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Synthesis of substrate analogues and inhibitors for phosphoribosyl anthranilate isomerase and indole-3-glycerolphosphate synthase.

Benjamin Joseph Mulchin
2008
Synthesis of substrate analogues and inhibitors for phosphoribosyl anthranilate isomerase and indole-3-glycerolphosphate synthase.

A thesis presented in partial fulfillment of the requirements for the degree of

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In
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Benjamin Joseph Mulchin
2008
Abstract

The general biosynthetic pathway for tryptophan is known. However, little information has been gathered on how substrates and enzymes interact when phosphoribosylanthranilate isomerase (PRAI) and indole-3-glycerolphosphate synthase (IPGS) convert a substituted phenyl ring, PRA, into an indole moiety, IGP, via 1-(O-carboxyphenylamino)-1-deoxyribulose-5-phosphate (CdRP). There has been no serious synthetic approach to develop methodology to produce a plethora of substrate and product analogues of CdRP. The studies described in this thesis cover methodology focusing on secondary aryl amine formation, using reductive amination, nucleophilic substitution and epoxide ring opening, leading to CdRP analogues. Reductive aminations with D-ribose failed to produce any aryl glycosylamine precursor, possibly due to the low nucleophilicity of aryl amines such as aniline. Removing the aromaticity and using cyclohexylamine produced secondary amines in moderate yield in the presence of benzylpentanal, and NaBH₃CN, at a pH of 5.5. This led to a successful reductive amination using anthranilate methyl ester. Secondary aryl amine synthesis via epoxide ring opening proved consistently reproducible. Using LiNTf₂ and high equivalents of cyclohexylamine or aniline in neat conditions opened protected epoxides. This has led to the formation of advanced secondary aryl amine synthons and the development of methodology leading to target compounds with functionality at the 1,2 and 5 positions. Nucleophilic substitution using caesium base, high equivalents aniline at room temperature, gave a moderate yield of secondary aryl amines from sulfonyl and bromide good leaving groups. Raising the reaction temperature improved yields using low equivalents of aniline, with the optimal temperature being 50 °C. Ultimately using both the high equivalents of aniline or anthranilate methyl ester and warming the reaction in DMF gave the highest yields of secondary aryl amines. No overalkylated tertiary amine was isolated when a caesium base was used. Boc N-protection of 1-phenylamino-4-pentene and asymmetric dihydroxylation gave the corresponding diol, which was phosphorylated giving the protected target 1,4,5 compound. The methodology leading to the protected target 1,4,5 compound synthesis provides a means to the synthesis additional of CdRP analogues.
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# Table of contents

**Abbreviations** x

**Index of figures** xv

**Index of schemes** xvi

**Index of tables** xxii

**Index of graphs** xxiii

## CHAPTER 1: Tryptophan biosynthesis.

1.1. Thesis introduction: 1

1.1.2. Roles of tryptophan and other aromatic amino acids: 1

1.2. Pathways: 2

1.2.1. Shikimate pathway: 2

1.2.2. Biosynthesis of tryptophan: 4

1.3. Enzyme structure basics of PRAI and IGPS: 7

1.3.1. Introduction: 7

1.3.2. Sources of PRAI and IGPS: 7

1.3.3. PRAI and IGPS enzymes: 7

1.4. Biochemical details of PRAI: 8

1.4.1. Enzyme kinetics for PRAI: 8

1.4.2. Proposed mechanism catalysed by PRAI – The Amadori rearrangement: 10

1.4.3. X-ray structural analysis of product analogue rCdRP crystallized in rPRAI: 11

1.5. Biochemical details of IGPS: 12

1.5.1. Enzyme kinetics for IGPS: 12

1.5.2. Proposed mechanism catalysed by IGPS – indole ring formation: 14

1.5.3. Residue interactions and model studies of intermediates of indole ring formation: 16

1.5.4. Reaction catalysed by IGPS – indole ring formation: 17
1.6. Previous synthetic research on PRA and CdRP:

1.6.1. PRA synthesis: 18
1.6.2. Synthesis of PRA derivatives: 19
1.6.3. CdRP synthesis: 20
1.6.4. Synthesis of CdRP derivatives: 21
1.6.5. rCdRP synthesis: 22

1.7. Target compounds:

1.7.1. PRA analogue targets for the investigation of PRAI reaction: 23
1.7.2. CdRP analogue targets for the investigation of PRAI and IGPS: 24
1.7.3. Target 1,2,5 compounds for the investigation of the PRAI and IGPS: 26
1.7.4. Target 1,4,5 compounds for the investigation of the PRAI and IGPS: 27

1.8. Synthetic ideas:

1.8.1 Synthetic goals: 28
1.8.2. Retrosynthesis of CdRP like compounds: 28

1.9. Formation of secondary amines:

1.9.1. Introduction: 29
1.9.2. Condensation: 30
1.9.3. N-alkylation via nucleophilic substitution: 31
1.9.4. Nucleophilic substitution with metal coordination: 34
1.9.5. Epoxide ring opening: 35
1.9.6. Imine formation: 36
1.9.7. Solid phase synthesis: 37

1.10. Summary of thesis aims: 39

CHAPTER 2: Reductive aminations.

