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# Synthesis and chemistry of cyclopentenoid antibiotics

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Abstract A new and simple method has been developed for the preparation of α -methylene cyclopentenones and presently provides the most convenient route to sarkomycin. The work has, in addition, led to a better understanding of the vinylogous Dieckmann condensation, the course of Michael addition to α -methylene cyclopentenones and the behavior of cyclopentenoid endocyclic and exocyclic dienolates towards electrophiles.

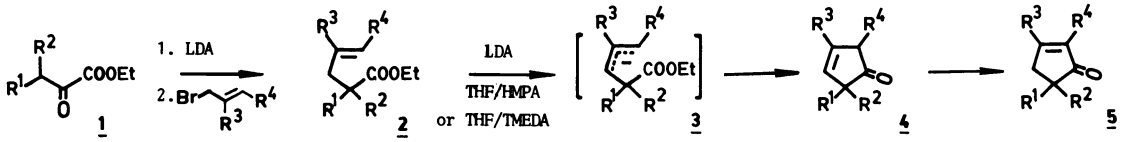
## INTRODUCTION

The chemistry of "cyclopentenoid antibiotics",[1] a small class of compounds isolated from the culture broth of streptomyces species, has recently attracted much attention from chemists. Despite the success of existing methods,[2] there have been recent reports on various alternative approaches to the synthesis of the cyclopentenoid nucleus, reflecting strong interest in this significant unit which is also found in a variety of other biologically important naturally occurring compounds. The work about to be described is from part of an on-going program being carried out in our laboratory.

## A THREE-CARBON ANNELATION ROUTE TO CYCLOPENTENONES

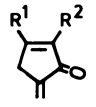
A few years ago we came across a very simple and effective method for the construction of disubstituted cyclopentenones (e.g. 4 or 5) via a three-carbon annelation as outlined below (Scheme 1).[3]

*Scheme 1*



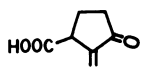

The mechanism of the above annelation is regarded as involving rapid cyclisation of the allyl anion 3. Various attempts to trap the anion 3 have failed, the reaction directly giving 4 and/or its thermodynamically more stable product 5.

Recognizing its potential, we decided to use the above reaction for the synthesis of α -methylene cyclopentenones 6, including methylenomycin B 7[4] and "the deceptive" sarkomycin 8.[5] Now, up until that time all the syntheses of α -methylene cyclopentenones have invariably involved two compulsory steps: construction of the five-membered ring and subsequent formation of the exo-methylene group via an elimination reaction (Figure A). In our study, however, the desired sequence was achieved by simply reacting the propene unit with a masked α -methylene carbonyl function (Figure B, Scheme 2, and Table 1).

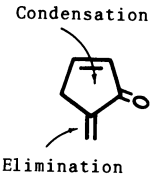


6

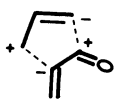
7



8



A

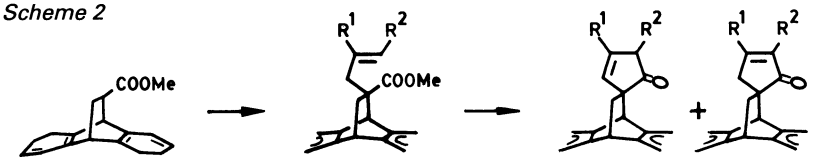


B

*Table 1*

| Entry | Substituents | Ratio of 11 : 12 | % Yield |
|---|---|---|---|
| a | $R^1 = R^2 = Ph$ | 0 : 1 | 92 |
| b | $R^1 = H$, $R^2 = Ph$ | 0 : 1 | 68 |
| c | $R^1 = H$, $R^2 = m$-OMe-$C_6H_4$ | 0 : 1 | 70 |
| d | $R^1 = Me$, $R^2 = H$ | 1 : 1 | 87 |
| e | $R^1 = R^2 = H$ | 1.2 : 1 | 82 |
| f | $R^1 = H$, $R^2 = Me$ | 1 : 1 | 79 |

