

Figure 1

Modular Total Synthesis of Tetracyclines

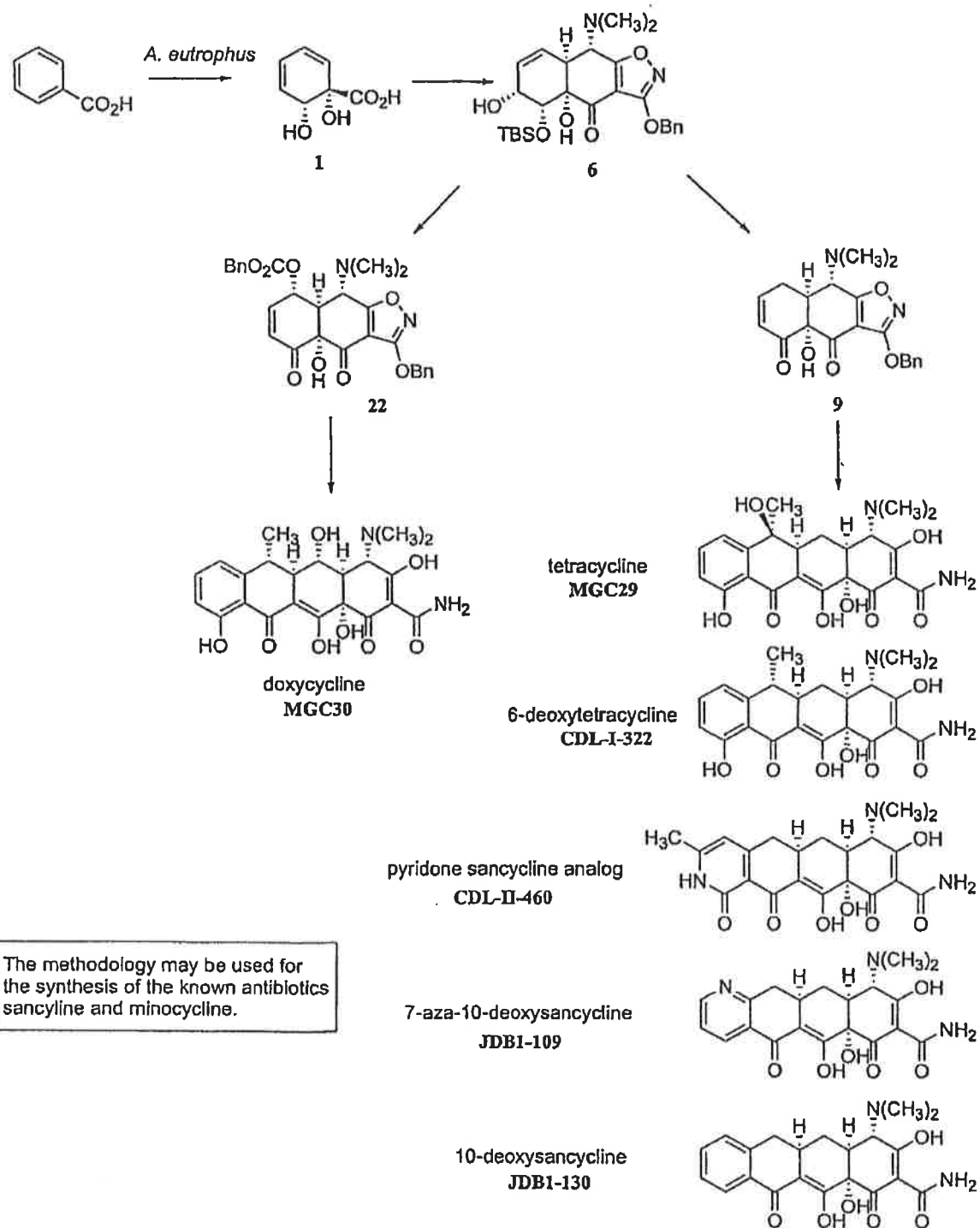


Figure 2
Total Synthesis of Tetracycline

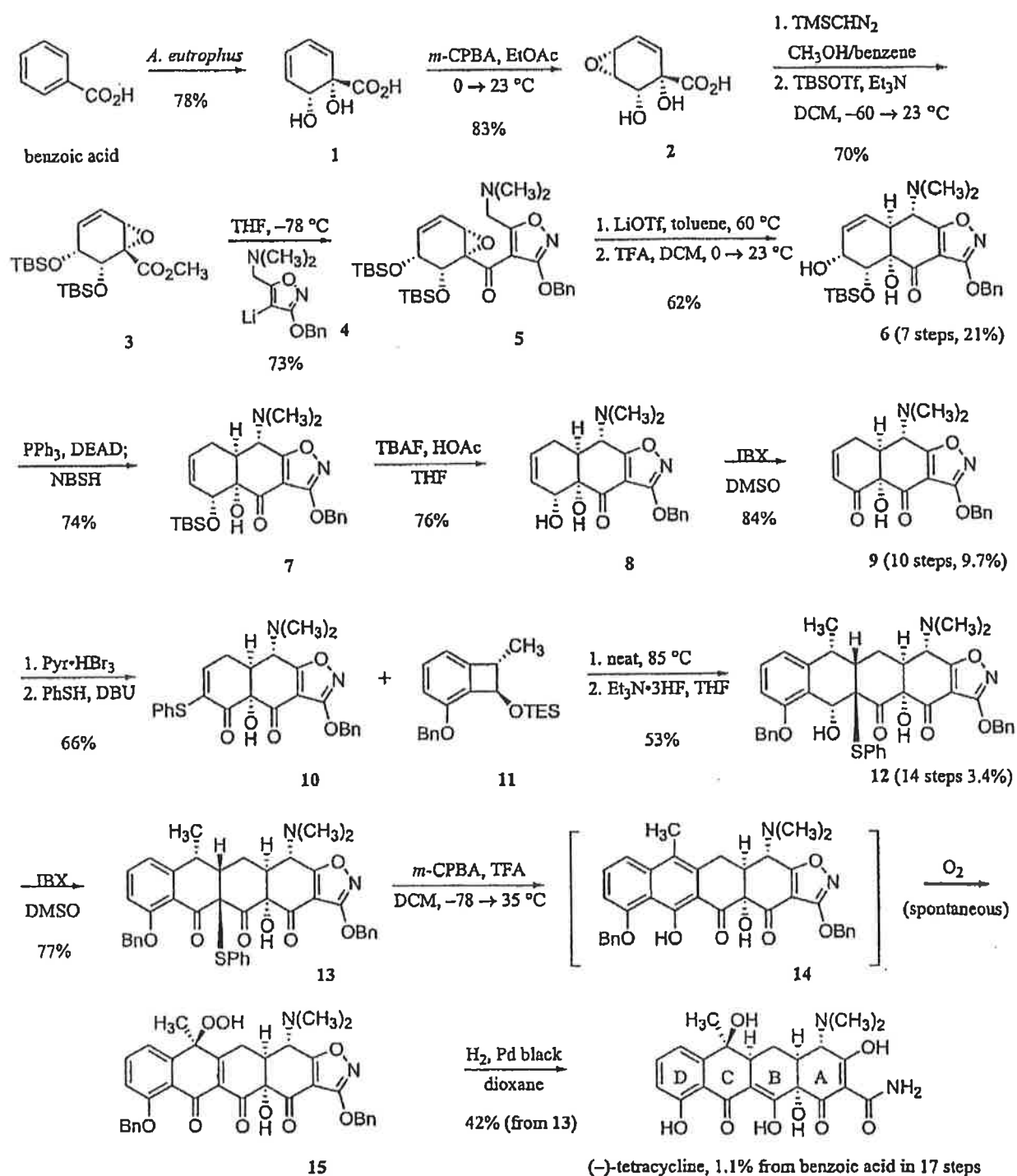
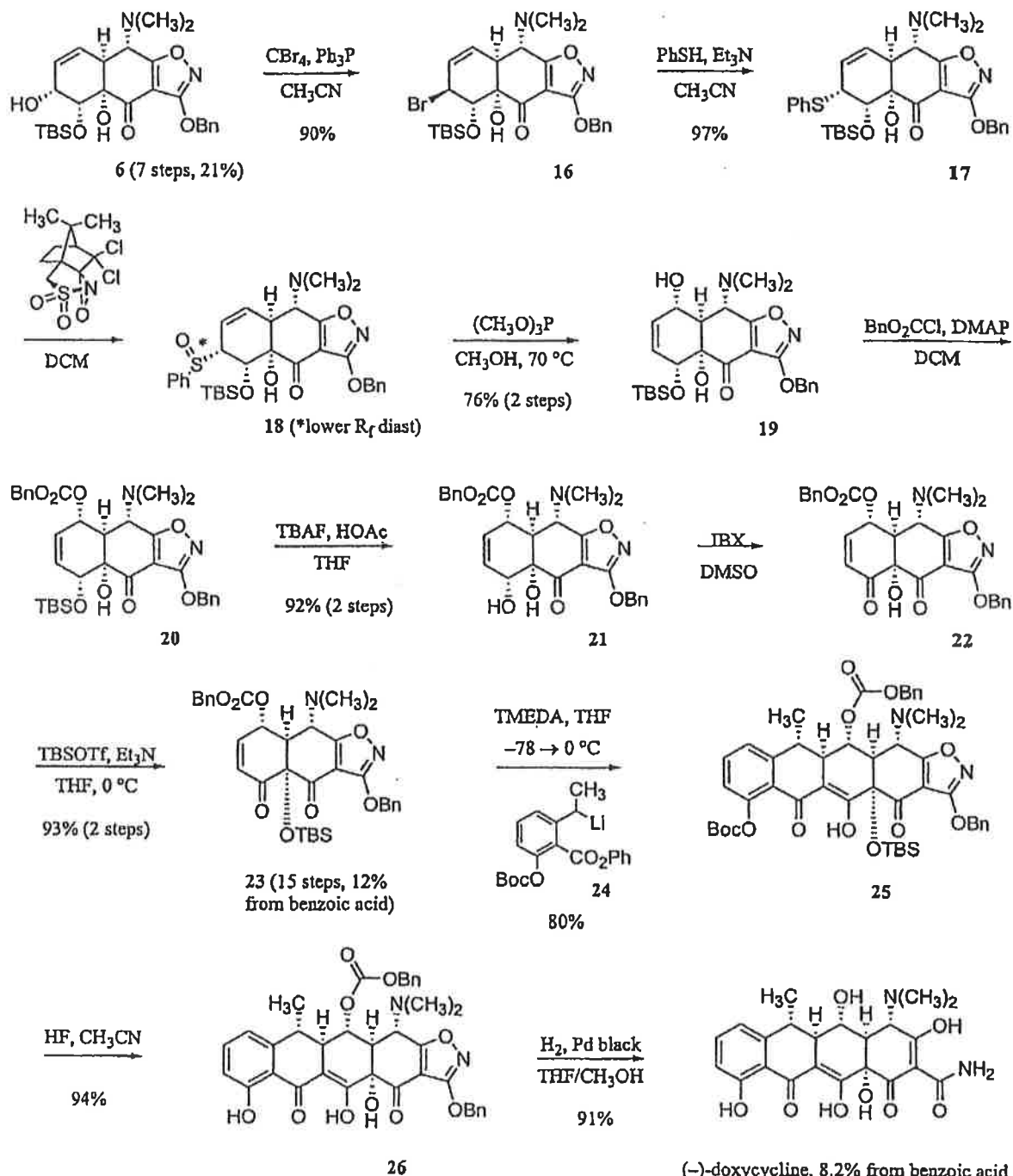


