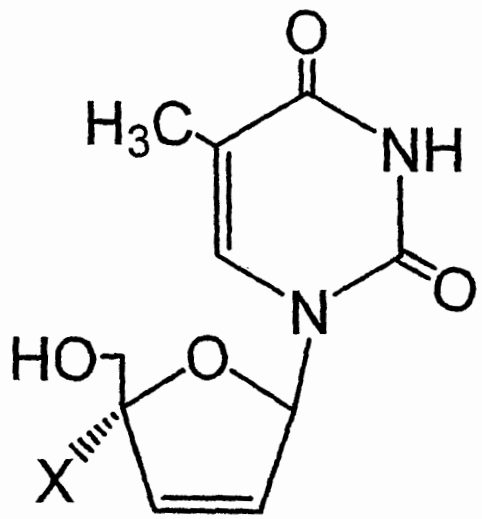
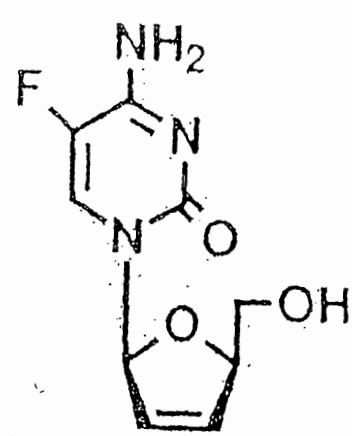
FIGURE 1

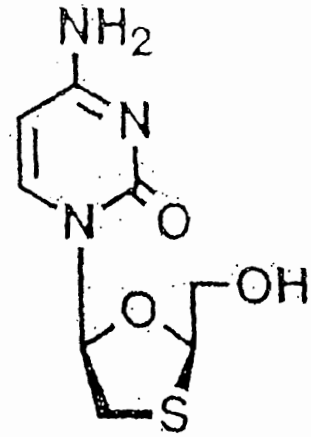


X	Name
-H	D4T
$-CH_3$	4'-methyl D4T
$-C{=}CH_2$	4'-vinyl D4T
$-C{\equiv}CH$	4'-ethynyl D4T
$-C{\equiv}CCH_3$	4'-ethynylmethyl D4T
$-C{\equiv}CCl$	4'-ethynylchloro D4T
$-CH_2CH{=}CH_2$	4'-allyl D4T
-CN	4'-cyano D4T

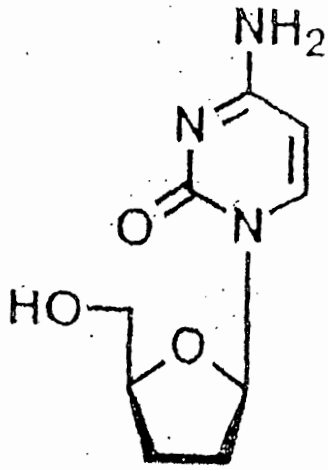
FIGURE 2



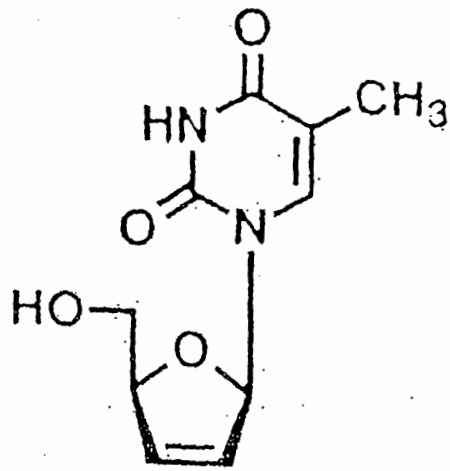
L(-)Fd4C



L(-)SddC
(3TC)



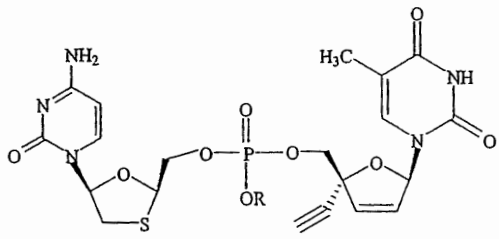
ddC



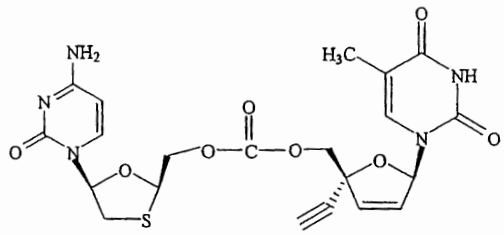
D4T

FIGURE 3

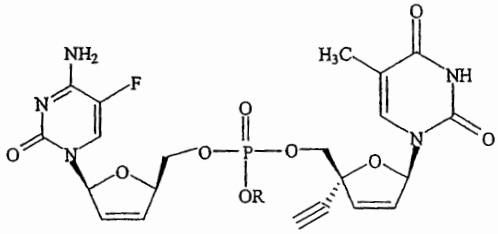
Dinucleoside Prodrugs



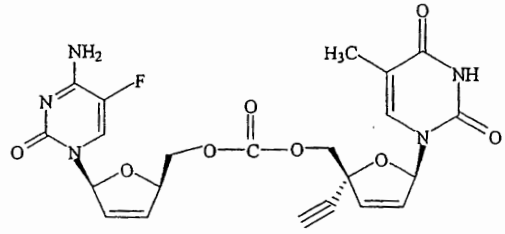
3TC and TKD-4-114 Dinucleoside Phosphate



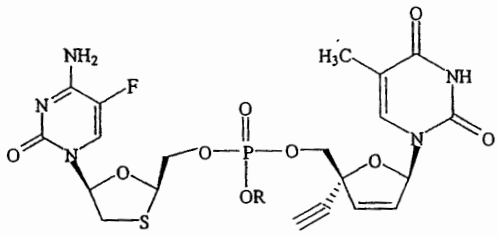
3TC and TKD-4-114 Dinucleoside Carbonate



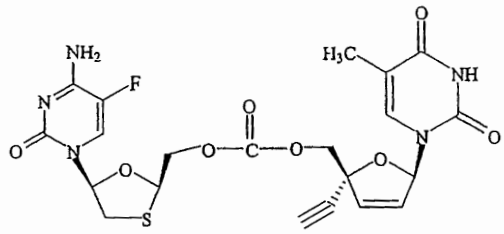
BLFd4C and TKD-4-114 Dinucleoside Phosphate



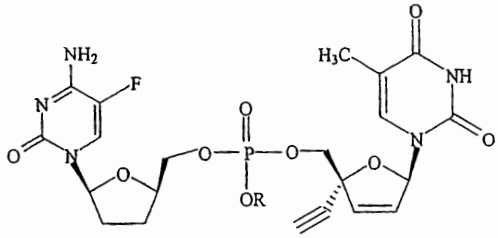
BLFd4C and TKD-4-114 Dinucleoside Carbonate



