A Stereoselective Synthesis of (±)-Pestalotin

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(±)-Pestalotin (1) was synthesized by employing a stereoselective reduction of a 5-alkyltetronate derivative (3) and a two-carbon elongation reaction of the aldehyde (13) with ethyl diazoacetate in the presence of stannous chloride as key steps.

Keywords (±)-pestalotin; tetronate; syn-glycol; stereoselective reduction; ethyl diazoacetate

Pestalotin (1) was isolated from culture filtrate of a phytopathogenic fungus, Pestalotia cryptomeriaeola, as an active principle showing gibberellin-synergistic activity.1) Pestalotin has been the target of several syntheses owing to its interesting biological activity and syn-glycol structural feature.2,3) We describe here a stereoselective synthesis of (±)-pestalotin using a catalytic reduction of a 5-alkyltetronate to construct the syn-glycol system as a key reaction.

Since the alkylation of tetronate has been established to afford the 5-alkylated product site-selectively,3) methoxy-methyl tetronate (2) was reacted with crotyl bromide in the presence of lithium cyclohexyl isopropylamide to give the desired compound (3) in 61% yield. In contrast, similar alkylation of 2 with n-butyl bromide yielded a trace amount of alkylated product. Catalytic reduction of the tetrone (3) over 5% rhodium on alumina under medium pressure (7 atm) of hydrogen provided the lactones (4 and 5) in 76 and 22% yields, respectively, where the reduction occurred predominantly from the opposite side to the substituent at the 5-position.4)

Thus, the desired syn-glycol system was constructed stereoselectively, and we next attempted the conversion of 4 into (±)-pestalotin as follows.

Reduction of 4 with lithium aluminum hydride gave the diol (6) whose mono-silylation with tert-butyldimethylsilyl chloride and triethylamine afforded the silyl ether (7) in 78% yield from 4. The secondary hydroxy group of 7 was then benzylation in a usual manner with benzyl bromide and sodium hydride to give the benzyl ether, which (without
further purification) was subjected to desilylation with tetrabutylammonium fluoride to afford the alcohol (8) in 80% yield in two steps. Although we first employed 8 as a starting material, difficulties were encountered in removal of the methoxymethyl protecting group in the later stage of this synthesis. Compound 8 was, therefore, treated with benzoyl chloride in pyridine to give the benzoox (9), which, on treatment with aqueous hydrochloric acid, followed by silylation of the resulting alcohol (10) with tert-butyldimethylsilyl chloride and imidazole, gave the silyl ether (11) in 67% yield from 8. Alkaline hydrolysis of 11 afforded the primary alcohol (12), which was subjected to oxidation with pyridinium chlorochromate (PCC) to provide the aldehyde (13). Two-carbon elongation reaction was achieved by treatment of 13 with ethyl diazoacetate in the presence of a catalytic amount of stannous chloride to form the β-keto ester (14) in 94% yield. The silyl group of 14 was deprotected with aqueous hydrochloric acid, furnishing the alcohol (15), which on hydrolysis with 10% sodium hydroxide, followed by neutralization with 10% hydrochloric acid, brought about δ-lactone formation to give 16 in 72% yield from 14. Finally, methylation of 16 with dimethyl sulfate and potassium carbonate in acetone gave benzyl pestalitin (17) whose spectroscopic data were identical with those reported. Since compound 17 has already been transformed into (+)-pestalitin, this synthesis constitutes a formal total synthesis of 1.

The stereoselective reduction of a tetronate derivative yielding a syn-glycol system was thus applied successfully to the synthesis of (+)-pestalitin.

Experimental

Infrared (IR) spectra were measured in CHCl₃ solution and recorded with a Hitachi 260-10 spectrophotometer. Proton nuclear magnetic resonance (1H-NMR) spectra were determined with a JEOL PMX GXS 270 spectrometer and δ values are quoted relative to tetramethylsilane. Mass spectra (MS) were measured with a JEOL JMS D300.

Methoxymethyl 5-Crotyltetronate (3) A solution of methoxymethyl tetronate (2) (5 g, 34.72 mmol) in dry tetrahydrofuran (THF) (10 mL) was added to a stirred solution of lithium cyclohexylisopropylamide (1.2 eq) prepared from cyclohexyl isopropylamine and n-butyl lithium (50 mmol) at −78 °C and the mixture was stirred for 2 h at −20 °C. After addition of crotyl bromide (4.46 mL, 45.09 mmol) at −78 °C, this solution was further stirred for 3 h at −20 °C. The reaction mixture was treated with aqueous NH₄Cl and extracted with CHCl₃. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (4:1) as the eluant to afford 3 (4.2 g, 61.1%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1720, 1610. 1H-NMR (CDCl₃) δ: 1.60 (3H, d, J = 5.5 Hz, Me), 2.26–2.63 (2H, m, 6-H), 3.45 (3H, s, OMe), 4.74–4.81 (1H, m, 5-H), 5.09 (1H, d, J = 6.1 Hz, OCH₃), 5.11 (1H, d, J = 6.1 Hz, OCH₃), 5.30–5.38 (1H, m, 7-H), 5.50–5.61 (1H, m, 8-H). MS m/z: 198 (M⁺).

