

Figure 1

Modular Total Synthesis of Tetracyclines

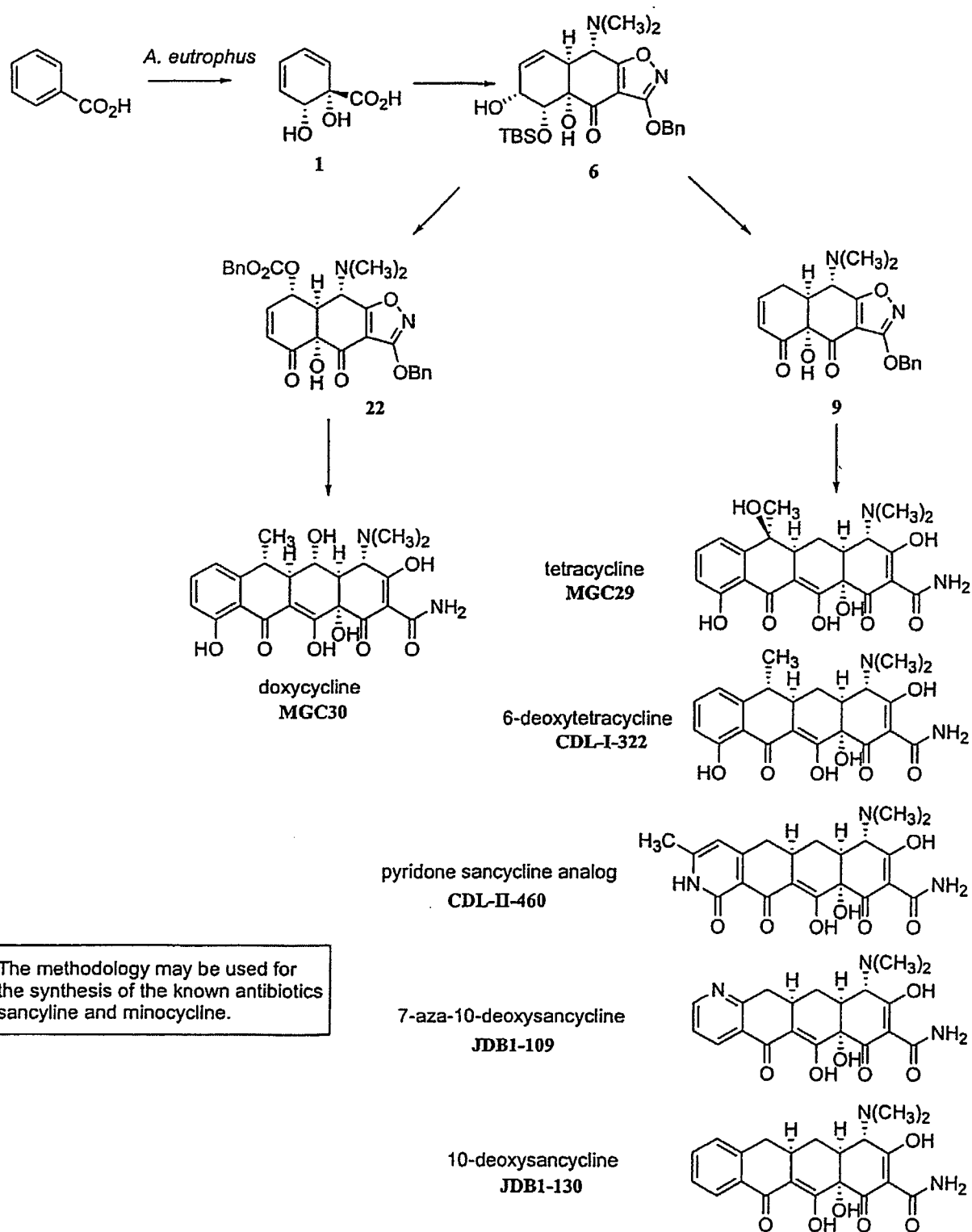


Figure 2
Total Synthesis of Tetracycline

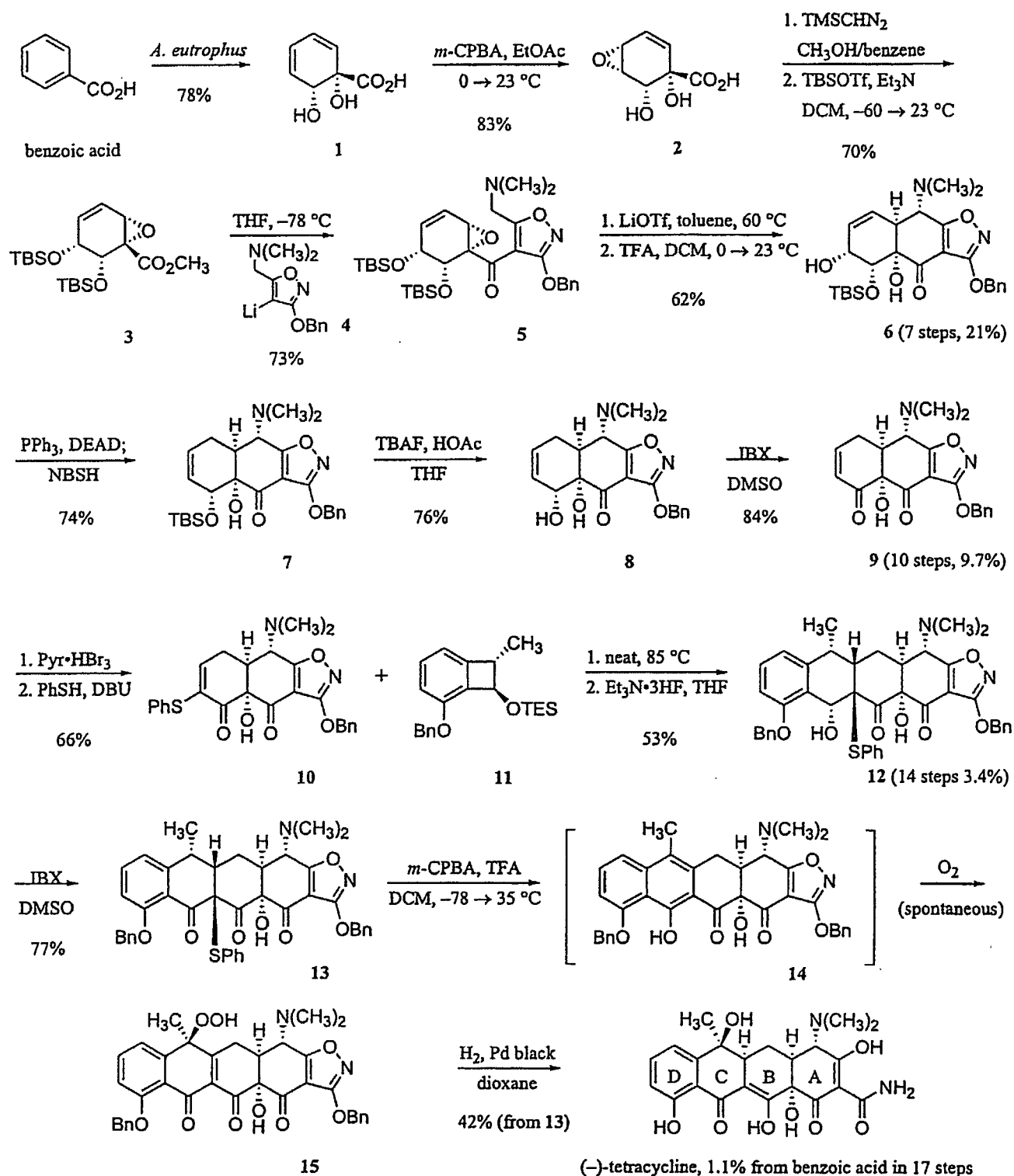


Figure 3
Total Synthesis of Doxycycline

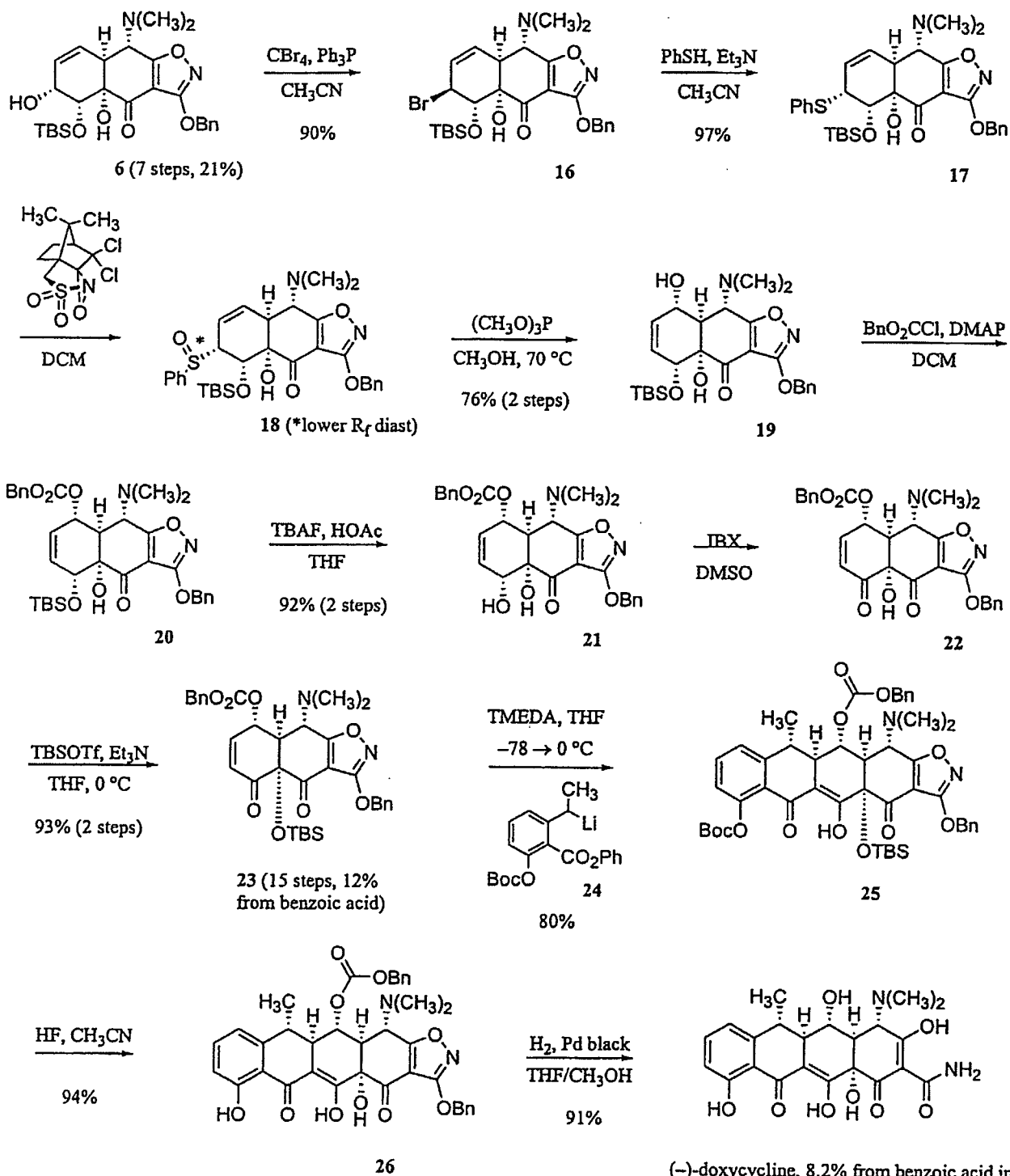
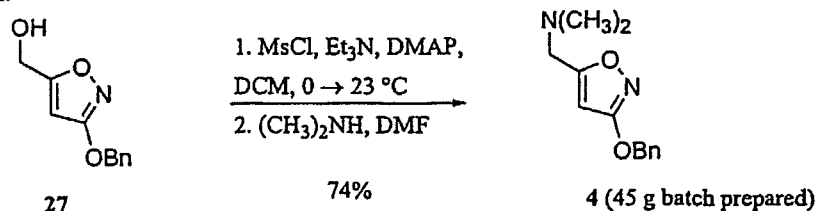


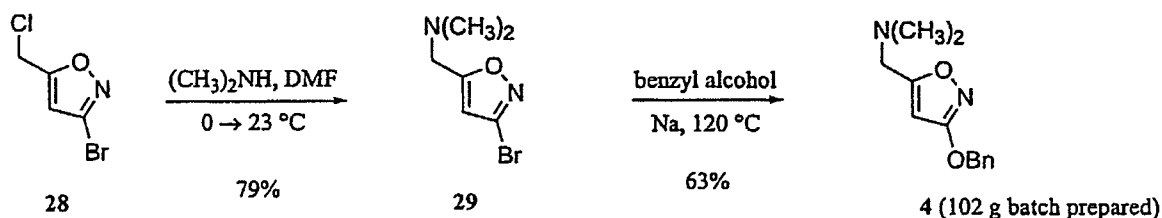
Figure 4
Synthesis of Isoxazole 4

First Generation:



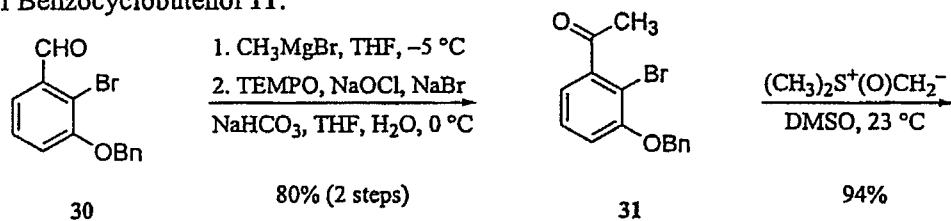
27: prepared in 3 steps from dimethylacetylene dicarboxylate and *N*-hydroxyurea
Synthesis 1985, 1100-1104.
Eur. J. Org. Chem. 1998, 473-479.

Second Generation:

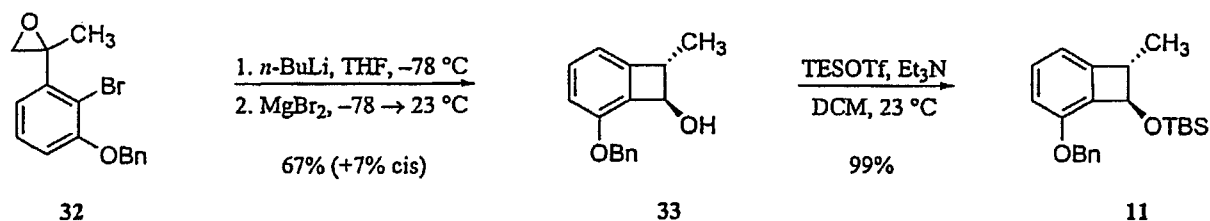


28: prepared in 2 steps from glyoxylic acid and 2,3-dichloro-1-propene
Synth. Commun. 1992, 22, 1939-1948.
Tetrahedron Lett. 1984, 25, 487-490.

Figure 5
Synthesis of Benzocyclobutenol 11:



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

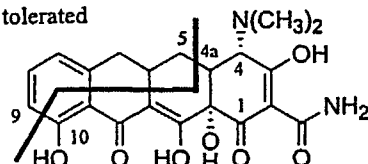


cyclization from 32 to 33 based on: (a) Akgün, E.; Glinski, M. B.; Dhawan, K. L.; Durst, T. *J. Org. Chem.* 1981, 46, 2730.
 (b) Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* 1980, 45, 922.