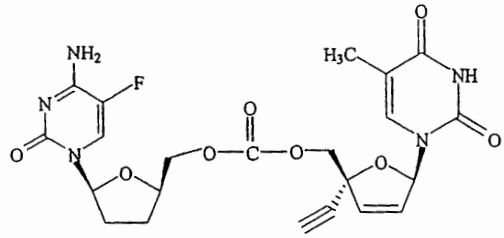
FTC and TKD-4-114 Dinucleoside Phosphate



FTC and TKD-4-114 Dinucleoside Carbonate

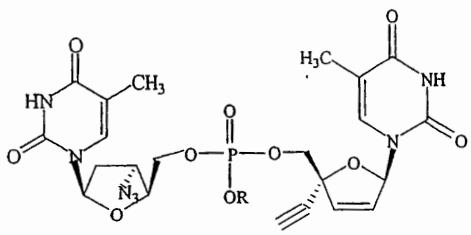


BLFddC and TKD-4-114 Dinucleoside Phosphate

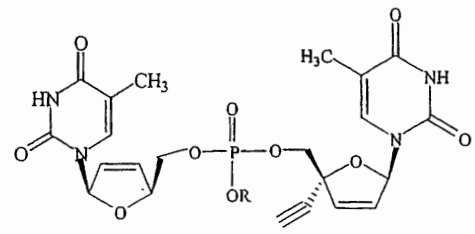


BLFddC and TKD-4-114 Dinucleoside Carbonate

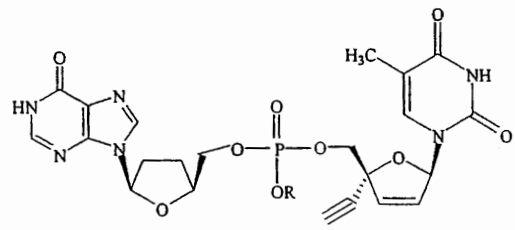
FIGURE 3 (cont'd)



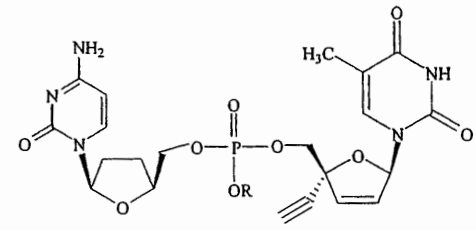
AZT and TKD-4-114 Dinucleoside Phosphate



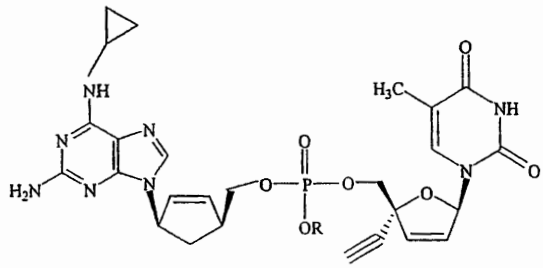
d4T and TKD-4-114 Dinucleoside Phosphate



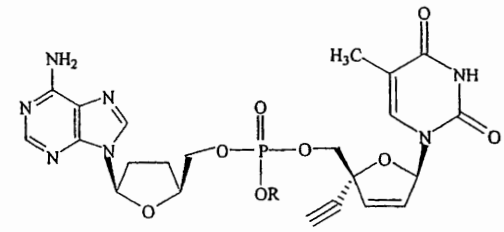
ddI and TKD-4-114 Dinucleoside Phosphate



