

TOTAL SYNTHESSES OF NATURAL PRODUCTS FROM FIVE-MEMBERED
HETEROCYCLIC COMPOUNDS AS STARTING MATERIALS

Tetsuji Kametani^{*} and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama,
Sendai 980, Japan

Total syntheses of natural products, in which the carbon-unit generated by ring opening of five-membered heterocyclic compounds is either a starting material or a key intermediate, are described.

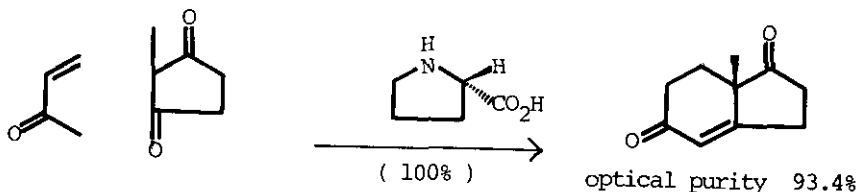
CONTENTS

- I Introduction
- II Syntheses from Furans and Hydrofurans
 - 1. Furans
 - 1.1 Acidic Hydrolysis Method
 - 1.2 Syntheses via 2,5-Dihydrofurans
 - 1.3 Syntheses by an Oxidative Ring Opening of Furans
 - 1.4 Syntheses by a Cycloaddition of Furans
 - 2. 2,3-Dihydrofurans and Tetrahydro-2-hydroxyfurans
- III Syntheses Using Thiophenes
- IV Syntheses Using Pyrroles
- V Syntheses from Oxazoles
- VI Syntheses from Isoxazoles
- VII Syntheses from Thiazoles and Isothiazoles
- VIII References

I. Introduction

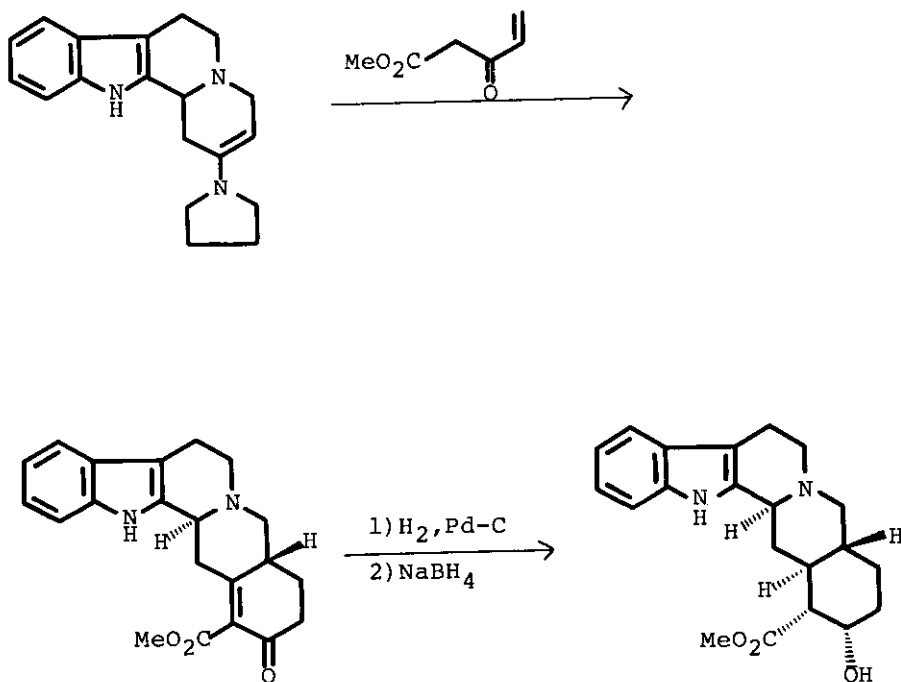
It is well known that there are more than three millions of organic compounds and a great number of new compounds has been born by a synthesis or an isolation from nature. Heterocyclic compounds occupy an important position in organic chemistry and, especially, have been widely used in synthesis. For example, tetrahydrofuran has been employed as a solvent, dihydropyran as a reagent to protect hydroxyl groups, pyridine and piperidine have functioned as a base for dehydrohalogenation or carbon-carbon bond formation, and recently, L-proline has been applied as a catalyst for an asymmetric synthesis as shown in the following Chart.¹

Chart 1



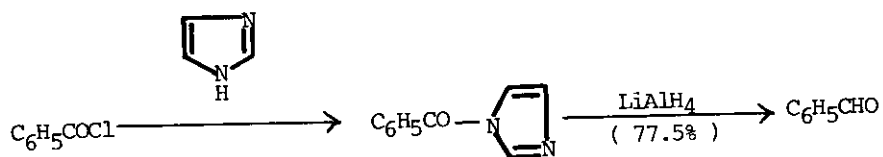
The use of pyrrolidine, morpholine and piperidine enamines was developed by Stork² and is an important synthetic reaction. As an example of this method in the synthesis of natural products Chart 2 shows the preparation of yohimbine³. In contrast to the activation of substrates by enamine formation, imidazole has

Chart 2



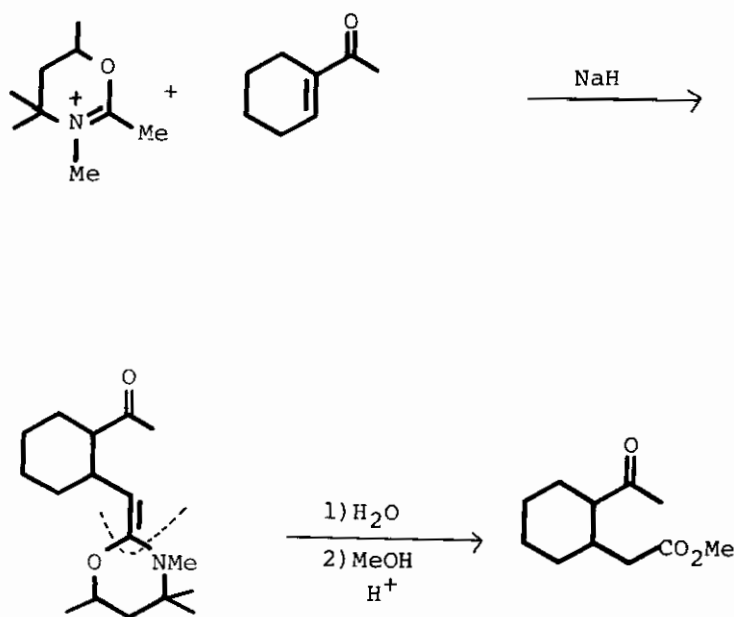
been used as deactivating group in the lithium aluminium hydride reduction of carboxylic acids to aldehydes.⁴

Chart 3



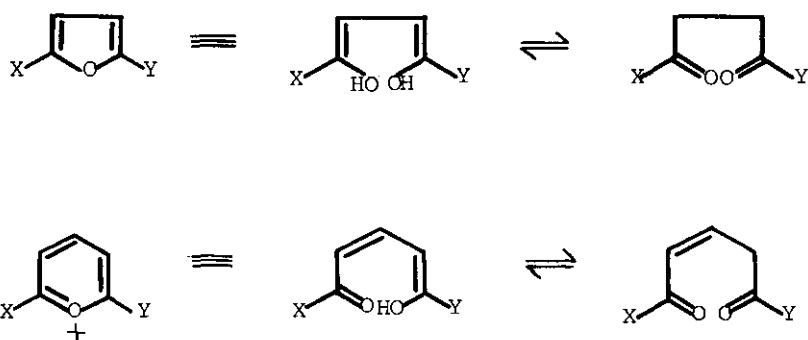
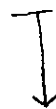
In the above examples, the heterocyclic compounds do not form any parts of the products. However in some cases, part of the heterocyclic system constitutes a carbon unit to the reaction products.⁵

Chart 4



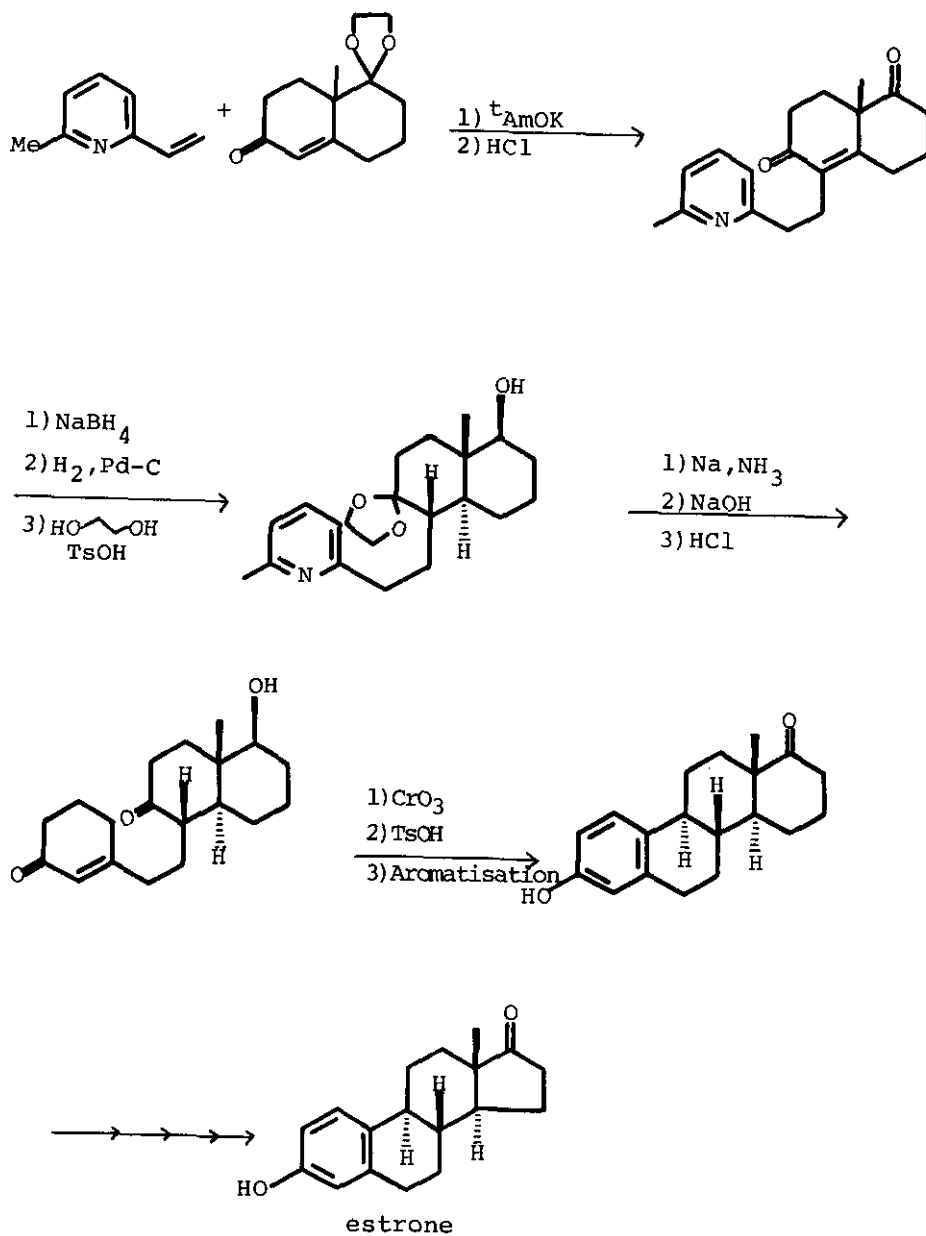
As shown in the Chart 5, some kinds of heterocyclic compounds are chemical equivalents with carbonyl derivatives and suggests

Chart 5



that such heterocyclic compounds can provide a means of introducing side chain. Thus, a heterocyclic compound can be used to construct a nonheterocyclic system.⁶ A typical example is shown in the total synthesis of estrone by Danishefsky and coworkers where picoline is converted into ring A of the target compound.⁷

Chart 6



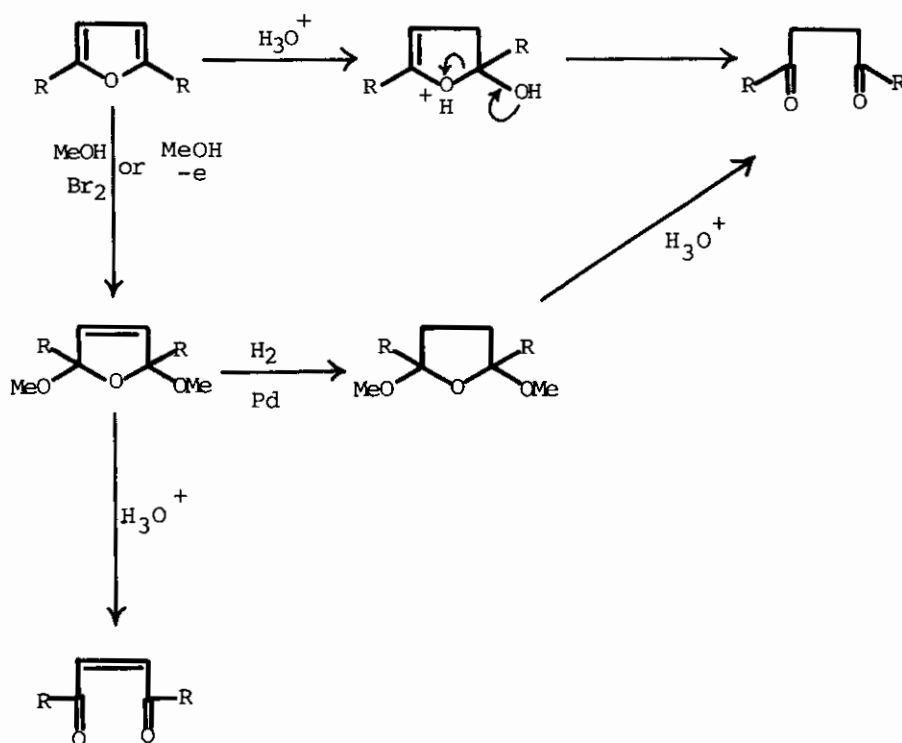
In this review, we will describe the total syntheses of natural products via a carbon-carbon chain formed by elimination of the hetero atom through decomposition of a five-membered heterocyclic system.

II Syntheses from Furans and Hydrofurans

1. Furans

The furan nucleus is sensitive to mineral acids and forms the corresponding ring-opened 1,4-dicarbonyl compound.^{8,9} However,

Chart 7

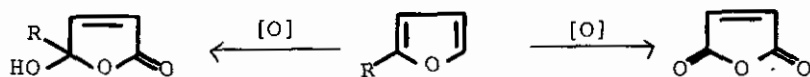


since this reaction, until recently, was of little preparative value because of extensive polymerisation, the following indirect method has been used in the conversion of furans into 1,4-dicarbonyl compounds.¹⁰

Thus, a disubstituted furan is transformed by treatment with bromine in methanol or by electrolytic oxidation into the 2,5-dihydro-2,5-dimethoxyfuran and then the products are reduced catalytically followed by acidic hydrolysis to give the 1,4-dicarbonyl compounds. In some cases, direct hydrolysis of the intermediate 2,5-dihydro-furans with acid has provided unsaturated 1,4-diketones.

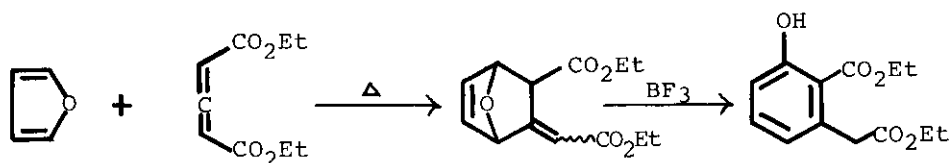
The second method for ring opening the furan ring is based on oxidation to give, depending on reaction conditions, γ -lactones or maleic acid derivatives.

Chart 8



The other synthetic reaction using furans is Diels-Alder reaction with appropriate dienophiles and has been employed in the synthesis of six-membered ring compounds.¹¹

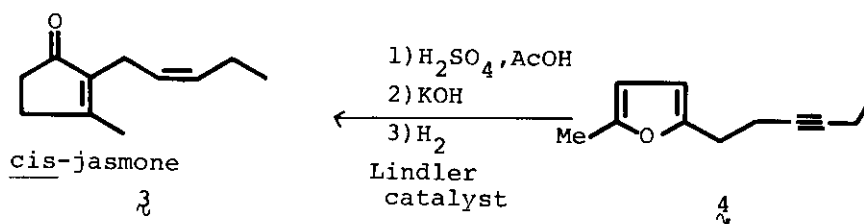
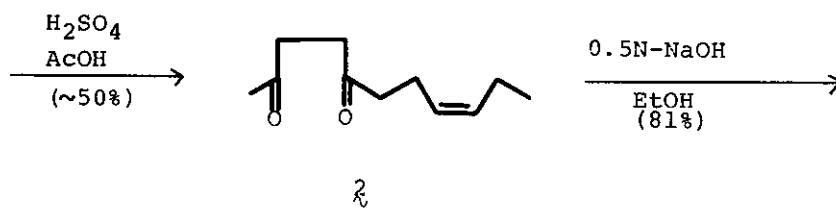
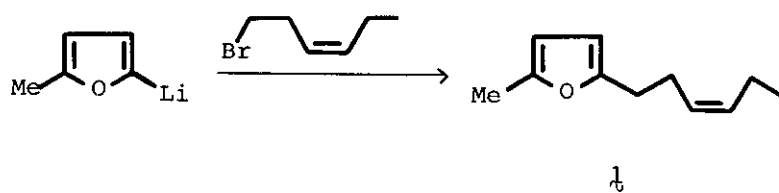
Chart 9



1.1 Acidic Hydrolysis Method

As mentioned above, acidic treatment of furans gives easily by ring opening 1,4-dicarbonyl compounds which form upon basic treatment cyclopentenones via aldol condensation. By using this sequence, Büchi and Wüest¹² synthesised cis-jasmone (3) from 2-methylfuran in 40 % overall yield. The hexenylfuran 1, obtained by metallation of 2-methylfuran and then alkylation with 2-hexenyl bromide, was treated with a trace of sulphuric acid in acetic acid at 120° for 3 hr to give the 1,4-diketone 2, which was cyclised to cis-jasmone (3) under the influence of ethanolic sodium hydroxide at room temperature for 5 hr. Birch and coworkers¹³ also synthesised cis-jasmone from 2-methylfurylpropionate via 2-carboxymethyl-3-methylcyclopentenone by the same reaction sequence. Moreover, Takano and associates¹⁴ succeeded in the conversion of 2-methylfuran into cis-jasmone via 5-methylfurylpropionaldehyde and the acetylene derivative 4.

Chart 10

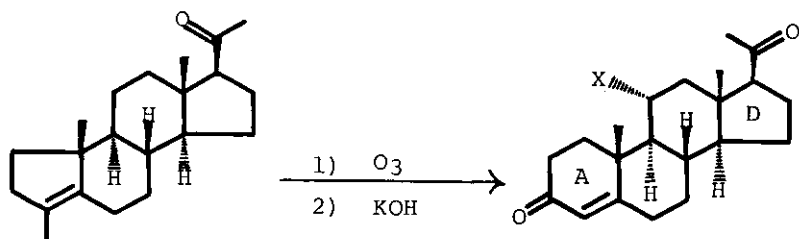
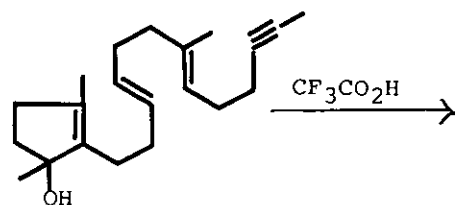
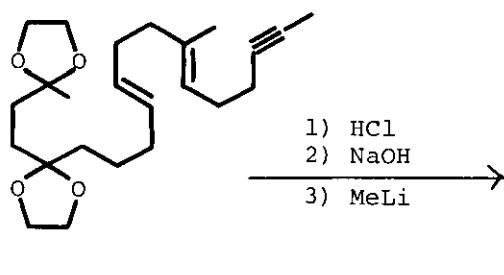
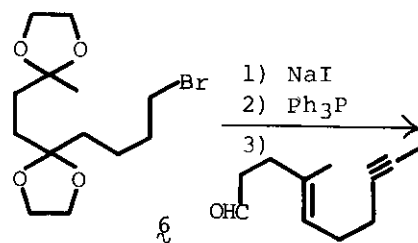
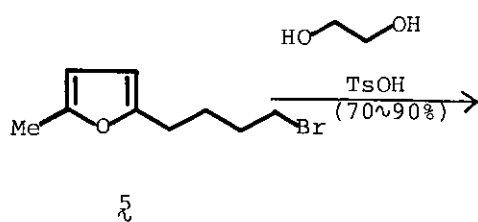


A biogenetic type synthesis of progesterone (7) has been achieved by Johnson and colleagues¹⁵ who utilized 2-methylfuran as the carbon source for ring A formation. Alkylation of 2-methylfuran with 1,4-dibromobutane gave the 2-bromobutylfuran 5 which was treated with a small amount of *p*-toluenesulphonic acid in ethylene glycol and benzene in the presence of hydroquinone to afford the bis-ketal 6 in 70 ~ 90 % yield. After introduction of the appropriate carbon-chain for the formation of rings B,C and D, deketalisation, aldol condensation and then methylation, the cyclopentane derivative was converted into progesterone (7) as shown in Chart 11. It is noteworthy that the 1,4-diketone arising from the direct acid cleavage of furan ring was protected as the diketal in order to prevent polymerisation and the formation of side products. In a similar manner¹⁶, 11 α -hydroxyprogesterone (8) was obtained from the chloride corresponding to 6. (Chart 11)

Further, since the cyclopentene portion derived from the bis-ketal (6) corresponds to ring D of steroids, it was utilized in the total synthesis of estrone (9) as shown in Chart 12.¹⁷

A convenient synthesis of the prostaglandin precursor 12 is available from the ω -furfuryl alcohol 10 readily prepared by condensation of furan with *tert*-butyl ω -formylheptanoate. The furfuryl alcohol 10 was rearranged with polyphosphoric acid in acetone at 50° to the cyclopentenone 11 followed by isomerisation with alumina to give the prostaglandin E₁ precursor 12.¹⁸

