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Concise, regiocontrolled synthesis of yangjinhualine A

John Boukouvalas *, Lucas C. McCann

Département de Chimie, Université Laval, Quebec City, Que., Canada G1V 0A6

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ABSTRACT

The first synthesis of yangjinhualine A, a recently isolated α,β-disubstituted γ-hydroxybutenolide from the Chinese medicinal herb *Datura metel* L., has been accomplished in concise, entirely regiocontrolled fashion through the combined use of Suzuki–Miyaura cross-coupling and 2-silyloxyfuran oxyfunctionalization.

Datura metel L. (Solanaceae) is a shrubby perennial herb praised throughout Southern Asia for its therapeutic benefits.[1] In traditional Chinese medicine, its dried flowers, known as 'yangjinhua', have been prescribed since antiquity as a remedy for asthma, cough, convulsions, pain, and insanity.[1a] At present, yangjinhua is clinically used in China for the treatment of psoriasis.[2] Its antipsoriatic properties were recently shown to reside in the non-alkaloid fraction which displays strong anti-inflammatory and anti-anaphylactic activities.[2b,3]

In 2008, Feng and co-workers reported the isolation of a novel component of this fraction, named yangjinhualine A (**1**), along with some previously known terpenoids.[3] Structurally, **1** belongs to a growing family of naturally occurring α,β-disubstituted γ-hydroxybutenolides[4,5] that also includes antrocinnamomin D (**2**),[6] the microperfuranones (**3** and **4**)[7], and chloraniolide A (**5**)[8] (Fig. 1).

Only minute amounts of **1** could be obtained from the natural source (0.000027% of dry weight) after multiple chromatography steps.[3] Although its biological effects have yet to be investigated, many γ-hydroxybutenolides, including antrocinnamomin D (**2**),[6] are known to possess potent anti-inflammatory properties.[9] In fact, a founding member of this class, the marine natural product manoalide, has been evaluated in phase II clinical trials for the treatment of psoriasis.[10] Moreover, several γ-hydroxybutenolides are endowed with other significant biological properties,[4b] including antitumor,[9b] antidiabetic[11], and antifungal activities.[4c,g]

It comes as no surprise, then, that these molecules have attracted considerable attention by the synthetic community.[12,13] Even so, regiocontrolled access to unsymmetrically α,β-disubstituted γ-hydroxybutenolides is still a challenge,[14] as illustrated by Clive's synthesis of microperfuranone (**3**) from phenylsuccinic acid (6 steps, ca. 1% overall yield), which provides **3** together with its regiomer **7** (1:1 mixture) via oxidation of furan **6** (Eq. 1).[15] As yet, there have been no other reports on the synthesis of **3** or any of its relatives depicted in Figure 1.

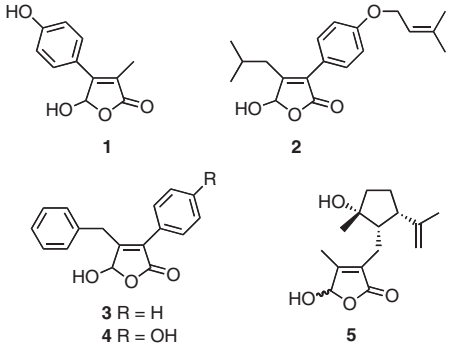
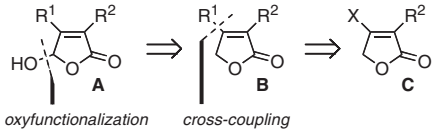


Figure 1. Yangjinhualine A (**1**) and related natural products.



Scheme 1. Plan for regiocontrolled assembly of **A**.

* Corresponding author. Tel.: +1 418 656 5473; fax: +1 418 656 7916.
E-mail address: john.boukouvalas@chm.ulaval.ca (J. Boukouvalas).

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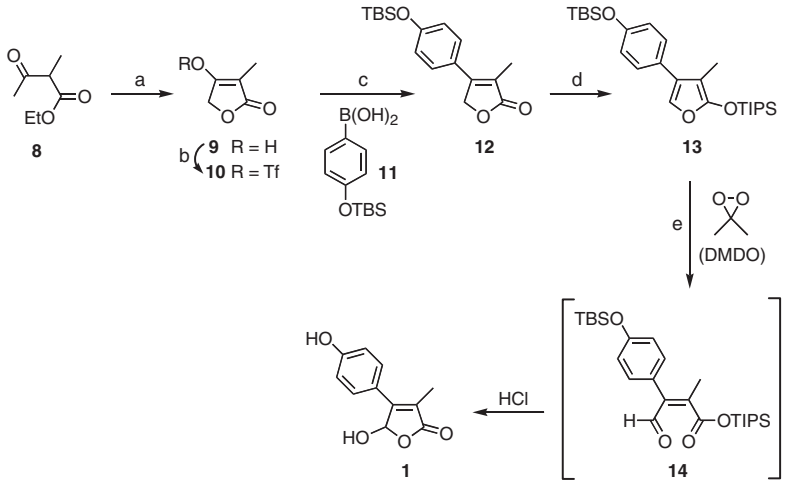
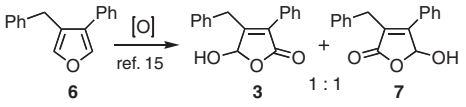