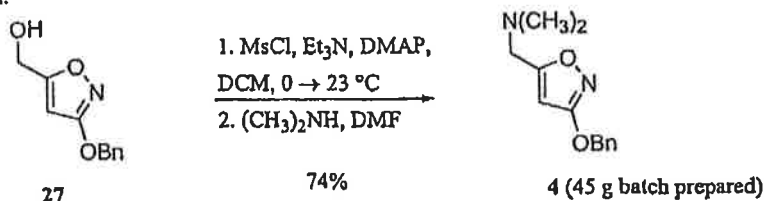
Figure 3
Total Synthesis of Doxycycline



(-)-doxycycline, 8.2% from benzoic acid in 18 steps (the first 7 steps are identical to the first 7 steps of the tetracycline synthesis)

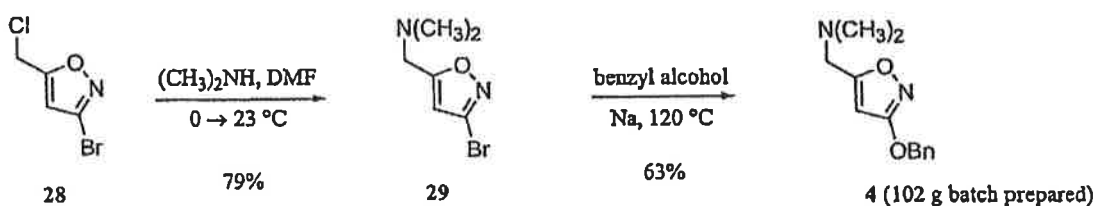
Figure 4
Synthesis of Isoxazole 4

First Generation:



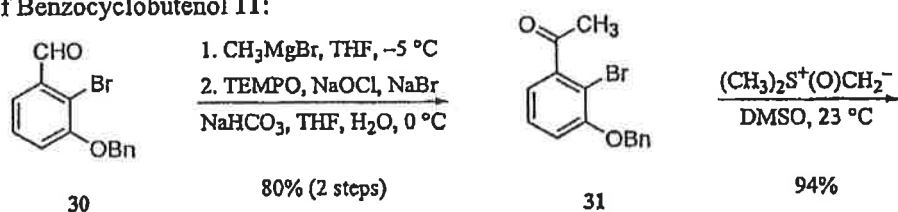
27: prepared in 3 steps from dimethylacetylene dicarboxylate and *N*-hydroxyurea
Synthesis 1985, 1100-1104.
Eur. J. Org. Chem. 1998, 473-479.

Second Generation:

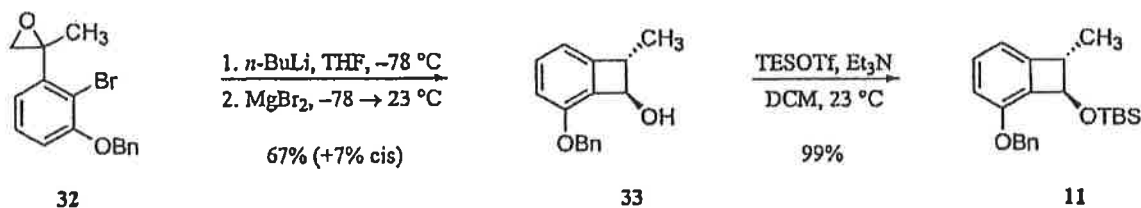


28: prepared in 2 steps from glyoxylic acid and 2,3-dichloro-1-propene
Synth. Commun. 1992, 22, 1939-1948.
Tetrahedron Lett. 1984, 25, 487-490.

Figure 5
Synthesis of Benzocyclobutenol 11:



30 prepared in 2 steps from 3-(benzyloxy)benzyl alcohol
J. Org. Chem. 1994, 59, 6703-6709.

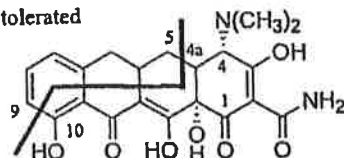


cyclization from 32 to 33 based on: (a) Akgün, E.; Glinski, M. B.; Dhawan, K. L.; Durst, T. *J. Org. Chem.* 1981, 46, 2730.
(b) Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* 1980, 45, 922.

Figure 6
Selected Analogs Accessible by our Modular Synthesis

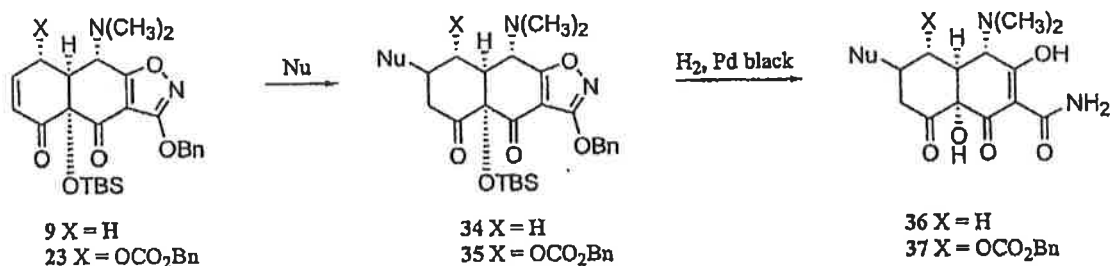
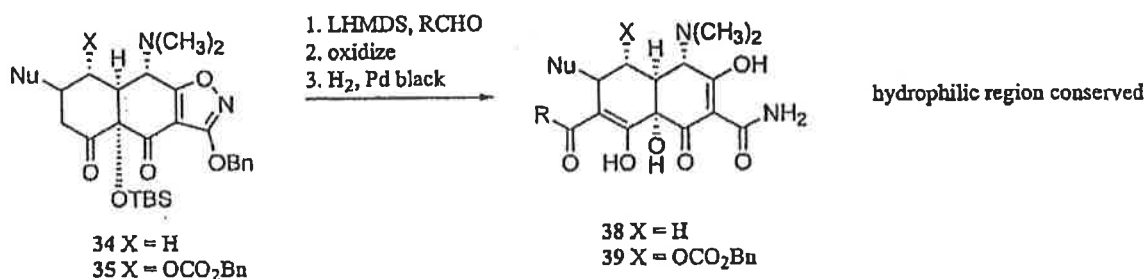
Paradigm for Antibiotic Activity of the Tetracyclines

hydrophobic region:
modifications are generally tolerated



hydrophilic region:
modifications are generally not tolerated

Summary of Targeted "Dicyclines"



Scope:

Nu = any soft alkyl, aryl, vinyl, or heterocyclic nucleophile. For example alkyl and aryl cuprates and Grignard reagents.
R = any alkyl, aryl, or heterocyclic structure. Basically anything that does not have acidic protons.

