Synthesis of Norbornane Bisether Antibiotics via Silver-mediated Alkylation

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All norbornane-based compounds are named using the Von-Baeyer system of nomenclature. All other parts of the structure are named following the IUPAC guidelines. Numbering of norbornane protons follows the general structure shown below. Protons on carbon 7 are labelled either syn (s) or anti (a).
2-Methylisothiouronium iodide\(^2\) (18)

\[\text{[CAS Reg. No. 14257-47-7]}\]

A mixture of thiourea (10.098 g, 0.133 mol), iodomethane (8.2 mL, 0.133 mol) and MeOH (100 mL) was heated at 65 °C for 90 min. The MeOH was removed \textit{in vacuo} and the resulting yellow solid was transferred to a sintered glass funnel and washed with Et\(_2\)O (5 × 50 mL) under vacuum to afford compound 18 (28.261 g, 99\%) as an amorphous white powder.

m.p: 115.3–117.6 °C (lit. 117 °C).\(^3\)

\(^1\)H NMR (270 MHz, DMSO-\(d_6\)) \(\delta\) 2.56 (3H, s, CH\(_3\)), 8.89 (4H, br s, NH\(_2\)).

\(^{13}\)C NMR (67.5 MHz, DMSO-\(d_6\)) \(\delta\) 13.3, 171.1.

\(N,N'\)-Bis(\textit{tert}-butoxycarbonyl)-S-methylisothiourea\(^2\) (19)

\[\text{[CAS Reg. No. 107819-90-9]}\]

To a stirring solution of 2-methylisothiouronium iodide 18 (9.820 g, 45.03 mmol) in sat. NaHCO\(_3\) (50 mL) and CH\(_2\)Cl\(_2\) (105 mL) was added Boc\(_2\)O (19.668 g, 90.12 mmol) using CH\(_2\)Cl\(_2\) (3 × 25 mL). After 48 h the reaction mixture was transferred to a separatory funnel and the organic phase was isolated and the aqueous phase was extracted using CH\(_2\)Cl\(_2\) (2 × 50 mL). The combined organic phase was dried (MgSO\(_4\)), filtered, and concentrated \textit{in vacuo}. The crude solid was stirred (EtOH/H\(_2\)O, 1:9, 100 mL) for 1 h before the mixture was cooled to 0 °C and solid was collected by vacuum filtration, washing with H\(_2\)O (EtOH/H\(_2\)O, 1:9, 50 mL) gives the title compound (12.257 g, 94\%) as a white powder.

m.p: 122.3–123.8 °C (lit. 127 °C).\(^4\)

\(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 1.51 (9H, br s, \textit{t}-Bu), 1.53 (9H, br s, \textit{t}-Bu), 2.40 (3H, s, CH\(_3\)), 11.61 (1H, br s, NH).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.6, 28.2, 81.1, 83.4, 150.9, 160.9, 171.6.

HRMS (ESI, \(m/z\)) for C\(_{12}\)H\(_{22}\)N\(_2\)O\(_4\)S [M + Na]\(^+\) calc. 313.1193; found 313.1186.

2-\{2,3-\textit{Bis(\textit{tert}-butoxycarbonyl)guanidino}\}ethylamine\(^5\) (14)

3
A solution of \(N,N'\)-Bis(tert-butoxycarbonyl)-S-methylisothiourea 19 (20.404 g, 70.27 mmol) in CH\(_2\)Cl\(_2\) (110 mL) was added in one portion to a stirred solution of 1,2-ethylenediamine (11.7 mL, 176 mmol) in CH\(_2\)Cl\(_2\) (150 mL). The reaction was allowed to stir at 21 °C for 90 min. The reaction mixture was then transferred to a separatory funnel and washed with H\(_2\)O (2 × 80 mL), brine (80 mL), then dried (MgSO\(_4\)) and filtered. The solvent was removed \textit{in vacuo} at ambient temperature to afford 14 (20.696 g, 97%) as a white powder.

m.p: 96.2–100.1 °C.

\(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 1.50 (9H, br s, t-Bu), 1.51 (9H, br s, t-Bu), 2.90 (2H, t, \(J = 6.2\) Hz, CH\(_2\)), 3.49 (2H, app. q, \(J_{app} = 5.5\) Hz, CH\(_2\)), 8.67 (1H, br s, NH), 11.51 (1H, br s, NH).

\(^{13}\)C NMR (67.5 MHz, CDCl\(_3\)) \(\delta\) 28.2, 28.4, 41.1, 43.5, 79.4, 83.2, 153.3, 156.5, 163.7.

HRMS (ESI, m/z) for C\(_{13}\)H\(_{26}\)N\(_4\)O\(_4\) [M + H]\(^+\) calc. 303.2027; found 303.2032.