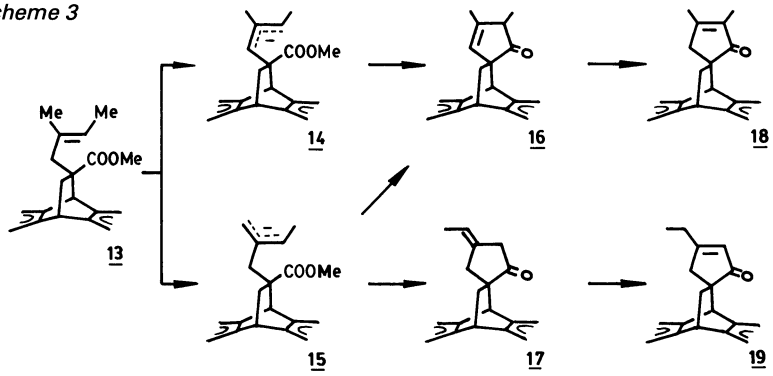
*Scheme 2*



9 10 11 12

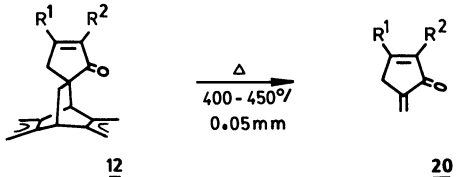
After studying a series of examples according to Schemes 1 and 2 a very interesting feature of the cyclisation was recognized, which is that two types of allyl anions, leading to two different cyclopentenones, would prevail if $R^1$ in 10 (or $R^3$ in 2) were not a tertiary carbon. Thus treatment of 13 with LDA in THF/TMEDA (4 : 1) solution gave only a minor amount of 18 (10%) while the major product (61%) was identified as 19. The formation of 19 can be explained in terms of preferred cyclisation at the less steric nucleophilic centre of 15 (Scheme 3).

*Scheme 3*



13 14 15 16 17 18 19

The problem of the poor yield of 18 (the required methylenomycin B precursor) from the cyclisation of 13 can be circumvented by a slight modification, by employing specific α- methylation of the lithium dienolate derived from 11d to yield solely 18. Subsequent retro-Diels-Alder reaction of the spirocyclopentenones 12 under flash vacuum pyrolysis conditions (400-450°/0.05mm) went smoothly giving the corresponding α-methylene cyclopentenones 20 in nearly quantitative yields. In this manner methylenomycin B 7 was obtained from the pyrolysis of 18.[6]

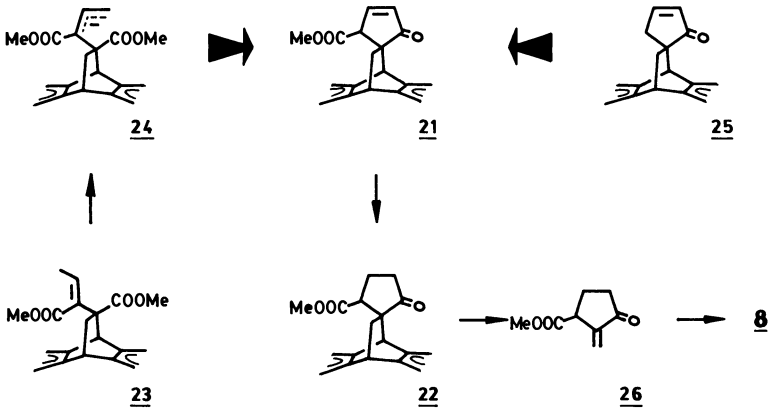



12 20

**Synthesis of sarkomycin (ref. 7)**

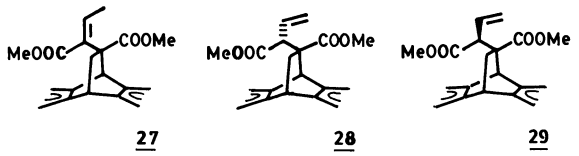
Unlike methylenomycin B 7, sarkomycin 8 contains a carboxylic acid group attached to the carbon adjacent to the methylene group, hence the obvious precursor of 8 would be the adduct 22, the dihydro derivative of the spirocyclopentenone 21. In principle it should be possible to obtain 21 either from the cyclisation of the anion 24 or from the specific $\gamma$-alkylation of 25, which is the equivalent of introducing the -COOR group into the molecule either before or after the cyclisation step (Scheme 4).

