A Unified Strategy for the Regiospecific Assembly of Homoallyl-Substituted Butenolides and γ-Hydroxybutenolides: First Synthesis of Luffariellolide

John Boukouvalas,* Joël Robichaud, François Maltais

Département de Chimie, Université Laval, Quebec City, Quebec G1K 7P4, Canada
Fax +1(418)6567916; E-mail: john.boukouvalas@chm.ulaval.ca

Received 31 May 2006

Abstract: The first synthesis of the antiinflammatory marine natural product luffariellolide has been achieved by a convergent pathway involving sp^3–sp^3 cross-coupling and silyloxyfuran oxyfunctionalisation as key steps. An illustration of the inherent flexibility of this strategy is provided by a simple synthesis of α,β-acariolide and its γ-hydroxylated derivative from a common silyloxyfuran precursor.

Key words: cross-coupling, Grignard reagents, lactones, oxyfunctionalisation, 2-silyloxyfurans

First isolated in 1987 from the Palauan sponge *Luffariella* sp.,[1] luffariellolide (**1**, Figure 1) is a non-steroidal sesterterpene γ-hydroxybutenolide that has attracted considerable synthetic[2,3] and biomedical[4] interest on account of its potent in vivo antiinflammatory activity through partially reversible inhibition of phospholipase A_2 (PLA_2).[1] The inhibition of PLA_2 by **1** and related natural products, such as manoalide,[5] does not appear to involve binding at the active site, but reaction of the aldehyde tautomer of the γ-hydroxybutenolide moiety with lysine residues at the surface of PLA_2, thereby preventing the enzyme from moving across membranes.[4a,6] Recently, luffariellolide and some of its relatives, e.g. acantholide B (**2**),[7] were found to exhibit broad antimicrobial activity in vitro,[7a] while the non-hydroxylated butenolide cyclolinteinone (**3**)[8] has been shown to reduce COX-2 and iNOS protein expression,[9] and may thus represent a new lead for the pharmacological control of inflammation.

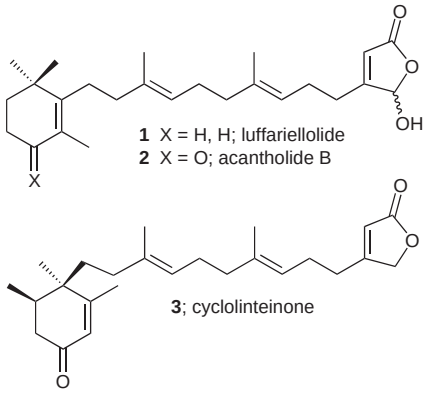
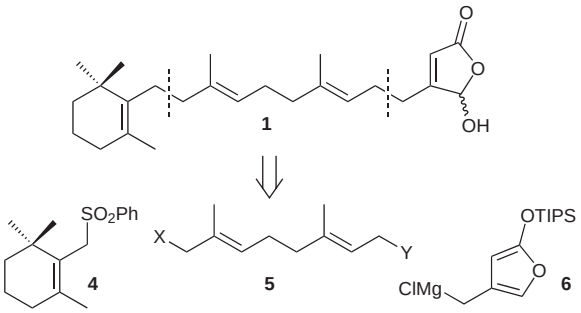


Figure 1

SYNLETT 2006, No. 15, pp 2480–2482
Advanced online publication: 08.09.2006
DOI: 10.1055/s-2006-949641; Art ID: S12006ST

Herein we report the first synthesis of luffariellolide (**1**) by a convergent, versatile strategy that should be useful for preparing related butenolides with or without a γ-hydroxyl substituent (cf. **2** and **3**).

As indicated in Scheme 1, we envisioned assembly of **1** by the union of fragments **4**–**6** and subsequent application of our silyloxyfuran oxyfunctionalisation protocol for unmasking the γ-hydroxybutenolide.[10,11] The versatility of this approach stems from the latent functionality hidden within the silyloxyfuran ring, making **6** the reagent of choice for either synthon **A** or **B** (Figure 2).



