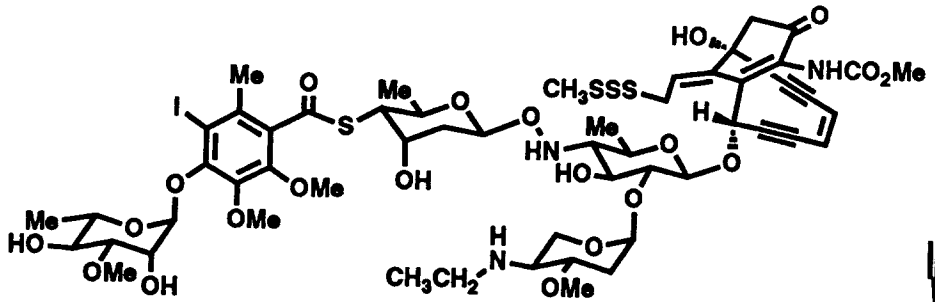
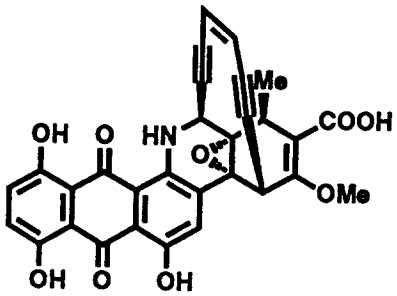
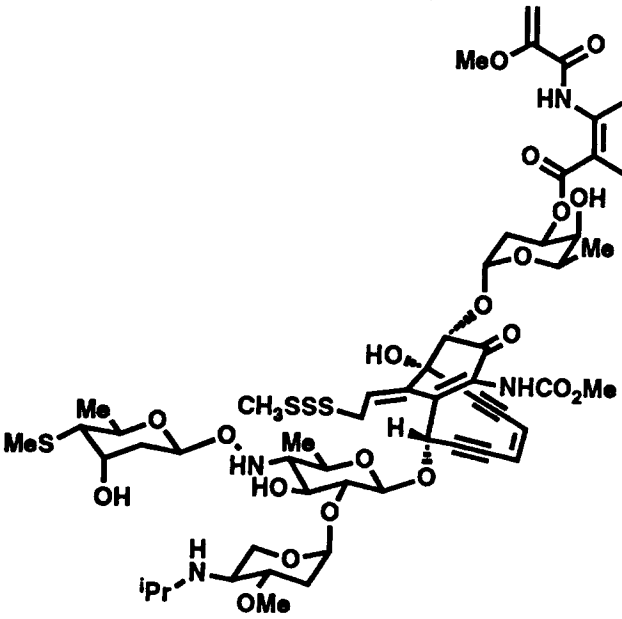
Chart 1



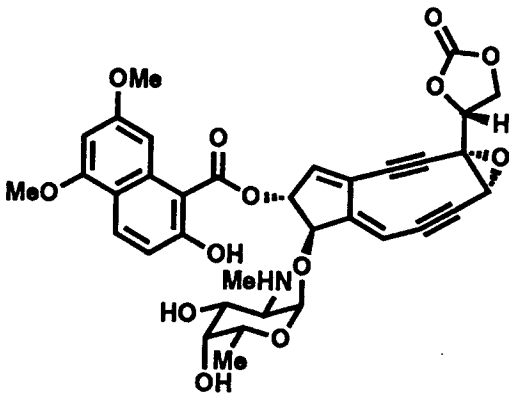
Calicheamicin γ_1^I (1)



Dynemicin A (4)

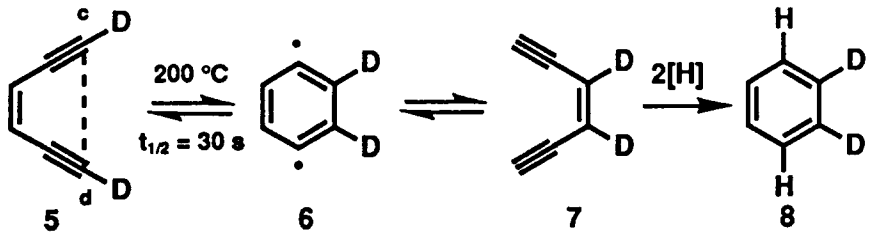


Esperamicin A_1 (2)

