Studies toward a Total Synthesis of Rhizoxin D: Stereoselective Preparation of the C11–C19 Fragment

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Abstract: The C11–C19 fragment of rhizoxin D was synthesized efficiently and stereoselectively. Stereoselective induction at C13 was achieved by means of the Crimmins protocol, whereas a substrate-controlled lithium aldol reaction gave the desired selectivity at the C17 position.

Key words: acyl thiazolidinone, lithium aldol reaction, Crimmins protocol, rhizoxin D

Rhizoxin D (2), a 16-membered anti-tumor macrolide and biogenetic precursor of rhizoxin (1), was isolated from the fungus *Rhizopus chinensis* by Iwasaki and co-workers.2 The biological profile of this molecule is characterized by a strong cytotoxic activity against human tumor cell lines.3–5 All the congeners of this family share a common carbon skeleton, i.e. a 16-membered macrolactone, but differ in the numbers of epoxy groups present. The interesting biological activity and challenging macrolide structure have prompted several groups to attempt syntheses of rhizoxin D, and eight total syntheses of rhizoxin D has been reported,6 along with syntheses of several fragments of the molecule.7 Here, we report details of our stereoselective synthesis of the C11–C19 fragment.

Our synthesis began with the addition of allyl(tributyl)tin8 to the known aldehyde 3 in the presence of tin(IV) chloride to give alcohol 4 in 92% yield and 36:1 diastereoselectivity. Protection of the allyl alcohol followed by oxidative cleavage of the terminal olefin by using osmium tetroxide/sodium periodate in the presence of 2,6-dimethylpyridine gave aldehyde 6. The C13 stereocenter was introduced with the desired stereochemistry by means of the Crimmins aldol protocol.9 Addition of a titanium enolate derived from 4-benzyl-3-propionyl-1,3-oxazolidin-2-one to aldehyde 6 resulted in formation of the *syn*-aldol product 7 in a 85% yield and excellent diastereoselectivity ( 96%). Reductive removal of the chiral auxiliary with sodium borohydride in tetrahydrofuran10 gave the corresponding alcohol 8 in a good yield. Regioselective cleavage11 of the acetal group of 8 by diisobutylaluminium hydride in dichloromethane gave alcohol 9 (Scheme 1).

Tosylation of alcohol 9 gave the tosylate 10, which was converted into the corresponding terminal olefin 11 by heating with sodium iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene in 1,2-dimethoxyethane.12 The synthesis of compound 11 from compound 9 helped us in determining the stereochemistry and the anti-relationship between the C13 and C15 alcohol groups by single-crystal X-ray diffraction analysis.13

As the stereochemistry at C13 chiral center was correct, we converted fragment 9 into the C11–C19 fragment as shown in Scheme 2. Alcohol 9 was silylated to give the protected derivative 12, which was debensylated with Raney nickel under hydrogen to give the corresponding alcohol 13. This was converted into the aldehyde 14 by treatment with Dess–Martin periodinane.14 The tert-butyllithium-mediated reaction of aldehyde 14 with 2-bromopropane provided the required homologation to give the protected C11–C19 fragment 15. A lithium aldol addition reaction of the *anti*-substituted aldehyde 14 gave the expected Felkin diastereomer with a good level of selectivity (80:20) at the C-17 position.15
In conclusion, we synthesized the key C11–C19 fragment of rhizoxin D from the known aldehyde 3. The route involved the Crimmins aldol protocol, a Lewis acid mediated stereochemical induction, and a substrate-controlled lithium aldol reaction to introduce the desired stereo-centers at C13, C15, and C17, respectively. This flexible approach provides us with a robust route toward a total synthesis of rhizoxin D and its structural analogues for biological studies, which are currently underway in our laboratory.

Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 25 °C. Concentrations (c) are quoted in g/100 mL. IR spectra were recorded on a Schimadzu IR Prestige 21 FT-IR spectrometer, and the absorption bands are reported in cm⁻¹. ¹H NMR spectra were determined on a Varian Mercury Plus spectrometer at 400 MHz, and ¹³C NMR spectra were determined on a Varian Gemini-2000 spectrometer at 200 MHz; CDCl₃ was used as a solvent in both cases. Proton chemical shifts (δ) are reported relative to TMS (δ = 0.00) as internal standard, and expressed in ppm. The spin multiplicities are given as s (singlet), d (doublet), t (triplet), m (multiplet), and br s (broad singlet), and the coupling constants (J) are given in Hz. Coupling constants were rounded to the first place after the decimal point. ESI-MS spectra were obtained on a Perkin-Elmer API 3000 spectrometer. Column chromatography was carried out with silica gel (grade 60-120, 100–200 mesh). Reactions were monitored by TLC on silica gel plates (60 F₂₅₄), and spots were visualized by UV irradiation or staining with alkaline KMnO₄. Unless

Scheme 1  Reagents and conditions: (a) CH₂CH=CHSnBu₃, SnCl₄, CH₂Cl₂, −90 °C to 0 °C, 1 h, 92%; (b) TBDPSCl, imidazole, DMF, r.t., 10 h, 95%; (c) OsO₄, NaIO₄, 2,6-dimethylpyridine, THF–H₂O (3:1), r.t., 5 h, 85%; (d) TiCl₄, (−)-sparteine, CH₂Cl₂, −78 °C to 0 °C, 2 h, 90%; (e) NaBH₄, MeOH–THF (>200:1), r.t., 4 h; (f) 4-MeOC₆H₄CH(OMe)₂, CSA, CH₂Cl₂, r.t., 16 h, 74% (two steps); (g) DIBAL-H, CH₂Cl₂, 0 °C, 2 h, 90%; (h) TsCl, py, r.t., 3 h, 93%; (i) NaI, DBU, MeO(CH₂)₂OMe, 85 °C, 2.5 h, 96%.

Scheme 2  Reagents and conditions: (a) TBSCI, imidazole, DMF, r.t., 10 h, 91%; (b) H₂, Raney-Ni, EtOH, r.t., 24 h, 81%; (c) Dess–Martin periodinane, CH₂Cl₂, r.t., 0.5 h, 89%; (d) 2-bromopropene, t-BuLi, THF, −78 °C to 0 °C, 4 h, 63%.
stated otherwise, reactions were performed under N₂. All other reagents were purchased from Aldrich at the highest commercial quality, and used without further purification.

(2R,3S)-1-Benzoyloxy-2-methylhex-5-en-3-ol (4)
A 1.0 M soln of SnCl₂ in CH₂Cl₂ (117.99 mL, 117.99 mmol) was added rapidly from a syringe to a soln of allyltributylstannane (37.7 mL, 117.95 mmol) in CH₂Cl₂ (200 mL) at –78 °C. When the addition was complete, the soln was cooled from –78 °C to –90 °C, a soln of (R)-3-benzoyloxy-2-methylpropanol (15.0 g, 84.26 mmol) in CH₂Cl₂ (100 mL) was added dropwise, and the mixture was kept at –90 °C for 0.5 h. Sat. aq NaHCO₃ (160 mL) was added, the mixture was warmed to r.t., and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3 × 150 mL), and the combined extracts were filtered through a pad of Florisil. The filtrate was concentrated, and the residue was purified by column chromatography [silica gel, EtOAc–hexanes (20:80) to give a single diastereomer of hexane (3:97)] to give a colorless oil; yield: 0.385 g (92.7%); [α]D²⁰ = 5.91 (c 1.23, CHCl₃).

IR (neat): 3457, 2905, 1640, 1454, 1363 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 0.93 (d, J = 6.8 Hz, 3 H), 1.89 (m, 1 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 3.07 (d, J = 3.6 Hz, 1 H, OH), 3.50 (dd, J = 9.6, 7.2 Hz, 1 H), 3.61 (m, 2 H), 4.52 (s, 2 H), 5.13 (m, 2 H), 5.90 (m, 1 H), 7.32 (m, 5 H).