2.1. The initial retrosynthetic plan:

2.1.2. Phosphorylation introduction: 41
CHAPTER 3: Nucleophilic substitution of good leaving groups.

3.1. Synthesis of rCdRP-like target compounds:
   3.1.2. Synthesis of secondary rCdRP-like aryl amines: 97
   3.1.3. Proposed synthesis of secondary rCdRP-like aryl amines: 102

3.2. Synthesis of sulfonyl good leaving groups:
   3.2.2. Preparation of sulfonyl good leaving groups on pentan-1,5-diol: 105
   3.2.3. Preparation of sulfonyl good leaving groups on 4-penten-1-ol: 109

3.3. N-nucleophilic substitution of sulfonyl good leaving groups:
   3.3.2. Nucleophilic substitution of sulfonyl good leaving groups on pentan-1,5-diol by aniline: 112
   3.3.3. Nucleophilic substitution of sulfonyl good leaving groups on 4-penten-1-ol by aniline: 114

3.4. N-nucleophilic substitution of bromide moieties:
   3.4.2. N-nucleophilic substitution of
           5-O-para-methoxybenzyl bromopentanol and bromo-4-pentene: 118
   3.4.3. Synthesis of a target 1,4,5 compound
           \( N\text{-}\text{tert-butyloxy carbonyl-1-phenylamino-5-diethyl phosphate-4-pentanol:} \) 121

3.5. Nucleophilic substitution of \( O\)- and \( C\)-nucleophiles:
   3.5.1. Substitution of good leaving groups on
pentan-1,5-diol moieties by O- and C-nucleophiles: 127
3.5.2. Attempted synthesis of target 1,4,5 compound using a C-nucleophile: 130
3.6. Conclusions: 132

CHAPTER 4: Epoxide ring opening.
4.1. Introduction: 135
   4.1.2. Retrosynthetic plan: 135
4.2. Literature on epoxide ring formation: 136
   4.2.1. Good leaving groups: 136
   4.2.2. Epoxidation from alkenes: 137
4.3. Formation of protected epoxide: 137
   4.3.1. 1-O-tert-Butyldimethylsilyl-4,5-epoxypentanol: 139
   4.3.2. 1-O-tert-Butyldiphenylsilyl-4,5-epoxypentanol: 141
4.4. Literature on epoxide ring opening: 143
4.5. Epoxide ring opening: 146
   4.5.1. Ring opening of 1-O-tert-butyldimethylsilyl-4,5-epoxypentanol: 146
   4.5.2. Ring opening of 1-O-tert-butyldiphenylsilyl-4,5-epoxypentanol: 152
4.6. Conclusions: 152

CHAPTER 5: Summary of thesis.
5.1. Overall conclusions: 154
   5.1.2. Conclusions of reductive amination chemistry: 154
   5.1.3. Conclusions of nucleophilic substitution of good leaving groups: 160
   5.1.4. Conclusions of epoxide ring opening methodology: 169
5.2. Possible future experiments: 171
CHAPTER 6: Experimental.

6.1. General Methods:

6.1.2. Reagents and solvents: 173
6.1.3. Synthetic methods: 175
6.1.4. Chromatography: 175
6.1.5. Characterisation: 176

6.2. Experiments described in Chapter Two:

5-O-Triphenylmethyl-D-ribonolactone 2.09: 177
2,3-Bis-O-tert-butyldimethylsilyl-5-O-triphenylmethyl
-D-ribonolactone 2.12: 178
2-O-tert-Butyldiphenylsilyl-5-O-triphenylmethyl-D-ribonolactone 2.28: 179
2,3-O-Dibenzyl-5-O-triphenylmethyl-D-ribonolactone 2.35: 180
2-O-Benzyl-5-O-triphenylmethyl-D-ribonolactone 2.36: 181
2,3-O-iso-Propylidene-D-ribo-1,4-lactone 2.44: 182
3,4-O-iso-Propylidene-D-ribo-1,5-lactone 2.45: 182
Methyl-2,3-O-iso-propylidene-β-D-ribofuranoside 2.48: 183
Methyl-2,3-O-iso-propylidene-5-O-benzyl-β-D-ribofuranoside 2.49: 184
Methyl-2,3-O-iso-propylidene-5-O-diphenylphosphate-β-
D-ribofuranoside 2.50: 185
Anthranilate methyl ester 2.51: 186
5-Diphenyl phosphate pentanol 2.72: 187
5-Diphenyl phosphate pentanal 2.73: 188
5-O-Benzylpentanol 2.76: 189
5-O-Benzylpentanal 2.77: 189
5-O-Benzylpentylcyclohexylamine 2.83: 190
5-O-Benzylpentyl anthranilate methyl ester 2.85: 191

6.3. Experiments described in Chapter Three:

(2S,3R,4R)-3,4-Bis-O-tert-butyldimethylsilyl-1-O-triphenylmethyl
tetrahydrofuran 3.06: 192
3,4-Bis-\textit{O-}\textit{tert}-butyldimethylsilyl-2,5-bis-\textit{O}-toluenesulfonyl-1-\textit{O}-triphenylmethyl-D-ribitol 3.08:

(2S,3R,4S)-\textit{N}-5-Anthranilate methyl ester-3,4-bis-
\textit{O-}\textit{tert}-butyldimethylsilyl-1-\textit{O}-triphenylmethyl 3.10:

5-\textit{O-}\textit{tert}-Butyldiphenylsilyl-D-ribonolactone 3.14:

5-Tetrahydropyran-3-yloxy pentanol 3.21:

5-\textit{O-}\textit{tert}-Butyldimethylsilyl pentanol 3.23:

5-\textit{O-}\textit{tert}-Butyldimethylsilyl-1-\textit{O}-methanesulfonyle pentanol 3.24:

5-\textit{O-}\textit{tert}-Butyldimethylsilyl-1-\textit{O}-toluenesulfonyle pentanol 3.25:

4-Pentenyl methanesulfonyle 3.26:

4-Pentenyl toluenesulfonyle 3.27:

5-\textit{O-}\textit{tert}-Butyldimethylsilyl-1-phenylamino-pentane 3.37:

5-\textit{O-}\textit{tert}-Butyldimethylsilyl-1-\textit{O}-trifluoro-methanesulfonyle pentanol 3.38:

1-Phenylamino-4-pentene 3.39:

Bromopentan-5-ol 3.40:

5-\textit{O-}\textit{para}-Methoxybenzyl bromopentanol 3.42:

Bromo-4-pentene 3.43:

5-\textit{O-}\textit{para}-Methoxybenzyl-1-phenylamino-pentane 3.44:

5-\textit{O-}\textit{para}-Methoxybenzyl pentylyclohexylamine 3.46:

Anthranilate methyl ester-4-pentene 3.47:

\textit{N}-9-Fluorenlymethoxycarbonyl-1-phenylamino-4-pentene 3.48:

\textit{N}-9-Fluorenlymethoxycarbonyl-1-phenylamino-4,5-pentan-diol 3.54:

\textit{N-}\textit{tert}-Butyloxyxycarbonyl-1-phenylamino-4-pentene 3.55:

\textit{N-}\textit{tert}-Butyloxyxycarbonyl-1-phenylamino-4,5-pentan-diol 3.56:

\textit{N-}\textit{tert}-Butyloxyxycarbonyl-1-phenylamino-5-diethyl phosphate-4-pentanol 3.57:

\textit{N-Tert}-butyloxyxycarbonyl-1-phenylamino-4-diethyl phosphate-5-pentanol 3.58:

5-\textit{O-}\textit{tert}-Butyldimethylsilyl-1-phenoxy-pentane 3.60:

5-\textit{O-}\textit{para}-Methoxybenzyl-1-phenoxy-pentane 3.61:

1-Phenoxy-pentanol 3.63:
2-(5-Hydroxy-pentyl)-phenol \textbf{2.64}: \hspace{1cm} 215
5-\textit{O-}tert-Butyldimethysilyl-1-phenyl-hexane \textbf{3.66}: \hspace{1cm} 216
Hex-5-enylbenzene \textbf{3.67}: \hspace{1cm} 217
5,6-Epoxyhexylbenzene \textbf{3.68}: \hspace{1cm} 217

\textbf{6.4. Experiments described in Chapter Four:} \hspace{1cm} 218
1-\textit{O-}tert-Butyldimethylsilyl-4-penten-1-ol \textbf{4.11}: \hspace{1cm} 218
1-\textit{O-}tert-Butyldiphenylsilyl-4-penten-1-ol \textbf{4.17}: \hspace{1cm} 219
1-\textit{O-}tert-Butyldimethylsilyl-4,5-epoxypentanol \textbf{4.12}: \hspace{1cm} 220
1-\textit{O-}tert-Butyldiphenylsilyl-4,5-epoxypentanol \textbf{4.16}: \hspace{1cm} 220
5-\textit{O-}Benzylpentene \textbf{4.18}: \hspace{1cm} 221
5-\textit{O-}tert-Butyldimethylsilyl-1-phenylamino-pentan-2-ol \textbf{4.31}: \hspace{1cm} 222
5-\textit{O-}tert-Butyldimethylsilyl-1-cyclohexylamino-pentan-2-ol \textbf{4.33}: \hspace{1cm} 223
5-\textit{O-}tert-Butyldiphenylsilyl-1-phenylamino-pentan-2-ol \textbf{4.34}: \hspace{1cm} 224

