JOC The Journal of Organic Chemistry

JAMES COOK UNIVERSITY AUSTRALIA

Subscriber access provided by JAMES COOK UNIVERSITY LIBRARY

Article

Asymmetric Total Synthesis of (–)-Pavidolide B via a Thiyl-Radical-Mediated [3+2] Annulation Reaction

Pengpeng Zhang, Yuan-He Li, Zhiming Yan, Jianxian Gong, and Zhen Yang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02230 • Publication Date (Web): 21 Nov 2019

Downloaded from pubs.acs.org on November 23, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Asymmetric Total Synthesis of (–)-Pavidolide B via a Thiyl-Radical-Mediated [3+2] Annulation Reaction

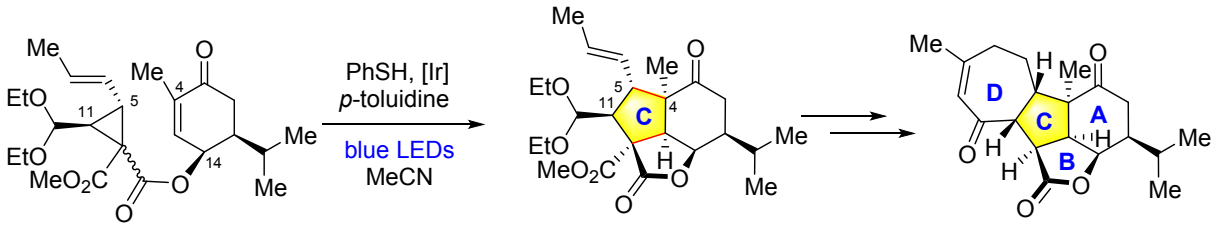
Pengpeng Zhang,[†] Yuanhe Li[‡], Zhiming Yan,[†] Jianxian Gong,[†,§] and Zhen Yang,*[†,‡,§]*

[†]*Key Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China*

[‡]*State Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry and the Peking University, Beijing 100871, China*

§Laboratory for Marine Drugs and Bioproducts of Qingdao National Laboratory for Marine Science and Technology, Qingdao 266237, China

RECEIVED DATE



- Mild visible-light conditions
- Fully functionalized five-membered ring C
- Two C-C bonds, two rings and four stereocenters

10 LLS
16% overall yield
300 mg synthesized

ABSTRACT: The development of an efficient strategy for the asymmetric total synthesis of the bioactive marine natural product (–)-pavidolide B is described in detail. The development process and detours leading to the key thiyl-radical-mediated [3+2] annulation reaction, which constructed the central C ring with 4 contiguous stereogenic centers in one step, is depicted. Subsequently, the seven-membered D ring is constructed via a ring-closing metathesis reaction followed by a Rh(III)-catalyzed isomerization. This strategy enables the total synthesis of (–)-pavidolide B in a longest linear sequence of 10 steps.

INTRODUCTION

The cembranoid family is one of the largest and most diverse marine metabolite families. To date, hundreds of cembrane-based derivatives have been isolated from marine soft corals, particularly of the genera *Sinularia* and *Sarcophyton*.[1] In 2012, a structurally diverse set of cembranoids, namely, pavidolides A–E (**Figure 1**), were isolated from the marine soft coral *Sinularia pavida*.[2] A preliminary biological study with a panel of tumor cell lines indicated that tetracyclic diterpenoid (–)-pavidolide B (**1**) shows selective inhibition against human promyelocytic leukemia cell line HL-60 (IC_{50} = 2.7 μg/mL).[2] Structurally, (–)-pavidolide B (**1**) possesses an unprecedented highly rigid 6,5,7-tricarbocyclic core, which includes a fully functionalized five-membered C-ring, seven contiguous stereocenters, and a quaternary bridgehead carbon center. The stereocontrolled construction of such a highly functionalized five-membered ring system with five contiguous stereogenic centers is the primary synthetic challenge for the total synthesis of this natural product. Herein, we describe our efforts to develop a concise strategy for the asymmetric total synthesis of (–)-pavidolide B (**1**),[3a] which was enabled by a thiyl-radical-mediated intramolecular [3+2] annulation reaction of a vinylcyclopropane (VCP) under visible-light irradiation. More recently, Ding and coworkers also realized the total synthesis of (–)-pavidolide B by constructing the 6,5,7-tricarbocyclic core through a pinacol rearrangement[3b] and ring contraction strategy[3c] respectively.

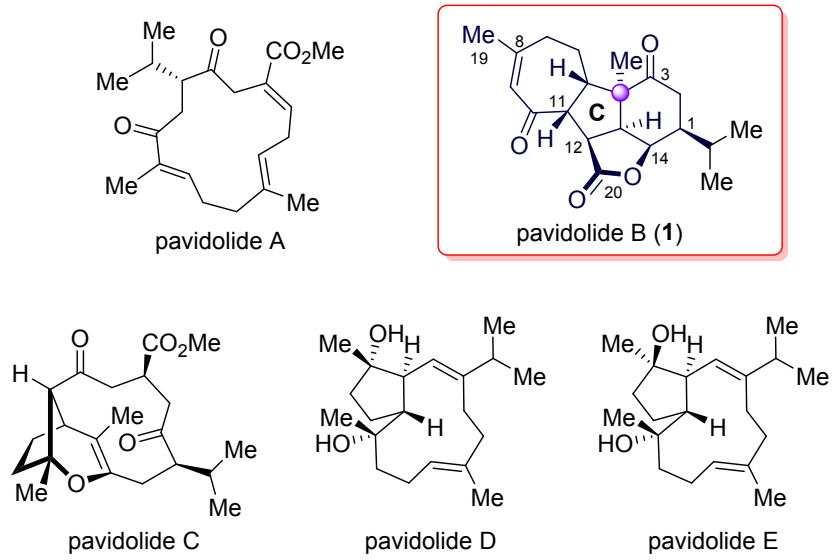


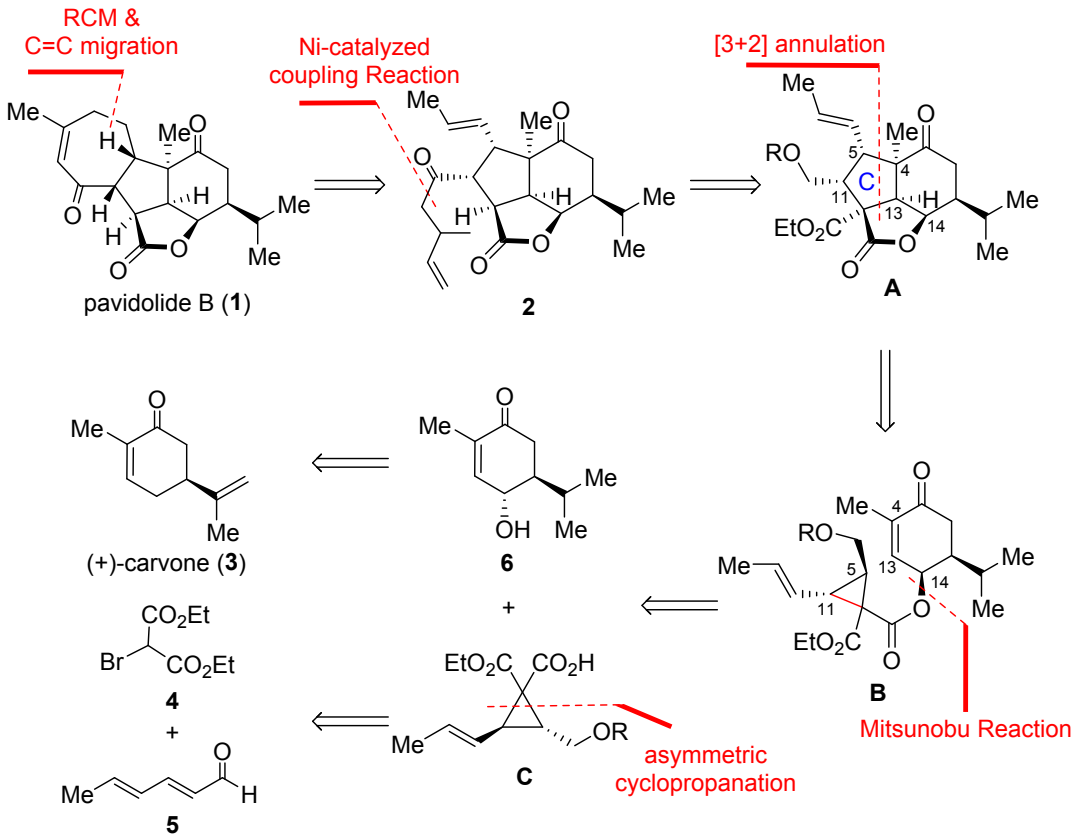
Figure 1. Structures of pavidolides A–E.

RESULTS AND DISCUSSION

Retrosynthetic Analysis of Pavidolide B (1)

Given the concise and powerful features of the [3+2] annulation reaction of VCPs[4] with alkenes for the stereoselective construction of highly substituted cyclopentanoids, we envisaged applying this reaction as the key disconnection strategy for the stereoselective construction of the 5-membered ring core of pavidolide B (**1**). To get the correct stereochemistry at C4 and C13, the VCP part needs to approach the enone from the top side, which is, however, hindered by the isopropyl group. To overcome the steric effect of *i*Pr group, the intermolecular [3+2] annulation reaction was designed as an intramolecular reaction with an ester linker, where the stereochemistry of C14 controls the stereoselectivity at C4 and C13.

Scheme 1. Retrosynthetic Analysis of Pavidolide B (**1**)



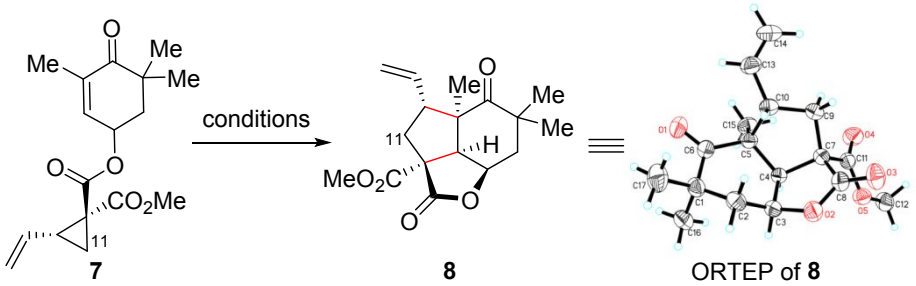
Scheme 1 illustrates our retrosynthetic analysis. We envisioned that **1** could be made from compound **2** via a ring-closing metathesis (RCM) reaction[5] followed by a double-bond migration reaction[6]. The compound **2**, in turn, could be assembled via a Ni-catalyzed cross-coupling reaction[7] of an aldehyde derived from compound **A**. We expected that compound **A** bearing the core structure of the five-membered ring could be generated directly from its corresponding VCP-tethered cyclohexanone (**B**) through an intramolecular [3+2] annulation reaction described above. The correct stereochemistry of C14 in substrate **B** could be made easily from alcohol **6** and acid **C** via a Mitsunobu reaction. Enantiopure alcohol **6** could then be prepared stereoselectively from (+)-carvone (**3**), whereas acid **C**

could be prepared from bromide **4** and aldehyde **5** via a reported protocol for organocatalyzed asymmetric cyclopropanation[8].

Model Study of the [3+2] Annulation Reaction

With this proposed route in mind, we first conducted a model study to test the key reaction by using **7** as a simplified substrate, which can be easily prepared in one step from known compounds[9] (see Supporting Information for details). In the beginning, we attempted Pd-catalyzed [3+2] cycloaddition reaction[4b,4e,10] with Pd(0) and various phosphine ligands (Table 1). When P(*n*-Bu)$_3$ and dppf (1,1'-bis(diphenylphosphino)ferrocene) were used as ligands, no desired product was observed (entries 1–2). When dppe (1,2-bis(diphenylphosphino)ethane) ligand was used, a small amount of desired product **8** was detected (entry 3); however, most of the substrate decomposed, which may be due to the coordination of Pd to the enone double bond followed by cleavage of the C–O bond. Lowering the temperature prevented the decomposition of the starting material but no desired product was formed (entry 4). To promote the selective coordination of Pd to the VCP double bond over the enone double bond and probably reducing substrate decomposition, more hindered Trost ligand[10] was used, but no reaction occurred (entry 5).

Table 1. Model Study of [3+2] the Annulation Reaction



entry	conditions	temp	result[a]
1	$Pd_2(dba)_3 \cdot CHCl_3$, P(*n*-Bu)$_3$, DCM	20 °C to reflux	no reaction
2	$Pd_2(dba)_3 \cdot CHCl_3$, dppf, DCM	30 °C	decomposed
3	$Pd_2(dba)_3 \cdot CHCl_3$, dppe, DCM	30 °C	trace[b]
4	$Pd_2(dba)_3 \cdot CHCl_3$, dppe, DCM	10 °C	no reaction
5	$Pd_2(dba)_3 \cdot CHCl_3$, Trost ligand[c], DCM	30 °C	no reaction
6	PhSH, ABVN[d], toluene	80 °C	30%

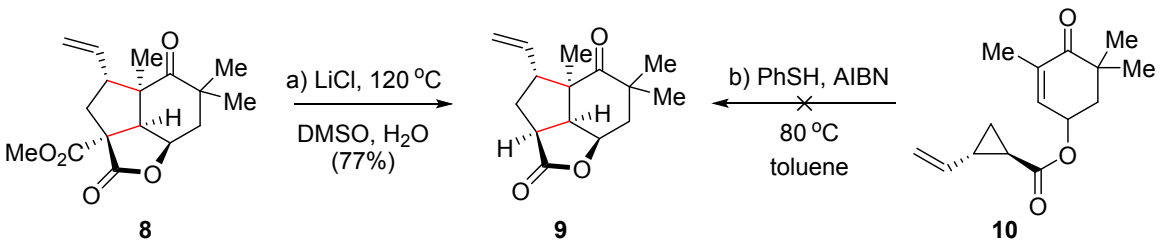
7	PhSSPh, AIBN, sunlamp, toluene	50 °C	23%
8	PhSH, AIBN, toluene	80 °C	47%[e]

[a]Isolated yield; [b]Reagents and conditions: **7** (0.5 mmol), solvent (0.05 M for substrate), catalyst (5 mol%), ligand (10 mol%), under a nitrogen atmosphere for 3 h; [c]Trost ligand = (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*'-bis(2'-diphenylphosphinobenzoyl); [d]AVBN = 2,2'-Azobis (2,4 dimethylvaleronitrile); [e]Slow addition of the mixture of PhSH (1.2 equiv) and AIBN (0.3 equiv) in toluene to the substrate.

