ORGANIC LETTERS

2008
Vol. 10, No. 11
2115−2118

Stereocontrolled Synthesis of the Sterically Encumbered F Ring of Lancifodilactone G

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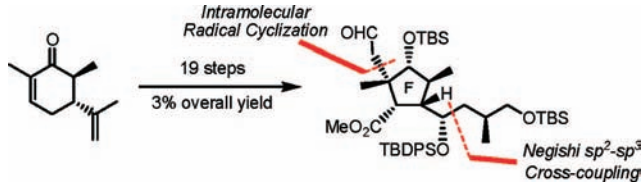
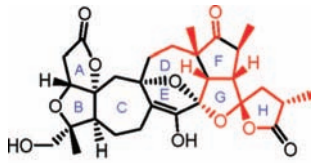
Received February 22, 2008

ABSTRACT



A stereochemically linear strategy has been developed to prepare the heavily congested F-ring sector of lancifodilactone G (1) from commercially inexpensive (*R*)-carvone. Prominent operations in our synthesis include Negishi-type sp²−sp³ cross-coupling and intramolecular free-radical cyclization for the purpose of appending the sidearm links of the D and H rings onto the F platform.

In the preceding letter,[1] a concise synthesis of the ABC network of lancifodilactone G (**1**, Figure 1) was disclosed.[2] Needless to say, our attention subsequently shifted to the eastern sector of this intricate target. Inspection of its right-hand region revealed a highly congested F ring which held significant hurdles for chemical synthesis. Also recognized was a 2-fold anomerically stabilized bis-spiro system[3] having anticipated sensitivity to acidic and/or basic conditions. In so doing, it became paramount that select pendant side chains be incorporated onto the F platform as progress was realized. Herein, a synthesis of the key building block **2** with full utilization of stereochemically linear tactics is described.[4]



Lancifodilactone G (**1**)

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

A retrosynthetic overview of the significant strategic operations is depicted in Scheme 1. According to our plan, **2** was to arise from cyclic acetal **3** whose stereogenic centers at C13 and C14 were to be properly established by intramolecular free-radical cyclization[5] of bromide **4**, a step envisioned to enable controlled introduction of the challenging quaternary carbon center (C13)[6] in this compact system. Compound **4** was to be derived from aldehyde **5** by way of conventional procedures. Application of Negishi sp²−sp³

(1) For our preliminary results on synthesis of ABC fragment of lancifodilactone G, see: Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 2111–2114.

(2) 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.

(3) For a review of anomeric effects in natural product synthesis, see: Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.

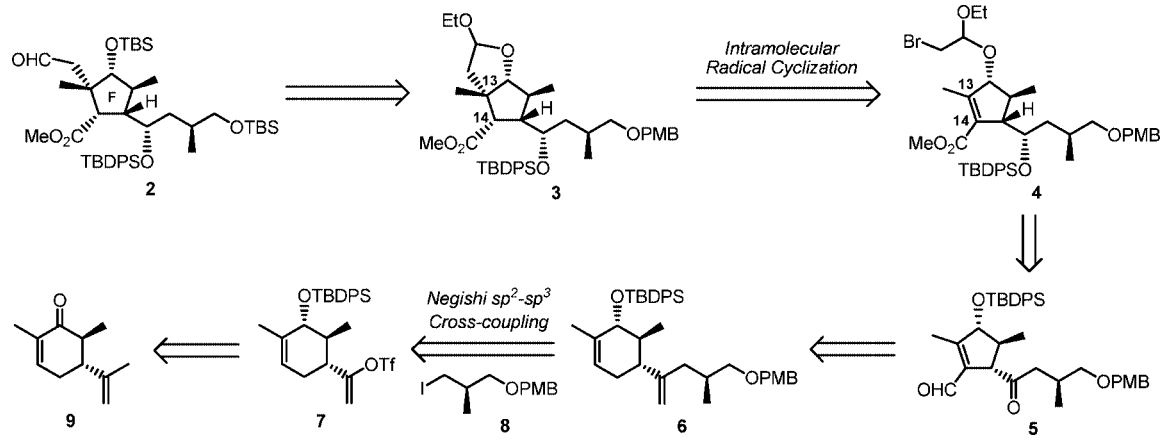
(4) For an early application of stereochemically linear strategy, see: Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269.

(5) (a) Stock, G.; Mook, R.; Biller, S. A., Jr.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(6) The carbon numbering is accorded to the system of the parent natural product in ref 2.