Figure 6
Selected Analogs Accessible by our Modular Synthesis

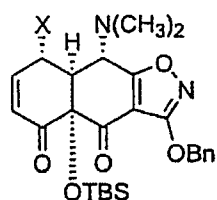
Paradigm for Antibiotic Activity of the Tetracyclines

hydrophobic region:
modifications are generally tolerated

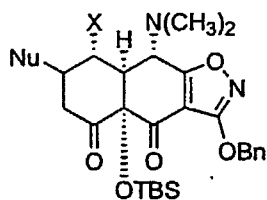


hydrophilic region:
modifications are generally not tolerated

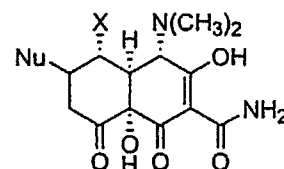
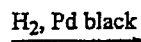
Summary of Targeted "Dicyclines"



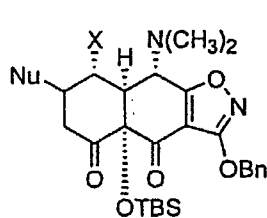
9 X = H
23 X = OCO₂Bn



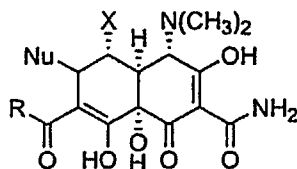
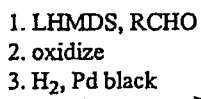
34 X = H
35 X = OCO₂Bn



36 X = H
37 X = OCO₂Bn



34 X = H
35 X = OCO₂Bn



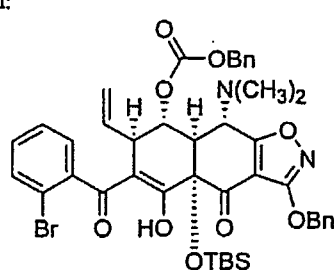
38 X = H
39 X = OCO₂Bn

hydrophilic region conserved

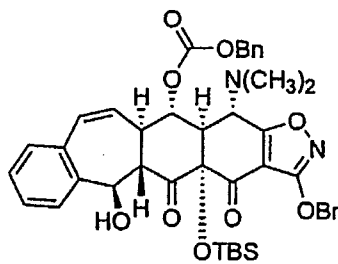
Scope:

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:

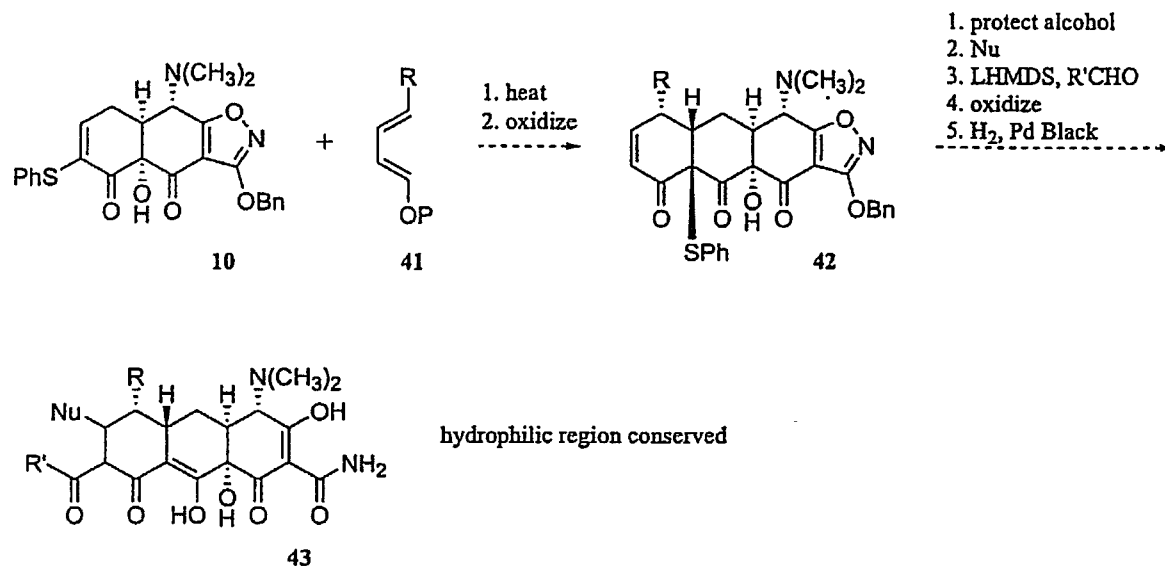


40



40b

Figure 7
Summary of Targeted "Tricyclines"



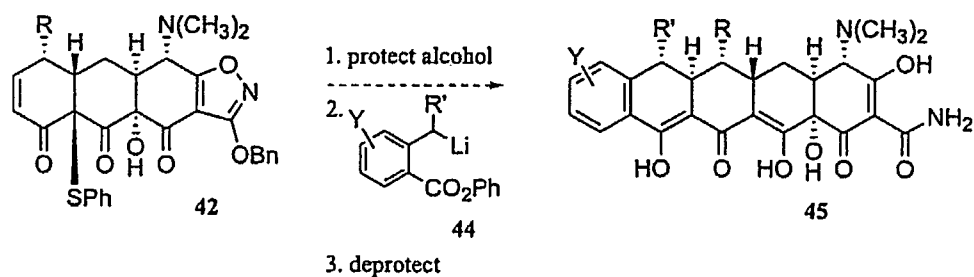
Scope:

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.

