Asymmetric Total Synthesis of Cerorubenic Acid-III

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Supplementary Materials

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I. General Information

Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere under anhydrous conditions and all reagents were purchased from commercial suppliers without further purification. Solvent purification was conducted according to *Purification of Laboratory Chemicals* (Perrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by Yantai Chemicals (China) using UV light as visualizing agent, an ethanolic solution of phosphomolybdic acid, or basic aqueous potassium permanganate (KMnO₄), and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200-300 mesh) supplied by Tsingtao Haiyang Chemicals (China). NMR spectra were recorded on Bruker AV-500 and calibrated using residual undeuterated solvent as an internal reference (CHCl₃, δ 7.26 ppm ¹H NMR, δ 77.16 ¹³C NMR; CH₂Cl₂, δ 5.32 ppm ¹H NMR, δ 54.00 ¹³C NMR; C₆D₆, δ 7.15 ppm ¹H NMR, δ 128.00 ¹³C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet, td = triplet of doublets, dt = doublet of triplets.

Melting points were obtained on an MP450-01 micro-melting point apparatus (Hanon Instrument, Shandong, China) without correction. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Infrared spectra were recorded on a Shimadzu IR Prestige 21, using thin films of the sample on KBr plates. Optical rotations were recorded on a Perkin-Elmer 351 polarimeter at 589 nm, 100 mm cell at 25 °C. Data were reported as follow: optical rotation (c (g/100 mL), solvent).

The 4-bromofuraldehyde was bought in 1 Kg at a price of 5.3 $ per 1 g from Alfachem company (http://alfachem.company.lookchem.cn/).
II. Experimental Procedures

Synthesis of S1

To a mixture of proline-derived catalyst (12, 1.3 g, 3.9 mmol, 5 mol%) and ethyl 3,4-dihydroxy benzoate (13, 2.8 g, 15.6 mmol, 20 mol%) at 0 °C was added a precooled mixture of S-citronellal (11, 12 g, 77.9 mmol) and methyl vinyl ketone (9.7 mL, 116.9 mmol, 1.5 equiv). The resulting homogeneous solution was stirred at 0 °C for 48 h and the reaction mixture was directly purified by flash-column chromatography on silica gel (hexane:EtOAc = 5:1) to afford the keto-aldehyde S1 (13.8 g, 79%, >95% de) as a colorless oil. Spectral data were identical to previously reported.\(^1\)

\(R_f = 0.52\) (hexane:EtOAc = 2:1);

**Major diastereomer:**

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 9.63\) (d, \(J = 2.7\) Hz, 1H), 5.05 (m, 1H), 2.51 (ddd, \(J = 17.8, 8.8, 5.6\) Hz, 1H), 2.36 (ddd, \(J = 17.8, 8.5, 6.6\) Hz, 1H), 2.19 – 2.15 (m, 1H), 2.12 (s, 3H), 2.04 – 1.83 (m, 4H), 1.75 – 1.69 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.42 (m, 1H), 1.28 – 1.21 (m, 1H), 0.98 (d, \(J = 6.9\) Hz, 3H);

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 207.9, 205.2, 205.2, 131.8, 123.7, 56.2, 41.3, 33.8, 33.2, 29.9, 25.6, 25.4, 19.6, 17.5, 16.8;

**HRMS (ESI)** \(C_{14}H_{24}NaO_2\) [M+Na\(^+\)]: 247.1668; found 247.1663.

Synthesis of 10
Lithium hydroxide monohydrate (LiOH, 375 mg, 8.9 mmol, 10 mol%) was added to a solution of S1 (20 g, 89.3 mmol) in isopropyl alcohol (1.5 L). The suspension was stirred at 25 °C until a light-yellow color appeared and was further stirred for 1h, or until TLC (hexane/EtOAc, 2:1) showed a completion of the reaction. The reaction was quenched with a saturated ammonium chloride solution (NH₄Cl, 50 mL). The mixture was directly concentrated in vacuo to remove of the isopropyl alcohol and then the residue was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL) and dried with anhydrous sodium sulfate (Na₂SO₄). The dried solution was filtered and concentrated. The residue was purified by flash-column chromatography on silica gel (hexane/EtOAc = 5:1) to afford 10 (16.7 g, 91%, de = 93%) as a colorless oil. Spectral data were identical to previously reported.¹

\[ R_f = 0.63 \text{ (hexane:EtOAc = 2:1);} \]

**Major diastereomer:**

¹H NMR (500 MHz, CDCl₃) \( \delta \) 6.86 (dd, \( J = 10.3, 1.9 \text{ Hz, 1H} \)), 6.01 (dd, \( J = 10.3, 2.8 \text{ Hz, 1H} \)), 5.13 – 5.03 (m, 1H), 2.50 (dt, \( J = 16.7, 4.1 \text{ Hz, 1H} \)), 2.42 – 2.40 (m, 1H), 2.34 (ddd, \( J = 16.8, 13.7, 5.1 \text{ Hz, 1H} \)), 2.05 – 1.90 (m, 3H), 1.84 – 1.75 (m, 1H), 1.68 (s, 3H), 1.66 – 1.62 (m, 1H), 1.60 (s, 3H), 1.44 – 1.34 (m, 1H), 1.27 – 1.23 (m, 1H), 0.92 (d, \( J = 7.1 \text{ Hz, 3H} \));

¹³C NMR (126 MHz, CDCl₃) \( \delta \) 200.0, 154.2, 131.7, 129.8, 124.0, 41.5, 37.6, 35.9, 33.8, 25.7, 25.7, 25.6, 17.6, 16.4;

HRMS (ESI) Calcd for C₁₄H₂₃O [M+H]^+: 207.1743; Found: 207.1749.

**Synthesis of S3**

\[
\begin{align*}
\text{4-bromofuran-2-carboxaldehyde} & \xrightarrow{\text{Dibal-H, DCM, -76 °C}} \text{TBSO} \xrightarrow{\text{then copper(II) tartrate hydrate, TBSCI, imidazole 89%}} \text{S2} \\
\text{Br} & \xrightarrow{n-\text{BuLi ethylene oxide BF}_3\text{Et}_2\text{O, Et}_2\text{O 80%}} \text{TBSO} \xrightarrow{\text{OH}} \text{S3}
\end{align*}
\]

\( n-\text{BuLi (2.4 M in hexanes, 15 mL, 36.2 mmol) was added dropwise to a solution of S2}^2 \) (10 g, 34.5 mmol, synthesized from commercially-available 4-bromofuran-2-
carbaldehyde in one-pot reaction by the known method\(^2\) in anhydrous Et\(_2\)O at -78 °C. After stirred at the same temperature for 1 hour, ethylene oxide (4.0 M in THF, 17.3 mL, 69.0 mmol) and boron trifluoride etherate (BF\(_3\)•Et\(_2\)O, 6.4 mL, 51.8 mmol) were added to the mixture subsequently. The reaction was stirred at -78 °C for another 5 minutes. The reaction was quenched with a saturated Na\(_2\)CO\(_3\) solution (100 mL), washed with sodium hydroxide (0.5M solution, 100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na\(_2\)SO\(_4\). The dried solution was filtered and concentrated. The residue was purified by flash-column chromatography on silica gel (hexane/EtOAc, 10:1) to provide S3 (7.1 g, 80%) as a yellow oil.

\(R_f = 0.24\) (hexane:EtOAc = 5:1);

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.23 (s, 1H), 6.15 (s, 1H), 4.59 (s, 2H), 3.76 (t, \(J = 6.4\) Hz, 2H), 2.64 (t, \(J = 6.4\) Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H);

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 154.9, 139.5, 122.0, 108.8, 62.6, 58.4, 28.5, 26.0, 18.6, -5.1;

HRMS (ESI) Calcd for C\(_{13}\)H\(_{25}\)O\(_5\)Si [M+H]\(^+\): 257.1567; Found: 257.1560.

Synthesis of 9

![Chemical structure of S3 and 9](image)

2-Iodoxybenzoic acid (IBX, 40.8 g, 145.6 mmol) was added to a solution of S3 (12.4 g, 48.5 mmol) in EtOAc (300 mL). The resulting suspension was immersed in an oil bath set to 80 °C and stirred vigorously for 5 hours. Then the reaction was cooled to 25 °C and filtered through a medium glass frit. The filter cake was washed with EtOAc (3 × 50 mL), and the combined filtrates were concentrated to yield 9 (12.4 g, >95% yield, >95% pure by \(^1\)H NMR) as a yellow oil, which was used in the next step directly
without further purification.

\( R_f = 0.45 \) (hexane:EtOAc = 5:1);

\(^1H\) NMR (500 MHz, CD\(_2\)Cl\(_2\)) \( \delta 9.71 - 9.67 \) (m, 1H), 7.34 (t, \( J = 1.0 \) Hz, 1H), 6.19 (s, 1H), 4.59 (s, 2H), 3.53 – 3.47 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H);

\(^13C\) NMR (126 MHz, CD\(_2\)Cl\(_2\)) \( \delta 199.2, 155.8, 140.7, 116.8, 109.5, 58.5, 40.4, 26.1, 18.8, -5.1; \)

HRMS (ESI) Calcd for C\(_{13}\)H\(_{23}\)OSi [M+H]^+: 255.1411; Found: 255.1406.

**Synthesis of 8**

Potassium bis(trimethylsilyl)amide (KHMDS, 1.0 M in THF, 110 mL, 110 mmol) was added to a solution of S\(_4\) (35 g, 100.5 mmol) in anhydrous THF (150 mL) at -78 °C. After the mixture was stirred for 10 minutes, benzyl bromide (15.5 mL, 130.6 mmol) and triethylamine (Et\(_3\)N, 16.8 mL, 120 mmol) were added to the solution concurrently. The resulting mixture was warmed to 0 °C and stirred for another 1 hour. The reaction was quenched by addition of saturated NH\(_4\)Cl (100 mL). The aqueous layer was extracted with EtOAc (3 \times 80 mL). The combined organic layers were washed with brine (100 mL) and dried over Na\(_2\)SO\(_4\). The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on basic aluminium oxide (hexane:EtOAc = 100:1) to afford 8 (43.0 g, 98%) as a colorless oil. Spectral data were identical to previously reported.

\( R_f = 0.7 \) (hexane:EtOAc = 50:1);

\(^1H\) NMR (500 MHz, CDCl\(_3\)) \( \delta 7.41 - 7.33 \) (m, 4H), 7.32 – 7.27 (m, 1H), 6.33 - 5.97 (m, 2H), 4.52 (s, 2H), 4.06 (dd, \( J = 5.1, 1.5 \) Hz, 2H), 1.51 – 1.49 (m, 6H), 1.35 – 1.27 (m, 6H), 0.89 (m, 15H);

\(^13C\) NMR (126 MHz, CDCl\(_3\)) \( \delta 144.6, 138.5, 131.6, 128.5, 128.0, 127.7, 74.1, 72.1, \)

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Synthesis of 14

\[ n\text{-BuLi (2.4 M in hexanes, 42 mL, 101 mmol) was added dropwise to a solution of } (E)-(3-(benzyloxy)prop-1-en-1-yl)tributylstannane 8 (42.5 g, 97 mmol) in anhydrous THF (150 mL) at -50 °C and the mixture was stirred at the same temperature for 1 hour. The resultant solution was transferred via cannula to another flask, containing a suspension of copper cyanide (CuCN, 8.7 g, 97 mmol) in anhydrous THF (100 mL, also cooled to -50 °C). The mixture was stirred for 15 minutes and then treated with MeLi (1.6 M in diethyl ether, 61 mL, 97 mmol), stirred for additional 15 minutes and cooled to -78 °C. A solution of enone 10 (10 g, 48.5 mmol) in THF (50 mL) was added over 30 minutes and the mixture was stirred for additional 30 minutes. Chlorotrimethylsilane (TMSCl, 8.4 mL, 97 mmol) was then added and after 15 minutes, this was followed by Et\textsubscript{3}N (16.8 mL, 120 mmol). The reaction was quenched by poured into a 10% aqueous solution of NH\textsubscript{4}Cl (200 mL). The mixture was filtrated through a pad of Celite by the aid of EtOAc. The organic layer of the filtrate was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. The residue was passed through a short silica gel column with EtOAc/hexane (1:100 - 1:50) quickly. The eluate was concentrated to give the trimethylsilyl enol ether 10a, which was used for the next step without further purification.

To a solution of the crude trimethylsilyl enol ether 10a in anhydrous THF (150 mL) was added \textit{n}-BuLi (2.4 M in hexanes, 20 mL, 48.5 mmol) at -78 °C and stirring was continued at -30 °C for 1 hour. Then, the mixture was cooled to -78 °C and a
solution of ZnBr$_2$ (12 g, 53.4 mmol) in THF (60 mL) was added dropwise. After stirred at the same temperature for 30 minutes, a solution of aldehyde 9 (12.3 g, 48.5 mmol) in THF (50 mL) was added over 30 minutes and the mixture was stirred for additional 30 minutes. Then, diisobutylaluminium hydride (DIBAL-H, 1.5 M in toluene, 76 mL, 115 mmol) was added to the solution dropwise. After being stirred at the same temperature for 30 minutes, the reaction was poured into a saturated aqueous solution of potassium sodium tartrate (300 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na$_2$SO$_4$. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 15:1) to afford 14 (14.8 g, 50% for two steps) as a colorless oil.

$R_f = 0.35$ (hexane:EtOAc = 5:1);

$[\alpha]^{25}_D = -34$ (c = 1.0, CH$_2$Cl$_2$);

IR (film) 2929, 2862, 1556, 1454, 1276, 839 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.27 (m, 5H), 7.20 (s, 1H), 6.08 (s, 1H), 5.68 (dt, $J = 15.5, 5.9$ Hz, 1H), 5.27 (ddt, $J = 15.5, 10.2, 1.4$ Hz, 1H), 5.10 – 5.05 (m, 1H), 4.54 (s, 2H), 4.50 (s, 2H), 4.40 (d, $J = 2.7$ Hz, 1H), 4.02 (td, $J = 5.9, 2.6$ Hz, 3H), 2.78 (dd, $J = 14.4, 9.0$ Hz, 1H), 2.69 (q, $J = 10.8$ Hz, 1H), 2.54 (dd, $J = 14.4, 5.1$ Hz, 1H), 2.00 (t, $J = 7.8$ Hz, 1H), 1.93 – 1.89 (m, 1H), 1.82 – 1.76 (m, 1H), 1.71 – 1.67 (m, 1H), 1.65 (d, $J = 1.4$ Hz, 3H), 1.56 (d, $J = 1.3$ Hz, 3H), 1.50 (td, $J = 12.9, 3.4$ Hz, 1H), 1.46 – 1.41 (m, 2H), 1.36 – 1.30 (m, 1H), 1.30 – 1.24 (m, 1H), 1.21 (dt, $J = 11.3, 2.3$ Hz, 1H), 1.12 – 1.10 (m, 1H), 1.02 – 0.95 (m, 1H), 0.92 – 0.90 (m, 1H), 0.89 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 155.1, 139.6, 138.5, 136.2, 131.2, 129.0, 128.5, 127.8, 127.7, 125.2, 122.2, 108.8, 72.9, 72.0, 70.7, 66.5, 58.4, 48.1, 47.6, 40.4, 33.4, 33.1, 31.1, 30.1, 26.6, 26.0, 25.9, 18.6, 18.5, 18.3, 17.8, -5.1;

HRMS (ESI) Calcd for C$_{37}$H$_{58}$NaO$_5$Si [M+Na]$^+$: 633.3946; Found: 633.3942.

