Supporting Information

Construction of key building blocks towards the synthesis of cortistatins

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1. **Experimental Details:**

Preparation of enones 20 and 24:

It was observed that the hydrogenation of the sulfone S10 leading to S12 lacked reproducibility in our hands, as the reduced sulfone underwent facile elimination leading to the enone 20, which was subsequently reduced once again in the same reaction medium to provide saturated products, which were of no use to our purpose. But such problems were not encountered with the hydrogenation of enedione S9 and hence we moved forward with enedione 24, rather than enone 20.
Table S1: Attempted epoxide opening

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<th>Entry</th>
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<th>Conditions</th>
<th>Result</th>
</tr>
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<tr>
<td>1</td>
<td>None</td>
<td>Et₂O, 0 °C – rt</td>
<td>SM remained</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂</td>
<td>Et₂O, 0 °C – rt</td>
<td>SM remained</td>
</tr>
<tr>
<td>3</td>
<td>CuCN</td>
<td>THF, rt – reflux</td>
<td>SM remained</td>
</tr>
<tr>
<td>4</td>
<td>CuCl₂</td>
<td>LiCl, THF, rt – reflux</td>
<td>SM remained</td>
</tr>
<tr>
<td>5</td>
<td>Me₃Al</td>
<td>DCM, 0 °C – rt</td>
<td>SM remained</td>
</tr>
</tbody>
</table>

It was evident from the crystal structure of the diester 28 that the epoxide was highly hindered by the angular methyl group and this explains the difficulty faced in the epoxide opening. The nucleophile was required to attack from the direction of the axial site of the 6-membered carbocycle, where the reagents were faced with the steric hindrance of the methyl group.

Synthesis of D-glucose derived aldehydes 29 and 30:

Starting from D-glucose diacetonide, the free secondary alcohol was converted into the corresponding (2-naphthyl)methyl ether, followed by hydrolysis of the primary acetonide to generate the diol S15. Treatment under oxidative conditions using NaIO₄ cleaved the diol to generate the aldehyde 29, which was used for further transformations. Detailed procedures for the above sequence have been given in Section 3.
A similar sequence was repeated for the preparation of the corresponding benzylated aldehyde 30 as reported in literature.3,4

2. Experimental Procedures and Characterization of Products:

(3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(naphthalen-2-ylmethoxy)tetrahydrofuro[2,3-d][1,3]dioxole (S14):

A flame-dried 2-necked round bottomed flask was charged with NaH (230 mg, 5.77 mmol, 60% in mineral oil) and anhydrous DMF (10 mL) was added. After cooling to 0 °C, a solution of glucose diacetonide (1 g, 3.85 mmol) in DMF (5 mL) was added in drop wise manner and the resulting solution was stirred for 1 h at the same temperature. Finally a pinch of TBAI and a solution of 2-(bromomethyl)naphthalene (1.28 g, 5.77 mmol) in DMF (5 mL) were added and the resulting mixture was stirred to room temperature for 12 hs. Finally the reaction was quenched with saturated NH₄Cl solution and work-up was done with EtOAc to obtain the crude mixture. Purification was done through silica gel column chromatography using 5% EtOAc/hexanes to obtain 1.3 g (84%) of the compound S14 as a white solid.

R_f : 0.70 (25% EtOAc/hexanes)

[α]_D^20 : −32.4 (c 0.5, CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃): δ 7.86–7.80 (m, 4H), 7.52–7.45 (m, 3H), 5.94 (d, J = 3.7 Hz, 1H), 4.83 (ABq, Δδ_AB = 21.9 Hz, J_AB = 12.0 Hz, 2H), 4.64 (d, J = 3.7 Hz, 1H), 4.46–4.39 (m, 1H), 4.20–4.13 (m,
2H), 4.09 (d, J = 3.1 Hz, 1H), 4.04 (dd, J = 8.6, 5.8 Hz, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 135.1, 133.3, 133.1, 128.2, 127.9, 127.7, 126.5, 126.2, 126.0, 125.7, 111.8, 109.1, 105.4, 82.7, 81.7, 81.4, 72.6, 72.5, 67.5, 26.9, 26.8, 26.3, 25.5. IR ν (neat, cm$^{-1}$): 2987, 2931, 1635, 1603, 1456, 1381, 1373, 1254, 1217, 1078, 1020, 851.

HRMS (ESI-QTOF): m/z for C$_{23}$H$_{28}$NaO$_6$, [M+Na]$^+$ calcd. 423.1778, found 423.1773.

