Synthesis of Gymnoascolide A

Md. Merajuddin Baag, Narshinha P. Argade*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India
E-mail: np.argade@ncl.res.in

Received 14 September 2007; revised 1 October 2007

Abstract: Recently isolated 4-benzyl-3-phenylfuran-2,5-dione and antifungal gymnoascolide A have been synthesized using the chemoselective S_N2' coupling of phenylmagnesium bromide with dimethyl 2-(bromomethyl)fumarate, chemoselective allylic substitution of bromide in 3-(bromomethyl)-4-phenylfuran-2,5-dione with phenylmagnesium bromide and regioselective N-Selectride-induced reduction of 3-benzyl-4-phenylfuran-2,5-dione as the key reactions.

Key words: dimethyl (bromomethyl)fumarate, S_N2' Grignard coupling reaction, functionalized maleic anhydrides, regioselective reduction, gymnoascolide A

Recently, gymnoascolides A–C (**1**, **2a**, **2b**) were isolated from the Australian soil ascomycete *Gymnoascus reessii*[1] and *Malbranchea filamentosa* IFM41300.[2] 3-Benzyl-4-phenylfuran-2,5-dione was isolated from *Aspergillus nidulans*.[3] Gymnoascolides A–C possess moderate activity against the pathogenic plant fungus *Septoria nodorum*.[1] Gymnoascolide A also possesses vasodilatory activity and it inhibits Ca^{2+}-induced vasocintraction in aortic rings pretreated with high K^+ or norepinephrine.[2] 3-Benzyl-4-phenylfuran-2,5-dione possesses plant growth regulatory activity and it effectively accelerates the root elongation of radish seedlings.[3] The gymnoascolides possess a rare structural motif, only a few examples are known in the literature such as eutypoid A (**3**), isolated from a south China sea marine fungus of the genus *Eutypa*[4] and microperfuranone (**4**), isolated from terrestrial fungi *Anixiella micropertusa*[5] (Figure 1).

Earlier, 3-benzyl-4-phenylfuran-2,5-dione was synthesized by Momose and co-workers.[6] In order to study the structure–activity relationship of these types of natural and unnatural molecules, a flexible synthetic approach that will allow mono, dialkyl, allyl, benzyl, or aryl functionalization of both the vinylic carbons, with the presence of several types of heteroatom in the five-membered ring needs to be developed. In continuation of our studies on the synthesis of structurally interesting and biologically important natural and unnatural products using cyclic anhydrides as potential precursors,[7] we herein report the synthesis of gymnoascolide A (Scheme 1).

We planned to use dimethyl (bromomethyl)fumarate (**5**)[7d] as a potential starting material for the stepwise construction of natural product gymnoascolides. The chemoselective S_N2' coupling reaction of phenylmagnesium bromide with **5** exclusively gave the desired dimethyl 2-methylene-3-phenylsuccinate (**6**) in 73% yield. The base-catalyzed hydrolysis of diester **6** to diacid **7** (92%) followed by acetic anhydride induced ring closure gave the expected anhydride **8** in nearly 100% yield. In this reaction, both the formation of the succinic anhydride intermediate and carbon–carbon double-bond migration took place in one pot. The *N*-bromosuccinimide bromination of the allylic carbon in the anhydride **8** furnished the required bromo anhydride **9** in 80% yield. We did not observe any bromination of the phenyl ring under our reaction conditions. The chemoselective allylic substitution of the bromo atom in anhydride **9** with phenylmagnesium bromide gave 3-benzyl-4-phenylfuran-2,5-dione (**10**) in 45% yield. In anhydride **10**, one of the carbonyl groups is in conjugation with the phenyl ring, while the other one is sterically hindered because of an adjacent phenyl ring. Hence the regioselective reduction of one of the carbonyls to obtain **1** is a challenging task. In our hands sodium borohydride reduction of anhydride **10** was not selective and we obtained an inseparable mixture of both regioisomers in 74% yield (ratio desired/undesired = 1:2, by ^1H NMR). Fortunately, N-Selectride regioselectively reduced the unhindered carbonyl in anhydride **10** at –78 °C and exclusively furnished the natural product gymnoascolide A (**1**) in 90% yield.

