A palladium-mediated cascade cyclisation approach to the CDE cores of rubriflordilactone A and lancifodilactone G†‡

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Palladium-mediated cascade cyclisation reactions have been applied to the synthesis of the CDE-ring cores of two anti-HIV natural products, rubriflordilactone A and lancifodilactone G.

Lancifodilactone G[1] (**1**, Fig. 1) and rubriflordilactone A[2] (**2**) are two members of a growing family of natural products isolated by Sun and co-workers from Chinese herbal plants of the *Schisandra* genus. They are characterised by highly oxygenated, complex fused-ring architectures, and many have been found to possess anti-HIV activity (*e.g.* EC_{50} = 95 μg mL^{-1} for lancifodilactone G). This disease affects some 33 million people worldwide, and causes around 3 million deaths each year,[3] yet there remains no cure. The discovery of new candidates for drug development is thus of great importance.[4]

We recently reported a versatile palladium-mediated cascade cyclisation[5] which accesses bi- and tricyclic fused ring systems using the combined efficiency of organopalladium and pericyclic processes.[6] This reaction was in fact inspired by consideration of approaches to the challenging fused ring skeletons found in the *Schisandra* natural products. We envisaged these could be formed *via* a common strategy,[7] involving single-step construction of the 7,8- or 7,6-fused CD rings, with simultaneous appendage of a 5-membered E-ring. We report here the realisation of this strategy to prepare the CDE-cores of both natural products (*e.g.* **3** and **4**, Fig. 1), together with the observation of unusual pericyclic cascades.

Our approach to the rubriflordilactone core targeted two CDE-skeletons (**4** and **5**, Scheme 1), which would be formed using a fully intramolecular cascade cyclisation of appropriate bromoenediynes. The first of these (tricycle **5**) was designed to evaluate the efficiency of the cyclisation reaction to prepare 7,6,5-cores. The synthesis of **5** commenced with the monosilylation of 1,6-hexadiyne, followed by lithiation and addition to aldehyde **6** to give alcohol **7**. Following protecting group and oxidation state manipulation, a $Ba(OH)_2$-mediated Horner–Wadsworth–Emmons (HWE) olefination[8] delivered enoate **9**, the cascade cyclisation substrate (81% over four steps, $E : Z$ = 6.5 : 1). Although intramolecular bromoenediyne cyclisations have precedent in the elegant work of the groups of Negishi and de Meijere,[9] they have rarely been applied to substrates containing a 7-membered tether, and certainly not in natural product total synthesis.[10] We were therefore pleased to find that treatment of **9** with $Pd(PPh_3)_4$ in acetonitrile in the presence of triethylamine (the conditions of de Meijere)[10] effected smooth cyclisation to the tricycle **5** (77%).

Satisfied that 7,6,5-fused ring formation could indeed be achieved, we next examined installation of the D-ring oxygen of rubriflordilactone A. It seemed that this might be introduced through Tamao–Fleming oxidation[11] of a suitable arylsilane, which would in turn require the preparation of the corresponding silyl alkyne. The dimethylisopropoxysilyl group was selected, as it was anticipated to be sufficiently stable for handling as the silyl alkyne, but also susceptible to oxidation once it had been converted to the arylsilane.

This route commenced with oct-4-yn-1,8-diol **10**, prepared in three steps from 1,4-butynediol according to a literature procedure.[12] **10** was oxidised to give a dialdehyde, which was prone to degradation under prolonged storage. However, if used immediately and without purification, this aldehyde underwent a moderate-yielding mono-olefination to the corresponding enoate;[8] subsequent addition of the lithium anion of dimethylisopropoxysilyl acetylene[13] to the remaining aldehyde led to the allylic alcohol **11** (89%). To circumvent the problems of the low yielding HWE, we were also able to employ an alternative strategy involving mono-protection of diol **10**, which led to alcohol **11** in six steps.[14]

