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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.

Keywords

b-diketones; tautomers; acylation; oxidative cleavage; enol ethers

The structure of the natural product (+)-rishirilide B (**1**)^{1,2} 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 b and g sites of an α -methylated cyclohexanone core and conjoined at the d and e positions with an aromatic ring. Danishefsky and co-workers have reported a synthesis of its racemic core³ and later a synthesis of the (–)-enantiomer from (*R*)-3-methylcyclohexanone.⁴ 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.

We chose to begin with the known naphthoquinones **2** and **3** (Scheme 1).⁵ 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 (m) is more stable and more representative of the inherent reactivity and structure. Addition of isoamylmagnesium 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 CHCl₃) 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 ¹H NMR analysis, a mixture of tautomers **5** and **6** arise in deuteriochloroform. However, over time in dimethyl sulfoxide-*d*₆ only a single tautomer **6** becomes visible. In deuteriochloroform the tautomers are distinguished by the relative chemical shift for H_a in their ¹H NMR spectra (δ = 8.03 for **6**, δ = 8.12 for **5**). However, even if only tautomer **6** of the compound is visible by ¹H 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 converted into a single vinylogous ester.⁶ The process works again in this instance. Treatment of the tautomeric mixture (0.15 M in CHCl₃ at 25 °C) with diethylcarbamoyl chloride (**7**) (1.5 equiv) and Hünig's base (4.0 equiv) provides compound **9**. From our experimentation with this and its structural analogues, we believe that both **9** and its regioisomer **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 α -hydroxycarboxylic acid has ample precedent.⁷ The corresponding reaction among esters is known, but more rare.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 **10**⁹ (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 α -hydroxyvinyl ether **12** (96% isolated yield). Alternatively, addition of an excess of the lithiated enol ether **11**¹⁰ (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 β -aliphatic side chain and the β -methine functionality as well as protons within the α -enol ether and α -methyl residue. While both enol ethers **12** and **13** can be purified by chromatography, the methoxymethyl enol ether **13** is significantly more stable towards silica gel than the ethyl analogue **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 *syn* cleaving reagents such as sodium periodate and their formation attests to the directing power of its neighboring alkoxide. Furthermore, isolation of amides **14** and **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 **12** (0.4 M in MeCN–CCl₄–H₂O, 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 **17** along with the ketone **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 **13** proves marginally better in this regard. Similar conditions afford a 1.5:1 ratio of the corresponding ester **18** and the ketone **16** in a combined 68% yield. The methoxymethyl ester **18** (0.12 M in Et₂O) succumbs to cleavage with magnesium bromide (2.0 equiv) and affords the acid **19**, which is converted into the corresponding methyl ester **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 CH₂Cl₂ 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 a-hydroxycortisone.¹¹ To begin, the enol ether **12** (0.25 M in acetone) is first converted into the a-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-chloroper-oxybenzoic 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**.

This unexpected sequence of events suggests a straightforward solution to accomplish the task at hand; enter the cascade at a lower oxidation state. Thus, a-hydroxy ketone **22** is reduced with a freshly prepared solution of sodium triacetoxyborohydride at 5 °C (Scheme 5).¹² The tetrol **27** emerges from these conditions as a single diastereomer of unassigned configuration. This material (0.08 M in CH₂Cl₂-H₂O, 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-60^{F-250}. Visualization was effected by UV light (254 nm) and staining [stain: phosphomolybdic acid (25 g), cerium sulfate (10 g), H₂SO₄ (60 mL), H₂O (940 mL)]. In reactions where H₂O 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 utilized 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 (d = 7.27) or DMF-*d*₇ (d = 2.92). ¹³C NMR spectra were recorded at (100 MHz) with a solvent resonance of CDCl₃ (d = 77.23). IR spectra were recorded on a Shimadzu FT infrared spectrophotometer with 2 cm resolution in a solution cell (CH₂Cl₂). In some instances, flash chromatography was performed using a Jones Flashmaster Solo model 605. MS were recorded on a VG-7035 mass spectrometer at an ionizing voltage of either 70 or 20 eV.

Tautomers 5 and 6

To a cooled (dry ice/acetone), vigorously stirring soln 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 soln was maintained for 20 min and then allowed to stir at r.t. for an additional 2 h. The resulting burgundy soln was then poured into cold 1 M HCl and the mixture was extracted with EtOAc (2 • 100 mL) and dried (Na₂SO₄). Concentration afforded a red semisolid. The vinylogous acid **6** was purified by crystallization (hot CHCl₃) to give a flaky light yellow solid; yield: 55–65%; R_f = 0.2 tailing (30% EtOAc–hexane).

