

Concise Enantioselective Synthesis of (–)-Gloeosporone from (S)-O-Benzylglycidol [(S)-Benzyloxymethyloxirane]

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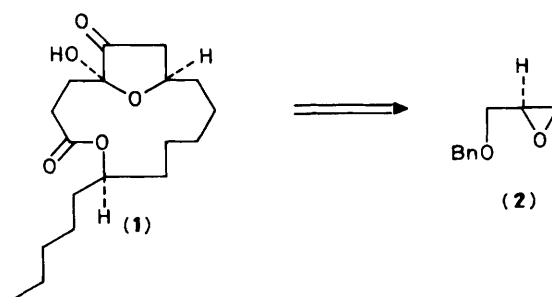
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Concise enantioselective synthesis of (–)-gloeosporone, a germination self-inhibitor isolated from *Colletotrichum gloeosporioides*, has been established using (S)-O-benzylglycidol as a chiral template.

The structure of gloeosporone (1), a germination self-inhibitor isolated from the spores of the fungus *Colletotrichum gloeosporioides*,¹ has been determined by X-ray analysis² and synthesis of the un-natural (+)-antipode from (S)-malic acid.³ We report here the enantioselective synthesis of (–)-gloeosporone (1) in naturally occurring forms using (S)-O-benzylglycidol⁴ (2) as a chiral template.

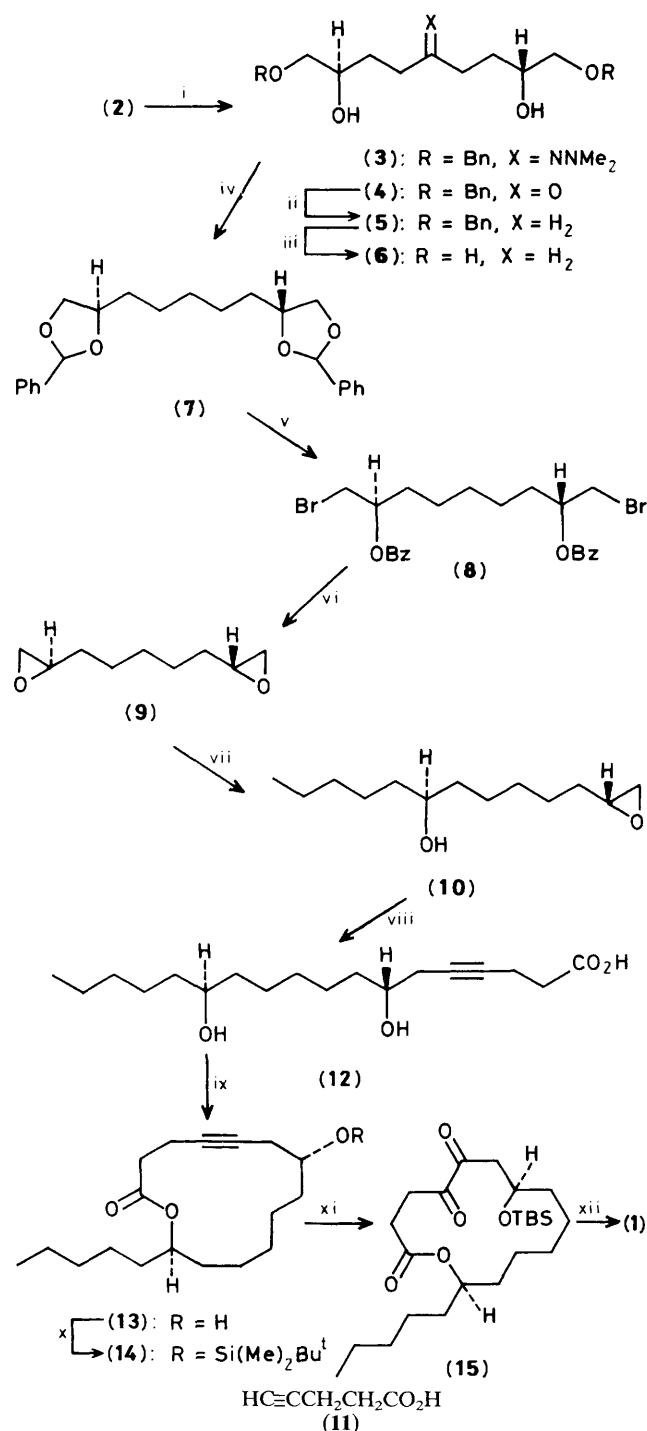
Acetone dimethylhydrazone was successively treated with two equivalents of (S)-O-benzylglycidol (2) in the presence of n-butyl-lithium⁵ to give the ketodiols (4)[†] in 59% yield after hydrolytic treatment with aqueous acetic acid. Thus, the carbanion, generated from the hydrazone (19.2 mmol) in

tetrahydrofuran (THF) (80 ml) with n-butyl-lithium (19.2 mmol) at –60 °C (40 min), was reacted with (2)



Scheme 1. Bn = benzyl.

[†] Satisfactory spectral [i.r., ¹H n.m.r. (90 and 500 MHz), mass] and analytical (combustion and/or high resolution m.s.) data were obtained for all new compounds.



