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Metal-Catalyzed Syntheses of Abridged CDE Rings of Rubriflordilactones A and B

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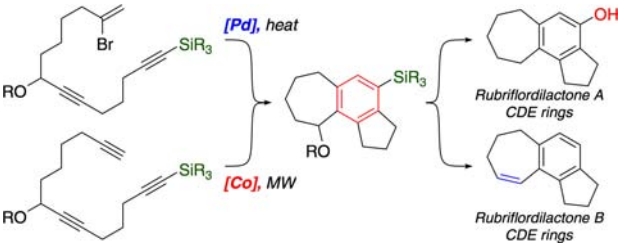
ABSTRACT



The development of complementary palladium- and cobalt-catalyzed approaches to tricyclic arylsilanes suitable for elaboration into the CDE ring systems of rubriflordilactones A and B is reported. Microwave conditions are required to effect a cobalt-catalyzed triyne cyclotrimerization, which critically depends on the substitution pattern of the triyne termini. Mild conditions to elaborate these arylsilanes to the CDE cores of the natural products are described.

Rubriflordilactones A and B (Figure 1) are triterpenoid natural products isolated from *Schisandra rubriflora*.[1] Although related in structure and biosynthetic origin to a large family of terpenoids isolated from this genus of Chinese herbal plants,[2] they are the only two which feature aromatic D rings. These molecules have attracted attention due to their anti-HIV properties, for which rubriflordilactone B represents one of the more active family members (EC_{50} = 9.75 μg mL^{-1} for inhibition of HIV-induced syncytium formation). Interestingly, rubriflordilactone A shows limited antiviral activity, which may suggest a structure–activity relationship that depends on the CDEFG framework of these molecules, rather than the AB rings which are common to the two.

The centerpiece of the rubriflordilactone skeleton is the aromatic D-ring, which is flanked by 7- and 5-membered carbocycles (the C and E rings) and, in the case of rubriflordilactone A, a pyran. The two aromatic cores are distinguished by the presence or absence of arene oxygenation, and by the adjacent unsaturation that is featured in the C ring of rubriflordilactone B. The synthetic challenge posed by this family of natural products is highlighted by the solitary total synthesis of (±)-schindilactone A,[3] despite the numerous synthetic strategies that have been described.[4] Our own studies focused on palladium-catalyzed cascade cyclization of a bromoenediyne to form the CDE core,[5] methodology which is well-established in the field of palladium-catalyzed cascade reactions,[6] but which has not been applied in total synthesis. We report here refinements of this strategy and an alternative cyclotrimerization

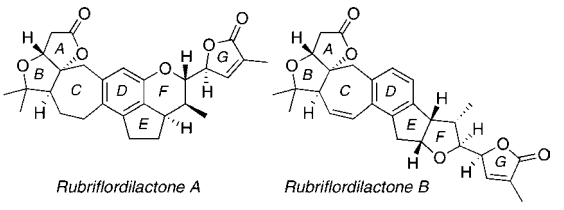


Figure 1. Rubriflordilactone family of natural products.

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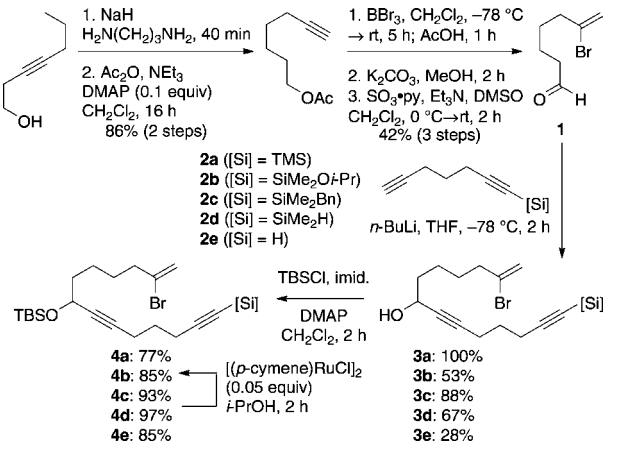
Scheme 1. Synthesis of Bromoendiynes **3a**–**e** and **4a**–**e**

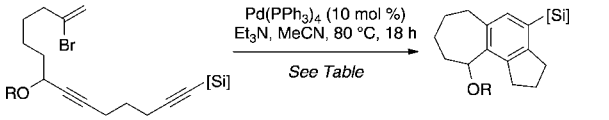


approach to the CDE rings, the success of which depends not only on the substitution pattern of the triyne substrate but also on the mode of heating. We also detail elaboration of the cyclized products to the different functionalities found in the rubriflordilactone CDE cores.

