INVITED REVIEW

J. Sci. Soc. Thailand, 12 (1986) 195–212

THE USE OF ANTHRACENE ADDUCTS IN THE SYNTHESIS OF NATURAL PRODUCTS*

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(Received 25 August 1986)

Abstract

The development of the "anthracene adduct" for use in the synthesis of natural products is described. This stable intermediate is easily prepared from cheaply available starting materials and can be readily converted into various structure forms. This high versatility is demonstrated by its use in the synthesis of cyclopentenoid antibiotics (e.g. methylenomycins and sarkomycin), α-methylene lactones and acetylenic compounds. Thus the anthracene adduct provides a simple and economical route to compounds hitherto difficult to synthesize.

Background

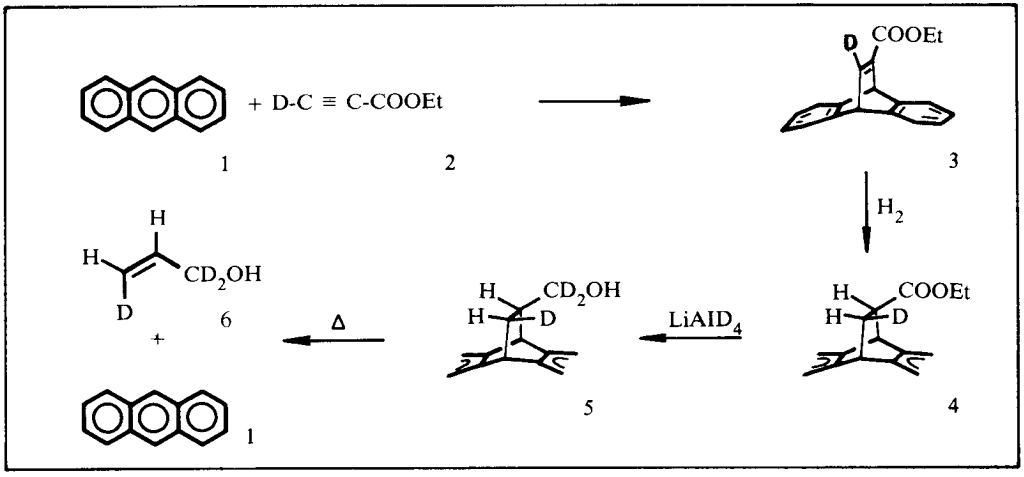
To write here about events leading up to the use of anthracene adducts in the synthesis of natural products makes me think as far back as twelve years, over the period of luring and persuading students to invest their postgraduate years tending "plants" that I somehow believed could bear magic fruit.

It all began in 1974 when we needed specifically deuteriated allyl alcohol **6** for use in our studies and I asked my Malaysian M.Sc. student, Miss Zuriati Bt Zakaria (now Dr. Zakaria at the National University of Malaysia), to prepare the alcohol by the method of Schleyer[1] **(Scheme I).**

The overall reaction is, in fact, a conversion of **2** to **6,** a conversion otherwise difficult, if not impossible, to perform if complete stereospecificity in product **6** were

* Based on the Outstanding Scientist of Thailand Award Lecture, Bangkok, 18 August 1986.

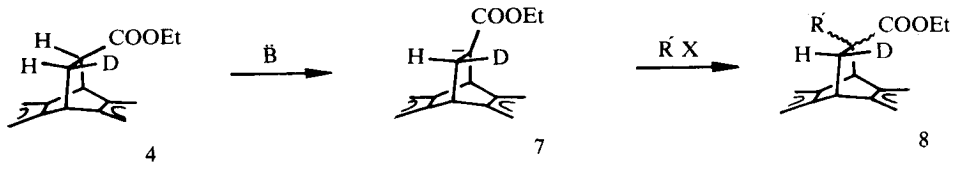
SCHEME I



required. As illustrated in **Scheme I,** anthracene **1** is used as a handle to hold the starting material **2** in the form of the Diels-Alder adduct **3** upon which simple stereospecific chemical manipulations can be carried out. The handle is then removed and recovered in the very last step.

While carrying out the above sequence of reactions three very important features caught our attention. We found that not only was anthracene, the host molecule, cheap and easily available, but that all of its adducts (**3, 4,** and **5**) were also stable crystalline solids which were easy to purify and, most important of all, gave clearly distinguishable first order nuclear magnetic resonance spectra even under low resolution (60 MHz) NMR conditions. These facts combine to make the use of such adducts an ideal chemical research project for a country such as Thailand where both budget and spectroscopic instruments are limited. Secondly, it was found that the retro Diels-Alder reaction (**5** → **6** + **1**) proceeded very smoothly, contrary to our former apprehensions. Our previous search through the literature had confirmed wide use of the Diels-Alder reaction (e.g. **1** + **2** → **3**) but relatively few reports on the use of the retro Diels-Alder reaction could be found. Apparently one excuse that many chemists found for avoiding the reaction was that the technique required too high a temperature and thus might harm the product. However, such was not the case in our synthesis of a fairly small molecule, and in our hands the reaction gave **6** in very high yield with complete retention of stereochemistry and without any trace of deuterium scrambling.