Chart 11



X=H progesterone 7
 X=OH 8

Chart 12

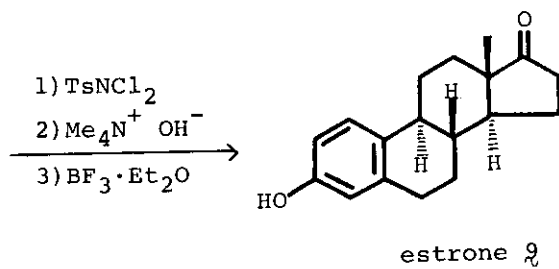
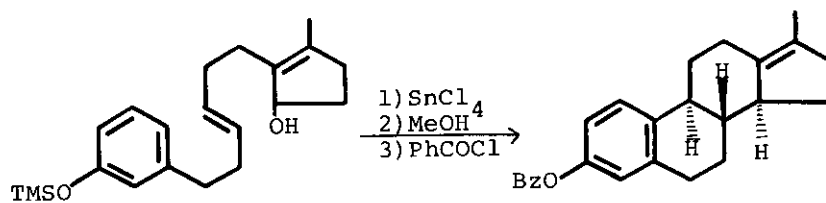
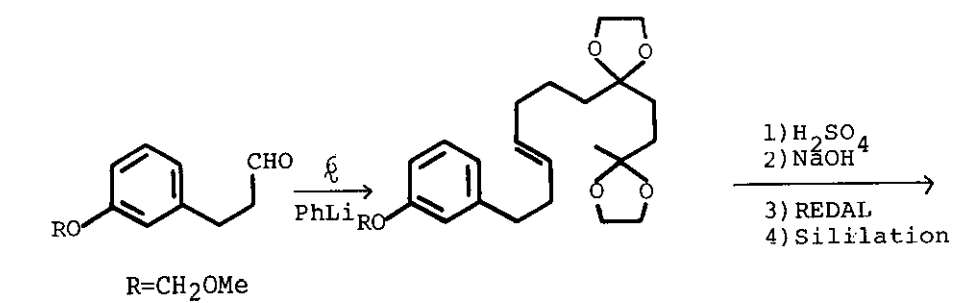
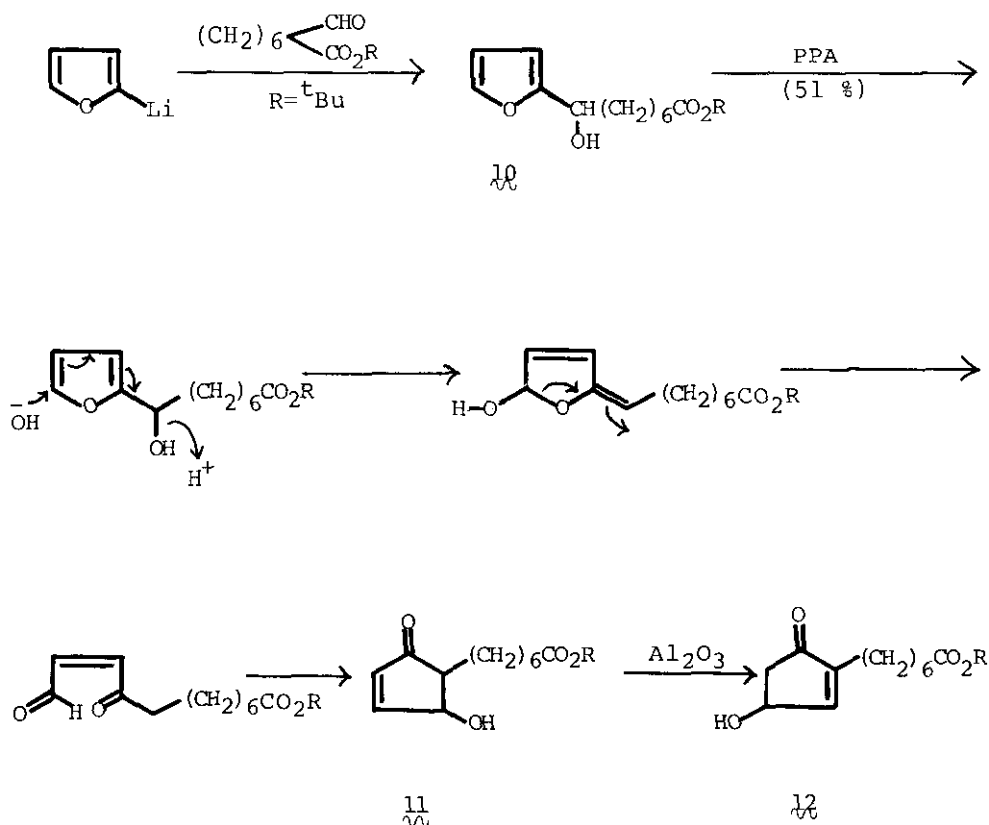
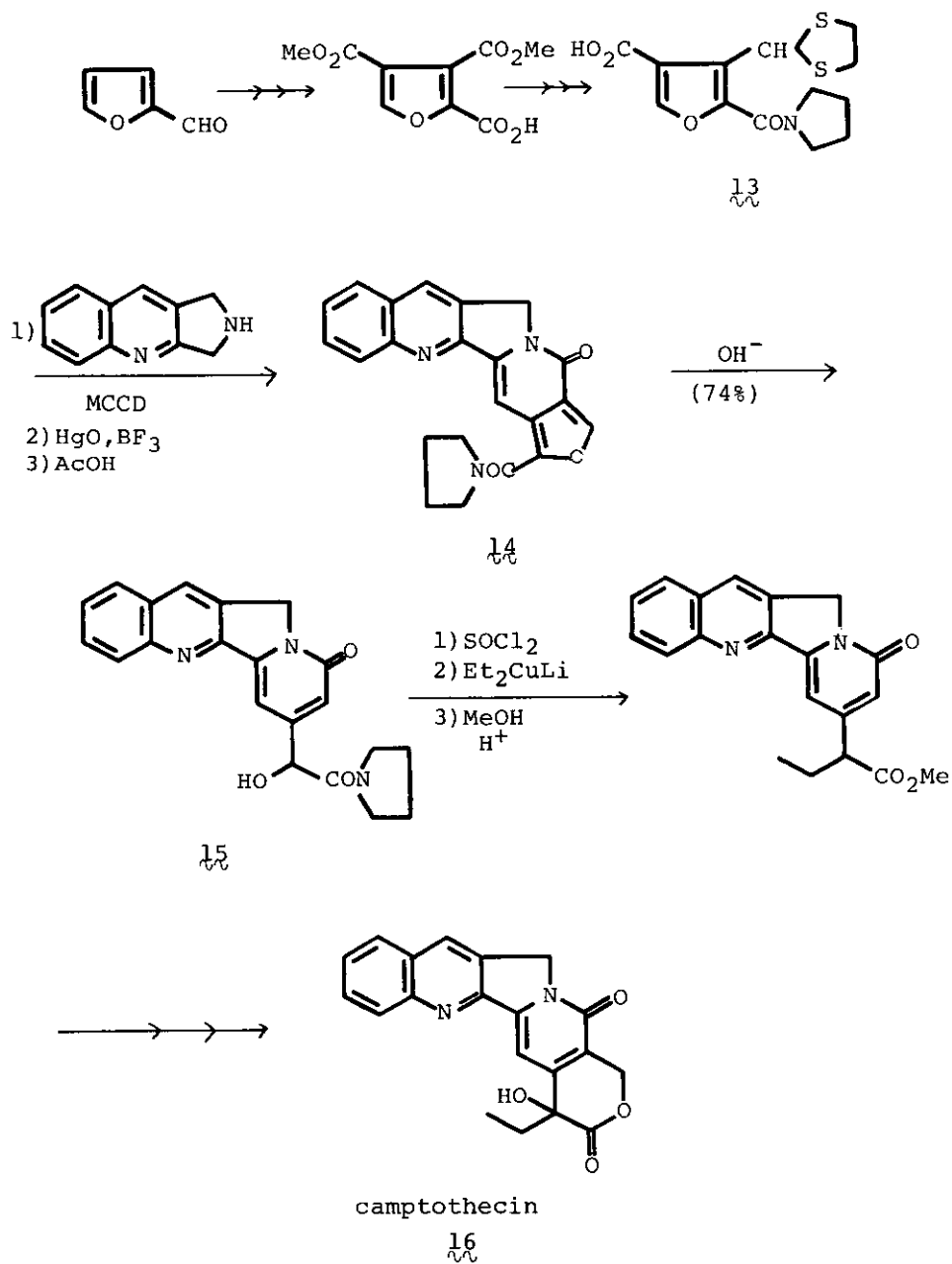


Chart 13



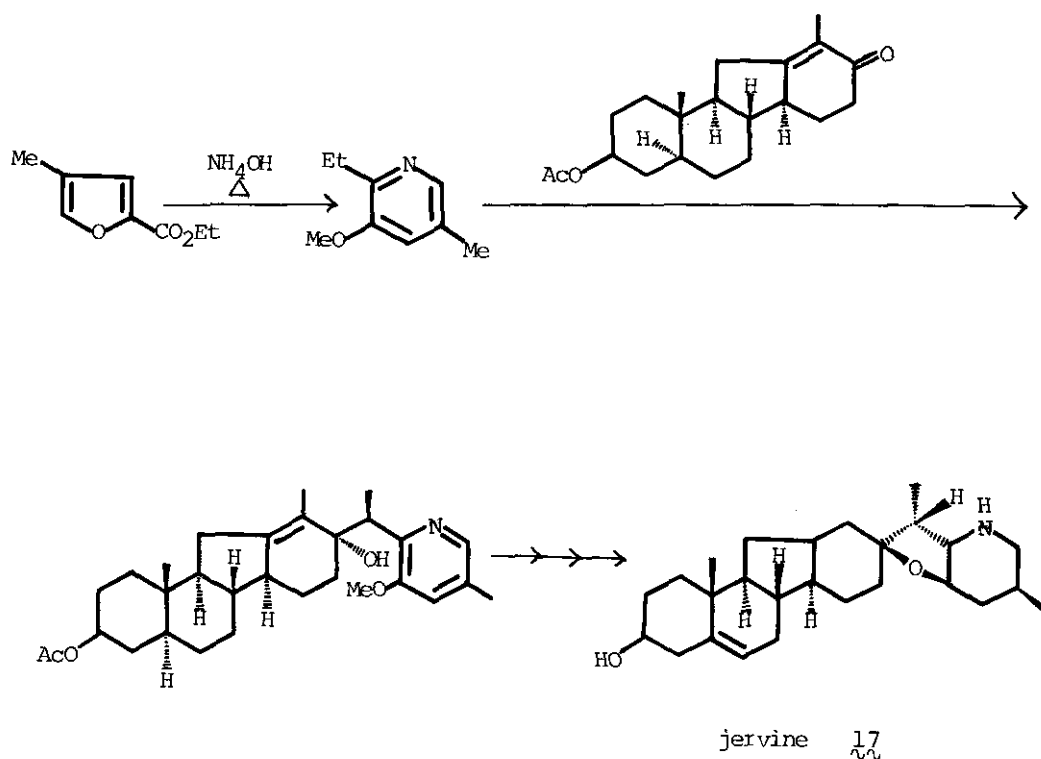
Kende and colleagues¹⁹ achieved a total synthesis of camptotecin (**16**) by using the furan nucleus to form ring E of this alkaloid. The amidofuran **13**, obtained from furfural in several steps, was treated with pyrrolo[2,3-*c*]quinoline and the condensation product was cyclised to the pentacyclic intermediate **14**. Alkali treatment of **14** produced the amino-alcohol **15** in 74 % yield by cleavage of furan ring and subsequent deformylation. After introduction of ethyl group, the resulting product was converted in the usual manner into camptothecin.

Chart 14



In the synthesis of jervine (17) by Kutney and coworkers²⁰ 5-methyl-2-propionylfuran was easily transformed into the key starting material 2-ethyl-3-methoxy-5-methylpyridine.

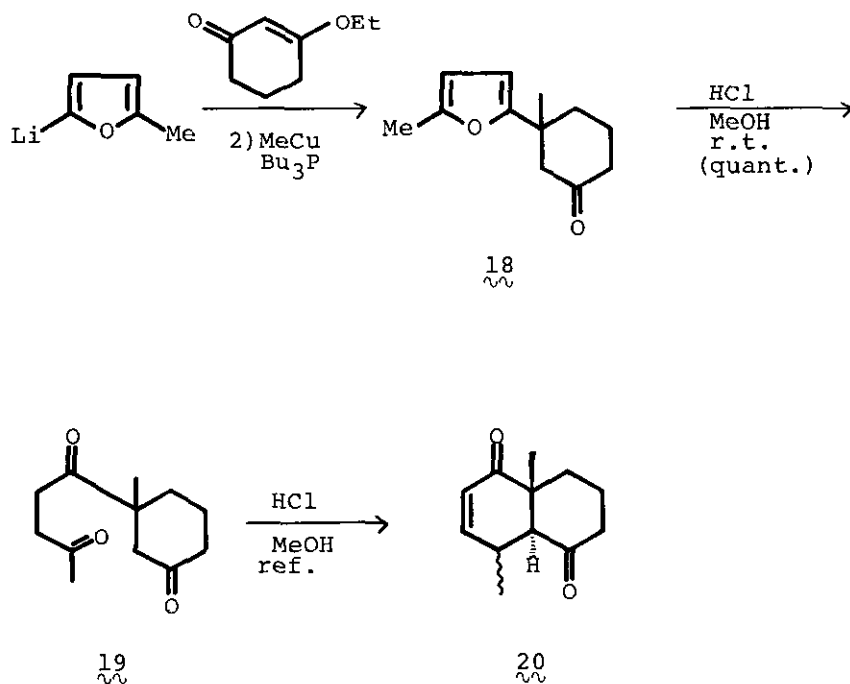
Chart 15



The furan ring has also been utilized as a functional group where the carbon chain participated in annelation.^{21 ~ 23} For example, the bicyclic dione 20, an important starting material for sesquiterpenes, was obtained in four-steps from 2-methylfuran and

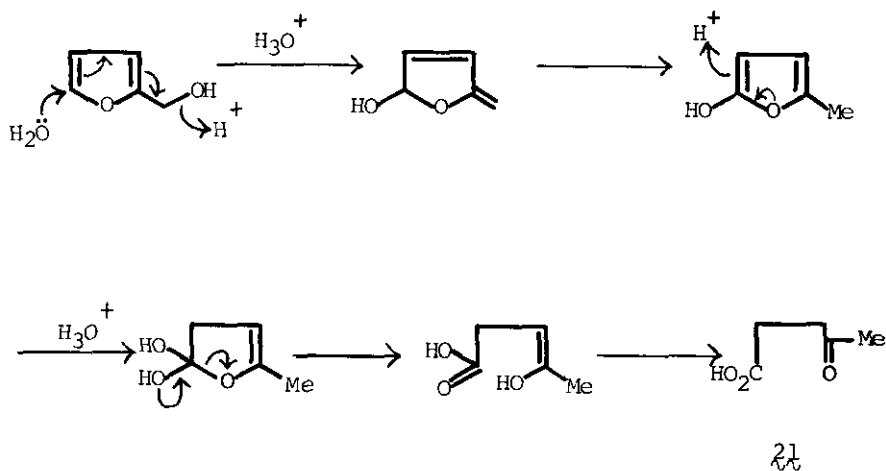
3-ethoxycyclohexenone. Condensation of 2-methylfuran with cyclohexenone followed by methylation provided the 2,5-disubstituted furan 18 with the necessary carbon content for annelation. Treatment of 18 with concentrated hydrochloric acid in methanol at room temperature produced the triketone 19 which was subjected to annelation with hydrochloric acid in boiling methanol to give the product 20.²⁴

Chart 16



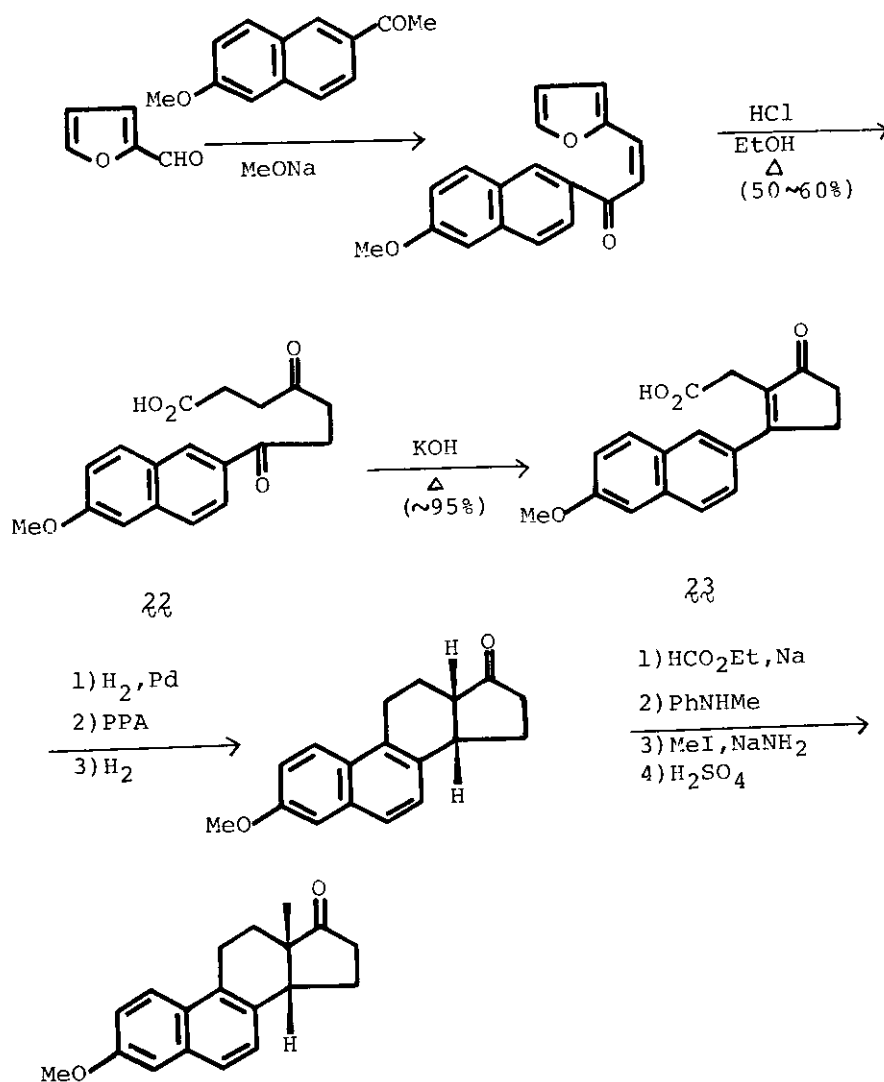
Although ring opening reaction of furans with acids produces 1,4-dicarbonyl compounds, levulinic acids are formed by the same treatment of α -furfuryl alcohols or α -vinylfurans as shown in Chart 17.²⁵

Chart 17



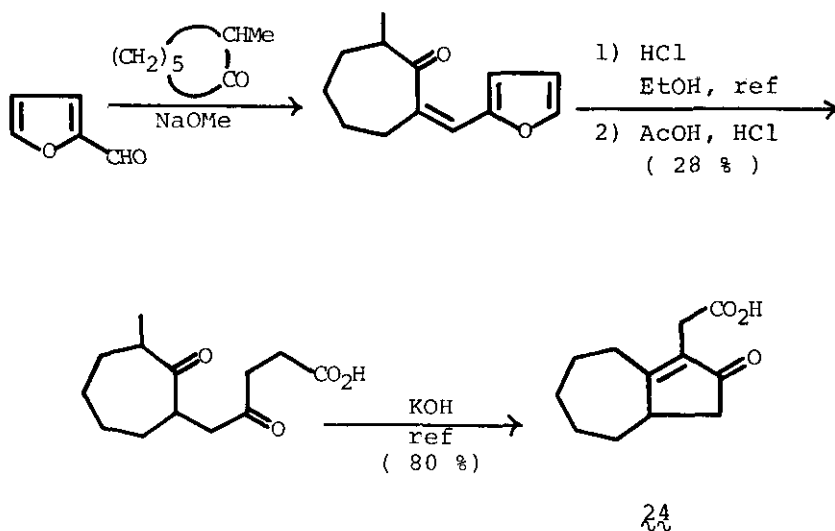
Birch and Subba Rao²⁶ reported a synthesis of steroids by using this type reaction. Thus, aldol condensation of furfural with β -acetylnaphthalene gave the furfurylidene derivative which opened up in ethanolic hydrochloric acid to the diketone acid 21 followed by cyclisation with potassium hydroxide to the cyclopentenone derivative 23 which was converted into the steroid as shown in Chart 18. Similar approaches to steroids were also reported by Coombs and Bhatt²⁷ and Kapoor and Mehta.²⁸

Chart 18



A synthesis of the bicyclo[5.3.0]decanone 24, a basic structure in certain sesquiterpenes, was accomplished in 17 % yield by ring opening of the condensation product of furfural with 1-methylcyclopentanone followed by annelation of the resulting diketo acid. In this sequence an unusual intramolecular oxidation-reduction occurred where the double bond in the condensation product is reduced while the terminal aldehyde derived from furan is oxidised to the carboxyl group.²⁷

Chart 19

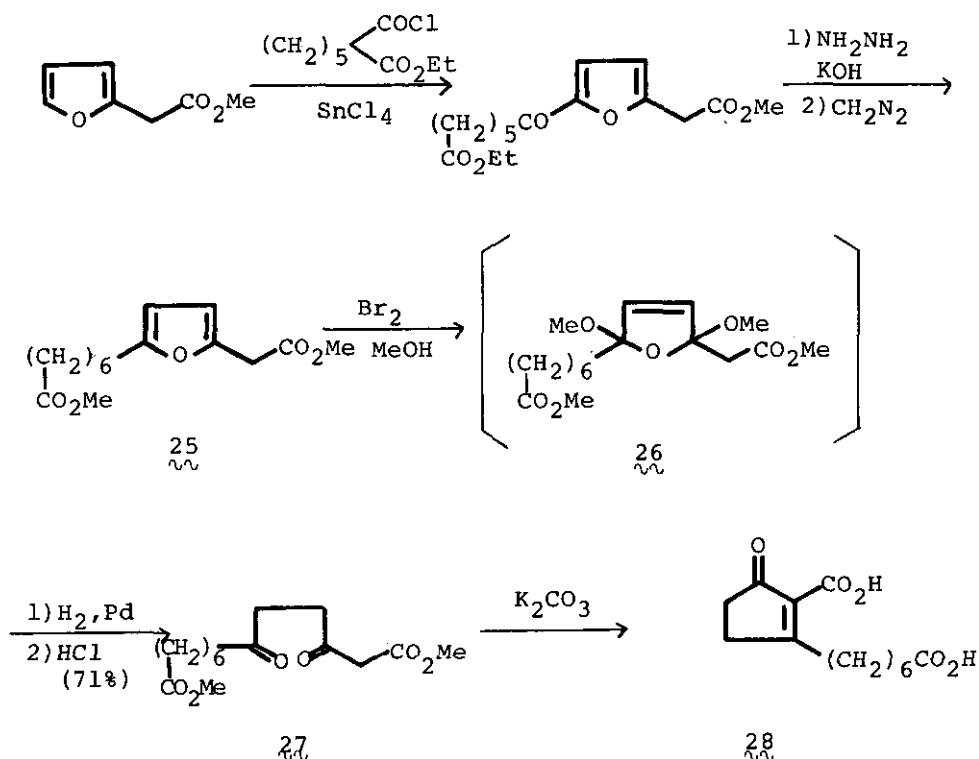


1.2 Syntheses via 2,5-Dihydrofurans

As shown in Chart 7, the second approach to 1,4-dicarbonyl compounds from furans involves the hydrolysis of 2,5-dialkoxy-2,3,4,5-tetrahydrofurans. This method has been employed in the synthesis of the prostaglandin precursor 28. Acylation of 2-furylacetic acid introduced on the furan ring the carbon skeleton which became the

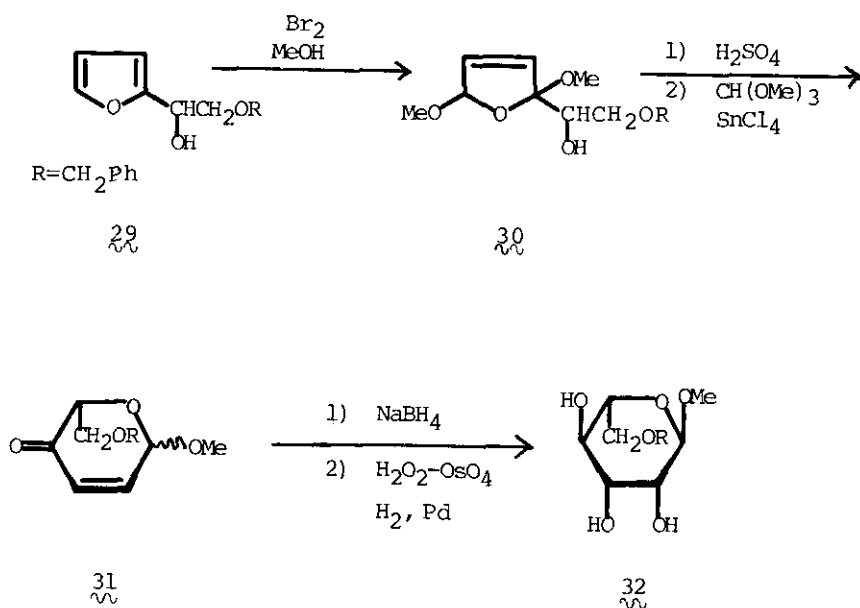
substituent at the 3 position of 28. The product was reduced by Wolff-Kishner reaction and then methylated with diazomethane to produce the furandimethyl ester 25. Treatment of the latter with bromine in methanol gave the 2,5-dihydro-2,5-dimethoxyfuran 26, which, without purification, was reduced on palladium and then hydrolysed with hydrochloric acid to provide the diketone 27. Finally, cyclisation of 27 was carried out with potassium carbonate to afford the prostaglandin precursor 28.²⁹

Chart 20



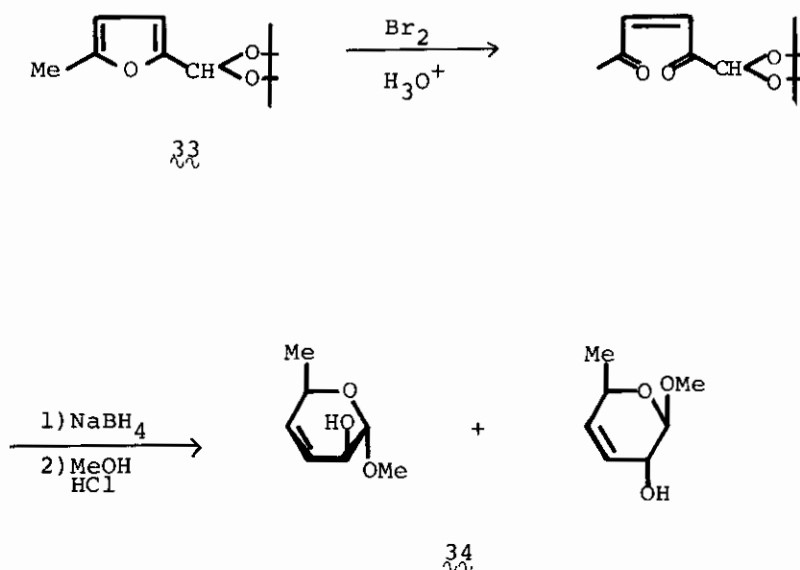
Achmatowicz and coworkers^{30,31} developed a new route to saccharides by using 2,5-dihydro-2,5-dimethoxyfurans in a ring opening reaction. The 2,5-dihydrofuran derivative **29**, available easily from the furfuryl alcohol **28** was hydrolysed with 2 % sulphuric acid at room temperature to provide the six-membered compound, isolated as the acetal **31**. Reduction of the latter followed by cis-hydroxylation with osmium tetroxide and hydrogen peroxide gave the monosaccharide **32**.