(R)-1-((3aR,5R,6S,6aR)-2,2-dimethyl-6-(naphthalen-2-ylmethoxy)tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethane-1,2-diol (S15):

![Diagram of S15]

The diacetonide S14 (1.3 g, 3.25 mmol) was dissolved in 60% AcOH (30 mL) and the resulting mixture was stirred at room temperature overnight. After complete consumption of the starting material, the acetic acid was evaporated by azeotrope formation with toluene and concentration of the organic solvents under high pressure afforded the crude diol. Purification was done through silica gel column chromatography using 60% EtOAc : hexanes as the eluent to obtain 1.17 g (quantitative yield) of the diol S15 as a colourless liquid.

$R_f$ : 0.10 (50% EtOAc/hexanes)

$[\alpha]_{D}^{20}$ : $-30.0$ (c 2.0, CH$_2$Cl$_2$)

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.87–7.78 (m, 4H), 7.53–7.47 (m, 2H), 7.45 (dd, J = 8.4, 1.5 Hz, 1H), 5.96 (d, J = 3.8 Hz, 1H), 4.80 (ABq, $\Delta\delta_{AB} = 84.1$ Hz, $J_{AB} = 11.9$ Hz, 2H), 4.67 (d, J = 3.8 Hz, 1H), 4.18–4.12 (m, 2H), 4.10–4.05 (m, 1H), 3.86–3.69 (m, 2H), 2.65 (bs, 1H), 2.33 (bs, 1H), 1.49 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 134.5, 133.2, 133.1, 128.7, 127.9, 127.8, 126.9, 126.4, 126.3, 125.5, 111.9, 105.2, 82.2, 72.0, 80.0, 72.3, 69.3, 64.4, 26.8, 26.3. IR ν (neat, cm$^{-1}$): 3466, 3015, 2930, 1602, 1509, 1457, 1376, 1219, 1076, 1021. HRMS (ESI-QTOF): m/z for C$_{20}$H$_{24}$NaO$_6$, [M+Na]$^+$ calcd. 383.1465, found 383.1467.

(3aR,5S,6S,6aR)-2,2-dimethyl-6-(naphthalen-2-ylmethoxy)tetrahydrofuro[2,3-d][1,3]dioxole-5-carbaldehyde (29):
The crude diol S15 (1.17 g, 3.25 mmol) from the previous step was dissolved in methanol (30 mL) and water (10 mL) and to this solution was added NaIO₄ (834 mg, 3.9 mmol) in portion wise manner at 0 °C. The resulting suspension was stirred to room temperature over 1 h after which the solid residues were filtered off under vacuum and the filtrate was collected. The methanol was removed and the product was extracted from the aqueous layer with dichloromethane. The combined organic layer was concentrated under vacuum to obtain the crude aldehyde. Purification was done through silica gel column chromatography using 40% EtOAc : hexanes as the eluent to obtain 900 mg (85%) of the aldehyde 29 as a colourless liquid.

Rf : 0.4 (50% EtOAc/hexanes)

[α]D²⁰ : −81.0 (c 2.0, CH₂Cl₂)

¹H NMR (500 MHz, CDCl₃): δ 9.71 (d, J = 1.2 Hz, 1H), 7.84 (d, J = 7.7 Hz, 3H), 7.70 (s, 1H), 7.52–7.47 (m, 2H), 7.35 (dd, J = 8.4, 1.2 Hz, 1H), 6.15 (d, J = 3.5 Hz, 1H), 4.71 (ABq, Δδ_AB = 62.4 Hz, J_AB = 12.0 Hz, 2H), 4.69 (d, J = 3.5 Hz, 1H), 4.59 (dd, J = 3.6, 1.0 Hz, 1H), 4.39 (d, J = 3.8 Hz, 1H), 1.47 (s, 3H), 1.34 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 200.1, 134.2, 133.3, 133.3, 128.7, 128.1, 127.9, 127.0, 126.5, 126.4, 125.6, 112.8, 106.4, 84.8, 83.7, 82.4, 72.7, 27.2, 26.6. IR ν (neat, cm⁻¹): 2986, 2935, 1738, 1455, 1374, 1223, 1074, 871. HRMS (ESI-QTOF): m/z for C₁₉H₂₀NaO₅, [M+Na]⁺ calcd. 351.1208, found 351.1212.