To this end, we synthesized a range of alkynylsilanes suitable for cyclization (Scheme 1). This began with zipper isomerization of hept-3-yn-1-ol,[7] followed by an alkyne bromoboration[8]/oxidation sequence to aldehyde **1**, to which was added a range of lithiated silyldiynes **2a**–**d** and the unsubstituted diyne **2e**. While the isopropoxy and dimethylsilane groups **2b** and **2d** were tolerated in this addition, superior results were obtained with the trimethyl and benzyldimethylsilanes **2a** and **2c**. Although it was not yet clear whether the propargylic alcohol would require protection during cyclization, the TBS ethers **4a**–**e** could be obtained in good yields, with **4b** being prepared via ruthenium-catalyzed etherification of silane **4d**.[9,10]

With a selection of silylated bromoendiynes in hand, we examined their palladium-catalyzed cyclization to tricyclic arylsilanes (Table 1). This revealed that the free propargylic hydroxyl (**3a**) was indeed incompatible with the cyclization conditions. However, the equivalent TBS ether **4a** underwent successful cyclization (entries 1, 2). Of the various alkynylsilanes, benzyldimethylsilane **4c** proved most effective, delivering **6c** in 76% yield (entry 4). Hydrosilane **4d** did not survive the reaction conditions (entry 5), possibly due to competitive oxidative addition into the Si–H bond. Terminal alkyne **4e** also decomposed (entry 6), implying that a post-cyclization desilylation strategy would be needed to access rubriflordilactone B.

Table 1. Cyclization of Bromoendiynes to Tricyclic Arylsilanes



3a (R = H)
4a-e (R = TBS)

5a (R = H)
6a-e (R = TBS)

entry	substrate	R	[Si]	product	yield (%)
1	**3a**	H	TMS	**5a**	dec.
2	**4a**	TBS	TMS	**6a**	62
3	**4b**	TBS	$SiMe_2Oi$-Pr	**6b**	41
4	**4c**	TBS	$SiMe_2Bn$	**6c**	76
5	**4d**	TBS	$SiMe_2H$	**6d**	dec.
6	**4e**	TBS	H	**6e**	dec.

These cyclizations had revealed the scope and limitations (with respect to the crucial silane substituent) of the bromoendiyne route to rubriflordilactone-like tricyclic arylsilanes. However, we were mindful of other methods for the assembly of fused-ring arenes, such as alkyne cyclotrimerization. While this process has rich precedent in synthesis[11] and is well-known to tolerate simple alkynylsilanes, its use in total synthesis for the preparation of rings larger than 6-membered is, to our knowledge, unknown. It was certainly unclear whether the nature of the substituents at the alkyne termini, which we presumed might direct the order of events in the cyclotrimerization, would be of importance.

A screen of cyclotrimerization conditions was undertaken using triyne **7a**[12] (featuring a TMS substituent at the triyne terminus where 5-membered ring formation occurs) with a particular focus on methods suitable for the

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(10) Attempted formation of **4c** from **3c** using TBSCl/imidazole led to formation of a disiloxane at the alkyne terminus.

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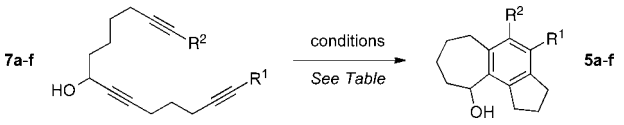
(12) See the Supporting Information for the synthesis of **7a**.

Table 2. Cyclotrimerization of Triynes to Tricyclic Arylsilanes[a]



entry	substrate	R^1	R^2	catalyst (mol %)	solvent	temp (°C)	time	product	yield (%) (conversion (%))
1	**7a**	TMS	H	$Rh(PPh_3)_3Cl$ (3)	PhMe/EtOH (10:3)	80	5.5 h	**5a**	dec (n.d.)
2	**7a**	TMS	H	$Rh(PPh_3)_3Cl$ (10)	EtOH[b]	80	24 h	**5a**	dec (n.d.)
3	**7a**	TMS	H	$Co_2(CO)_8$ (10)	PhMe[b]	110	20 h	**5a**	10 (30)
4	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (100)	dioxane	100	48 h	**5a**	10 (67)
5	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (100)	PhMe	110	24 h	**5a**	30 (87)
6	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl	150[d]	30 min	**5a**	67 (100)
7	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl[b]	150[d]	30 min	**5a**	55 (100)
8	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl[c]	150[d]	30 min	**5a**	53 (100)
9	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl	150[d]	15 min	**5a**	63 (73)
10	**7a**	**TMS**	**H**	**$CpCo(CO)_2$/2 PPh_3 (20)**	**PhCl**	**150[d]**	**25 min**	**5a**	**80 (100)**
11	**7a**	TMS	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl	150[d]	25 min	**5a**	19 (47)[e]
12	**7a**	**TMS**	**H**	**$CpCo(CO)_2$/2 PPh_3 (20)**	**PhCl**	**150[f]**	**25 min**	**5a**	**70 (86)[e]**
13	**7d**	$SiMe_2H$	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl	150[d]	25 min	**5d**	20 (100)
14	**7c**	**$SiMe_2Bn$**	**H**	**$CpCo(CO)_2$/2 PPh_3 (20)**	**PhCl**	**150[d]**	**25 min**	**5c**	**87 (100)**
15	**7e**	H	H	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl	150[d]	25 min	**5e**	10 (100)
16	**7f**	H	TMS	$CpCo(CO)_2$/2 PPh_3 (20)	PhCl	150[d]	25 min	**5f**	trace

