Diastereoselective Synthesis of a Simplified Core of Rishirilide B

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Abstract: A route enabling the synthesis of the stereo-triad of rishirilide B (1) from 2-hydroxy-3-methylnaphthalene-1,4-dione, is reported. Key transformations include the regioselective 1,2-Grignard addition to a tautomeric mixture of o- and p-quinones, regioselective carbamoylation of a tautomeric mixture, and a synopsis of the methods explored to convert various terminal vinyl ethers into the corresponding carboxylic acid by cleavage.

Key words: β-diketones, tautomers, acylation, oxidative cleavage, enol ethers

The structure of the natural product (+)-rishirilide B (1) presents several interesting synthetic challenges (Figure 1). Among these is a triad of stereochemical centers that include two adjacent tertiary alcohols distributed in an anti arrangement at β and γ sites of an α-methylated cyclohexanone core and conjoined at the δ and ε positions with an aromatic ring. Danishefsky and co-workers have reported a synthesis of its racemic core and later a synthesis of the (−)-enantiomer from (R)-3-methylcyclohexanone. Due to the lack of a general synthetic solution for the (+)-enantiomer, we began to consider some alternative approaches. Herein, we report a concise diastereoselective solution for this unique atom arrangement and reveal some unexpected reactivity of this core structure. These findings enable efficient access to the fully elaborated core structure of rishirilide B (1), albeit in racemic form.

Scheme 1

We chose to begin with the known naphthoquinones 2 and 3 (Scheme 1). While this starting material, which is available in one step, can be considered as a tautomeric mixture of the o-quinone and the p-quinone, the latter compound with a lesser dipole (μ) is more stable and more representative of the inherent reactivity and structure. Addition of isoamyilmagnesium bromide (4) (3.0 equiv, 1.5 M in THF) to the quinones 2 and 3 (0.1 M in THF, 0 °C) affords after workup with 1 M hydrochloric acid and crystallization (hot CHCl$_3$) a mixture of the tautomers 5 and 6 in 55–65% isolated yield. Presumably, addition of the first equivalent of the Grignard reagent causes deprotonation of the vinylogous acid and insulates the carbonyl groups at sites a and b from subsequent 1,2-reactivity. Nucleophilic addition occurs at the only remaining electrophilic site c. To the best of our knowledge, this reaction of compounds 2 and 3 and structures similar to it had been unknown with carbon nucleophiles.

By $^1$H NMR analysis, a mixture of tautomers 5 and 6 arise in deuterochloroform. However, over time in dimethyl sulfoxide-d$_6$ only a single tautomer 6 becomes visible. In deuterochloroform the tautomers are distinguished by the relative chemical shift for H$_a$ in their $^1$H NMR spectra (δ = 8.03 for 6, δ = 8.12 for 5). However, even if only tautomer 6 of the compound is visible by $^1$H NMR, addition of diazomethane will usually afford an approximate 1:1 mixture of the corresponding methyl ethers. Despite this problematic reactivity, we recently discovered a process that enables the mixture of tautomers 5 and 6 to be con-
verted into a single vinylogous ester.\textsuperscript{6} The process works again in this instance. Treatment of the tautomeric mixture (0.15 M in CHCl\textsubscript{3} at 25 °C) with diethylcarbamoyl chloride (7) (1.5 equiv) and Hüning’s base (4.0 equiv) provides compound 9. From our experiment with this and its structural analogues, we believe that both 9 and its regioisomer \textsuperscript{8} initially form. However, over time the mixture of products transforms into 9 with assistance from the nucleophilic nitrogen atom of the base used in the reaction. It should be noted, that compound 9 proves unstable towards both chromatography and aqueous conditions, whereupon it reverts to the tautomeric mixture of 5 and 6. Therefore, the reaction mixture is simply concentrated under reduced pressure (0.01 Torr, 12 h) and used in crude form for subsequent reactions with organolithium reagents.