Scheme 2. Reagents and conditions: (a) (i) Br_2, H_2O/ice, 0 °C → rt; (ii) cat. HBr, 100 °C (80%, 2 steps, Ref. 19); (b) Tf_2O/Et_3N (1.2 equiv each), CH_2Cl_2, 0 °C → rt, 2 h (81%); (c) **11** (1.2 equiv), $Pd(OAc)_2/P(Cy)_3$ (0.05 equiv each), Na_2CO_3 (3.0 equiv), THF/H_2O (20:1), rt, 3 h (77%); (d) TIPSOTf/Et_3N (1.3 equiv each), CH_2Cl_2, −78 °C → rt, 1 h (74%); (e) (i) DMDO in acetone (ca. 0.07 M, 1.5–2 equiv), CH_2Cl_2, −78 °C → rt; 1 h; (ii) THF/aq 10% HCl (2:1), rt, 18 h (92%, one-pot procedure).



(1)

Clearly, the development of a more utilitarian, potentially general pathway to these natural products would be worthwhile. We envisaged that such targets (**A**) should be accessible with complete regiocontrol from butenolides **B** by application of our oxyfunctionalization protocol.[13a] Practical access to **B** was in turn envisioned from **C** (X = Br or OTf)[16,17] using cross-coupling tactics[18] (Scheme 1).

Described herein is the successful implementation of this strategy to the first synthesis yangjinhualine A (**1**). As shown in Scheme 2, our endeavor began with the conversion of inexpensive ethyl 2-methylacetoacetate (**8**) to methyltetronic acid **9** using the two-step procedure of Stoltz.[19] Treatment of **9** with triflic anhydride and triethylamine afforded the known triflate **10**[17a,b] in 81% yield after purification by flash chromatography.[20]

In keeping with our previous findings on the arylation of 3-chlorotetronic acid triflate,[18g] the Suzuki–Miyaura coupling of **10** with commercially available 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid (**11**, Aldrich) proceeded smoothly in the presence of $Pd(OAc)_2/P(Cy)_3$ at room temperature, albeit under slightly modified conditions (THF–water), to deliver butenolide **12** in a yield of 77%.[21]

Exposure of **12** to TIPSOTf/Et_3N provided 2-silyloxyfuran **13** (74%),[22] thereby setting the stage for one-pot oxyfunctionalization with concomitant deprotection of the phenol moiety. Thus, treatment of **13** with an acetone solution of dimethyldioxirane (DMDO)[13,23] gave the silyl ester **14**, which was not purified but subjected to the action of aq HCl in THF, to afford after flash chromatography racemic yangjinhualine A (**1**, 92%) whose ^1H and ^{13}C NMR properties[24] were in full agreement with those reported for the natural product.[3]

In conclusion, the first synthesis of yangjinhualine A has been accomplished in concise, entirely regiocontrolled fashion from commercially available starting materials (6 steps, 34% overall yield). Our synthesis makes this scarce natural product easily accessible for biological studies and demonstrates the serviceability of the general plan outlined in Scheme 1 for constructing unsymmetrically α,β-disubstituted γ-hydroxybutenolides. Further work in this area is underway and will be reported in due course.

Acknowledgments

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20. *Data for* **10**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (s, 2H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 160.5, 120.2, 117.1 (q, J_{CF} = 321 Hz), 66.8, 7.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.4; HRMS: Calcd for $C_6H_5F_3O_5S$ (*m/z*): 245.9810, Found: 245.9809. Although this is a known compound, its ^{13}C NMR data have not been reported (Refs. 17a,b).
21. *Data for* **12**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.03 (s, 2H), 2.13 (s, 3H), 0.99 (s, 12H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 157.9, 154.6, 129.0, 124.8, 121.0, 70.6, 25.8, 18.5, 10.7, −4.1; HRMS: Calcd for $C_{17}H_{24}O_3Si$ (*m/z*): 304.1495, Found: 304.1486.
22. *Data for* **13**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 2.00 (s, 3H), 1.30 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 18H), 1.03 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 153.9, 128.6, 128.3, 127.3, 126.9, 120.4, 91.4, 26.0, 18.5, 17.9, 12.6, 8.4, −4.1; HRMS: Calcd for $C_{26}H_{44}O_3Si_2$ (*m/z*): 460.2829, Found: 460.2837.
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24. *Data for* **1**: amorphous solid (mp 210–212 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.38 (d, *J* = 1.0 Hz, 1H), 2.06 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.5, 160.7, 156.8, 131.7, 123.7, 122.6, 116.7, 99.1, 10.6; HRMS: Calcd for $C_{11}H_{10}O_4$ (*m/z*): 206.0579, Found: 206.0579.