Communication

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Asymmetric Total Synthesis of Lancifodilactone G Acetate

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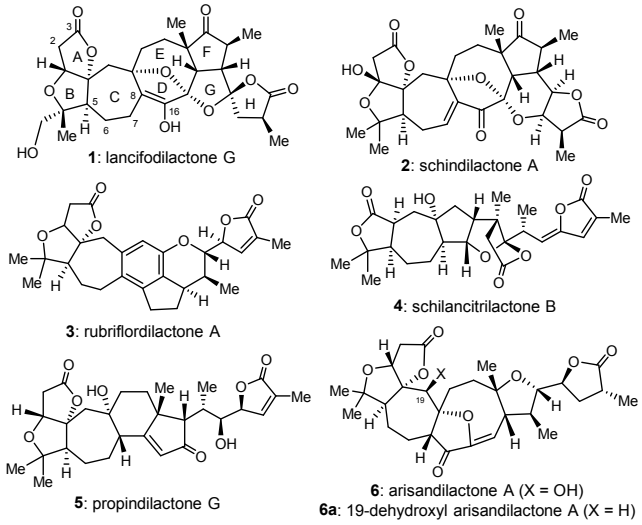
Supporting Information Placeholder

ABSTRACT: Asymmetric total synthesis of structurally intriguing and highly oxygenated lancifodilactone G acetate (**7**) has been achieved for the first time in 28 steps from cheap commodity chemical 2-(triisopropylsiloxy)-1,3-butadiene.

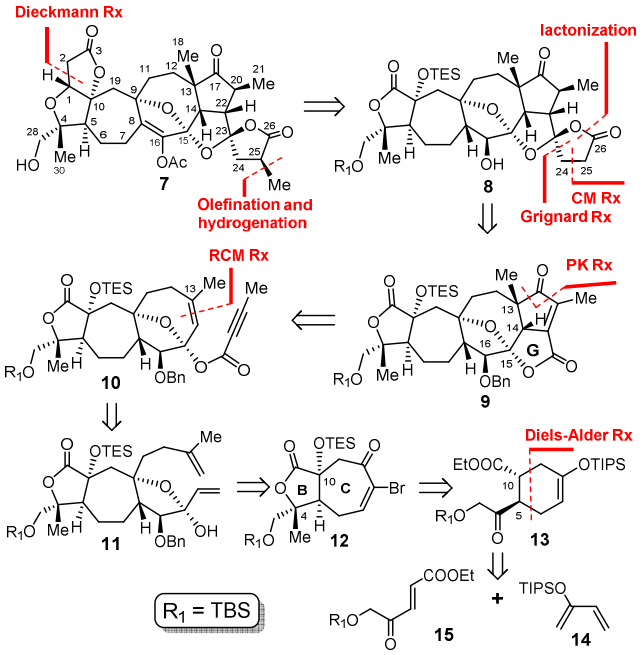
Lancifodilactone G (**1**, Figure 1) was isolated from the medicinal plant *Schisandra lancifolia* by Sun and co-workers in 2005, and its structure has been determined by X-ray crystallographic analysis.[1] Unlike the other members of the schinortriterpenoids family (such as **2**-**6**, Figure 1), **1** contains a CD ring that bears a rare non-resonance-stabilized aliphatic enol (C-8/C-16),[2] a highly congested FGH tricyclic ring system containing six contiguous stereogenic centers, and an unusual two-fold anomerically stabilized bis-spiro system.[3]

Figure 1: Naturally occurring schinortriterpenoids.



