Natural Product Synthesis

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Total Synthesis of Rubriflordilactone B

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Dedicated to Professor Han-Dong Sun

Abstract: *Taking advantage of a 6π electrocyclization–aromatization strategy, we accomplished the first and asymmetric total synthesis of rubriflordilactone B, a heptacyclic Schisandraceae bisnortriterpenoid featuring a tetrasubstituted arene moiety. The left-hand fragment was accessed through a chiral-pool-based route, and linked to the right-hand fragment by a Sonogashira coupling. The cis geometry of the electrocyclization substrates was established by hydrogenation or hydrosilylation of the alkyne. An electrocyclization–aromatization sequence finally built the multisubstituted arene. The hydrosilylation approach was of significant advantage in terms of reaction scale, reproducibility, and intermediate stability. The structure of synthetic rubriflordilactone B was validated by X-ray crystallographic analysis, and found to be consistent with that reported for the authentic natural product based on an independent X-ray crystallographic analysis. However, obvious differences in the NMR spectra of the synthetic and authentic samples suggest that the authentic samples subjected to X-ray crystallography and NMR spectroscopy were two different compounds.*

Constructing multisubstituted arenes remains a challenge in natural product synthesis. Conventional strategies based on substitution-type reactions, such as Friedel–Crafts, S_N2Ar, and cross-coupling reactions, are limited by the availability and electronic properties of the corresponding substrates and the positional selectivity of these transformations, despite being recently reinforced by transition-metal- or radical-mediated C–H bond functionalization. The groups of Nicolaou and others have elegantly demonstrated the power of electrocyclization in natural product synthesis.[1–3] The combination of 6π electrocyclization and oxidative aromatization for constructing multisubstituted arenes is of significant advantage from the following aspects: 1) strong driving force, 2) no functionalization (e.g., halogenation or metalation) required, 3) separating stereochemical problems from connectivity issues, 4) eliminating torquoselectivity issues, and 5) enhanced convergence. Thus, such strategies were creatively applied by a number of groups in synthesizing natural products containing multisubstituted arenes,[4,5] which recently inspired us to explore this area.[6,7] However, the geometrically controlled formation of the prerequisite triene substrates is a considerable challenge for executing the electrocyclization strategy. Partial-hydrogenation reagents (e.g., Lindlar catalyst, diazene, activated Zn) suffer from incompatibility issues with functionalized diene-ynes and result in poor yields of the desired *cis*-trienes. Precursors of penta- and hexasubstituted arenes pose even greater difficulties in controlling the geometry of the more substituted olefin substrates.

The *Schisandraceae* triterpenoids (e.g., **1**–**4**; Figure 1) are a class of structurally and biologically attractive compounds;[8] the total synthesis of these compounds[9] was pioneered by Yang and co-workers.[9a–e] Rubriflordilactone B (**4**) is a bisnortriterpenoid featuring a tetrasubstituted arene moiety, and was isolated by Sun et al. from *Schisandra rubriflora* along with its congener rubriflordilactone A (**3**).[10] The structures of both compounds were determined by X-ray crystallography. Recently, the synthesis of **3** was independently achieved by us[6a] and Anderson et al.,[9g] but endeavors[11,12] towards the synthesis of **4** have not been successful. Right before we submitted this manuscript, Xie et al. reported an elegant synthesis of a truncated model of **4** with the undesired configuration at the C5 position by a rhodium-catalyzed [2+2+2] cycloaddition.[12b] Herein, we report the first and asymmetric total synthesis of **4**, which features a 6π electrocyclization–aromatization strategy.

In a retrosynthetic analysis (Figure 1), we envisioned an initial disconnection of **4** at the C8–C14 bond leading to *cis* olefin **5** as the electrocyclization substrate, which could be further disassembled into two segments, **6** and **7**. Triflate **6** may be obtained from ketone **8**, which was traced back to cycloheptenone **9** via the intermediacy of nitrile **10**. Commercially available (−)-perillyl alcohol (**11**) was suggested to be a precursor of **9**. Alkyne **7** could be obtained from lactol **12** and phosphonate **13** through a one-pot olefination/oxa-Michael addition process.[13] Simplification of **12** gave alcohol **14** as a Johnson–Claisen substrate, which should be readily available from enantioenriched enone **15**.