The elaboration of a ketone into an $\alpha$-hydroxycarboxylic acid has ample precedent.\textsuperscript{7} The corresponding reaction among esters is known, but more rare.\textsuperscript{8} To the best of our knowledge, the functional group transformation we required for the vinylogous ester in 9 had been unknown, presumably due to the likelihood of elimination. However, as shown in Scheme 2 an excess of the lithiated enol ether \textsuperscript{10} (30 equiv, 1.72 M in THF) combines with the vinylogous ester 9 (0.15 M in THF at −78 °C to 25 °C, 2 h). Brine workup reveals the $\alpha$-hydroxyvinyl ether \textsuperscript{12} (96% isolated yield). Alternatively, addition of an excess of the lithiated enol ether \textsuperscript{11} (30 equiv, 1.72 M in THF) to 9 (0.15 M in THF at −78 °C to 25 °C, 2 h) affords 13 upon similar workup (94% isolated yield). Only one stereoisomer appears to emerge from both reactions. The relative configuration among these products was assigned by a combination of transannular nuclear Overhauser effects observed for the $\beta$-aliphatic side chain and the $\beta$-methine functionality as well as protons within the $\alpha$-enol ether and $\alpha$-methyl residue. While both enol ethers \textsuperscript{12} and \textsuperscript{13} can be purified by chromatography, the methoxymethyl enol ether \textsuperscript{13} is significantly more stable towards silica gel than the ethyl analogue \textsuperscript{12}.

Both preceding reactions prove to be very clean affording benign volatile side products. Therefore, these compounds can be used in subsequent reactions without further purification. The relative anti stereochemistry in these 1,2-diols was further confirmed by their stability towards $\text{syn}$ cleaving reagents such as sodium periodate and their formation attests to the directing power of its neighboring alkoxide. Furthermore, isolation of amides \textsuperscript{14} and \textsuperscript{15} from the corresponding reactions confirms the existence of an enolate intermediate.

Next, we investigated cleavages of these enol ethers (Scheme 3). The enol ether \textsuperscript{12} (0.4 M in MeCN–CCl\textsubscript{4}–H\textsubscript{2}O, 2:1:1) undergoes reaction with catalytic ruthenium tetroxide, generated by the combination of ruthenium(III) chloride (0.2 equiv) with sodium periodate (3.0 equiv), to afford the ethyl ester \textsuperscript{17} along with the ketone \textsuperscript{16} in 1:1 ratio and a combined yield of 64%. Attempts to prevent the formation of the ketone by using a buffered aqueous solution proved utterly unsuccessful. The more robust methoxymethyl vinyl ether \textsuperscript{13} proves marginally better in this regard. Similar conditions afford a 1.5:1 ratio of the corresponding ester \textsuperscript{18} and the ketone \textsuperscript{16} in a combined 68% yield. The methoxymethyl ester \textsuperscript{18} (0.12 M in Et\textsubscript{2}O) succumbs to cleavage with magnesium bromide (2.0 equiv) and affords the acid \textsuperscript{19}, which is converted into the corresponding methyl ester \textsuperscript{20} with diazomethane to facilitate spectral characterization. While this sequence might be applicable to rishirilide B (1) and its analogues, the loss of half of the material from the synthetic stream as the ketone
16 would be very unappealing. Therefore, we investigated a few other sequences. Ozonolysis of 12 (0.06 M in CH$_2$Cl$_2$ at −78 °C) provides the ethyl ester 17, which undergoes saponification (0.6 M in THF, 10 equiv 1 M LiOH) to afford the acid 19 after workup. However, it seemed doubtful that this sequence of reactions could be employed with the fully elaborated rishirilide core, which is expected to undergo oxidation with ozone and is reported to be unstable towards saponification with aqueous lithium hydroxide.