Schinortriterpenoids are reported to exhibit anti-hepatitis, antitumor, and anti-HIV agents.[4] As a result, much effort has been paid to their total syntheses,[5] with the aim of accelerating the evaluation of their pharmacological potential. This has recently culminated in the total syntheses of **2**-**5**[5] and **6a**.[6]

As one of the most important member of the schinortriterpenoids family, **1** represents the most challenging target for total synthesis owing to the difficulties associated with the construction of its highly congested FGH tricyclic ring and its unusual 7–5–7 tricyclic ring (CDE) system. The ring system has not yet been assembled in the laboratory and represents a noteworthy target for both synthetic[7] and computational[8] chemists. Herein a 28-step route to lancifodilactone G acetate **7** (Scheme 1) is documented, in which the central poly-fused ring system is constructed through a sequence of key reactions featuring a ring-closing metathesis reaction and Pauson-Khand reaction.

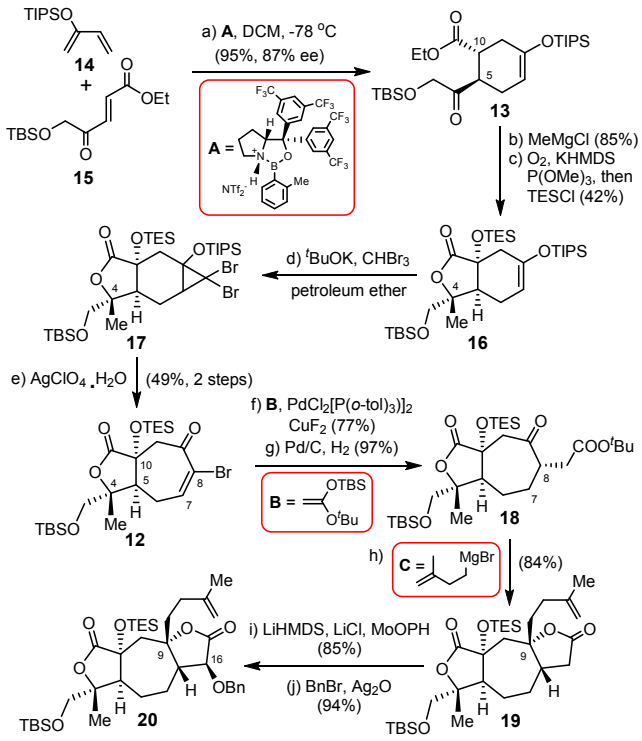


Scheme 1: Strategic bond disconnections of **7**.

A retrosynthetic overview of the main strategic operations is depicted in Scheme 1. Our strategy involved the following steps: (1) oxidation of the alcohol at C-16 to give a ketone, followed by acetylation to afford **7**; (2) a sequence of reactions, featuring a Grignard reaction, cross-metathesis reaction, and lactonization to form the two-fold anomerically stabilized bis-spiro system in **8**; (3) a

tetramethyl thiourea (TMTU)/$Co_2(CO)_8$-catalyzed Pauson–Khand reaction[9] of enyne **10** for the stereoselective construction of highly congested bicyclo[6.3.0]undecan-2-one[10] **9**, which bears an all-carbon quaternary chiral center at C-13; (4) a ring-closing metathesis (RCM) reaction to form the tri-substituted olefin based on an oxa-bridged eight-membered ring in **10**; and (5) an oxazaborolidine-catalyzed[11] asymmetric intermolecular Diels–Alder reaction[12] of diene **14** with dienophile **15** for the enantioselective synthesis of ketoester **13** with 87% ee.

Scheme 2. Synthesis of compound **20**.



