SYNTHETIC STUDIES ON HETEROANTHRACYCLINES

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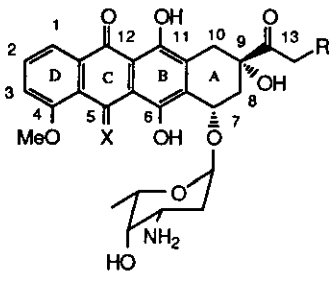
Abstract - This review summarizes the synthetic studies on the new anthracycline analogs which have heterocyclic ring systems in their aglycones.

1. INTRODUCTION

Anthracycline antibiotics, such as daunomycin (**1a**) and adriamycin (**1b**), are important antitumor agents that are widely used in clinics to treat several cancers.[1] However, they have some severe side effects, such as bone marrow suppression and dose-related cardiotoxicity.[2] Consequently, there are many synthetic studies on new anthracycline derivatives to decrease the side effects and to increase their anticancer activities. In this review, we summarize synthetic studies of new analogs of anthracyclines that have heterocyclic ring systems in their aglycones (heteroanthracyclines).

It is suggested that the antitumor activity and cardiotoxicity are caused by some reactive oxygen species such as oxygen anion radicals, hydrogen peroxide, and hydroxy radicals, which are formed by a cyclic redox reaction of anthracyclines.[3] The C-ring quinone moiety of anthracyclines plays an important role in the redox reaction, and it is expected that the C-ring modification effects the biological activity of anthracyclines. In fact, 5-imino derivatives (**2a** and **2b**) showed strong antitumor activity and significantly reduced cardiotoxicity.[4] From this point of view, many research groups have studied C-ring heterocyclic analogs of anthracyclines.



Daunomycin (**1a**): R=H, X=O
Adriamycin (**1b**): R=OH, X=O
2a: R=H, X=NH
2b: R=OH, X=NH

Figure 1

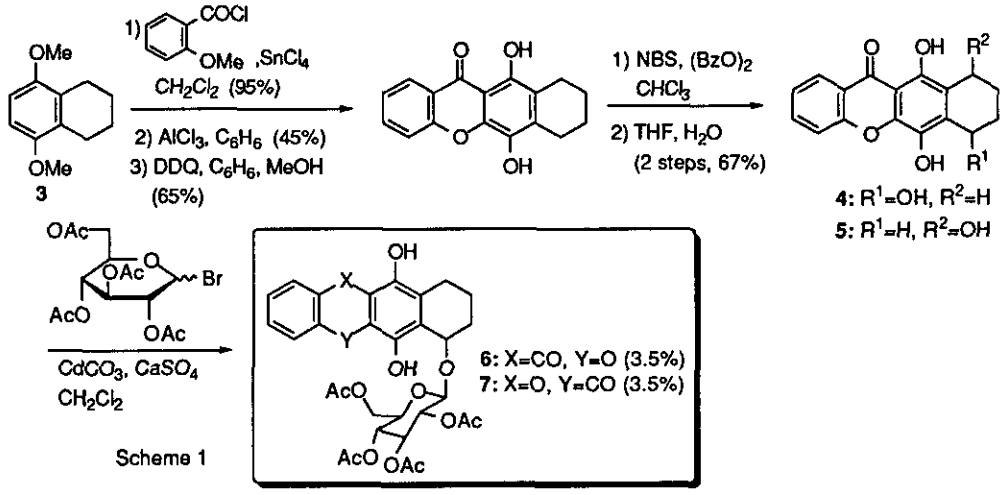
† Dedicated to the memory of late professor Shun-ichi Yamada.

In the first chapter, we summarize the synthetic studies on C-ring heteroanthracyclines. The B or D-ring modification of the chromophore is also expected to have some effect on the C-ring quinone moiety and the redox reaction, because 1 l-deoxy- [5] and 4-demethoxyanthracyclines[6] are well recognized to exhibit higher values of therapeutic index than natural anthracyclines. Although the synthetic studies on B-ring heterocyclic analogs of anthracyclines have not been examined at all, several kinds of the D-ring heteroanthracyclines have been synthesized. In the second chapter, the synthetic studies on D-ring heteroanthracyclines are reviewed. The A-ring modification is also interesting not only for the biological activities but also from the stereochemical and conformational point of view. The A-ring heteroanthracyclines are handled in the last chapter.

2. C-RING HETEROCYCLIC ANALOGS

2-1. ANALOGS HAVING A XANTHONE MOIETY

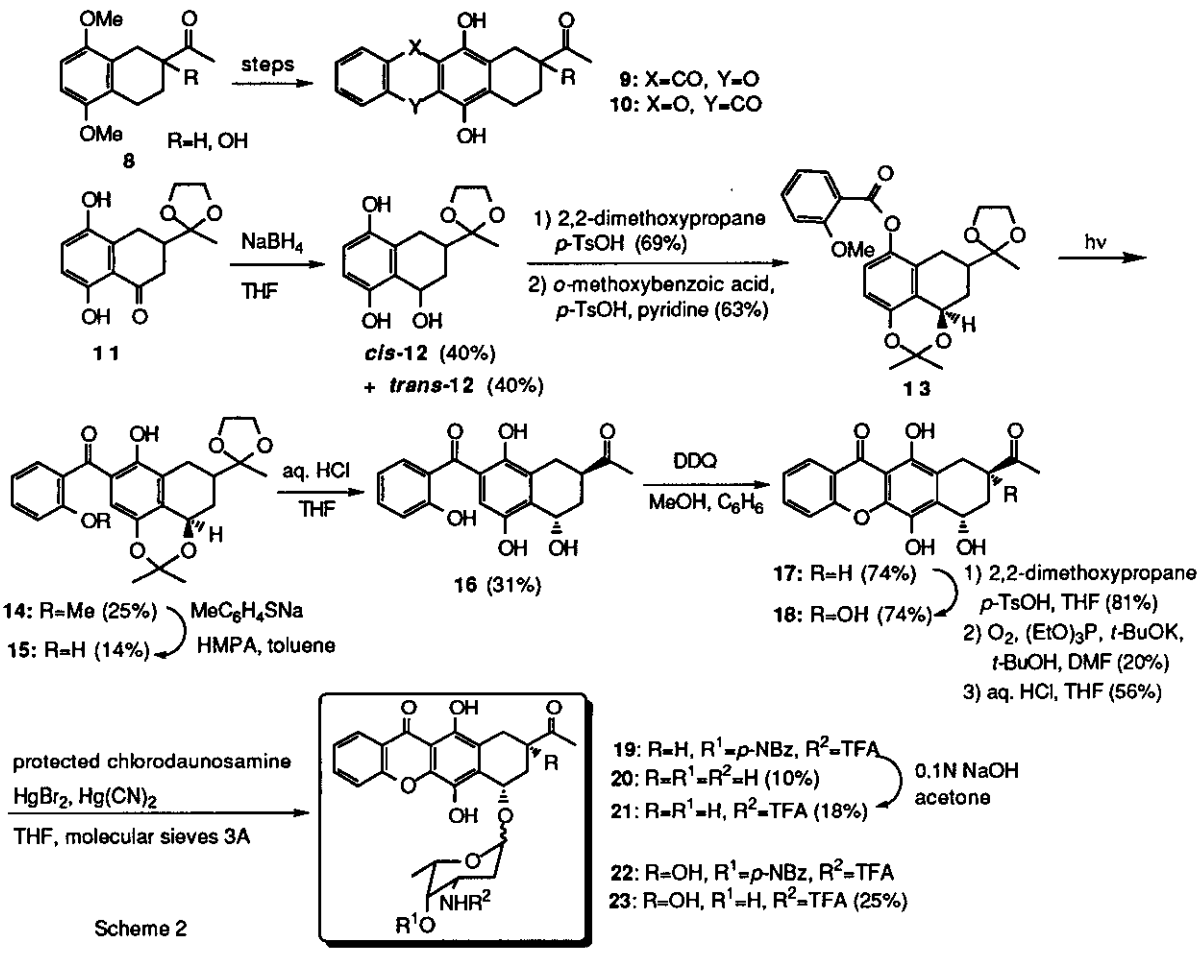
Lown's group planned to synthesize the C-ring heteroanthracyclines having a xanthone moiety. At first, they prepared **6** and **7** as the model compounds.[7] The tetracyclic xanthone compound was synthesized from 5,8-dimethoxytetraline (**3**) utilizing the Freidel-Crafts acylation and the oxidative xanthone formation induced by DDQ. Radical bromination and hydration afforded the hydroxy derivatives (**4** and **5**). Coupling of **4** and **5** with the protected sugar could be effected using cadmium carbonate to afford **6** and **7**, but the yields of the products were quite low.



