Natural Products

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Total Synthesis of Schilancitrilactones B and C**

*Liang Wang, Hengtao Wang, Yihang Li, and Pingping Tang**

Abstract: *The first total syntheses of schilancitrilactones B and C have been accomplished in 17 steps (longest linear sequence) from commercially available materials. Key steps include an intramolecular radical cyclization to provide the seven-membered ring, late-stage iodination, and an intermolecular radical addition reaction to complete the total synthesis.*

Schilancitrilactones B and C (**1** and **2**; Figure 1)[1] were isolated in 2012 by Sun and co-workers from the stems of *Schisandra Lancifolia*, which have been used in traditional Chinese medicine for the treatment of neurasthenia and related diseases.[2] Preliminary biological assays indicated that schilancitrilactone C showed biological activities for inhibiting HIV-1 while schilancitrilactone B was not bioactive. The structures of these compounds were striking in that they contain a 5/7/5/5/5-fused pentacyclic ring system bearing nine stereogenic centers. In addition, the three *cis*-fused five-membered rings (rings C–E), all with the envelope conformations, and seven contiguous chiral centers (including two quaternary centers) form a structurally rigid tricyclic ring system. Construction of these highly oxygenated unique motifs remains challenging. Herein, we present the first total synthesis of schilancitrilactones B and C. The key steps include the successful implementation of an intramolecular radical cyclization to prepare a seven-member ring, late-stage iodination, and an intermolecular radical C–C bond formation.

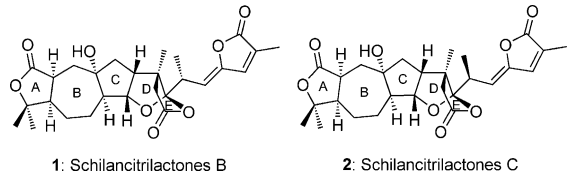
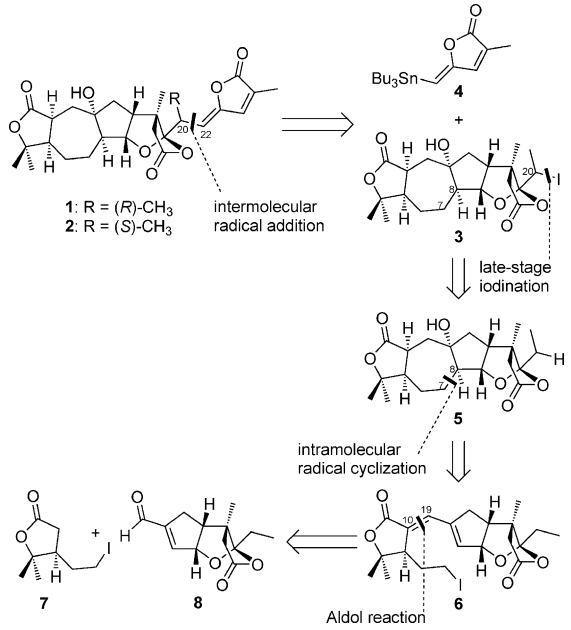


Figure 1. Schilancitrilactones B and C.

Recently, the total synthesis of *Schisandraceae* triterpenoids has been of great interest to synthetic organic chemists because of the intriguing structures and diverse biological activities.[3] In 2011, Yang and co-workers reported the first total synthesis of schindilactone A.[4] Recently, the group of Li disclosed the first asymmetric total synthesis of rubriflordilactone A.[5] Herein we report our efforts on developing a new strategy to solve the chemical synthesis of **1** and **2**, and a pathway for the synthesis of their analogues and derivatives for medicinal studies. Our retrosynthetic analysis is shown in Scheme 1. It was hypothesized that **1** and **2** might be accessible by an intermolecular radical addition reaction between the alkyl iodide **3** and vinyl stannane **4**. The alkyl iodide **3** was expected to arise by late-stage iodination at C20 from the compound **5**, which in turn could be prepared from the compound **6** by a series of steps including an intramolecular radical cyclization at the C7–C8 bond to prepare the seven-membered ring.[6] The compound **6** was further deconstructed at the C10–C19 bond into the two simple building blocks **7** and **8**, which could be put together by an aldol reaction. The building blocks **4**, **7**, and **8** could be prepared from the commercially available compounds citraconic anhydride (**16**), L-carvone (**9**), and 1,3-cyclohexadiene (**19**), respectively.



Scheme 1. Retrosynthetic analysis of schilancitrilactones B and C.

