Synthesis of 7-epi-Goniodiol by Proline-Catalyzed Diastereoselective Direct Aldol Reaction

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Abstract: A simple organocatalytic approach was developed for the total synthesis of 7-epi-goniodiol. The strategy involves L-proline-catalyzed diastereoselective direct aldol reaction and Baeyer–Villiger oxidation as key steps for the construction of chiral lactone.

Key words: styryllactones, 7-epi-goniodiol, proline, aldol reaction, Baeyer–Villiger oxidation

Styryl lactones are heterocyclic natural products mainly isolated from plants of the genus Goniothalamus (Annonaceae) and possess activities including antitumor, antifungal, and antibiotic properties. The biological activities and interesting structural features of styryl lactones have attracted attention for their synthesis. 7-epi-Goniodiol (1) along with leiocarpin B (2) and leiocarpin C (3, Figure 1) was isolated by Mu and co-workers (from the ethanolic extract of stem barks of Goniothalamus leiocarpus, a tropical plant widespread in the south of the Yunnan province in China. The structure of 1 was elucidated and its stereochemistry was defined based on spectroscopic methods, X-ray crystallographic analysis, and some chemical transformations. It contains three stereocenters (6R,7S,8R) and an α,β-unsaturated pyrone ring system. 7-epi-Goniodiol (1) exhibited strong inhibitory activity against HL-60 at a low concentration (11 g/mL) and displayed selective activities in the trypan blue dye exclusion test.

In recent years, the proline-catalyzed asymmetric aldol reaction has been extensively studied and has emerged as an impressive protocol for the synthesis of various natural products. We report herein the total synthesis of 1 using a proline-catalyzed diastereoselective direct aldol reaction as the key step.

The retrosynthetic analysis of 1 is shown in Scheme 1. The lactone moiety in 1 was envisaged to be accessible through Baeyer–Villiger oxidation of ketone 4, which could be derived from L-proline-catalyzed diastereoselective direct aldol reaction between aldehyde 5 and cyclopentanone (6). Thus, the main points of this synthetic strategy are the C–C bond formation between 5 and 6, ring expansion of the ketone to a lactone, and introduction of the olefinic double bond, en route to the construction of the α,β-unsaturated lactone of the target molecule.

The stereocenter at C-8 was envisaged to be derived from (R)-mandelic acid, while, the C-6, C-7 vic-diol would be generated through the proline-catalyzed aldol reaction. Baeyer–Villiger oxidation was expected to permit efficient expansion of the ketone to the lactone, while the un-
saturation would be created through a selenation–deselenation protocol.

Thus, the synthesis of \( 1 \) began with the known alcohol \( 7 \) (Scheme 2). Accordingly, oxidation of \( 7 \) with IBX in EtOAc and DMSO at reflux for two hours gave the corresponding aldehyde \( 5 \) which was subjected to L-proline-catalyzed diastereoselective direct aldol reaction with cyclopentanone \( 6 \) at room temperature for 12 hours to afford a diastereomeric mixture of \( 8a \) and \( 8b \). After purification by flash column chromatography on silica gel (11% EtOAc in PE), diastereomers \( 8a \) and \( 8b \) were obtained in 82% yield in a ratio of 88:12, respectively.

The major diastereomer \( 8a \) was subjected to FeCl\(_3\)-6H\(_2\)O in CH\(_2\)Cl\(_2\) at room temperature for five hours, afforded the acetonide \( 9 \) in 78% yield (Scheme 2). The absolute stereochemistry of \( 9 \) was confirmed from its specific rotation value \([\alpha]_D^{25} +97.0 \text{ (c 0.95, CHCl}_3\})\], comparable with the reported \([\alpha]_D^{25} +96.4 \text{ (c 0.3, CHCl}_3}\})\]. The spectroscopic and physical data of synthetic \( 1 \) were consistent with the data reported in the literature.

Thus, in conclusion, a simple organocatalytic route, catalyzed by L-proline, for the total synthesis of 7-epi-gonio-diol \( 1 \) has been achieved. Of the three stereocenters, two are obtained from the proline-catalyzed diastereoselective direct aldol reaction, while the third stereocenter was derived from L-mandelic acid. This strategy has significant potential for the synthesis of a variety of other biologically important styrylpyrones.

Finally, deprotection of the MOM groups in \( 11 \) was affected by reaction with FeCl\(_3\)-6H\(_2\)O in CH\(_2\)Cl\(_2\) at room temperature for two hours to afford \( 1 \) in 78% yield \([\alpha]_D^{25} +107.6 \text{ (c 0.3, CHCl}_3\})\]. The spectroscopic and physical data of synthetic \( 1 \) were consistent with the data reported in the literature.

