

Figure 1

Modular Total Synthesis of Tetracyclines

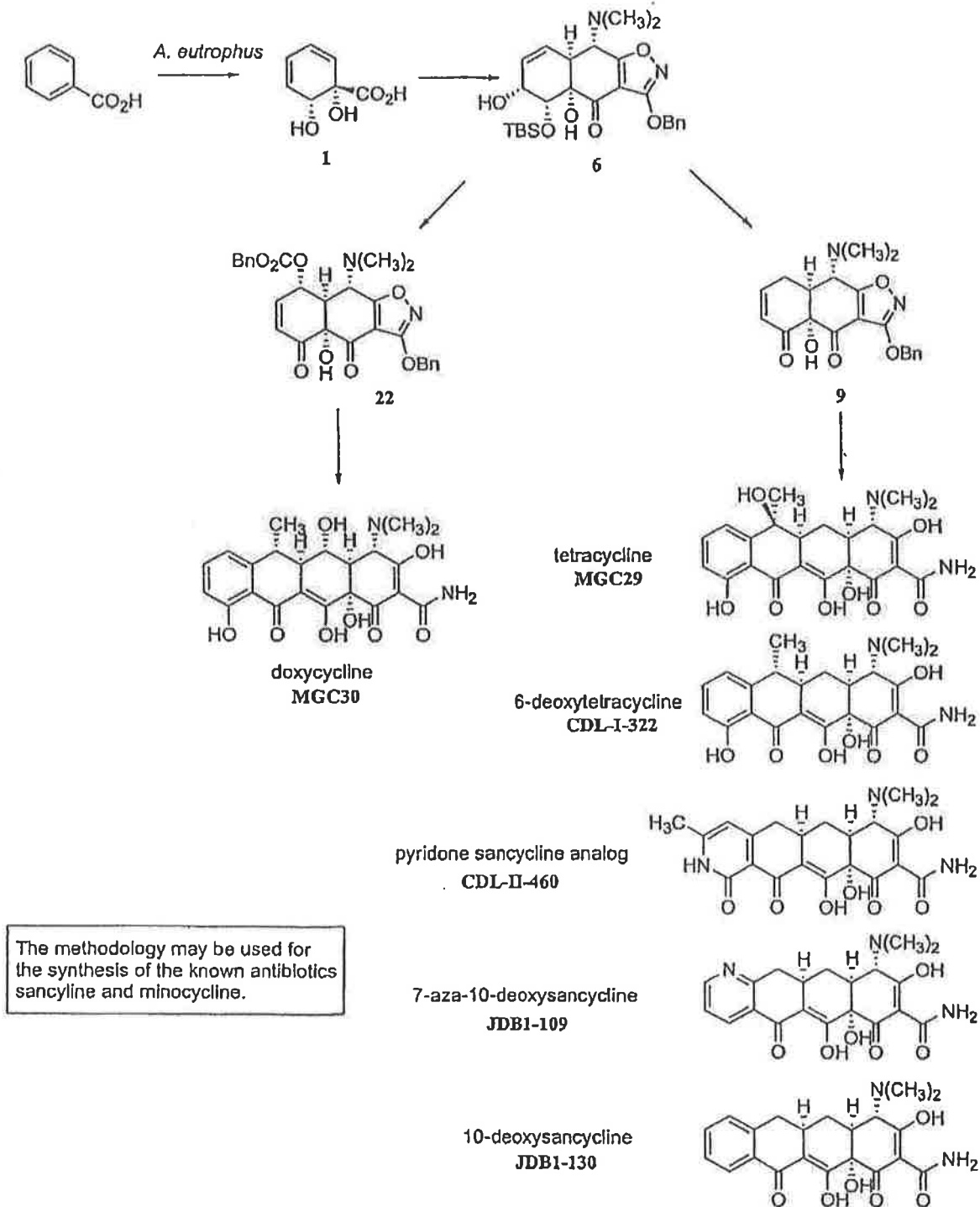


Figure 2
Total Synthesis of Tetracycline

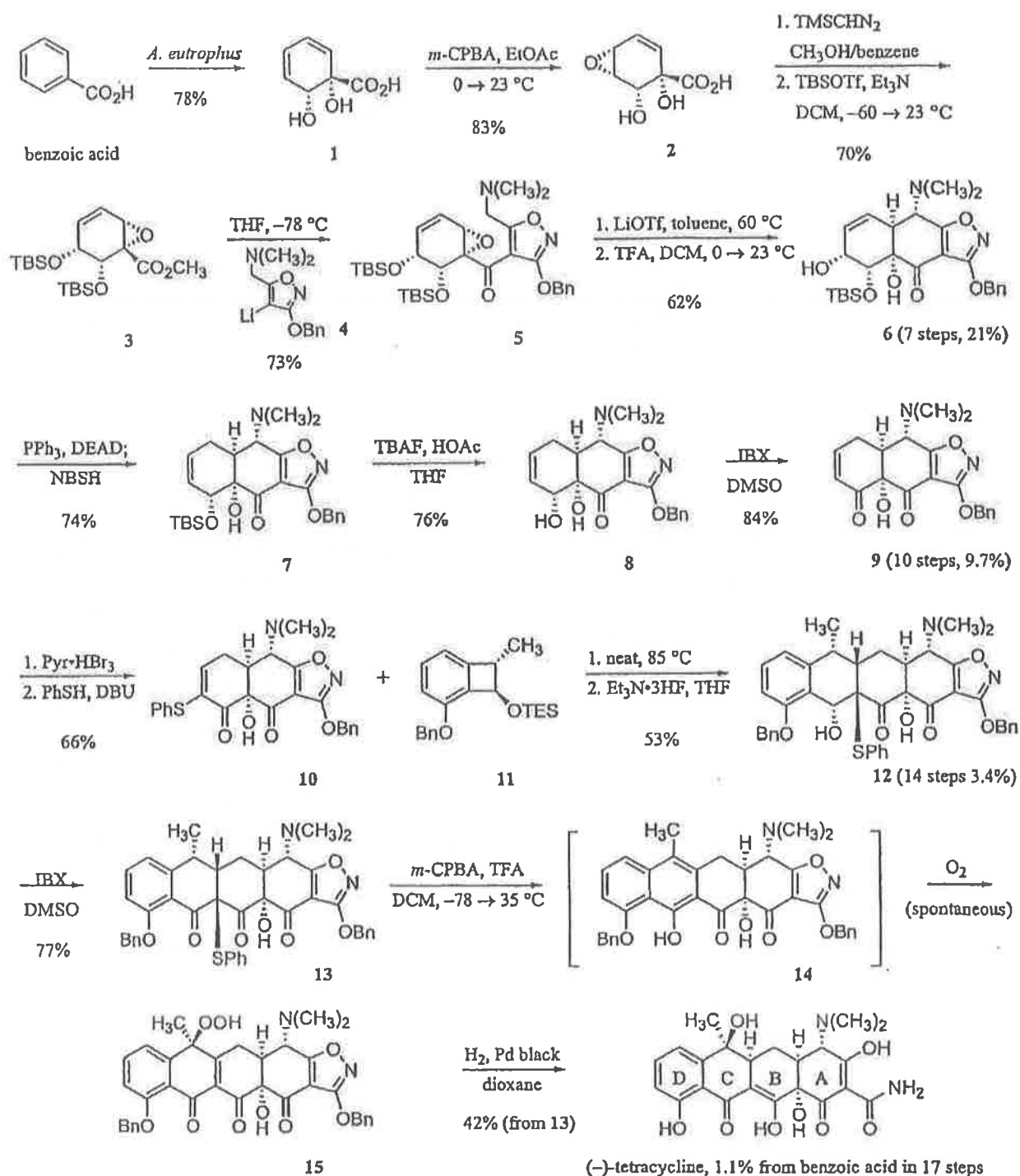
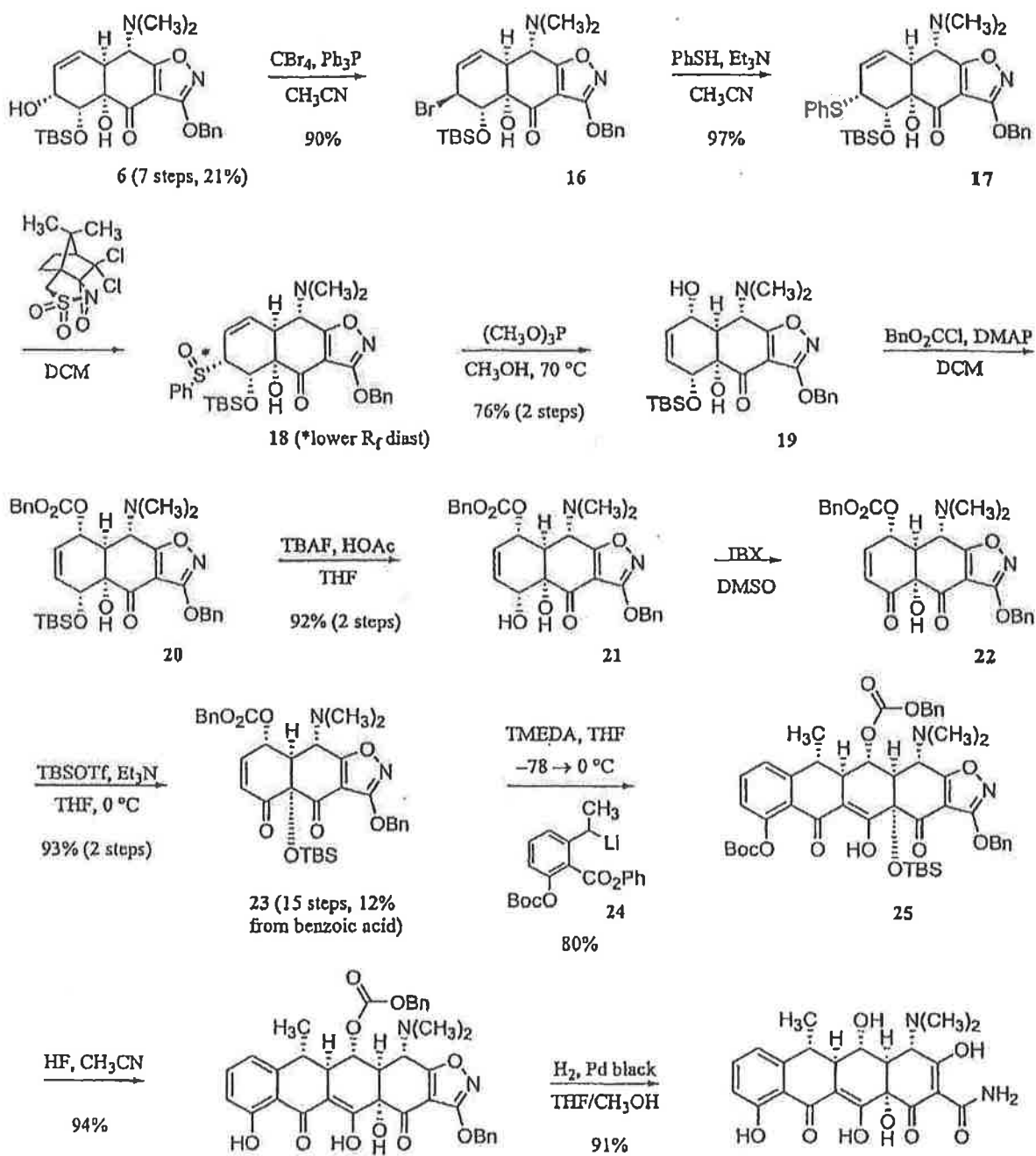