The synthesis was commenced with constructing the left-hand segment **6** (Scheme 1). Exposure of **11** to $P(OEt)_3$ and ZnI_2 at 140 °C resulted in an Arbuzov-type reaction to afford phosphonate **16** in 94% yield, which underwent ozonolysis and intramolecular Horner–Wadsworth–Emmons (HWE) olefination to yield cycloheptenone **17** with acceptable overall efficiency. The ozonolysis preferentially cleaved the trisub-

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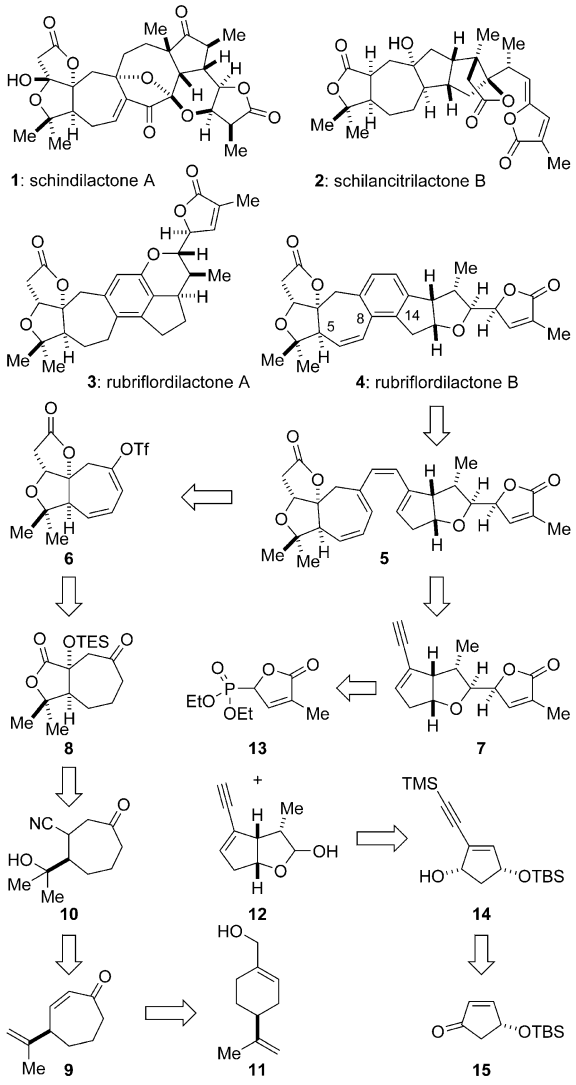
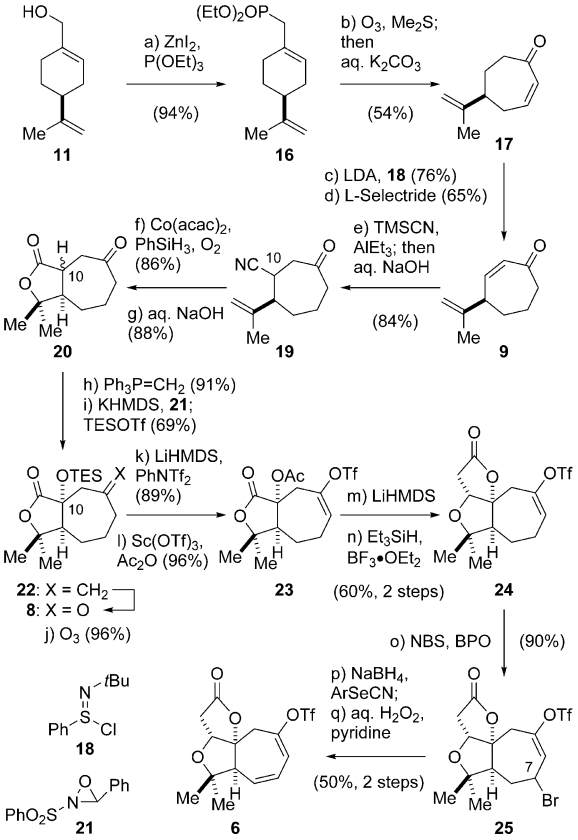


