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

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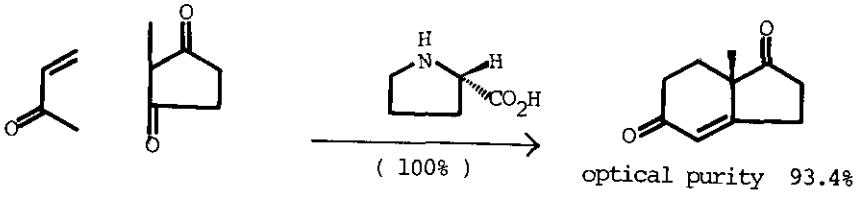
Total syntheses of natural products, in which the carbon-unit generated by ring opening of five-membered heterocyclic compounds is either a starting material or a key intermediate, are described.

CONTENTS

I. Introduction

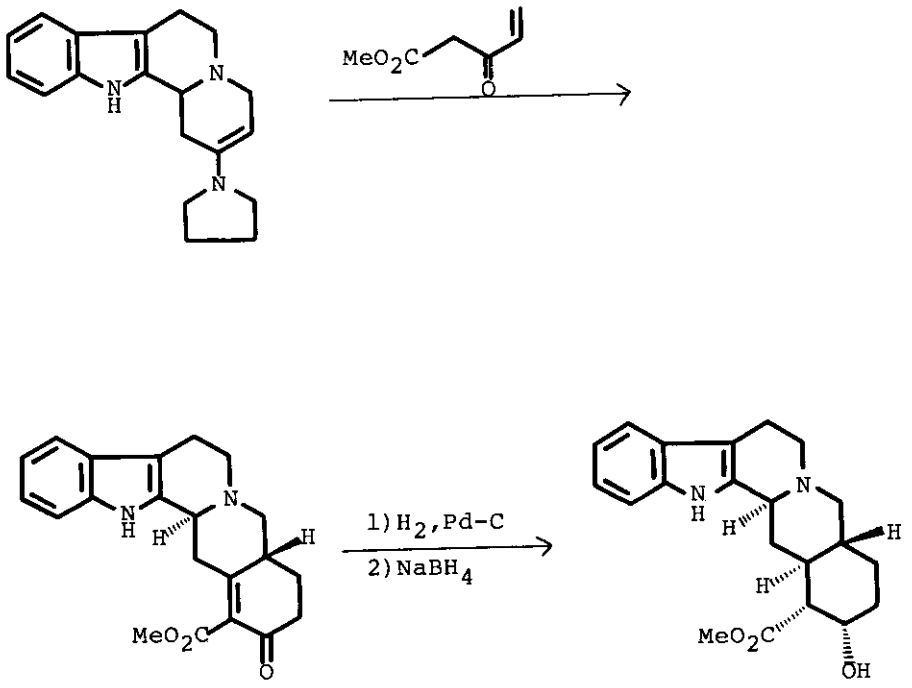
It is well known that there are more than three millions of organic compounds and a great number of new compounds has been born by a synthesis or an isolation from nature. Heterocyclic compounds occupy an important position in organic chemistry and, especially, have been widely used in synthesis. For 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



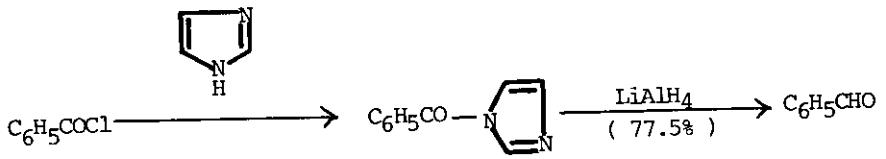
The use of pyrrolidine, morpholine and piperidine enamines was developed by Stork[2] and is an important synthetic reaction. As an example of this method in the synthesis of natural products Chart 2 shows the preperation of yohimbine[3]. In contrast to the activation of substrates by enamine formation, imidazole has

Chart 2



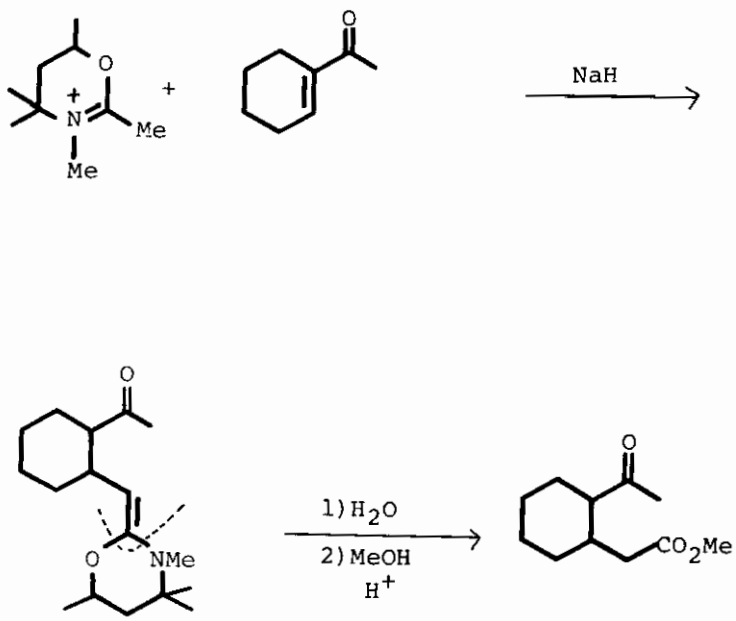
been used as deactivating group in the lithium aluminium hydride reduction of carboxylic acids to aldehydes.[4]

Chart 3



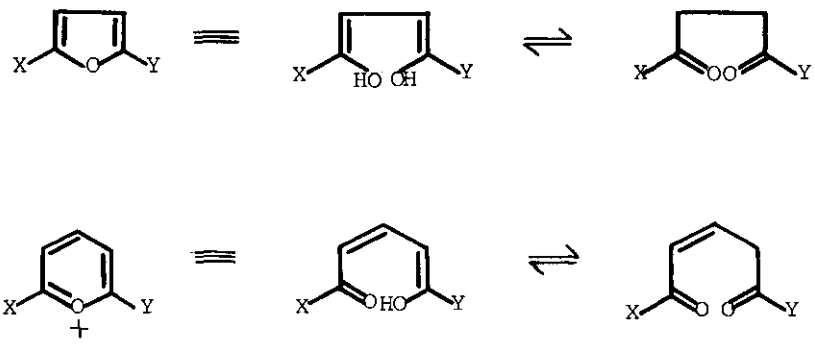
In the above examples, the heterocyclic compounds do not form any parts of the products. However in some cases, part of the heterocyclic system constitutes a carbon unit to the reaction products.[5]

Chart 4



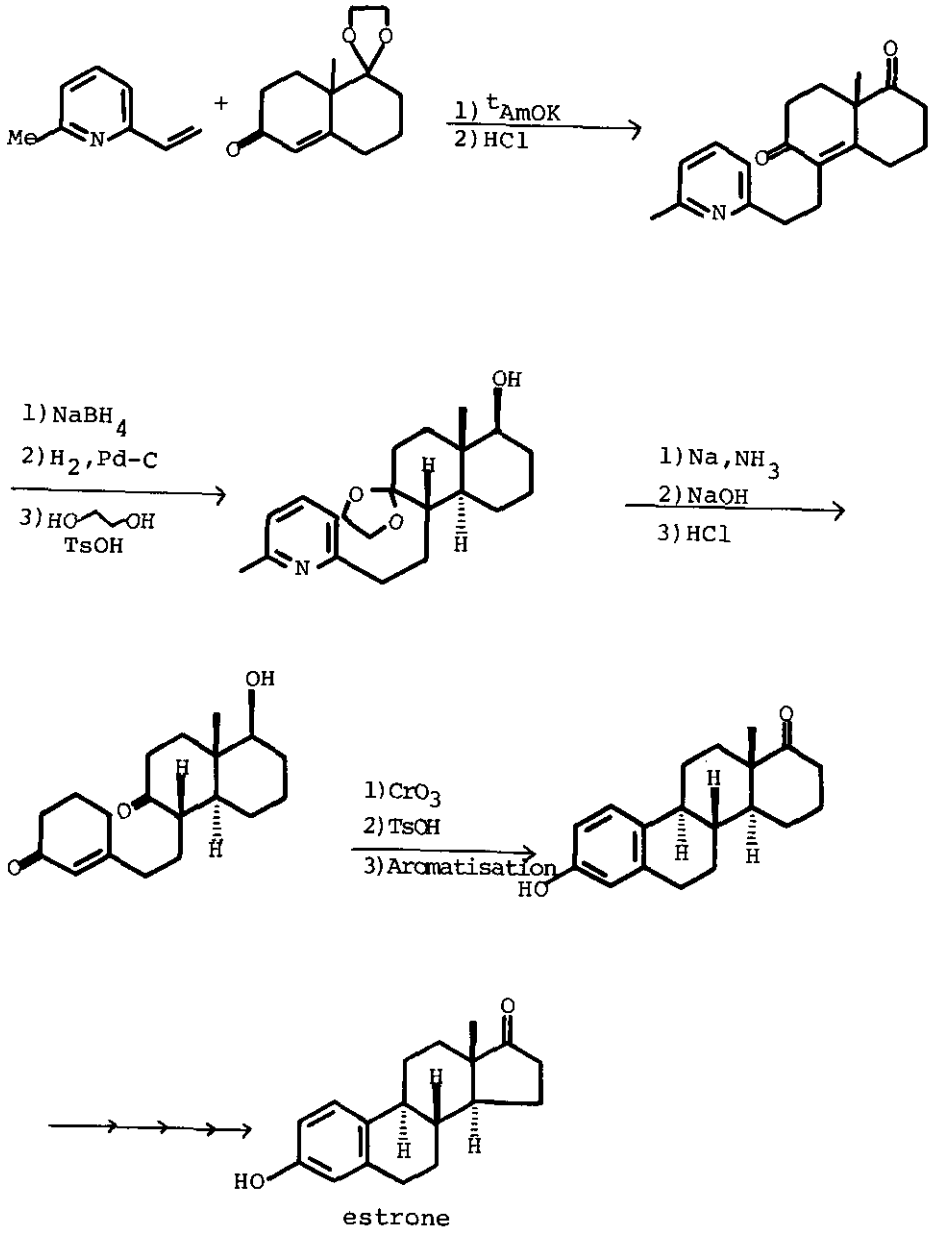
As shown in the Chart 5, some kinds of heterocyclic compounds are chemical equivalents with carbonyl derivatives and suggests

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



estrone

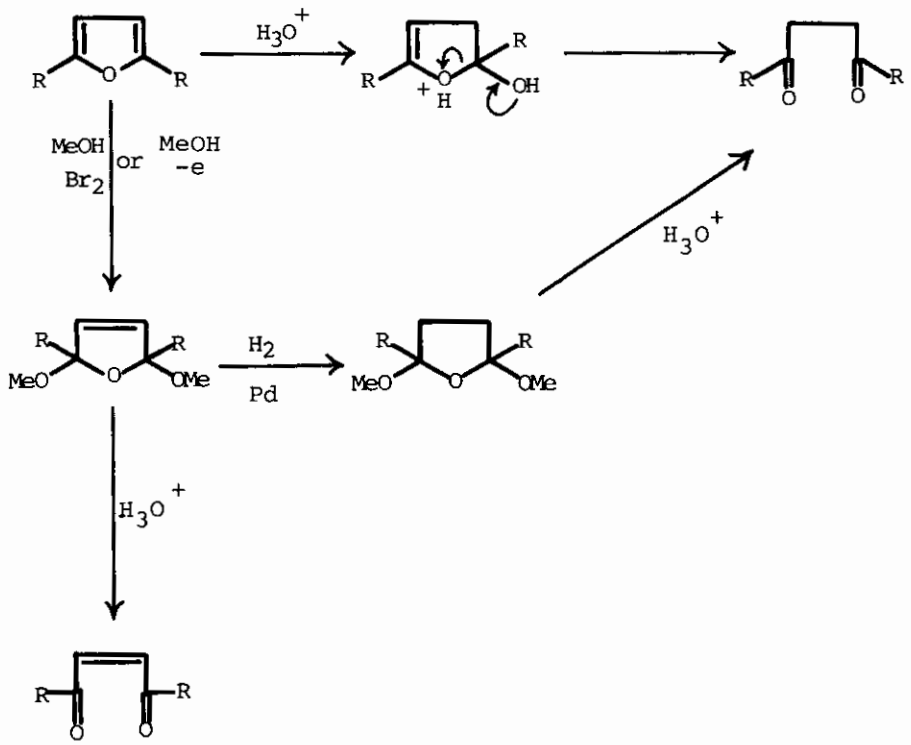
In this review, we will describe the total syntheses of natural products via a carbon-carbon chain formed by elimination of the hetero atom through decomposition of a five-membered heterocyclic system.