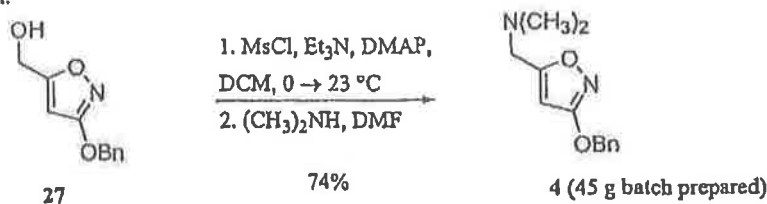
Figure 3
Total Synthesis of Doxycycline



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

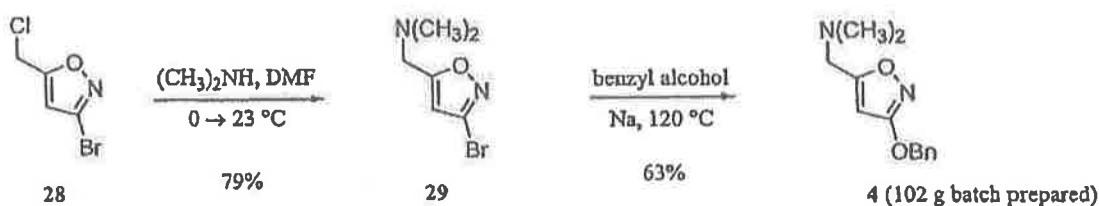
Figure 4
Synthesis of Isoxazole 4

First Generation:



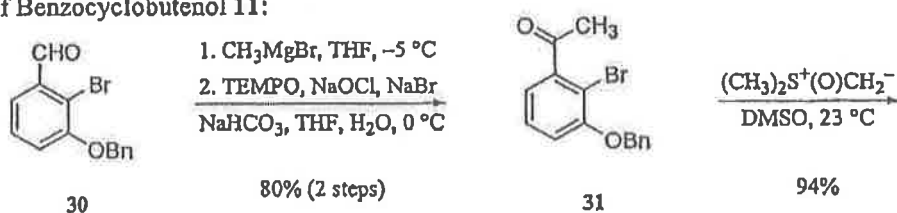
27: prepared in 3 steps from dimethylacetylene dicarboxylate and *N*-hydroxyurea
Synthesis 1985, 1100-1104.
Eur. J. Org. Chem. 1998, 473-479.

Second Generation:

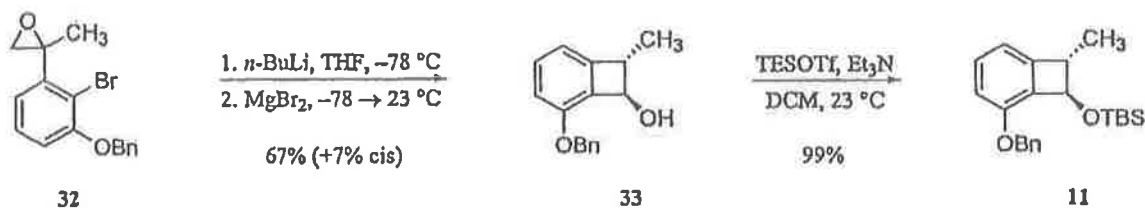


28: prepared in 2 steps from glyoxylic acid and 2,3-dichloro-1-propene
Synth. Commun. 1992, 22, 1939-1948.
Tetrahedron Lett. 1984, 25, 487-490.

Figure 5
Synthesis of Benzocyclobutenol 11:



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

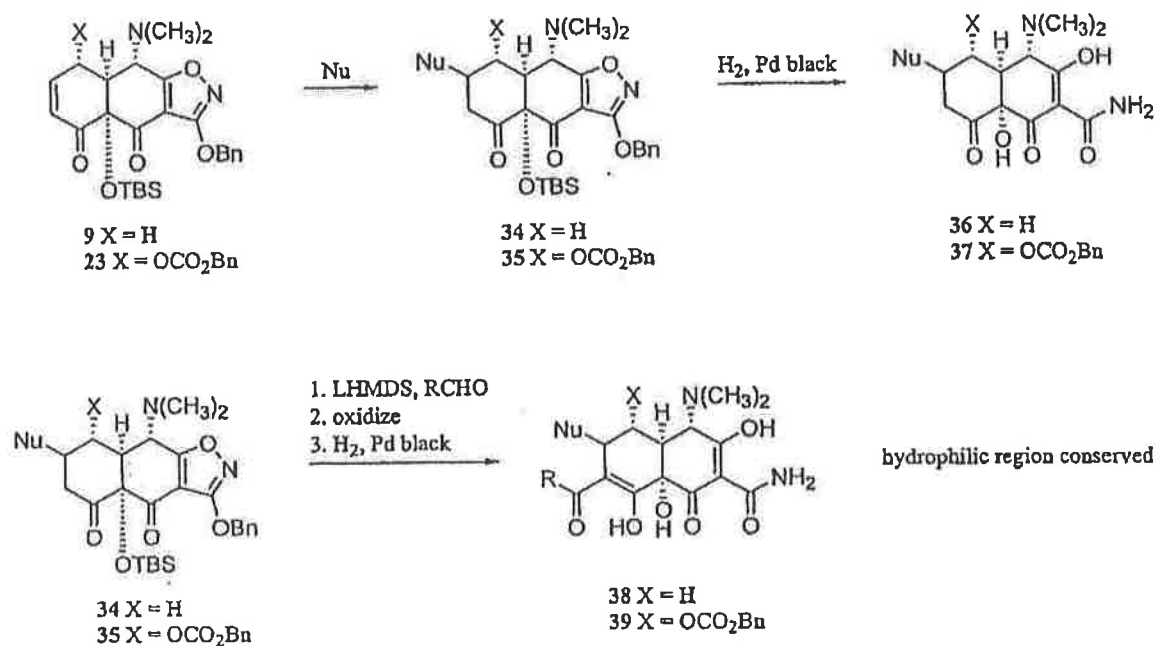


cyclization from 32 to 33 based on: (a) Akgün, E.; Glinski, M. B.; Dhawan, K. L.; Durst, T. *J. Org. Chem.* 1981, 46, 2730.
(b) Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* 1980, 45, 922.