\textbf{References:} \hspace{1cm} 225

\textbf{Abbreviations}

\begin{itemize}
\item Ac \hspace{1cm} Acetyl
\item ACE-Cl \hspace{1cm} \(\alpha\)-Chloroethyl chloroformate
\item AD-mix \hspace{1cm} Asymmetric dihydroxylation reagent
\item Aq \hspace{1cm} Aqueous
\item Arg \hspace{1cm} Arginine
\item Asn \hspace{1cm} Asparagine
\item Asp \hspace{1cm} Aspartic acid
\item BINAP \hspace{1cm} 2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
\item bmim \hspace{1cm} 1-Butyl-3-methylimidazolium
\item Bn \hspace{1cm} Benzyl
\item Boc \hspace{1cm} \textit{tert}-Butyloxycarbonyl
\item BTP \hspace{1cm} 1,3-Bis(tris(hydroxymethyl)methylamino)propane
\item Bz \hspace{1cm} Benzoyl
\end{itemize}
CdRP \hspace{1cm} 1-(O-Carboxyphenylamino)-1-deoxyribulose-5-phosphate
\[ ^1H/\hspace{0.2cm}^1H \text{ COSY} \] \hspace{1cm} Proton correlation spectroscopy
\[ m-\text{CPBA} \] \hspace{1cm} meta-Chloroperoxybenzoic acid
CSA \hspace{1cm} Camphorsulfonic acid
Cys \hspace{1cm} Cysteine
DAHP \hspace{1cm} 3-Deoxy-D-arabino-heptulosonate 7-phosphate
DAH7P \hspace{1cm} 3-Deoxy-D-arabino-heptulosonate 7-phosphate
DCP \hspace{1cm} 1,2-Dichloropropane
DDQ \hspace{1cm} 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAE \hspace{1cm} Diethylamino ethanol
DHP \hspace{1cm} 3,4-Dihydro-2H-pyran
DHQ \hspace{1cm} Dehydroquinate
(DHQ)\text{2-PHAL} \hspace{1cm} Dihydroquinine phthalazine
DHS \hspace{1cm} Dehydroshikimate
Diab-H \hspace{1cm} Disiamylborane
Dibal-H \hspace{1cm} Di-iso-butylaluminum hydride
DIEA \hspace{1cm} Di-iso-propylethylamine
DMAP \hspace{1cm} 4-Dimethylaminopyridine
DMF \hspace{1cm} N,N-Dimethylformamide
DMP \hspace{1cm} 2,2-Dimethoxypropane
DMP \hspace{1cm} Dess-Martin periodinane
DMSO \hspace{1cm} Dimethyl sulfoxide
\[ e\text{IGPS} \] \hspace{1cm} Escherichia coli IGPS
\[ e\text{PRAI} \] \hspace{1cm} Escherichia coli PRAI
E4P \hspace{1cm} D-Erythrose 4-phosphate
EDG \hspace{1cm} Electron-donating groups
EDTA \hspace{1cm} Ethylenediamine tetra-acetic acid (di-sodium salt)
EPSP \hspace{1cm} 5-Enolpyruvyl-shikimate 3-phosphate
Eq \hspace{1cm} Equivalent
EWG \hspace{1cm} Electron-withdrawing groups
Fmoc \hspace{1cm} 9-Fluorenylmethoxycarbonyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>GL</td>
<td>Good leaving group</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamic acid</td>
</tr>
<tr>
<td>His</td>
<td>Histidine</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoric triamide</td>
</tr>
<tr>
<td>HREIMS</td>
<td>High Resolution Electron Impact Mass Spectrometry</td>
</tr>
<tr>
<td>$^1$H/$^{13}$C HMQC</td>
<td>Heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>IEX</td>
<td>Ion exchange chromatography</td>
</tr>
<tr>
<td>IGPS</td>
<td>Indole-3-glycerolphosphate synthase</td>
</tr>
<tr>
<td>Ile</td>
<td>Isoleucine</td>
</tr>
<tr>
<td>im</td>
<td>Imidazole</td>
</tr>
<tr>
<td>$k_{cat}$</td>
<td>Catalytic rate/turnover number</td>
</tr>
<tr>
<td>$k_{cat}/K_M$</td>
<td>Catalytic efficiency</td>
</tr>
<tr>
<td>KDO8P</td>
<td>3-Deoxy-D-manno-octulosonate 8-phosphate</td>
</tr>
<tr>
<td>$K_i$</td>
<td>Enzyme inhibitor affinity</td>
</tr>
<tr>
<td>$K_M$</td>
<td>Michaelis constant</td>
</tr>
<tr>
<td>$K_p$</td>
<td>Enzyme product affinity</td>
</tr>
<tr>
<td>L. Pet.</td>
<td>Light petroleum</td>
</tr>
<tr>
<td>Leu</td>
<td>Leucine</td>
</tr>
<tr>
<td>Lys</td>
<td>Lysine</td>
</tr>
<tr>
<td>MEM</td>
<td>$\beta$-Methoxyethoxymethyl</td>
</tr>
<tr>
<td>4 Å M.S.</td>
<td>4 Å Molecular sieves</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl, methanesulfonate</td>
</tr>
<tr>
<td>N. P.</td>
<td>No product</td>
</tr>
<tr>
<td>NMP</td>
<td>$N$-Methyl pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>PB</td>
<td>Pyridine-borane</td>
</tr>
<tr>
<td>PEP</td>
<td>Phosphoenolpyruvate</td>
</tr>
</tbody>
</table>
Ph Phenyl
Phe Phenylalanine
pK\text{a} Acid dissociation constant
PMB \textit{para}-Methoxybenzyl
PMHS Polymethylhydrosiloxane
PPG Primary protecting groups
ppm Parts per million
Pro Proline
PRAI Phosphoribosyl anthranilate isomerase
Psi Pounds per square inch
py Pyridine
rCdRP 1-(\textit{O}-Carboxyphenylamino)-1-deoxyribose-5-phosphate
R\text{f} Retardation factor/retention factor
R5P D-Ribose 5-phosphate
RT Room temperature
sIGPS \textit{Sulfolobus solfataricus} IGPS
Ser Serine
tIGPS \textit{Thermotoga maritima} IGPS
tPRAI \textit{Thermotoga maritima} PRAI
TBAB Tetrabutylammonium bromide
TBAF Tetrabutylammonium fluoride
TBAI Tetrabutylammonium iodide
TBDMS \textit{tert}-Butyldimethylsilyl
TBDPS \textit{tert}-Butyldiphenylsilyl
TBHP \textit{tert}-Butyl hydroperoxide
Tf Trifluoromethane sulfonate
TFA Trifluoroacetyl
THCP Tributylammonium hydrobenzoin cyclic phosphate
THF Tetrahydrofuran
THP Tetrahydropyran
TLC Thin layer chromatography
TMS  Tetramethylsilane
TMSBr  Trimethylsilyl bromide
Tr  Trityl, triphenyl methyl
Trp  Tryptophan
Ts  Tosyl, toluene-sulfonate
pTSA  para-Toluenesulfonic acid
Tyr  Tyrosine
UV  Ultraviolet
$V_{\text{max}}$  Maximum reaction velocity
$y$PRAI  Saccharomyces cerevisiae PRAI

