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Enantioselective Synthesis of the Predominant AB Ring System of the *Schisandra* Nortriterpenoid Natural Products

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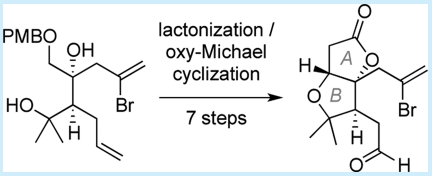
Supporting Information

ABSTRACT: An enantioselective synthesis of the AB ring system common to the majority of the *Schisandra* nortriterpenoid natural products is reported. Key steps include a stereospecific ring opening of a trisubstituted epoxide and the use of a β-lactone to enable installation of the *gem*-dimethyl functionality of the B ring. An acetalization strategy played a key role in a late-stage biomimetic AB ring bicyclization.

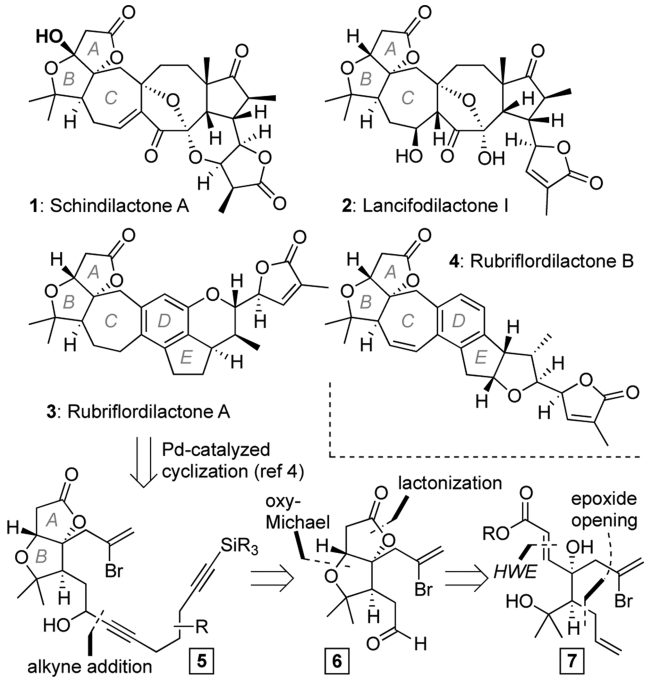


Extracts from the *Schisandra* genus of herbal plants have long been used in Chinese herbal medicines. Studies by Sun et al. over the past decade have resulted in the isolation of more than 120 bioactive nortriterpenoids from these plants, many of which have anti-HIV or other bioactivities.[1] While these properties make them attractive targets for synthetic endeavors,[2] it is the challenge posed by their beautiful and complex skeletons which has driven organic chemistry research in this field—a challenge that is underlined by the solitary total synthesis to date of just one family member, (±)-schindilactone A (**1**, Scheme 1).[3] Common to almost all of these natural products is a highly oxygenated [3.3.0] bicyclic lactone AB ring system, epitomized by lancifodilactone I and rubriflordilactones A and B (**2**–**4**). In this respect, schindilactone A in fact represents a structural outlier in featuring an additional alcohol substituent at the AB ring junction, an attribute that played a key role in the formation of its A ring via aldol cyclization in the work of Yang et al.[3]

The rubriflordilactones and lancifodilactones are longstanding synthetic targets within our group and have inspired the development of various metal-catalyzed methods for the formation of their CDE ring systems.[4] In planning for an assault on the full framework of these natural products, we ideally required a preformed AB ring system, onto which appropriate functionality could be attached in readiness for CDE ring cyclization. It is notable that all previous approaches to the ABC rings have used a preformed C ring (or equivalent) as a template,[2] a strategy that we were keen to avoid due to the skeletal diversity that might be introduced from CDE cyclization subsequent to AB ring formation. Here we report an enantioselective route to the AB rings that permits such future explorations, which is characterized by biomimetic lactonization/oxy-Michael transformations.