Scheme 1

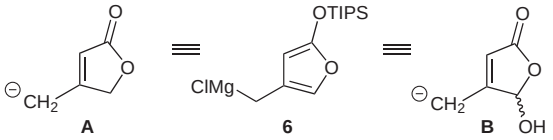
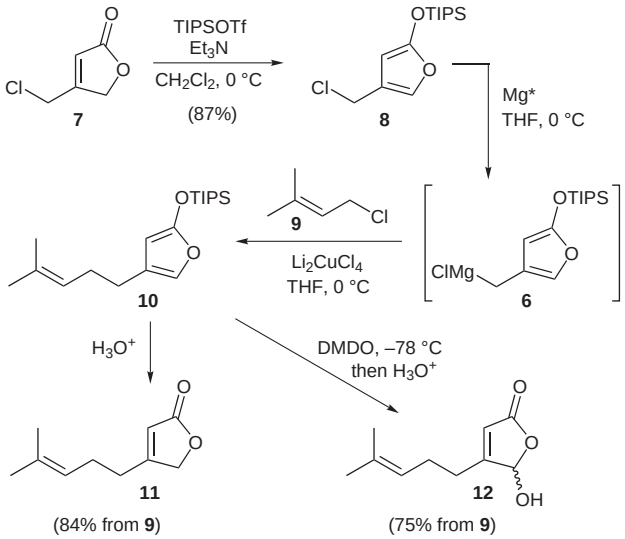


Figure 2

To probe the feasibility of this strategy, especially the crucial sp^3-sp^3 cross-coupling of the hitherto unknown Grignard reagent **6** with an allylic partner,[12] we initially chose as targets the structurally simple natural products α,β-acariolide (**11**)[13] and its γ-hydroxyl derivative[14] **12** (Scheme 2). The precursor of **6**, 4-(chloromethyl)-2-(triisopropylsilyloxy)furan (**8**),[15] was prepared from the readily available butenolide **7**[16] as previously described.[10] After several futile attempts to generate **6** from **8** by conventional means,[12] an effective procedure was ultimately found involving treatment of **8** with properly activated magnesium turnings in tetrahydrofuran at 0 °C.[17] Subsequent reaction of **6** with prenyl chloride (**9**) in the presence of Kochi's catalyst[18] (Li_2CuCl_4) at 0 °C for 20 minutes delivered silyloxyfuran **10** which was hydrolyzed to give α,β-acariolide (**11**) in 84% yield after chromatography.[17]

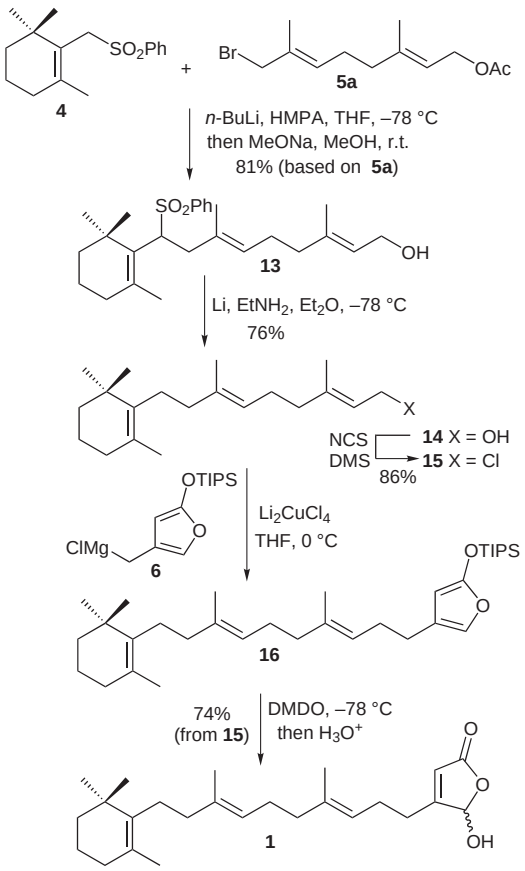
Alternatively, exposure of crude **10** to dimethyldioxirane (DMDO) in acetone at –78 °C and subsequent quenching with aqueous acetone/Amberlyst-15,[10] afforded hydroxybutenolide **12** in a yield of 75% over two steps.[17]



Scheme 2

Having established the viability of this strategy, the synthesis of luffariellolide began with the coupling of sulfone **4**[19] with bromide **5a**[20] (Scheme 3). Thus, reaction of the anion of **4** (1.5 equiv) with **5a** followed by treatment of the resulting mixture of alcohol **13** and its acetate with sodium methoxide in methanol, provided **13** in 81% yield. Removal of the phenylsulfonyl group was best accomplished by using the procedure of Sato[21] to furnish alcohol **14** which was subsequently converted to chloride **15** on treatment with *N*-chlorosuccinimide and dimethyl sulfide.[22] In a manner analogous to that described for the synthesis of hydroxybutenolide **12** (vide supra), coupling of **15** with **6** and ensuing oxyfunctionalisation of silyloxyfuran **16**[23] delivered luffariellolide (**1**, 74%) whose spectral properties (IR, ^{1}H and ^{13}C NMR) were in full agreement with those reported for authentic samples of the natural product.[1,7a]

In summary, the first synthesis of luffariellolide has been achieved in highly convergent fashion by the combined use of sp^3-sp^3 cross-coupling and silyloxyfuran oxyfunctionalisation. The strategy offers considerable flexibility, allowing regiospecific access to both butenolides and γ-hydroxylbutenolides. It should prove useful for preparing several related natural products[7,8] and new analogues for biological studies.