*Scheme 4*

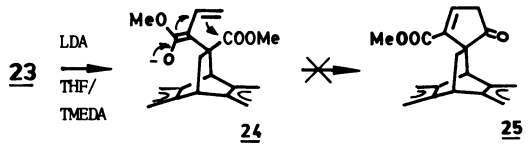



(a) Attempted cyclisation of 24 and related reactions[8]

When 23 was subjected to standard cyclisation conditions no trace of any cyclised product (e.g. 21 or its double bond isomer) could be observed but, instead, the starting material 23 together with 27, 28, and 29 were obtained in 12, 16, 14, and 27% purified yields respectively.

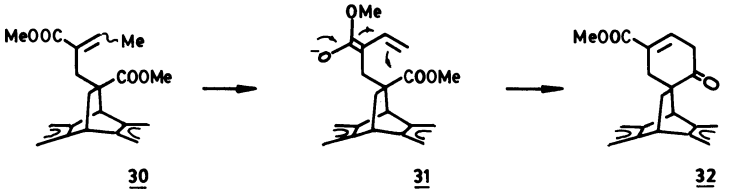



*Scheme 5*



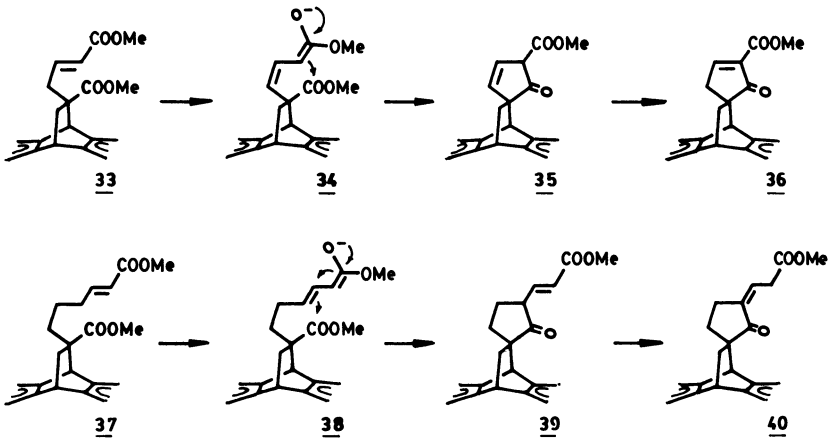

The isolation of isomeric 23, 27, 28, and 29 from the attempted cyclisation of 23 is strong indication that the dienolate 24 was formed but failed to cyclise. Upon close examination it was realized that the transition state of the required reaction is equivalent to a 5-(enolendo)-exo-trig cyclisation which has been described by Baldwin as a disfavoured process (Scheme 5).[9] However, there is no report on whether or not these concepts can be extended to conjugate enolate systems and having observed that the cyclisation of 24 is inhibited, it bacame of interest to further test such vinylogous Dieckmann condensation reactions. For example a 6-(enolendo)-exo-trig cyclisation is known to be a favoured process[9] and, indeed, we found that when compound 30, the homologue of 23, was subjected to the same reaction conditions, the cyclised product 32 was obtained in 64% yield (Scheme 6).

*Scheme 6*



Having differentiated between the vinylogous 5- and 6- (enolendo)-exo-trig cyclisations (Schemes 5 and 6) we then turned to scrutinize the (enolexo)-exo-trig process as outlined in Scheme 7. True to prediction, upon treatment with base both 33 and 37 smoothly cyclised in a manner equivalent to the 5-(enolexo)-exo-trig process followed by double bond isomerization to yield 36 and 40 respectively.