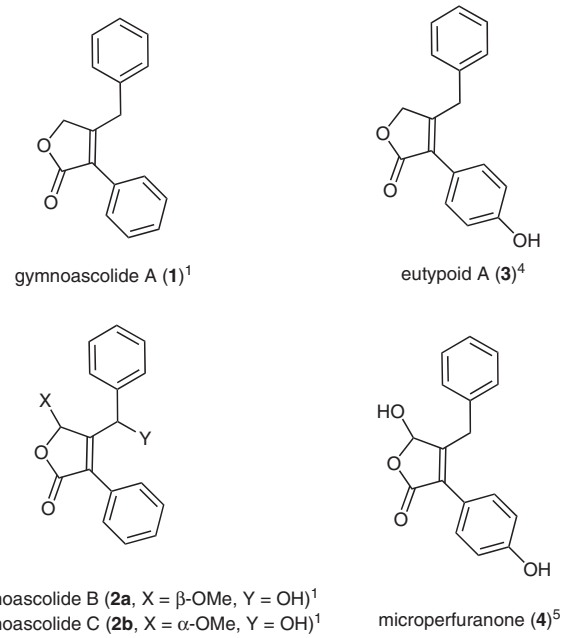
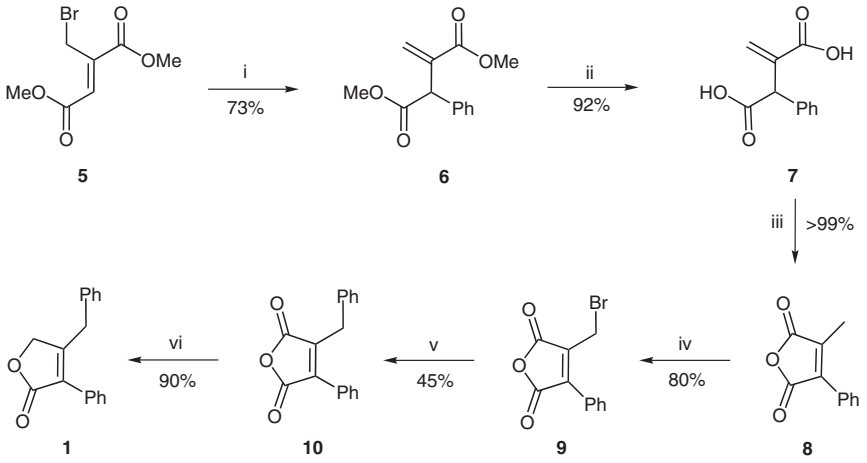


Figure 1 Naturally occurring bioactive butenolactones **1**–**4**

SYNTHESIS 2008, No. 1, pp 0026–0028
Advanced online publication: 15.11.2007
DOI: 10.1055/s-2007-990901; Art ID: Z21407SS



Scheme 1 *Reagents and conditions*: (i) PhMgBr (1.50 equiv), THF, HMPA, 0 °C, 0.5 h; (ii) (a) LiOH (10.00 equiv), THF–H_2O (3:1), r.t., 18 h; (b) H^+/HCl; (iii) Ac_2O, reflux, 1.5 h; (iv) NBS (1.50 equiv), $(BzO)_2$ (10 mol%), CCl_4, reflux, 12 h; (v) PhMgBr (5.00 equiv), THF, HMPA, CuI, 0 °C, 8 h; (vi) N-Selectride (3.00 equiv), THF, –78 °C, 1 h.

The analytical and spectral data obtained for these natural products **10** and **1** were in complete agreement with the reported data.[1–3,6]

In summary, we have demonstrated the synthesis of natural 3-benzyl-4-phenylfuran-2,5-dione (**10**) (5 steps, 24%) and the first synthetic approach to bioactive natural product gymnoascolide A (**1**) (6 steps, 22%). In the present synthesis, the selective Grignard reagent coupling reactions and N-Selectride reduction are noteworthy. We feel that our present approach is general and will be useful to design congeners of gymnoascolides in the search for new lead molecules with better activity.

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 NMR spectrometer using TMS as an internal standard. ^{13}C NMR spectra were recorded on Bruker AC 200 (50 MHz), Bruker AC 300 (75 MHz). or Bruker AC 500 NMR spectrometers (125 MHz). FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrophotometer. Column chromatographic separations were carried out on silica gel (60–120 mesh) eluting with petroleum ether (PE; bp 60–80 °C) and EtOAc. Commercially available citraconic anhydride, bromobenzene, Mg turnings, HMPA, NBS, $(BzO)_2$, Ac_2O, and N-Selectride were used.

Dimethyl 2-Methylene-3-phenylsuccinate (6)

A fresh soln of PhMgBr in THF was prepared as follows. A soln of bromobenzene (3.76 g, 24.00 mmol) in anhyd THF (30 mL) was added in 3 equal portions at 10 min intervals to Mg turnings (1.73 g, 72.00 mmol) in THF (10 mL) under argon at r.t. with constant stirring. The mixture was further stirred at r.t. for 4 h. This freshly generated Grignard reagent was added dropwise to a soln of **5** (3.79 g, 16.00 mmol) and HMPA (14.34 g, 80.00 mmol) in anhyd THF (30 mL) under argon at 0 °C and the mixture was stirred at this temperature for 30 min. The reaction was quenched by the addition of sat. NH_4Cl soln (30 mL). EtOAc (50 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, PE–EtOAc, 9:1) to give **6** (2.73 g, 73%) as a thick oil.

IR (neat): 1738, 1724, 1634, 1448, 1250 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.78 (s, 3 H), 4.84 (s, 1 H), 5.40 (s, 1 H), 6.41 (s, 1 H), 7.20–7.45 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.2, 52.4, 53.0, 127.8, 128.1, 128.8, 129.0, 135.7, 138.8, 166.7, 172.2.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.49; H, 5.88.