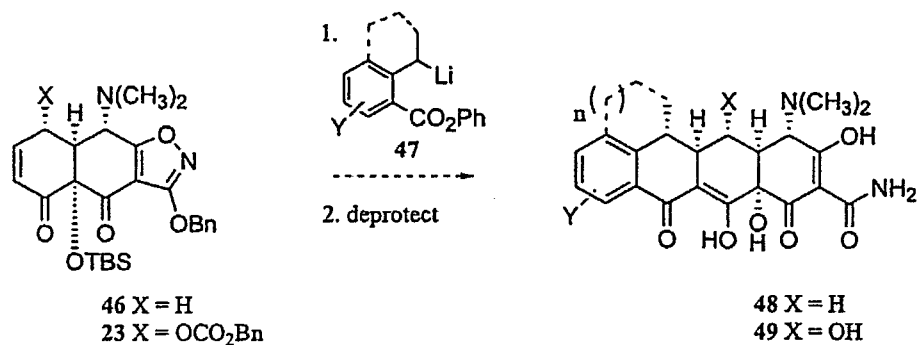
Figure 8
Summary of Targeted "Pentacyclines"



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

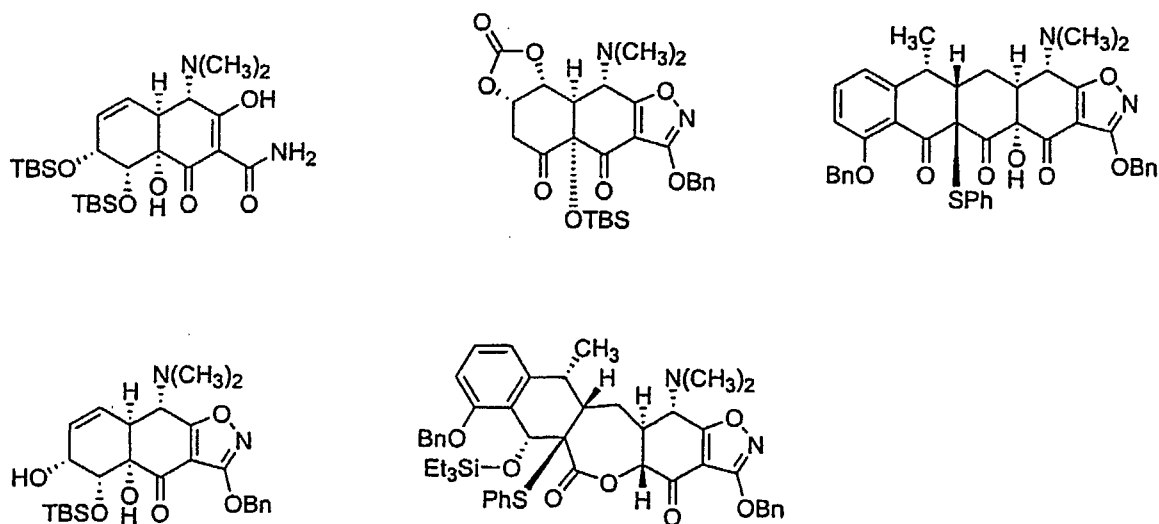


Figure 11
Total Synthesis of a Pyridone Sancycline Analog

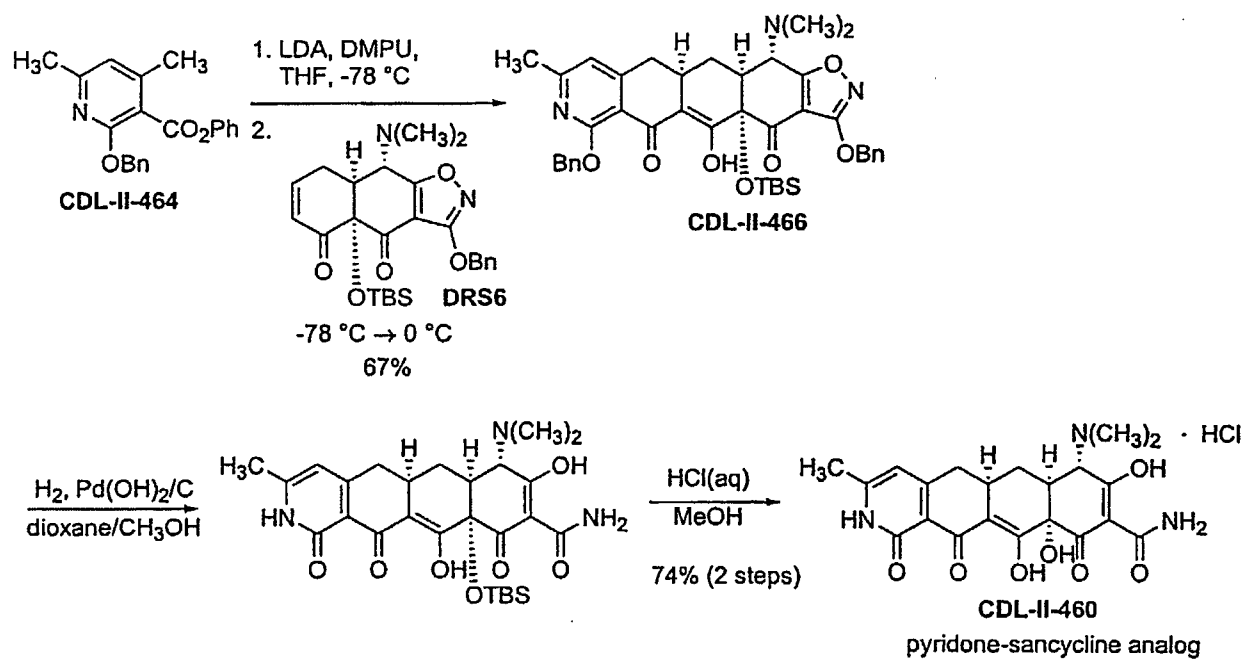
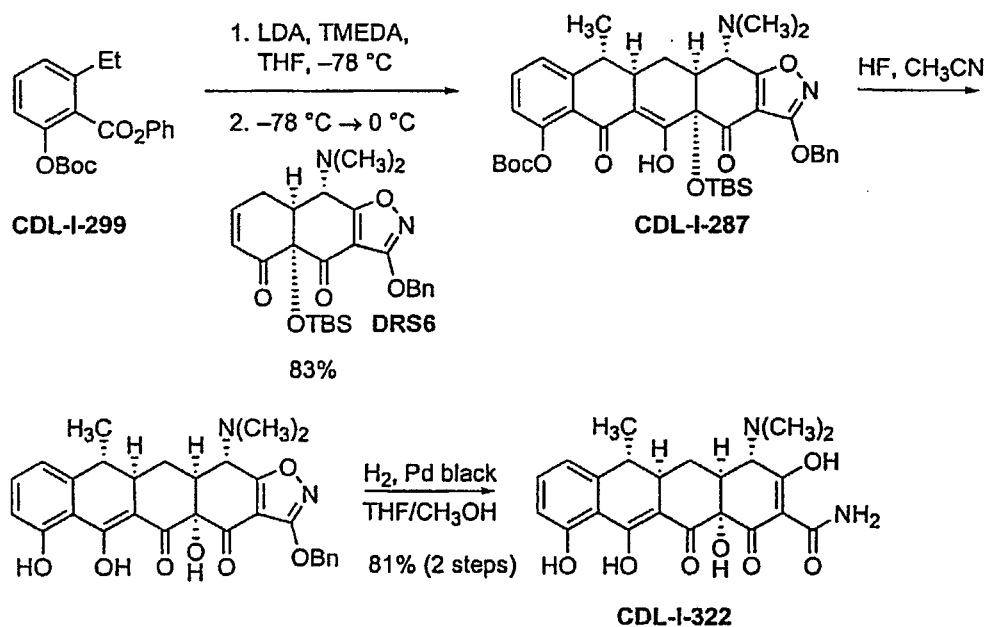