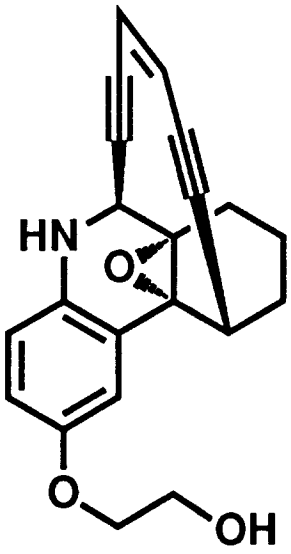


Neocarzinostatin Chromophore (3)

Figure 1



The Bergman cyclization reaction (1972). The distance between the centers *c* and *d* in the educt calculated by MM2 is 4.12 Å.



76

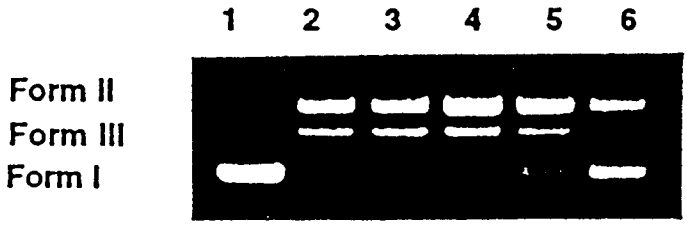
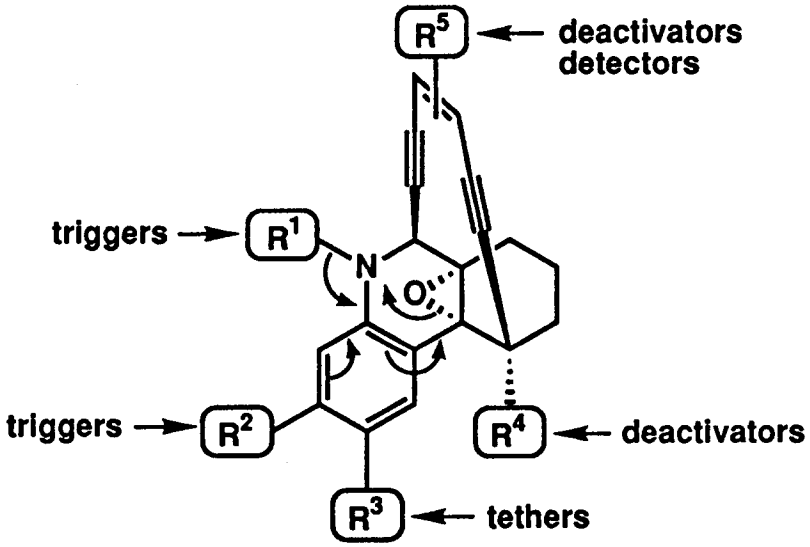


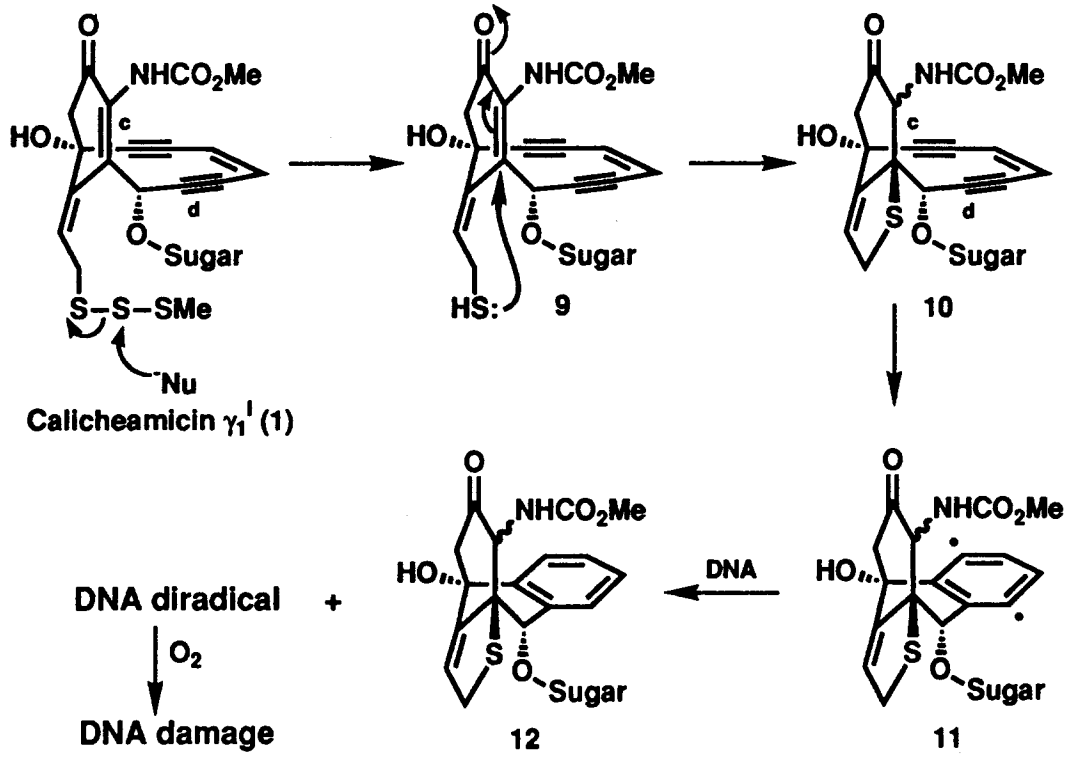
Figure 2. ΦX174 Form I DNA (50 μM per base pair) was incubated for 4 h at 37 °C with compound **76** (in 10% EtOH in phosphate buffers, pH 7.4, 50 mM) and analyzed by gel electrophoresis (1% agarose, ethidium bromide stain). Lane 1, control; lanes 2-6, 5000, 2000, 1000, 500, 100 μM of **76**, respectively. Key: I, form I DNA; II, form II DNA, III, form III DNA.