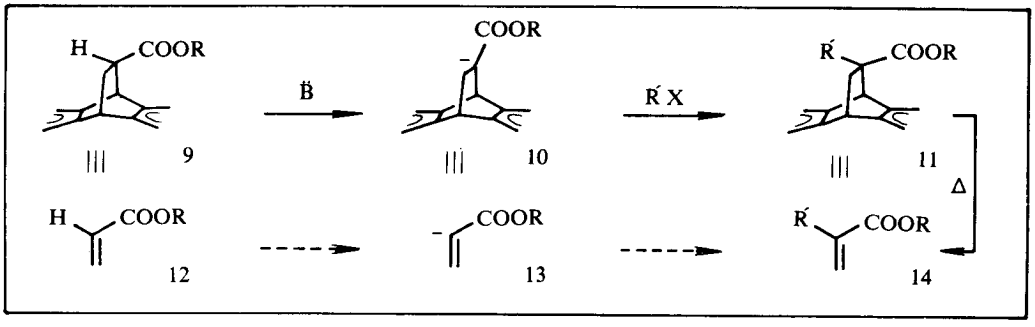
Lastly, for some curious reason I had treated the adduct **4** with base and observed that the resulting basic mixture could be alkylated with an alkyl halide, giving **8** in low yield. The course of reaction can be represented by the following equation:



4 7 8

The potential of this reaction suddenly dawned on me: anion **7** was, in fact, a "masked acrylate anion". **Scheme II** illustrates how such an anion **(10)** could be employed as the acrylate anion **(13)** equivalent with the proviso that i) the alkylation process (**9** to **11** via **10**) proceeded in high yield and ii) optimum conditions were established for the retro Diels-Alder reaction **(11 → 14).**

SCHEME II



Let me enlarge a little further on this subject.

The masked acrylate anion has, since the nineteen seventies, caught interest as a favourable candidate for the methylene synthon and its application has been studied by several groups.[2] This activity is easily understood upon looking round at the large number of naturally occurring antitumor agents and antibiotics which contain the acrylate unit (or related group), for example the potent α -methylene- γ -butyrolactones **15** and the related cyclopentenoid antibiotics **16**[3].

16

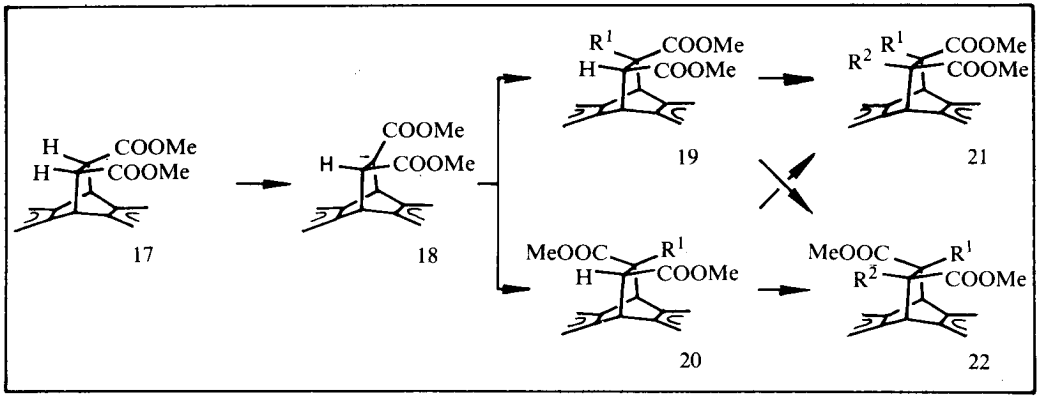
Nevertheless, I did not have time to investigate in more detail and what happened was that this interesting reaction was set aside for two years! The reason, of course, was that our reasearch group was already engaged in other research problems and then my subsequent absence during a year abroad doing post-doctoral training added further to the time lapse. Looking back, however, I now realize that my post-doctoral training in organo-metallic chemistry could not have come at a more opportune time since I returned to Thailand armed with the latest techniques in handling unstable and air-sensitive materials as well as in performing chemical reactions under completely anhydrous conditions, all of which proved essential to the success in my later work.

Having discovered the right kind of "seeds" and having learned the "method" to grow them, the task for my research group, since then, has been to tend the plants and harvest the "fruits" which marked the beginning of the use of anthracene adducts in the synthesis of natural products.

Anthracene adducts as the building block for substituted acrylate, maleate and fumarate[4]

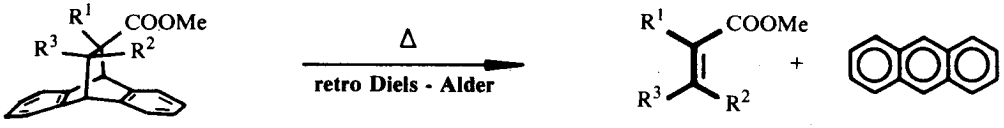
The "masked acrylate anion" concept illustrated in **Scheme II** can be extended to include "masked maleate" and "masked fumarate" anion by simply starting with the dicarboxylate adduct **17** instead of the monocarboxylate adduct **9**[5]. **Scheme III** shows how this was successfully carried out.

SCHEME III



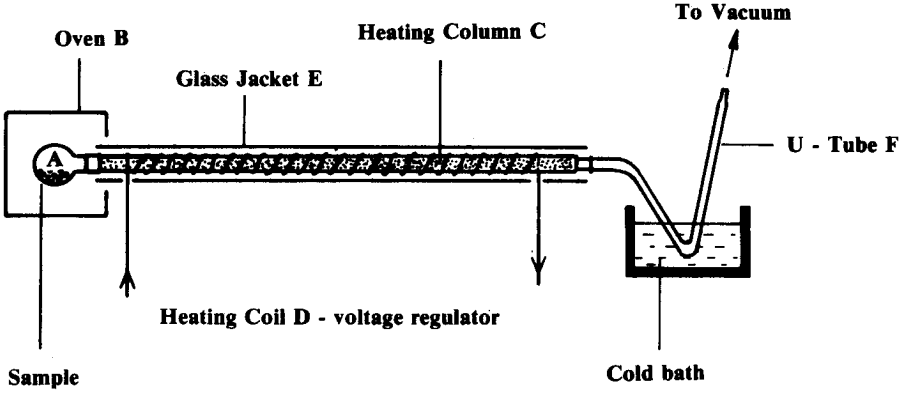
Having prepared a series of adducts, **11** and **19 - 22,** our next task was to find how to efficiently induce the retro Diels-Alder reaction of these compounds as summarized in **Scheme IV.**