Scheme 1

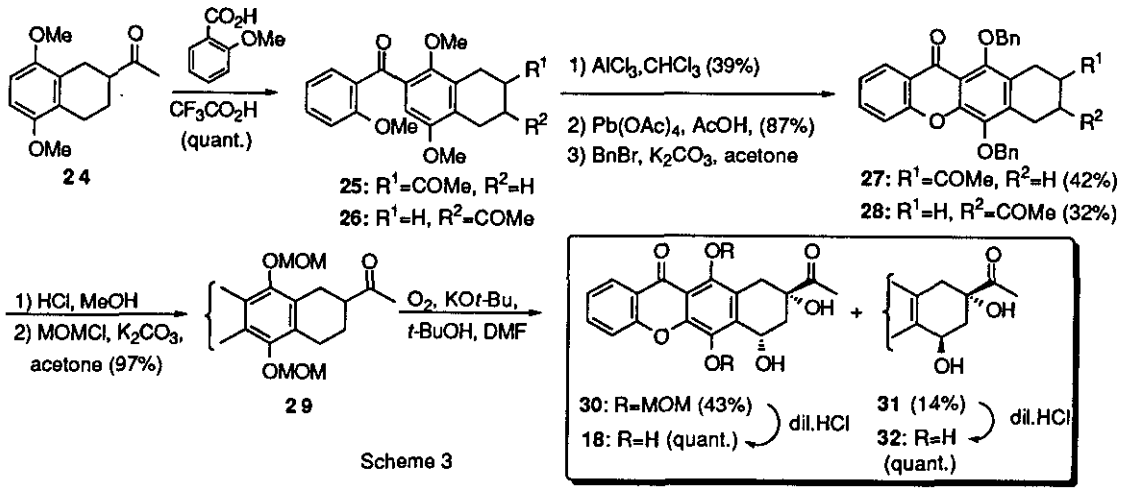
Although A-ring substituted heteroanthracyclinones (**9** and **10**) could be prepared from **8** by the same procedure as the synthesis of **4** and **5**, all attempts to functionalize at C-7 failed.[7] They tried to introduce the C-7 hydroxy function in the initial synthon for the synthesis of heteroanthracyclinone.[8] The *cis* alcohol (*cis*-**12**) obtained from $NaBH_4$ reduction of **11** was converted into **13**, and irradiation with UV lamps caused photo-Fries rearrangement to afford **14**. Demethylation of **14** with $AlCl_3$, HCl or BBr_3 was not successful. Nucleophilic demethylation of **14** with sodium thiocresolate afforded the desired **15** in low yield. DDQ oxidation of **16** afforded the tetracyclic **17**. The hydroxy group was introduced into the A-ring by means of

oxidation with molecular oxygen to give **18**. Glycosidation of **17** and **18** with the protected chlorodaunosamine by using the Koenigs-Knorr method gave the glycosides (**19**) and (**22**) as a mixture of α and β anomers. Alkaline deprotection of a sugar moiety afforded **20, 21,** and **23**. These glycosides (**19-23**) exhibited cytotoxicity against leukemia L1210 cells grown in culture with ID_{50} values in a range up to 10 mg / mL. The antileukemic activity of these compounds is lower than that of the parent **1a**.[9]



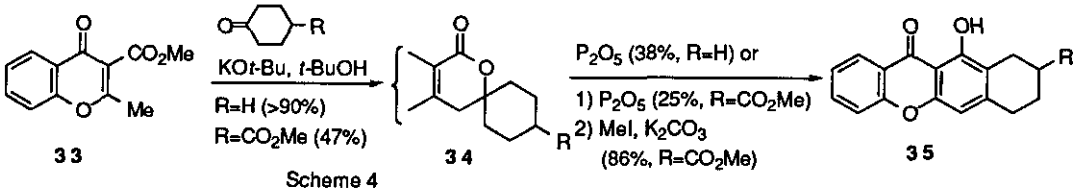
Scheme 2

Wong's group synthesized the C-ring heteroanthracyclinones having a xanthone moiety (**18** and **32**).[10] The Freidel-Crafts acylation of **24** and successive oxidative cyclization gave tetracyclic xanthone as a mixture of two regioisomers (**25** and **26**). A large scale separation of regioisomers was accomplished by column chromatography of their corresponding dibenzyl ethers (**27** and **28**) on silica gel. Hydrolysis of **27** followed by methoxymethylation gave **29**, which was oxidized by molecular oxygen in the presence of *t*-BuOK to give **30** and **31**. Hydrolysis of **30** and **31** afforded **18** and **32**, respectively, which show a weak cytotoxicity against tumor cells MCF-7 (*in vitro*).



Scheme 3

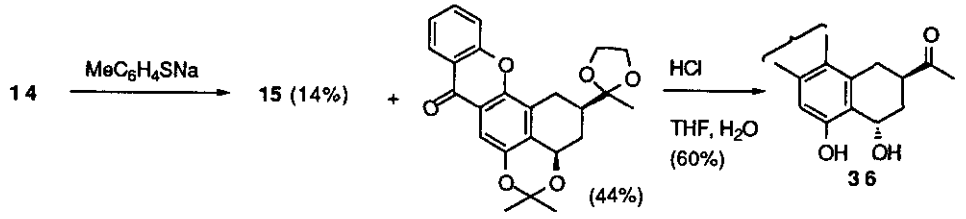
Charlton's group synthesized the tetracyclic **35** that has the xanthone ring system from the spirolactone (**34**) obtained by the condensation reaction of **33** with cyclohexanone.[11] They tried to introduce substituents in the A ring, but all attempts were unsuccessful.

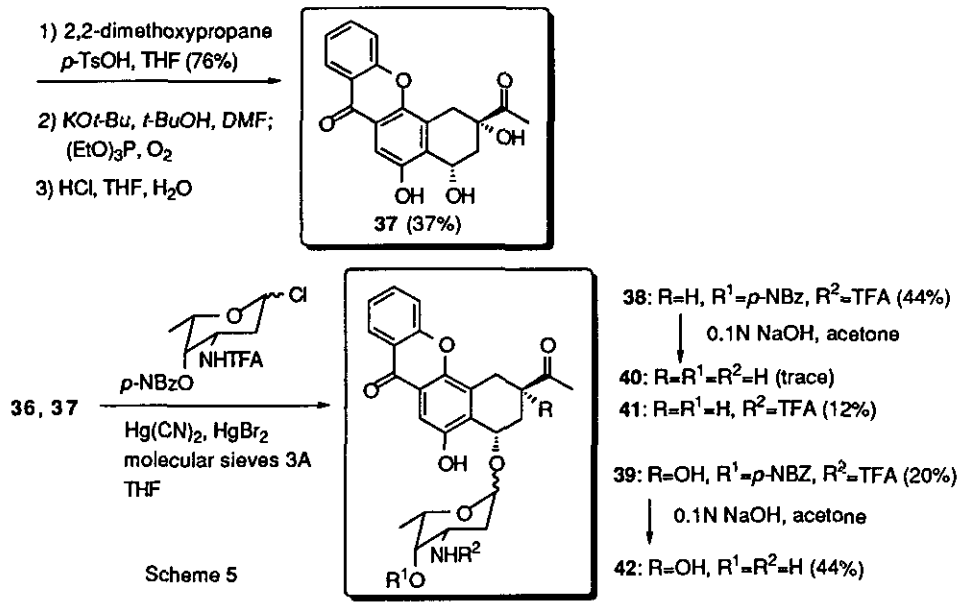


Scheme 4

2-2. ANALOGS HAVING AN ANGULAR XANTHO[2,3-*g*]TETRALINE SYSTEM

Lown's group synthesized the heteroanthracyclines having an angular xantho[2,3-*g*]tetraline ring system (**39-43**).[12] As described in Chapter **2-1**, they obtained the angular compound (**36**). A hydroxy group was introduced into the A-ring of **36** by means of molecular oxygen oxidation. Glycosidation of **36** and **37** with the protected chlorodaunosamine was performed under the Koenigs-Knorr conditions to afford **38** and **39**, which were deprotected to give **40**, **41**, and **42**. These glycosides (**38-42**) exhibit low cytotoxicity against leukemia L 1210 cells grown in culture with ID_{50} values in the range of 1 - 10 mg / mL.

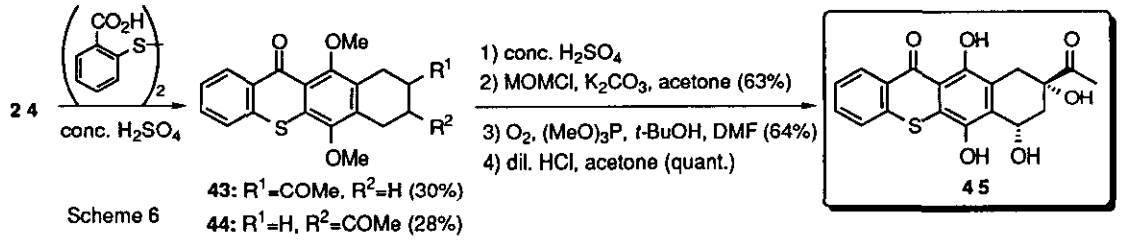




Scheme 5

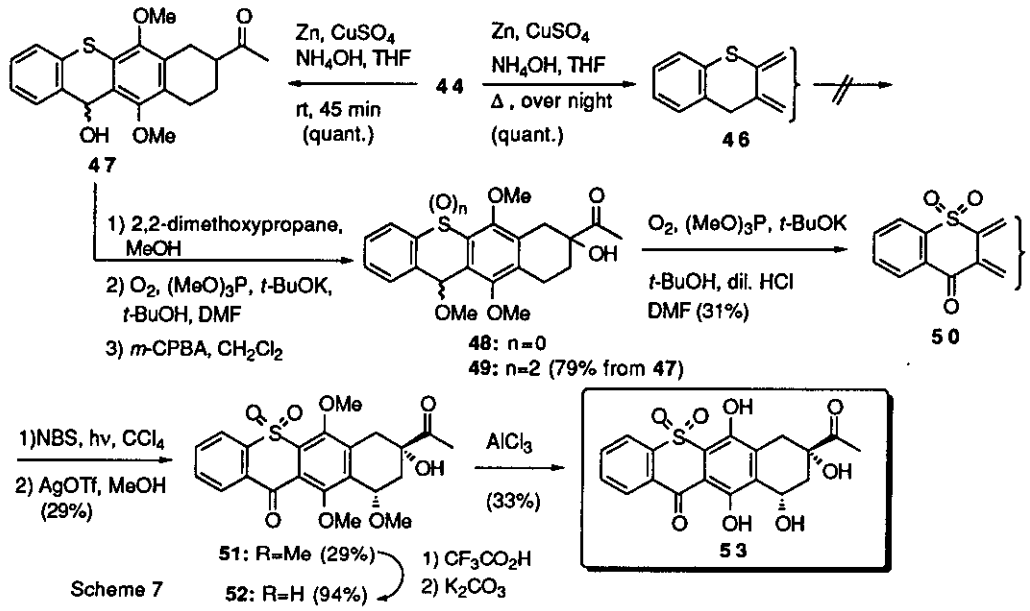
2-3 ANALOGS HAVING A THIOXANTHONE RING SYSTEM

Wong's group synthesized the heteroanthracyclines having a thioxanthone ring system.[13] Condensation of **24** with 2,2'-dithiosalicylic acid in conc. H_2SO_4 gave the separable tetracyclic **43** and **44**. Demethylation, realkylation and oxidation of **43** gave a mixture of *cis*- and *trans*-diols. Hydrolysis of *cis*-diol gave the desired **45**.