Figure 3



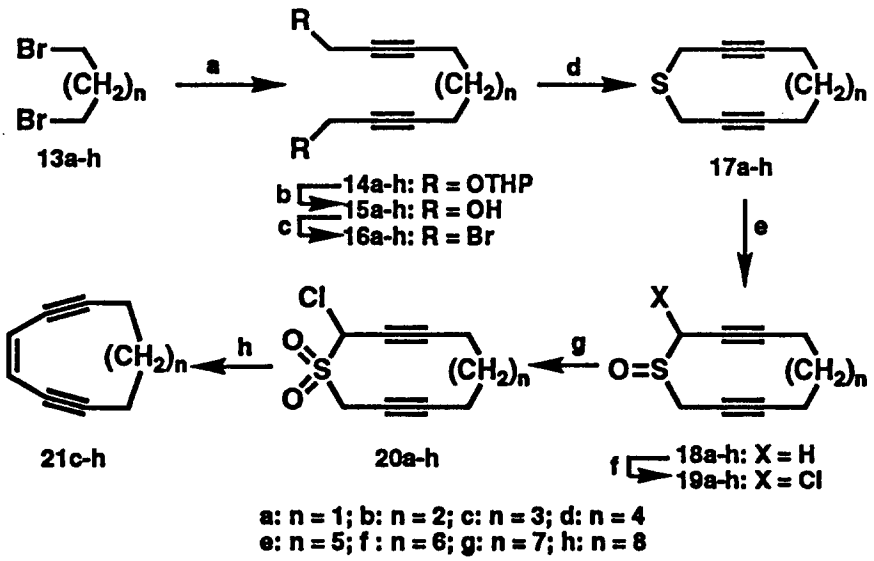
Molecular design of dynemicin A model systems.

Scheme I



Mechanism of DNA cleavage by 1.

