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Collective Synthesis of Schilancidilactones A, B and Schilancitrilactones A, B, C, 20-*epi*-Schilancitrilactone A

Hengtao Wang,[a] Liang Wang,[a] Yihang Li[a], Xiunan Zhang[a] and Pingping Tang*[a,b]

ABSTRACT Schisandraceae triterpenoids are novel natural products that contain highly fused ring systems bearing multiple chiral centers surrounding. Some of them exhibit promising bioactivities, such as antitumor, anti-HIV etc. In this article, we describe our efforts to the collective total synthesis of schilancidilactones A, B, schilancitrilactones A, B, C, and 20-*epi*-schilancitrilactone A from common precursors. An intramolecular radical cyclization, late-stage halogenation and AIBN-mediated or Ni-catalyzed intermolecular radical cross coupling reaction was employed as the key steps.

KEYWORDS total synthesis, radical cyclization, nickel-catalyzed cross coupling, late-stage halogenation, triterpenoids

Introduction

Schisandraceae, containing genera Schisandra and Kadsura, was widely distributed in Southeast Asia and North America. 29 species of this family spread over southwest part in China, and the most famous is Schisandra chinensis, called *wuweizi* in Chinese, which has been used as traditional Chinese medicine for the treatment of asthenia and insomnia for thousands of years. [1] With the enormous medical value, this family of plants has attracted many chemists' attention. Over the last forty years, many chemists devoted their efforts to the extraction of valuable bioactive molecules from schisandraceae.[2] So far, more than 200 schisandraceae nortriterpenoids were isolated, many of which possessed fascinating bioactivities, such as antitumor, antihepatitis, anti-HIV-1.[2] Besides fascinating bioactivities, most schisandraceae nortriterpenoids shared novel skeletons with highly fused ring system bearing multiple vicinal stereocenters.[2,3,4] Therefore, many research groups have made considerable efforts towards the synthesis of schinortriterpenoids during the last two decades.[3,4].

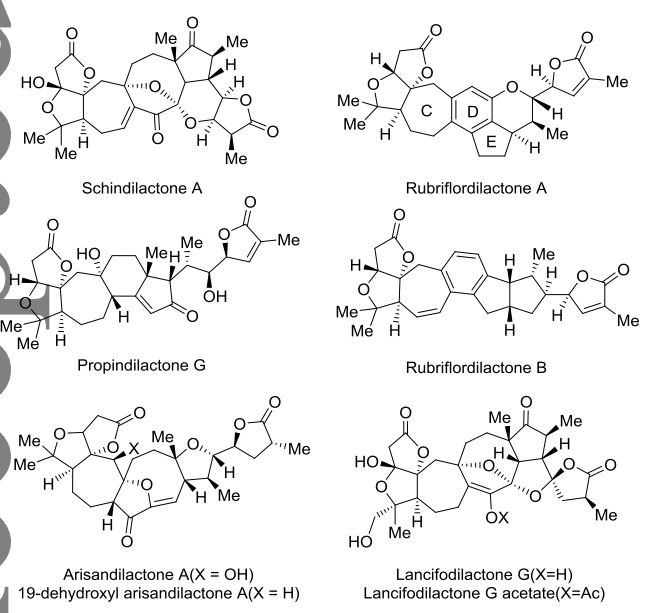

Figure 1 Schindilactone A, rubriflordilactone A and B, propindilactone G, arisandilactone A, lancifodilactone G.

The breakthrough of the synthesis of schinortriterpenoids was the complete synthesis of schindilactone A by Yang and coworkers in 2011 [4a] (Figure 1). From then on, reports about the total synthesis of molecules in this family blossomed over the last 8 years. In 2014, Li[4e] group disclosed the synthesis of rubriflordilactone A, in which 6π-electrocyclization/aromatization was adopted as the key transformation to constructed the challenging pentasubstituted arene. Anderson[4f] group also accomplished the rubriflordilactone A featured a Pd- or Co-catalyzed cyclization to form the CDE rings in one step in 2015. In the follow years, the total synthesis of propindilactone G,[4h] rubriflordilactone B,[4l] 19-dehydroxyl arisandilactone A[4m] lancifodilactone G[4n,4q] acetate and schiglautone A[4p] were successively completed. In 2015 and 2017, we briefly reported the total synthesis of schilancidilactones A, B[4o] and schilancitrilactones A, B, C,[4g] 20-*epi*-schilancitrilactone A (Figure 2). In this article, we will represent a more detailed discussion.

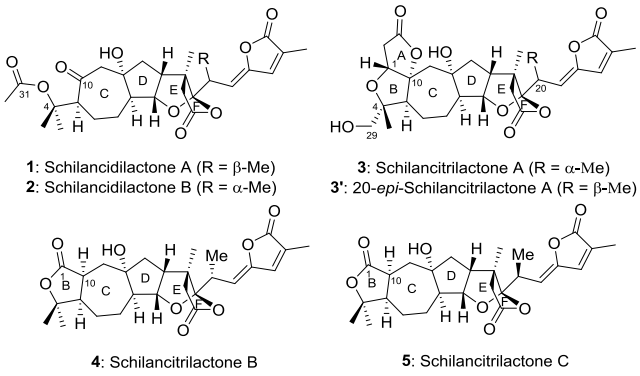

Figure 2 Schilancidilactones A, B and schilancitrilactones A, B, C, 20-*epi*-schilancitrilactone A.

Results and Discussion

From the structural point of view, compounds **1**-**5** (Figure 2) all share highly fused ring systems and highly oxidative state.[5,6] There are lots of chiral centers in these molecules, many of which are adjacent to other. Thus, to complete the total synthesis of compounds **1**-**5** is a challenging work. From another point of view, these five compounds are of great similarity to each other. All these molecules share the same 7/5/5/5-fused CDEF ring systems and the same side lactone. The main difference of the five compounds lies in the left part, of which schilancidilactones A, B are open-ring system, schilancitrilactone A is 5/5-fused ring system, schilancitrilactones B, C are 5-member ring system. Herein, we tend to apply the same synthetic strategy to achieve these five

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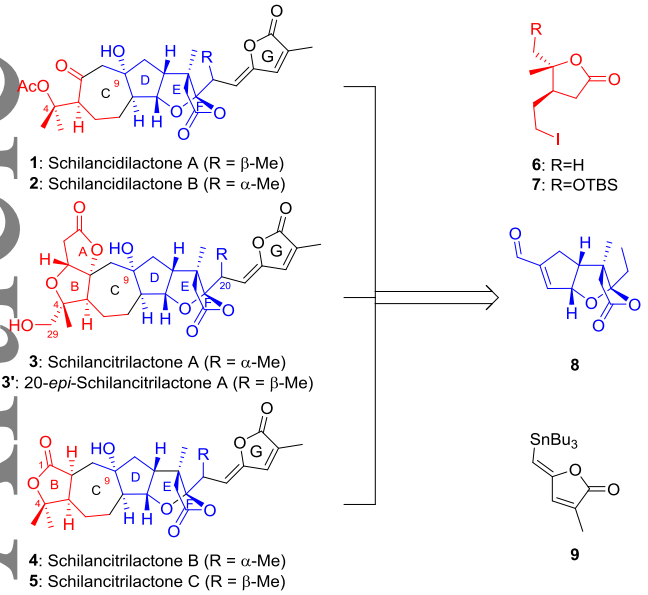
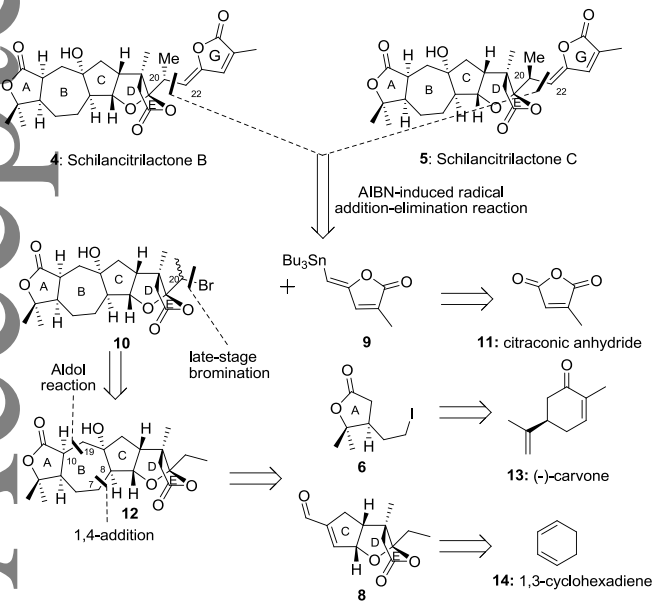
molecules. We pursued to take part of these molecules into three components, namely left fragments **6** and **7**, middle fragment **8** and right fragment **9** as shown in Scheme 1. On the whole, the left fragment **6** or **7** was sequentially connected to the middle fragment **8** and right fragment **9**, and then underwent later-stage transformation to achieve molecules **1**-**5**.



Scheme 1 Retrosynthetic analysis of compounds **1**-**5**.

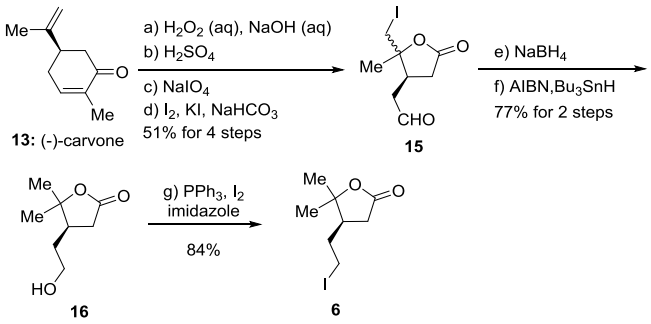
Total synthesis of schilancitrilactones B, C



Scheme 2 Retrosynthetic analysis of schilancitrilactones B and C.

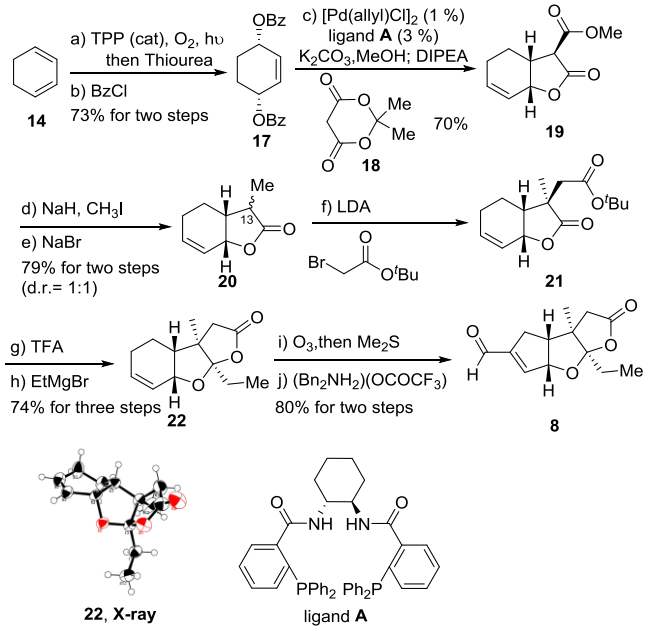
Based on our retrosynthetic analysis, we initially decided to choose schilancitrilactones A and B (**4**, **5**, Scheme 2) as first goal. Both molecules possessed a challenging backbones with 5/7/5/5/5-fused ring system and 9 stereocenters. We hypothesized that branched domain G of molecules **4** and **5** could be raised by AIBN-induced radical addition-elimination reaction of alkyl bromide **10** and right fragment **9**[7] as shown in Scheme 2.

