers (C-12) in a ratio of 1.5/1. The stereochemical configuration of the C12 chiral center would be ablated in the ensuing annulation reaction and we did not attempt to control this stereochemistry. A Mitsunobu reaction of alcohol **5** with acid **6** was achieved using diethyl diazodicarboxylate (DEAD) and PPh_3 in THF, affording ester **4** in 74% yield.

We next explored the synthesis of the key intermediate **3** from ester **4**. Initially, we used the protocol developed by Oshima and coworkers, involving exposure of **4** to a mixture of PhSH (1.5 equiv) and AIBN (0.3 equiv)[5a,12] in a degassed toluene at 60 °C for 9 h. Under these conditions, a trace amount of **3** was observed, and most of the substrate **4** was decomposed (Table 1, entry 1). We then performed the reactions at higher temperature under otherwise identical conditions. In these reactions, substrate **4** was completely consumed (Table 1, entries 2-4), and the desired product **3** could be isolated in 35% yield, together with the decomposition of substrate **4**, when the reaction was carried out at 120 °C for 3h (entry 4). The structure of **3** was confirmed by X-ray analysis of its analog **12** (Scheme 2). This clean control of all the relative stereochemistries at the C ring of **3** and the installation of the C4 quaternary carbon provided a basis for testing the viability of our designed approach to the synthesis of (−)-pavidolide B (**1**).

Table 1: Screening of the Reaction Conditions



entry	conditions	solvent	temp	time	yield[a]
1	PhSH, AIBN	toluene	60 °C	9 h	trace
2	PhSH, AIBN	toluene	80 °C	6 h	32%
3	PhSH, AIBN	toluene	100 °C	3 h	31%
4	PhSH, AIBN	toluene	120 °C	3 h	35%
5	PhSSPh, AIBN, UV (250 W)	toluene	25 °C	5 h	32%
6	PhSSPh, AIBN, UV (250 W), $AlMe_3$	toluene	25 °C	3 h	40-48%
7	PhSSPh, BPO,[b] UV (250 W)	toluene	25 °C	5 h	23%
8	PhSH, $Ru(bpy)_3Cl_2$, *p*-toluidine blue LEDs	MeCN	25 °C	4 h	30%
9	PhSH, $Ir(ppy)_2(dtbbpy)PF_6$ *p*-toluidine, blue LEDs	MeCN	25 °C	5 h	47%
10	PhSH, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ *p*-toluidine, blue LEDs	MeCN	25 °C	2 h	50%[c]
11	benzyl mercaptan, *p*-toluidine, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, blue LEDs	MeCN	25 °C	5 h	23%
12	methyl thiolglycolate, *p*-toluidine, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, blue LEDs	MeCN	25 °C	2 h	25%

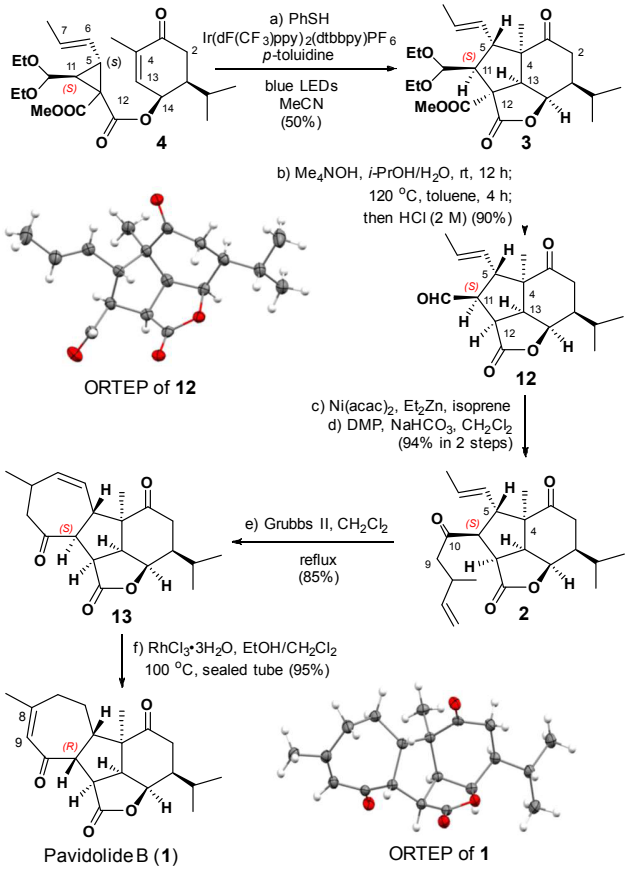
[a]Isolated yield; [b]BOP = benzoyl peroxide; [c]Reaction conditions: **4** (0.5 mmol), PhSH (1.1 equiv), *p*-toluidine (0.5 equiv), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (0.5 mol %) in CH_3CN (30 mL) at 25 °C for 2 h.

We then performed systematic screening to identify the reaction parameters (thiyl radical precursor, radical initiator, solvent, and temperature) that would affect the annulation of **4**; the results are listed in Table 1. Because of the thermal instability of the VCP[13] moiety in **4**, we tested the reaction at room temperature under irradiation with UV light[14] (250 W) (entries 5–7). The desired annulation of **4** proceeded when the reaction was performed in the

presence of PhSSPh and AIBN under irradiation with UV light in toluene at 25 °C (entry 5). Under these conditions, the reaction was complete within 5 h, giving product **3** in 32% yield. The use of $AlMe_3$[5b,15] as a Lewis acid improved the yield of **3** to 40-48% (entry 6). However, the yield of **3** was variable using $AlMe_3$, which is sensitive to moisture and its quality cannot be controlled, suggesting that more reliable reaction conditions had to be identified for achieving the total synthesis.