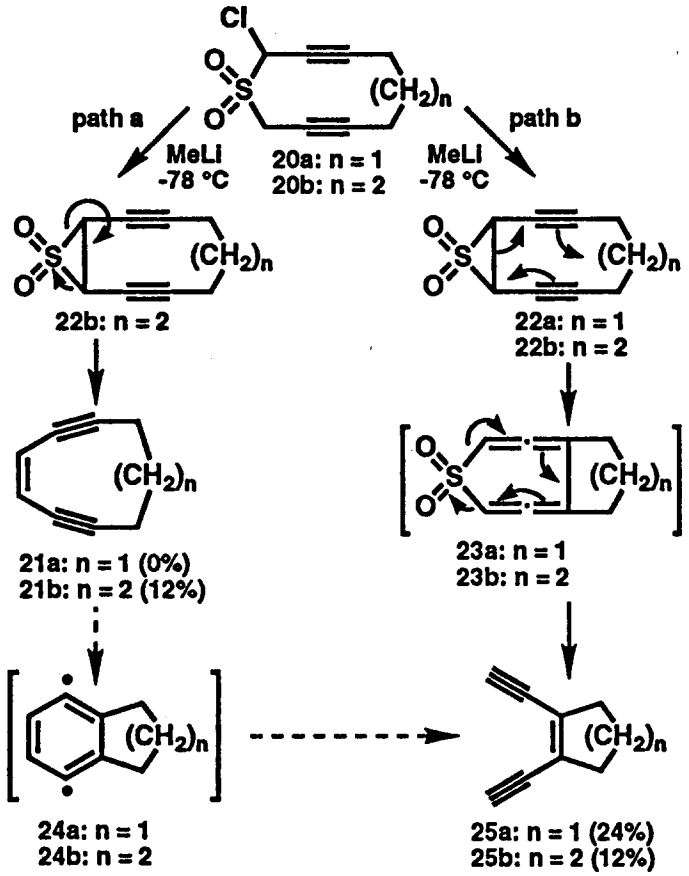
Scheme II[a]



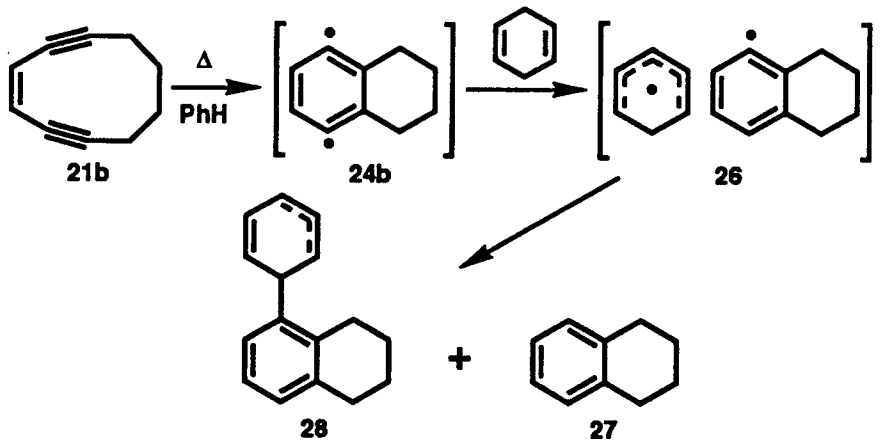
a: n = 1; b: n = 2; c: n = 3; d: n = 4
e: n = 5; f : n = 6; g: n = 7; h: n = 8

Reagents and conditions: (a) $THPOCH_2CCH$, *n*-BuLi, HMPA, THF, -78 °C; (b) PPTS, MeOH; (c) *n*-Bu_3P, CBr_4, Et_2O, 0 °C; (d) $Na_2S{\cdot}9H_2O$, EtOH, H_2O, 25 °C; (e) *m*CPBA, CH_2Cl_2, -78 °C; (f) SO_2Cl_2, Pyr., CH_2Cl_2, -78 °C; (g) *m*CPBA, CH_2Cl_2, 0 °C; (h) 1.2 equiv. of KO^tBu, THF, -78 °C.