SCHEME IV



11	R^1 = alkyl, R^2 = R^3 = H	**23**
19	R^1 = alkyl, R^2 = COOMe, R^3 = H	**24**
21	R^1 = R^3 = alkyl, R^2 = COOMe	**25**
20	R^1 = alkyl, R^2 = H, R^3 = COOMe	**26**
22	R^1 = R^2 = alkyl, R^3 = COOMe	**27**

After numerous attempts and uncountable failures we finally decided to use the flash vacuum pyrolysis technique to effect the retro Diels-Alder reaction. For this we asked the glass blower to make a very simple vacuum pyrolysis apparatus which I still consider the most valuable and vital piece of apparatus in this whole project. As demonstrated in the drawing below, the compound to be pyrolysed was placed in a round bottom flask (**A**) connected to a heating column (**C**) which was packed with glass chips, wrapped with a heating coil (**D**) and enclosed in a glass jacket (**E**). A U-tube (**F**), attached to a vacuum line, was connected to the end of the heating column and immersed in a dry-ice/acetone bath. The temperature of the heating column (**C**) was controlled by a voltage regulator while oven (**B**) controlled the sublimation temperature of the starting material in flask (**A**).



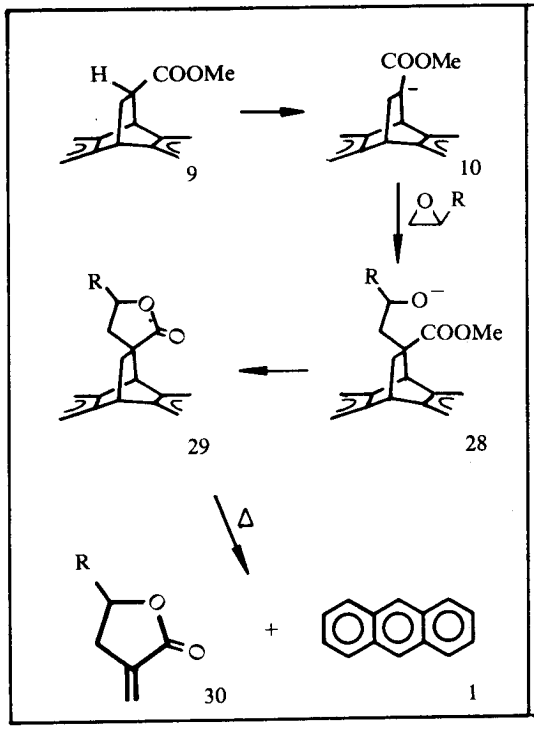
The product of pyrolysis consisted of anthracene which invariably deposited at the end of the heating column, and a substituted unsaturated ester (as shown in **Scheme IV**) which collected in the U-tube. Yields were in general good to excellent. Thus the anthracene adducts proved to be exceptionally good substrates upon which we could build the acrylate unit and then release the completed molecule as required.

Synthesis of α-methylene - γ - butyrolactone[6]

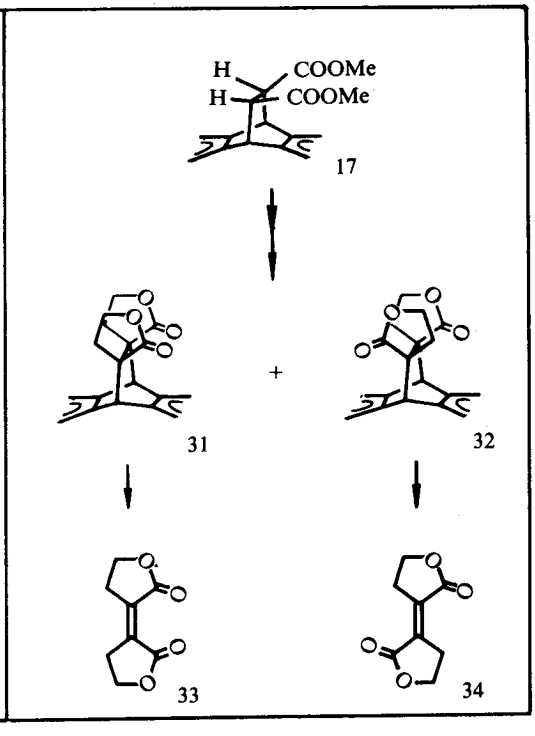
Armed with the "anthracene adduct process" described above we were now in a position to explore its application to the synthesis of natural products. The first synthesis we embarked upon was that of α -methylene- γ -butyrolactones, a very important unit responsible for the anti-cancer activity found in various natural products.