ddC and TKD-4-114 Dinucleoside Phosphate



Abacavir and TKD-4-114 Dinucleoside Phosphate



ddA and TKD-4-114 Dinucleoside Phosphate

FIGURE 4

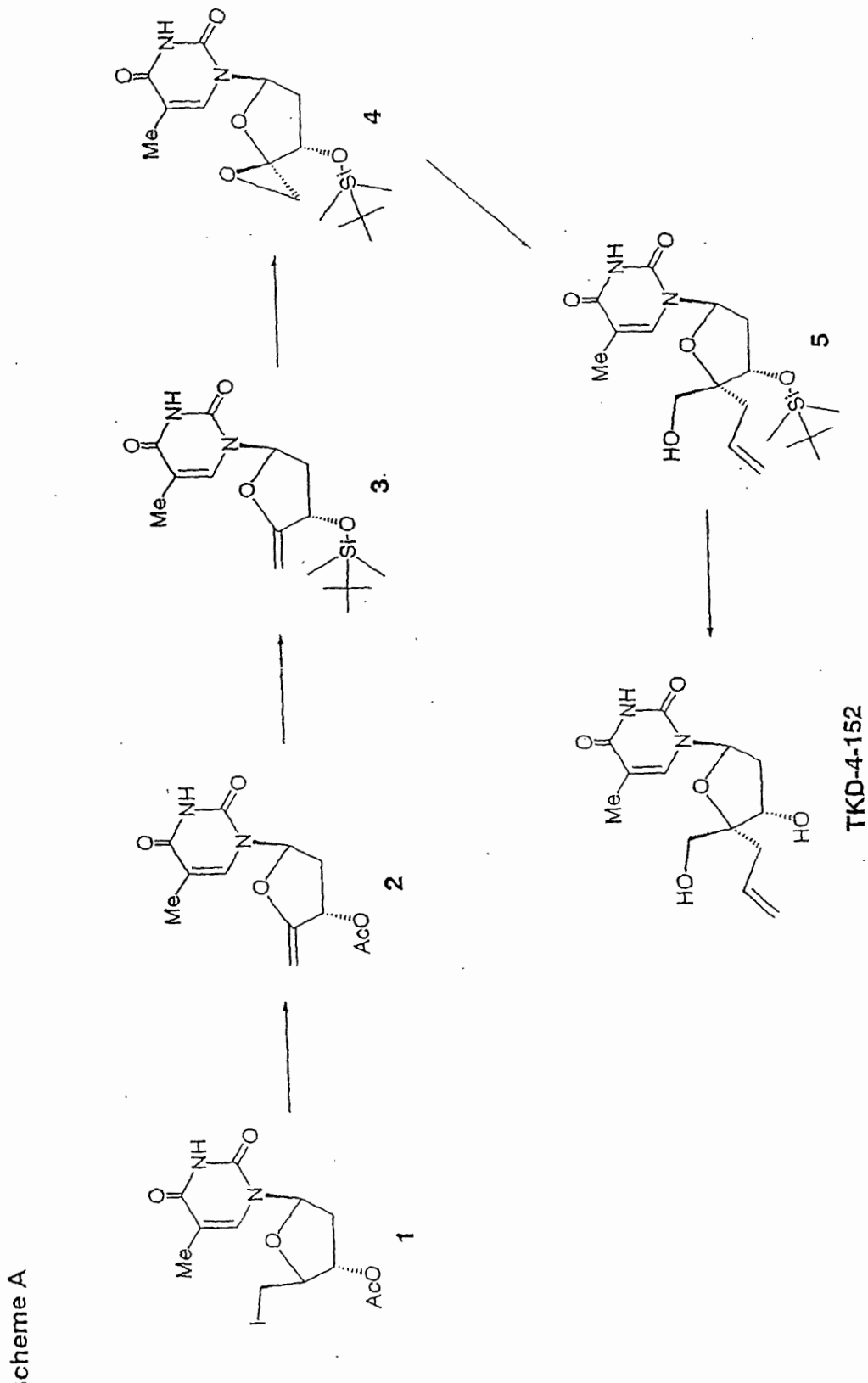


FIGURE 5

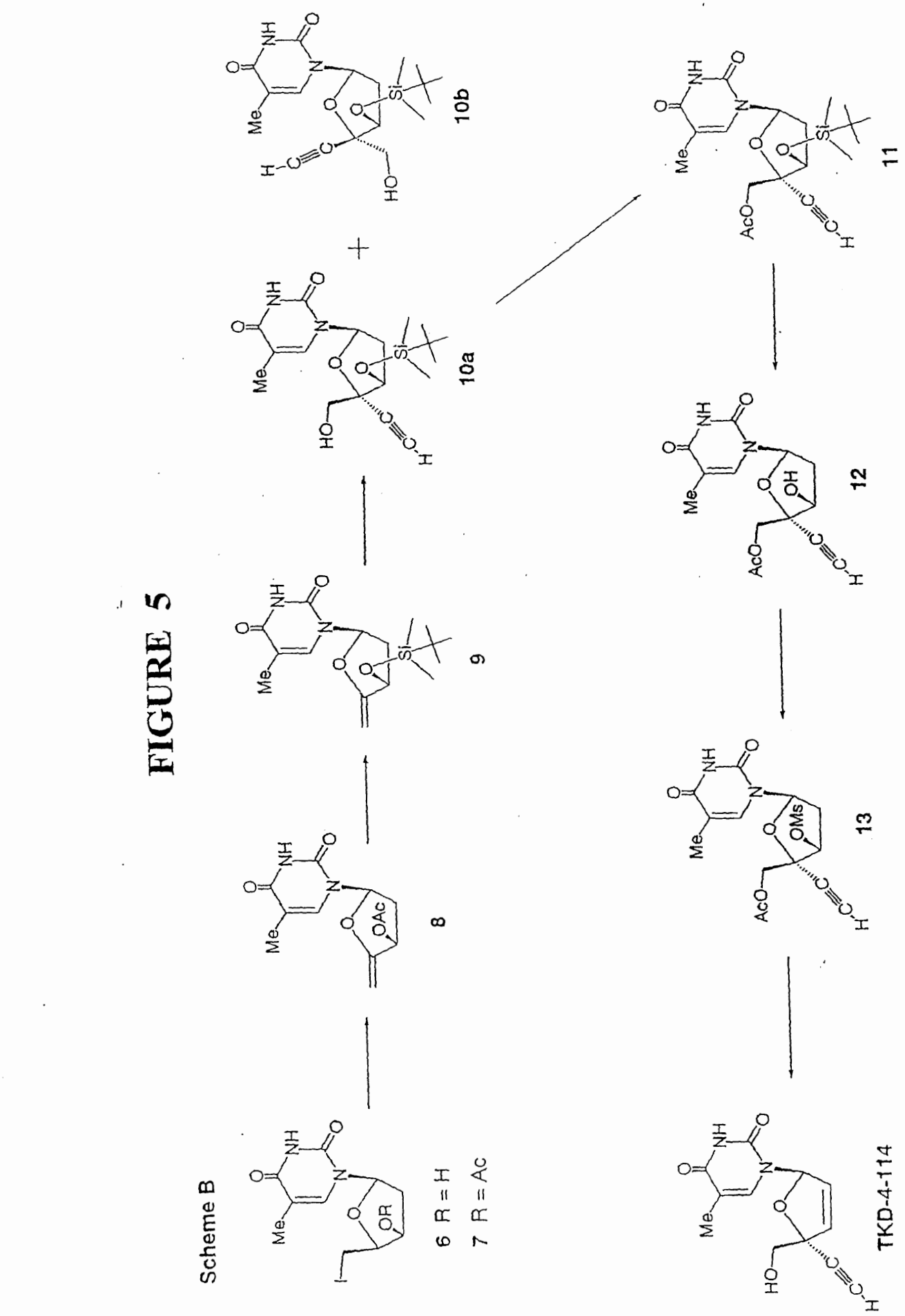
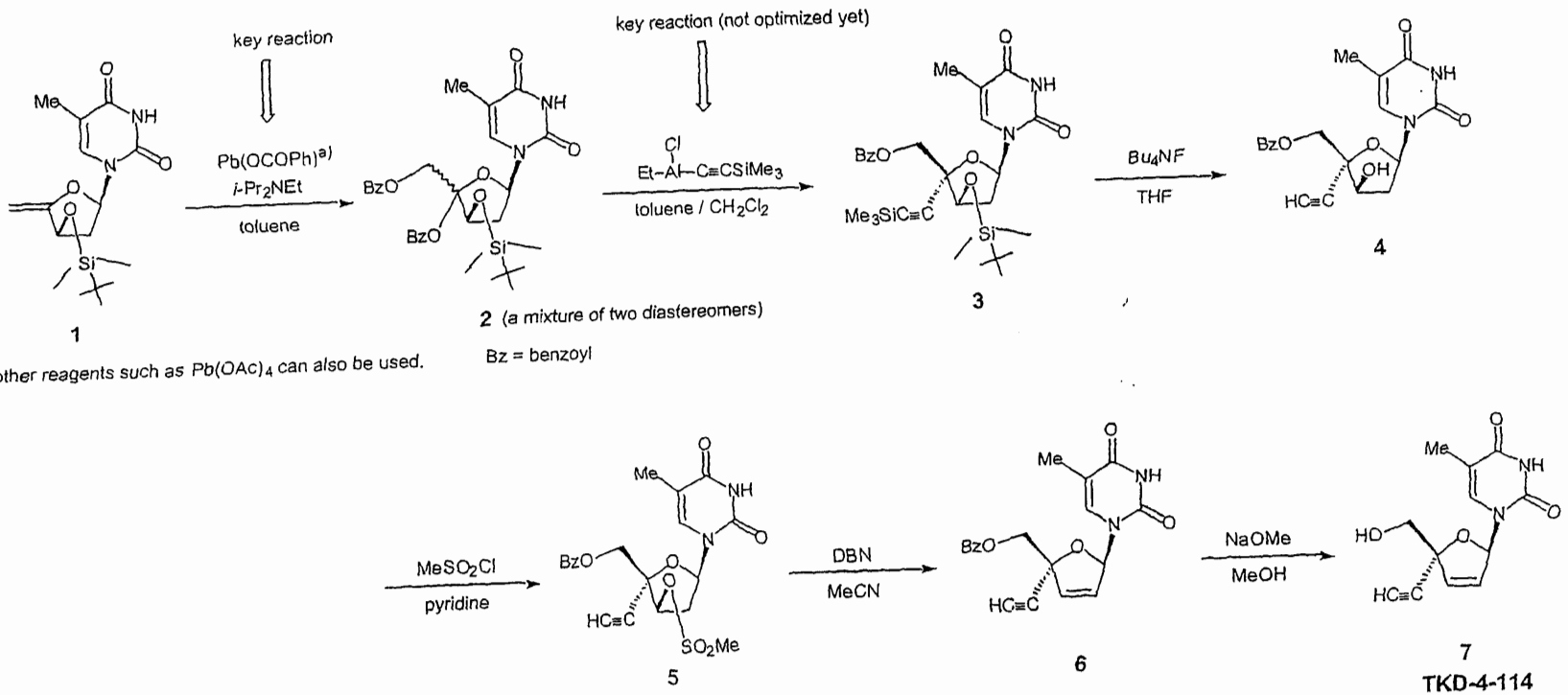


FIGURE 5A

Alternative Synthesis of TKD-4-114



a) other reagents such as $Pb(OAc)_4$ can also be used.