13C NMR (50 MHz, CDCl₃): δ = 22.7, 41.8, 48.1, 51.2, 53.5, 69.4, 72.7, 72.8, 72.9, 74.6, 74.9, 117.1, 126.7, 127.6, 128.4, 137.8.

HRMS: m/z calcd for C₂₉H₃₆NaO₃Si [M + Na⁺]: 483.2331; found: 483.2326.

(4R)-4-Benzyl-3-[[(2R,3S,5S,6R)-7-benzoyloxy]-5-[(tert-butyldiphenylsilyloxy)-3-hydroxy-2,6-dimethylpentanoyl]-1,3-o xoazolidin-2-one (7)
TiCl₄ (0.102 mL, 0.934 mmol) was added dropwise over 5 min to a stirred soln of 4-benzyl-3-propionyl-1,3-oxazolidin-2-one (0.207 g, 0.98 mmol) in CH₂Cl₂ (5 mL) at 0 °C under argon. A 2 M soln of LiBH₄ in THF (1.26 mL, 2.52 mmol) was added dropwise to the yellow slurry, and the resulting dark red enolate was stirred for 20 min at 0 °C. Aldehyde 6 (0.45 g, 0.97 mmol) in CH₂Cl₂ (1 mL) was added dropwise, and the mixture was stirred for 1 h at 0 °C. The reaction was then quenched with half-sat. aq NH₄Cl (5 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash column chromatography [silica gel, EtOAc–hexane (25:75)] to give compound 7 as a colorless thick liquid; yield: 0.63 g (93%); [α]D²⁰ = 69.2 (c 0.5, CHCl₃).

IR (neat): 3519, 2932, 2923, 1783, 1695, 1385, 1208 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 0.95 (d, J = 6.8 Hz, 3 H), 1.04 (s, 9 H), 1.10 (d, J = 7.2 Hz, 3 H), 1.59 (m, 2 H), 2.09 (m, 1 H), 2.72 (dd, J = 13.2, 9.2 Hz, 2 H), 3.17 (dd, J = 6.4, 3.6 Hz, 1 H), 3.20 (m, J = 6.4, 3.2 Hz, 1 H), 3.45 (dd, J = 9.6, 6.8 Hz, 1 H), 3.53 (dd, J = 7.2, 3.6 Hz, 1 H), 3.93 (dd, J = 9.6 Hz, 1 H), 4.05 (m, 3 H), 4.35 (s, 2 H), 4.58 (m, 1 H), 7.30 (m, 15 H), 7.67 (m, 5 H).

13C NMR (50 MHz, CDCl₃): δ = 10.2, 10.8, 12.9, 27.1, 38.0, 38.8, 41.8, 42.9, 55.0, 65.9, 68.3, 68.7, 72.3, 72.8, 72.4, 127.4, 127.5, 125.8, 128.9, 129.4, 129.6, 133.6, 134.4, 135.1, 136.0, 138.4, 152.9, 176.5.

HRMS: m/z calcd for C₃₀H₃₈NaO₃Si [M + H⁺]: 694.3585; found: 694.3585.

7-O-Benzyl-5-O-[(tert-butylidiphenylsilyl)-2,4,6-trideoxy-1,3-O-(4-methoxybenzylidene)-2,6-dimethyl-d-gluco-heptitol (8)
A 2 M soln of LiBH₄ in THF (1.26 mL, 2.52 mmol) was added dropwise to a soln of aldol adduct 7 (0.7 g, 1.008 mmol) and anhyd MeOH (0.1 mL, 2.52 mmol) in anhyd THF (20 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, and then the reaction was quenched with 2 M aq NaOH (70.6 mL). The mixture was stirred for 18 h at r.t., the volatiles were removed under a vacuum, and the resulting slurry was extracted with Et₂O (5 × 150 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Without further purification, the diol was dissolved in 3:1 dioxane–H₂O (2 mL) and treated with 4-MeOC₆H₄CH(OMe)₂ (0.21 mL, 1.26 mmol) and CSA (0.017 g, 0.08 mmol) at r.t., and the mixture was stirred for a further 12 h. The reaction was quenched with sat. aq NaHCO₃ (10 mL), and the mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexanes (1:99)] to give a colorless oil; yield: 0.476 g (74%); [α]D²⁰ = –18.2 (c 0.5, CHCl₃).