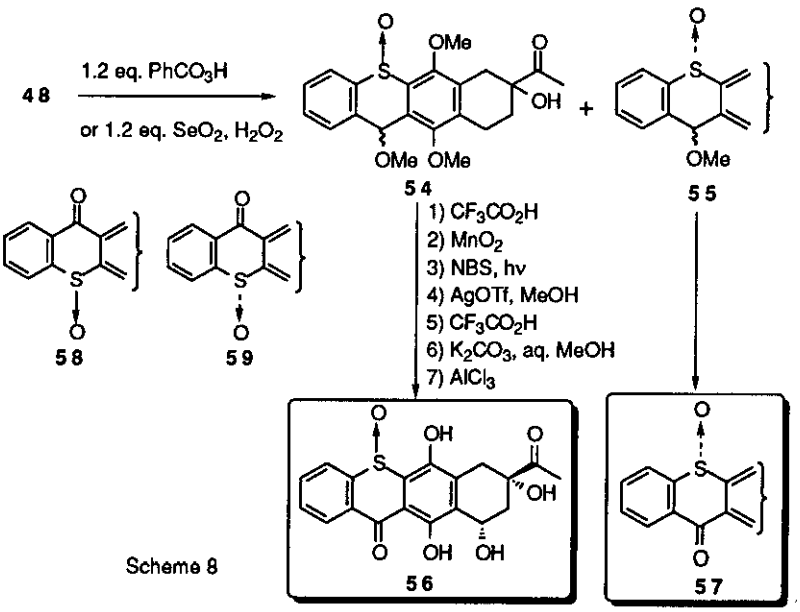
Scheme 6

Wong *et al.* synthesized the 12-sulfone and sulfoxide analogs of **1a**.[14,15] All their attempts to oxidize **44** into the corresponding sulfone or sulfoxide failed. Therefore, they tried to remove the C-5 carbonyl function. The reduction of **44** with zinc and $CuSO_4$ afforded **46**, but further conversion failed. When the reduction was carried out at room temperature, the product was a mixture of isomers (**47**). A hydroxy group was introduced into the A-ring by means of molecular oxygen. Further oxidation of **48** by *m*-CPBA gave the separable sulfone (**49**). Oxidation of **49** by molecular oxygen, followed by the addition of dil. HCl and $(MeO)_3P$, regenerated the C-5 carbonyl function to form **50**. Introduction of the methoxy group to C-7 was accomplished by bromination with NBS and subsequent methanolysis in the presence of AgOTf. Treatment of **51** with CF_3CO_2H and then with aq. K_2CO_3 gave **52** which was demethylated to provide the aglycones (**53**).[14]



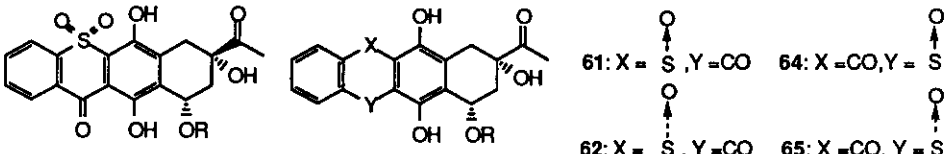
Scheme 7

Alternatively, oxidation of **48** with $C_6H_5CO_3H$ or SeO_2/H_2O_2 afforded a mixture of the sulfoxides (**54** and **55**), which was converted into **56** and **57**. The regioisomeric aglycones (**58** and **59**) were prepared by the same procedure. [15]



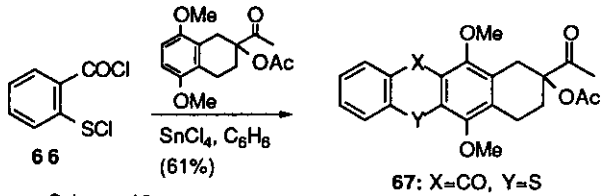
Scheme 8

The aglycone (**53**) was coupled with the protected chlorodaunosamine in the presence of AgOTf to give the glycoside, which was deproteced by aq. NaOH to give the desired **60**. The related glycosides (**61**-**65**) were synthesized by the same procedure.[15]



Scheme 9

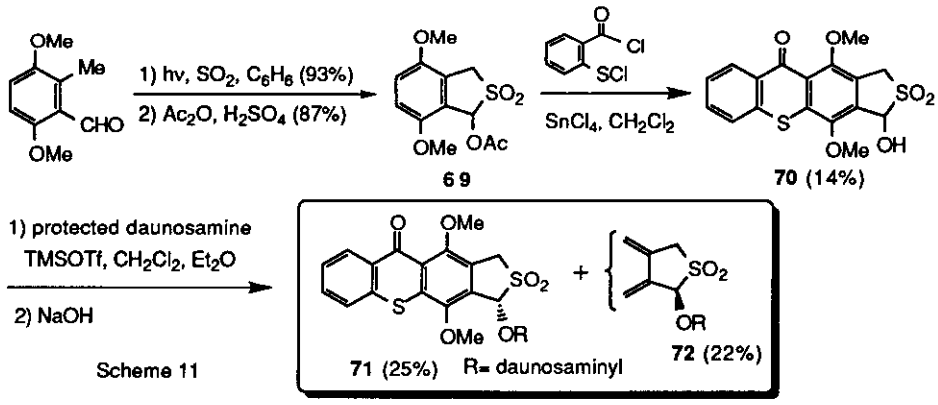
Belleau's group synthesized the tetracyclic **67** and **68** which have a thioxanthone ring system by means of the Freidel-Crafts reaction of **66**.[16]



Scheme 10

They also reported the total synthesis of the heteroanthracycline having heterocyclic ring systems in its A and C rings. Photochemical irradiation of 2,5-dimethoxy-6-methylbenzaldehyde in a solution of SO_2 in benzene and subsequent acetylation gave **69**.[17] A double Freidel-Crafts reaction of **69** gave **70**. The glycosidation of **70** with the protected daunosamine under the conditions developed by Terashima *et al.*[18] afforded the two α-glycosides, and deprotection of them afforded **71** and **72**.

The heteroanthracycline (**71**) was subjected to an *in vitro* cytotoxicity evaluation against several tumor cells and showed a wide spectrum of neoplasm-inhibiting activity.



Scheme 11

2-4. ANALOGS HAVING OTHER HETEROCYCLES

Antitumor properties have been reported for several phenazine 5,10-dioxides (**73** and derivatives) against Ehrlich ascites carcinoma in mice.[19] Therefore, Acton's group tried to synthesize the anthracycline analog that has the phenazine 5,10-dioxide structure (**74**).[20] At first, they tried to synthesize heteroanthracyclines from **75-78**, but all their attempts were unsuccessful.

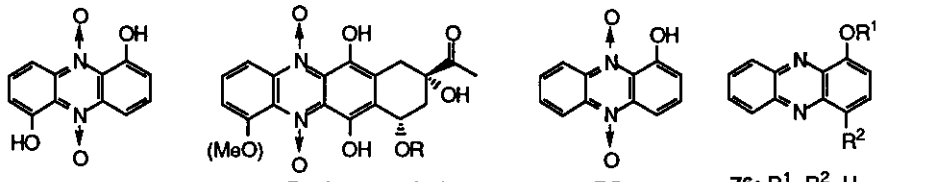
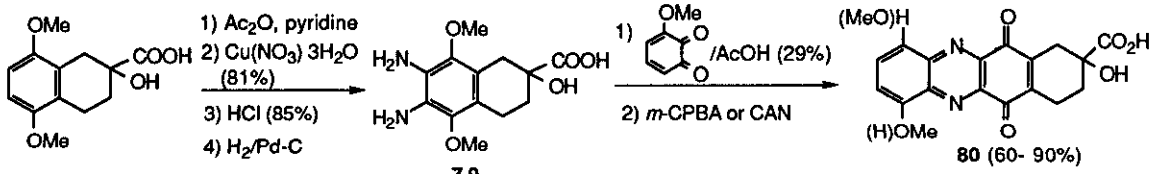


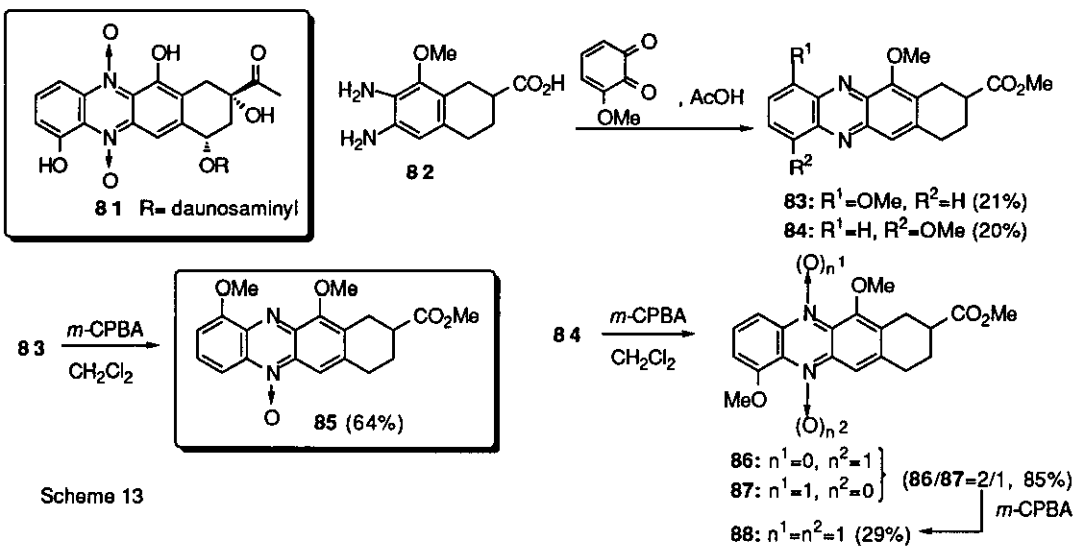
Figure 2

An alternative approach, which contains the reaction of **79** with 3-methoxy-1,2-quinone as a key step, gave the tetracyclic **80** as a mixture of regioisomers, but their attempts at *N*-oxidation of **80** were unsuccessful.