Chart 21



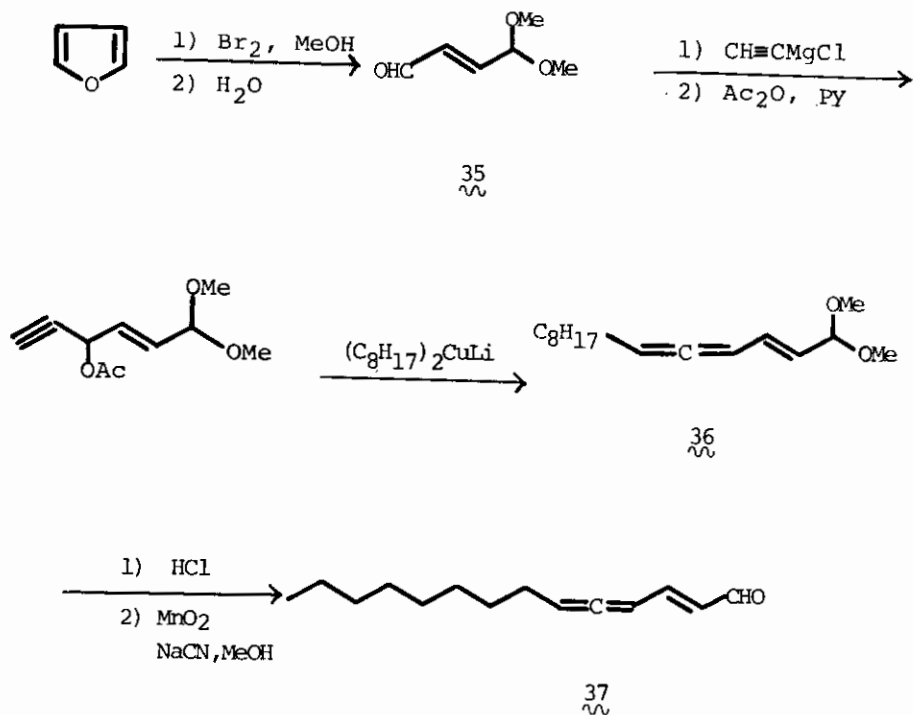
Similarly, 3,4,6-trideoxyhex-3-enopyranoside **34** has been synthesised from 5-methylfurfural ethyleneacetal **33** via the ring-opened diketone.³²

Chart 22



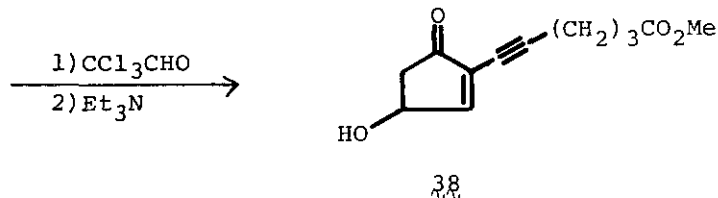
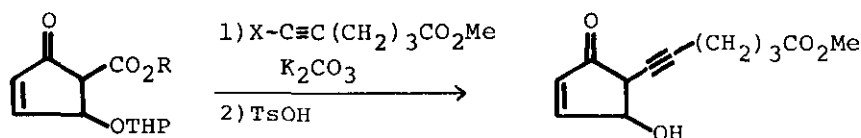
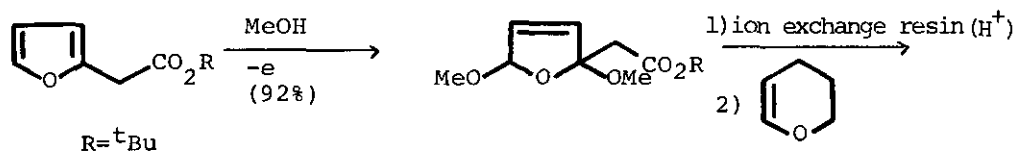
Furthermore, the direct hydrolysis method of 2,5-dihydro-2,5-dialkoxyfurans³³ has been applied to the synthesis of the insect pheromone 37.³⁴ Treatment of furan with bromine in methanol at $-45 \sim -10^{\circ}\text{C}$ followed by mild hydrolysis gave the aldehyde 35 which was converted via the key allene intermediate 36 as shown in Chart 23 into the pheromone 37.

Chart 23



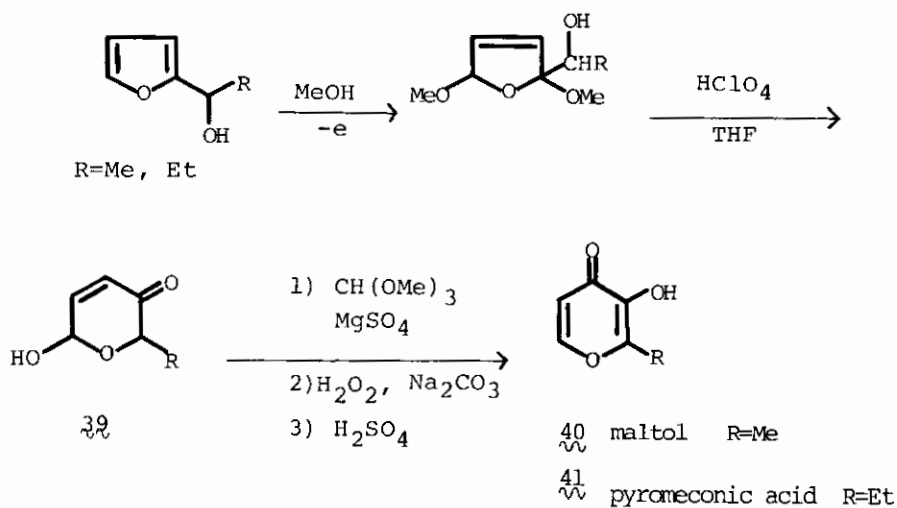
Electrolytic oxidation of furans in methanol is also a useful approach to 2,5-dihydro-2,5-dimethoxyfuran. Shono and associates³⁵ reported a synthesis of rethrolones from furan derivative via ring opening and recyclisation. The prostaglandin precursor 38 was also obtained by this method from the furylacetate as shown in Chart 24.³⁶

Chart 24



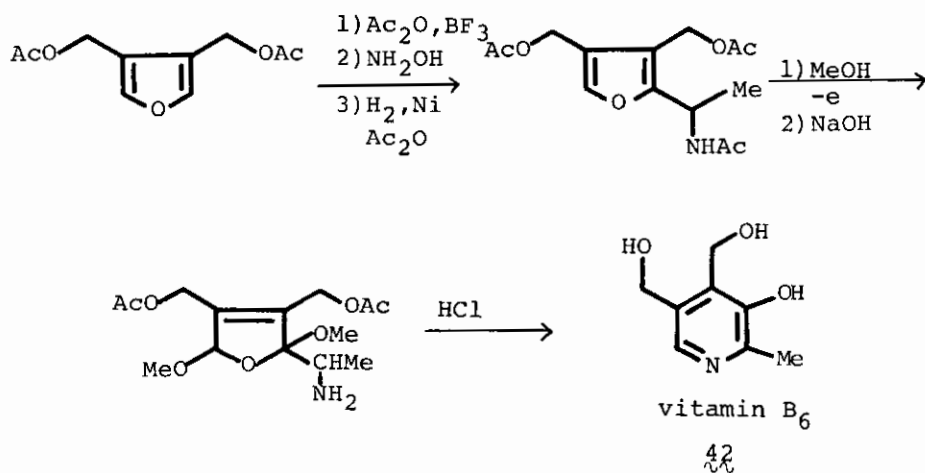
As electrochemical method has also been employed in the synthesis of maltol (40) and pyromeconic acid (41). Thus, electrolytic oxidation of the substituted furfuryl alcohol in methanol followed by acid treatment produced the pyran 39 which was subjected to methylation, epoxidation and rearrangement with acid to give maltol (40) and pyromeconic acid (41).³⁷ Maltol (40) was also synthesised by Shono and Matsumura³⁸ in a similar way.

Chart 25



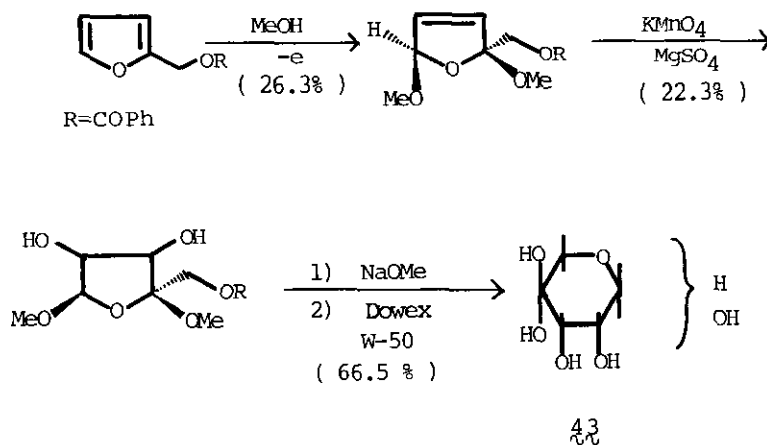
Vitamin B₆ (42) was obtained from 3,4-diacetoxymethylfuran by using electrolysis as the key reaction. Ring opening and recyclisation were carried out with hydrochloric acid without isolation of intermediates.³⁹

Chart 26



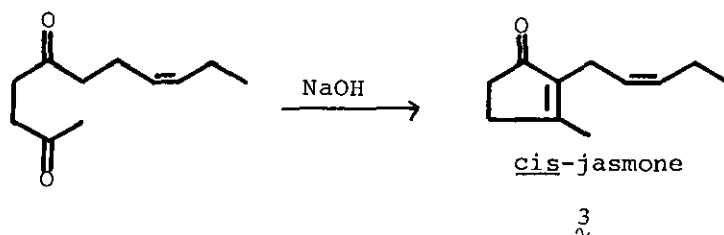
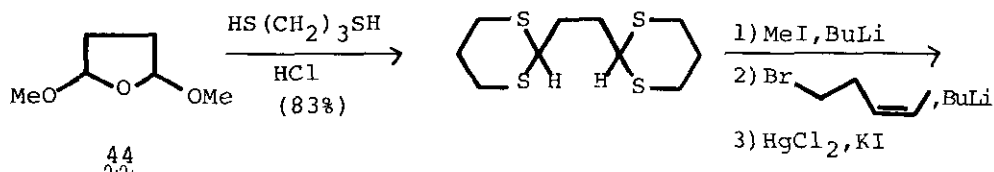
Srogl and collaborators⁴⁰ succeeded in synthesizing the 4-ketopentose (43) by rearrangement of the acetal derivative formed by cis-hydroxylation of dihydrofuran derived by the electrolytic oxidation of furfuryl benzoate. Moreover, Shono and associates⁴¹ reported a new synthetic route to 2-hydroxycyclopentenone by reduction and rearrangement of an electrooxidation product of furan.

Chart 27



2,3,4,5-Tetrahydro-2,5-dimethoxyfuran (44), obtained by electrooxidation of furan followed by reduction of the resulting dihydrofuran, is chemically equivalent to succinaldehyde, and has been converted into cis-jasmone (3)⁴² and squalene.⁴³ For example, reaction of 44 with propanedithiol in the presence of hydrogen chloride gas formed succinaldehyde dithioketal. Introduction of the methyl and pentenyl group followed by regeneration of the carbonyl functions gave the diketone which was smoothly transformed with alkali into cis-jasmone (3).⁴²

Chart 28



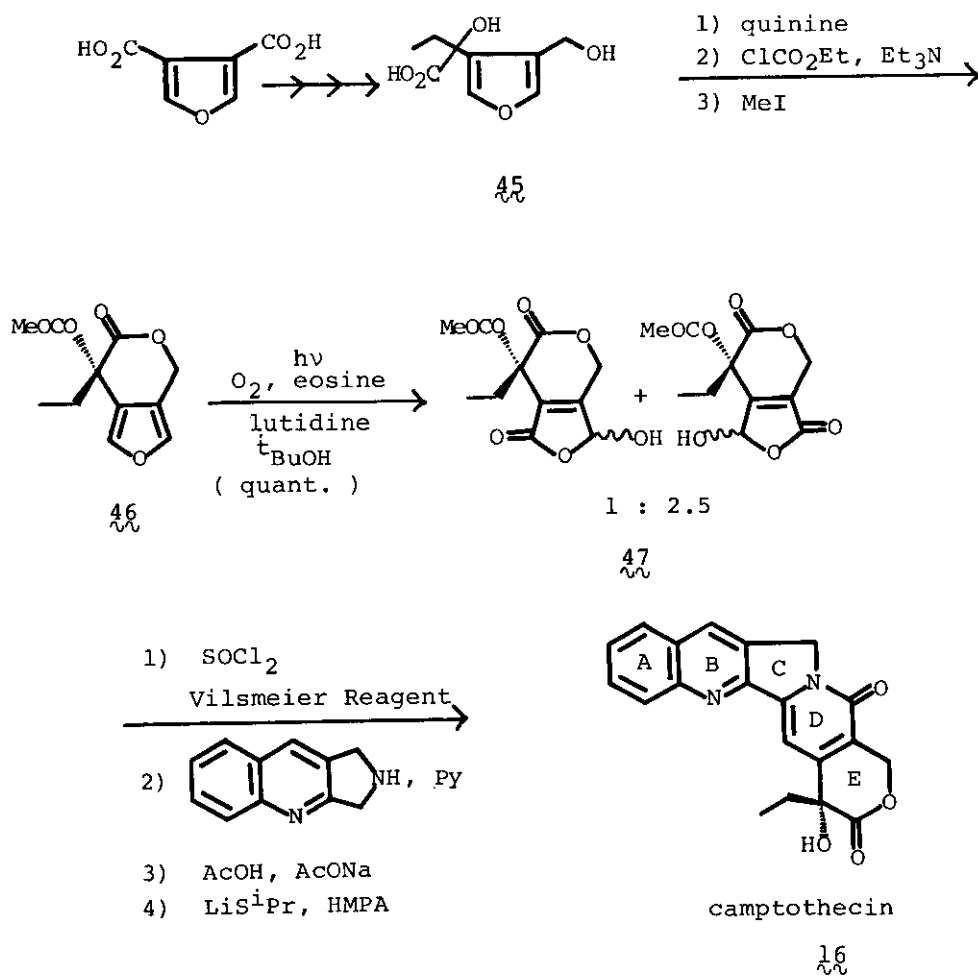
1.3 Syntheses by an Oxidative Ring Opening of Furans

Furans are sensitive to oxidation and leads to γ -lactone or ring opened compounds depending on the conditions used. However, the process must be controlled to minimize tar formation.

Corey and associates⁴⁴ achieved a total synthesis of camptothecin (16) by using the carbon skeleton of the bis-lactone 47, derived from the furan 46 of oxidation, to form ring D of the product. Thus, the furan-3-acetic acid derivative 45, obtained from furan-3,4-dicarboxylic acid, was converted into the optically active lactone 46 in the presence of quinine as shown which was subjected

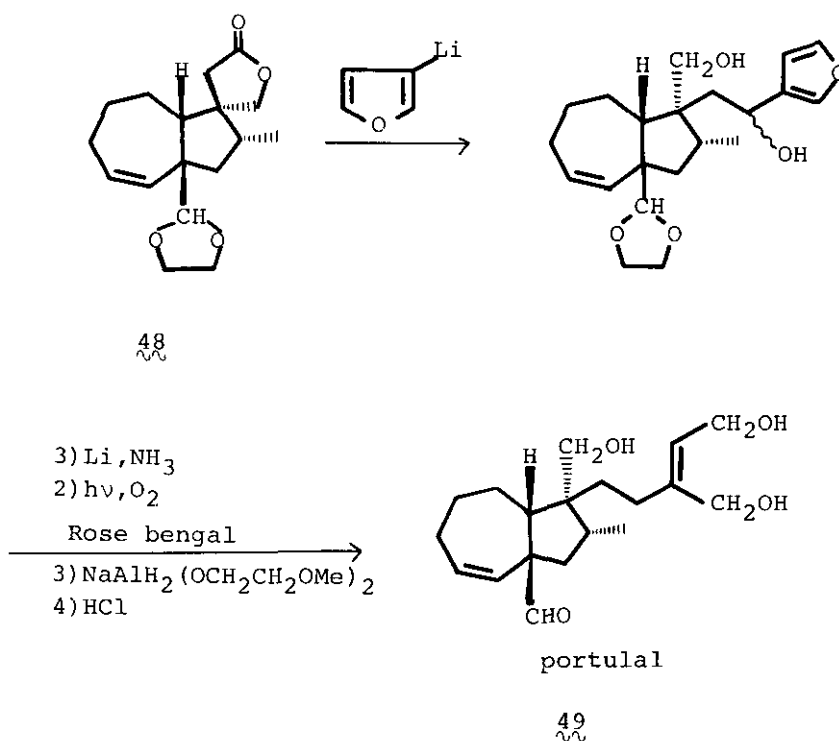
to photo-oxidation in tert-butanol in the presence of eosine and lutidine at 25°C to form the bis-lactones 47. The latter were condensed with pyrroloquinoline followed by removal of the protecting group to give camptothecin 16.

Chart 29



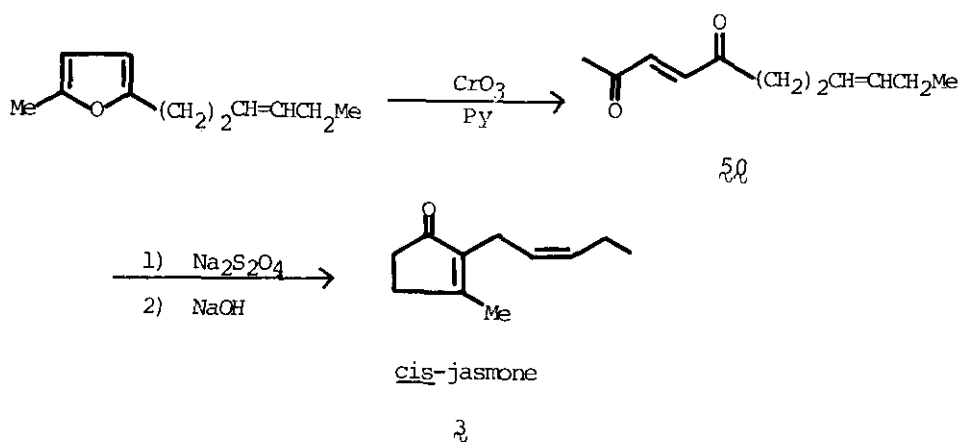
Oxidation of furans has been utilized to form the butenolide antheridiol⁴⁵. Tokoroyama and coworkers⁴⁶ reported a stereoselective synthesis of cis-2-butene-1,4-diol from furans by photo-oxidation and reduction. They used this reaction sequence for a total synthesis of portulal (49) via the condensation product of the hydroazulene 48 with furan as shown in Chart 30.

Chart 30



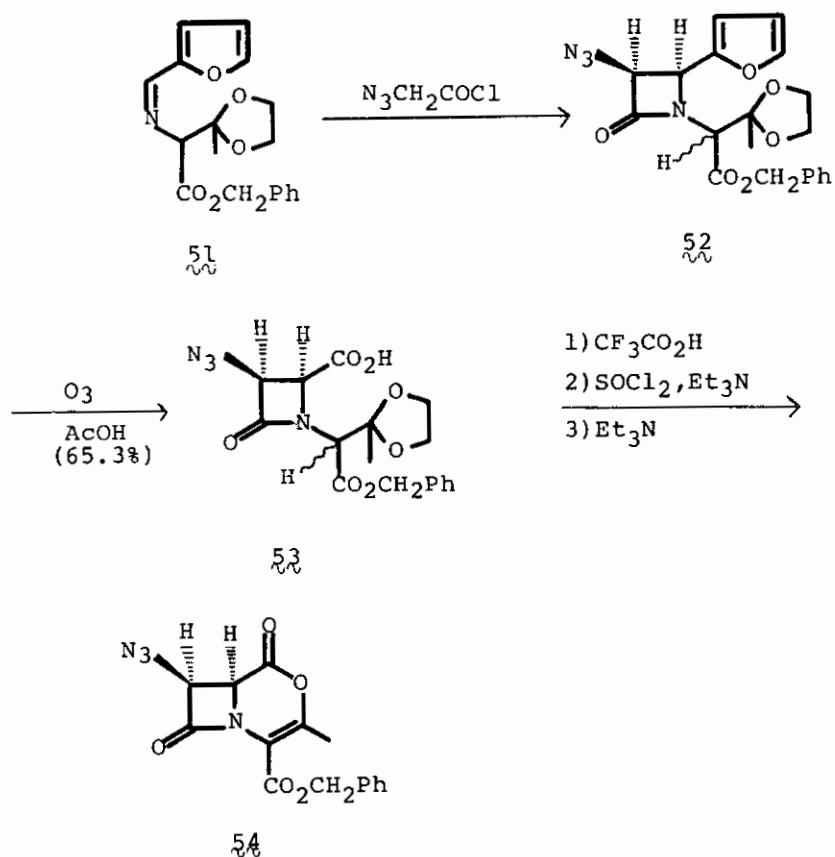
Birch and associates¹³ reported a simple synthesis of cis-jasmone (3) by oxidation of 2-methyl-5-heptenylfuran with Collins reagent followed by reduction and aldol condensation of the resulting diketone 50.

Chart 31



In a synthesis of the 1-oxo- Δ^3 -isocephem 54 by Doyle and colleagues ⁴⁷, only one carbon atom from the furan ring was incorporated into the six-membered ring. The Schiff base 51 was converted in the usual way into the β -lactam 52 which was oxidised with ozone to give by an elimination of the atoms on 1,3,4 and 5 positions of the furan nucleus the carboxylic acid 53 . The latter was then transformed into the 1-oxo- Δ^3 -isocephem 54 as shown in Chart 32.

