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Synthetic Study of Rubriflordilactone B: Highly Stereoselective Construction of the C-5-epi ABCDE Ring System

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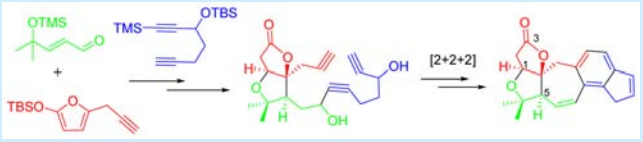
Supporting Information

ABSTRACT: A highly stereocontrolled construction of the C-5-epi ABCDE-ring system of rubriflordilactone B has been developed. The present synthesis features a convergent strategy to construct the C-5-*epi* AB-ring utilizing Mukaiyama−Michael reaction and forge the CDE ring in one step using intramolecular [2 + 2 + 2] cycloaddition of triynes.



The fruits of *Schisandra chinensis*, named "Wu-Wei-Zi" in Chinese, have been used in traditional medicine for the treatment of hepatitis for over 2000 years in China.[1] Its family, Schisandraceae, has gained the interest of the medicinal chemistry and drug discovery community. Chemical investigations of the plants of this family have led to the isolation of over 120 triterpenoids with different oxygenated skeletons and significant biological activities, including anti-HIV activity.[1] These nortriterpenoid natural products with attractive architectures also represent a formidable synthetic challenge; the pioneering work for the total synthesis of schindilactone A was first reported by Yang in 2011.[2] Recently, schilancitrilactones B and C and propindilactone G were synthesized by Tang and Yang, respectively.[3] The rubriflordilactones A (**1**) and B (**2**), another two nortriterpenoid natural products isolated from the leaves and stems of *Schisandra rubriflora* by Sun et al. in 2006, possess a modified aromatic D-ring as an unique structure[4] (Figure 1). Compound **1** showed weak anti-HIV-1

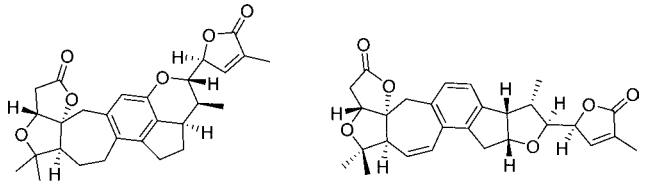
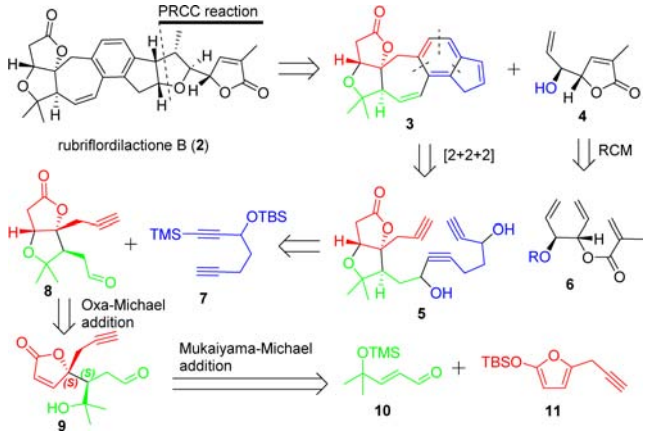


Figure 1. Rubriflordilactones A (**1**) and B (**2**).

activity, and compound **2** exhibited a fairly strong bioactivity against HIV-1 replication with an EC_{50} value of 9.75 μg/mL (SI = 12.39) and low cytotoxicity.[4] Their attractive architectures and bioactivities have drawn particular attention from the synthetic community. Many synthetic approaches have been developed for the synthesis of its framework.[5] An elegant asymmetric synthesis of rubriflordilactone A via 6π electrocyclization to assemble the challenging pentasubstituted D-ring arene has been completed by Li et al.[6] Very recently, Anderson's group also disclosed the total synthesis of rubriflordilactone A, which used palladium- or cobalt-catalyzed cyclization to form the CDE rings.[7] It is noteworthy that rubriflordilactone B exhibits better anti-HIV activity than A, which was chosen as our target molecular. Herein, we report our progress on the synthetic study of the ABCDE ring system.