Index of figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>Aromatic amino acids.</td>
</tr>
<tr>
<td>1.02</td>
<td>Stereoview of substrate CdRP bound to the active site of sIGPS.</td>
</tr>
<tr>
<td>1.03</td>
<td>Stereoview of the bound catalytic intermediate 1 (a) and intermediate 2 (b) from molecular models of the active site in sIGPS.</td>
</tr>
<tr>
<td>1.04</td>
<td>Ring analogue target compounds for potential inhibition of PRAI.</td>
</tr>
<tr>
<td>1.05</td>
<td>PRAI carbohydrate analogues target compounds for potential inhibition of PRAI.</td>
</tr>
<tr>
<td>1.06</td>
<td>rCdRP carbohydrate-analogue target compounds for potential inhibition of PRAI and IGPS.</td>
</tr>
<tr>
<td>1.07</td>
<td>Ring analogue target compounds for product inhibition of PRAI.</td>
</tr>
<tr>
<td>1.08</td>
<td>Ring analogue target compounds for PRAI.</td>
</tr>
<tr>
<td>1.09</td>
<td>Target 1,4,5 compounds for inhibition of PRAI and IGPS.</td>
</tr>
<tr>
<td>2.01</td>
<td>Mono-protected product.</td>
</tr>
<tr>
<td>2.02</td>
<td>Resonance structures for aniline 2.65, lowering pK_{a}.</td>
</tr>
<tr>
<td>2.03</td>
<td>Effects of steric hindrance by groups on the phenyl ring.</td>
</tr>
<tr>
<td>2.04</td>
<td>Primary and secondary amines.</td>
</tr>
</tbody>
</table>
2.05. Tertiary amine by-product 2.84.

3.01. Selective removal of trityl groups in the presence of acetals. 102

3.02. Chiral ligand of AD-mix-α. 123

4.01. Target 1,2,5 compounds. 135

4.02. Jacobsen’s catalyst$^{333-335}$ 4.13, a cobalt-based salen ligand complex. 139

6.01. Chiral ligand of AD-mix-α. 175

## Index of schemes

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>The shikimate pathway. 3</td>
</tr>
<tr>
<td>1.02</td>
<td>Chorismate, the precursor to the aromatic amino acids and aromatic compounds. 4</td>
</tr>
<tr>
<td>1.03</td>
<td>Formation of anthranilate 1.02 via bicyclic derivative 1.03. 4</td>
</tr>
<tr>
<td>1.04</td>
<td>Formation of anthranilate 1.02 via Michael-type addition and loss of pyruvate. 5</td>
</tr>
<tr>
<td>1.05</td>
<td>Tryptophan biosynthesis. 6</td>
</tr>
<tr>
<td>1.06</td>
<td>Plausible mechanism of the Amadori rearrangement forming CdRP 1.06. 11</td>
</tr>
<tr>
<td>1.07</td>
<td>Indole ring formation showing substrate interactions with Lys 53, Lys 110, and Glu 159 from sIGPS. 15</td>
</tr>
<tr>
<td>1.08</td>
<td>First synthesis of PRA 1.05 by Creighton.$^{42}$ 18</td>
</tr>
<tr>
<td>1.09</td>
<td>Berger et al.$^{48}$ synthesis of ribosyl aniline 1.09. 19</td>
</tr>
<tr>
<td>1.10</td>
<td>Synthesis of dephosphorylated PRA 1.10. 20</td>
</tr>
<tr>
<td>1.11</td>
<td>Heat-induced synthesis of CdRP 1.06. 20</td>
</tr>
<tr>
<td>1.12</td>
<td>Synthesis of 1-(O-carboxyphenylamino)-1-deoxyribulose 1.11. 21</td>
</tr>
<tr>
<td>1.13</td>
<td>Inhibition of IGPS by 1-(phenylamino)-1-deoxyribulose 5’-phosphate 1.12. 22</td>
</tr>
<tr>
<td>1.14</td>
<td>Successful reduction of CdRP 1.06 to rCrRP 1.13. 23</td>
</tr>
<tr>
<td>1.15</td>
<td>Retrosynthesis of CdRP-like compounds. 29</td>
</tr>
<tr>
<td>1.16</td>
<td>Retrosynthesis of secondary amines. 30</td>
</tr>
<tr>
<td>1.17</td>
<td>Okahara et al.$^{74}$ N-alkylation to form aryl secondary amine 1.29. 32</td>
</tr>
</tbody>
</table>
1.18 Example of Ullmann$^{269}$ and Goldberg$^{270}$ couplings by Buchwald $et$ $al$.$^{77}$