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

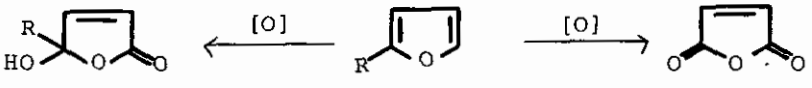


since this reaction, until recently, was of little preparative value because of extensive polymerisation, the following indirect method has been used in the conversion of furans into 1,4-dicarbonyl compounds.[10]

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-dihydrofurans with acid has provided unsaturated 1,4-diketones.

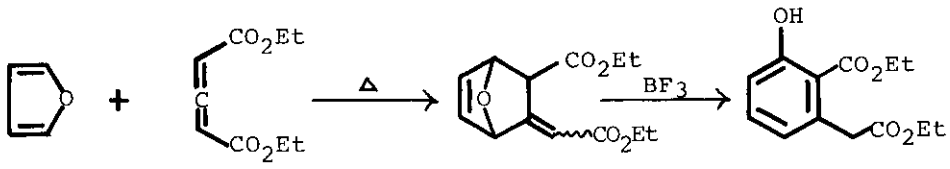
The second method for ring opening the furan ring is based on oxidation to give, depending on reaction conditions, γ-lactones or maleic acid derivatives.

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]

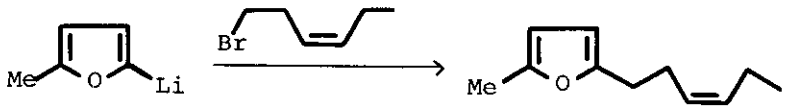
Chart 9



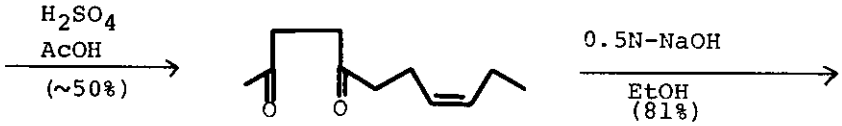
1,1 Acidic Hydrolysis Method

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 Wüest[12] 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 coworkers[13] also synthesised *cis*-jasmone from 2-methylfurylpropionate *via* 2-carboxymethyl-3-methylcyclopentenone by the same reaction sequence. Moreover, Takano and associates[14] succeeded in the conversion of 2-methylfuran into *cis*-jasmone *via* 5-methylfurylpropionaldehyde and the acetylene derivative 4.

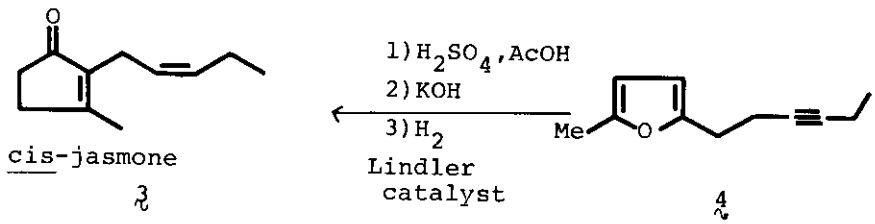
Chart 10



1



2



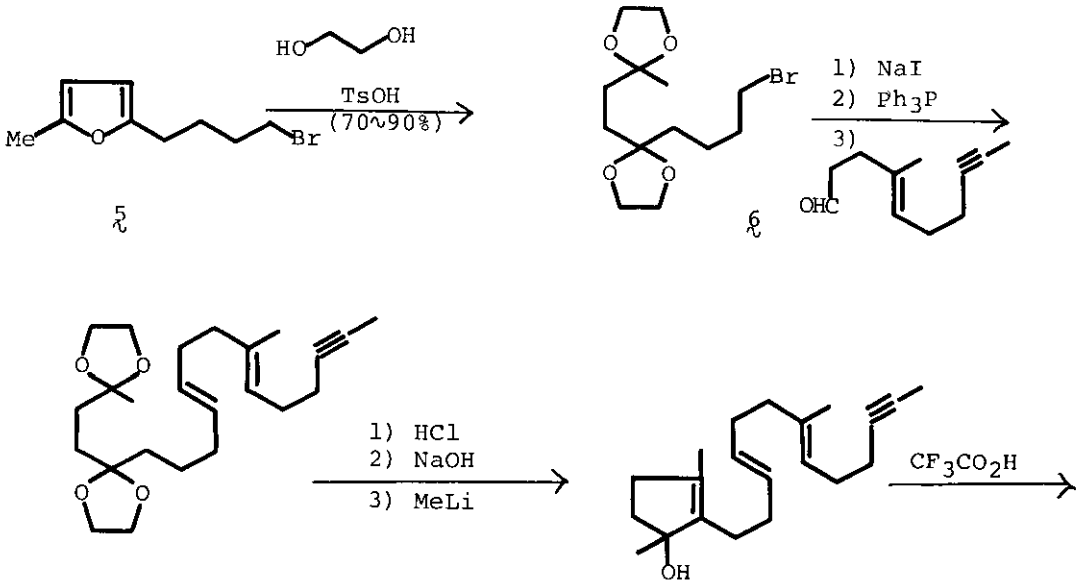
3 4

A biogenetic type synthesis of progesterone (7) has been achieved by Johnson and colleagues[15] who utillized 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 cleavege of furn ring was protected as the diketal in order to prevent polymerisation and the formation of side products. In a similar manner[16], 11α-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 conveninet 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 actone at 50° to the cyclopentenone 11 followed by isomerisation with alumina to give the prostaglanding E_1 precursor 12.[18]