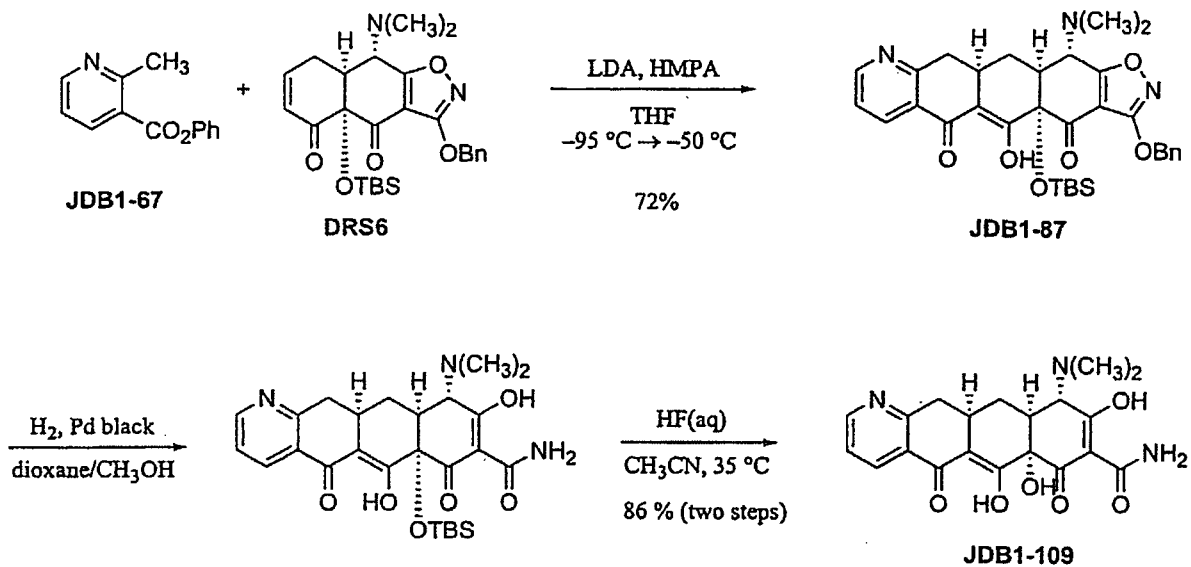
Figure 12
Total Synthesis of 6-Deoxytetracycline



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

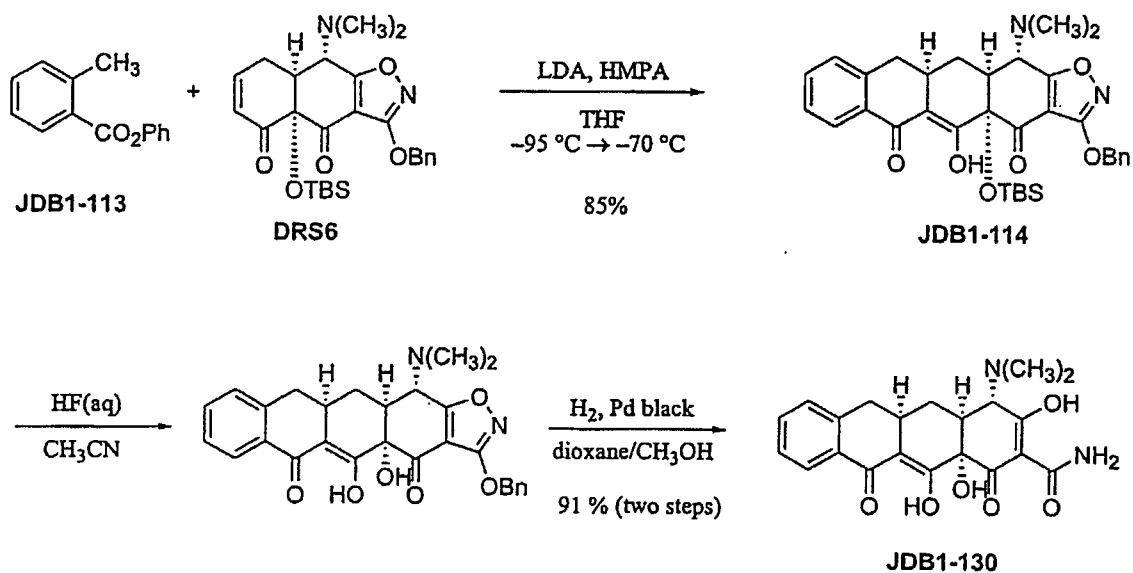
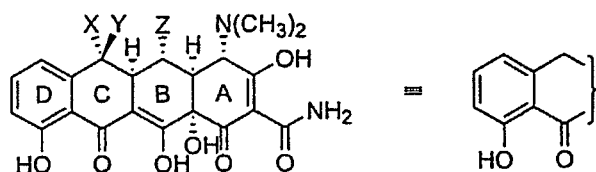


Figure 14A
Representative Structures



D-ring modifications

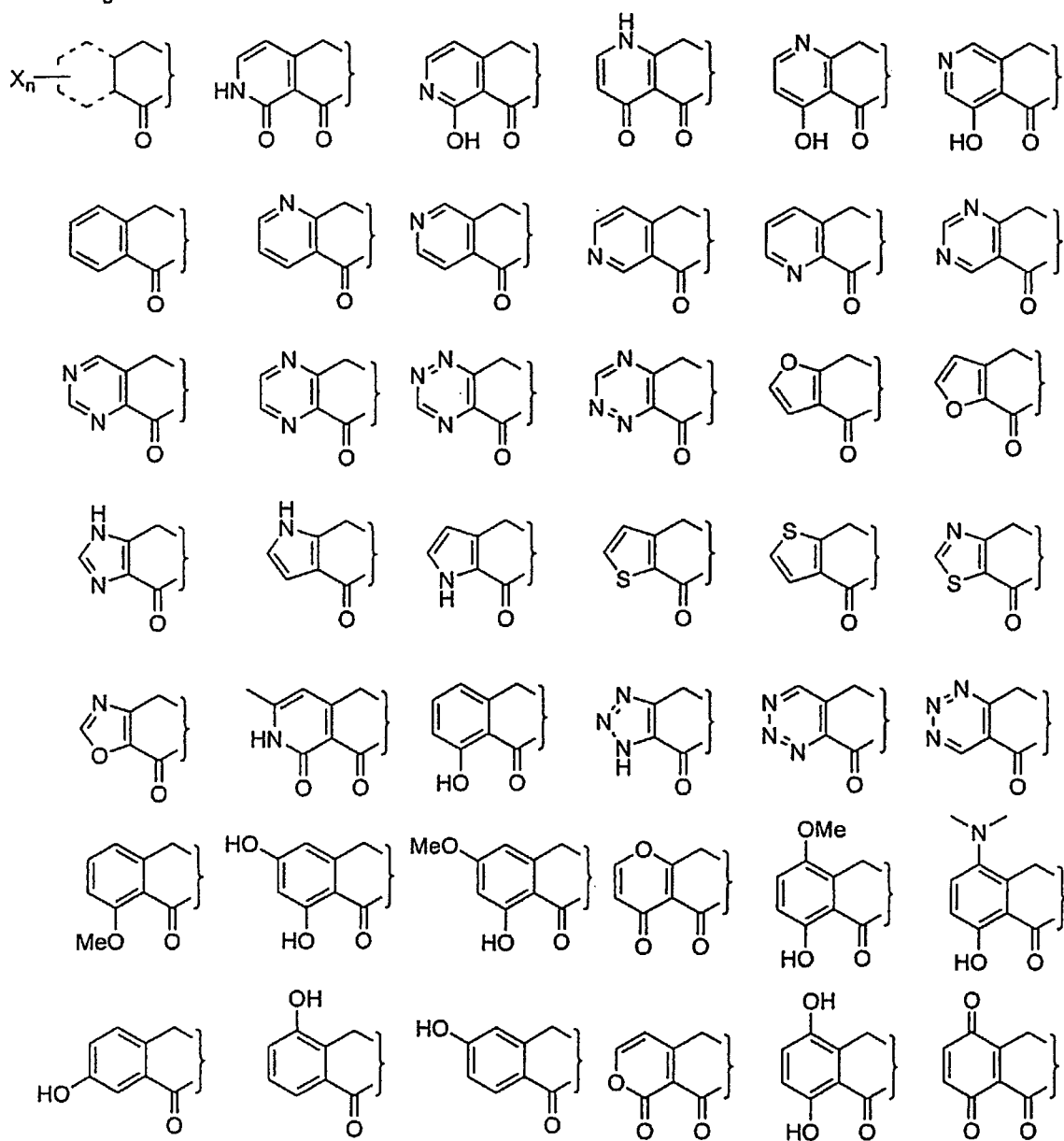
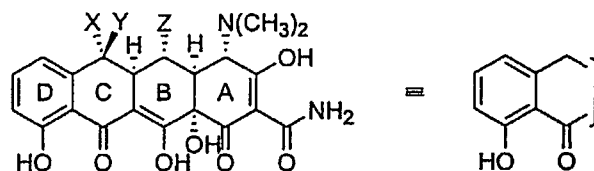


Figure 14B
Representative Structures



penta- and polycyclines:

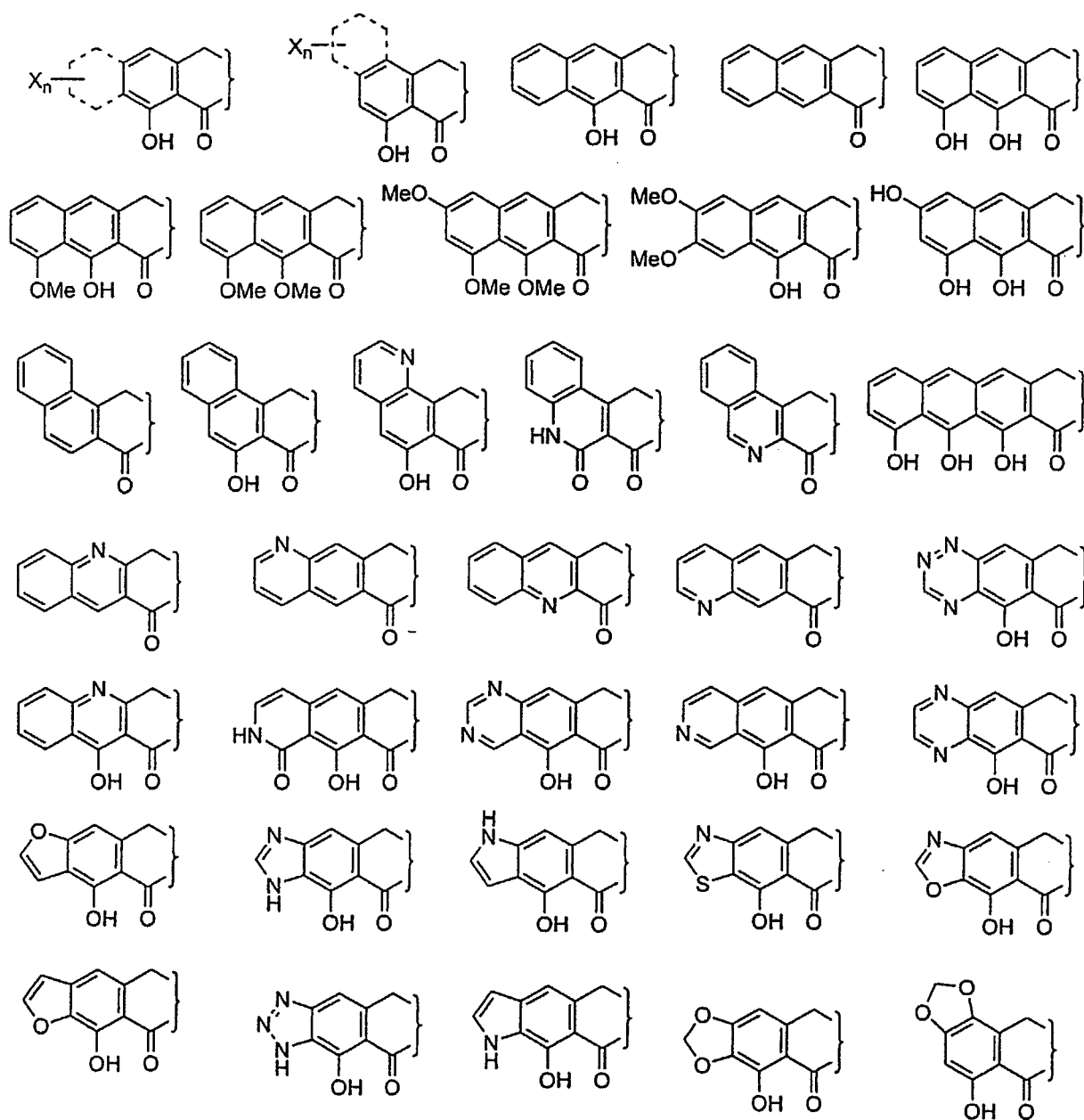


Figure 15

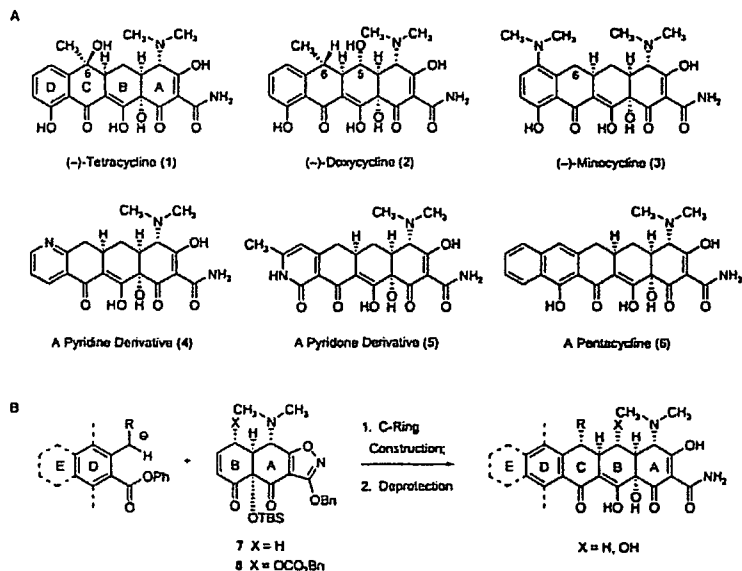


Figure 16

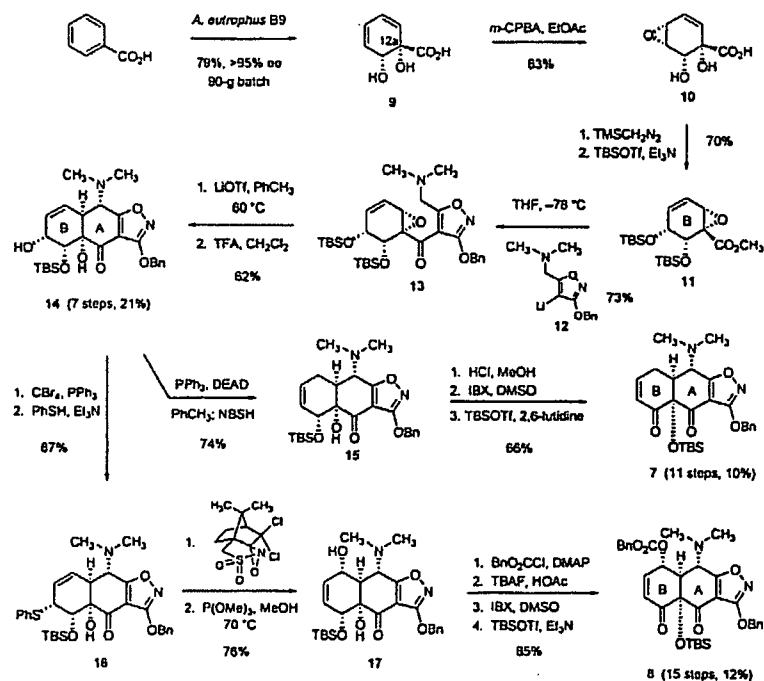


Figure 17

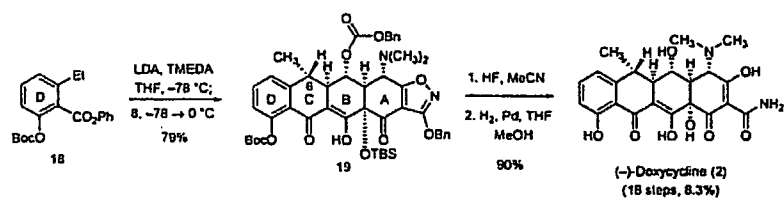


Figure 18

Bacterial Strains Tested				
Gram-Positive Organisms				
<i>S. aureus</i> ATCC 29213	<i>S. epidermidis</i> ACH-0016	<i>S. hemolyticus</i> ACH-0013	<i>E. faecalis</i> ATCC 70682	<i>B. subtilis</i> ATCC 7059
Gram-Negative Organisms				
<i>P. aeruginosa</i> ATCC 27853	<i>K. pneumoniae</i> ATCC 13833	<i>E. coli</i> ATCC 25922	<i>E. coli</i> ACH-0095	<i>E. coli</i> pBR122

Entry	D-Ring Precursor	Conditions	Tetracycline Analog	MIC (μg/mL)										
1		1. LDA, TMEDA; 7 -78 → 0 °C (81%) 2. HF, MeCN 3. H2, Pd (85%)		<table border="1"> <tr> <td>1</td><td>0.5</td><td>2</td><td>10</td><td>16</td> </tr> <tr> <td>>64</td><td>8</td><td>16</td><td>16</td><td>16</td> </tr> </table>	1	0.5	2	10	16	>64	8	16	16	16
1	0.5	2	10	16										
>64	8	16	16	16										
(-)-6-Deoxytetracycline (14 steps, 7.0%)														
2		1. LDA, DMPU; 7 -78 → 0 °C (67%) 2. H2, Pd(OH)2 3. HCl, MeOH (74%)		<table border="1"> <tr> <td>1</td><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><td>ND</td> </tr> </table>	1	ND	ND	ND	ND	>64	ND	>64	ND	ND
1	ND	ND	ND	ND										
>64	ND	>64	ND	ND										
A Pyridone Derivative (5) (14 steps, 5.0%)														
3		1. 7; HMPA -85 → -50 °C (76%) 2. H2, Pd 3. HF, MeCN (78%)		<table border="1"> <tr> <td>1</td><td>2</td><td>8</td><td>2</td><td>16</td> </tr> <tr> <td>>64</td><td>16</td><td>2</td><td>>64</td><td>64</td> </tr> </table>	1	2	8	2	16	>64	16	2	>64	64
1	2	8	2	16										
>64	16	2	>64	64										
7-Aza-10-Deoxysancycline (4) (14 steps, 6.1%)														
4		1. 7; n-BuLi -100 → -70 °C (81%) 2. HF, MeCN 3. H2, Pd (83%)		<table border="1"> <tr> <td>16</td><td>16</td><td>>64</td><td>8</td><td>16</td> </tr> <tr> <td>>64</td><td>ND</td><td>12</td><td>ND</td><td>ND</td> </tr> </table>	16	16	>64	8	16	>64	ND	12	ND	ND
16	16	>64	8	16										
>64	ND	12	ND	ND										
10-Deoxysancycline (14 steps, 6.8%)														
5		1. 7; n-BuLi -100 → 0 °C (75%) 2. HF, MeCN 3. H2, Pd 4. BBr3, CH2Cl2 -78 → 23 °C (74%)		<table border="1"> <tr> <td>1</td><td>0.5</td><td>1</td><td>1</td><td>16</td> </tr> <tr> <td>>64</td><td>>64</td><td>>64</td><td>>64</td><td>>64</td> </tr> </table>	1	0.5	1	1	16	>64	>64	>64	>64	>64
1	0.5	1	1	16										
>64	>64	>64	>64	>64										
A Pentacycline (6) (15 steps, 5.6%)														
Testing Control:				<table border="1"> <tr> <td>1</td><td>1</td><td>2</td><td>1</td><td>16</td> </tr> <tr> <td>12</td><td>32</td><td>1</td><td>>64</td><td>>64</td> </tr> </table>	1	1	2	1	16	12	32	1	>64	>64
1	1	2	1	16										
12	32	1	>64	>64										
(-)-Tetracycline (1)														