Compounds Prepared:

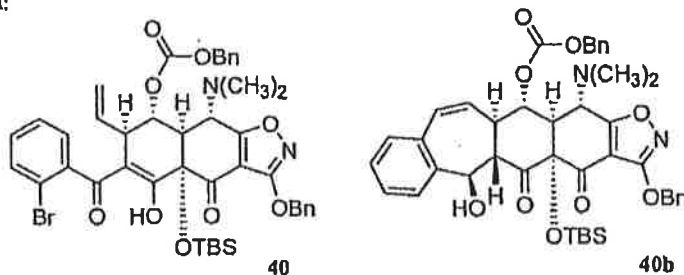
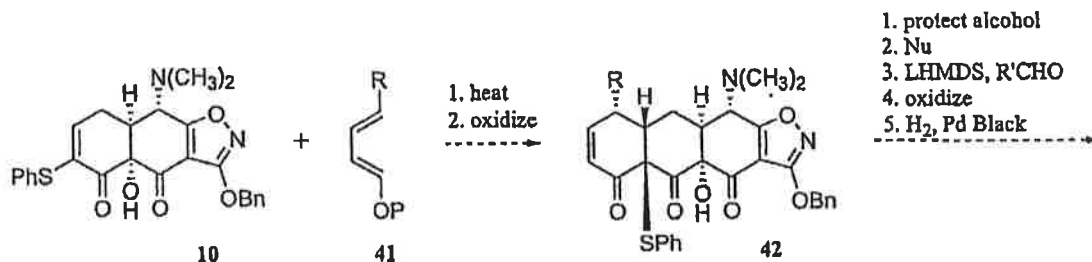
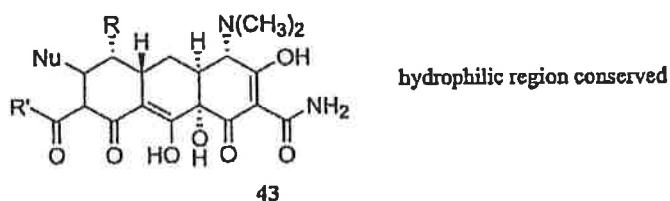


Figure 7
Summary of Targeted "Tricyclines"



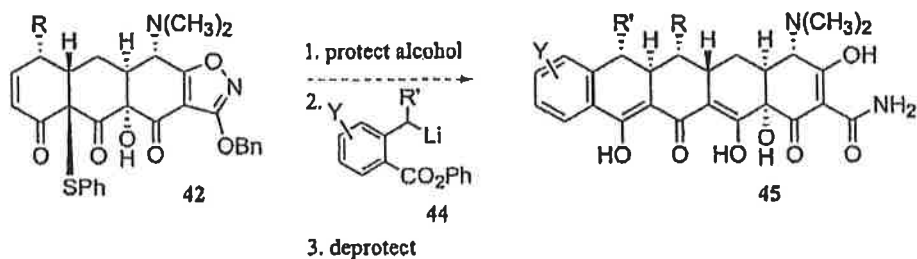
Scope:

Nu = any soft alkyl, aryl, vinyl, or heterocyclic nucleophile. For example alkyl and aryl cuprates and Grignard reagents.

R = sterically non-remanding alkyl or substituted group. Aryl less reasonable.

R' = any alkyl, aryl, or heterocyclic structure. Basically anything that does not have acidic protons.

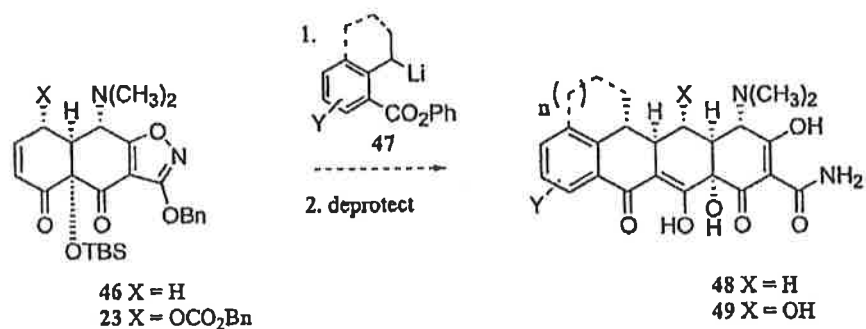
Figure 8
Summary of Targeted "Pentacyclines"



Scope:

Same as other Michael-Dieckmann reactions.

Figure 9
Summary of Targeted "Bridged-Pentacyclines"



Scope:
Same as other Michael-Dieckmann reactions.

Figure 10
Synthesized Compounds as Potential Analog Platforms

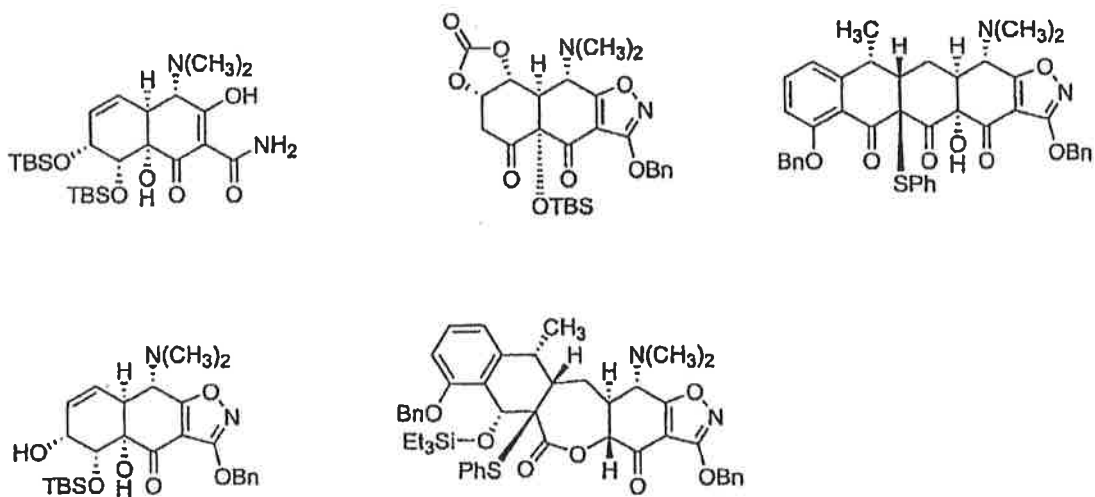


Figure 11
Total Synthesis of a Pyridone Sancycline Analog

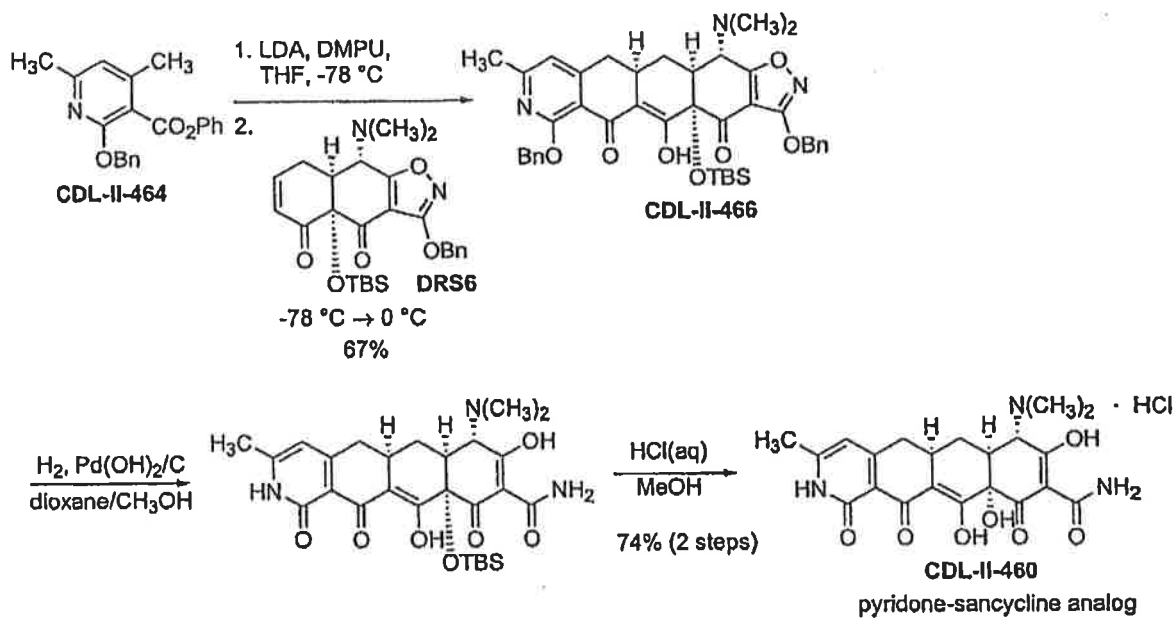
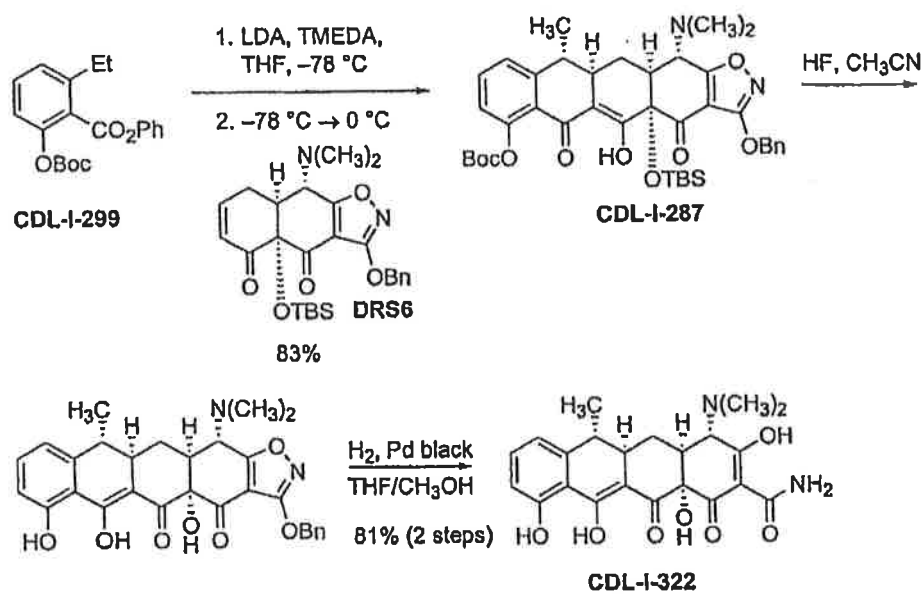