Scheme V shows how a slight modification of the process, i.e. alkylating the anion **10** with an epoxide instead of an alkyl halide, led to the spiro-lactone **29** which yielded α -methylene- γ -butyrolactone **30** when subjected to flash vacuum pyrolysis. The scope of this reaction was studied in detail and several methylene lactones of general skeleton **30** were synthesized, including the rather interesting syn- and anti-bislactones **33** and **34** formed via double lactonization of **17 (Scheme VI).**

SCHEME V



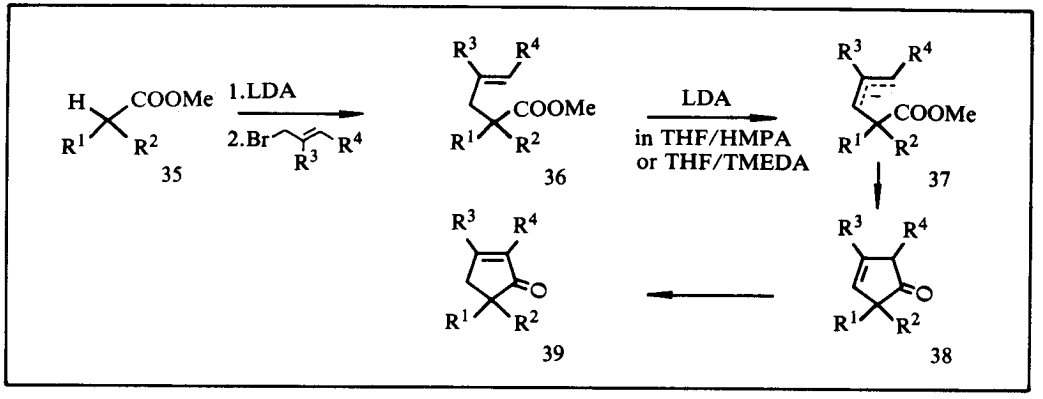
SCHEME VI



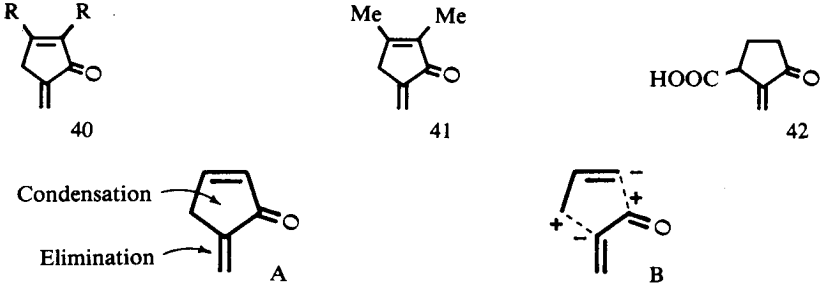
Novel route to α -methylene cyclopentenones:[7] high yield synthesis of methylenomycin B[8]

Here I must recount that we had earlier, in another area of research, come across a very simple and effective method for the construction of disubstituted cyclopentenones (e.g. **38** or **39**) via a three-carbon annelation as outlined in **Scheme VII.**

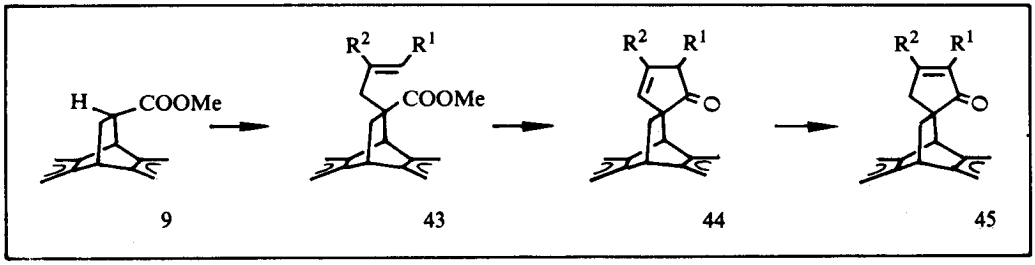
SCHEME VII



Recognizing its potential, we decided to use this reaction in our planned synthesis of α -methylene cyclopentenones **40,** the prime targets being methylenomycin B **41**[9] and the "deceptive" sarkomycin **42.**[10] These latter two compounds belong to a class of "cyclopentenoid antibiotics" which were isolated from the culture broth of *Streptomyces* species and have since attracted much attention due to their important biological activities.



SCHEME VIII

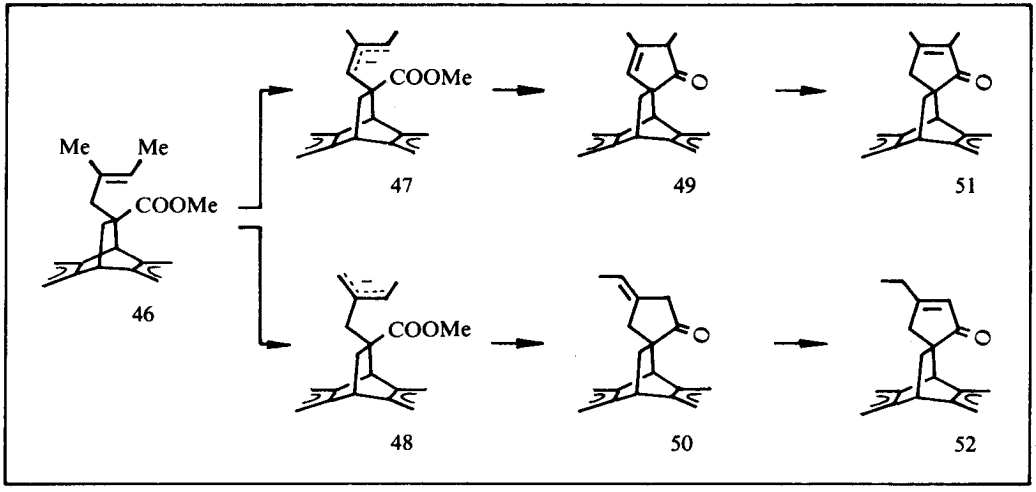


Now, up until that time all syntheses of α -methylene cyclopentenones had in variably involved two compulsory steps: construction of the five-membered ring and subsequent formation of the exo-methylene group via an elimination reaction (structure **A**). In our plan, however, the desired sequence was to be achieved by simply reacting the propene unit with our masked α -methylene carbonyl function (the anthracene adduct) as schematized in structure **B.**

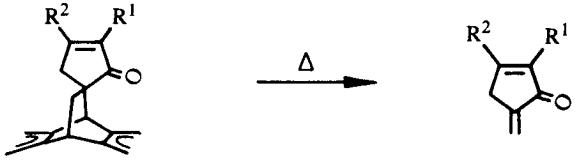
Our first implementation of this plan was not without problems. However, without going into technical details here I would like to say that with certain modifications and manipulations we finally discovered the right conditions for the reaction, thence followed the synthesis of α-methylene cyclopentenone precursors **45** as outlined in **Scheme VIII.**

A glimpse of the problems that we had to tackle can be seen in **Scheme IX** which shows how two products are obtained from the cyclisation of the allyl anions derived from **46,** with the required product being obtained as the minor component.