(3S,4S,5S)-4-Butyl-3-methoxymethoxy-γ-butyrolactone (4) and (3S,4S,5R)-4-Butyl-3-methoxymethoxy-γ-butyrolactone (5) A solution of 3 (2.2 g, 11.1 mmol) in AcOEt (20 mL) containing 5% rhodium on alumina (0.45 g) was stirred under medium pressure (7 atm) of hydrogen for 4 h and the insoluble material was filtered off. The filtrate was concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (10:1) afforded 4 (1.7 g, 75%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1760. 1H-NMR (CDCl₃) δ: 0.90–1.85 (9H, m, n-Bu), 2.62 (1H, dd, J = 1.8, 17.7 Hz, 3-H), 2.72 (1H, dd, J = 4.9, 17.7 Hz, 3-H), 3.38 (3H, OMe), 4.33–4.47 (2H, m, 4-H, 5-H), 4.62, 4.67 (each 1H, dd, J = 6.7 Hz, OCH₃). MS m/z: 141 (M⁺–OMOM).

(3S,4S,5S)-1-Benzoyloxy-4-benzylxy-3-methoxymethoxyoctane (9) A solution of 8 (550 mg, 1.86 mmol), benzyl chloride (0.35 mL, 3.02 mmol) and pyridine (0.35 mL, 3.02 mmol) in THF (10 mL) was added slowly to the THF (2 h) saturated with NH₄Cl. This reaction mixture was stirred at ambient temperature for 6 h, then poured into aqueous NH₄Cl and extracted with AcOEt. The organic layer was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (20:1) as the eluant to afford 7 (2.43 g, 78.3%) as a colorless oil. IR (CHCl₃) cm⁻¹: 3300. 1H-NMR (CDCl₃) δ: 0.88–1.92 (11H, m, n-Bu, 2-H₂), 3.41 (3H, s, OMe), 3.55–3.76 (4H, m, 1-H, 3-4, 4-H), 4.71 (2H, s, OCH₂O). MS m/z: 259 (M⁺–OMOM).

(3S,4S,5S)-1-Benzoyloxy-4-benzylxy-3-methoxymethoxyoctane (10) A solution of 9 (70 mg, 0.18 mmol) and 10% HCl in THF (5 mL) was heated at reflux for 2 h, and then diluted with AcOEt. The combined organic layer was washed with aqueous NaHCO₃ and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (8:1) as the eluant to afford 10 (51 mg, 81.9%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1710. 1H-NMR (CDCl₃) δ: 0.87–2.11 (21H, m, n-Bu, 2-H₂), 3.43 (3H, OMe), 4.05–4.46 (2H, m, 4-H, 5-H), 4.66 (2H, s, OCH₃). MS m/z: 356 (M⁺–OMOM).

(3S,4S,5S)-1-Benzoyloxy-4-benzylxy-3-hydroxyoctane (11) A solution of 10 (40 mg, 0.25 mmol), 2-butyldimethylsilyl chloride (114 mg, 0.76 mmol) and imidazole (52 mg, 0.76 mmol) in dry THF (5 mL) was stirred at room temperature for 6 h, then the mixture was poured into ice-cooled water and extracted with AcOEt. The extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave a residue,
which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (30:1) afforded 11 (102 mg, 85.9%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1710. ¹H-NMR (CDCl₃) δ: 0.69 (6H, s, SiMe₃), 0.89 (9H, s, tert-Bu), 0.93–2.14 (11H, m, n-Bu, 2-H), 3.37 (1H, dd, J = 2.4, 4.9, 9.2 Hz, 4-H), 4.01–4.08 (1H, m, 3-H), 4.28–4.53 (2H, m, 1-H), 4.55, 4.61 (each 1H, each d, J = 11.6 Hz, CH₃Ph), 7.24–8.05 (10H, m, aromatic protons). MS m/z: 308 (M⁺→tert-Bu).