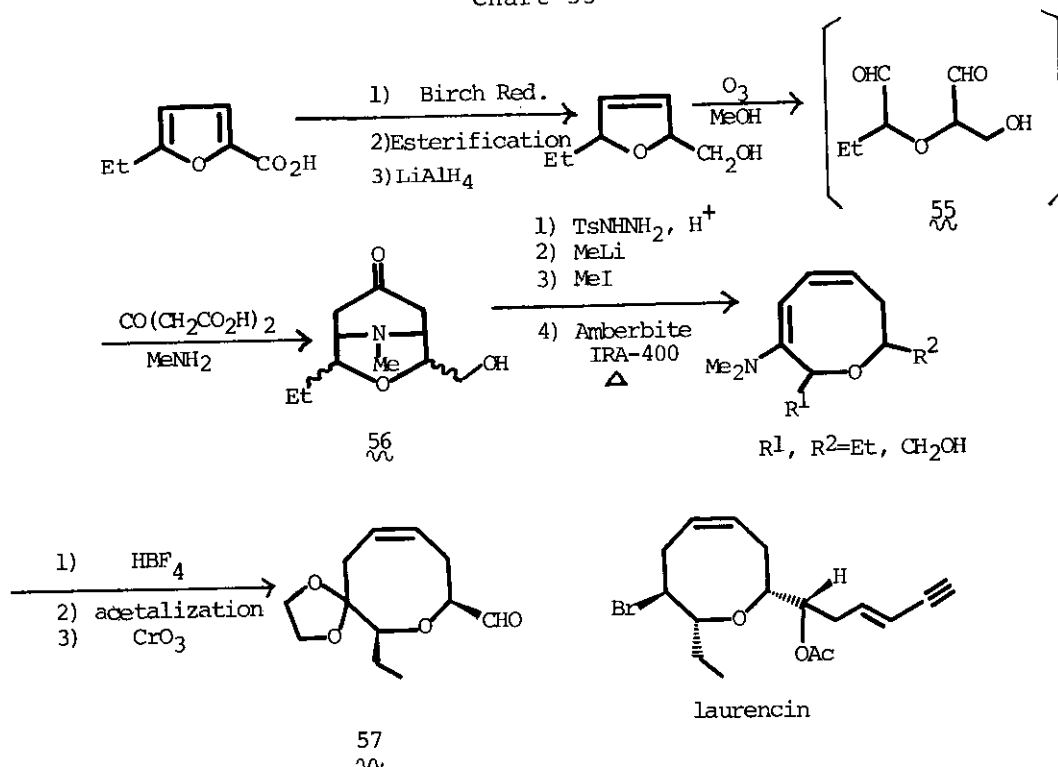
Chart 32



Another interesting example of the synthesis using dialdehydes generated by an oxidative cleavage of the $\text{C}_3\text{-C}_4$ bond of 2,5-dihydrofurans was reported Masamune and colleagues.⁴⁸ In the synthesis of the 9-aza-3-oxabicyclo[3.3.1]nonanone 56, an intermediate for the laurencin-type 57, Birch reduction of 5-ethylfuran-2-carboxylic acid followed by esterification and reduction gave 5-ethyl-2,5-

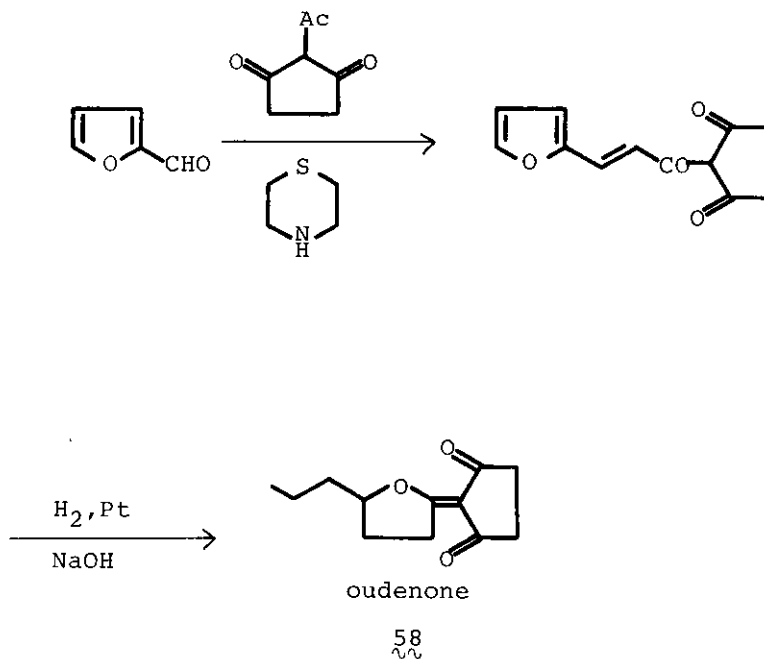
dihydrofurfuryl alcohol which on ozonolysis in methanol provided the dialdehyde 55. Robinson-Schöpf reaction of 55 with 3-keto-glutaric acid and methylamine produced the bicyclononanone 56 which was then converted into the laurencin-type 57.

Chart 33



Reductive ring-opening between the carbon and oxygen bond in furans has also been reported. For example, oudenone (58) has been obtained in poor yield from furfural in two steps as shown in Chart 34.⁴⁹

Chart 34



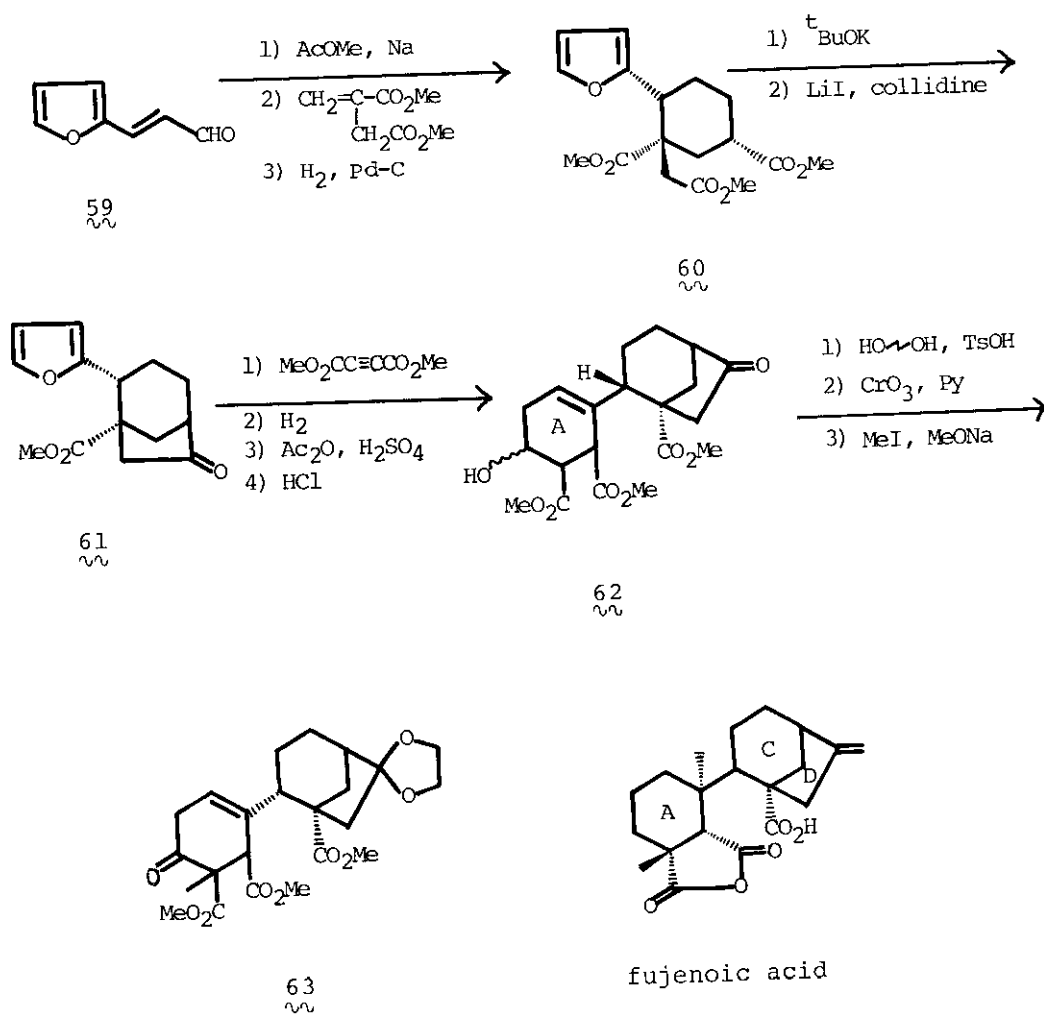
1.4 Syntheses by Cycloaddition of Furans

Furan, an effective diene in cycloaddition reactions, forms six-membered ring compounds by treatment with dienophiles. This suggests that furans can be employed as carbon sources in the synthesis of the cyclic compounds. Moreover, the carbon-oxygen bond in the cycloaddition products is an effective functional group for introducing substituents. By utilizing these properties,

several approaches to the synthesis of natural products have been reported.

Kitahara and coworkers^{50,51} utilized furan in a Diels-Alder reaction with acetylenedicarboxylic acid to form ring A in fujenoic acid. The 2-cyclohexylfuran **60**, obtained from 2-furylacetylaldehyde

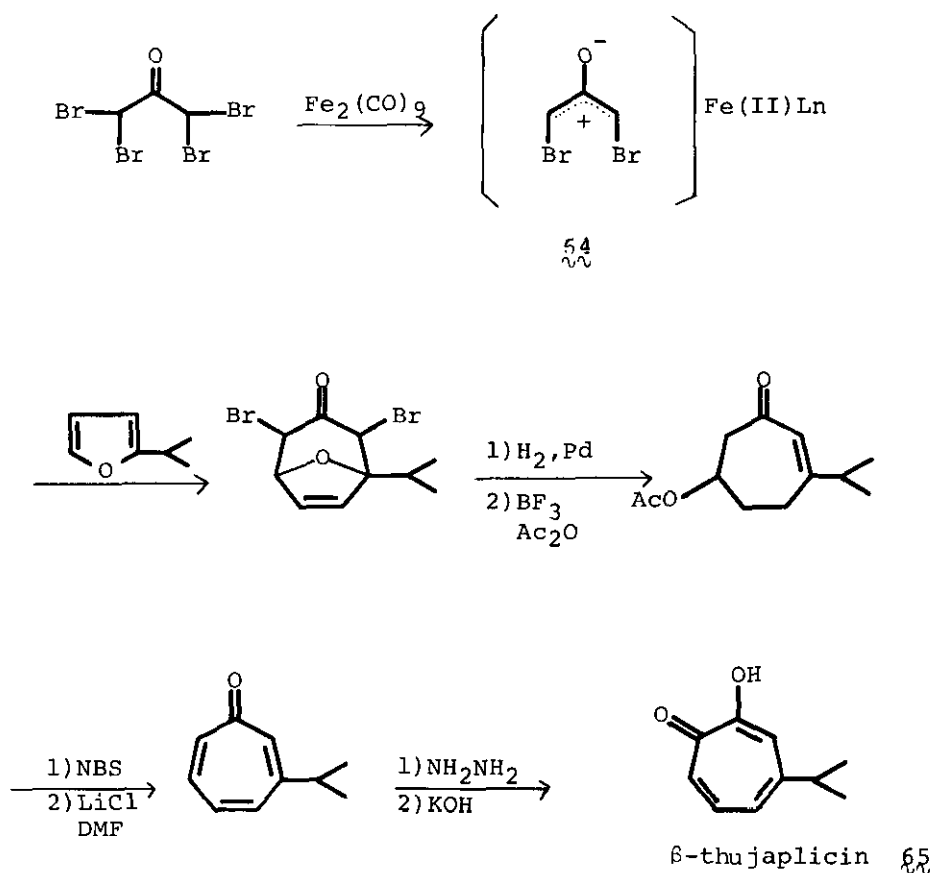
Chart 35



59, was subjected to a Dieckmann condensation to give the 2 α -furyl-6-oxobicyclo[3.2.1]octane 61, which was treated in a Diels-Alder reaction with an acetylene derivative followed by catalytic hydrogenation and acid treatment to afford 62 as basic skeleton of fujenoic acid that was easily converted into the demethylfujenoic acid analogue 63.

Oxyallyl species (cf. 64) which are generated by reaction of α,α -dibromoketones with iron carbonyls, are reactive intermediates

Chart 36



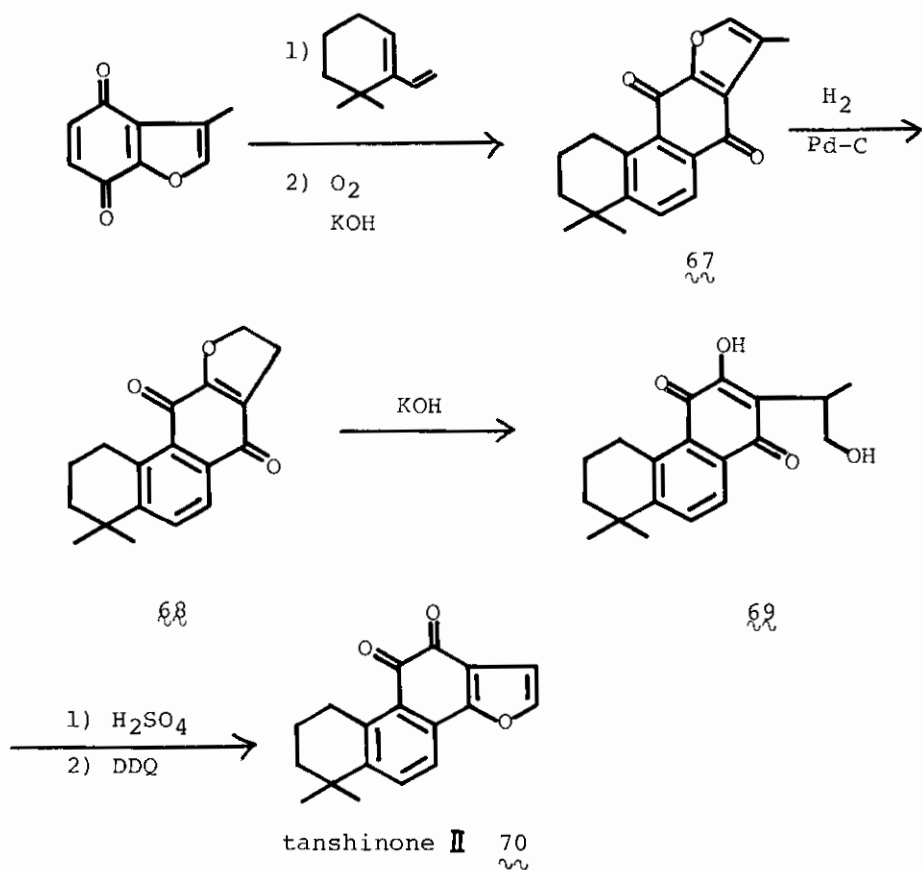
due to the 2π electron system which promotes cycloaddition with dienes. Noyori synthesised the seven-membered compounds by $(3\pi + 4\pi)$ cycloaddition where the furan and oxyallyl species were the four and three-carbon sources, respectively, and the products were converted into β -thujaplicin (**65**)⁵², α -thujaplicine⁵² and nezukone⁵³ as shown in Chart 36.

2. 2,3-Dihydrofurans and Tetrahydro-2-hydroxyfurans

2,3-Dihydrofurans and γ -lactols are chemically equivalent to γ -ketoalcohols. The reaction of tetrahydrofurfuryl chloride with bases gives easily by ring opening the C_5 -unit having a suitable functional group at the terminal position. Based on these facts, hydrofurans have been used as a carbon source in synthetic reactions.

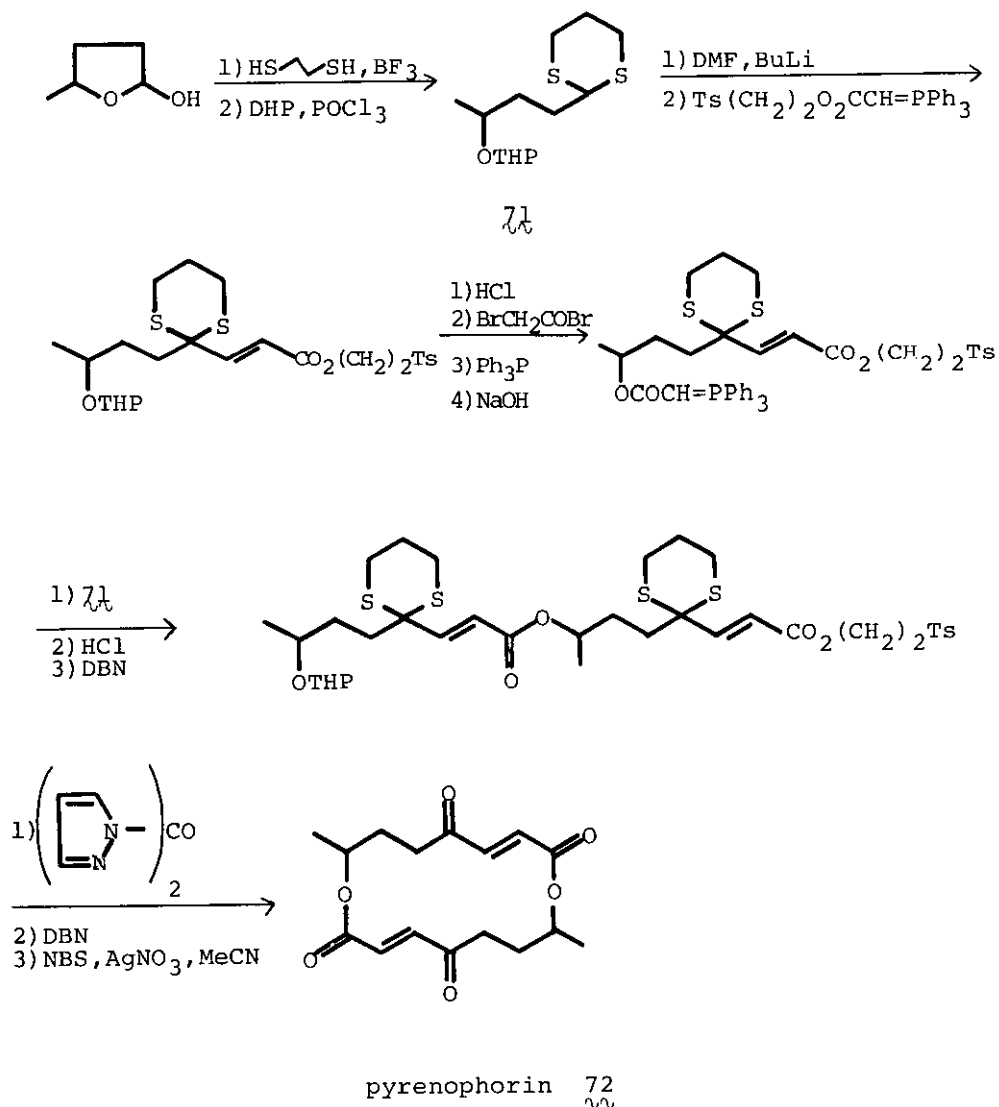
In the synthesis of tanshinone II (**70**), Diels-Alder reaction of the furanobenzoquinone with 3,3-dimethyl-2-vinylcyclohexene, followed by an air oxidation produced isotanshinone (**67**) which was hydrogenated to the 2,3-dihydrofuran derivative **68** followed by hydrolysis with potassium hydroxide to provide the γ -ketoalcohol **69**. Successive ring opening and ring closure of **69** with sulphuric acid followed by dehydrogenation with dichlorodicyanobenzoquinone afforded tanshinone II (**70**).⁵⁴

Chart 37



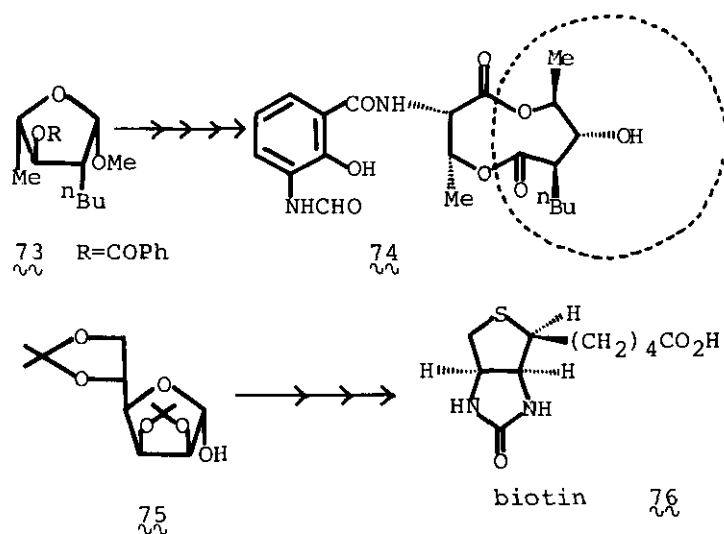
γ -Lactols, which are chemically equivalent to γ -ketoalcohols, are starting materials for pyrenophyryl (72)⁵⁵ and the polyacetate in Anthemidal.⁵⁶ For example, Raphael and coworkers⁵⁵ achieved a total synthesis of pyrenophorin (72) in which the main portion of the product was prepared from two units of 5-methyl- γ -lactol.