Scheme 12

They redesigned the target *N*-isosters to avoid the *p*-dihydroxy substituent that is incompatible with *N*-oxidation. Their final target was **81**, and they synthesized the substituted 7,8,9,10-tetrahydrobenzo[*b*]phenazine *N*-oxides (**85-87**) and the *N*-dioxide (**88**).[21] They tried to synthesize **88** by the condensation of the *o*-phenylenediamine (**82**) containing the relevant AB moiety and an appropriately substituted 1,2-benzoquinone. Diamine (**82**) was condensed with 3-methoxy-1,2-benzoquinone to give the two separable regioisomers (**83**) and (**84**). *N*-Oxidation of **83** gave the 5-oxide (**85**), but an attempted conversion to the 5,12-dioxide failed. Under the same conditions, **84** was converted to a 2:1 mixture of the 5- and 12-oxides (**86** and **87**). Retreatment of this isolated mixture with *m*-CPBA yielded the 5,12-dioxide (**88**). They have not reported further transformations from **88**.



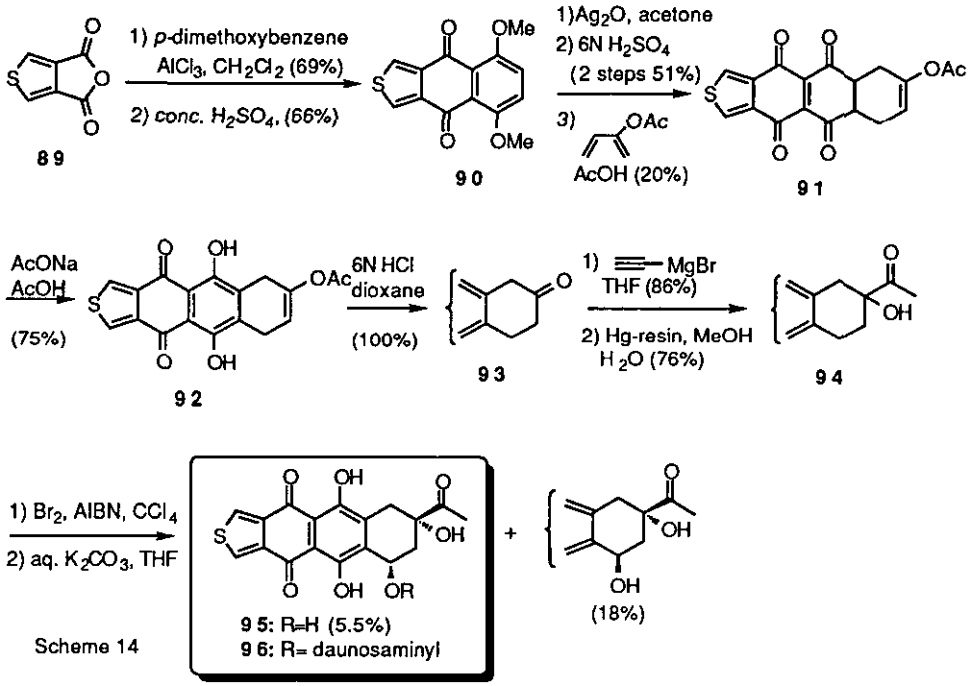
Scheme 13

3. D-RING HETEROCYCLIC ANALOGS OF ANTHRACYCLINE

3-1. ANALOGS HAVING A THIOPHENE MOIETY

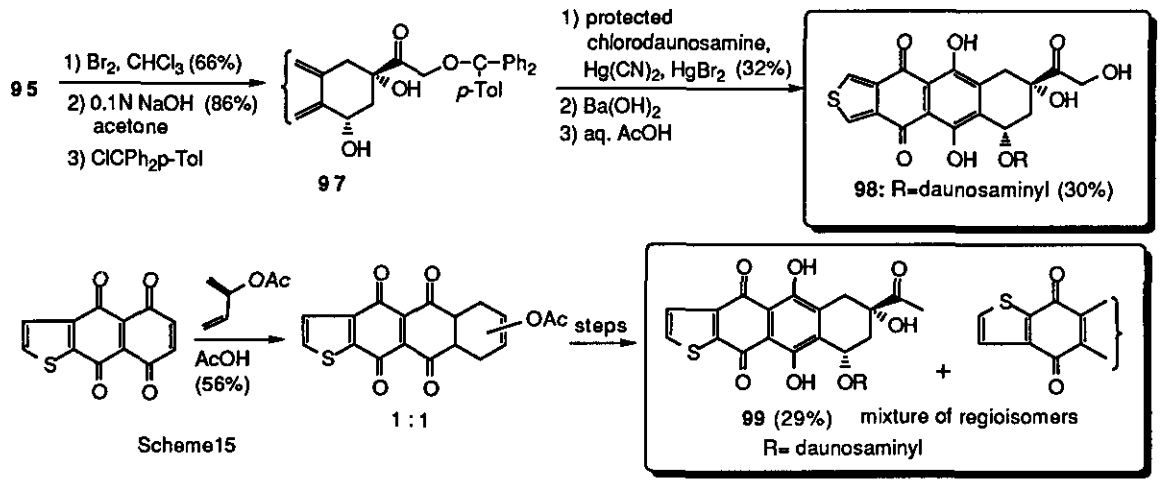
Kende's group synthesized several kinds of the D-ring thiophene analogs of anthracyclines.[22]

The anhydride (**89**) was treated with *p*-dimethoxybenzene under the Friedel-Crafts condition followed by treatment with H_2SO_4 to produce the tricyclic **90**. The oxidation of **90** with Ag_2O and condensation with diene gave **91** that was isomerized by NaOAc to give **92**. Tricarbonyl compound (**93**) was converted into **94**. Hydroxylation into the A-ring of **94** was accomplished by radical bromination and hydration to give the tetracyclic **95**. The undesirable *trans*-diol was epimerized by CF_3CO_2H in 90% yield. The glycosidation of **95** and 4-*O*-*p*-nitrobenzoyl-3-*N*-trifluoroacetyldaunosaminyl chloride under the Koenigs-Knorr conditions gave a mixture of the α- and β-anomers in 37% and 27% yields, respectively. The deprotection of the α-anomer gave **96** which has an antitumor activity toward mouse's leukemia P-388 (T/C%=174, optimal dosage=2.5mg/Kg).



Scheme 14

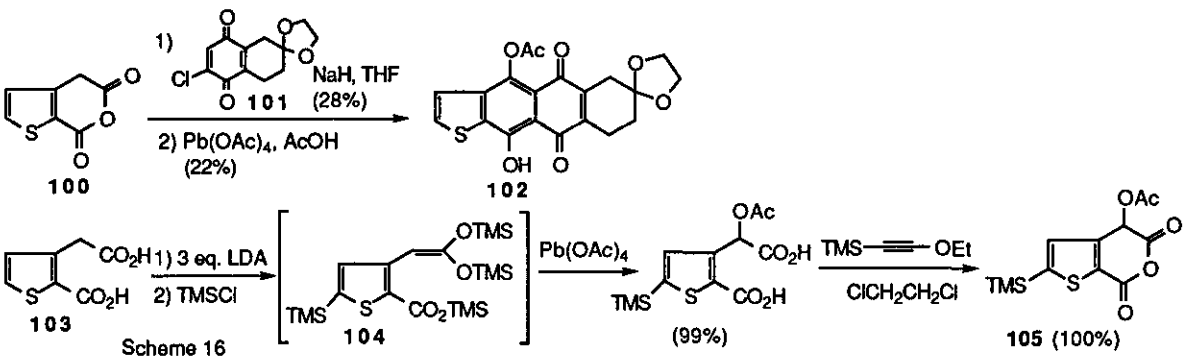
The compound (**95**) was converted into the protected adriamycinone analog (**97**) which was coupled with the protected chlorodaunosamine to give the corresponding glycoside. The glycoside was deprotected to give **98**. They also synthesized an inseparable regioisomeric mixture of heteroanthracyclines (**99**) by similar procedures.