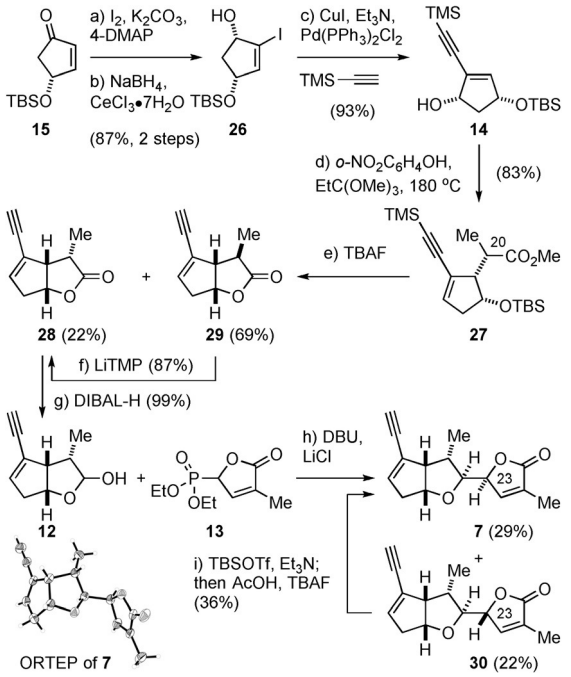
Figure 1. Structures of selected *Schisandraceae* triterpenoids and a retrosynthetic analysis of rubriflordilactone B (**4**). TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.



Scheme 1. Construction of triflate **6**. acac = acetylacetonate, BPO = benzoyl peroxide, LDA = lithium diisopropylamide, LiHMDS = lithium hexamethyldisilazide, NBS = *N*-bromosuccinimide, Tf = trifluoromethanesulfonyl.

stituted C=C bond, presumably owing to electronic effects. The C=C bond of **17** was then switched to the other side of the carbonyl group. Mukaiyama dehydrogenation[14] (LDA, **18**) furnished a bis-enone, and L-selectride reduction selectively saturated the less hindered enone moiety to form **9**. Addition to **9** with in situ generated Et_2AlCN gave nitrile **19** [84% yield, ca. 1.7:1 d.r. at C10 (inconsequential)]; base treatment ensured full conversion of overreacted cyanohydrins back into the desired ketone. Compound **19** was subjected to Mukaiyama hydration conditions [$Co(acac)_2$, $PhSiH_3$, O_2, 10 °C] to afford a tertiary alcohol,[15] which underwent lactonization upon exposure to aqueous NaOH at 80 °C to give compound **20** [ca. 2.2:1 d.r. at C10 (inconsequential)] with good efficiency. A low concentration of **19** was crucial to the success of the Mukaiyama hydration, as it suppressed undesired bimolecular radical addition pathways. Notably, treatment of **19** with strong aqueous acid directly delivered **20**, presumably through olefin hydration–cyclization as well. However, the enantiopurity of the obtained product was significantly lower; a plausible mechanism is that the tertiary carbocation reversibly migrated to the neighboring carbon atom and thus lost the stereochemical information inherited from the chiral pool. Methylenation of **20** followed by hydroxylation of the lactone enolate with Davis oxaziridine **21** and in situ silylation provided compound **22** as a single diastereomer at C10. At this point, the enantiopurity of the left-hand fragment was determined by HPLC analysis of an aromatic derivative of **22** (96% *ee*, see the Supporting Information). Ozonolysis of **22** gave intermediate **8**, which afforded tricycle **24** after a four-step sequence.[6a] Dehydrogenation of **24** was achieved by allylic functionalization and then elimination. Radical bromination (NBS, BPO, 85 °C) occurred at the less hindered C7 position and furnished compound **25** (90% yield, ca. 2.8:1 d.r.). Exposure to bases resulted in undesired 1,4-elimination. Selenide attack (o-$NO_2C_6H_4SeCN$, $NaBH_4$) followed by oxidation and elimination gave diene **6** in 50% yield over the two steps. An enone generated by a [2,3]-sigmatropic rearrangement of the selenoxide intermediate was detected as a side product.