Note: Compound 7 is sensitive to acid and base. When it was purified by silica gel,
large part of it underwent cyclization to give 7a. When compound 7 was subjected to the Wittig reaction, it was found to give products 7c and 7d.

Synthesis of 15

$p$-Toluenesulfonic acid (TsOH, 2.7 g, 15.8 mmol) was added to a solution of diol 14 (10 g, 15.8 mmol) in acetone (50 mL). The mixture was stirred at 25 °C for 3 hours. Then tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 47.4 mL, 47.4 mmol) was added and stirred for 1 hour at 25 °C until the end of the reaction. The reaction was diluted by EtOAc, washed with saturated NH₄Cl (2 × 100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue was purified by flash-column chromatography on silica gel (hexane:EtOAc = 6:1) to afford 15 (7.2 g, 85%) as a colorless oil.

$R_f = 0.3$ (hexane:EtOAc = 3:1);

$[\alpha]_{D}^{25} = -23 \, (c = 1.0, \text{CHCl}_3)$;
IR (film) 3435, 2981, 2854, 1456, 1377, 1105 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 7.17 (s, 1H), 6.16 (s, 1H), 5.65 – 5.55 (m, 1H), 5.23 (dd, J = 15.5, 10.1 Hz, 1H), 5.11 – 5.01 (m, 1H), 4.49 (s, 2H), 4.45 (s, 2H), 4.10 (t, J = 5.5 Hz, 2H), 3.94 (q, J = 3.2 Hz, 1H), 3.68 – 3.61 (m, 1H), 2.59 (dd, J = 15.0, 3.5 Hz, 1H), 2.50 (dd, J = 15.0, 7.8 Hz, 1H), 2.28 (q, J = 10.6 Hz, 1H), 2.04 – 1.96 (m, 1H), 1.93 – 1.83 (m, 2H), 1.79 (dd, J = 15.0, 7.6 Hz, 1H), 1.66 (s, 3H), 1.64 – 1.60 (m, 1H), 1.57 (s, 3H), 1.46 – 1.43 (m, 2H), 1.37 (d, J = 5.5 Hz, 1H), 1.36 (s, 6H), 1.32 – 1.26 (m, 2H), 1.02 – 0.10 (m, 1H), 0.97 – 0.91 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 153.6, 140.0, 138.4, 136.3, 131.2, 128.5, 128.3, 127.8, 127.7, 125.1, 122.8, 110.2, 100.3, 73.5, 72.3, 70.6, 64.0, 57.7, 46.6, 46.0, 45.5, 33.0, 31.7, 30.4, 29.9, 26.5, 26.5, 25.9, 24.6, 19.2, 18.4, 17.7;

HRMS (ESI) Calcd for C₃₄H₄₈NaO₅ [M+Na]⁺: 559.3394; Found: 559.3380.

Synthesis of 6

To a solution of 15 (5.0 g, 9.3 mmol) and tert-butyl hydroperoxide (TBHP, 5.5 M in decane, 2.5 mL, 14.0 mmol) in anhydrous DCM (40 mL) was added vanadyl acetylacetonate (VO(acac)₂, 123 mg, 0.47 mmol) at 0 °C, and the mixture was stirred at the same temperature for 15 minutes, followed by stirring at 25 °C for 4 hours. Then the reaction was cooled to 0 °C, Et₃N (2.0 mL, 14.0 mmol), 4-dimethylaminopyridine (DMAP, 1.0 g, 9.3 mmol) and acetic anhydride (Ac₂O, 1.3 mL, 14.0 mmol) were added to the reaction in sequence. Then mixture was stirred in the same temperature until the end of reaction. The reaction was quenched by saturated NH₄Cl (30 mL) and the mixture was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue was purified by flash-column chromatography on silica gel.
(hexane:EtOAc = 10:1) to afford 6 (3.9 g, 71%) as a colorless oil.

$$R_f = 0.5 \text{ (hexane:EtOAc = 5:1)};$$

$$[\alpha]^{25}_D = -8 \text{ (c = 0.25, CH}_2\text{Cl}_2);$$

IR (film) 2929, 2862, 1751, 1375, 1211 cm\(^{-1}\);

Mixture of the diastereomers (dr \(\approx 1:1.4\)):

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.27 (m, 5H), 6.49 (s, 0.58 H), 6.48 (s, 0.42 H), 6.13 (s, 0.58H), 6.12 (s, 0.42H), 5.65 – 5.62 (m, 1H), 5.32 – 5.21 (m 1H), 5.08 – 5.02 (m, 1H), 4.53 (s, 1.2H), 4.50 (s, 0.8H), 4.36 (d, \(J = 17.0\) Hz, 0.42H), 4.31 (d, \(J = 16.9\) Hz, 0.58H), 4.10 (d, \(J = 16.9\) Hz, 0.58H), 4.09 (d, \(J = 17.0\) Hz, 0.42H), 3.97 (d, \(J = 4.6\) Hz, 1.7H), 3.95 (d, \(J = 6.0\) Hz, 1.3H), 3.74 – 3.70 (m, 0.42H), 3.62 – 3.58 (m, 0.58H), 2.51 – 2.31 (m, 2H), 2.31 – 2.18 (m, 2H), 2.10 (s, 1.7H), 2.09 (s, 1.3H), 2.04 – 1.96 (m, 1H), 1.92 (dd, \(J = 14.9, 3.3\) Hz, 1H), 1.82 – 1.74 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.53 – 1.41 (m, 3H), 1.39 (s, 1.3H), 1.36 (s, 1.7H), 1.31 (s, 1.3H), 1.30 (s, 1.7H), 1.29 – 1.24 (m, 2H), 1.05 – 0.97 (m, 1H), 0.96 – 0.90 (m, 1H), 0.88 (d, \(J = 6.9\) Hz, 3H);

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 194.0, 193.9, 169.9, 169.8, 156.6, 156.0, 138.4, 138.0, 135.6, 131.3, 128.6, 128.5, 127.9, 127.8, 126.6, 126.1, 125.0, 125.0, 100.9, 100.9, 89.2, 88.5, 73.3, 72.6, 72.5, 71.0, 70.3, 70.1, 66.4, 64.0, 63.9, 47.6, 46.6, 46.5, 46.0, 45.9, 39.6, 39.1, 32.9, 32.9, 30.3, 30.0, 26.4, 26.1, 26.1, 25.9, 23.9, 23.9, 21.1, 21.1, 19.2, 19.2, 18.4, 18.4, 17.7;

HRMS (ESI) Calcd for C\(_{36}\)H\(_{50}\)NaO\(_7\) [M+Na]\(^+\): 617.3449; Found: 617.3436.

Synthesis of 5

To a dried sealed tube with anhydrous acetonitrile (CH\(_3\)CN, 500 mL) was added 6 (1.5 g, 2.5 mmol) and 2,2,6,6-tetramethylpiperidine (TMP, 0.63 mL, 3.8 mmol). Then
the mixture was heated at 170 °C for 20 hours. The reaction was worked up by transferred the solution to a round-bottomed flask and the solvents were removed under reduced pressure, and the residue was purified by flash-column chromatography on silica gel (hexane:EtOAc = 10:1) to afford 5 (0.96 g, 72%) as a white foam.

**Note:** Using the described route, 20 g of 5 was prepared readily after twenty parallel operations.

\[ R_f = 0.45 \text{ (hexane:EtOAc = 5/1);} \]

\[ [\alpha]_D^{25} = -143 \text{ (c = 1.0, CHCl}_3\text{);} \]

**IR (film)** 2922, 1683, 1456, 1381, 1228, 1028 cm\(^{-1}\);

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.27 (m, 5H), 5.97 (s, 1H), 5.04 – 4.96 (m, 1H), 4.74 (d, \(J = 6.9\) Hz, 1H), 4.58 – 4.49 (m, 2H), 4.48 (s, 1H), 3.97 (ddd, \(J = 7.1, 4.5, 3.1\) Hz, 1H), 3.46 (dd, \(J = 9.3, 4.2\) Hz, 1H), 3.37 (td, \(J = 10.2, 5.6\) Hz, 1H), 3.28 (t, \(J = 9.6\) Hz, 1H), 2.78 (dd, \(J = 11.1, 5.6\) Hz, 1H), 2.52 (td, \(J = 11.0, 1.3\) Hz, 1H), 2.07 – 2.03 (m, 1H), 2.00 – 1.94 (m, 2H), 1.86 (dt, \(J = 14.7, 7.8\) Hz, 1H), 1.82 – 1.73 (m, 2H), 1.65 (s, 3H), 1.60 (s, 3H), 1.56 – 1.51 (m, 1H), 1.45 – 1.37 (m, 1H), 1.34 (s, 3H), 1.34 (s, 3H), 1.30 – 1.19 (m, 3H), 1.18 – 1.10 (m, 2H), 0.99 – 0.89 (m, 1H), 0.79 (d, \(J = 6.7\) Hz, 3H).

**\(^13\)C NMR** (126 MHz, CDCl\(_3\)) \(\delta\) 196.1, 162.7, 138.1, 132.6, 128.6, 127.8, 127.8, 124.5, 124.3, 101.2, 85.0, 80.8, 75.1, 73.1, 71.7, 64.8, 56.2, 47.3, 46.7, 45.5, 41.8, 40.9, 32.5, 31.6, 27.9, 25.9, 25.8, 24.1, 24.0, 18.8, 17.9, 17.3;

**HRMS (ESI)** Calcd for C\(_{34}\)H\(_{47}\)O\(_5\) [M+H]\(^+\): 535.3418; Found: 535.3421.

**Synthesis of 16**

![Diagram](image)

To a solution of 5 (10 g, 18.8 mmol) in anhydrous THF (100 mL) was added DIBAL-H (1.5 M in toluene, 28.2 mL, 28.2 mmol) dropwise at -78 °C. After being
stirred at the same temperature for 15 mins, the reaction was quenched by addition of potassium sodium tartrate saturated solution (100 mL). The mixture was warmed to 25 °C and stirred for 3 hours. Then it was transferred to a separatory funnel and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (60 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 5:1) to afford 16 (9.8 g, 98%) as a white foam.

\[ R_f = 0.25 \] (hexane:EtOAc = 3:1);

\[ [\alpha]_{D}^{25} = -164 \] (c = 1.0, CH₂Cl₂);

IR (film) 3460, 2935, 2856, 1456, 1379, 1105 cm⁻¹;

\( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) 7.35 – 7.27 (m, 5H), 5.41 (s, 1H), 5.19 – 5.09 (m, 1H), 4.69 – 4.62 (m, 1H), 4.52 (d, \( J = 1.8 \) Hz, 2H), 4.36 (d, \( J = 6.3 \) Hz, 1H), 4.30 (d, \( J = 5.6 \) Hz, 1H), 3.93 (dt, \( J = 7.2, 4.0 \) Hz, 1H), 3.45 (dd, \( J = 9.1, 3.7 \) Hz, 1H), 3.36 (td, \( J = 10.1, 5.4 \) Hz, 1H), 3.29 (t, \( J = 9.8 \) Hz, 1H), 2.62 – 2.54 (m, 1H), 2.51 (dd, \( J = 11.9, 5.5 \) Hz, 1H), 2.18 (t, \( J = 11.4 \) Hz, 1H), 2.09 – 1.98 (m, 2H), 1.92 (dt, \( J = 15.1, 7.6 \) Hz, 1H), 1.80 (dt, \( J = 9.4, 6.1 \) Hz, 1H), 1.76 – 1.71 (m, 1H), 1.68 (s, 3H), 1.67 – 1.62 (m, 2H), 1.62 (s, 3H), 1.45 – 1.39 (m, 2H), 1.39 – 1.35 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.31 (s, 1H), 1.27 (d, \( J = 14.5 \) Hz, 1H), 1.10 – 1.03 (m, 1H), 1.01 – 0.95 (m, 1H), 0.85 (d, \( J = 6.7 \) Hz, 3H);

\( ^{13}C \) NMR (126 MHz, CDCl₃) \( \delta \) 139.6, 138.2, 131.6, 128.6, 127.8, 127.8, 124.9, 123.8, 100.8, 82.1, 79.6, 75.3, 73.1, 73.1, 67.4, 64.8, 57.6, 47.1, 45.3, 43.9, 40.9, 40.2, 33.0, 31.7, 27.9, 26.4, 25.8, 24.3, 24.1, 18.9, 17.9, 17.7;

HRMS (ESI) Calcd for C₃₄H₄₈NaO₅ [M+Na]⁺: 559.3394; Found: 559.3391.