*Scheme 7*




The described investigation of vinylogous Dieckmann condensations equivalent to (enolexo)-exo-trig and (enolendo)-exo-trig cyclisations ascertains that these systems obey Baldwin's rules and thus clarifies why five membered rings are smoothly obtained from the former while the latter cyclisations occur only with six and not with five membered ring systems.

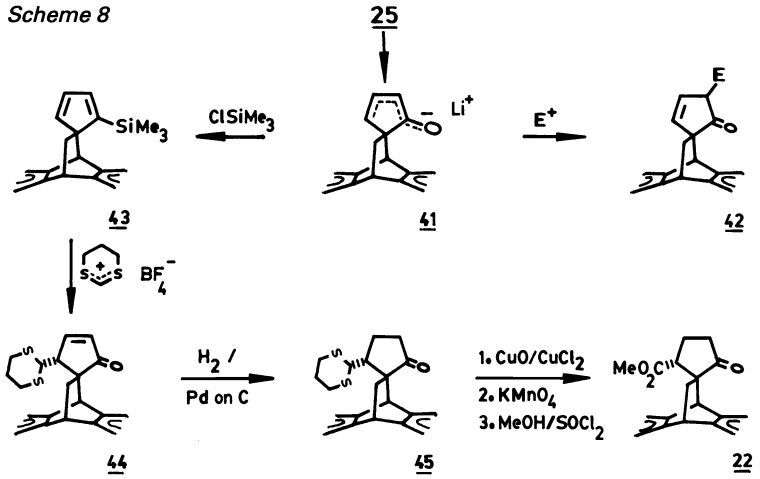
Results from the above study thus leaves the synthetic plan for sarkomycin via the three-carbon annelation technique outlined in Scheme 4 with only one option, that is, the specific γ-alkylation of 25. This goal has since been achieved and, moreover, two other methods of sarkomycin synthesis have also been successfully developed as will be briefly described below.

(b) Route 1 to sarkomycin : Specific γ-alkylation of 25[10]

As expected, alkylation of the lithium dienolate 41 derived from 25 with various electrophiles invariably took place at the α -position to give 42. However, we finally found that the reaction of the stable silyl dienol ether 43 with dithienium tetrafluoroborate,[11] which was both stereo-specific and regiospecific, led to the γ-alkylation product 44.

Having obtained 44, its subsequent conversion to the sarkomycin precursor 22 was then a straight forward process as shown in Scheme 8.

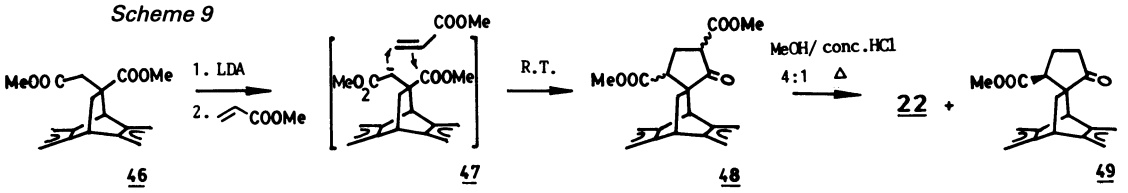
*Scheme 8*



(c) Route 2 to sarkomycin : A tandem Michael addition-Dieckmann condensation approach[10]

A shorter route to 22 and its stereoisomer 49 was developed using the dimethyl itaconate-anthracene adduct 46.[12] Here construction of the cyclopentenone nucleus was accomplished by tandem Michael addition-Dieckmann condensation between the anion derived from 46 and methyl acrylate. The crude cyclisation product 48 was then subjected to partial hydrolysis and subsequently decarboxylated by boiling in methanol/conc. HCl (4 : 1) to give 22 and 49 in a ratio of 1 : 3 (Scheme 9).

