J|A|C|S
COMMUNICATIONS

Published on Web 10/27/2005

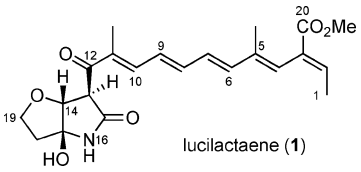
Total Synthesis of Lucilactaene, A Cell Cycle Inhibitor Active in p53-Inactive Cells

Robert S. Coleman,* Matthew C. Walczak, and Erica L. Campbell

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210-1185

Received September 9, 2005; E-mail: coleman@chemistry.ohio-state.edu

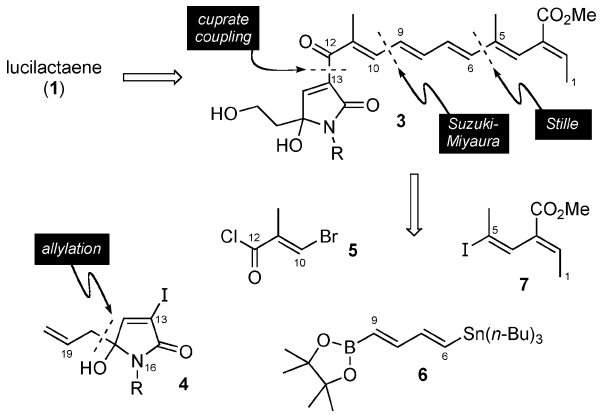
Fungi of the genus *Fusarium* have been a rich source of biologically active natural products. In 2001, Osada and co-workers[1] reported the isolation of lucilactaene (**1**) from a strain of *Fusarium* and demonstrated this cytotoxic natural product induced cell cycle to arrest in a p53-independent manner in cells possessing a temperature-sensitive p53 protein.[2] Lucilactaene is related to other *Fusarium* natural products, including epolactaene,[3] fusarins A,[4] C,[5] D,[6] and F,[7] L-755,807,[8] and NG-391,[9] which possess a γ-lactam nucleus with a polyunsaturated side chain. Hayashi and co-workers demonstrated that lucilactaene occurs naturally as the racemate by synthesis of **1** from NG-391 in seven steps (3.7% overall).[10]



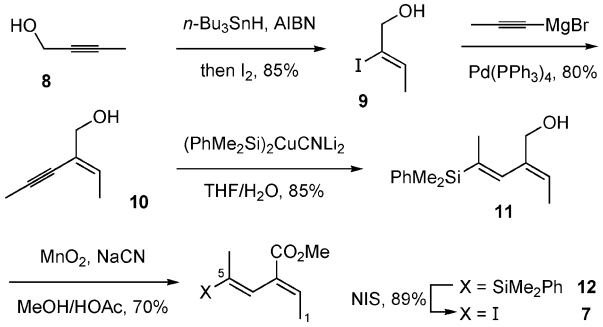
The tumor suppressor gene p53 is mutated and inactive in many human tumors.[11] This gene normally controls cell cycle progression and is responsible for a wide variety of processes that are critical for maintenance of cell integrity, including apoptosis and DNA repair.[12] In programmed cell death, p53 provides a key link between nuclear damage and mitochondrial release of further signaling molecules. In cells lacking functional p53, control of cell division is lost, and such cells are often resistant to chemotherapy because of defects in the damage-induced apoptotic pathway due to lack of p53 function.[13] Agents that reestablish or mimic p53 function could be useful in cancer therapy by restoring the normal apoptotic p53 response to DNA damage.[14]

Our strategy for the synthesis of lucilactaene was formulated to achieve maximum convergence. Late-stage conjugate addition of the primary alcohol of **3** would form the tetrahydrofuran ring. Under thermodynamic control, this reaction should provide the more stable *cis*-fused ring system with the pentaenone side chain in the pseudoequatorial position. The 2-hydroxyethyl side chain of **3** would arise from the alkene of **4**, the product of allylation of an N-protected iodomaleimide. Introduction of the pentaene side chain would rely on a convergent series of cross-coupling reactions between olefin partners **5**, **6**, and **7**. Cuprate-coupling[15] between C12 of acid chloride **5** and C13 of iodide **4** would effect ketone installation; Stille coupling[16] of dienyl iodide **7** with the C6 vinyl stannane of the dissymmetrically substituted bis-metalated 1,3-butadiene **6**[17] would serve as a linchpin in the assembly of the terminal tetraene fragment of **3**; Suzuki-Miyaura coupling[18] of the C9 vinyl boronate of **6** with C10 of vinyl bromide **5** will accomplish construction of the C1−C12 pentaene side chain. The synthesis of **1** would result from an orchestrated series of sp^2-sp^2 bond formation events within a triply convergent synthetic strategy [(**6** + **7**) + (**4** + **5**)]. Herein, we report the total synthesis of lucilactaene.