Facing the difficulty with Pd catalyzed cyclization methods, we turned our attention to thiyl-radical mediated reactions. Fortunately, treating substrate **7** with PhSH and ABVN,[11] we successfully obtained the desired product **8** with 30% yield (entry 6). The relative stereochemistry of newly formed 4 stereocenters was confirmed to be consistent with that in natural product **1** by X-ray crystallography. Modification of the procedure[12] by slow addition of the mixture of PhSH and AIBN in toluene to the solution of the substrate at 80 °C increased the yield of product **8** to 47% (entry 8). Subsequently, product **8** underwent Krapcho decarboxylation[13] smoothly at 120 °C to give compound **9** in 77% yield (Scheme 2), which indicate the applicability of those reactions in total synthesis of pavidolide B.

To avoid the need of following high-temperature decarboxylation reaction, we investigated whether the mono-ester substrate could also work in this [3+2] annulation reaction. Mono-ester **10** was synthesized from simple starting materials[14]. However, under the similar reaction conditions (Scheme 2), only trace amounts of desired product **9** were detected, and further optimization of the reaction conditions did not give better results. This poor yield may due to the decomposition of the highly reactive radical intermediate from **10** without stabilization of the diester.

Scheme 2. Synthesis of Compound **9**[a]

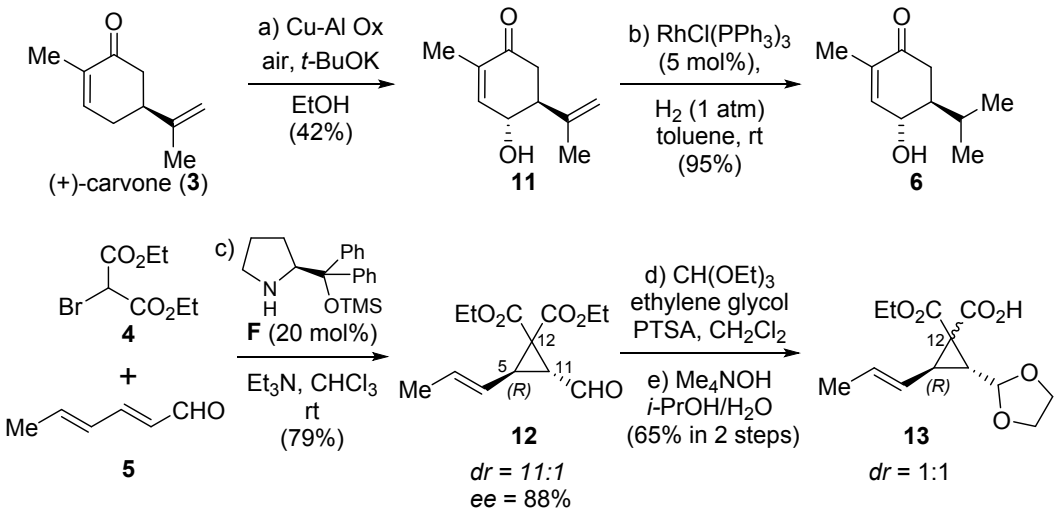


[a]Reagents and conditions: (a) LiCl (5.0 equiv), H_2O (10.0 equiv), DMSO, 120 °C, 5 h, 77%; (b) PhSH (1.2 equiv), AIBN (0.3 equiv), toluene, 80 °C, trace.

Preparation of Asymmetric Precursors

The success of the model study with substrate **7** provided a basis for testing the viability of our designed approach for the synthesis of **1**. Our total synthesis began with the preparation of two enantiopure fragments, **13** and **6** as shown in Scheme 3. The preparation of enantiopure alcohol **6** commenced from commercially available (+)-carvone (**3**), which was subjected to enone allylic hydroxylation catalyzed by a copper-aluminum mixed oxide[15] in the presence of oxygen in ethanol to give alcohol **11** in 42% yield, followed by selective hydrogenation with Wilkinson's catalyst[16] to selectively remove the terminal double bond in excellent yield.

Scheme 3. Asymmetric Synthesis of Alcohol **6** and Acid **13**[a]



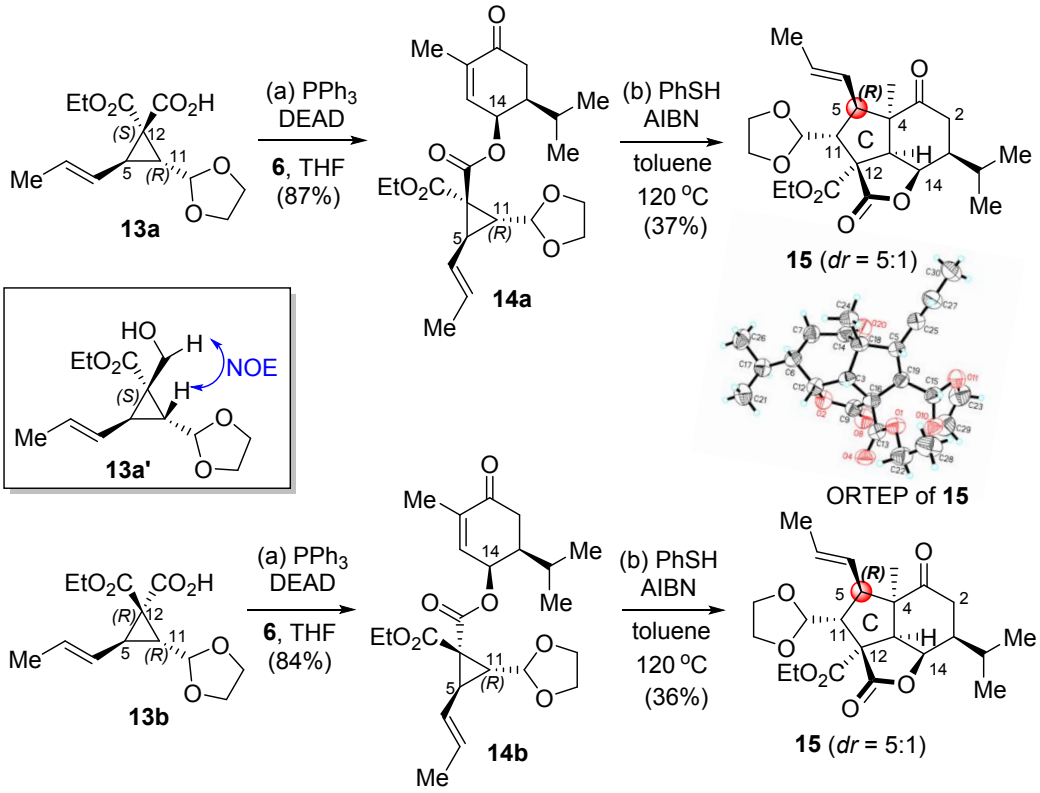
[a]Reagents and conditions: (a) Cu–Al Ox (84 mg per mmol of carvone **3**), air, *t*-BuOK (0.5 equiv), EtOH, rt, 36 h, 42%; (b) $RhCl(PPh_3)_3$ (5 mol%), H_2 (1 atm), toluene, rt, 14 h, 95%; (c) (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine **F** (20 mol%), **5** (1.2 equiv), Et_3N (1.0 equiv), $CHCl_3$, rt, 6 h, 79%; (d) $CH(OEt)_3$ (1.5 equiv), ethylene glycol (2.0 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, 65% for two steps.

Aldehyde **12** was synthesized in 79% yield by following a reported protocol[8], and then protected with ethylene glycol in the presence of PTSA and $CH(OEt)_3$ in CH_2Cl_2. The hydrolysis of the ethyl-ester with Me_4NOH in a mixed solvent of *i*-PrOH and H_2O afforded mono-acids **13** in 80% overall yield as a pair of diastereomers at C12 (**13a**:**13b** = 1:1). As the C12 stereogenic centre will be rebuilt in the following [3+2] annulation reaction, we envisioned that this lack of diastereoselectivity would not affect the asymmetric total synthesis of our final target.

The control of C5 stereochemistry in the [3+2] Annulation Reaction

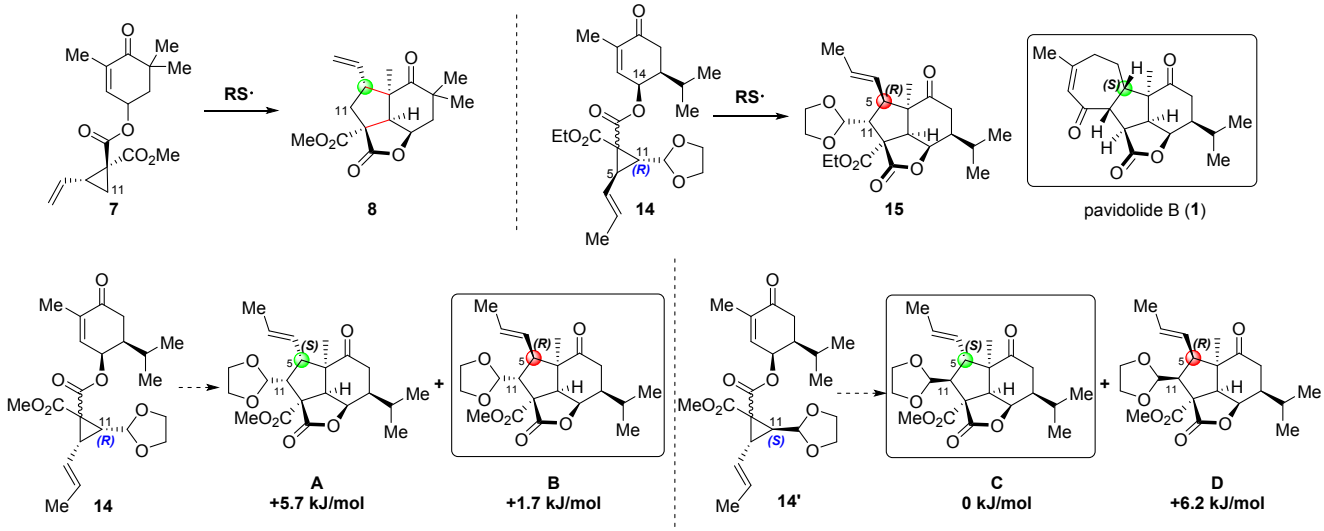
To verify our hypothesis, acids **13a** (the stereochemistry of C12 was determined by the NOE-NMR analysis of its reduced derivative **13a'**, see Supporting Information for details)[19] and **13b** were separated and subjected to a typical Mitsunobu reaction[20] with alcohol **6** in the presence of diethyl azodicarboxylate (DEAD) and PPh_3 in THF, respectively, providing **14a** in 87% yield and **14b** in 84% yield (Scheme 4). Then the [3+2] annulation reaction was performed under the same conditions of model study by treating **14a** or **14b** with thiophenol and AIBN at 80 °C. However, both reactions occurred slowly in low yields. When we performed the reactions at a higher temperature of 120 °C, both **14a** and **14b** gave the same tricyclic product **(15)** in similar yields and diastereoselectivities (*dr* = 5:1). These results confirmed that the lack of diastereoselectivity at C12 in precursors would not affect the following [3+2] annulation reaction. Unfortunately, further X-ray crystallographic analysis of the major product **15** showed that the stereochemistry of C5 (*R*) was opposite to that of the natural product pavidolide B (**1**).

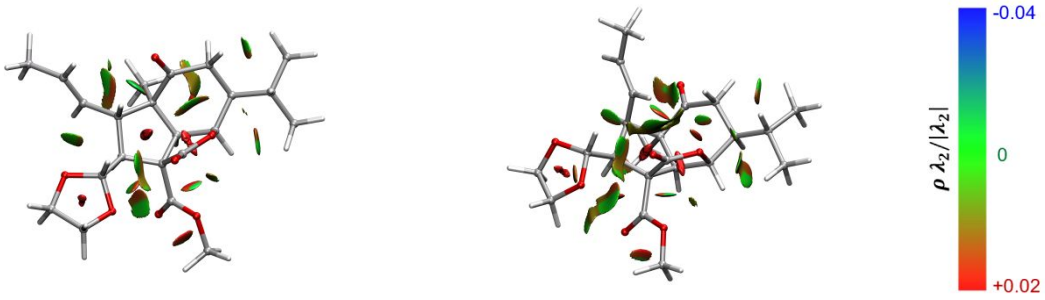
Scheme 4. [3+2] Annulation of Ethylene-Glycol-Protected C11-(*R*) Precursor **14**



[a]Reagents and conditions: (a) PPh_3 (2.0 equiv), DEAD (2.0 equiv), **6** (1.1 equiv), THF, 0 °C to rt, overnight; (b) PhSH (1.2 equiv), AIBN (0.3 equiv), toluene, 120 °C, 6 h.