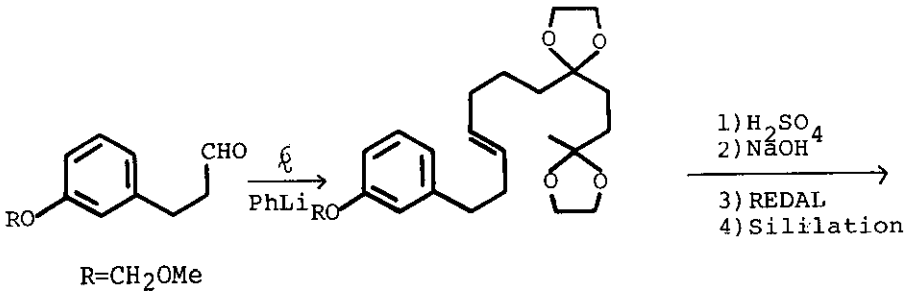
Chart 11



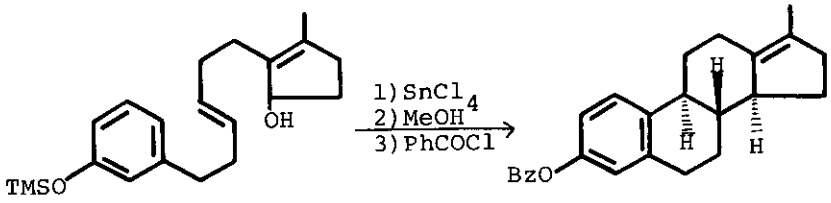
X=H progesterone 7

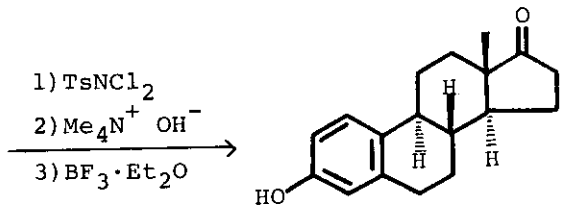
X=OH 8

Chart 12



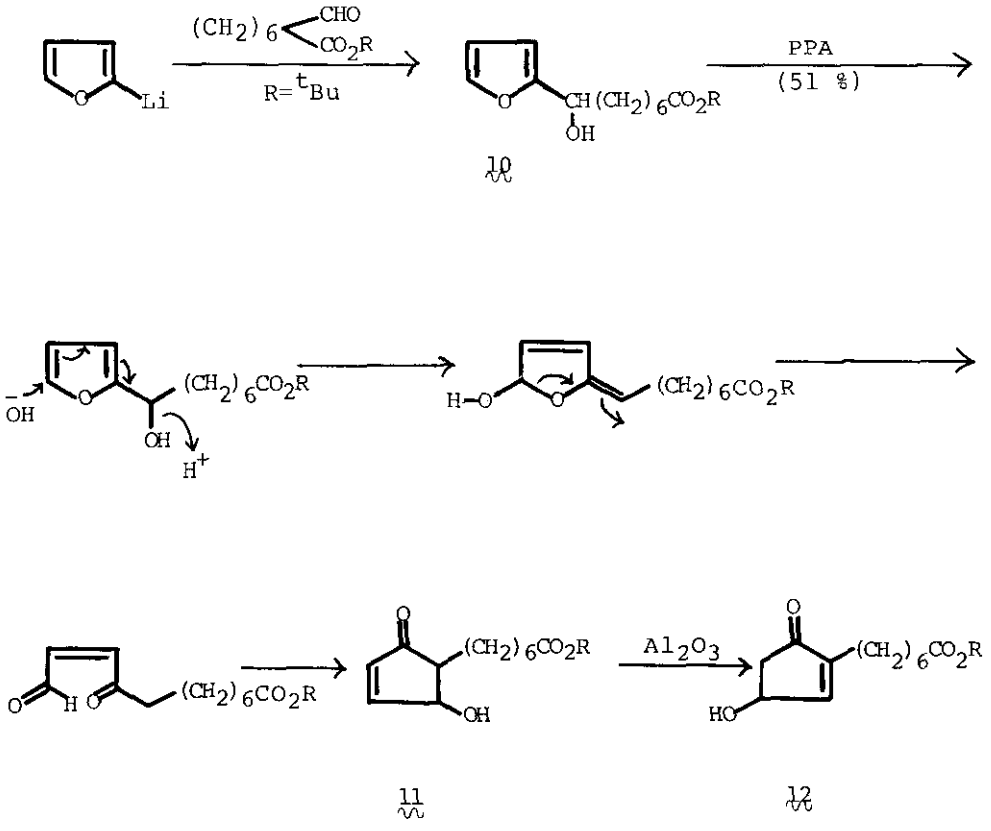
R=CH_2OMe





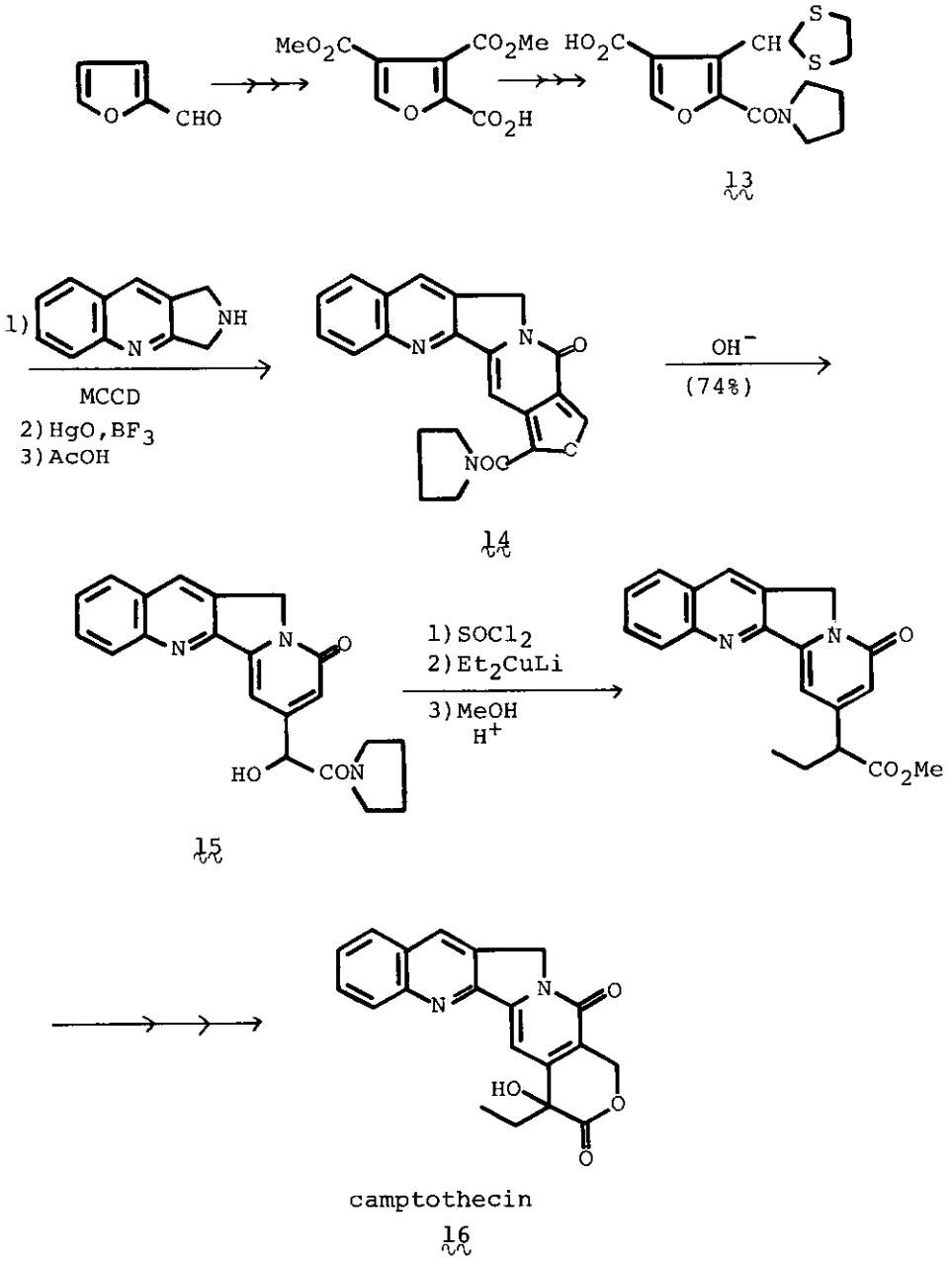
estrone 9

Chart 13



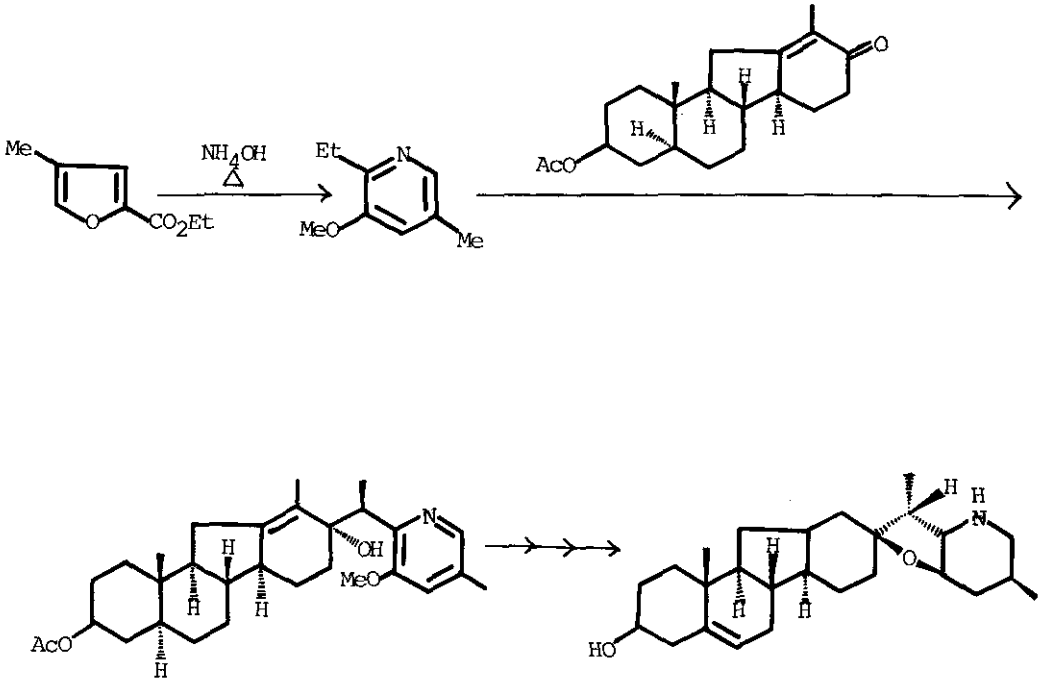
Kende and colleagues[19] achieved a total synthesis of camptotecin (16) by using the furan uncleus to form ring E of this alkaloid. The amidofuran 13, obtained from furfural in several steps, was treated with pyrrolo[2,3-c]quinoline and the condensation product was cyclised to the pentacyclic intermediate 14. Alkali treatment of 14 produced the amino-alcohol 15 in 74 % yield by cleavage of furn ring and subsequent deformylation. After introduction of ethyl group, the resulting product was converted in the usual manner into camptothecin.

Chart 14


MeO2C
CO2Me
HO2C
CH
S
S
CHO
CO2H
CON
13
1)
NH
N
MCCD
2) HgO, BF3
3) AcOH
O
OH−
(74%)
NOC
14
HO
1) SOCl2
2) Et2CuLi
3) MeOH
H+
CO2Me
15
HO
camptothecin
16

In the synthesis of jervine (17) by Kutney and coworkers[20] 5-methyl-2-propionylfuran was easily transformed into the key sarting material 2-ethyl-3-methoxy-5-methylpyridine.

Chart 15

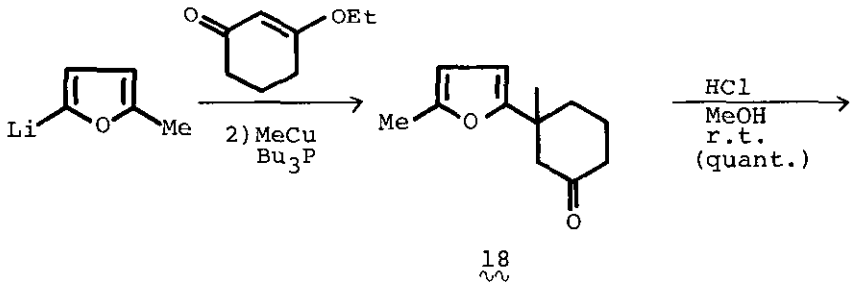


jervine 17

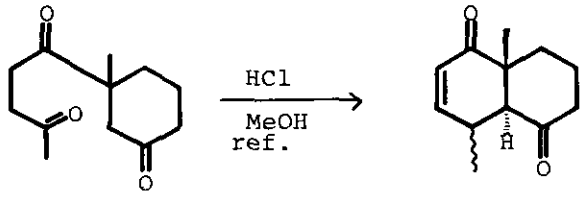
The furan ring has also been utilized as a functional group where the carbon chain participated in annelation.[21 ~ 23] For example, the bicyclic dione 20, an important starting material for sesquiterpenes, was obtained in four-steps from 2-methylfuran and

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 aicd in boiling methanol to give the product 20.[24]

Chart 16



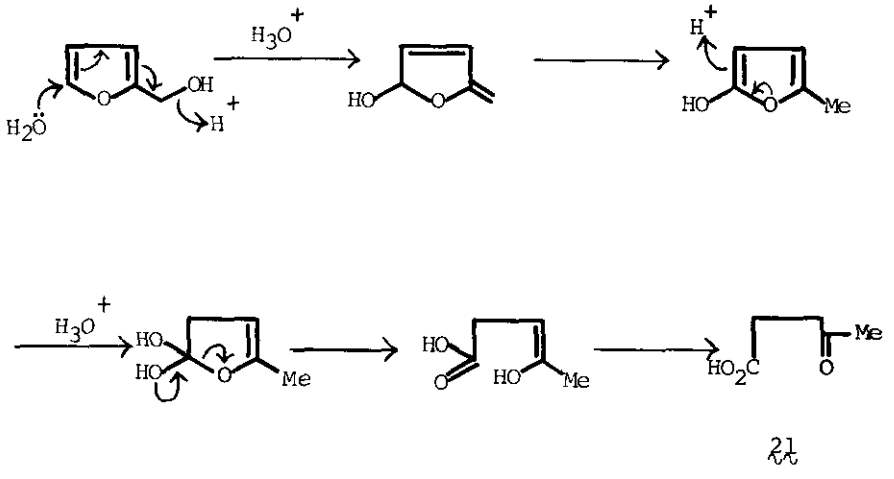
18



19 20

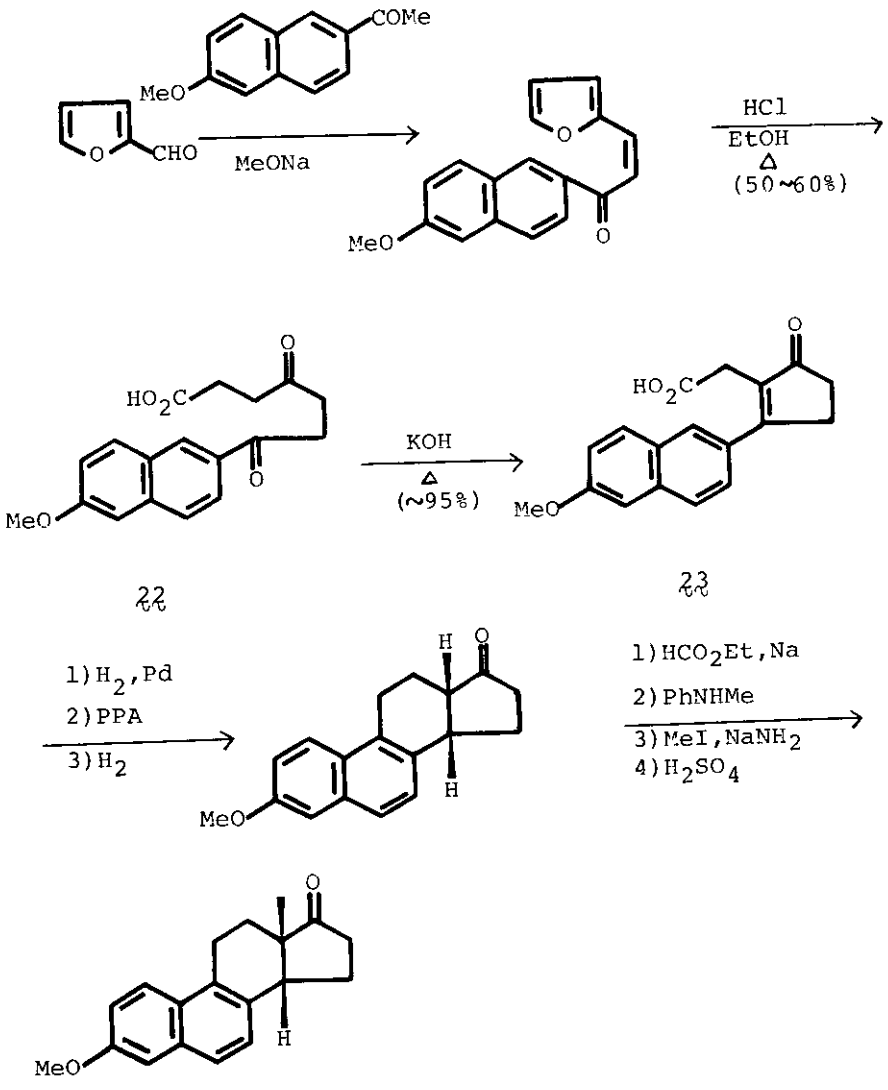
Although ring opening reaction of furans with acids produces 1,4-dicarbonyl compounds, levulinic acids are formed by the same treatment of α-furfuryl alcohols or α-vinylfurans as shown in Chart 17.[25]

Chart 17



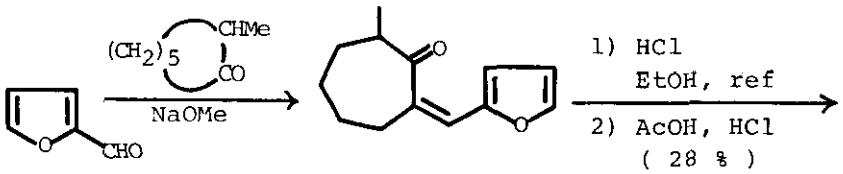
Birch and Subba Reo[26] reported a synthesis of steroids by using this type reaction. Thus, aldol condensation of furfural with β-acetylnaphthalene gave the furfurylidene derivative which opened up in ethanolic hydrochloric acid to the diketo acid 22 followed by cyclisation with potassium hydroxide to 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 Bhatt[27] and Kapoor and Mehta.[28]

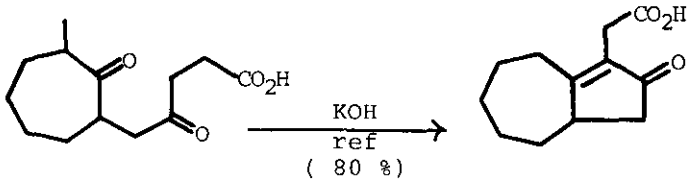
Chart 18


COMe
MeO
CHO
MeONa
HCl
EtOH
Δ
(50~60%)
MeO
HO2C
KOH
Δ
(~95%)
22
23
1) H2, Pd
2) PPA
3) H2
1) HCO2Et, Na
2) PhNHMe
3) MeI, NaNH2
4) H2SO4
MeO
MeO

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-methyl-cyclopentanone 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





