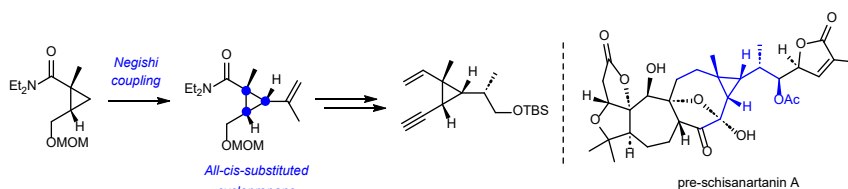


Toward the Total Synthesis of Schinortriterpenoids: Construction of the all-*cis*-substituted cyclopropane unit

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Abstract As a step toward total synthesis of pre-schisanartanins and arisanlactones, we successfully synthesized a right fragment of *Schisandra* nortriterpenoids bearing a distorting all-*cis*-substituted cyclopropane from a chiral lactone. The key step in this synthesis was diastereoselective construction of an all-*cis*-substituted cyclopropane via Negishi coupling using an amide as a directing group.

Keywords cyclopropane, *Schisandra* nortriterpenoid, Negishi coupling, pre-schisanartanin, arisanlactone, diastereoselective synthesis

The dried mature fruits of *Schisandra* species have been used in traditional Chinese medicine for more than 2000 years.¹ They are a rich source of biologically active triterpenoids called *Schisandra* nortriterpenoids (SNTs). SNTs have attracted the interest of many synthetic chemists because of their unique skeleton and important biological activities, including anti-viral, cytotoxic, and immunosuppressive activities.² All-*cis*-substituted cyclopropanes³ have all bulky substituents on the cyclopropane orientated in the same direction. We are interested in SNTs containing this unique structure, such as pre-schisanartanins,^{4a} arisanlactones,^{4b} schincarin A,^{4c} spiroschincarin,^{4d} and schincalactones^{4e} (Figure 1). Pre-schisanartanin A has anti-HIV activity (EC₅₀ = 13.81 µg/mL), and spiroschincarins and schincalactones have weak immunosuppressive activity. Schincalactones are assumed to be biosynthetically produced from pre-schisanartanin P via oxidative cleavage and cyclization. The synthesis of these SNTs is challenging because the all-*cis*-substituted cyclopropane could be highly reactive. Yang et al. reported a ring-opening of all-*cis*-substituted cyclopropane to construct the unique 7,9,5-membered fused ring system in the synthesis of 19-dehydroxyl arisandilactone A.^{2k} The total synthesis of pre-schisanartanin C has been achieved by Yang et al.^{2r} They successfully constructed the all-*cis*-substituted cyclopropane structure using a gold-catalyzed enyne cyclization. Other SNTs

containing an all-*cis*-substituted cyclopropane have not yet been synthesized.

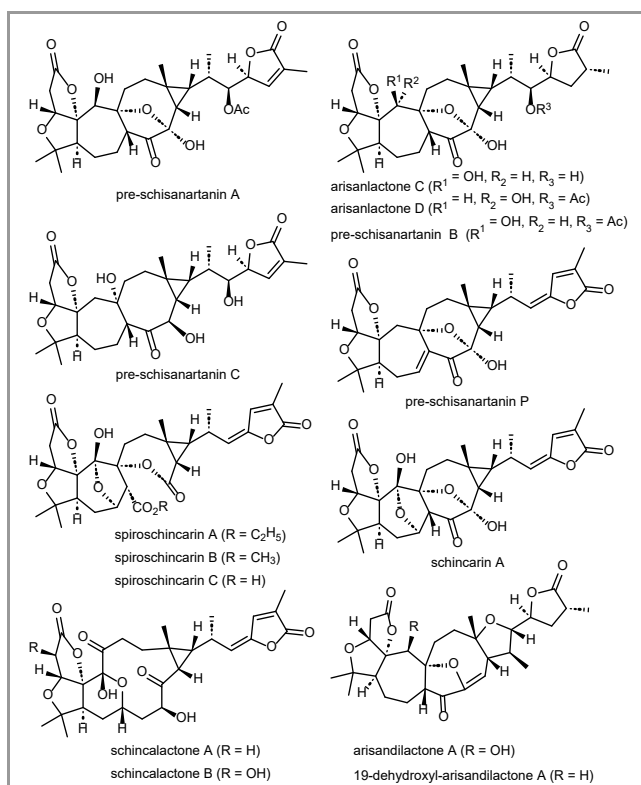
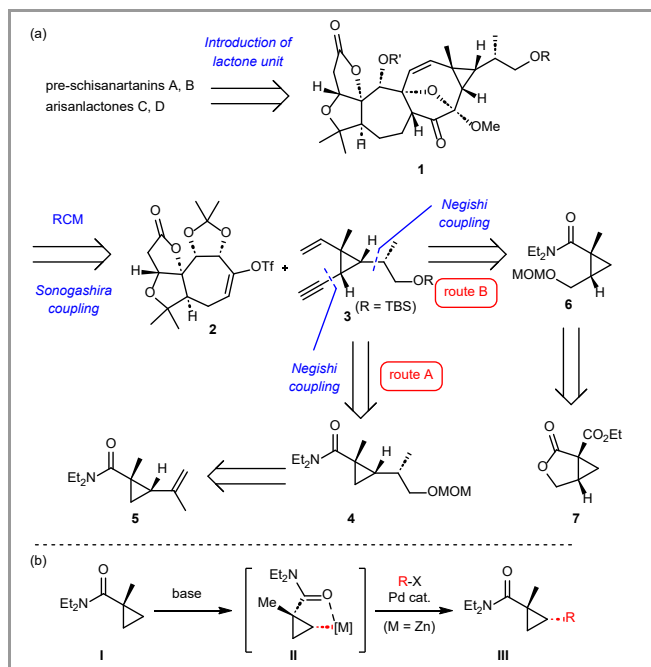