1.19 General scheme of palladium-catalysed secondary amine formation.

1.20 Glycosylamine formation via an epoxide.

1.21 Imine formation and subsequent formation of secondary amine.

1.22 General synthesis of secondary amine via resin 1.40.

2.01 General synthetic strategy.

2.02 Phosphorylation route options.

2.03 Carbohydrate phosphate formation by use of
diphenyl phosphorochloridate at room temperature (RT).

2.04 Phosphorylation by triethyl phosphate and iodine.

2.05 Example of electrophilic phosphorylation.

2.06 Phosphorylation of C5-hydroxyl using the phosphoramidite method.

2.07 Failed synthesis of D-ribonolactone-5-diphenyl phosphate 2.07.

2.08 D-Ribonolactone modification from Taylor $et$ $al$.134

2.09 Primary tritylation of D-ribonolactone.

2.10 Formation of intermediate 2.10 from catalytic DMAP.

2.11 Disilylation of trityl 2.09.

2.12 Retrosynthesis for the reductive amination of lactol.

2.13 Dibal-H reduction of disilyl protected lactone 2.12.

2.14 Desilylation by Dibal-H.

2.15 Dibal-H reduction by Ley $et$ $al$.144

2.16 Dibal-H reduction by Ireland and Wilcox.145

2.17 Dibal-H ester reduction by Pamies and Backvall.146

2.18 Dibal-H acetate reduction by Yamada $et$ $al$.147

2.19 Dibal-H acetal reduction by Iqbal $et$ $al$.148

2.20 Dibal-H desilylation by Xu and Newcomb.151

2.21 Dibal-H reduction in the presence of TBDPS.


2.25 TBDPSCI protection of diol 2.09.
2.26 Lactone benzylation using BnBr and NaH.
2.27 Cis diol benzylation using BnBr and Ag₂O.
2.28 Reaction 5 - the best conditions for the formation of
dibenzylated lactone 2.35.
2.29 Attempts at tribenzylating D-ribonolactone 2.03.
2.30 Potential benzylidene acetal products.
2.31 Unprotected C5 hydroxyl group leads to acid-catalysed rearrangement.
2.32 Dibal-H reduction of iso-propylidene acetal D-ribonolactone moieties.
2.33 Potential iso-propylidene acetal products
2.34 Retrosynthesis of protected lactol via D-ribose methyl glycoside.
2.35 One-step formation of 2,3-O-iso-propylidene-β-D-ribofuranoside 2.48
from D-ribose 2.47.
2.36 Primary hydroxyl group benzylation.
2.37 Primary hydroxyl group phosphorylation.
2.38 Methyl esterification of anthranilic acid.
2.39 Methyl esterification of 4-aminobenzoic acid.
2.40 Esterification via isolated acid chloride.
2.41 Imine formation and subsequent formation of secondary amine.
2.42 Platinum oxide use in indirect reductive amination.
2.43 Retrosynthesis of potential inhibitors via D-ribose 2.47.
2.44 Glycosylamine formation using D-ribose 2.47.
2.45 Glycosylamine 2.64 formation using anthranilate ethyl ester.
2.46 Parameters used in reductive aminations involving D-ribose 2.47.
2.47 Aldehyde equilibrium and formation of the imine 2.68 before
reduction to the aryl glycosylamine precursor 2.66.
2.48 Retrosynthetic pathway of 5-phosphonopentyl anthranilic acid 2.74.
2.49 Synthesis of mono phosphorylated product 2.72.
2.50 Synthesis of aldehyde 2.73.
2.51 Attempted synthesis of 5-phosphonopentyl anthranilate methyl ester 2.75.
2.52 Synthesis of benzyl-protected product 2.76.
2.53 Synthesis of protected aldehyde 2.77.
2.54 Unsuccessful synthesis of benzyl-protected pentyaminophenyl 2.78.
2.55 Harrison’s attempts at synthesis of benzyl-protected hexylamino-acetic ethyl ester 2.81.
2.56 Successful synthesis of benzyl-protected pentylcyclohexyl amine 2.83.
2.57 Successful synthesis of benzyl-protected pentyl anthranilate methyl ester 2.85.
2.58 Formation of benzyl-protected pentyl anthranilate methyl ester 2.85 over three steps.
3.01 Literature synthesis by Taylor et al. 134
3.02 General retrosynthetic strategy for CdRP-like compounds.
3.03 Initial attempts at forming a primary-mono good-leaving group.