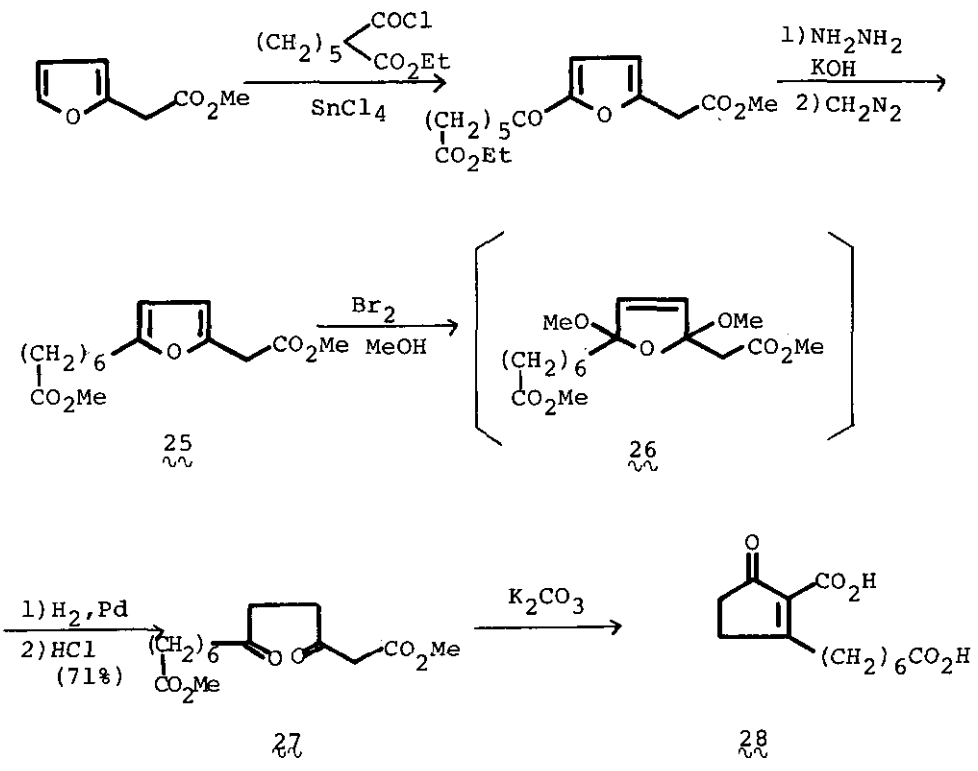
24

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

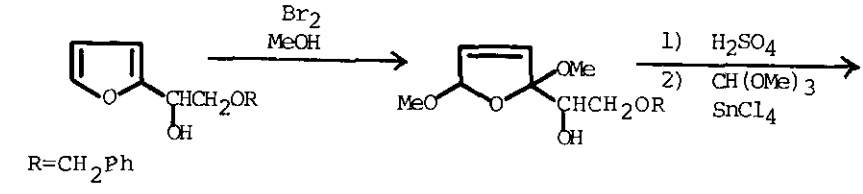
substituent at the 3 position of 28. The product was reduced by Wolff-Kishner reaction and then methylated with diazomethane to produce the furandimethyl ester 25. Treatment of the latter with bromine in methanol gave the 2,5-dihydro-2,5-dimethoxyfuran 26, which, without purification, was reduced on 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

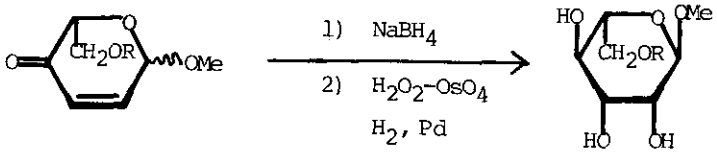


Achmatowicz and coworkers[30,31] developed a new route to saccharides by using 2,5-dihydro-2,5-dimethoxyfurans in a ring opening reaction. The 2,5-dihydrofuran derivative 30, available easily from the furfuryl alcohol 29 was hydrolysed with 2 % sulphuric acid at room temperature to provide the six-membered 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



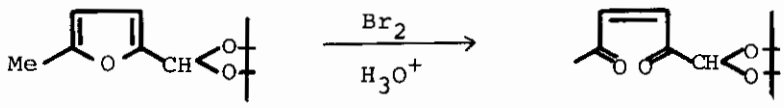
29 30



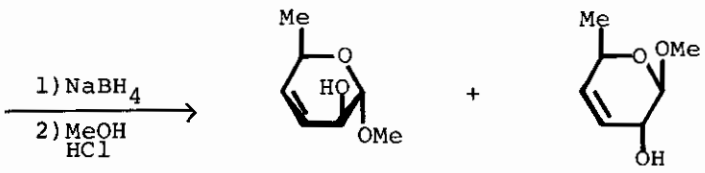
31 32

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

Chart 22



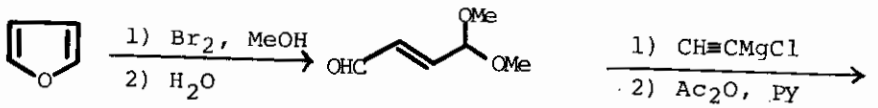
33



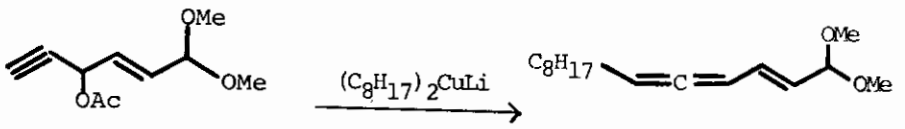
34

Furthermore, the direct hydrolysis method of 2,5-dihydro-2,5-dialkoxyfurans[33] has been applied to the synthesis of the insect pheromone 37.[34] Treatment of furan with bromine in methanol at -45 ∿ -10°C followed by mild hydrolysis gave the aldehyde 35 which was converted via the key allene intermidate 36 as shown in Chart 23 into the pheromone 37.

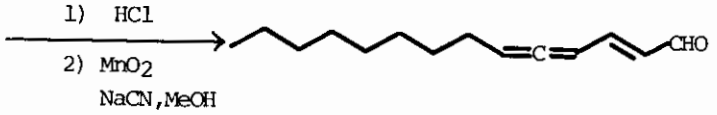
Chart 23



35



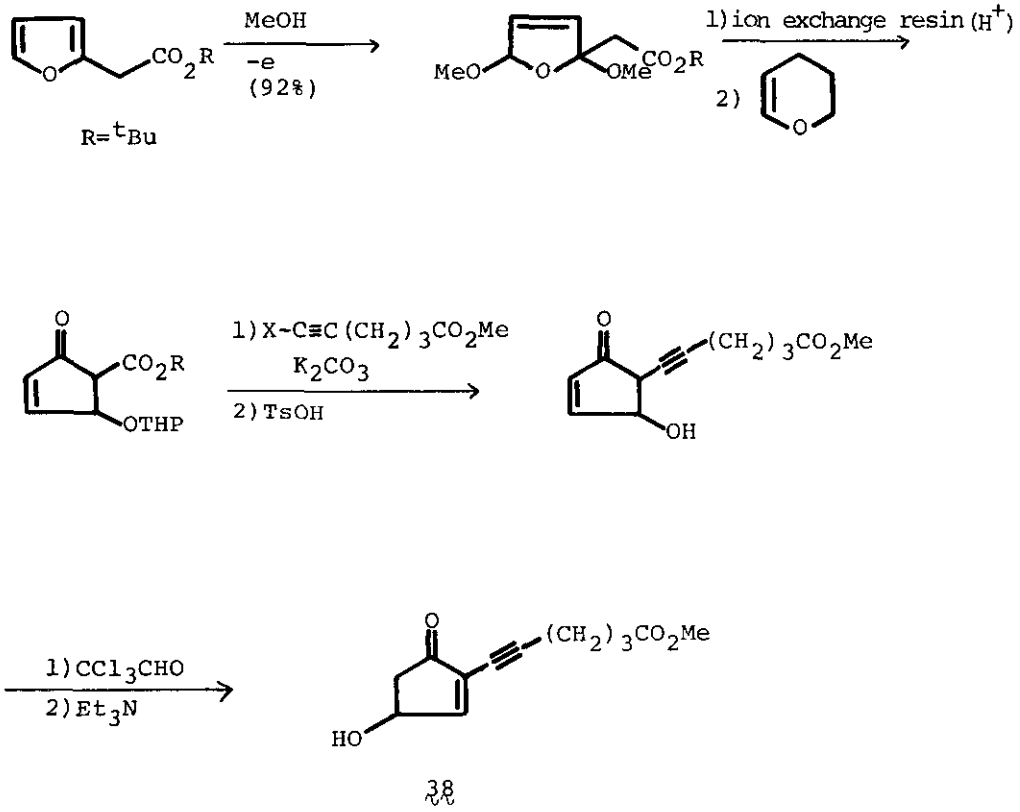
36



37

Electrolytic oxidation of furans in methanol is also a useful approach to 2,5-dihydro-2,5-dimethoxyfuran. Shono and associates[35] 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]

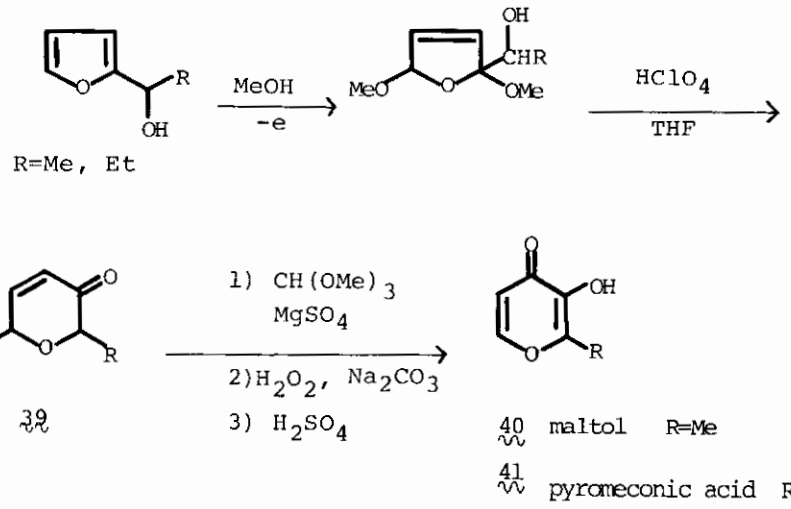
Chart 24



38

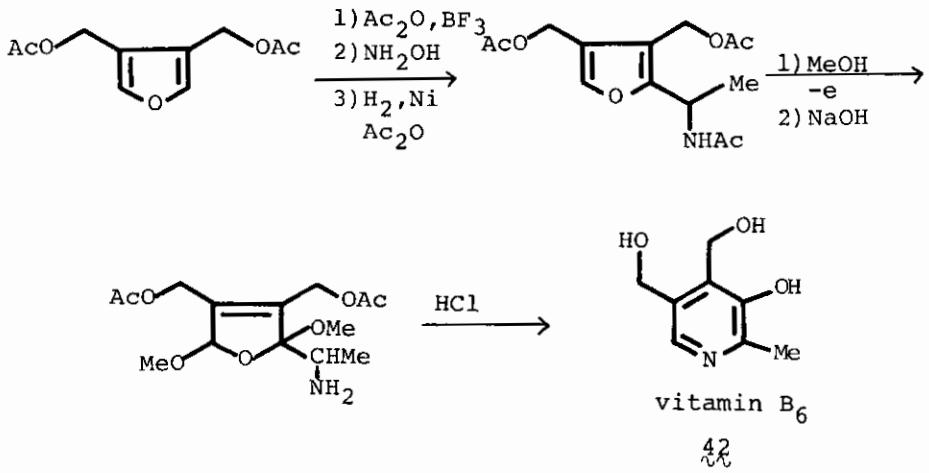
As electrochemical method has also been employed in the synthesis of maltol (40) and pyromeconic acid (41). Thus, electrolytic oxidation of the substituted furfuryl alcohol in methanol followed by acid treatment produced the pyran 39 which was subjected to methylation, epoxidation and rearrangement with acid to give maltol (40) and pyromeconic acid (41).[37] Maltol (40) was also synthesised by Shono and Matsumura[38] in a similar way.

Chart 25



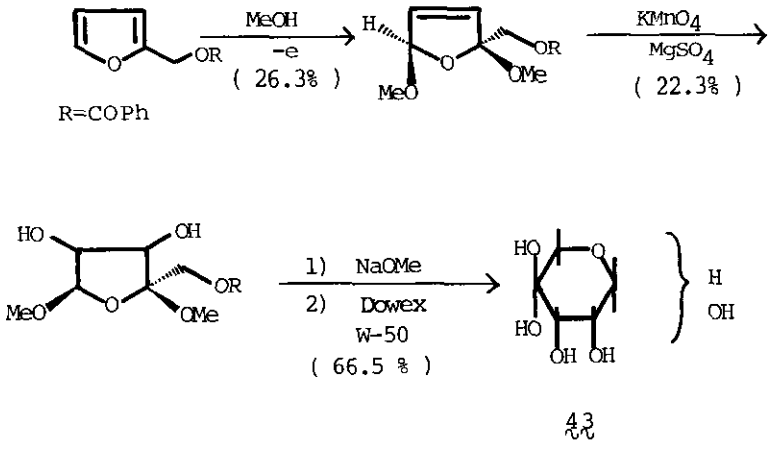
Vitamin B_6 (42) was obtained from 3,4-diacetoxymethylfuran by using electrolysis as the key reaction. Ring opening and recyclisation were carried out with hydrochloric acid without isolation of intermediates.[39]

Chart 26



Srogl and collaborators[40] 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 associates[41] reported a new synthetic route to 2-hydroxycyclopentenone by reduction and rearrangement of an electroxidation product of furan.