Our work began with the synthesis of the alkyl iodide **7** (Scheme 2). Following the procedure by Fukuyama and co-workers,[7] L-carvone (**9**) was converted into the correspond-

[*] L. Wang, H. Wang, Y. Li, Prof. Dr. P. Tang
State Key Laboratory and Institute of Elemento-Organic Chemistry
Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University
Tianjin 300071 (China)
E-mail: ptang@nankai.edu.cn

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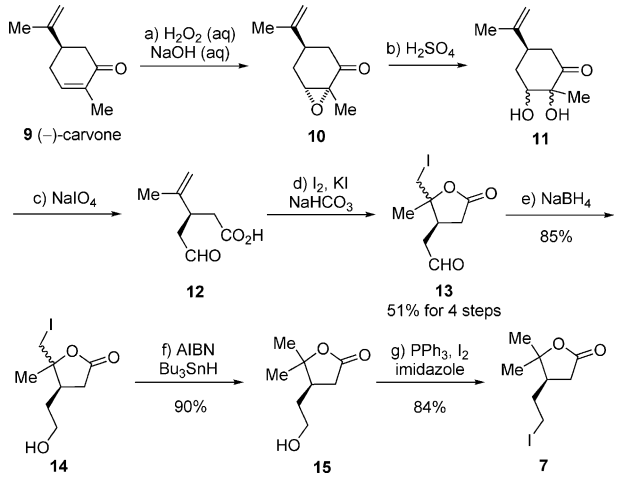
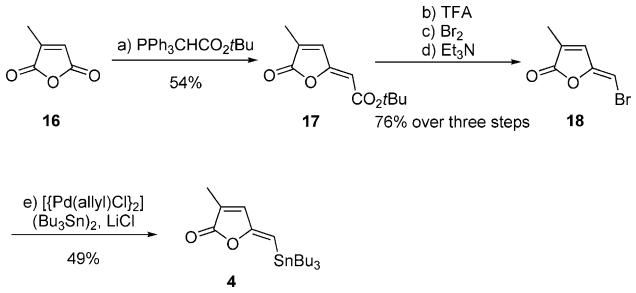


Scheme 2. Reagents and conditions: a) 30% H_2O_2, NaOH (aq), MeOH, 0°C; b) H_2SO_4, THF/H_2O (5:1), reflux; c) $NaIO_4$, *i*PrOH/H_2O (1:1), 0°C to RT; d) I_2, KI, $NaHCO_3$, CH_2Cl_2/H_2O (1:3), 0°C, 51% for 4 steps; e) $NaBH_4$, MeOH, 0°C, 85%; f) AIBN, Bu_3SnH, toluene, 100°C, 90%; g) PPh_3, I_2, imidazole, 0°C to RT, THF, 84%. AIBN = 2,2′-azobis(2-methylpropionitrile), THF = tetrahydrofuran.

ing aldehyde **13** in a four-step sequence involving epoxidation, epoxide hydrolysis, oxidative cleavage of diols, and iodolactonization in 51% overall yield (4 steps). The aldehyde **13** was selectively reduced with $NaBH_4$ to provide the alcohol **14** in 85% yield. The deiodination of **14** with AIBN and Bu_3SnH afforded the compound **15**, which was converted into the corresponding **7** with I_2 in the presence of Ph_3P and imidazole in 84% yield.[8]

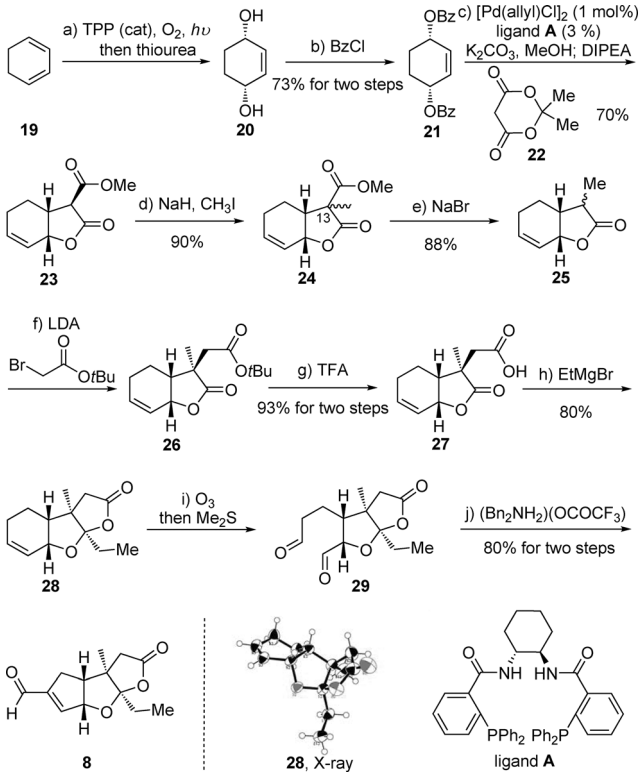
Depicted in Scheme 3 is the construction of the vinyl stannane compound **4**. The vinyl bromide **18** was prepared



Scheme 3. Reagents and conditions: a) PPh_3CHCO_2tBu, toluene, RT, 54%; b) TFA, CH_2Cl_2, 0°C; c) Br_2, TFA, $CDCl_3$/CCl_4 (1:1), RT; (d) Et_3N, DMF, 0°C to RT, 76% for 3 steps; (e) [{Pd(allyl)Cl}$_2$] (5 mol%), $(Bu_3Sn)_2$, LiCl, 1,4-dioxane, RT, 49%. DMF = *N*,*N*-dimethylformamide, TFA = trifluoromethanesulfonyl.