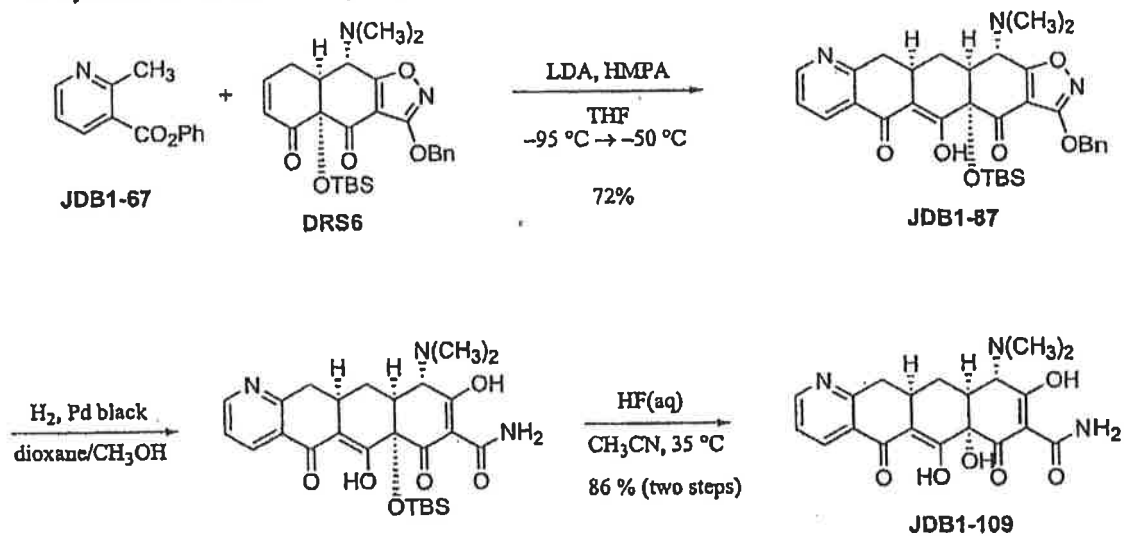
Figure 12
Total Synthesis of 6-Deoxytetracycline



6-deoxycycline, 8% from benzoic acid in 14 steps (the first 10 steps are identical to the first 10 steps of the tetracycline total synthesis)

Figure 13

A. Synthesis of 7-Aza-10-deoxysancycline



B. Synthesis of 10-Deoxysancycline

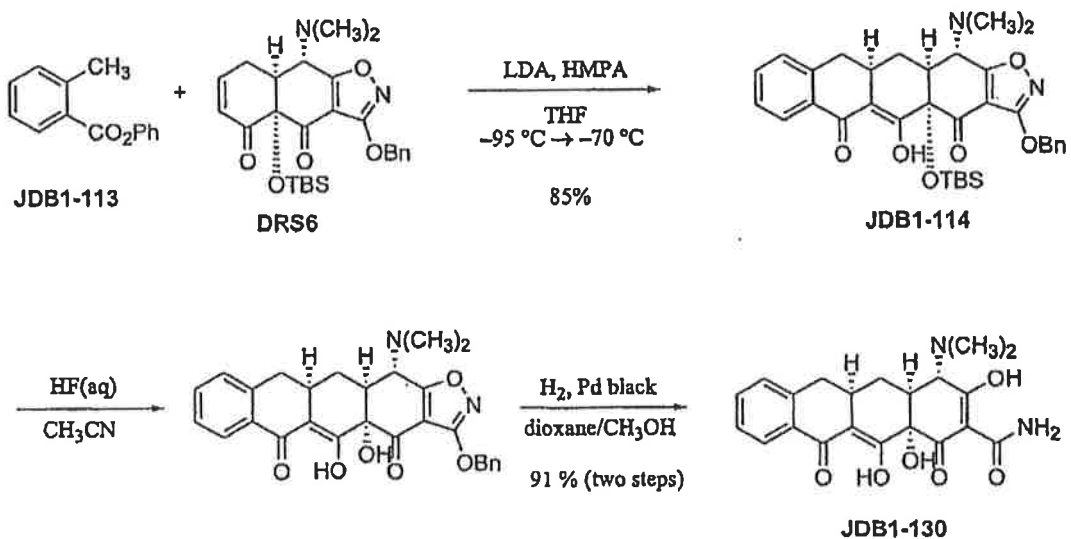
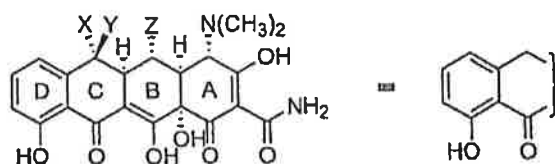


Figure 14A
Representative Structures



D-ring modifications

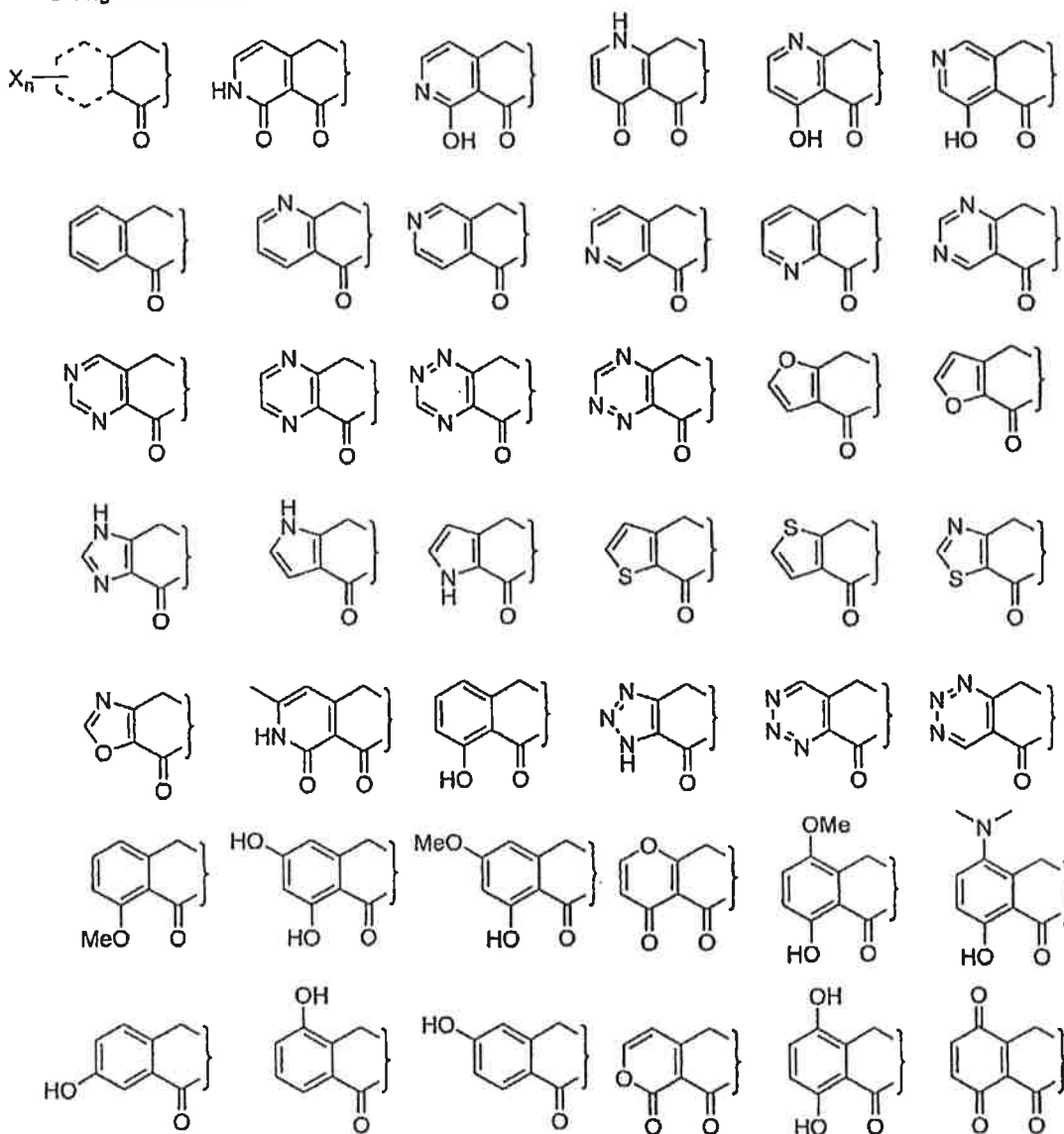
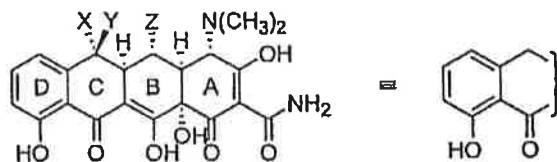