A retrosynthetic analysis that depicts these considerations in the context of rubriflordilactone A is illustrated in Scheme 1, the CDE rings of which could arise from a generalized bromoendiyne precursor **5**. This disconnection reveals the

Scheme 1. Representative *Schisandra* Nortriterpenoid Natural Products and Our AB Ring Retrosynthetic Analysis



'unified' nature of our synthetic plan, as addition of a variety of alkynes into aldehyde **6** could lead to different cyclization substrates (including **5**) and therefore different natural products. Aldehyde **6** in turn was envisaged to arise from possible biomimetic processes such as an oxy-Michael addition and lactonization from diol-enoate **7**. The two stereocenters in this enoate could be installed from a regioselective ring opening

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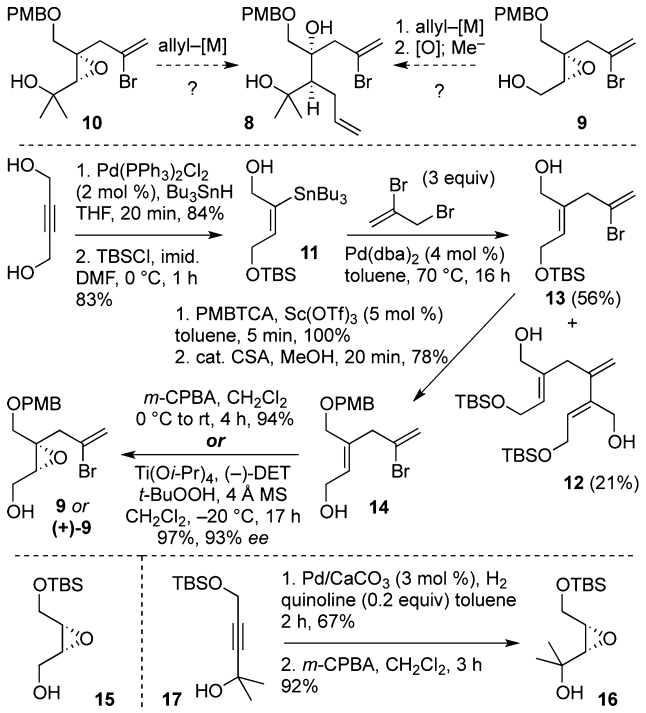
of an appropriate trisubstituted epoxide with an allyl organometallic reagent. The synthesis of aldehyde **6**, which is key to all our future synthetic work, forms the focus of this paper.

Our work commenced with an exploration of this epoxide ring opening. An ideal precursor to **7** would be a diol such as **8** (Scheme 2), which we might approach either from a hydroxyl-

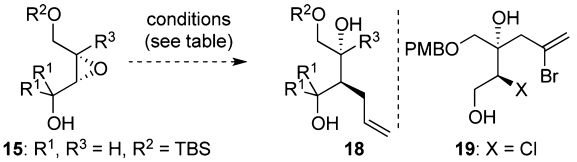
Scheme 2. Epoxide Synthesis



(or steric-) directed ring opening[5] of hydroxymethyl epoxide **9**, followed by oxidation and dimethylation, or from a direct but challenging opening of a more hindered epoxide such as **10**. The route to **9** began with a Pd-catalyzed hydrostannylation[6] of but-2-yne-1,4-diol, followed by regioselective monosilylation. Subsequent π-allyl Stille coupling[7] of stannane **11** with 2,3-dibromopropene proved surprisingly challenging. Despite the use of an excess of 2,3-dibromopropene (3 equiv), a significant amount of byproduct **12** was produced (21%) which arises from a second Stille coupling of desired product **13**, implying that the vinyl bromide in **13** is at least as reactive toward Pd(0) as the allylic bromide in 2,3-dibromopropene. Fortunately, these products were easily separable, and **13** could be isolated in a respectable 56% yield on multigram scale. In order to reveal the hydroxyl group required to direct epoxide opening and also mediate an asymmetric epoxidation, a protecting group switch afforded **14**; epoxidation with *m*-CPBA, or a Sharpless AE (97%, 93% *ee*), delivered epoxide **9** in racemic and enantioenriched form, respectively.[8] For comparison in the ring-opening reactions, disubstituted epoxide **15** was prepared in two steps from *cis*-butene-1,4-diol, and disubstituted epoxide **16**, which would enable us to evaluate the tolerance of steric effects around the 'directing' alcohol adjacent to the site of nucleophilic attack, was prepared in two steps from acetone adduct **17**.[9]