(3R,4S,5S)-4,5-bis(naphthalen-2-ylmethoxy)hept-1-en-6-yn-3-ol (S18):
The dibromo compound 39 (50 mg, 0.086 mmol) was dissolved in dry THF (5 mL) and cooled to -78 °C and to this solution was added n-BuLi (0.1 mL, 1.0 M in THF, 0.1 mmol) in drop wise manner and the resulting solution was stirred for 1 h. The reaction was quenched with saturated NH₄Cl solution and work-up was done with EtOAc to obtain the crude product. Purification was done through silica gel column chromatography using 12% EtOAc/hexanes as the eluent to obtain 20 mg (54%) of the terminal alkyne as a pale yellow solid.

R_f : 0.15 (10% EtOAc/hexanes)

[α]D²₀ : +54.8 (c 1.0, CH₂Cl₂)

1H NMR (500 MHz, CDCl₃): δ 7.87−7.73 (m, 8H), 7.51−7.42 (m, 6H), 5.91 (ddd, J = 17.2, 10.5, 5.4 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.18 (d, J = 10.5 Hz, 1H), 4.98 (ABq, Δδ_AB = 130.6 Hz, J_AB = 11.3 Hz, 2H), 4.90 (ABq, Δδ_AB = 156.0 Hz, J_AB = 11.8 Hz, 2H), 4.54 (bs, 1H), 4.49 (dd, J = 6.7, 2.1 Hz, 1H), 4.36 (dd, J = 6.7, 3.2 Hz, 1H), 2.66 (d, J = 2.1 Hz, 1H), 2.41 (bs, 1H).

13C NMR (125 MHz, CDCl₃): δ 138.1, 135.6, 135.1, 133.5, 133.4, 133.3, 128.5, 128.4, 128.2, 127.9, 127.9, 127.3, 127.2, 126.4, 126.4, 126.3, 126.2, 126.2, 116.5, 83.5, 80.6, 77.0, 75.6, 72.4, 71.7, 70.7. IR ν (KBr, cm⁻¹): 3494, 3288, 3057, 2953, 2115, 1601, 1508, 1461, 1271, 1082, 856, 818. HRMS (ESI-QTOF): m/z for C₂₉H₂₆NaO₃, [M+Na]⁺ calcd. 445.1774, found 445.1777.

(3R,4S,5S)-4,5-bis(benzyloxy)hept-1-yn-6-ol (S19):

R_f : 0.50 (25% EtOAc/hexanes)

1H NMR (400 MHz, CDCl₃): δ 7.40−7.26 (m, 10H), 5.88 (ddd, J = 17.1, 10.5, 5.4 Hz, 1H), 5.32 (d, J = 17.2 Hz, 1H), 5.18 (d, J = 10.5 Hz, 1H), 4.80 (ABq, Δδ_AB = 112.0 Hz, J_AB = 11.1 Hz, 2H), 4.73 (ABq, Δδ_AB = 125.9 Hz, J_AB = 11.7 Hz, 2H), 4.52−4.46 (m, 1H), 4.41 (ddd, J = 6.5, 2.1 Hz, 1H), 3.60 (dd, J = 6.5, 3.4 Hz, 1H), 2.62 (d, J = 2.1 Hz, 1H), 2.41 (bs, 1H). 13C NMR (100 MHz, CDCl₃): δ 138.1, 138.0, 137.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 116.4, 83.4, 80.5, 76.6, 75.5, 72.3, 71.4, 70.5. IR ν (neat, cm⁻¹): HRMS (ESI-QTOF): m/z for C₂₁H₂₂NaO₃, [M+Na]⁺ calcd. 345.1461, found 345.1471.

((3S,4R,5R)-3,4-bis(benzyloxy)-5-((triisopropylsilyl)oxy)hept-6-en-1-yn-1-yl)triisopropylsilane (S20):
Some proportion of the TMS-TIPS exchange product S20 was also observed in some of the reaction batches which had to be carefully separated from compound 44 (eluted with 2% EtOAc : hexanes), the data for which is given below.

\[ R_f : 0.8 \text{ (10\% EtOAc/hexanes)} \]

\[ [\alpha]_D^{20} : +23.8 \text{ (c 1.0, CH}_2\text{Cl}_2) \]