Chart 38



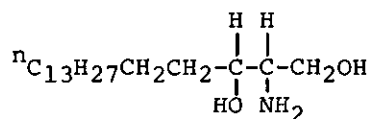
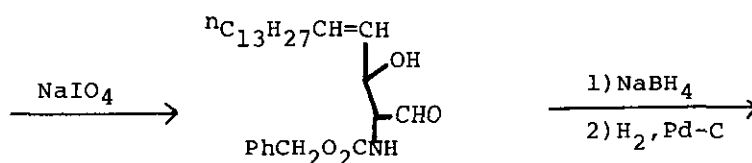
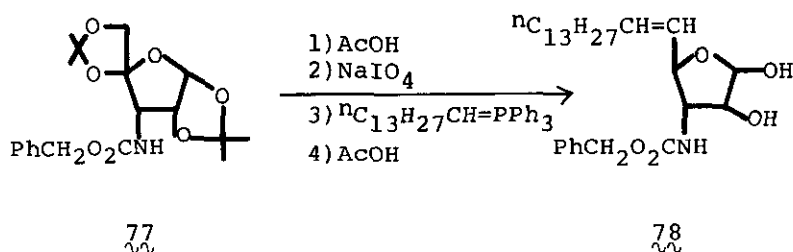
The three ring carbons in arabinofuranoside **73** was utilized to form the nine-membered ring in the synthesis of deisovaleryl-blastmycin (**74**)⁵⁷ and α -D-mannofuranose (**75**) was transformed via an asymmetric synthesis into the thiophene portion of (+)-biotin (**76**).⁵⁸

Chart 39



The 2,3-dihydroxytetrahydrofuran derivative **78** obtained from the allofuranose **77** in four steps, was easily converted into the β -hydroxyaldehyde via an elimination of one-carbon by the Criegee reaction followed by successive reductions to give D-dihydro-sphingosine (**79**).⁵⁹

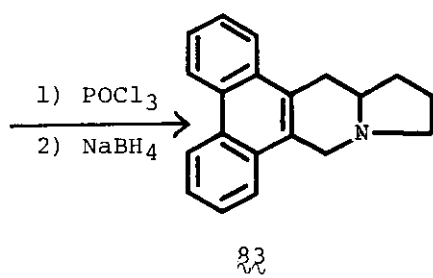
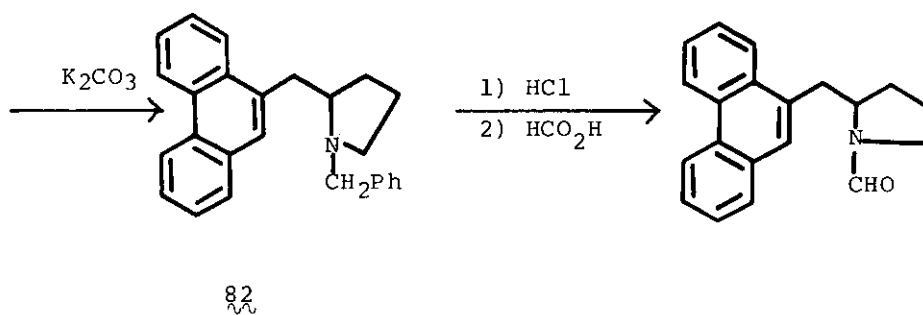
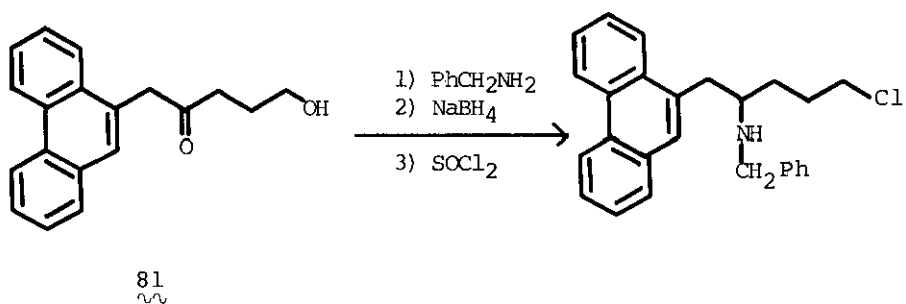
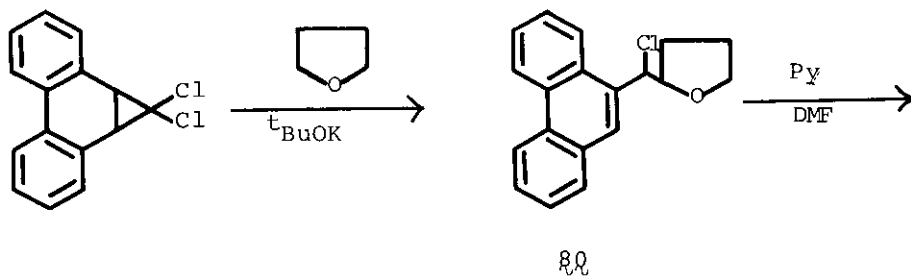
Chart 40



79

Tetrahydrofuryl chlorides are easily converted into the linear alcohols having a functional group at the γ -position. This reaction has been applied by Takano and associates⁶⁰ to the synthesis of 93 a tylophorine-type compound. Tetrahydrofuran was condensed with the 9,10-dihydrophenanthrene derivative and the resulting tetrahydrofurfuryl chloride 80 was treated with pyridine to give the γ -ketoalcohol 81, which was converted via the γ -amino

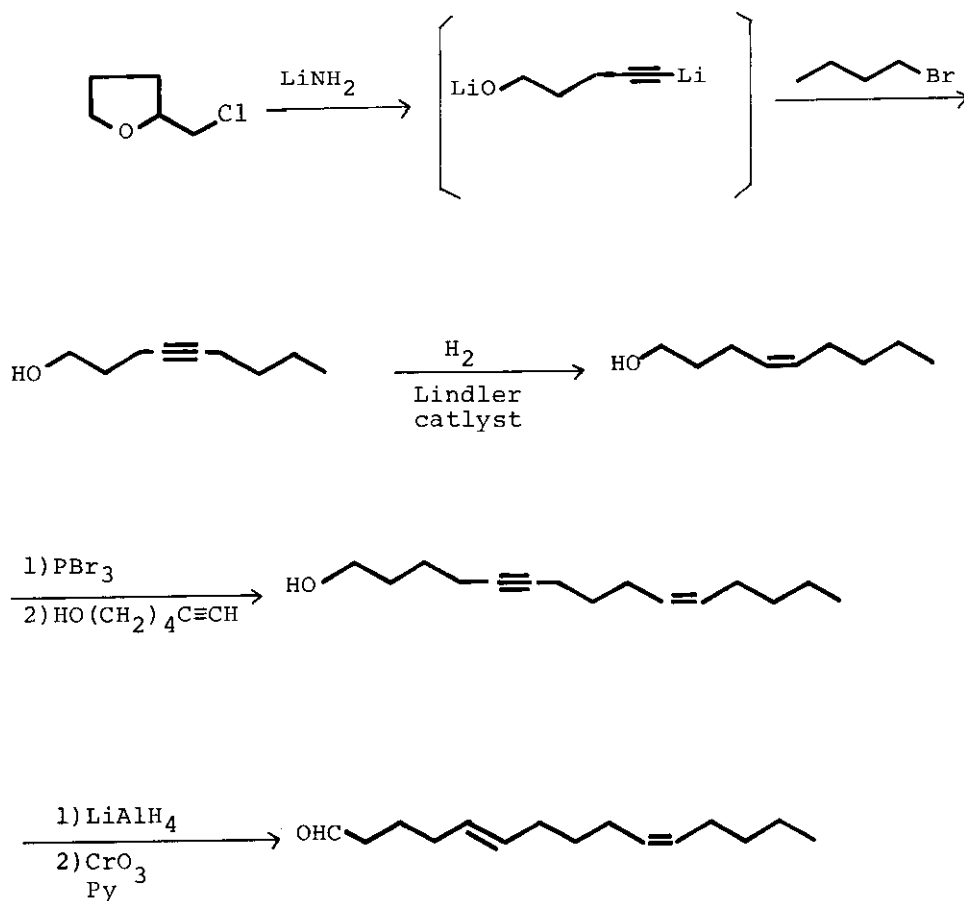
Chart 41



chloride into the pyrrolidine derivative 82. The latter was then smoothly transformed in four steps into the tylophorine-type compound 83.

Ohloff and coworkers⁶¹ succeeded in a stereoselective synthesis of a natural product from Abies pectinate by a condensation of n-butyl bromide with the acetylene derivative generated in situ from

Chart 42

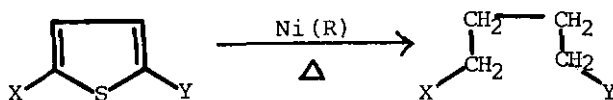
84

tetrahydrofurfuryl chloride by a treatment with lithium amide as shown in Chart 42.

III Syntheses Using Thiophenes

Reductive desulphurisation of thiophenes produces in good yield a four-carbon unit (Chart 43) and has been widely used as a method

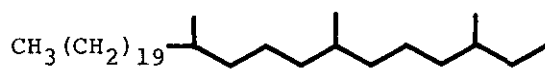
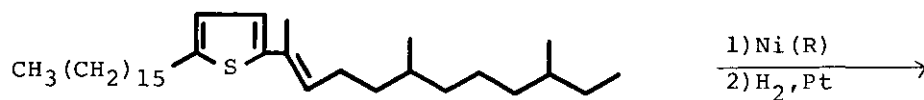
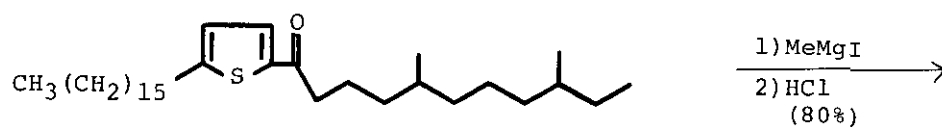
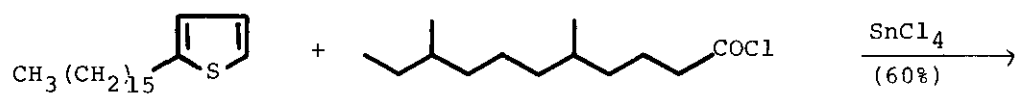
Chart 43



to extend the chain of a hydrocarbon. Usually, the reaction has been carried out by condensation of substrates with a thiophene derivative followed by desulphurisation on Raney nickel.^{6,62}

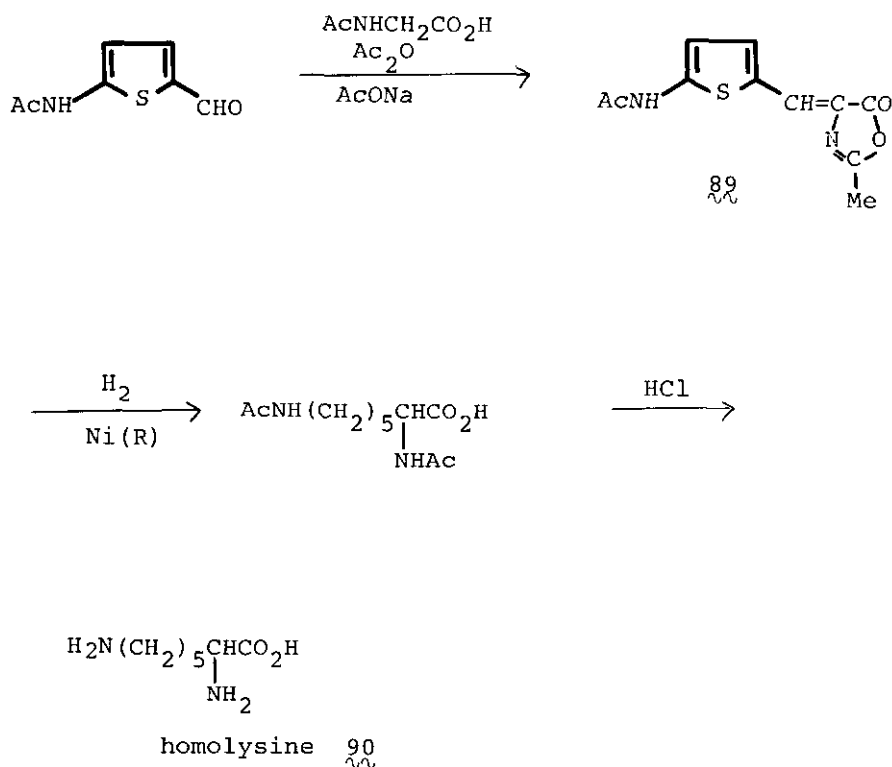
Syntheses of natural products by this method has been applied to compounds having a long aliphatic side chain Martin and MacConnell⁶³ utilized the thiophene ring to construct as shown in Chart 44 3,7,11-trimethylhentriacontane (85), a major component of Atta columbica.

Chart 44



85

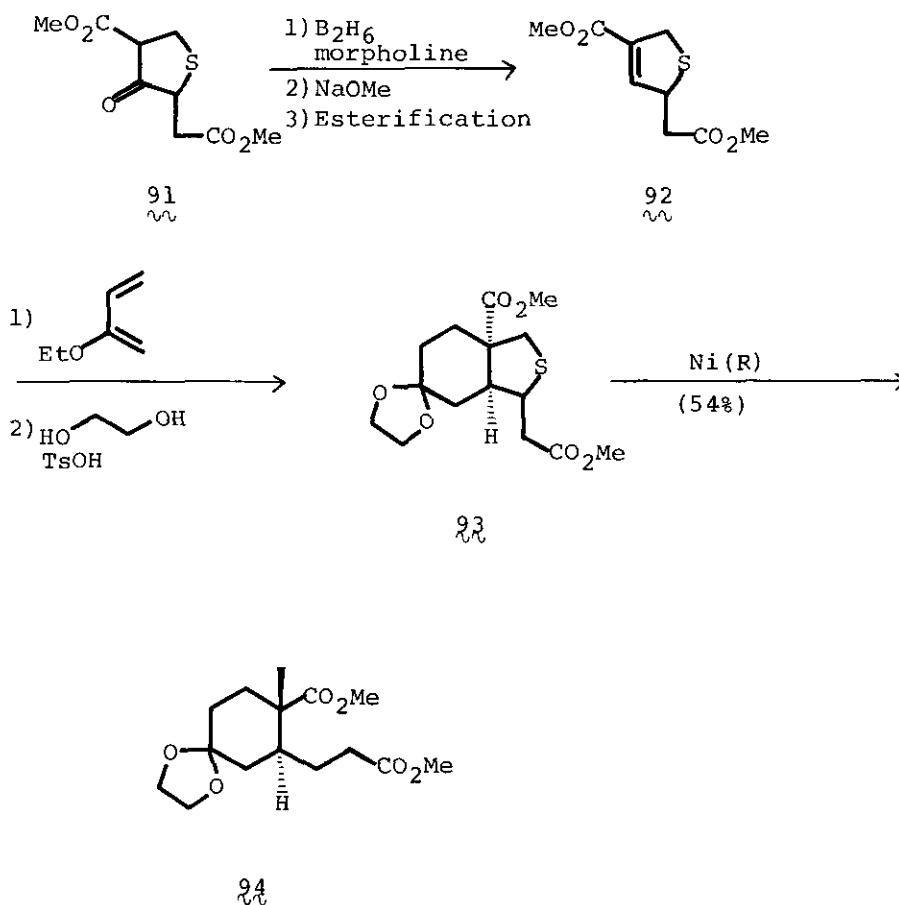
Chart 46



Similar to thiophenes, reductive desulphurisation of 2,5-dihydrothiophenes gives rise to a four-carbon unit. Based on this and the fact that 2,5-dihydrothiophenes behave as dienophiles, Stork and Stotter⁶⁸ obtained stereoselectively a potential intermediate to rings C and D for the synthesis of steroids. Thus, the 2,3,4,5-tetrahydro-3-ketothiophene 91, easily available from

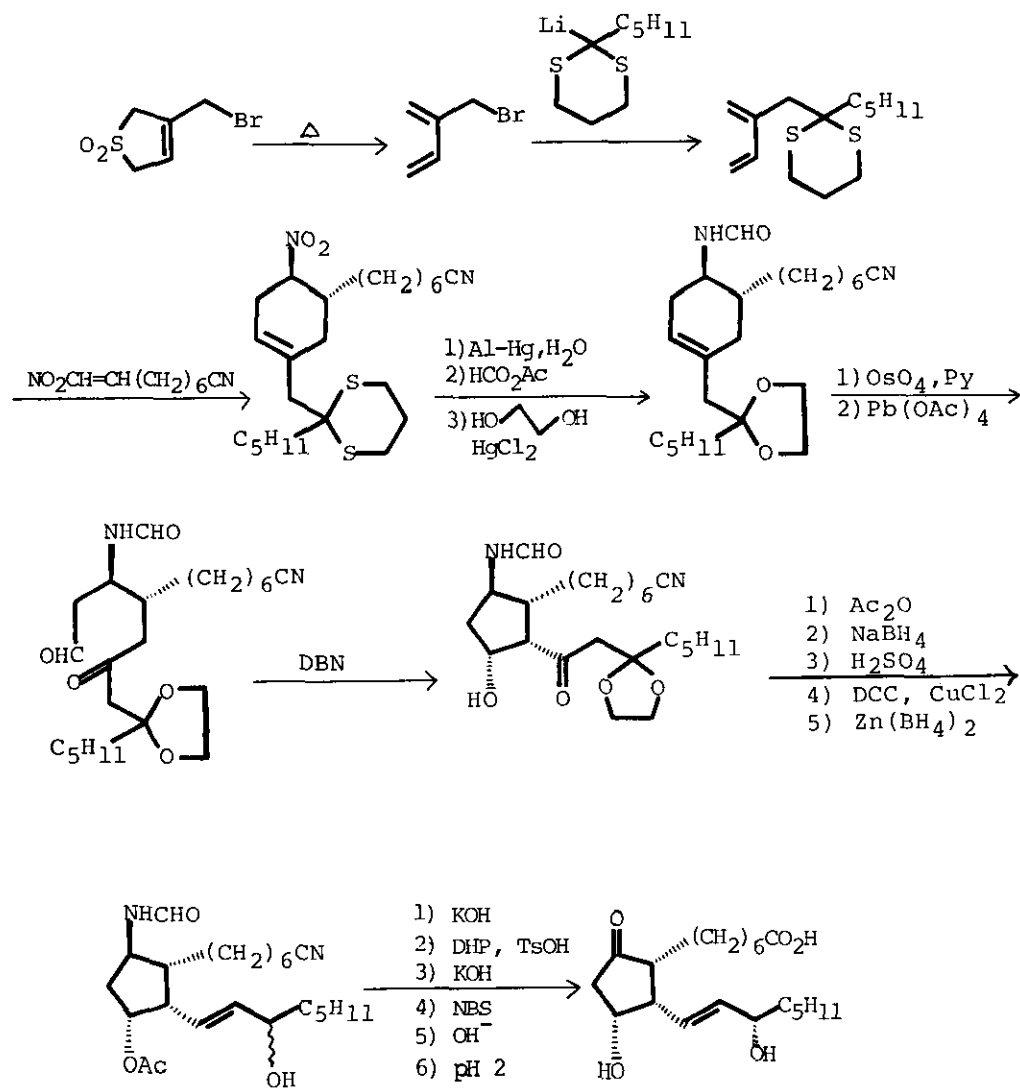
mercaptopropionic acid and dimethyl maleate, was transformed in three steps into the 2,5-dihydrothiophene **92** followed by a Diels-Alder reaction with 2-ethoxybutadiene to give the bicyclic compound **93**. Finally, desulphurisation of **93** provided the key compound which has the correct stereochemistry constructing rings C and D of steroids.

Chart 47



It is well known that heating sulfolenes forms butadienes by a disrotatory ring opening. For example, Corey and associates⁷⁰

Chart 48

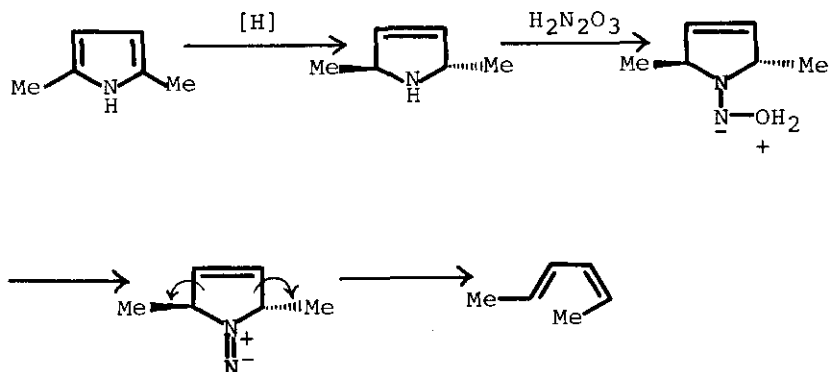


synthesised prostaglandin E_1 (96), as shown in Chart 48, where the starting 2-bromomethyl-1,3-butadiene was prepared in good yield by a thermolytic extrusion of sulphur dioxide from 3-bromomethyl-sulfolene 95 which was obtained by bromination of 3-methylsulfolene with N-bromosuccinimide.

IV Syntheses Using Pyrroles

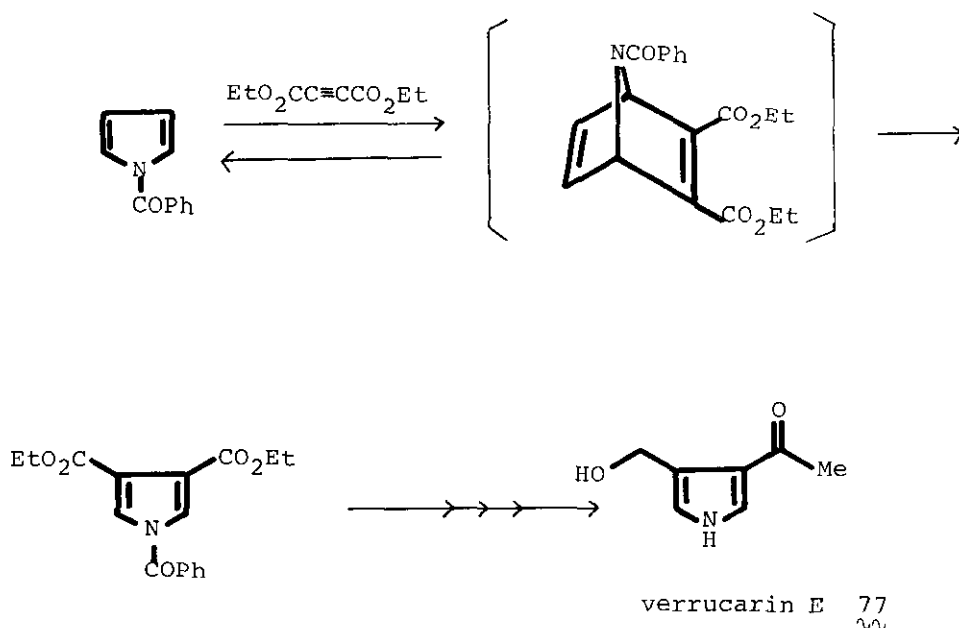
Generation of open chain compounds by direct elimination of the hetero atom in pyrroles is impossible. However, dienes are formed in high yield from 3-pyrrolines, obtained from pyrroles, by treatment with nitrohydroxylamine. Usually, 3-pyrrolines are synthesised by reduction with zinc in acidic medium or a Birch type reaction followed by ring opening, generally called a cheletropic reaction, which proceeds stereoselectively in a disrotatory manner⁷¹, as shown in Chart 49.

Chart 49



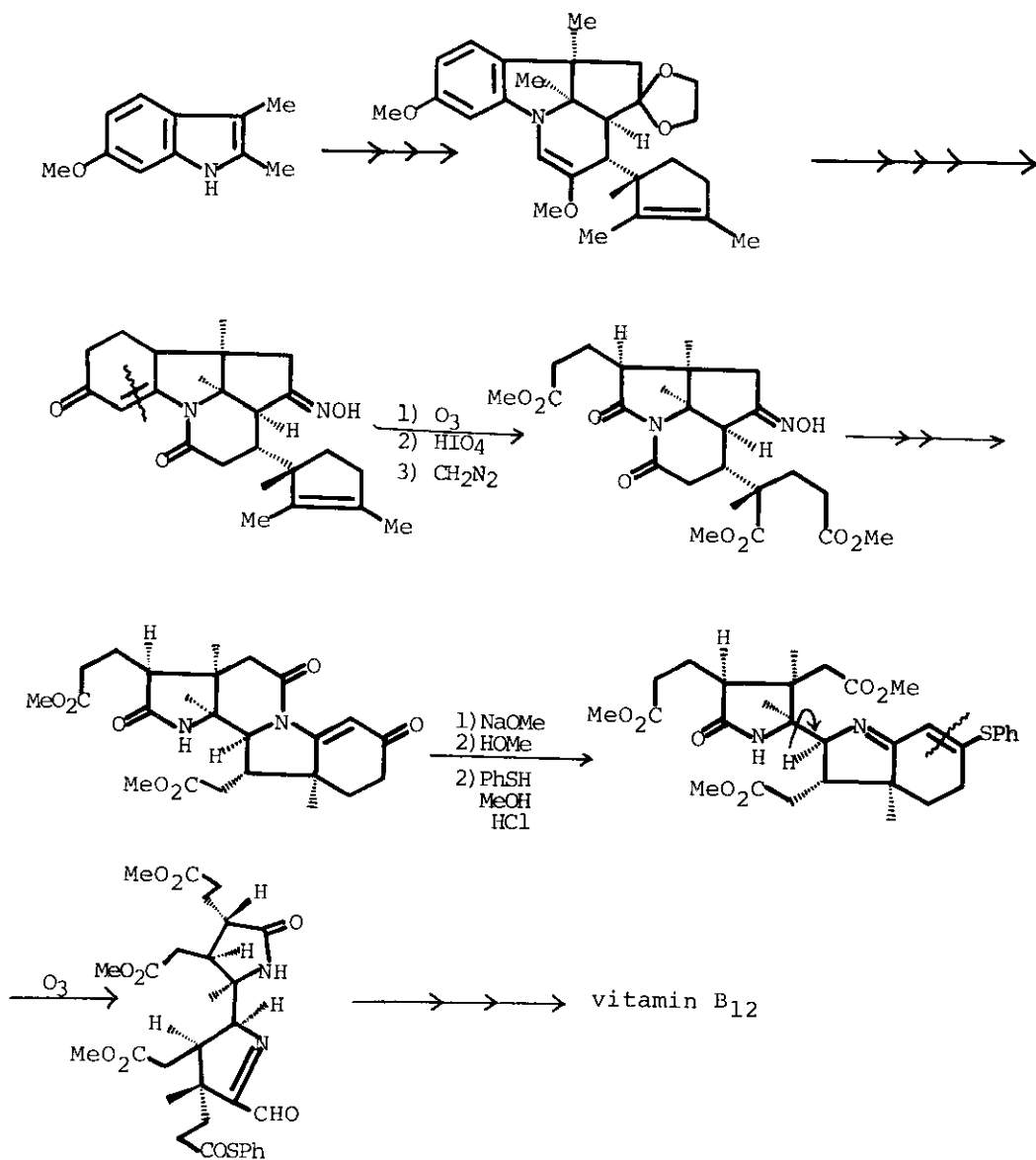
Usually, the Diels-Alder reaction does not occur with pyrroles since they react poorly with dienophiles. However, N-acylpyrroles form adducts upon reaction with acetylenedicarboxylate in the presence of Lewis acids.⁷² Verrucarin E (97) has been obtained by using this type of Diels-Alder reaction.⁷³

Chart 50



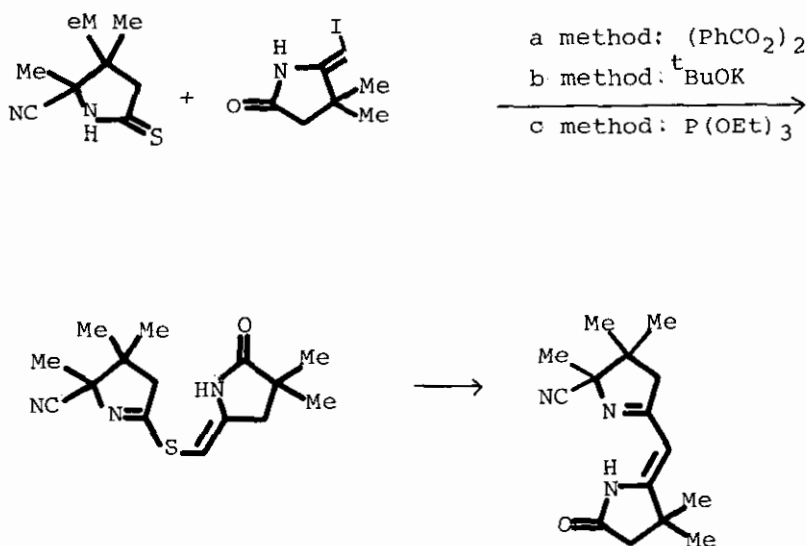
Woodward⁷⁴ reported the total synthesis of Vitamin B₁₂ from 2,3-dimethyl-6-methoxyindole in which the benzene ring in the indole derivative was cleaved with ozone after Birch reduction of 98.