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

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.4 (br s, OH), 7.88 (d, *J* = 7.5 Hz, 1 H), 7.67 (d, *J* = 7.4 Hz, 1 H), 7.57 (t, *J* = 6.7 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 6.03 (br s, OH), 2.10 (m, 1 H), 1.79 (m, 5 H), 1.24 (m, 2 H), 0.67 (d, *J*₁ = 6.6 Hz, 3 H), 0.62 (d, *J* = 6.6 Hz, 3 H).

¹³C NMR (200 MHz, DMSO-*d*₆): δ = 183.9, 170.7, 144.9, 131.7, 130.3, 127.3, 125.6, 124.4, 109.7, 71.7, 32.1, 27.3, 22.3, 7.9.

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

Compounds 12 and 13; General Procedure

To a soln of vinylogous acids **5** or **6** (0.769 mmol) in CHCl₃ (5 mL) at r.t. was sequentially added, diethylcarbomoyl chloride (1.15 mmol) and *i*-Pr₂NEt (3.07 mmol) in a dropwise fashion. The orange colored soln was stirred overnight. All volatiles were removed under vacuum and the resulting oil was resuspended in dry THF (5 mL) and cooled (dry ice/acetone). In a separate 50-mL round-bottom flask, THF (11 mL) and the respective vinyl ether (23.0 mmol) were combined and cooled (dry ice/acetone). Dropwise addition of *t*-BuLi (19.2 mmol) immediately gave rise to a bright yellow colored soln corresponding to the THF-*t*-BuLi complex. The cooling bath was removed, and the color of the soln was carefully monitored. Upon disappearance of the yellow color, the soln was cooled (dry ice/acetone) and the compound **9** was added via cannula. The soln was allowed to stir for 15 min at -78 °C and subsequently warmed to 25 °C. The mixture was stirred for 1 h and then it was poured into brine and extracted with EtOAc (2 • 50 mL), washed with H₂O, dried (Na₂SO₄), and concentrated in vacuo. The corresponding enol ethers could be purified using chromatography (silica gel) or used directly.

Enol Ether 12

Colorless oil; yield: 96% (over two steps); R_f = 0.23 (15% EtOAc–hexane).

IR (CH₂Cl₂): 3558, 3051, 2958, 2869, 1685, 1620, 1600, 1103 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.92 (dd, *J*₁ = 1.3 Hz, *J*₂ = 7.5 Hz, 1 H), 7.57 (t, *J* = 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*₁ = 6.4 Hz, *J*₂ = 13.0 Hz, 1 H), 2.87 (br s, OH), 2.33 (br s, OH), 2.26 (dt, *J*₁ = 3.8 Hz, *J*₂ = 13 Hz, 1 H), 1.63 (dt, *J*₁ = 3.8 Hz, *J*₂ = 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 (t, *J* = 7 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 197.4, 161.6, 145.6, 132.5, 132.2, 127.1, 126.2, 125.5, 86.1, 83.0, 76.7, 63.5, 48.6, 35.5, 31.8, 28.5, 22.8, 22.6, 13.3, 9.8.

HRMS (ESI-TOF): calcd for $C_{20}H_{28}NaO_4$ $[(M + Na)^+]$: 355.1876; found: 355.1879.

Enol Ether 13

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

IR (KBr): 3421, 3056, 2958, 2935, 1703, 1683, 1600, 1361 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J_1 = 1 Hz, J_2 = 7.9 Hz, 1 H), 7.60 (dd, J_1 = 0.85, J_2 = 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, J_1 = 3.6 Hz, J_2 = 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).

^{13}C NMR (200 MHz, $CDCl_3$): 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, 56.1, 48.6, 35.6, 31.9, 28.6, 22.8, 22.6, 9.7.

HRMS (ESI-TOF): calcd for $C_{20}H_{28}NaO_5$ $[(M + Na)^+]$: 371.1834; found: 371.1837.

Compounds 16–18 by Ruthenium Tetroxide Oxidation; General Procedure

$RuCl_3$ (0.2 equiv) and $NaIO_4$ (2.9 equiv) were stirred in $MeCN-CCl_4-H_2O$ (2:2:1) at r.t. for 15 min. The appropriate enol ether **12** or **13** (0.4 M in $MeCN$) was added to the biphasic mixture of RuO_4 and the mixture stirred at r.t. for 1 h.

Ketone 16

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

IR (KBr): 3421, 3056, 2958, 2935, 1703, 1683, 1600, 1361 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 7.9 Hz, 1 H), 7.73 (d, J = 7.9 Hz, 1 H), 7.67 (t, J = 7.3 Hz, 1 H), 7.47 (t, J = 7.3 Hz, 1 H), 5.10 (s, 1 H), 3.11 (q, J = 7 Hz, 1 H), 2.26 (m, 2 H), 1.78 (dt, J_1 = 5.1 Hz, J_2 = 12.5 Hz, 1 H), 1.56 (s, 3 H), 1.42–1.30 (m, 2 H), 1.15 (d, J = 7 Hz, 3 H), 0.83 (m, 4 H), 0.75 (d, J = 6.4 Hz, 3 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 208.7, 197.4, 144.6, 134.2, 131.0, 128.3, 127.4, 127.1, 88.3, 48.6, 37.6, 31.5, 28.8, 28.4, 22.8, 22.6, 9.8.