Therefore, we investigated processes where periodic acid or ruthenium tetroxide or other related oxidants had been reported to cleave between the ketone and the primary alcohol functionality such as found in α-hydroxycortisone.$^{11}$ To begin, the enol ether 12 (0.25 M in acetone) is first converted into the α-hydroxy ketone 22 by the addition of aqueous sodium hydrogen carbonate (20 equiv, 5 M) and Oxone (3.0 equiv) to generate 21 in situ (Scheme 4). Under these conditions the reaction proceeds to 22 in >95% isolated yield. Commercial 3-chloroperbenzoic acid was found to lead to hydrolysis and affords the unwanted ketone 16. Despite the myriad of references to the contrary, exposure of 22 to ruthenium tetroxide (generated as before) or to periodic acid (2.2 equiv) affords a mixture of diones 5 and 6 and starting material. This result would seem to suggest preferential cleavage between the more encumbered tertiary alcohol and carbonyl moiety. Therefore, we paused to consider an explanation for this unusual reactivity. Thoughtful analysis of the reaction reveals the initial oxidation of 22 proceeds as expected to the glyoxal 23. This material should have undergone hydration and then cleavage. Instead, it undergoes closure to the lactol 24, which succumbs to oxidation and affords compound 25. Under the reaction conditions, this compound affords the hydrate 26, which has been fully characterized and is a rather interesting isoelectronic analogue of rishirilide. However, with this arrangement of hydroxy groups, hydrate 26 suffers cleavage between the hydrate and the tertiary alcohol and thereby produces the starting tautomeric mixture of 5 and 6.

![Scheme 4](image_url)

This unexpected sequence of events suggests a straightforward solution to accomplish the task at hand; enter the cascade at a lower oxidation state. Thus, α-hydroxy ketone 22 is reduced with a freshly prepared solution of sodium triacetoxyborohydride at 5 °C (Scheme 5).$^{12}$ The tetroxide 27 emerges from these conditions as a single diastereomer of unassigned configuration. This material (0.08 M in CH$_2$Cl$_2$–H$_2$O, 5:1, 25 °C) undergoes the desired cleavage with sodium periodate on silica gel (2.0 equiv) to cleanly afford the aldehyde 28.$^{13}$ The aldehyde in turn is smoothly transformed into the acid 19 using Kraus’s modification of the Lindgren oxidation.$^{14}$ Methylation of the acid 19 with diazomethane in diethyl ether affords the methyl ester 20 in 91% overall yield. While the sequence leading from the enol ether 12 to the methyl ester 20 via the acid 19 is lengthy, we find that the innate architecture of this triad of stereocenters presents few other synthetic options. However, the combined efficiency and simplicity of this strategy [3 → 6 → 9 → 12 → 22 → 27 → 28 → 19 → 20] may prove useful in the future.

Reactions were monitored by analytical TLC on EM-Science hard layer silica gel-60F$^{254}$. Visualization was effected by UV light (254 nm) and staining [stain: phosphomolybdic acid (25 g), cerium sulfate (10 g), H$_2$SO$_4$ (60 mL), H$_2$O (940 mL)]. In reactions where H$_2$O

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was not present by solvent, reagent, or byproduct. Vessels were flame-dried under a slow N2 flow and a slight positive pressure of dry N2 was maintained during the course of the reaction. If the product was nonvolatile, trace solvents were removed by a Labconco freeze dryer system at a pressure of approximately 0.01 Torr. EtOAc (anhyd) and DMF (anhyd) were used directly from the bottle. Ozone was generated using Yanco Industries Ozonizer (OL 80W-PY). CDCl3 was filtered through basic alumina prior to use.

NMR spectra were recorded at 400 MHz on a Varian spectrometer. Chemical shifts are reported in ppm from TMS with the solvent resonance of CDCl3.