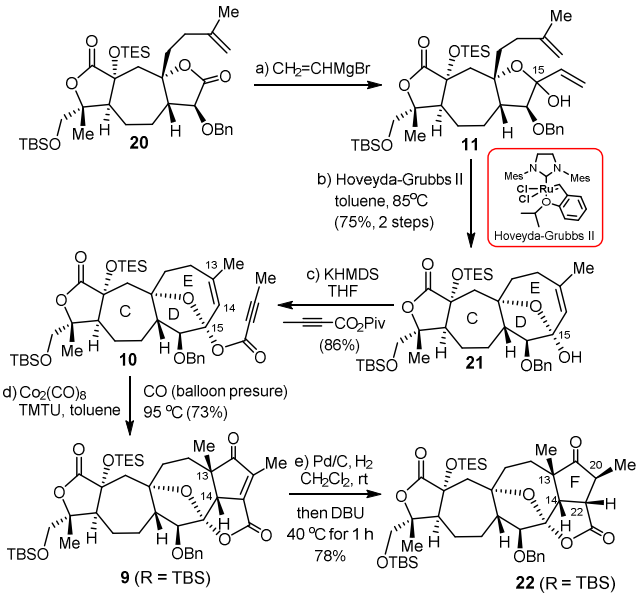
Reagents and conditions: (a) **14** (1.5 equiv.), **15** (1.0 equiv.), **A** (20 mol %), CH_2Cl_2, -78 °C, 12 h, 95% (87% ee); (b) MeMgCl (2.0 equiv.), THF, -78 °C to -20 °C, 0.5 h, 85% (dr = 1.7 : 1); (c) KHMDS (2.0 equiv.), THF, -78 °C to 0 °C followed by addition of $P(OMe)_3$ (2.0 equiv.), O_2, 0 °C, 1 h; then, TESCl (1.5 equiv.), 42% and 38% C-4 isomer; (d) KO^{t}Bu (6.0 equiv.), $CHBr_3$ (6.0 equiv.), petroleum ether, -20 °C, 2 h; (e) $AgClO_4$•H_2O (2.0 equiv.), acetone, rt, 12 h, 49% for two steps; (f) (1-tert-butoxyvinyloxy)-(*tert*-butyl)di-methylsilane (3.0 equiv.), $PdCl_2$/[P(*o*-tol)$_3$]$_2$ (0.1 equiv.), CuF_2 (3.0 equiv.), THF, reflux, 12 h, 77%; (g) Pd/C (10 wt%), H_2, EtOAc, 50 °C, 1 h, 97%; (h) Grignard reagent (5.0 equiv.), THF, -78 °C to 0 °C, 84%; (i) LiHMDS (3.5 equiv.), LiCl (5.0 equiv.), THF, -78 °C, MoOPH (3.5 equiv.), 2h; 85%; (j) Ag_2O (2.0 equiv.), BnBr (2.0 equiv.), 35 °C, 12 h, 94%.

Scheme 2 shows our synthesis of *bis*-lactone **20**. Knowing that the enantioselective synthesis of ketoester **13** using a Diels–Alder reaction with an acyclic ketone as the dienophile is challenging,[13] we conducted a systematic investigation. Pleasingly, enantioselective synthesis was achieved when the Diels–Alder reaction was carried out in the presence of oxazaborolidine **A**[14] as the catalyst, and **12** was obtained in 95% yield with 87% ee. This reaction worked well on a 100-g scale, and provided a good foundation from which to pursue the total synthesis of **1**. To construct lactone **16**, **13** was reacted with MeMgCl, and the resultant lactone was treated with KHMDS followed by reaction with O_2 in the presence of $P(OMe)_3$,[15] and quenching with TESCl to give gave silyl ether **16** in 36% overall yield, together with its diastereoisomer in 33%, respectively.

We then turned our attention to the later steps in the synthesis of **20**. Reaction of **16** with dibromomethylene (derived from $CHBr_3$ and KO^{t}Bu in petroleum ether[16]) was followed by ring-expansion of resulting dibromocyclopropane **17** with $AgClO_4$[17] to afford vinyl bromide **12** in 49% yield over two steps, and the ee value of **12** is 99% after recrystallization from a mixed solvent of CH_2Cl_2 and hexane.

The ester side chain in **18** was extended through two discrete operations that involved a Pd-catalyzed cross-coupling reaction of **12** with vinyloxy silane **B** in the presence of CuF_2,[18] followed by Pd-catalyzed hydrogenation. As a result, ketoester **18** was formed in 75% overall yield. Grignard reaction of **18** with Grignard reagent **C** afforded a tertiary alcohol, which then underwent an intramolecular lactonization to give **19**. Lastly, treatment of **19** with LiHMDS and oxidation of the resulting enolate with MoOPH,[19] followed by treatment with Ag_2O/BnBr[20] for the benzylation to give the desired product **20** in 80% yield. Notably, both the Grignard reaction and the oxidative hydroxylation used for the formation of **19** and **20** were diastereoselective owing to the steric effect of the OTES group at C-10 (the conformation analysis is provided in SI). The structure of **19** was confirmed by X-ray crystallographic analysis.