Chart 51



On the other hand, Eschenmoser and coworkers⁷⁵ used the pyrrolidone derivative in a synthesis of the corrin group of compounds as shown in Chart 52.

Chart 52

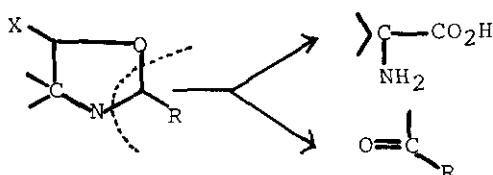


V Syntheses from Oxazoles⁷⁶

Syntheses of natural products from oxazoles are divided into two groups; one where a carbon unit is incorporated along with the hetero atom(s) into the product while the other uses only the carbon atoms. The former is exemplified by the formation of amino

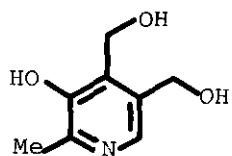
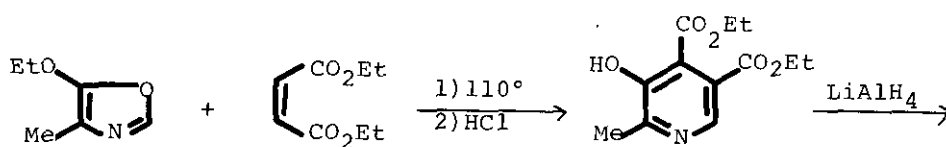
acid.⁷⁷ The latter reaction which utilizes the carbon at the 2 position in the oxazole ring as source for carbonyl or carboxyl functions was developed by Meyers.

Chart 53



Total synthesis of natural products using all the atoms of the oxazole ring system is found in a simple synthesis of vitamin B₆ (42) via a Diels-Alder reaction of the appropriately substituted isoxazole with diethyl maleate.⁷⁸ Vitamin B₆ has also been prepared

Chart 54

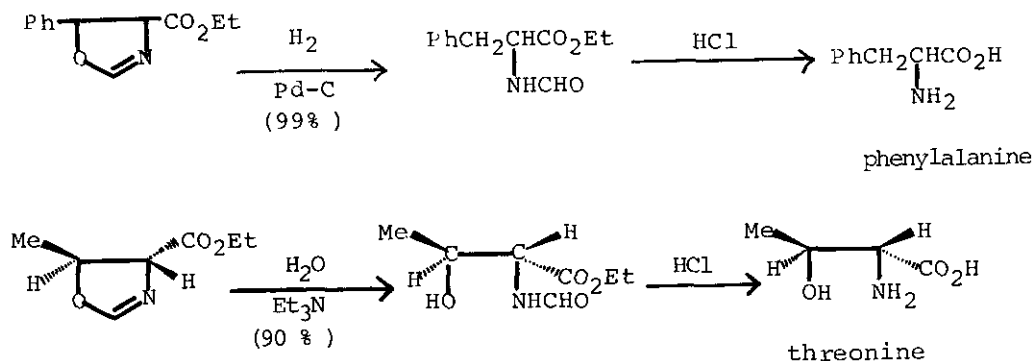


vitamin B₆ 42

in one step by a Diels-Alder reaction with fumaronitrile or 2,5-dihydrofuran with butene-1,4-diol as the dienophile. In a similar manner, many types of norpyridoxals have been synthesised by Morisawa and colleagues⁷⁹ who also examined the steric effect of dienophiles in the Diels-Alder reaction.

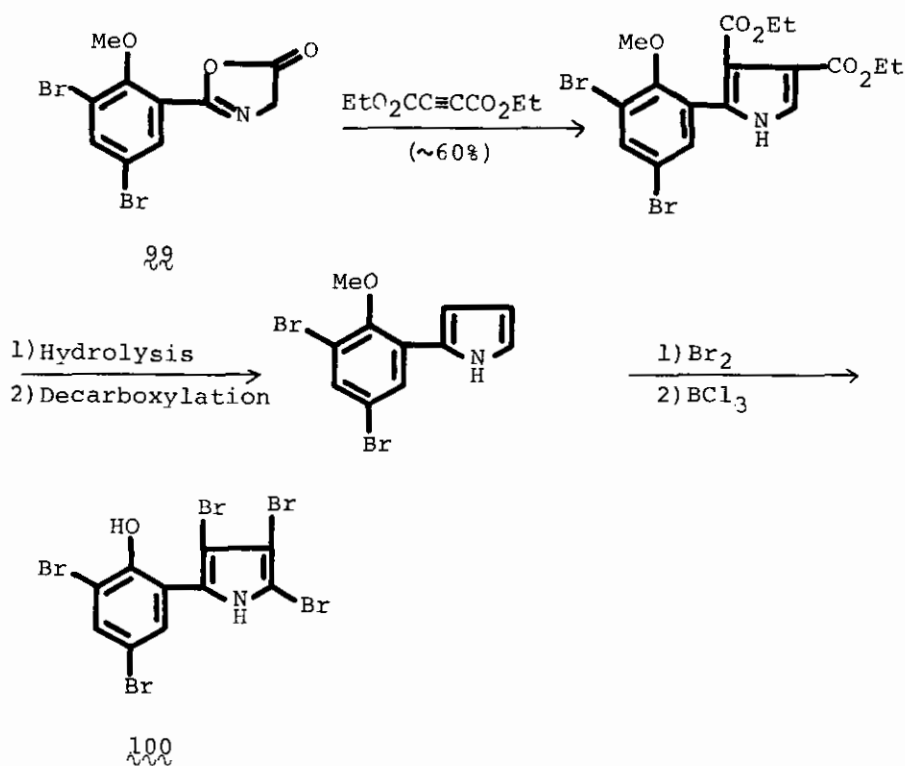
Schöllkopf and Hoppe⁸⁰ reported a synthesis of α -amino acids from oxazolines by hydrogenolysis of 5-phenyloxazoline-4-carboxylate and successive hydrolysis of the product to afford phenylalanine. On the other hand, mild hydrolysis of 5-methyloxazoline-4-carboxylate in the presence of a catalytic amount of triethylamine provided N-formyl- β -hydroxy- α -amino acid ester which was easily converted into threonine by treatment with hydrochloric acid.⁸¹

Chart 55



Reaction of acetylenedicarboxylate with the substituted oxazoline 99, is the first step in the synthesis of the antibiotic isolated from Pseudomonas bromoutilis, and incorporates the C₂-N-C₃ portion of oxazoline into the intermediate (100).⁸²

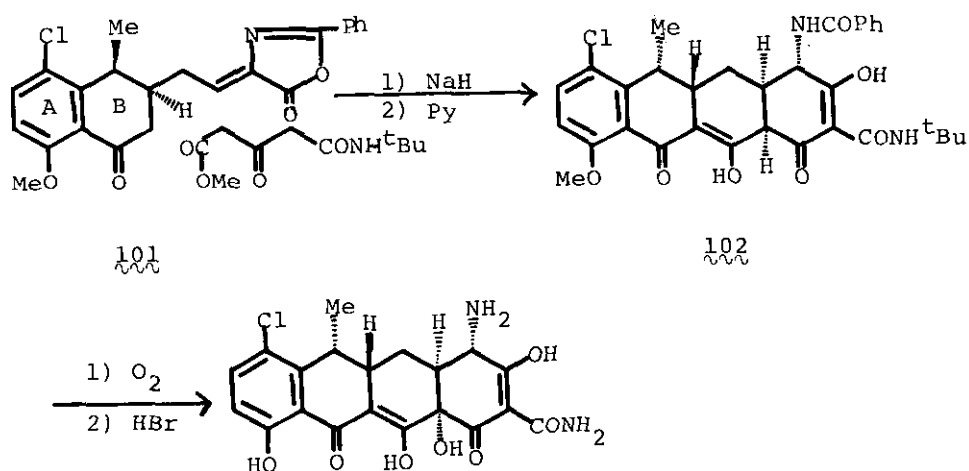
Chart 56



The C₄-C₅ unit in oxazolones has been utilized in forming the ring D in tetracycline. Martin and coworkers⁸³ treated the ring

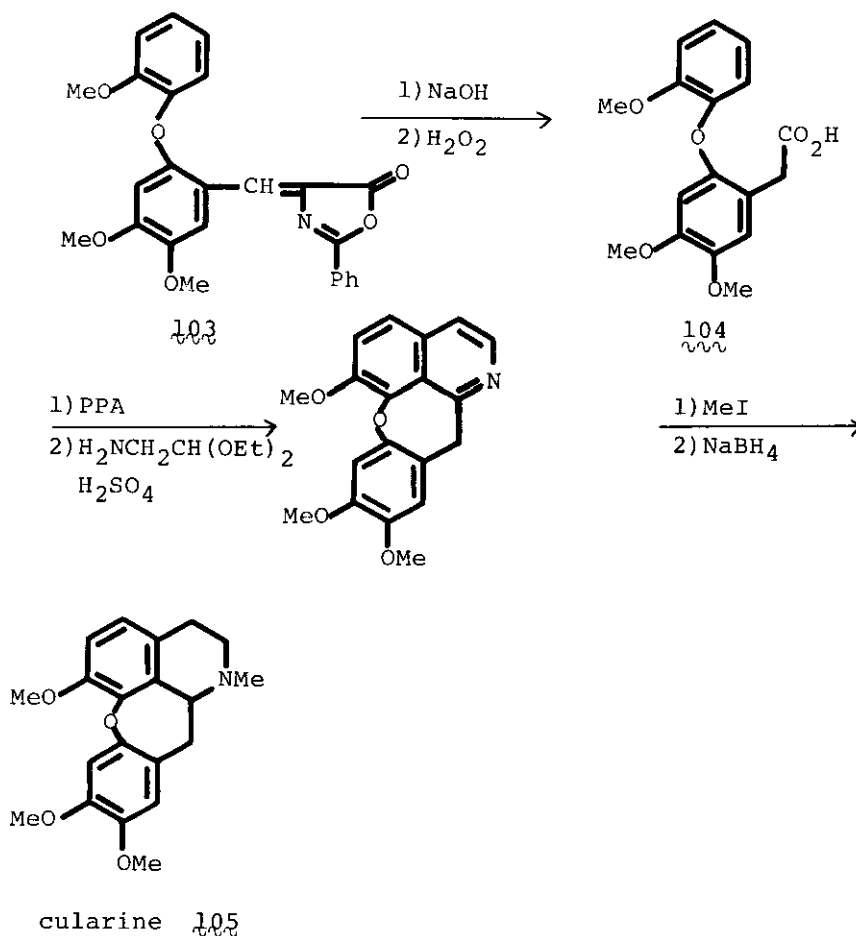
A and B substituted oxazolone 101 with acetonedicarboxylate and thus obtained directly the linear tetracyclic compound 102.

Chart 57



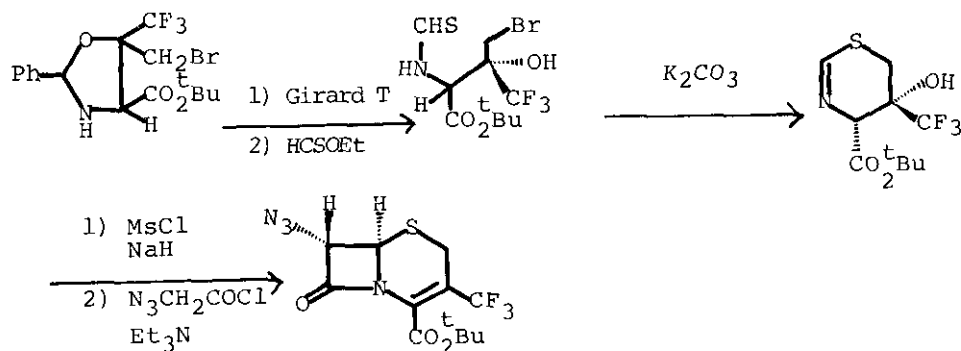
It is well known that oxazolones are useful precursors for α -amino acids^{5,77}. Recently, Battersby and associates reported a stereospecific synthesis of C₃-labelled α -amino acids with deuterium and tritium.⁸⁴ Moreover, phenylacetic acids are obtained from oxazolones, and the Chart 58 shows an example where cularine (105), a natural product, is synthesised from the oxazolones 103 via the corresponding phenylacetic acid 104.⁸⁵

Chart 58



Tetrahydrooxazole ring opens easily to form β -hydroxy- α -amino acids. Watanabe and colleagues reported the synthesis of a cephalosporin-type compound from tetrahydrooxazole via the amino acid and thiazine as shown in Chart 59.⁸⁶

Chart 59



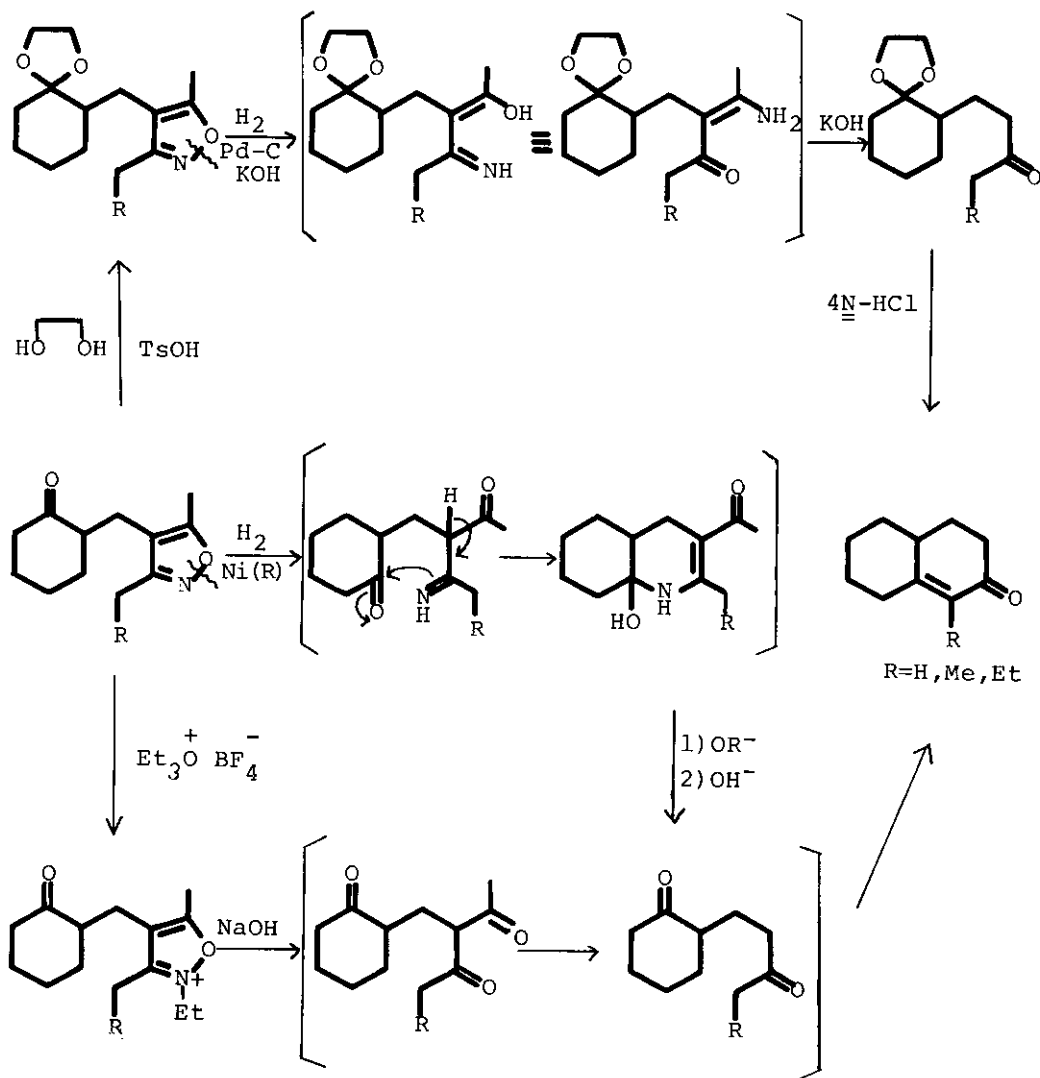
VI Syntheses from Isoxazoles

Many examples in organic synthesis using isoxazoles as starting material are reported.⁶ These can be divided into two reaction patterns; one which utilizes only the carbon atoms on the isoxazole ring while the other employs all the ring atoms via bond cleavage between the 1 and 2 positions.

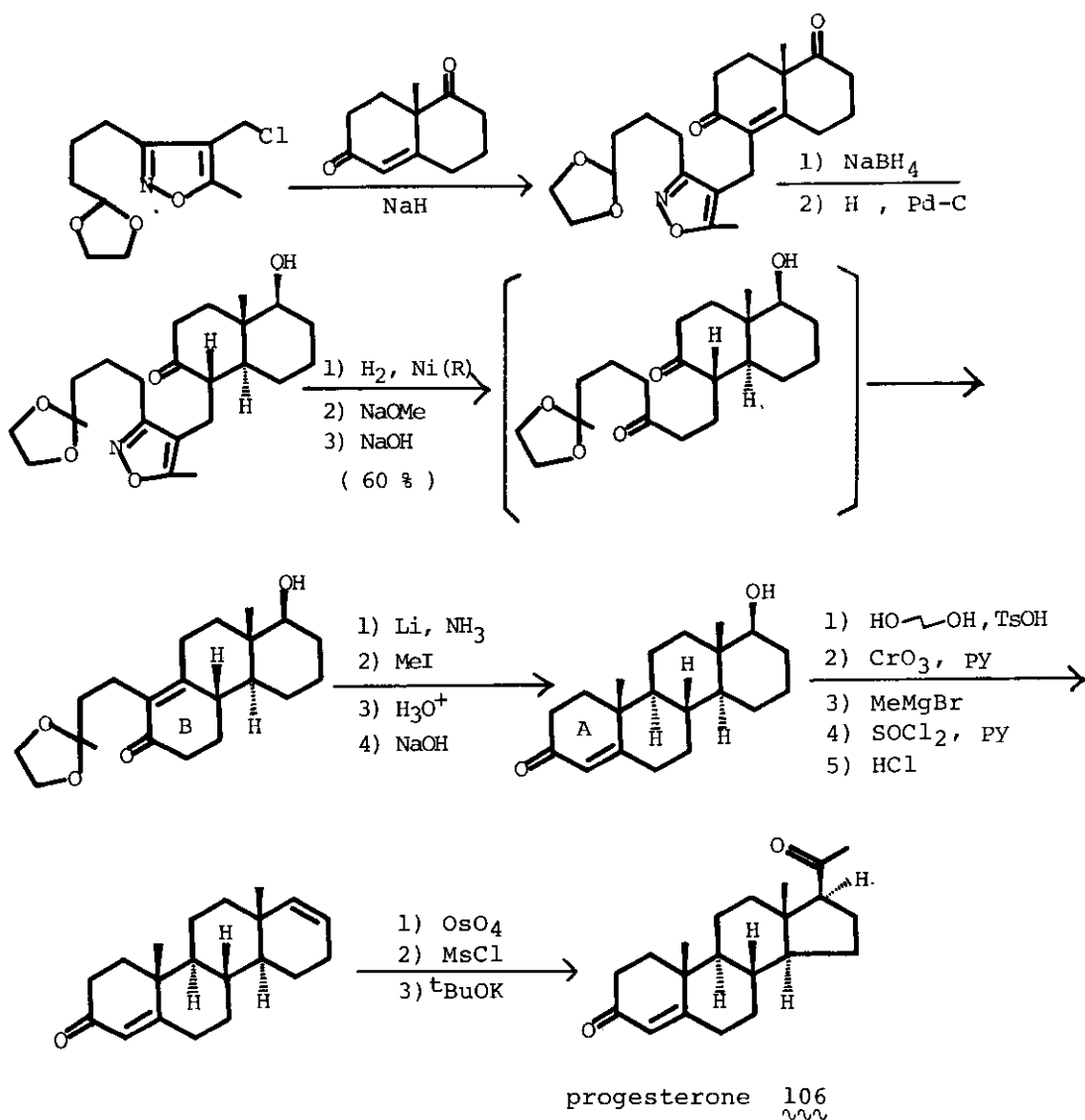
3-Methylisoxazoles with a halogenomethyl group at the 4-position condense easily with cyclohexanones followed by selective hydrogenolytic cleavage of the N-O bond and successive treatment with alcoholate and alkaline hydroxide to give 2-octalones^{89,90}. Some modifications of this reaction have been reported. For example, 2-octalones are obtained by an alkaline treatment of the quaternary salts derived from the condensation product and triethyl-oxonium fluoroborate⁸⁸. Moreover, hydrogenolysis of the ketals of the condensation products and then hydrolysis with alkali, followed

by aldol condensation forms annelation products.⁸⁸

Chart 60



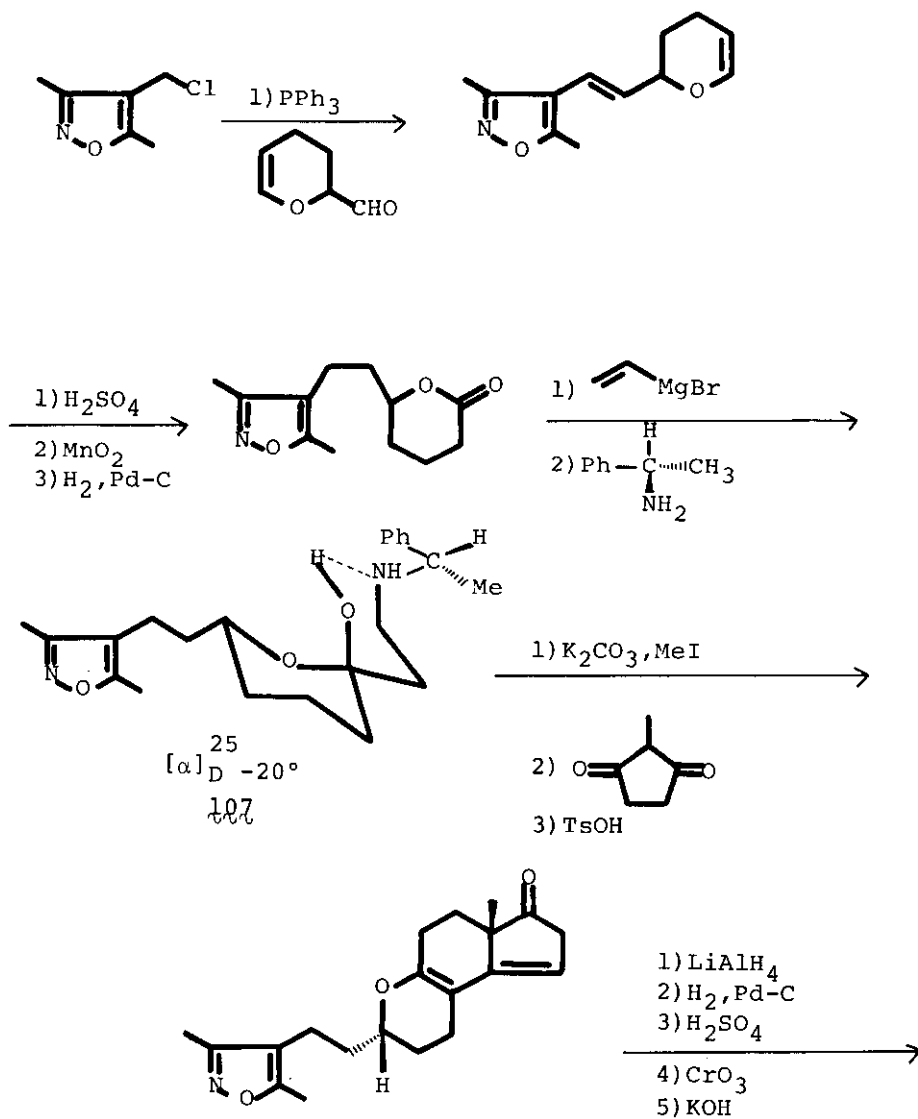
This type of annelation reaction²¹ has been developed by Stork, and the four-carbon unit consisting C₃, C₃-methyl, C₄ and C₄-methylene is utilized in this reaction.^{87,90} Since 2-octalones



