Convergent Total Syntheses of (−)-Rubriflordilactone B and (−)-pseudo-Rubriflordilactone B

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Abstract: A highly convergent strategy for the synthesis of the natural product (−)-rubriflordilactone B, and the proposed structure of (−)-pseudo-rubriflordilactone B, is described. Late stage coupling of diynes containing the respective natural product FG rings with a common AB ring aldehyde precedes rhodium-catalyzed [2+2+2] alkyn cyclotrimerization to form the natural product skeleton, with the syntheses completed in just one further operation. This work resolves the uncertainty surrounding the identity of pseudo-rubriflordilactone B and provides a robust platform for further synthetic and biological investigations.

Plants of the genus Schisandra produce an array of nortriterpenoids characterized by densely functionalized polycyclic skeletons. Extracts from these plants feature prominently in traditional Chinese medicine, and many of their natural products have been found to display antiviral and anticancer activities. Stimulated by their structures and properties, syntheses of a number of these molecules have been achieved. Among the many family members, rubriflordilactones A and B (isolated by Sun and co-workers from Schisandra rubriflora) are of interest due to their contrasting anti-HIV bioactivities and, from a synthetic perspective, the challenge of efficient assembly of their polysubstituted arene cores. Syntheses of rubriflordilactone A were described by the Li group, and by ourselves. However, the subsequent completion of rubriflordilactone B (I, Scheme 1) by Li et al. revealed a structural ambiguity: the NMR spectroscopic data of synthetic 1 (the form of the natural product characterized by X-ray crystallographic analysis) did not match that recorded for rubriflordilactone B by the Sun group. This finding appeared to imply the existence of two rubriflordilactone B natural products—one corresponding to the X-ray structure, and the other to the NMR spectroscopic data.

Subsequent computational work by Kaufman and Sarti suggested that the difference between the two forms of rubriflordilactone B lies at C16 and C17 in the EF rings, leading to the proposal of 2, dubbed pseudo-rubriflordilactone B, as the most likely candidate to fit the NMR data reported in the isolation paper. Herein, we describe our efforts to solve this stereochemical puzzle, first by establishing a robust synthetic route to rubriflordilactone B, and second by modification of this route to access the proposed structure of pseudo-rubriflordilactone B. In combination with studies from the Li group, we demonstrate that this proposed structure is indeed the likely identity of this natural product.

Our strategy towards these targets derived from our studies on rubriflordilactone A, with the central arene D ring being a focal point for scaffold disconnection. Specifically, we viewed the [2+2+2] cyclotrimerization of suitable triynes 1 as offering a convergent and stereocemically flexible approach to the natural products. These triynes conveniently derive from the common AB ring aldehyde 4 and diynes such as 5 (required for rubriflordilactone B, 1) and 6 (required for pseudo-rubriflordilactone B, 2). Mindful of the potential sensitivity of these fragments under the basic conditions required for their union with 4, we also contemplated equivalent iodoalkynes 7 and 8 which would enable a milder Nozaki–Hiyama–Kishi connection.

Diyne 7 was selected as our initial target. A particular challenge in this fragment is the need to install four contiguous stereocenters on the tetrahydrofuran ring, three of which we envisaged could be created using a diaionic
IRELAND–CLAISEN RINGING OF THE D (+)-ENOLATE OF A SUITABLE ESTER. Starting from aldehyde 9 (Scheme 2), enantioselective [2+2] cycloaddition of ketene afforded β-lactone 10. Ring-opening of this lactone with the magnesium alkoxide of enantioenriched alcohol 11 (obtained by enzymatic resolution) afforded ester 12. Dianionic Ireland–Claisen rearrangement followed by treatment with TMS diazomethane gave ester 13, featuring three of the required F ring stereocenters, and was confirmed by X-ray crystallographic analysis. The formation of all four isomers greatly aided assignment of stereochemistry at the new F and G ring stereocenters by a combination of 1H NMR (with high selectivity (dr 35%), presumably reflecting the base-sensitivity of the iodoketone 16). Ring-closure of the terminal alkyne in 16 with iodine and morpholine afforded the butenolide G ring through palladium- and cobalt-catalyzed cyclizations of bromoendiynes and triynes, respectively. The former proved more effective than through the alkynyllithium (which in the present context would necessitate later stage arene desilylation), and also temporary protection of the propargylic alcohol. Under cobalt catalysis, the challenge of 7-membered C-ring formation called for microwave heating, which limited scalability, and alternative catalyst systems were therefore considered. Rhodium-catalyzed [2+2+2] alkyne cyclotrimerization also has a rich history in synthetic contexts, and subsequent to our work on rubriflordilactone A, was reported to promote efficient cyclization to a truncated rubriflordilactone B fragment.