The alkyl bromide **10** was expected to be installed by late-stage C (sp^3)-H bromination[8] at the C20 (α-position of the ketal) from the lactone **12**. Stannane **9** was intended to be synthesized from the citraconic anhydride **11** according to Benneche's work.[9] The lactone **12** was expected to be synthesized from left fragment **6** and right fragment **8** by intermolecular 1, 4-addition of organozincs[10,11] or ogranolithiums[12] derived from **6** to form C7-C8 bond, and the given enolate anions was going to be trapped by TMSCl followed by Rubottom[13] oxidation to install the hydroxyl group at C9. The resulting formyl lactone underwent intramolecular aldol reaction to obtain lactone **12**. Fragments **6** and **8** could be synthesized from 1, 3-cyclohexadiene (**14**) and (-)-carvone (**13**), respectively.[9b]



Scheme 3 Synthesis of left fragment **6**.

The total synthesis of schilancitrilactones A and B was commenced with the synthesis of alkyl iodide **6** (Scheme 3) from the commercially avaliable (-)-carvone (**13**). Following Fukuyama's work, [14] (-)-carvone (**13**) was converted to the aldehyde **15** over four steps in overall 51% yield. Aldehyde **15** was reduced with $NaBH_4$ followed by deiodination with AIBN and Bu_3SnH to give compound **16**. Alcohol **16** was then reacted with I_2, Ph_3P and imidazole to afford the left fragment **6** in 84% yield.[15]

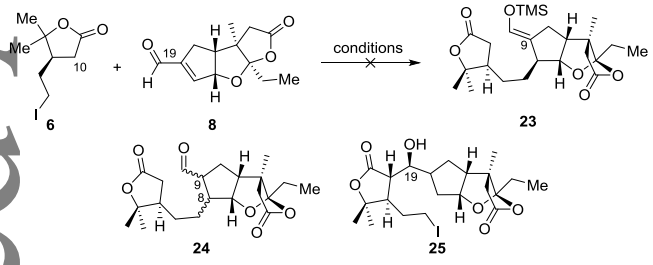


Scheme 4 Synthesis of middle fragment **8**.

The total synthesis of aldehyde **8** was shown in Scheme 4.

Starting from 1, 3-cyclehexadiene (**14**), we sequentially applied the O_2-participated Diels-Alder reaction, thiourea-participated reduction to give the diol, which was then protected by benzoyl chloride to afford the compound **17** in overall 79% yield. Using asymmetric palladium catalyzed allylic alkylation developed by Trost and co-workers,[16] the compound **17** was converted to lactone **19** in 70% yield. Lactone **19** was treated with NaH followed by methyl iodide to give a methylated product, which underwent decarboxylation by treated with NaBr to afford the lactone **20** in overall 79% yield (d.r.= 1:1 at C13). Alkylation of lactone **20** was achieved by sequentially adding LDA and *t*-butyl bromoacetate to produce a single diastereomer **21**. The latter underwent deprotection with trifluoroacetic acid and addition of ethyl magnesium bromide followed by acidic workup to afford tricycle **22** in 74% yield, in which an ethyl group was installed stereoselectively into the tricyclic framework.[17] The absolute configuration of tricycle **22** was determined by X-ray crystallographic analysis. After oxidative cleaved of double bond by ozonolysis in compound **22**, the resulting dialdehyde was directly subjected to intramolecular aldol condensation to afford ring-closed unsaturated aldehyde **8** in overall 80% yield for two steps.[18]

Table 1 Conditions for assemble blocks **6** and **8**

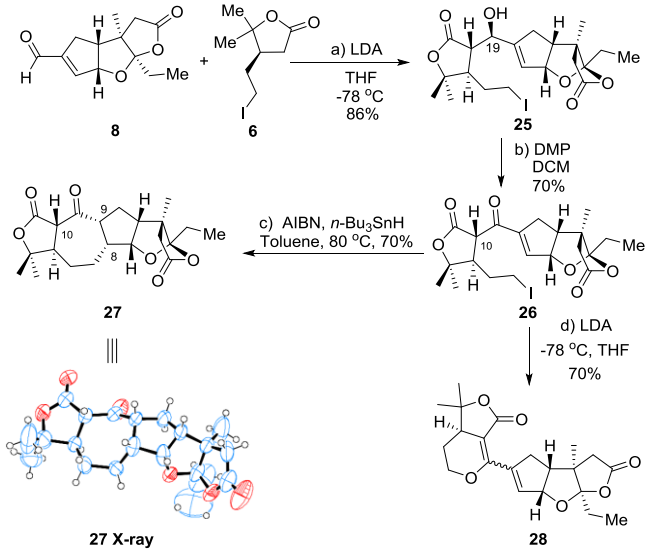


Entry	Conditions	Yield (%)[a]
1	Li, naphthalene, CuCN, TMSCl	**23**,0
2	Zn, CuCN, TMSCl	**23**,0
3	Et_2Zn, CuI or CuCN, TMSCl	**23**,0
4	$PdCl_2$(dppf), Et_2Zn, CuCN, TMSCl	**23**,0
5	$Ni(acac)_2$, Et_2Zn, CuCN, TMSCl	**23**,0
6	*fac*-Ir(ppy)$_3$, Hantzsch ester, Bu_3N, MeCN, visible light	**24**,0
7	Zn, CuI in EtOH and water	**24**,48%
8	*t*-BuLi, CuCN, TMSCl	**23**,0

[a]Yields refer to isolated product.

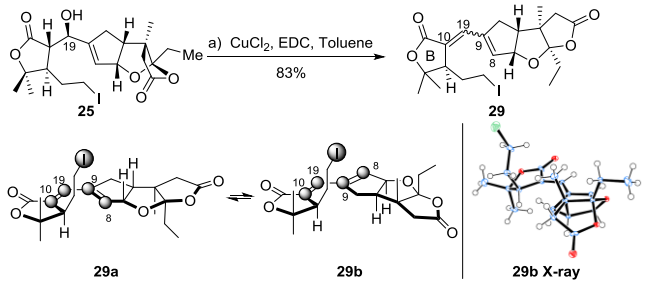
We then moved to assemble left fragment **6** and middle fragment **8** (Table 1). Firstly, we intended to prepared organozincs or organolithiums from iodide **6** in situ, [11a, b] which reacted with fragment **8** through Michael addition in the presence of copper salt, followed by addition of TMSCl to give the silyl enol ether **23**. However, no desired product was observed (entry 1 and 2). We also investigated to generate organozincs with diethylzinc, [11e] but only ethyl-Michael additional product was observed (entry 3 to 5). In addition, photo-redox catalyst was used, such as Ir-induced radical Michael reaction,[19] and no desired product was obtained (entry 6). Under Luche's[20] conditions [Zn, CuI, Pyridine, H_2O], we were pleased to observe two inseparable conjugated products **24** (entry 7). The absolute configuration at C8 and C9 on compound **24** could not be confirmed. However, the following hydroxylation at C9 on compound **24** was not achieved under Rubottom,[13a] Davis,[13b] MoOPH[11d,e], Blackmond's oxidation[13g], and Armando's conditions[13h]. Under condition listed in entry 8, an aldol product **25**[12e,f] was observed implying a new strategy to connect left fragment **6** and middle fragment **8**.

Scheme 5 depicted our new strategy to schilancitrilactones B and C based on the aldol product **25**. Iodide **6** was subjected to LDA to give the lithium enolate which reacted with aldehyde **8** to achieve compound **25** (d.r. =17:1 at C19). Alcohol **25** underwent Dess-Martin[21] oxidation to obtain ketone **26**, which in turn was subjected to AIBN-induced radical cyclization[22] to give cycloketone **27**. The structure of the ketone **27** was unambiguously confirmed by X-ray crystallographic analysis. Disappointedly, the absolute configurations at C8, C9 and C10 were not coincident with schilancitrilactones B and C. The unwelcomed α-face selectivity of the intramolecular conjugated addition might be affected by the (*S*)-configuration at C10. Thus, we intended to convert the (*S*)-configuration to the corresponding (*R*)-configurations. However, intramolecular cyclization[23] of **26** occurred to give 2-dihydropyran **28** under basic condition as shown in Scheme 5.



Scheme 5 Synthetic route to the compound **27**.

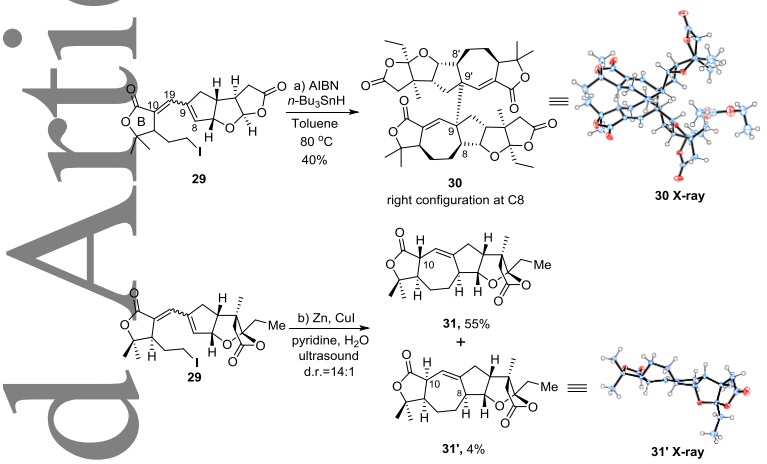
Herein, we intended to introduce the double bond at C10 and C19 in order to set the iodine atom above the plane. After optimization, we treated alcohol **25** with $CuCl_2$ and EDC in toluene under 80 °C (Scheme 6) to give the dienes **29** in 83% yield.[24] ^{1}H NMR analysis showed that the 1, 3-dienes **29** were a mixture of two inseparable isomers. Fortunately, the structure of **29-b** was confirmed by X-ray crystallographic analysis. From the X-ray structure of **29-b**, the alkyl iodide chain of B ring was above to the face of C10-C19-C9-C8 of 1, 3-diene, which might give the right chirality at C8 during the subsequently cyclization reaction.