We then synthesized the right-hand fragment **7** (Scheme 2). Enone **15** (>99% *ee*)[16] was subjected to iodination and Luche reduction conditions to give alcohol

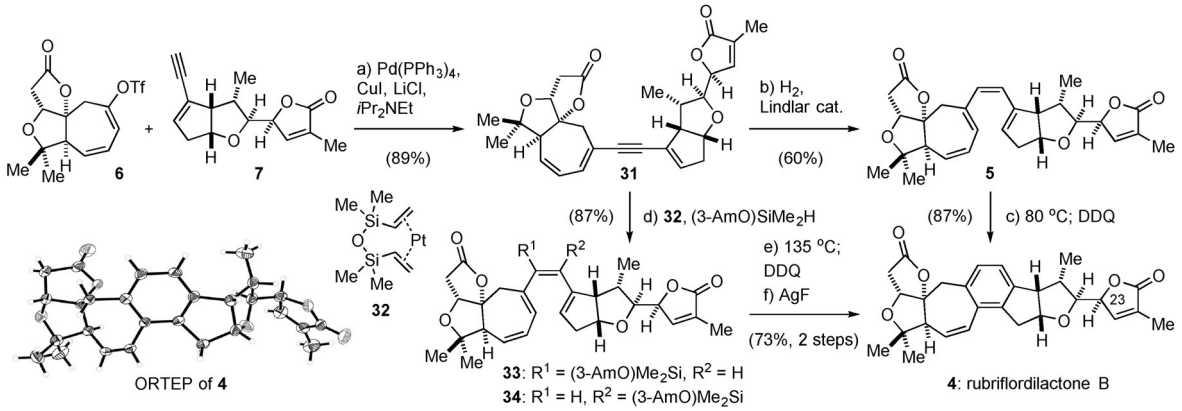


Scheme 2. Preparation of alkyne **7**. DIBAL-H = diisobutylaluminum hydride, 4-DMAP = 4-dimethylaminopyridine, LiTMP = lithium tetramethylpiperidide, TBAF = tetrabutylammonium fluoride.

26 (87% overall yield, > 20:1 d.r.). Sonogashira coupling with TMS–acetylene furnished **14** as a single diastereomer, which underwent Johnson–Claisen rearrangement at 180 °C in the presence of $EtC(OMe)_3$ and *o*-$NO_2C_6H_4OH$ (cat.)[17] to yield ester **27** (83% yield, ca. 2.7:1 at C20). Exposure of **27** to TBAF led to global desilylation and lactonization, providing a pair of chromatographically separable epimers, compounds **28** and **29**. Undesired **29** was efficiently converted into **28** upon treatment with LiTMP followed by aqueous workup.[9a] DIBAL-H reduction of **28** furnished lactol **12**, which reacted with phosphonate[18] **13** under Masamune–Roush conditions (DBU, LiCl) to give a pair of C23 epimers, **7** and **30**, in moderate yields, presumably through a one-pot HWE olefination/oxa-Michael addition process.[13] The facial selectivity of the conjugate addition was excellent, whereas the protonation at C23 was poorly controlled. The structure of the desired compound **7** was confirmed by X-ray crystallographic analysis (Scheme 2).[19] We partially converted undesired **30** into **7** through a sequence of silyl ether formation and desilylation, which also corroborated the structural relationship between **7** and **30**.