The C1−C5 terminal dienoate fragment **7** was synthesized in five steps (36% overall) from 2-butyn-1-ol (**8**) by an efficient and

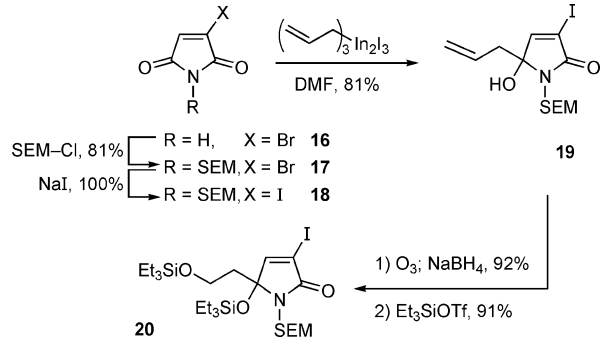


stereocontrolled reaction sequence. Regioselective *anti*-hydrostannylation[19] followed by in situ iododestannylation of the resulting vinylstannane (I_2, CCl_4, −10 °C, 10 min) provided allylic alcohol **9**, predominantly as the *Z*-isomer (96:4 *Z*/*E*). Palladium-promoted coupling of propynylmagnesium bromide and the vinylic iodide of **9** (THF, 50 °C, 4 h)[20] afforded enyne **10**. *Syn*-selective silylcupration[21] of the alkyne triple bond in the presence of water to effect protonolysis of the intermediate vinylcuprate (−10 °C, 3 h) provided silyldiene **11** as a separable mixture of stereoisomers (85:15). Corey-Ganem oxidation[22] of **11** afforded methyl dienoate **12**. Subsequent iododesilylation of **12** (2,6-lutidine, $(CF_3)_2CHOH$, −10 °C, 90 s)[23] installed the C5 iodide to afford the target **7**.

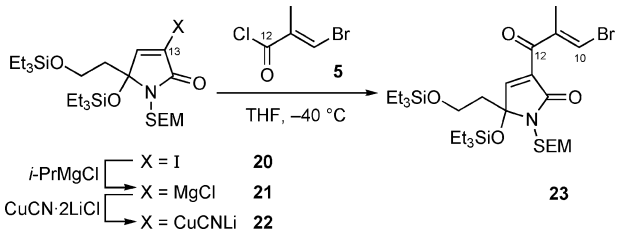


The heterocyclic fragment **20** was synthesized in high yield from bromomaleimide (**16**).[24] Protection of the imide nitrogen with the trimethylsilylethoxymethyl (SEM) group[25] (*i*-Pr_2NEt, DMF, −45 °C, 3 h) afforded **17**. Bromide to iodide conversion (5 equiv of NaI, acetone, reflux, 12 h) quantitatively afforded protected iodomaleimide **18**. Regioselective allylation of the carbonyl distal to the iodine was achieved using allylindium in DMF (−15 °C, 3 days)[26] to afford **19** as a separable 8:1 mixture of regioisomers. Ozonolysis of the terminal alkene (O_3, CH_2Cl_2, −78 °C) and reduction of the ozonide with sodium borohydride (CH_2Cl_2/MeOH, 0 °C, 2 h) afforded the corresponding diol, which was protected as the bis-triethylsilyl ether (2,6-lutidine, CH_2Cl_2, −45 to 25 °C, 2 h) to provide **20** in five steps (55% overall) from bromomaleimide.

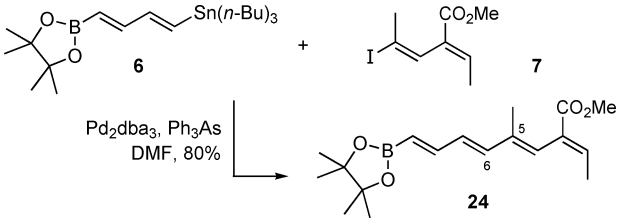
10.1021/ja056217g CCC: $30.25



Connection of the pyrroline core with the C12 acyl group of **5** was achieved using a cuprate/acid chloride coupling.[15] Formation of Grignard reagent **21** occurred upon reaction of iodide **20** with isopropylmagnesium chloride (THF, −60 °C, 20 min); transmetalation to the corresponding cuprate **22** occurred upon treatment with cuprous cyanide (−40 °C, 20 min). Reaction of cuprate **22** with acid chloride **5**[27] (−40 °C, 1 min) achieved formation of the C12−C13 bond and provided *β*-bromoenone **23** in good yield (65%). Compound **23** was the result of six synthetic transformations (36% overall) from bromomaleimide.

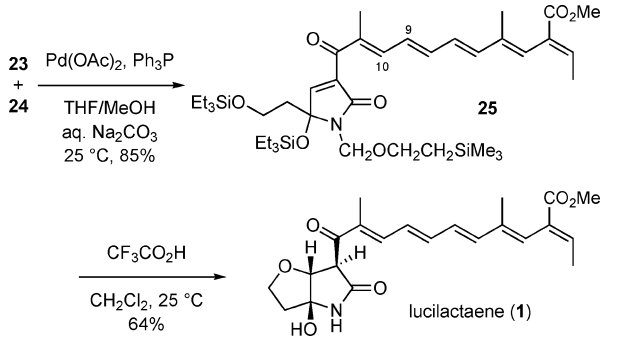


Two reasonable options existed for the ordering of the final alkene couplings as a consequence of the necessary connections between both C5−C6 and C9−C10: [diene **6** + diene **7**] + enone **23** or [enone **23** + diene **6**] + diene **7**. Chemoselective Stille coupling of the vinylstannane of **6**[28] with the vinyl iodide of **7** was achieved using triphenylarsine as the ligand for palladium (DMF, 25 °C, 18 h), and tetraene **24** was obtained in good yield. Tetraene **24** is six steps from 2-butyn-1-ol (29% overall).