Scheme 6 Synthetic route to the compound **29**.

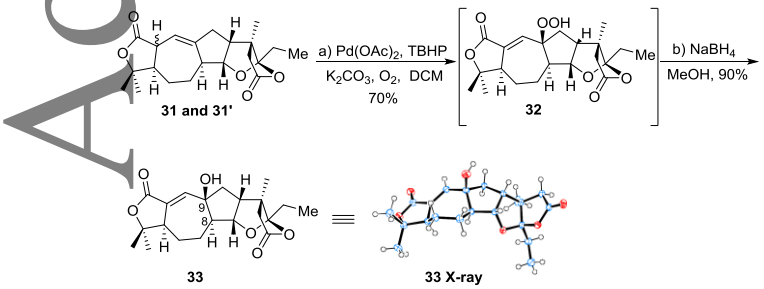
Herein, we started to investigate the intramolecular cyclization reaction to form the seven-membered ring. Firstly, we

subject 1, 3-dienes **29** with AIBN, *n*-Bu_3SnH[22] in toluene at 80 °C (Scheme 7) and trace amounts of desired cylization product was observed. Interestingly, the unexpected dimer **30** was isolated in 40% yield. The structure of dimer **30** was exactly confirmed by X-ray crystallographic analysis. This reaction brought us great confidence because the chirality at C8 was identical to natural products. We envisioned that the dimerization could be prevented when a mild condition was used. To our delight, cyclization products of two isomers **31** and **31'** were obtained under the Luche's [25] conditions in 59% total yield (d.r.=14:1 at C10). The choice of pyridine and water as solvents was crucial to this transformation, while no desired product was detected without water. When ethanol or tetrahydrofuran was used instead of pyridine, large amounts of starting material remained unreactive. The structure of **31'** was confirmed by X-ray crystallographic analysis and the chirality at C8 was in line with expectation.



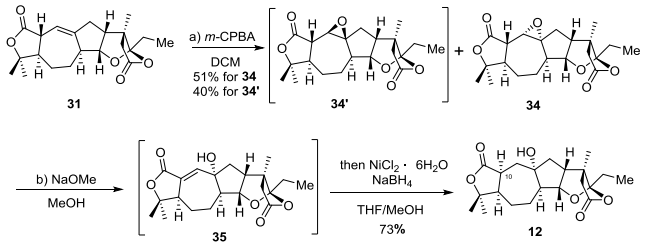
Scheme 7 Synthetic route to the compounds **31** and **31'**.

We next moved to the installation of the hydroxyl group at C9 (Scheme 8). Interestingly, the isomers **31** easily transformed to the peroxide **32** just by standing the solution in $CDCl_3$ under air for a couple of days. However, the auto-oxidation underwent in low yield when the reaction was carried out in large scale. Under the method [$Pd(OAc)_2$, *t*-BuOOH, K_2CO_3, O_2] discovered by Corey,[26] peroxide **32** was gained in 70% yield. The latter was then subjected to $NaBH_4$[27] to achieve the reductive product **33**, the structure of which was confirmed by X-ray crystallographic analysis. Unfortunately, the chirality at C9 was opposite to schilancitrilactones B (**4**) and C (**5**). The β-face selectivity might resulted from the less steric hindrance of the β-face. Thus, we had to pursue other method to overcome the problem.



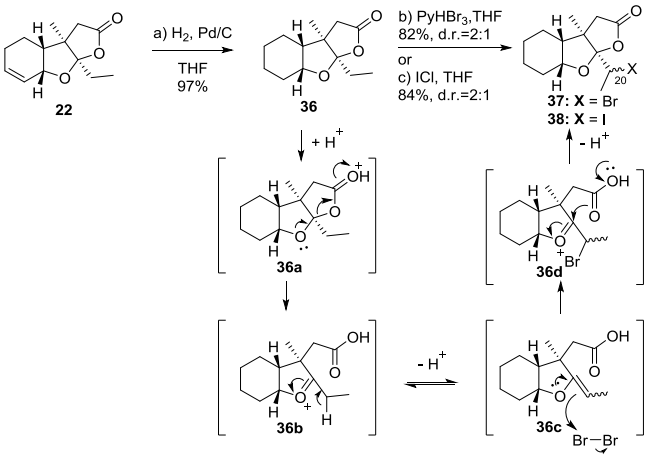
Scheme 8 Synthetic route to the compound **33**.

After careful investigation, we established a roundabout approach to install the hydroxyl group at C9 as shown in Scheme 9. Lactone **31** was treated with *m*-CPBA[28] to give the epoxide **34** in 51% yield coupled with its isomer **34'** in 40% yield, and the former was then underwent NaOMe-induced rearrangement to give an ally alcohol **35**, which then underwent $NiCl_2$-$NaBH_4$ mediated reduction[29, 30] to give the alcohol **12** in 73% yield.



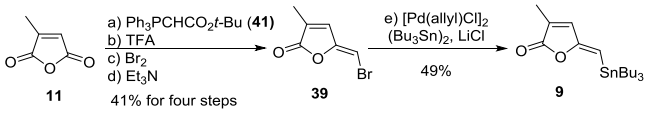
Scheme 9 Synthetic route to the compound **12**.

We decided to introduce model reactions to test the final coupling reaction. Bromide **37** and iodide **38** were chosen as model substrates which could be easy achieved through two successive steps from lactone **22** as shown in Scheme 10. Lactone **22** underwent Pd/C-catalyzed hydrogenation to give the compound **36** in 97% yield. Under Scholz's condition,[8] the bromine atom could be successfully introduced at α-position of ketal in 82% yield (d.r.=2:1 at C20) and the mechanism of this conversion was considered as an acid-promoted ring opening process as shown below. Lactone **36** underwent ring opening process to give the intermediate **36b**, which undertook isomerization to give the carboxylic acid **36c**. The latter was trapped by bromine to achieve intermediate **36d**, which subsequently underwent cyclization to obtain the final product **37**. Iodoketal **38** was also obtained in 84% yield (d.r.=2:1 at C20) when ICl was used as an electrophile.



Scheme 10 Synthetic route to the model substrates **37** and **38**.

The right fragment **9** was synthesized in 5 steps from commercial available compound citraconic anhydride (**11**) as shown in Scheme 11. Citraconic anhydride (**11**) underwent a reported four-step process [9] to give the bromide **39** in overall 41% yield coupled with its E-isomer 5% yield. The latter was then subjected to $[Pd(allyl)Cl]_2$ and $(Bu_3Sn)_2$ to afford vinyl stannane **9** in 49% yield and no isomer was observed.[31] It is noteworthy that vinyl stannane **9** is not stable during the purification and low isolated yield was observed.

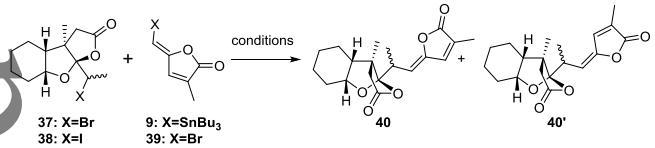


Scheme 11 Synthetic route to the right frament **9**.

With model substrates **37**, **38** and right fragment **9**, **39** in hand, we then moved to the model reaction. Optimized conditions were shown in Table 2. We first tested Zn-mediated reductive coupling

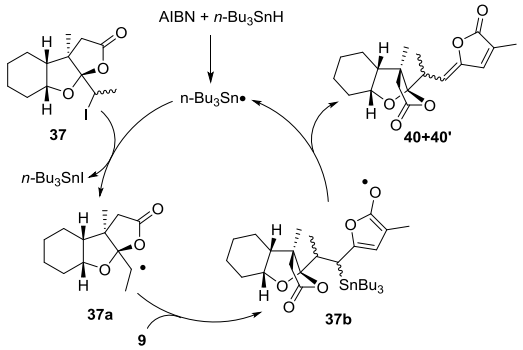
reactions[30c-i] of bromides **37** and **39** (entry 1-5). Under Lipshutz's condition (entry 1), no reaction occurred. Bromide **39** was then subjected to activate Zn firstly, followed by addition of compound **37**, but only debromination of **39** occurred (entry 2-3). Bromide **37** also underwent debromination when first subjected to activate Zn (entry 4). Under Luche's condition, no ideal product was gained (entry 5 and 11). When traditional radical conditions were applied, no assembled products **40**/**40'** were detected (entry 6 and 7) [7a] and the bromide **37** underwent debromination to give lactone **36**. Considering that toluene might be source of the proton, we then tested different solvents without activated proton, such as benzotrifluoride, benzene (entry 8 and 9). Disappointedly, no desired product was detected. When Et_3B/O_2 was applied to initiated the reaction (entry 10),[25,30] no coupling product was gained. Excitedly, when iodide **38** was used instead of bromide **37**, the coupling products **40**/**40'** were observed in trace yield (entry 12). By addition of *n*-Bu_3SnH and 4 Å molecular sieves (entry 13 and 14), the yield could be finally increased to 75% in total. We considered the mechanism of this transformation as a $\bullet SnBu_3$ mediated addition-elimination process as shown in table 2. The $\bullet SnBu_3$ was generated in situ, which further reacted with iodide **37** to give the intermediate **37a.** Subsequently intermediate **37a** underwent 1, 6-addition with stannane **9** to afford **37b**. The following elimination occurred to achieve the product **40** and **40'** and regenerated $\bullet SnBu_3$.

Table 2 Conditions for model reactions

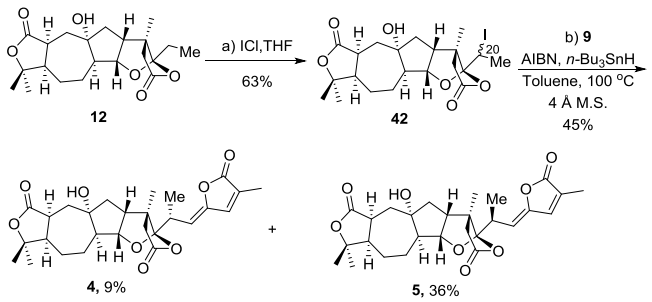


Entry	Conditions	Yield/%(**40**/**40'**)[a]
1	**37**, **39**, Zn, TMEDA, $PdCl_2$(Amphos), 2% PTS/H_2O	0
2	**39**, Zn, LiCl, TMSCl, THF; **37**, $TMSCH_2MgCl$, $FeCl_3$, TMEDA	0
3	**39**, Zn, LiCl, TMSCl, 1, 2-dibromoethane, THF; **37**, $Ni(cod)_2$, PyBox, TMEDA	0
4	**37**, Zn, THF; **39**, $Pd(dba)_2$, dtbpf	0
5	**37, 39**, CuI, Zn, *i*-PrOH, H_2O	0
6	**37**, AIBN, Toluene, 80°C	0
7	**37**, AIBN, *n*-Bu_3SnH, Toluene, 80°C	0
8	**37**, AIBN, *n*-Bu_3SnH, Benzotrifluoride, 80°C	0
9	**37**, AIBN, *n*-Bu_3SnH, Benzene, 80°C	0
10	**37**, Et_3B, O_2, Et_2O	0
11	**37**, Zn, CuI, Bu_4NI, *i*-PrOH-H_2O, ultrasound	0
12	**38**, AIBN, Toluene, 86°C	trace
13	**38**, AIBN, *n*-Bu_3SnH, Toluene, 80°C	38/28
14	**38**, AIBN, *n*-Bu_3SnH, 4 Å M.S., Toluene, 80°C	41/34

[a]Yields were determined by ^1H NMR spectroscopy with benzyl chloride as the internal standard.