SCHEME IX



Retro Diels-Alder reaction of the spirocyclopentenones **45** under flash vacuum pyrolysis conditions gave the corresponding α -methylene cyclopentenones **40** in nearly quantitative yields. In this manner methylenomycin B **41** was obtained from the pyrolysis of **51.**



45 40

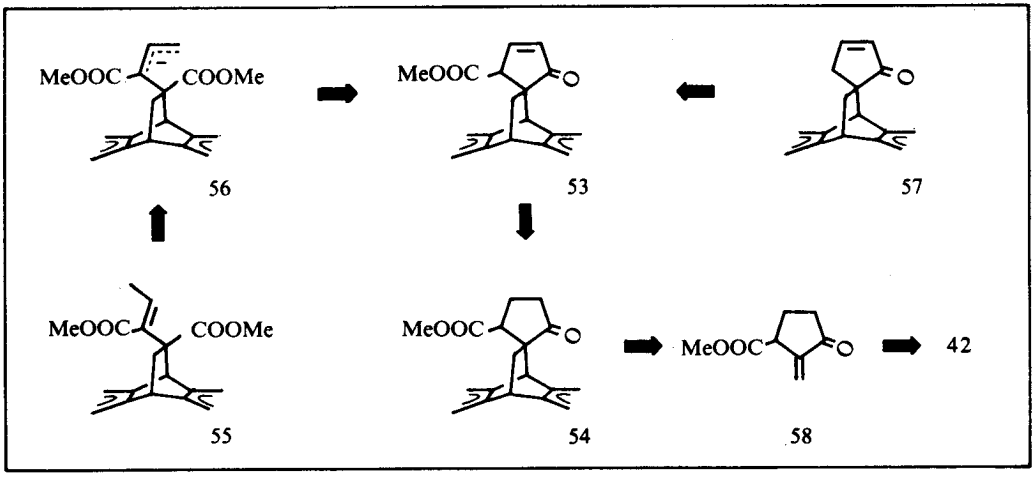
Synthesis of sarkomycin[11]

Sarkomycin **41,** a simple - looking molecule which has been called "deceptive", displays interesting biological activities in being both antitumor and antibiotic, and hence has attracted much interest. Indeed, the recent years have seen several different methods reported for the synthesis of sarkomycin.[10] Unfortunately, however, the methods are usually only suitable for very small-scale operations, employing exotic chemicals and/or highly sophisticated experimental procedures, and as a result of the paucity of material, the reported NMR data of sarkomycin **42** and that of its methyl ester, which are frequently cited in the literature, appear to be oddly inconsistent.

To solve these problems we decided to find a more suitable method for the synthesis of sarkomycin, one that would conveniently accomplish large-scale preparations of the target molecule for further biological testings.

Upon looking at the molecule, the first striking feature is that, unlike methylenomycin B **41,** sarkomycin **42** contains a carboxylic group attached to the carbon adjacent to the methylene group. In principle it should be possible to introduce this carboxylic group into the molecule either before or after formation of the five-membered ring. Both these approaches were planned as outlined in **Scheme X.**

SCHEME X

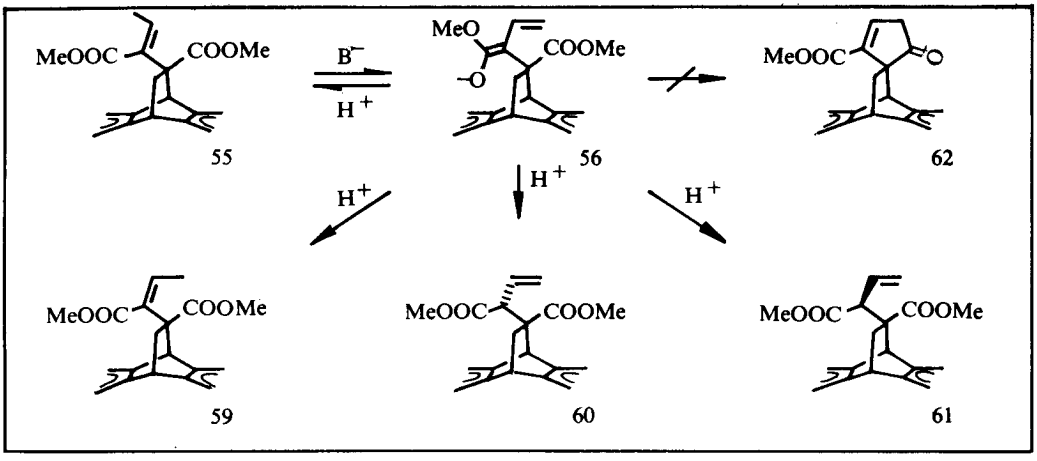


The attractiveness of these two approaches lie in the availability of large quantities of cheap starting materials and in the volatility of the sarkomycin methyl ester **58**, which is expected to be high enough as not to cause any difficulty in the retro Diels-Alder reaction of **54** under flash vacuum pyrolysis conditions. Furthermore, the subsequent acid-catalyzed conversion of **58** to sarkomycin **42** is also a known process.