10.1021/ol800419v CCC: $40.75
Published on Web 05/03/2008

Scheme 1. Retrosynthetic Analysis of Aldehyde **2**

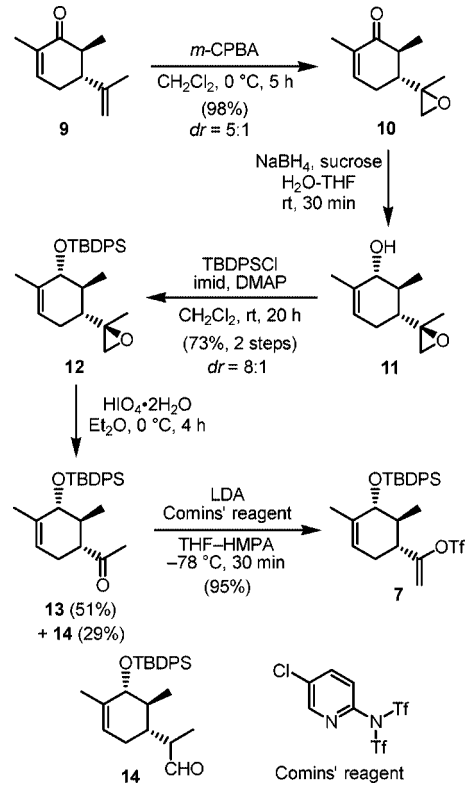


cross-coupling technology[7] to append the known iodide **8**[8] to vinyl triflate **7** was expected to provide access to **6**; the latter in turn was thought to be well suited to ring contraction via a series of steps designed to deliver cyclopentene **5**.

Our point of departure entailed the stereoselective epoxidation[9] of the readily available carvone derivative **9**.[10] The use of *m*-CPBA afforded a 5:1 mixture of epoxides in near quantitative yield[11] (Scheme 2). The major isomer **10** was subjected to sucrose-controlled $NaBH_4$ reduction[12] (dr = 8:1), and the resultant alcohol **11** was protected with TBDPSCl to give the corresponding silyl ether **12** in stereochemically homogeneous form after chromatographic purification. Oxidative cleavage of the epoxide **12** was achieved using periodic acid as the only workable conditions uncovered and formed the desired methyl ketone **13** accompanied by a significant amount of unwanted aldehyde **14** which originated from facile [1,2] hydride shift.[13] The requisite vinyl triflate **7** was prepared directly from methyl ketone **13** using Comins' reagent in combination with LDA and HMPA.[14]

With vinyl triflate **7** in hand, the time had arrived to effect cross-coupling to the organozinc species **15** as illustrated in Scheme 3.[7] Extensive optimization was necessary to realize a high yield. Especially critical was the premixing of iodide **8**[8] with $ZnCl_2$ prior to addition of three equivalents of *t*-BuLi. This finding implicates the *tert*-butylzinc species **15** as the actual alkyl donor in this reaction.[15] Another factor essential to success was the utilization of lithium chloride in order to mediate the cross-coupling under mild conditions.[16,17]

Scheme 2. Preparation of Vinyl Triflate **7**



A further central strategic transformation consisted of contracting the six-membered ring present in **6** into the five-membered keto aldehyde **5** by adoption of Schreiber's two-directional tactic.[18] The three discrete operations involved the bis-dihydroxylation of diene **6**,[19] ensuing oxidative cleavage of tetraol **16** to generate **17**, and intramolecular aldol

(7) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(8) Heckrodt, T. J.; Mulzer, J. *Synthesis* **2002**, 1857.

(9) Smitt, O.; Högberg, H.-E. *Tetrahedron* **2002**, *58*, 7691.

(10) Gabriëls, S.; Haver, D. V.; Vandewalle, M.; Clercq, P. D.; Verstuyf, A.; Bouillon, R. *Chem. Eur. J.* **2001**, *7*, 520.