As shown in figure 2, compared with the stereoselectivity exhibited in the model study (product **8**), radical cyclization with substrate **14** gave compound **15** as product, where the C5 stereochemistry is inverted. We reasoned that the product might preferably form with the substitution on C5 *anti* to that of C11. Although a thermodynamic analysis doesn't guarantee the corresponding kinetic preference, we do believe that similar interaction exists in the stereoselectivity-determining transition state. To gain confidence in this analysis, computational studies were carried out at DSD-PBEP86-D3/def2-TZVP//PBE0/def2-SV(P) level with SMD solvation in MeCN to evaluate the thermodynamic preference of C5, C11 diastereomers. For products derived from compound **14**, the undesired C5-(*R*) configuration **B** is thermodynamically favored by 4.1 kJ/mol. On the contrary, if the stereogenic centre at C11 is inverted (compound **14'**), compound **C** with an (*anti,syn)*-configuration would be the thermodynamically favored one over the (*syn,anti*)-product **D** by 6.2 kJ/mol. Based on conformational search, in the most stable conformation of product **D**, the acetal group is forced to occupy the out-of-plain carbon of the cyclopentane ring to minimize the steric interaction of the acetal group with the lactone and alkenyl chain. According to the RDG analysis, this will increase the strain of the tricyclic skeleton itself, causing the alkenyl chain to occupy the axial position of the cyclopentane envelope conformation which sterically contacts the other part of the tricyclic skeleton. In product **C**, steric repulsion between the alkenyl chain and the *cis*-methyl group positively contributes to the overall free energy, albeit to a lesser extent. Thus, we decided to prepare the C11-(*S*) substrate and see whether it would give the desired stereochemistry at C5. With this strategy, however, the stereochemistry of C11 will be opposite to that of the natural product, but we reasoned that C11, adjacent to a carbonyl group, could be epimerized later.



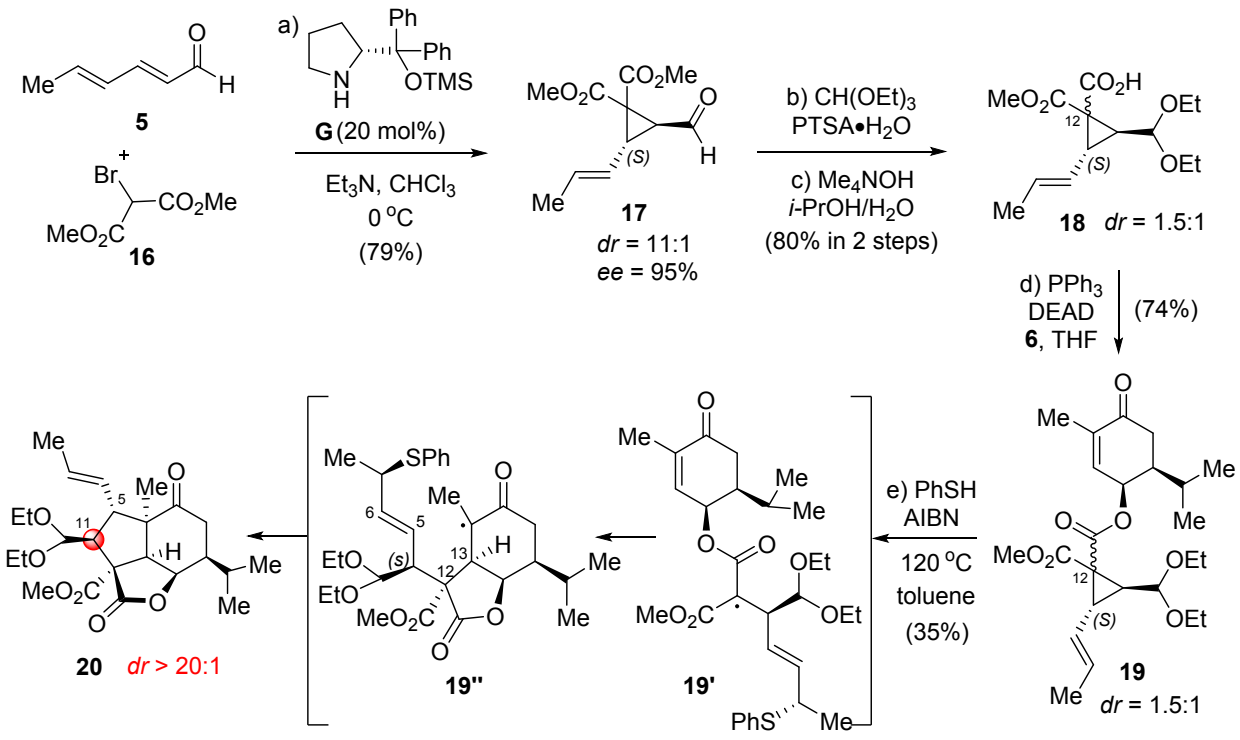


RDG analysis of **C** RDG analysis of **D**

Figure 2. Different diastereoselectivity in model and real system, calculated thermodynamic preference and RDG analysis for product with inversed stereochemistry at C11 .

C11-(*S*) substrate **17** was prepared by similar procedures using (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine **G** as catalyst (Scheme 5). Meanwhile, dimethyl 2-bromomalonate **16** was chosen instead of diethyl 2-bromomalonate to guarantee milder conditions for the later decarboxylation[13b]. After screening of a series of protecting groups[18], aldehyde **17** was protected with a diethoxyl group in the presence of PTSA and $CH(OEt)_3$ in CH_2Cl_2. This protecting group has an enhanced steric effect that could ensure higher diastereoselectivity at C5 in the following [3+2] annulation reaction. After similar hydrolysis and Mitsunobu reaction sequences, precursor **19** was prepared as a pair of diastereomers (*dr* = 1.5:1) at C12. Then, this mixture was treated with thiophenol and AIBN at 120 °C to undergo the [3+2] annulation reaction. Fortunately, tricyclic product **20** was isolated in 35% yield as a single diastereomer, in which stereochemistry of C5 was consistent with pavidolide B (**1**). This clean control of all the relative stereochemistries in the C ring of **20** and the installation of the C4 quaternary carbon ultimately provided a concise access to pavidolide B (**1**).[3a]

Scheme 5. [3+2] Annulation Reaction of C11-(*S*) Substrate **19**[a]

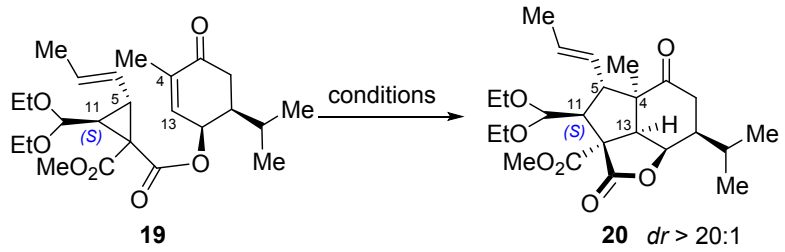


[a]Reagents and conditions: (a) (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine **G** (20 mol%), **5** (1.2 equiv), Et_3N (1.0 equiv), $CHCl_3$, 0 °C, 6 h, 79%; (b) $CH(OEt)_3$ (1.5 equiv), PTSA (0.1 equiv), CH_2Cl_2, rt, 2 h; (c) Me_4NOH (1.1 equiv), *i*-PrOH/H_2O = 10:1, rt, 12 h, 80% in two steps; (d) PPh_3 (2.0 equiv), DEAD (2.0 equiv), **6** (1.1 equiv), THF, 0 °C to 45 °C, overnight, 74%; (e) PhSH (1.2 equiv), AIBN (0.3 equiv), toluene, 120 °C, 35%.

Optimization of the [3+2] Annulation Reaction Conditions

With the success of the key [3+2] annulation reaction for the stereoselective formation of the tricyclic core of **1**. We tried to vary the conditions to thermally generate the thiyl radical[12], involving the treatment of **19** with a mixture of PhSH (1.5 equiv) and AIBN (0.3 equiv) in degassed toluene at various temperatures. We found that substrate **19** was completely consumed at 60 °C after 9 h, but only a trace amount of the desired product **20** was detected (Table 2, entry 1). When the reaction was conducted at 120 °C for 3 h, the desired product **20** was isolated in 35% yield, along with decomposition of the substrate (entry 4).

Table 2. Thermal Conditions Screening for the [3+2] Annulation Reaction



19 **20** *dr* > 20:1

entry	conditions[a]	solvent	temp (°C)	time (h)	yield (%)[b]
1	PhSH, AIBN	toluene	60	9	trace
2	PhSH, AIBN	toluene	80	6	32
3	PhSH, AIBN	toluene	100	3	31
4	PhSH, AIBN	toluene	120	3	35

[a] Reaction conditions: **19** (0.5 mmol) in toluene (20 mL), slow addition of PhSH (1.5 equiv) and AIBN (0.3 equiv) in toluene (10 mL); [b] Isolated yield.

To gain insight into this highly stereospecific annulation reaction, we carried out DFT calculation at DSD-PBEP86-D3/def2-TZVP//PBE0-D3/def2-SV(P) level with SMD solvation in MeCN for the pathways from **19** to **20**. [21a-f] As shown in Figure 3, the calculation indicates that the rate-determining step is the 5-*exo* conjugate addition of intermediate **IM2** (**19'**, Scheme 5) forming **IM3** (**19''**, Scheme 5). The activation Gibbs free energy is 72.3 kJ/mol from (12*S*)-**19**, and 59.6 kJ/mol from (12*R*)-**19** (for all possible pathways, see Supporting Information). Similar to what's predicted by the thermodynamic data, with (11*S*)-**19** as the substrate, product **20** is favored over 5-*epi*-**20** in all pathways. This preference is inverted when (11*R*)-**19** was used as the substrate, shown in the right part of Figure 3. The substrate dependence of stereoselectivity in this reaction demonstrated that C5 stereocenter is controlled by the C11 acetal group during the cyclization process.

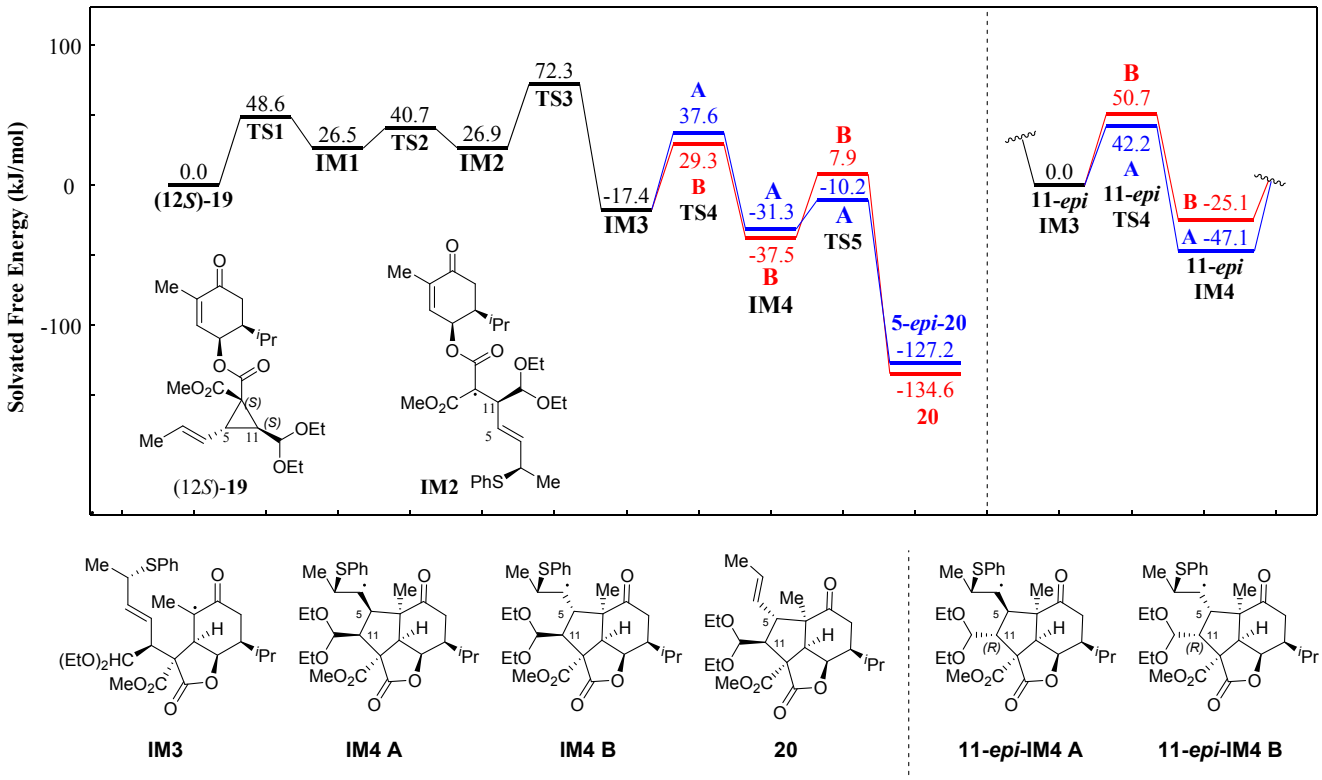
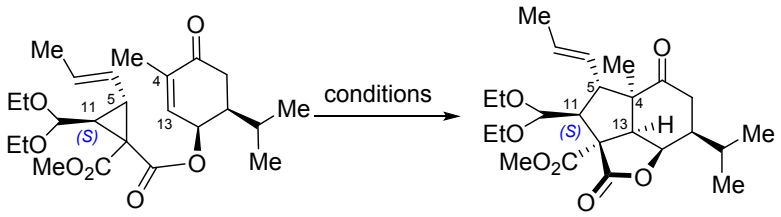


Figure 3. DFT calculation of PhS· initiated cyclization reaction from (12*S*)-**19** and 11-*epi*-**19**

Besides the rate-determining step and the origin of diastereoselectivity, the computational study shown in Figure 3 also indicates that the cyclization process, once initiated, requires less than 75 kJ/mol of activation Gibbs free energy, which means the cyclization could occur rapidly at room temperature. Thus, combined with the fact that the VCP moiety in the substrate is thermally unstable,[22] we next attempted to optimize this reaction by room temperature radical initiation methods. We first tested irradiation with UV light[23] (entries 1-6, Table 3). The desired annulation proceeded smoothly when the reaction was performed in the presence of PhSSPh and AIBN under UV-light irradiation in toluene at 25 °C for 5 h (entry 1), giving product **20** in 32% yield. According to Feldman's work[24], the addition of $AlMe_3$ as a Lewis acid could promote this reaction and, to our delight, the yield of **20** was improved to 40%–48% with a shorter reaction time (entry 2). However, the yield of **20** was variable when using this approach, as $AlMe_3$ is sensitive to moisture and its quality is difficult to control. The screen of other Lewis acids, such as $Zn(OTf)_2$, $Sc(OTf)_2$, and $Ti(O\textit{i}\text{-}Pr)_4$, failed to promote this reaction. Solvent screening showed that toluene was the best solvent. Even the reaction gave similar yield (47%) in cyclohexane, the yield declined in a larger scale due to the lower solubility in cyclohexane. When we tested BPO as an initiator[25] (entry 5), the desired product **20** was generated in only 20% yield. Interestingly, when a higher-power UV light (500 W) was used (entry 6), the yield of **20** dropped to

35%. We recognized that high-energy UV irradiation may lead to some side reactions, which could potentially be minimized by using lower-energy visible-light irradiation.