Paradigm for Antibiotic Activity of the Tetracyclines

CN(C)C1=C(O)C(=O)C2=C1C(=O)C3=C2C(=O)C4=C3C(=O)C5=C4C(=O)C6=C5C(=O)C7=C6C(=O)C8=C7C(=O)C9=C8C(=O)C10=C9C(=O)C11=C10C(=O)C12=C11C(=O)C13=C12C(=O)C14=C13C(=O)C15=C14C(=O)C16=C15C(=O)C17=C16C(=O)C18=C17C(=O)C19=C18C(=O)C20=C19C(=O)C21=C20C(=O)C22=C21C(=O)C23=C22C(=O)C24=C23C(=O)C25=C24C(=O)C26=C25C(=O)C27=C26C(=O)C28=C27C(=O)C29=C28C(=O)C30=C29C(=O)C31=C30C(=O)C32=C31C(=O)C33=C32C(=O)C34=C33C(=O)C35=C34C(=O)C36=C35C(=O)C37=C36C(=O)C38=C37C(=O)C39=C38C(=O)C40=C39C(=O)C41=C40C(=O)C42=C41C(=O)C43=C42C(=O)C44=C43C(=O)C45=C44C(=O)C46=C45C(=O)C47=C46C(=O)C48=C47C(=O)C49=C48C(=O)C50=C49C(=O)C51=C50C(=O)C52=C51C(=O)C53=C52C(=O)C54=C53C(=O)C55=C54C(=O)C56=C55C(=O)C57=C56C(=O)C58=C57C(=O)C59=C58C(=O)C60=C59C(=O)C61=C60C(=O)C62=C61C(=O)C63=C62C(=O)C64=C63C(=O)C65=C64C(=O)C66=C65C(=O)C67=C66C(=O)C68=C67C(=O)C69=C68C(=O)C70=C69C(=O)C71=C70C(=O)C72=C71C(=O)C73=C72C(=O)C74=C73C(=O)C75=C74C(=O)C76=C75C(=O)C77=C76C(=O)C78=C77C(=O)C79=C78C(=O)C80=C79C(=O)C81=C80C(=O)C82=C81C(=O)C83=C82C(=O)C84=C83C(=O)C85=C84C(=O)C86=C85C(=O)C87=C86C(=O)C88=C87C(=O)C89=C88C(=O)C90=C89C(=O)C91=C90C(=O)C92=C91C(=O)C93=C92C(=O)C94=C93C(=O)C95=C94C(=O)C96=C95C(=O)C97=C96C(=O)C98=C97C(=O)C99=C98C(=O)C100=C99C(=O)C101=C100C(=O)C102=C101C(=O)C103=C102C(=O)C104=C103C(=O)C105=C104C(=O)C106=C105C(=O)C107=C106C(=O)C108=C107C(=O)C109=C108C(=O)C110=C109C(=O)C111=C110C(=O)C112=C111C(=O)C113=C112C(=O)C114=C113C(=O)C115=C114C(=O)C116=C115C(=O)C117=C116C(=O)C118=C117C(=O)C119=C118C(=O)C120=C119C(=O)C121=C120C(=O)C122=C121C(=O)C123=C122C(=O)C124=C123C(=O)C125=C124C(=O)C126=C125C(=O)C127=C126C(=O)C128=C127C(=O)C129=C128C(=O)C130=C129C(=O)C131=C130C(=O)C132=C131C(=O)C133=C132C(=O)C134=C133C(=O)C135=C134C(=O)C136=C135C(=O)C137=C136C(=O)C138=C137C(=O)C139=C138C(=O)C140=C139C(=O)C141=C140C(=O)C142=C141C(=O)C143=C142C(=O)C144=C143C(=O)C145=C144C(=O)C146=C145C(=O)C147=C146C(=O)C148=C147C(=O)C149=C148C(=O)C150=C149C(=O)C151=C150C(=O)C152=C151C(=O)C153=C152C(=O)C154=C153C(=O)C155=C154C(=O)C156=C155C(=O)C157=C156C(=O)C158=C157C(=O)C159=C158C(=O)C160=C159C(=O)C161=C160C(=O)C162=C161C(=O)C163=C162C(=O)C164=C163C(=O)C165=C164C(=O)C166=C165C(=O)C167=C166C(=O)C168=C167C(=O)C169=C168C(=O)C170=C169C(=O)C171=C170C(=O)C172=C171C(=O)C173=C172C(=O)C174=C173C(=O)C175=C174C(=O)C176=C175C(=O)C177=C176C(=O)C178=C177C(=O)C179=C178C(=O)C180=C179C(=O)C181=C180C(=O)C182=C181C(=O)C183=C182C(=O)C184=C183C(=O)C185=C184C(=O)C186=C185C(=O)C187=C186C(=O)C188=C187C(=O)C189=C188C(=O)C190=C189C(=O)C191=C190C(=O)C192=C191C(=O)C193=C192C(=O)C194=C193C(=O)C195=C194C(=O)C196=C195C(=O)C197=C196C(=O)C198=C197C(=O)C199=C198C(=O)C200=C199C(=O)C201=C200C(=O)C202=C201C(=O)C203=C202C(=O)C204=C203C(=O)C205=C204C(=O)C206=C205C(=O)C207=C206C(=O)C208=C207C(=O)C209=C208C(=O)C210=C209C(=O)C211=C210C(=O)C212=C211C(=O)C213=C212C(=O)C214=C213C(=O)C215=C214C(=O)C216=C215C(=O)C217=C216C(=O)C218=C217C(=O)C219=C218C(=O)C220=C219C(=O)C221=C220C(=O)C222=C221C(=O)C223=C222C(=O)C224=C223C(=O)C225=C224C(=O)C226=C225C(=O)C227=C226C(=O)C228=C227C(=O)C229=C228C(=O)C230=C229C(=O)C231=C230C(=O)C232=C231C(=O)C233=C232C(=O)C234=C233C(=O)C235=C234C(=O)C236=C235C(=O)C237=C236C(=O)C238=C237C(=O)C239=C238C(=O)C240=C239C(=O)C241=C240C(=O)C242=C241C(=O)C243=C242C(=O)C244=C243C(=O)C245=C244C(=O)C246=C245C(=O)C247=C246C(=O)C248=C247C(=O)C249=C248C(=O)C250=C249C(=O)C251=C250C(=O)C252=C251C(=O)C253=C252C(=O)C254=C253C(=O)C255=C254C(=O)C256=C255C(=O)C257=C256C(=O)C258=C257C(=O)C259=C258C(=O)C260=C259C(=O)C261=C260C(=O)C262=C261C(=O)C263=C262C(=O)C264=C263C(=O)C265=C264C(=O)C266=C265C(=O)C267=C266C(=O)C268=C267C(=O)C269=C268C(=O)C270=C269C(=O)C271=C270C(=O)C272=C271C(=O)C273=C272C(=O)C274=C273C(=O)C275=C274C(=O)C276=C275C(=O)C277=C276C(=O)C278=C277C(=O)C279=C278C(=O)C280=C279C(=O)C281=C280C(=O)C282=C281C(=O)C283=C282C(=O)C284=C283C(=O)C285=C284C(=O)C286=C285C(=O)C287=C286C(=O)C288=C287C(=O)C289=C288C(=O)C290=C289C(=O)C291=C290C(=O)C292=C291C(=O)C293=C292C(=O)C294=C293C(=O)C295=C294C(=O)C296=C295C(=O)C297=C296C(=O)C298=C297C(=O)C299=C298C(=O)C300=C299C(=O)C301=C300C(=O)C302=C301C(=O)C303=C302C(=O)C304=C303C(=O)C305=C304C(=O)C306=C305C(=O)C307=C306C(=O)C308=C307C(=O)C309=C308C(=O)C310=C309C(=O)C311=C310C(=O)C312=C311C(=O)C313=C312C(=O)C314=C313C(=O)C315=C314C(=O)C316=C315C(=O)C317=C316C(=O)C318=C317C(=O)C319=C318C(=O)C320=C319C(=O)C321=C320C(=O)C322=C321C(=O)C323=C322C(=O)C324=C323C(=O)C325=C324C(=O)C326=C325C(=O)C327=C326C(=O)C328=C327C(=O)C329=C328C(=O)C330=C329C(=O)C331=C330C(=O)C332

Summary of Targeted "Dicyclines"



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:

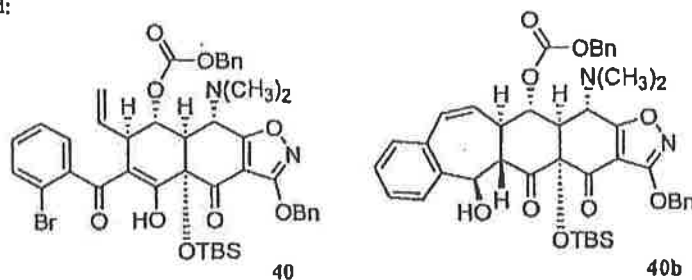
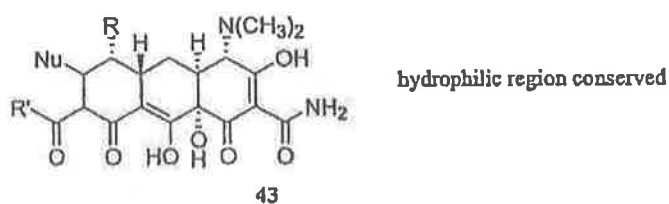
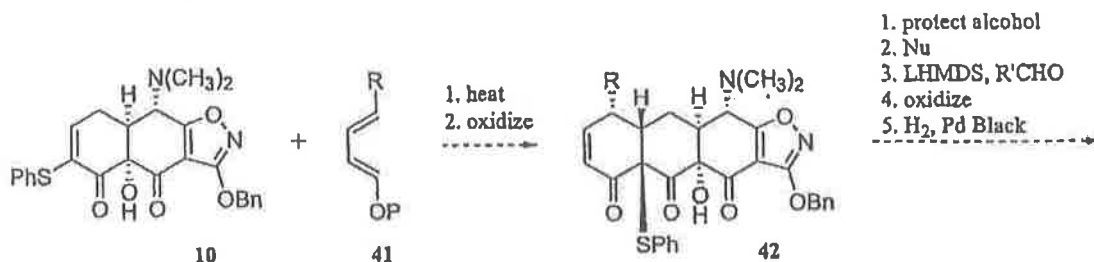


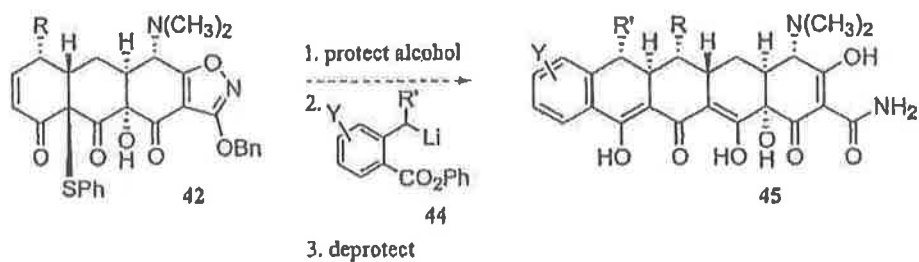
Figure 7
Summary of Targeted "Tricyclines"



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.

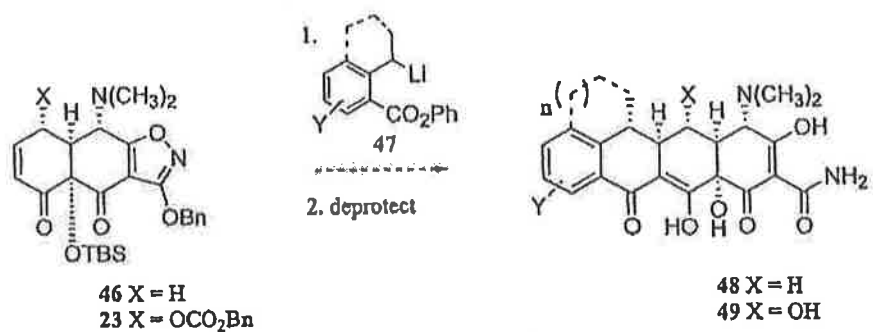
Figure 8
Summary of Targeted "Pentacyclines"