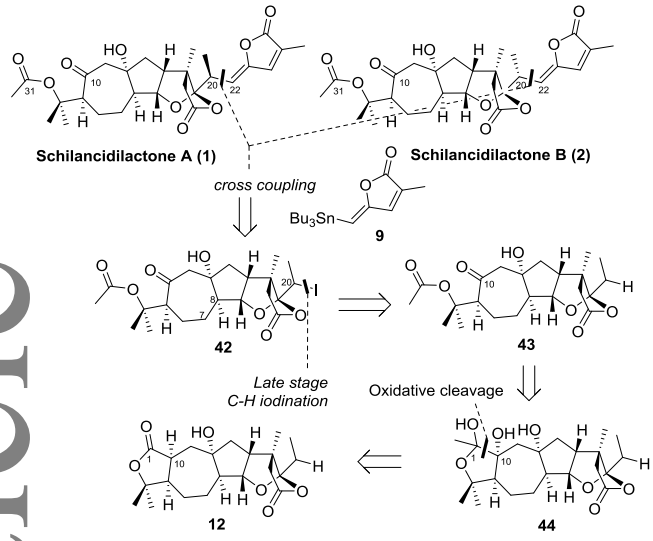
Having established the suitable conditions for the late-stage halogenation and intermolecular radical addition reaction, we then attempted to complete the total synthesis of the natural products as shown in Scheme 12. Alcohol **12** was subjected to ICl to give the iodides **42** in 63% yield as a mixture of diastereomers (d.r.=1.5:1 at C20), and the resulted iodides **42** was then treated with AIBN, *n*-Bu_3SnH in toluene to finish the total synthesis of schilancitrilactones B (**4**) and C (**5**) in overall 45% yield. The characterization data of synthetic schilancitrilactones B and C were in accord with the natural products.



Scheme 12 Synthetic route to schilancitrilactones B and C.

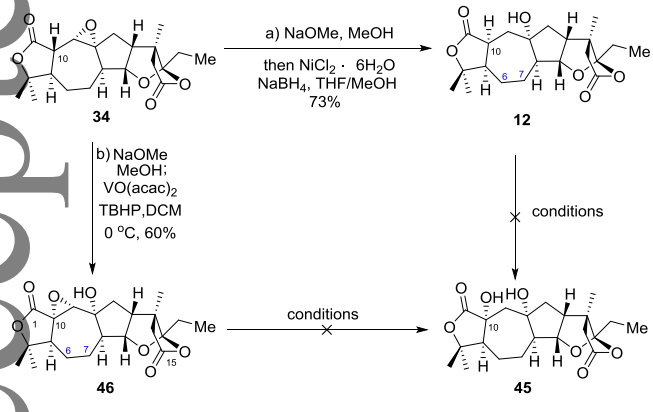
Total synthesis of schilancidilactones A, B

With the accomplishment of schilancitrilactones B and C, we next turned our attention to the synthesis of schilancidilactones A and B. Based on our former retrosynthetic analysis, we decided to applied latter-stage modification to transfer key intermediate above to achieve schilancidilactones A and B as shown in Scheme 13. These two target molecules were expected to be assembled from the iodides **42** and right fragment **9** through radical-induced coupling reaction. The iodides **42** in turn would be raised from the acetyl lactone **43** by late-stage iodination which was going to be synthesized from lactone **12** through methylation at C1 followed by oxidative cleavage at C1-C10 bond of triol **44**.



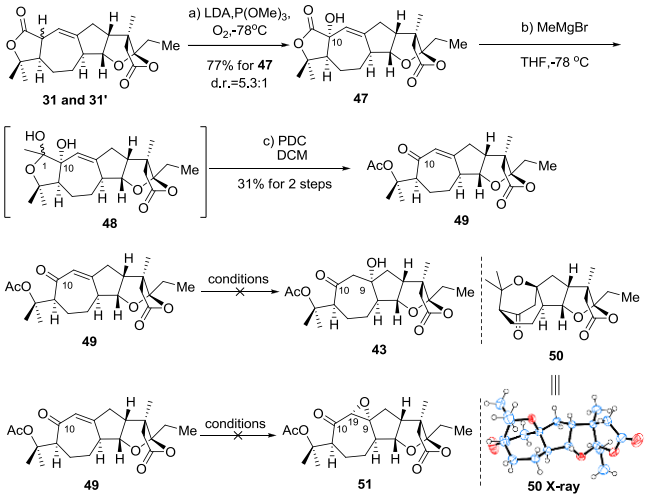
Scheme 13 Retrosynthetic analysis of schilancidilactones A and B.

Beyond our expectation, the installation of hydroxyl group at C10 was not smoothly (Scheme 14). When we subjected alcohol **12** to KHMDS, $P(OMe)_3$, O_2,[32] no reaction occurred with the recovery of starting material. Different bases (LDA, NaOMe) under different temperature (-78 °C, 0 °C, 25 °C) were also tested, no desired product **45** was obtained. Epoxide **34** was then converted to intermediate **46** by rearrangement with NaOMe followed by epoxidation with $VO(acac)_2$, TBHP.[33] Disappointedly, the reduction of epoxide **46** was not achieved under many conditions[34] ($NiCl_2$•$6H_2O$, $NaBH_4$; Red-Al; H_2, Pd/C; $LiAlH_4$; DIBAL-H; H_2, PtO_2). We thought the major problem was the steric hindrance caused by C6 and C7.



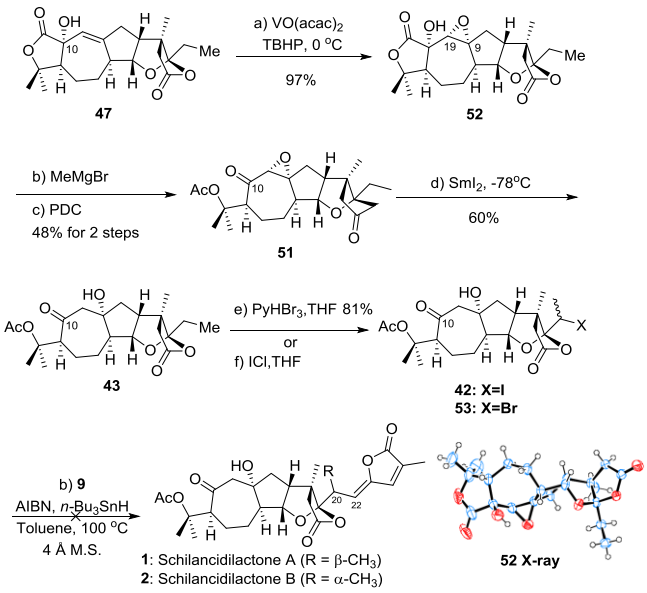
Scheme 14 Attemption to synthesize compound **45**.

Thus, an alternative method was raised to install the hydroxyl group at early stage as shown in Scheme 15. Lactone **31/31'** could be easily converted to the corresponding alcohol **47** under LDA, $P(OMe)_3$, O_2[32] in 77% yield with a diastereoselectivity 5.3:1. The favorable β-face selectivity might be resulted from the less steric hindrance of β-face. Alcohol **47** underwent selective methylation at C1 followed by PDC-mediated oxidative cleavage[35] at C1-C10 bond to give ketene **49** in 31% yield for two steps. However, the introduction of oxygen atom at C9 position again encountered problems. We attempted to apply direct hydration[36] to install the hydroxyl ketone **43**. However, no reaction occurred when Ag_2O, HFIP or AcOH was used as the reagents. While TfOH or TsOH was applied, intramolecular cyclization occurred to give the ketone **50**, which might arise from acid catalyzed deprotection of acyl group followed by intramolecular 1, 4-addition. Epoxidation[37] of ketene **49** was also investigated and no desired product **51** was detected.



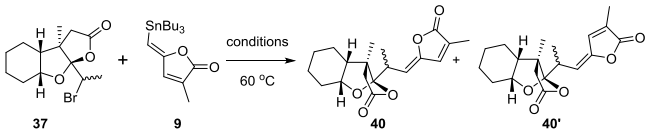
Scheme 15 Attemption to synthesize compounds **43** and **51**.

Upon former investigation, we intended to introduce the epoxy group in the early stage as shown in Scheme 16. Alcohol **47** underwent epoxidation[33] with the $VO(acac)_2$ and TBHP to give the epoxide **52** in 97% yield, of which the structure was unambiguously confirmed by X-ray crystallographic analysis. The epoxide **52** was then treated with MeMgBr followed by oxidative cleavage with PDC to give the ketone **51**. To our delight, epoxide **51** could be easily transformed to alcohol **43** by reductive ring opening with SmI_2 in 60% yield.[38] However, the desired iodide **42** was not achieved when ICl was applied as electrophilic reagent. Careful investigation showed that the iodide **42** might formed under low temperature (-20 °C) as being monitored by ^1H NMR but being destroyed upon quenching. The more stable bromides **53** could be achieved in 81% yield when alcohol **42** was treated with $PyHBr_3$. When we applied the bromides **53** to the radical coupling reaction with vinyl stannane **9**, no desired products was gained.



Scheme 16 Attemption to synthesize schilancidilactones A and B.

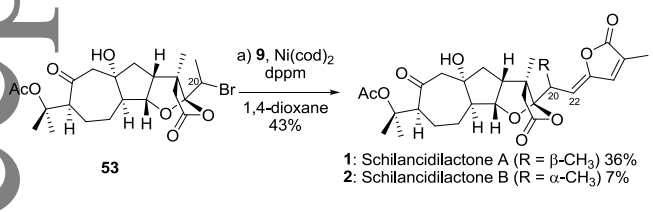
Table 3 Investigation of conditions for the cross coupling



Entry	Conditions	Yield/%(**40**/**40'**)[a]
1	$NiCl_2$, 2,2-bipyine,KO*t*-Bu, *t*-BuOH/*i*-BuOH	0
2	$Ni(cod)_2$ (10 mol%), 2,2-bipyridine, dioxane	0
3	$Ni(cod)_2$ (10 mol%), dppm, dioxane	28/28
4	$Ni(cod)_2$ (10 mol%), dppp, dioxane	0
5	$Ni(cod)_2$ (40 mol%), dppm, dioxane	40/40

[a]Yields were determined by ^{1}H NMR spectroscopy with benzyl chloride as the internal standard.