**Compounds 12 and 13; General Procedure**

To a cooled (dry ice/acetone), vigorously stirring solution of 2-hydroxy-3-methyl-1,4-naphthoquinone (330 mg, 1.75 mmol) in THF (20 mL) was added 1.5 M isoamylmagnesium bromide in Et2O (5.26 mmol) in a dropwise fashion. The temperature of the solution was allowed to stir for 15 min at –78 °C and subsequently warmed to r.t. was sequentially added, diethylcarbamoyl chloride (1.15 mmol) and water (0.23 mL). The colored solution corresponding to the THF–HCl and the mixture was extracted with EtOAc (2 × 100 mL) and dried (Na2SO4). Concentration afforded a red semisolid. The vinyl ether corresponding to the THF–HCl was purified by crystallization (hot CHCl3) to give a colorless oil; yield: 96% (over two steps); Rf = 0.2 tailing (30% EtOAc–hexane).

**IR (KBr):** 3267, 2952, 1742, 1644, 1617, 1591, 1567, 1385, 1227, 1038 cm⁻¹.

**HRMS (ESI-TOF):** calcd for C16H20NaO3 [(M + Na)⁺]: 283.1412; found: 283.1305.

**1H NMR (400 MHz, CDCl3):** δ = 7.92 (dd, J1 = 1.3 Hz, J2 = 7.5 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.31 (t, J = 6 Hz, 1 H), 4.41 (d, J = 2.7 Hz, 1 H), 4.17 (d, J = 2.7 Hz, 1 H), 3.39 (m, 1 H), 3.23 (m, 1 H), 3.04 (q, J = 6.4 Hz, J2 = 13.0 Hz, 1 H), 2.87 (br s, OH), 2.33 (br s, OH), 2.26 (d, J1 = 3.8 Hz, J2 = 13 Hz, 1 H), 1.63 (dt, J1 = 3.8 Hz, J2 = 13 Hz, 1 H), 1.45–1.27 (m, 6 H), 0.88–0.80 (m, 3 H), 0.71 (d, J = 6.4 Hz, 3 H), 0.59 (d, J = 7 Hz, 3 H).

**13C NMR (CDCl3):** δ = 197.4, 161.6, 145.6, 135.2, 132.2, 127.1, 126.2, 125.5, 86.1, 83.0, 76.7, 63.5, 48.6, 35.8, 31.5, 28.8, 22.8, 13.3, 9.8.


**Enol Ether 13**

Colorless oil; yield: 94% (over 2 steps); Rf = 0.15 (20% EtOAc–hexane).

**IR (KBr):** 3426, 3056, 2958, 2935, 1703, 1683, 1600, 1361 cm⁻¹.

**HRMS (ESI-TOF):** calcd for C18H24NaO4 [(M + Na)⁺]: 327.1557; found: 327.1505.

**1H NMR (400 MHz, CDCl3):** δ = 8.01 (dd, J1 = 1 Hz, J2 = 7.9 Hz, 1 H), 7.60 (dd, J1 = 0.85, J2 = 7.9 Hz, 1 H), 7.51 (t, J = 7.2 Hz, 1 H), 7.34 (t, J = 7.2 Hz, 1 H), 4.58–4.52 (m, 3 H), 4.41 (d, J = 6.4 Hz, 1 H), 3.09 (q, J = 6.6 Hz, 1 H), 2.73 (s, 3 H), 2.34 (br s, OH), 2.27 (dt, J1 = 3.6 Hz, J2 = 9.6 Hz, 2 H), 1.32–1.40 (m, 5 H), 0.83–0.91 (m, 4 H), 0.74 (d, J = 6.8 Hz, 3 H).

**13C NMR (200 MHz, CDCl3):** δ = 197.0, 159.5, 145.2, 132.6, 132.1, 127.4, 126.2, 125.8, 93.8, 89.6, 83.2, 76.6, 51.6, 48.6, 35.6, 31.9, 28.6, 22.8, 22.6, 9.7.