2-Methylene-3-phenylsuccinic Acid (7)

A soln of LiOH (2.40 g) in H_2O (20 mL) was added to a soln of **6** (2.34 g, 10.00 mmol) in THF (30 mL) at r.t. and the mixture was stirred for 18 h. The mixture was concentrated in vacuo and EtOAc (50 mL) was added and then it was acidified to pH 2 with 2 M HCl. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, PE–EtOAc, 6:4) to give **7** (1.89 g, 92%) as a white solid; mp 145 °C.

IR (Nujol): 2700–2500, 1713, 1693, 1634, 1463, 1304 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.78 (s, 1 H), 5.36 (s, 1 H), 6.54 (s, 1 H), 7.25–7.50 (m, 5 H), 11.12 (br s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.4, 128.2, 129.1, 129.2, 130.8, 134.4, 138.6, 172.2, 178.5.

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.92; H, 5.02.

3-Methyl-4-phenylfuran-2,5-dione (8)

A soln of **7** (1.65 g, 8.00 mmol) in Ac_2O (15 mL) was gently refluxed for 1.5 h and the mixture was concentrated under vacuo at 50 °C. The residue was diluted with EtOAc (40 mL) and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to give **8** (1.50 g, ~100%) as a yellow solid; mp 100 °C (Lit.[8] 94.5 °C).

IR (Nujol): 1774, 1759, 1643, 1460, 1377 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 7.50–7.58 (m, 3 H), 7.62–7.71 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 127.4, 129.0, 129.4, 131.0, 138.7, 139.9, 164.8, 166.2.

Anal. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.28. Found: C, 70.10; H, 4.37.

3-(Bromomethyl)-4-phenylfuran-2,5-dione (9)
A mixture of **8** (940 mg, 5.00 mmol), NBS (1.34 g, 7.50 mmol), and a catalytic amount of $(BzO)_2$ (122 mg, 10 mol%) in CCl_4 (50 mL) was gently refluxed for 12 h. The mixture was left overnight at r.t. and then filtered. The residue was washed with CCl_4 (25 mL) and the combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 9:1) to give **9** (1.07 g, 80%) as a yellow solid; mp 72 °C.

IR (Nujol): 1761, 1636, 1601, 1512, 1460 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.35 (s, 2 H), 7.50–7.70 (m, 3 H), 7.75–7.90 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9, 126.6, 129.4, 129.7, 132.1, 136.2, 141.2, 163.9 (2 C).

Anal. Calcd for $C_{11}H_7O_3Br$: C, 49.47; H, 2.64. Found: C, 49.39; H, 2.55.

3-Benzyl-4-phenylfuran-2,5-dione (10)
A fresh soln of PhMgBr in THF was prepared as follows. A soln of bromobenzene (785 mg, 5.00 mmol) in anhyd THF (20 mL) was added in 3 equal portions at 10 min intervals to Mg turnings (600 mg, 25.00 mmol) in THF (5 mL) under argon at r.t. with constant stirring. The mixture was further stirred at r.t. for 4 h. This freshly generated Grignard reagent was added dropwise to a soln of **9** (267 mg, 1.00 mmol) and CuI (19 mg, 0.10 mmol) in THF (10 mL) and HMPA (1 mL) under argon at 0 °C over 15–20 min with stirring. The mixture was allowed to reach r.t. and stirred for 8 h. The mixture was diluted with EtOAc (10 mL) and acidified with 2 M H_2SO_4 (20 mL) and the aqueous layer was further extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, PE–EtOAc, 9.5:0.5) to give **10** (118 mg, 45%) as a white solid; mp 65 °C (Lit.[3] 67–68 °C).

IR ($CHCl_3$): 1769, 1656, 1508, 1215, 758 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.04 (s, 2 H), 7.15–7.35 (m, 5 H), 7.45–7.70 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.4, 127.1, 127.3, 128.4, 129.0, 129.1, 129.3, 131.2, 135.4, 140.6, 141.1, 164.8, 165.8.

Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.57. Found: C, 77.13; H, 4.44.

4-Benzyl-3-phenylfuran-2(*5H*)-one (Gymnoascolide A, 1)
To a stirred soln of **10** (50 mg, 0.19 mmol) in anhyd THF (10 mL) at –78 °C, was added 1 M N-Selectride in THF (0.60 mL, 0.60 mmol) over a period of 10 min. The mixture was maintained at this temperature for 1 h. The reaction was quenched with H_2O (5 mL) at –78 °C and allowed to reach to r.t. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, PE–EtOAc, 9:1) to give gymnoascolide A (**1**) (42 mg, 90%) as a thick oil.

IR ($CHCl_3$): 1751, 1655, 1522, 1215, 768 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 2 H), 4.70 (s, 2 H), 7.10–7.20 (m, 2 H), 7.25–7.35 (m, 3 H), 7.40–7.60 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.0, 71.1, 127.4, 127.6, 128.5, 128.7, 128.8, 128.9, 129.2, 129.6, 136.1, 159.7, 173.3.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.62; H, 5.49.

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