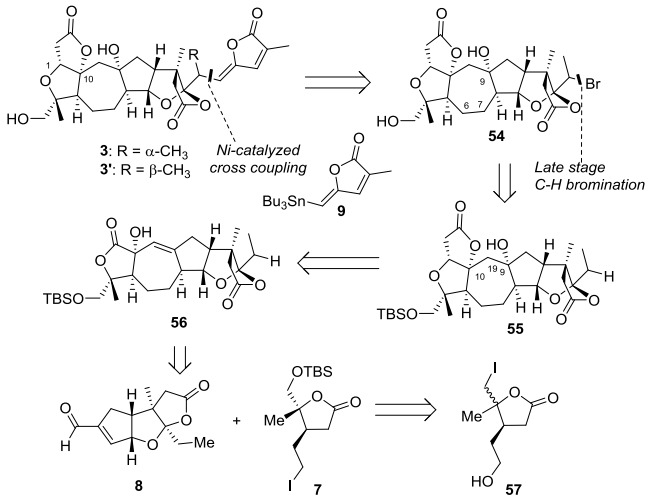
Herein, a new method to connect bromides **53** and right fragment **9** was required. As having been discussed in detail in the previous report,[4o] here was only a concise introduction. Inspired by Fu's reports[39] on the nickel catalyzed cross coupling of alkyl halides with stannane for the formation of C-C bond, we insisted that this strategy could be applied in our final coupling reaction. We then systematically evaluated different solvents, ligands, catalyst's loadings, and temperature (see ESI of the previous report for details).[4o] As being listed in Table 3, no product was gained under Fu's standard conditions. After careful screening different catalysts and ligands, $Ni(cod)_2$ and dppm were found to give the desired product in 56% total yield (entry 3). When 2, 2-bipyridine or dppp was used instead of dppm, no desired products were observed. When the catalyst's loading increased to 40% mol, the yield could be up to 80% in total. Gratifyingly, when bromides **53** and vinyl stannane **9** were involved, this Ni-catalyzed reaction proceeded smoothly to give the schilancidilactones A (**1**) and B (**2**) in 43% total yield (Scheme 17). The characterization data of synthetic **1** and **2** were identical with those reported data of the natural products.



Scheme 17 Synthetic route to schilancidilactones A and B.

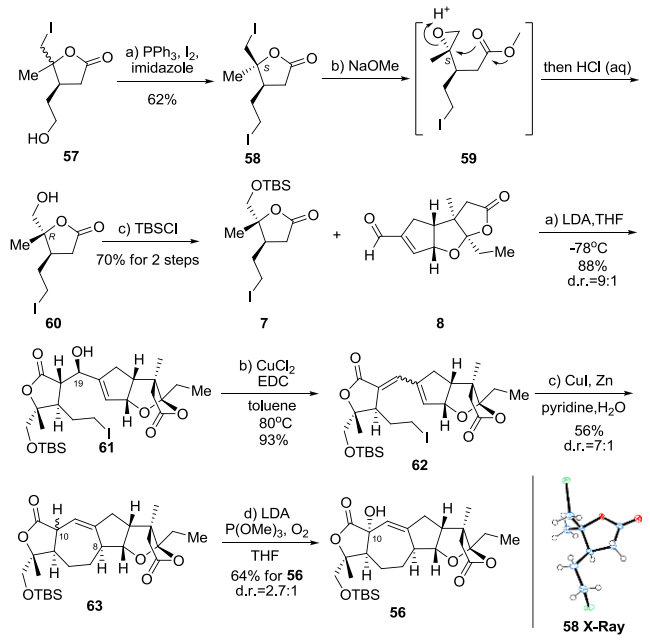
Total synthesis of schilancitrilactone A

Having successfully completed the synthesis of schilancidilactones A and B, schilancitrilactones B and C, we then turned our attention to schilancitrilactone A. The retrosynthetic analysis was shown in Scheme 18. Schilancitrilactone A (**3**) was intended to be assmbled from bromides **54** and stannane **9** through Ni-catalyzed cross coupling reaction. Bromides **54** was expected to be synthesized by late-stage C-H bromination from lactone **55**, which in turn was going to be raised from lactone **56** through a intramolecular Dieckmann condensation. The OTBS group on lactone **56** was going to be introduced in the stage when we constructed the left fragment **7**. The iodide **7** was going to be connected with middle fragment **8** to form the C10-C19 bond through the intermolecular aldol reaction followed by CuI-Zn induced radical cyclization to give the intermediate **56**, both of which were the same to former reaction applied in the synthesis of schilancidilactones A and B, schilancitrilactones B and C. The left fragment **7** was going to be synthesized from compound **57**.[4g]



Scheme 18 Retrosynthetic analysis of schilancitrilactone A.

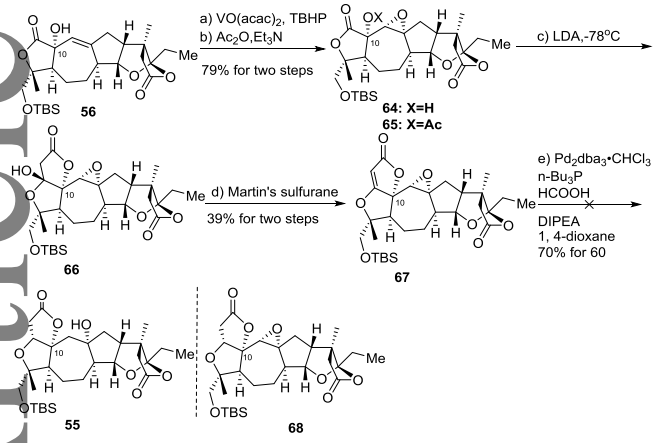
Scheme 19 illustrated the construction of key intermediate **58**. Started with alcohol **57**, we applied three steps procedure to the left fragment **7**. Iodonation of the hydroxyl group in **57** with PPh_3 and I_2 to give the iodide **58** in 62% yields, which was sequentially treated with MeONa and HCl to give the iodoalcohol **60**.[40] The free alcohol was then protected by TBSCl to achieve the left fragment **7** in overall 70% yield. Upon being treated with LDA, iodide **7** and aldehyde **8** was connected to give the alcohol **61** in 88% yield (d.r.=9:1 at C19), which underwent elimination by treating with $CuCl_2$ and EDC to afford the dienes **62** in 93% yields. Under Luche's condition, we successfully closed the seven member ring of the dienes **62** to give the lactone **63** in 56% yield (d.r.=7:1 at C10). Finally, hydroxyl group at C10 was then introduced by treating with LDA , $P(OMe)_3$ under oxygen atmosphere to give the alcohol **56** in 64% yield (d.r.=2.7:1 at C10, 64% yield for **56**).



Scheme 19 Synthetic route to alcohol **56**.

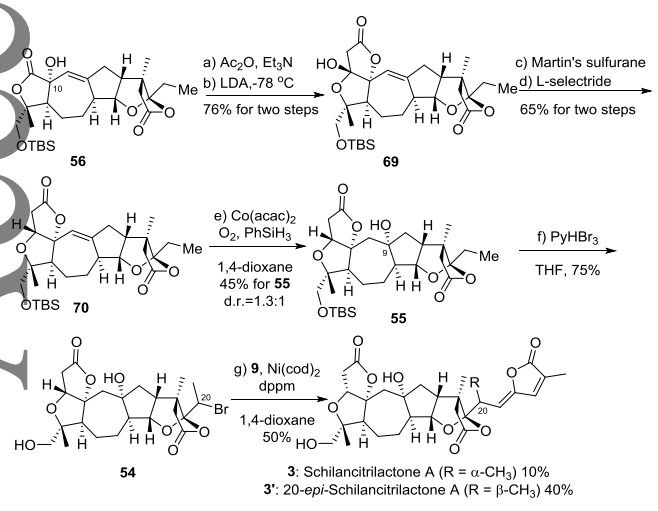
We then shifted our attention to synthesize intermediate **55** as illustrated in Scheme 20. The alcohol **56** was sequentially treated with $VO(acac)_2$, TBHP and Ac_2O to afford the acetate **65** in 79% yield for two steps. And the acetate was then underwent

intramolecular Dieckmann-type condensation and Martin's elimination[41] to afford compound **67** in overall 39% yield. However, our attempt to convert the lactone **67** to hydroxide **55** by reducing the C=C double bond and ring-opening of epoxide through Pd-catalyzed hydrogenation[42] in one pot was unachieved, only double bond being reduced to give the epoxide **68**. Many conditions were tested to open the epoxide, but failed.



Scheme 20 Attempt to synthesize compound **55**.

Herein, we intended to directly introduce the hydroxyl group at C9 from the C=C double bond through Mukaiyama hydration[43] as illustrated in Scheme 21. Alcohol **56** underwent acetylation and intramolecular Dieckmann-type condensation to give the compound **69** in 76% yield for two steps. The lactone **69** was then sequentially subjected to Martin's sulfurane[41] and L-selectride to generate the lactone **70**. Under Mukaiyama hydration[43] condition[$Co(acac)_2$, $PhSiH_3$, O_2], the tertiary hydroxyl group at C9 was successfully installed to give alcohol **55** in 45% yield (d.r.=1.3:1 at C9, 45% yield for **55**). Finally, we completed the synthesis of schilancitrilatone A (**3**) and its C20-epimer (**3'**) by late-stage $C(sp^3)$-H bromination and nickel-catalyzed cross coupling reaction. The spectra and physical properties of the schilancitrilacetone A (**3**) are identical with those reported of the natural product.



Scheme 21 Synthetic route to Schilancitrilactone A and 20-*epi*-Schilancitrilactone A.

Conclusions

In summary, the collective total synthesis of schilancidilactones A, B and schilancitrilactones A, B, C, 20-*epi*-schilancitrilactone A has been accomplished from a common precursor (**8**). The key steps included intermolecular radical cyclization, late-stage halogenation (Br or I), AIBN, *n*-Bu_3SnH-induced intermolecular cross coupling or nickel-catalyzed intermolecular cross coupling of alkyl halide with vinyl stannane in the late stage. In this way, the right hand moieties present in this family of natural products were prepared in the final step of each total synthesis. This strategy shows promise for entry into other derivatives and analogues by way of a common intermediate, which may facilitate the biological studies on schisandraceae triterpenoids.