Scheme15

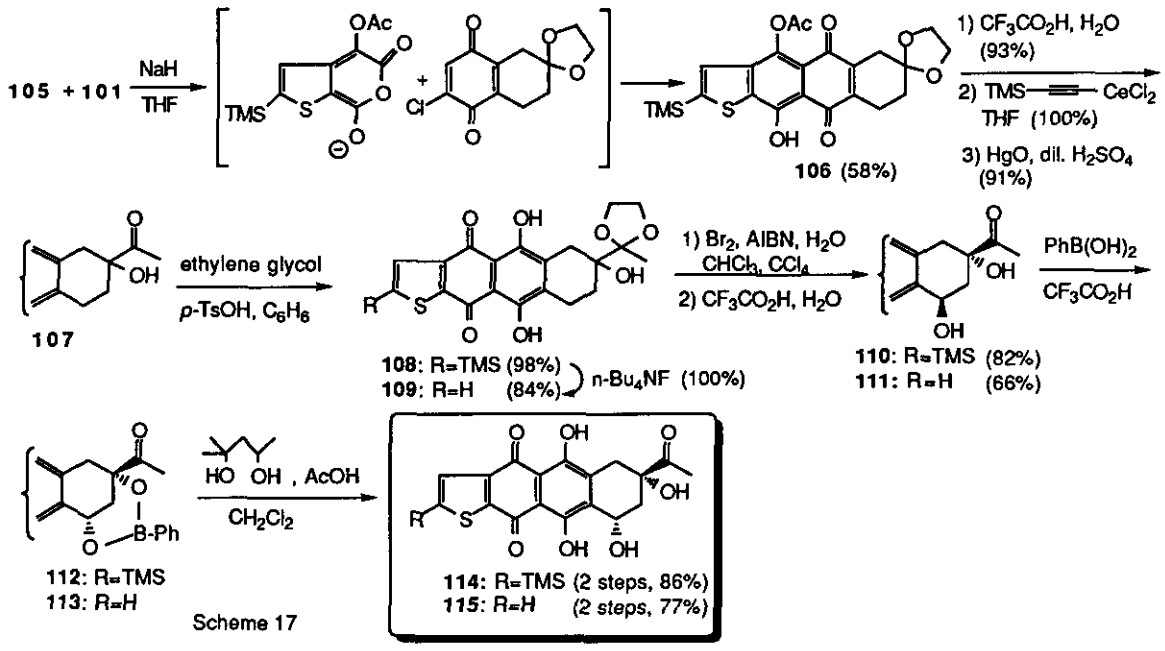
The authors' group accomplished the regiospecific total synthesis of the D-ring thiophene analogs of **1a**.[23] Synthetic strategy was based on a strong base-induced cycloaddition of homophthalic anhydrides, which was developed by the authors' group. [24]

At first, we used the known anhydride (**100**) for the cycloaddition to **101** and obtained the tetracyclic **102** regioselectively. However, the yields of the cycloaddition and the next oxidation were quite low. Therefore, we developed an alternative synthesis using a cycloaddition of the previously C_2-acetoxylated anhydrides and quinones. The anhydride (**105**) was prepared in an excellent yield from **103** through a $Pb(OAc)_4$ oxidation of **104** and dehydration with (trimethylsilyl)ethoxyacetylene.



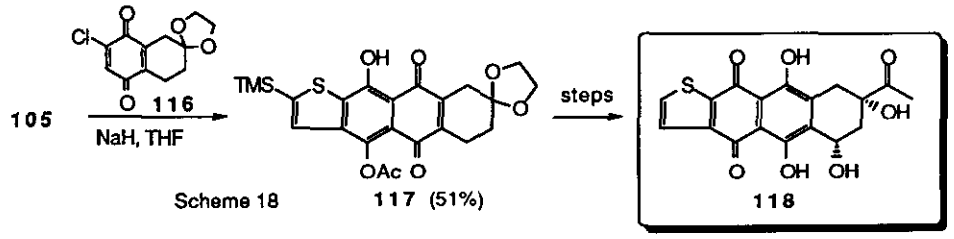
Scheme 16

Treatment of the sodium enolate of **105** with **101** gave the regiospecific cycloadduct (**106**). Acid hydrolysis of **106** led to the tricarbonyl compound, then trimethylsilylethynylation with a cerium(III) reagent gave the corresponding carbinol, which was hydrolyzed to give **107**. Attempts to convert the monoacetals (**108** and **109**) into the desired aglycone having the *cis*-diols in their A-ring by radical bromination and the hydration gave an unexpected *trans*-diols (**110** and **111**). Epimerization was accomplished when **110** and **111** were treated with benzeneboronic acid in the presence of CF_3CO_2H. The resulting *cis*-boronates (**112** and **113**) were deprotected with 2-methylpentane-2,4-diol and acetic acid to give the desired aglycones (**114** and **115**), regioselectively.



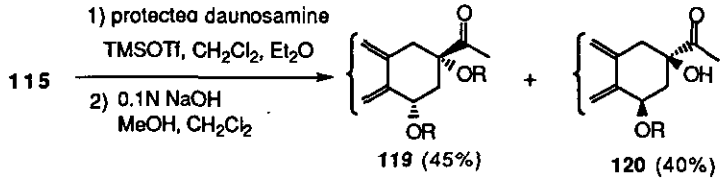
Scheme 17

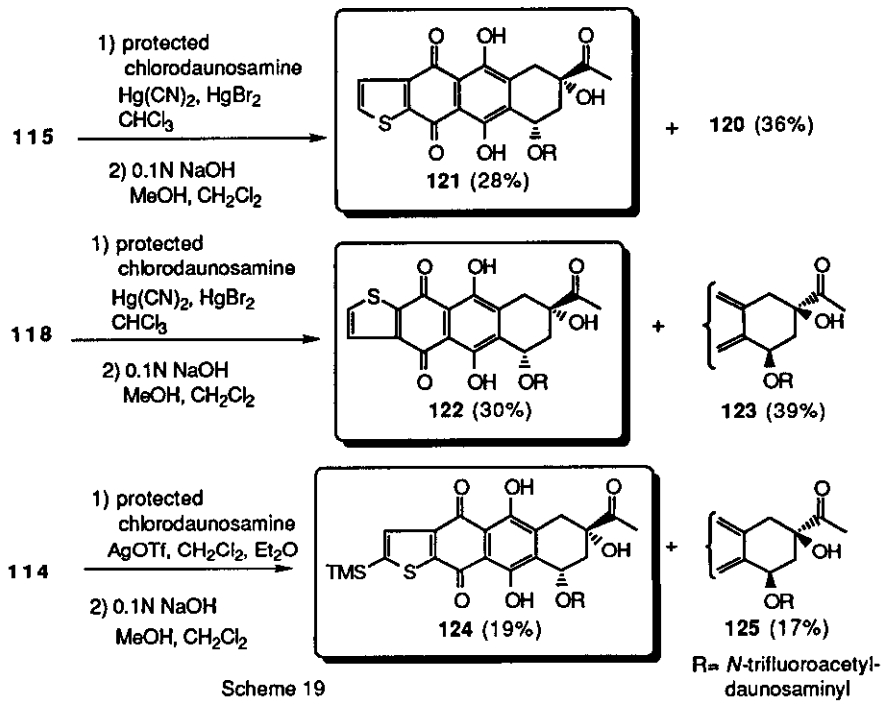
Similarly regioisomeric aglycone (**118**) was prepared from the adduct (**117**) obtained by the reaction of **105** and **116**.



Scheme 18

The glycosidation of **115** with the appropriately protected L-daunosamine using TMSOTf gave the natural type of bisglycoside (**119**) and the unnatural type of monoglycoside (**120**). Employment of the classical Koenigs-Knorr method for the glycosidation gave the desired natural-type α-glycoside (**121**). The regioisomeric glycosides (**122** and **123**) were obtained from **118** by the same Koenigs-Knorr method. The silylated glycosides (**124** and **125**) were synthesized by the modified Koenigs-Knorr method using AgOTf. Heteroanthracyclines (**121**, **122**, and **124**) which are a natural type of monoglycosides showed strong inhibitory activity against L-1210 and P-388 cell growth (*in vitro*) comparable to that of **1b**.

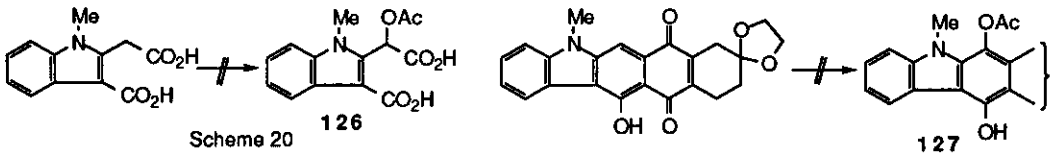




Scheme 19

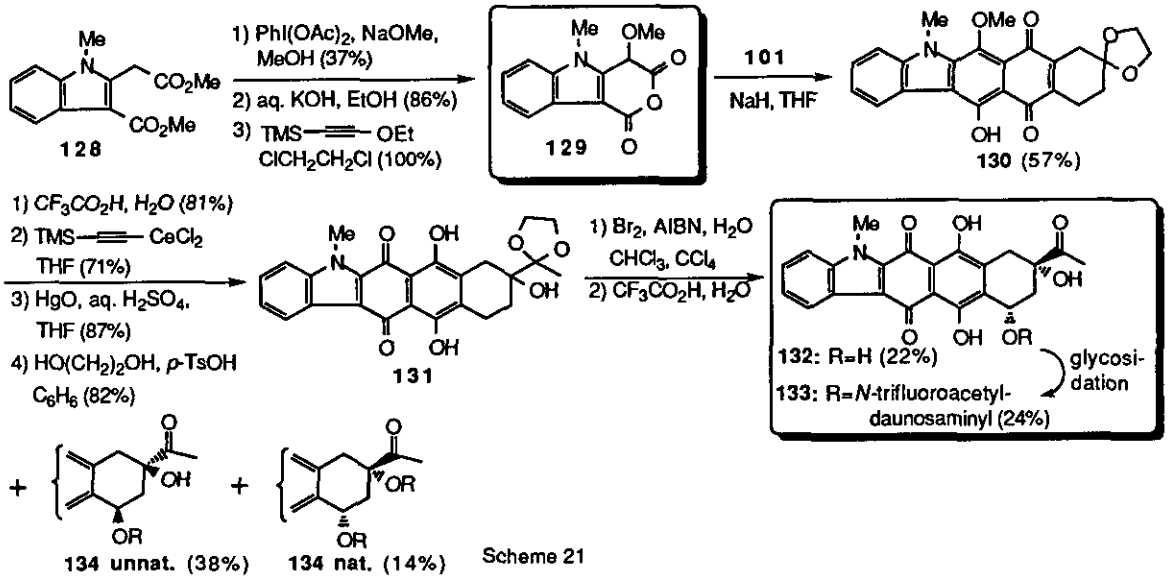
3-2. ANALOGS HAVING AN INDOL MOIETY[25]

The authors' group also synthesized the D-ring indole analog of **1a** regioselectively. Our initial attempts to obtain **126** and **127** by methods similar to those used for the synthesis of the D-ring thiophene analogs failed due to the instability of the indole ring against the $Pb(OAc)_4$ oxidation.