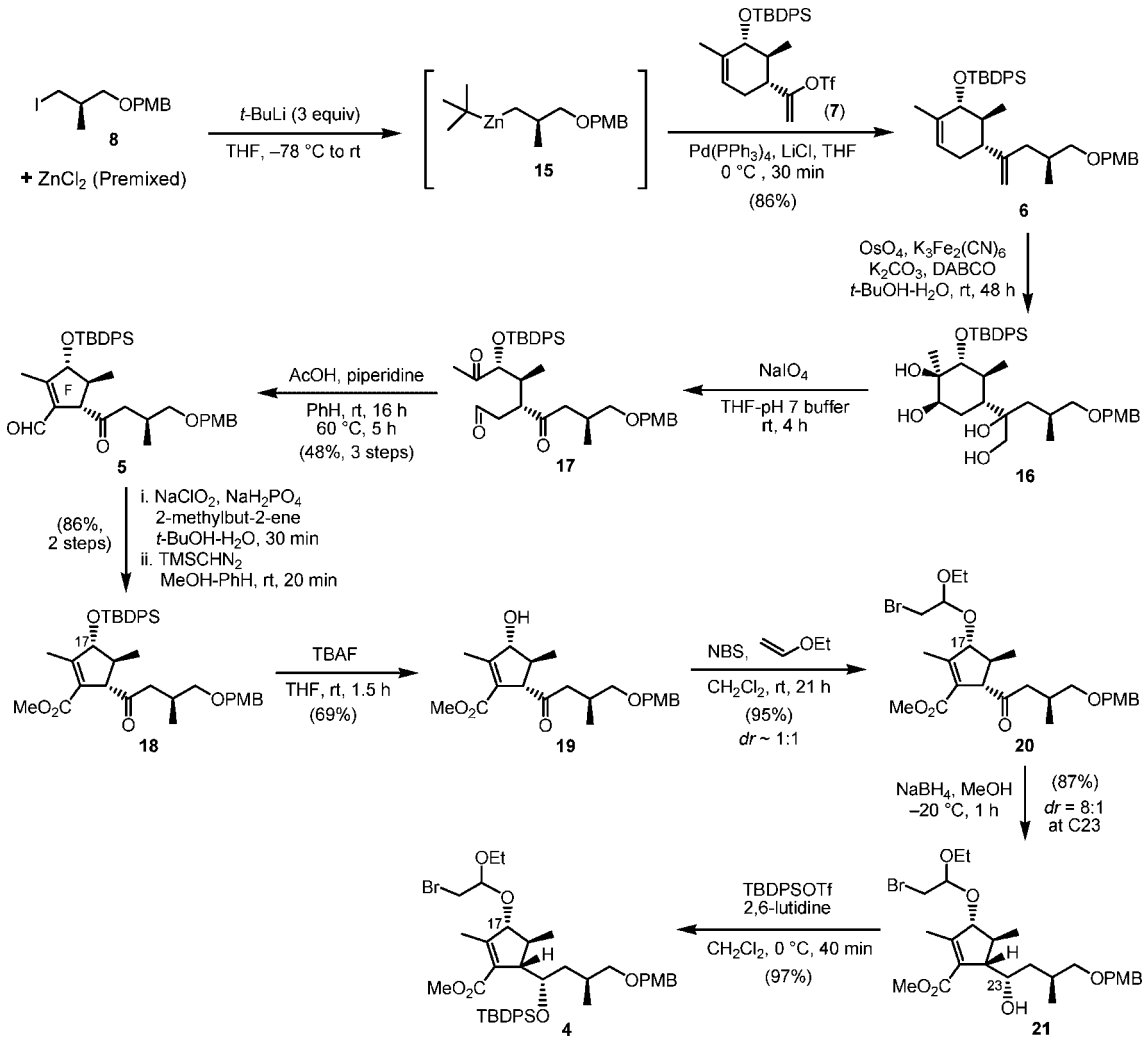
(11) The stereochemical outcome was not determined. The major isomer was separated by column chromatography and was used for the subsequent reduction reaction.

(12) Denis, C.; Laignel, B.; Plusquellec, D.; Le Marouille, J.-Y.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53.

(13) For periodic acid oxidative cleavage, see: Davisson, V. J.; Neal, T. R.; Poulter, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 1235.

(14) (a) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

Scheme 3. Preparation of Bromo Acetal **4**



cyclization—elimination under Corey's conditions.[20] This sequence delivered the targeted keto aldehyde in 48% overall yield with only a single column chromatographic purification. Subsequent Pinnick oxidation[21] of **5** delivered the corresponding carboxylic acid which was treated with TMSCHN$_2$[22] to afford methyl ester **18**. Removal of the TBDPS protecting group within **18** with TBAF resulted in liberation of the secondary alcohol **19**, the action of NBS and ethyl vinyl ether on which produced the bromo acetal **20**. Chelation-controlled reduction of the ketone carbonyl in **20** with NaBH$_4$ at −20 °C in MeOH pleasingly gave the secondary alcohol **21** in 87% yield with 8:1 diastereoselectivity. Subsequent silylation of the resultant alcohol **21** with TBDPSOTf and 2,6-lutidine delivered the pivotal precursor **4**.

The next task was to set up the two continuous stereogenic centers at C-13 and C-14 of **4** via an intramolecular free-radical cyclization (Scheme 4).[5] Treatment of bromide **4** under typical radical conditions (*n*-Bu$_3$SnH and AIBN) made available the sterically congested system **3** as an inseparable mixture in good yield. The stereoselectivity encountered in this step can be rationalized in terms of intermediate **22**. Approach of the radical-bearing side chain to the acceptor π-bond from the bottom face sets up the quaternary center at C13 and precedes final delivery of a hydrogen atom from the more accessible convex face.[23]

(15) For precedent speculation regarding the formation of mixed *tert*-butylalkylzinc species in the Negishi reaction, see: Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.