Formation of the C9/C10 carbon−carbon bond by Suzuki-Miyaura coupling[18] of the vinyl boronate of tetraene **24** with the vinyl bromide of pyrrolinone **23** afforded pentaene **25**, completing construction of the lucilactaene framework. Final treatment of **25** with trifluoroacetic acid (25 °C, 5 h) effected removal of the silyl ethers and nitrogen protecting group, with concomitant conjugate addition of the primary alcohol, and afforded lucilactaene (**1**).

The synthesis of the *Fusarium* metabolite lucilactaene was achieved using a synthetic approach that is a significant departure from existing work in the field with respect to methodology, strategy, and synthetic efficiency.[10,29] The synthesis of **1** was achieved in eight linear steps and 17 total synthetic operations in 19% overall yield from commercially available compounds. The convergent nature of this synthetic route wherein three organometallic-based cross-coupling reactions of the four fragments [(iodide **20** + acid chloride **5**) + (diene **6** + diene **7**)] will allow for efficient, modular preparation of related agents for mechanistic evaluation.



Acknowledgment. This work was supported by a grant from the National Cancer Institute (NIH CA91904).

Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kakeya, H.; Kageyama, S.-I.; Nie, L.; Onose, R.; Okada, G.; Beppu, T.; Norbury, C. J.; Osada, H. *J. Antibiot.* **2001**, *54*, 850.
(2) Winters, Z. E.; Ongkeko, W. M.; Harris, A. L.; Norbury, C. J. *Oncogene* **1998**, *17*, 673.
(3) Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 733.
(4) Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1985**, *17*, 1189.
(5) Gelderblom, W. C. A.; Marasas, W. F. O.; Steyn, P. S.; Thiel, P. G.; van der Merwe, K. J.; van Rooyen, P. H.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1984**, 122.
(6) Gelderblom, W. C. A.; Thiel, P. G.; Van der Merwe, K. J. *Food Chem. Toxicol.* **1988**, *26*, 31−6.
(7) Savard, M. E.; Miller, J. D. *J. Nat. Prod.* **1992**, *55*, 64.
(8) Lam, Y. K. T.; Hensens, O. D.; Ransom, R.; Giazobbe, R. A.; Polishook, J.; Zink, D. *Tetrahedron* **1996**, *52*, 1481.
(9) Hayashi, Y.; Yamaguchi, J.; Shoji, M. *Tetrahedron* **2002**, *58*, 9839.
(10) Yamaguchi, J.; Kakeya, H.; Uno, T.; Shoji, M.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 3110.
(11) (a) Slee, E. A.; O'Connor, D. J.; Lu, X. *Oncogene* **2004**, *23*, 2809. (b) Hofseth, L. J.; Hussain, S. P.; Harris, C. C. *Trends Pharmacol. Sci.* **2004**, *25*, 177. (c) Levine, A. J.; Finlay, C. A.; Hinds, P. W. *Cell* **2004**, *116*, S67−S69. (d) Jäättelä, M. *Oncogene* **2004**, *23*, 2746.
(12) Norbury, C. J.; Zhivotovsky, B. *Oncogene* **2004**, *23*, 2797.
(13) Gasco, M.; Crook, T. *Drug Resist. Updates* **2003**, *6*, 323.
(14) Wang, W.; Rastinejad, F.; El-Deiry, W. S. *Cancer Biol. Ther.* **2003**, *2*, S55.
(15) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.
(16) (a) Stille, J. K.; Milstein, D. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Mitchell, T. N. *Synthesis* **1992**, 803. (d) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (e) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
(17) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289.
(18) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
(19) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.
(20) (a) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135. (b) White, J. D.; Hanselmann, R.; Wardrop, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1106.
(21) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
(22) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(23) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.
(24) Nicolaus, R. A.; Nicoletti, R. *Rend. Acad. Sci. Fis. Mater.* (Soc. Nazl. Sci., Napoli) **1959**, *26*, 148.
(25) Saito, S.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 9628.
(26) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633.
(27) Dzierba, C. D.; Zandi, K. S.; Möllers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 4711.
(28) 1,3-Butadiene **6** was prepared in 76% overall yield from propargyl aldehyde diethyl acetal by stannylcupration and Takai olefination; see ref 17.
(29) (a) Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998**, 313. (b) Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443. (c) Kuramochi, K.; Nagata, S.; Itaya, H.; Matsubara, Y.; Sunoki, T.; Uchiro, H.; Takao, K.-I.; Kobayashi, S. *Tetrahedron* **2003**, *59*, 9743.

JA056217G