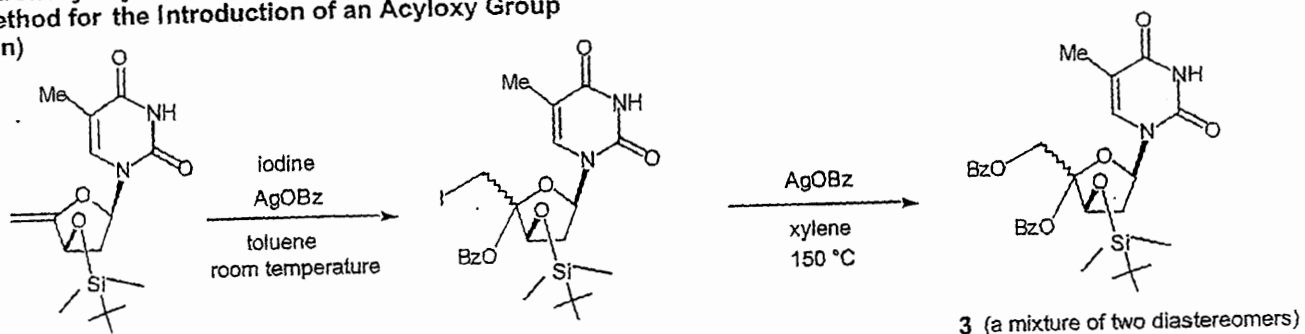
Bz = benzoyl

Elemental analysis data for compounds 3-6 have not been obtained yet.

DBN = 1,5-diazabicyclo[4.3.0]non-5-ene

FIGURE 5B

Preparation of 4'-Benzoyloxy nucleosides
(an Alternative Method for the Introduction of an Acyloxy Group into the 4'-Position)



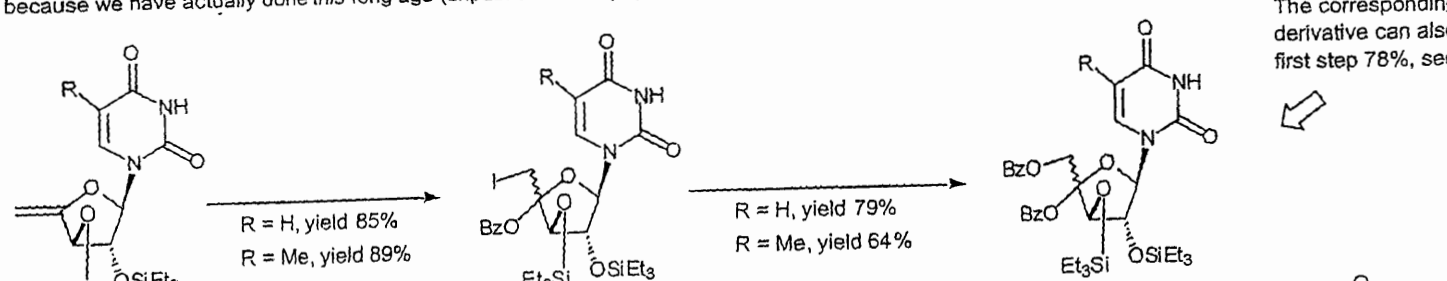
1

2 (a mixture of two diastereomers)

Bz = benzoyl

3 (a mixture of two diastereomers)

The above reaction sequence can avoid the use of toxic lead reagents, and should work because we have actually done this long ago (unpublished data) by using the following compounds.



The corresponding N^6-pivaloyladenine derivative can also be prepared: first step 78%, second step 56%.