Figure 1 *Schisandra* nortriterpenoids (SNTs) containing an all-*cis*-substituted cyclopropane.

For a convergent synthesis of pre-schisanartanins and arisanlactones, we planned to use Sonogashira coupling of a 5/5/7-membered-ring fused system **2** with all-*cis*-substituted cyclopropane **3**, ring-closing metathesis to construct an 8-membered-ring of **1**, and introduction of a five-membered lactone unit (Scheme 1a). For triflate **2**, we have already

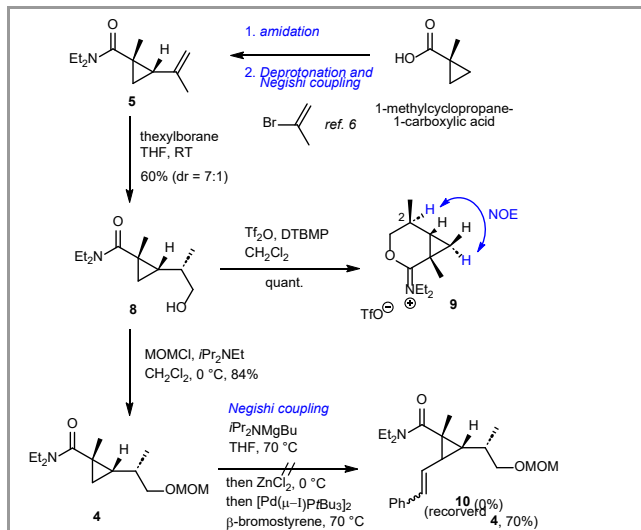
reported the synthesis of the precursor ketone.⁵ We previously reported a synthetic strategy for constructing a *cis*-cyclopropane, in which the cyclopropane ring of **1** was stereoselectively deprotonated using diethylamide as a directing group, followed by introduction of the substituent via Negishi coupling (Scheme 1b, **II**→**III**).⁶ Two synthetic pathways were envisioned for the synthesis of the all-*cis*-substituted cyclopropane **3** using this strategy. In route A, the substituent that would become the alkyne moiety would be introduced onto compound **4**, which would be synthesized from compound **5**. In route B, the substituent that would become the alkyl chain would be introduced onto compound **6**, which would be derived from the known compound **7**. In both routes, the alkene substituent would be synthesized from a diethylamide. Because the three-membered ring of all SNTs shares the common all-*cis* substituted structure, the synthesis of **3** would lead to the synthesis of other SNTs. In this report, we describe in detail the synthesis of compound **3**.



Scheme 1 (a) Retrosynthesis of pre-schisanartanins A and B, and arisanlactones C and D. (b) Direct introduction of a substituent onto cyclopropane via Negishi coupling.