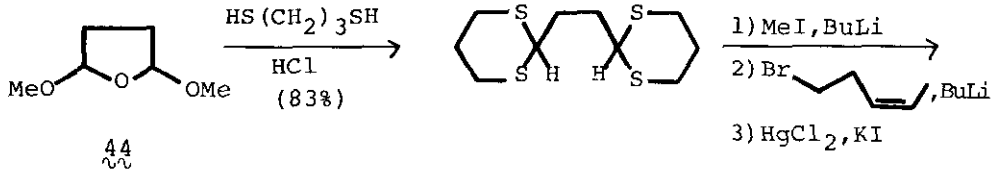
Chart 27



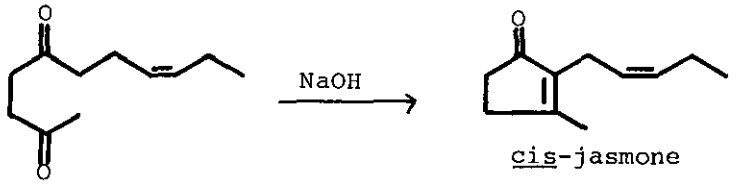
43

2,3,4,5-Tetrahydro-2,5-dimethoxyfuran (44), obtained by electroxidation 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



44



cis-jasmone

3

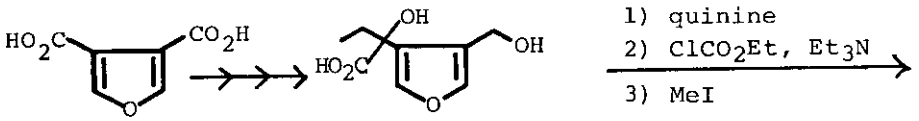
1.3 Syntheses by an Oxidative Ring Opening of Furans

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.

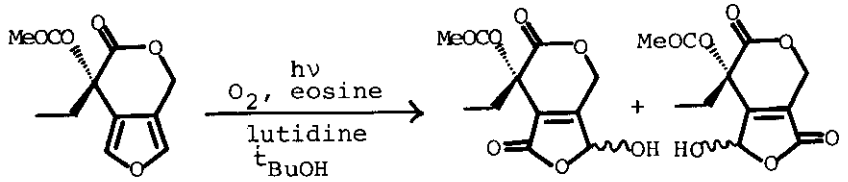
Corey and associates[44] achieved a total synthesis of camptothecin (16) by using the carbon skeleton of the bis-lactone 47, derived from the furan 46 of oxidation, to form ring D of the product. Thus, the furan-3-acetic acid derivative 45, obtained from furan-3,4-dicarboxylic acid, was converted into 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



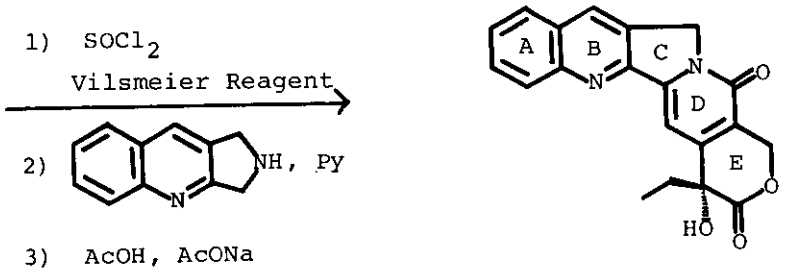
45



46

1 : 2.5

47

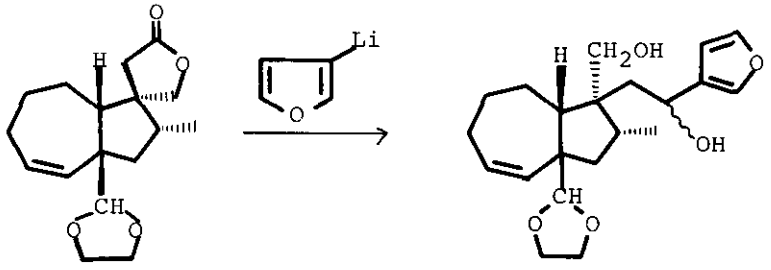


camptothecin

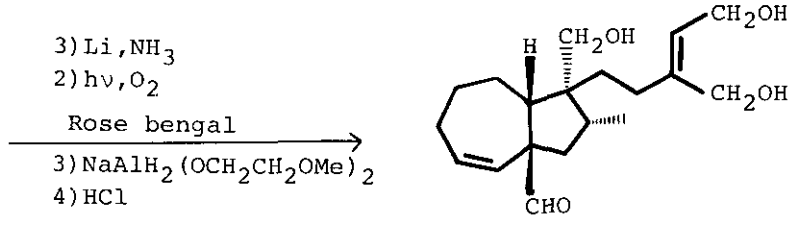
16

Oxidation of furans has been utilized to form the butenolide antheridiol[45]. Tokoroyama and coworkers[46] 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



48

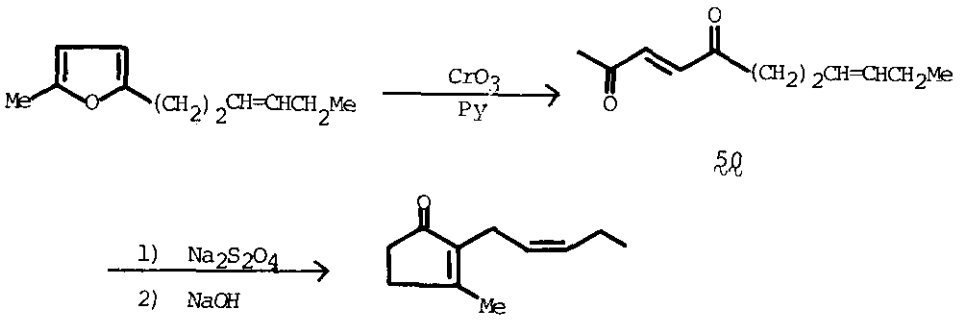


portulal

49

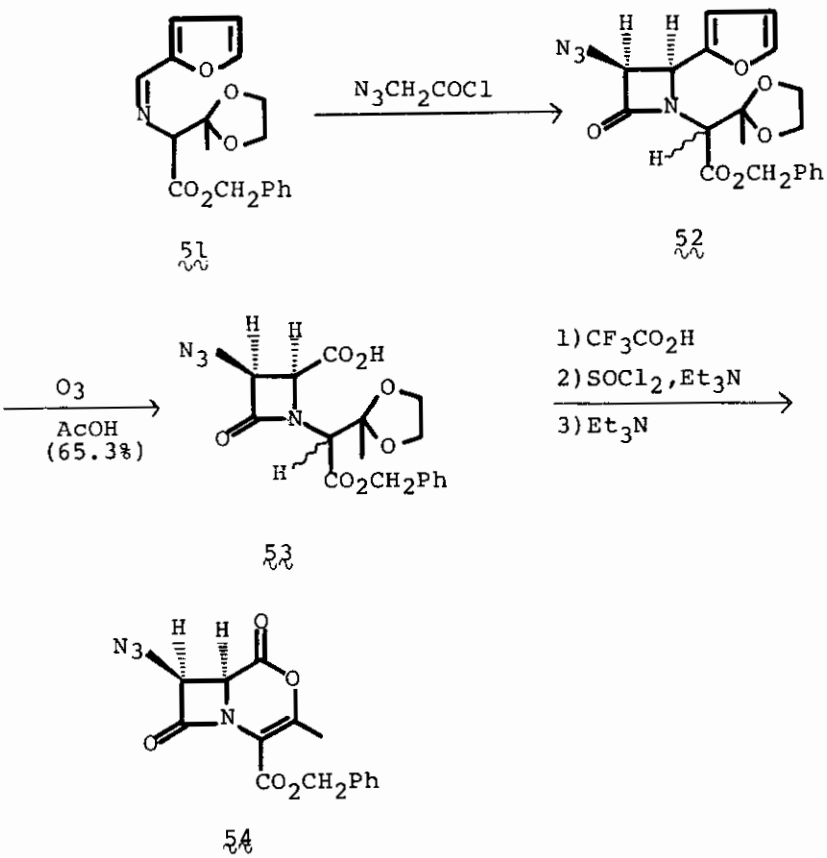
Birch and associates[13] reported a simple synhtesis of cis-jasmone (3) by oxidaiton of 2-methyl-5-heptenylfuran with Collins reagent followed by reduction and aldol condensation of the resulting diketone 50.

Chart 31



In a synthsis of the 1-oxo-Δ^3-isocephem 54 by Doyle and colleagues [47], only one carbon atom from the furan ring was incorported 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.

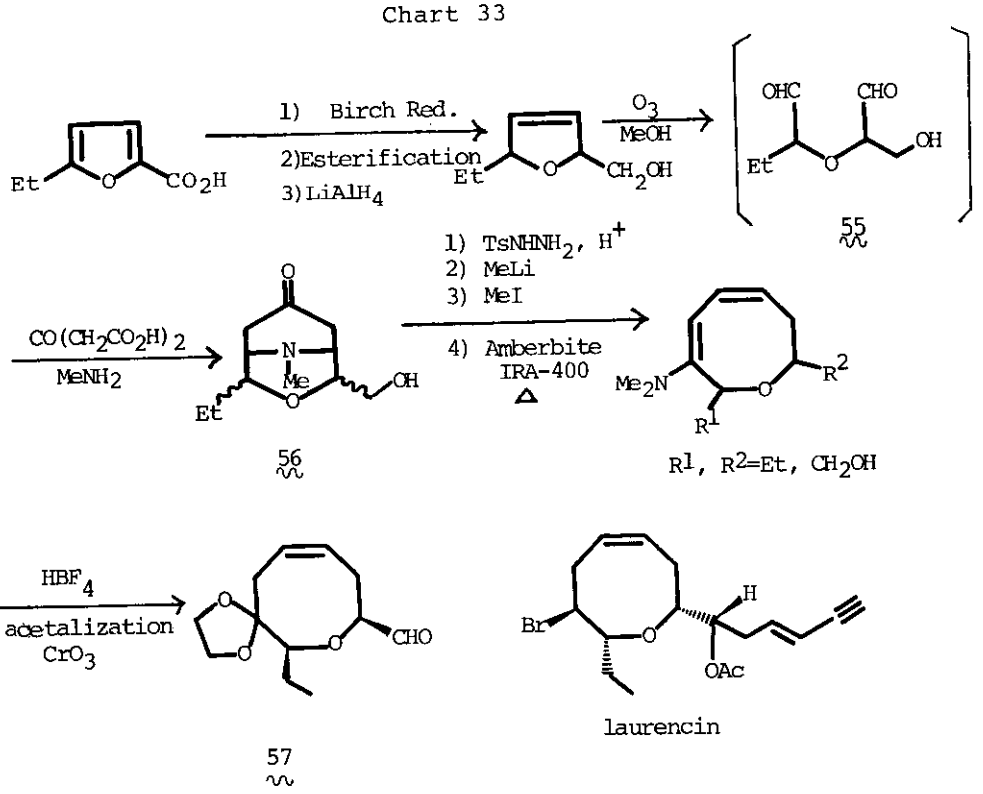
Chart 32



Another interesting example of the synthesis using dialdehydes generated by an oxidative cleavage of the C_3-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-

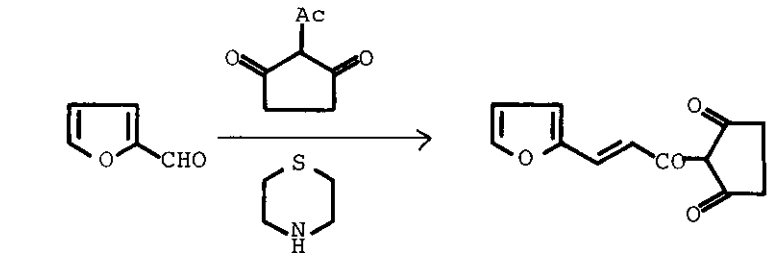
dihydrofurfuryl alcohol which on ozonolysis in methanol provided the dialdehyde 55. Robinson-Schöpf reaction of 55 with 3-keto-glutaric acid and methylamine produced the bicyclononanone 56 which was then converted into the laurencin-type 57.