However, when **55** was subjected to standard cyclisation conditions no trace of any cyclised product (e.g. **53** or its double bond isomer) could be observed but, instead, the starting material **55** together with **59**, **60**, and **61** were obtained. **(Scheme XI).**

This isolation of the isomeric **55**, **59**, **60**, and **61** from the reaction indicated that the dienolate **56** was in fact formed, but somehow failed to cyclise. We have since studied the physical organic chemistry problem concerning this cyclisation reaction in detail and our results have been published in the literature.[12]

SCHEME XI

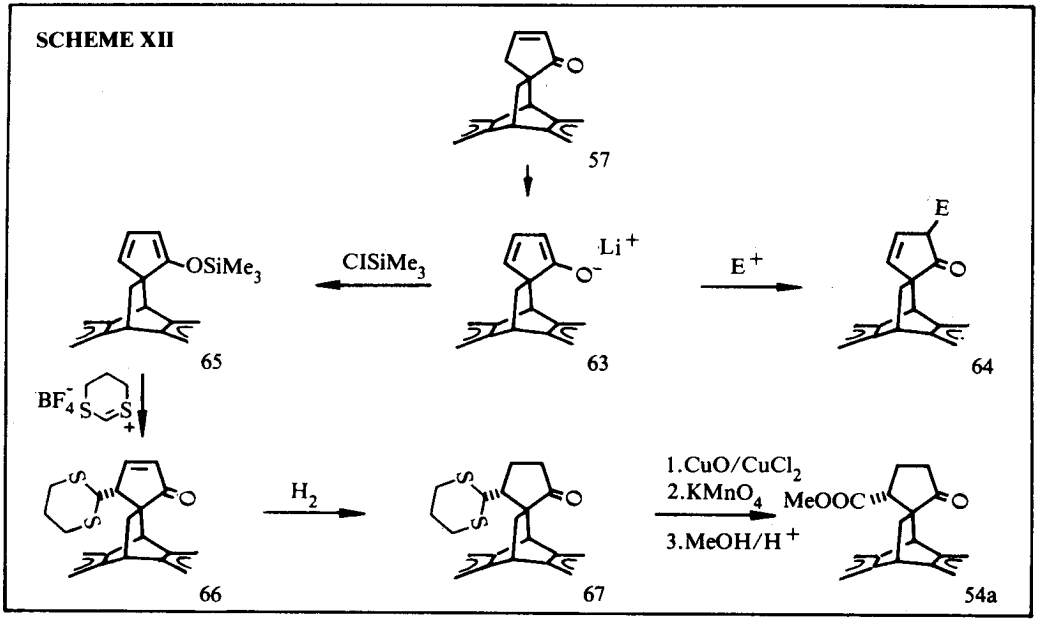


Scheme X was therefore left with only one option, that of the specfic γ -alkylation of **57.** This goal was successfully achieved but this synthesis of sarkomycin has, since then, been surpassed by two better and more efficient syntheses which we finally developed. All three routes to sarkomycin are briefly described below.

Route 1 to Sarkomycin : Specific γ -Alkylation of 57[11]

As expected, alkylation of lithium dienolate **63** derived from **57** with various electrophiles invariably took place at the α - position to give **64.** However, we eventually found that the reaction of the stable silyl dienol ether **65** with dithienium tetrafluoroborate[13] (which was both stereospecific and regiospecific), led to the γ -alkylation product **66.**

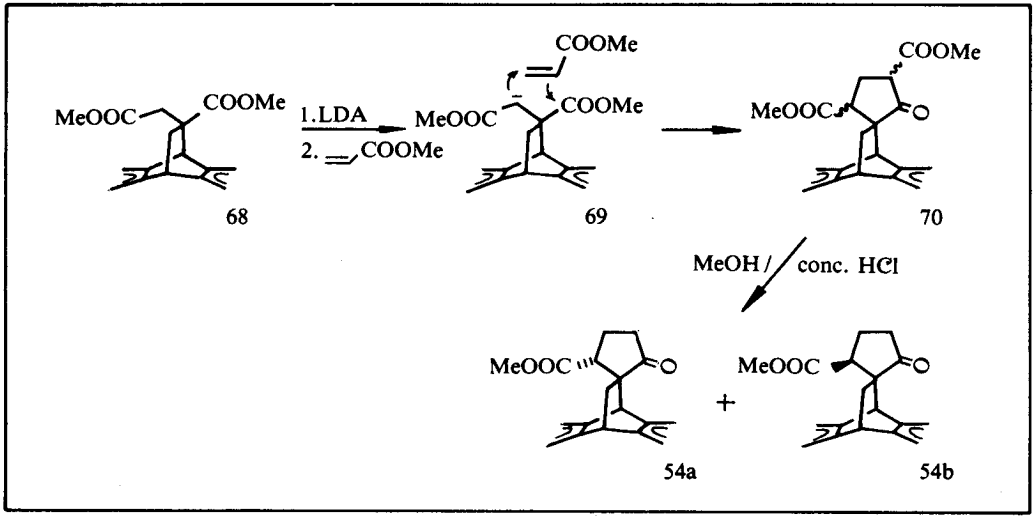
Once **66** was obtained, its subsequent conversion to the sarkomycin precursor **54a** was then a straightforward process as shown in **Scheme XII.**