Experimental

Total synthesis of schilancitrilactone A

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene and 1, 4-dioxane were distilled immediately before use from sodium-benzophenone ketyl. Methylene chloride (CH_2Cl_2), triethylamine (Et_3N), N, N–dimethylformide (DMF) were distilled from calcium hydride and stored under an argon atmosphere. Methanol (MeOH) was distilled from magnesium and stored under an argon atmosphere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents for chromatography were used as supplied by Tianjin Reagents chemical. Reactions were monitored by thin layer chromatography (TLC) carried out on silica gel Huanghai HSGF254 plates using UV light as visualizing agent and aqueous phosphomolybdic acid or basic aqueous potassium permanganate as developing agent. 200-300 mesh silica gel purchased from Qingdao Haiyang Chemical Co., China was used for flash column chromatography. Semipreparative HPLC was performed on an UltiMate 3000 liquid chromatography with a Thermo HG-C18, 21.2 mm × 15 cm column. NMR spectra were recorded on Bruker AVANCE AV 400 (400 MHz, 101 MHz and 376 MHz) instrument and calibrated by using residual undeuterated chloroform (δ_H=7.26 ppm) and $CDCl_3$ (δ_C=77.16 ppm) as internal references. The following abbreviations are used to designate multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, quint=quintet, br=broad. IR spectra were recorded on a Bruker Tensor 27 instrument. High-resolution mass spectra (HRMS) were obtained on Varian 7.0T FTMS. Circular dichroism spectra (CD) were obtained from JASCO J-715 Spectropolarmeter. Optical rotations were measured with an Insmark IP 120 digital polarimeter. X-ray diffraction was realized on a Rigaku 007 Saturn 70 instrument.

Synthesis of aldehydes 24. To a 5 mL schlenk tube was sequentially added compound **6** (155.3 mg, 0.579 mmol, 3.00 equiv), compound **8** (45.6, 0.193 mmol, 1.00 equiv), Zn (75.8 mg, 1.160 mmol, 6.00 equiv), CuI (73.6 mg, 0.193 mmol, 2.00 equiv), EtOH (592 μL) and H_2O (319 μL). The mixture was degassed with N_2 for 3 times and stirred for another 10 hours before filtered through celite pad. The extract was evaporated and purified by silica gel column chromatography (EA/PE = 1/4 to 1/2) to give aldehydes **24** (35.0 mg, 0.0925 mmol, 48%) as a yellow oil. **24-major**: Rf = 0.3 (silica, EA/PE = 1/2); $[\alpha]_D^{25}$ = - 35.6 (c = 0.15 in $CHCl_3$); IR (film): ν_{max} = 3501, 2960, 2926, 2870, 2855, 1769, 1462, 1377, 1261, 1214, 1098, 1028, 937, 912, 874, 799, 756, 705, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.63 (d, *J* = 2.0 Hz, 1H), 4.29 (dd, *J* = 5.8, 2.3 Hz, 1H), 2.74 (d, *J* = 18.5 Hz, 1H), 2.67 – 2.46 (m, 4H), 2.42 – 2.17 (m, 3H), 2.02 – 1.87 (m, 2H), 1.81 – 1.71 (m, 2H), 1.55 – 1.50 (m, 1H), 1.45 (s, 3H), 1.40 (t, *J* = 9.2 Hz, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.4, 175.3, 173.9, 120.9, 87.4, 86.7, 58.6, 55.2, 49.7, 45.9, 45.7, 45.7, 35.0, 31.6, 28.5, 28.0, 27.6, 22.1, 19.8, 7.7. HRMS (m/z): $[M + H]^+$ calcd for $C_{21}H_{30}O_6H^+$ 379.2115, found 379.2116.

Synthesis of ketone 26. To a stirred solution of compound **25** (282 mg, 0.560 mmol, 1.00 equiv) in DCM (30 mL) in THF was added DMP (474 mg, 1.120 mmol, 2.00 equiv) under N_2 at room temperature. 5 hours later, TLC showed the disappearance of starting material. The mixture was filtered through a celite pad, evaporated, and purified by flash silica gel column chromatography (EA/PE = 1/2 to 1/1) to give ketone **26** (197 mg, 0.392 mmol, 70%) as a white solid.; **26**: m.p. unknown (decomposed > 170 °C); Rf = 0.5 (silica, EA/PE = 7:3); $[\alpha]_D^{25}$= + 15.9 (c = 0.63 in $CHCl_3$); IR (film): ν_{max} = 2979, 1765, 1671, 1618, 1466, 1438, 1189, 1117, 912, 873, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, *J* = 1.5 Hz, 1H), 5.46 (d, *J* = 7.9 Hz, 1H), 4.04 (d, *J* = 11.5 Hz, 1H), 3.08 – 2.85 (m, 4H), 2.80 – 2.42 (m, 4H), 2.09 (m, 1H), 1.93 (m, 1H), 1.71 (m, 2H), 1.53 (s, 3H), 1.31 (s, 3H), 1.09 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.8, 171.7, 168.8, 144.8, 140.8, 119.9, 87.1, 83.9, 53.9, 49.5, 48.08, 46.9, 43.8, 33.0, 30.1, 26.3, 26.3, 21.8, 15.5, 6.2; HRMS (m/z): $[M + Na]^+$ calcd for $C_{21}H_{27}IO_6Na^+$ 525.0750, found 525.0748.

Synthesis of ketone 27. To a roundbottom flask containing compound **26** (197 mg, 0.392 mmol, 1.00 equiv), AIBN (12.9 mg, 0.0784 mmol, 0.20 equiv) was added toluene (10.0 mL) under N_2. *n*-Bu_3SnH (0.126 mL, 0.470 mmol, 1.20 equiv) was added, and the mixture was heated to reflux. After stirring for 5 hours at that temperature, the solvent was removed under reduced pressure. The resulted mixture was purified by silica gel column chromatography (EA/PE = 1/5 to 1/2) to give the product **27** (103 mg, 0. 274mmol, 70%) as a white solid; **27**: m.p. 116-117 °C; Rf = 0.40 (silica, EA/PE = 7:3); ^1H NMR (400 MHz, $CDCl_3$): δ 4.64 (t, *J* = 5.0 Hz, 1H), 3.70 (d, *J* = 13.4 Hz, 1H), 3.20 (dd, *J* = 17.3, 10.4 Hz, 1H), 2.70 (dd, *J* = 58.4, 18.7 Hz, 4H), 2.39 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.30 – 1.94 (m, 3H), 1.90 – 1.70 (m, 4H), 1.55 – 1.40 (m, 4H), 1.40 – (m, 7H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.5, 174.2, 170.5, 119.6, 85.1, 83.8, 58.1, 57.8, 55.3, 53.5, 49.3, 45.2, 42.2, 29.3, 28.3, 26.8, 26.6, 25.9, 21.8, 19.6, 7.8; HRMS (m/z): $[M + Na]^+$ calcd for $C_{21}H_{28}O_6Na^+$ 399.1784, found 399.1782.

Synthesis of dihydropyran 28. To a solution of lithium diisopropylamide (0.2 mL, c = 2.00 M in THF, 0.400 mmol, 2.00 equiv) in THF (11.5 mL) was slowly added a solution of compound **26** (101 mg, 0.200 mmol, 1.00 equiv) in tetrahydrofuran (15.0 mL) at -78 °C. After stirring at that temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc (3 × 20.0 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/4 to 1/2) to give dihydropyran **28** (52.0 mg, 0.139 mmol, 70%) as a colorless oil. **28**: Rf = 0.47 (silica, EA/PE = 7:3); $[\alpha]_D^{25}$ = + 4.0 (c = 0.60 in $CHCl_3$); IR (film): ν_{max} = 3421, 2976, 2933, 1768, 1629, 1466, 1270, 1249, 1140, 1104, 901, 867, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.50 (s, 1H), 5.31 (d, *J* = 7.8 Hz, 1H), 4.44 (dd, *J* = 11.2, 2.1 Hz, 1H), 4.01 – 3.82 (m, 1H), 3.11 (d, *J* = 17.7 Hz, 1H), 3.01 – 2.80 (m, 2H), 2.75 – 2.45 (m, 3H), 1.95 (dd, *J* = 13.0, 5.8 Hz, 1H), 1.84 – 1.57 (m, 4H), 1.50 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5, 168.3, 156.4, 139.2, 134.2, 121.5, 103.3, 88.0, 83.2, 66.06, 50.8, 49.7, 45.5, 45.2, 33.1, 27.5, 27.1, 22.8, 21.4, 16.72, 7.4; HRMS (m/z): $[M + Na]^+$ calcd for $C_{21}H_{26}O_6Na^+$ 397.1627, found 377.1625.

Synthesis of dimer 30. To a roundbottom flask containing compounds **29** (30.4 mg, 0.625 mmol, 70%) and AIBN (2.1 mg, 0.0125 mmol, 0.20 equiv) was added toluene (2.0 mL), *n*-Bu_3SnH (20.1 µL, 0.075 mmol, 1.20 equiv). The mixture was heated to 80 °C and stirring continued for 5 hours at that temperature. The solvent was evaporated. The remainder was resolved in MeCN (10.0 Ml) and washed with hexane (3 × 4 mL). MeCN was removed under reduced pressure, the crude product was purified by silica gel column chromatography (EA/PE = 1/2 to 1/1) to give the product **30** (17.9 mg, 0.249 mmol, 40 %) as a colorless oil. **30**: Rf = 0.60 (silica, EA/PE = 7:3); $[\alpha]_D^{25}$ = + 8.6 (c = 0.37 in $CHCl_3$); IR (film): ν_{max} = 2971, 2927, 1768, 1669, 1458, 1375, 1237, 1164, 1118, 906, 877, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.66 (d, *J* = 2.3 Hz, 2H), 4.56 (dd, *J* = 7.2, 5.4 Hz, 2H), 2.83 – 2.51 (m, 6H), 2.45 (dt, *J* = 18.2, 9.0 Hz, 2H), 2.36 (s, 2H), 2.26 (d, *J* = 14.3 Hz, 2H), 2.00 – 1.75 (m, 8H), 1.70 – 1.45 (m, 6H), 1.38 (s, 6H), 1.23 (s, 6H), 1.21 (s, 6H), 1.12 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 170.1, 144.4, 135.7, 121.4, 84.4, 83.9, 61.6, 50.9, 50.4, 49.5, 45.4, 37.7, 28.2, 27.4, 27.1, 24.3, 22.3, 18.9, 7.6; HRMS (m/z): $[M + Na]^+$ calcd for $C_{42}H_{54}O_{10}Na^+$ 741.3615, found 741.3612.