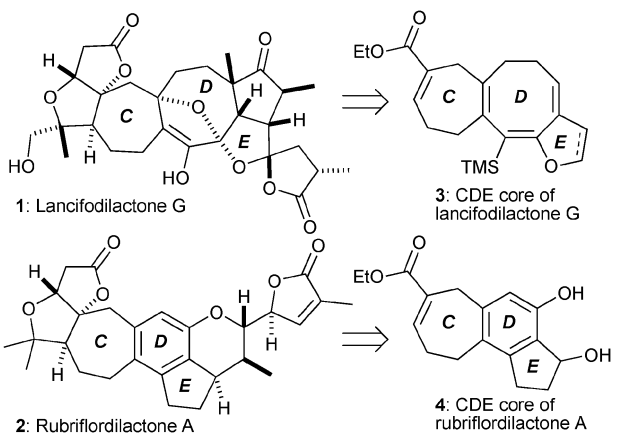

Fig. 1

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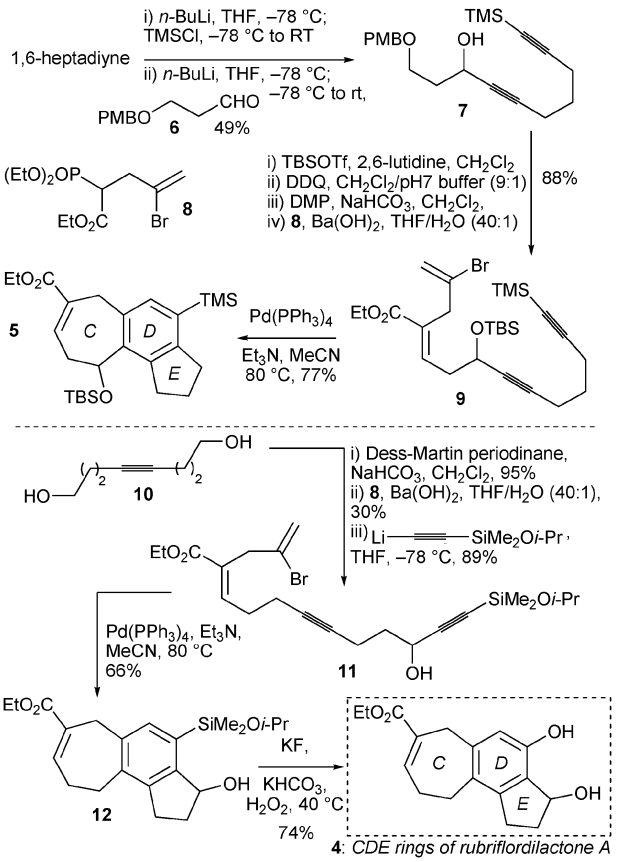
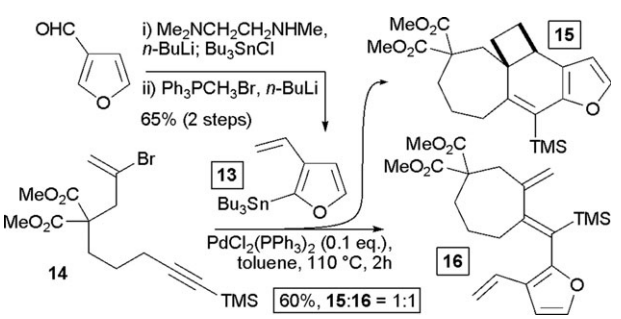
‡ Electronic supplementary information (ESI) available: Preparation and characterisation of key intermediates and products, and selected ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b814360a



Scheme 1

With **11** in hand, the key cascade cyclisation was attempted. Pleasingly, the use of identical cyclisation conditions gave the pentasubstituted 7,6,5-core **12** in 66% yield. In addition, we were able to validate the use of the dimethylisopropoxysilyl group as a masked phenol, as it was smoothly oxidised to the fully functionalised CDE core **4** of rubriflordilactone A under standard Tamao conditions (74%).

Our approach to the 7,8,5-CDE core of lancifodilactone G called for a cascade cyclisation terminating in an 8π-electrocyclisation.[15] In the course of methodology development, we had already prepared 7,8-fused bicyclic ring systems *via* cascade cyclisation,[6] and now sought to annulate an additional ring through coupling with a cyclic (furanyl) stannane. Towards this end, stannane **13** (Scheme 2) was prepared in two steps from commercially available 3-furaldehyde, *via* directed lithiation/stannylation using Comins' protocol,[16] and Wittig olefination (65%, 2 steps).



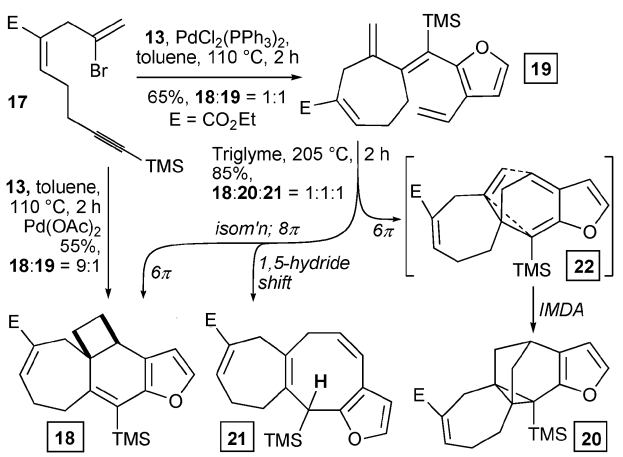
Scheme 2

Treatment of bromoenyne **14** with this stannane under our standard reaction conditions ($PdCl_2(PPh_3)_2$, toluene, reflux) led not to the expected CDE rings, but to a mixture of two compounds. The first was identified as the 7,6,4,5 tetracycle **15**, which had arisen from a cascade 8π/6π-electrocyclisation, a rather surprising result given that the previously prepared 7,8-bicycles had not undergone this secondary 6π-process (although we had observed a similar outcome from a related 5-membered ring substrate).[6] This process is likely driven by rearomatisation of the furan ring upon 6π-electrocyclisation of the intermediate cyclooctatriene,[15,17] despite the inevitable increase in ring strain. The second product was identified as the isomeric triene **16**[18] which, in keeping with our previous observations, seemed to have arisen from isomerisation of an intermediate palladium species. The ratio of **15** and **16** varied,[19] but was typically around 1 : 1 (60% yield).