A Crystalline Michael Adduct

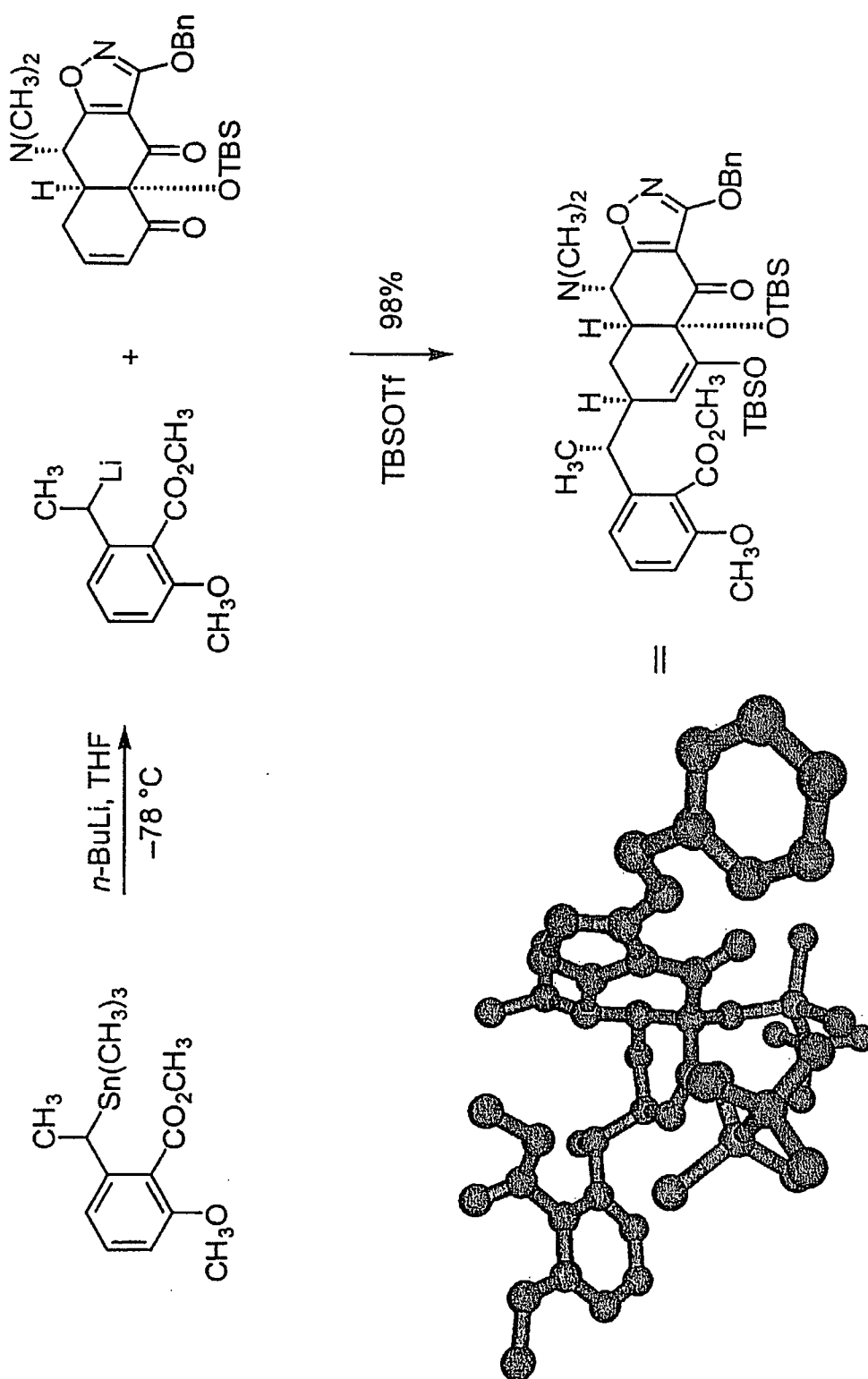


Figure 19

Synthesis of a Pentacycline

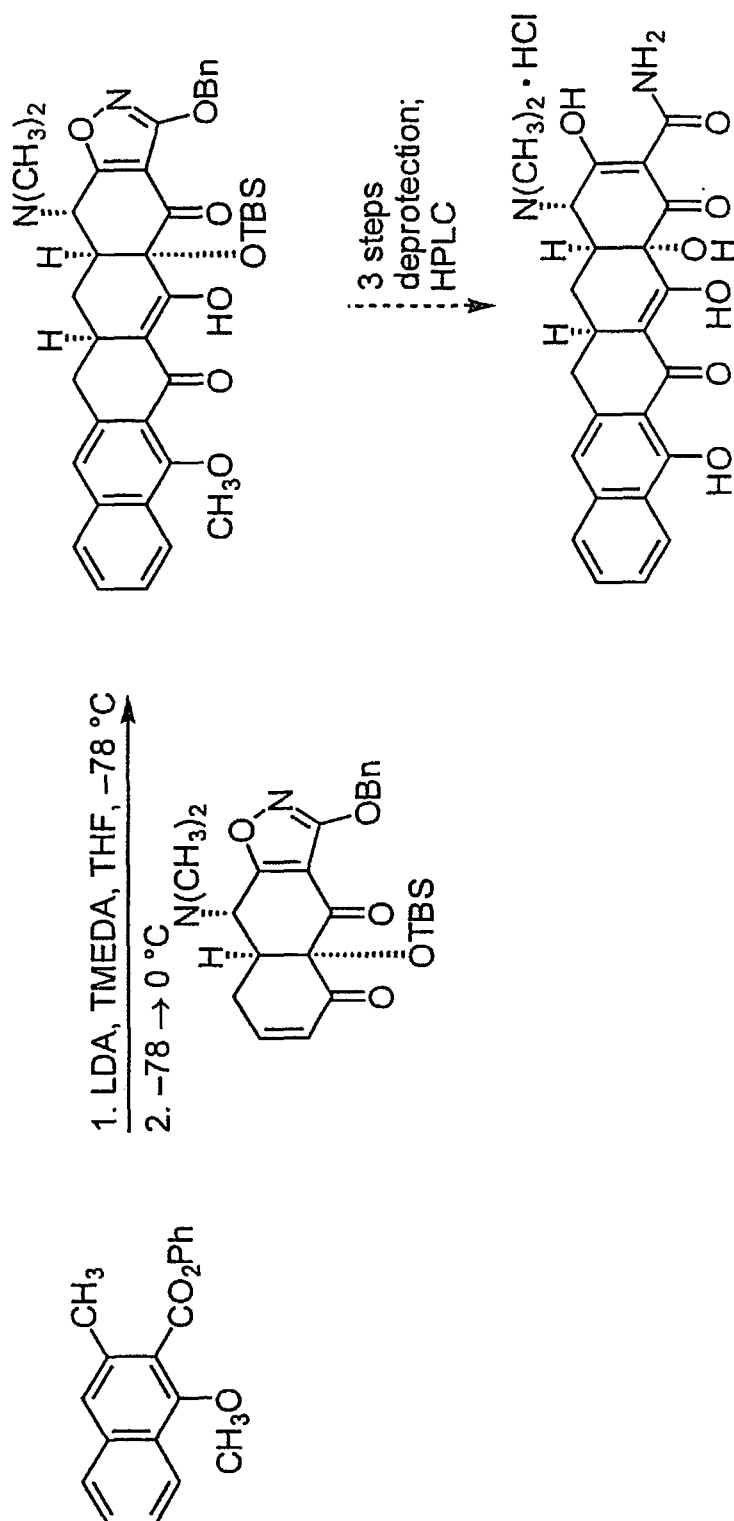
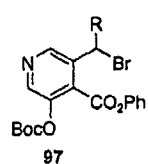
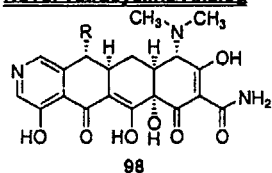
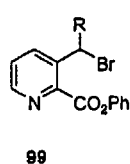
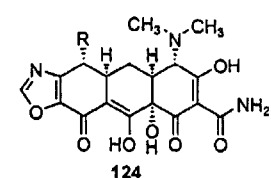
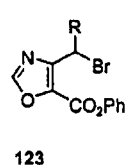
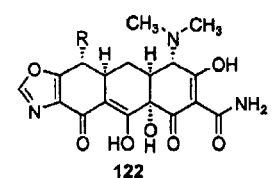
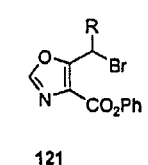
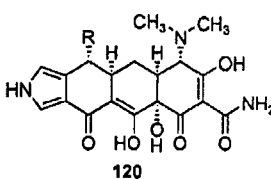
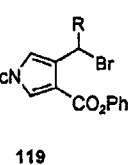
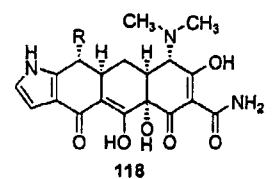
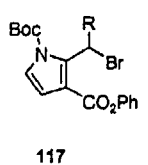
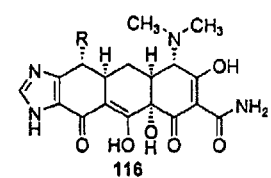
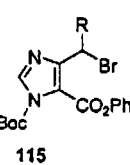
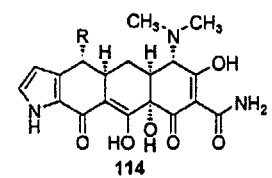
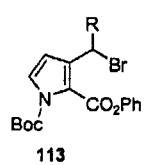
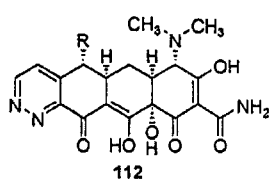
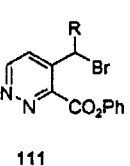
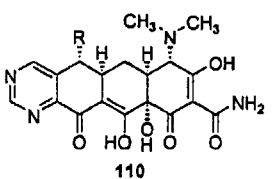
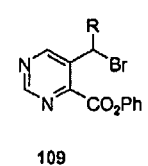
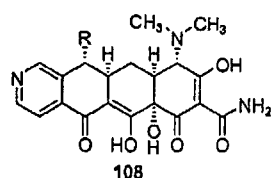
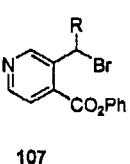
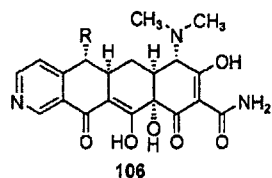
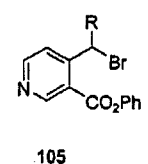
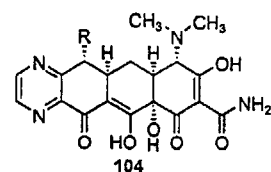
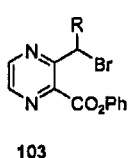
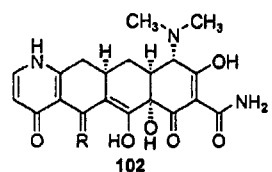
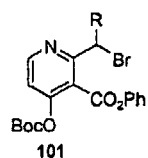
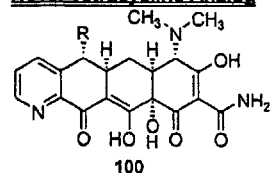
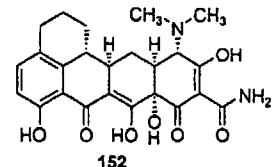
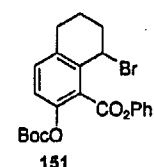
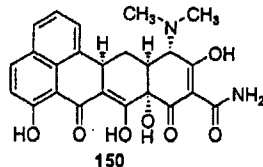
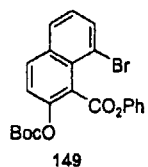
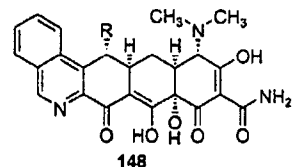
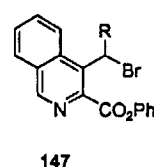
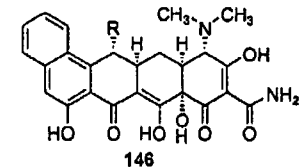
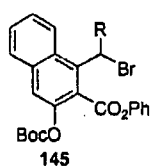
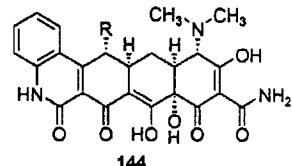
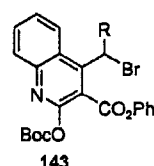
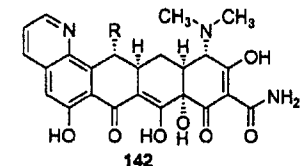
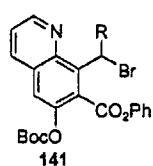
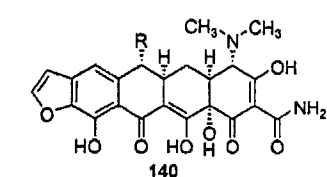
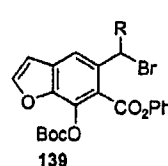
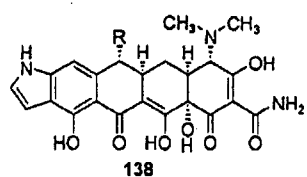
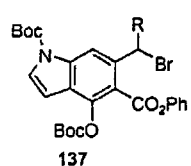
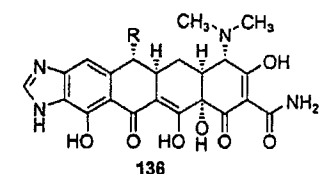
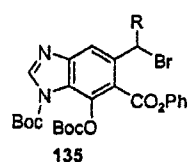
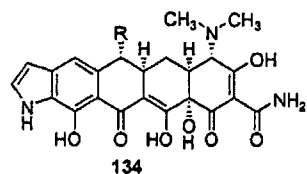
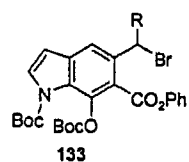
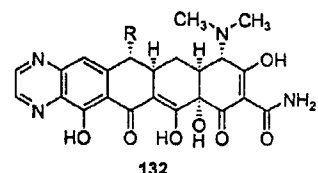
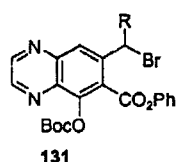
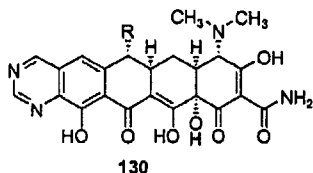
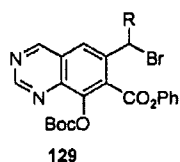
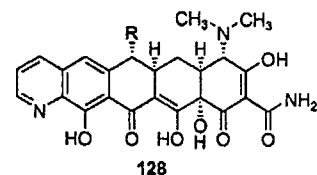
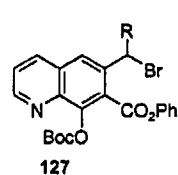
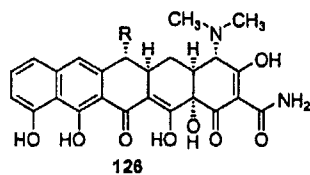
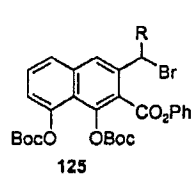