Synthesis of 17
To a solution of 16 (40.0 mg, 0.07 mmol) in anhydrous DCM (5 mL) was added Et₃N (0.016 mL, 0.11 mmol) and DMAP (7.9 mg, 0.07 mmol) at 0 ºC. After being stirred at the same temperature for 5 minutes, 4-nitrobenzoyl chloride (26.0 mg, 0.14 mmol) was added to the reaction. The mixture was warmed to 25 ºC and stirred for 10 minutes. The reaction was quenched by addition of saturated NH₄Cl (5 mL). Then the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 10:1) to afford 17 (44.1 mg, 92%) as a white solid.

\[
R_f = 0.55 \text{ (hexane:EtOAc = 3:1)}; \\
\]

\(^1\)H NMR (500 MHz, CDCl₃) δ 8.16 – 8.06 (m, 4H), 7.26 – 7.22 (m, 3H), 7.19 – 7.15 (m, 2H), 5.92 (dd, \(J = 5.4, 2.6 \text{ Hz}, 1\)H), 5.59 (q, \(J = 1.7 \text{ Hz}, 1\)H), 5.09 (d, \(J = 1.5 \text{ Hz}, 1\)H), 4.64 (dt, \(J = 5.6, 1.2 \text{ Hz}, 1\)H), 4.50 (d, \(J = 6.3 \text{ Hz}, 1\)H), 4.49 – 4.35 (m, 2H), 4.02 – 3.95 (m, 1H), 3.50 (dd, \(J = 9.0, 3.3 \text{ Hz}, 1\)H), 3.44 (dt, \(J = 10.1, 5.1 \text{ Hz}, 1\)H), 3.37 (dd, \(J = 10.6, 9.0 \text{ Hz}, 1\)H), 2.65 – 2.56 (m, 2H), 2.32 – 2.26 (m, 1H), 2.14 – 2.06 (m, 1H), 1.91 (dt, \(J = 9.6, 6.0 \text{ Hz}, 1\)H), 1.80 – 1.72 (m, 3H), 1.69 (d, \(J = 8.9 \text{ Hz}, 1\)H), 1.67 – 1.65 (m, 3H), 1.55 (s, 3H), 1.49 – 1.41 (m, 4H), 1.37 (s, 3H), 1.37 (s, 3H), 1.16 (td, \(J = 7.5, 3.9 \text{ Hz}, 1\)H), 1.03 – 0.98 (m, 1H), 0.93 (d, \(J = 6.7 \text{ Hz}, 3\)H), 0.89 – 0.85 (m, 1H);

\(^1\)C NMR (126 MHz, CDCl₃) δ 164.3, 150.5, 143.2, 138.3, 135.6, 131.8, 130.7, 128.4, 127.7, 127.5, 124.7, 123.5, 119.1, 100.9, 80.1, 79.8, 75.2, 73.5, 73.2, 71.7, 64.8, 57.5, 47.1, 46.2, 45.0, 41.5, 40.1, 34.1, 32.0, 29.8, 27.4, 25.7, 24.2, 24.1, 19.0, 17.8, 17.5;

HRMS (ESI) Calcd for C₄₁H₅₂NO₈ [M+H]^+: 686.3687; Found: 686.3677.

Synthesis of 18
KHMDS (1.0 M in THF, 13.8 mL, 13.8 mmol) was added to a solution of 16 (3.7 g, 6.9 mmol) in anhydrous THF (35 mL) at 0 °C. After being stirred at the same temperature for 10 minutes, the mixture was added a solution of N-tosylimidazole (Ts-Im, 4.6 g, 20.7 mmol) in anhydrous THF (10 mL) and stirred for another 30 minutes. Then anhydrous lithium bromide (LiBr, 6.0 g, 69 mmol) was added to the reaction at 0 °C and stirred for another 1 hour at 25 °C. The reaction was quenched by addition of saturated NH₄Cl (20 mL). Then it was transferred to a separatory funnel and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 15:1) to afford 18 (5.5 g, 67%) as a white foam.

**Note:** Using the described route, 11 g of 18 was prepared readily after two parallel operations.

$R_f = 0.62$ (hexane:EtOAc = 5:1);

$[\alpha]_{B}^{25} = -159$ ($c = 1.8$, CH₂Cl₂);

**IR (film)** 2943, 2856, 1455, 1381, 1227, 1030 cm⁻¹;

$\text{dr} \approx 10:1$, the major was displayed:

$^1\text{H NMR}$ (500 MHz, CD₂Cl₂) δ 7.43 – 7.30 (m, 5H), 5.72 (d, $J = 4.2$ Hz, 1H), 5.23 – 5.11 (m, 1H), 4.65 – 4.37 (m, 5H), 3.94 (dd, $J = 7.1$, 3.7 Hz, 1H), 3.45 (dd, $J = 9.2$, 3.5 Hz, 1H), 3.33 (td, $J = 10.1$, 5.5 Hz, 1H), 3.24 (t, $J = 9.8$ Hz, 1H), 2.58 (dd, $J = 11.8$, 5.7 Hz, 1H), 2.25 (t, $J = 11.3$ Hz, 1H), 2.13 – 2.05 (m, 1H), 2.00 – 1.92 (m, 2H), 1.87 (dt, $J = 10.9$, 5.9 Hz, 1H), 1.77 (d, $J = 4.1$ Hz, 1H), 1.73 (s, 3H), 1.65 (s, 3H), 1.62 – 1.55 (m, 1H), 1.44 – 1.37 (m, 2H), 1.33 (d, $J = 7.6$ Hz, 6H), 1.30 – 1.26 (m, 1H), 1.26 – 1.19
(m, 1H), 1.15 – 1.03 (m, 2H), 0.93 (dt, J = 17.3, 6.2 Hz, 2H), 0.88 (d, J = 6.8 Hz, 3H);

**13C NMR** (126 MHz, CD₂Cl₂) δ 141.7, 138.8, 132.3, 128.9, 128.3, 128.2, 125.2, 121.9, 101.1, 84.5, 80.0, 75.8, 73.7, 73.4, 65.2, 59.6, 54.4, 54.2, 54.0, 53.8, 53.6, 51.0, 50.7, 47.6, 45.4, 41.7, 40.8, 33.2, 32.1, 28.4, 26.7, 26.2, 24.3, 24.3, 19.0, 18.0, 17.6;

**HRMS (ESI)** Calcd for C₃₄H₄₈BrO₄ [M+H]⁺: 599.2730; Found: 599.2728.

**Synthesis of 20**

Sodium naphthalenide was prepared freshly in advance: sodium (2.1 g, 91.3 mmol) was added to a solution of naphthalene (11.6 g, 90.3 mmol) in anhydrous THF (80 mL), which was then sonicated for 1.5 hours to give a dark blue solution. Meanwhile, compound 18 (2.7 g, 4.5 mmol) was dissolved in a mixed solution of THF (40 mL) and H₂O (0.24 mL, 13.5 mmol), which was degassed with Ar for 0.5 hour. Then the sodium naphthalenide was added to the solution of 18 at 25 °C and stirred at the same temperature for 0.5 hour. The reaction was quenched by bubbling with an air balloon until the dark blue faded, followed by addition of saturated NH₄Cl. The mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 4:1) to afford 20 (1.5 g, 78%) as a white foam.
Note:

1. Using the described route, 4.5 g of 20 was prepared readily after three parallel operations.

2. When no H$_2$O participated in the reaction, mainly gave the intermediate compound 19. Compound 19 could also be converted to 20 when it was subjected to the Na-naphthalenide condition again, but the yield was not good as one pot process.

3. The absolute stereochemistry at C24 in ring opening product 20 was established to be R configuration by its nOe experiments.

![Figure S1. Key NOESY correlations of 20](image)

4. Here is a short summary for synthesis of 20 (as shown below). Our initial attempt was to cleavage the C-O bond at C4 in enone 5. However, treatment of enone 5 with SmI$_2$ in various solvent did not provide the desired product 5A. While chloride 5B, which was prepared from enone 5 in two steps with a yield of 41%, could indeed be converted to the desired C-O bond breaking compound 5C, but the yield was low and hard to repeat. Subsequently, we switched to the bromide 18, which was considered to be more reactive than its chloride substrate from a point view of electronegativity. Unfortunately, the yield did not seem to be improved under SmI$_2$ or t-BuLi conditions. Eventually, we found that treatment of 18 with Na-naphthalenide in THF-H$_2$O system smoothly afforded diol 20 in 78% yield.
$R_f = 0.35$ (hexane:EtOAc = 2:1);

$[\alpha]_D^{25} = -41 (c = 1.0, \text{CH}_2\text{Cl}_2)$;

**IR (film)** 2924, 2362, 1456, 1379, 1226, 1022 cm$^{-1}$;

$^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 5.70 (dd, $J = 8.7, 3.8$ Hz, 1H), 5.24 – 5.15 (m, 1H), 4.45 (d, $J = 2.2$ Hz, 1H), 4.01 (dt, $J = 8.6, 6.9$ Hz, 1H), 3.72 (dd, $J = 10.6, 3.2$ Hz, 1H), 3.60 (dd, $J = 10.6, 6.5$ Hz, 1H), 3.39 – 3.33 (m, 1H), 2.78 – 2.67 (m, 1H), 2.38 (dd, $J = 11.0, 3.4$ Hz, 1H), 2.23 (td, $J = 10.9, 2.4$ Hz, 1H), 2.14 (dt, $J = 12.9, 7.1$ Hz, 1H), 2.09 – 1.98 (m, 2H), 1.95 – 1.89 (m, 2H), 1.86 – 1.77 (m, 2H), 1.72 (s, 3H), 1.66 (s, 3H), 1.64 – 1.58 (m, 3H), 1.57 – 1.50 (m, 2H), 1.49 – 1.43 (m, 1H), 1.42 – 1.35 (m, 1H),
1.32 (s, 3H), 1.30 (s, 3H), 1.27 – 1.23 (m, 2H), 1.10 (dtd, J = 13.0, 11.1, 4.9 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H);

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 138.4, 131.1, 127.6, 125.0, 100.0, 73.6, 72.1, 66.9, 65.6, 47.9, 46.7, 45.2, 44.5, 44.3, 35.4, 32.8, 30.6, 26.3, 25.9, 25.5, 24.7, 23.9, 23.6, 23.1, 18.9, 18.3, 17.3;

HRMS (ESI) Calcd for C$_{27}$H$_{44}$NaO$_4$ [M+Na]$^+$: 455.3132; Found: 455.3139.

**Synthesis of S5**

Compound 20 (4.5 g, 10.4 mmol) was dissolved in anhydrous THF (50 mL) at -78 °C, then Et$_3$N (2.9 mL, 20.9 mmol) was added to the solution, which was followed by dropwise addition of t-butyldimethylsilyl triflate (TBSOTf, 2.5 mL, 10.8 mmol). After being stirred at -78 °C for 10 minutes, KHMDS (1.0 M in THF, 31 mL, 31 mmol) was added to the solution and stirred for another 15 minutes. Then a solution of N-tosylimidazole (Ts-Im, 9.2 g, 41.4 mmol) in anhydrous THF (50 mL) was added to the mixture, which was then warmed to 0 °C. After 30 minutes, the reaction was warmed to 25 °C, and MeOH (2.0 mL) and TBAF (1.0 M in THF, 54 mL, 54 mmol) was added to the reaction in sequence. The reaction was stirred overnight before being quenched by saturated NH$_4$Cl (80 mL). The aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine (80 mL) and dried over Na$_2$SO$_4$. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 8:1) to afford S5 (3.6 g, 60%) as a white foam.

$R_f = 0.54$ (hexane:EtOAc = 3:1);
$[\alpha]_b^{25} = -11 \ (c = 1.0, \text{CH}_2\text{Cl}_2);$

**IR (film)** 2924, 2858, 2370, 1560, 1174, 1020 cm$^{-1};$

**$^1$H NMR** (500 MHz, CD$_2$Cl$_2$) $\delta$ 7.75 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 5.57 (dd, $J = 9.2$, 3.6 Hz, 1H), 5.18 – 5.10 (m, 1H), 4.91 (d, $J = 1.8$ Hz, 1H), 3.96 (dt, $J = 9.3$, 7.1 Hz, 1H), 3.63 (dt, $J = 10.7$, 3.5 Hz, 1H), 3.50 – 3.41 (m, 1H), 3.27 – 3.21 (m, 1H), 2.53 – 2.47 (m, 1H), 2.43 (s, 3H), 2.25 (dd, $J = 11.3$, 3.3 Hz, 1H), 2.14 – 2.04 (m, 1H), 2.02 – 1.93 (m, 2H), 1.86 – 1.81 (m, 1H), 1.79 – 1.71 (m, 3H), 1.68 (s, 3H), 1.66 – 1.60 (m, 2H), 1.57 (s, 3H), 1.54 (d, $J = 11.5$ Hz, 1H), 1.49 – 1.45 (m, 1H), 1.44 – 1.39 (m, 2H), 1.36 (dd, $J = 6.4$, 4.3 Hz, 1H), 1.32 – 1.27 (m, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 1.16 – 1.09 (m, 1H), 1.08 – 1.02 (m, 1H), 0.97 – 0.93 (m, 1H), 0.85 (d, $J = 6.7$ Hz, 3H);

**$^{13}$C NMR** (126 MHz, CD$_2$Cl$_2$) $\delta$ 145.4, 134.6, 132.8, 131.7, 130.3, 128.2, 125.4, 100.6, 100.5, 82.0, 73.1, 67.4, 65.1, 48.8, 46.4, 44.9, 44.3, 44.2, 35.3, 33.3, 31.0, 26.7, 26.0, 25.8, 24.8, 24.3, 24.1, 23.4, 21.9, 19.2, 18.4, 17.8;

**HRMS (ESI)** Calcd for C$_{34}$H$_{50}$NaO$_6$S [M+Na]$^+$: 609.3220; Found: 609.3219.

**Synthesis of 21**

To a solution of S5 (3.6 g, 6.1 mmol) in DCM (60 mL) at 25 °C was added sodium bicarbonate (NaHCO$_3$, 7.8 g, 23.9 mmol) and Dess-Martin periodinane (DMP, 5.2 g, 12.2 mmol) in sequence. The mixture was stirred for 1.0 hour and quenched by addition of saturated NH$_4$Cl (40 mL). Then it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (40 mL) and dried over Na$_2$SO$_4$. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 8:1) to afford 21 (3.3 g, 92%) as a white foam.
\[ R_f = 0.4 \text{ (hexane:EtOAc = 5:1)}; \]

\[ [\alpha]^{25}_D = -38 \text{ (c = 1.0, CH}_2\text{Cl}_2); \]

**IR (film)** 2929, 2875, 1722, 1375, 1224, 1178 cm\(^{-1}\);

**\(^1\)H NMR** (500 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 9.68 (s, 1H), 7.71 (d, \(J = 8.1\) Hz, 2H), 7.33 (d, \(J = 8.1\) Hz, 2H), 5.68 (dd, \(J = 9.1, 5.2\) Hz, 1H), 5.06 (d, \(J = 4.0\) Hz, 1H), 5.03 (s, 1H), 3.99 (d, \(J = 5.7\) Hz, 1H), 3.24 – 3.17 (m, 1H), 2.58 – 2.50 (m, 1H), 2.46 (d, \(J = 4.7\) Hz, 2H), 2.43 (s, 3H), 2.19 (dd, \(J = 11.3, 4.0\) Hz, 1H), 2.14 – 2.08 (m, 1H), 2.04 – 1.97 (m, 1H), 1.90 (t, \(J = 11.4\) Hz, 1H), 1.87 – 1.83 (m, 1H), 1.83 – 1.78 (m, 1H), 1.78 – 1.68 (m, 2H), 1.63 (s, 3H), 1.60 – 1.58 (m, 4H), 1.56 (s, 3H), 1.35 – 1.30 (m, 2H), 1.28 (s, 3H), 1.26 (s, 3H), 1.25 – 1.22 (m, 1H), 1.12 – 1.05 (m, 1H), 1.03 – 0.96 (m, 1H), 0.93 (d, \(J = 6.6\) Hz, 3H);

**\(^{13}\)C NMR** (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 203.5, 145.7, 134.2, 134.0, 133.0, 132.2, 130.3, 128.2, 124.7, 101.2, 83.2, 77.3, 66.1, 54.1, 49.2, 46.5, 43.8, 43.3, 38.9, 32.7, 30.9, 28.5, 26.1, 26.0, 24.4, 23.8, 22.5, 22.2, 22.0, 19.7, 19.2, 17.8;

**HRMS (ESI)** Calcd for C\(_{34}\)H\(_{48}\)NaO\(_6\)S [M+Na]\(^+\): 607.3064; Found: 607.3056.

**Synthesis of 4**

To a stirred solution of the aldehyde 21 (2.1 g, 3.6 mmol) in tert-butanol (\(t\)-BuOH, 50 mL, degassed with Ar for 0.5 hour) was added potassium tert-butoxide (\(t\)-BuOK, 1.8M in THF, 5.6 mL, 10.1 mmol) at 25 °C. and the mixture was stirred at the same temperature for 4 hours. The reaction was quenched by addition of saturated NH\(_4\)Cl (30 mL). The aqueous layer was extracted with EtOAc (3 \(\times\) 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na\(_2\)SO\(_4\). The dried solution was filtered and concentrated. The residue obtained was purified by flash-column
chromatography on silica gel (hexane:EtOAc = 15:1) to afford 4 (1.2 g, 78%) as a white foam.