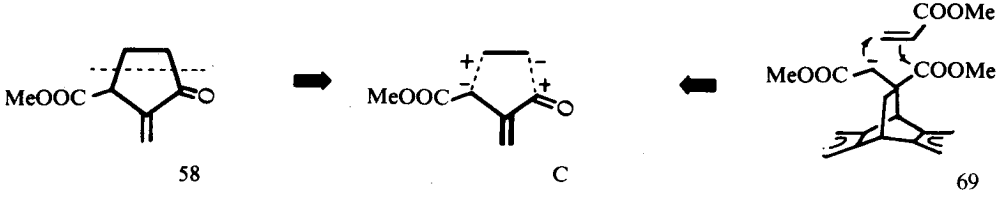
Route 2 to sarkomycin : a tandem Michael addition - Dieckmann condensation approach[11]

A shorter route to **54a** and its stereoisomer **54b** was then developed using the dimethyl itaconate - anthracene adduct **68.** Here construction of the cyclopentanone nucleus was accomplished by tandem Michael addition - Dieckmann condensation between the anion derived from **68** and methyl acrylate (see **69**). The crude cyclisation product **70** was subjected to partial hydrolysis and subsequently decarboxylated by boiling in methanol/concentrated hydrochloric acid to give **54a** and **54b** in a ratio of 1:3 **(Scheme XIII).**

SCHEME XIII



This synthesis of sarkomycin via *Route 2* deserves special comments. It should be emphasized that the tandem Michael addition - Dieckmann condensation reaction shown above is extremely attractive and the selective hydrolysis-decarboxylation in the last step (**70** → **54**) is particularly efficient and straightforward. Here the dimethyl itaconate - anthracene adduct **68** is used as the C-5 and methyl acrylate as the C-2 synthons in the overall synthesis (structure **C.**).

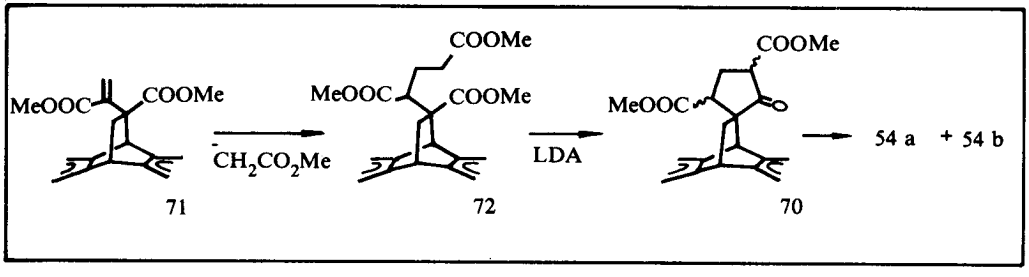


Very recently we have further demonstrated the versatile use of this tandem Michael addition-Dieckmann condensation reaction in the construction of other naturally occurring carbocycles and the results have appeared in the literature.[14]

Route 3 to Sarkomycin : an alternative Michael addition - Dieckmann condensation Route[15]

Treatment of the methylene diester **71** with methyl acetate anion gave the Michael addition product **72** in 78% isolated yield. Subsequent base-induced Dieckmann condensation of **72** afforded **70** which, upon selective hydrolysis and decarboxylation, yielded **54a** and **54b** in a ratio of 2.6 : 1 as shown in **Scheme XIV.**

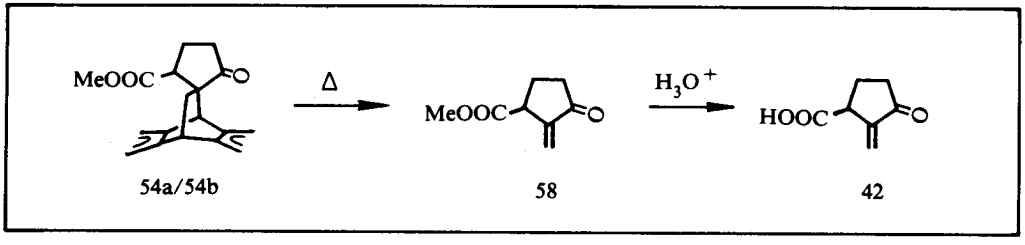
SCHEME XIV



It can be seen that *Route 3* is, in fact a variation of *Route 2* which still remains the shortest route to sarkomycin. However, it should be noted that the isomeric product ratio (**54a : 54b**) obtained from these two routes do differ markedly, **54a** being the major product in *Route 3* while **54b** is the predominant isomer in *Route 2*. Hence these two modes of synthesis are complimentary and an appropriate choice can thus be made according to the stereochemistry required in the final product.

All three synthetic routes described above merge in a common final step: the retro Diels-Alder reaction. Thus, having obtained the sarkomycin precursors **54a** and **54b** via the three routes, the synthesis of sarkomycin was at its final stage. Flash vacuum pyrolysis of **54a** and **54b,** performed either on the single or mixed isomers, quantitatively yielded sarkomycin methyl ester **58,** which upon acid hydrolysis afforded sarkomycin **42.**

SCHEME XV



Contrary to the reported spectra[10a,c,g,h] which have been cited in the literature[10b,d], in our hands sarkomycin **42** exibited an NMR spectrum identical with only that obtained by Tsuji[10f]. As already mentioned, up until this time there had been much controversy surrounding the NMR spectra of sarkomycin and its methyl ester, probably due to the difficulties in their synthesis which resulted in insufficient quantities and badly contaminated materials. With our new simple routes, however, we were able to easily prepare large quantities of pure compounds, and, with the aid of a Europium shift reagent (EuFOD), prove and clarify each proton's absorption.

Thus the controversy concerning the NMR spectra of sarkomycin and its methyl ester was settled, ironically by using the lowest resolution NMR spectrophotometer available (60 MHz), it being the only NMR instrument we have in our chemistry department, and is, in fact, on loan from The Office of Narcotics Control Board.