Scheme 3. Synthesis of compound **22**.



Reagents and conditions: (a) vinylmagnesium bromide (3.0 equiv.), THF, 0 °C, 1 h; (b) Hoveyda-Grubbs II catalyst (8 mol%), toluene, 85 °C, 12 h, 76% for two steps; (c) KHMDS (2.0 equiv.), but-2-ynoic pivalic anhydride (5.0 equiv.), THF, 0 °C, 1 h, 86%; (d) $Co_2(CO)_8$ (0.2 equiv.), TMTU (1.5 equiv. toluene, under a balloon pressure of CO, toluene, 95 °C, 8 h, 73%; (e) Pd/C (10 wt%), H_2, CH_2Cl_2, rt, 1 h,; then, DBU, 40 °C, 1 h, 78%.

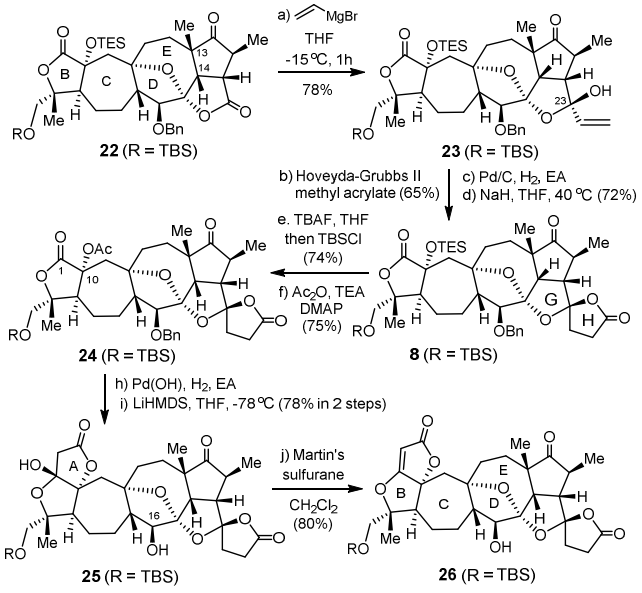
With **20** in hand, we then proceeded to the synthesis of the most challenging intermediate, **22**. Aside from the obvious difficulties posed by the high steric demand of the F ring in **22**, a unique issue associated with the formation of the oxabicyclo[4.2.1]nonene core[21] bearing a sterically hindered tri-substituted olefin in **21** also made this synthesis challenging. Initial attempts to construct **21** from **11** through RCM reactions[22] using the Grubbs I and Grubbs II catalysts failed to afford any of the desired product. However, when the Hoveyda–Grubbs II[23] catalyst (8 mol%) was used, the expected annulation proceeded smoothly. Exposure of lactone **20** to vinyl magnesium bromide at 0 °C resulted in the formation of dienes **11** as a pair of diastereoisomers in a ratio of 5:1. These diastereoisomers were treated without separation with the Hoveyda–Grubbs II catalyst (8 mol%) at 85 °C in toluene for 8 h to give **21**, which was obtained in 76% overall yield as a single isomer. This *in situ* epimerization[24] was remarkable and in line with our early observation,[6] and might be of general utility in similarly challenging synthetic contexts.