Synthesis of alcohol 33. To a roundbottom flask containing compounds **31** and **31'** (38.6 mg, 0.107 mmol, 1.00 equiv) in DCM, $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 0.05 equiv) and K_2CO_3 (43.0 mg, 0.120 mmol, 1.12 equiv) was added (5.00 mL) under O_2 at room temperature. 70% aqueous *t*-BuOOH (0.30 mL) was then added, and stirring continued for 3 hours. The reaction mixture was filtered and the organic solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 2/1 to 1/1) to give compound **32** (27.4 mg, 0.0749 mmol, 70%). To a solution of freshly prepared compound **32** (27.4 mg, 0.0749 mmol, 1.00 equiv) in MeOH (3.00 mL) was slowly added $NaBH_4$ (8.5 mg, 0.225 mmol, 3.00 equiv). After 30 min later, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the resulted mixture was extracted with EtOAc (3 × 15.0 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/4 to 1/2) to give the product **33** (25.5 mg, 0.0677 mmol, 90%) as a red solid. **33**: m.p. 79-80 °C; Rf = 0.25 (silica, EA/PE = 7:3); $[\alpha]_D^{25}$ = + 9.5 (c = 0.55 in $CHCl_3$); IR (film): ν_{max} = 3442, 2934, 1752, 1676, 1465, 1375, 1264, 1178, 1132 910, 871, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, *J* = 3.3 Hz, 1H), 4.42 (dd, *J* = 7.2, 4.0 Hz, 1H), 2.87 (m, 2H), 2.64 (dd, *J* = 76.7, 18.0 Hz, 2H), 2.10 (m, 2H), 1.98 (m, 2H), 1.85 – 1.70 (m, 6H), 1.49 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 1.08 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 170.3, 139.0, 136.7, 121.9, 89.2, 85.4, 81.3, 52.0, 51.1, 48.8, 48.6, 45.7, 41.5, 28.2, 27.0, 25.1, 24.6, 23.8, 19.1, 7.6; HRMS (m/z): $[M + Na]^+$ calcd for $C_{21}H_{28}O_6Na^+$ 399.1784, found 399.1784.

Synthesis of iodides 38. To a stirred solution of compound **36** (150.0 mg, 3.65 mmol, 1.00 equiv) in THF (5.0 mL) was added ICl (148 mg, 0.911 mmol, 1.35 equiv). Stirring continued for 20 min before the organic solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (silica, EA/PE/Et_3N = 1/4/0.05) to give the diastereisomers of compounds **38** (198 mg, 0.565 mmol, 84%, 2:1) as a yellow oil. **38-Minor:** Rf = 0.5 (silica, EA/PE = 1:4); $[\alpha]_D^{25}$ = –8.5 (c = 0.20 in $CHCl_3$); IR (film): ν_{max} = 2930, 2857, 1770, 1733, 1645, 1455, 1418, 1378, 1362, 1319, 1294, 1260, 1229, 1189, 1160, 1089, 1059, 1019, 966, 953, 936, 864, 800, 760, 740, 700, 668, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.40 (q, *J* = 7.0 Hz, 1H), 4.21 (dd, *J* = 6.9, 3.4 Hz, 1H), 2.82 (d, *J* = 19.0 Hz, 1H), 2.65 (d, *J* = 19.0 Hz, 1H), 2.18-2.10 (m, 1H), 2.07 (t, *J* = 7.0 Hz, 3H), 1.94 – 1.87 (m, 1H), 1.78-1.69 (m, 1H), 1.67-1.53 (m, 3H), 1.60 – 1.54 (m, 1H), 1.43 (s, 3H), 1.25-1.21 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5, 116.4, 74.6, 51.7, 50.3, 46.1, 27.4, 24.9, 24.6, 24.2, 24.1, 20.2, 19.6. HRMS (m/z): $[M + H]^+$ calcd for $C_{13}H_{19}IO_3H^+$ 351.0452, found 351.0450.

Synthesis of epoxide 46. To a stirred solution of compound **34** (24.0 mg, 0.637 mmol, 1.00 equiv) in methanol (2.0 mL) was added NaOMe (17.2 mg, 3.185 mmol, 5.00 equiv), stirring continued for 0.5 h at room temperature. 2.0 mL H_2O was added, and the resulted mixture was extracted with EtOAc (3 × 2.0 mL). The combined extracts were evaporated to give the crude product **35** (24.0 mg). The crude product **35** was used for the next step without further purification. To a roundbottom flask containing compound **35** (24.0 mg, 0.637 mmol, 1.00 equiv) and

$VO(acac)_2$ (1.7 mg, 0.0637 mmol, 0.10 equiv) was added DCM (2.0 mL) under N_2 at 0°C. TBHP (25% v/v in DCM, 735 μL, 1.911 mmol, 3.00 equiv) was slowly added, and the mixture was stirring for 3 hours. The solvent was evaporated and the crude product was purified by silica gel column chromatography (EA/PE = 1/1 to 2/1) to give the product **46** (15.0 mg, 0.382 mmol, 60% yield) as a colorless oil. **46**: Rf = 0.2 (silica, EA/PE = 1:1); $[\alpha]_D^{25}$ = 41.6 (c = 0.57 in $CHCl_3$); IR (film): ν_{max} = 3501, 2960, 2926, 2870, 2855, 1769, 1462, 1377, 1261, 1214, 1098, 1028, 937, 912, 874, 799, 756, 705, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.36 (dd, *J* = 6.7, 3.7 Hz, 1H), 3.49 (s, 1H), 2.85 (s, 1H), 2.71 (d, *J* = 17.3 Hz, 1H), 2.63 (dd, *J* = 15.8, 8.1 Hz, 1H), 2.56 (d, *J* = 18.0 Hz, 1H), 2.52-2.42 (m, 1H), 2.25 – 2.20 (m, 1H), 2.11 (s, 1H), 2.09 (s, 1H), 1.87 – 1.67 (m, 4H), 1.52 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 172.1, 121.4, 87.2, 86.1, 80.8, 64.0, 62.3, 52.5, 50.8, 50.5, 46.0, 45.6, 40.2, 29.2, 28.0, 25.1, 23.7, 22.4, 19.7, 7.6. HRMS (m/z): $[M + H]^+$ calcd for $C_{21}H_{28}O_7H^+$ 393.1908, found 393.1903.

Synthesis of ketene 49. To a stirred solution of compound **47** (50.0 mg, 0.133 mmol, 1.00 equiv) in THF (2.2 mL) was slowly added MeMgBr (3.0 M in THF, 0.1 mL, 0.300 mmol, 2.25 equiv) at 0 °C under the atmosphere of N_2. 3 hours later, the reaction mixture was quenched with MeOH (1.0 mL). The resulting mixture was carefully evaporated under reduced pressure. The remainder was filtered with silica gel (EtOAc), and the solvent was evaporated to give the crude products **48** (dr=1.5:1 at C1). The crude products were purified by silica gel column chromatography (EA/PE = 1/1) to give the products **48** (22.0 mg, 0.0561 mmol, dr=1.5:1 at C1, 42% yield). To a stirred solution of compounds **48** (22.0 mg, 0.0561 mmol, 1.00 equiv) in DCM (4.0 mL) was slowly added PDC (63.3 mg, 0.168 mmol, 3.00 equiv). After stirring for 3 hours, the reaction mixture was filtered through silica gel and the residue was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/4 to 2/5) to give the product **49** (16 mg, 0.425 mmol, 75% yield) as a colorless oil; **49**: Rf = 0.3 (silica, EA/PE = 1:2); $[\alpha]_D^{25}$ = 2.7 (c = 0.23 in $CHCl_3$); IR (film): ν_{max} = 3397, 2952, 2923, 2854, 1768, 1728, 1660, 1462, 1367, 1258, 1109, 1022, 938, 909, 800, 760, 721, 666, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 4.40–4.34 (m, 1H), 3.74–3.66 (m, 1H), 3.13–3.04 (m, 1H), 2.77 (d, *J* = 18.6 Hz, 1H), 2.72–2.54 (m, 3H), 2.53–2.44 (m, 1H), 2.22–2.11 (m, 1H), 2.06–1.94 (m, 4H), 1.87–1.73 (m, 2H), 1.64 (s, 3H), 1.55-1.50 (m, 1H), 1.49 (s, 3H), 1.45 – 1.36 (m, 1H), 1.29 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 174.0, 170.7, 165.1, 128.1, 119.9, 89.0, 84.2, 54.5, 53.8, 50.1, 46.7, 45.2, 37.7, 29.6, 29.1, 25.1, 23.7, 22.7, 22.0, 19.9, 7.9. HRMS (m/z): $[M + H]^+$ calcd for $C_{22}H_{30}O_6H^+$ 391.2115, found 391.2118.

Synthesis of ketone 50. To a solution of compound **49** (3.0 mg, 0.00768 mmol, 1.00 equiv) in H_2O (1.0 mL) was added TfOH (2.0 μL, 0.0230 mmol, 0.30 equiv). The reaction mixture was heated to reflux and stirring continued for 30 min. The resulted mixture was extracted with EtOAc (3 × 2.0 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/1) to give the product **50** (2.2 mg, 0.00607 mmol, 79% yield) as a white solid. **50**: m.p. 65-66 °C; Rf = 0.4 (silica, EA/PE = 1:1); $[\alpha]_D^{25}$ = -15.0 (c = 0.17 in $CHCl_3$); IR (film): ν_{max} = 3459, 2958, 2923, 2852, 1767, 1728, 1713, 1468, 1453, 1378, 1260, 1091, 938, 863, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.88 (d, *J* = 18.5 Hz, 1H), 2.84 – 2.75 (m, 2H), 2.59 (d, *J* = 18.7 Hz, 1H), 2.36 (d, *J* = 18.5 Hz, 1H), 2.28 (d, *J* = 7.8 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.08 – 2.02 (m, 1H), 1.87 (ddd, *J* = 14.3, 11.5, 5.7 Hz, 3H), 1.79 – 1.71 (m, 2H), 1.70-1.62 (m, 3H), 1.36 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.09 (t, *J* = 7.3 Hz, 3H; ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.0, 174.4, 120.3, 89.6, 84.2, 75.2, 56.0, 55.2, 54.7, 49.3, 47.5, 45.6, 42.5, 32.7, 29.3, 27.3, 26.4, 25.3, 20.0, 7.9. HRMS (m/z): $[M + H]^+$ calcd for $C_{22}H_{28}O_5H^+$ 349.2010, found 349.2007.