Having assembled a selection of epoxides, we moved to the challenge of epoxide ring opening (Table 1). We first confirmed that typical Cu-catalyzed hydroxyl-directed epoxide opening could be achieved on disubstituted epoxide **15** (entry 1) using conditions employed by Paquette et al. for the opening of a trisubstituted epoxide with a butenyl Grignard reagent (cat. CuCN, allylMgCl, THF).[2i] This ring opening proceeded uneventfully, with product **18** isolated in good yield. However, application of these conditions to the more hindered epoxide **16** failed, resulting in no observable reaction even in the presence of excess nucleophile and stoichiometric Cu(I) salt (entries 2, 3). Hindered ring openings of this nature are unprecedented and suggest that neopentylic steric considerations prohibit nucleophile approach. This result thus dictated that we would need to install the B ring *gem*-dimethyl group into tertiary alcohol **8** *after* allylation.

Table 1. Allyl Organometallic Epoxide Opening



15: R^1, R^3 = H, R^2 = TBS
16: R^1 = Me, R^2 = TBS, R^3 = H
9: R^1 = H, R^2 = PMB, R^3 = CH_2CBrCH_2 **21**
18
19: X = Cl
20: X = Br

entry	substrate	conditions	product	yield (%)
1	TBSO, HO, O (**15**)	CuCN (0.3 equiv) AllylMgCl (3 equiv) THF, –40 °C, 4 h	**18**	69
2	TBSO, HO, O (**16**)	CuCN (0.3 equiv) AllylMgCl (3 equiv) THF, –40 °C to rt, 4 h	no reaction	
3	TBSO, HO, O (**16**)	CuCN (1 equiv) AllylMgCl (3 equiv) THF, –40 °C to rt, 4 h	no reaction	
4	PMBO, HO, O, Br (**9**)	CuCN (0.3 equiv) AllylMgCl (3 equiv) THF, –40 °C, 7 h	**19**	61
5	PMBO, HO, O, Br (**9**)	CuCN (0.3 equiv) AllylMgBr (3 equiv) THF, –40 °C, 6 h	**20**	89
6	PMBO, HO, O, Br ((+)-**9**)	AllylMgCl (4 equiv) THF, 0 °C, 10 min	**21**	94

With this in mind, we turned to trisubstituted epoxide **9**. Again, the use of the previously successful copper(I) cyanide promoted conditions failed; these, and indeed any other Cu-catalyzed methods,[10] led only to the halohydrin product **19** or **20** in good-to-excellent yields (entries 4, 5), where the halide derives from the counterion of the Grignard reagent. Halohydrins have been reported by Hatakeyama et al. in the opening of a related epoxide with an allyl Grignard reagent; their solution simply involved exclusion of the copper salt from the reaction.[11] To our delight this also proved effective for us, delivering the targeted epoxide **21** in excellent yield (94%, entry 6) and in a short time scale.