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

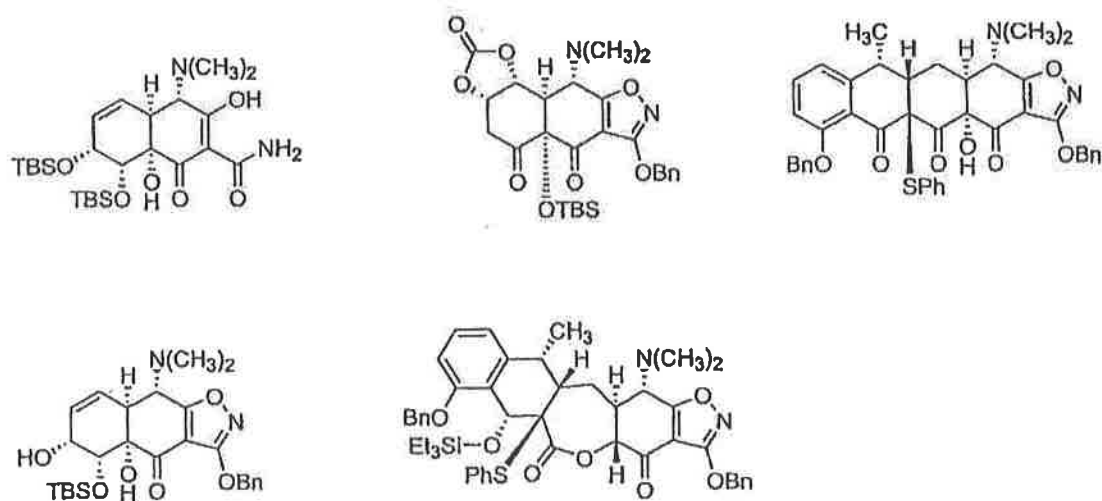


Figure 11
Total Synthesis of a Pyridone Sancycline Analog

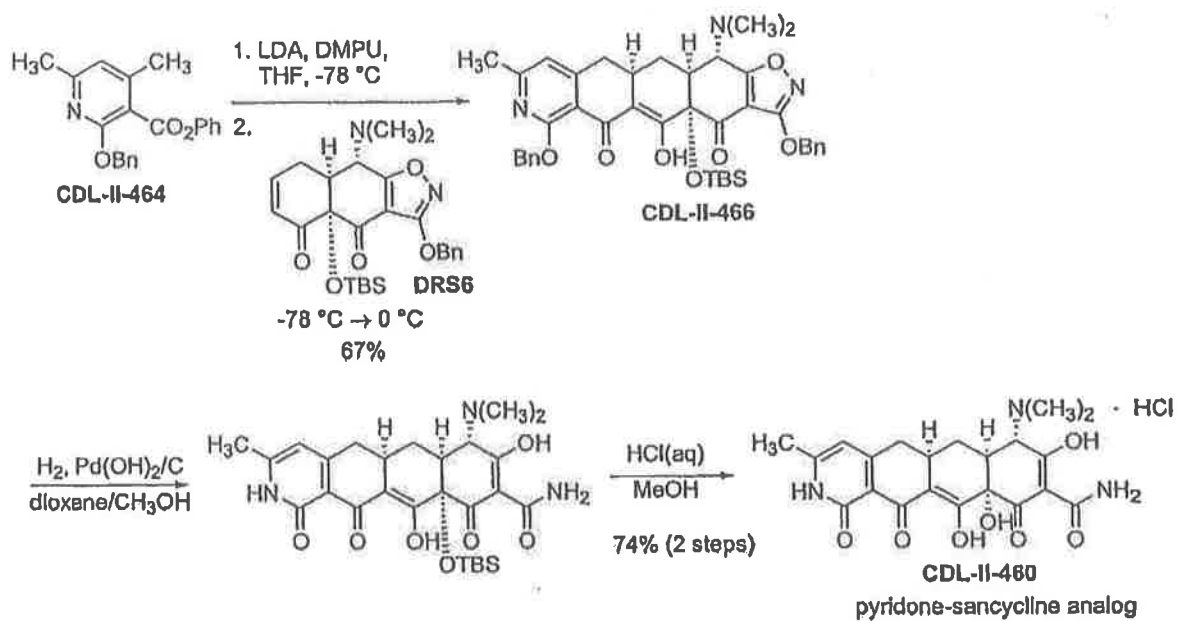


Figure 12
Total Synthesis of 6-Deoxytetracycline

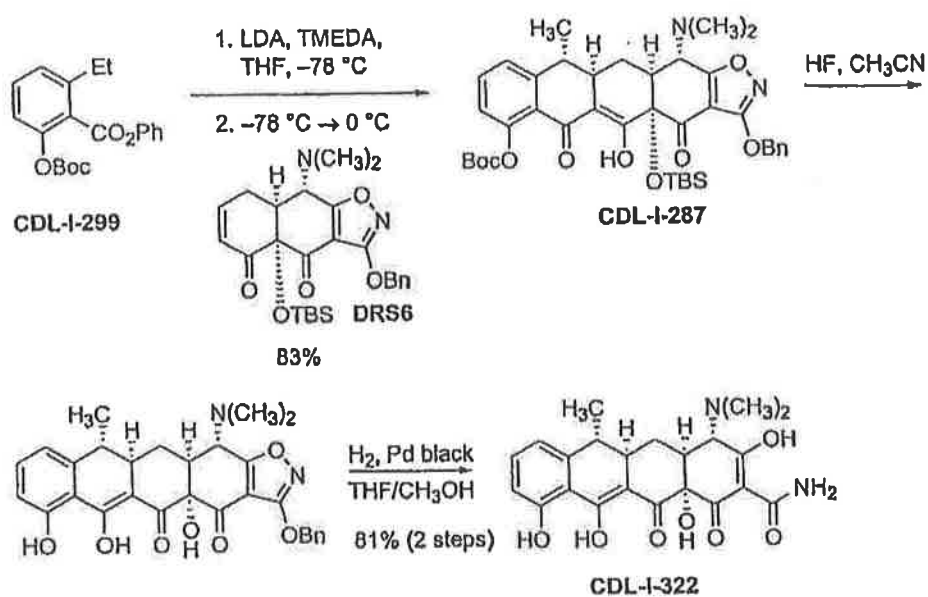
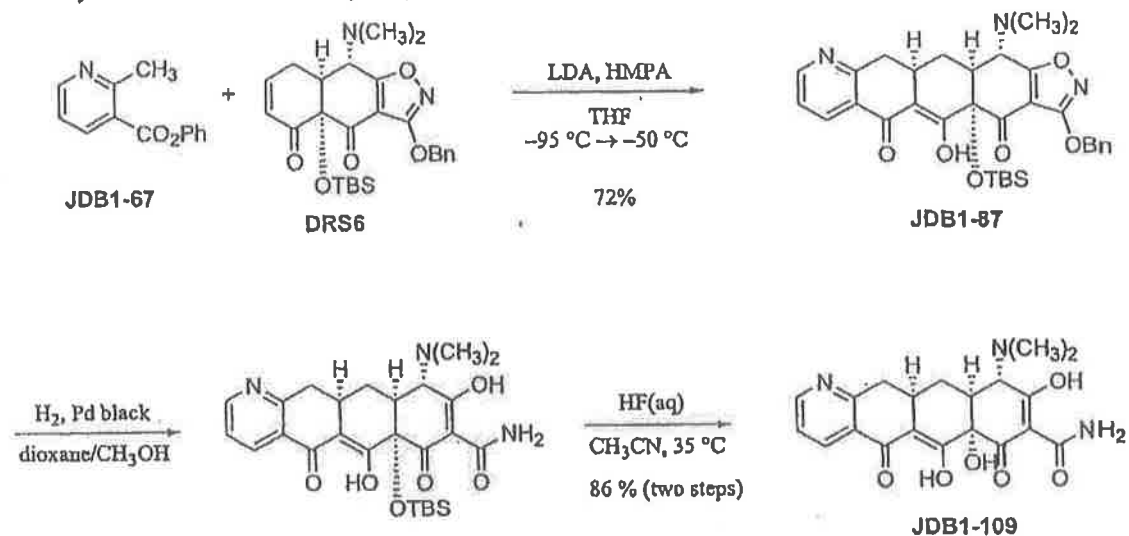


Figure 13

A. Synthesis of 7-Aza-10-deoxysancycline



B. Synthesis of 10-Deoxysancycline

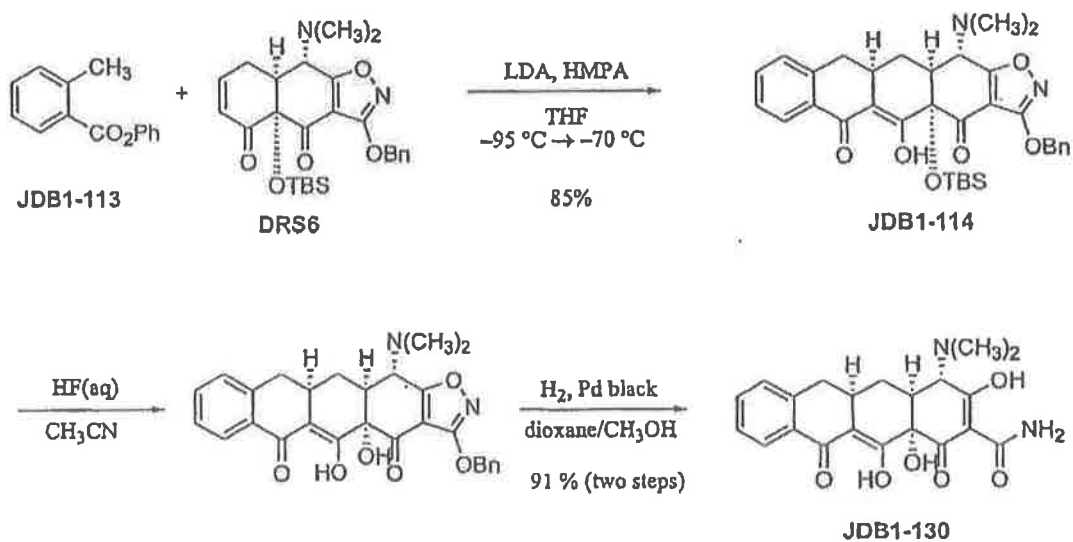
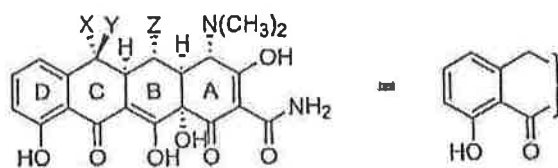