Table 3. Optimization for UV-initiated [3+2] Annulation Reaction at Room Temperature



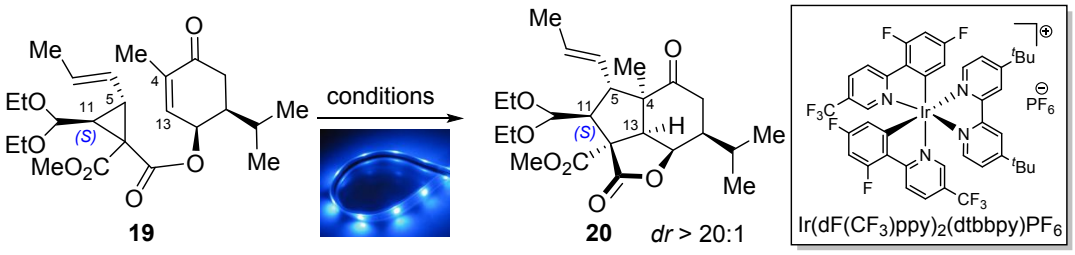
19 **20** *dr* > 20:1

entry	conditions	solvent	additive	time (h)	yield (%)[a]
1	PhSSPh, AIBN, UV (250 W)	Toluene		5	32
2	PhSSPh, AIBN, UV (250 W)	toluene	$AlMe_3$	3	40–48[b]
3	PhSSPh, AIBN, UV (250 W)	MeCN	$AlMe_3$	6	37
4	PhSSPh, AIBN, UV (250 W)	cyclohexane	$AlMe_3$	3	47[c]
5	PhSSPh, BPO, UV (250 W)	toluene	$AlMe_3$	5	20
6	PhSSPh, AIBN, UV (500 W)	toluene	$AlMe_3$	3	35

[a]Isolated yield; [b]Reaction conditions: **19** (0.5 mmol), $AlMe_3$ (1.0 equiv), PhSSPh (1.2 equiv), AIBN (0.5 equiv), toluene (30 mL), UV (250 W) irradiation. [c]the yield dropped in larger scale due to the poor solubility.

Recently, the couplings of thiols and alkenes were realized by using transition-metal catalysts[26] or organic photocatalysts[27] under visible-light irradiation[28], representing state-of-the-art chemical transformations promoted by low-cost energy. Motivated by this recent progress, we applied similar conditions to our thiyl-radical-mediated [3+2] annulation reaction (Table 4). To this end, several commercially available photoredox catalysts[29] were screened (entries 1–3). Under irradiation of low-energy blue light-emitting diodes (LEDs), when $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (0.5 mol%) was selected as the catalyst, desired product **20** was obtained in 50% yield. In contrast, when alkyl thiols, such as benzyl mercaptan and methyl thioglycolate (entries 4 and 5) were used as the thiyl-radical source, the yield of **20** declined, probably because of the higher bond dissociation energy (BDE) of S–H bonds in alkyl thiols than that of PhSH[12c].

Table 4. Screening of Visible-Light Irradiation Conditions

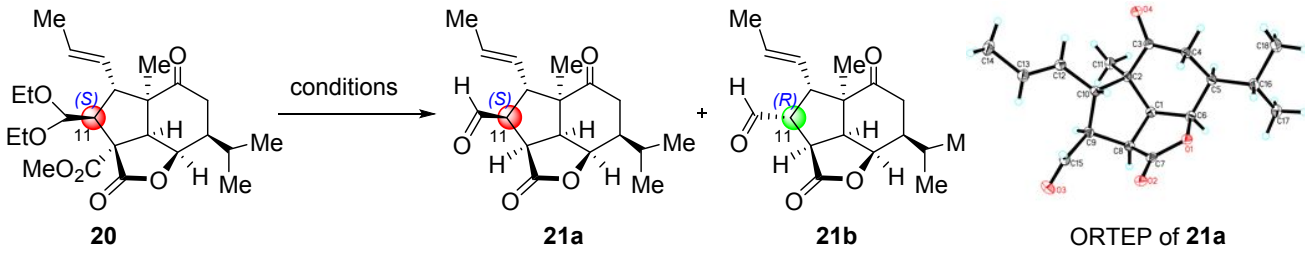


entry	conditions	time (h)	yield (%)[a]
1	PhSH, $Ru(bpy)_3Cl_2$, *p*-toluidine	4	30
2	PhSH, $Ir(ppy)_2(dtbbpy)PF_6$, *p*-toluidine	4	47
3	PhSH, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, *p*-toluidine	2	50[b]
4	benzyl mercaptan, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, *p*-toluidine	5	23
5	methyl 2-mercaptoacetate, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, *p*-toluidine	2	25

[a]Isolated yield; [b]Reaction conditions: **19** (0.5 mmol), PhSH (1.1 equiv), *p*-toluidine (0.5 equiv), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (0.5 mol%), MeCN (30 mL), 25 °C, 2 h.

Building the Tetracyclic Core

Table 5. Screening of Krapcho Decarboxylation Reaction Conditions

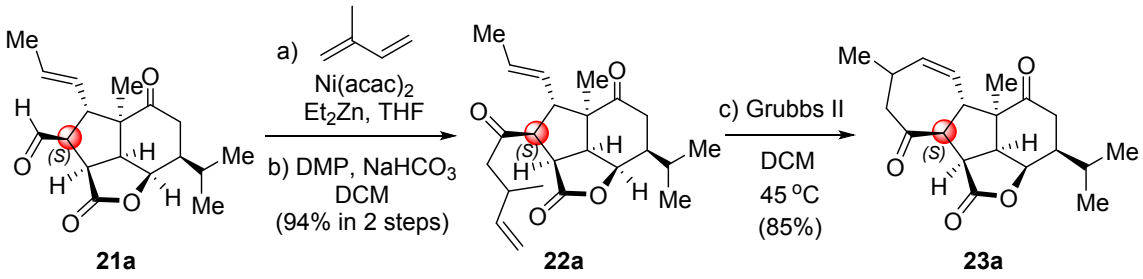


entry	conditions	temp (°C)	time (h)	yield of **21a** (%)[a]	ratio (**21a**:**21b**)
1	LiCl, DMAc, H_2O	120	12	<10	-
2	LiCl, DMSO, H_2O	120	12	<10	-
3	LiCl, DMAc, H_2O	160	6	20	1.3:1
4	LiI, DMAc, H_2O	160	6	28	1.3:1
5	NaI, DMAc, H_2O	160	4.5	38[b]	1.6:1
6	NaI, DMF, H_2O	160	4.5	32	1.5:1

[a]Yield of isolated product; [b]Reagents and conditions: NaI (5.0 equiv), H_2O (10.0 equiv), DMAc, 160 °C, 4.5 h.

To remove the extra C12 carboxylic ester needed for the [3+2] cyclization reaction, compound **20** was treated under Krapcho decarboxylation reaction conditions.[13] Various halogen salts, such as LiCl, NaCl, LiBr, LiI, and NaI, were tested in different solvents at high temperatures. Interestingly, we found that the deprotection of the aldehyde occurred simultaneously to give aldehyde **21a** in low yields (Table 5, entries 1–3). The stereochemistry of product **21a** was assigned by X-ray crystallography. After careful examination of the other messy byproducts, we found that aldehyde **21b** was formed at the same time (entry 3), in which all seven contiguous stereocenters are the same as those in the target molecule **1**. However, attempts to drive further epimerization of **21a** to **21b** under several basic or acidic conditions led to a mixture of diastereomers, with a ratio of **21a**:**21b** = 1:1.5 (see Supporting Information for details). These results indicate that equilibrium may exist between **21a** and **21b**.

Scheme 6. Building the Tetracyclic Skeleton **23a** from aldehyde **21a**[a]

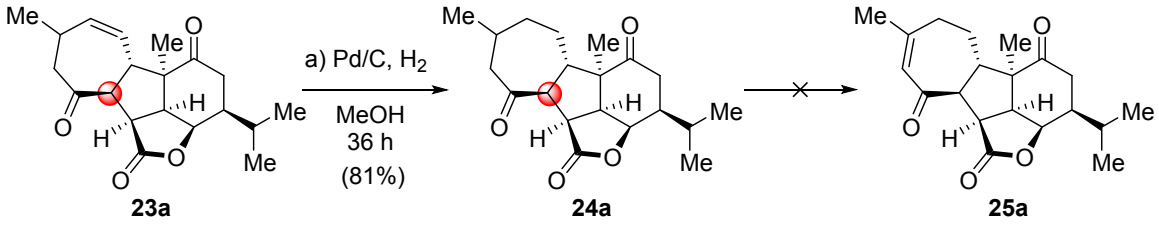


[a]Reagents and conditions: (a) $Ni(acac)_2$ (20 mol%), isoprene (4.0 equiv), Et_2Zn (2.4 equiv), THF, rt, 4 h; (b) $NaHCO_3$ (5.0 equiv), Dess−Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 4 h, 94% in two steps; (c) Grubbs II catalyst (2 mol%), CH_2Cl_2, reflux, 6 h, 85%.

With key intermediates **21a** and **21b** in hand, we focused on constructing the seven-membered ring D of **1**. We adopted the Ni-catalyzed reductive coupling reaction of aldehydes with 1,3-dienes developed by Tamaru and co-workers[7] to install the alkene side chain. When aldehyde **21a** was coupled with isoprene in the presence of $Ni(acac)_2$ and Et_2Zn in THF at room temperature for 2 h, the expected homoallylic product was obtained in almost quantitative yield. Then DMP oxidation of this product without purification gave diene **22a** in 94% yield over two steps (Scheme 6). Then, the intramolecular RCM reaction[5] of diene **22a** was explored with several catalysts. The Grubbs II catalyst gave the best result, with an 85% annulation yield for product **23a**, thus completing the tetracyclic skeleton of **1**.[3a]

Final trip to pavidolide B (1)

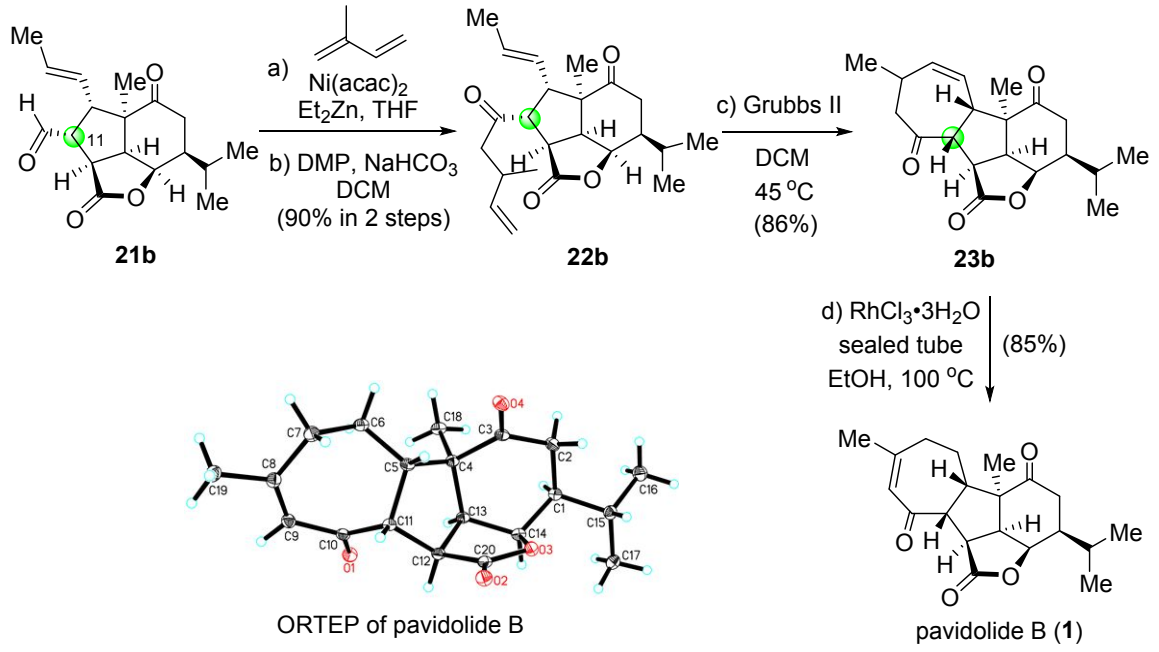
Scheme 7. Hydrogenation and Oxidation Sequence[a]



[a]Reagents and conditions: (a) Pd/C (20 wt%), H_2 (1 atm), MeOH, 36 h, 81%.

To build the enone moiety, we first tried a hydrogenation and oxidation sequence, proposing the less hindered carbonyl group on 7-membered ring may be more prone to be activated. As shown in Scheme 7, hydrogenation of the C-C double bond of **23a** in the presence of Pd/C in a hydrogen atmosphere (1 atm) provided product **24a** in 81% yield. Unfortunately, several methods to build the enone moiety[30] were investigated, including Saegusa oxidation,[31] selenylation,[32] IBX oxidation,[33] and Stahl's palladium-catalyzed dehydrogenation,[34] but these conditions failed to generate desired product **25a,** resulting in decomposition or no reaction.

