Total Syntheses of (±)-Vestitol and Bolusanthin III Using a Wittig Strategy

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Received 28 January 2011

Abstract: An intramolecular Wittig olefination was utilized to produce the key isoflav-3-ene intermediate needed to prepare (±)-vestitol and bolusanthin III in ca. 30% and 20% respective yields after eight steps.

Key words: vestitol, bolusanthin III, total syntheses, intramolecular Wittig olefination

Often displaying phytoestrogenic and antioxidant properties, polyphenolic isoflavans remain of interest for potential use as selective estrogen receptor modulators (SERM) and as cancer preventative agents.[1] Within this structural theme, vestitol and bolusanthin III (**1** and **2** in Figure 1, respectively) are a closely-related pair of isoflavonoids that differ in their degree of conformational rigidity and extent of conjugation between two similarly appended phenolic hydroxyl groups. The levorotatory[2] and dextrorotatory[3] enantiomers of isoflavan **1** have been isolated from various sources, as has its achiral isoflavene relative **2**.[4] Both (–)-**1** and **2** are present in the common licorice *Glycyrrhiza pallidiflora*.[5] Vestitol, in particular, has been found to have significant activity against antibiotic resistant *H. pylori* while licorice extracts, in general, are considered to be potentially useful as chemopreventatives for peptic ulcer and gastric cancer.[6] Given their structural similarity to human estrogen receptor ligands, such as estradiol and diethylstilbestrol (**3** and **4** in Figure 1, respectively), we have undertaken a multistep, total synthesis of racemic **1** and **2** in order to generate quantities that can be deployed to further scope their potential anticancer profile and to ascertain if they have demonstrable phytoestrogenic properties. Although **1** has been synthesized previously,[1a,2d,7] to our knowledge this is the first report of a total synthesis for **2**.

Drawing from our evolving studies pertaining to the syntheses of various pterocarpan phytoalexins,[8a–d] we imagined that an intramolecular Wittig reaction could be used to form the isoflav-3-ene system in **2**. Reduction of the latter can readily yield (±)-**1**.[5] This synthetic strategy is shown in Scheme 1.

4-Methoxy-2-hydroxyacetophenone was protected with a benzyl group under mildly basic conditions and then subjected to selective α-iodination using either Selectfluor[8c] or copper oxide[9] to provide intermediate **5**.[10] As we have done previously, selective benzylation of 2,4-dihydroxybenzaldehyde at the *para* position was followed by reduction with sodium borohydride to provide the salicyl alcohol intermediate **6**.[8c,d] Coupling of **5** and **6** was accomplished by a nucleophilic substitution reaction[11] to form ether **7**.[12] The latter was converted to a Wittig salt by treatment with triphenylphosphine hydrobromide[13] and used in an intramolecular olefination reaction[8c,d–i] to obtain the key, penultimate intermediate **8**.[14] A total synthesis of racemic vestitol was then achieved in eight steps upon catalytic hydrogenation[5] which simultaneously reduced the olefin while cleaving the two benzyl-protecting groups. The overall yield was 29%.[15]

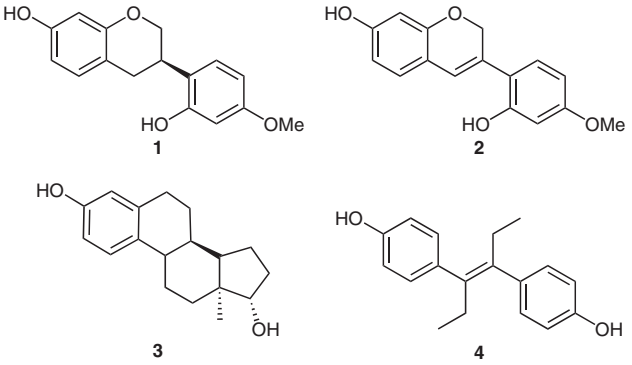
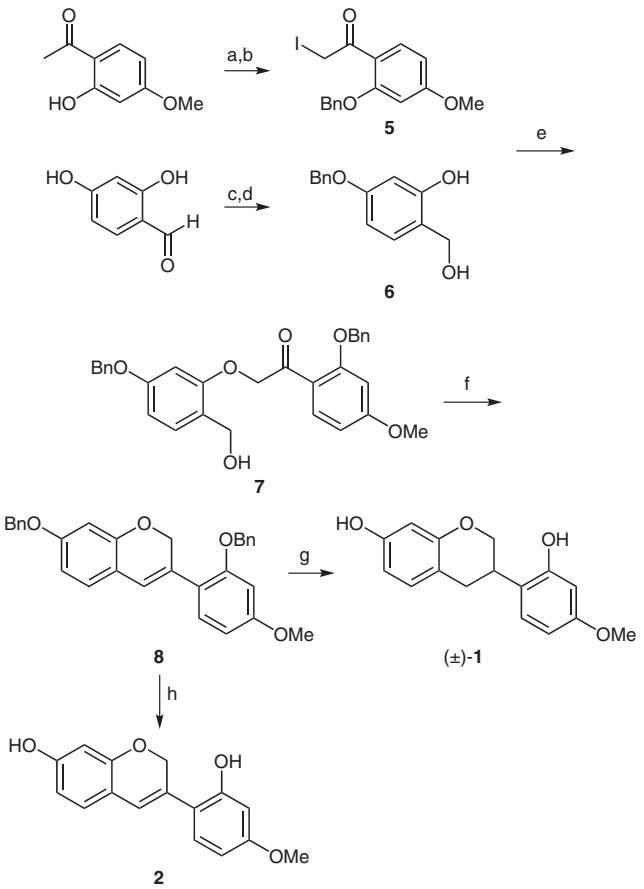