HRMS (ESI-TOF): calcd for $C_{18}H_{24}NaO_4$ $[(M + Na)^+]$: 327.1557; found: 327.1557.

Esters 17, 18 Using Ozone

The appropriate enol ether **12** or **13** was dissolved in CH_2Cl_2 (0.5 M) and cooled (dry ice/acetone). Ozone was bubbled into the soln until it displayed a bluish tint. Bubbling was ceased and N_2 was then bubbled through the soln for a short while until the color dissipated and then Me_2S (3 equiv) was added. The soln was vigorously stirred at r.t. for 15 min. and then concentrated under vacuum. The colorless oil was chromatographed to provide the corresponding ester.

Ethyl Ester 17

Isolated yield from ozonolysis: 74%; R_f = 0.15 (35% EtOAc–hexane).

1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J_1 = 0.4 Hz, J_2 = 7.7 Hz, J_3 = 8.2 Hz, 1 H), 7.52–7.63 (m, 2 H), 7.39 (dt, J_1 = 1.4 Hz, J_2 = 7.7 Hz, J_3 = 8.5 Hz, 1 H), 4.25 (br s, OH), 3.83–3.99 (m, 2 H), 3.07 (q, J = 6.8 Hz, 1 H), 2.25 (dt, J_1 = 3.8 Hz, J_2 = 13.8 Hz, J_3 = 16 Hz, 1 H), 1.69

(dt, $J_1 = 3.8$ Hz, $J_2 = 13.8$ Hz, $J_3 = 16$ 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 C₁₉H₂₇O₅ [(M + H)⁺]: 335.1848; found: 335.1858

MOM Ester 18

Isolated yield from ozonolysis reaction: 71%; $R_f = 0.2$ (40% EtOAc–hexane).

¹H NMR (400 MHz, CDCl₃): d = 8.07 (dd, $J_1 = 0.9$ Hz, $J_2 = 7.8$ Hz, 1 H), 7.66 (dd, $J_1 = 0.9$ Hz, $J_2 = 7.8$ Hz, 1 H), 7.57 (dt, $J_1 = 1.4$ Hz, $J_2 = 7.3$ Hz, $J_3 = 7.8$ Hz, 1 H), 7.39 (dt, $J_1 = 1.2$, $J_2 = 7.7$ Hz, $J_3 = 8.5$, 1 H), 4.99 (dd, $J_1 = 5.5$ Hz, $J_2 = 18.4$ Hz, 2 H), 4.26 (s, OH), 3.08 (q, $J = 6.6$ Hz, 1 H), 2.86 (s, 3 H), 2.44 (br s, OH), 2.26 (dt, $J_1 = 3.8$ Hz, $J_2 = 6.5$ Hz, $J_3 = 13.8$ Hz, 1 H), 1.76 (dt, $J_1 = 3.8$ Hz, $J_2 = 6.5$ Hz, $J_3 = 13.8$ Hz, 1 H), 1.29–1.43 (m, 2 H), 1.28 (d, $J = 6.8$ Hz, 3 H), 0.83–0.94 (m, 4 H), 0.75 (d, $J = 6.5$ Hz, 3 H).

¹³C NMR (200 MHz, CDCl₃): d = 196.7, 173.3, 144.1, 133.1, 131.3, 127.6, 126.7, 126.5, 92.6, 84.8, 57.7, 48.2, 36.7, 31.6, 28.5, 22.8, 22.6, 9.9.

HRMS (ESI-TOF): calcd for C₁₉H₂₆NaO₆ [(M + Na)⁺]: 373.3959; found: 373.1531.

Deprotection of the MOM Ester 18

To a soln of MOM ester **18** (0.062 mmol) in dry Et₂O (0.5 mL) was added MgBr₂ (0.125 mmol) and the mixture allowed to stir for 2 h. The resulting soln was then diluted with H₂O, extracted with Et₂O (2 • 20 mL), and dried (Na₂SO₄) and concentrated in vacuo to give acid **19**.