Figure 14A
Representative Structures



D-ring modifications

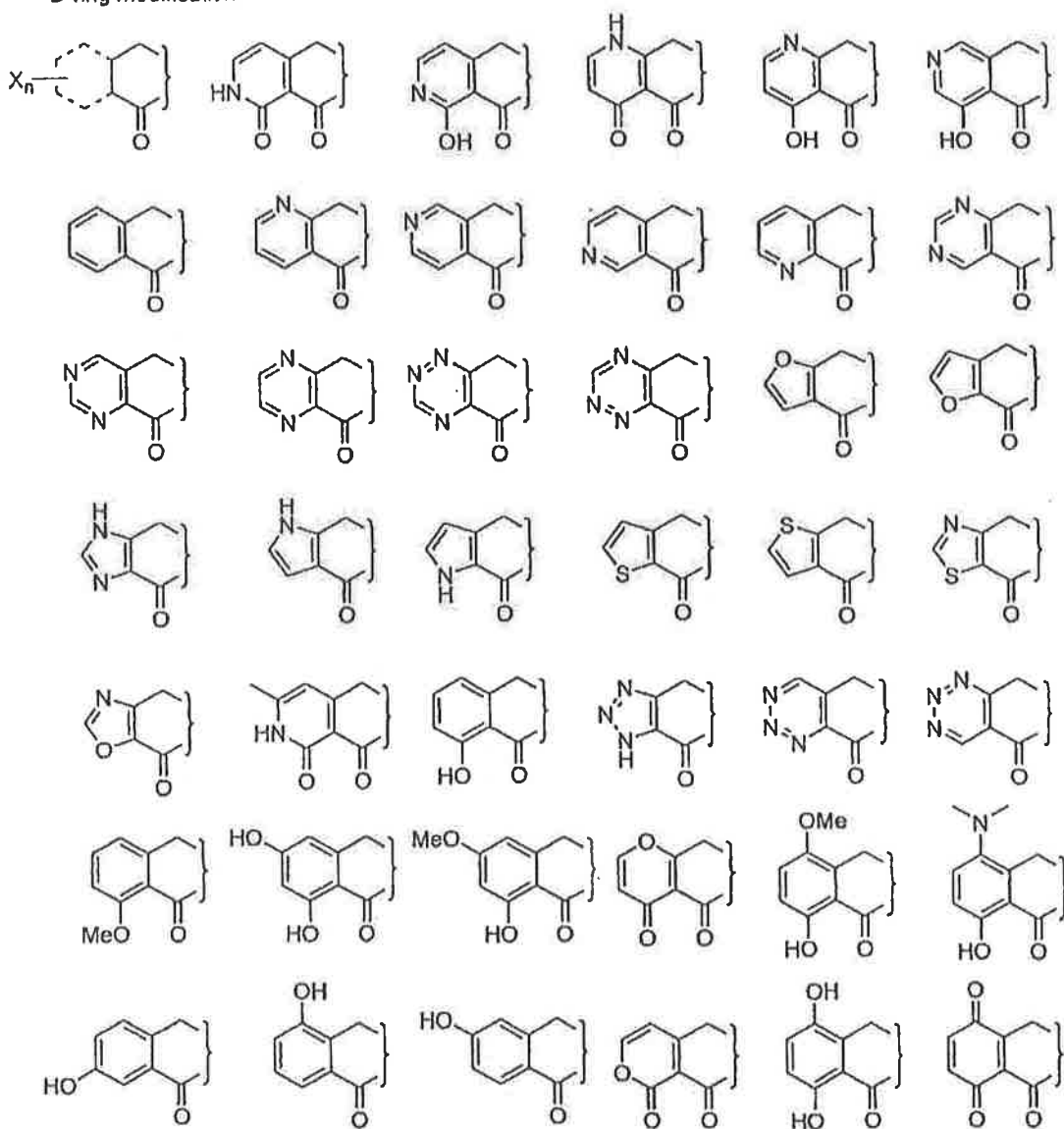
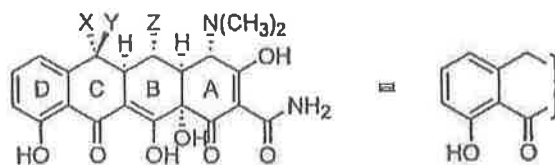


Figure 14B
Representative Structures



penta- and polycyclines:

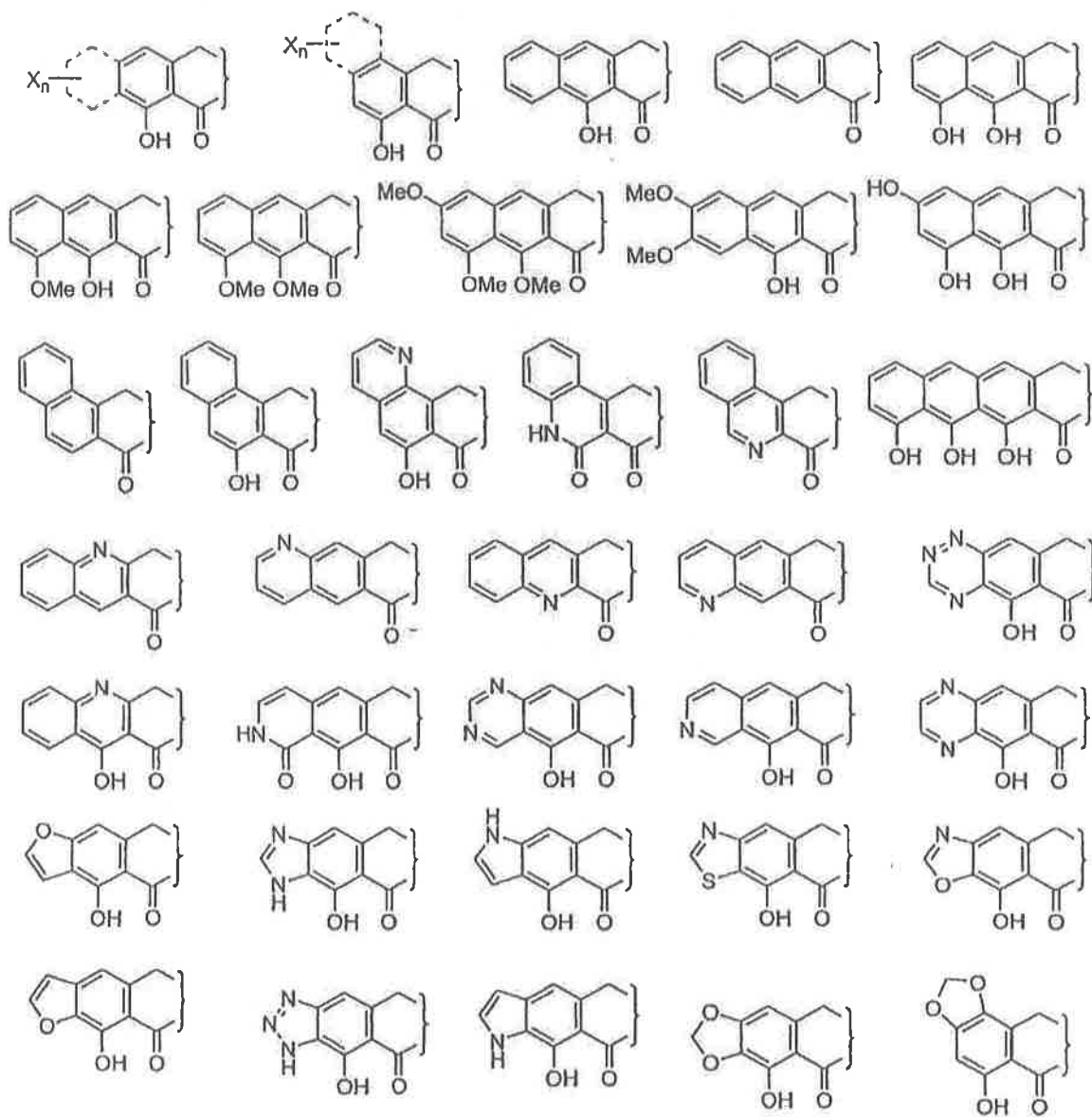


Figure 15

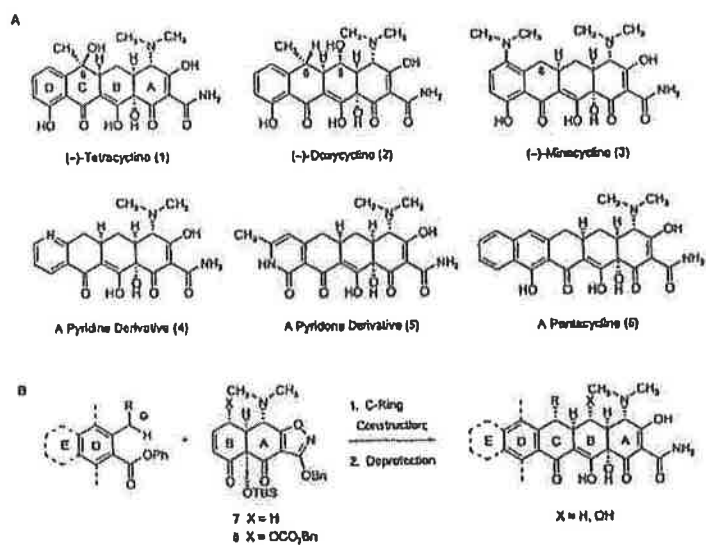


Figure 16

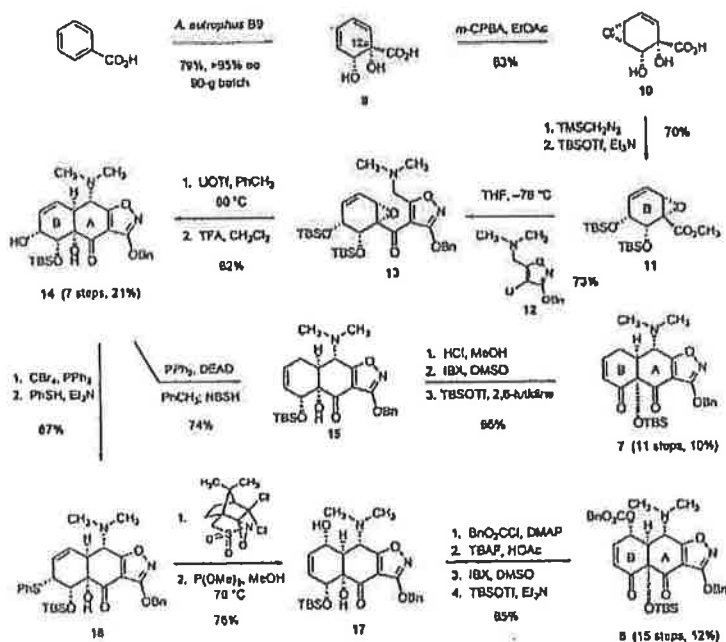


Figure 17

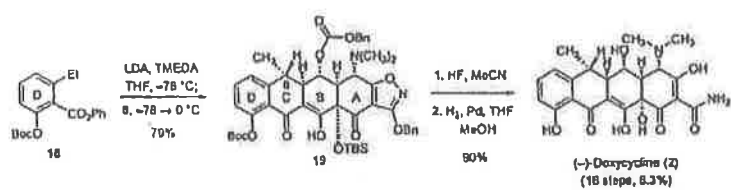


Figure 18

Convergent Assembly of
Structurally Diverse
Tetracyclines

Bacterial Strains Tested				
Gram-Positive Organisms				
<i>S. aureus</i> ATCC 29213	<i>S. epidermidis</i> ACH-4016	<i>S. pneumoniae</i> ACH-2913	<i>E. faecalis</i> ATCC 29222	<i>S. Lacti</i> ATCC 11801
Gram-Negative Organisms				
<i>P. aeruginosa</i> ATCC 27853	<i>P. aeruginosa</i> ATCC 27853	<i>P. aeruginosa</i> ATCC 27822	<i>E. coli</i> ATCC 25922	<i>E. coli</i> BR322