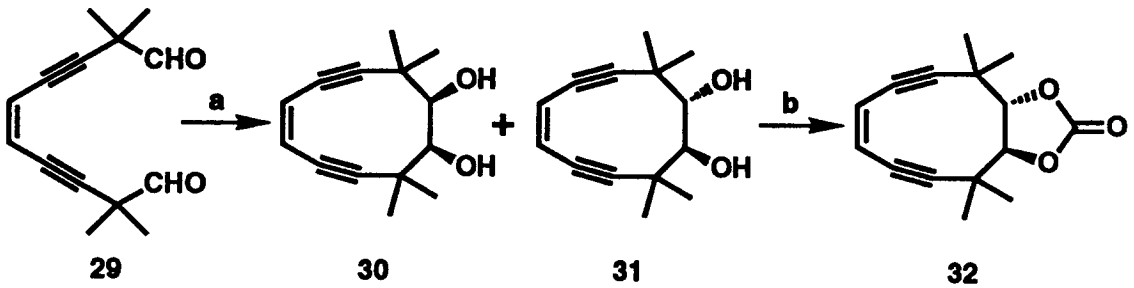
Scheme III



Scheme IV

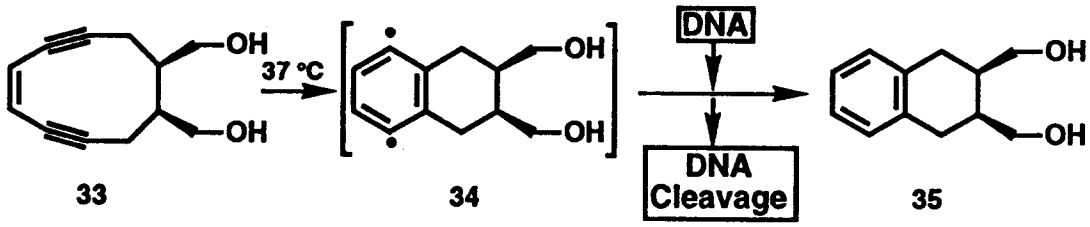


Scheme V[a]



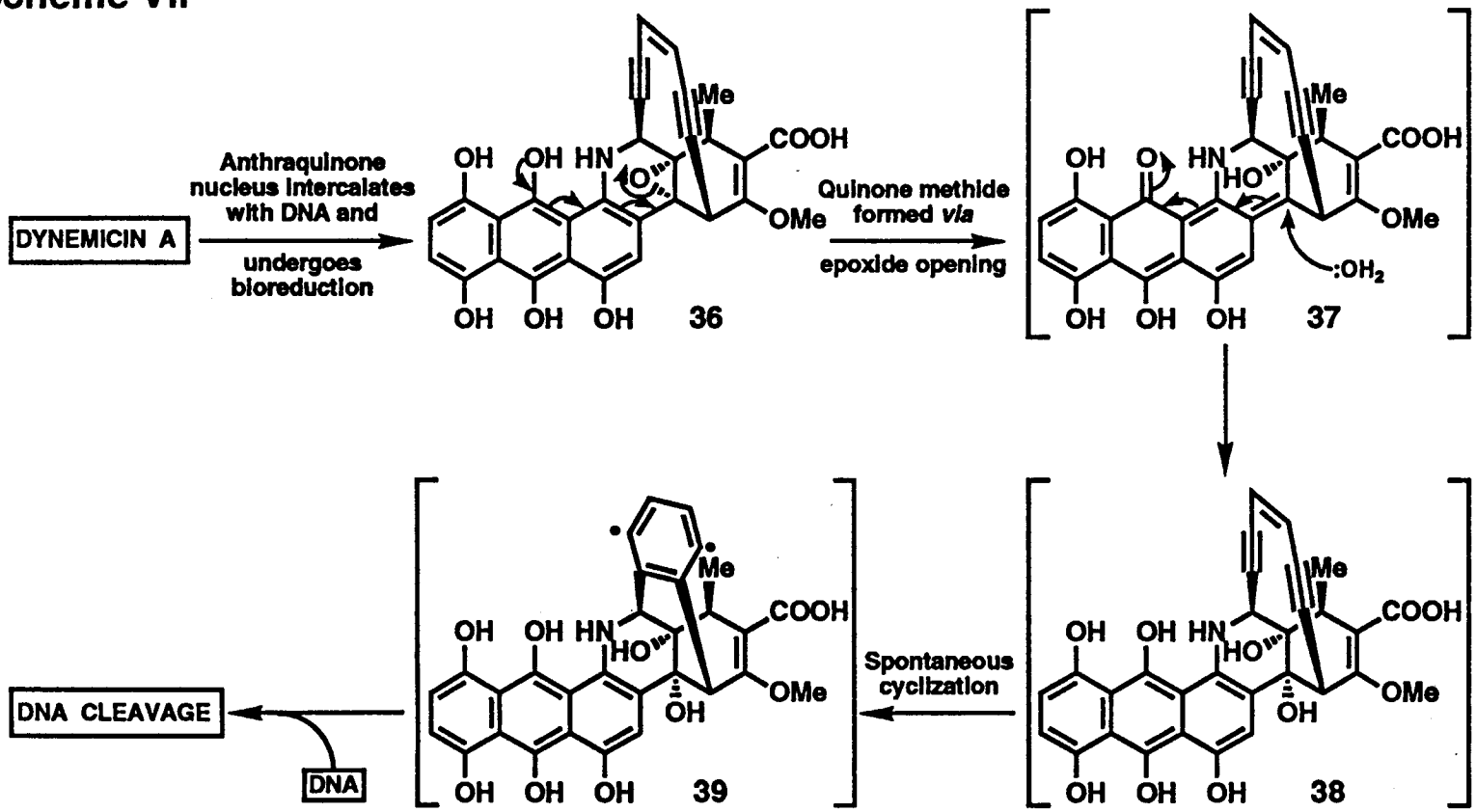
aReagents and conditions: (a) 5.0 equiv. of SmI_2, THF, 25 °C, 1 h, 42% (trans/cis, ~20:1); or excess Ti(O) [from TiCl3•3/2DME and Zn-Cu couple], DME, 25 °C, 12 h, 45% (trans/cis, ~1:2.6); (b) 1.1 equiv. of (COCl)2, 2.1 equiv. of Et3N, CH_2Cl_2, 0 °C, 15 min, 85%.