Synthesis of epoxide 64. To a round–bottom flask covered with tinfoil was added compound **56** (90.0 mg, 0.178 mmol, 1.00 equiv) and $VO(acac)_2$ (13.7 mg, 0.0533 mmol, 0.30 equiv), DCM (4.5 mL). A solution of TBHP (25% v/v in DCM, 0.8 mL, 2.131 mmol, 12.0 equiv) was slowly added to the reaction mixture. After stirring for 3.5 hours, TLC showed the disappearance of the starting material and the reaction mixture was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 2/3 to 1/1) to give the product **64** (74.0 mg, 0.142 mmol, 88% yield) as a colorless oil; **64**: Rf = 0.2 (silica, EA/PE = 1/1); $[\alpha]_D^{25}$ = 22.5 (c = 0.08 in $CHCl_3$); IR (film): ν_{max} = 3467, 2960, 2926, 2854, 1771, 1463, 1412, 1377, 1260, 1096, 1020, 939, 800, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, *J* = 5.5 Hz, 1H), 3.62 (dd, *J* = 31.5, 10.6 Hz, 2H), 3.38 (s, 1H), 3.22 (s, 1H), 2.80 – 2.69 (m, 2H), 2.62 – 2.52 (m, 3H), 2.24 (dd, *J* = 16.0, 10.7 Hz, 1H), 1.96 – 1.80 (m, 3H), 1.76 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.72 – 1.64 (m, 1H), 1.58 – 1.45 (m, 1H), 1.41 – 1.31 (m, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.13 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 173.9, 120.6, 89.3, 85.5, 74.0, 68.9, 68.4, 56.9, 52.4, 50.89, 48.1, 45.7, 43.6, 33.4, 28.4, 25.9, 25.0, 22.9, 20.8, 19.6, 18.3, 7.7, -5.3, -5.4. HRMS (m/z): $[M + H]^+$ calcd for $C_{27}H_{42}O_8SiH^+$ 523.2722, found 523.2723.

Synthesis of acetyl epoxide 65. To a stirred solution of compound **64** (70.0 mg, 0.134 mmol, 1.00 equiv) in DCM (1.4 mL) was sequentially added NEt_3 (270 μL, 2.678 mmol, 20.0 equiv) and Ac_2O (75.5 μL, 0.804 mmol, 6.00 equiv) at room temperature. After stirring for 3 hours, the reaction was quenched with saturated aqueous $NaHCO_3$. The resulted mixture was extracted with DCM (3 × 3.0 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/3 to 1/2) to give the product **65** (68.0 mg, 0.120 mmol, 90% yield) as a colorless oil; **65**: Rf = 0.3 (silica, EA/PE = 1/1); $[\alpha]_D^{25}$ = 31.2 (c = 0.17 in $CHCl_3$); IR (film): ν_{max} = 2958, 2927, 2855, 1777, 1746, 1463, 1376, 1260, 1221, 1094, 1049, 1021, 935, 800, 702, 685, 663, 618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, *J* = 5.2 Hz, 1H), 3.74 (s, 2H), 3.15 (s, 1H), 2.79 – 2.67 (m, 3H), 2.64 – 2.53 (m, 2H), 2.24 (dd, *J* = 15.9, 10.7 Hz, 1H), 2.15 (s, 3H), 1.95 – 1.65 (m, 5H), 1.63 – 1.54 (m, 1H), 1.44 – 1.37 (m, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.15 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.06 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 171.7, 169.5, 120.6, 89.7, 85.0, 78.0, 69.9, 67.0, 56.3, 52.7, 50.9, 48.2, 45.6, 43.2, 33.6, 28.5, 25.9, 24.7, 23.7, 21.4, 21.2, 19.7, 18.3, 7.7, -5.4. HRMS (m/z): $[M + H]^+$ calcd for $C_{29}H_{44}O_9SiH^+$ 565.2827, found 565.2834.

Synthesis of alcohol 66. To a stirred solution of compound **65** (63.2 mg, 0.112 mmol, 1.00 equiv) in THF (4.0 mL) was slowly added LDA (2.0 M in THF, 1.7 mL, 0.340 mmol, 3.00 equiv) at –78 °C under the atmosphere of N_2. After stirring for 3 h, the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc (3 × 5.0 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/2 to 1/1) to give the product **66** (30.1 mg, 0.0533 mmol, 48% yield) as a colorless oil; **66**: Rf = 0.2 (silica, EA/PE = 1:1); $[\alpha]_D^{25}$ = –3.8 (c = 0.10 in $CHCl_3$); IR (film): ν_{max} = 3398, 2958, 2924, 2853, 1778, 1767, 1462, 1413, 1377, 1260, 1096, 1019, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (d, *J* = 6.3 Hz, 1H), 3.69 (s, 1H), 3.50 – 3.41 (m, 2H), 2.97 (d, *J* = 17.5 Hz, 1H), 2.89 – 2.67 (m, 4H), 2.54 (d, *J* = 17.7 Hz, 1H), 2.44 – 2.26 (m, 3H), 1.94 – 1.83 (m, 1H), 1.83 – 1.66 (m, 3H), 1.60 – 1.55 (m, 1H), 1.36 – 1.30 (m, 1H), 1.29 – 1.24 (m, 4H), 1.22 (s, 3H), 1.13 (t, *J* = 7.3 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 171.2, 121.6, 107.9, 92.6, 88.8, 88.7, 69.9, 68.1, 52.7, 52.3, 51.9, 50.8, 46.1,

43.6, 42.7, 32.7, 27.8, 26.4, 25.9, 23.1, 21.2, 19.3, 18.6, 7.6, 0.1, -5.2, -5.4. HRMS (m/z): $[M + H]^+$ calcd for $C_{29}H_{44}O_9SiH^+$ 565.2827, found 565.2828.

Synthesis of lactone 67. To a stirred solution of compound **66** (26.6 mg, 0.0471 mmol, 1.00 equiv) in DCM (2.3 mL) was added Martin's sulfurane (57.1 mg, 0.0849 mmol, 1.80 equiv). After stirring for 3 hours, the reaction was quenched with saturated aqueous NH_4Cl. The resulted mixture was extracted with DCM (3 × 5.0 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/3 to 1/1) to give the product **67** (21.0 mg, 0.384 mmol, 82% yield) as a colorless oil; **67**: Rf = 0.3 (silica, EA/PE = 1:1); $[\alpha]_D^{25}$ = – 26.9 (c = 0.16 in $CHCl_3$); IR (film): ν_{max} = 2959, 2925, 2854, 1772, 1653, 1462, 1377, 1358, 1261, 1095, 1021, 939, 802, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.37 (d, *J* = 5.3 Hz, 1H), 3.66 (d, *J* = 11.1 Hz, 1H), 3.53 (d, *J* = 11.1 Hz, 1H), 3.20 (s, 1H), 2.82 (dd, *J* = 10.0, 6.2 Hz, 1H), 2.77 – 2.53 (m, 4H), 2.18 (dd, *J* = 15.7, 10.3 Hz, 1H), 2.06 – 1.93 (m, 1H), 1.93 – 1.71 (m, 3H), 1.71 – 1.62 (m, 1H), 1.54 – 1.48 (m, 2H), 1.43 (s, 3H), 1.24 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.05 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 173.9, 173.6, 120.8, 101.9, 90.6, 87.6, 84.3, 69.0, 67.7, 57.5, 53.0, 50.8, 46.2, 45.6, 43.5, 34.1, 28.6, 25.8, 24.2, 22.3, 20.8, 19.5, 18.3, 7.7, -5.3, -5.4. HRMS (m/z): $[M + H]^+$ calcd for $C_{29}H_{42}O_8SiH^+$ 547.2722, found 547.2730.

Synthesis of lactone 68. Preparation of solution A: Pd_2dba_3·$CHCl_3$ (15.0 mg, mmol) and *n*-Bu_3P (7.0 μL, mmol) was dissolved in 1, 4-dioxane (0.5 mL), and stirring continued for 10 min.

Preparation of solution B: HCOOH (52.0 μL, mmol) and DIPEA (92.0 μL, mmol) were dissolved in 1, 4-dioxane (0.36 mL), and stirring continued for 10 min.

To a stirred solution of compound **67** (11.3 mg, 0.0207 mmol, 1.00 equiv) in 1, 4-dioxane (0.4 mL) was sequentially added 100.0 μL of solution A and 50.0 μL of solution B under N_2.The reaction mixture was heated to 45 °C, and stirring continued for another 10 hours. The resulted mixture was filtered, and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (EA/PE = 1/5 to 1/2) to give the product **68** (6.0 mg, 0.0109 mmol, 53% yield) as a colorless oil; **68**: Rf = 0.3 (silica, EA/PE = 1/1); $[\alpha]_D^{25}$ = 7.8 (c = 0.15 in $CHCl_3$); IR (film): ν_{max} = 2957, 2926, 2855, 1778, 1768, 1462, 1453, 1377, 1259, 1209, 1168, 1101, 1064, 1032, 933, 874, 837, 802, 760, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 11.4, 5.9 Hz, 2H), 3.59 – 3.50 (m, 2H), 3.05 (s, 1H), 2.87 – 2.74 (m, 2H), 2.70 (dd, *J* = 17.4, 11.9 Hz, 2H), 2.54 (d, *J* = 17.7, 1H), 2.44 (t, *J* = 10.1 Hz, 1H), 2.30 (dd, *J* = 16.3, 10.9 Hz, 2H), 1.92 – 1.79 (m, 2H), 1.76 – 1.67 (m, 2H), 1.48-1.37 (m, 1H), 1.37 – 1.24 (m, 2H), 1.21 (d, *J* = 3.7 Hz, 3H), 1.16 – 1.09 (m, 6H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 173.8, 121.5, 92.1, 88.8, 86.8, 81.3, 69.2, 67.8, 55.0, 54.5, 52.4, 50.8, 46.0, 43.0, 35.7, 32.5, 27.8, 26.2, 25.9, 23.0, 19.3, 18.4, 17.6, 7.6, -5.2, -5.4. HRMS (m/z): $[M + H]^+$ calcd for $C_{29}H_{44}O_8SiH^+$ 549.2878, found 549.2884.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Entry for the Table of Contents

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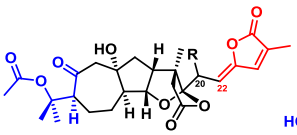
Collective Synthesis of Schilancidilactones A, B and Schilancitrilactones A, B, C, 20-*epi*-Schilancitrilactone A

Hengtao Wang, Liang Wang, Yihang Li, Xiunan Zhang, Pingping Tang*



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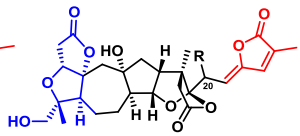

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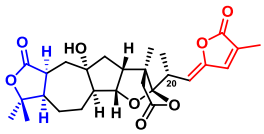

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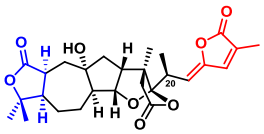

Schilancitrilactone C

The collective total synthesis of schilancidilactones A, B, schilancitrilactones A, B, C, and 20-*epi*-schilancitrilactone A were accomplished. The key steps include intermolecular radical cyclization, late-stage halogenation, intermolecular cross coupling of alkyl halide with vinyl stannane.