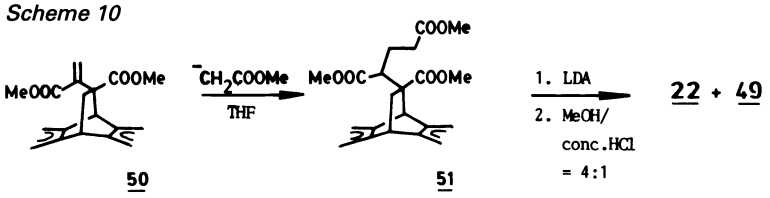
*Scheme 9*




(d) Route 3 to sarkomycin : An alternative Michael addition-Dieckmann condensation route[13]

Treatment of the methylene diester 50 (prepared in the same manner as 23)[8] with methyl acetate anion gave the Michael addition product 51 in 78% isolated yield. Subsequent base induced Dieckmann condensation of 51 afforded 48, which upon selective hydrolysis and decarboxylation yielded 22 and 49 in a ratio of 2.6 : 1 (65% from 51) as shown in Scheme 10.

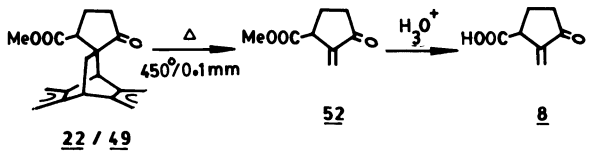
*Scheme 10*



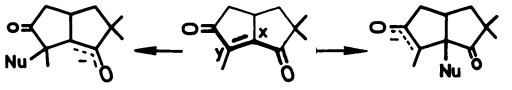

(e) Flash vacuum pyrolysis of sarkomycin precursors

Flash vacuum pyrolysis of the isomeric precursors 22 and 49, performed on the single or the mixed isomers, quantitatively yielded sarkomycin methyl ester 52. Upon acid hydrolysis[7f] the ester afforded sarkomycin 8.

*Scheme 11*




*Scheme 12*

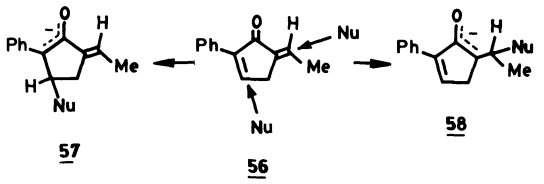



## NUCLEOPHILIC ADDITION TO α-METHYLENE CYCLOPENTENONES (ref. 14)

It has been reported[15] that nucleophiles react with the unsymmetrical enedione 53 in a Michael addition fashion at the bridge-head carbon x and not at carbon y, the products from such reactions being uniformly derived from the enolates 54. The direction of addition is believed to be governed by strain in the developing enolate, the formation of enolate 54 being less strained than the enolate 55 with an $SP^2$ bridge-head carbon. In considering this difference in regiochemistry it can be appreciated that nucleophilic attack at carbon x to give 54 is, in fact, an addition to the endocyclic transoid-enone double bond, while the same process at carbon y yielding 55 is the attack at the exocyclic cisoid-enone double bond.

Since Michael additions to both types of enones are well documented we became curious to test the regiospecificity of such additions to the methylene cyclopentenone system. Compound 56[16] was selected as our study model because inspection of its molecular model showed almost no strain in either of the transition states leading to the enolate 57 or 58 from nucleophilic attack at the two respective electrophilic centres.

*Scheme 13*

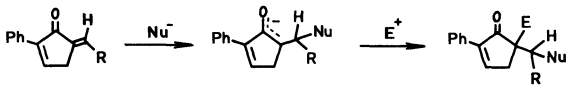


The reaction of various nucleophiles with 56 proceeded smoothly in THF solution at -78° and the results are summarized in Table 2.

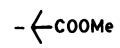
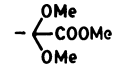
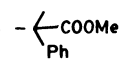
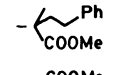
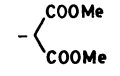
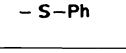
It was found that the additions specifically occurred at the exocyclic double bond of the cisoid-enone in 56. We were able to trap the resulting enolate 58 with the proton, as well as with other electrophiles, to yield 59.