We tested the key annulation reaction in the presence of transition-metal catalysis under visible light.[16] Several commercially available catalysts[17] were screened (entries 8-12). The use of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$[18] (0.5 mol%) as the catalyst (0.5 mol %) gave the best result, and product **3** was obtained in 50% yield under irradiation with low-energy blue-light-emitting diodes (LEDs) (entry 10).

Scheme 2. Asymmetric Total Synthesis of Pavidolide B (**1**)[a]



[a]Reagents and conditions: (a) PhSH (1.1 equiv), *p*-toluidine (0.5 equiv), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (0.5 mol %), MeCN, blue LEDs, 2 h, 50%; (b) Me_4NOH (1.1 equiv), *i*-PrOH/H_2O = 10:1, rt, 12 h; then toluene, 120 °C, 4 h, then HCl (2.0 M), THF, rt, 2 h, 90%; (c) $Ni(acac)_2$ (20 mol %), isoprene (4.0 equiv), Et_2Zn (2.4 equiv), THF, rt, 4 h; (d) $NaHCO_3$ (5.0 equiv), Dess-Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 4 h, 94% in two steps; (e) Grubbs II catalyst (20 mol %), CH_2Cl_2, reflux, 6 h, 85%; (f) $RhCl_3$•$3H_2O$ (20 mol %), EtOH/CH_2Cl_2 = 6:1, 100 °C, sealed tube, 5 h, 95%.

To gain insights into this highly stereoselective reaction for forming four stereocenters (C4, C5, C12, and C13) in **3**, we performed density functional theory calculations for the annulation of **4**[19] (the located transition states and intermediates of this radical cyclization are given in the Supporting Information). The results show that the rate determining step of this cascade reaction is 5-*exo* conjugated addition of a radical in intermediate **A** to its enone moiety to give the kinetically favored intermediate **B** (Figure 2), with an activation Gibbs free energy of 17.3 kcal/mol from (12*S*)-**4**, or 14.3 kcal/mol from (12*R*)-**4**, forming the two contiguous stereogenic centers of at C12 and C13. Formation of the chiral centers at C5 and C4 proceeded via 5-*exo* radical addition of intermediate **B** to the allyl sulfane moiety to generate, after loss of the thiyl radical, product **3**, bearing a thermos-dynamically stable *trans* alkene.[20]

With **3** in hand, we then concentrated on the total synthesis of pavidolide B (**1**). Hydrolysis of the ester group in **3** was achieved by exposure of **3** to a mixed solvent of isopropanol–H_2O in the presence of Me_4NOH at room temperature. The resultant acid was heated at 120 °C in toluene to initiate a thermal decarboxylation; the resultant mixture was treated with a HCl solution to hydrolyze its acetal, giving rise to aldehyde **12** in 90% yield. For the synthesis of diene **2**, aldehyde **12** was coupled with isoprene in the presence of $Ni(acac)_2$ and Et_2Zn[7] in THF at room temperature, and the resultant homoallylic product, without purification, underwent a DMP-oxidation to give diene **2** in 94% yield in two steps. It is worth mentioning that when triethylborane[7b] was used as the reducing agent, the Ni-catalyzed homoallylation reaction of aldehyde **12** did not proceed.

To complete the total synthesis, diene **2** was annulated with Grubbs II catalyst to give product **13** in 85% yield, building the tetracyclic core of pavidolide B (**1**). Subsequent isomerization of the γ,δ-unsaturated enone in **13** to the more stable α,β-unsaturated enone in pavidolide B (**1**) and epimerization of the C11 stereocenter were accomplished by treatment of **13** with $RhCl_3$•$3H_2O$ (20 mol %)[21] in absolute ethanol (a small amount of CH_2Cl_2 was used as a co-solvent) at 100 °C for 5 h, giving the natural product pavidolide B (**1**) in 95% yield (verified by X-ray crystallography,[22] $[\alpha]_D^{26}$ = - 146, c = 0.42 in MeOH). The synthesized pavidolide B was tested against a panel of tumor cell lines including HL-60, HepG2, A549, and showed selective inhibition against A549 with IC_{50} of 45μg/mL.

In summary, the asymmetric total synthesis of pavidolide B (**1**) was achieved for the first time in 10 linear steps with 16% overall yield. The key step is a radical-based cascade annulation of ester **4**. This reaction assembles the fully functionalized tricyclic C ring of pavidolide B with formation of two C–C bonds, two rings in a single step, and four stereocenters including the C4 quaternary center.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, compound characterization data, and the X-ray crystallographic data for compound **1** (CIF) and **12** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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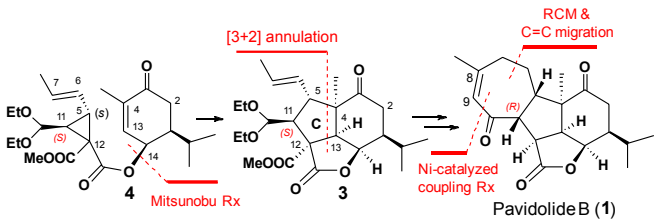
(23) CCDC 1562355 contains the supplementary crystallographic data for pavidolide B and is available free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

TOC


[3+2] annulation
RCM &
C=C migration
Mitsunobu Rx
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coupling Rx
4
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Pavidolide B (1)