whereas

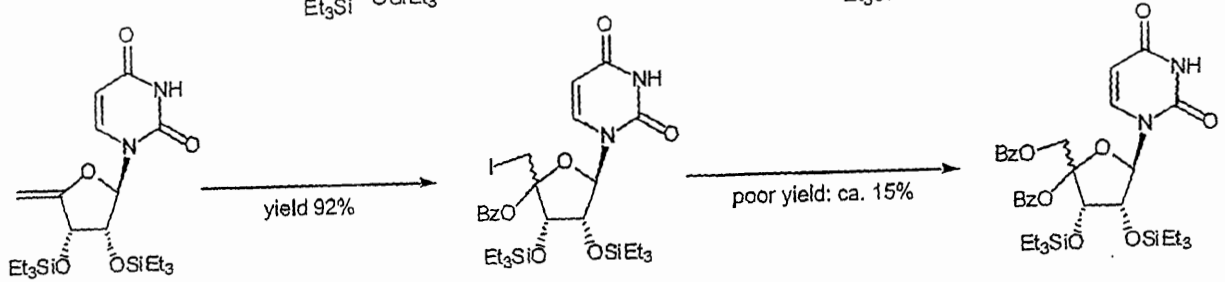


FIGURE 6

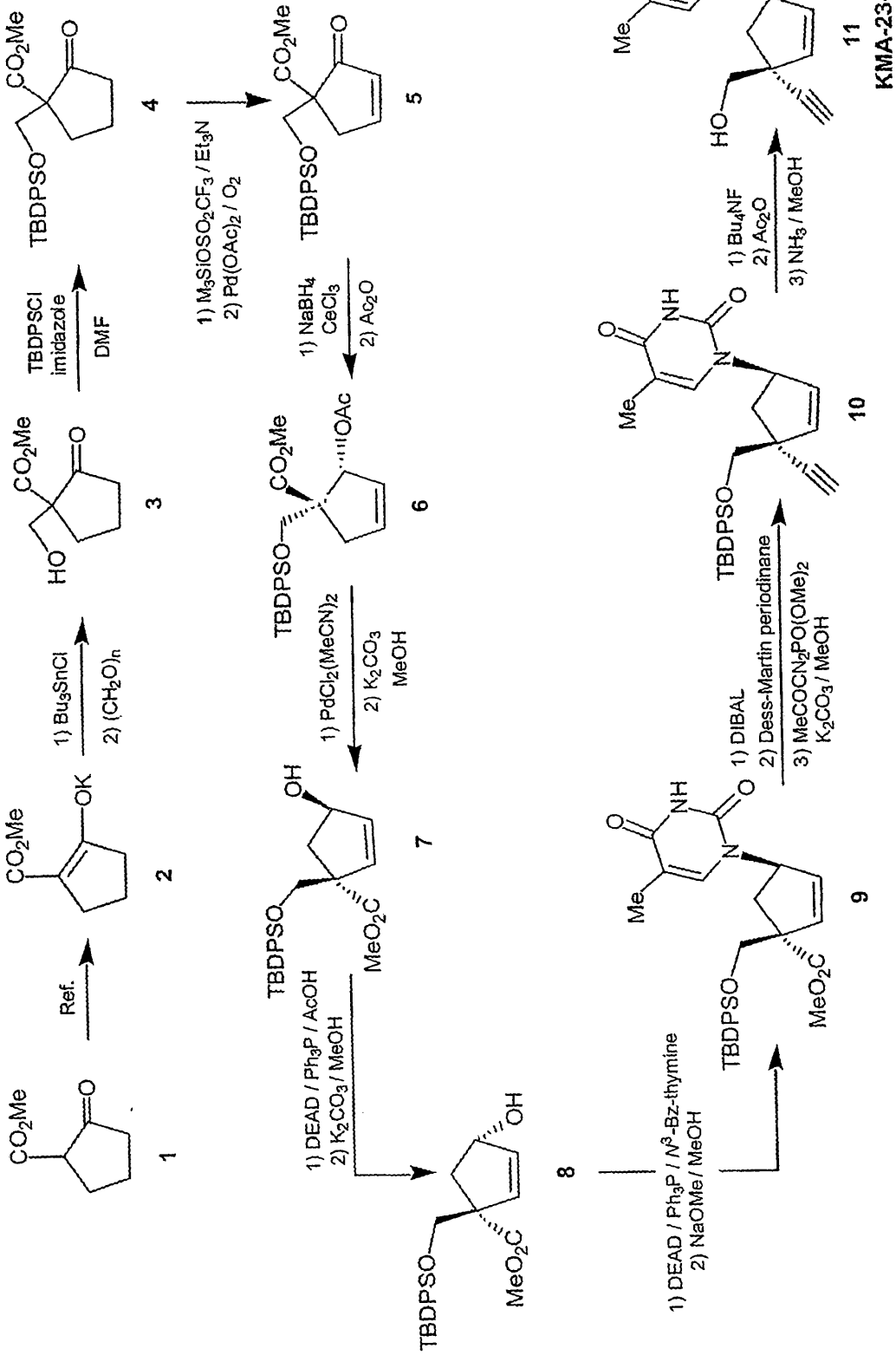
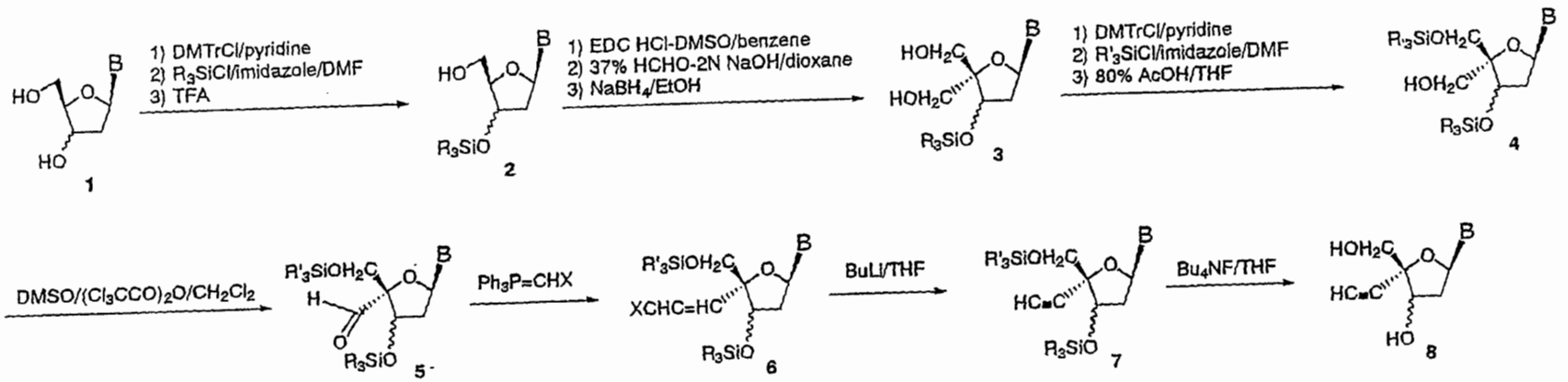

Ref.
1) Bu3SnCl
2) (CH2O)n
TBDPSCl
imidazole
DMF
1) M3SiOSO2CF3 / Et3N
2) Pd(OAc)2 / O2
1) NaBH4
CeCl3
2) Ac2O
1) PdCl2(MeCN)2
2) K2CO3
MeOH
1) DEAD / Ph3P / AcOH
2) K2CO3 / MeOH
1) DEAD / Ph3P / N3-Bz-thymine
2) NaOMe / MeOH
1) DIBAL
2) Dess-Martin periodinane
3) MeCOCN2PO(OMe)2
K2CO3 / MeOH
1) Bu4NF
2) Ac2O
3) NH3 / MeOH
KMA-23-153

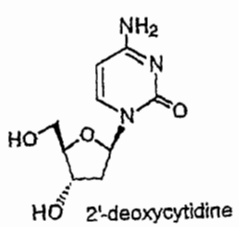
FIGURE 7A

Scheme 1. Synthesis of 4'-ethynyl-2'-deoxynucleosides from 2'-deoxynucleosides



<Comments>

This synthetic route has been published in the case of **1** = 2'-deoxycytidine:
Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *J. Med. Chem.* **1999**, *42*, 2901-2908.