Dimethyl bicyclo[2.2.1]hept-5-ene-3-endo-2-exo-dicarboxylate (17)


\(\text{Method A}^6\)

To the stirring solution of dimethyl fumarate (65.290 g, 0.453 mol) in THF (200 mL), was added freshly cracked cyclopentadiene (40 mL, 0.476 mol), and the reaction was stirred at ambient temperature for 16 h. The solvent was removed under reduced pressure to give the title compound (95.230 g, 99%) as a clear oil.

\(\text{Method B}^7\)

A 35 mL microwave vial was charged with dicyclopentadiene (2.0 mL, 15.0 mmol), dimethyl fumarate (2.883 g, 20.0 mmol) and hydroquinone (100 mg, 0.90 mmol), and heated using microwave irradiation to 150 °C for 2 h. The resulting orange oil was purified by flash column chromatography (10% EtOAc in pet. spirits) to give a clear oil (4.137 g, 98%).

\(R_f = 0.32\) (10% EtOAc in pet. spirits).
$^1$H NMR (400 MHz, CDCl$_3$) δ 1.45 (1H, dd, $J = 8.8, 1.7$ Hz, H7s), 1.61 (1H, d, $J = 8.8$ Hz, H7a), 2.68 (1H, dd, $J = 3.1, 1.2$ Hz, H2), 3.12 (1H, br s, H4), 3.25 (1H, br s, H1), 3.37 (1H, app. t, $J = 5.6$ Hz, H3), 3.64 (3H, s, Me), 3.71 (3H, s, Me), 6.06 (1H, dd, $J = 5.6, 2.8$ Hz, H6), 6.27 (1H, dd, $J = 5.6, 3.1$ Hz, H5).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 45.5, 46.9, 47.2, 47.5, 47.7, 51.1, 135.3, 137.7, 174.0, 175.2.

HRMS (ESI, $m/z$) for C$_{11}$H$_{14}$O$_4$ [M + Na]$^+$ calc. 233.0784; found 233.0785.

Dimethyl 5,6-exo-dihydroxybicyclo[2.2.1]heptane-3-endo-2-exo-dicarboxylate (6)

[CAS Reg. No. 1228039-59-5]

Method A

The dimethyl ester 17 (3.054 g, 14.53 mmol) and NMO-H$_2$O (1.87 g, 16.0 mmol) were dissolved in a solution of H$_2$O/acetone (1:4, 36 mL) to which OsO$_4$ (4% in H$_2$O, 730 µL, 0.40 mol%) was added. The reaction was stirred for 3 d and was then quenched with sat. NaHSO$_3$ (30 mL). The suspension was extracted with EtOAc (4 × 25 mL), and the combined organic phase was washed with brine (25 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo to give the title compound (3.337 g, 94%) as a white solid.

Method B

To a stirring solution at 0 °C of dimethyl ester 17 (270 mg, 1.28 mmol), t-BuOH (4.7 mL) and H$_2$O (1.2 mL), a solution of KMnO$_4$ (405 mg, 2.56 mmol), K$_2$CO$_3$ (212 mg, 1.54 mmol) in H$_2$O (6.0 mL) was added dropwise. The reaction was stirred for a further 25 min before the reaction mix was quenched with sat. NaHSO$_3$ (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo to afford the title compound (181 mg, 58%) as a white solid. m.p: 89.9–92.3 °C (lit. 81–84 °C).

$^1$H NMR (270 MHz, CDCl$_3$) δ 1.33 (1H, d, $J = 11.0$ Hz, H7s), 1.78 (1H, dd, $J = 11.0, 1.2$ Hz, H7a), 2.40 (1H, br s, H1), 2.46 (1H, dd, $J = 4.5, 1.2$ Hz, H4), 2.63 (1H, d, $J = 4.9$ Hz, H2), 3.11 (1H, app. t, $J = 5.1$ Hz, H3), 3.62 (3H, s, Me), 3.64 (3H, s, Me), 3.71–3.77 (1H, m, H6), 3.85 (1H, br s, H5).

$^{13}$C NMR (67.5 MHz, CDCl$_3$) δ 31.8, 44.8, 46.2, 46.4, 48.2, 52.3, 52.5, 70.2, 73.3, 173.2, 174.2.