Scheme VI



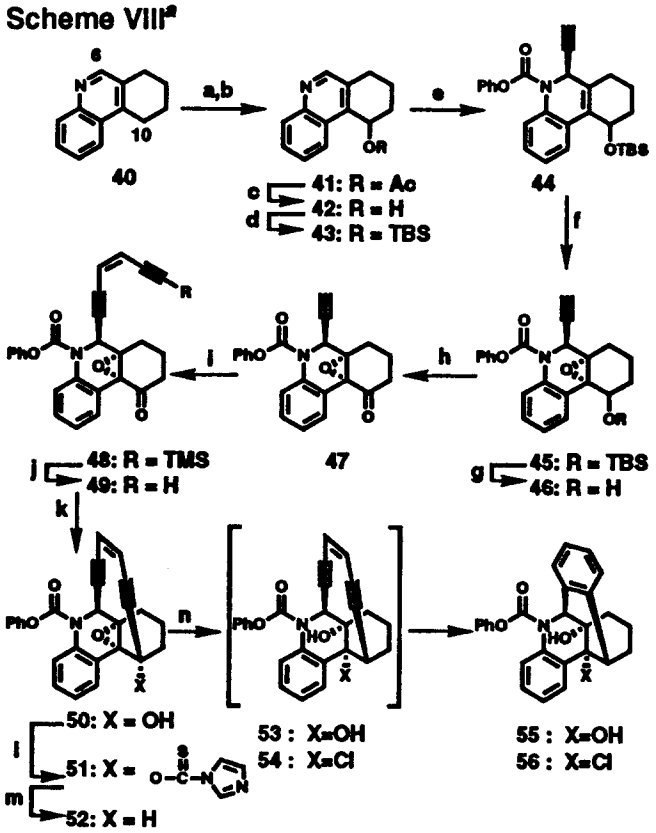
Model 10-membered ring enediynes.

Scheme VII



Proposed mechanism of DNA cleavage by dynemicin A.

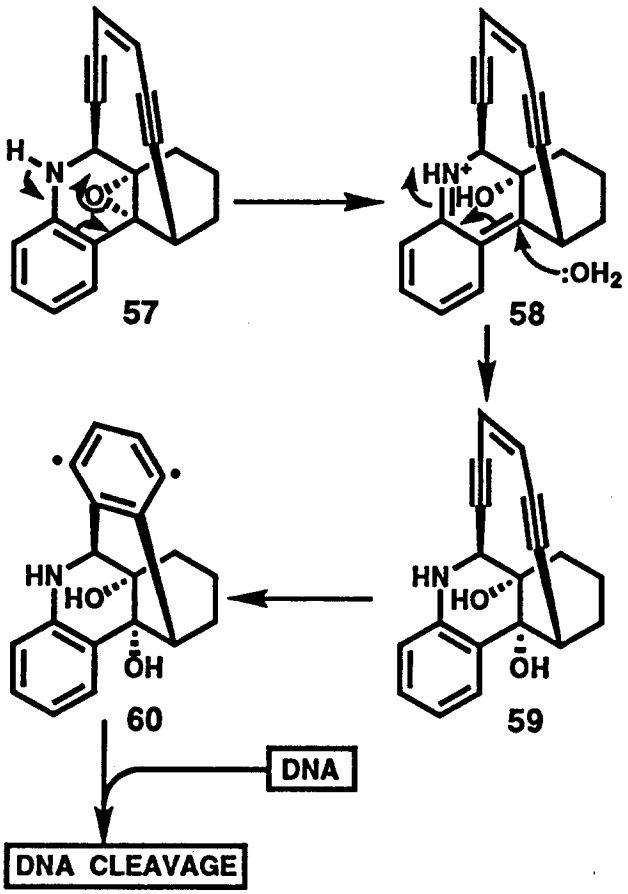
Scheme VIII[a]