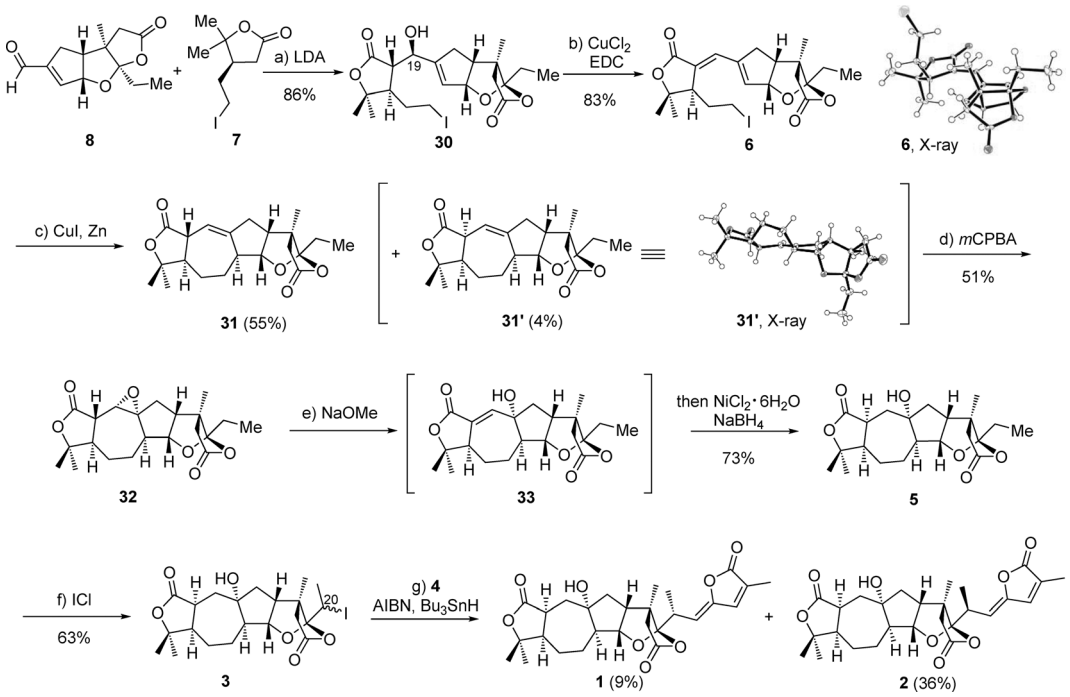
from the commercially available compound citraconic anhydride (**16**) in a reported four-step process in a 41% overall yield.[9] Stannylation of **18** was achieved and afforded **4** with [{Pd(allyl)Cl}$_2$] and $(Bu_3Sn)_2$ in 49% yield.[10] It is noteworthy that **4** is not stable during purification, thus resulting in a low yield.

We then moved on to construct the aldehyde compound **8** (Scheme 4). By using the reaction conditions developed by



Scheme 4. Reagents and conditions: a) TPP, O_2, hυ, CCl_4, −10°C then thiourea, MeOH; b) BzCl, Et_3N, DMAP, CH_2Cl_2, RT, 73% for 2 steps; c) [{Pd(allyl)Cl}$_2$] (3 mol%), ligand **A**, **22**, K_2CO_3, MeOH, THF, 0°C; then DIPEA, 55°C; 70%; d) NaH, CH_3I, DMF, 0°C, 90%, d.r. (at C13) = 4:1; e) NaBr, DMF, 180°C, 88%, d.r. (at C13) = 1:1; f) LDA, $BrCH_2CO_2tBu$, THF, −78°C; g) TFA, CH_2Cl_2, 0°C to RT, 93% for 2 steps; h) EtMgBr, THF/Et_2O (1:1), −78°C to RT, 80%; i) O_3, CH_2Cl_2/MeOH (1:1), −78°C, then Me_2S, −78°C to RT; j) $(Bn_2NH_2)(OCOCF_3)$, toluene, 63°C, 80% for 2 steps. Bz = benzoyl, DIPEA = diisopropylethylamine, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, LDA = lithium-diisopropyl amide, TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine. Thermal ellipsoids are shown at 50% probability.[21]