Scheme 8. Realizing the Total Synthesis of Pavidolide B (**1**) through Double-Bond Migration[a]



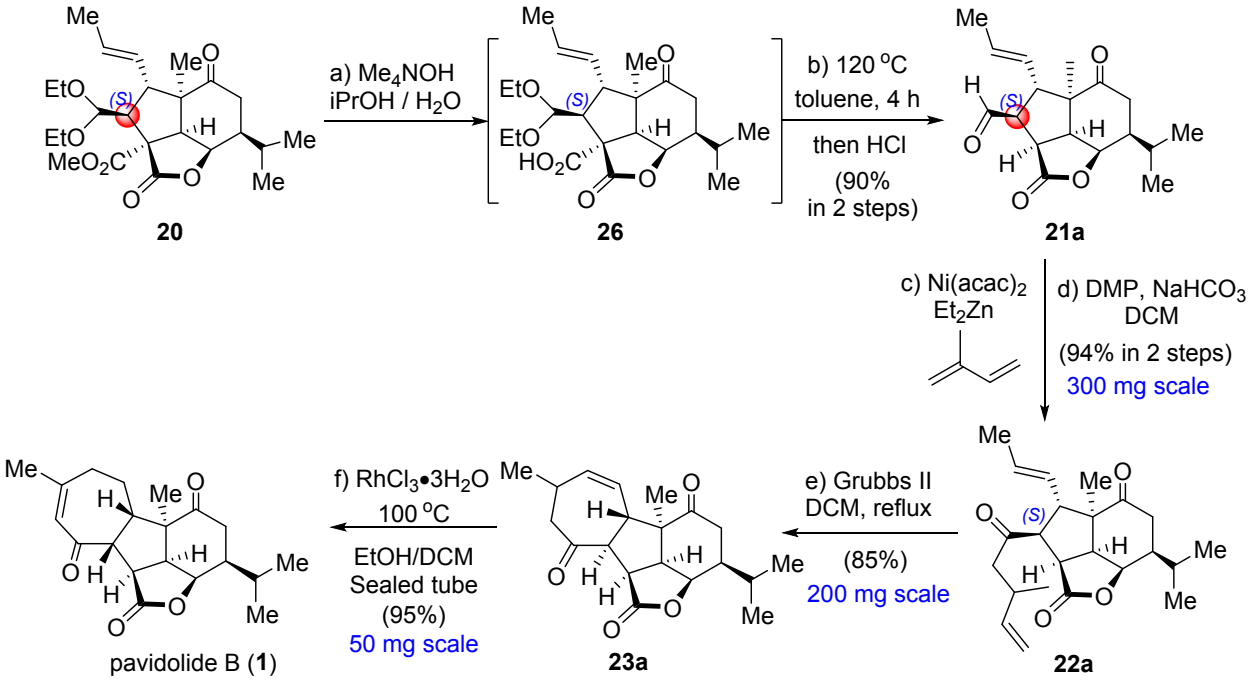
[a]Reagents and conditions: (a) $Ni(acac)_2$ (20 mol%), isoprene (4.0 equiv), Et_2Zn (2.4 equiv), THF, rt, 4 h; (b) $NaHCO_3$ (5.0 equiv), Dess−Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 4 h, 90% in two steps; (c) Grubbs II catalyst (2 mol%), CH_2Cl_2, reflux, 6 h, 86%; (d) $RhCl_3 \cdot 3H_2O$ (20 mol%), EtOH, 100 °C, sealed tube, 5 h, 85%.

As an alternative, we thought that double-bond migration[6] of the *α,β*-unsaturated enone to the more stable *α,β*-unsaturated enone would be a more efficient and direct strategy. We tested this idea by using C11-(*S*) aldehyde **21b** as substrate, with all seven contiguous stereocenters the same as those in

pavidolide B (**1**). Following a similar procedure, tetracyclic compound **23b** was prepared from **21b** smoothly in three steps (Scheme 8). After screening various olefin isomerization catalysts[6, 35], including Ru, Rh, and Pd catalysts, we were glad to find that when **23b** was treated with $RhCl_3 \cdot 3H_2O$ (20 mol%) in absolute ethanol at 100 °C in a sealed-tube for 5 h[35a], the target molecular **1** was generated in 85% yield ([α]26 D = -146, *c* = 0.42 in MeOH). The structure of the synthesized product was unambiguously confirmed by X-ray crystallography to match that of the isolated (–)-pavidolide B (**1**).

Optimization of Synthetic Route

Scheme 9. Revised Synthetic Route[a]



[a]Reagents and conditions: (a) Me_4NOH (1.1 equiv), *i*-PrOH/H_2O = 10:1, rt, 12 h; then toluene, 120 °C, 4 h; (b) 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, 90% in two steps; (e) Grubbs II catalyst (20 mol%), CH_2Cl_2, reflux, 6 h, 86%; (f) $RhCl_3 \cdot 3H_2O$ (20 mol%), EtOH/CH_2Cl_2 = 6:1, 100 °C, sealed tube, 5 h, 95%.

After successfully realizing the total synthesis of **1**, we attempted to improve the efficiency of this synthetic route (Scheme 9). To improve the yield of the decarboxylation reaction, the methyl ester of compound **20** was selectively hydrolyzed by treatment with Me_4NOH in a mixed solvent of *i*-PrOH and H_2O at room temperature. Without purification, the resultant acid **26** was subjected to decarboxylation[36] by heating at 120 °C in toluene and then deprotection with HCl solution (3 N) in situ

to furnish **21a** in 90% yield over two steps. Following the same procedure, **21a** was transformed into tetracyclic **23a** on the scale of hundreds of milligrams. When **23a** was treated with $RhCl_3 \cdot 3H_2O$ (20 mol%) in ethanol (with a small amount of CH_2Cl_2 as a cosolvent) at 100 °C for 5 h, to our delight, epimerization of C11 occurred simultaneously with double-bond migration to give natural product **1** in 95% yield. Thus, the entire synthetic route was shortened to 10 linear steps and the overall yield was improved to 16%. Finally, 300 mg of pavidolide B (**1**) was synthesized for further bioactivity studies.

CONCLUSIONS

In summary, the asymmetric total synthesis of (–)-pavidolide B (**1**) was realized in 10 steps in 16% overall yield. In this work, a thiyl-radical-mediated [3+2] annulation reaction under visible-light irradiation conditions was used for the concise construction of a highly substituted cyclopentane core structure, with two C–C bonds, two rings, and four stereocenters, including one quaternary all-carbon center, formed in one step. The four newly formed stereocenters were cleanly controlled through the logical design of the substrate. This cascade radical reaction provides a powerful strategy for the construction of highly substituted five-membered rings under mild conditions with good functional-group tolerance, which may have broad potential applications in organic synthesis.

EXPERIMENTAL SECTION

General Experimental Information. Unless otherwise mentioned, all reactions were carried out under an argon atmosphere in oven-dried glassware with dry solvents. An oil bath was used as the heating source for the reactions that require heating. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents purification was conducted according to Purification of Laboratory Chemicals (Peerrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (GF-254) and visualized under UV light at 254 nm. Staining was performed with an ethanolic solution of phosphomolybdic acid (PMA) and cerium sulfate, or by oxidative staining with an aqueous basic potassium permanganate ($KMnO_4$) solution and subsequent heating. Tsingdao silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. NMR spectra were recorded on either a Brüker Advance 400 MHz or Brüker Advance

500 MHz NMR spectrometer. All ^{1}H-NMR data are reported in δ units, parts per million (ppm), and all ^{13}C-NMR data were obtained with ^{1}H decoupling unless otherwise stated. They were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR = 7.26 ppm, ^{13}C NMR = 77.2 ppm; Acetone-d6: ^{1}H NMR = 2.05 ppm, ^{13}C NMR = 206.3 ppm; DMSO-d6: ^{1}H NMR =2.50 ppm, ^{13}C NMR = 40.0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on an IR Prestige-21 FTIR spectrometer with a KBr disc. Melting points (m.p.) are uncorrected and were recorded on a SGWX-4B apparatus. High resolution mass spectrometric (HRMS) data were recorded on a Brüker Apex IV RTMS instrument and a VG Auto Spec-3000 spectrometer using quadrupole analyzer, respectively. CD spectrum was measured using the Applied Photophysics Chirascan with a 150W Xe lamp (165 nm – 900 nm). Optical rotation values were recorded on a Rudolph Research Analytical Autopol I polarimeter (Rudolph Research Co.).

4,4,5a-trimethyl-6-vinyloctahydroindeno[7,1-bc]furan-1,5-dione (9):

A flame dried round-bottom flask containing a solution of **7** (300 mg, 1.0 mmol, 1.0 equiv, see Supporting Information for details) in toluene (20 mL) under N_2 was heated to 80 °C in an oil bath. Then a mixture solution of PhSH (150 μL, 1.5 mmol, 1.5 equiv) and AIBN (50 mg, 0.3 mmol, 0.3 equiv) in toluene (10 mL) was added dropwise by syringe pump over 5 h at 80 °C. The reaction mixture was stirred at the same temperature for an additional 30 min. After cooling to ambient temperature, the solvent was removed under vacuum and the residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give the desired product **8** (141 mg, 47%) as a crystalline solid. Compound **8**: R_f = 0.50 (silica gel, hexane/EtOAc = 4:1, $KMnO_4$); m.p.: 106.2–107.5 °C; IR (thin film, ν cm^{-1}): 3000, 2961, 2918, 2850, 1772, 1759, 1377, 1250, 1243, 1054, 800; HRMS (ESI)**:** m/z calcd for $C_{17}H_{23}O_5^+$ $[M+H]^+$: 307.1540; found: 307.1532. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 – 5.74 (m, 1H), 5.17 – 5.14 (m, 1H), 5.08 (td, *J* = 9.2, 7.0 Hz, 1H), 5.02 – 4.98 (m, 1H), 3.81 (s, 3H), 3.25 (d, *J* = 9.3 Hz, 1H), 2.65 – 2.58 (m, 2H), 2.50 – 2.39 (m, 1H), 2.33 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.04 (dd, *J* = 14.5, 9.2 Hz, 1H), 1.18 (s, 3H), 1.15 – 1.08 (m, 3H), 1.05 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 213.0, 175.0, 169.9, 133.8, 117.8, 74.6, 61.3, 55.8, 54.6, 53.5, 50.1, 42.4, 39.1, 36.4, 25.9, 25.0, 20.3 ppm.

To a stirred solution of **8** (100 mg, 0.33 mmol, 1.0 equiv) in DMSO (10 mL) was added LiCl (138 mg, 3.3 mmol, 10.0 equiv) and H_2O (0.3 mL, 16.5 mmol, 50.0 equiv), and the resultant reaction mixture was

then heated to 120 °C in an oil bath, and stirred for 5 h. After cooling to ambient temperature, the mixture was extracted with Et_2O (5 x 30 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 6:1) to give the desired product **9** (66 mg, 77%) as a viscous oil. Compound **9**: R_f = 0.45 (silica gel, hexane/EtOAc = 4:1, $KMnO_4$); IR (thin film, ν cm^{-1}): 2961, 2929, 2854, 1765, 1661, 1472, 1243, 1018; HRMS (ESI)**:** m/z calcd for $C_{15}H_{20}NaO_3^+$ $[M+Na]^+$: 271.1305; found: 271.1305. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.76 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.13 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.97 (M, 2H), 3.30 (td, *J* = 10.3, 1.7 Hz, 1H), 3.07 (t, *J* = 9.9 Hz, 1H), 2.70 – 2.55 (m, 1H), 2.38 – 2.21 (m, 2H), 2.19 – 2.09 (m, 1H), 2.05 – 2.00 (m, 1H), 1.18 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 213.9, 179.3, 134.4, 117.5, 75.0, 56.3, 50.2, 48.6, 44.0, 42.4, 39.4, 33.2, 25.9, 25.0, 20.2 ppm.

(2*R*,3*R*)-2-(1,3-dioxolan-2-yl)-1-(ethoxycarbonyl)-3-((*E*)-prop-1-en-1-yl)cyclopropane-1-carboxylic acid (13):

Compound **12** was prepared by following known procedures[8] in 79% yield as a colorless oil, which is an inseparable 11:1 mixture of diastereomers. (For the determination of enantiomeric excess of **12**, see Supporting Information.) To a stirred solution of aldehyde **12** (2.84 g, 11.2 mmol, 1.0 equiv) in dry DCM (100 mL) was added triethyl orthoformate (2.23 mL, 13.4 mmol, 1.2 equiv), ethylene glycol (1.14 mL, 22.4 mmol, 2.0 equiv) and PTSA•H_2O (213 mg, 1.12 mmol, 0.1 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion, the mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered and concentrated under vacuum. The residue can be used directly for the next step without further purification.