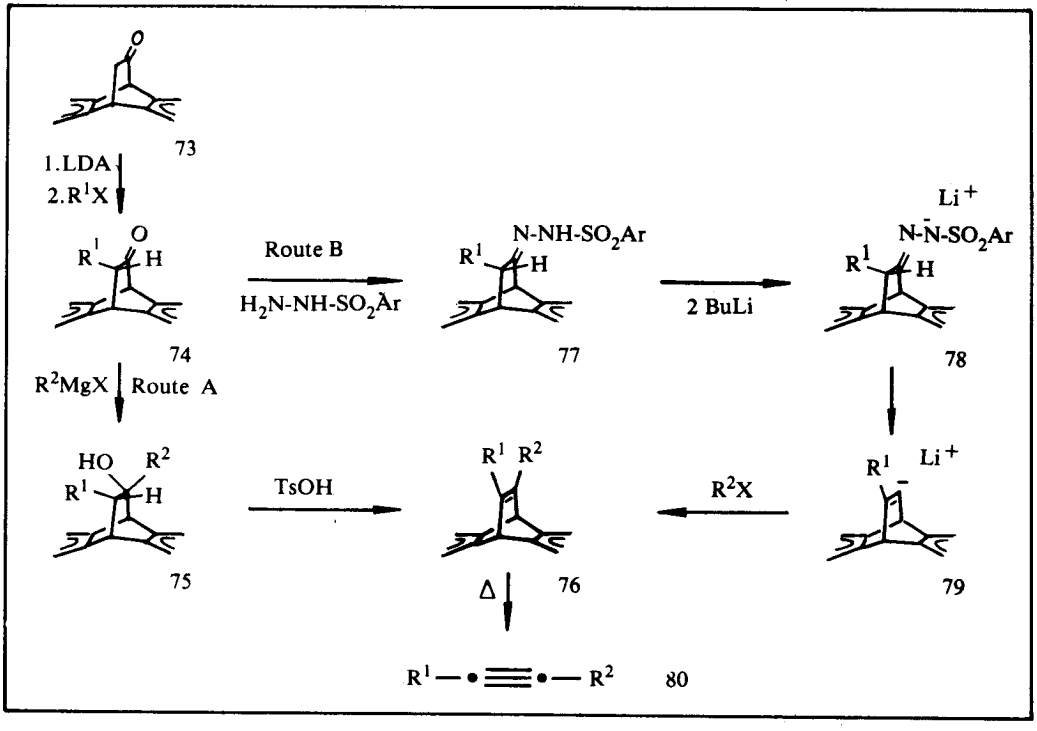
Ketene - Anthracene adduct : a novel route to substituted acetylenes[16]

Before concluding I would like to just mention some other use of the anthracene adduct, to give an idea of its high versatility.

For example, a few years ago we showed that the ketene-anthracene adduct **73,** a well known candidate for ketene precursor,[17] was a convenient starting block for the preparation of substituted acetylenes. The method provided a novel approach to the acetylenic bond, whose construction normally employed elimination reactions.

Our synthetic sequence is illustrated in **Scheme XVI.** Direct alkylation of the ketene adduct **73** via its lithium enolate gave **74** which could be converted to the acetylene precursor **76** via either Route A or B.

The retro Diels-Alder reaction of **76** offered no difficulty and the crude pyrolysates were shown to be pure acetylenes. It might be interesting to note that, in **Scheme XVI,** we in fact employed the ketene-anthracene adduct **73** as both the $^{-}C = C^{+}$ (Route A) and the $^{-} C = C ^{-}$ (Route B) synthons.



Conclusion

The work described above revolves around the synthetic utility of anthracene adducts and as a result of the study, methods have now been successfully developed for the syntheses of α -methylene- γ -butyrolactones, α -methylene cyclopentenones (including the antibiotics Methylenomycin B and Sarkomycin) and substituted acetylenes, amongst others. The study has led us to discover novel reactions such as the three-carbon annelation and the tandem Michael addition-Dieckmann condensation, which superbly complement each other in the construction of the cyclopentenoid nucleus and have made possible, for the first time, the preparation of large quantities of "cyclopentenoid antibiotics". In addition, the research has also provided much information relating to the understanding of several mechanistic problems[18-21] which, however, is beyond the scope of this present topic and is therefore not included here.

Acknowledgement

I consider myself fortunate in having always had excellent students who worked very long hours, wise friends who provided stimulating discussions and valuable advice

and a wonderful wife who not only took care of everything, but, as a chemistry partner, also played a major part in all my research work.

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บทคัดย่อ

การพัฒนาสาร *"แอนธราซีน แอดดักส์"* เพื่อนำมาใช้ในการสังเคราะห์พวกสารที่เป็นผลิตผลจากธรรมชาติ นั้นได้กระทำจนประสบผลสำเร็จ สารแอดดักส์ดังกล่าวนี้เตรียมได้โดยง่ายจากสารตั้งต้นที่มีราคาถูก และเมื่อเตรียมขึ้นแล้วก็เสถียรและสามารถใช้ทำปฏิกิริยาสังเคราะห์โครงสร้างต่าง ๆ ได้มากมาย ประโยชน์ดังกล่าวนี้จะเห็นได้จากตัวอย่างการใช้สารแอดดักส์นี้สังเคราะห์พวกยาปฏิชีวนะ เมทธิลิโนมัยซิน และ ซาร์โคมัยซิน พวกสารอัลฟ่า-เมทธิลีนแลคโทน และพวกสารประกอบ อะเซ็ทธิลีน ต่าง ๆ เป็นต้น ดังนั้น สารแอนธราซีน แอดดักส์ จึงสามารถใช้แก้ปัญหาในการสังเคราะห์ โดยทำให้สามารถเตรียมสารประกอบต่าง ๆ ที่มีคุณค่าได้โดยง่ายและประหยัด