Figure 1 Target compounds (±)-vestitol [**1**, depicted as the (–)-enantiomer obtained from licorice] and bolusanthin III (**2**), and their structural similarities to human estrogen receptor ligands estradiol (**3**) and diethylstilbestrol (**4**)

Alternatively, to produce bolusanthin III, we first attempted to remove the benzyl groups in **8** by treatment with pentamethylbenzene/trifluoroacetic acid (PMB/TFA)[16] and with boron tribromide (BBr_3).[17] However, both reagents proved too harsh and resulted in degradation of **8** to multiple side products without providing detectable levels of desired material (TLC). A possible mechanism for this ready decomposition could involve the allylic ether either becoming protonated in the case of TFA or chelated with the Lewis acid in the case of BBr_3. Either species can collapse to a benzyl carbocation that leads to multiple decomposition pathways. Ultimately, the synthesis of **2** was achieved by treating **8** with BCl_3 in the presence of PMB at –78 °C.[18] An eight-step procedure leading to **2** was thus accomplished in 21% overall yield.[19] Unlike the previous isolations of **2** from natural sources, the synthesized product can be obtained conveniently as a free-

SYNLETT 2011, No. 11, pp 1605–1607
Advanced online publication: 10.06.2011
DOI: 10.1055/s-0030-1260783; Art ID: S01011ST



Scheme 1 Synthesis of racemic vestitol and bolusanthin III. *Reagents and conditions*: (a) BnBr, K_2CO_3, MeCN, reflux, 24 h, 96%; (b) Selectfluor, I_2, CH_2Cl_2–MeOH (1:5), r.t., 20 h, 84%; (c) BnBr, $KHCO_3$, MeCN, reflux, 15 h, 85%; (d) $NaBH_4$, EtOH, 0 °C 1 h, r.t., 10 h, 58%; (e) K_2CO_3, Me_2CO, reflux, 16 h, 78%; (f) (i) Ph_3P·HBr, MeCN, r.t., 1 h; (ii) KO*t*-Bu, MeOH, reflux, 24 h, 70% across two steps; (g) 10% Pd/C, EtOAc, H_2 (2.4 bar), r.t., 14 h, 84%; (h) BCl_3, PMB, CH_2Cl_2, –78 °C, 15 min, 61%.

flowing powder that displays a discernable melting point. This constitutes the first published report[20] for the total synthesis of bolusanthin III.

Acknowledgment

We are thankful to the USDA ARS SRRC for financial support.

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(10) **1-(2′-Benzyloxy-4-methoxyphenyl)ethanone**
To a solution of 4-methoxy-2-hydroxyacetophenone (5.0 g, 30 mmol) in MeCN (80 mL), K_2CO_3 (5.0 g, 36 mmol) and benzyl bromide (5.0 g, 29 mmol) were added. The reaction mixture was stirred under reflux while progress was followed by TLC and ^{1}H NMR. After 24 h solvent was evaporated under vacuum. The off-white residue was dissolved in EtOAc and washed with 2 M NaOH, 0.1 M HCl, H_2O, and brine. After drying over anhyd Na_2SO_4 and then filtration, the volatiles were evaporated under vacuum to obtain the desired ketone (7.4 g, 28.8 mmol, 96%) as a white solid; mp 84–88 °C. TLC: R_f = 0.40 (EtOAc–hexanes = 1:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.85 (1 H, d, *J* = 8.4 Hz), 7.40 (5 H, m), 6.53 (2 H, m), 5.13 (2 H, s), 3.83 (3 H, s), 2.56 (3 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.8, 164.3, 160.1, 135.9, 132.7, 128.7, 128.2, 127.6, 121.4, 105.3, 99.4, 70.6, 55.5, 32.2
Compound 5
To a solution of protected ketone from the previous step (22.7 g, 88.6 mmol) in anhyd CH_2Cl_2 (100mL) and anhyd MeOH (500 mL), Selectfluor™ (18.9 g, 53.3 mmol) was added followed by addition of elemental iodine (11.25 g, 44.3 mmol). The reaction mixture was stirred for 20 h. Progress was monitored by TLC and ^{1}H NMR. After completion, the reaction mixture was filtered and the precipitate was washed with CH_2Cl_2. The combined filtrate was evaporated under vacuum, and the solid residue was dissolved in CH_2Cl_2 (200 mL) and washed with freshly prepared 10% $Na_2S_2O_3$ solution (3 × 125 mL). The organic layer was dried over anhyd Na_2SO_4, filtered, and evaporated to dryness. The solid residue was purified by recrystallization from Me_2CO–MeOH (1:10, 100 mL) to obtain **5** (28.4 g, 74.3 mmol, 84%) as yellowish crystals; mp 96–100 °C. TLC: R_f = 0.54 (EtOAc–hexanes = 1:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (1 H, d, *J* = 9.0 Hz), 7.44 (5 H, m), 6.57 (1 H, dd, *J* = 9.0 Hz), 6.53 (1 H, d, *J* = 2.4 Hz), 5.17 (2 H, s), 4.40 (2 H, s), 3.84 (3 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.1, 159.7, 135.5, 134.1, 128.8, 128.5, 127.9, 117.4, 106.0, 99.3, 71.0, 55.6, 9.9. Anal. Calcd (%) for