Epoxidation of Enol Ethers 12 and 13

Aq NaHCO₃ (3 mL, 15.3 mmol) was added to a crude soln of enol ether (0.769 mmol) in acetone (3 mL). The resulting soln was cooled (0 °C) and Oxone (2.3 mmol) was added in one portion as a solid. Consumption of the enol ether was monitored by TLC and the reaction was typically complete in 1.5 h. The mixture was then concentrated in vacuo and resuspended in THF (5 mL). The resulting epoxide was then treated with 2 M HCl (4 mL), stirred for 1 h then extracted with EtOAc and dried (Na₂SO₄). The desired hydroxy ketone **22** was collected in almost quantitative yield from purified enol ether.

α -Hydroxy Ketone 22

$R_f = 0.2$ (40% EtOAc–hexane).

¹H NMR (400 MHz, CDCl₃): d = 8.09 (dd, $J_1 = 1.8$ Hz, $J_2 = 7.8$ Hz, 1 H), 7.63–7.69 (m, 2 H), 7.48 (m, 1 H), 4.68 (br s, OH), 3.61 (s, 2 H), 3.07 (q, $J = 7.0$ Hz, 2 H), 2.76 (br s, OH), 2.24 (dt, $J_1 = 3.8$ Hz, $J_2 = 13.9$ Hz, $J_3 = 17.6$ Hz, 1 H), 1.72 (dt, $J_1 = 3.8$ Hz, $J_2 = 13.9$ Hz, $J_3 = 17.6$ Hz, 1 H), 1.18–1.41 (m, 3 H), 1.16 (d, $J = 7.0$ Hz, 3 H), 0.81–0.90 (m, 4 H), 0.74 (d, $J = 6.4$ Hz, 3 H).

¹³C NMR (200 MHz, CDCl₃): d = 211.4, 196.5, 143.6, 134.3, 130.8, 128.7, 127.5, 127.2, 87.9, 77.0, 68.0, 48.8, 36.8, 31.4, 28.5, 22.9, 22.7, 9.9.

HRMS (ESI-TOF): calcd for C₁₈H₂₄NaO₅ [(M + Na)⁺]: 343.1531; found: 343.1515.

Hydrate 26

IR (CH₂Cl₂): 3529, 3055, 2958, 1782, 1697, 1311 cm⁻¹.

^1H NMR (400 MHz, CDCl_3): δ = 8.01 (d, J = 7.8 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.45 (t, 7 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, J_1 = 5 Hz, J_2 = 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).

^{13}C NMR (200 MHz, CD_3NO_3): 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 $\text{C}_{18}\text{H}_{22}\text{NaO}_6$ [(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. NaBH_4 (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 soln was diluted with H_2O , extracted with Et_2O (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 NaIO_4 (0.2 mL, 0.168 mmol) was added to a suspension of silica gel (500 mg) in CH_2Cl_2 (0.5 mL) and stirred for 15 min. The crude tetrol **27** (0.084 mmol) in CH_2Cl_2 (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 organics were dried (Na_2SO_4). Removal of solvents yielded the aldehyde **28** as the only product visible by NMR; isolated yield: 80% (over two steps); R_f = 0.2 (10% EtOAc–hexane).

IR (CH_2Cl_2): 3055, 2956, 2929, 2869, 1724, 1685, 1421 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 9.33 (s, 1 H), 8.10 (dd, J_1 = 1.6 Hz, J_2 = 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, J_1 = 3.6 Hz, J_2 = 12.8 Hz, J_3 = 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).

^{13}C NMR (CDCl_3): 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 $\text{C}_{17}\text{H}_{22}\text{O}_4$: 290.1506; found: 290.1518.

Oxidation of Aldehyde and Methylation of Acid

To a soln of aldehyde **28** (0.072 mmol) in *t*-BuOH– H_2O (5:1, 0.5 mL) were added NaH_2PO_4 (0.108 mmol), NaClO_2 (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 H_2O and extracted with CH_2Cl_2 (2 • 10 mL), dried (Na_2SO_4), and concentrated. The crude carboxylic acid (0.072 mmol) was dissolved in Et_2O (1 mL total) and cooled (ice/water). Freshly prepared diazomethane (0.5 mmol) was added. After 40 min, the reaction was quenched with MgSO_4 , filtered, and the volatiles were removed. Purification by chromatography (silica gel) afforded a colorless oil; isolated yield of methyl ester: 91%; R_f = 0.3 (20% EtOAc–hexane).

^1H NMR (400 MHz, CDCl_3): 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), 2.25 (dt, J_1 = 3.8 Hz, J_2 = 13 Hz, J_3 = 16 Hz, 1 H), 1.74 (dt, J_1 = 3.8 Hz, J_2 = 13 Hz, J_3 = 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).

^{13}C NMR (CDCl_3): 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 $\text{C}_{18}\text{H}_{24}\text{NaO}_5$ $[(\text{M} + \text{Na})^+]$: 343.1517; found: 343.1515.

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(+)-rishirilide B (1)

Figure 1.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.