Figure 20

D-Ring PrecursorNovel Tetracycline AnalogD-Ring PrecursorNovel 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

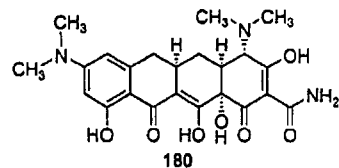
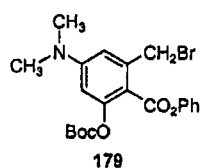
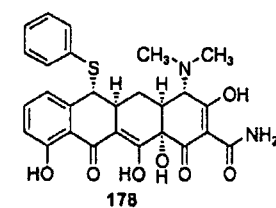
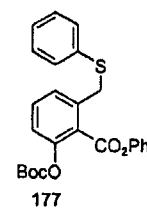
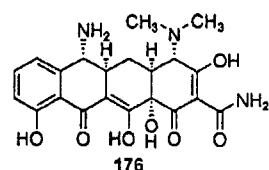
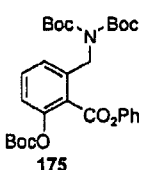
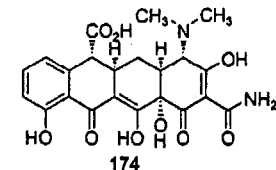
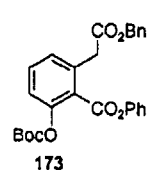
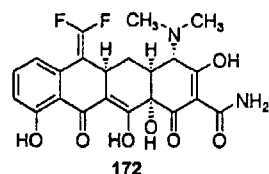
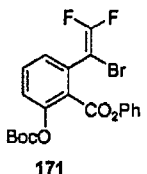
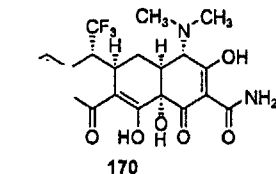
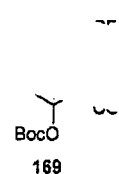
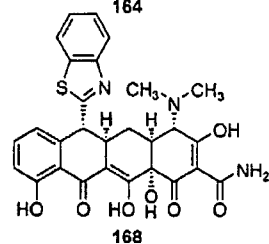
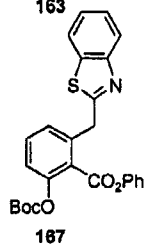
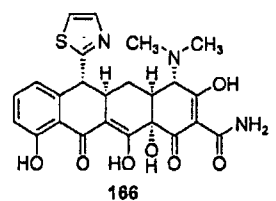
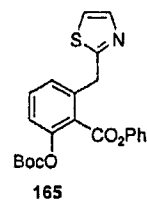
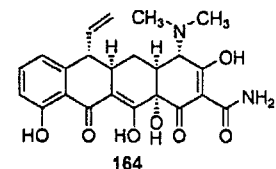
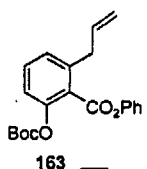
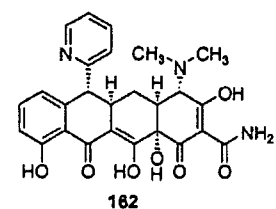
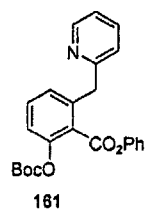
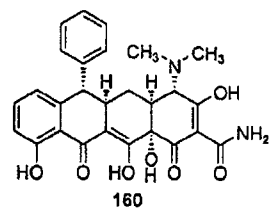
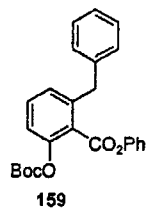
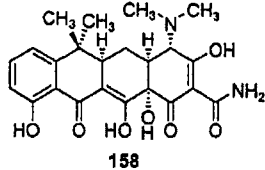
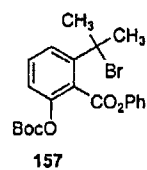
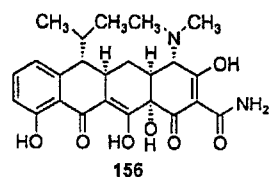
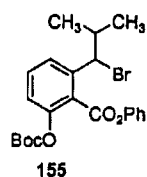
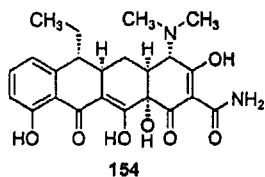
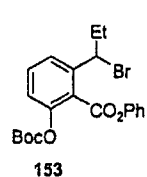
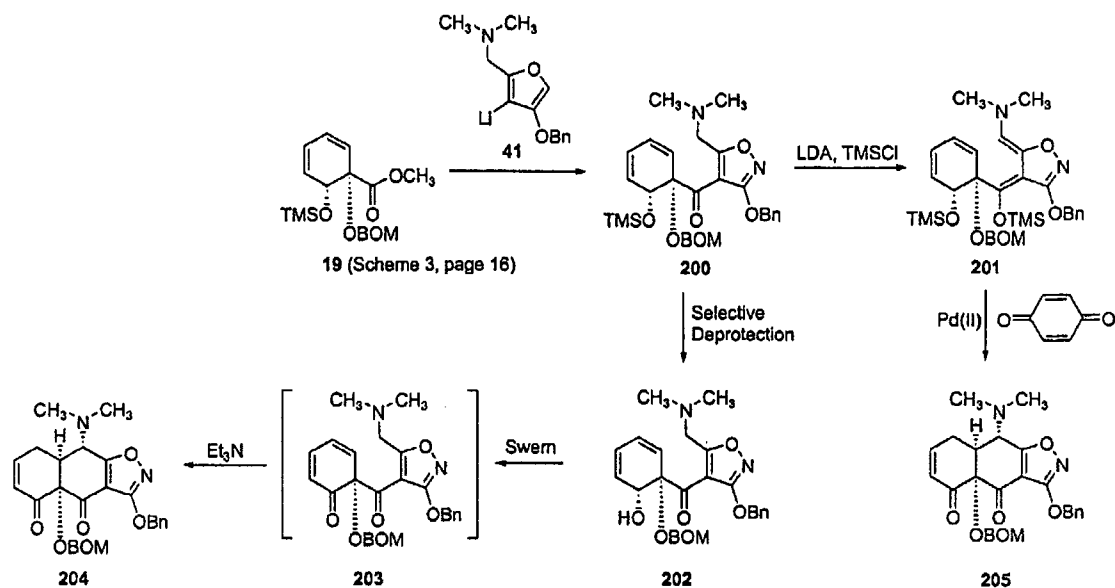
D-Ring PrecursorNovel Tetracycline AnalogD-Ring PrecursorNovel Tetracycline Analog