A simpler (but arguably not as good) model molecule 60 was also subjected to study. Again, additions cleanly produced 62, confirming that nucleophiles react preferentially at the exocyclic site even though reaction at the endocyclic transoid-enone would have given an electronically more stable enolate (e.g. 57).

*Table 2*



56, R = Me; 60, R = H — 58, R = Me; 61, R = H — 59, R = Me; 62, R = H

| | NUCLEOPHILE | ELECTROPHILE | % of 59[a] | % of 62[a] |
|---|---|---|---|---|
| i. |  | a. $H_3O^+$ | 91 | 90 |
| | | b. $CH_3I$ | 85 | 76 |
| | | c $H_2C=CH-CH_2-Br$ | 82 | 74 |
| | | d. $Ph-CH_2-Br$ | 64 | 73 |
| ii. |  | a. $H_3O^+$ | 90 | 71 |
| | | b. $CH_3I$ | 85 | *b* |
| | | c. $H_2C=CH-CH_2-Br$ | 81 | *b* |
| | | d. $Ph-CH_2-Br$ | 58 | *b* |
| iii. |  | a. $H_3O^+$ | 84 | 73 |
| | | b. $CH_3I$ | *b* | 68 |
| | | c. $H_2C=CH-CH_2-Br$ | *b* | 77 |
| | | d. $Ph-CH_2-Br$ | *b* | 78 |
| iv. |  | $H_3O^+$ | 86 | 72 |
| v. |  | $H_3O^+$ | 82 | 94 |
| vi. |  | $H_3O^+$ | 95 | 97 |

[a] The yields shown are isolated yields after purification by Prep. TLC (silica gel, 7 : 3 $CH_2Cl_2$ : hexane). Where several diastereomers were possible it was found that one isomer always predominated (indicated by nmr). Separation of isomers were performed in cases 62-iii-b, 62-iii-c, 62-iii-d, each of which afforded two stereomers. No attempt was made to assign their stereochemistry.

[b] This reaction has not been performed.

*Scheme 14*

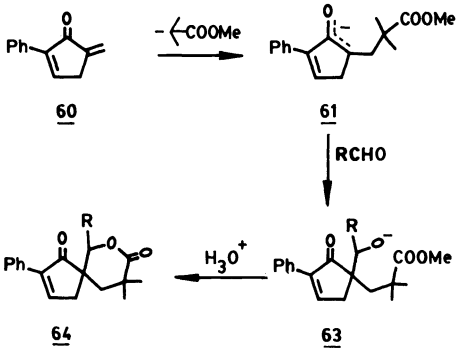
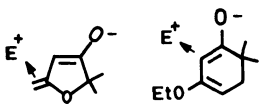


*Table 3*

| | ALDEHYDE | % yield of 64 |
|---|---|---|
| i. | PhCHO | 60 |
| ii. | $CH_3CHO$ | 53 |
| iii. | $CH_3CH_2CHO$ | 72 |
| iv. | $CH_3CH=CHCHO$ | 56 |
| v. | PhCH=CHCHO | 51 |
| vi. | 4-OMe-$C_6H_4CHO$ | 69 |
| vii. | 3-OMe-$C_6H_4CHO$ | 74 |
| viii. | 2,3-di-OMe-$C_6H_3CHO$ | 61 |
| ix. | 3,4-di-OMe-$C_6H_3CHO$ | 63 |
| x. | 3,4,5-tri-OMe-$C_6H_2CHO$ | 58 |

Trapping the intermediate 61 with aldehydes gave a rather interesting result. Here the enolate ion 61, generated by the addition of methyl isobutyrate to 60, reacted with aldehyde to give, via the alkoxide 63, the spirolactone 64 in reasonable yield (Table 3). High resolution nmr data revealed that the product in each case was homogeneous, which indicated that the reaction was, stereospecific, producing, in each case, only one pair of racemate. However, no attempt was made to assign the stereochemistry.