[a] Reaction conditions: **7** (30 mg) in degassed solvent; Concentration, unless otherwise stated: $Rh(PPh_3)_3Cl$, 0.05 M; $Co_2(CO)_8$, 0.1 M; $CpCo(CO)_2$/2 PPh_3, 0.04 M. [b] 0.1 M. [c] 0.02 M. [d] MW power: 150 W. [e] Performed using 210 mg of **7**. [f] MW power: 300 W.

formation of 7-membered rings (Table 2). Our survey began with Wilkinson's catalyst, but despite a precedent for the formation of a benzannulated bridged 7-membered ring,[11e] only decomposition was observed (entries 1, 2). The use of cobalt catalysts led to some success, with small amounts of arene **5a** isolated using dicobalt octacarbonyl (entry 3), albeit with incomplete conversion; similar results were obtained with stoichiometric amounts of $CpCo(CO)_2$/PPh_3, a reagent which had enabled the formation of a benzooxepane (entries 4, 5).[13] To our delight, significant improvement was observed on moving to microwave irradiation.[14] While the role of microwave heating in cyclotrimerization remains the subject of some debate,[15] its benefit was clear, with reaction at 150 °C proceeding to completion in 30 min using 20 mol % of catalyst, affording **5a** in 67% yield (entry 6). Although varying the concentration did not lead to further improvement (entries 7, 8), the reaction time proved to be critical: incomplete conversion was observed after 15 min, but with an optimized irradation period of 25 min, **5a** was produced in 80% yield (entries 9, 10). Both conversion and yield diminished on scale-up. However, this problem could be solved by increasing the microwave power to 300 W, which gave **5a** in 70% yield (entries 11, 12).

A series of other triynes were examined to determine the effect of position and nature of the silane substituent. Whereas hydrosilane **7d** gave a poor return of arylsilane **5d**, benzyldimethylsilane **7c** delivered **5c** in an excellent 87% yield (entries 13, 14). From a mechanistic perspective, it is of interest that the unsubstituted triyne **7e**, and triyne **7f** (in which the silyl substituent is installed at the 1,8-diyne terminus), gave low yields or only a trace product, implying that a sterically demanding substituent at R^1, but not R^2, is crucial (entries 15, 16). In contrast to the bromoendiyne cyclizations, protection of the propargylic alcohol was not necessary.

These successful cyclizations may be explained by two possible mechanistic pathways (Scheme 2).[16] The first initiates with kinetically favored complexation of the 1,6-diyne, leading to cobaltacycle **8**. Intramolecular [4 + 2] cycloaddition with the remote unsubstituted alkyne in **8** then outcompetes intermolecular reaction with another molecule of substrate, unless the substrate is also unsubstituted at the 1,6-diyne terminus (as in **7e** and **7f**) or, worse, substituted at the 1,8-diyne terminus (**7f**). Alternatively, complexation of the 1,8-diyne (which might be expected to be favored by silylation of the 1,6-diyne terminus) leads to cobaltacycle **9**, the alkyne of which, due to its shorter tether, is then able to compete successfully with intermolecular reactions, affording **5**.