Scheme 20

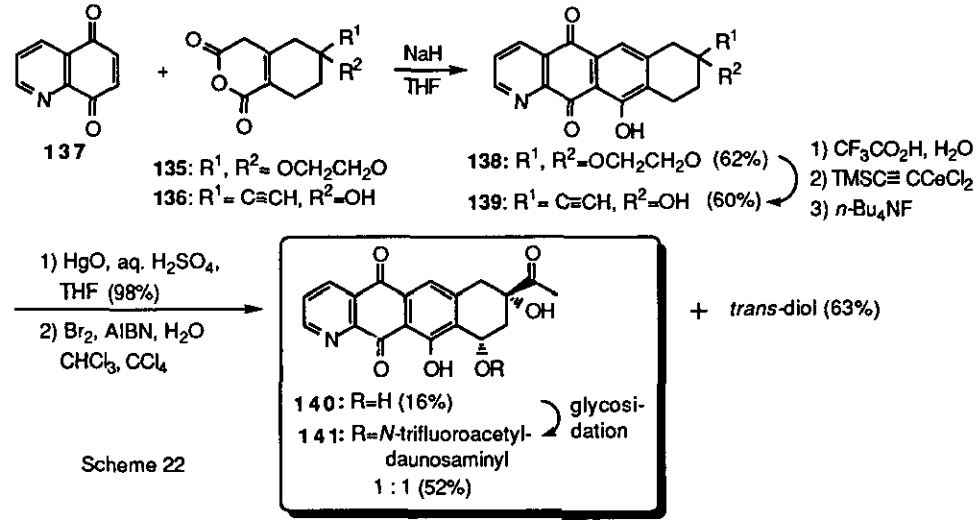
The useful anhydride (**129**) was obtained by hypervalent iodine oxidation of **128** and subsequent hydrolysis and dehydration. The sodium enolate of **129** reacted with the chloroquinone acetals regioselectively. The cycloadduct (**130**) led to the key intermediate (**131**) by the procedures that are shown in Scheme 17. Radical bromination and subsequent hydration of **131** gave the *cis*-diol (**132**). Glycosidation of **132** and the appropriately protected daunosamine using TMSOTf gave the natural-type α-glycoside (**133**), the unnatural-type α-glycoside (**134 un.**) and the natural-type α-bisglycoside (**134 nat.**). The heteroanthracycline (**133**) showed inhibitory activity against L-1210 and P-388 cell growth (*in vitro*) comparable to that of **Ib**.



Scheme 21

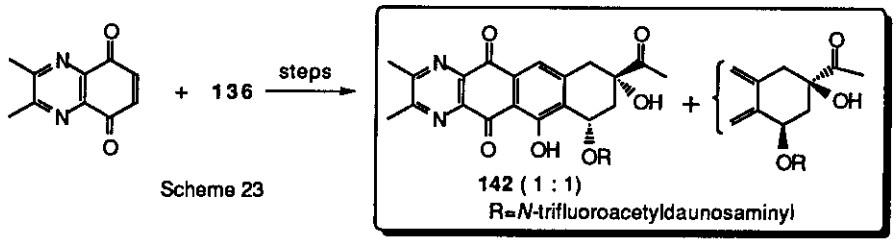
3-3. ANALOGS HAVING PYRIDINE AND PYRAZINE MOIETIES[26]

Our group had succeeded in the total synthesis of l l-deoxydaunomycin.[27] Therefore we tried to synthesize the D-ring heterocyclic analogs of l l-deoxyanthracycline using this method. The cycloaddition of 7-bromo- and 7-chloro-5,8-dihydro-5,8-dioxoquinolines with the tetrahydrohomophthalic anhydride (**135** and **136**) under strongly basic conditions gave a complex mixture. However, the reaction of **135** with unsubstituted quinone (**137**) gave a single cycloadduct (**138**) regiospecifically. The structure of **138** was determined by ^{13}C-*NMR and X-ray analysis. Similarly, the reaction of* **136** *with* **137** regiospecifically gave **139**, which was identical with the compound obtained from **138** by acid hydrolysis and ethynylation. The desired *cis*-diol (**140**) and *trans*-diol were obtained from **139**. The *trans*-diol was epimerized to **140** *via* the *cis*-boronate intermediate. The condensation of **140** and the appropriately protected daunosamine using TMSOTf gave the α-glycoside (**141**) as an inseparable diastereomeric mixture.



Scheme 22

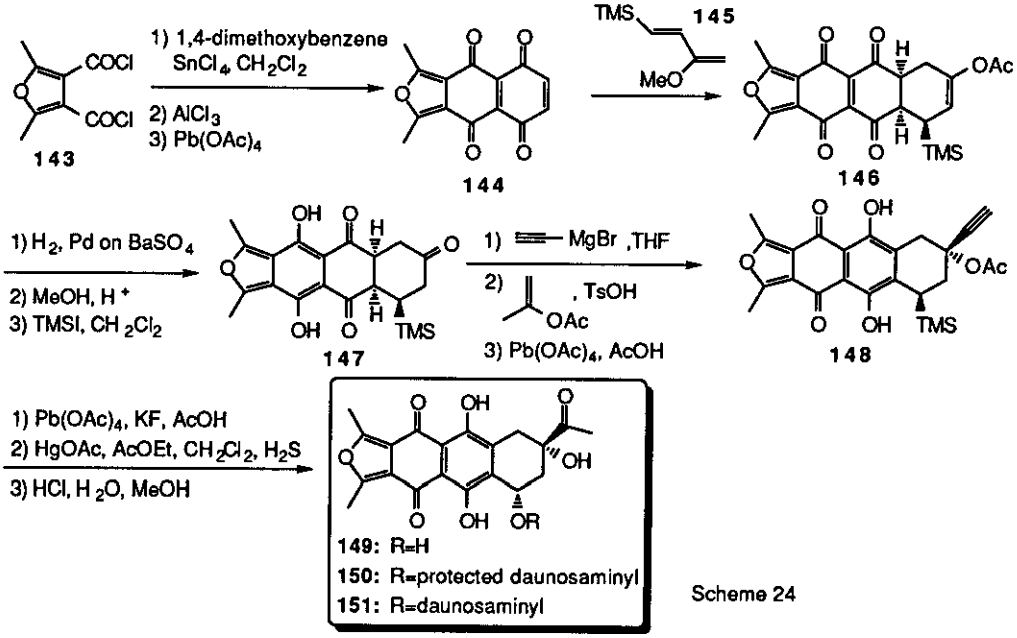
Similarly, the D-ring pyrazine analog (**142**) was obtained.



Scheme 23

3-4. ANALOGS HAVING A DIMETHYLFURANE MOIETY

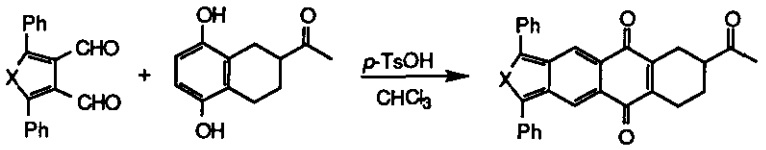
Lee synthesized the heteroanthracyclines that have dimethylfuran in their D-ring.[28] Freidel-Crafts reaction of **143** with 1,4-dimethoxybenzene, and subsequent demethylation and oxidation gave the tetracarbonyl compound (**144**). Diels-Alder reaction of **144** with the diene (**145**) gave the tetracyclic **146**. Hydrogenation, acetalization and demethylation gave the tricarbonyl compound (**147**). Ethynylation of **147** with ethynylmagnesium bromide and subsequent oxidation with $Pb(OAc)_4$ produced **148**. The trimethylsilyl group in **148** was converted into the acetoxy group using $Pb(OAc)_4$ and KF. Hydration of the ethynyl group and subsequent acid treatment afforded the aglycone (**149**), which was coupled with the protected chlorodaunosamine under the Koenigs-Knorr conditions to yield a mixture of the separable α- and β-anomers. The separated α-anomer (**150**) was deprotected with aq. NaOH to give the heteroanthracycline (**151**), which showed an antitumor activity against melanotic melanoma B16 (T/C%=157, optimal dosage=5.0 mg/kg).