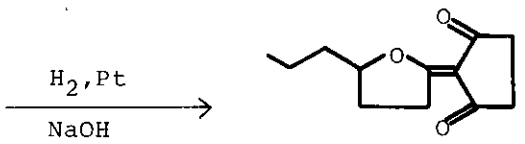
Chart 33



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





oudenone

58

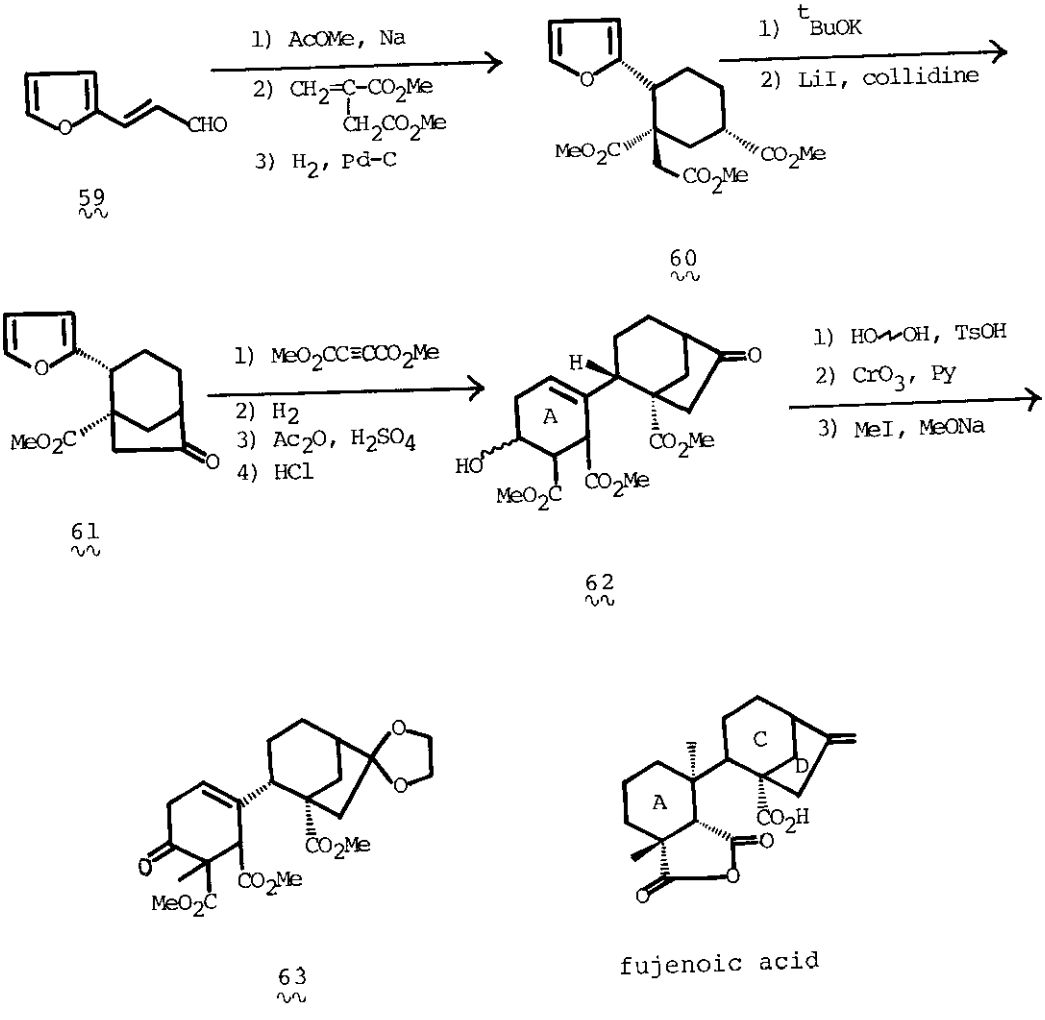
1.4 Syntheses by Cycloadditon of Furans

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-furylacylylaldehyde

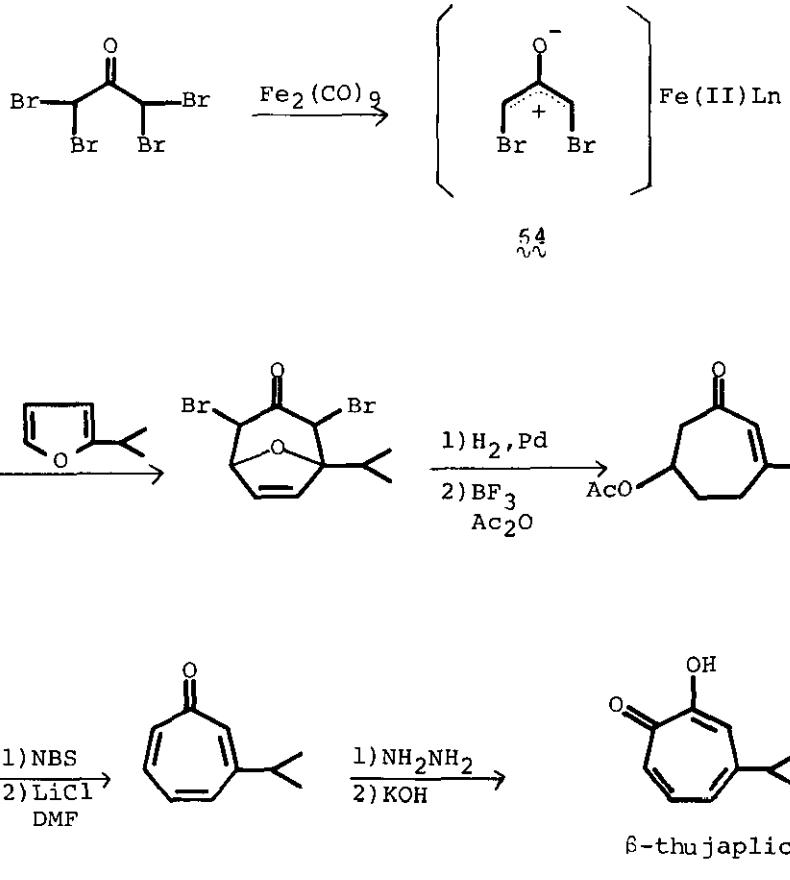
Chart 35



59, was subjected to a Dieckmann condensation to give the 2α-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



54

β-thujaplicin 65

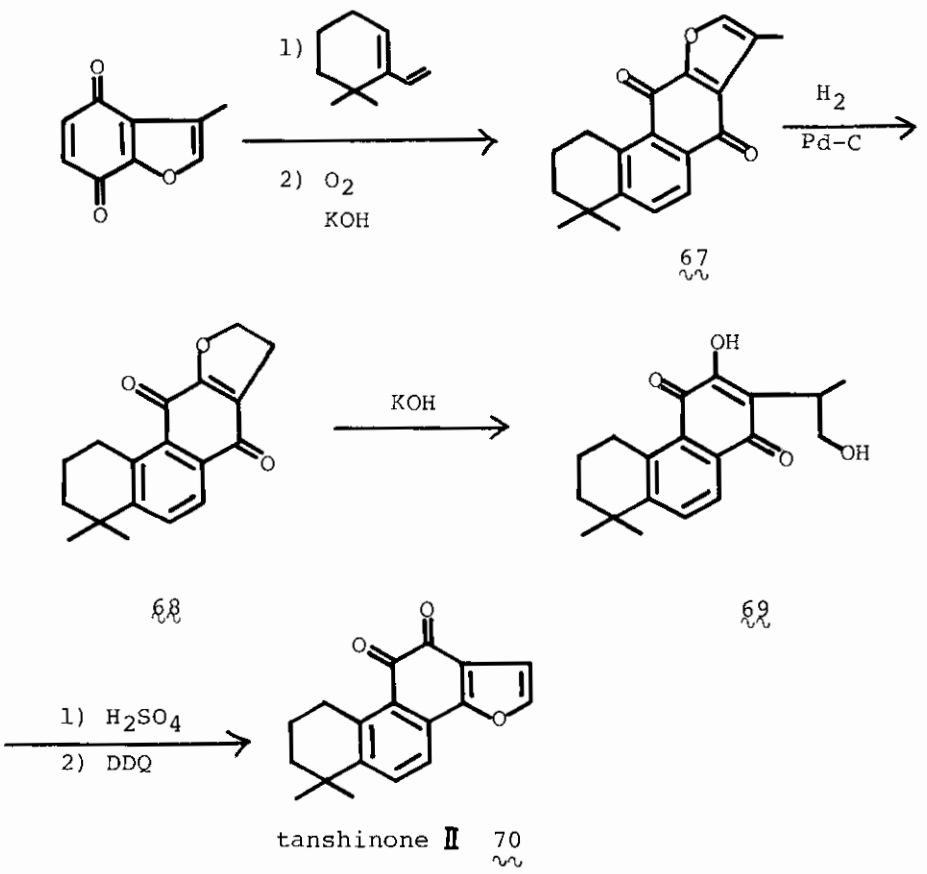
due to the 2π electron system which promotes cycloaddition with dienes. Noyori synthesised the seven-membered compounds by (3π + 4π) cycloaddition where the furan and oxyallyl species were the four and three-carbon sources, respectively, and the products were converted into β-thujaplicin (65)[52], α-thujaplicine[52] and nezukone[53] 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



67

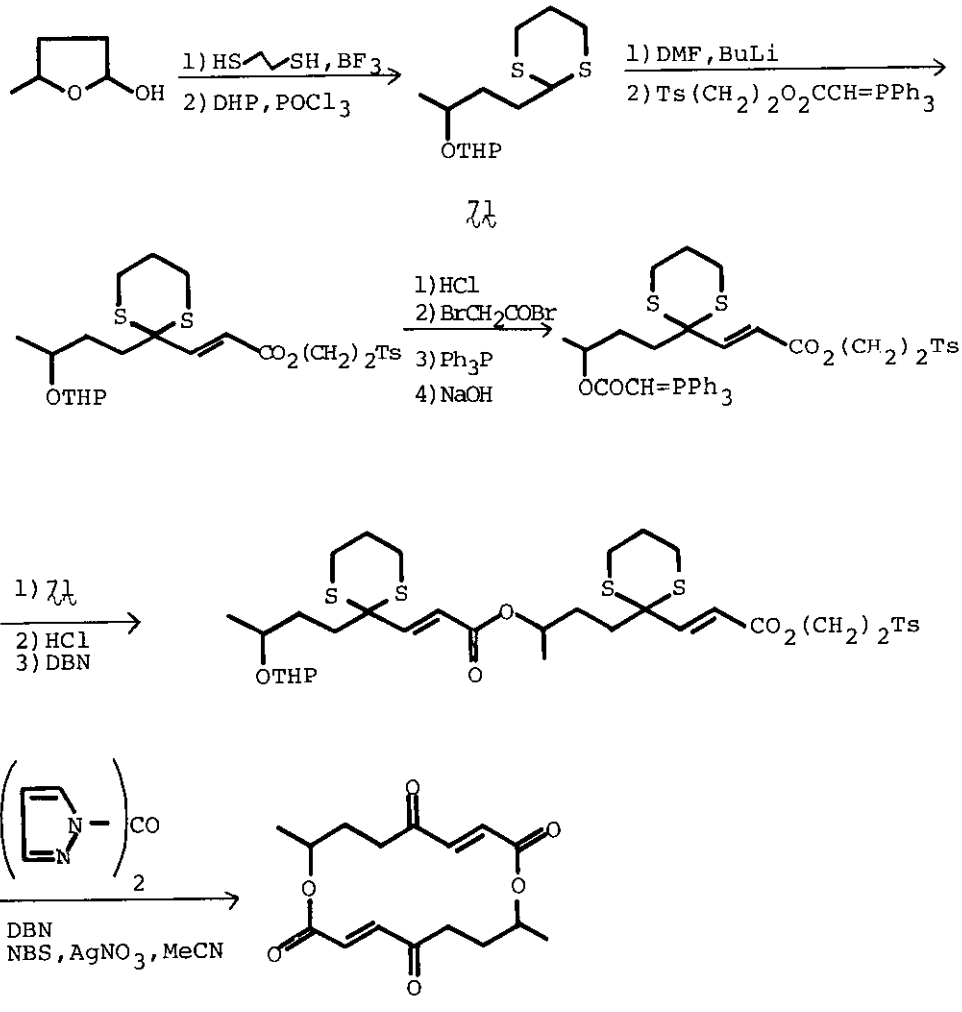
68

69

tanshinone Ⅱ 70

γ-Lactols, which are chemically equivalent to γ-ketoalcohols, are starting materials for pyrenophyrin (72)[55] and the polyacetate in Anthemidal.[56] For example, Raphael and coworkers[55] 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.