Thus, in conclusion, a simple organocatalytic route, catalyzed by L-proline, for the total synthesis of 7-epi-gonio-diol \( 1 \) has been achieved. Of the three stereocenters, two are obtained from the proline-catalyzed diastereoselective direct aldol reaction, while the third stereocenter was derived from L-mandelic acid. This strategy has significant potential for the synthesis of a variety of other biologically important styrylpyrones.  

\( \text{(R)}-2-[(\text{IR,2R})-1-Hydroxy-2-(methoxymethoxy)-2-phenylethyl]cyclopentanone (8a) \) and \( \text{(R)}-2-[(\text{S,2R})-1-Hydroxy-2-(methoxymethoxy)-2-phenylethyl]cyclopentanone (8b) \)  

A suspension of IBX (11.5 g, 41.1 mmol) in DMSO (5.0 mL) was cooled to 0 °C, treated with a solution of alcohol \( 7 \) (5 g, 27.4 mmol) in EtOAc (60 mL) and stirred at r.t. for 2 h. The reaction mixture was filtered through a Celite® pad and washed with EtOAc (4 × 20 mL). The organic layers were washed with \( \text{H}_2\text{O} \) (2 × 30 mL), brine (40 mL), dried (\( \text{Na}_2\text{SO}_4\)), filtered, and evaporated to give the corresponding aldehyde \( 5 \), which was directly used for the next reaction.

A mixture of aldehyde \( 5 \) (4.9 g, 27.2 mmol), cyclopentanone (6, 5 mL), and L-proline (0.94 g, 8.1 mmol) were stirred at r.t. for 12 h. The reaction mixture was quenched with \( \text{H}_2\text{O} \) (10 mL) and extracted with CHCl\(_3\) (4 × 20 mL). The combined extracts were dried (\( \text{Na}_2\text{SO}_4\)), filtered, evaporated, and the residue purified by column chromatography (60–120 mesh silica gel, 11% EtOAc in PE) to afford 5.19 g of \( 8a \) (\( R_f = 0.50 \)) and 0.71 g of \( 8b \) (\( R_f = 0.45 \)) in 82% yield.

Compound \( 8a \): \([\alpha]_D^{25} +40.1 \text{ (c 0.5, CHCl}_3\})\). IR (neat): 3351, 2823, 2857, 1689, 1447 cm\(^{-1}\). \( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta = 7.33–7.16 \), 7.01–6.87, 5.48–4.89, 4.35–4.09, 3.91–3.79, 3.74–3.69, 3.66–3.40, 3.38–3.24, 3.13–2.97, 2.82–2.58, 2.46–2.27, 2.10–1.82, 1.96–1.07, 1.03–0.86 ppm.
(m, 5 H, ArH), 4.51 (q, 2 H, J = 6.9, 13.8 Hz, OCH2), 4.36 (d, 1 H, J = 9.3 Hz, OCH), 4.27 (dd, 1 H, J = 1.9, 8.8, 10.8 Hz, OCH), 3.31 (s, 3 H, CH3). 13C NMR (75 MHz, CDCl3): δ = 138.3, 128.2, 128.0, 127.9, 94.9, 79.7, 75.9, 55.9, 48.7, 39.5, 27.3, 20.8. HRMS: m/z calculated for C17H24O5Na+ [M + Na]+: 287.1259; found: 287.1265.

Compound 8b: [a]25D = −102.5 (c = 0.08, CHCl3). IR (neat): 3351, 2823, 1689, 1447 cm–1. 1H NMR (300 MHz, CDCl3); δ = 7.35–7.26 (m, 5 H, ArH), 4.70 (q, 2 H, J = 6.7, 9.4 Hz, OCH2), 4.30 (d, 1 H, J = 8.8 Hz, OCH), 4.24–4.20 (m, 1 H, OCH), 3.26 (s, 3 H, OCH3), 2.17–1.86 (m, 5 H, 2 × CH2, CH), 1.60–1.51 (m, 2 H, CH2). 13C NMR (75 MHz, CDCl3): δ = 137.6, 128.6, 128.5, 127.6, 94.5, 81.3, 73.3, 55.7, 49.7, 38.7, 22.2, 20.6. HRMS: m/z calculated for C17H24O5Na+ [M + Na]+: 287.1259; found: 287.1260.

