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Pinacol Macrocyclization-Based Route to the Polyfused Medium-Sized CDE Ring System of Lancifodilactone G

Leo A. Paquette* and Kwong Wah Lai

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette@chemistry.ohio-state.edu

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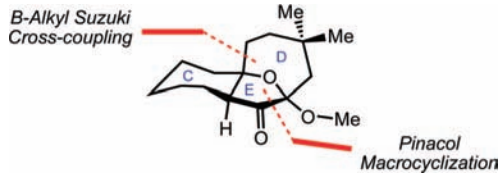
ABSTRACT



The polyfused medium-sized CDE ring system of lancifodilactone G is assembled via *B*-alkyl Suzuki−Miyaura cross-coupling and SmI_2-mediated pinacol macrocyclization as the key strategic steps.

Lancifodilactone G (**1**) is an architecturally unique nortriterpenoid recently isolated from the medicinal plant *Schisandra lancifolia*.[1] Its structure and relative stereochemistry were unambiguously determined by X-ray crystallography.[2,3] Lancifodilactone G (**1**) attracted our attention not only because of its intricate cyclic connectivity but also because of its unprecedented 7−5−7 polyfused ring system (red bonds, Figure 1). The latter has hitherto not been assembled in the laboratory and represents a noteworthy target.

Very recently, we have published our preliminary results dealing with construction of the ABC and F segments of lancifodilactone G (**1**).[4] As a continuation of this work, we have now investigated a mode of assembly of the core eight-membered carbocyclic architecture residing in **1**.[5,6] In early 2008, Yang's group reported a synthesis of the 7−8 fused ring platform in micrandilactone A based on TRIBAL-

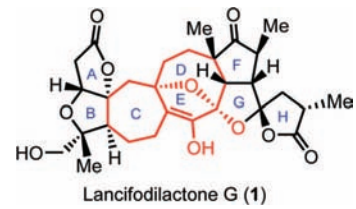


Figure 1. Chemical structure of lancifodilactone G (**1**).

(1) For the isolation and biological evaluation of lancifodilactone G, see: Xiao, W.-L.; Zhu, H.-J.; Shen, Y.-H.; Li, R.-T.; Li, S.-H.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q. T. *Org. Lett.* **2005**, *7*, 2145.

(2) The original structural assignment for lancifodilactone G has been revised. See: Xiao, W.-L.; Zhu, H.-J.; Shen, Y.-H.; Li, R.-T.; Li, S.-H.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q. T. *Org. Lett.* **2006**, *8*, 801.

(3) The absolute configuration of lancifodilactone G has been deduced from that of micrandilactone B. See: Huang, S.-X.; Li, R.-T.; Liu, J.-P.; Lu, Y.; Chang, Y.; Lei, C.; Xiao, W.-L.; Yang, L.-B.; Zheng, Q.-T.; Sun, H.-D. *Org. Lett.* **2007**, *9*, 2079.

(4) (a) Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 2111. (b) Lai, K. W.; Paquette, L. A. *Org. Lett.* **2008**, *10*, 2115.

(5) For reviews of medium-sized ring synthesis, see: (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Patasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

(6) For reviews of eight-membered ring carbocycle construction, see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881.

(7) Zhang, Y.-D.; Ren, W.-W.; Lan, Y.; Xiao, Q.; Wang, K.; Xu, J.; Chen, J.-J.; Yang, Z. *Org. Lett.* **2008**, *10*, 665.

(8) Tribal-catalyzed Claisen ring expansions, see: (a) Paquette, L. A.; Sun, L.-Q.; Friedrich, D.; Savage, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 8438. (b) Sollogoub, M.; Mallet, J.-M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 360. (c) Wang, W.; Zhang, Y.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2466. (d) Wang, W.; Zhang, Y.; Zhou, H.; Blériot, Y.; Sinaÿ, P. *Eur. J. Org. Chem.* **2001**, 1053. (e) Sisu, E.; Sollogoub, M.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron* **2002**, *58*, 10189.

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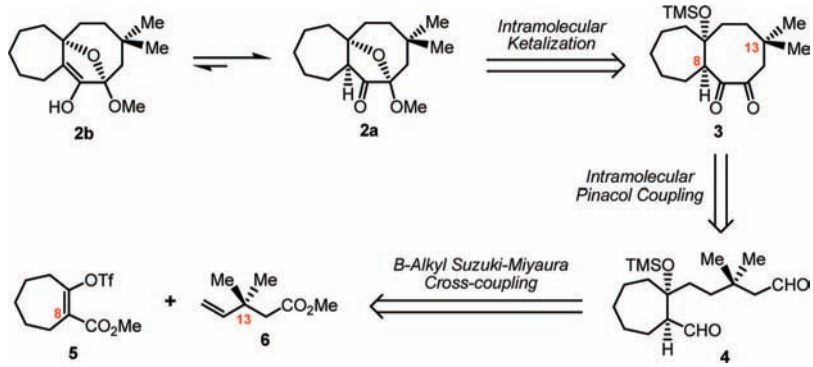
Scheme 1. Retrosynthetic Analysis of Tricycle **2a**/**2b**