**Note:** THF is not important in this case since its content is relatively small compared to the huge amount of t-BuOH solvent. On the contrary, it is critical to select t-BuOH as the solvent because the starting material was not consumed if the solvent was changed from t-BuOH to THF, even with prolonged reaction time.

\[ R_f = 0.45 \] (hexane:EtOAc = 10:1);

\[ [\alpha]_D^{25} = -87 \text{ (c = 0.15, CH}_2\text{Cl}_2) \];

**IR (film)** 2930, 2856, 1710, 1379, 1224, 1018 cm\(^{-1}\);

**\(^1\text{H NMR}\)** (500 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 8.80 (s, 1H), 5.85 (t, \(J = 5.2\) Hz, 1H), 5.10 (td, \(J = 8.0, 2.3\) Hz, 1H), 3.99 – 3.94 (m, 1H), 3.23 – 3.15 (m, 1H), 2.84 – 2.77 (m, 1H), 2.48 (dd, \(J = 11.4, 3.8\) Hz, 1H), 2.23 (t, \(J = 11.3\) Hz, 1H), 2.08 – 2.00 (m, 1H), 1.98 – 1.89 (m, 3H), 1.88 – 1.82 (m, 1H), 1.79 – 1.71 (m, 2H), 1.69 – 1.65 (m, 3H), 1.63 – 1.57 (m, 3H), 1.50 (m, 2H), 1.44 – 1.36 (m, 2H), 1.30 (s, 3H), 1.30 (s, 3H), 1.26 (s, 1H), 1.22 (dd, \(J = 16.2, 4.3\) Hz, 1H), 1.18 – 1.13 (m, 1H), 1.13 – 1.07 (m, 1H), 1.07 – 0.94 (m, 2H), 0.90 (d, \(J = 6.8\) Hz, 3H), 0.87 – 0.83 (m, 1H);

**\(^{13}\text{C NMR}\)** (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 201.5, 133.2, 131.5, 129.2, 125.4, 101.5, 78.4, 65.9, 50.9, 50.8, 42.7, 42.2, 40.2, 35.1, 33.4, 32.0, 31.5, 27.3, 26.0, 24.9, 24.6, 24.3, 24.0, 22.2, 19.3, 17.8;

**HRMS (ESI)** Calcd for C\(_{27}\)H\(_{41}\)O\(_3\) [M+H]\(^+\): 413.3050; Found: 413.3047.

**Note:** Hypothetically intermediate 22 and product 4 are presented in a three-dimensional way in order to better understand the unusual vinylcyclopropane formation process. As shown in the scheme below, the OTs leaving group is in the same face with the nucleophile generated in situ from deprotonation of the aldehyde under basic condition, thus a S\(_{N2}\) reaction could not happen in this case. So, we prefer to consider the vinylcyclopropane formation process as a S\(_{N1}\) mechanism: first, the C-OTs bond ionized with help from the polar, protic solvent (t-BuOH), then si face of enolate attacks the empty p orbital of the solvated allylic carbocation. And this transannular process
proceeded with complete stereochemical control on the configuration of the two stereogenic centers generated across the newly formed C–C bond. We believed that the polycyclic nature of the substrate plays an important role in this transannular process. We also agreed that the orbital alignment of enolate and the carbocation was feasible for the bond formation, as shown in below.

**Synthesis of 23a**

Solid potassium hydroxide (KOH, 122 mg, 2.2 mmol) and hydrazine hydrate (0.2 mL) were added to a solution of aldehyde 4 (30 mg, 0.07 mmol) in ethylene glycol dimethyl ether (4 mL), and the mixture was heated to 130 °C with stirring for 30 minutes before elevated to 190 °C for another 3 hours. Then, the reaction was cooled
to 25 °C and quenched with saturated NaHCO₃ (5 mL). Then it was transferred to a separatory funnel and extracted with Et₂O (3 × 5 mL). The combined organic phase was washed with H₂O, brine, dried over anhydrous Na₂SO₄, and evaporated to give a crude product. The residue was purified by flash-column chromatography on silica gel (hexane:EtOAc = 20:1) to afford 23a (23 mg, 84%) as a white solid.

\[ R_f = 0.3 \text{ (hexane:EtOAc = 20:1);} \]

**m.p.** (DCM/hexane): 97 – 99 °C;

\[ [\alpha]_{D}^{25} = -189 \text{ (c = 1.0, CH}_2\text{Cl}_2); \]

**IR (film)** 2934, 2858, 1456, 1379, 1228, 1074 cm⁻¹;

**¹H NMR** (500 MHz, CD₂Cl₂) δ 5.79 (d, \( J = 7.4 \text{ Hz}, 1\text{H}), 5.14 – 5.10 (m, 1H), 3.94 – 3.90 (m, 1H), 3.15 – 3.09 (m, 1H), 2.40 (dd, \( J = 11.1, 3.8 \text{ Hz}, 1\text{H}), 2.20 – 2.12 (m, 1H), 2.11 – 2.01 (m, 2H), 1.85 – 1.76 (m, 4H), 1.68 (s, 3H), 1.64 (dd, \( J = 4.0, 2.2 \text{ Hz}, 1\text{H), 1.60 \text{ (s, 3H}), 1.51 – 1.44 \text{ (m, 1H), 1.37 \text{ (dt, J = 10.3, 3.8 Hz, 2H), 1.28 \text{ (s, 3H), 1.28 \text{ (s, 3H), 1.27 – 1.20 \text{ (m, 2H), 1.11 \text{ (s, 3H), 1.07 – 0.98 \text{ (m, 3H), 0.95 \text{ (d, J = 6.9 Hz, 3H), 0.90 – 0.81 \text{ (m, 2H), 0.56 \text{ (t, J = 9.0 Hz, 1H);}}\]

**¹³C NMR** (126 MHz, CD₂Cl₂) δ 137.4, 131.2, 129.0, 125.7, 101.2, 78.7, 66.1, 51.4, 51.3, 43.4, 42.8, 36.0, 33.2, 32.0, 31.8, 31.2, 27.5, 27.1, 26.0, 24.5, 24.5, 24.3, 24.1, 22.8, 19.5, 19.5, 17.8;

**HRMS (ESI)** Calcd for C₂₇H₄₃O₂ [M+H]⁺: 399.3258; Found: 399.3258.

**Synthesis of 23**

Solid potassium hydroxide (KOH, 4.9 g, 87 mmol) and hydrazine hydrate (7.5 mL) were added to a solution of aldehyde 4 (1.2 g, 2.9 mmol) in ethylene glycol dimethyl ether (50 mL), and the mixture was heated to 130 °C with stirring for 30 minutes before
elevated to 190 °C for another 3 hours. Then, the reaction was cooled to 25 °C and
diluted with THF (50 mL) and H2O (100 mL), which was followed by addition of AcOH
(200 mL). The mixture was stirred for four days at 25 °C before being quenched by
saturated KOH. Then it was transferred to a separatory funnel and extracted with Et2O
(3 × 200 mL). The combined organic phase was washed with water (3 × 30 mL) and
brine, dried over anhydrous Na2SO4, and evaporated to give a crude product. The
residue was purified by flash-column chromatography on silica gel (hexane:EtOAc =
10:1) to afford 23 (830 mg, 80%) as a white foam.

Note: We have been alerted to the instability of vinylcyclopropane moiety under acid
conditions, even in CDCl3 which contains trace hydrochloride accompanied by its
thermo- or photolysis. The deketalization product 23 was found to be unexpectedly
stable in THF-AcOH-H2O system, it did not decompose even it was stirred for a week.
However, the THF-HCl(aq)-H2O system induced a partial decomposition. Acidity
difference between HCl and AcOH might account for the observed phenomenon. It is
very lucky for us to found that the vinylcyclopropane moiety is relatively stable in the
presence of AcOH.

\[ R_f = 0.25 \text{ (hexane:EtOAc = 5:1); } \]

\[ [\alpha]_{25}^D = -48 \text{ (c = 1.6, CHCl}_3); \]

**IR (film)** 2929, 2856, 2362, 1454, 1377, 1020 cm\(^{-1}\);

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 5.71 (d, \( J = 7.0 \) Hz, 1H), 5.14 – 5.05 (m, 1H), 4.35 –
4.25 (m, 1H), 3.46 (td, \( J = 10.1, 4.6 \) Hz, 1H), 2.64 (dd, \( J = 11.4, 4.5 \) Hz, 1H), 2.22 (t, \( J =
11.0 \) Hz, 1H), 2.12 – 1.96 (m, 4H), 1.91 (dd, \( J = 13.5, 3.4 \) Hz, 1H), 1.81 – 1.72 (m, 3H), 1.67 (s,
3H), 1.64 – 1.59 (m, 1H), 1.58 (s, 3H), 1.48 (td, \( J = 9.4, 3.4 \) Hz, 1H), 1.43
– 1.34 (m, 2H), 1.33 – 1.27 (m, 1H), 1.24 (dt, \( J = 10.2, 6.7 \) Hz, 2H), 1.19 – 1.12 (m,
2H), 1.11 (s, 3H), 0.95 (d, \( J = 6.8 \) Hz, 3H), 0.93 – 0.89 (m, 2H), 0.43 (t, \( J = 8.6 \) Hz, 1H);

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 135.6, 130.8, 126.4, 125.3, 76.6, 67.1, 52.6, 52.0, 45.4,
40.6, 33.2, 32.7, 32.2, 31.9, 30.2, 27.2, 27.0, 25.9, 25.5, 23.8, 21.3, 19.5, 17.7, 17.2;

**HRMS (ESI)** Calcd for C\(_{24}\)H\(_{39}\)O\(_2\) [M+H]\(^+\): 359.2945; Found: 359.2943.
Synthesis of S6

To a solution of 23 (830 mg, 2.3 mmol) in DCM (15 mL) at 0 °C was added Et\textsubscript{3}N (0.49 mL, 3.5 mmol) and DMAP (146 mg, 1.2 mmol) subsequently. Then Ac\textsubscript{2}O (0.24 mL, 2.5 mmol) was added to the solution and stirred at 0 °C for 45 minutes. Then, NaHCO\textsubscript{3} (0.9 g, 10.5 mmol) was added to the reaction, which was followed by addition of DMP (1.5 g, 3.5 mmol). The mixture was warmed to 25 °C and stirred for 1 hour before being quenched by saturated NH\textsubscript{4}Cl (10 mL). Then the aqueous layer was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 20:1) to afford S6 (824 mg, 90%) as a white foam.

$R_f = 0.32$ (hexane:EtOAc = 10:1);

$[\alpha]_{D}^{25} = -154$ (c = 1.0, CHCl\textsubscript{3});

**IR (film)** 2929, 2858, 1735, 1448, 1375, 1022 cm\textsuperscript{-1};

**\textsuperscript{1}H NMR** (500 MHz, CD\textsubscript{2}Cl\textsubscript{2}) $\delta$ 5.76 (d, $J$ = 7.2 Hz, 1H), 5.15 – 5.08 (m, 1H), 4.69 (td, $J$ = 10.3, 5.4 Hz, 1H), 3.84 – 3.81 (m, 1H), 2.59 (dd, $J$ = 11.7, 5.4 Hz, 1H), 2.26 (t, $J$ = 11.2 Hz, 1H), 2.12 (d, $J$ = 4.5 Hz, 1H), 2.05 (s, 3H), 2.03 – 1.97 (m, 1H), 1.88 – 1.75 (m, 4H), 1.67 (s, 3H), 1.66 – 1.61 (m, 1H), 1.59 (s, 3H), 1.42 – 1.29 (m, 5H), 1.23 (td, $J$ = 12.8, 5.8 Hz, 1H), 1.16 (d, $J$ = 10.9 Hz, 1H), 1.13 (s, 3H), 0.98 (s, 1H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.90 – 0.82 (m, 1H), 0.44 (t, $J$ = 9.1 Hz, 1H);

**\textsuperscript{13}C NMR** (126 MHz, CD\textsubscript{2}Cl\textsubscript{2}) $\delta$ 172.0, 134.6, 131.1, 127.2, 125.7, 78.1, 66.5, 52.9, 50.8, 42.1, 39.6, 33.2, 33.0, 32.4, 32.2, 30.3, 27.6, 27.1, 26.4, 26.0, 24.1, 21.7, 21.7, 19.7, 17.8, 17.5;
**HRMS (ESI)** Calcd for C_{26}H_{39}O_{3} [M+H]^+: 399.2894; Found: 399.2892.