Figure 14B
Representative Structures



penta- and polycyclines:

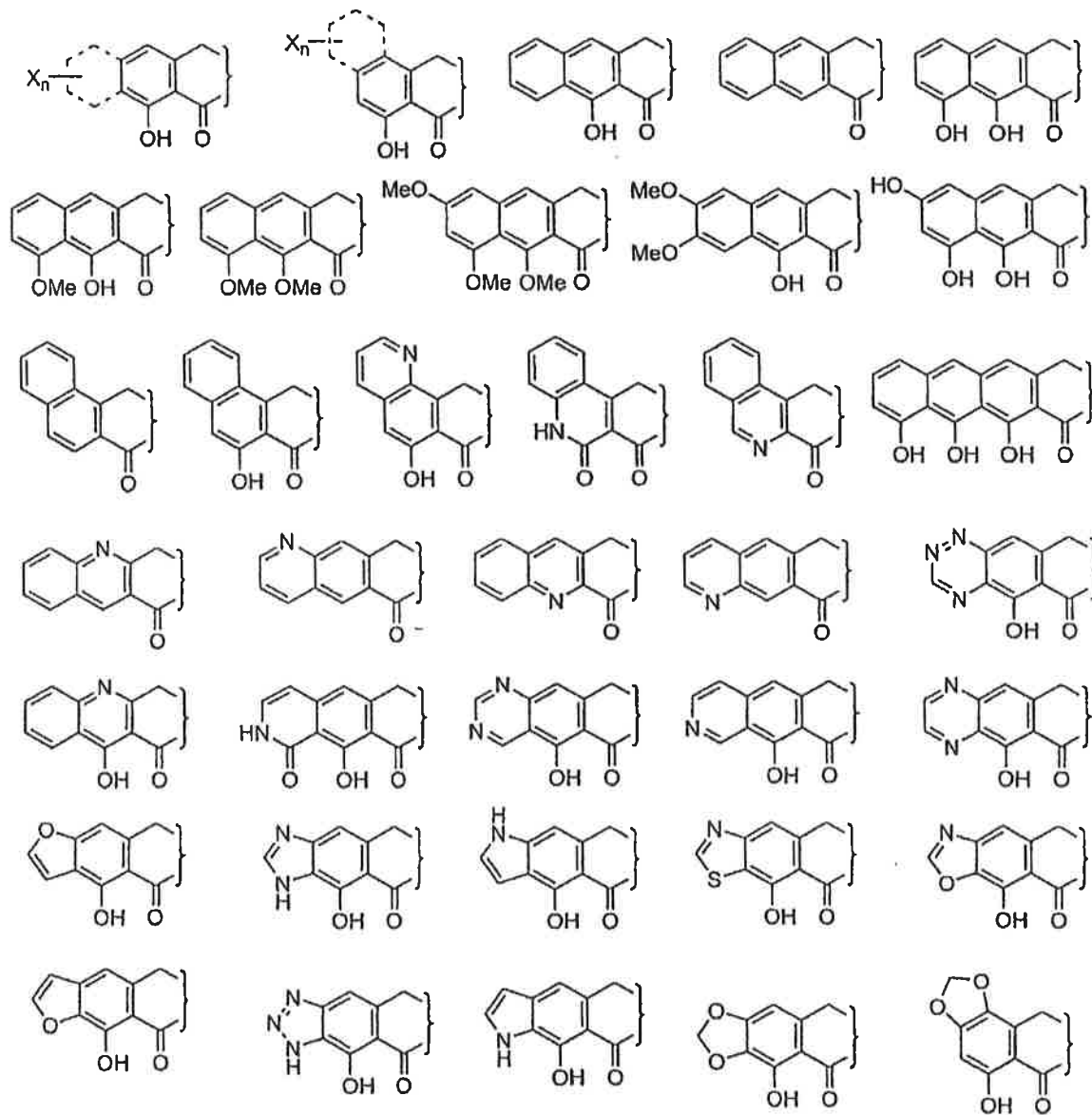


Figure 15

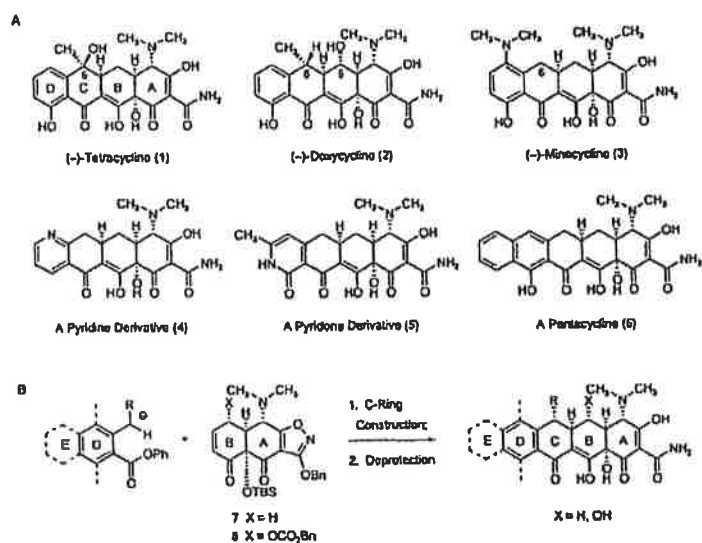


Figure 16

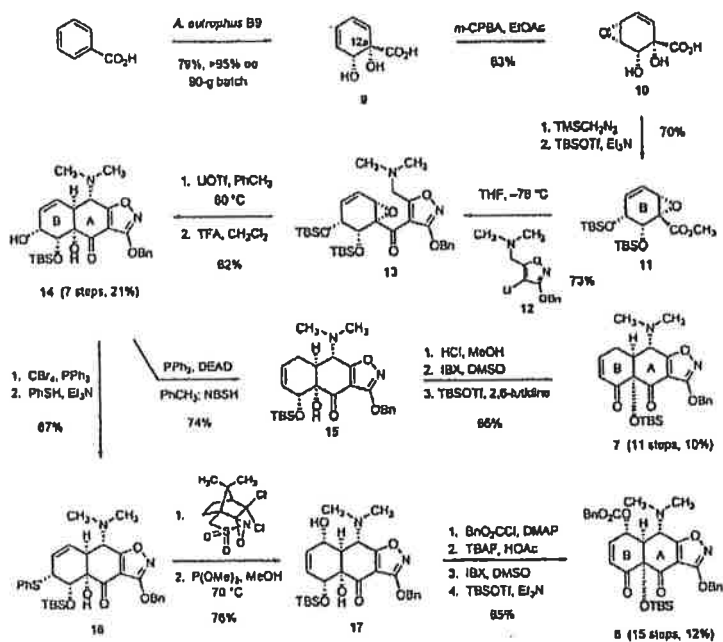


Figure 17

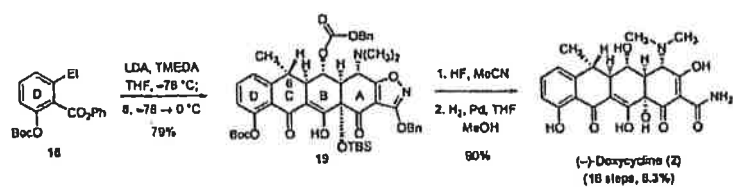


Figure 18

Convergent Assembly of
Structurally Diverse
Tetracyclines

Bacterial Strains Tested				
Gram-Positive Organisms				
<i>S. aureus</i> ATCC 29212	<i>S. epidermidis</i> ACH-0016	<i>S. pneumoniae</i> ACH-0013	<i>E. faecalis</i> ATCC 705802	<i>S. pneumoniae</i> ATCC 6305
Gram-Negative Organisms				
<i>P. aeruginosa</i> ATCC 27853	<i>K. pneumoniae</i> ATCC 13883	<i>E. coli</i> ATCC 25922	<i>E. coli</i> ACH-0095	<i>E. coli</i> pBR322