[a]Reagents and conditions: (a) 1.0 equiv. of mCPBA, CH_2Cl_2, 25 °C, 1 h, 80%; (b) Ac_2O, reflux, 20 h, 77%; (c) K_2CO_3 (catalytic), MeOH, 25 °C, 1 h, 100%; (d) 1.2 equiv. of $^tBuMe_2SiOTf$, 1.4 equiv. of 2,6-lutidine, CH_2Cl_2, 0.5 h, 92%; (e) 3.0 equiv. of ethynylmagnesium bromide, 3.0 equiv. of PhOCOCl, THF, -78 → 25 °C, 1 h, 92%; (f) 2.0 equiv. of mCPBA, CH_2Cl_2, 25 °C, 3 h, 85%; (g) 1.2 equiv. of TBAF, THF, 42 °C, 3 h, 95%; (h) 3.0 equiv. of PCC, CH_2Cl_2, 4Å MS, 25 °C, 1 h, 81%; (i) 1.4 equiv. of (*Z*)-(4-chloro-3-buten-1-ynyl)trimethylsilane, 1.5 equiv. of *n*-$BuNH_2$, 0.25 equiv. of PPh_3, 0.05 equiv. of $Pd(OAc)_2$, 0.2 equiv. of CuI, PhH, 25 °C, 4 h, 88%; (j) 4.0 equiv. of $AgNO_3$, 7.0 equiv. of KCN, H_2O, EtOH, THF, 25 °C, 10 min, 90%; (k) 1.1 equiv. of LDA, toluene, -78 °C, 1 h, 80% based on 25% recovery of 49. (l) 3 equiv. of thiocarbonyl-diimidazole, 0.5 equiv. of DMAP, CH_2Cl_2, 25 °C, 48 h, 91%; (m) 2 equiv. of *n*-Bu_3SnH, AIBN (catalytic), toluene, 75 °C, 2 h, 75%; (n) (i) 0.05 M in benzene – 1,4-cyclohexadiene (4:1), 1.2 equiv. of $TsOH.H_2O$, 24 h, 25 °C, 86% (X=OH); or (ii) HCl(g), 40 equiv. of 1,4-cyclohexadiene, CH_2Cl_2, 1 min, 25 °C, 82% (X=Cl).

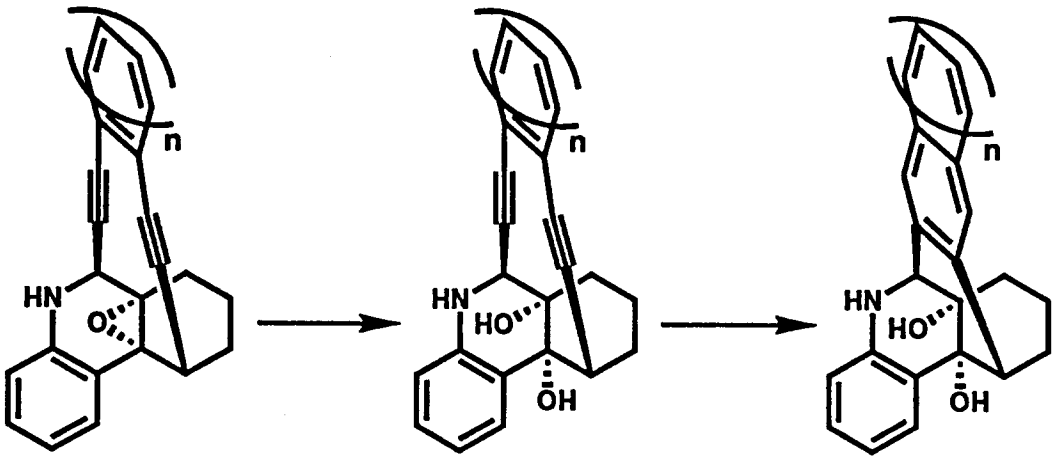
Synthesis of dynemicin A model systems.

Scheme IX[a]



[a]Proposed mechanism of DNA cleavage by dynemicin A model 57.