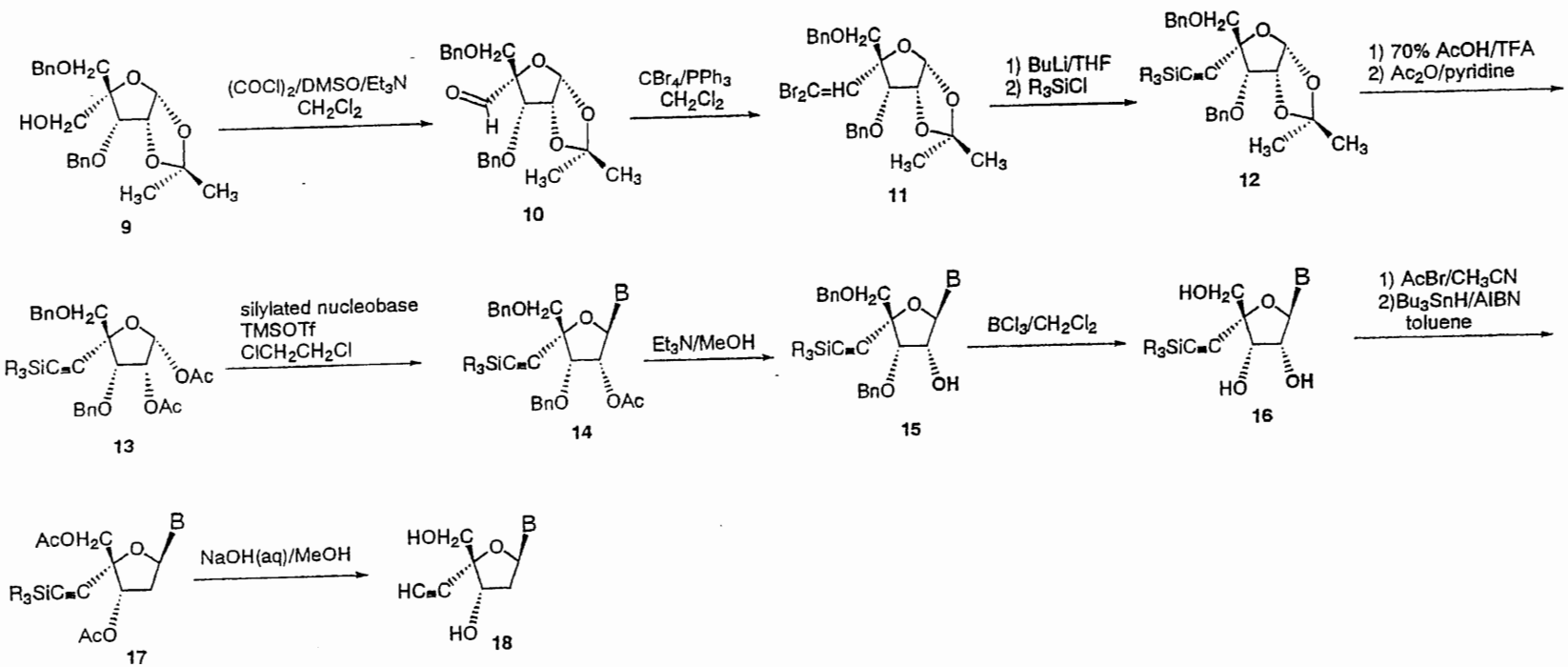
"B" denotes nucleobase moiety, such as uracil-1-yl, thymin-1-yl, cytosin-1-yl, adenin-9-yl, guanin-9-yl, and hypoxanthin-9-yl.

SiR_3 is typically *tert*-butyldimethylsilyl group, whereas SiR'_3 is typically *tert*-butyldiphenylsilyl group.

X is halogen atom, such as chlorine.

FIGURE 7B

Scheme 2. Synthesis of 4'-ethynyl-2'-deoxynucleosides from sugar precursor



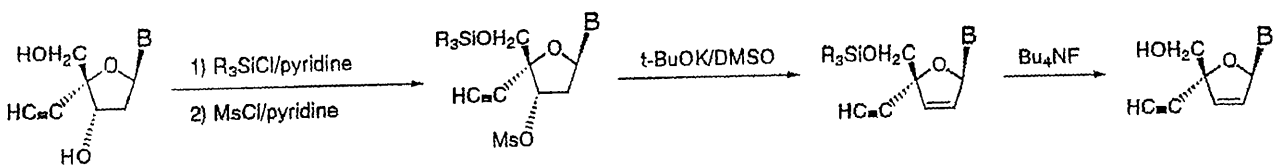
<Comments>

This synthetic route has been published in the synthesis of 18 where B is thymin-1-yl:
Ohrui, H.; kohgo, S.; kitano, K.; Sakata, K.; Kodama, E.; Yoshimura, K.; Matsuoka, m.; Shigeta, s.; Mitsuya, S. *J. Med. Chem.*, **2000**, *43*, 4516-4525.

R_3Si is typically triethylsilyl group.

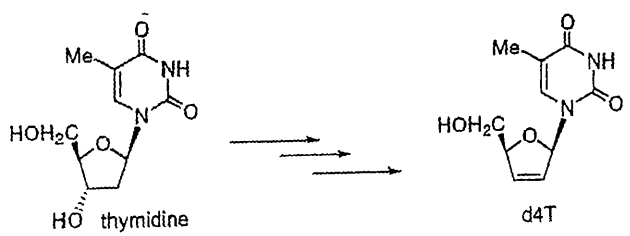
FIGURE 7C

Scheme 3. Introduction of the 2',3'-double bond: synthesis of 2',3'-didehydro-3'-deoxy-4'-ethynylthymidine (4'-ethynyl-d4T, TKD-4-114)



<Comments>

This route has been used for the conversion of thymidine to d4T: Horwitz, J. P.; Chua, J.; Rooge, M. A. D.; Noel, M.; Klundt, I. *J. Org. Chem.* **1966**, *31*, 205.



R_3Si is typically *tert*-butyldimethylsilyl group.