Entry	D-Ring Precursor	Conditions	Tetracycline Analog	MIC (μg/mL)								
1		1. LDA, TMEDA; 7 -78 → 0 °C (81%) 2. HF, MeCN 3. H ₂ , Pd (85%)	 (-)-6-Deoxytetracycline (14 steps, 7.0%)	<table border="1"><tr><td>10.5</td><td>2</td><td>0.5</td><td>16</td></tr><tr><td>>64</td><td>ND</td><td>16</td><td>>64</td></tr></table>	10.5	2	0.5	16	>64	ND	16	>64
10.5	2	0.5	16									
>64	ND	16	>64									
2		1. LDA, DMPU; 7 -78 → 0 °C (87%) 2. H ₂ , Pd(OH) ₂ 3. HCl, MeOH (74%)	 A Pyridone Derivative (5) (14 steps, 5.0%)	<table border="1"><tr><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>>64</td><td>ND</td><td>>64</td><td>ND</td></tr></table>	ND	ND	ND	ND	>64	ND	>64	ND
ND	ND	ND	ND									
>64	ND	>64	ND									
3		1. 7; LDA, HMPA -85 → -50 °C (75%) 2. H ₂ , Pd 3. HF, MeCN (78%)	 7-Azo-10-Deoxysansancycline (4) (14 steps, 6.1%)	<table border="1"><tr><td>ND</td><td>2</td><td>0.5</td><td>16</td></tr><tr><td>>64</td><td>16</td><td>2</td><td>>64</td></tr></table>	ND	2	0.5	16	>64	16	2	>64
ND	2	0.5	16									
>64	16	2	>64									
4		1. 7; n-BuLi -100 → -70 °C (81%) 2. HF, MeCN 3. H ₂ , Pd (83%)	 10-Deoxysansancycline (14 steps, 6.0%)	<table border="1"><tr><td>16</td><td>16</td><td>16</td><td>16</td></tr><tr><td>>64</td><td>ND</td><td>>64</td><td>ND</td></tr></table>	16	16	16	16	>64	ND	>64	ND
16	16	16	16									
>64	ND	>64	ND									
5		1. 7; n-BuLi -100 → 0 °C (75%) 2. HF, MeCN 3. H ₂ , Pd 4. BB ₃ , CH ₂ CH ₃ -78 → 23 °C (74%)	 A Pentacycline (9) (15 steps, 5.6%)	<table border="1"><tr><td>0.5</td><td>0.5</td><td>16</td><td>16</td></tr><tr><td>>64</td><td>>64</td><td>>64</td><td>>64</td></tr></table>	0.5	0.5	16	16	>64	>64	>64	>64
0.5	0.5	16	16									
>64	>64	>64	>64									
Testing Control:			 (-)-Tetracycline (1)	<table border="1"><tr><td>10.5</td><td>16</td><td>16</td><td>16</td></tr><tr><td>32</td><td>32</td><td>16</td><td>>64</td></tr></table>	10.5	16	16	16	32	32	16	>64
10.5	16	16	16									
32	32	16	>64									

A Crystalline Michael Adduct

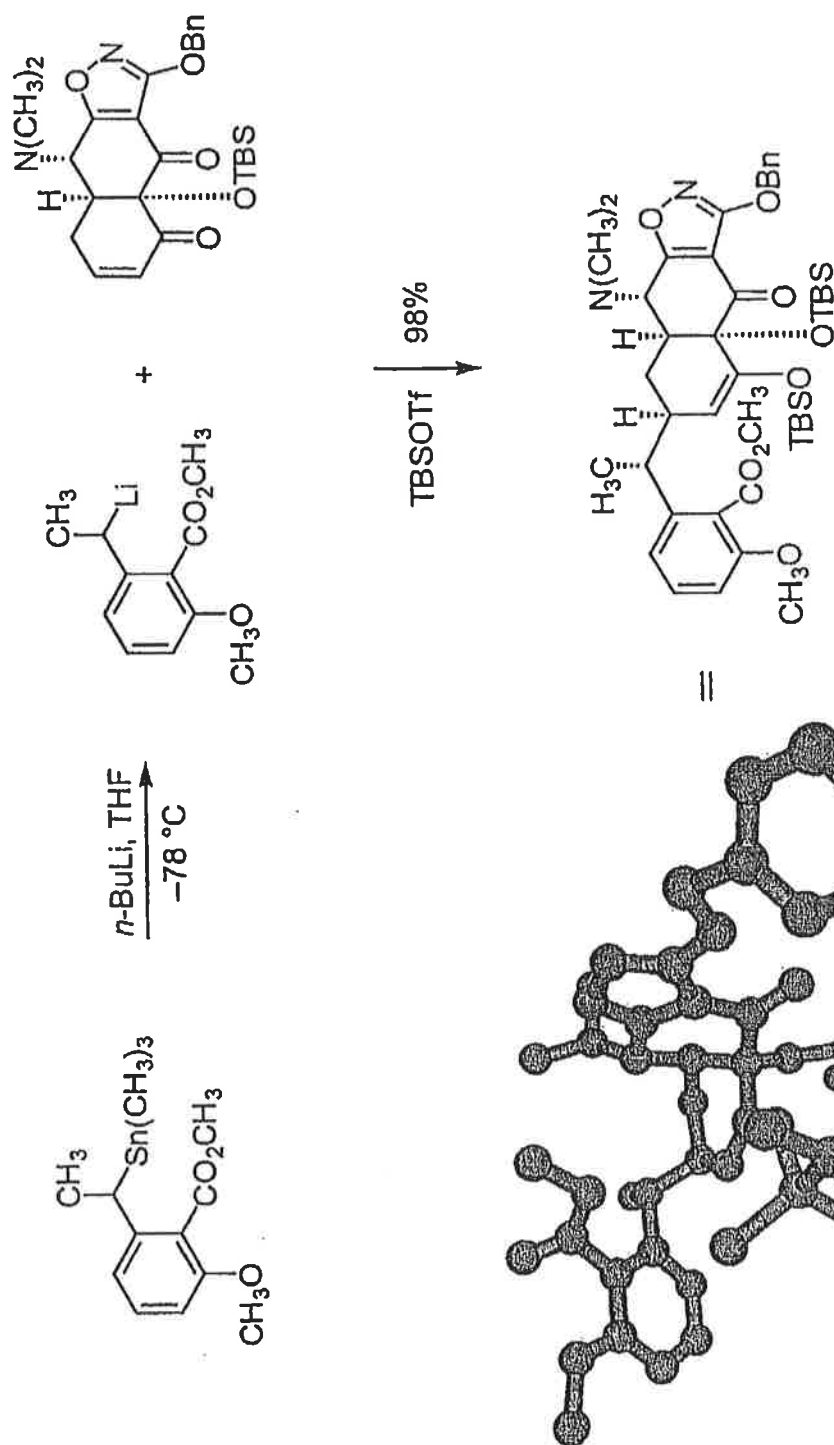
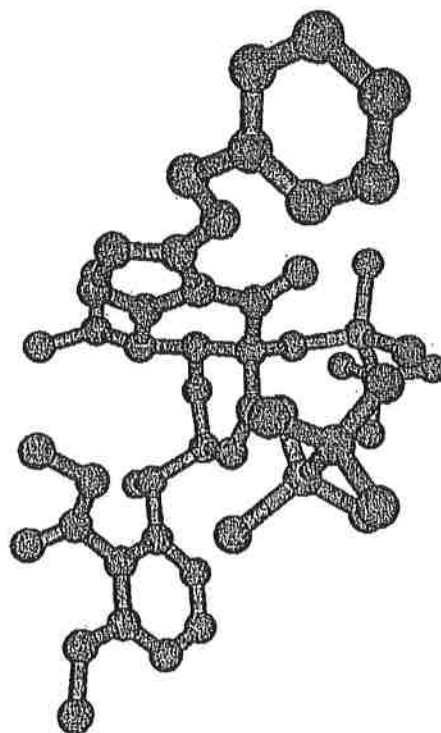
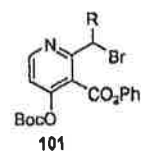
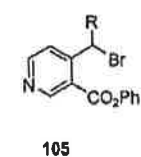
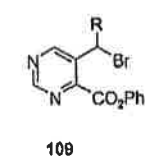
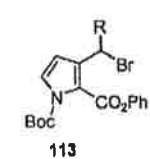
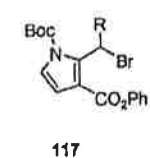
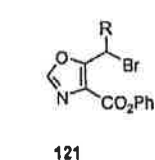
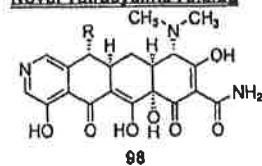
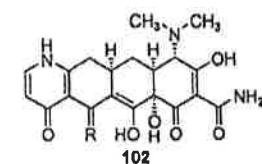
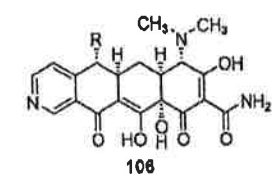
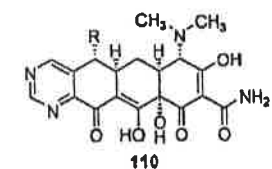
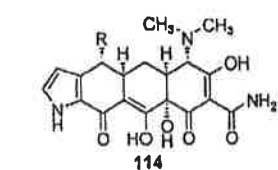
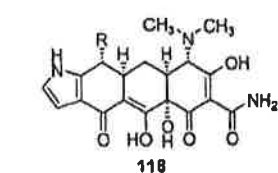
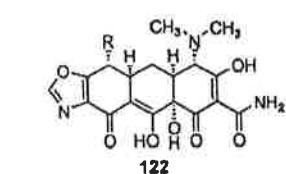


