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

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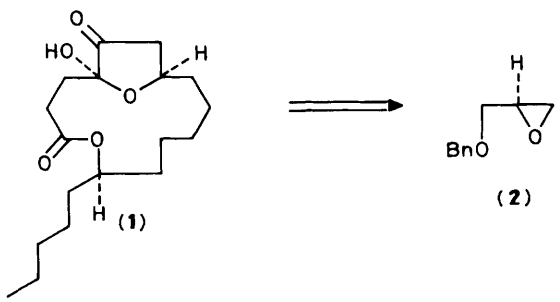
Concise enantioselective synthesis of (−)-gloeosporone, a germination self-inhibitor isolated from *Colletotrichum gloeosporioides*, has been established using (*S*)-*O*-benzylglycidol as a chiral template.

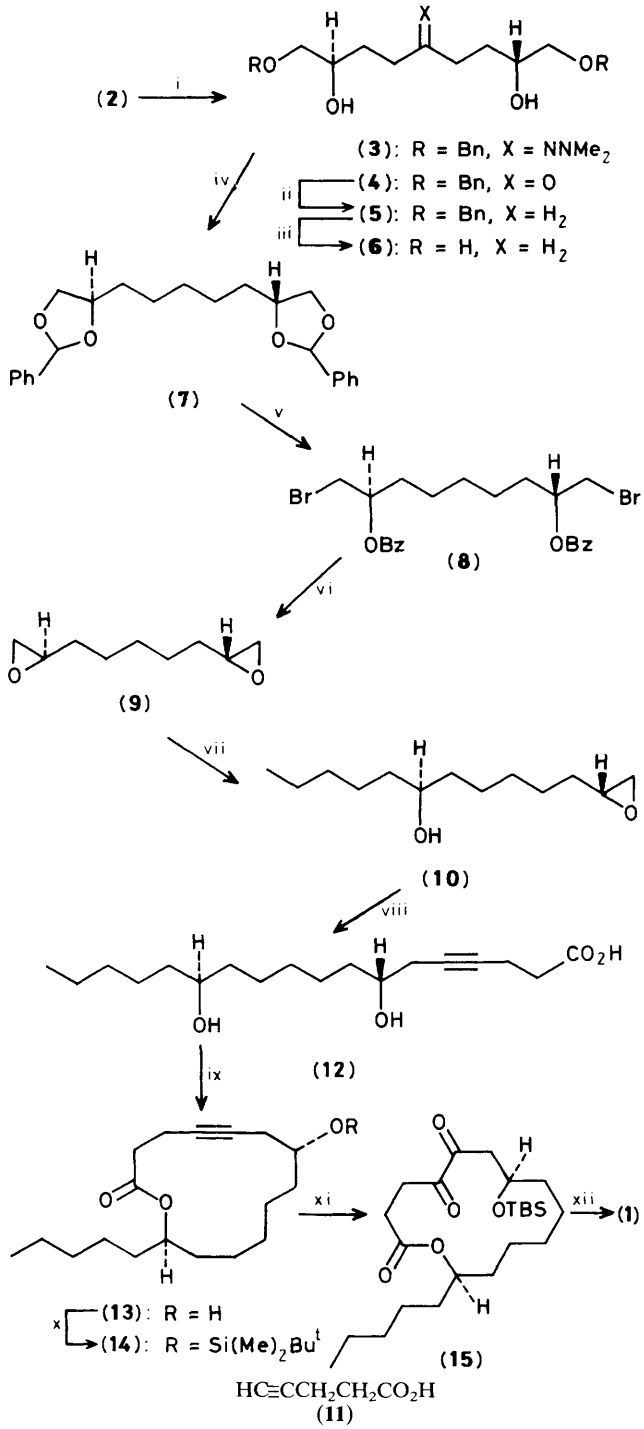
The structure of gloeosporone (**1**), a germination self-inhibitor isolated from the spores of the fungus *Colletotrichum gloeosporioides*,[1] has been determined by *X*-ray analysis[2] and synthesis of the un-natural (+)-antipode from (*S*)-malic acid.[3] We report here the enantioselective synthesis of (−)-gloeosporone (**1**) in naturally occurring forms using (*S*)-*O*-benzylglycidol[4] (**2**) as a chiral template.

Acetone dimethylhydrazone was successively treated with two equivalents of (*S*)-*O*-benzylglycidol (**2**) in the presence of n-butyl-lithium[5] to give the ketodiol (**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., ^{1}H 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, $Me_2C{=}NNMe_2$ (1.4 equiv.), Bu^nLi (1.4 equiv.), tetrahydrofuran (THF), −60 °C, then (**2**) (1 equiv.), −60 °C—room temp., then Bu^nLi (1.1 equiv.), −60 °C to −20 °C, (**2**) (1.5 equiv.), −60 °C—room temp., aq. AcOH, THF; ii, $H_2NNH_2{\cdot}H_2O$, KOH, diethyleneglycol, 120—220 °C; iii, H_2, $Pd(OH)_2$, EtOH (cat. $CHCl_3$); iv, PhCHO (2.2 equiv.), cat. *p*-TsOH, benzene, reflux; v, *N*-bromosuccinimide (NBS) (3 equiv.), CCl_4; vi. K_2CO_3 (3 equiv.), MeOH; vii, Bu_2^nCuLi (1.2 equiv.), THF, −70 °C; viii, (**11**) (10 equiv.), Bu^tLi (20 equiv.), hexamethylphosphoramide (HMPA) (10 equiv.), THF, −28 °C—room temp.; ix, diethylazodicarboxylate (DEAD) (2 equiv.), Ph_3P (2 equiv.), benzene, 0 °C, 10 min; x, Bu^tMe_2SiCl (2 equiv.), imidazole (4 equiv.), dimethylformamide (DMF); xi, $RuCl_3{\cdot}3H_2O$ (cat.), $NaIO_4$ (4.1 equiv.), MeCN–CCl_4–H_2O (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 ^{1}H n.m.r. δ ($CDCl_3$) 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**), $[\alpha]_D^{25}$ −5.91° (*c* 1.014, $CHCl_3$), which was debenzylated [H_2, $Pd(OH)_2$] 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**), $[\alpha]_D^{26}$ + 20.43° (*c* 1.008, $CHCl_3$), in 78% yield:[4] 90 MHz ^{1}H n.m.r. δ ($CDCl_3$) 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**), $[\alpha]_D^{25}$ +9.17° (*c* 1.046, $CHCl_3$) [*ca.* 100% enantiomeric excess (e.e.)]† in 40% yield [74% yield based on recovered (**9**)]: 90 MHz ^{1}H n.m.r. δ ($CDCl_3$) 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-butyl-lithium (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 ^{1}H n.m.r. δ ($CDCl_3$) 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 conditions[3] afforded the desired 14-membered compound (**13**), $[\alpha]_D^{24}$ +27.30° (*c* 0.63, $CHCl_3$) (*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 method[3] (**13**) could be converted into (−)-gloeosporone (**1**), m.p. 119—120 °C; $[\alpha]_D^{24}$ −82.95° (*c* 0.50, benzene) {lit.[3] for (+)-enantiomer: m.p. 117—118 °C; $[\alpha]_D$ + 79° (*c* 0.40, benzene)},§ *via* the silyl ethers (**14**) and (**15**).

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

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