Scheme 1 outlines our retrosynthetic analysis of rubriflordilactone B (**2**). First, the target molecular is cleaved at the

Scheme 1. Retrosynthetic Plan of Rubriflordilactone B (2)



indenyl tetrahydrofuran motif, giving two key intermediates alkene **3** and alkenol **4**. Polar-radical-crossover cycloaddition (PRCC)[8] of **3** and **4** is envisioned to install the tetrahydrofuran motif in the final step. The compound **4** in turn could potentially be derived from **6** via ring-closing metathesis (RCM) reaction. The tetrasubstituted arene **3** could be formed from the triyne **5** by intramolecular [2 + 2 + 2] cycloaddition of triynes under transition-metal catalysis and subsequent dehydration. The compound **5** was considered synthesizable

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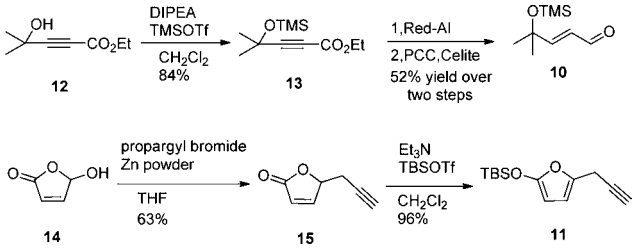
through intermolecular coupling of the diyne **7** and aldehyde **8** followed by a deprotection protocol. We also envisaged that aldehyde **8** could be derived from the α, β-unsaturated ester **9** by oxa-Michael reaction, which could prepared from the α,β-unsaturated aldehyde **10** and silyloxyfuran **11** by using a stereoselective Mukaiyama−Michael reaction as the crucial step.

The substrates **10** and **11** were constructed as illustrated in Scheme 2. We started our synthesis from the known ester **12**.[9]

Scheme 2. Synthesis of Compounds 10 and 11

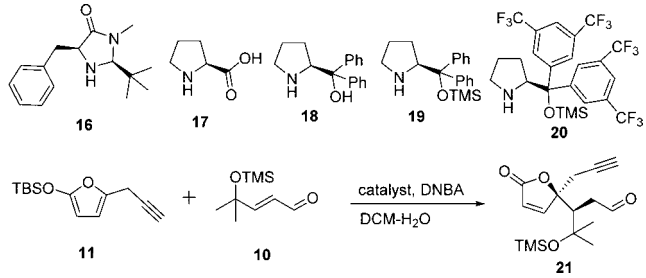


After the protection of tertiary alcohol by the TMS group,[10] the corresponding ether **13** was obtained in 84% yield. Subsequent concomitant reduction of the ester and alkynyl functionalities of **13** by Red-Al produced the *trans* allylic alcohol.[11] The alcohol was oxidized without further purification by treating with PCC and NaOAc to give the α,β-unsaturated aldehyde **10** on 10-g scale.[12] The silyloxyfuran **11** could be obtained from **15** smoothly,[13] which could be prepared easily via Barbier reaction[14] from commercially available 3-brompropyne and known 5-hydroxyfuran-2(5*H*)-one.[15]

With compounds **10** and **11** in hand, we attempted the key Mukaiyama−Michael reaction to construct the two vicinal chiral centers (one of them is a quaternary carbon center) in 4-substituted butenolides. The first enantioselective version of this type of reaction has been reported by Katsuki in 1997 with *anti*-selectivity as major products.[16a,b] Recently, several methods were developed for constructing the two vicinal chiral centers in 4-substituted butenolides with anti- or syn-selectivity.[16c−j] At the outset of our study, we used the Lewis acid promoted Michael addition of silyloxyfurans to α,β-unsaturated aldehydes.[16a−c] To our disappointment, it did not work no matter what Lewis acid and temperature we chose. We then tried Macmillan's method, which could contribute the adjacent chiral center in anti- or syn-selectivity.[16d] Perhaps due to the steric hindrance effects, the coupling of silyloxyfuran **11** and α,β-unsaturated aldehyde **10** did not occur under Macmillan's conditions. However, after changing the aldehyde **10** to crotonaldehyde, the conjugate addition indeed occurred with moderate yield.