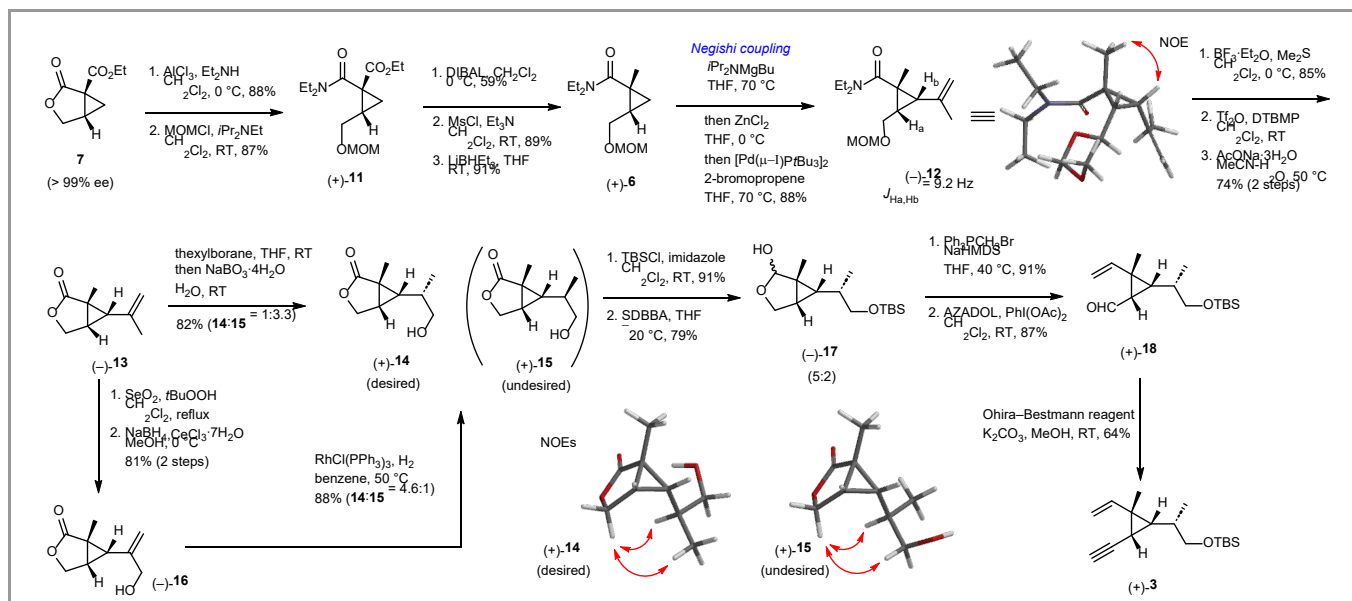
To investigate route A, we commenced with hydroboration of *cis*-cyclopropane **5**, which was synthesized from 1-methylcyclopropane-1-carboxylic acid by amidation and Negishi coupling (Scheme 2).⁶ The reaction gave the desired alcohol **8** along with a small amount of its diastereomer (dr 7:1).⁷ To confirm the newly generated stereochemistry, **8** was treated with Ti_2O and di-*tert*-butylmethylpyridine to give cyclic imide **9**. NOESY results for **9** indicated that the stereocenter of C2 was in the desired *S* configuration. After compound **8** was converted to methoxymethyl (MOM) ether **4**, introduction of the third substituent onto the cyclopropane ring was examined. However, the Negishi reaction with β -bromostyrene under the previously established conditions did not give the desired compound **10**, and the starting material **4** was recovered in 70% yield. In our previous report, Negishi reaction of a

substrate having a non-branched substituent with β -bromostyrene proceeded under the same conditions.⁶ We assumed that the branched alkyl substituent on the cyclopropane ring was too bulky to approach β -bromostyrene. Thus, we turned our attention to route B, which used a less bulky substituent on the cyclopropane.



Scheme 2 An initial attempt to construct all-*cis*-substituted cyclopropane **10** via route A.

Although racemic substrate **6** could be prepared from 1-methylcyclopropane-1-carboxylic acid by following the method in our previous report,⁶ we started the synthesis from an optically active known compound **7** for asymmetric synthesis (Scheme 3).⁸ After ring-opening of lactone by treatment with AlCl_3 and Et_2NH , the resultant alcohol was protected as MOM ether to give (+)-**11**. Reduction of (+)-**11** with diisobutylaluminum hydride was followed by mesylation and reductive desulfonyloxylation with LiBHET_3 to give (+)-**6**. As expected, an isopropenyl group as a third substituent was successfully introduced by treatment with $i\text{Pr}_2\text{NMgBu}$ and then bromopropene and $[\text{Pd}(\mu\text{-I})\text{PtBu}_3]_2$.^{9,10} The stereochemistry on the cyclopropane ring of (–)-**12** was confirmed using NOESY and the coupling constant between H_a and H_b (Scheme 3). To convert the amide functionality, (–)-**12** was converted to lactone (–)-**13** through removal of the MOM group, formation of a cyclic imide, and hydrolysis. Unfortunately, hydroboration of (–)-**13** gave the desired alcohol (+)-**14** only as a minor product that was separable from its diastereomer (+)-**15**. Thus, allylic oxidation of (–)-**13** with SeO_2 and $t\text{BuOOH}$ followed by 1,2-reduction was used. Hydrogenation of the resultant alcohol (–)-**16** using Wilkinson catalyst¹¹ gave the desired (+)-**14** as a major product. Finally, silylation of (+)-**14** and reduction of lactone with sodium diisobutyl-*t*-butoxyaluminum hydride¹² gave lactol (–)-**17**, which was converted to the right fragment (+)-**3** through a Wittig reaction, oxidation of a resultant alcohol, and treatment with the Ohira-Bestmann reagent.¹³ We found that (+)-**3** was unstable at 70 °C and it needed to be stored at < 0 °C.^{14,15}



Scheme 3 Synthesis of all-*cis*-substituted cyclopropane (+)-**3** through route B.