mediated Claisen ring expansion technology.[7,8] Earlier studies by us likewise have demonstrated successful application of the thermally induced Claisen rearrangement to construction of the CDEF ring system of lancifodilactone G (**1**).[9,10] However, this methodology suffers from harsh reaction conditions, and its TRIBAL-induced alternative proved not to be suitable for acid-labile substrates.[9] As a result, we were prompted to design a mild synthetic alternative to reach the eight-membered core of lancifodilactone G (**1**).

At the outset, we speculated that lancifodilactone G (**1**) exists in its enol form due in part to the potential hydrogen-bond network between the enol proton and the G ring oxygen atom, together with associated conformational issues. For these reasons, we devised instead a realistic model aimed at preparation of the potentially interconvertible ketone **2a** and enol **2b**. Retrosynthetically, **2a**/**2b** were considered accessible via intramolecular ketalization of α-diketone **3** as depicted in Scheme 1. The plan involved the building of **3** from dialdehyde **4** via SmI_2-mediated pinacol macrocyclization as the key strategic step.[11] SmI_2-mediated pinacol macrocyclization reactions of keto aldehydes have been inadequately utilized for the construction of eight-membered rings. Further, to the best of our knowledge, no one has utilized this particular dialdehyde reduction in the area of natural product synthesis.[12] Finally, dialdehyde **4** can be traced back to vinyl triflate **5** and terminal olefin **6** by means of *B*-alkyl Suzuki−Miyaura cross-coupling.[13] It is imperative to note that the olefin partner **6** was judiciously chosen in the hope to induce the *gem*-dimethyl effect[14] and hence facilitate the subsequent pinacol ring closure operation. In this Letter, we report the synthesis of an exemplary oxatricyclic medium-sized CDE ring system of lancifodilactone (**1**).

The synthesis commenced with preparation of enol triflate **5** (Scheme 2). To this end, treatment of cycloheptanone (**7**) with LiHMDS and $NCCO_2Me$, followed by reaction with Tf_2O delivered **5**. The next task called for *B*-alkyl Suzuki−Miyaura cross-coupling.[13] Despite the steric bulk of the geminal dimethyl groups housed in the olefin partner **6**, the hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeded smoothly at ambient temperature to give the corresponding *B*-alkylboron species.[15] The latter was subjected to the palladium-catalyzed Suzuki reaction in the presence of K_3PO_4 as base to yield the cross-coupling product **8** in excellent yield (Scheme 2). The proper oxidation state of the tetrasubstituted olefin **8** was set up using *m*CPBA to furnish the epoxide **9** efficiently.

The next task turned to reductive opening of the epoxide **9**. Delightfully, SmI_2-induced reduction of α,*β*-epoxy ester **9** in the presence of water as a proton source yielded *β*-hydroxy ester **10** in a highly regioselective fashion by adaptation of a modification of Inanaga's procedure.[16,17]

(9) For thermal Claisen ring expansion for synthesis of the CDEF ring system of **1**, see: Paquette, L. A.; Lai, K. W. *Heterocycles* **2009**, accepted.

(10) For previous applications of Claisen ring expansion for construction of eight-membered ring systems from our laboratory, see: (a) Paquette, L. A. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, England, 1994; pp 313−336. (b) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7352. (c) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610. (d) Paquette, L. A.; Sweeney, T. J. *Tetrahedron* **1990**, *46*, 4487. (e) Friedrich, D.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 3831. (f) Paquette, L. A.; Friedrich, D.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 3841. (g) Paquette, L. A.; Philippo, C. M. G.; Vo, N. H. *Can. J. Chem.* **1992**, *70*, 1356. (h) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021.

(11) For a review of intramolecular SmI_2-mediated reactions, see: (a) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (b) For a comprehensive review of SmI_2 chemistry, see: Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351.

(12) The only report that utilizes the pinacol macrocyclization of dialdehydes is found in the synthesis of a C8-carbasugar. See: Andriuzzi, O.; Gravier-Pelletier, C.; Vogel, P.; Merrer, V. L. *Tetrahedron* **2005**, *61*, 7094.