Next, we screened a number of known iminium/enamine-type catalysts (Table 1). Finally, we were delighted to find that the two substrates were carried out with catalyst **19** at 0 °C, which could produce **21** smoothly in high diastereoselectivity (dr >20:1) (entries 4 and 10). Then we tried to assign the absolute stereochemistry of the compound **21**. After all of the efforts to get the crystals of related compounds were in vain, we undertook the synthesis of three known products[16d] by this procedure to confirm the Mukaiyama−Micheal addition's stereochemistry (detailed in the Supporting Information). Based on the reaction mechanism, we confirmed that the absolute stereochemistry of compound **21** was inferred as shown in this paper. Notably, using catalyst **19** alone gave a

Table 1. Catalyst Screening for the Mukaiyama−Michael Reaction

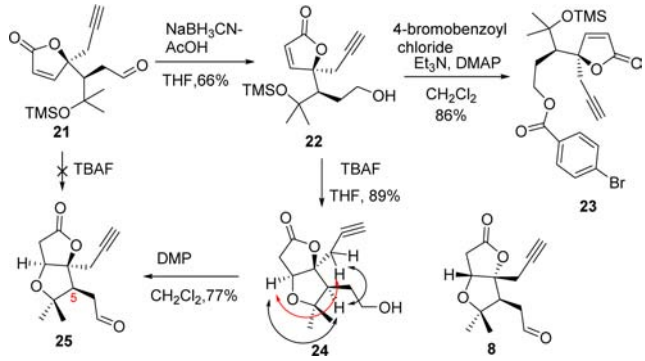


entry	cat.	DNBA (equiv)	temp (°C)	yield[a] (%)	ee[b]	dr[c]
1	**16**		−40 to rt	0		
2	**17**		−40 to rt	0		
3	**18**		−40 to rt	trace		
4	**19**		−40 to 0	68	97	>20:1
5	**20**		−40 to rt	0		
6	**16**	0.2	−40 to rt	0		
7	**17**	0.2	−40 to rt	0		
8	**18**	0.2	−40 to rt	trace		
9	**19**	0.2	−40 to rt	trace		
10	**20**	0.2	−40 to +10	52	99	>20:1

[a]Isolated yields after purification by flash chromatography. [b]Determined of compound **23** by chiral column AD-H. See the Supporting Information for further experimental details. [c]Determined by ^{1}H, ^{13}C NMR spectra.

better yield than using catalyst **20** combined with DNBA (2,4-dinitrobenzoic acid). As shown in Scheme 3, compound **21** was

Scheme 3. Synthesis of Compounds 23 and 25



reduced by $NaBH_3CN/AcOH$[17] to give the alcohol **22**, which was acylated with 4-bromobenzoyl chloride obtain the ester **23**. After detecting the ee of the compound **23**, we knew that using catalyst **20** combined with DNBA gave better enantioselectivity than using catalyst **19** alone (entries 4 and 10).

When we treated compound **21** with TBAF, we got a complex mixture. We realized that the carbonyl group in compound **21** impacted the O-Michael addition. Thus, the aldehyde was then treated with $NaBH_3CN/AcOH$ at 0 °C to give a primary alcohol **22**.[17] At this time, desilylation of **22** with TBAF resulted in the corresponding O-Michael additional product **24**,[18] which was converted into the aldehyde **25** by treatment with Dess−Martin periodinane in 77% yield (Scheme 3).[19] The assignment of stereochemistry to compound **24** was based on analysis of its NMR spectral data. Significant NOE enhancements observed among the

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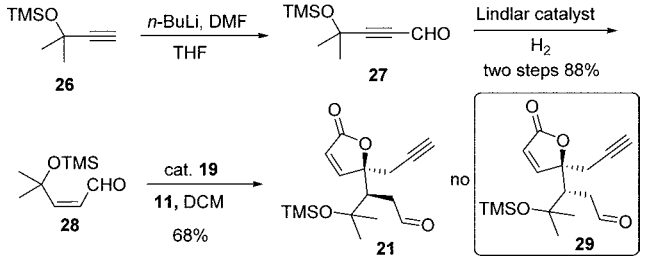
marked protons of **24** indicated that the chirality center of C-5 was undesired. The stereochemistry of **25** was confirmed by comparing the spectral data of **25** with those of the reported compound **8**.[7]