With an enantioselective route to diol **21** in place, installation of the *gem*-dimethyl group was next addressed. We first attempted a stepwise oxidation/methylation sequence via intermediate ketone **22** (Scheme 3). However, the second addition of MeMgBr to **22** proved surprisingly low yielding (24%),[12] and we further found that recovered 'unreacted'

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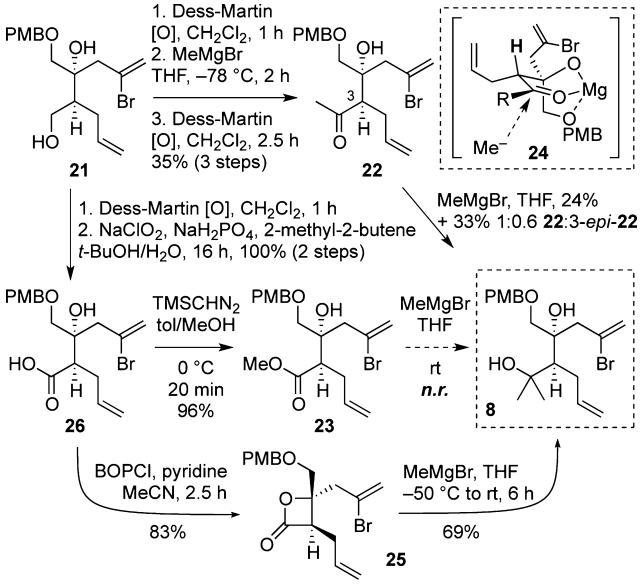
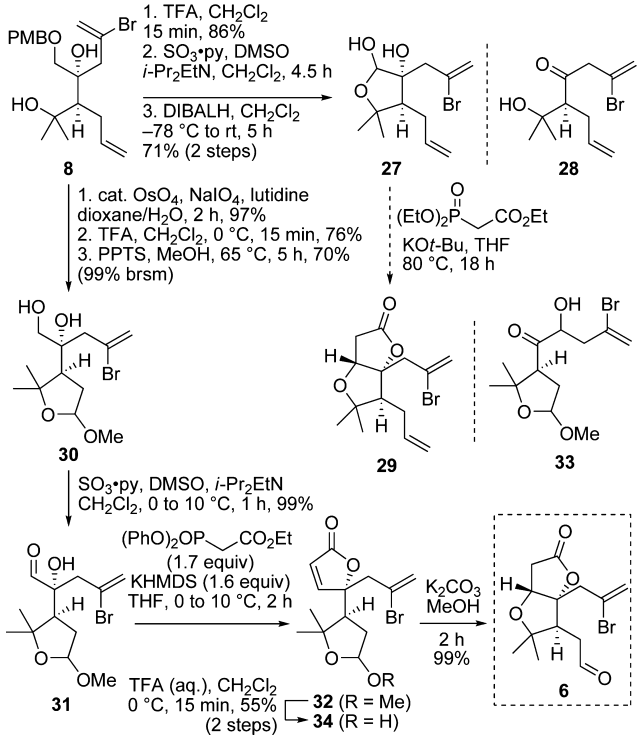
Scheme 3. Installation of the B Ring *gem*-Dimethyl Group



Scheme 4. Completion of the AB Ring Fragment 6



ketone from this reaction had undergone partial epimerization at the allyl-bearing C3 stereocenter, indicating preferential enolization over nucleophilic addition.[13] An alternative strategy of oxidation to the methyl ester **23**, followed by treatment with methylmagnesium bromide, proved even less fruitful; **23** was resistant to the Grignard reagent even at or above rt. We ascribe the epimerization of **22** and the surprisingly low reactivity of **23** to a chelated reactive conformation **24** (box, Scheme 3), which on stereoelectronic grounds requires addition of a methyl nucleophile to the hindered concave face of this bicyclic complex; meanwhile, the C–H bond α to the ketone is ideally aligned for enolization. A solution to this problem presented itself first by serendipity[14] and then by design in the form of β-lactone **25**, which could be produced in high yield from acid **26** using BOPCl. This strained lactone does not suffer from the immediate problem of forming chelate complex **24** and, to our delight, indeed underwent successful double addition of methylmagnesium bromide to give the targeted tertiary alcohol **8** (69%).