(13) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Org. Chem.* **1989**, *111*, 314. For a review of the *B*-alkyl Suzuki−Miyaura reaction in natural product synthesis, see: (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

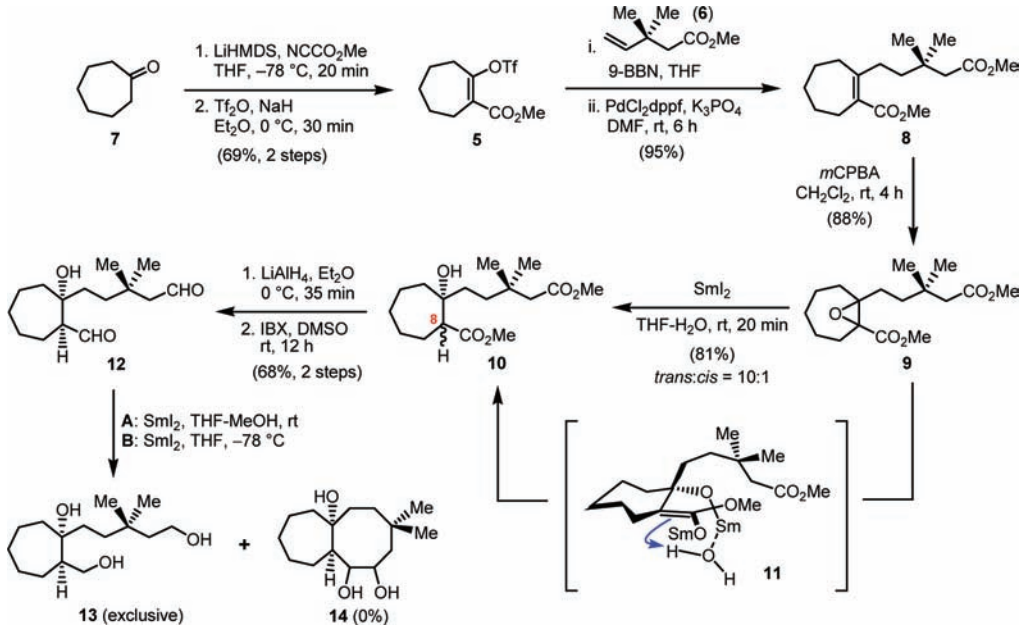
(14) Apart from inducing the *gem*-dimethyl effect, the quaternary carbon center at C-13 (ref 18) in **6** was intended to impose a steric environment comparable to that in **1**. For the *gem*-dimethyl effect, see: (a) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701. (b) Galli, C.; Giovannelli, G.; Illuminati, G.; Mandolini, L. *J. Org. Chem.* **1979**, *44*, 1258.

(15) (a) Brown, H. C.; Gundu Rao, C.; Kulkarni, S. U. *Synthesis* **1980**, 151. (b) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.

(16) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437. (b) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.

(17) In contrast to Inanaga's work (ref 16a), we found that no chelating agent such as DMAE (*N*,*N*-dimethylaminoethanol) is required to suppress the formation of the unwanted α-hydroxy ester.

Scheme 2. Attempted Synthesis of Cyclooctane-1,2,4-triol **14**



Most notably, a good diastereoselectivity ratio of 10:1 was seen. Though of no major consequence to the ensuing synthetic operations, structural characterization was thereby facilitated. The stereochemistry (C-8)[18] of the major isomer **10a** was established by NMR data analysis involving the advanced compound **2a**. To explain the observed *trans*-selectivity of this reaction, we propose the plausible chelated transition structure **11**.[19] The model postulates coordination of water to the Sm(III) alkoxide and internal delivery of the acidic proton to the α-face of the Sm(III) enolate. Full reduction of diester **10a** with $LiAlH_4$ proceeded smoothly and gave the triol which without purification was subjected to IBX oxidation, leading to the cyclization precursor **12** in reasonably good yield.

With the key dialdehyde **12** in hand, we were at the stage to attempt the SmI_2-mediated macrocyclization. Disappointingly, exposure of **12** to SmI_2 in a solvent mixture of THF−MeOH at ambient temperature led exclusively to the exhaustively reduced product **13** instead of to the desired cyclooctane-1,2,4-triol **14**. A decrease in reaction temperature continued to furnish **13** instantaneously as the only product (^{1}H NMR and HRMS analyses). We are not certain why this phenomenon materialized in this case but herein propose that the internal tertiary hydroxyl group within **12** may act as a bulky Lewis base capable of displacing the labile iodide ligands on the oxophilic SmI_2 to the outer sphere. In addition, chelation with the carbonyl oxygens could increase the reducing power of the samarium reagent. To probe this hypothesis, the interfering hydroxyl moiety was masked with a silyl protecting group, and the alternative routing described in Scheme 3 was developed.