Scheme 3

Acknowledgment

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), Merck Frosst Canada and Eisai Research Institute (MA, USA) for financial support.

References and Notes

(1) Albizati, K. F.; Holman, T.; Faulkner, D. J.; Glaser, K. B.; Jacobs, R. S. *Experientia* **1987**, *43*, 949.
(2) (a) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2733. (b) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 7007.
(3) For the synthesis of a simpler luffariellolide relative (dictyodendrillin-B), see: Gerlach, K.; Hoffmann, H. M. R. *Synlett* **1998**, 682.
(4) (a) Potts, B. C. M.; Faulkner, D. J.; de Carvalho, M. S.; Jacobs, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 5093. (b) Mann, I. *Nature (London)* **1992**, *358*, 540. (c) Hope, W. C.; Chen, T.; Morgan, D. W. *Agents Actions* **1993**, *39*, C39. (d) Blanchard, J. L.; Epstein, D. M.; Boisclair, M. D.; Rudolph, J.; Pal, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2537. (e) Capasso, A.; Casapullo, A.; Randazzo, A.; Gomez-Paloma, L. *Life Sci.* **2003**, *73*, 611. (f) Izzo, I.; Avallone, E.; Della Monica, C.; Casapullo, A.; Amigo, M.; De Riccardis, F. *Tetrahedron* **2004**, *60*, 5587.
(5) For the synthesis of manoalide see: Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P. J. *J. Org. Chem.* **2003**, *68*, 4008; and references therein.
(6) Faulkner, D. J.; Newman, D. J.; Cragg, G. M. *Nat. Prod. Rep.* **2004**, *21*, 50.
(7) (a) Elkhayat, E.; Edrada, R.; Ebel, R.; Wray, V.; van Soest, R.; Wiryowidagdo, S.; Mohamed, M. H.; Müller, W. E. G.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 1809. (b) See also: Cao, S.; Foster, C.; Lazo, J. S.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2005**, *13*, 5094.