Scheme 2. Reagents and conditions: i, Me₂C=NNMe₂ (1.4 equiv.), BuⁿLi (1.4 equiv.), tetrahydrofuran (THF), -60°C, then (2) (1 equiv.), -60°C—room temp., then BuⁿLi (1.1 equiv.), -60°C to -20°C, (2) (1.5 equiv.), -60°C—room temp., aq. AcOH, THF; ii, H₂NNH₂·H₂O, KOH, diethyleneglycol, 120–220°C; iii, H₂, Pd(OH)₂, EtOH (cat. CHCl₃); iv, PhCHO (2.2 equiv.), cat. *p*-TsOH, benzene, reflux; v, *N*-bromosuccinimide (NBS) (3 equiv.), CCl₄; vi, K₂CO₃ (3 equiv.), MeOH; vii, BuⁿCuLi (1.2 equiv.), THF, -70°C; viii, (11) (10 equiv.), BuⁿLi (20 equiv.), hexamethylphosphoramide (HMPA) (10 equiv.), THF, -28°C—room temp.; ix, diethylazodicarboxylate (DEAD) (2 equiv.), Ph₃P (2 equiv.), benzene, 0°C, 10 min; x, Bu^tMe₂SiCl (2 equiv.), imidazole (4 equiv.), dimethylformamide (DMF); xi, RuCl₃·3H₂O (cat.), NaIO₄ (4.1 equiv.), MeCN–CCl₄–H₂O (2:2:3); xii, (HF)_x Py, (Py = pyridine), THF. Bn = benzyl; Bz = benzoyl.

(13.7 mmol) at the same temperature, and after 4 h at room temperature, cooled to -60°C and treated with *n*-butyllithium (15.1 mmol) followed by (2) (20.5 mmol) at the same temperature. After stirring at room temperature (6 h), the mixture was treated with 10% aqueous acetic acid (50 ml) to give (4): 90 MHz ¹H n.m.r. δ (CDCl₃) 7.32 (s, 10H), 4.53 (s, 4H), 3.75 (m, 2H), 3.35 (m, 4H), 2.62 (br.s, 2H, exchangeable), 2.60 (t, *J* 7 Hz, 4H), 2.0–1.5 (m, 4H). The ketone (4) was reduced with hydrazine hydrate (90%) and potassium hydroxide in hot diethyleneglycol to give the diol (5), [α]_D²⁵ -5.91° (c 1.014, CHCl₃), which was debenzylated [H₂, Pd(OH)₂] to give the tetraol (6) in 99% overall yield. Bis-benzylidenation of (6), followed by treatment of the resulting acetal (7) with *N*-bromosuccinimide afforded the bis-bromobenzoate (8) which was stirred with potassium carbonate in methanol at room temperature to give the bis-epoxide (9), [α]_D²⁶ +20.43° (c 1.008, CHCl₃), in 78% yield: 90 MHz ¹H n.m.r. δ (CDCl₃) 2.90 (m, 2H), 2.75 (dd, *J* 4.8 and 4.4 Hz, 2H), 2.48 (dd, *J* 4.8 and 2.7 Hz, 2H), 1.7–1.1 (m, 10H). Treatment of (9) with one equivalent of lithium dibutyl cuprate gave the epoxy alcohol (10), [α]_D²⁵ +9.17° (c 1.046, CHCl₃) [*ca.* 100% enantiomeric excess (e.e.)]† in 40% yield [74% yield based on recovered (9)]: 90 MHz ¹H n.m.r. δ (CDCl₃) 3.60 (m, 1H), 2.90 (m, 1H), 2.75 (dd, *J* 4.8 and 4.4 Hz, 1H), 2.48 (dd, *J* 4.8 and 2.7 Hz, 1H), 1.7–1.1 (m, 19H), 0.90 (br.t, *J* 7 Hz, 3H). When an excess of the cuprate was used, the unusable bis-adduct was obtained in place of (9) which may be recycled. The monoepoxide (10) (2.0 mmol) was then reacted with an excess of the dianion, generated from 4-pentynoic acid (11) (20.0 mmol) with *t*-butyllithium (40.0 mmol) in THF (60 ml) containing hexamethylphosphoric triamide (10.0 mmol), at -20°C for 4 h and room temperature for 4 days to give the diol (12) in 72% yield: 90 MHz ¹H n.m.r. δ (CDCl₃) 5.95 (br.s, 3H, exchangeable), 3.67 (m, 2H), 2.6–2.2 (m, 6H), 1.65–1.15 (m, 18H), 0.9 (br.t, *J* 8 Hz, 3H). Lactonization of (12) under the Mitsunobu conditions³ afforded the desired 14-membered compound (13), [α]_D²⁴ +27.30° (c 0.63, CHCl₃) (*ca.* 100% e.e.)‡§ in 44% yield as the only detectable product of which the enantiomer was obtained by Seebach and co-workers.³ Employing the established method³ (13) could be converted into (-)-gloeosporone (1), m.p. 119–120°C; [α]_D²⁴ -82.95° (c 0.50, benzene) [lit.³ for (+)-enantiomer: m.p. 117–118°C; [α]_D²⁴ +79° (c 0.40, benzene)],§ *via* the silyl ethers (14) and (15).

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† Optical purity was determined by ¹H n.m.r. analysis of the α-methoxy-α-(trifluoromethyl)phenylacetyl(MTPA) ester.

§ ¹H n.m.r. spectrum (500 MHz) was identical with that (300 MHz) of the authentic material provided by Professor Seebach.