As illustrated, generation of the TMS ether followed by sequential $LiAlH_4$ reduction and IBX oxidation constituted a three-step sequence that yielded **4** efficiently. Our first attempt to induce pinacol macrocyclization of **4** with SmI_2 at low temperature (−78∼0 °C) only returned starting material. This result was expected in that SmI_2 alone does not reduce aldehyde functionalities at low temperature. Actually, we know that additives such as hexamethylphosphoramide (HMPA) are capable of raising the reducing property of SmI_2.[20] Gratifyingly, the pinacol macrocyclization of **4** with HMPA (10 equiv) as additive and *t*-BuOH (2.5 equiv) as a proton source afforded the desired 8-membered compound **15** as an inseparable mixture of diastereoisomers. To facilitate structural characterization, the crude diol **15** was carried forward into the subsequent IBX oxidation step, and diketone **3** was obtained in 32% yield (65% brsm) over two steps.[21] It is noteworthy that recourse to high dilution techniques (0.003 M) effectively eliminates operation of the intermolecular pinacol process and gives rise very predominately to α-diketone **3**.

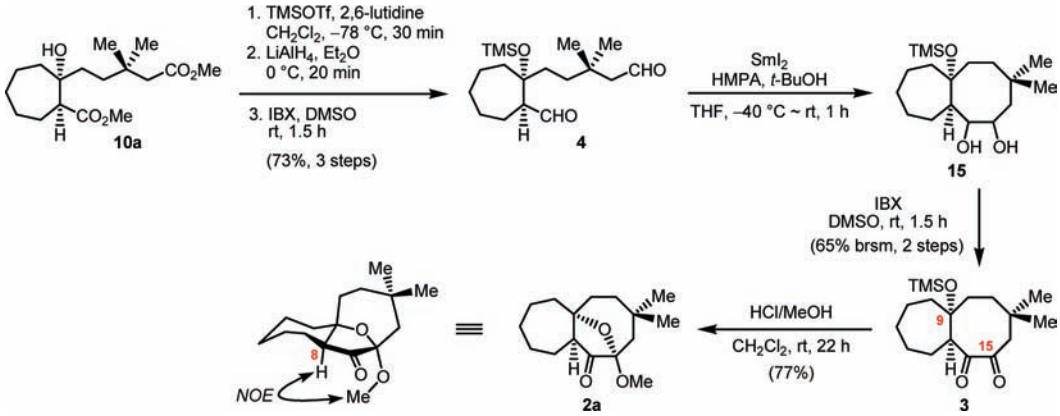
(18) The carbon numbering is according to the system used for the parent natural product in ref 1.

(19) We have found no precedent in an attempt to explain the stereochemical outcome of the SmI_2-mediated epoxide opening of α-substituted α,β-epoxy carbonyl compounds.

(20) The role of HMPA in SmI_2-promoted reactions is extensively documented. See: (a) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717. (b) Hou, Z.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1205. (c) Shotwell, J. B.; Sealy, J. M.; Flowers, R. A., II. *J. Org. Chem.* **1999**, *64*, 5251. (d) Shabangi, M.; Kuhlman, M. L.; Flowers, R. A., II. *Org. Lett.* **1999**, *1*, 2133. (e) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2000**, *122*, 7718.

(21) Oxidation of diol **15** using the modified Swern conditions (DMSO and trifluoroacetic anhydride) furnished the vicinal dione **3** in only 16% yield (**4** → **3**, 2 steps). This unsatisfactory result may be attributed in part to formation of the enol tautomers of **3**. Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851.

Scheme 3. Synthesis of Tricycle **2a**



The final task called for introduction of an oxa-bridge across C9−C15 in **3**. Removal of the labile TMS protecting group within **3** with acidic methanol provided the tertiary alcohol (not shown) which was subject to in situ methoxy ketalization to deliver the tricycle **2a** as the sole isolatable product. No enol isomer **2b** was detected. The chemical structure of **2a** and its relative stereochemistry were unambiguously confirmed by virtue of 1D and 2D NMR experiments. In particular, mutual NOE interactions were noted between the bridgehead hydrogen at C-8 and the ketal methoxy group, and thus indirectly elucidated the stereochemical outcome on the SmI_2-mediated epoxide opening step (**9** → **10**, see Scheme 2).

In summary, a unique route for acquiring the polyfused medium-sized CDE ring system of lancifodilactone G (**1**) has been developed. The key steps involve a *B*-alkyl Suzuki−Miyaura cross-coupling reaction and SmI_2-mediated pinacol macrocyclization. These combined methodologies warrant more effective application to the synthesis of members of the lancifodilactone family and other cyclooctane-containing natural products. The discovery that a neighboring tertiary hydroxyl group can profoundly boost the reducing capability of SmI_2 and foster aldehyde reduction at low temperatures holds particular interest. Follow-up investigations of this reactivity profile are being pursued, and its deeper integration into the crafting of **1** is currently underway.

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Supporting Information Available: Experimental procedures and spectral data for all stable new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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