Trost and co-workers,[11] the lactone **23** was obtained in a reported three-step process from the commercially available 1,3-cyclohexadiene (**19**). The steps included asymmetric palladium-catalyzed allylic alkylation. Methylation of **23** with NaH and CH_3I provided the compound **24** in 90% yield with 4:1 diastereoselectivity at C13, and was then subjected to decarboxylation mediated by NaBr to produce a 1:1 mixture of the lactone **25** in 88% yield. Alkylation of **25** with *tert*-butyl bromoacetate gave the single diastereomer **26**. Deprotection of **26** was achieved using trifluoroacetic acid and gave the acid **27** in 93% yield (two steps). Addition of ethyl magnesium bromide followed by acidic workup gave rise to the tricycle **28**, having an ethyl group installed stereoselectively onto the tricyclic framework.[12] The absolute configuration of **28** was determined by X-ray crystallographic analysis. The cyclohexene ring in **28** was oxidatively cleaved by ozonolysis and the resulting dialdehyde **29** was directly subjected to intramolecular aldol condensation, thus yielding the ring-closed unsaturated aldehyde **8** (80% yield for two steps).[13]



Scheme 5. Reagents and conditions: a) LDA, THF, −78 °C, then **8**, 86%, d.r. (at C19) = 17:1; b) $CuCl_2$, EDC, toluene, 80 °C, 83%; c) CuI, Zn, Pyr/H_2O (1:4), ultrasound, RT, 55% for **31**, 4% for **31′**; d) *m*CPBA, $NaHCO_3$, CH_2Cl_2, −15 °C, 51%; e) NaOMe, MeOH, RT; then $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH/THF (1:5), −15 °C, 73%; (f) ICl, THF, RT, 63%, d.r. (at C20) = 1.5:1; (g) **4**, AIBN, Bu_3SnH, toluene, 4 Å M.S., 100 °C, 9% for **1**, 36% for **2**. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidem *m*CPBA = *m*-chloroperbenzoic acid. Thermal ellipsoids are shown at 50% probability.[21]

With the key intermediates **4**, **7**, and **8** in hand, we finished the total synthesis of schilancitrilactones B and C as shown in Scheme 5. The iodo compound **7** was converted into the lithium enolate with LDA at −78 °C and then reacted with **8** to give the aldol adduct **30** in 86% yield (d.r. = 17:1 at C19). Dehydration of **30** with 2 equivalents of EDC and a catalytic amount of $CuCl_2$ provided a 2:1 mixture of the inseparable diene lactone **6** in 83% yield.[14] The structure of the *E* isomer was confirmed by X-ray crystallographic analysis. Then we investigated the intramolecular radical cyclization to form the seven-membered ring. Initially, the conventional radical conditions (AIBN, Bu_3SnH) led to rapid decomposition of **6** and trace amounts of cyclization product was observed. Photoredox catalysis[15] was also evaluated and no desired product was found. By using the method (CuI, Zn under ultrasound) for conjugate additions in aqueous media discovered by Luche et al.,[16] we were pleased to observe the cyclization product **31** in 55% yield, together with the isomer **31′** in 4% yield. The structure of **31′** was confirmed by X-ray crystallographic analysis. We reasoned that the conformation of **6** was suited for cyclization to give the seven-membered ring over the five-membered ring.[17] Epoxidation of **31** with *m*CPBA provided the epoxide **32** in 51% yield, and underwent ring opening with $NaOMe/NiCl_2{\cdot}6H_2O/NaBH_4$ to give the alcohol **5** in 73%.[18] During this transformation, the epoxide **32** was converted into the intermediate **33** with NaOMe and then further reduced to give the desired product **5** with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$. Finally, we investigated the late-stage iodination and intermolecular radical addition reaction. It was found that treatment of **5** with ICl delivered the iodo compound **3** as a mixture of diastereomers (d.r. = 1.5:1 at C20) in 63% yield,[18] and when **3** was heated with the vinyl stannane **4**, AIBN, and Bu_3SnH provided the schilancitrilactones B (**1**, 9%) and C (**2**, 36%) in 45% total yield. Around 25% yield of other isomers were observed based on the ^1H NMR analysis of the crude reaction mixture.[20] The characterization data obtained for synthetic **1** and **2** were in accord with the reported data for the natural products.

In summary, the first total synthesis of schilancitrilactones B and C has been accomplished by employing an intramolecular radical cyclization, late-stage iodination, and intermolecular radical addition as key steps in the 17 step synthesis (longest linear sequence) from commercially available materials. This strategy opens a pathway for the syntheses of other compounds related to schilancitrilactones B and C, as well as their derivatives and analogues.

Keywords: cyclizations · natural products · radical chemistry · total synthesis · terpenoids

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[21] CCDC 1034710 (**28**), 1046754 (**6**), and 1034713 (**31′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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