Clinical efficacy of daunomycin (lA), adriamycin (lB)
and carminomycin (lC) in the treatment of human tumors
has attracted the attention of synthetic organic chemists
all over the world. However the use of these drugs in
chemotherapy is known to be hampered by dose dependent
cardiotoxicity. This has made it therefore necessary
for a continuous search for better drugs which show low
cardiotoxicity and/or better therapeutic indices. Recently
Arcamone et al. have isolated 11-deoxyanthracyclines
(11-deoxydaunomycin 1d etc.) from Micromonospora peucetica
which are related to aclacinomycin A. Clinical studies
of aclacinomycin A showed that it has a low incidence
of cumulative dose-dependent cardiomyopathy, in comparison
with adriamycin. Recent findings indicate that 4-demethoxy-
daunomycin (1e), a synthetic compound, is eight times
more effective compared to daunomycin and adriamycin.
Similar observations were also made with 4-demethoxy-11-
deoxydaunomycin (lf).

Anthracyclines on mild hydrolysis will give the
corresponding aglycones (anthracyclinones) and aminosugar,
L-daunosamine. Practical synthesis of L-daunosamine from
sugar as well as non-sugar precursors and its coupling with
1. a. $R=OCH_3, X=OH, R_1=H$
b. $R=OCH_3, X=R_1=OH$
c. $R=X=OH, R_1=H$
d. $R=OCH_3, X=R_1=H$
e. $R=R_1=H, X=OH$
f. $R=R_1=X=H$

2. a. $R=OCH_3, X=OH$
b. $R=OCH_3, X=H$

3. a. $R=H, X=OH$
b. $R=X=H$
anthracyclinones to give anthracyclines are well established.

Therefore much efforts have been made for the synthesis of these anthracyclinones, which resulted in many new approaches for their synthesis. In 1979, Kelly published a comprehensive review on anthracyclines [Ann. Rep. Med. Chem., 14, 288 (1979)]. Various methods reported on the synthesis of anthracyclinones (recemic) after the report of Kelly are reviewed in this chapter.

CHAPTER II - REGIOSPECIFIC SYNTHESIS OF (+)ll-DEOXY-DAUNOMYCINONE

A regiospecific synthesis of (+)ll-deoxydaunomycinone is discussed in this chapter. It is based on the synthesis of functionalised AB synthon and construction of the tetracyclic system by taking the advantage of regiospecific Fries migration. The key intermediate AB synthon, 2-acetyl-8-bromo-5-hydroxy-1,2,3,4-tetrahydronaphthalene-4-one (4) was first prepared starting from 2-bromo-5-hydroxybenzaldehyde. It was condensed with acetyl acetone in presence of piperidine to give 3-acetyl-4(2-bromo-5-hydroxyphenyl)buten-2-one.
which on hydrogenation and methylation afforded diketone 5. Alkylation of 5 with ethylbromoacetate in presence of sodium hydride gave the ester 6, which on treatment with aqueous sodium hydroxide afforded the acid 7. Compound 7 was cyclized with HF to give 2-acetyl-5-bromo-5-methoxy-1,2,3,4-tetrahydronaphthalene-4-one. It was treated with B\(_3\)F\(_3\)-etherate to afford 4.

The key intermediate 4 was also prepared by an alternative route starting from 4-bromo-3-methylphenol (8) by a more simple method. 8 after acetylation was brominated by N-bromosuccinimide to afford 9. Treatment of 9 with acetyl acetone in presence of potassium carbonate in acetone gave diketone 10. Second alkylation on 10 with
ethyl bromoacetate in similar conditions gave the ester 11. Treatment of 11 with alcoholic potassium hydroxide afforded the acid 12, which on treatment with conc. sulfuric acid afforded 4.

\[
\begin{align*}
\text{Br} & \quad \text{OAc} \\
\text{OEt} & \quad \text{O} \\
\text{OAc} & \quad \text{O}
\end{align*}
\]

Hydrogenation of 4 with Pd on charcoal afforded debrominated product 13 in 36% yield. The reduction of C-4 carbonyl was achieved by first protecting the free acetyl ketone of 13 with ethyleneglycol and resulting ketal was subjected to Wolff-Kishner reduction followed by acid work-up to give the AB synthon 14 in 30% yield.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

D-ring synthon, methyl-2-carboxy-3-methoxy benzoate (15) was prepared starting from 3-hydroxy benzoic acid. Chloromethylation of 3-hydroxy benzoic acid afforded 4-hydroxy
phthalide, which on methylation gave 4-methoxyphthalide. It was oxidised with alkaline potassium permanganate to give 3-methoxyphthalic acid which on treatment with BF₃-methanol gave 15.

Acid chloride of 15 and 14 in presence of pyridine in benzene afforded the benzoate 16. Alternatively 16 was also obtained by treatment of acid 15 with 14 in trifluoroacetic anhydride. 16 on refluxing with BF₃-etherate afforded a dihydroxy tetracyclic compound 17, which on partial methylation gave a mixture of 18 and 19 along with starting material. When the reaction was carried out under milder conditions (BF₃-etherate, 126°, 5 min.), it gave the
keto-ester 20 which on hydrolysis, followed by cyclisation with conc. sulfuric acid, boric acid gave 18. As the methods are available for hydroxylation at C-7 and C-9 this furnishes the total synthesis of (+)11-deoxydaunomycinone.

