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CLAISEN RING EXPANSION APPROACH TOWARD THE CDEF RING SYSTEM OF LANCIFODILACTONE G‡

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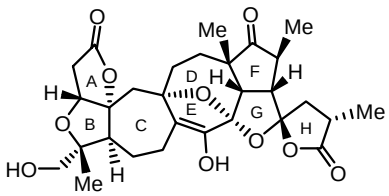
Abstract – The fused CDEF ring system of lancifodilactone G is assembled via a Nozaki-Hiyama-Kishi cross-coupling reaction and a Petasis-Claisen ring expansion sequence as the key strategic steps.

Lancifodilactone G (**1**, Figure 1) is an architecturally novel, highly oxygenated nortriterpenoid that was isolated from the medicinal plant *Schisandra lancifolia* by Sun and co-workers in 2005 (Figure 1).[1] Its structure and relative stereochemistry were determined on the basis of extensive one- and two-dimensional NMR spectroscopy and mass spectral data, coupled with single-crystal X-ray analysis.[2] Its absolute configuration was recently deduced on the basis of the existing biogenetic connectivity to its congener micrandilactone B.[3] Lancifodilactone G (**1**) exerts minimal cytotoxicity against C8166 cells (CC_{50} > 200 μ/mL) while demonstrating anti-HIV activity with an EC_{50} = 95.47 ± 14.19 μ/mL and a selectivity index in the range of 1.82–2.46. For these reasons, we have become engaged in its total synthesis.[4] Herein, we define a route to the fused CDEF ring system of lancifodilactone G (**1**) based on a combination of the Nozaki-Hiyama-Kishi (NHK) cross-coupling reaction[5] and Petasis-Claisen ring expansion technology.[6]



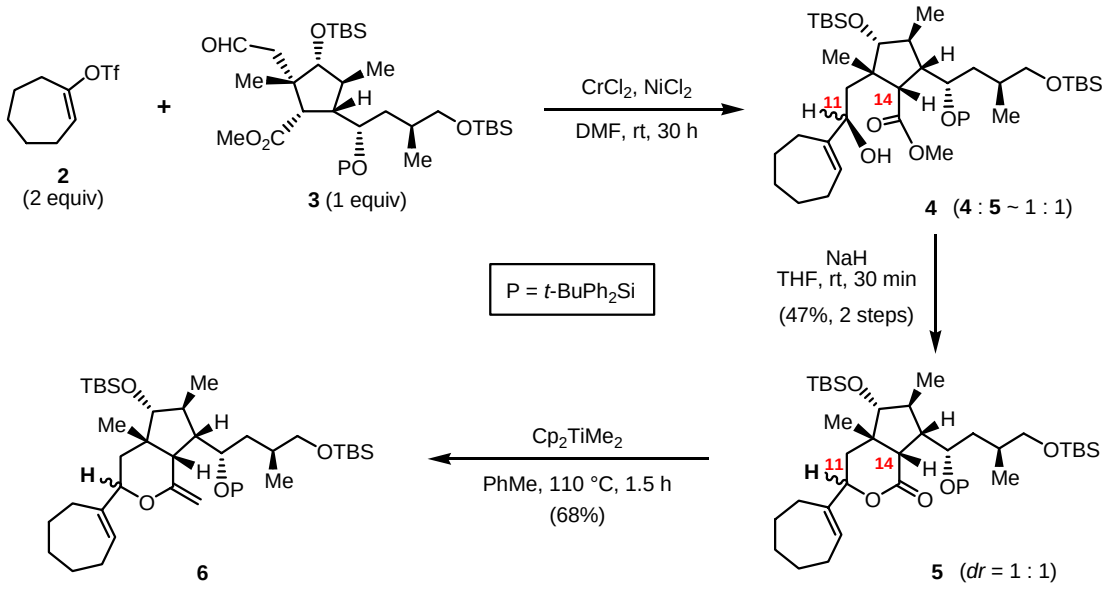
lancifodilactone G (**1**)

Figure 1. Chemical structure of lancifodilactone G (**1**).

‡This paper is dedicated to the memory of Dr. John Daly.