In summary, we successfully synthesized **3**, a possible common intermediate for SNTs containing an all-*cis*-substituted cyclopropane, with direct introduction of the side chain onto the cyclopropane ring as the key step. It was difficult to introduce a third substituent onto cyclopropanes with branched alkyl side chains, and it was necessary to employ a substrate with a less bulky substituent. We are currently investigating the coupling of fragments **2** and **3** to construct a core structure for pre-schisanartanines and will report the results in the future.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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- (10) **Compound 12**: To a $n\text{Bu}_2\text{Mg}$ (1 M heptane solution, 4.53 mL, 4.53 mmol) was added $i\text{Pr}_2\text{NH}$ (0.600 mL, 4.27 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to 50 °C and stirred for 10 min. The solution was cooled to room temperature, added the solution of **6** (281 mg, 1.23 mmol) in anhydrous THF (4.00 mL). The solution was warmed to 70 °C and stirred for 3 h. The solution was cooled to 0 °C, added ZnCl_2 (1 M THF solution, 4.63 mL, 4.63 mmol) and stirred for 20 min at the same temperature. The solution were added the solution of $[\text{Pd}(\mu\text{-I})\text{PtBu}_3]_2$ (117 mg, 0.134 mmol) in anhydrous toluene (4.00 mL) and 2-bromopropene (0.450 mL, 5.17 mmol). The solution was warmed to 70 °C and stirred for 19 h. The reaction was quenched with saturated aqueous NH_4Cl . The mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20–50% EtOAc/hexane) to afford **12** (290 mg, 88%) as a brown oil: $[\alpha]_{\text{D}}^{17}$ -54.1 (*c* 0.480, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 4.82 (1H, s), 4.60 (2H, dd, J = 28.2, 6.4 Hz), 4.42 (1H, s), 4.11 (1H, dd, J = 11.2, 4.2 Hz), 3.71–3.61 (2H, m), 3.47–3.38 (1H, m), 3.32 (3H, s), 3.34–3.23 (2H, m), 1.88 (3H, s), 1.57 (1H, d, J = 9.2 Hz), 1.38 (1H, ddd, J = 13.6, 9.5, 4.2 Hz), 1.34 (3H, s), 1.21 (3H, t, J = 7.2 Hz), 1.10 (3H, t, J = 7.1 Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 170.5, 140.9, 110.1, 96.6, 64.3, 55.1, 41.8, 38.5, 35.5, 31.0, 30.2, 26.0, 26.0, 13.9, 12.2; HRMS (FAB, m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_3$, 270.2069 found 270.2071.
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- (15) **Compound 3**: To a solution of **18** (2.7 mg, 9.6 μmol) in anhydrous MeOH (1.00 mL) was added K_2CO_3 (20.0 mg, 0.145 mmol) at room temperature under N_2 atmosphere. The solution was stirred at room temperature for 5 min. The solution was added Ohira-Bestmann reagent (15.0 μL , 0.0999 mmol) and stirred for 3 h at the same temperature. The reaction mixture was quenched with aqueous saturated NaHCO_3 and extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2% Et $_2\text{O}$ /hexane) to afford **3** (1.7 mg, 64%) as a colorless oil: $[\alpha]_{\text{D}}^{21}$ +83.4 (*c* 0.160, CHCl_3); ^1H NMR (400 MHz, C_6D_6) δ 6.14 (1H, dd, J = 17.4, 11.0 Hz), 5.21–5.11 (2H, m), 3.59 (1H, dd, J = 9.5, 3.6 Hz), 3.41 (1H, dd, J = 9.5, 6.9 Hz), 1.94–1.83 (1H, m), 1.73 (1H, d, J = 2.2 Hz), 1.35 (1H, dd, J = 8.7, 2.2 Hz), 1.27 (3H, d, J = 6.6 Hz), 0.97 (9H, s), 0.92 (3H, s), 0.70 (1H, dd, J = 11.1, 8.7 Hz), 0.05 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 138.4, 114.1, 81.5, 69.0, 66.8, 35.3, 33.5, 27.2, 25.8, 22.3, 19.9, 18.2, 16.5, -5.5, -5.6; HRMS (APCI, m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{31}\text{OSi}$, 279.2139 found 279.2138.