Entry	D-Ring Precursor	Conditions	Tetracycline Analog	MIC ($\mu\text{g/mL}$)										
1		1. LDA, TMEDA; 7 -78 $\rightarrow$ 0 $^{\circ}\text{C}$ (81%) 2. HF, MeCN 3. H_2 , Pd (85%)	 (-)-8-Deoxytetracycline (14 steps, 7.0%)	<table border="1"><tr><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr><tr><td>>64</td><td>32</td><td>32</td><td>16.5</td><td>16.5</td></tr></table>	16.5	16.5	16.5	16.5	16.5	>64	32	32	16.5	16.5
16.5	16.5	16.5	16.5	16.5										
>64	32	32	16.5	16.5										
2		1. LDA, DMPU; 7 -78 $\rightarrow$ 0 $^{\circ}\text{C}$ (87%) 2. H_2 , Pd(OH) ₂ 3. HCl, MeOH (74%)	 A Pyridone Derivative (5) (14 steps, 6.0%)	<table border="1"><tr><td>32</td><td>16</td><td>16</td><td>16</td><td>16</td></tr><tr><td>>64</td><td>16</td><td>32</td><td>16</td><td>16</td></tr></table>	32	16	16	16	16	>64	16	32	16	16
32	16	16	16	16										
>64	16	32	16	16										
3		1. 7; LDA, HMPA -95 $\rightarrow$ -50 $^{\circ}\text{C}$ (76%) 2. H_2 , Pd 3. HF, MeCN (78%)	 7-Aza-10-Deoxytetracycline (4) (14 steps, 6.1%)	<table border="1"><tr><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr><tr><td>>64</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr></table>	16.5	16.5	16.5	16.5	16.5	>64	16.5	16.5	16.5	16.5
16.5	16.5	16.5	16.5	16.5										
>64	16.5	16.5	16.5	16.5										
4		1. 7; n-BuLi -100 $\rightarrow$ -70 $^{\circ}\text{C}$ (81%) 2. HF, MeCN 3. H_2 , Pd (83%)	 10-Deoxytetracycline (14 steps, 6.0%)	<table border="1"><tr><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr><tr><td>>64</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr></table>	16.5	16.5	16.5	16.5	16.5	>64	16.5	16.5	16.5	16.5
16.5	16.5	16.5	16.5	16.5										
>64	16.5	16.5	16.5	16.5										
5		1. 7; n-BuLi -100 $\rightarrow$ 0 $^{\circ}\text{C}$ (75%) 2. HF, MeCN 3. H_2 , Pd 4. BBr_3 , CH_2Cl_2 -78 $\rightarrow$ 23 $^{\circ}\text{C}$ (74%)	 A Pentacycline (8) (15 steps, 5.6%)	<table border="1"><tr><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr><tr><td>>64</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr></table>	16.5	16.5	16.5	16.5	16.5	>64	16.5	16.5	16.5	16.5
16.5	16.5	16.5	16.5	16.5										
>64	16.5	16.5	16.5	16.5										
Testing Control:			 (-)-Tetracycline (1)	<table border="1"><tr><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td><td>16.5</td></tr><tr><td>32</td><td>32</td><td>32</td><td>16.5</td><td>16.5</td></tr></table>	16.5	16.5	16.5	16.5	16.5	32	32	32	16.5	16.5
16.5	16.5	16.5	16.5	16.5										
32	32	32	16.5	16.5										

A Crystalline Michael Adduct

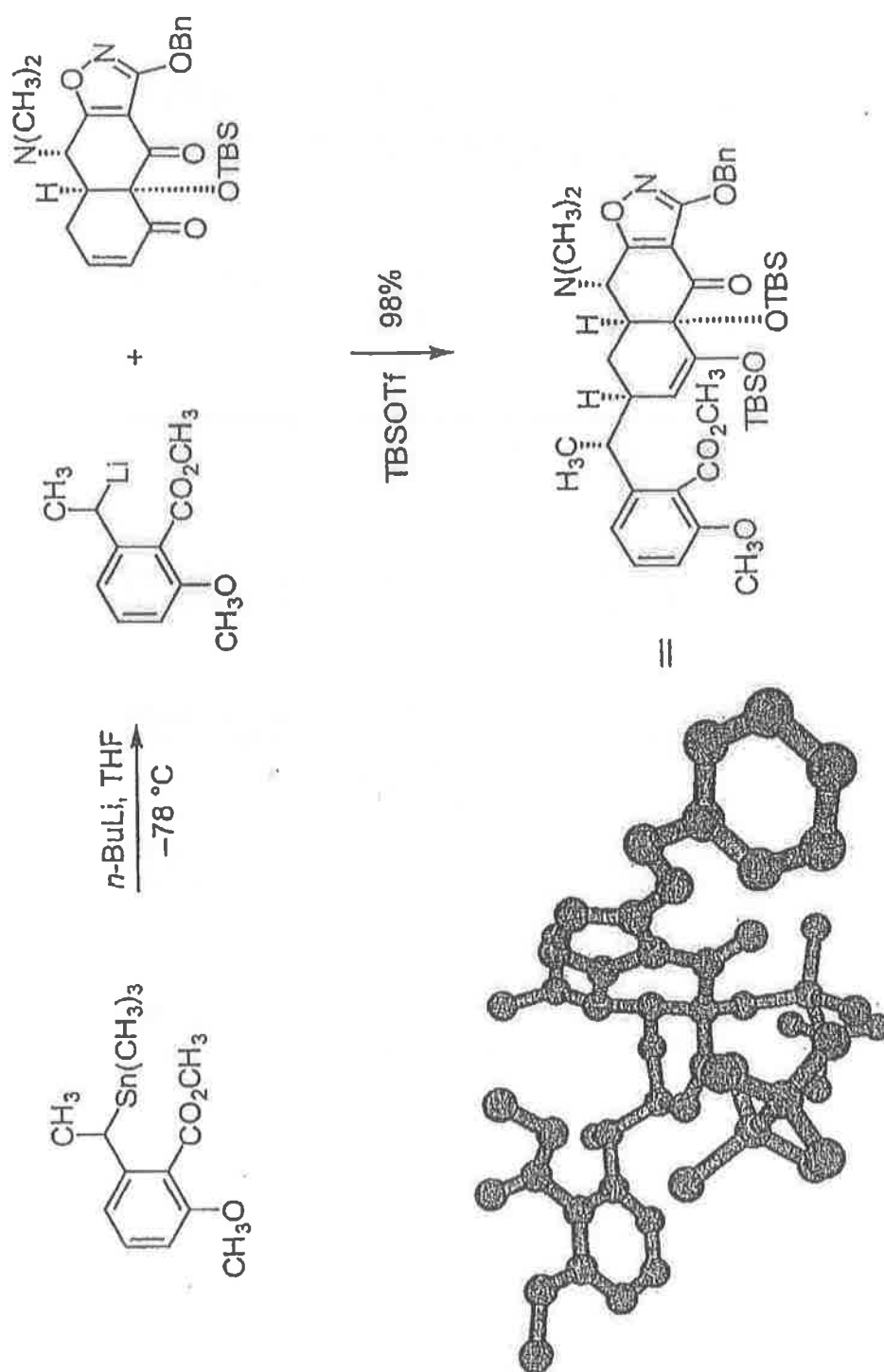


Figure 19

Synthesis of a Pentacycline

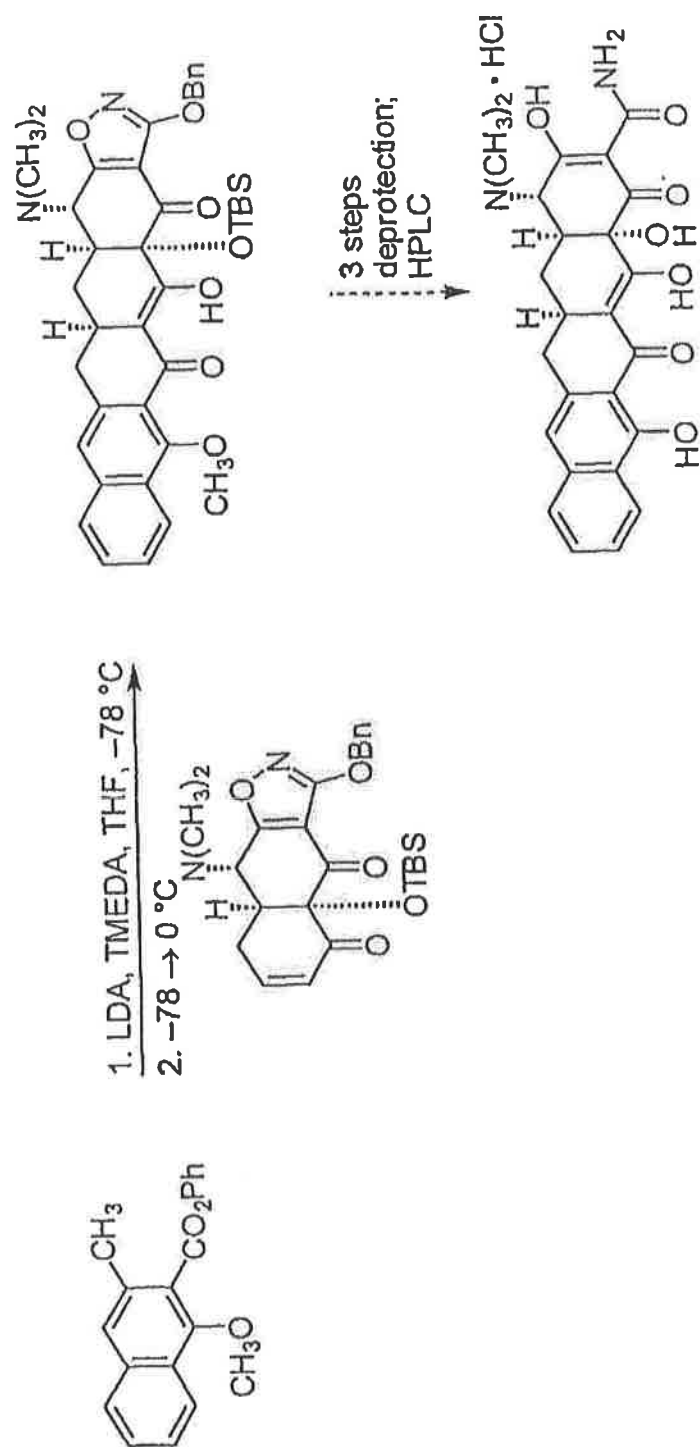
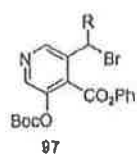
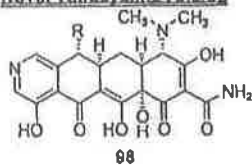