To make **22**, **21** was treated with KHMDS in THF at 0 °C for 15 min, and the resultant alkoxide was reacted with but-2-ynoic pivalic anhydride[25] to afford enyne **10** in 86% yield. Thus, under the optimized PKR conditions, **10** was treated with the complex of tetramethyl thiourea (TMTU) and $Co_2(CO)_8$ in dry toluene under a balloon pressure of CO[26] at 95 °C for 8 hours, enone **9** was obtained in 73% yield as a sole isomer. This stereoselectively TMTU/Co-catalyzed PKR that yielded enone **9**[27] in such a high yield

is truly remarkable. The structure of **9** was confirmed by X-ray crystallographic analysis of the crystals derived from its racemic sample (see SI for details). The next mission was to stereoselectively introduce the contiguous stereogenic centers at C-20 and C-22 in **22** involving Pd/C catalyzed hydrogenation. Thus, approach of the catalyst to the double bond from the more accessible top face within **9** set up the stereogenic centers at C-20 and C-22, and the opposite stereochemistry at C-20 in the resultant product was inverted by the treatment with DBU[28] to afford **22** in 78% yield.

The construction of the *bis*-spiro system was another strategic transformation, and involved three discrete operations: chemo- and stereo-selective vinylation, intermolecular cross-metathesis[29] using the Hoveyda–Grubbs II catalyst, and Pd-catalyzed hydrogenation–lactonization. This sequence delivered desired siproketal **8** in 37% overall yield. Removal of the silyl protecting groups with anhydrous TBAF, followed by selective silylation with TBSCl, resulted in a tertiary alcohol, which was then protected with Ac_2O/TEA/DMAP to give acetate **24** in 56% yield over two steps.

Scheme 4. Synthesis of compound **26.**



Reagents and conditions: (a) vinylmagnesium bromide (3.0 equiv.), THF, -15 °C, 0.5 h, 78%; (b) methyl acrylate (20.0 equiv.), Hoveyda-Grubbs II catalyst (5 mol %), toluene, 88 °C, 12 h, 66%; (c) Pd/C (10 wt%), H_2, EtOAc, rt, 1 h; (d) Sodium hydride (10.0 equiv.), THF, 40 °C, 72% for two steps; (e) TBAF (2.0 equiv.), THF; TBSCl (5.0 equiv.), 40 °C, 6 h, 74%; (f) Ac_2O (5.0 equiv.), Et_3N, DMAP (1.0 equiv.), 60 °C, 76%; (g) $Pd(OH)_2$/C (10 wt%), EtOAc, rt, 1 h; (h) LiHMDS (5.0 equiv.), THF, -78 to -20 °C, 78% for two steps; (i) Martin's sulfuran (1.2 equiv.), CH_2Cl_2, rt, 5 min, 80%.

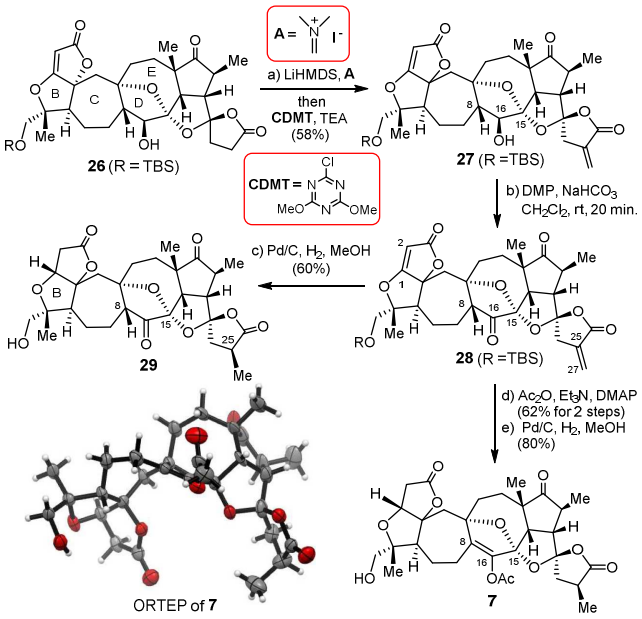
To apply the Dieckmann-type condensation[30] for the formation of the A ring, the benzyl group in **24** was removed by hydrogenation and the resultant product was treated with LiHMDS in THF at –78 °C to give lactone **25** in 78% yield. It is imperative that the benzyl group in **24** is removed to allow the carbonyl group at C-1 and the acetate at C-10 to come closer together and thus facilitate the subsequent ring closing reaction. Thereafter, further treatment of **25** with Martin's sulfurane[31] resulted in the formation of α,β-unsaturated lactone **26** in good yield.