**Synthesis of 24**

To a solution of S6 (820 mg, 2.1 mmol) in anhydrous THF (30 mL) at 0 °C was added KHMDST (1.0 M in THF, 2.1 mL, 2.1 mmol) and stirred at the same temperature for 5 minutes. The reaction was quenched by addition of saturated NH_{4}Cl (20 mL) and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_{2}SO_{4}. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography on silica gel (hexane:EtOAc = 20:1) to afford 24 (632 mg, 89%) as a white foam.

\[ R_f = 0.57 \text{ (hexane:EtOAc = 10:1);} \]

\[ [\alpha]_D^{25} = -92 \text{ (c = 0.5, CH}_2\text{Cl}_2); \]

**IR (film)** 2926, 2858, 1705, 1458, 1199, 810 cm\(^{-1}\);

\[ ^1\text{H NMR} \text{ (500 MHz, CD}_2\text{Cl}_2) \delta 6.71 (d, J = 3.7 \text{ Hz, 1H}), 5.75 (d, J = 6.9 \text{ Hz, 1H}), 5.18 - 5.06 (m, 1H), 3.29 - 3.20 (m, 1H), 3.14 - 3.08 (m, 1H), 2.81 - 2.70 (m, 1H), 2.45 - 2.39 (m, 1H), 2.27 - 2.17 (m, 1H), 2.13 - 2.05 (m 2H), 1.93 - 1.86 (m, 1H), 1.83 (dt, J = 13.3, 6.8 Hz, 1H), 1.79 - 1.74 (m, 2H), 1.73 - 1.69 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.51 (td, J = 13.3, 4.6 Hz, 1H), 1.36 - 1.29 (m, 3H), 1.15 (s, 3H), 1.05 - 0.99 (m, 2H), 0.99 (d, J = 6.8 Hz, 3H), 0.92 (dd, J = 12.9, 4.8 Hz, 1H);

\[ ^{13}\text{C NMR} \text{ (126 MHz, CD}_2\text{Cl}_2) \delta 201.9, 141.3, 140.7, 137.0, 131.5, 125.9, 125.4, 49.0, 42.0, 39.9, 39.3, 36.1, 32.5, 32.0, 30.0, 27.1, 27.0, 26.0, 24.4, 24.3, 22.4, 21.3, 19.3, 17.8;\]

**HRMS (ESI)** Calcd for C_{24}H_{35}O [M+H]^+: 339.2682; Found: 339.2681.
Synthesis of 1

To a stirred solution of enone 24 (110 mg, 0.32 mmol) in MeOH (20 mL) was added nickel(II) chloride hexahydrate (NiCl₂ • 6H₂O, 175 mg, 0.64 mmol) at 25 °C. The mixture was cooled to -40 °C, sodium borohydride (NaBH₄, 61 mg, 1.6 mmol) was added over 10 min. After stirring was continued for 30 min at the same temperature, the reaction mixture was slowly warmed to 25 °C over 1 h. The reaction mixture was stirred at 25 °C for 2 hours before diluted with Et₂O (50 mL) and celite (50.0 mg) was added. After being stirred for another 30 min, the mixture was then filtered through celite-pad and the filtrate was concentrated in vacuo. The residue was purified quickly by column chromatography on silica gel (hexane:EtOAc = 20:1) to afford the desired ketone (Rᶠ = 0.26 (hexane:EtOAc = 5:1)) and an inseparable mixture of unidentified byproducts. The desired ketone was not characterized and was used directly in the next step.

To a dispersion of methyltriphenylphosphonium bromide (628 mg, 1.8 mmol) in THF (20 mL) at 0 °C was added n-BuLi (1.6 M in hexanes, 1.0 mL, 1.6 mmol), and the mixture was stirred for 1 h. The mixture was cooled to -78 °C and a solution of ketone (obtained in last step above) in THF (10 mL) was added. Then the reaction was gradually warmed up to 25 °C and stirred for another 2 h at the same temperature. The reaction was quenched with water, and the aqueous layer extracted with Et₂O (3× 20 mL). The organic extracts were washed with brine (20 mL), dried over Na₂SO₄, and
concentrated. The residue obtained was purified quickly by flash-column chromatography on silica gel (hexane) to afford the crude 3 ($R_f = 0.91$ (hexane)), which was used directly in the next step. For characterization of compound 3, the crude sample was further purified by preparative HPLC to give small amounts of 3 for data collection. Preparative HPLC was carried out on an Agilent 1260 instrument equipped with MWD detector (Agilent 1260, MWDVL, USA, 214 nm) and a Cosmosil 5C18-MS-II column (5 μm, 4.6 mm I. D. × 250 mm; NacalaiTesque, JPN) with a phase of 98% acetonitrile-water (v/v).

$R_f = 0.91$ (hexane);

$[α]^{25}_D = -65$ ($c = 0.32$, CH₂Cl₂);

IR (film) 2926, 2854, 2358, 1637, 1377, 1259 cm⁻¹;

$^1$H NMR (500 MHz, CD₂Cl₂) δ 5.65 (dt, $J = 7.2, 2.3$ Hz, 1H), 5.14 – 5.07 (m, 1H), 4.75 (s, 1H), 4.69 (m, 1H), 2.51 – 2.40 (m, 1H), 2.33 – 2.29 (m, 1H), 2.23 – 2.17 (m, 3H), 2.15 – 2.10 (m, 1H), 2.09 – 1.97 (m, 2H), 1.91 – 1.76 (m, 3H), 1.67 (s, 3H), 1.63 (t, $J = 4.3$ Hz, 2H), 1.60 (s, 3H), 1.57 (d, $J = 7.3$ Hz, 1H), 1.51 – 1.46 (m, 1H), 1.45 – 1.38 (m, 2H), 1.36 (dd, $J = 13.2, 4.4$ Hz, 1H), 1.21 – 1.14 (m, 1H), 1.10 (s, 3H), 1.05 – 0.97 (m, 1H), 0.95 (d, $J = 8.9$ Hz, 1H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.68 (dd, $J = 10.6, 9.2$ Hz, 1H);

$^{13}$C NMR (126 MHz, CD₂Cl₂) δ 152.6, 141.0, 131.5, 125.6, 124.6, 106.2, 45.1, 40.8, 36.5, 34.4, 33.1, 32.9, 32.4, 31.3, 29.0, 28.9, 27.5, 26.1, 26.0, 25.0, 24.3, 24.3, 21.0, 18.3, 17.8;

HRMS (ESI) Calcd for C₂₅H₃₉ [M+H]⁺: 339.3046; Found: 339.3046.

To a solution of 3 in anhydrous DCM (20 mL) was added methacrylaldehyde (0.29 mL, 3.5 mmol) and Grubbs II catalyst (81 mg, 0.1 mmol) subsequently. The reaction was sealed and heated at 52 °C for 15 hours. After cooled to 25 °C, the volatiles were removed under vacuo and the residue was re-dissolved in EtOH (6 mL). To the vigorously stirred solution was added a solution of silver nitrate (82 mg, 0.48 mmol) in water (3 mL), which was followed by addition of a solution of sodium hydroxide (38 mg, 0.96 mmol) in water (3 mL) dropwise. After stirring for 1 h, the
mixture was carefully acidified with AcOH and filtered. The filtrate was concentrated in vacuo and the residue was extracted with ether. The combined organic layers were washed with brine (5 mL) and dried over Na₂SO₄. The dried solution was filtered and concentrated. The residue obtained was purified quickly by flash-column chromatography on silica gel (hexane:EtOAc = 3:1) to afford 1 as a colorless oil (32 mg, 27% for three steps).

**Note:** For the last reaction, to our surprise, when the relatively pure CM product (purified by chromatography) was subjected to Ag₂O oxidation, only trace cerorubenic acid-III was produced. However, when the crude sample was used as described in the supporting information, the oxidation proceeded smoothly to give 1.

*Rf* = 0.45 (hexane:EtOAc = 5:1);

|α|²⁵ = -38 (c = 0.32, CH₂Cl₂);

**IR (film)** 2929, 2358, 2339, 1695, 1452, 1028 cm⁻¹;

**NMR data collected with C₆D₆:**

**¹H NMR** (500 MHz, C₆D₆) δ 7.01 (d, *J* = 6.4 Hz, 1H), 5.72 – 5.67 (m, 1H), 4.90 (d, *J* = 1.8 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.29 – 2.21 (m, 3H), 2.19 – 2.12 (m, 2H), 2.10 – 2.08 (m, 1H), 1.86 – 1.83 (m, 1H), 1.81 (s, 3H), 1.78 (td, *J* = 4.7, 2.4 Hz, 1H), 1.65 – 1.62 (m, 1H), 1.61 – 1.58 (m, 1H), 1.58 – 1.50 (m, 3H), 1.43 – 1.38 (m, 3H), 1.34 (s, 1H), 1.21 – 1.14 (m, 1H), 1.06 (s, 3H), 0.90 – 0.88 (m, 1H), 0.88 – 0.84 (m, 1H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.71 (dd, *J* = 10.5, 9.1 Hz, 1H);

**¹³C NMR** (126 MHz, C₆D₆) δ 172.8, 151.3, 145.4, 140.5, 124.4, 106.9, 44.8, 40.6, 36.3, 32.8, 32.8, 32.4, 28.9, 28.7, 27.3, 26.7, 24.8, 24.2, 23.9, 20.7, 18.0, 12.1 (the signal for the enoate carbon 19 is obscured by solvent peaks);

**NMR data collected with CD₂Cl₂:**

**¹H NMR** (500 MHz, CD₂Cl₂) δ 6.90 (t, *J* = 7.6 Hz, 1H), 5.69 – 5.62 (m, 1H), 4.76 (d, *J* = 2.0 Hz, 1H), 4.70 (d, *J* = 2.1 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.34 – 2.29 (m, 1H), 2.29 – 2.23 (m, 1H), 2.25 – 2.08 (m, 5H), 2.03 – 1.94 (m, 1H), 1.84 (m, 1H), 1.83 (s,
$3H$), 1.81 – 1.76 (m, 1H), 1.72 – 1.60 (m, 3H), 1.59 – 1.53 (m, 2H), 1.50 – 1.45 (m, 1H), 1.39 – 1.32 (m, 1H), 1.21 – 1.17 (m, 1H), 1.16 – 1.12 (m, 1H), 1.10 (s, 3H), 0.96 (d, $J = 9.2$ Hz, 1H), 0.91 (d, $J = 6.7$ Hz, 3H), 0.68 (t, $J = 9.9$ Hz, 1H);

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 173.2, 152.3, 146.1, 140.9, 127.1, 124.6, 106.4, 45.0, 40.8, 36.5, 33.0, 32.9, 32.8, 32.6, 31.2, 29.1, 28.9, 27.5, 27.1, 25.0, 24.3, 24.2, 21.0, 18.2, 12.3;

HRMS (ESI) Calcd for C$_{25}$H$_{37}$O$_2$ [M+H]$^+$: 369.2788; Found: 369.2788.

Note: Based on the analysis of dept-135, HSQC, $^1$H-$^1$H COSY, HMBC and NOESY spectra (Figure S2-S3), the $^1$H and $^{13}$C NMR data of 1 were assigned as shown in Table S1, which was not reported by Naya and coworkers previously.\textsuperscript{5}

Figure S2. Key $^1$H-$^1$H COSY and HMBC correlations of cerorubenic acid-III (1)
Figure S3. Key NOESY correlations of cerorubenic acid-III (1)
Table S1. $^1$H (500 MHz) and $^{13}$C (126 MHz) NMR data of cerorubenic acid-III (1) in CD$_2$Cl$_2$ ($\delta$ in ppm, $J$ in Hz)$^a$

| position | $\delta_H$          | $\delta_C$ |
|----------|---------------------|------------|
| 1        | 1.84 (m, 1H)        | 36.5       |
| 2        | 0.68 (t, $J = 9.9$ Hz, 1H) | 31.2       |
| 3        | –                   | 21.0       |
| 4        | 1.63 (m, 1H), 1.35 (m, 1H) | 29.1       |
| 5        | 2.00 (m, 1H), 1.79 (m, 1H) | 24.3       |
| 6        | 5.69 – 5.62 (m, 1H) | 124.6      |
| 7        | –                   | 140.9      |
| 8        | 2.49 – 2.42 (m, 1H) , 2.20 (m, 1H) | 33.0       |
| 9        | 2.20 (m, 1H), 1.50 (m, 1H) | 28.9       |
| 10       | 2.32 (m, 1H)        | 40.8       |
| 11       | –                   | 152.3      |
| 12       | 2.20 (m, 1H), 2.15 (m, 1H) | 32.9       |
| 13       | 1.65 (m, 1H), 1.57 (m, 1H) | 24.2       |
| 14       | 1.20 (m, 1H)        | 45.0       |
| 15       | 1.70 (m, 1H)        | 32.6       |
| 16       | 1.56 (m, 1H), 1.16 (m, 1H) | 32.8       |
| 17       | 2.27 (m, 1H), 2.12 (m, 1H) | 27.1       |
| 18       | 6.90 (t, $J = 7.6$ Hz, 1H) | 146.1      |
| 19       | –                   | 127.1      |
| 20       | –                   | 173.2      |
| 21       | 1.83 (s, 3H)        | 12.3       |
| 22       | 0.91 (d, $J = 6.7$ Hz, 3H) | 18.2       |
| 23       | 1.10 (s, 3H)        | 27.5       |
| 24       | 0.96 (d, $J = 9.2$ Hz, 1H) | 25.0       |
| 25       | 4.76 (d, $J = 2.0$ Hz, 1H), 4.70 (d, $J = 2.1$ Hz, 1H) | 106.4      |

$^a$ Overlapped signals are reported without designating multiplicity.
Synthesis of cerorubenic acid-III methyl ester (2)

To a solution of 1 (10 mg, 0.03 mmol) in hexane (2.5 mL) and MeOH (2.5 mL) was added a solution of TMSCHN₂ (2M in hexane, 27 μL, 0.05 mmol). The solution was stirred at room temperature for 40 minutes and quenched with AcOH until no bubbles came out. The volatiles were removed under vacuo and the residue was purified by flash-column chromatography on silica gel (hexane:EtOAc = 20:1) to afford the cerorubenic acid-III methyl ester (2) as a colorless oil (9.8 mg, 95%).

Rf = 0.59 (hexane:EtOAc = 20:1);

[α]²⁵° = -50 (c = 1.0, CH₂Cl₂), [α]²⁵° = -22 (c = 0.16, CHCl₃); -28 (c = 0.054, CHCl₃); {lit⁶ [α]²⁵° = -139 (c= 0.16, CHCl₃); lit⁶ -124 (c = 0.001, CHCl₃); lit⁶ [α]²⁵° = -60 (c = 0.001, CHCl₃)};

Note: We confirmed that our sample of cerorubenic acid-III methyl ester was partially decomposed during optical rotation test using CHCl₃ as solvent. To avoid acidic decomposition, we did optical rotation test of the cerorubenic acid-III methyl ester in CH₂Cl₂ (([α]²⁵° = -50 (c = 1.0, CH₂Cl₂)).