Figure 20

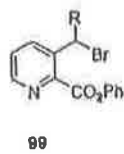
D-Ring Precursor



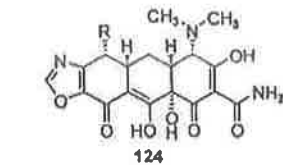
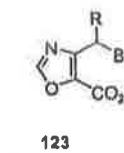
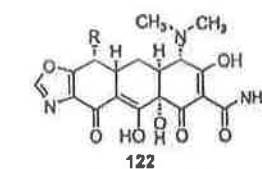
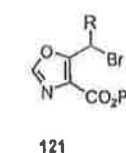
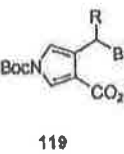
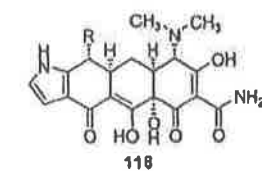
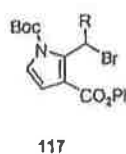
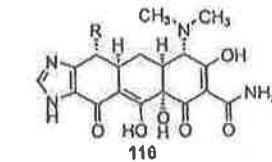
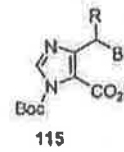
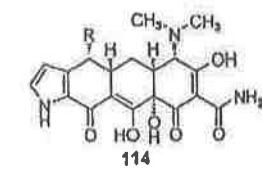
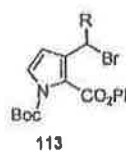
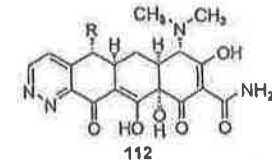
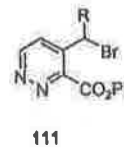
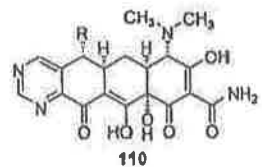
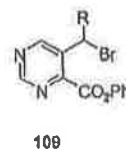
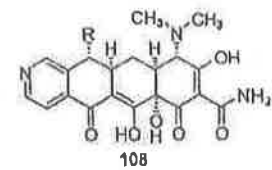
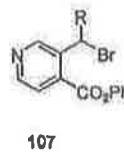
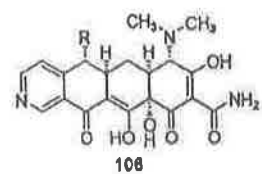
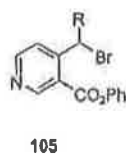
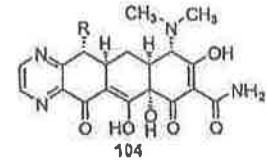
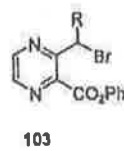
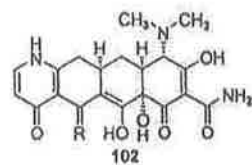
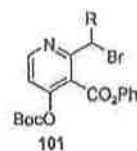
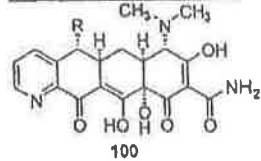
Novel Tetracycline Analog



D-Ring Precursor

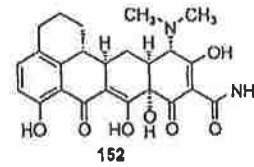
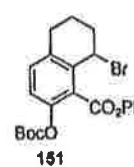
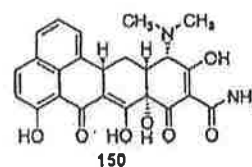
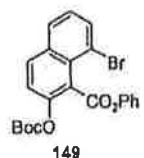
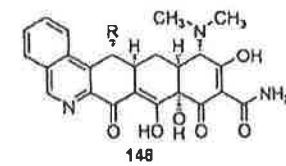
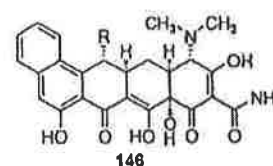
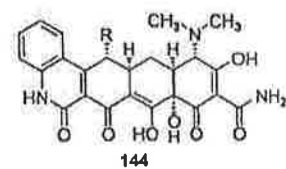
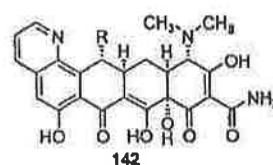
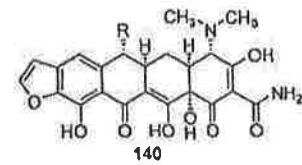
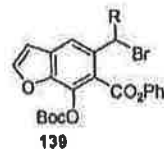
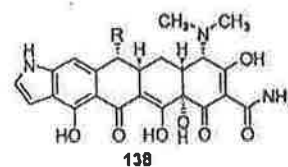
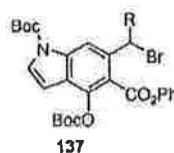
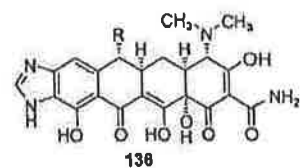
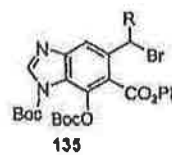
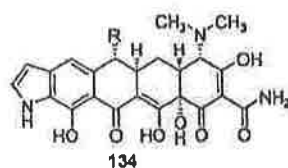
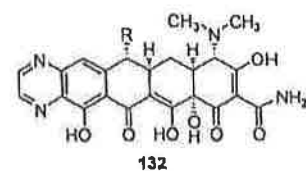
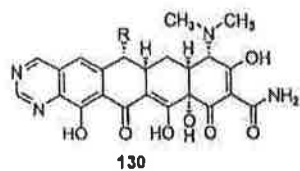
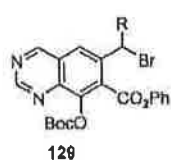
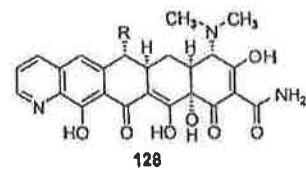
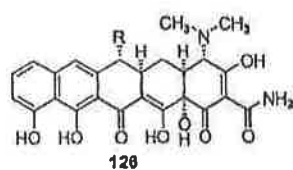
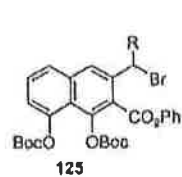


Novel Tetracycline Analog



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

Figure 21A

D-Ring PrecursorNoval Tetracycline AnalogD-Ring PrecursorNoval Tetracycline Analog