Scheme 24

3-5. ANALOGS HAVING OTHER HETEROCYCLES

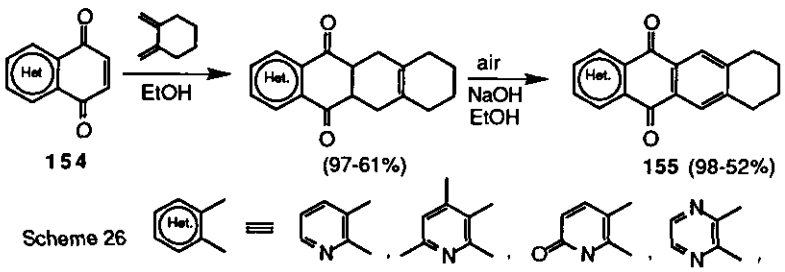
Lepge's group synthesized some fused quinones (**152** and **153**) that have heteroaromatic rings by the cycloaddition of hydroquinones with 1,4-dialdehydes.[29]



Scheme 25

152: X=O (66%)
153: X=S (98%)

Kobayashi's group prepared tetracyclic **155** that have heterocyclic rings by Diels-Alder reaction of 1,2-dimethylenecyclohexane with **154**. Their attempts to introduce hydroxy groups in the B-ring were not successful.[30]

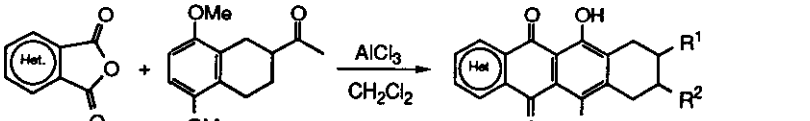


154 (97-61%) **155** (98-52%)

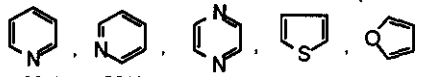
Scheme 26

Het. ≡

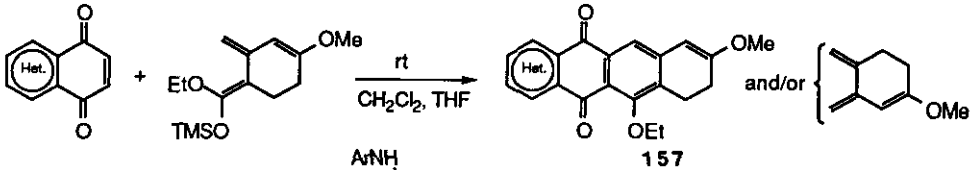
Several tetracyclic compounds (**156** and **157**) were prepared by Preston's group utilizing Freidel-Crafts reaction and Diels-Alder reaction. [31]



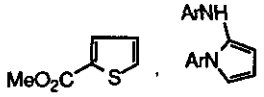
156 inseparable mixture
(R^1=COMe, R^2=H; R^1=H, R^2=COMe)

Het. ≡ 

62% 69% 4% 73% 85%



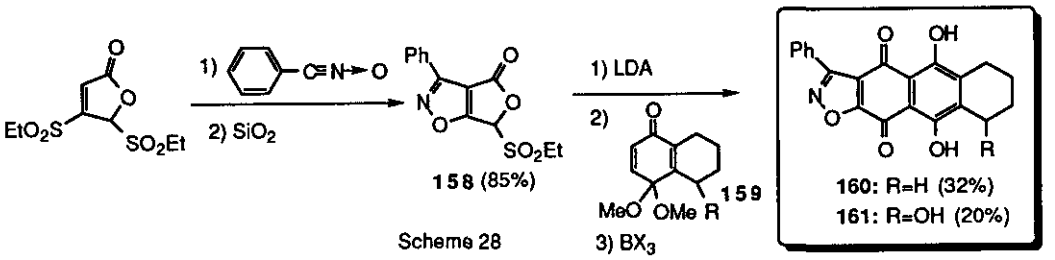
157

Het. ≡ 

6% 8%

Scheme 27

Martin *et al.* prepared 6-ethylsulfonyl-3-phenylfuro[3,4-*d*]isoxazol-4(*6H*)-one (**158**) *via* 1,3-dipolar cycloaddition of benzonitrile oxide. The anion generated from **158** reacted with **159** to afford **160** and **161**.[32]

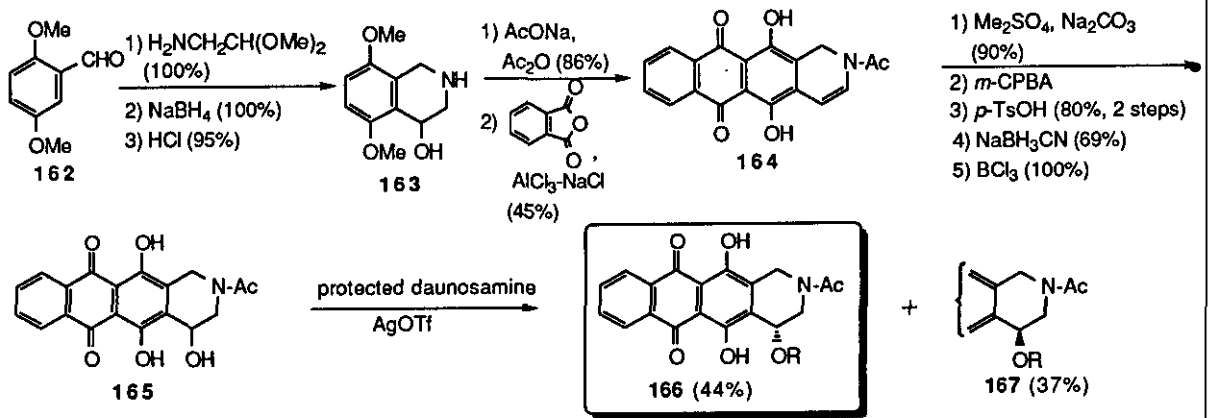


Scheme 28

4. A-RING HETEROCYCLIC ANALOGS OF ANTHRACYCLINES

4-1. 9-AZA ANALOGS[33]

Mitscher's group synthesized 9-aza analogs of *N*-trifluoroacetyl-4-demethoxydaunomycin (**166, 167**) from **162**. Pomeranz-Fritsch condensation of **162** followed by $NaBH_4$ reduction and acid-catalyzed cyclization led to **164**. Selective *N*-acetylation of **163** and subsequent Freidel-Crafts reaction produced the tetracyclic **164**, which was protected as its dimethyl ether, epoxidized, dehydrated, reduced with $NaBH_3CN$, and demethylated with BCl_3 to give **165**. Glycosidation of **165** with *N,O*-bis(trifluoroacetyl)-daunosamine bromide and AgOTf gave **166** and **167**. Unexpectedly, both **166** and **167** were inactive *ip* in mice carrying the P-388 leukemia.



Scheme 29

4-2. 9-OXA ANALOGS[34]

The pyranonaphthoquinone antibiotics such as kalafungin[35] or its enantiomer nanaomycin D[35] have some antineoplastic activities as a bioreducing agent. Koch and co-workers tried to synthesize analogs of **1a** with an oxygen in the A ring (**168**).

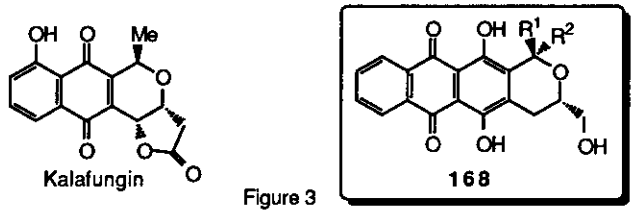
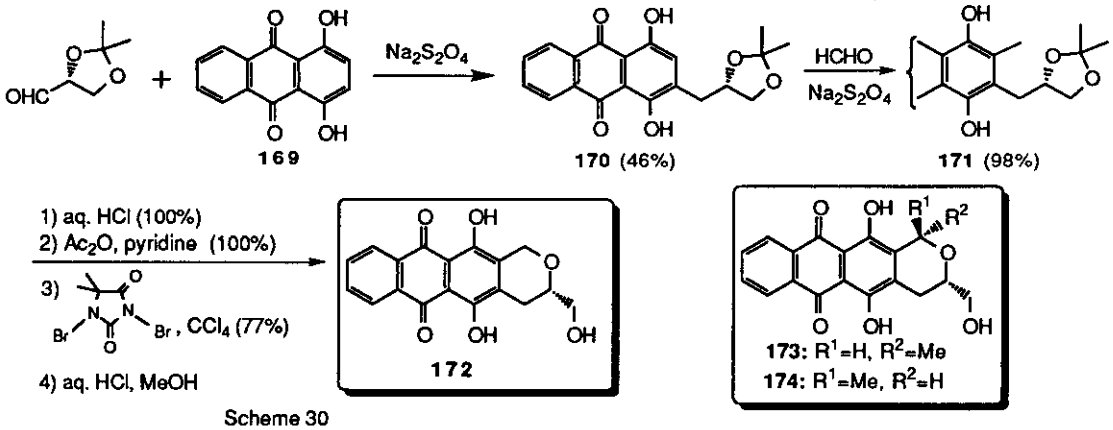


Figure 3

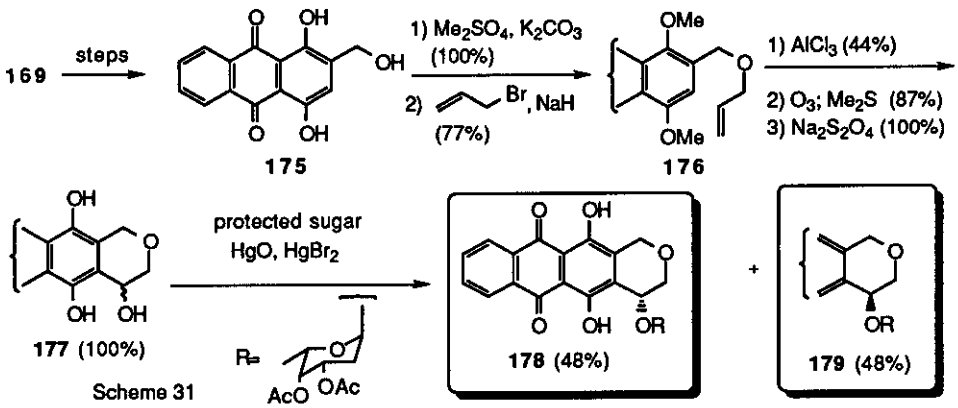
They estimated that intercalation with native DNA must be less marked with **168** than with **1a** and **1b**. Although it has been shown that 9-OH and 13-C=O of anthracyclines strongly participate in the intercalation, pyranonaphthoquinone antibiotics act as powerful alkylating agents after bioreduction. Aldol condensation of the optically active glyceraldehyde with the anion of **169** gave **170** under Marschalk conditions.[36] A second alkylation of **170** under Marschalk conditions with HCHO, afforded **171**. Deacetalization, acetylation, bromination and acid treatment gave **172**. Following to a similar procedure, they obtained a mixture of diastereomers (**173** and **174**). They made several glycoside derivatives with aminodeoxysugars or deoxysugars, but they had no significant antibiotic or antitumor activity.