\textbf{\textsuperscript{1}H NMR (500 MHz, CDCl}\textsubscript{3}):} \( \delta 7.42-7.35 \text{ (m, 4H), 7.34-7.29 \text{ (m, 4H), 7.29-7.25 \text{ (m, 2H), 6.02 \text{ (ddd, } J = 17.3, 10.5, 7.1 \text{ Hz, 1H), 5.16 \text{ (d, } J = 17.3 \text{ Hz, 1H), 5.06 \text{ (d, } J = 10.5 \text{ Hz, 1H), 4.87 \text{ (ABq, } \Delta \delta_{AB} = 119.1 \text{ Hz, } J_{AB} = 11.8 \text{ Hz, 2H), 4.73 \text{ (ABq, } \Delta \delta_{AB} = 127.6 \text{ Hz, } J_{AB} = 11.7 \text{ Hz, 2H), 4.50 \text{ (d, } J = 4.4 \text{ Hz, 1H), 4.47 \text{ (dd, } J = 6.9, 4.7 \text{ Hz, 1H), 3.59 \text{ (t, } J = 4.6 \text{ Hz, 1H), 1.18-1.07 \text{ (m, 3H), 1.12 \text{ (s, 18H), 1.03-0.95 \text{ (m, 3H), 0.99 \text{ (s, 18H).}}}} \text{ IR v (neat, cm}^{-1}) \text{:} \]

\textbf{HRMS (ESI-QTOF):} \( m/z \) for C\textsubscript{39}H\textsubscript{62}NaO\textsubscript{3}Si\textsubscript{2}, [M+Na]\textsuperscript{+} calcd. 657.4135, found 657.4149.
3. Crystallographic Data:

Table S2. Selected crystallographic data for compound 28:

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<td>b (Å)</td>
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5. **References:**


6. Spectral Data:

![1H NMR spectrum of compound 22 in CDCl₃](image)

H NMR (500 MHz, CDCl₃)

![13C NMR spectrum of compound 22 in CDCl₃](image)

13C NMR (125 MHz, CDCl₃)
$\text{23}$

$^1\text{H NMR (400 MHz, CDCl}_3\text{)}$

$\text{23}$

$^{12}\text{C NMR (100 MHz, CDCl}_3\text{)}$
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
Figure S15

$^1$H NMR (500 MHz, CDCl$_3$)

Figure S15

$^{13}$C NMR (125 MHz, CDCl$_3$)
33a (Non-polar anomer)
$^1$H NMR (500 MHz, CDCl$_3$)

33a (Non-polar anomer)
$^{13}$C NMR (125 MHz, CDCl$_3$)
33b (Polar anomer)

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \]
35a (Non-polar anomer)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)

$^{12}$C NMR (125 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (100 MHz, CDCl$_3$)
COSY (500 MHz, CDCl₃)
34 (Major anomer)

$^1$H NMR (400 MHz, CDCl$_3$)

34 (Major anomer)

$^{13}$C NMR (100 MHz, CDCl$_3$)
36 (Major anomer)

$^1$H NMR (500 MHz, CDCl$_3$)

36 (Major anomer)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$\text{HO\cdots\text{BnO}}$  
$\text{O\cdots\text{OBn}}$

\textbf{S19}  

$^1\text{H NMR (400 MHz, CDCl}_3\text{)}$

![NMR Spectrum](image)

$\text{HO\cdots\text{BnO}}$  
$\text{O\cdots\text{OBn}}$

\textbf{S19}  

$^{13}\text{C NMR (100 MHz, CDCl}_3\text{)}$

![NMR Spectrum](image)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (100 MHz, CDCl$_3$)
44

$^1$H NMR (500 MHz, CDCl$_3$)

44

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
62

$^1$H NMR (400 MHz, CDCl$_3$)

\[ \text{signal peaks at } \delta \text{ ppm} \]

62

$^{13}$C NMR (100 MHz, CDCl$_3$)

\[ \text{signal peaks at } \delta \text{ ppm} \]
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
65

$^1$H NMR (500 MHz, CDCl$_3$)

65

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
69

$^1$H NMR (400 MHz, C$_6$D$_6$)

69

$^{13}$C NMR (100 MHz, C$_6$D$_6$)
63

$^1$H NMR (500 MHz, CDCl$_3$)

63

$^{13}$C NMR (125 MHz, CDCl$_3$)
1H NMR (400 MHz, C6D6)

13C NMR (100 MHz, C6D6)
\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \text{)} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \text{)} \]
\[ \text{79} \]

$^1$H NMR (500 MHz, CDCl$_3$)

\[ \text{79} \]

$^{13}$C NMR (125 MHz, CDCl$_3$)
\[ 81 \]

$^1$H NMR (400 MHz, CDCl$_3$)

\[ 81 \]

$^{13}$C NMR (100 MHz, CDCl$_3$)