Figure 19

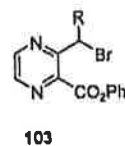
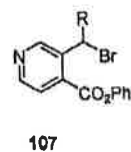
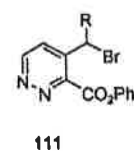
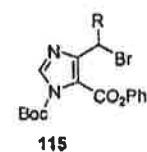
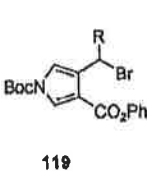
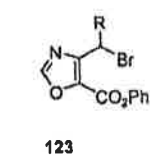
D-Ring Precursor



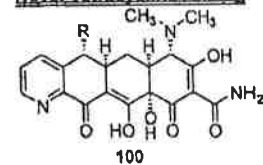
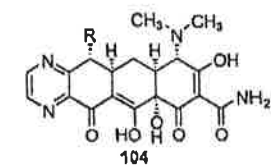
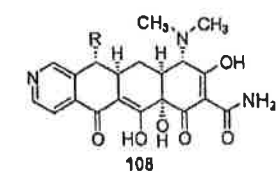
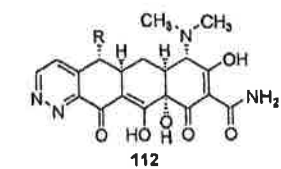
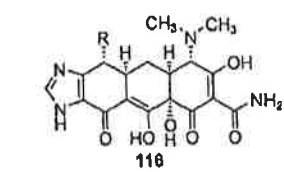
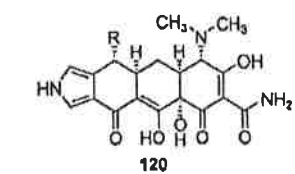
Novel Tetracycline Analog



D-Ring Precursor

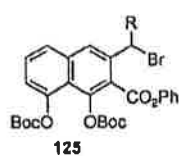
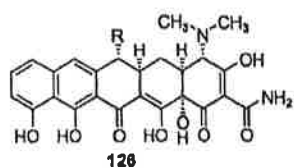
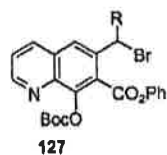
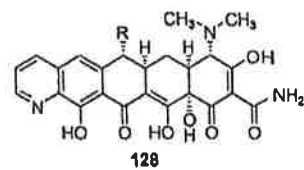
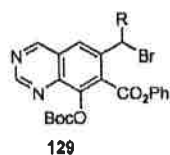
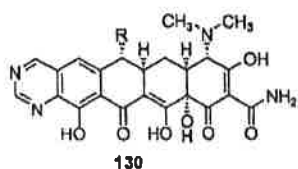
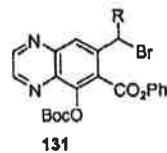
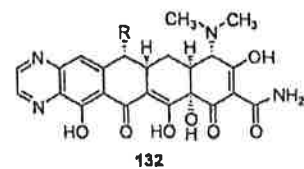
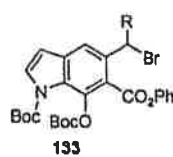
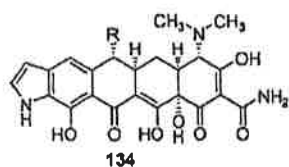
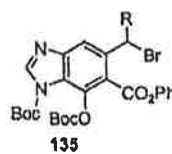
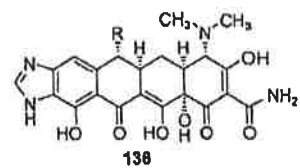
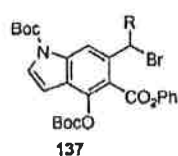
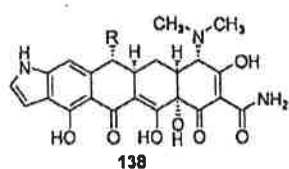
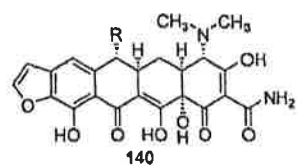
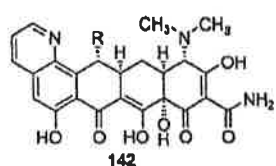
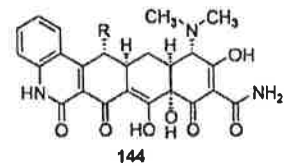
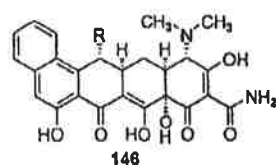
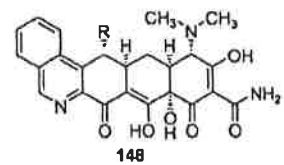
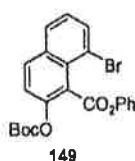
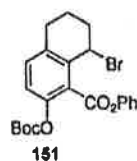
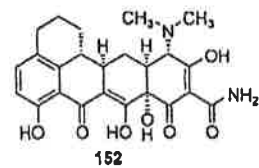


Novel Tetracycline Analog



R = H, simple alkyl, branched alkyl, aryl, heteroaryl, arylalkyl.

Figure 21A

D-Ring PrecursorNovel Tetracycline AnalogD-Ring PrecursorNovel Tetracycline Analog

R = H, simple alkyl, branched alkyl, aryl, heteroaryl, arylalkyl.

Figure 21B

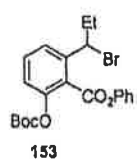
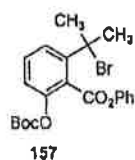
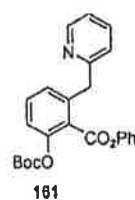
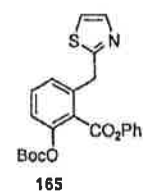
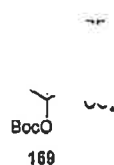
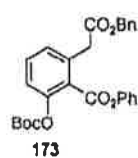
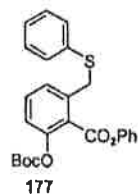
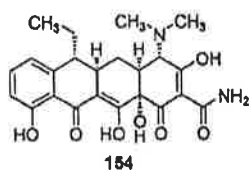
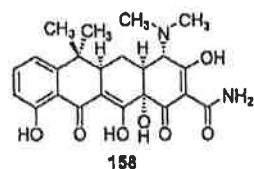
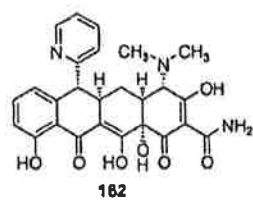
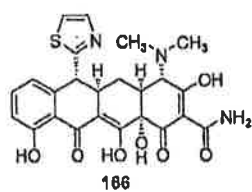
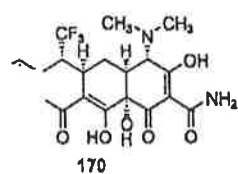
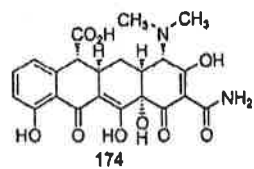
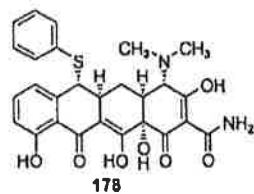
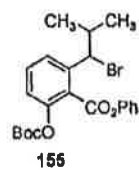
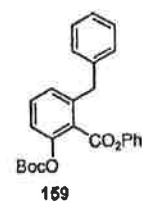
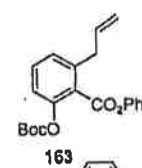
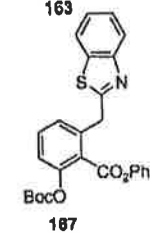
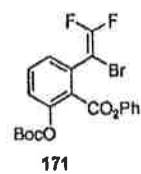
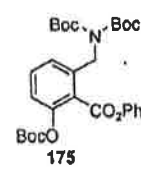
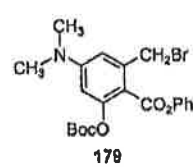
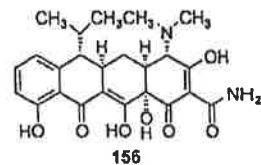
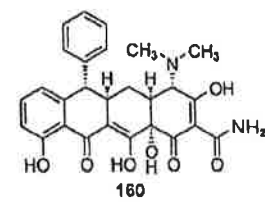
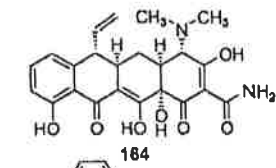
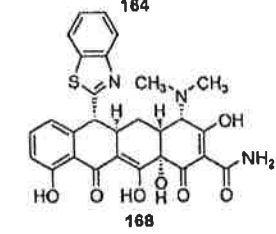
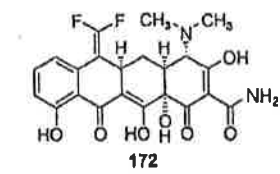
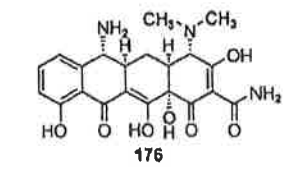
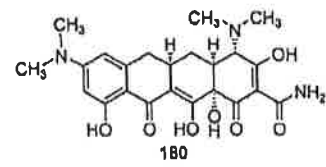
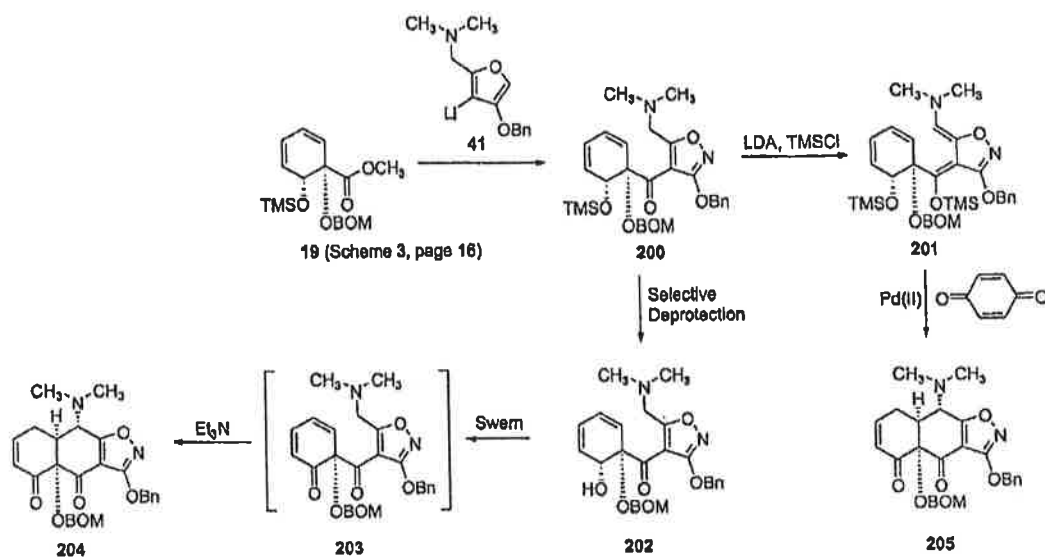
D-Ring PrecursorNovel Tetracycline AnalogD-Ring PrecursorNovel Tetracycline Analog