$C_{16}H_{15}IO_3 \cdot 0.5H_2O$: C, 49.13; H, 4.12. Found: C, 48.82; H, 3.78.

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(12) **Compound 7**
To a solution of salicyl alcohol **6** (0.19 g, 0.82 mmol) and α-iodo ketone **5** (0.28 g, 0.74 mmol) in Me_2CO (15 mL), K_2CO_3 (0.14 g, 0.98 mmol) was added under a flow of N_2. The reaction mixture was refluxed for 16–18 h. Progress was followed by TLC. After completion, the solvent was evaporated under reduced pressure. The solid residue was dissolved in EtOAc (120 mL) and washed with 1 M NaOH, H_2O, brine, dried over anhyd Na_2SO_4, and evaporated to dryness under vacuum. The solid residue was purified using flash column chromatography to obtain **7** (0.28 g, 0.57 mmol, 78%) as off-white solid; mp 150–153 °C. TLC: R_f = 0.17 (EtOAc–hexanes = 1:2). ^{1}H NMR [600 MHz, $(CD_3)_2CO$)]: δ = 7.89 (1 H, d, *J* = 8.4 Hz), 7.45 (10 H, m), 7.22 (1 H, d, *J* = 9.0 Hz), 6.83 (1 H, d, *J* = 2.4 Hz), 6.68 (1 H, dd, *J* = 2.4, 9.0 Hz), 6.56 (1 H, dd, *J* = 2.4, 8.4 Hz), 6.26 (1 H, d, *J* = 2.4 Hz), 5.33 (2 H, s), 5.21 (2 H, s), 4.99 (2 H, s), 4.57 (2 H, d, *J* = 6.6 Hz), 4.15 (1 H, t, *J* = 6.6 Hz), 3.90 (3 H, s). ^{13}C NMR [100 MHz, $(CD_3)_2CO$): δ = 193.7, 161.7, 160.1, 158.0, 138.2, 137.0, 133.2, 129.6, 129.5, 129.3, 129.2, 129.1, 128.6, 107.5, 106.0, 101.0, 99.8, 74.6, 71.7, 70.5, 60.9, 56.1. Anal. Calcd (%) for $C_{30}H_{28}O_6 \cdot 0.25H_2O$: C, 73.68; H, 5.87. Found: C, 73.33; H, 5.71.

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(14) **Compound 8**
To a suspension of **7** (97 mg, 0.2 mmol) in anhyd MeCN (4 mL), $Ph_3P \cdot HBr$ (70 mg, 0.2 mmol) was added under a flow of N_2. The reaction mixture was stirred at r.t. and followed by TLC. After completion, solvent was evaporated under vacuum to obtain an off-white residue which was directly used in the next step without further purification.
To a solution of the above phosphonium salt in anhyd MeOH (15 mL), KO*t*-Bu (45 mg, 0.4 mmol) was added under a flow of N_2. The reaction mixture was refluxed for 16–20 h. Progress was monitored by TLC. After completion, the mixture was reduced to one-third of original volume under vacuum and then filtered. The precipitate was dissolved in CH_2Cl_2 (30 mL). The organic phase was washed with H_2O, brine, dried over anhyd Na_2SO_4, and evaporated to dryness under vacuum to obtain **8** (50 mg, 0.11 mmol, 70% over 2 steps) as an off-white solid; mp 119–122 °C. TLC: R_f = 0.65 (EtOAc–hexanes = 1:2). ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: δ = 7.41 (10 H, m), 7.28 (1 H, d, *J* = 8.4 Hz), 7.01 (1 H, d, *J* = 7.8 Hz), 6.70 (1 H, d, *J* = 2.4 Hz), 6.60 (1 H, s), 6.57 (2 H, m), 6.46 (1 H, d, *J* = 1.8 Hz), 5.16 (2 H, s), 5.10 (2 H, s), 4.93 (2 H, s), 3.80 (3 H, s). ^{13}C NMR [150 MHz, $(CD_3)_2CO$]: δ = 161.7, 160.3, 158.2, 155.5, 138.2, 137.8, 130.0, 129.9, 129.3, 129.4, 129.23, 128.7, 128.6, 128.5, 128.3, 128.2, 121.5, 121.4, 118.1, 108.9, 106.3, 102.8, 100.5, 71.0, 70.4, 68.9, 55.6. Anal. Calcd (%)for $C_{30}H_{26}O_4 \cdot 0.5H_2O$: C, 78.41; H, 5.92. Found: C, 78.30; H, 5.69.