To a solution of the residue in *i*-PrOH/H_2O = 50 mL/5 mL, tetramethylammonium hydroxide (5.5 mL, 25% w/w solution in H_2O, 12.0 mmol, 1.1 equiv) was added at room temperature. The reaction mixture was heated to 40 °C in an oil bath and stirred for 12 h. After completion, the solution was extracted with DCM (2 × 20 mL). The organic phase was discarded and the water phase was acidified with 2 N aq. HCl at 0 °C to pH = 2, and extracted with DCM (3 × 50 mL). The combined organic layer were dried over Na_2SO_4. The solvent was removed under vacuum to give acid **13** (1.97 g, 65% yield in two steps) as a colorless oil, which is a 1:1 mixture of diastereomers, and can be separated by flash column

chromatography (PE:EA = 2:1) to afford **13a** and **13b**. Compound **13a**: R_f = 0.40 (silica gel, hexane/EtOAc = 1:1, PMA). **[α]25 D** = + 2.4 (c = 0.5, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2974, 2925, 2857, 1726, 1713, 1453, 1374, 1292, 1211, 1113, 966; HRMS (ESI)**:** m/z calcd for $C_{13}H_{18}NaO_6^+$ $[M+Na]^+$: 293.0996; found: 293.0998. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.86 – 5.77 (m, 1H), 5.37 – 5.31 (m, 1H), 4.88 (d, *J* = 6.7 Hz, 1H), 4.29 – 4.24 (m, 2H), 4.01 – 3.98 (m, 2H), 3.90 – 3.81 (m, 2H), 2.83 (t, *J* = 8.3 Hz, 1H), 2.43 (dd, *J* = 8.1, 6.7 Hz, 1H), 1.68 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 169.4, 131.6, 123.7, 102.4, 65.1, 65.0, 62.4, 37.9, 36.7, 35.7, 17.9, 13.8 ppm. Compound **13b**: R_f = 0.30 (silica gel, hexane/EtOAc = 1:1, PMA). **[α]25 D** = - 6.4 (c = 0.5, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2964, 2922, 2853, 1722, 1445, 1374, 1266, 1096, 1022, 800; HRMS (ESI)**:** m/z calcd for $C_{13}H_{18}NaO_6^+$ $[M+Na]^+$: 293.0996; found: 293.0998. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.88 – 5.79 (m, 1H), 5.34 – 5.24 (m, 1H), 5.09 (d, *J* = 7.0 Hz, 1H), 4.35 – 4.18 (m, 2H), 4.05 – 3.98 (m, 2H), 3.92 – 3.83 (m, 2H), 2.95 (t, *J* = 8.3 Hz, 1H), 2.48 – 2.44 (m, 1H), 1.68 (dd, *J* = 6.6, 1.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 170.7, 169.6, 132.2, 123.9, 101.8, 65.1, 65.1, 62.6, 37.8, 37.6, 37.0, 18.0, 14.0 ppm.

1-ethyl 1-((1*R*,6*S*)-6-isopropyl-3-methyl-4-oxocyclohex-2-en-1-yl) (1*R*,2*R*,3*R*)-2-(1,3-dioxolan-2-yl)-3-((*E*)-prop-1-en-1-yl)cyclopropane-1,1-dicarboxylate (14a) and 1-ethyl 1-((1*R*,6*S*)-6-isopropyl-3-methyl-4-oxocyclohex-2-en-1-yl) (1*S*,2*R*,3*R*)-2-(1,3-dioxolan-2-yl)-3-((*E*)-prop-1-en-1-yl)cyclopropane-1,1-dicarboxylate (14b):

To a solution of **13a** (576 mg, 2.1 mmol, 1.0 equiv), alcohol **6** (430 mg, 2.56 mmol, 1.2 equiv) and PPh_3 (1.9 g, 4.2 mmol, 2.0 equiv) in THF, was added DEAD (0.66 mL, 4.2 mmol, 2.0 equiv) dropwise at 0 ^oC. Then the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of a saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20:1) to give **14a** (767 mg, 87% yield) as a colorless oil. Compound **14a**: R_f = 0.60 (silica gel, hexane/EtOAc = 4:1, UV & PMA). **[α]25 D** = + 261 (c = 0.6, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2964, 2925, 1724, 1683, 1459, 1370, 1285, 1204, 1110, 1051, 907; HRMS (ESI): m/z calcd for $C_{23}H_{32}NaO_7^+$ $[M+Na]^+$: 443.2040; found: 443.2041; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.86 – 6.78 (m, 1H), 5.81 – 5.71 (m, 1H), 5.41 (dd, *J* = 5.7, 2.9 Hz, 1H), 5.10 – 5.01 (m, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.20 – 4.02 (m, 2H), 4.00 – 3.93 (m, 2H), 3.85 – 3.73 (m, 2H), 2.69 (t, *J* = 8.0 Hz, 1H), 2.58 (dd, *J* =

16.9, 3.3 Hz, 1H), 2.34 (dd, *J* = 16.9, 12.8 Hz, 1H), 2.27 – 2.19 (m, 1H), 1.77 (d, *J* = 1.6 Hz, 3H), 1.75 –1.70 (m, 1H), 1.60 (dd, *J* = 6.6, 1.4 Hz, 3H), 1.24 – 1.17 (m, 1H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.86 (dd, *J* = 13.2, 6.6 Hz, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 199.3, 166.9, 166.4, 138.9, 138.6, 130.8, 124.0, 102.2, 67.7, 65.1, 65.0, 61.7, 44.5, 39.3, 37.6, 33.6, 32.0, 28.2, 20.2, 19.8, 17.9, 15.4, 13.8 ppm.

Compound **14b** was prepared through the same procedure from **13b** in 84% yield as a colorless oil. Compound **14b**: R_f = 0.70 (silica gel, hexane/EtOAc = 4:1, UV & PMA). **[α]25 D** = + 40 (c = 1.0, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2965, 2926, 1727, 1684, 1459, 1371, 1286, 1205, 1110, 1051, 908; HRMS (ESI)**:** m/z calcd for $C_{23}H_{32}NaO_7^+$ $[M+Na]^+$: 443.2040; found: 443.2041; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 (dd, *J* = 5.8, 1.2 Hz, 1H), 5.81 – 5.72 (m, 1H), 5.43 – 5.42 (m, 1H), 5.15 – 5.06(m, 1H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.14 – 4.04 (m, 2H), 4.00 – 3.93 (m, 2H), 3.85 – 3.72 (m, 2H), 2.68 – 2.59 (m, 2H), 2.41 – 2.29 (m, 1H), 2.27 (t, *J* = 7.1 Hz, 1H), 1.80 (s, 3H), 1.64 – 1.62 (m, 3H), 1.29 – 1.20 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.1 Hz, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 199.5, 166.9, 166.6, 138.8, 138.7, 130.8, 123.7, 102.3, 68.1, 65.1, 64.9, 61.6, 44.8, 39.1, 37.6, 33.8, 31.7, 28.1, 20.3, 20.0, 17.9, 15.5, 14.0 ppm.

ethyl (2a*R*,2a^{1}*R*,3*R*,4*R*,4a*R*,7*S*,7a*R*)-3-(1,3-dioxolan-2-yl)-7-isopropyl-4a-methyl-2,5-dioxo-4-((*E*)-prop-1-en-1-yl)octahydroindeno[7,1-bc]furan-2a(2H)-carboxylate (15):

A flame dried three-necked round-bottom flask containing solution of mixture **14** (100 mg, 0.25 mmol, 1.0 equiv) in toluene (20 mL) was heated to 120 °C in an oil bath under N_2. Then a solution of PhSH (31 μL, 0.3 mmol, 1.2 equiv) and AIBN (50 mg, 0.3 mmol, 0.3 equiv) in toluene (10 mL) was added dropwise by syringe pump over 5 h at 120 °C. The reaction mixture was stirred at the same temperature for an additional 30 min. After cooling to ambient temperature, the solvent was removed under vacuum and the residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give the desired product **15** (37 mg, 37%, *dr* = 5:1) as a crystalline solid. Compound **15** (major): R_f = 0.40 (silica gel, hexane/EtOAc = 4:1, $KMnO_4$). m.p.: 146.1-148.2 °C. **[α]25 D** = + 18 (c = 1.0, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2968, 2916, 2850, 1774, 1733, 1710, 1022; HRMS (ESI)**:** m/z calcd for $C_{23}H_{32}NaO_7^+$ $[M+Na]^+$: 443.2040; found: 443.2041; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.95 – 5.86 (m, 1H), 5.46 – 5.36 (m, 1H), 5.24 (d, *J* = 5.1 Hz, 1H), 4.87 (d, *J* = 6.9 Hz, 1H), 4.30 – 4.21 (m, 2H), 4.00 – 3.92 (m, 2H), 3.88 – 3.73 (m, 2H), 3.23 (d, *J* = 6.8 Hz, 1H), 2.68 – 2.54 (m, 2H), 2.44 (dd, *J* = 11.9, 9.5 Hz, 1H), 2.17 – 1.99 (m, 2H), 1.78 (dd, *J* = 11.3, 4.6 Hz, 1H), 1.69 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.36 – 1.25 (m, 6H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ =

212.0, 174.0, 168.7, 128.8, 127.5, 104.0, 75.0, 65.3, 64.3, 62.5, 62.4, 58.9, 57.3, 55.7, 52.4, 43.4, 38.2, 30.4, 23.0, 20.6, 20.4, 17.8, 13.9 ppm.

General procedure of [3+2] annulation under visible light irradiation conditions.

To a stirred solution of compound **19**[3a] (110 mg, 0.25 mmol, 1.0 equiv) and *p*-toluidine (13.4 mg, 0.12 mmol, 0.5 equiv), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (0.5 mol %) in dry MeCN (15 mL) under argon atmosphere was added a solution of aryl or alkyl thiols (0.27 mmol, 1.1 equiv) in dry MeCN (5 mL) dropwise. The reaction mixture was stirred at room temperature at a distance of approximately 3 cm from blue LED strips (λ_{max} = 465 nm, 0.5m, 11.52W/m). Upon completion of the reaction, the solution was washed with aq. NaOH solution (10%, 5 mL) to remove unreacted thiol. The aqueous layers were extracted with Et_2O (4 × 10 mL), and the combined organic layers were washed with brine (5 mL), and dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give the desired product **20** as a colorless oil. The yields are shown in the table 4. Compound **20**: R_f = 0.40 (silica gel, hexane/EtOAc = 4:1, $KMnO_4$); [α]25 D = - 48 (c = 0.5, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2965, 2922, 1781, 1748, 1733, 1683, 1260, 1065, 1011, 771; HRMS (ESI): m/z calcd for $C_{24}H_{36}NaO_7^+$ $[M+Na]^+$: 459.2353; found: 459.2353. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.30 – 5.10 (m, 2H), 4.80 (s, 1H), 4.78 (s, 1H), 3.86 – 3.76 (m, 4H), 3.67 (dq, *J* = 14.1, 7.0 Hz, 2H), 3.45 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.12 (dd, *J* = 12.6, 8.1 Hz, 1H), 2.81 (d, *J* = 6.6 Hz, 1H), 2.59 (t, *J* = 14.3 Hz, 1H), 2.41 – 2.30 (m, 2H), 1.92 – 1.77 (m, 1H), 1.65 (dd, *J* = 6.1, 1.1 Hz, 3H), 1.63 – 1.60 (m, 1H), 1.15 – 1.09 (m, 9H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 208.9, 173.0, 170.5, 128.2, 127.0, 104.1, 76.4, 65.3, 64.8, 63.8, 58.5, 56.0, 53.6, 53.2, 52.7, 45.8, 35.0, 30.2, 29.9, 20.7, 20.5, 18.1, 15.4, 15.3 ppm.

(2a*R*,2a[1]*S*,3*S*,4*S*,4a*R*,7*S*,7a*R*)-7-isopropyl-4a-methyl-2,5-dioxo-4-((*E*)-prop-1-en-1-yl)decahydroindeno[7,1-bc]furan-3-carbaldehyde (21a) and (2a*R*,2a1*S*,3*R*,4*S*,4a*R*,7*S*,7a*R*)-7-isopropyl-4a-methyl-2,5-dioxo-4-((*E*)-prop-1-en-1-yl)decahydroindeno[7,1-bc]furan-3-carbaldehyde (21b):

To a solution of compound **20** (218 mg, 0.5 mmol, 1.0 equiv) in DMAc (5.0 ml) and H_2O (0.05 mL, 2.5 mmol, 5.0 equiv) was added NaI (375 mg, 2.5 mmol, 5.0 equiv). Then the sealed tube was heated to 160 °C in oil bath and stirred for 12 hours under N_2. After completion, the mixture was diluted with 20 mL Et_2O and washed with H_2O (5 ×10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by a flash column

chromatography on silica gel (hexane/EtOAc = 6:1) to give the aldehyde **21a** (58 mg, 38% yield) as a colorless crystal and aldehyde **21b** (36 mg, 24% yield) as a white solid.

Optimized procedure: To a solution of **20** (0.87 g, 2.0 mmol, 1.0 equiv) in *i*-PrOH (20 mL) and H_2O (2 mL) was added Me_4NOH (25% w/w solution in H_2O, 0.84 mL, 2.2 mmol, 1.1 equiv) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After completion, the solution was acidified by the slow addition of 2 N aq. HCl solution at 0 °C until pH = 2. The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was dissolved in toluene and heated to 120 °C for 4 h under N_2. After cooling to room temperature, THF (5 mL) and 2 N aq. HCl solution (2 mL) was added to the solution and stirred for 2 h. After completion, the mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 6:1) to give the aldehyde **21a** (0.54 g, 90% yield in 2 steps) as a colorless crystal. Compound **21a**: R_f = 0.35 (silica gel, hexane/EtOAc = 2:1, PMA); [α]25 D = - 65 (c = 0.5, $CHCl_3$); m.p.: 138.9–140.2 °C; IR (thin film, *v* cm^{-1}): 2993, 2917, 2851, 1762, 1726, 1693, 1276, 1204; HRMS (ESI): m/z calcd for $C_{18}H_{25}O_4^+$ $[M+H]^+$: 305.1747; found: 305.1748. ^1H NMR (500 MHz, Acetone) δ = 9.76 (d, *J* = 2.9 Hz, 1H), 5.48 – 5.39 (m, 1H), 5.25 – 5.14 (m, 1H), 5.06 (d, *J* = 6.7 Hz, 1H), 3.88 (t, *J* = 8.1 Hz, 1H), 3.15 – 3.03 (m, 2H), 2.99 (dd, *J* = 12.1, 7.5 Hz, 1H), 2.73 (t, *J* = 14.3 Hz, 1H), 2.27 (dd, *J* = 14.5, 1.9 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.84 – 1.76 (m, 1H), 1.61 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, Acetone) δ = 210.1, 201.6, 177.4, 130.1, 127.2, 79.7, 56.4, 56.0, 53.6, 50.8, 49.9, 46.7, 35.6, 31.2, 21.2, 21.0, 20.7, 18.4 ppm.