(8) Carotenuto, A.; Fattorusso, E.; Lanzotti, V.; Magno, S.; Carnuccio, R.; D'Acquisto, F. *Tetrahedron* **1997**, *53*, 7305; and cited references.
(9) D'Acquisto, F.; Lanzotti, V.; Carnuccio, R. *Biochem. J.* **2000**, *346*, 793.
(10) Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31.
(11) For previous applications in natural product synthesis, see: (a) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228. (b) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Basabe, P.; Hernández, F. A.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 369. (c) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.* **2004**, *69*, 9100. (d) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; García, N.; Escola, M. A.; Basabe, P.; Conde, A.; Moro, R. F.; Urones, J. G. *Synthesis* **2005**, 3301. (e) Boukouvalas, J.; Wang, J.-X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670.
(12) Tanis, S. P. *Tetrahedron Lett.* **1982**, *23*, 3115.
(13) Tarui, H.; Mori, N.; Nishida, R.; Okabe, K.; Kuwahara, Y. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 135.
(14) Díaz, J. G.; Barba, B.; Herz, W. *Phytochemistry* **1994**, *36*, 703.
(15) Data for **8**: TLC, R_f = 0.42 (100% hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (s, 1 H), 5.22 (s, 1 H), 4.38 (s, 2 H), 1.23 (m, 3 H) 1.09 (d, J = 7.1 Hz, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 129.6, 123.5, 84.2, 38.1, 17.4, 12.0.
(16) LaLonde, R. T.; Parakyla, H.; Hayes, M. P. *J. Org. Chem.* **1990**, *55*, 2847.
(17) **Experimental Procedure:** Magnesium turnings (212 mg, 8.70 mmol) were activated by washing successively with aq 10% HCl, H_2O, acetone and Et_2O, and dried in a vacuum desiccator. The turnings were then flame-heated under an atmosphere of dry nitrogen, allowed to cool, and 1,2-dibromoethane (75 μL, 0.87 mmol) and anhyd THF (4 mL) were added. The mixture was heated to reflux, stirred for 15 min, and the THF was cannulated out and replaced with anhyd THF (3 mL). The resulting suspension was cooled to 0 °C and silyloxyfuran **8** (835 mg, 2.89 mmol), which was purified on a short column (SiO_2) before use, was added. Stirring was continued at 0 °C for 1 h, at which time no more starting material was detected by TLC. Anhyd THF (2 mL) was added, and the mixture was divided into two equal parts and placed into two separate dry vials at 0 °C. In each vial was then added prenyl chloride (**9**; 80 μL, 0.70 mmol) at 0 °C, followed immediately by a solution of Li_2CuCl_4 (0.1 M, 350 μL, 0.035 mmol) in THF. Each reaction mixture was stirred for 20 min at 0 °C and then poured (in parallel fashion) into H_2O (50 mL) and Et_2O (50 mL), and a solution of aq sat. NH_4Cl was added until the two layers separated. The product was extracted with Et_2O (3 × 50 mL), washed with brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford silyloxyfuran **10** as a yellowish oil that was carried forward without further purification. TLC, R_f = 0.81 (EtOAc–hexanes, 1:9). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (s, 1 H), 5.12 (t, J = 7.0 Hz, 1 H), 5.02 (s, 1 H), 2.31 (m, 2 H), 2.18 (t, J = 7.3 Hz, 2 H), 1.66 (s, 3 H), 1.57 (s, 3 H), 1.24 (m, 3 H), 1.07 (d, J = 7.0 Hz, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 131.6, 127.5, 126.5, 123.9, 85.1, 28.1, 25.8, 25.5, 17.4, 15.1, 12.0.
Preparation of α,β-Acariolide (11): To a solution of **10** (112 mg) in acetone (10 mL) and H_2O (5 drops) was added Amberlyst-15 (25 mg) and the mixture was stirred at r.t. for 45 min. The resin was filtered, washed with acetone (15 mL), and the solvent was evaporated in vacuo. The resulting oil was purified by flash chromatography (EtOAc–hexanes, 15:85, then 2:8) to afford **11** as a colourless oil (98 mg, 84%); TLC: R_f = 0.24 (EtOAc–hexanes, 2:8), whose NMR data matched those reported in ref. 13.
Preparation of γ-Hydroxybutenolide 12: To a solution of **10** (112 mg) in anhyd CH_2Cl_2 (10 mL) at –78 °C was added an acetone solution of DMDO (ca. 0.1 M, 0.4 mL). The mixture was stirred at –78 °C for 1 h and concentrated in vacuo at –78 °C. The crude oil was dissolved in acetone (10 mL) and H_2O (5 drops) was added followed by Amberlyst-15 (25 mg). The mixture was stirred at r.t. for 1.5 h, the resin was filtered off, washed with acetone (15 mL), and the solvent was evaporated in vacuo. The resulting oil was purified by flash chromatography (EtOAc–hexanes, 2:8, then 25:75) to afford **12** as a colourless oil (88 mg, 75%); TLC: R_f = 0.32 (EtOAc–hexanes, 3:7), whose NMR data matched those reported in ref. 14.
(18) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(19) (a) Prepared in two steps from geranyl bromide: Torii, S.; Uneyama, K.; Ishihara, M. *Chem. Lett.* **1975**, 479. (b) For the coupling of sulfone **4** with allylic halides see: Jeong, Y. C.; Ji, M.; Lee, J. S.; Yang, J.-D.; Jin, J.; Baik, W.; Koo, S. *Tetrahedron* **2004**, *60*, 10181; and references therein.
(20) Prepared in two steps from geranyl acetate: Dauben, W. G.; Saugier, R. K.; Fleishhauer, I. *J. Org. Chem.* **1985**, *50*, 3767.
(21) Sato, K.; Inoue, S.; Onishi, A.; Uchida, N.; Minowa, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 761.
(22) For an alternative synthesis of alcohol **14** and its conversion to chloride **15**, see: Demotie, A.; Fairlamb, I. J. S.; Lu, F.-J.; Shaw, N. J.; Spencer, P. A.; Southgate, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2883.
(23) Data for **16**: TLC, R_f = 0.77 (100% hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.58 (s, 1 H), 4.94−5.21 (m, 3 H), 1.89−2.37 (m, 14 H), 1.53−1.65 (m, 11 H), 1.42 (m, 2 H), 1.17−1.31 (m, 3 H), 1.09 (d, J = 7.1 Hz, 18 H), 1.06 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 137.1, 135.9, 135.3, 127.6, 126.8, 126.5, 123.8, 123.5, 85.1, 40.2, 39.7, 39.6, 34.9, 32.6, 29.6, 28.5, 28.0, 27.8, 26.5, 25.9, 19.7, 19.4, 17.4, 15.9, 12.1, 10.5.