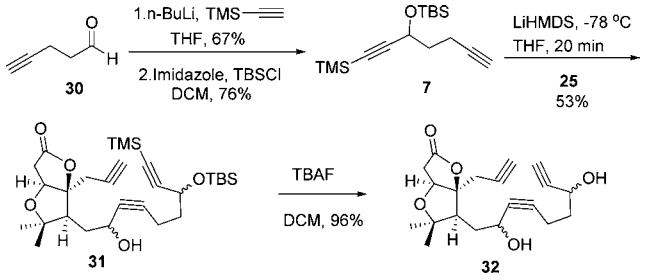
In order to revise the chirality of C-5, (*Z*)-*α*,*β*-unsaturated aldehyde **28** was prepared for the Mukaiyama−Michael reaction from alkyne **26** via a two-step procedure (Scheme 4). However, to our confusion, the product was still compound **21** and not compound **29**. The synthesis of compound **29** is currently underway in our laboratory.

Scheme 4. Attempted Synthesis of Compound 29



With compound **25** in hand, our efforts were focused on construction of the triyne substrate (Scheme 5). Terminal

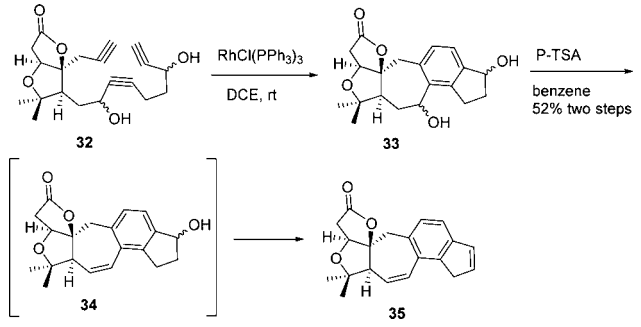
Scheme 5. Synthesis of Compound 31



monoalkyne **30** was converted into the corresponding alcohol by treatment with ethynyltrimethylsilane in the presence of *n*-BuLi. Followed by silylation with TBSCl and imidazole, this protocol resulted in a pair of enantiomers **7** in 51% yield in two steps.[20] As our synthetic plan, the lithiated terminal alkyne **7** was added to the aldehyde **25**. This protocol resulted in four stereoisomers **31**. As the new generated chiral centers would disappear by dehydroxylation in the next step, the resulting mixture of stereoisomers **31** was directly used for the cycloaddition reaction to construct the tetrasubstituted arene. However, using *n*-BuLi as lithiated reagent produced a complex mixture as shown by TLC. When LiHMDS was used as the lithiated reagent, the desired product was obtained in 18% yield. After optimization, compound **31** was obtained in 53% yield. Treatment of **31** with TBAF in THF gave diol **32**,[18] which was used as a substrate for construction of the tetrasubstituted arene via intramolecular [2 + 2 + 2] cycloaddition of triynes.

Several transition metals were used to catalyze the intramolecular [2 + 2 + 2] cycloaddition of triynes to polysubstituted arenes, such as ruthenium,[21] cobalt,[22] rhodium,[23] palladium,[24] nickel,[25] niobium,[26] and iridium.[27] Metal free formal [2 + 2 + 2] cycloaddition of triynes to polysubstituted arene was also reported.[28] Anderson's group ingeniously applied cobalt-catalyzed [2 + 2 + 2] cycloaddition of triynes to build the CDE ring in the total synthesis of rubriflordilactone A.[7] On the basis of these references, the transition-metal catalysts were screened. The rhodium-catalyzed condition was found to give the best results.[23] After optimization, the crude mixture of stereoisomers **33** was obtained in 76% yield (contained some catalyst) (Scheme 6).

Scheme 6. Synthesis of C-5-epi ABCDE core of Rubriflordilactone B



Efforts toward the purification of compound **33** were unsuccessful, as the R_f value of the catalyst and product was equal. Finally, compound **35** was obtained by treating all stereoisomers of **33** with *p*-TSA in 9 h.[29] It was noteworthy that compound **33** was first transferred to compound **34** and then **35**. Thus, the C-5-*epi* ABCDE core of rubriflordilactone B was synthesized.

In conclusion, a stereoselective synthesis of the C-5-epi ABCDE-ring system of rubriflordilactone B via Mukaiyama−Michael reaction and intramolecular [2 + 2 + 2] cycloaddition of triynes has been achieved in the longest linear sequence of 10 steps. On the basis of the present results, further investigation toward total synthesis of rubriflordilactone B is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00057.

^{1}H, ^{13}C, NOE, and HPLC spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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