FIGURE 8

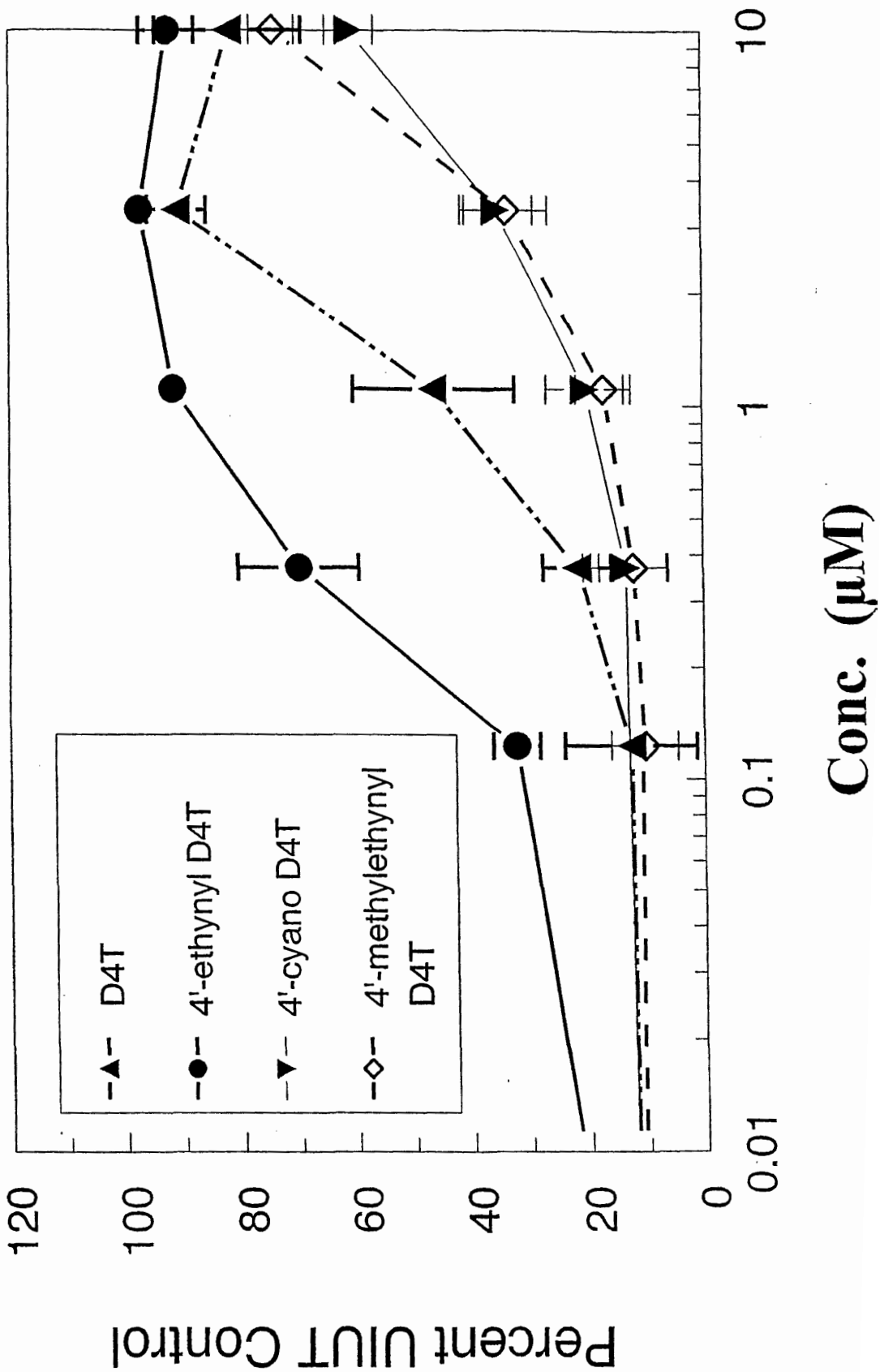

Percent UUT Control
120
100
80
60
40
20
0
0.01
0.1
1
10
Conc. (μM)
D4T
4'-ethynyl D4T
4'-cyano D4T
4'-methylethynyl D4T

FIGURE 9

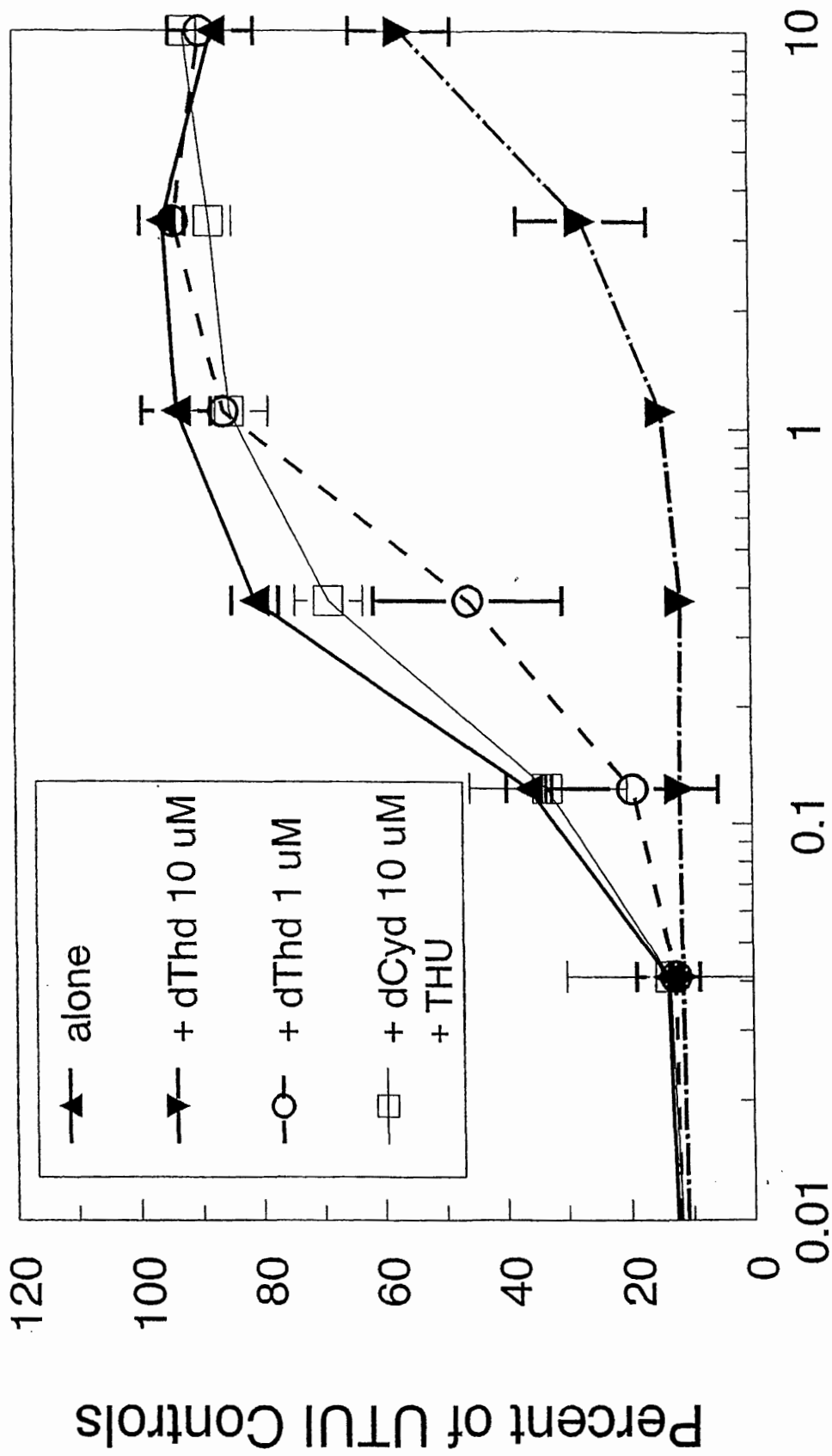
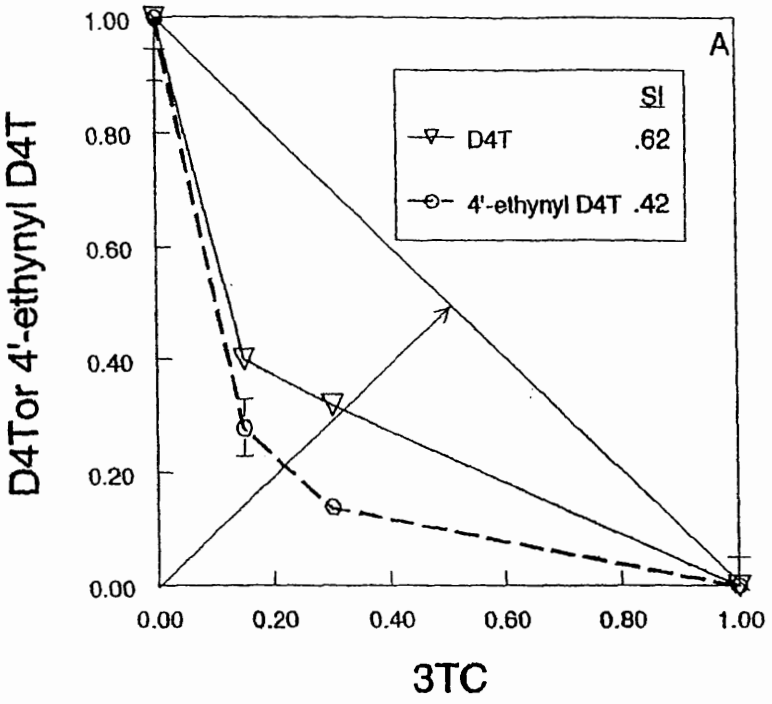