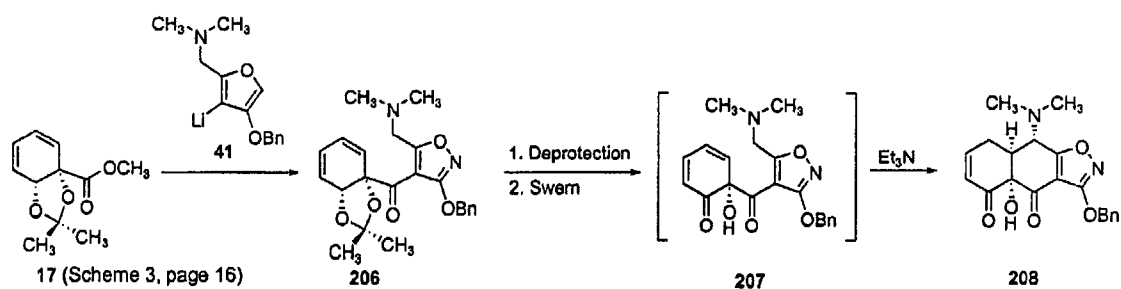
Figure 21C

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

A.



B.



C.

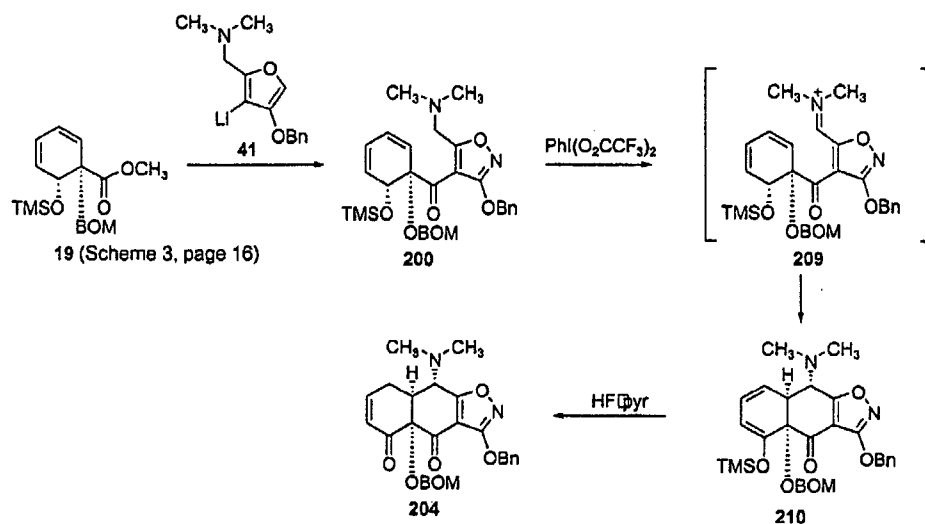
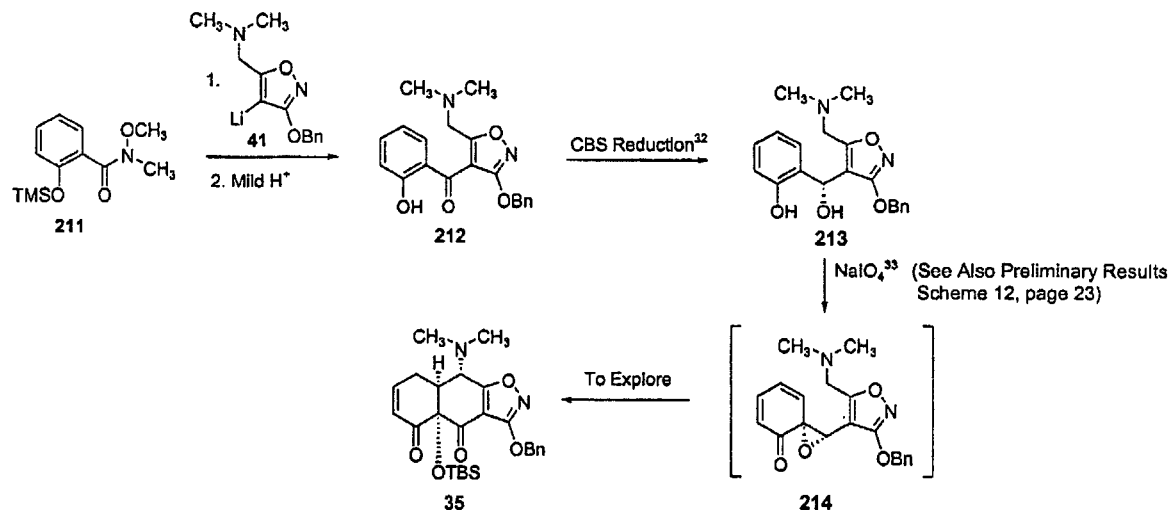


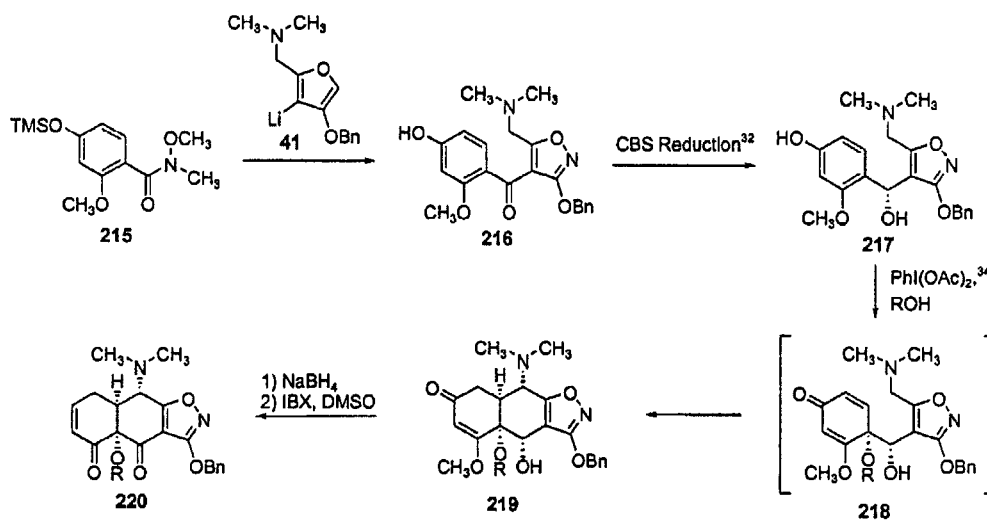
Figure 22

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

A.



B.



C.

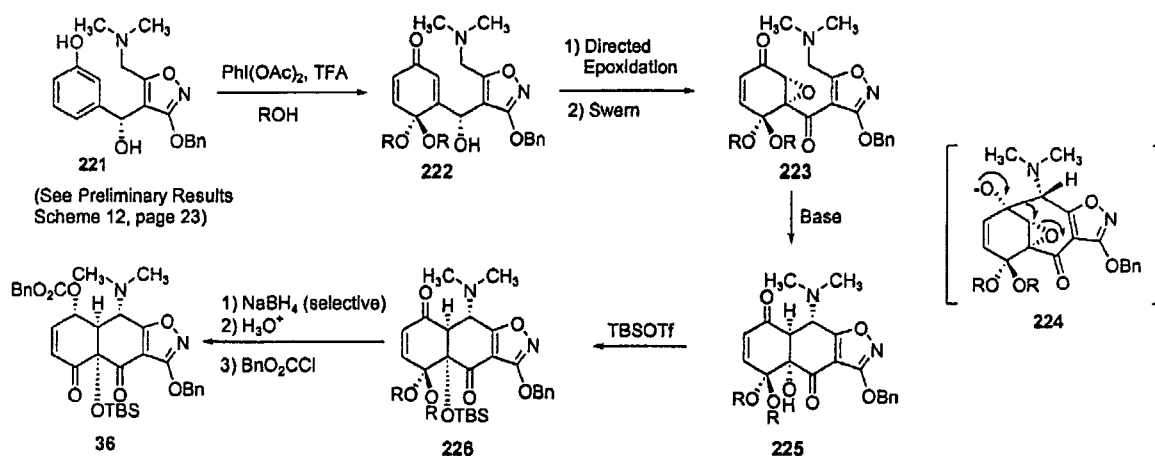


Figure 23