We next examined the cyclisation of enone **17**, which contains functionality more relevant to our strategy towards lancifodilactone G. Again, varying ratios of tetracycle **18** and tetraenylfuran **19** were isolated (typically ratios of **18** : **19**, 1 : 1–3 : 1), with the nature of the catalyst seeming to play an important role.

The degree of isomerisation (to give **19**) was rather surprising given the rate of reaction (<2 h) and relative ease with which furanylstannanes undergo transmetallation, which we would have predicted to lead to little isomerisation based on our previous work. Theorising that the bulk of the palladium ligand sphere and/or the rate of transmetallation might affect the degree of isomerisation, we repeated the reaction using ligand-free conditions ($Pd(OAc)_2$). This resulted in almost exclusive formation of the tetracycle **18** (55%), with very little of the isomer **19** being detected.

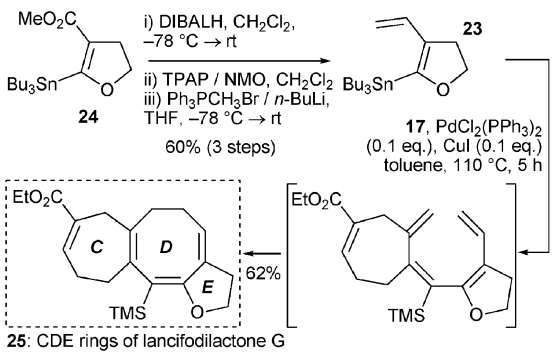
On several occasions, **19** could be isolated as the sole product (70–92%). Although this was also not a consistent result, it permitted a definitive confirmation of the undesired geometry of the tetrasubstituted olefin using NOE experiments.[18] Further heating of this tetraene in toluene (in the presence or absence of Pd catalyst) led to no further reaction. However, a report by van Leusen on electrocyclisations of 4-nitropyrroles[20] prompted us to test higher boiling solvents, and we were pleased to find that heating pure tetraene **19** in triglyme at 205 °C for 2 h led to complete consumption of



Scheme 3

starting material (Scheme 3). *Three* inseparable products were isolated (85%, 1 : 1 : 1): tetracycle **18**, the remarkable hexacycle **20**, and the 7,8,5-tricycle **21**. Hexacycle **20** likely arises from an initial 6π-electrocyclisation to form a spirocyclic 7,6-ring system **22**, which then undergoes an intramolecular Diels–Alder reaction with the proximal *exo*-methylene group, again driven by restoration of aromaticity to the furan. This mode of cascade cyclisation was initially discovered by Marvell *et al.*,[21] and has undergone a revival in the context of the pyrone-polypropionate natural products.[22] The formation of tetracycle **18** and tricycle **21** (the latter containing the targeted lancifodilactone CDE core) can be rationalised by an initial thermal isomerisation of **19**, followed by 8π-cyclisation; the intermediate cyclooctatriene then undergoes either 6π-cyclisation to give **18**, or a 1,5-hydride shift to tricycle **21**.[23]

Although interesting from the viewpoint of construction of unusual molecular skeletons, these side reactions are not productive in terms of efficient synthesis of the natural product core. We recognised that their driving force (rearomatisation of the furan) could be removed through use of the dihydrofuran analogue of stannane **13**. To this end, stannane **23** (Scheme 4) was prepared in three steps from the known methyl ester **24**,[24] *via* DIBALH reduction, reoxidation (TPAP/NMO)[25] and Wittig olefination (60%). With **23** in hand, the crucial cyclisation was re-examined. This time, to our delight, the desired 7,8,5-tricycle **25** could be isolated cleanly (62%), although transmetallation of the dihydrofuranyl stannane **23** was markedly slower than **13**, requiring catalytic copper(I) iodide. This reaction completes the 7,8,5-CDE core of lancifodilactone G for the first time.



Scheme 4

In conclusion, we have prepared the highly functionalised CDE cores of the natural products rubriflordilactone A and lancifodilactone G, the latter featuring a 7,8,5-fused ring system ripe for further functionalisation. In the course of this work, we also observed three remarkable rearomatisation-driven pericyclic processes, leading to the formation of polycylic ring systems. Ongoing studies towards advanced synthetic intermediates and total syntheses of these intruiging natural products will be reported in due course.

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