3.04 Synthesis of bis-mesyl 3.07 and bis-tosyl 3.08 compounds.
3.05 Lack of aryl amine reactivity at room temperature.
3.06 Nucleophilic substitution forming pyrrolidine derivative 3.10.
3.07 Synthesis of precursor towards formation of a primary good leaving group.
3.08 Formic acid removal of trityl group by Taylor et al. 134
3.09 Attempted removal of trityl group.
3.11 Proposed alternative strategy to primary good leaving group 3.18.
3.13 Retrosynthetic pathway for target 1,4,5 compounds from 4-penten-1-ol 3.20.
3.14 Pentan-1,5-diol 3.19 protection with DHP in hexanes.
3.15 Silylation of pentan-1,5-diol 3.19 using NaH.
3.16 Mesylation of mono silyl 3.23.
3.17 Tosylation of mono silyl 3.23.
3.18 Formation of good leaving groups on 4-penten-1-ol 3.20.
3.19 Protection/deprotection strategy leading to the synthesis of secondary amine 3.29.
3.20 Chemoselectivity of secondary amine 3.34 by caesium base.  111
3.21 Use of caesium carbonate and low equivalents of aniline 3.36 in the synthesis of secondary aryl amine 3.37.  112
3.22 Synthesis of 5-O-tert-butyldimethylsilyl-1-O-trifluoro-methanesulfonyl pentanol 3.38.  113
3.23 Use of higher equivalents of aniline 3.36 in the synthesis of secondary aryl amine 3.37.  113
3.24 Use of low equivalents of aniline 3.36 in the synthesis of secondary aryl amine 3.39.  114
3.25 Neat aniline 3.36 in the synthesis of secondary aryl amine 3.39.  115
3.26 Synthesis of 5-O-para-methoxybenzyl bromopentanol 3.42 from pentan-1,5-diol 3.19.  116
3.27 Synthesis of bromo-4-pentene 3.43 by PBr₃ and pyridine.  117
3.28 Secondary amine 3.46 synthesis using low equivalents of cyclohexylamine 3.45.  118
3.29 Synthesis of secondary aryl amine 3.44 via heating.  119
3.30 Synthesis of 1-phenylamino-4-pentene 3.39 using heat and high equivalents of aniline 3.36.  120
3.31 Synthesis of anthranilate methyl ester-4-pentene 3.47 using heat and high equivalents of anthranilate methyl ester 3.09.  121
3.32 Synthesis of N-9-fluorenylmethoxycarbonyl -1-phenylamino-4-pentene 3.48.  122
3.33 Overview of asymmetric dihydroxylation using either AD-mix-α or β.  122
3.34 Catalytic cycle of the AD reaction with K₃Fe(CN)₆ as the cooxidant.  123
3.35 Synthesis of N-9-fluorenylmethoxycarbonyl-1-phenylamino -4,5-pentan-diol 3.54 using AD-mix-α.  124
3.36 Synthesis of N-tert-butyloxy carbonyl-1-phenylamino -4-pentene 3.55 using a heterogeneous system and NaOH.  125
3.37 Synthesis of N-tert-butyloxy carbonyl-1-phenylamino -4,5-pentan-diol 3.56 using AD-mix-α.  126
3.38 Synthesis of N-tert-butyloxy carbonyl-1-phenylamino
-5-diethyl phosphate-4-pentanol \textbf{3.57}.

3.39 Substitution of mesyl \textbf{3.24} by phenol \textbf{3.59} at room temperature.

3.40 Substitution of bromide \textbf{3.42} by phenol \textbf{3.59} at room temperature.

3.41 Mixture of products formed when phenol \textbf{3.59} substituted bromopentan-5-ol \textbf{3.40}.

3.42 Substitution of mesyl \textbf{3.24} with benzyl magnesium bromide \textbf{3.65}.

3.43 Synthesis of hex-5-enylbenzene \textbf{3.67} via substitution of 4-pentenyl methanesulfonyl \textbf{3.26} with benzyl magnesium bromide \textbf{3.65}.

3.44 Synthesis of 5,6-epoxyhexylbenzene \textbf{3.68} by \textit{m}-CPBA.

3.45 Epoxide ring opening by inorganic phosphate described by Bolte \textit{et al.}\textsuperscript{325}

3.46 Attempted ring opening of 5,6-epoxyhexylbenzene \textbf{3.68} with inorganic phosphate.

3.47 Synthesis of a protected target 1,4,5 compound \textbf{3.57} over 5 steps.

4.01 General retrosynthetic strategy.

4.02 Epoxide formation from good leaving group.

4.03 4,5-Epoxypentan-1-ol formation from \textit{m}-CPBA.