With **8** in hand, the route to the AB rings now appeared straightforward (Scheme 4). First, acidic deprotection of the PMB ether (which proved more efficient than oxidative methods) and a two-step oxidation sequence afforded the lactols **27**. Notably, the choice of oxidant in this step (SO_3·py) was crucial to avoid the formation of ketone **28** via oxidative fragmentation of the intermediate triol under other conditions (e.g., Dess-Martin); precedent for this side reaction is found in Dess and Martin's own work[15] and in a mechanistic study by Santagostino et al.[16] We presumed (on the basis of literature precedent of a related C ring-tethered lactol)[21] that **27** would be well-suited to a Wittig or HWE olefination/*in situ* cascade cyclization to the AB rings. Indeed, this exciting transformation led, on a single occasion, to a product that was tentatively assigned as the AB rings **29**. However, this success proved irreproducible, and despite many attempts, only decomposition pathways were observed. It would appear that without the imposed conformational influence of a template C ring, Thorpe–Ingold effects (from the two quaternary carbons in lactol **27**) strongly disfavor the equilibrium of the lactol anion with the open chain aldehyde and thus prevent **27** from participating in productive olefination.

This seemingly insurmountable obstacle necessitated a change of strategy. Given that the allyl side chain in **8** was eventually destined for oxidative cleavage to reveal an aldehyde, we realized that this aldehyde could also provide a transient means to prevent the formation of the troublesome B ring lactol by sequestering the tertiary alcohol as an acetal. Thus, oxidative cleavage of the alkene in **8** gave an epimeric mixture of γ-lactols. After acidic cleavage of the PMB ether, treatment with acidic methanol led to the methyl acetals **30** as the exclusive regioisomers (despite the presence of two other hydroxyl groups which might form cyclic acetals), tying up the B ring oxygen and, we hoped, allowing A ring construction. This required the oxidation of the primary alcohol in **30** to form aldehyde **31**, which again required Parikh–Doering conditions to avoid similar oxidative fragmentation as observed previously (see **28**) and gave aldehyde **31** in quantitative yield.

Although an (*E*)-selective Horner–Wadsworth–Emmons reaction and subsequent cascade cyclization on **31** should afford the AB rings, we recognized that a (*Z*)-selective olefination and *in situ* A ring lactonization would render the subsequent B ring oxy-Michael cyclization stereospecific (a strategy related to the work of other researchers where the C ring template is present),[2b,g] rather than relying on an equilibrium situation to control B ring formation. We tested both the Still–Gennari[17] and Ando phosphonates[18] and found that while the Still–Gennari olefination was moderately stereoselective, affording butenolide **32** as the major product along with some of the noncyclized (*E*)-alkene, the Ando variant gave exclusively the desired (*Z*)-olefination product **32**. An excess of phosphonate reagent (>1.5 equiv) was necessary to drive the reaction to completion, as otherwise a significant amount of byproduct **33** (30–55%), formed by a base-promoted rearrangement of the aldehyde **31**, was observed.

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Separation of the excess phosphonate proved difficult, but after deprotection of the methyl acetal **32** with TFA, the lactols **34** were isolated cleanly. Completion of the AB ring fragment **6** required only ring opening of the lactol in α,β-unsaturated lactone **34** and subsequent oxy-Michael addition of the tertiary alcohol onto the α,β-unsaturated lactone. To our delight, this reaction was triggered under mild basic conditions to afford **6** in 99% yield. The structure and stereochemistry of this product was confirmed by NMR spectroscopy, including ^{1}H NMR NOE experiments.[19]

In summary, we have established an enantioselective synthesis of the AB rings common to many of the *Schisandra* nortriterpenoid natural products, using an oxy-Michael/lactonization strategy. The final aldehyde product is well suited to a subsequent diversity-oriented approach to members of this family, the details of which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for novel compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

§B.G. and S.S.G. contributed equally.

Notes

The authors declare no competing financial interest.

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