HRMS (ESI, $m/z$) for C$_{11}$H$_{16}$O$_6$ [M + Na]$^+$ calc. 267.0839; found 267.0836.
Norbornane diester dibenzyl ether
SMH05-081F-1H

[Chemical structure image]

[1H NMR spectrum image]
Norbornane diester dibenzyl ether
SMH05-081F-13C
c13CPD CDCl3 \(\text{c:\Gail\nmr 13}\)
Norbornane diester di benzyl-3-bromo
SMH66-123B - 13C
c13CP0 CDC03 (c:\Data_500\Shane) nmr 1

$\text{Br}$ $\text{Br}$

$\text{O}$ $\text{O}$

$\text{OMe}$ $\text{OMe}$

$9g$

$174.077$ $173.077$

$140.761$ $140.705$

$130.830$ $130.816$ $130.771$ $130.100$ $130.089$ $126.331$ $126.187$

$82.042$ $78.344$

$71.887$ $71.729$

$52.481$ $52.322$ $46.320$ $45.056$ $44.153$ $33.350$

$\delta (\text{ppm})$

$200$ $190$ $180$ $170$ $160$ $150$ $140$ $130$ $120$ $110$ $100$ $90$ $80$ $70$ $60$ $50$ $40$ $30$ $20$ $10$ $0$
SMH07-123A
SMH07-123A - 1H
PROTON DMSO (C:\Data_500\Shane) nmr 3
Shane/SMH06-139B-13C
Single Pulse with Broadband Decoupling

[Diagram of chemical structure]

[Graph with peaks at various ppm values]
Figure S1: VT $^1$H NMR (500 MHz) of 12c in DMSO-$d_6$ (20–110 °C)
Figure S2: Expansion (1.76–1.98 ppm) of VT $^1$H NMR (500 MHz) of 12c in DMSO-$d_6$ (20–110 °C)
Figure S3: Expansion (2.14–2.29 ppm) of VT $^1$H NMR (500 MHz) of 12c in DMSO-$d_6$ (20–110 °C)
Figure S4: Expansion (3.56–3.79 ppm) of VT $^1$H NMR (500 MHz) of 12c in DMSO-$d_6$ (20–110 °C)
Figure S5: Expansion (4.26–4.78 ppm) of VT $^1$H NMR (500 MHz) of 12c in DMSO-$d_6$ (20–110 °C)
Table S1: Ester by-products of bis-alkylation step

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkylating Agent (RX)</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>12a</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>PhBr</td>
<td>12b</td>
<td>37 (7)</td>
</tr>
<tr>
<td>3</td>
<td>MePhBr</td>
<td>12c</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;PhBr</td>
<td>12d</td>
<td>51 (6)</td>
</tr>
<tr>
<td>5</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>12e</td>
<td>55 (12)</td>
</tr>
<tr>
<td>6</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>12f</td>
<td>25 (9)</td>
</tr>
<tr>
<td>7</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;F</td>
<td>12g</td>
<td>24 (8)</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>12h</td>
<td>28 (12)</td>
</tr>
</tbody>
</table>
Yield calculated over two steps.
Figure S6. Thermal ellipsoid plot of one of the two independent molecules of 12h. Ellipsoids are at the 20% probability level.

Crystal data for 12h. 2(C_{23}H_{22}Br_{2}O_{6}). (CH_{3}CH_{2}OH), M = 1138.52, T = 130.0 K, λ = 1.54180, 554.22, space group P c, a = 13.3929(1) b = 5.4658(1), c =33.5433(4) Å, β = 97.438(1)° V = 2434.81(6) Å³, Z = 4, Z’ = 2, Dc = 1.512 Mg M⁻³ μ(Cu-Kα) = 4.519 mm⁻¹, F(000) =1112, crystal size 0.54 x 0.49 x 0.38 mm³, 16695 reflections measured, 8602 independent reflections [R(int) = 0.0230], the final R was 0.0431 [I > 2σ(I)8569 data] and wR(F²) was 0.1162 (all data), Absolute structure parameter 0.15(2) .
<table>
<thead>
<tr>
<th>Organism</th>
<th>Strain</th>
<th>Strain description</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>ATCC 25922</td>
<td>FDA strain Seattle 1946</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>ATCC 13883</td>
<td>Control strain</td>
<td>DD</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>ATCC 700603</td>
<td>Multi-drug resistant</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>ATCC 19606</td>
<td>Type strain</td>
<td>MIC/DD</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>ATCC 27853</td>
<td>Type strain</td>
<td>MIC/DD</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>ATCC 43300</td>
<td>MRSA (methicillin resistant <em>S. aureus</em>)</td>
<td>MIC/DD</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>ATCC 700221</td>
<td>VRE (vancomycin resistant Enterococcus)</td>
<td>DD</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Clinical isolate</td>
<td>mMRSA (multi-resistant methicillin resistant <em>S. aureus</em>)</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>NARSA-NRS 17</td>
<td>GISA (glycopeptide-intermediate <em>S. aureus</em>)</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>NARSA-NRS 1</td>
<td>VISA (vancomycin-intermediate <em>S. aureus</em>)</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Clinical isolate</td>
<td>MRSA</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>NARSA-VRS 10</td>
<td>Glycopeptide resistant</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>ATCC 700677</td>
<td>Multi-drug resistant</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>Clinical isolate</td>
<td>VanA (vancomycin resistant)</td>
<td>MIC</td>
</tr>
</tbody>
</table>
References