4.04 4,5-Epoxypentan-1-ol formation from oxaziridinium salt.

4.05 Protected epoxide \textbf{4.12} formation by Yang \textit{et al.}\textsuperscript{331}

4.06 Hydrolytic kinetic resolution of racemic epoxide \textbf{4.12}.

4.07 Synthesis of protected epoxide \textbf{4.12}.

4.08 Synthesis of 1-\textit{O-}tert\textendash butyldiphenylsilyl-4,5-epoxypentanol \textbf{4.16}.

4.09 Synthesis of 5-\textit{O}-benzylpentene \textbf{4.18}.

4.10 Lewis acid catalytic cyclic for epoxide ring opening.

4.11 Parameters to form secondary aryl amine \textbf{4.26}.

4.12 Parameters to form secondary aryl amine \textbf{4.28}.

4.13 Epoxide ring opening by refluxing aniline.

4.14 Parameters for epoxide ring opening by aryl amines.

4.15 Low-yielding opening of TBDMS-protected epoxide \textbf{4.12} using aniline \textbf{4.24}, and ZnCl\textsubscript{2} in refluxing MeCN.

4.16 Cyclohexylamine \textbf{4.32} opening of the TBDMS-protected epoxide \textbf{4.12}.

4.17 Aniline \textbf{4.24} opening of TBDMS-protected epoxide \textbf{4.12}.
4.18 Aniline 4.24 opening of TBDPS-protected epoxide 4.16.
4.19 Formation of secondary aryl amine synthon 4.31 over three steps.
5.01 Failed Dibal-H reduction of disilyl protected lactone 2.12.
5.02 Parameters used in reductive aminations involving D-ribose 2.47.
5.03 Hirota et al.252 glycosylamine formation using D-ribose 2.47.
5.04 Synthesis of 5-O-benzylpentyl anthranilate methyl ester 2.85.
5.05 Formation of the furan derivative 3.06, after attempting to synthesise a sulfonyl leaving group on diol 3.02 primary hydroxyl group.
5.06 Nucleophilic substitution forming pyrrolidine derivative 3.10.
5.07 Use of caesium carbonate and low equivalents of aniline 3.36 in the synthesis of secondary aryl amine 3.37.
5.08 Neat aniline 3.36 in the synthesis of secondary aryl amine 3.39.
5.09 Synthesis of secondary aryl amine 3.44 via heating.
5.10 Synthesis of anthranilate methyl ester-4-pentene 3.47 using heat and high equivalents of anthranilate methyl ester 3.09.
5.11 Synthesis of a protected target 1,4,5 compound 3.57.
5.12 Substitution of bromide 3.42 by phenol 3.59 at room temperature.
5.13 Attempted ring opening of 5,6-epoxyhexylbenzene 3.68 with inorganic phosphate.
5.14 Formation of secondary aryl amine synthon 4.31 over three steps.
5.15 Proposed alternative strategy to primary good leaving group 3.18.

**Index of tables**

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>Enzyme kinetics of PRAI enzymes.</td>
</tr>
<tr>
<td>1.02</td>
<td>Enzyme kinetic parameters of IGPS enzymes.</td>
</tr>
<tr>
<td>2.01</td>
<td>Conditions used in benzylation reactions.</td>
</tr>
<tr>
<td>2.02</td>
<td>Conditions used in iso-propylidene acetal reactions.</td>
</tr>
<tr>
<td>2.03</td>
<td>Conditions used in esterification reactions.</td>
</tr>
<tr>
<td>2.04</td>
<td>Conditions used in lactol reductive amination reactions.</td>
</tr>
<tr>
<td>2.05</td>
<td>pKₐ of different potential nucleophiles at 25 °C.</td>
</tr>
</tbody>
</table>
3.01 Conditions used in silylation of pentan-1,5-diol \textbf{3.19} using NaH. 107
3.02 Conditions used in silylation of pentan-1,5-diol \textbf{3.19} using imidazole. 108
3.03 Conditions used in the synthesis of bromopentan-5-ol \textbf{3.40}. 116
3.04 Conditions used in the synthesis of secondary aryl amine \textbf{3.44}. 119
3.05 Conditions used in the synthesis of 1-phenylamino-4-pentene \textbf{3.39}. 120
4.01 Conditions used in silylation reactions. 140
4.02 Conditions used in epoxidation reactions. 141
4.03 Reactions using low equivalents of aryl amine at room temperature to open the TBDMS-protected epoxide \textbf{4.12}. 147
4.04 Reactions using low equivalents of aryl amine at reflux to open the protected epoxide \textbf{4.12}. 149
4.05 Reactions using high equivalents of neat aryl amine at room temperature to open the TBDMS-protected epoxide \textbf{4.12}. 151

\textbf{Index of graphs}

<table>
<thead>
<tr>
<th>Graph</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.01</td>
<td>\textsuperscript{1}H NMR spectrum of secondary aryl amine \textbf{4.31} between 3.0 and 7.15 ppm.</td>
</tr>
</tbody>
</table>