(15) **Racemic vestitol [(±)-1]**
To a solution of **8** (50 mg, 0.11 mmol) in EtOAc (15 mL) at 0 °C, 10% w/w Pd/C (15–20 mg) was added. The mixture was stirred at r.t. under hydrogen atmosphere (2.4 bar). Progress was followed by TLC. After completion, the reaction mixture was passed through a pad of Celite. Solvent was evaporated under vacuum, and the residue further purified using flash column chromatography (EtOAc–hexanes = 1:1) to obtain (±)-**1** (25 mg, 90 μmol, 84%) as an off-white powder; mp 172–179 °C (lit.[2d] 171–173 °C). TLC: R_f = 0.44 (EtOAc–hexanes = 1:1). ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: δ = 8.52 (1 H, br), 8.10 (1 H, br), 7.05 (1 H, d, *J* = 8.4 Hz), 6.88 (1 H, d, *J* = 8.4 Hz), 6.50 (1 H, d, *J* = 2.4 Hz), 6.42 (1 H, dd, *J* = 2.4, 8.4 Hz), 6.35 (1 H, dd, *J* = 2.4, 8.4 Hz), 6.27 (1 H, d, *J* = 2.4 Hz), 4.23 (1 H, m), 3.97 (1 H, t, *J* = 10.2 Hz), 3.71 (3 H, s), 3.47 (1 H, m), 2.96 (1 H, m), 2.79 (1 H, m). ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = 160.3, 157.4, 156.6, 156.0, 130.9, 128.6, 120.8, 114.2, 108.6, 105.5, 103.4, 102.4, 70.4, 55.2, 32.5, 30.9. Anal. Calcd (%) for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.22; H, 5.98.

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(19) **Bolusanthin III (2)**
To a solution of **8** (0.45 g, 1 mmol) and pentamethylbenzene (1.48 g, 10 mmol) in anhyd CH_2Cl_2 (30 mL) at –78 °C, BCl_3 (0.2 mmol) was added dropwise under N_2. The mixture was stirred at –78 °C, and after 15–20 min the reaction was quenched with a $CHCl_3$–MeOH (10:1, 20 mL) mixture. The resulting mixture was warmed to r.t. The organic solvent was evaporated under vacuum. The residue was purified by column chromatography [silica gel 35 mm dia, 8 inch thick, EtOAc–hexanes (1:2)] to obtain **2** (0.17 g, 0.61 mmol, 61%) as a brownish solid; mp 150–154 °C (lit. reports an amorphous material[5] or a brown paste[4] after isolation from natural sources). TLC: R_f = 0.48 (EtOAc–hexanes = (1:2). ^{1}H NMR (600 MHz, CD_3OD): d = 7.14 (1 H, d, *J* = 8.4 Hz), 6.88 (1 H, d, *J* = 8.4 Hz), 6.53 (1 H, s), 6.42 (1 H, dd, *J* = 2.4, 8.4 Hz), 6.37 (1 H, d, *J* = 2.4 Hz), 6.33 (1 H, dd, *J* = 2.4, 8.4 Hz), 6.24 (1 H, d, *J* = 1.8 Hz), 4.94 (2 H, s), 3.74 (3 H, s). ^{13}C NMR (150 MHz, CD_3OD): d = 161.8, 159.1, 157.3, 155.9, 130.1, 130.0, 128.4, 121.4, 119.9, 117.6, 109.4, 106.1, 103.4, 102.4, 69.2, 55.6. Anal. Calcd (%) for $C_{16}H_{14}O_4 \cdot 0.1H_2O$: C, 70.63; H, 5.26. Found: C, 70.42; H, 5.20.

(20) Portions of this work were described previously as a poster presentation at the 239th American Chemical Society meeting in San Francisco during March, 2010. The published abstract was denoted as ORGN-941.