IR (film) 2926, 2355, 2345, 1717, 1436, 1266 cm⁻¹;

¹H NMR (500 MHz, C₆D₆) δ 6.93 (dt, J = 1.5, 8.0 Hz, 1H), 5.71 – 5.65 (m, 1H), 4.95 (s, 1H), 4.89 (d, J = 1.8 Hz, 1H), 3.45 (s, 3H), 2.53 – 2.46 (m, 1H), 2.25 – 2.13 (m, 5H), 2.11 – 2.03 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.87 (s, 3H), 1.83 (dt, J = 10.3, 5.2 Hz, 1H), 1.80 – 1.73 (m, 1H), 1.66 – 1.31 (m, 8H), 1.19 (dt, J = 6.7, 4.4 Hz, 1H), 1.05 (s, 3H), 0.92 (d, J = 8.5 Hz, 1H), 0.81 (d, J = 6.7 Hz, 3H), 0.71 (dd, J = 10.5, 9.1 Hz, 1H);

¹³C NMR (126 MHz, C₆D₆) δ 168.1, 151.3, 142.6, 140.5, 127.7, 124.4, 106.9, 51.3, 44.9, 40.6, 36.3, 32.9, 32.8, 32.6, 32.2, 31.1, 28.9, 28.6, 27.3, 26.5, 24.8, 24.2, 23.9,
20.7, 18.1, 12.6. (127.7, the signal of the enoate carbon 19, is obscured by solvent peaks, and it was elucidated by the correlations of H21 and C19 in the HMBC spectrum);

**HRMS (ESI)** Calcd for C_{26}H_{39}O_{2} [M+H]^+: 383.2945; Found: 383.2944.

**Note:** Based on the analysis of dept-135, HSQC, {\textsuperscript{1}}H-{\textsuperscript{1}}H COSY, HMBC and NOESY spectra (Figure S4-S5), the {\textsuperscript{1}}H and {\textsuperscript{13}}C NMR data of 2 were assigned as shown in Table S2, which was not reported by Naya and coworkers previously.\textsuperscript{5}

![Figure S4](image1.png)

**Figure S4.** Key {\textsuperscript{1}}H-{\textsuperscript{1}}H COSY and HMBC correlations of cerorubenic acid-III methyl ester (2)

![Figure S5](image2.png)

**Figure S5.** Key NOESY correlations of cerorubenic acid-III methyl ester (2)
Table S2. $^1$H (500 MHz) and $^{13}$C (126 MHz) NMR data of cerorubenic acid-III methyl ester (2) in C$_6$D$_6$ ($\delta$ in ppm, $J$ in Hz)$^a$

| position | $\delta_H$ | $\delta_C$ |
|----------|------------|------------|
| 1        | 1.83 (m, 1H) | 36.3       |
| 2        | 0.71 (dd, $J = 10.5$, 9.1 Hz, 1H) | 31.1       |
| 3        | –          | 20.7       |
| 4        | 1.62 (m, 1H), 1.43 (m, 1H) | 28.9       |
| 5        | 2.09 (m, 1H), 1.77 (m, 1H) | 24.2       |
| 6        | 5.71 – 5.65 (m, 1H) | 124.4      |
| 7        | –          | 140.5      |
| 8        | 2.53 – 2.46 (m, 1H), 2.15 (m, 1H) | 32.9       |
| 9        | 2.22 (m, 1H), 1.51 (m, 1H) | 28.6       |
| 10       | 2.23 (m, 1H) | 40.6       |
| 11       | –          | 151.3      |
| 12       | 2.19 (m, 1H), 2.16 (m, 1H) | 32.8       |
| 13       | 1.58 (m, 1H), 1.40 (m, 1H) | 23.9       |
| 14       | 1.19 (m, 1H) | 44.9       |
| 15       | 1.55 (m, 1H) | 32.2       |
| 16       | 1.37 (m, 1H), 1.34 (m, 1H) | 32.6       |
| 17       | 1.98 (m, 1H), 1.91 (m, 1H) | 26.5       |
| 18       | 6.93 (dt, $J = 1.5$, 8.0 Hz, 1H) | 142.6      |
| 19       | –          | 127.7$^b$ |
| 20       | –          | 168.1      |
| 21       | 1.87 (s, 3H) | 12.6       |
| 22       | 0.81 (d, $J = 6.7$ Hz, 3H) | 18.1       |
| 23       | 1.05 (s, 3H) | 27.3       |
| 24       | 0.92 (d, $J = 8.5$ Hz, 1H) | 24.8       |
| 25       | 4.95 (s, 1H), 4.89 (d, $J = 1.8$ Hz, 1H) | 106.9      |
| OMe      | 3.45 (s, 3H) | 51.3       |

$^a$ Overlapped signals are reported without designating multiplicity. $^b$ the signal of the enoate carbon 19 is obscured by solvent peaks, and it was elucidated by the correlations of H21 and C19 in the HMBC spectrum.
**Table S3.** Compared NMR data of synthetic cerorubenic acid-III methyl ester (2) between this work (500 MHz, C₆D₆) and Paquette’s work (300 MHz, C₆D₆).⁶

![Cerorubenic acid-III methyl ester (2)](image)

|                  | this work (500M) | Paquette (300M) | error (this - Paquette) | this work (126M) | Paquette (75M) | error (this - Paquette) |
|------------------|------------------|-----------------|-------------------------|------------------|----------------|-------------------------|
| **1H & ppm (J)** |                  |                 |                         |                  |                |                         |
| 6.93 (dt, J = 1.5, 8.0 Hz, 1H) | 6.92 (dt, J = 1.4, 7.5 Hz, 1H) | 0.01 | 166.1 | 168.1 | 0 |
| 5.71 - 5.65 (m, 1H) | 5.70 - 5.67 (m, 1H) | 0.01 | 151.3 | 151.3 | 0 |
| 4.95 (s, 1H) | 4.95 (s, 1H) | 0 | 142.8 | 142.8 | 0 |
| 4.89 (d, J = 1.8 Hz, 1H) | 4.88 (d, J = 0.8 Hz, 1H) | 0.01 | 124.4 | 124.4 | 0 |
| 3.45 (s, 3H) | 3.45 (s, 3H) | 0 | 106.9 | 106.9 | 0 |
| 2.53 - 2.46 (m, 1H) | 2.55-2.48 (m, 1H) | -0.02 | 51.3 | 51.2 | 0.1 |
| **13C & ppm** |                  |                 |                         |                  |                |                         |
| 1.90 (m, 1H) | 2.34 - 1.72 (series of m, 13H) | 32.9(32.859) | 32.8 | 32.8 | 0 |
| 1.87 (s, 3H) | 2.34 - 1.72 (series of m, 13H) | 32.8(32.765) | 32.6 | 32.6 | 0 |
| 1.83 (dt, J = 10.3, 5.2 Hz, 1H) | 2.34 - 1.72 (series of m, 13H) | 32.2 | 32.2 | 0 |
| 1.80 - 1.73 (m, 1H) | 2.34 - 1.72 (series of m, 13H) | 31.1 | 31.1 | 0 |
| 1.66 - 1.31 (m, 8H) | 1.65-1.30 (m, 8H) | 0.01 | 28.9 | 28.9 | 0 |
| 1.19 (dt, J = 6.7, 4.4 Hz, 1H) | 1.23-1.17 (m, 1H) | 28.6 | 28.7 | -0.1 |
| 1.05 (s, 3H) | 1.05 (s, 3H) | 0 | 27.3 | 27.3 | 0 |
| 0.92 (d, J = 8.5 Hz, 1H) | 0.92 (d, J = 9.7 Hz, 1H) | 0 | 26.5 | 26.5 | 0 |
| 0.81 (d, J = 8.7 Hz, 3H) | 0.81 (d, J = 6.7 Hz, 3H) | 0 | 24.8 | 24.8 | 0 |
| 0.71 (dd, J = 10.5, 9.1 Hz, 1H) | 0.70 (dd, J = 10.2, 9.4 Hz, 1H) | 0.01 | 24.2 | 24.2 | 0 |
|                  |                  |                 |                         |                  |                |                         |

**Note:**

The optical rotation of the synthetic 2 in this work ([α]²⁵_D = -50 (c = 1.0, CH₂Cl₂), [α]³⁰_D = -28 (c = 0.054, CHCl₃)) was close to that of Naya’s work ([α]²⁵_D = -60 (c = 0.001, CHCl₃)), and Paquette’s work ([α]²⁰_D = -124 (c = 0.001, CHCl₃)). The ¹H spectra of 2 in this work were identical to those of Paquette’s work. The ¹³C NMR spectra of 2 in this work were almost identical to those of Paquette’s work except for the chemical shift of only one carbon (32.9 in this work and 30.0 in Paquette’s work) as shown in the Table S3.

Our efforts to get the copies of the original spectra of compound 2 from Prof. Paquette or Prof. Naya have all failed to date, because they have retired for a long time. In turn, we confirmed our structure of natural product (1) and its methyl ester (2) to be
the reported one based on the comprehensive analysis of $^1$H, $^{13}$C, dept-135, HSQC, $^1$H-$^1$H COSY, HMBC and NOESY spectra (Figure S2-S5 and Table S1-S2). We confirmed that chemical shift 32.9 is for C8 and chemical shift 32.8 is for C12 in compound 2.

Further analysis of the carbon spectrum in table S3, we preferred to believe that the carbon 32.8 (in Paquette’s work) was an overlapped single of two carbons (32.859 and 32.765 in this work), because of their imperceptible distance (less than 0.1 ppm) and the probably different dispersion of the 300MHz-NMR machine in more than 20 years ago. Meanwhile, the carbon 30.0 (in Paquette’s work) was likely a mistaken assignment of grease $^7$ (a frequently observed impurity in the spectrum, Figure S6) by the author because of the scarcity or inadequate purity of the sample. Proofs to the speculation above can be found in many papers, and two works $^8$-$^9$ of Paquette’s group was shown below (Figure S7 – S10) for examples. In the $^{13}$C-NMR data of the synthetic natural product citralitrione $^8$ (Figure 7), there is no shift beside 30.0. But in the copy of the $^{13}$C-NMR spectra (Figure S8), there is a distinct carbon of the impurity (30.162), which was correctly distinguished by the author this time. Furthermore, in the study toward to lancifodilactone G, $^9$ the signal of the impurity (29.65) in the copy of the $^{13}$C-NMR spectra of compound 24 (Figure S10) was distinguished by the author and was disappeared in the $^{13}$C-NMR data (Figure S9).

| carbon | THF-$d_4$ | CDCl$_3$ | DMSO | toluene-$d_8$ | CD$_2$Cl$_2$ | CHCl$_3$ | CD$_2$OD | D$_2$O |
|--------|-----------|-----------|-------|-------------|-------------|-----------|----------|-------|
| solvent signals | 67.2 | 53.84 | 77.16 | 173.48 | 128.87 | 128.25 | 125.13 | 20.43 |

acidic acid
CO
171.69
173.93
175.99
175.30
175.82
175.67
172.31
171.93
172.21
172.96
175.11
177.23

acetone
CO
204.19
206.78
207.07
208.04
205.43
204.83
205.87
206.31
207.43
32.35
209.67
215.94

acetonitrile
CN
116.79
119.68
122.43
125.76
116.02
115.93
147.07
117.90
119.71
118.26
119.95
119.06
119.68

benzene
CH
128.84
128.68
128.37
128.57
128.62
128.38
128.18
128.30
129.32
129.84
129.34

ter-butyl alcohol
(CH$_2$)$_3$C
67.50
69.11
69.15
65.12
65.19
68.19
68.13
66.88
66.74
72.35
64.40

carbon dioxide
CO$_2$
125.69
125.26
124.99
124.86
124.76
124.08
124.83
124.24
124.69
124.92
126.31

carbon tetrachloride
CCl$_4$
96.89
96.52
96.74
96.57
96.44
96.38
95.63
95.44
95.68
97.74
97.21

chloroform
CH
79.24
77.99
77.36
77.69
77.79
77.67
79.19
79.16
79.17
80.83
79.44

DMSO-6
71.2
70.47
70.25
70.86
70.30
70.55
71.23
69.85
71.22
70.80
71.45

ethanol
CH
57.57
58.73
59.01
59.62
58.86
58.42
58.77
57.98
58.90
59.00
58.67

glucose
C$_6$H$_12$O$_6$
56.14
60.31
60.51
60.94
65.94
65.79
66.12
67.05
66.12
67.55
68.08
69.42

glycine
C$_2$H$_5$O$_2$
59.72
58.95
59.01
59.62
58.86
58.42
58.77
57.98
58.90
59.00
58.67

dimethylformamide
CH$_3$N$_2$
163.98
163.37
162.62
162.95
162.83
162.01
162.79
162.29
163.41
166.01
164.75
164.53

DMF
C$_3$H$_6$N$_2$
153.65
156.36
156.30
152.22
152.35
153.45
156.15
153.73
156.37
157.66
156.89
157.24

$^1$H-NMR of synthetic natural product citralitrione $^8$ (Figure S7), there is no shift beside 30.0. But in the copy of the $^{13}$C-NMR spectra (Figure S8), there is a distinct carbon of the impurity (30.162), which was correctly distinguished by the author this time. Furthermore, in the study toward to lancifodilactone G, $^9$ the signal of the impurity (29.65) in the copy of the $^{13}$C-NMR spectra of compound 24 (Figure S10) was distinguished by the author and was disappeared in the $^{13}$C-NMR data (Figure S9).
**Figure S6.** NMR chemical shifts of trace impurities

$^1$H NMR (600 MHz, C$_6$D$_5$) $\delta$ 5.22 (s, 1 H), 3.85 (d, $J = 9.4$ Hz, 1 H), 3.10 (s, 1 H), 2.38-2.19 (m, 5 H), 2.10 (d, $J = 17.0$ Hz, 1 H), 1.87-1.82 (m, 1 H), 1.45 (d, $J = 1.5$ Hz, 3 H), 1.39 (s, 3 H), 1.29 (d, $J = 13.8$ Hz, 1 H), 1.20 (d, $J = 7.5$ Hz, 3 H), 0.70 (s, 3 H), 0.50 (s, 3 H); $^{13}$C NMR (150 MHz, C$_6$D$_5$) $\delta$ 216.9, 213.8, 207.2, 144.7, 129.1, 72.5, 67.8, 65.6, 55.5, 52.9, 46.8, 38.0, 37.0, 35.0, 34.2, 27.7, 23.2, 20.2, 16.2, 14.7; HRMS (ES) $m/z$ (M+Na)$^+$ calcd 353.1723, obsd 353.1694.