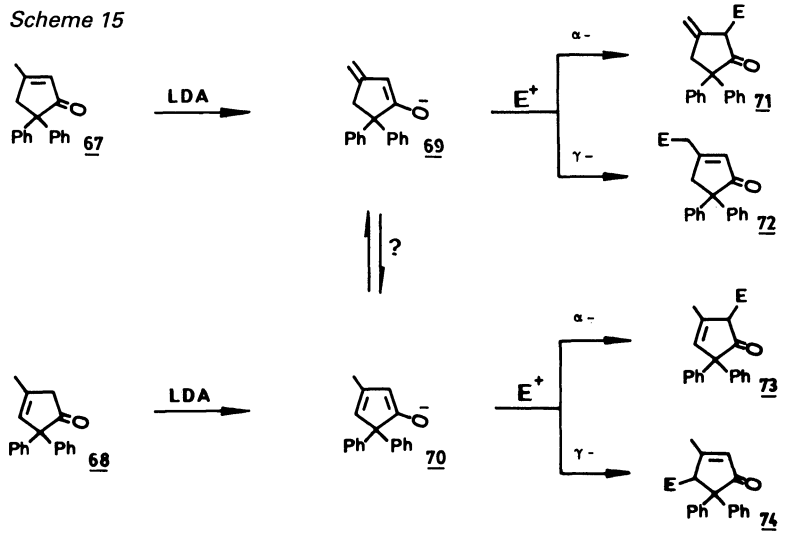
## BEHAVIOR OF EXOCYCLIC AND ENDOCYCLIC DIENOLATES TOWARDS ELECTROPHILES (ref. 17)



65 66

A very interesting observation by Smith[18] has revealed that the exocyclic dienolate (e.g. 65) reacts with alkyl halides preferentially at the γ- position while the endocyclic dienolate (e.g. 66) does so exclusively at the α- position. We ourselves came across some very unusual alkylation selectivity in the cyclopentenone system during our synthesis of methylenomycin B 7 and sarkomycin 8 as mentioned earlier. This led us to study the behavior of isomeric exocyclic and endocyclic dienolates towards electrophiles. The choice of isomeric cyclopentenones 67 and 68 as model compounds offered a two-fold advantage. The first is that treatment of 67 and 68 with base under kinetically controlled conditions would lead specifically to the respective exocyclic and endocyclic dienolates 69 and 70 and thus allow us to determine the individual regiospecificity towards electrophiles and the second is that it should also be possible to measure the extent of isomerisation, if any, of the dienolates 69 and 70 at various temperatures.

*Scheme 15*




Results from the study can be summarized as follows :

i. Generation of specific exocyclic and endocyclic dienolates 69 and 70 from the corresponding enones is feasible and these enolates can be employed in further reactions without isomerisation.

ii. The endocyclic dienolate 70 reacts regiospecifically with various electrophiles (alkyl chloroformates, acid chlorides, aldehydes, and alkyl halides) at α- position to yield 73 as the only product.

iii. Reaction regiospecificity of the exocyclic dienolate 69 is dependent on the type of electrophile employed. For example, 69 reacts with alkyl chloroformates and acid chlorides exclusively at the α- position to yield 71, while specific γ- addition to give 72 is observed in the case of aromatic and aliphatic aldehydes, yet alkylation of 69 with alkyl halides occurs both at the α- and γ- positions, the ratio of products 71 and 72 being dependent on the reaction conditions. These observations should find applications in organic synthesis with exocyclic and endocyclic dienolates.

## CONCLUSION

The work described above revolves around the synthesis and reactions of cyclopentenones and as a result of the study various methods have been successfully developed for the synthesis of sarkomycin. We have demonstrated that the tandem Michael addition-Dieckmann condensation works extremely well in the construction of the cyclopentenoid nucleus and thus allows large quantities of sarkomycin to be easily prepared. The retro-Diels-Alder reaction also proceeded efficiently under our employed conditions which is suitable for the fairly small molecules under study. Moreover, the research has provided much information and thereby enhanced our understanding of the vinylogous Dieckmann condensation, the Michael addition to α-methylene cyclopentenones, and the behavior of isomeric endocyclic and exocyclic dienolates towards electrophiles.