The final assembly of **4** by a 6π electrocyclization–aromatization strategy is depicted in Scheme 3. The two segments were forged by a Sonogashira coupling at 70 °C to afford the conjugated triene-yne **31** in 89% yield. The next challenge was to convert it into a *cis*-tetraene suitable for 6π electrocyclization. Partial hydrogenation of **31** suffered from two problems, namely 1) reaction reproducibility (especially on a large scale) and 2) product stability, which represent general difficulties for synthesizing *cis*-polyenes. On a small scale (10 mg), we managed to obtain **5** in 60% yield along with 12% of recovered **31** under carefully tuned conditions [Lindlar catalyst, MeOH/EtOAc (4:1), H_2 (50 bar), 40 °C]. However, this reaction often inexplicably ended up with one of the two opposite situations: poor conversion and overhydrogenation. Heating freshly prepared **5** at 80 °C for three hours effected the 6π electrocyclization, and the crude product was oxidized by DDQ to furnish the target compound **4** in 87% overall yield. To overcome the drawbacks of the above approach, we subjected **31** to the Karsted catalyst (1 mol%) and (3-AmO)$SiMe_2H$[6f] to obtain a mixture of regioisomers **33** and **34** (ca. 1:1, inconsequential) in 87% yield within 10 min.[20] The silyl tetraenes were easily prepared on a reasonable scale and could be stored at ambient temperature. (3-AmO)$SiMe_2H$ was designed for a balance of good reactivity and stability. The corresponding products were usually stable for chromatography and the following transformations as they are sterically hindered secondary silyl ethers, yet readily cleaved, oxidized, or halogenated under specific conditions. The mixture underwent electrocyclization (135 °C) and aromatization to give a mixture of pentasubstituted arenes, which were desilylated with AgF[21] to give **4** in 73% overall yield. A sample of *ent*-**4** was prepared through a similar route starting from *ent*-**6** and *ent*-**7**.

The structure of **4** was confirmed by X-ray crystallographic analysis (Scheme 3),[19] and found to be identical to the reported structure of authentic rubriflordilactone B



Scheme 3. Completion of the synthesis of **4**. 3-Am = 3-pentyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

derived from an independent X-ray crystallographic analysis.[10] However, the ^{1}H and ^{13}C NMR spectra of the synthetic and authentic samples were clearly different in deuterated chloroform and pyridine. The effects of pH, concentration, temperature, and impurities were carefully examined and excluded. Another important observation was that the synthetic sample displayed poor solubility ($\ll 1$ mg mL^{-1}) in MeOH, and thus the concentration for measuring the optical rotation ($c = 0.514$ in MeOH) described in the isolation report cannot be reached. Therefore, we speculated that the originally isolated sample of "rubriflordilactone B" was composed of two compounds. The minor and less soluble one may be crystallized and subjected to X-ray crystallographic analysis, the structure of which was then determined as that of rubriflordilactone B. The major one, possibly an isomer of rubriflordilactone B, could be responsible for the reported spectroscopic data and biological activities in the isolation paper. To differentiate between the two compounds, we call the latter pseudo-rubriflordilactone B. An obvious argument would be whether rubriflordilactone B is formed as an artifact of pseudo-rubriflordilactone B during the crystallizing process, which cannot be fully excluded at the current stage. We synthesized 23-*epi*-rubriflordilactone B from precursors **6** and **30**, which can potentially be converted into rubriflordilactone B by enolization and tautomerization. However, its spectra were different from those of pseudo-rubriflordilactone B as well. Uncovering the structural mystery of pseudo-rubriflordilactone B and confirming the spectroscopic and physical properties (in particular the sign of the optical rotation)[22] of rubriflordilactone B will have to rely on the re-isolation of reasonable amounts of both natural products, which is beyond the expertise of our group.

In summary, we have accomplished the total synthesis of rubriflordilactone B in a highly convergent fashion. A 6π electrocyclization–aromatization sequence served as a key step. Hydrosilylation of a conjugated triene-yne intermediate defined the *cis* geometry of the electrocyclization precursor, which constitutes a superior approach to the conventional method of partial hydrogenation. The Sonogashira–hydrosilylation–electrocyclization–aromatization sequence could be streamlined as a general and robust approach towards the synthesis of pentasubstituted arenes bearing silyl groups as versatile handles, considering that the regioselectivity of the hydrosilylation can be tuned by varying the ligands. The total synthesis suggests the existence of a naturally occurring sibling of rubriflordilactone B and provides efficient and flexible access to analogues of potential biological interest.

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[22] The absolute configuration of authentic **4** cannot be determined at this stage because its optical rotation is unavailable. We separated synthetic **4** and *ent*-**4** by HPLC (see the Supporting Information for details). The retention times could serve as accurate references to determine the absolute configuration of authentic **4** if it could be re-isolated from nature at some point.

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