Percent of UTUI Controls
120
100
80
60
40
20
0
0.01
0.1
1
10
4'-Ethynyl D4T (μM)
alone
+ dThd 10 uM
+ dThd 1 uM
+ dCyd 10 uM
+ THU

FIGURE 10


A
SI
D4T .62
4'-ethynyl D4T .42
D4Tor 4'-ethynyl D4T
3TC
1.00
0.80
0.60
0.40
0.20
0.00
0.00 0.20 0.40 0.60 0.80 1.00

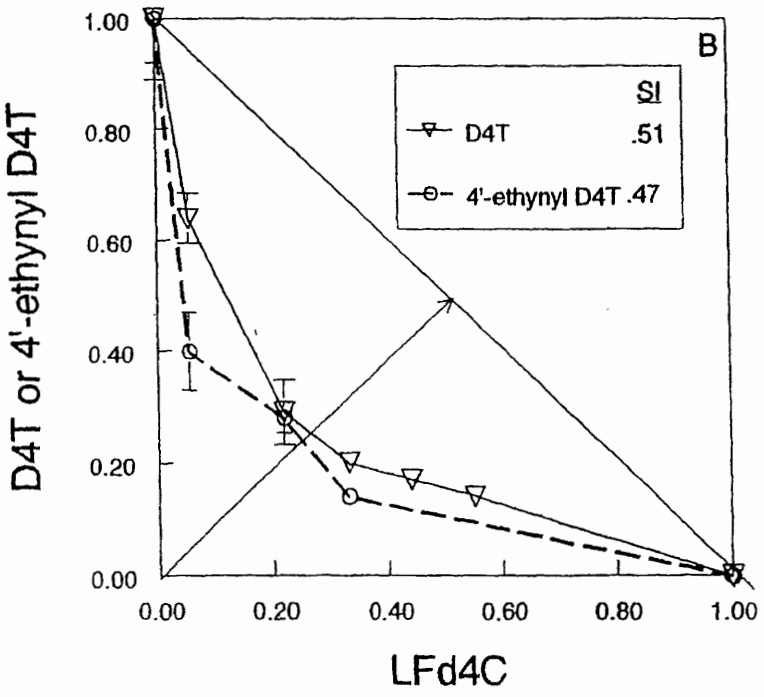
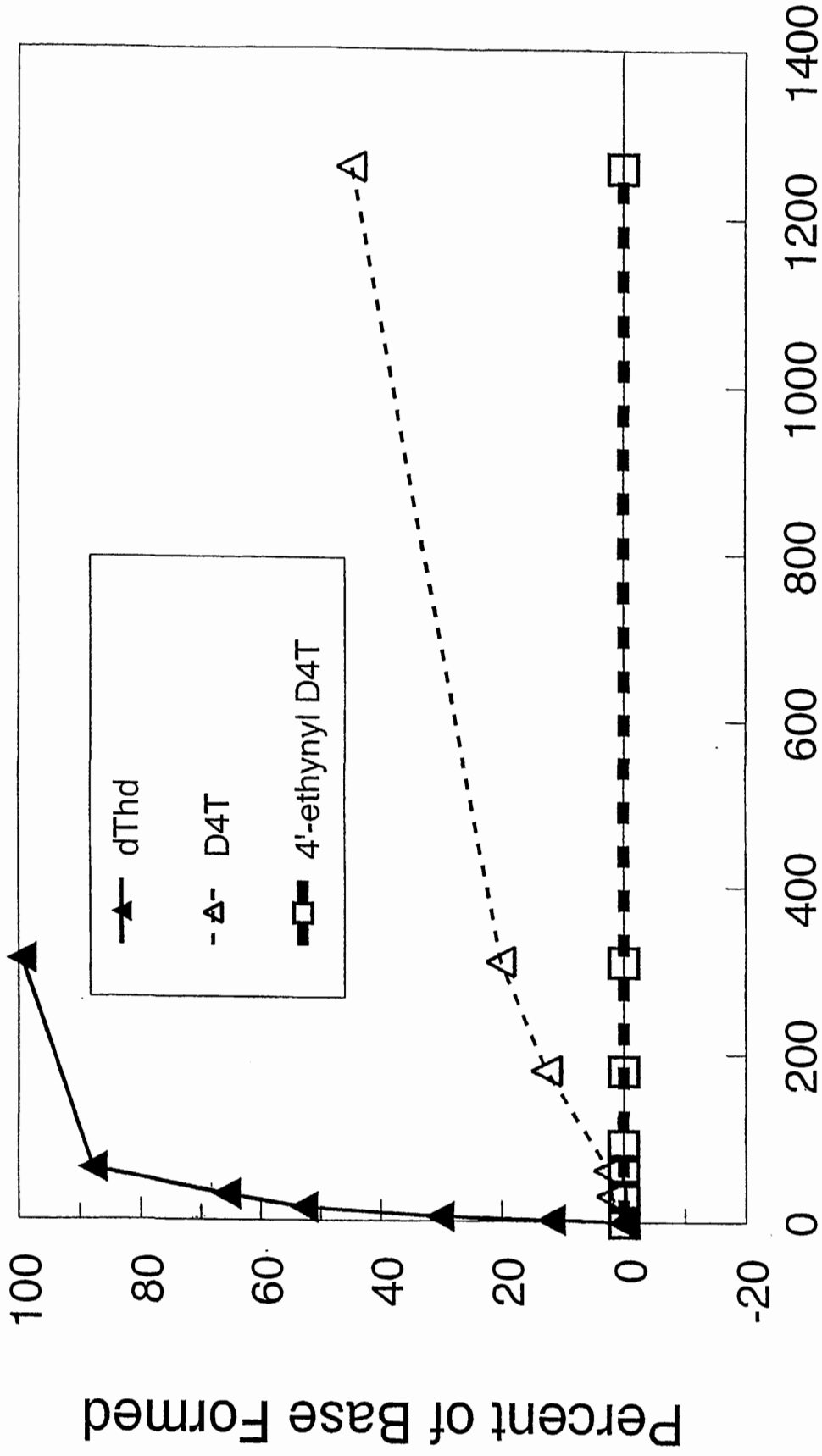

B
SI
D4T .51
4'-ethynyl D4T .47
D4T or 4'-ethynyl D4T
LFd4C
1.00
0.80
0.60
0.40
0.20
0.00
0.00 0.20 0.40 0.60 0.80 1.00

FIGURE 11


Percent of Base Formed
100
80
60
40
20
0
-20
0
200
400
600
800
1000
1200
1400
Time (Min.)
dThd
D4T
4'-ethynyl D4T