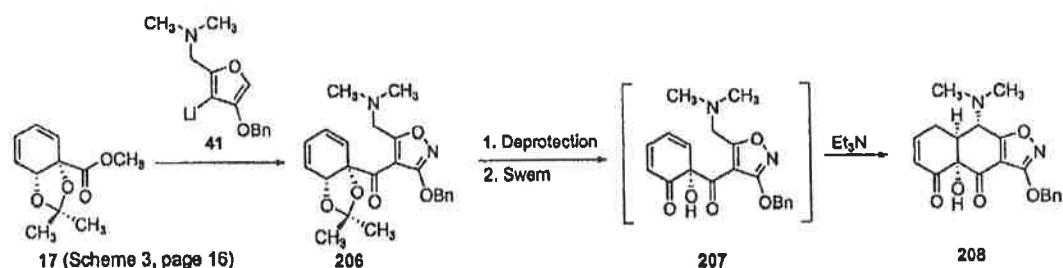
Figure 21C

Alternative Sequences to AB Enone Precursors from 1*S*,2*R*-*cis*-Dihydroxy Benzoic Acid

A.



B.



C.

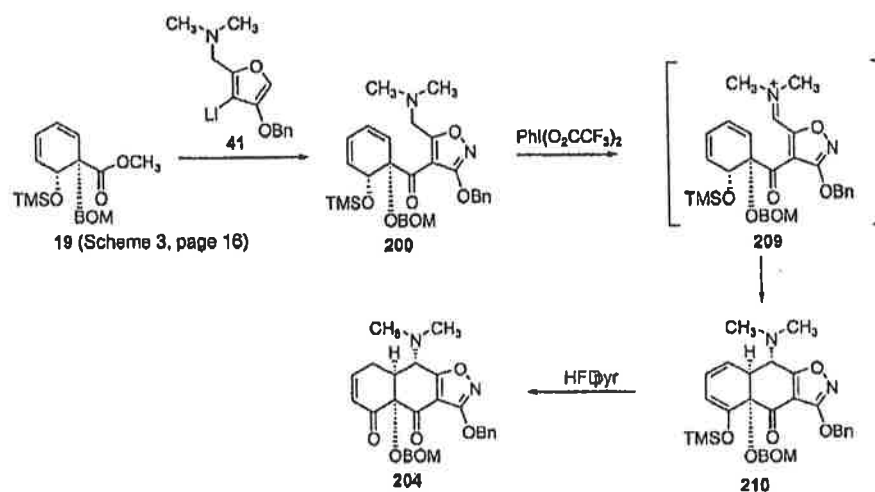
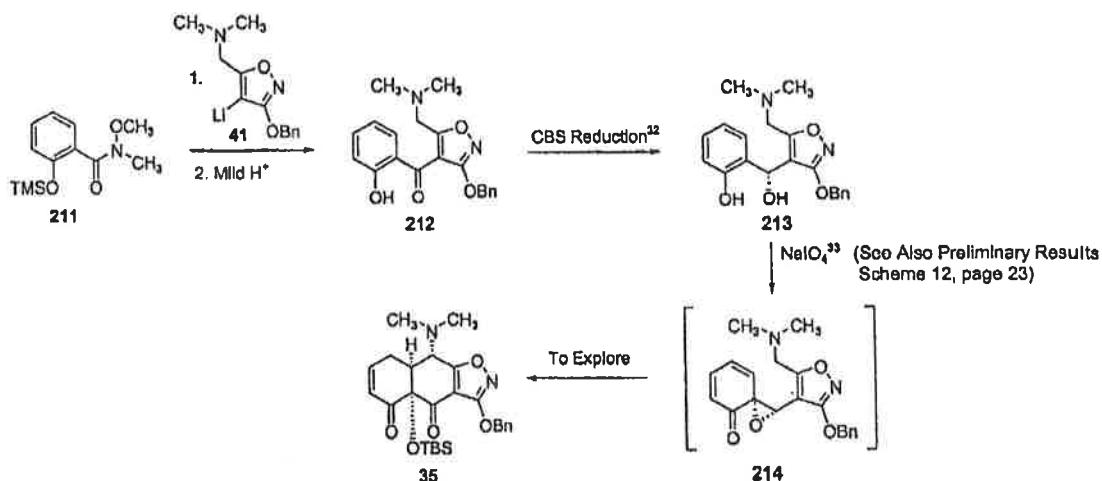


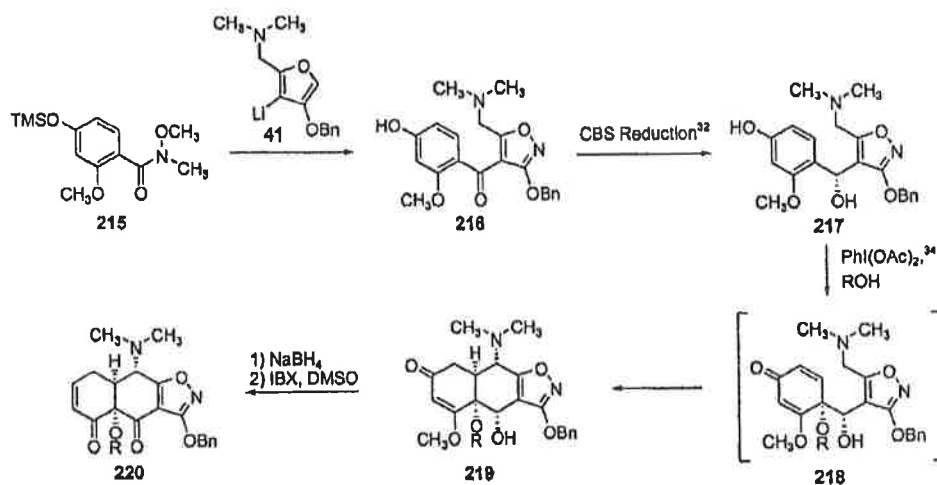
Figure 22

New Routes to AB Precursors That Do Not Involve Microbial Dihydroxylation of Benzoic Acid

A.



B.



C.

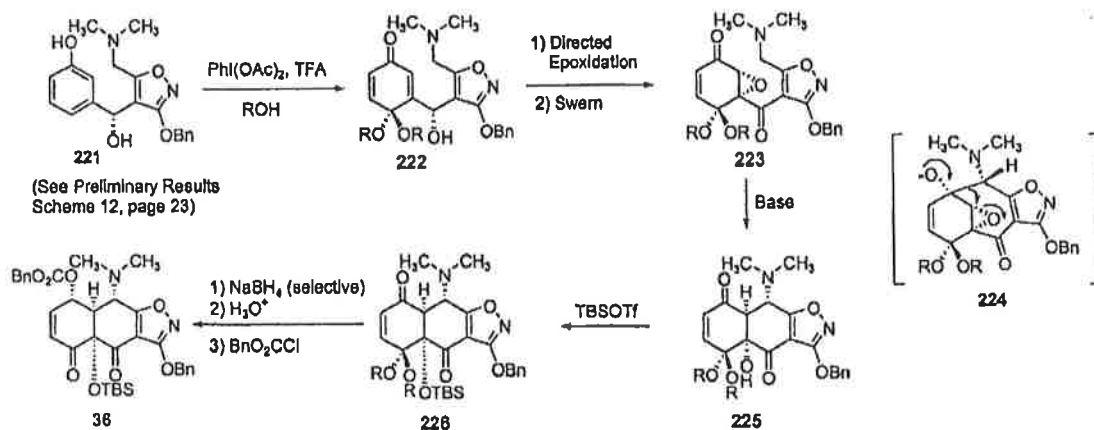


Figure 23