(16) For use of LiCl as additive, see: Piers, E.; Friesen, R. W.; Keay, B. A. *Tetrahedron* **1991**, *47*, 4555.

(17) The cross-coupling product **6** was contaminated with the inseparable deiodination compound derived from **8**.

(18) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–19.

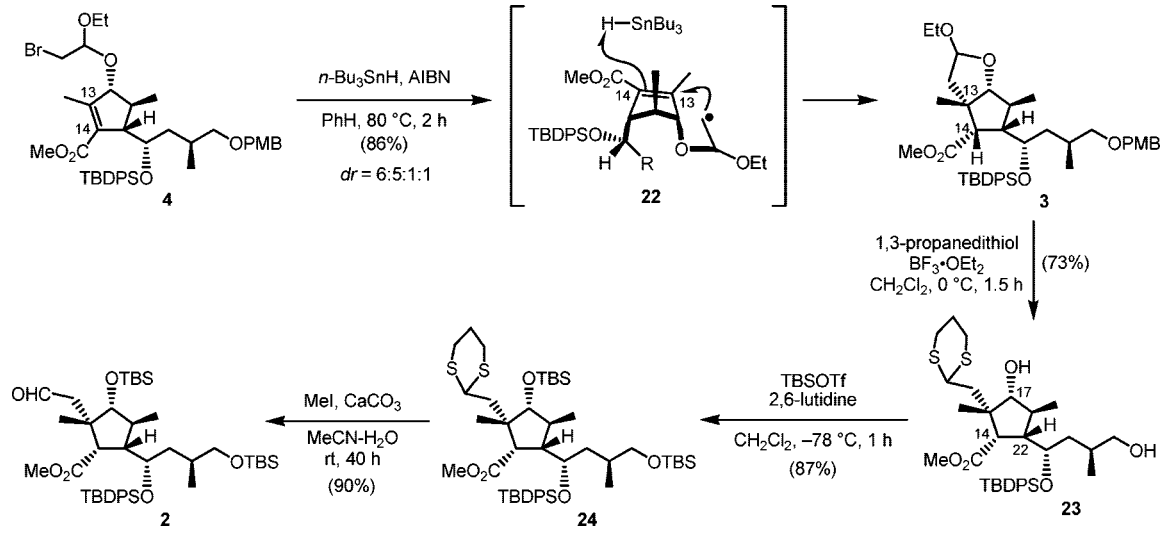
(19) (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) The use of 1,4-diazabicyclo[2.2.2]octane (DABCO) was essential to mediate dihydroxylation of the 1,1′-disubstituted olefin in **6**; see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(20) Corey, E. J.; Danheiser, R. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.

(21) Balkrishna, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(22) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

Scheme 4. Preparation of Aldehyde **2**



Formation of dithioketal **23** was achieved using 1,3-propanedithiol and BF_3•OEt_2 so as to promote concomitant deprotection of the PMB functional group and make diol **23** available as a single diastereoisomer in 77% isolated yield.[24,25] The stereochemical assignment to **23** was unambiguously corroborated on the basis of extensive COSY and NOESY NMR experiments.[26] The pair of hydroxyl groups within **23** were simultaneously masked as in **24**, with the ultimate aim of streamlining steps in the eventual end game. The subsequent dethioacetalization of **24** in the presence of excess MeI and $CaCO_3$ afforded the target aldehyde in excellent yield on modest scale.

In summary, a synthesis of the sterically congested F ring component **2** has been successfully realized from the known carvone derivative **9**. The present study underscores the utility of Smith's stereochemically linear and Schreiber's two-directional strategies. The routing involved 19 steps with an overall yield of 3%. Highlights of the synthesis include Negishi sp^2-sp^3 cross-coupling reaction, ring contraction sequence (**6** → **5**) and stereoselective intramolecular free radical cyclization. Pursuit of the union of aldehyde **2** with the ABC segment of lancifodilactone G is currently in progress.

Acknowledgment. We thank The Ohio State University for partial financial support and Robert Dura (The Ohio State University) for assistance with the NOE and 2D NMR experiments.

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.

OL800419V

(23) The stereo-outcome of this process was elucidated after the subsequent dithiane removal step.

(24) Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994**, *35*, 4271.

(25) The minor diastereoisomers were easily separated during column chromatography.

(26) Diagnostic NOE enhancements between H-14 and H-17, H-14 and H-22, and H-17 and H-22 were observed.