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## REFERENCES

1. Scarborough, R.M., Jr.; Toder, B.H.; Smith, A.B., III J. Am. Chem. Soc. 102, 3904 (1980).
2. Ellison, R.A. Synthesis 397 (1973).
3. Prempree, P.; Siwapinyoyos, T.; Thebtaranonth, C.; Thebtaranonth, Y. Tetrahedron Lett. 21, 1169 (1980).
4. (a) Haneishi, T.; Kitihara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. J. Antibiot. 27, 386 (1974). (b) Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. Ibid. 27, 393 (1974).
5. Umezawa, H.; Takeuchi, T.; Nitta, K.; Yamamoto, Y.; Yamaoka, S. J. Antibiot. 6, 101 (1953).
6. Siwapinyoyos, T.; Thebtaranonth, Y. J. Org. Chem. 47, 598 (1982).
7. Synthesis of sarkomycin: (a) Govindan, S.V.; Hudlicky, T.; Koszyk, F.J. J. Org. Chem. 48, 3581 (1983). (b) Hewson, A.T.; MacPherson, D.T. Tetrahedron Lett. 24, 647 (1983). (c) Marx, J.N.; Minaskanian, G. J. Org. Chem. 47, 3306 (1982). (d) Wexler, B.A.; Toder, B.H.; Minaskanian, G.; Smith, A.B., III Ibid. 47, 3333 (1982). (e) Barreiro, E.J. Tetrahedron Lett. 23, 3605 (1982). (f) Kobayashi, Y.; Tsuji, J. Ibid. 22, 4295 (1981). (g) Boeckman, R.K.; Naegely, P.C.; Arther, S.D. J. Org. Chem. 45, 752 (1980). (h) Marx, J.N.; Minaskenian, G. Tetrahedron Lett. 4175 (1979).
8. Kodpinid, M.; Thebtaranonth, Y. Tetrahedron Lett. 25, 2509 (1984).
9. (a) Baldwin, J.E. J. Chem. Soc. Chem. Comm. 734 (1976). (b) Baldwin, J.E.; Lusch, M.J. Tetrahedron 38, 2939 (1982). (c) House, H.O.; Phillips, W.V.; Sayer, T.S.B.; Yau, C.C. J. Org. Chem. 43, 700 (1978).
10. Kodpinid, M.; Siwapinyoyos, T.; Thebtaranonth, Y. J. Am. Chem. Soc. 106, 4862 (1984).
11. (a) Dauben, H.J., Jr.; Honnen, L.R.; Harmon, K.M. J. Org. Chem. 25, 1442 (1960). (b) Corey, E.J.; Walinsky, S.W. J. Am. Chem. Soc. 94, 8932 (1972). (c) Paterson, I.; Price, L.G. Tetrahedron Lett. 22, 2833 (1981).
12. Golfier, M.; Prange', T. Bull. Soc. Chim. Fr. 1158 (1974).
13. Unpublished results.
14. Siwapinyoyos, T.; Thebtaranonth, Y. Tetrahedron Lett., 25, 353 (1984).
15. Danishefsky, S.; Khan, M. Tetrahedron Lett. 22, 485 (1981).
16. Prepared according to the method described in reference 6.
17. For full details see: Thebtaranonth, Y.; Yenjai, C. Tetrahedron Lett., 26, 0000 (1985).
18. (a) Smith, A.B., III; Lavenberg, P.A..; Jerris, P.J.; Scarborough, R.M., Jr.; Wovkulish, P.M. J. Am. Chem. Soc. 103, 1501 (1981). (b) Smith, A.B., III; Scarborough, R.M., Jr. Tetrahedron Lett. 4193 (1978).