**Compounds 16–18 by Ruthenium Tetroxide Oxidation; General Procedure**

RuCl3 (0.2 equiv) and NaIO4 (2.9 equiv) were stirred in MeCN–CCl3–H2O (2:1:1) at t.r. for 15 min. The appropriate enol ether 12 or 13 (0.4 M in MeCN) was added to the biphasic mixture of RuO4 and the mixture stirred at t.r. for 1 h.

Ketone 16

Colorless oil; Rf = 0.18 (15% EtOAc–hexane).

**HRMS (ESI-TOF):** calcd for C18H24O4 [(M + Na)⁺]: 327.1505; found: 327.1557.

**Esters 17, 18 Using Ozone**

The appropriate enol ether 12 or 13 was dissolved in CH2Cl2 (0.5 M) and cooled (dry ice/acetone). Ozone was bubbled into the solution until it displayed a bluish tint. Bubbling was ceased and N2 was then bubbled through the solution for a short while until the color dissipated and then Me2S (3 equiv) was added. The solution was vigorously stirred at t.r. for 15 min. and then concentrated under vacuum. The colorless oil was chromatographed to provide the corresponding ester.

**Ethan Ester 17**

Isolated yield from ozonolysis: 74%; Rf = 0.15 (35% EtOAc–hexane).
1H NMR (400 MHz, CDCl₃): δ = 8.01 (dd, J₁ = 0.4 Hz, J₂ = 7.7 Hz, J₃ = 8.2 Hz, 1 H), 7.52–7.63 (m, 2 H), 7.39 (dt, J₁ = 1.4 Hz, J₂ = 7.7 Hz, J₃ = 8.5 Hz, 1 H), 4.25 (br s, OH), 3.83–3.99 (m, 2 H), 5.07 (q, J = 6.8 Hz, 1 H), 2.25 (dt, J₁ = 3.8 Hz, J₂ = 13.8 Hz, J₃ = 16.1 Hz, 1 H), 1.69 (dt, J₁ = 3.8 Hz, J₂ = 13.8 Hz, J₃ = 16 Hz, 1 H), 1.60 (br s, OH), 1.32–1.42 (m, 2 H), 1.26 (d, J = 6.9 Hz, 3 H), 0.76–0.92 (m, 4 H), 0.69–0.74 (m, 6 H).

HRMS (CI/CH₄): calcd for C₁₀H₁₀O₂ [(M + H)⁺]: 168.0392; found: 168.0384.

2H NMR (400 MHz, CDCl₃): δ = 8.01 (d, J = 7.8 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.45 (t, J = 7.1 Hz, 1 H), 4.71 (s, OH), 3.90 (s, OH), 3.43 (s, OH), 3.03 (q, J = 7 Hz, 2 H), 2.58 (dd, J₁ = 5 Hz, J₂ = 13 Hz, 1 H), 1.32–1.46 (m, 5 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.69–0.77 (m, 4 H).

13C NMR (200 MHz, CDNO₂): δ = 198.3, 175.7, 143.9, 136.8, 135.1, 131.7, 130.1, 128.1, 98.6, 92.0, 82.8, 50.6, 38.4, 35.5, 31.4, 24.3, 24.2, 10.3.

HRMS (ESI-TOF): calcd for C₁₀H₁₀NaO₂ [(M + Na)⁺]: 357.1317; found: 357.1308.

Preparation of Aldehyde 28
Chemoselective reduction: Glacial AcOH (0.25 mL) was placed in a round-bottom flask with a large overhead volume and cooled to approx. 5 °C to avoid freezing of the AcOH. NaBH₄ (0.169 mmol) was added slowly (reacted violently) and the contents were permitted to stir until bubbling ceased. The hydroxy ketone 22 (0.0843 mmol) was added and the mixture stirred at r.t. After 2 h, the solution was diluted with H₂O and extracted with CH₂Cl₂ (2 × 5 mL) then dried and concentrated in vacuo to afford the crude tetrol 27. Oxidative cleavage: In a separate flask an aq soln of NaIO₄ (0.2 mL, 0.168 mmol) was added to a suspension of silica gel (500 mg) in CH₂Cl₂ (0.5 mL) and stirred for 15 min. The crude tetrol 27 (0.084 mmol) in CH₂Cl₂ (0.5 mL) was then added to the suspension and allowed to stir for 2 h. The suspension was filtered through Celite, and the Celite was then washed with EtOAc. The collected organs where dried (Na₂SO₄). Removal of solvents yielded the aldehyde 28 as the only product visible by NMR; isolated yield: 80% (over two steps); R₂ = 0.2 (10% EtOAc–hexane).