**Figure S7.** Paquette’s $^{13}$C-NMR assignment data of the synthetic citralitrone

**Figure S8.** Paquette’s $^{13}$C-NMR copy of the synthetic citralitrone

30.2 ppm, impurity, not assigned
(s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.30, 136.13, 136.01, 134.37, 134.07, 129.50, 129.43, 127.42, 127.39, 89.28, 71.83, 68.69, 55.03, 51.94, 51.30, 48.36, 44.80, 43.91, 40.80, 37.11, 32.03, 31.40, 30.97, 28.79, 27.12, 25.93, 25.91, 25.68, 25.31, 19.64, 19.56, 18.24, 18.02, 15.92, –4.00, –4.31, –5.43, –5.48; HRMS (ES) calcd for C$_{25}$H$_{30}$O$_2$S$_2$Si$_2$Na$^+$ 895.4653, found 895.4687.

**Figure S9.** $^{13}$C-NMR data of compound 24 in the study toward to lancifodilactone G by Paquette

**Figure S10.** $^{13}$C-NMR copy of the spectra of compound 24 in the study toward to lancifodilactone G by Paquette
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III. Density functional theory (DFT) calculations

Computational Details

All density functional theory (DFT) calculations were carried out by Gaussian 09 package\textsuperscript{10}. M06-2X method combined with 6-31G* basis set was used to optimize all the structures in gas phase followed by harmonic frequency calculations.\textsuperscript{11} Then, single-point energy calculations by using M06 and B3LYP-D3 methods as well as by including solvent effect (acetonitrile) using SMD M06-2X method were also performed on the above-mentioned gas-phase optimized geometry.\textsuperscript{12-13} Overall, different methods give the same mechanistic conclusion.

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Figure S11. The optimized reactants, transition states and products of the two possible [5+2] cycloaddition pathways by the M06-2X method.

As shown in Figure S11, there is a more π-π interaction between the dipolar and Ph moieties in R5 than R5a. In addition, the two linear chains containing the dipolar and reacting alkene moieties in R5 adopt an energetically more favorable conformations (see dihedral angles C4-C3-C2-C1, C5-C4-C3-C2 & C6-C5-C4-C3: close to anti conformation (±180º) and not close to eclipsed conformation (0 or ±120º)) than R5a. These structural features are proposed to provide more thermostability towards R5 than R5a and, thus, promote the diastereocontrol addition.
Table S4. Absolute (in au) and relative (in kcal/mol) energies of all optimized structures in gas phase by M06-2X/6-31G* method.

|     | E   | E+ZPE | G   | ΔE  | ΔEZPE | ΔG  |
|-----|-----|-------|-----|-----|-------|-----|
| R5  | -   | -     | -   | 0.0 | 0.0   | 0.0 |
|     | 1698.612380 | 1697.862015 | 1697.936210 | - | - | - |
| TS5 | -   | -     | -   | 14.7| 15.1  | 16.3|
|     | 1698.588973 | 1697.838019 | 1697.910189 | - | - | - |
| 5   | -   | -     | -   | -40.9| -37.2 | -35.8|
|     | 1698.677527 | 1697.921346 | 1697.993284 | - | - | - |
| R5a | -   | -     | -   | 5.2 | 5.1   | 6.5 |
|     | 1698.604083 | 1697.853830 | 1697.925879 | - | - | - |
| TS5a| -   | -     | -   | 17.3| 18.1  | 21.2 |
|     | 1698.584820 | 1697.833228 | 1697.902460 | - | - | - |
| 5a  | -   | -     | -   | -41.2| -37.4 | -34.1|
|     | 1698.678102 | 1697.921624 | 1697.990631 | - | - | - |

Table S5. Absolute (in au) and relative (in kcal/mol) energies for the single-point calculations of all optimized structures by the M06, B3LYP-D3 and SMD M06-2X methods.

|     | M06  | ΔE  | ΔG  | B3LYP-D3 | ΔE  | ΔG  | SMD M06-2X | ΔE_{soln} | ΔG_{soln} |
|-----|------|-----|-----|----------|-----|-----|------------|-----------|-----------|
| R5  | -    | 0.0 | 0.0 | -        | 0.0 | 0.0 | -          | 0.0       | 0.0       |
|     | 1698.164260 | 1699.447268 | 1698.649817 | - | - | - |
| TS5 | -    | 15.5| 17.2| -        | 14.5| 16.1| -          | 15.0      | 16.7      |
|     | 1698.139512 | 1699.424178 | 1698.625838 | - | - | - |
| 5   | -    | -   | -   | -        | -   | -   | -          | -40.9     | -35.8     |
|     | 1698.226423 | 1699.496414 | 30.8 | 1698.714980 | - | - | - |
| R5a | -    | 6.0 | 7.3 | -        | 5.0 | 6.3 | -          | 4.4       | 5.7       |
|     | 1698.154644 | 1699.439315 | 1698.642801 | - | - | - |
| TS5a| -    | 18.6| 22.5| -        | 18.1| 21.9| -          | 17.0      | 20.9      |
|     | 1698.134651 | 1699.418491 | 1698.622722 | - | - | - |
| 5a  | -    | -   | -   | -        | -   | -   | -          | -40.6     | -33.5     |
|     | 1698.225198 | 1699.497319 | 1698.714446 | - | - | - |
Cartesian coordinates of the optimized stationary points:

|   | O   | -0.918428 | 2.405462 | H   | -0.975210 | -2.468361 | 3.412433 |
|---|-----|-----------|----------|-----|-----------|----------|----------|
| O | 0.655604 | -2.998180 | 0.512459 | C   | -0.139197 | -4.684270 | 1.932566 |
| O | -1.629704 | -3.036476 | 0.981003 | H   | -0.855696 | -4.932811 | 2.718991 |
| O | 1.897167  | 1.986604  | -1.471672 | H   | 0.876414  | -4.842178 | 2.303761 |
| O | 5.025562  | -0.399792 | -1.087544 | H   | 0.303943  | -5.345413 | 1.077567 |
| C | -5.923759 | 3.753688  | 3.065637  | C   | -1.670357 | -3.247399 | -0.425469 |
| H | -4.996088 | 4.322463  | 3.169247  | H   | -1.131449 | -4.172952 | -0.671131 |
| H | -5.994387 | 3.053452  | 3.907138  | C   | -3.119475 | -3.391455 | -0.862585 |
| H | -6.766282 | 4.449652  | 3.163359  | H   | -3.587807 | -4.169992 | -0.251453 |
| C | -5.984393 | 3.021448  | 1.751131  | H   | -3.122838 | -3.745659 | -1.902143 |
| C | -4.984171 | 0.309462  | 0.867176  | C   | -3.900447 | -2.080741 | -0.776224 |
| H | -4.109424 | 3.685730  | 1.141206  | H   | -3.975742 | -1.773606 | 0.274420 |
| C | -4.909145 | 2.393578  | -0.462598 | H   | -4.920313 | -2.242079 | -1.142152 |
| H | -4.351314 | 3.017636  | -1.173646 | C   | 0.537308  | 2.274071  | -1.759925 |
| H | -5.910863 | 2.268290  | -0.858040 | H   | 0.437756  | 2.186014  | -2.845822 |
| C | -4.211376 | 1.029777  | -0.350214 | H   | 0.318570  | 3.315036  | -1.474085 |
| H | -4.802900 | 0.390485  | 0.319975  | C   | 2.220606  | 2.152075  | -0.108113 |
| H | -3.242512 | 1.184205  | 0.141508  | H   | 1.896140  | 1.279536  | 0.480481 |
| C | -4.008048 | 0.329505  | -1.699413 | H   | 1.688015  | 3.032419  | 0.292106 |
| H | -3.410308 | 1.007167  | -2.327633 | C   | 3.705610  | 2.348121  | 0.064916 |
| C | -3.202721 | -0.982604 | -1.586729 | C   | 4.510710  | 2.758920  | -0.996945 |
| H | -3.079200 | -1.359058 | -2.617795 | H   | 4.062222  | 2.893950  | -1.975604 |
| C | -1.791137 | -0.769880 | -1.009901 | C   | 5.872130  | 2.977002  | -0.798818 |
| H | -1.887662 | -0.518689 | 0.056857  | H   | 6.493401  | 3.289481  | -1.633108 |
| C | -1.025387 | 0.322809  | -1.694835 | C   | 6.436282  | 2.803812  | 0.463731 |
| H | -0.916393 | 0.223092  | -2.779807 | C   | 7.496984  | 2.980487  | 0.616106 |
| C | -0.398854 | 1.321516  | -1.073750 | C   | 5.636659  | 2.387794  | 1.526139 |
| H | -0.509231 | 1.425333  | 0.007447  | H   | 6.068360  | 2.209709  | 2.505893 |
| C | 5.380246 | -0.507572 | 0.169276  | C   | 4.279940  | 2.153257  | 1.322978 |
| H | 6.397674 | -0.188941 | 0.357193  | H   | 3.673766  | 1.782044  | 2.146353 |
| C | 4.481101 | -0.941178 | 1.208899  | C   | 3.819884  | -0.718149 | -1.526690 |
| C | 3.217437 | -1.397643 | 0.675759  | H   | 3.686454  | -0.520829 | -2.580806 |
| H | 2.514502 | -1.844615 | 1.371381  | C   | -0.945538 | -2.063492 | -1.074213 |
| C | 2.885890 | -1.274673 | -0.665968 | H   | -0.751727 | -2.304750 | -2.130767 |
| C | 1.577436 | -1.734380 | -1.272554 | C   | -5.344565 | 0.098677  | -2.413308 |
| H | 1.723720 | -2.708904 | -1.756802 | H   | -6.077720 | -0.367756 | -1.744584 |
| H | 1.294304 | -1.021723 | -2.055583 | H   | -5.219251 | -0.556010 | -3.283145 |
| C | 0.399017 | -1.873202 | -0.318890 | H   | -5.774419 | 1.039674  | -2.767597 |
| H | 0.340911 | -0.965668 | 0.300930  | C   | -7.240895 | 2.218031  | 1.540373 |
| C | -0.323905 | -3.234316 | 1.513338  | H   | -7.241561 | 1.660256  | 0.601635 |
| C | -0.180895 | -2.276031 | 2.686860  | H   | -8.123755 | 2.868966  | 1.553498 |
| H | -0.270037 | -1.237757 | 2.355835  | H   | -7.370039 | 1.498123  | 2.357761 |
| H | 0.788406 | -2.415832 | 3.172740  |
TS5:

| Element | x  | y  | z  |
|---------|----|----|----|
| C       | -6.244698 | -2.320429 | 0.635481 |
| H       | -7.048064 | -1.580718 | 0.603055 |

O: 2.402723 -1.007537 2.230761
H: -3.943495 -2.653328 0.982035
C: -4.583584 -0.708240 -0.085740
O: 3.630533 -0.557052 -1.485450
C: 1.640657 -3.239250 -0.430765
C: -1.806414 6.168316 2.631638
H: -1.558033 5.589362 3.525171
C: -2.892579 6.321569 2.610588
H: -1.350300 7.161502 2.728009
C: -1.335823 5.482312 1.376677
C: -0.708290 4.302851 1.420312
H: -0.564132 3.899911 2.396512
C: -0.217627 3.513262 0.235280
H: 0.632721 2.889788 0.540734
H: 0.163819 4.185521 -0.541283
C: -1.308121 2.605687 -0.353762
H: -2.180676 3.221400 -0.612302
H: -1.649182 1.919495 0.433288
C: -0.836026 1.826162 -1.591393
H: 0.193827 1.503565 -1.400352
C: -1.679888 0.560133 -1.869938
H: -1.377857 0.191507 -2.864220
C: -1.361305 -0.603934 -0.858768
H: -1.223965 -0.145403 0.131053
C: -0.019075 -1.166155 -1.305004
H: -0.058542 -1.696527 -2.260873
C: 1.190939 -0.629479 -0.930923
H: 1.188159 0.093669 -0.115798
C: 2.249429 -2.290163 0.265987
H: 3.293633 -2.174982 0.000424
C: 1.746854 -1.801483 1.544916
C: 0.430641 -2.302689 1.860075
H: -0.001374 -2.046028 2.823820
C: -0.281164 -3.019558 0.930124
C: -1.728139 -3.363163 1.123952
H: -1.920825 -3.616307 2.170727
C: -2.016454 -4.227697 0.515367
C: -2.624842 -2.191568 0.741000
C: -2.401604 -1.345866 1.408071
C: -4.922283 -1.628750 0.934284
C: -4.976798 -0.839956 2.234735
H: -5.013476 -0.367772 2.442649
H: -5.239659 -1.503197 3.062294
O: -5.729164 -0.051604 2.152724
O: 1.503978 -2.101443 2.868251
O: -4.928204 -1.127825 0.740639