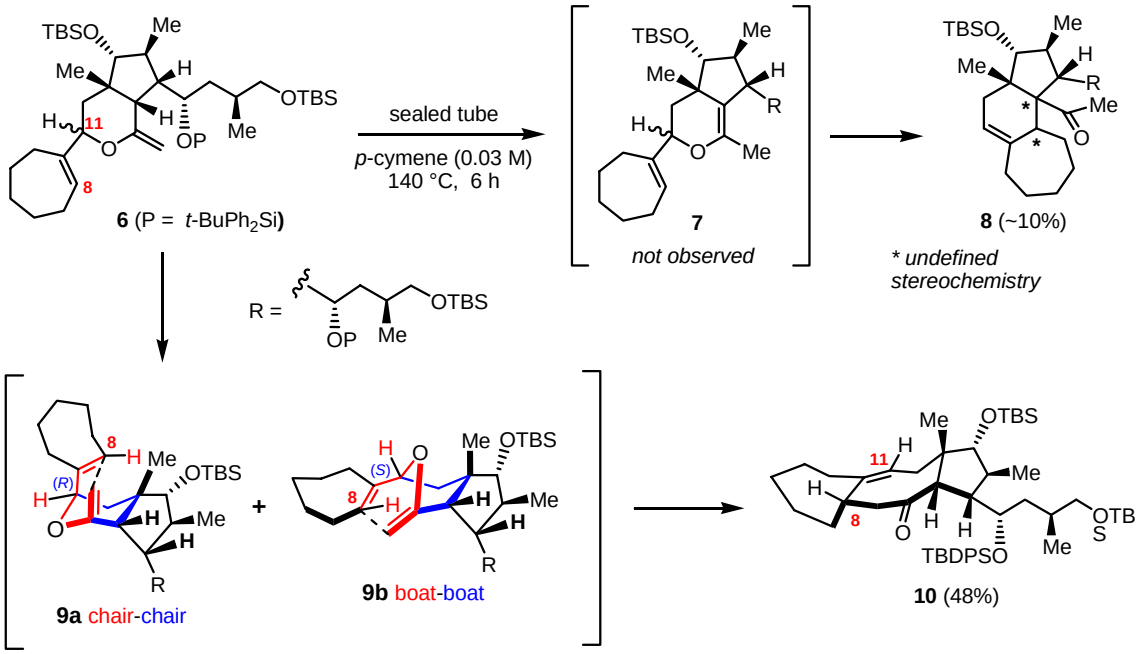
The synthesis commenced with the union of vinyl triflate (**2**)[7] and aldehyde (**3**)[4b] as depicted in Scheme 1. Initial attempts using THF as solvent failed to produce the NHK cross-coupling product at any appreciable rate due mostly to the poor solubility of the catalysts. To circumvent this issue, recourse was made to DMF (dried over activated 4Å MS). In this medium, the targeted allylic alcohol (**4**) was formed alongside an inseparable mixture of the *in situ* lactonization products (**5**). To facilitate structural characterization, the unpurified reaction mixture was treated directly with excess NaH to generate lactone (**5**) as a 1:1 mixture of diastereoisomers with no evidence of epimerization at C14. The next task called for methylenation of the six-membered lactone (**5**). To this end, successful reaction of **5** with the Petasis-Tebbe reagent required vigorous conditions to bring about conversion to the unstable enol ether (**6**).

Scheme 1



With the enol ether (**6**) in hand, its Claisen ring expansion was pursued.[6] Preliminary studies of this process revealed that exposure of **6** to TRIBAL in PhMe at 80 °C gave rise to a complicated mixture of unwanted products.[8] This failure is likely attributable to the acid-sensitivity of the substrate. As a result, the feasibility of the thermally-induced Claisen rearrangement was examined.[6] Thermolysis of **6** in dry *p*-cymene solution contained in potassium hydroxide-coated sealed tubes at 140 °C for 6 h resulted in smooth conversion to the eight-membered ring enone (**10**) in 48% isolated yield, presumably through the dual operation of chair-chair and boat-boat transition states **9a** and **9b** (Scheme 2). The identical stereochemical outcome of these mechanistic alternatives concisely rationalizes the unique formation of diastereomer (**10**) as the product of this 3,3-sigmatropic conversion. The absolute configuration of **10** was deduced with the aid of ^{13}C NMR, DEPT 135, COSY, NOESY and HMQC experiments.[9] In addition, a minor product tentatively identified as **8** results from competitive 1,3-hydrogen migration within **6** to form the *endo*-olefin intermediate (**7**) and Claisen rearrangement of the latter.

Scheme 2



In summary, we have successfully assembled the fused CDEF framework of lancifodilactone G (**1**). The synthetic strategy highlights the utility of the Nozaki-Hiyama-Kishi cross-coupling reaction and Petasis-Claisen ring expansion technology. Application of these methods to the total synthesis of lancifodilactone G (**1**) is in progress.

ACKNOWLEDGMENTS

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9. For **10**: IR (neat) 2924, 1710, 1462, 1256, 1086 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.70 (m, 4H), 7.45–7.34 (m, 6H), 5.37 (t, *J* = 8.5 Hz, 1H), 4.20–4.14 (m, 1H), 3.31 (d, *J* = 5.0 Hz, 1H), 3.07 (dd, *J* = 9.5, 5.0 Hz, 1H), 2.95 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.94–2.86 (m, 1H), 2.79 (d, *J* = 7.0 Hz, 1H), 2.57–2.33 (m, 4H), 2.10–2.00 (m, 4H), 1.85–1.75 (m, 1H), 1.75–1.61 (m, 3H), 1.53–1.42 (m, 1H), 1.40–1.20 (m, 6H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 0.96 (s, 9H), 0.96–0.85 (m, 1H), 0.84 (s, 9H), 0.43 (d, *J* = 6.5 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), –0.05 (s, 3H), –0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.55, 145.23, 136.13, 136.01, 134.91, 134.16, 129.49, 129.30, 127.47, 127.33, 124.28, 90.08, 72.49, 68.46, 62.51, 53.12, 52.65, 49.26, 45.68, 39.16, 38.59, 36.21, 34.91, 33.76, 31.89, 30.40, 30.16, 29.70, 28.62, 27.68, 27.30, 26.06, 25.97, 19.74, 18.29, 18.06, 16.79, –4.03, –4.11, –5.39.