Thiostrepton (1) is the most complex and best characterized member of the thiopeptide antibiotics whose structure has been secured by X-ray crystallography, degradative, and spectroscopic techniques. Thiostreptin (1) is active against gram-positive bacteria and exhibits antimalarial activity against Plasmodium falciparum, which is the parasite responsible for causing over 85% of human malarial infections. Isolated in 1955, thiostrepton itself still remains elusive to total synthesis, although the construction of its dehydropiperidine moiety has recently been reported.

**Retrosynthesis**

Thiostrepton (1) is retrosynthetically divided into three components: 5, 4, and 3. Component 5 is further divided into two parts: 2 and 4, with 2 being the main component. Component 3 is a separate entity.

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**References**

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Scheme 1

1. MeOH, SOCl₂, 99%  
2. PtO₂/H₂, 60%  
3. MeCHO, H₂O₂, FeSO₄, CF₃CO₂H, 99% → MeO₂C – N

1. B(OMe)₃, BH₃SMe₂, 95% (90% ee)  
2. TBSOTf, 2,6-lutidine 90%

1. LAH, 88%  
2. PivCl, 82%

1. m-CPBA, 99%  
2. TFAA, rt, 73%  
3. NaHCO₃(aq), 75%

1. NBS, AIBN, 63%  
2. DBU, 86%

1. TBSOTf, 88%  
2. K₂CO₃, MeOH, 99%  
3. TFAA, py then K₂CO₃, MeOH, 84%

1. IBX, 98%  
2. NaClO₂, NaH₂PO₄, 2-methyl-2-butene, 95%

Scheme 2

1. MsCl, 79%  
2. DBU, 81%  
3. LiOH, 92%
Scheme 3

\[ \text{HO-CH} \overset{\text{O}}{\text{NH}} \text{Boc} \quad \text{29} \quad \text{J. Bull. Chem. Soc. Jpn. 1998, 71, 1863.} \]

1. LiBH₄, LiCl, 88%.
2. PPh₃, imidazole, I₂, 92%.
3. NaN₃, DMF, 96%

\[ \begin{align*}
\text{HN} & \quad \text{HN} \\
\text{O} & \\
\text{O} & \\
\text{NHBoc} & \\
\end{align*} \]

\[ \text{30} \]

\[ \text{NH}_2 \]

\[ \begin{align*}
\text{N} & \\
\text{S} & \\
\text{CBzHN} & \\
\text{O} & \\
\text{O} & \\
\text{NHBoc} & \\
\end{align*} \]

\[ \text{3} \]

\[ \text{TFA} \]

\[ \text{H} \]

\[ \text{33} \]

\[ \text{29} \]

Scheme 4

\[ \text{NH}_2 \]

\[ \text{3} \]

\[ \text{CbzHN} \]

\[ \text{OH} \]

\[ \text{32} \]

\[ \text{EDC, HOBT} \]

\[ \text{72\%} \]

\[ \text{2,4,6-trichlorobenzoyl chloride, DMAP 71\%} \]

\[ \text{31} \]

\[ \text{OTBS} \]

\[ \text{TFA} \]

\[ \text{CO}_2\text{tBu} \]

\[ \text{5} \]

\[ \text{1. TFA, 86\%} \]

\[ \text{2. HATU, 2,4,6-collidine 30\%} \]