5:
| H       | 9459     | 8112     |
|---------|----------|----------|
| C       | 1.182055 | 3.000373 |
| H       | 3.380430 |
| C       | 1.155633 | 2.082835 |
| H       | 2.783512 |
| C       | 2.223088 | 1.483975 |
| H       | 1.074850 |
| H       | 3.215156 | 2.296783 |
| C       | 2.938880 | 3.626382 |
| C       | 3.312645 | 1.245686 |
| H       | 3.062430 |
| C       | 1.448721 | 1.912959 |
| C       | 2.536916 |
| H       | 0.641612 |
| C       | 1.656156 |
| H       | 0.717305 |
| C       | 1.556216 |
| H       | 0.044388 |
| C       | 0.249544 | 0.614955 |
| H       | 1.292785 |
| H       | 0.305011 | 1.686008 |
| C       | 0.627414 | -0.367670 |
| C       | 3.287408 |
| H       | 0.758371 |
| C       | 0.318720 | 0.717305 |
| H       | 0.545100 | 0.044388 |
| C       | 0.249544 | 0.614955 |
| H       | 1.292785 |
| H       | -0.240524 |
| C       | 0.669202 | 0.193520 |
| C       | -0.540985 |
| C       | -0.604395 |
| H       | -1.624591 |
| C       | -1.827504 |
| C       | 0.1959773 |
| C       | -3.617733 |
| C       | 0.363444 |
| C       | 0.372374 |
| C       | 0.286361 |
| C       | -0.027074 |
| H       | 1.026511 |
| C       | -1.431821 |
| C       | 0.1859777 |
| C       | 3.618440 |
| C       | 3.363444 |
| C       | 3.790605 |
| C       | 4.221152 |
| C       | 4.439543 |
| C       | 4.281232 |
| C       | 4.562753 |
| C       | 5.303552 |
| C       | 4.978302 |
| C       | 3.312645 |
| C       | 2.851137 |
| C       | 2.938880 |
| C       | 2.245034 |
| C       | 1.709029 |
| H       | 2.979485 |
| H       | 1.518127 |
| C       | 3.764133 |
| H       | 3.121186 |
| H       | 4.567136 |
| H       | 4.205501 |
| C       | 2.227803 |
| H       | 3.215156 |
| C       | 1.155633 |
| H       | 1.182055 |
| H       | -4.835532 |
| H       | -5.110812 |
| H       | -6.410362 |
| C       | -4.871590 |
| C       | -3.969895 |
| H       | -3.554833 |
| C       | -3.419490 |
| H       | -3.097269 |
| H       | -4.199019 |
| C       | -2.223088 |
| H       | -2.536916 |
| H       | -1.448721 |
| C       | -1.656156 |
| H       | -1.556216 |
| C       | -0.249544 |
| H       | 0.012954 |
| C       | 0.852157 |
| H       | 0.624951 |
| C       | 0.781823 |
| H       | 0.346053 |
| C       | 1.026511 |
| H       | 1.431821 |
| C       | 3.618440 |
| C       | 3.363444 |
| C       | 3.790605 |
| C       | 4.221152 |
| C       | 4.439543 |
| C       | 4.281232 |
| C       | 4.562753 |
| C       | 5.303552 |
| C       | 4.978302 |
| C       | 3.312645 |
| C       | 2.851137 |
| C       | 2.938880 |
| C       | 2.245034 |
| C       | 1.709029 |
| H       | 2.979485 |
| H       | 1.518127 |
| C       | 3.764133 |
| H       | 3.121186 |
| H       | 4.567136 |
| H       | 4.205501 |
| C       | 2.227803 |
| H       | 3.215156 |
| C       | 1.155633 |
| H       | 1.182055 |

**TS8a:**

| O       | 2.591004 |
| O       | 4.438991 |
| O       | 2.641505 |
| O       | 2.107527 |
| O       | 3.081242 |
| H       | -0.811646 |
| H       | -2.338199 |
| H       | -4.041832 |
| C       | -3.161576 |

**TS5a:**

| O       | 2.591004 |
| O       | 5.195941 |
| O       | 5.179686 |
| O       | 5.179686 |
| O       | 5.179686 |
| O       | 5.179686 |
| H       | 4.669117 |
| H       | 5.964372 |
| H       | 5.687094 |
| C       | 4.221863 |
| H | -3.744419 | 2.404072 | -1.323240 | C | 0.213664 | 0.057538 | 2.834307 |
| C | -1.662457 | 1.976414 | -0.891404 | H | 0.073410 | 0.440104 | 3.850801 |
| H | -1.663740 | 2.622875 | -0.002309 | H | 0.132499 | -1.037207 | 2.877492 |
| H | -0.703491 | 2.154342 | -1.395691 | C | -0.834602 | 0.614893 | 1.882740 |
| C | -1.787732 | 0.501337 | -0.483069 | H | -0.742742 | 1.707795 | 1.853626 |
| H | -1.708414 | -0.094808 | -1.399440 | H | -1.832734 | 0.377824 | 2.264377 |
| C | -0.670866 | 0.019570 | 0.480588 | C | -0.653884 | -2.421083 | -2.085571 |
| H | -0.806704 | -1.066689 | 0.581529 | H | -1.024671 | -1.770354 | -2.887417 |
| C | 0.750183 | 0.275540 | -0.076461 | H | -0.541428 | -3.434075 | -2.503713 |
| H | 0.797586 | 1.357605 | -0.267419 | C | -1.558043 | -3.553149 | -0.214972 |
| C | 0.957869 | -0.400389 | -1.456057 | H | -0.562939 | -3.610876 | 0.250125 |
| H | 0.289047 | 0.101307 | -2.166730 | H | -1.715608 | -4.482764 | -0.784383 |
| C | 0.731511 | -1.932185 | -1.637573 | C | -2.609720 | -3.374118 | 0.845650 |
| H | 1.017952 | -2.468886 | -0.723410 | C | -3.960053 | -3.439601 | 0.497134 |
| C | 1.743175 | -2.275361 | -2.788573 | H | -4.232182 | -3.676185 | -0.528259 |
| H | 1.300326 | -2.844807 | -3.609106 | C | -4.943798 | -3.174873 | 1.443119 |
| C | 2.926878 | -3.023822 | -2.198602 | H | -5.991803 | -3.222031 | 1.163555 |
| C | 3.797303 | -2.139760 | -1.396040 | C | -4.584726 | -2.842038 | 2.749011 |
| H | 4.607481 | -2.599600 | -0.835944 | H | -5.353157 | -2.631643 | 3.486575 |
| C | 3.500181 | -0.834911 | -1.287420 | C | -3.240992 | -2.783063 | 3.106050 |
| C | 4.186660 | 0.068215 | -0.311525 | H | -2.956319 | -2.526079 | 4.121856 |
| H | 4.847340 | 0.777436 | -0.825988 | C | -2.258425 | -3.050317 | 2.154742 |
| H | 4.800488 | -0.518982 | 0.378799 | H | -1.206887 | -3.000152 | 2.428053 |
| C | 3.154796 | 0.847111 | 0.501723 | C | 2.363955 | -0.255921 | -2.118066 |
| H | 2.795061 | 1.693150 | -0.102738 | H | 2.586680 | 0.774753 | -2.413803 |
| C | 3.091913 | 2.257801 | 2.414135 | C | 1.909985 | 0.007958 | 0.920644 |
| C | 3.090035 | 3.654935 | 1.811373 | H | 2.163818 | -1.062755 | 0.920241 |
| H | 2.658488 | 3.641988 | 0.807332 | C | -3.174727 | 0.205901 | 0.100973 |
| H | 4.110806 | 4.041443 | 1.761002 | H | -3.470843 | 0.965068 | 0.835700 |
| H | 2.482948 | 4.319170 | 2.431360 | H | -3.192506 | -0.772170 | 0.591227 |
| C | 3.720243 | 2.236342 | 3.799890 | H | -3.935233 | 0.192859 | -0.685371 |
| H | 3.196160 | 2.939152 | 4.451928 | C | -3.772675 | 5.076875 | -0.578939 |
| H | 4.774660 | 2.517143 | 3.738291 | H | -3.968711 | 4.104814 | -0.121783 |
| H | 3.654280 | 1.233918 | 4.230506 | H | -4.735721 | 5.557228 | -0.792047 |
| C | 1.608395 | 0.418534 | 2.370761 | H | -3.268431 | 5.702962 | 0.167398 |
| H | 2.351061 | -0.057454 | 3.025116 |
IV. X-ray Crystallographic Data

X-Ray data for 17: (CCDC 1869291)

Crystal data and structure refinement for 17.

| Property                              | Value                                      |
|---------------------------------------|--------------------------------------------|
| Identification code                   | A                                          |
| Empirical formula                     | C₄₁H₅₁NO₈                                  |
| Formula weight                        | 685.82                                     |
| Temperature/K                         | 100                                        |
| Crystal system                        | monoclinic                                 |
| Space group                           | P2₁                                        |
| a/Å                                   | 9.855(3)                                   |
| b/Å                                   | 13.243(3)                                  |
| c/Å                                   | 13.890(5)                                  |
| α/°                                   | 90                                         |
| β/°                                   | 101.25(2)                                  |
| γ/°                                   | 90                                         |
| Volume/Å³                             | 1777.9(9)                                  |
| Z                                      | 2                                           |
| ρ calcg/cm³                           | 1.281                                      |
| μ /mm⁻¹                               | 0.088                                      |
| F(000)                                | 736.0                                      |
| Crystal size/mm³                      | 0.52 × 0.5 × 0.48                          |
| Radiation                             | MoKα (λ = 0.71073)                         |
| 2θ range for data collection/°       | 4.668 to 55.244                            |
| Index ranges                          | -12 ≤ h ≤ 12, -17 ≤ k ≤ 17, -18 ≤ l ≤ 18  |
| Reflections collected                 | 25208                                      |
| Independent reflections               | 8135 [R_int = 0.0339, R_sigma = 0.0353]    |
| Data/restraints/parameters            | 8135/1/457                                 |
| Goodness-of-fit on F²                 | 1.086                                      |
| Final R indexes [I>=2 σ (I)]          | R₁ = 0.0567, wR₂ = 0.1443                  |
| Final R indexes [all data]            | R₁ = 0.0601, wR₂ = 0.1471                  |
| Largest diff. peak/hole / e Å⁻³       | 0.27/-0.22                                 |
| Flack parameter                       | -0.2(10)                                   |
X-Ray data for 23a (CCDC 1869292)

Crystal data and structure refinement for 23a

| Property                              | Value                      |
|---------------------------------------|----------------------------|
| Identification code                   | A                          |
| Empirical formula                    | C_{27}H_{42}O_{2}           |
| Formula weight                        | 398.60                     |
| Temperature/K                         | 115.0                      |
| Crystal system                        | orthorhombic               |
| Space group                           | P2_12_1_2_1                |
| a/Å                                   | 9.8763(17)                 |
| b/Å                                   | 15.381(3)                  |
| c/Å                                   | 15.448(3)                  |
| α/°                                   | 90                         |
| β/°                                   | 90                         |
| γ/°                                   | 90                         |
| Volume/Å³                             | 2346.6(7)                  |
| Z                                      | 4                          |
| \( \rho_{\text{calc}} \)/g/cm³      | 1.128                      |
| \( \mu \)/mm⁻¹                        | 0.068                      |
| F(000)                                | 880.0                      |
| Crystal size/mm³                      | 0.2 × 0.03 × 0.03          |
| Radiation                             | MoKα (\( \lambda = 0.71073 \)) |
| 2Θ range for data collection/°       | 4.896 to 52.908            |
| Index ranges                          | -12 ≤ h ≤ 12, -19 ≤ k ≤ 19, -19 ≤ l ≤ 19 |
| Reflections collected                 | 27498                      |
| Independent reflections               | 4814 [R_{int} = 0.0658, R_{sigma} = 0.0448] |
| Data/restraints/parameters            | 4814/0/269                 |
| Goodness-of-fit on \( F^2 \)          | 1.087                      |
| Final R indexes [I>=2σ (I)]          | R_1 = 0.0390, wR_2 = 0.0878 |
| Final R indexes [all data]           | R_1 = 0.0431, wR_2 = 0.0897 |
| Largest diff. peak/hole / e Å⁻³      | 0.20/-0.15                 |
| Flack parameter                       | 0.3(7)                     |
V. $^1$H and $^{13}$C NMR Spectra

(H-NMR, CDCl$_3$, 500 MHz)

(C-NMR, CDCl$_3$, 500 MHz)
(H-NMR, CDCl₃, 500 MHz)

(C-NMR, CDCl₃, 500 MHz)
S3
(H-NMR, CDCl₃, 500 MHz)

TBSO₅

H₂O

S3
(C-NMR, CDCl₃, 500 MHz)
TBSO
\[
\text{CHO}
\]
(H-NMR, CD\textsubscript{2}Cl\textsubscript{2}, 500 MHz)

TBSO
\[
\text{CHO}
\]
(C-NMR, CD\textsubscript{2}Cl\textsubscript{2}, 500 MHz)
$\text{Bu}_3\text{Sn} = \equiv \text{OBn}$

8
(H-NMR, CDCl$_3$, 500 MHz)

$\text{Bu}_3\text{Sn} = \equiv \text{OBn}$

8
(C-NMR, CDCl$_3$, 500 MHz)
OTBS

14
(H-NMR, CDCl₃, 500 MHz)

14
(C-NMR, CDCl₃, 500 MHz)
15 (HMBC, CDCl₃, 500 MHz)

15 (NOESY, CDCl₃, 500 MHz)
(H-NMR, CDCl₃, 500 MHz)

(C-NMR, CDCl₃, 500 MHz)
18 (H-NMR, CD$_2$Cl$_2$, 500 MHz)

18 (C-NMR, CD$_2$Cl$_2$, 500 MHz)
(1H-1H COSY, CD₂Cl₂, 500 MHz)

(HSQC, CD₂Cl₂, 500 MHz)
S5 (H-NMR, CD$_2$Cl$_2$, 500 MHz)

S5 (C-NMR, CD$_2$Cl$_2$, 500 MHz)
23a
(H-NMR, CD$_2$Cl$_2$, 500 MHz)

23a
(C-NMR, CD$_2$Cl$_2$, 500 MHz)
23 (H-NMR, CDCl₃, 500 MHz)

23 (C-NMR, CDCl₃, 500 MHz)
(H-NMR, CD$_2$Cl$_2$, 500 MHz)

(C-NMR, CD$_2$Cl$_2$, 500 MHz)

S79
cerorubenic acid-III (1)  
(H-NMR, C₆D₆, 500 MHz)



S80
cerorubenic acid-III (1)
(dept-135, CD$_2$D$_6$, 500 MHz)

(cerorubenic acid-III (1)
(H-NMR, CD$_2$Cl$_2$, 500 MHz))
cerorubenic acid-III (1)
(C-NMR, CD$_2$Cl$_2$, 500 MHz)

cerorubenic acid-III (1)
(dept-135, CD$_2$Cl$_2$, 500 MHz)
cerorubenic acid-III (1)
(\textsuperscript{1}H-\textsuperscript{1}H COSY, CD\textsubscript{2}Cl\textsubscript{2}, 500 MHz)

cerorubenic acid-III (1)
(HSQC, CD\textsubscript{2}Cl\textsubscript{2}, 500 MHz)
cerorubenic acid-III (1)
(HMBC, CD$_2$Cl$_2$, 500 MHz)

cerorubenic acid-III (1)
(NOESY, CD$_2$Cl$_2$, 500 MHz)
cerorubenic acid-III methyl ester (2)
(dept135-NMR, C₆D₆, 500 MHz)

(1H-1H COSY, C₆D₆, 500 MHz)
cerorubenic acid-III methyl ester (2)
(HMBC, C$_2$D$_2$, 500 MHz)

cerorubenic acid-III methyl ester (2)
(NOESY, C$_2$D$_2$, 500 MHz)