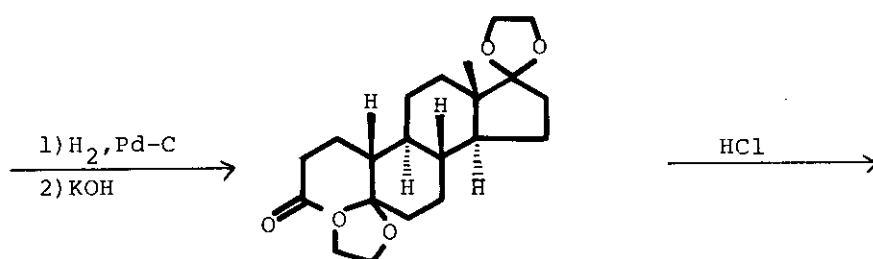
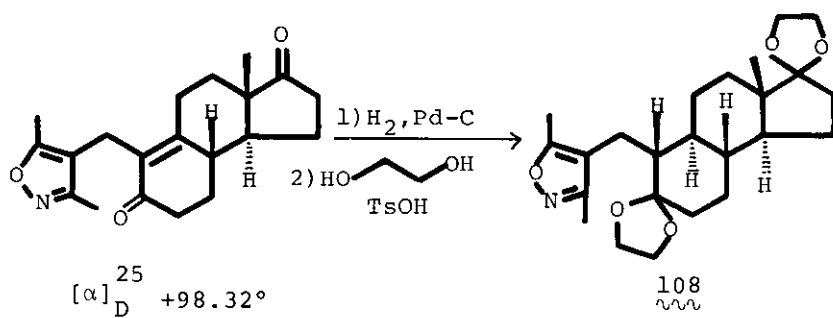
are obtained in good yield by an annelation reaction between 3-alkyl-4-chloromethylisoxazoles and cyclic ketones⁹¹, and therefore, it has been widely applied to the total synthesis of polycyclic natural products. A typical example is the total synthesis of progesterone (106) by Stork and McMurry⁹². Thus, the bicyclic diketone was treated with the chloromethylisoxazole to produce the alkylated compound which was converted into the key intermediate by sodium borohydride reduction and catalytic hydrogenation with palladium-carbon. Reduction on Raney nickel ruptured the highly labile N-O linkage and the product was hydrolysed with sodium methoxide to lead to the transient diketone which was annelated with sodium hydroxide to the tricyclic compound. Methylation of the latter followed by aldol condensation gave the tetracyclic product which was transformed into progesterone (106) in eight steps as shown in Chart 61. In this synthesis, the isoxazole ring system is used to construct ring B and the carbon chain at the C₃-position of the isoxazole was employed as the carbon unit for ring A formation.

Scott and colleagues^{93,94} used the oxazole moiety to form ring A of a steroid to obtain optically active (+)-estr-4-ene-3,17-dione (109). 4-Chloromethyl-3,5-dimethylisoxazole was subjected to a Wittig reaction and the resulting olefin was converted by hydration and oxidation into the lactone which was treated with vinylmagnesium bromide and then with the optically active α -phenethylamine to give the aminoethyl lactol 107. Hydrolysis and condensation of the latter with 2-methylcyclopentadiene afforded the oxazole derivative having all the carbons necessary for the final product 109. This

Chart 62



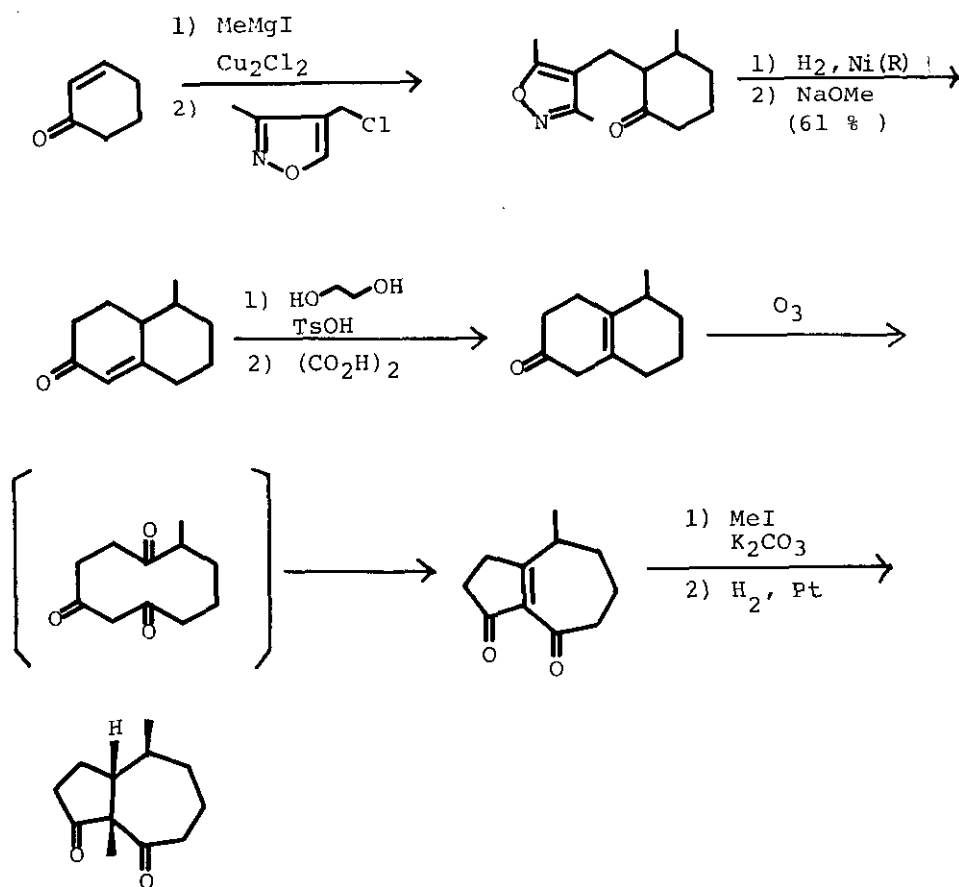
continued



was rearranged into the tricyclic system followed by reduction and ketalation to produce the key intermediate 108. Reductive cleavage of the isoxazole followed by hydrolysis of the carbinol amine and aldol condensation afforded the optically active steroidal system 109.

Annellation utilizing oxazoles has been applied to the synthesis

Chart 63

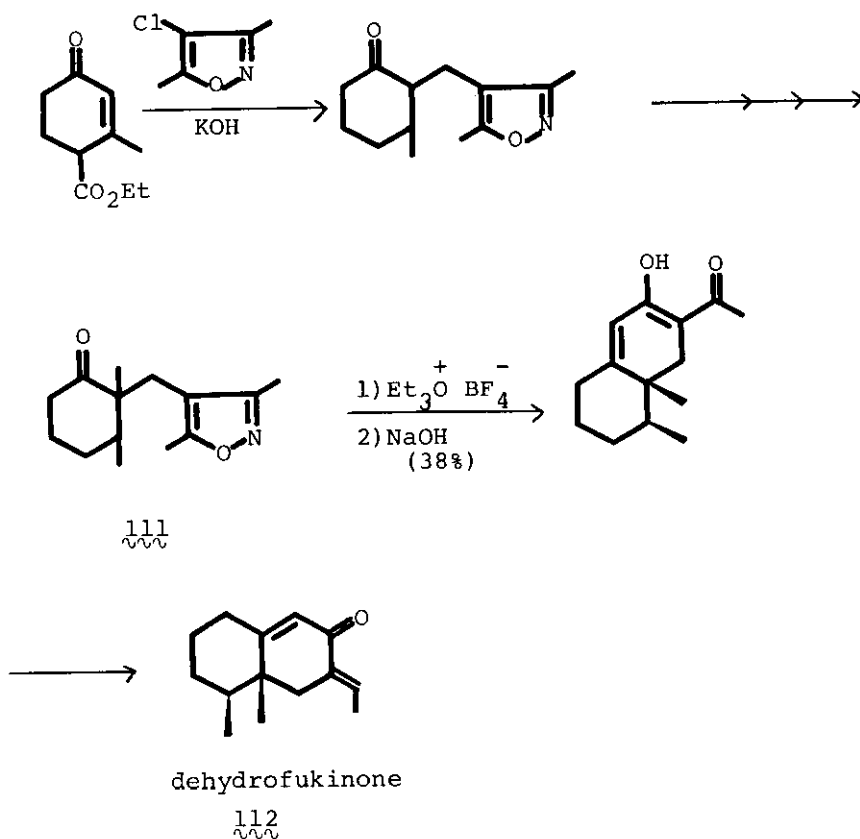


110

of terpenes. Kretchmer and Shafer⁹⁵ prepared 110, a potential intermediate to pseudoguaianolide, by annelation and ring transfer reactions as indicated in Chart 63.

In the above examples, an oxygen and a carbon of the isoxazole moiety were eliminated. However, all the atoms are sometimes utilized synthetically. Ohashi⁹⁶ employed oxazoles as a synthon for β -diketones in a synthesis of sesqui- and diterpenes. Thus,

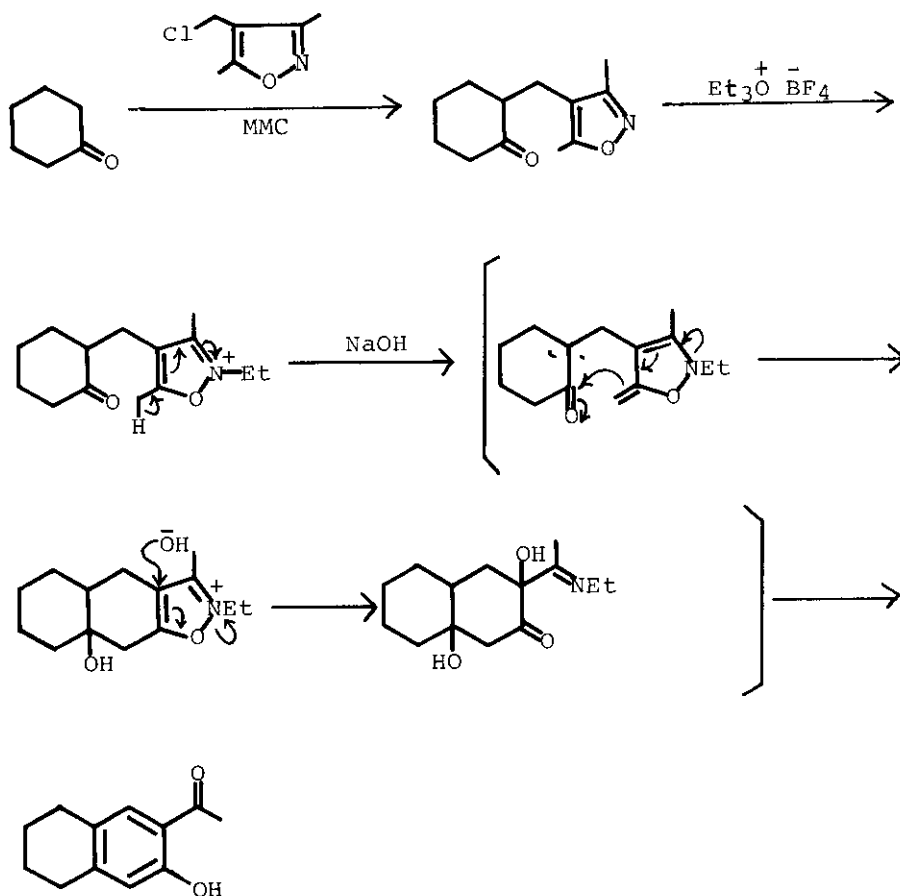
Chart 64



the isoxazole 111 was transformed into the quaternary salt with triethyloxonium fluoroborate and the product treated with sodium hydroxide to form by a ring opening of the isoxazole and annelation reaction dehydrofukinone (112).

The synthetic utility of the isoxazoles with regard to the annelation reaction has also been employed for the construction of the aromatic ring.⁹⁷ 4-Chloromethyl-3,5-dimethylisoxazole was

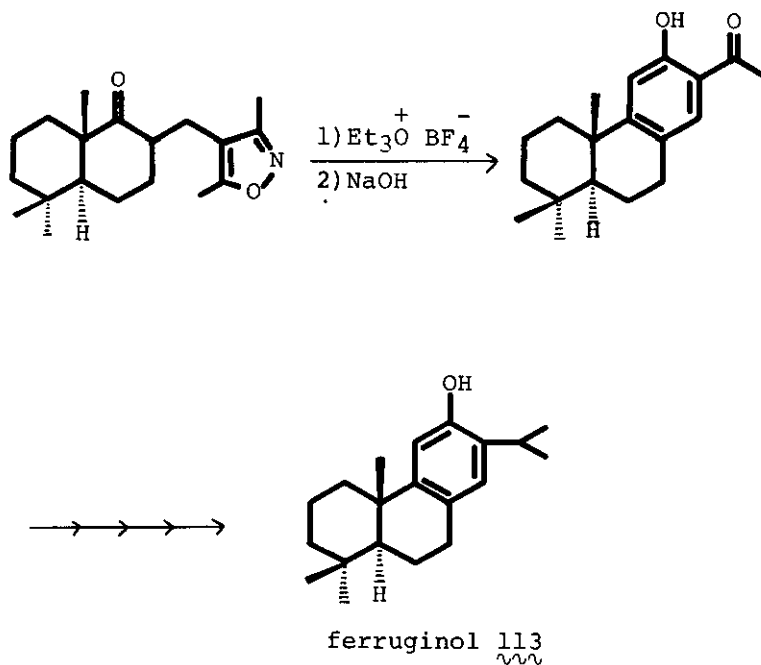
Chart 65



condensed with cyclohexanone and converted to the quaternary salt in the usual manner. Treatment with sodium hydroxide afforded the acylphenol in 40 - 50 % yield as shown in Chart 65.

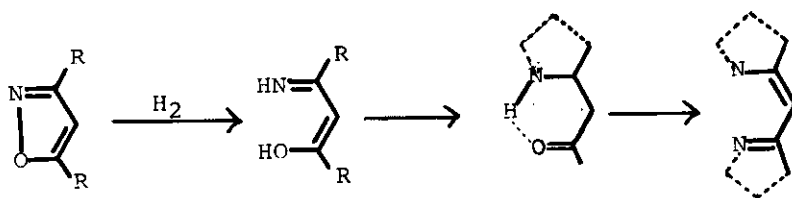
In this fashion ferruginol (113) has been synthesised by Ohashi and coworkers.⁹⁸

Chart 66



Reductive cleavage of the N-O bond of the isoxazole ring forms the α,β -unsaturated β -aminoketone system followed by amination to give β -iminovinylamines. Based on this sequence, Stevens and colleagues used isoxazoles to form ring-bridging vinylogous

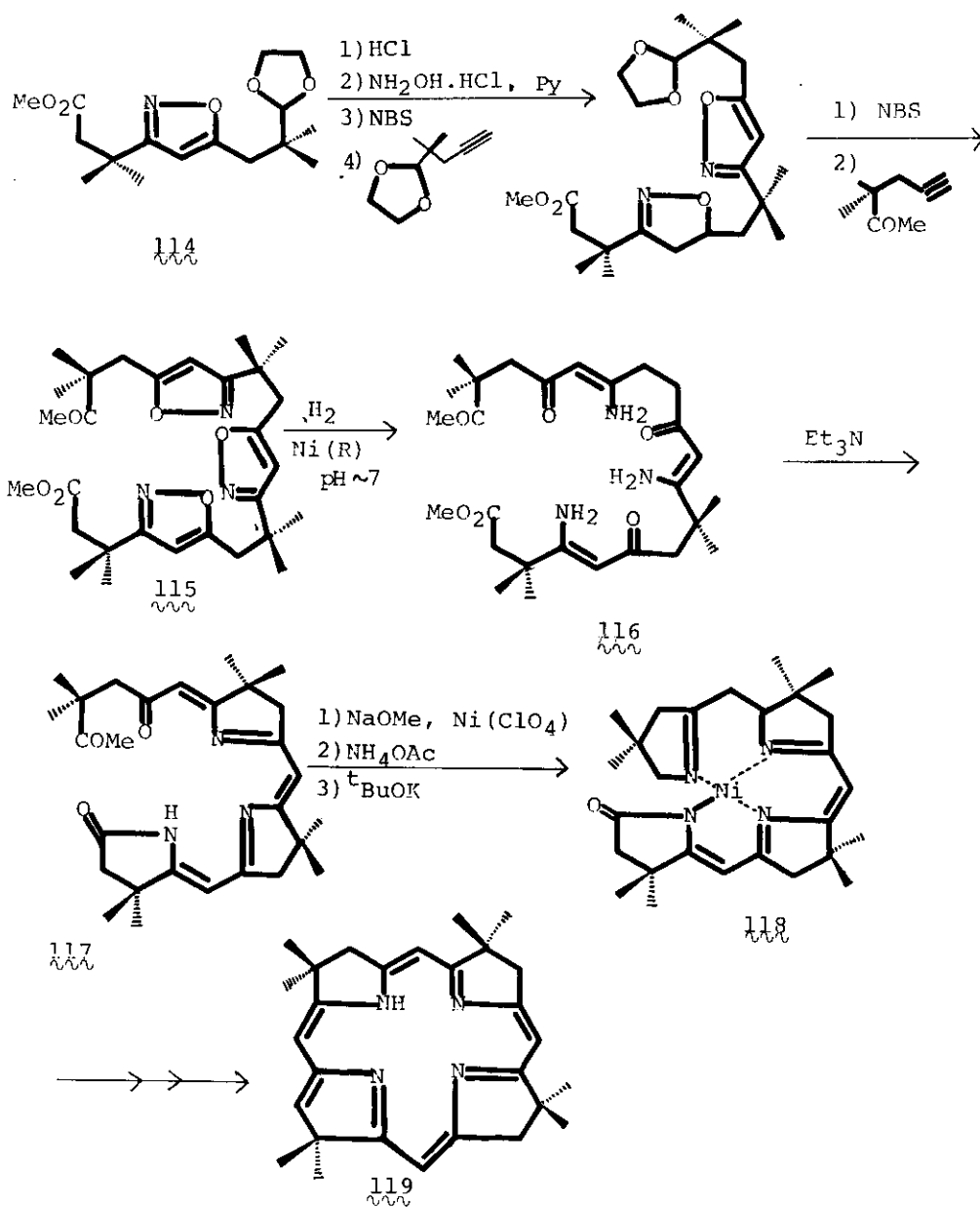
Chart 67



amidines.⁹⁹ Thus, the monoisoxazole 114 was stepwise converted via the di-isoxazole into the tri-isoxazole 115 and hydrogenolysed with Raney nickel to the triamino-triketone 116 followed by treatment with triethylamine to give the tripyrrole derivative (117). The latter was transformed via nickel precorphin complex (118) into octamethylcorphin (119).¹⁰⁰

Similarly, Traverso and associates¹⁰¹⁾ achieved a synthesis of semicorrin from isoxazole derivatives via reductive ring opening and ammonolysis.

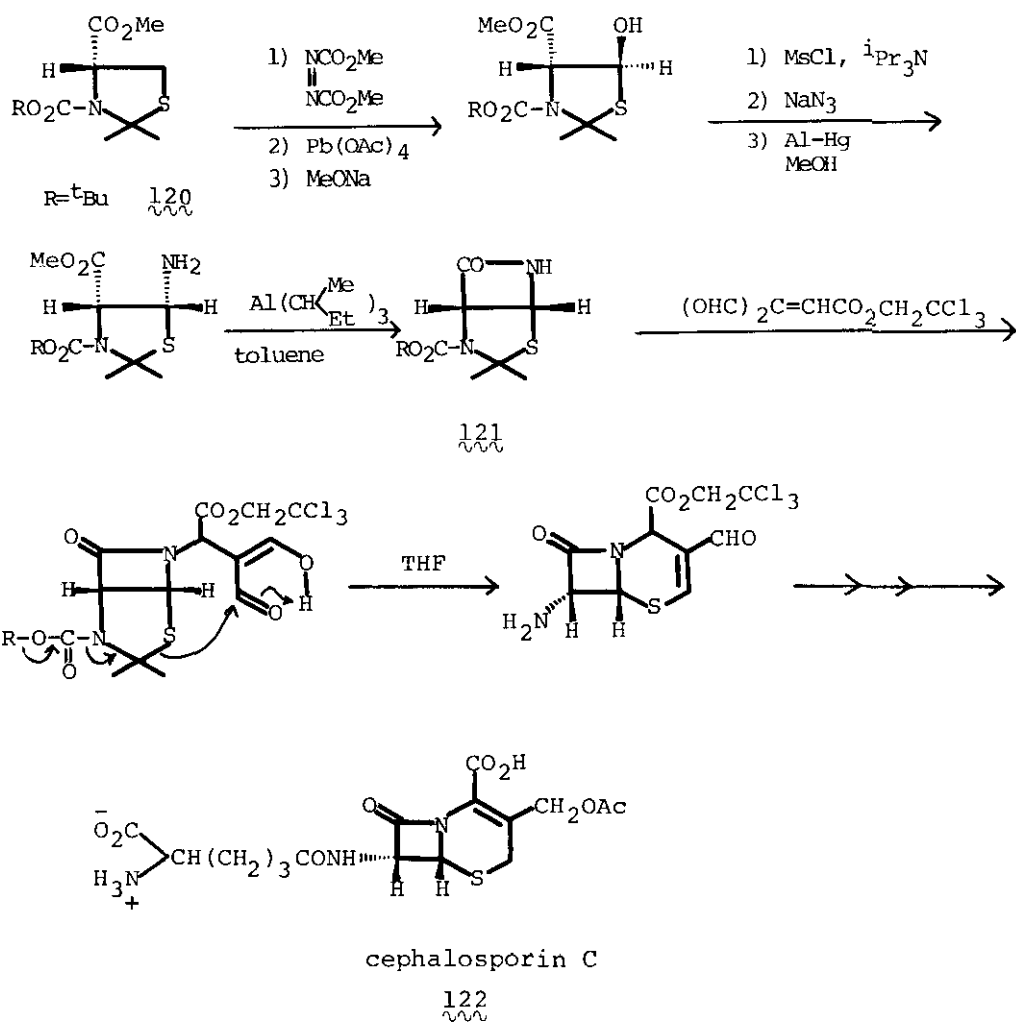
Chart 68



VII Syntheses from Thiazoles and Isothiazoles

Reductive ring opening of thiazoles produces β -aminomercaptans by elimination of carbon at the 2-position. The same reaction with isothiazoles cleaves the S-N bond and leads to β -aminomercaptans. Desulphurisation of these compounds with Raney nickel affords amines.