With a range of tricyclic arylsilanes in hand from both methodologies, we proceeded to study the divergent functionalization of the CD rings, in order to establish strategies

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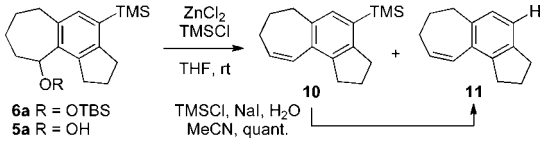
Table 3. Synthesis of an Abridged CDE Core of Rubriflordilactone B



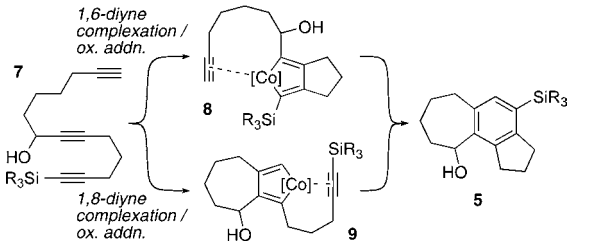
entry	substrate	$ZnCl_2$ equiv	TMSCl equiv	time (h)	product ratio[a]	yield (%)[b]
1	**6a**	1.5	2.0	2	90:10	78
2	**6a**	3.0	3.0	20	15:85	69
3	**5a**	1.5	2.0	2	100:0	99
4	**5a**	3.0	3.0	20	46:54	66

[a] Ratio of **10:11** based on integration of the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yield of **10** and **11**.

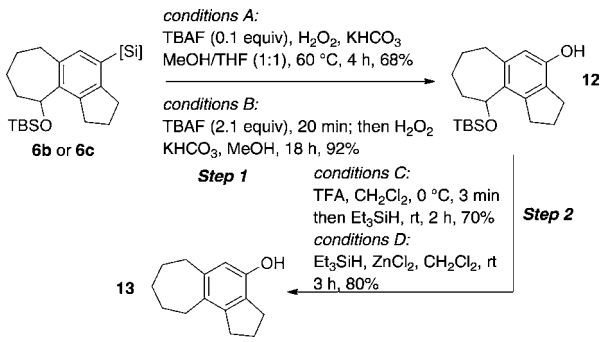
for the synthesis of either rubriflordilactone. We first investigated the CDE core of rubriflordilactone B, which would arise from desilylation, and elimination of the benzylic oxygen substituent. We were somewhat surprised to find that the arylsilane in **6a** was unaffected by a range of fluoride sources (e.g., TBAF, CsF), with only benzylic TBS ether cleavage observed upon heating. Acidic conditions (e.g., TFA/CH_2Cl_2, CSA/methanol) were also ineffective, although, in the latter case, methanolic substitution of the benzylic silyl ether was observed. This suggested that benzylic elimination might be facile, and pleasingly treatment of **6a** with $ZnCl_2$/TMSCl yielded **10** (Table 3, entry 1).[17] **10** could be desilylated using *in situ* generated TMSI to give **11**,[18] the tricyclic core of rubriflordilactone B, in 78% yield over two steps. By increasing the reaction time and reagent quantities, **6a** could be converted directly into **11** (entry 2), although this never proceeded to completion. This sequence could equally be applied to benzyl alcohol **5a**, delivering **11** in an excellent 99% yield (entry 3).

We anticipated that the CDE core of rubriflordilactone A could be obtained from tricyclic arylsilanes **6b** or **6c** by Tamao oxidation,[19] then benzylic reduction. In the event, oxidation of isopropoxydimethyl silane **6b** with catalytic TBAF was possible (Scheme 3, Step 1, conditions A)[20] but required heating and gave moderate yields of phenol **12**. A sequenced procedure was needed for the oxidation of benzyl dimethylsilane **6c**, with TBAF-mediated silanol formation preceding addition of H_2O_2;[21] simultaneous addition of all reagents gave this silanol as the sole product. Using this protocol with 2.1 equiv of TBAF (which was essential for the reaction to proceed to completion) gave **12** in 92% yield (Step 1, conditions B).

Scheme 2. Mechanistic Alternatives for Cyclotrimerization



Scheme 3. Synthesis of an Abridged CDE Core of Rubriflordilactone A



Finally, benzylic deoxygenation was investigated. We were delighted to find that ionic hydrogenation of phenol **12** with TFA/triethylsilane afforded the tricyclic core **13** of rubriflordilactone A, along with small amounts of the (separable) phenolic TES ether (Step 2, conditions C). The milder ionization conditions of $ZnCl_2$ also proved successful, giving **13** in 80% yield (Step 2, conditions D).

In summary, we have developed two transition metal-catalyzed routes to prepare tricyclic arylsilanes which are model precursors to the CDE rings of rubriflordilactones A and B. Highlights include the use of microwave-promoted cyclotrimerization to forge the challenging 7-membered C ring and the discovery of substituent effects which are critical to this reaction, an arylsilane oxidation which effectively employs alkynylsilanes as masked phenols, and the development of mild conditions for tricycle elaboration into the natural product cores.

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Supporting Information Available. Experimental procedures, 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.

The authors declare no competing financial interest.

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