CHAPTER III - A REGIOSPECIFIC AND FLEXIBLE APPROACH FOR THE SYNTHESIS OF (+)DAUNOMYCINONE AND (+)11-DEOXYDAUNOMYCINONE

The key intermediate 2-acetyl-3-bromo 5-hydroxy-1,2,3,4-tetrahydronaphthalene 21 was prepared from 4 by first protecting the acetyl ketone selectively with ethylene glycol and subjected the resulting ketal to Wolff-Kishner reduction followed by deketalisation. Important structural features of 21 were exploited for the synthesis of anthracyclinones.

First, 4-demethoxy analogues were prepared from 21 to assess the feasibility of constructing these tetracyclic systems from phthalic anhydride. Fusion of 21 with phthalic anhydride in AlCl₃-NaCl melt at 180° afforded the bromoquinone 22. Debromination of 22 by catalytic hydrogenation gave 23. Hydroxylation at C-3 was achieved by

\[
\begin{align*}
\text{4} & \quad \text{Br} \quad \text{O} \\
\text{Br} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{21} & \quad \text{Br} \\
\text{22} & \quad \text{R} = \text{H}, \text{X} = \text{Br} \\
\text{23} & \quad \text{R} = \text{X} = \text{H} \\
\text{24} & \quad \text{R} = \text{OH}, \text{X} = \text{H}
\end{align*}
\]
preparing its enolacetate by refluxing with acetic-anhydride and p-toluenesulfonic acid. It was epoxidised with m-chloroperbenzoic acid and the resulting epoxyacetate was treated successively with base and acid to give 4-demethoxy-7,11-dideoxydaunomycinone (24).

Bromoquinone 22 was further utilised for the synthesis of 4-demethoxy daunomycinone (3α). Methyl ether of 22 was treated with 1,2-ethanediathiol to give 25, which on treatment with sodium methoxide/methanol in pyridine in presence of cuprous chloride, followed by dethioketalisation produced 4-demethoxy 7,3-dideoxydaunomycinone dimethyl ether (26). 26 was already converted to 4-demethoxydaunomycinone (3α).

\[
\begin{align*}
25 & \quad R = \text{Br}; \quad X = -\text{SCH}_2\text{CH}_2\text{S}- \\
26 & \quad R = \text{OCH}_3, X = \text{O}
\end{align*}
\]

After successful synthesis of 4-demethoxy analogues from 21, it was further utilised for the regiospecific synthesis of daunomycinone (2α) and 11-deoxydaunomycinone (2b). Key step in controlling the regiospecificity was achieved by Friedel-
Crafts alkylation of bromophthalide 27 with 21 in presence of stannic chloride in dichloromethane to give phthalide 28. Ethylene ketal of 28 was subjected to zinc dust reduction in ethanolic potassium hydroxide solution to afford the bromo acid 23. Total methylation of 29, followed by hydrolysis afforded the acid 30. Cyclisation of 30 with trifluoroacetic anhydride in dichloromethane gave the anthrone, which on oxidation with Jones' reagent gave the bromoquinone 31. Treatment of 31 with 1,2-ethanedithiol afforded the thioketal, which on treatment with sodium methoxide/methanol in pyridine, in presence of cuprous chloride, followed by dethioketalisation gave 7,9-dideoxydaunomycinone dimethyl ether 32.
Alternatively ethylene ketal of 28, when subjected to zinc dust reduction in aq. 20% potassium hydroxide gave the debromo acid 32. Cyclisation of the acid 33 with HF afforded anthrone, which on Jones' oxidation gave 7,3,ll-trideoxydaunomycinone (18). Hydroxylation at C-9 was achieved by the procedure which was adopted for 4-demethoxy-ll-deoxydaunomycinone (enol acetate method) to give 34. Methods to convert 32 to (+)daunomycinone (2a) and 34 to (+)ll-deoxydaunomycinone (2b) are already reported.

Thus for the first time a flexible, yet simple synthesis of anthracyclinones was demonstrated starting from a common synthon.
CHAPTER IV - STUDIES DIRECTED TOWARDS THE ASYMMETRIC SYNTHESIS OF ANTHRACYCLINONES

A brief account of the available literature on optically active anthracyclinones is presented. Asymmetric synthesis of 4-demethoxydaunomycinone is undertaken. Synthesis of the key intermediate, R(-)2-acetyl-5,8-dimethoxy 2-hydroxy-1,2,3,4-tetrahydronaphthalene (35) is discussed.

The racemic allylic alcohol 2-(1-hydroxyethyl) 5,8-dimethoxy 3,4-dihydronaphthalene (36) was subjected to asymmetric epoxidation under Sharpless kinetic resolution condition. Reaction mixture was reduced with lithium aluminium hydride and separated by column chromatography and crystallisation. It afforded R(+)-36 and (-)2R[3]1-hydroxyethyl)R2-hydroxy-1,2,3,4-tetrahydronaphthalene 37 in optically pure forms. The undesired antipode (+)36 was inverted to the desired antipode (-)36 by using triphenyl phosphine, diethylidiazodicarboxylate and benzoic
acid, followed by hydrolysis of the resulting benzoate.

3(-)36 was epoxidised adopting similar condition to obtain the epoxide which was reduced with lithium aluminium hydride to get (-)37. Oxidation of (-)37 with Petizone reagent gave R(-)35, which on fusion with phthalic anhydride is known to furnish (-)4-demethoxy-7-deoxydaunomycinone.