Chart 69



Cephalosporins and penicillins have been synthesised by using this type of reaction.

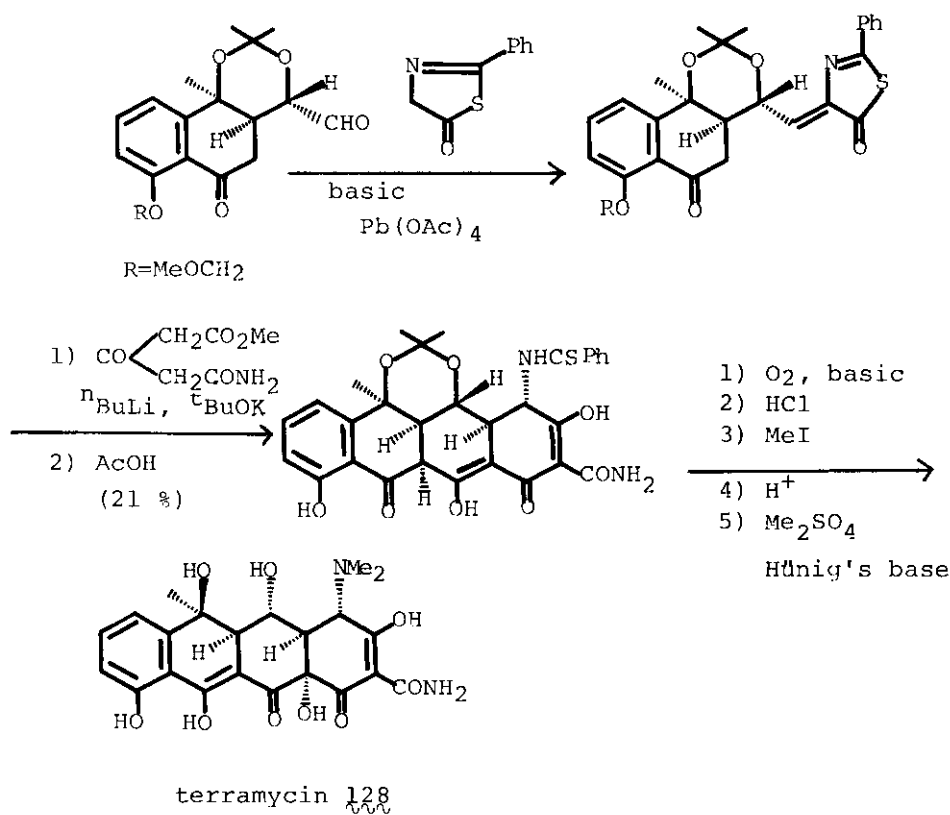
Woodward and coworkers¹⁰² accomplished the total synthesis of cephalosporin C (122) by converting the simple thiazolidine-4-carboxylate 120, derived from L-(+)-cysteine, into the β -lactam 121 and then introduced the carbon unit required for the construction of thiazine ring on the amide nitrogen. Treatment of the product with trifluoroacetic acid effected ring opening of the thiazoline system followed by recyclisation to the thiazine to give the cephalosporin skeleton, which was then converted into cephalosporin C (122).

Moreover, many cephams and penams have been prepared by cleavage of the thiazoline ring followed by recyclisation due to the nucleophilicity of the sulphur thus formed.¹⁰³ Stereospecific synthesis of d-biotin (76) from L-(+)-cystein via the thiazoline-4-carboxylate 123 has been reported by Uskokovic and coworkers.¹⁰⁴ Transformation of 123 into the 4-vinylthiazoline derivative 124, followed by bromination with pyridinium hydrobromide perbromide afforded via the sulphonium salt 125 the 4-amino-3-bromo-2,3,4,5-tetrahydrothiophene 126. The latter was then rearranged with hydrobromic acid and acetic acid and finally converted into d-biotin (76) as shown in Chart 70.



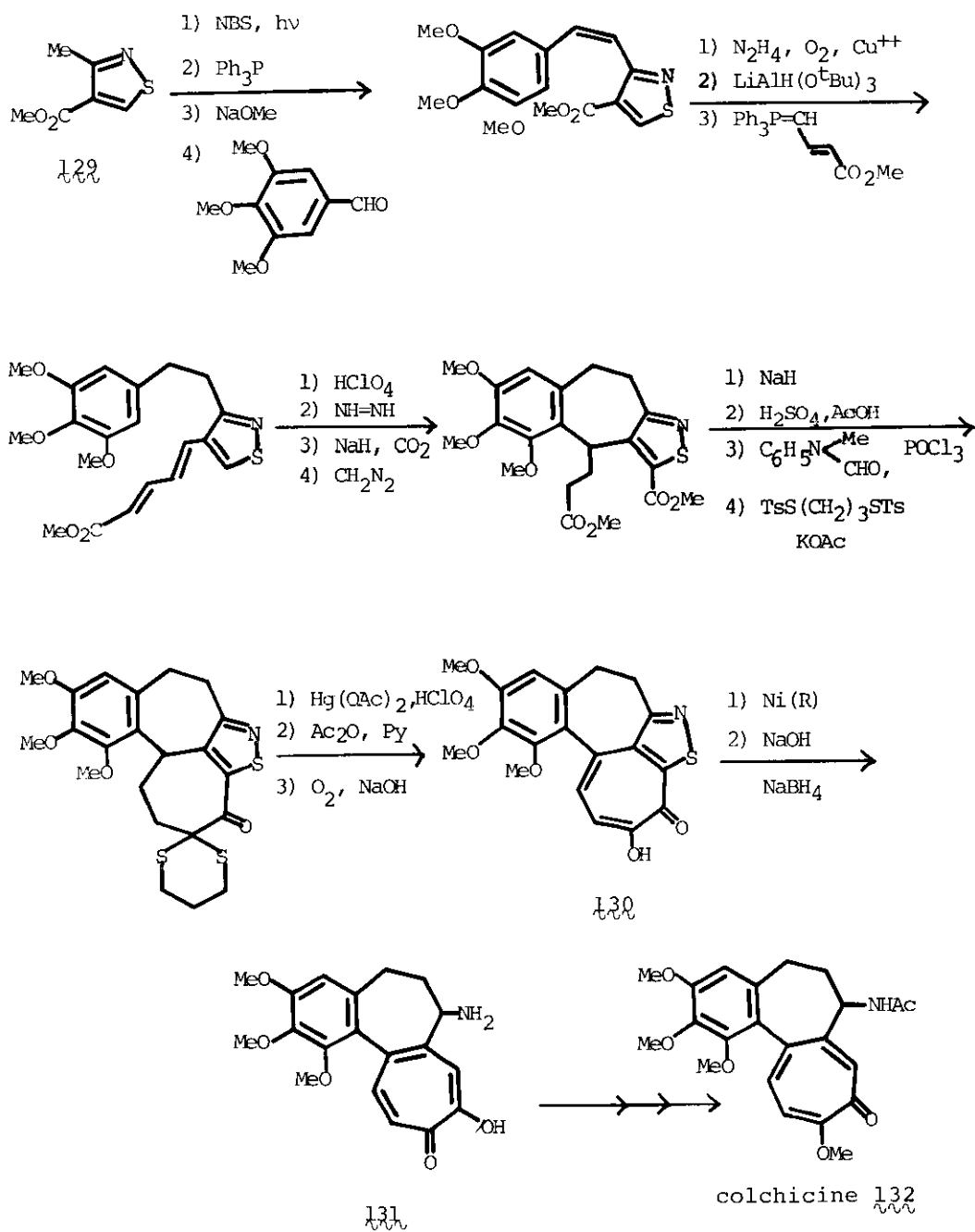
Muxfeldt and associates¹⁰⁵ achieved a total synthesis of terramycin (128) from a thiazolone derivative which was used to form ring D.

Chart 71



Isothiazole has been utilized by Woodward¹⁰⁶ in a total synthesis of colchicine (132). In this synthesis the nitrogen

Chart 72



atom in the isothiazole was transformed into the amine function and all the carbon atoms in heterocyclic system were used to build rings B and C of colchicine. 3-Methylisothiazole-4-carboxylate (129) was condensed with 3,4,5-trimethoxybenzaldehyde followed by conversion into the tetracyclic compound 130. The latter was subjected to reductive desulphurisation with Raney nickel in alkaline medium and then to sodium borohydride reduction to give descolchicine (131) which had previously been converted into the target compound colchicine (132).

VIII References

- 1 Z. G. Hajos and D. R. Parrish, J. Org. Chem., 1974, 39, 1615.
- 2 A. G. Cook, "Enamines: Their Synthesis, Structure, and Reactions", Marcel Dekker, New York, 1969.
- 3 T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, Chem. and Pharm. Bull. (Japan), 1975, 23, 2634.
- 4 H. A. Staab and H. Bräunling, Annalen, 1962, 654, 119.
- 5 A. I. Meyers and N. Nazarenko, J. Org. Chem., 1973, 38, 175.
- 6 A. I. Meyers, "Heterocycles in Organic Synthesis", Wiley-Interscience Publication, New York, 1974.
- 7 S. Danishefsky, P. Cain, and A. Nagel, J. Amer. Chem. Soc., 1975, 97, 380.
- 8 D. Lednicher, "Latent Functionality in Organic Synthesis" in Advances in Org. Chem., ed. by E. C. Taylor, Wiley-Interscience Publication, New York, Vol. 8, pp. 179, 1972.
- 9 P. Bosshard and C. E. Eugster, "Development of the Chemistry of Furans, 1952~1963" in Advances in Heterocyclic Chem., ed. by A. R. Katritzky, Academic press, New York, Vol. 7, pp. 377, 1966.
- 10 N. Elming, "Dialkoxy and Diacyloxydihydrofurans" in Advances in Org. Chem., ed. by R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience, New York, Vol.2, pp. 67, 1960.
11. A. P. Kozikovski, W. C. Floyd, and M. P. Kuniak, J. C. S. Chem. Comm., 1977, 582.
- 12 G. Büchi and H. Wüest, J. Org. Chem., 1966, 31, 977.
- 13 A. G. Birch, K. S. Koegh, and V. R. Mamdapur, Austral. J. Chem., 1973, 26, 2671.
- 14 S. Takano, T. Sugahara, M. Ishiguro, and K. Ogasawara,

Heterocycles, 1977, 6, 1141.

15 W. S. Johnson, M. B. Gravestock, and B. E. McCarry, J. Amer. Chem. Soc., 1971, 93, 4332.

16 W. S. Johnson, S. Escher, and B. W. Metcalf, J. Amer. Chem. Soc., 1976, 98, 1039.

17 P. A. Bartlett and W. S. Johnson, J. Amer. Chem. Soc., 1973, 95, 7501.

18 G. Piancatelli and A. Scettri, Tetrahedron Letters, 1977, 1131.

19 A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux, and I. Kubo, Tetrahedron Letters, 1973, 1307.

20 J. P. Kutney, J. Cable, W. A. F. Gladstone, H. W. Hanssen, G. V. Nair, E. J. Torupka, and W. D. C. Warnock, Canad. J. Chem., 1975, 53, 1796.

21 T. Kametani, H. Nemoto and K. Fukumoto, J. Org. Syn. Chem. (Japan), 1977, 35, 1009.

22 M. A. Tobias, J. Org. Chem., 1970, 35, 267.

23 A. M. Islam and M. T. Zemaity, J. Amer. Chem. Soc., 1957, 79, 6023.

24 T. Kametani, H. Nemoto, and K. Fukumoto, Heterocycles, 1974, 2, 639; T. Kametani, H. Nemoto, M. Takeuchi, S. Hibino, and K. Fukumoto, Chem. and Pharm. Bull. (Japan), 1976, 24, 1354.

25 R. Lukas and J. Srogl, Coll. Czech. Chem. Comm., 1961, 26, 2238; K. G. Lewis, J. Chem. Soc., 1961, 4690.

26 A. J. Birch and G. S. R. Subba Rao, Austral. J. Chem., 1970, 23, 547.

27 M. M. Coombs and T. S. Bhatt, J. C. S. Perkin I, 1973, 1251.

28 V. M. Kapoor and A. M. Mehta, J. C. S. Perkin I, 1973, 2420.

- 29 N. Finch, J. J. Fitt, and I. H. C. Hsu, J. Org. Chem., 1971, 36, 3191.
- 30 O. Achmatowicz and R. Bielski, Roczniki Chem., 1977, 51, 1389.
- 31 O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzchowska, and A. Zamojski, Tetrahedron, 1971, 27, 1973; O. Achmatowicz, G. Gryniewicz, and B. Szechner, Tetrahedron, 1976, 32, 1051;
- O. Achmatowicz, R. Bielski, and P. Burkowski, Roczniki Chem., 1976, 50, 1535.
- 32 R. Bogner and P. Herczegh, Carbohydrate Res., 1977, 54, 292.
- 33 S. M. Makin and N. J. Telegina, Zhur. obshchei. Khim., 1962, 32, 1104 [Chem. Abs., 1963, 58, 3308e].
- 34 C. Descoins, C. A. Henrick, and J. B. Siddall, Tetrahedron Letters, 1972, 3777.
- 35 T. Shono, Y. Matsumura, H. Hamaguchi, and K. Nakamura, Chem. Letters, 1976, 1249.
- 36 T. Shono, A. Hamaguchi, and K. Aoki, Chem. Letters, 1977, 1053.
- 37 S. Torii, H. Tanaka, T. Ando, and Y. Shimizu, Chem. Letters, 1976, 495.
- 38 T. Shono and Y. Matsumura, Tetrahedron Letters, 1976, 1363.
- 39 N. Elming and N. Clauson-Kaas, Acta Chem. Scand., 1955, 9, 23.
- 40 J. Srogl, M. Janda, I. Stibor, and J. Kucera, Coll. Czech. Chem. Comm., 1973, 38, 455.
- 41 T. Shono, Y. Matsumura, and H. Hamaguchi, J. C. S. Chem. Comm., 1977, 712.
- 42 B. A. Ellison and W. D. Woeshel, J. C. S. Chem. Comm., 1972, 529.

- 43 D. J. Faulkner and M. R. Petersen, J. Amer. Chem. Soc., 1973, 95, 553.
- 44 E. G. Corey, D. N. Crouse, and J. E. Anderson, J. Org. Chem., 1975, 40, 2140.
- 45 J. A. Edwards, J. Sundeen, W. Salmond, T. Iwadera, and J. H. Fried, Tetrahedron Letters, 1972, 781.
- 46 R. Kanazawa, H. Kotsuki, and T. Tokoroyama, Tetrahedron Letters, 1975, 3651.
- 47 T. W. Doyle, A. Martel, and B. Y. Luh, Canad. J. Chem., 1977, 55, 2708.
- 48 T. Masamune and H. Matsue, Chem. Letters, 1975, 895; T. Masamune, S. Numata, H. Matsue, A. Matsuyuki, T. Sato, and H. Murase, Bull. Chem. Soc. Japan, 1975, 48, 2294.
- 49 M. Ohno, M. Okamoto, N. Kawabe, H. Umezawa, T. Takeuchi, H. Iinuma, and S. Takahashi, J. Amer. Chem. Soc., 1971, 93, 1285.
- 50 T. Kato, T. Suzuki, N. Ototani, H. Maeda, K. Yamada, and Y. Kitahara, J. C. S. Perkin I, 1977, 206.
- 51 T. Kato, T. Suzuki, N. Ototani, and Y. Kitahara, Chem. Letters, 1976, 887.
- 52 R. Noyori, S. Makino, T. Okita, and Y. Hayakawa, J. Org. Chem., 1975, 40, 806.
- 53 Y. Hayakawa, M. Sakai, and R. Noyori, Chem. Letters, 1975, 509.
- 54 Y. Inoue and H. Kakisawa, Bull. Chem. Soc. Japan, 1969, 42, 3318.
- 55 E. W. Colvin, T. A. Purcell, and R. A. Raphael, J. C. S. Perkin I, 1976, 1718.
- 56 F. Bohlmann and G. Florentz, Chem. Ber., 1966, 99, 990.

- 57 S. Aburaki and M. Kinoshita, Chem. Letters, 1976, 701.
- 58 H. Ohruai and S. Emoto, Tetrahedron Letters, 1975, 2765.
- 59 E. J. Reist and P. H. Christie, J. Org. Chem., 1970, 35, 3521.
- 60 S. Takano, K. Yuta, and K. Ogasawara, Heterocycles, 1976, 4, 947.
- 61 G. Ohloff, C. Vial, F. Naf, and M. Pawlak, Helv. Chim. Acta, 1977, 60, 1161.
- 62 Recent examples: H. Stetter and B. Rajh, Chem. Ber., 1976, 109, 534; Z. Yoshida, Y. Yamada, and Y. Tamaru, Chem. Letters, 1977, 423.
- 63 M. M. Martin and J. G. MacConnell, Tetrahedron, 1970, 26, 307.
- 64 K. Murayama and T. Ohtsuki, Chem. Letters, 1977, 851.
- 65 B. D. Tilak and A. M. Malte, Indian J. Chem., 1969, 7, 1175.
- 66 Y. L. Goldfarb, B. P. Fabrichnyi, and I. F. Shalavina, Tetrahedron, 1962, 18, 21.
- 67 B. M. deMalleray, Helv. Chim. Acta, 1971, 54, 343.
- 68 G. Stork and P. L. Stotter, J. Amer. Chem. Soc., 1969, 91, 7780.
- 69 H. J. Backer and T. A. H. Blaas, Rec. Trav. chim., 1942, 61, 785.
- 70 E. J. Corey, N. H. Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, J. Amer. Chem. Soc., 1968, 90, 3245.
- 71 D. M. Lemal and S. D. McGregor, J. Amer. Chem. Soc., 1966, 88, 1335.
- 72 R. C. Bansal, A. W. McCulloch, and A. G. McInnes, Canad. J. Chem., 1970, 48, 1472.

- 73 J. K. Groves, N. E. Cundasawmy, and H. J. Anderson, Canad. J. Chem. 1973, 51, 1089.
- 74 R. B. Woodward, Pure Appl. Chem., 1973, 33, 145.
- 75 E. Gotschi, W. Hunkeler, H. J. Wild, P. Schneider, U. Fuhrer, J. Gleason, and A. Eschenmoser, Angew. Chem., 1973, 85, 950; E. Gotschi and A. Eschenmoser, Angew. Chem., 1973, 85, 952.
- 76 J. W. Cornforth, "Oxazolones" in Heterocyclic Compounds, ed. by R. C. Elderfield, Wiley, New York, Vol. 5, pp. 336, 1957; R. Filler, "Recent Advances in Oxazolone Chemistry" in Advances in Heterocyclic Chem., ed. by A. R. Katritzky, Academic Press, New York, Vol. 4, 75, 1965.
- 77 H. E. Carter, Org. Reactions, 1946, 3, 198.
- 78 E. E. Harris, R. A. Firestone, K. Fister, 3rd., R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, and W. Reuter, J. Org. Chem., 1962, 27, 2705; R. A. Firestone, E. E. Harris, and W. Reuter, Tetrahedron, 1967, 23, 943.
- 79 Y. Morisawa, M. Kataoka, and T. Watanabe, Chem. and Pharm. Bull. (Japan), 1976, 24, 1089.
- 80 U. Schöllkopf and D. Hoppe, Angew. Chem., 1970, 82, 483.
- 81 D. Hoppe and U. Schöllkopf, Angew. Chem., 1972, 84, 435.
- 82 J. W. ApSimon, D. G. Durham, and A. H. Rees, Chem. and Ind., 1973, 275.
- 83 W. Martin, H. Hartung, H. Urbach, and W. Durckheimer, Tetrahedron Letters, 1973, 3513.
- 84 A. R. Battersby, K. R. Hanson, R. H. Wightmann, and J. Staunton,

Chem. Comm., 1971, 185.

85 T. Kametani and K. Fukumoto, J. Chem. Soc., 1963, 4289.

86 T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto, M. Nagano, and T. Miyadera, Tetrahedron Letters, 1977, 3053.

87 J. E. McMurry, Org. Synth., 1973, 53, 59, 70.

88 G. Stork, S. Danishefsky, and M. Ohashi, J. Amer. Chem. Soc., 1967, 89, 5459.

89 M. Ohashi, H. Kamashi, H. Kakisawa, and G. Stork, J. Amer. Chem. Soc., 1967, 89, 5461; J. Org. Chem., 1971, 36, 2784.

90 G. Stork and J. E. McMurry, J. Amer. Chem. Soc., 1967, 89, 5463.

91 R. A. Kretchmer, E. D. Michelich, and J. J. Waldron, J. Org. Chem., 1972, 37, 4483.

92 G. Stork and J. E. McMurry, J. Amer. Chem. Soc., 1967, 89, 5464.

93 J. W. Scott and G. Saucy, J. Org. Chem., 1972, 37, 1652; J. W. Scott, P. Buchschacher, L. Labler, W. Meier, and A. Furst, Helv. Chim. Acta, 1974, 57, 1217.

94 J. W. Scott, R. Borer, and G. Saucy, J. Org. Chem., 1972, 37, 1659.

95 R. A. Kretchmer and W. M. Shafer, J. Org. Chem., 1973, 38, 95.

96 M. Ohashi, Chem. Comm., 1969, 893.

97 M. Ohashi, T. Muraishi, and H. Kakisawa, Tetrahedron Letters, 1968, 719.

98 S. Auricchio, S. Morrocchi, and A. Ricca, Tetrahedron Letters, 1974, 2793.

- 99 R. V. Stevens, L. E. Dupree, and M. P. Wentland, Chem. Comm., 1970, 821; R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, and L. E. Wentland, J. Amer. Chem. Soc., 1971, 93, 6629; R. V. Stevens, L. E. Dupree, W. L. Edmonson, L. L. Magid, and M. P. Wentland, J. Amer. Chem. Soc., 1971, 93, 6637; R. V. Stevens and E. B. Reid, Tetrahedron Letters, 1975, 4193; R. V. Stevens, J. M. Fitzpatrick, P. B. Germeraad, B. L. Harrison, and R. Lapalme, J. Amer. Chem. Soc., 1976, 98, 6313; R. V. Stevens, E. Chepreck, B. L. Harrison, J. Lai, and R. Lapalme, J. Amer. Chem. Soc., 1976, 98, 6317.
- 100 R. V. Stevens, C. G. Christensen, R. M. Cory, and E. Thorsett, J. Amer. Chem. Soc., 1975, 97, 5940.
- 101 G. Traverso, A. Barco, and G. P. Pollini, Chem. Comm., 1971, 926; G. Traverso, G. P. Pollini, G. Barco, and G. Degiuli, Gazzetta, 1972, 102, 243.
- 102 R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrügger, J. Amer. Chem. Soc., 1966, 88, 852.
- 103 J. E. Baldwin, M. A. Christie, S. B. Haber, and C. I. Kruse, J. Amer. Chem. Soc., 1976, 98, 3045; H. Tanino, S. Nakatsuka, and Y. Kishi, Tetrahedron Letters, 1976, 581; R. D. G. Cooper, J. Amer. Chem. Soc., 1972, 94, 1018; R. D. G. Cooper, and F. L. Jose, J. Amer. Chem. Soc., 1972, 94, 1021; R. Scartazzini, J. Gosteli, H. Bickel, and R. B. Woodward, Helv. Chim. Acta, 1972, 55, 2567; R. G. Micetich, and R. B. Morin, Tetrahedron Letters, 1976, 979.
- 104 Confalone, G. Pizzolato, E. G. Baggiolini, D. Lollar, and M. R. Uskokovic, J. Amer. Chem. Soc., 1975, 97, 5936.

- 105 H. Muxfeldt, G. Hardtmann, F. Kathawala, E. Vedejs, and J. B. Moovery, J. Amer. Chem. Soc., 1968, 90, 6534.
- 106 R. B. Woodward, "The Harvey Lectures", 1963, 31.

Received, 5th October, 1978