IR (CHCl₃): 3055, 2956, 2929, 2869, 1724, 1685, 1421 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 9.33 (s, 1 H), 8.10 (dd, J₁ = 1.6 Hz, J₂ = 8 Hz, 1 H), 7.70 (m, 2 H), 7.48 (t, J = 8 Hz, 1 H), 4.31 (s, OH), 3.17 (q, J = 7 Hz, 1 H), 2.39 (s, OH), 2.19 (dt, J₁ = 3.6 Hz, J₂ = 12.8 Hz, J₃ = 30.4 Hz, 1 H), 1.74 (m, 1 H), 1.41 (m, 2 H), 1.26 (m, 1 H), 1.16 (d, J = 7.2 Hz, 3 H), 0.89 (m, 5 H), 0.76 (d, J = 6.4 Hz, 3 H).

13C NMR (CDCl₃): δ = 202.6, 196.7, 143.3, 134.5, 130.4, 128.5, 127.6, 127.1, 86.6, 76.6, 47.7, 36.1, 30.8, 28.4, 22.8, 22.6, 9.7.

HRMS (EI) calcd for C₁₂H₁₂O₂: 290.1506; found: 290.1518.

Oxidation of Aldehyde and Methylation of Acid
To a soln of aldehyde 28 (0.072 mmol) in t-BuOH–H₂O (5:1, 0.5 mL) were added NaH₂PO₄ (0.084 mmol), NaClO₂ (0.217 mmol), and 2-methyl-2-butene (0.651 mmol). The mixture was stirred for 2 h and then the solvents were removed and the residue was diluted with H₂O and extracted with CH₂Cl₂ (2 × 10 mL), dried (Na₂SO₄), and concentrated. The crude carboxylic acid (0.072 mmol) was dissolved in EtO (1 mL total) and cooled (ice/water). Freshly prepared diazomethane (0.5 mmol) was added. After 40 min, the reaction was quenched with MgSO₄, filtered, and the volatiles were removed. Purification by chromatography (silica gel) afforded a colorless oil; isolated yield of methyl ester: 91%; R₂ = 0.3 (20% EtOAc–hexane).

1H NMR (400 MHz, CDCl₃): δ = 8.04 (d, J = 7.6 Hz, 1 H), 7.55–7.63 (m, 2 H), 7.40 (t, J = 7.6 Hz, 1 H), 4.22 (s, OH), 3.44 (s, 3 H), 3.05 (q, J = 6.7 Hz, 1 H), 2.40 (br s, OH), 2.29 (dt, J₁ = 3.8 Hz, J₂ = 13 Hz, J₃ = 16 Hz, 1 H), 1.74 (dt, J₁ = 3.8 Hz, J₂ = 13 Hz, J₃ = 16 Hz, 1 H), 1.19–1.42 (m, 5 H), 0.82–0.92 (m, 4 H), 0.75 (d, J = 6.4 Hz, 3 H).

13C NMR (CDCl₃): δ = 196.8, 173.1, 143.9, 133.2, 131.1, 127.6, 126.7, 126.2, 84.8, 53.4, 48.2, 36.7, 31.6, 28.5, 22.6, 10.0.

HRMS (ESI-TOF): calcd for C₁₂H₁₂NaO₂ [(M + Na)⁺]: 343.1517; found: 343.1515.
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