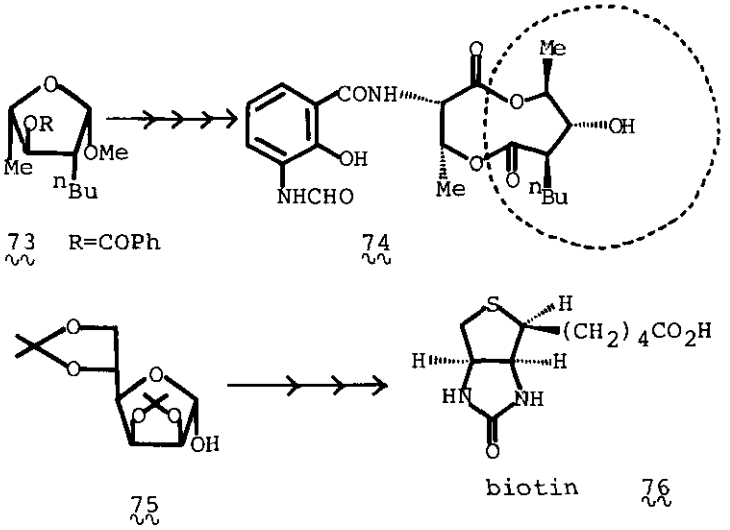
Chart 38



pyrenophorin 72

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



73 R=COPh

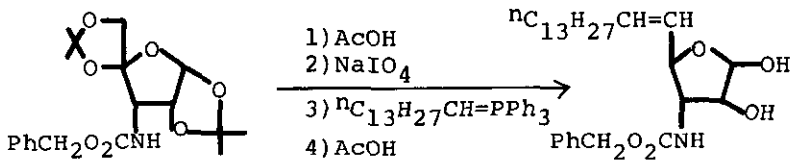
74

75

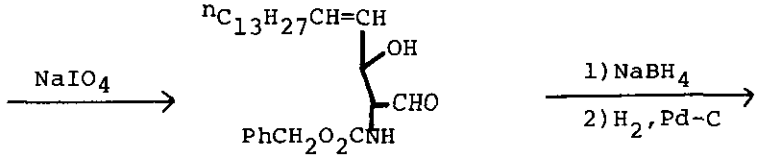
biotin 76

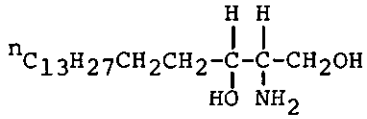
The 2,3-dihydroxytetrahydrofuran derivative 78 obtained from the allofuranose 77 in four steps, was easily converted into the β-hydroxyaldehyde via an elimination of one-carbon by the Criegee reaction followed by successive reductions to give D-dihydro-sphingosine (79).[59]

Chart 40



77 78

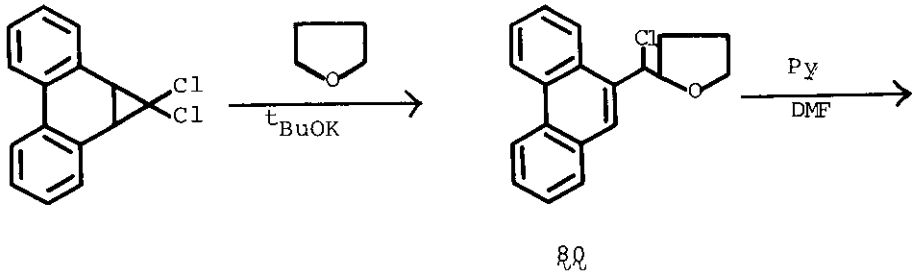




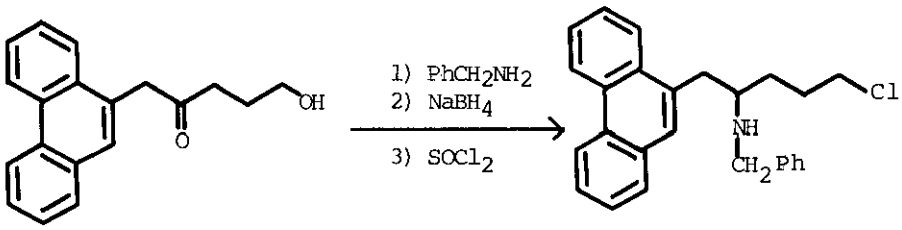
79

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 associates[60] 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

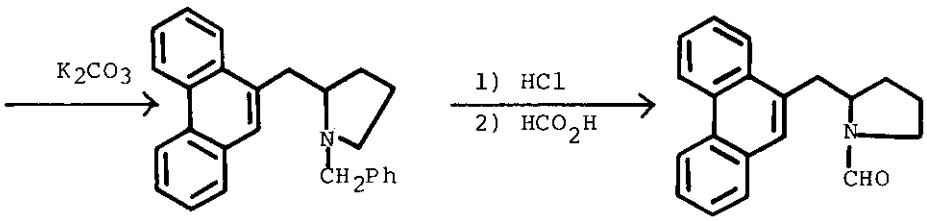
Chart 41



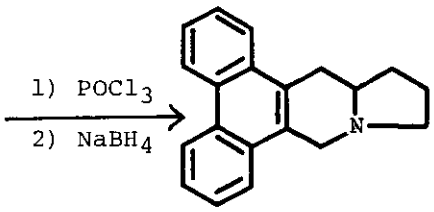
80



81



82

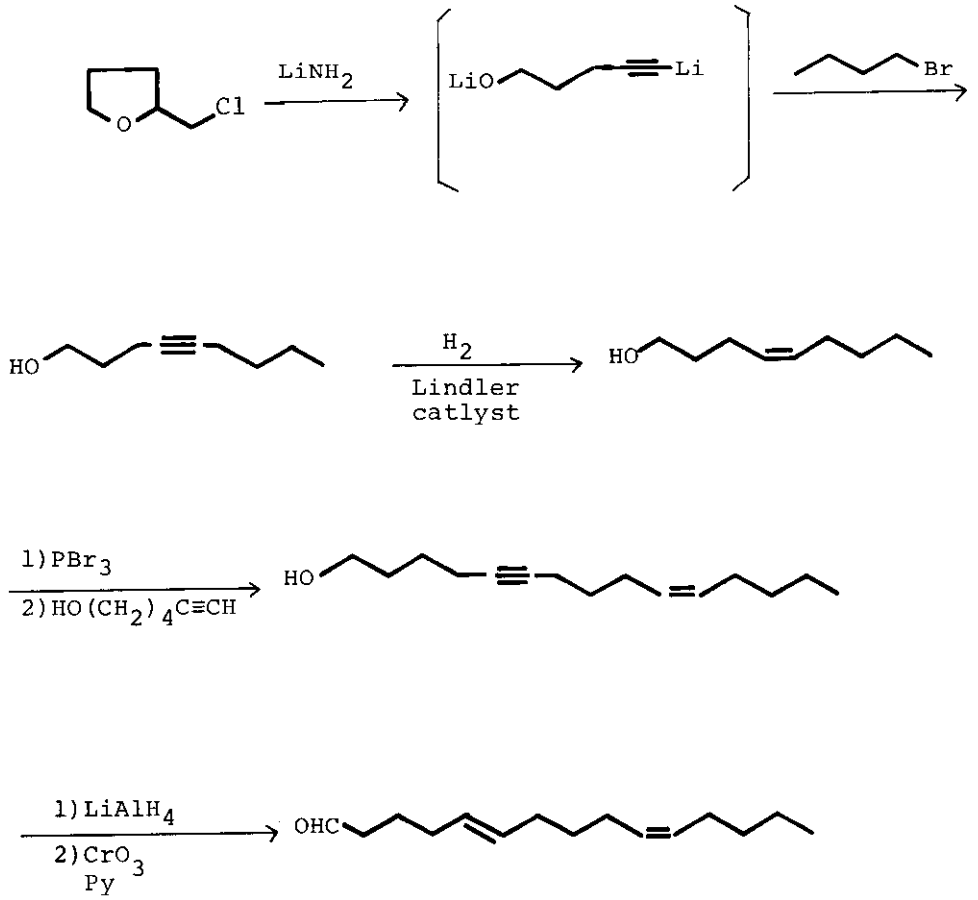


83

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

Ohloff and coworkers[61] 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



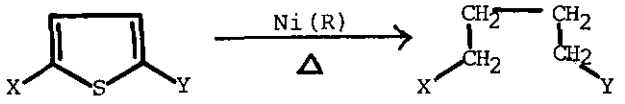
84

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

III Syntheses Using Thiophenes

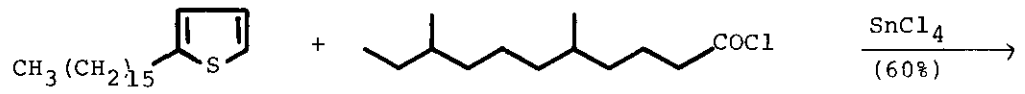
Reductive desulphurisation of thiophenes produces in good yield a four-carbon unit (Chart 43) and has been widely used as a method

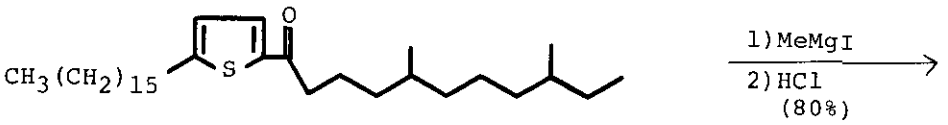
Chart 43

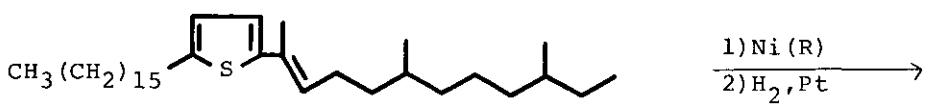


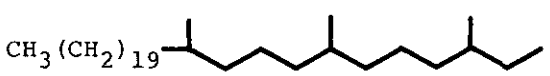
to extend the chain of a hydrocarbon. Usually, the reaction has been carried out by condensation of substrates with a thiophene derivative followed by desulphurisation on Raney nickel.[6,62] Syntheses of natural products by this method has been applied to compounds having a long aliphatic side chain Martin and MacConnell[63] utilized the thiophene ring to construct as shown in Chart 44 3,7,11-trimethylhentriacontane (85), a major component of Atta columbica.

Chart 44


CH3(CH2)15
S
+
COCl
SnCl4
(60%)


O
CH3(CH2)15
S
1)MeMgI
2)HCl
(80%)

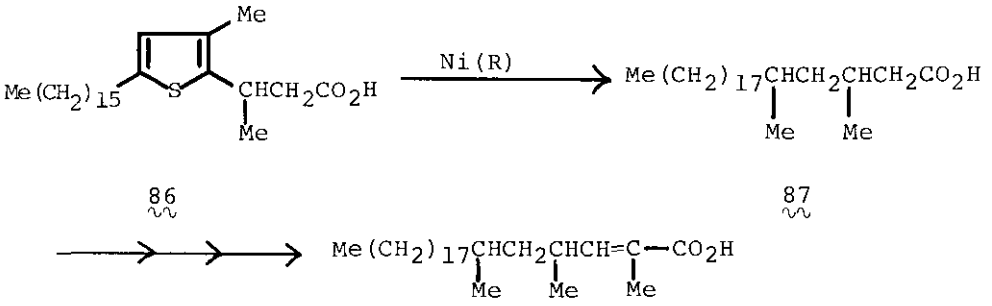

CH3(CH2)15
S
1)Ni(R)
2)H2,Pt


CH3(CH2)19

85

Natural quinone analogues have been obtained by the desulphurisation of the condensation product of 2,3-dichloro-1,4-naphthoquinone with thiophene.[64] Tilak and Malte[65] converted the 5-palomitylthienyl-2-propionic acid 86, derived from 3-methylthiophene in two steps, by desulphurisation with Raney nickel into the carboxylic acid 87 which was then transformed into mycolipenic acid (88).

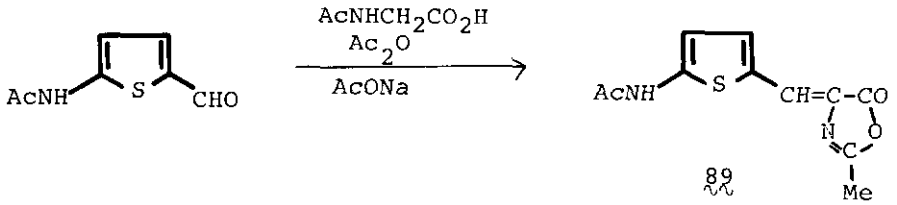
Chart 45



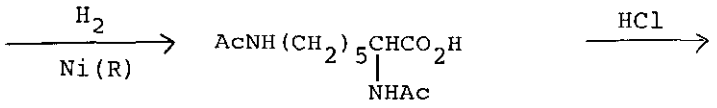
mycolipenic acid 88

Thienylglycines derived from 2-thenaldehydes by a Strecker reaction afforded on desulphurisation many kinds of α-amino acids.[66] Moreover, the azlactone 89 obtained from 5-acetylamino-thenaldehyde, in the usual manner was converted into the α-amino acid by reductive desulphurisation on Raney nickel followed by transformation into homolysine (90).[67]

Chart 46



89



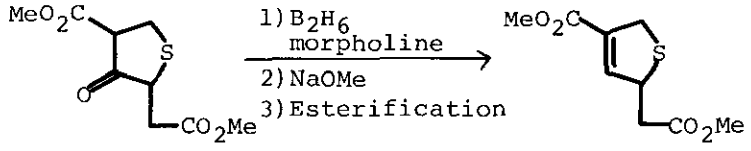
$H_2N(CH_2)_5CHCO_2H$
NH_2

homolysine 90

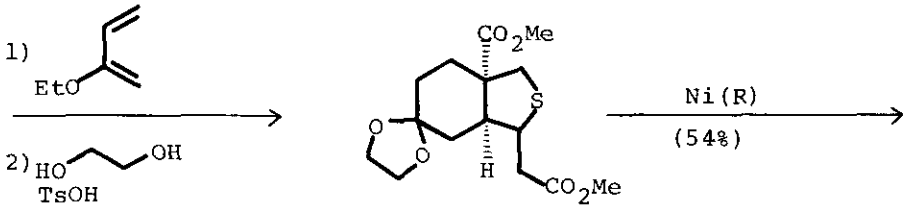
Similar to thiophenes, reductive desulphurisation of 2,5-dihydrothiophenes gives rise to a four-carbon unit. Based on this and the fact that 2,5-dihydrothiophenes behave as dienophiles, Stork and Stotter[68] obtained stereoselectively a potential intermediate to rings C and D for the synthesis of steroids. 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.