IR (neat): 2968, 2856, 1615, 1517, 1248 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 0.97 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.06 (s, 9 H), 1.23 (m, 1 H), 1.44 (dd, J = 11.2, 9.2, 1.6 Hz, 1 H), 1.61 (dd, J = 12.4, 10.4, 2.0 Hz, 1 H), 2.10 (m, 1 H), 3.25 (dd, J = 9.6, 6.8 Hz, 1 H), 3.35 (dd, J = 9.2, 7.2 Hz, 1 H), 3.70 (m, 2 H), 4.13 (dd, J = 9.6, 6.8 Hz, 1 H).

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7-O-Benzyl-5-O-[[tert-butyl(dipheny)silyl]-2,4,6-trideoxy-3-O-(4-methoxysulfonyl)-2,6-dimethyl-1-O-[4-(methylsulfonyl)sulfonyl]-d-gluco-heptitol (9)

A 1 M solution of DIBAL-H in toluene (2.97 mL, 2.97 mmol) was added dropwise to a stirred solution of acetal 8 (0.38 g, 0.59 mmol) in CH2Cl2 (20 mL) at 0 °C, and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with MeOH (0.54 mL) and a sat. soln of sodium potassium tartrate (15 mL) was added. The mixture was stirred vigorously for 6 h and then extracted with CH2Cl2 (4 × 6 mL). The organic layer was washed with brine (6 mL), dried (Na2SO4), and concentrated in vacuo. The residue that was purified by column chromatography [silica gel, EtOAc–hexane (25:75)] to give alcohol 9 as a colorless oil; yield: 0.35 g (91%); [α]c23 +10.5 (c 1.0, CHCl3).

IR (neat): 3425, 2927, 1512, 1453, 1248 cm−1.

HRMS: m/z calc for C44H46O5Si2 [M + H]+: 641.3667; found: 641.3667.

7-O-Benzyl-5-O-[[tert-butyl(dipheny)silyl]-2,4,6-trideoxy-3-O-(4-methoxysulfonyl)-2,6-dimethyl-1-O-[4-(methylsulfonyl)sulfonyl]-d-gluco-heptitol (10)

TsCl (0.15 g, 0.79 mmol) was added to a stirred soln of alcohol 9 (0.65 g, 1.01 mmol) in DMF (5 mL), and the mixture was stirred at rt. overnight. It was then treated with sat. aq NH4Cl (5 mL) and partitioned between Et2O (10 mL) and H2O (5 mL). The Et2O layer was washed with H2O (2 × 5 mL) and brine (2 × 5 mL), dried (Na2SO4), filtered, and concentrated. The residue was purified by flash chromatography [silica gel, EtOAc–hexane (9:5)] to give compound 10 as a colorless liquid; yield: 0.697 g (91%); [α]c23 +3.30 (c 1.0, CHCl3).

IR (neat): 2956, 2857, 1513, 1244 cm−1.

HRMS: m/z calc for C45H48O5Si2 [M + H]+: 650.4282; found: 650.4308.
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Hz, 2 H), 7.40 (m, 6 H), 7.70 (m, 4 H).

J = 4.20 (d, 3.78 (s, 3 H), 3.97 (d, J = 8.4 Hz, 2 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.40 (m, 6 H), 7.70 (m, 4 H).

IR (neat): 2931, 2857, 1725, 1513, 1248 cm–1.

MS (EI, 70 eV): 29.7, 36.9, 38.4, 51.4, 55.2, 64.3, 71.0, 72.5, 76.3, 113.5, 127.6, 139.5, 140.9, 153.8, 164.7, 183.5 cm–1.

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References

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HRMS: m/z calcd for C4H6O5Si [M + H]+: 705.4370; found: 705.4380.