To model the cyclization and synthesis endgame, diynes 16 and 17 were first added to hept-6-ynal (Scheme 4). This union proved far more efficient under Nozaki–Hiyama–Kishi conditions (with 17, 73% yield) than through the alkynyllithium (16, 35% yield), presumably reflecting the base-sensitivity of the diynes. After further transformations according to the previous route, led to lactone 21 with two substituents positioned on the β-face of this ring, methylation of the lactone enolate gave trisubstituted lactone 22 as a single stereoisomer, featuring three of the F-ring stereocenters required for the predicted natural product. After conversion of this lactone to acetal 23, completion of diyne 8 entailed an equivalent sequence of steps as employed for its diastereomer 7. In this case however, the final butenolide addition proceeded without stereocontrol, delivering the four diastereomeric FG diynes 8a–d in an approximately equimolar ratio. The formation of all four isomers greatly aided assignment of stereochemistry at the new F and G ring stereocenters by a combination of 1H NMR NOE enhancements around the tetrahydrofuran framework, and coupling constant analysis [15] 8b and 8c (the identity of the latter being confirmed by X-ray analysis) were isolated as single stereoisomers, but 8a and 8d proved inseparable.

In our previous work [4], we had constructed the arene D ring through palladium- and cobalt-catalyzed cyclizations of bromoendynes and triynes, respectively. The former proved more effective than through the alkynyllithium (which in the present context would necessitate later stage arene desilylation), and also temporary protection of the propargylic alcohol. Under cobalt catalysis, the challenge of 7-membered C-ring formation called for microwave heating, which limited scalability, and alternative catalyst systems were therefore considered. Rhodium-catalyzed [2+2+2] alkyne cyclotrimerization also has a rich history in synthetic contexts, and subsequent to our work on rubriflordilactone A, was reported to promote efficient cyclization to a truncated rubriflordilactone B fragment.

Scheme 2. Synthesis of rubriflordilactone B diyne fragments. Ac = acetyl; BAIB = Ph(OAc)₂; CSA = (±)-camphorsulfonic acid; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LDA = Li(N)i-Pr); LiHMDS = Li(N)(SiMe₃); NaHMDS, TMSCHN₂; NMO = N-methylmorpholine-N-oxide; PMB = 4-methoxybenzyl; TBAF = i-PrN(SiMe₃)₂; LiN(i-Pr)₂; TMS = SiMe₃.

Scheme 3. Synthesis of pseudo-rubriflordilactone B diyne fragments. DiBALH = i-Pr₂AlH; TBS = SiMe₃-i-Pr; TPAP = tetrapropylammonium perruthenate.
To our delight, subjection of the desilylated triyne derived from 27 to rhodium-catalyzed cyclotrimerization using Wilkinson’s catalyst (10 mol%) gave CDEF rings 28 in 73% yield. Dehydration of the benzylic alcohol was achieved on treatment with Martin sulfurane [23] (29), and finally bismuth(III)-promoted addition of furan 18 gave the CDEFG model 30 in 27% yield, along with its separable C23 epimer.

Encouraged by these results, an equivalent sequence was pursued using the AB ring aldehyde 4. Rhodium-catalyzed cyclotrimerization of adduct 31 again proceeded efficiently to give the corresponding hexacycle; due to co-elution with residual catalyst, this was carried directly to the next step after a short silica gel filtration. However, attempted dehydration of the resulting benzylic alcohol using Martin sulfurane surprisingly yielded the substitution product 33, likely reflecting the increased steric hindrance towards elimination (or subtle conformational effects) in this substrate compared to 28. Fortunately, elimination could be effected using the Grieco protocol [24], which gave 32 in 40% yield over the two steps. Bismuth-promoted reaction of 32 with furan 18 delivered rubriflordilactone B (1), and its C23 diastereomer epi-1. The former not only matched the spectroscopic data reported by the Li group, but X-ray crystallographic analysis of 1 enabled unambiguous confirmation of its structure and absolute configuration (Flack(ξ) parameter = −0.09(2)). [18]

Completion of pseudo-rubriflordilactone B (2) proved more challenging. As iodoalkynes 8a and 8d were inseparable, this necessitated addition of this 1:1 mixture to 4, which fortunately gave separable homopropargylic alcohols. Desilylation of the adduct destined for conversion to pseudo-rubriflordilactone B (36) proved somewhat capricious, and both the subsequent cyclotrimerization and acid-mediated dehydration required higher loadings of their respective catalysts, and/or extended reaction times, compared to rubriflordilactone B. This route nonetheless delivered 2, the predicted structure of pseudo-rubriflordilactone B. Diyne 8b was also carried through the sequence, giving the C23 epimer of pseudo-rubriflordilactone B, epi-2. Comparison of the NMR spectroscopic data of 2 (and epi-2) with data from the isolation paper revealed a high level of consistency for the
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Discrepancies were observed at H11, H12, C11, C12, and C15 compared to the natural product isolation NMR spectroscopic data, as were noted by Sarotti and Kaufman in Reference 8. It is our belief that these signals were misassigned in the original isolation work owing to the presence of phthalate impurities, and because of highly broadened peaks in the $^{13}$C NMR spectrum. See the Supporting Information for further discussion.
Communications

Total Synthesis

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Rubri B or not Rubri B? A convergent late-stage fragment coupling and rhodium-catalyzed [2+2+2] alkyne cyclotrimerization strategy provides access to the natural product (−)-rubriflordilactone B, and the proposed structure of (−)-pseudo-rubriflordilactone B. Thus, the uncertainty surrounding the identity of pseudo-rubriflordilactone B is resolved, and a synthetic platform that offers broad scope for the exploration of this natural product family is established.)