With key intermediate **26** in hand, we proceeded with the methylation at C-25, as illustrated in Scheme 5. This process involved α-methylenation of lactone as the key step. Briefly, **26** was treated with LiHMDS in THF at –78 °C, and then reacted with *N,N*-dimethyl- methyleneammonium iodide[32] (Eschenmoser's reagent). This was followed by treatment with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)[33] in the presence of TEA to afford methylene-containing **27** in 58% yield.

The final challenge in the total synthesis of lancifodilactone G (**1**) called for the introduction of an enol moiety. We speculated that, in the presence of water, the enol of lancifodilactone G (**1**) might form a hydrogen-bonded network involving the enol proton and the oxygen atom in the G ring, which could facilitate enolization from the ketone to the enol form. With this chemistry in mind, we oxidized **27** with DMP, and unstable intermediate **28** immediately underwent a Pd-catalyzed stereoselective hydrogenation that removed both double bonds at C-1/C-2 and C-25/C-27, as well as the TBS group,[34] to give ketone **29**. However, attempts to convert ketone **29** to its enol under various conditions did not result in the expected enolization, and in most cases **29** simply decomposed.

To promote the enolization, ketone **28** was treated with Ac_2O/Et_3N and, to our delight, the expected enol acetate was obtained. This compound then underwent a Pd/C-catalyzed hydrogenation reaction to give lancifodilactone G acetate (**7**). The structure of **7** was confirmed by X-ray single crystallography.

Scheme 5. Total synthesis of lancifodilactone G acetate **7**.



Reagents and conditions: (a) LiHMDS (5.0 equiv.), THF, -78 °C, then Eschenmoser's salt (6.0 equiv.), -78 to 0 °C; (b) CDMT (5.0 equiv.), Et_3N (10.0 equiv.), CH_2Cl_2, 0.5 h, 58%; (b) DMP (3.0 equiv.), $NaHCO_3$ (5.0 equiv.), CH_2Cl_2, rt, 20 min; (c) Pd/C (100 wt%), MeOH, rt, 3 h, 60% for two steps; (d) Ac_2O (8.0 equiv.), DMAP (1.5 equiv.), Et_3N (10 equiv.), 62% from **27**; (e) Pd/C (100 wt%), MeOH, rt, 3 h, 80%.

In summary, the asymmetric total synthesis of lancifodilactone G acetate **7** has been completed in 28 steps. Salient features of this work include: (1) development of a highly enantioselective oxazaborolidine-catalyzed Diels–Alder reaction using substituted (E)-4-oxopent-2-enoates **15** as the dienophile to synthesize key intermediate **13**; (2) demonstration of the efficiency of the RCM approach for accessing a oxabicyclo[4.2.1]nonene core bearing a sterically hindered tri-substituted olefin; and (3) application of our Co/TMTU-catalyzed Pauson-Khand reaction to the stereoselective synthesis of the highly congested F ring of **7**, which bears an all-carbon quaternary chiral center at C-13. We currently work on the conversions of compounds **29** and **7** to lancifodilactone G (**1**), and the results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization (cif, pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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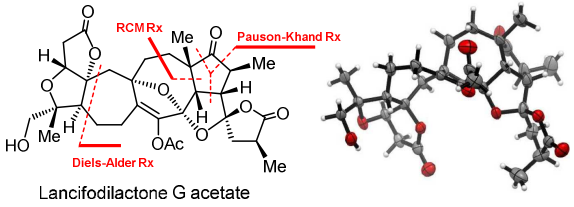

Lancifodilactone G acetate