Compound **21b**: R_f = 0.6 (silica gel, hexane/EtOAc = 2:1, PMA). [α]25 D = 86 (c = 0.5, $CHCl_3$); m.p.: 87.4–93.0 °C; IR (thin film, *v* cm^{-1}): 2995, 2918, 2853, 1765, 1727, 1695, 1207; HRMS (ESI): m/z calcd for $C_{18}H_{25}O_4^+$ $[M+H]^+$: 305.1747; found: 305.1748; ^1H NMR (400 MHz, Acetone) δ = 9.63 (d, *J* = 0.4 Hz, 1H), 5.76 – 5.61 (m, 1H), 5.26 – 5.13 (m, 2H), 3.93 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.61 (dd, *J* = 10.9, 7.2 Hz, 1H), 3.30 (dd, *J* = 10.5, 7.4 Hz, 1H), 3.04 (dd, *J* = 12.1, 5.4 Hz, 1H), 2.72 – 2.62 (m, 1H), 2.24 – 2.12 (m, 2H), 1.75 – 1.67 (m, 1H), 1.65 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.11 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, Acetone) δ = 211.3, 199.0, 177.8, 130.4, 125.7, 76.0, 57.8, 56.4, 51.6, 50.3, 43.5, 42.7, 35.9, 30.4, 20.3, 19.8, 19.6, 17.0 ppm.

(2a*R*,2a^1*S*,3*R*,4*S*,4a*R*,7*S*,7a*R*)-7-isopropyl-4a-methyl-3-(3-methylpent-4-enoyl)-4-((*E*)-prop-1-en-1-yl)octahydroindeno[7,1-bc]furan-2,5-dione (22b):

To a flame-dried flask under N_2 containing $Ni(acac)_2$ (51.4 mg, 0.2 mmol, 0.2 equiv) was introduced a solution of aldehyde **21b** (304 mg, 1.0 mmol 1.0 equiv) in THF (10 mL) and isoprene (0.4 mL, 4.0 mmol, 4.0 equiv) via syringe at room temperature. Then Et_2Zn (1 M in hexane, 2.4 mL, 2.4 mmol, 2.4 equiv) was added dropwise at 0 ^oC.[6] The mixture was stirred at room temperature for 4 h, during which the reaction was monitored by TLC. After dilution with ethyl acetate (10 mL), the mixture was washed successively with aq. HCl solution (1N, 10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4 and concentrated under vacuum. The residual oil was used directly for the next step without further purification. To a solution of this crude alcohol in DCM (10 mL) was added $NaHCO_3$ (0.42 g, 5.0 mmol, 5.0 equiv) and Dess-Martin periodinane (2.54 g, 6.0 mmol, 1.2 equiv) at 0 ^oC. The reaction mixture was stirred for 4 h at room temperature. After completion, the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 6:1) to give compound **22b** (332 mg, 94% yield for 2 steps) as a viscous oil. Compound **22b**: R_f = 0.50 (silica gel, hexane/EtOAc = 2:1, PMA); [α]25 D = - 110 (c = 0.5, $CHCl_3$); IR (thin film, ν cm^{-1}): 2961, 2930, 2880, 2853, 1771, 1710, 1372, 1120; HRMS (ESI): m/z calcd for $C_{23}H_{32}NaO_4^+$ $[M+Na]^+$: 395.2193; found: 395.2197; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.80 – 5.69 (m, 1H), 5.62 – 5.51 (m, 1H), 5.05 – 4.90 (m, 4H), 4.04 (dd, *J* = 10.8, 7.4 Hz, 1H), 3.58 (dd, *J* = 11.0, 6.9 Hz, 1H), 3.15 – 3.01 (m, 2H), 2.75 – 2.62 (m, 2H), 2.49 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.35 – 2.18 (m, 2H), 2.02 – 1.93 (m, 1H), 1.84 – 1.73 (m, 1H), 1.63 (d, *J* = 5.4 Hz, 3H), 1.09 (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 212.4, 204.9, 178.2, 142.9, 131.0, 125.1, 113.0, 75.7, 57.8, 57.5, 53.5, 49.9, 49.4, 45.0, 42.9, 36.3, 32.5, 30.3, 22.0, 20.7, 20.4, 19.7, 17.8 ppm.

(2a*R*,2a^1*S*,3*S*,5a*R*,5b*S*,10a*R*,10b*R*)-3-isopropyl-5a,8-dimethyl-2a,2a1,3,4,5a,5b,8,9,10a,10b-decahydro-1H-cyclohepta[2,3]indeno[7,1-bc]furan-1,5,10-trione (23b):

To an N_2-purged flask containing Grubbs II catalyst (100 mg, 0.12 mmol, 0.2 equiv) was introduced a solution of **22b** (220 mg, 0.6 mmol) in DCM via syringe. The solution was refluxed for 6 h. After completion, the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give **23b** (170 mg, 86% yield) as colorless viscous oil. Compound **23b**: R_f = 0.5 (silica gel, hexane/EtOAc = 2:1, PMA); IR (thin film, ν cm^{-1}):

2961, 2922, 1765, 1695, 1168; HRMS (ESI): m/z calcd for $C_{20}H_{26}NaO_4^+$ $[M+Na]^+$: 353.1723; found: 353.1723; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.64 – 5.60 (m, 1H), 5.34 (dt, *J* = 11.5, 2.5 Hz, 1H), 4.93 (d, *J* = 6.7 Hz, 1H), 4.05 (d, *J* = 8.5 Hz, 1H), 3.80 (d, *J* = 8.9 Hz, 1H), 3.09 – 2.99 (m, 1H), 2.98 – 2.88 (m, 2H), 2.61 (dd, *J* = 18.7, 3.6 Hz, 1H), 2.54 – 2.33 (m, 3H), 1.88 – 1.78 (m, 1H), 1.74 – 1.66 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 211.0, 209.6, 179.4, 137.7, 125.3, 77.9, 56.6, 54.9, 53.1, 51.4, 49.2, 47.6, 45.5, 34.7, 30.0, 27.1, 21.5, 21.5, 20.5, 20.2 ppm.

(2a*R*,2a^1*S*,3*S*,5a*R*,5b*S*,10a*S*,10b*R*)-3-isopropyl-5a,8-dimethyldodecahydro-1H-cyclohepta[2,3]indeno[7,1-bc]furan-1,5,10-trione (24a):

To a Ar-purged flask containing Pd/C catalyst (12 mg, 20 wt%) was introduced a solution of **23a**[3a] (57.5 mg, 0.17 mmol, 1.0 equiv) in MeOH via syringe. The solution was bubbled with H_2 balloon and was stirred for 36 h under H_2 atmosphere. After completion, the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give **24a** (45 mg, 85% yield) as a viscous oil. Compound **24a:** R_f = 0.45 (silica gel, hexane/EtOAc = 2:1, PMA); [α]26 D = - 142 (c = 0.5, $CHCl_3$); IR (thin film, *v* cm^{-1}): 2961, 2922, 2854, 1765, 1700, 1462, 1221, 1162, 1009; HRMS (ESI): m/z calcd for $C_{20}H_{26}NaO_4^+$ $[M+Na]^+$: 355.1880; found: 355.1877; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.86 (dd, *J* = 4.8, 1.6 Hz, 1H), 3.70 (dd, *J* = 8.3, 6.9 Hz, 1H), 2.86 (dd, *J* = 13.0, 2.2 Hz, 1H), 2.79 – 2.61 (m, 3H), 2.59 – 2.52 (m, 1H), 2.39 – 2.34 (m, 1H), 2.24 – 2.16 (m, 1H), 1.91 – 1.78 (m, 2H), 1.78 – 1.66 (m, 2H), 1.65 – 1.52 (m, 1H), 1.06 – 1.00 (m, 6H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 210.6, 176.9, 77.8, 57.7, 54.3, 51.3, 50.7, 50.2, 47.8, 46.0, 35.5, 34.7, 29.9, 29.6, 28.3, 22.6, 20.5, 20.2, 19.4, 17.2 ppm.

Rh(III)-catalyzed double bond migration

To a flame-dried microwave vial equipped with a magnetic stir bar was charged with $RhCl_3•3H_2O$ (8.0 mg, 0.03 mmol, 0.2 equiv), capped with a rubber septum, and evacuated and backfilled with N_2 three times. Then a solution of compound **23b** (50.0 mg, 0.15 mmol, 1.0 equiv) in ethanol (3 mL) and DCM (0.5 mL) was added to the vial. The vial was heated to 100 °C in an oil bath for 5 h. After completion, the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 6:1) to give Pavidolide B (**1**) (42.5 mg, 85% yield) as colorless crystals. Pavidolide B (**1**): R_f = 0.40 (silica gel, hexane/EtOAc = 2:1, UV); [α]25 D = -146 (c = 0.42, MeOH); mp : 179.6–180.9 °C; IR (thin film, *v* cm^{-1}): 2960, 2924, 1764, 1707, 1695, 1195, 1170; HRMS

(ESI): m/z calcd for $C_{20}H_{26}NaO_4^+$ $[M+Na]^+$: 353.1723; found: 353.1723; ^1H NMR (400 MHz, DMSO) δ = 5.90 (s, 1H), 4.98 (d, *J* = 6.9 Hz, 1H), 3.71 (d, *J* = 9.0, 1H), 3.41 (d, *J* = 9.4 Hz, 1H), 2.96 (dd, *J* = 9.0, 6.8 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.50 – 2.43 (m, 2H) 2.33 (dd, *J* = 17.8, 6.2 Hz, 1H), 2.17 (dd, *J* = 15.2, 2.5 Hz, 1H), 1.97 (s, 3H), 1.94 – 1.82 (m, 1H), 1.72 – 1.63 (m, 2H), 1.32 (dd, *J* = 24.7, 12.5 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ = 211.5, 199.2, 179.9, 164.4, 128.3, 78.1, 59.2, 54.4, 53.8, 48.1, 46.8, 44.2, 34.7, 33.7, 30.2, 27.7, 26.3, 20.7, 20.7, 20.4 ppm.

ASSOCIATED CONTENT

Supporting Information. Additional experiments, NMR spectra, computational data, X-ray crystallography data and CIF files-are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

gongjx@pku.edu.cn

zyang@pku.edu.cn

ORCID

Zhen Yang: 0000-0001-8036-934X

Jianxian Gong: 0000-0003-4331-0976

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by National Science Foundation of China (Grant Nos. 21632002, 21572009, and U1606403), Guangdong Natural Science Foundation (Grant No. 2016A030306011), Shenzhen Basic Research Program (Grant Nos. JCYJ20170818090044432, JCYJ20160226105337556 and GRCK2017042414425972), and Qingdao National Laboratory for Marine Science and Technology

(Nos. 2015ASKJ02 and LMDBKF201703). The hardware for the computational study was supported by the high-performance computing platform of Peking University (PKU-HPC)

REFERENCES

(1) (a) Li, Y.; Pattenden, G. Perspectives on the structural and biosynthetic interrelationships between oxygenated furanocembranoids and their polycyclic congeners found in corals. *Nat. Prod. Rep*. **2011**, 28, 1269–1310. (b) Iwagawa, T.; Nakashima, R.; Takayama, K.; Okamura, H.; Nakatani, M. New cembranes from the soft coral sarcophyton species. *J. Nat. Prod.* **1999**, *62*, 1046–1049.

(2) Shen, S.; Zhu, H.; Chen, D.; Liu, D.; van Ofwegen, L.; Proksch, P.; Lin, W. Pavidolides A–E, new cembranoids from the soft coral sinularia pavida. *Tetrahedron Lett*. **2012**, *53*, 5759–5762.

(3) (a) Zhang, P.-P.; Yan, Z.-M.; Li, Y.-H.; Gong, J.; Yang Z. Enantioselective total synthesis of (−)-pavidolide B. *J. Am. Chem. Soc.* **2017**, *139*, 13989–13992. (b) He, C.; Xuan, J.; Rao, P.; Xie, P.-P.; Hong, X.; Lin, X.; Ding, H. Total syntheses of (+)-sarcophytin, (+)-chatancin, (−)-3-oxochatancin, and (−)-pavidolide B: A Divergent Approach. *Angew. Chem. Int. Ed.* **2019**, *58*, 5100–5104. (c) Rao, P.; Hu, J.; Xuan, J.; Ding, H. Total synthesis of (−)-pavidolide B: a ring contraction strategy. *J. Org. Chem.* **2019**, *84*, 9385−9392.

(4) For free-radical-mediated annulation of VCPs and alkenes, see: (a) Dowd, P.; Zhang, W. Free radical-mediated ring expansion and related annulations. *Chem. Rev*. **1993**, *93*, 2091–2115. For transition metal-catalyzed annulation between activated VCPs and electron-deficient alkenes, see: (b) Shimizu, I.; Ohashi, Y.; Tsuji, J. Palladium-catalyzed [3+2] cycloaddition reaction of vinylcyclopropanes with *α,β*-unsaturated esters or ketones. *Tetrahedron Lett.* **1985**, *26*, 3825–3828. (c) Jiao, L.; Yu, Z.-X. Vinylcyclopropane derivatives in transition-metal-catalyzed cycloadditions for the synthesis of carbocyclic compounds. *J. Org. Chem.* **2013**, *78*, 6842–6848. For recent applications of VCP [3+2] annulations in natural product synthesis, see: (d) Zhang, H.; Curran, D. P. A short total synthesis of (±)-epimeloscine and (±)-meloscine enabled by a cascade radical annulation of a divinylcyclopropane. *J. Am. Chem. Soc*. **2011**, *133*, 10376–10378. (e) Goldberg, A. F. G.; Stoltz, B. M. A palladium-catalyzed vinylcyclopropane [3+2] cycloaddition approach to the melodinus alkaloids. *Org. Lett*. **2011**, *13*, 4474–4476.

(5) (a) Grubbs, R. H. Handbook of Metathesis, Vols. 1, 2; Wiley-VCH: Weinheim, **2003**. (b) Grubbs, R. H. Olefin metathesis. *Tetrahedron* **2004**, *60*, 7117–7140.

(6) For reviews: (a) Vilches-Herrera, M.; Domke, L.; Börner, A. Isomerization–hydroformylation tandem reactions. *ACS Catal.* **2014**, *4*, 1706–1724. (b) Larionov, E.; Li, H.; Mazet, C. Well-defined transition metal hydrides in catalytic isomerizations. *Chem. Commun.* **2014**, *50,* 9816–9826.