(35S,45S)-4-Benzyloxy-3-tert-butyldimethylsiloxoyoctanal (12) A solution of 11 (120 mg, 0.26 mmol) and 10% aqueous NaOH (0.5 ml) in MeOH (5 ml) was stirred at room temperature for 2h, and then treated with water. The mixture was extracted with AcOEt and the extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (9:1) as the eluant to afford 12 (81 mg, 86.7%) as a colorless oil. IR (CHCl₃) cm⁻¹: 3300. ¹H-NMR (CDCl₃) δ: 0.02, 0.05 (each 3H, each s, SiMe₃), 0.86–1.97 (11H, m, n-Bu, 2-H), 2.36 (1H, br s, OH), 3.33–3.59 (1H, m, 3-H), 3.71 (2H, br s, 1-H), 3.97 (1H, dt, J = 4.3, 7.9 Hz, 4-H), 4.55, 4.61 (each 1H, each d, J = 11.6 Hz, CH₃Ph), 7.28–7.35 (5H, m, aromatic protons). MS m/z: 309 (M⁺→tert-Bu).

(35S,45S)-4-Benzyloxy-3-tert-butyl(dimethyl)siloxyoctanal (13) A solution of 12 (105 mg, 0.29 mmol) in CH₂Cl₂ (10 ml) was added to a stirred suspension of PCC (180 mg, 0.84 mmol) and sodium acetate (20 mg, 0.24 mmol) in CH₂Cl₂ (70 ml) at room temperature and the mixture was further stirred for 1 h. After dilution with Et₂O, the mixture was filtered through a Celite pad to remove insoluble material and the filtrate was concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (20:1) gave 13 (95 mg, 91.0%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1720. ¹H-NMR (CDCl₃) δ: 0.02, 0.04 (each 3H, each s, SiMe₃), 0.85 (9H, s, tert-Bu), 0.86–1.67 (9H, m, n-Bu), 2.49 (1H, dd, J = 2.2, 7.9, 15.8 Hz, 2-H), 2.68 (1H, dd, J = 1.8, 4.3, 15.8 Hz, 2-H), 3.32–3.38 (1H, m, 3-H), 3.49 (1H, dd, J = 3.7, 4.3, 7.9 Hz, 4-H), 4.52, 4.57 (each 1H, each d, J = 11.6 Hz, CH₃Ph), 7.28–7.38 (5H, m, aromatic protons), 9.76 (1H, dd, J = 1.8, 2.2 Hz, CHO). MS m/z: 307 (M⁺→tert-Bu).

Ethyl (55S,65S)-6-Benzyloxy-5-tert-butyl(dimethyl)siloxy-3-oxo-decanate (14) A solution of 13 (30 mg, 0.08 mmol) in CH₂Cl₂ (5 ml) was added dropwise to a stirred solution of ethyl diazoacetate (20 mg, 0.16 mmol) and a catalytic amount of SnCl₂ in CH₂Cl₂ (5 ml) at ambient temperature over a period of 10 min. The mixture was further stirred for 4 h, and then poured into aqueous NH₄Cl solution and extracted with CH₂Cl₂. The extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (20:1) gave 14 (35 mg, 94%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1720. ¹H-NMR (CDCl₃) δ: 0.04, 0.06 (each 3H, each s, SiMe₃), 0.89 (9H, s, tert-Bu), 0.91–1.71 (12H, m, n-Bu, Me), 2.66 (1H, dd, J = 7.9, 15.9 Hz, 4-H), 2.81 (1H, dd, J = 3.7, 15.9 Hz, 4-H), 3.33–3.38 (1H, m, 5-H), 3.47 (2H, s, 2-H), 4.22 (2H, q, J = 7.3 Hz, OCH₂Me), 4.46–4.53 (1H, m, 6-H), 4.50, 4.62 (each 1H, each d, J = 11.6 Hz, CH₃Ph), 7.30–7.41 (5H, m, aromatic protons). MS m/z: 393 (M⁺→tert-Bu).

Ethyl (55S,65S)-6-Benzylxy-5-hydroxy-3-oxodecanate (15) A solution of 14 (156 mg, 0.35 mmol) and 10% HCl (10 drops) in EtOH (1 ml) was stirred at room temperature for 2h, and the mixture was extracted with an excess of CH₂Cl₂. The organic layer was washed with aqueous NaHCO₃ and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (5:1) to afford 15 (103.5 mg, 88.9%) as a colorless oil. IR (CHCl₃) cm⁻¹: 1720. ¹H-NMR (CDCl₃) δ: 0.91 (3H, t, J = 7.3 Hz, Me3), 1.24–1.71 (9H, m, CH₃(CH₂)₃, CH₃), 2.62–2.74 (3H, m, 4-H, OH), 3.32–3.45 (1H, m, 6-H), 3.51 (2H, s, 2-H), 4.12–4.17 (1H, m, 5-H), 4.18 (2H, q, J = 7.3 Hz, OCH₂Me), 4.49, 4.63 (each 1H, each d, J = 11.6 Hz, CH₃Ph), 7.26–7.39 (5H, m, aromatic protons). MS m/z: 318 (M⁺→H₂O).

References