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

Figure 21B

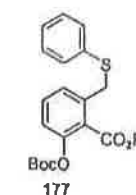
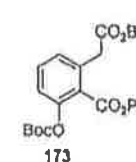
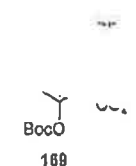
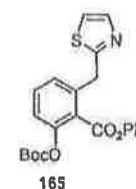
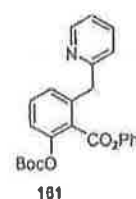
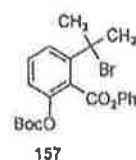
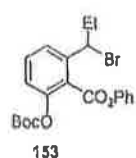
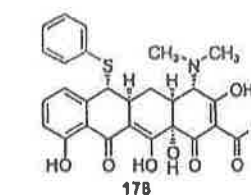
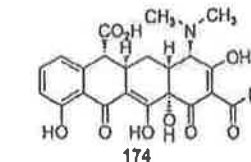
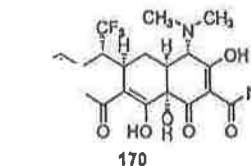
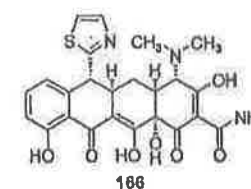
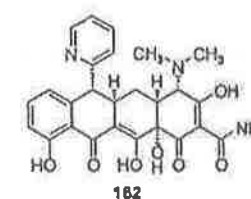
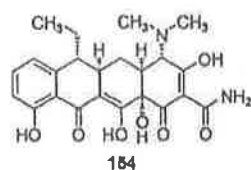
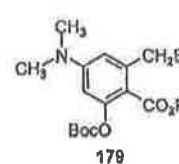
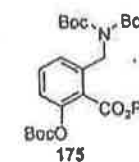
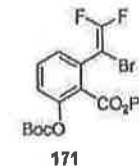
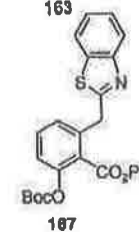
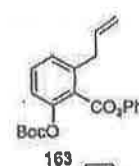
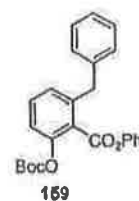
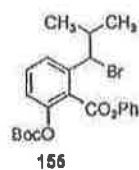
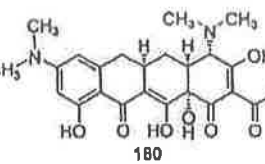
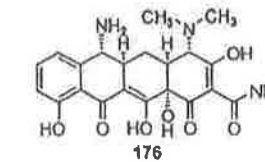
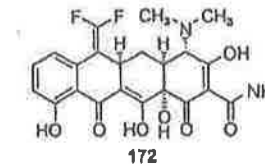
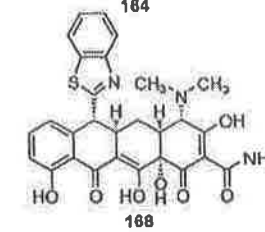
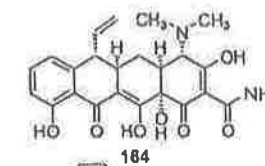
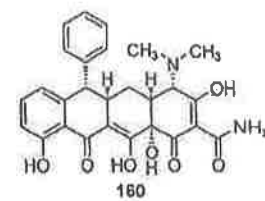
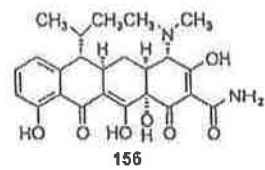
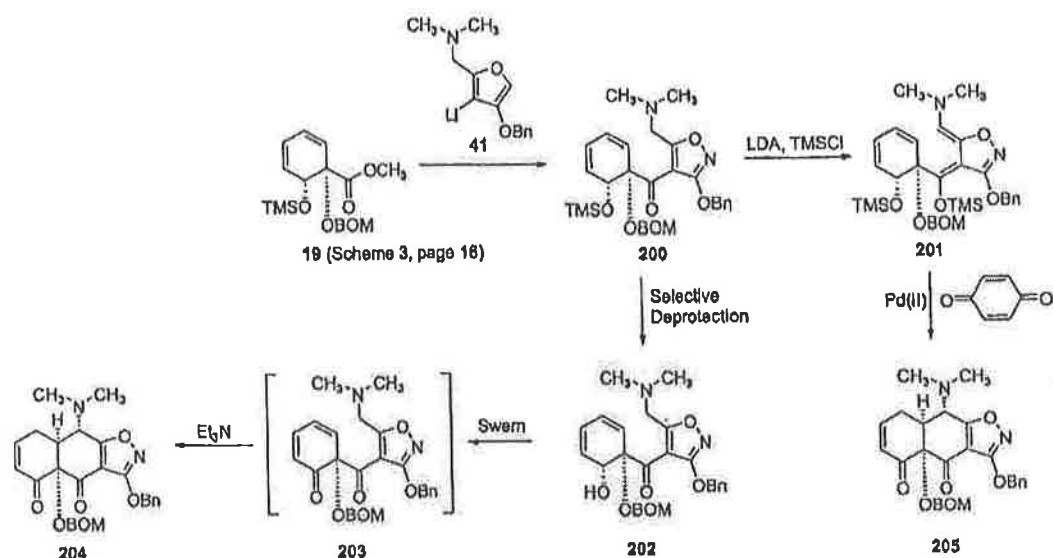
D-Ring PrecursorNovel Tetracycline AnalogD-Ring PrecursorNovel Tetracycline Analog

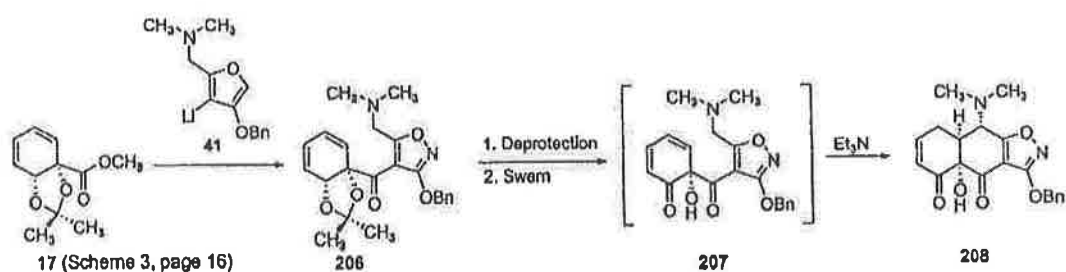
Figure 21C

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

A.



B.



C.

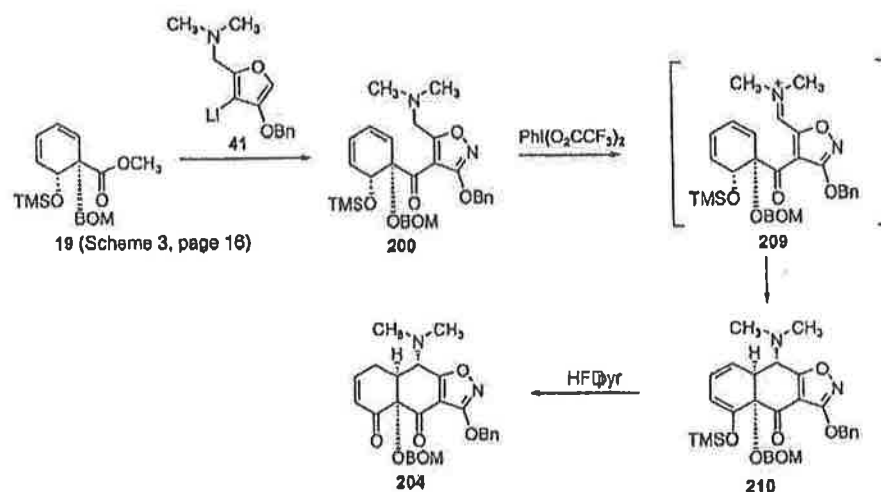
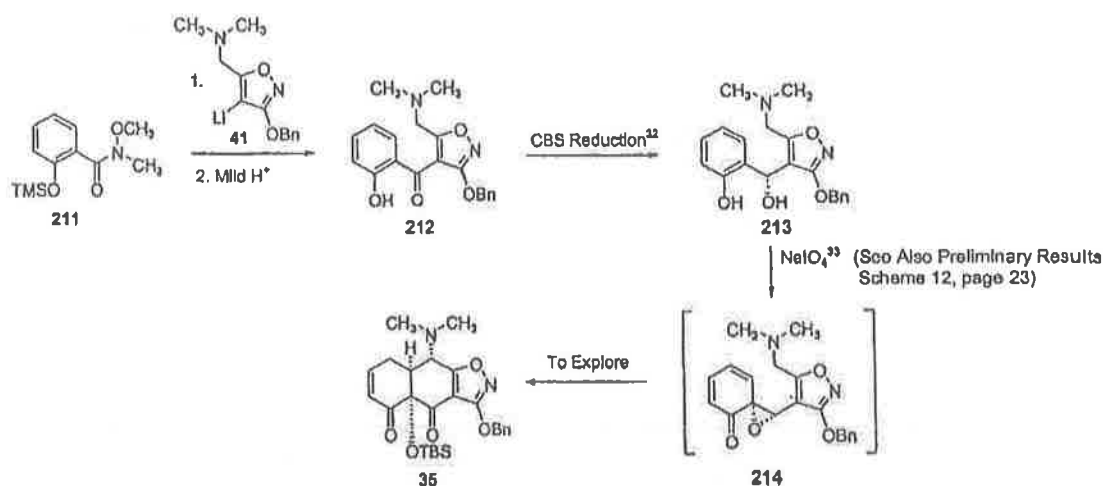


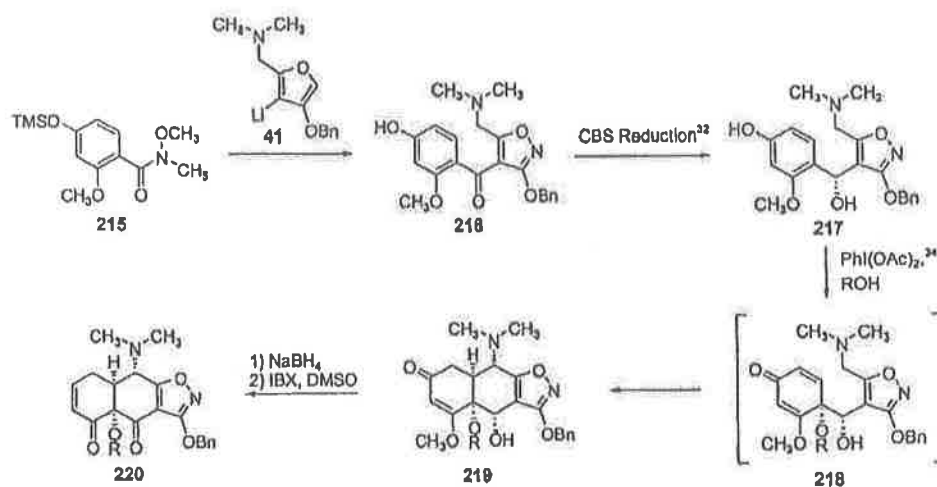
Figure 22

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

A.



B.



C.

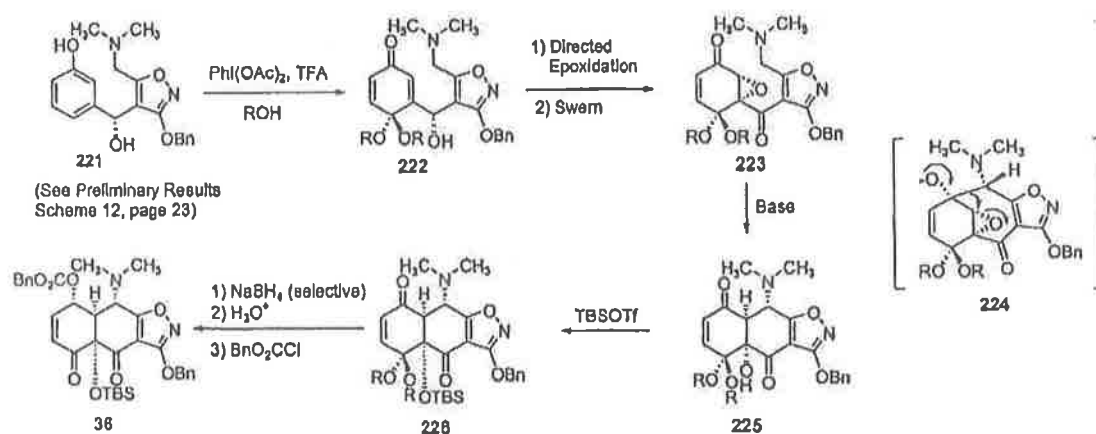


Figure 23