(R)-2-[(4R,SR)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)cyclopentanone (9)
To a solution of MOM ether 8a (0.05 g, 0.18 mmol) in CHCl3 (1.5 mL) was added FeCl3·6H2O (10 mol%, 0.005 g) at 0 °C, and the reaction mixture was stirred at r.t. for 2 h. It was then quenched with NaHCO3 (aq, 8 mL), H2O (aq, 10 mL), brine (aq, 10 mL), and dried (Na2SO4). After filtration, the solvent was evaporated, and the residue purified by flash column chromatography (60–120 mesh silica gel, 6% EtOAc in PE) to afford 9 (0.03 g, 78%) as a pale brown oil; [α]25D = +98.0 (c = 0.95, CHCl3). IR (neat): 3448, 2956, 2925, 2854, 1734, 1642 cm–1. 1H NMR (500 MHz, CDCl3): δ = 7.40–7.31 (m, 5 H, ArH), 4.51 (d, 1 H, J = 5.5 Hz, OCH), 4.45 (d, 1 H, J = 6.9 Hz, OCH2), 4.30 (d, 1 H, J = 7.6 Hz, OCH), 3.24 (s, 3 H, OCH3), 2.63–2.54 (m, 1 H, CH2). 13C NMR (75 MHz, CDCl3): δ = 138.7, 128.4, 127.4, 98.3, 94.4, 82.4, 79.2, 79.4, 56.3, 55.8, 29.8, 22.8, 21.1, 18.4. HRMS: m/z calculated for C17H20O4Na+ [M + Na]+: 347.1470; found: 347.1472.

(R)-6-[(5R,6R)-6-Phenyl-2,4,7,9-tetraoxadecan-5-yl]-5,6-dihydro-2H-pyran-2-one (10)
To a stirred solution of LiHMDS (1.4 mL, 1.07 mmol) in THF (1.5 mL) at –78 °C was added, dropwise, a solution of 10 (0.25 g, 0.77 mmol) in THF (3.5 mL). After 30 min, phenylselenenyl bromide (0.27 g, 1.06 mmol) was added and the reaction stirred for 1 h. The mixture was then quenched with aq NH4Cl (4 mL), distilled H2O (8 mL) and extracted with Et2O (20 mL). The combined organic extracts were filtered through a pad of silica gel (eluting with Et2O) and evaporated to give a slightly orange oil.

To a stirred solution of the above compound in CH2Cl2 (5 mL) at 0 °C, aq H2O2 (30%, 2 mL) was added, and the mixture was stirred at r.t. for 10 min. It was extracted with CH2Cl2 (20 mL) and dried (Na2SO4). After filtration, the solvent was evaporated, and the residue purified by flash chromatography (60–120 mesh silica gel, 8% EtOAc in PE) to afford 11 (0.17 g, 72%) as a colorless oil; [α]25D = +148.0 (c = 0.95, CHCl3). IR (neat): 2968, 2933, 1720, 1494, 1438, 1380, 1263, 1030 cm–1. 1H NMR (500 MHz, CDCl3); δ = 7.40–7.31 (m, 5 H, ArH), 6.86–6.78 (m, 1 H, CH=CH), 5.95–5.91 (m, 1 H, CH=CH), 4.82 (d, 1 H, J = 5.5 Hz, OCH), 4.66–4.58 (m, 4 H, OCH2), 4.38 (d, 1 H, J = 7.0 Hz, OCH), 3.33 [d, 6 H, J = 7.8 Hz (OCH3)], 2.63–2.54 (m, 1 H, CH), 2.28–2.19 (m, 1 H, CH). 13C NMR (75 MHz, CDCl3); δ = 145.5, 128.7, 128.3, 127.3, 120.8, 98.2, 94.4, 81.5, 76.8, 76.4, 56.3, 55.9, 31.4, 29.6, 24.9. HRMS: m/z calculated for C17H24O6Na+ [M + Na]+: 345.1315; found: 345.1308.

7-epi-Goniodiol (11)
To a solution of 11 (0.03 g, 0.09 mmol) in CH2Cl2 (1 mL) at 0 °C, FeCl3·6H2O (10 mol%, 0.02 g) was added, and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with H2O (1 mL) and extracted with CH2Cl2 (2 × 12 mL). The combined organic layers were washed with brine (10 mL), dried (Na2SO4), filtered, and evaporated. The residue was purified by column chromatography (60–120 mesh silica gel, 50% EtOAc in PE) to afford 11 (0.19 g, 78%) as a viscous liquid; [α]25D = +107.6 (c = 0.3, CHCl3); lit. [a]25D = +96.4 (c = 0.3, CHCl3). IR (neat): 3451, 2986, 1719, 1645, 1440, 1375, 1210, 1058 cm–1. 1H NMR (500 MHz, CDCl3); δ = 7.39–7.37 (m, 5 H, ArH), 6.95–6.89 (m, 1 H, CH=CH), 6.02–5.97 (m, 1 H, CH=CH), 4.93 (d, 1 H, J = 3.9 Hz, OCH), 4.46–4.40 (m, 1 H, OCH), 4.24–4.18 (m, 1 H, OCH), 2.64–2.58 (m, 1 H, CH), 2.54–2.49 (m, 1 H, CH). 13C NMR (75 MHz, CDCl3); δ = 145.2, 138.7, 128.3, 127.3, 120.8, 98.2, 94.4, 81.5, 76.8, 76.4, 56.3, 55.9, 31.4, 29.6, 24.9. HRMS: m/z calculated for C17H24O6Na+ [M + Na]+: 345.1315; found: 345.1308.

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References