(7) (a) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. nickel-catalyzed homoallylation of aldehydes and ketones with 1,3-dienes and complementary promotion by diethylzinc or triethylborane. *Angew. Chem., Int. Ed.* **1999**, *38*, 397–400. (b) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. Regio- and stereoselective nickel-catalyzed homoallylation of aldehydes with 1,3-dienes. *J. Am. Chem. Soc.* **2006**, *128*, 8559–8568. (c) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. Nickel catalysis: Synergy between method development and total synthesis. *Acc. Chem. Res.* **2015**, *48*, 1503–1514. (d) Tasker, S. Z.; Standley, E. A., Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299–309. (e) Montgomery, J. Nickel-catalyzed reductive cyclizations and couplings. *Angew. Chem. Int. Ed*. **2004**, *43*, 3890–3908.

(8) (a) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. Organocatalytic enantioselective cascade michael-alkylation reactions: synthesis of chiral cyclopropanes and investigation of unexpected organocatalyzed stereoselective ring opening of cyclopropanes. *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894. (b) Rios, R.; Sunden, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Cordova, A. A simple organocatalytic enantioselective cyclopropanation of *α,β*-unsaturated aldehydes. *Adv. Synth. Catal*. **2007**, *349*, 1028–1032. (c) Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sunden, H.; Dziedzic, P.; Cordova, A. One-pot organocatalytic domino michael/α-alkylation reactions: Direct catalytic enantioselective cyclopropanation and cyclopentanation reactions. *Chem.-Eur. J.* **2008**, *14*, 7867–7879.

(9) (a) Tanaka, A.; Yamamoto, H.; Oritani, T. Lipase-catalyzed asymmetric synthesis of (*R*)- and (*S*)-4-tert-butyldimethylsilyloxy-2,6,6-trimethyl-2-cyclohexenone and their dihydro derivatives. *Tetrahedron: Asymmetry* **1995**, *6*, 1273-1278. (b) Karadeolian, A.; Kerr, M. A. Total synthesis of (+)-isatisine A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1133–1135.

(10) Trost, B. M.; Morris, P. J.; Sprague, S. J. Palladium-Catalyzed Diastereo- and Enantioselective Formal [3+2]-Cycloadditions of Substituted Vinylcyclopropanes *J. Am. Chem. Soc.* **2012**, *134*, 17823–17831.

(11) Li, S.; Zhang, P.; Li, Y.; Lu, S.; Gong, J.; Yang Z. Diastereoselective synthesis of diquinanes and triquinanes bearing vicinal quaternary carbon stereocenters from acyclic allene-based precursors via a cascade reaction. *Org. Lett.* **2017**, *19*, 4416–4419.

(12) (a) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. Triprenylstannyl radical or benzenethiyl radical promotedtransformation of 1,1-dialk oxycarronyl-2-(1,3-butadienyl)cyclopropanes into 2-ethenyl-3-cyclopentenes. *Tetrahedron Lett.* **1988**, *29*, 1543−1546. (b) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. Synthesis of vinylcyclopentanes from vinylcyclopropanes and alkenes promoted by benzenethiyl radical. *Tetrahedron Lett*. **1988**, *29*, 5135−5138. For the utility of thiyl radical in organic synthesis, see: (c) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl radicals in organic synthesis. *Chem. Rev.* **2014**, *114*, 2587−2693. (d) Glass, R. S. Sulfur radicals and their application. *Top. Curr. Chem. (Z)* **2018**, *376*, 22–42.

(13) (a) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. The decarbethoxylation of geminal dicarbethoxy compounds. *Tetrahedron Lett.* **1967**, *8*, 215–217. (b) Teng, M.; Zi, W.; Ma, D. Total synthesis of the monoterpenoid indole alkaloid (±)-aspidophylline A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1814–1817.

(14) Kirmse, W.; Chiem, P.; Henning, P.-G. The diazo route to 2-vinylcyclopropylidenes. *Tetrahedron*, **1985**, *41*, 1441–1451.

(15) García-Cabeza, A. L.; Marín-Barrios, R.; Azarken, R.; MorenoDorado, F. J.; Ortega, M. J.; Vidal, H.; Gatica, J. M.; Massanet, G. M.; Guerra, F. M. DoE (design of experiments) assisted allylic hydroxylation of enones catalysed by a copper-aluminium mixed oxide. *Eur. J. Org. Chem.* **2013**, *2013*, 8307−8314.

(16) Ireland, R. E.; Bey, P. Homogeneous catalytic hydrogenation: dihydrocarvone. *Org. Synth.* **1973**, *53*, 63–63.

(17) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Enantioselective organocatalyzed α sulfenylation of aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 794−797. (b)

Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol silyl ethers as efficient organocatalysts for the asymmetric michael reaction of aldehydes and nitroalkenes. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212−4215.

(18) When 2,2-dimethylpropane-1,3-diol was used to protect the aldehyde **12**, excellent diastereoselectivity was achieved in the [3+2] reaction, but the deprotection in latter stage was failed under various conditions.

(19) Prantz, K.; Mulzer, J. Synthesis of (Z)-trisubstituted olefins by decarboxylative grob-type fragmentations: epothilone D, discodermolide, and peloruside A. *Chem. Eur. J.* **2010**, *16*, 485−506.

(20) (a) Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis* **1981**, *1981*, 1−28. (b) Appendino, G.; Minassi, A.; Daddario, N.; Bianchi, F.; Tron, G. C. Chemoselective esterification of phenolic acids and alcohols. *Org. Lett*. **2002**, *4*, 3839−3841.

(21) The calculation was performed with Gaussian 09 D.01 and ORCA 4.0.0.2 or ORCA 4.0.0 program. (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; et al., *Gaussian 09, Revision D.01*. Wallingford CT, **2009** (for a complete list of authors, see Supporting Information). (b) Neese, F. The ORCA program system. *Comput. Mol. Sci.* **2012,** *2*, 73−78. For references of the methods and basis sets: (c) Goerigk, L.; Grimme, S. Efficient and accurate Double-Hybrid-Meta-GGA density functionals-evaluation with the extended GMTKN30 database for general main group thermochemistry, kinetics, and noncovalent interactions. *J. Chem. Theory Comput.* **2011,** *7*, 291−309. (d) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, 7, 3297−3305. (e) Perdew, J. P.; Ernzerhof, M.; Burke, K. Rationale for mixing exact exchange with density functional approximations. *J. Chem. Phys.* **1996,** *105*, 9982−9885. (f) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009,** *113* (18), 6378−6396. The RDG analysis is performed with the Multiwfn program package:

(g) Lu, T., Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.* **2012**, *33*, 580−592. (h) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. Revealing noncovalent interactions. *J. Am. Chem. Soc.* **2010**, *132*, 6498−6506.

(22) Schneider, M.; Merz, I. Thermolyse und photolyse von *exo*-4-vinyl-2,3-diazabicyclo [3.3.0]oct-2-en. zugang zu der vinylcyclopropan-cyclopenten-umlagerung bicyclischer system. *Tetrahedron Lett.* **1974**, *15*, 1995−1998.

(23) (a) Feldman, K. S.; Berven, H. M.; Romanelli, A. L.; Parvez, M. Macrocyclization through radical-mediated vinylcyclopropane/alkene condensation. facile entry into the brefeldin ring system. *J. Org. Chem*. **1993**, *58*, 6851−6856. (b) Jung, M. E.; Rayle, H. L. Generation of [5.5.n] tricyclic ring systems by radical-promoted inter- and intramolecular [3+2] cycloadditions. *J. Org. Chem*. **1997**, *62*, 4601−4609.

(24) (a) Feldman, K. S.; Ruckle, R. E., Jr.; Romanelli, A. L. Vinylcyclopentene synthesis via phenylthio radical catalyzed addition of electron deficient alkynes to substituted vinylcyclopropanes. *Tetrahedron Lett.* **1989**, *30*, 5845−5848. (b) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. Cyclopentane synthesis via free radical mediated addition of functionalized alkenes to substituted vinyl cyclopropanes. *J. Am. Chem. Soc.* **1988**, *110*, 3300−3302.

(25) Hashimoto, T.; Kawamata, Y.; Maruoka, K. An Organic thiyl radical catalyst for enantioselective cyclization. *Nature Chem*, **2014**, *6*, 702−705.

(26) (a) Keylor, M. H.; Park, J. E.; Wallentin, C.-J.; Stephenson, C. R. J. Photocatalytic initiation of thiol–ene reactions: synthesis of thiomorpholin-3-ones. *Tetrahedron* **2014**, *70*, 4264−4269. (b) Xu, J.; Boyer, C. Visible light photocatalytic thiol-ene reaction: an elegant approach for fast polymer postfunctionalization and step-growth polymerization. *Macromolecules* **2015**, *48*, 520−529. (c) Tyson, E. L.; Ament, M. S.; Yoon, T. P. Transition metal photoredox catalysis of radical thiol-ene reactions. *J. Org. Chem.* **2013**, *78*, 2046−2050. (d) Tyson, E. L.; Niemeyer, Z. L.; Yoon, T. P. Redox Mediators in visible light photocatalysis: photocatalytic radical thiol-ene additions. *J. Org. Chem.* **2014**, *79*, 1427−1436.

(27) (a) Zhao G.; Kaur, S.; Wang, T. Visible-light-mediated thiol-ene reactions through organic photoredox catalysis. *Org. Lett*. **2017**, *19*, 3291-3294. (b) Limnios, D.; Kokotos, C. G. Photoinitiated thiol-ene "click" reaction: an organocatalytic alternative. *Adv. Synth. Catal.* **2017**, *359*, 323−328.

(28) For visible-light-mediated thiol-ene reaction through other types of catalysis, see: (a) Bhat, V. T.; Duspara, P. A.; Seo, S.; Abu Bakar, N. S. B.; Greaney, M. F. Visible light promoted thiol-ene reactions using titanium dioxide. *Chem. Commun.* **2015**, *51*, 4383−4385. (b) Fadeyi, O. O.; Mousseau, J. J.; Feng, Y.; Allais, C.; Nuhant, P.; Chen, M. Z.; Pierce, B.; Robinson, R. Visible-light-driven photocatalytic initiation of radical thiol-ene reactions using bismuth oxide. *Org. Lett.* **2015**, *17*, 5756−5759.

(29) Selected reviews on photoredox catalysis, see: (a) Ravelli, D.; Protti, S.; Fagnoni, M. Carbon-carbon bond forming reactions via photogenerated intermediates. *Chem. Rev*. **2016**, *116*, 9850−9913. (b) Yoon, T. P. Photochemical stereocontrol using tandem photoredox-chiral lewis acid catalysis. *Acc. Chem. Res.* **2016**, *49*, 2307−2315. (c) Staveness, D.; Bosque, I.; Stephenson, C. R. J. Free radical chemistry enabled by visible light-induced electron transfer. *Acc. Chem. Res*. **2016**, *49*, 2295−2306.

(30) For recent reviews on carbonyl dehydrogenation: (a) Turlik, A.; Chen, Y.; Newhouse, T. R. Dehydrogenation adjacent to carbonyls using Pd-Allyl intermediates. *Synlett* **2016**, *27*, 331−336. (b) Iosub, A. V.; Stahl, S. S. Palladium-catalyzed aerobic dehydrogenation of cyclic hydrocarbons for the synthesis of substituted aromatics and other unsaturated products. *ACS Catal.* **2016**, *6*, 8201−8213.

(31) (a) Ito, Y.; Hirao, T.; Saegusa, T. Synthesis of *α,β*-unsaturated carbonyl compounds by Palladium(II)-catalyzed dehydrosilylation of silyl enol ethers. *J. Org. Chem.* **1978**, *43*, 1011−1013.

(32) (a) Reich, H. J.; Reich, I. L.; Renga, J. M. Organoselenium chemistry. *α*-phenylseleno carbonyl compounds as precursors for *α,β*-unsaturated ketones and esters. *J. Am. Chem. Soc.* **1973**, *95*, 5813−5815. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. Electrophilic and nucleophilic organoselenium reagents. new routes to *α, β*-unsaturated carbonyl compounds. *J. Am. Chem. Soc.* **1973**, *95*, 6137−6139.

(33) (a) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. A New method for the one-step synthesis of *α, β*-unsaturated carbonyl systems from saturated alcohols and carbonyl compounds. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. Iodine (V) reagents in organic synthesis. Part 4. *o*-iodoxybenzoic acid as a chemospecific tool for single electron transfer-based oxidation processes. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. Modulation of the reactivity profile of ibx by ligand complexation: Ambient temperature dehydrogenation of aldehydes and ketones to *α,β*-unsaturated carbonyl compounds. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996. (d) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. Oxidation of silyl enol ethers by using IBX and IBX·N-oxide complexes: A mild and selective reaction for the synthesis of enones. *Angew. Chem., Int. Ed.* **2002**, *41*, 996−1000. (e) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. HIO3 and I2O5: Mild and selective alternative reagents to IBX for the dehydrogenation of aldehydes and ketones. *Angew. Chem., Int. Ed*. **2002**, *41*, 1386−1389.

(34) Diao, T. Stahl, S. S. Synthesis of cyclic enones via direct palladium-catalyzed aerobic dehydrogenation of ketones *J. Am. Chem. Soc*. **2011**, *133*, 14566−14569.

(35) (a) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. Remote double bond migration via rhodium catalysis: a novel enone transposition. *J. Am. Chem. Soc.* **1976**, 98, 7102−7104. (b) Ohlmann, D. M.; Gooßen, L. J.; Dierker, M. Regioselective synthesis of *β*-aryl- and *β*-amino-substituted aliphatic esters by rhodium-catalyzed tandem double-bond migration/conjugate addition. *Chem. - Eur. J.* **2011**, *17*, 9508−9519.

(36) Li, W. Total Synthesis of harringtonolide-introducing antidihydroxy group and forming the lactone. *Asian J. Chem*. **2012**, *24*, 1411-1412.