Scheme 30

Koch *et al.* also synthesized 9-oxa-anthracyclines bearing no side chain at the C-8 but a glycoside substituent at the C-7a.[37]

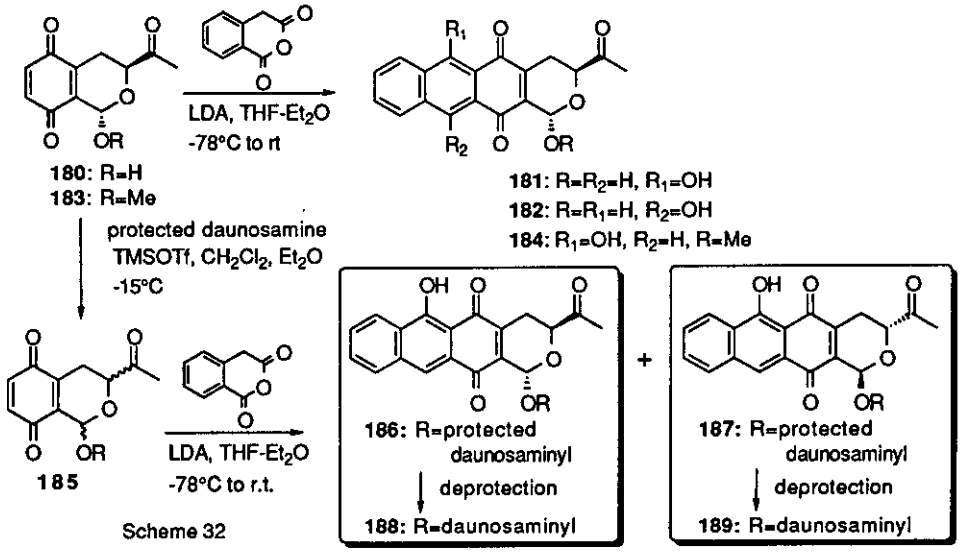
Quinizaline (**169**) was converted into **175** in two steps according to Krohn's procedure.[38] Methylation of **175** followed by condensation with allyl bromide afforded **176**. Ozonolysis of the demethylated compound led to the aldehyde, which was subjected to intramolecular alkylation under Marschalk conditions to afford **177**. Glycosidation of **177** with 3,4-di-*O*-acetyl-2-deoxy-L-fucopyranosyl chloride led to a mixture of two diastereomeric α-glycosides (**178** and **179**). Their deacetylated glycosides had no significant antitumor activity.



Scheme 31

4-3. 8-HETERO ANALOGS

Lavallee's group succeeded in the convergent and regioselective synthesis of 5-deoxypyranoanthracyclines using our strong base-induced cycloaddition of homophthalic anhydride to **185**.[39] Treatment of the quinone (**180**) with the lithium enolate of homophthalic anhydride produced an inseparable mixture (**181** and **182**) (2:1 ratio). Although the methyl ether (**183**) led to regioisomer (**184**) in 55% yield with high regiochemical control, it was not easy to hydrolyze **184** to **181**. The yield of glycosidation of **181** was quite low, mainly because of the very low solubility of **181**. This problem was solved by carrying out the glycosidation reaction with **180** affording **185** as a diastereoisomeric mixture. The reaction of homophthalic anhydride enolate with **185** produced **186** and **187** in 35-40% overall yields from **180**. Deprotection of **186** and **187** by usual method gave the desired **188** and **189**.

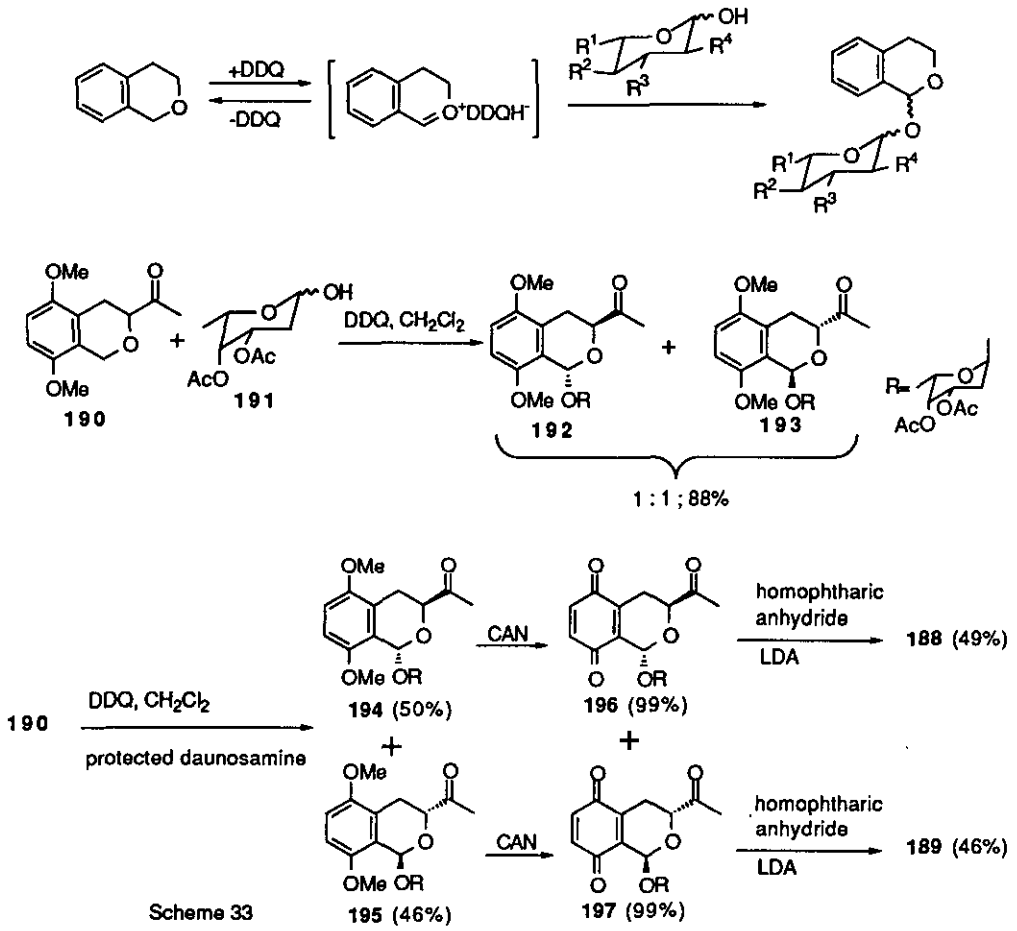


Scheme 32

They developed a novel method for the oxidative glycosidation at the heterosubstituted benzylic positions with DDQ and applied this reaction to the synthesis of heteroanthracyclines.[40] This reaction is stereospecific with 3-substituted isochromanes and isothiochromanes, as well as diastereoselective with

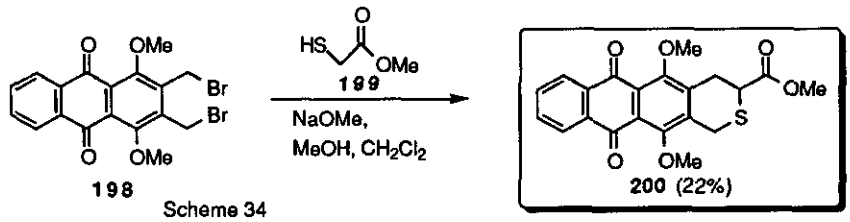
none 3-substituted isochromans. When the racemic isochroman (**190**) was treated with a 1:1 mixture of α- and β-anomers of sugar (**191**) in the presence of DDQ, oxidative glycosidation took place to give two *trans* diastereomeric α-glycosides (**192** and **193**) in high yield and a small amount of two *trans* diastereomeric β-glycosides. When the reaction was carried out with a longer reaction time or at elevated temperature, only *trans* diastereomeric α-glycosides were obtained. Furthermore, 5-glycosides could be converted to α-glycosides under the conditions that mimic the original glycosidation. These results suggest that the selectivity of this reaction was thermodynamically controlled.

Oxidative glycosidation of **190** with the protected daunosamine afforded two 1,3-*trans*-glycosides (**194, 195**) in high yield in a 1:1 ratio. Oxidative demethylation with CAN gave the pyranoquinones (**196, 197**). Treatment of **196** and **197** with the lithium enolate of homophthalic anhydride gave **188** and **189**.



Scheme 33

The Bio Chem Pharma group developed a simple synthetic method for the preparation of 3-substituted isothiochromane and extended this method to the synthesis of heteroanthracyclinone.[41] Reaction of tricyclic dibromide (**198**) with **199** in the presence of NaOMe afforded the tetracyclic compound (**200**) that is a heterocyclic analog of anthracyclinone with the CH_2 at position 8 replaced by a sulfur atom.



Scheme 34

5. CONCLUSIONS

Synthetic studies on the heteroanthracyclines are reviewed by focussing the classification of A-D ring constitutions. Modification of the sugar part also plays an important role for the antitumor activities and the side effect, but it is not included here since the preparation is limited.

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