Scheme X

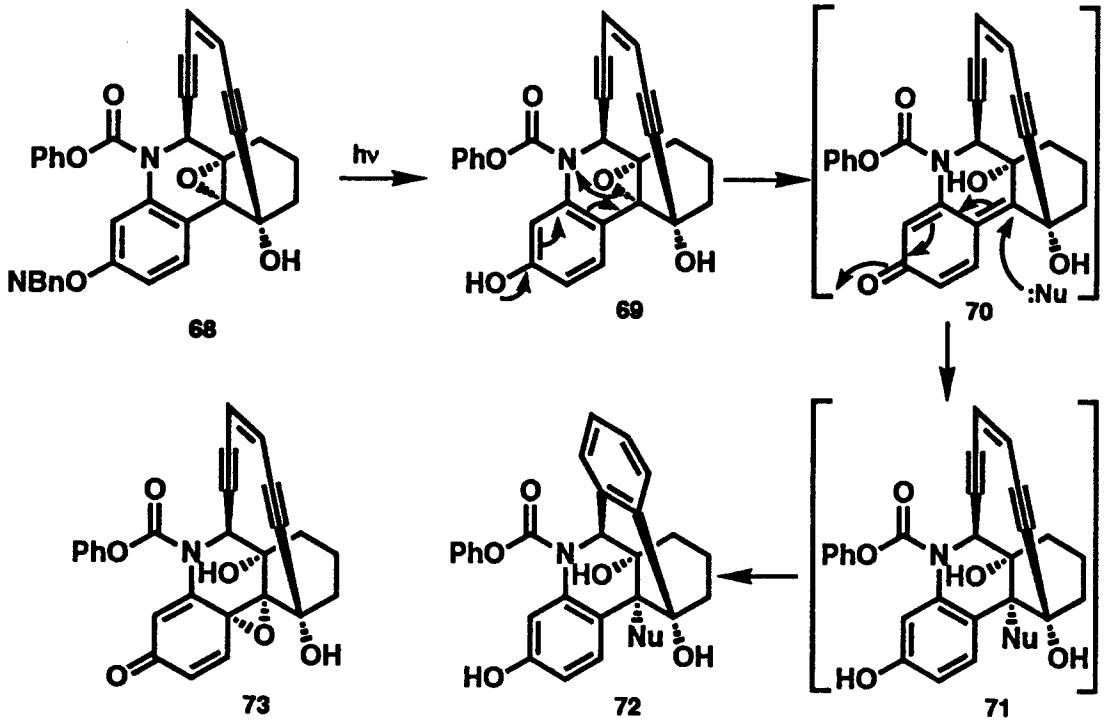


57: n = 0
61: n = 1
62: n = 2

59: n = 0
63: n = 1
64: n = 2

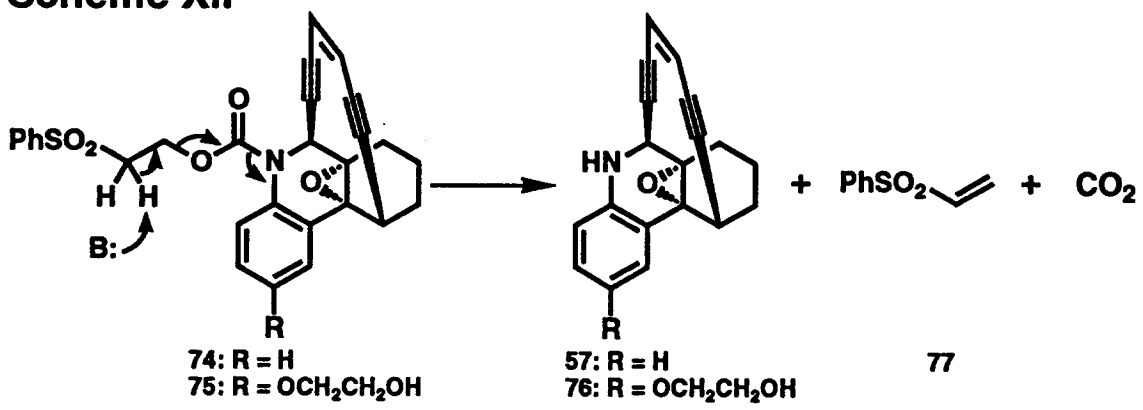
65: n = 0
66: n = 1
67: n = 2

Scheme XI



Photoinitiation of the dynemicin cascade.

Scheme XII



Base induced liberation of reactive dynemicin models.