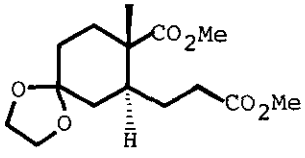
Chart 47



91 92



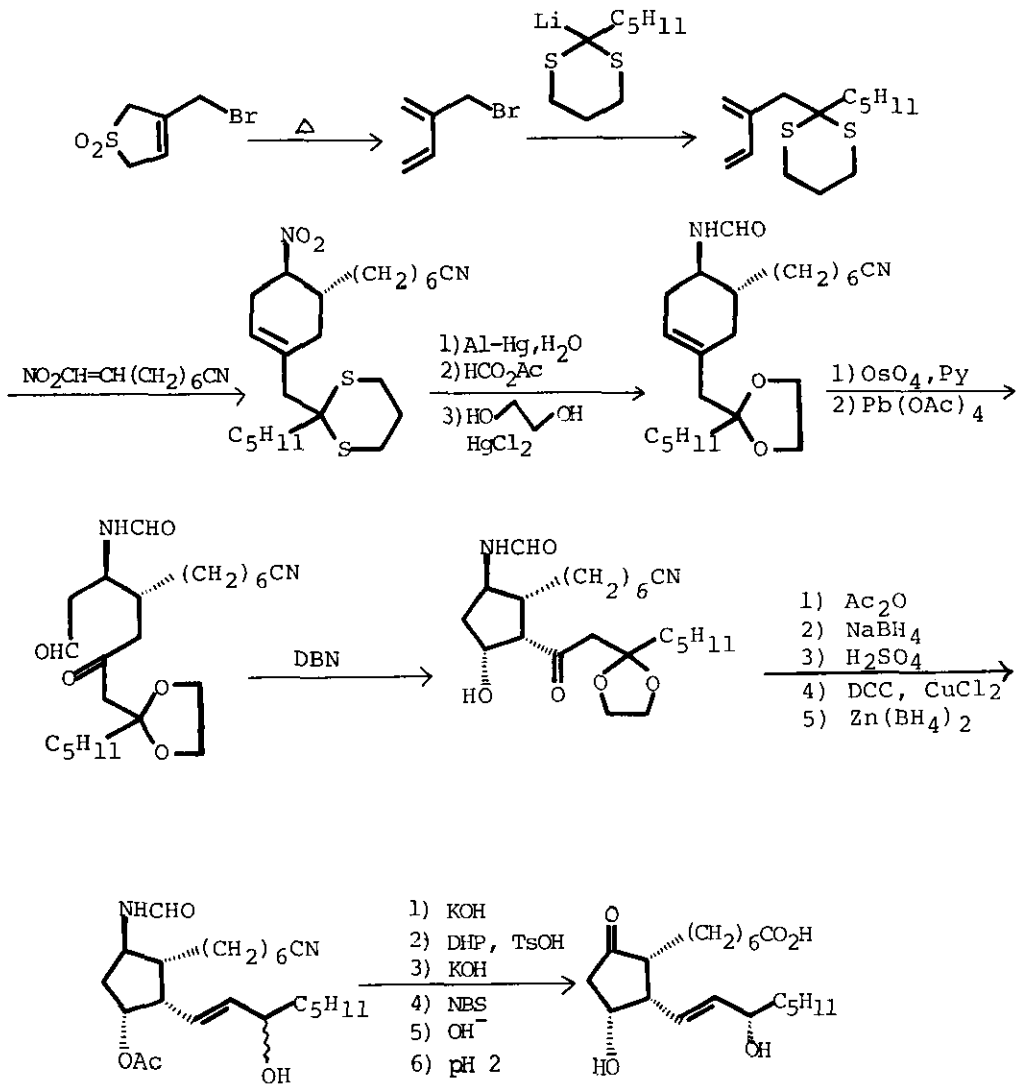
93



94

It is well known that heating sulfolenes forms butadienes by a disrotatory ring opening. For example, Corey and associates[70]

Chart 48



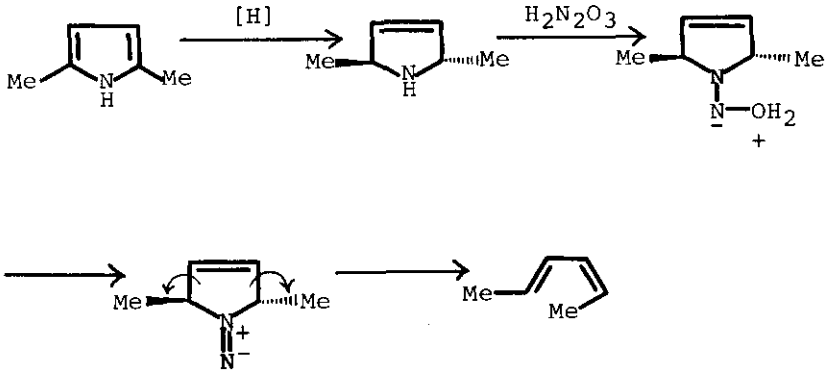
96

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

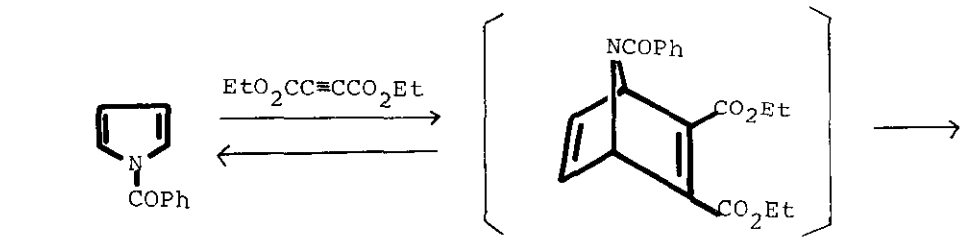
Generation of open chain compounds by direct elimination of the hetero atom in pyrroles is impossible. However, dienes are formed in high yield from 3-pyrrolines, obtained from pyrroles, by treatment with nitrohydroxylamine. Usually, 3-pyrrolines are synthesised by reduction with zinc in acidic medium or a Birch type reaction followed by ring opening, generally called a cheletropic reaction, which proceeds steroselectively in a disrotatory manner[71], as shown in Chart 49.

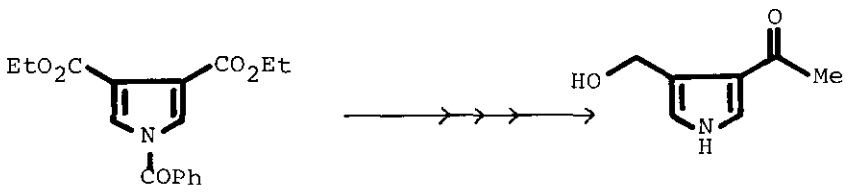
Chart 49



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

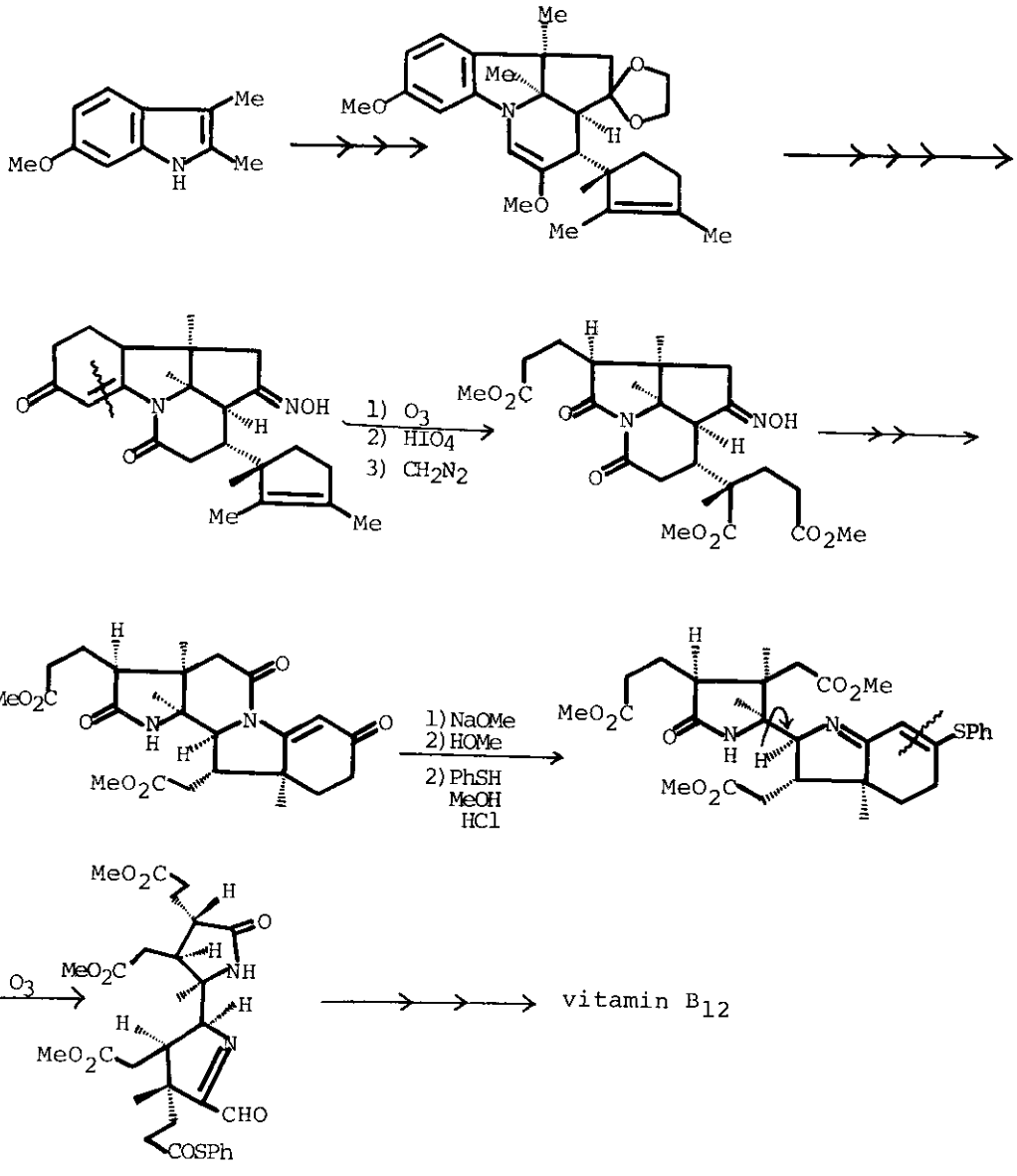




verrucarin E 77

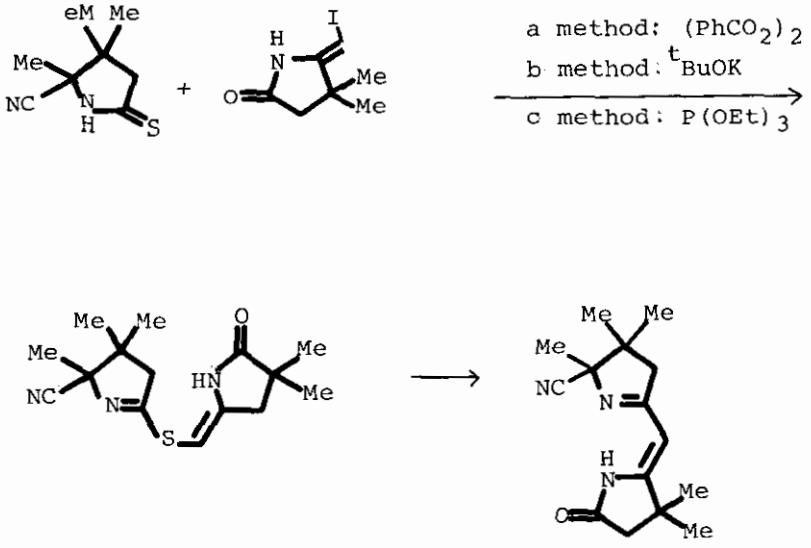
Woodward[74] reported the total synthesis of Vitamin B_{12} from 2,3-dimethyl-6-methoxyindole in which the benzene ring in the indole derivative was cleaved with ozone after Birch reduction of 98.

Chart 51


Me
MeO
N
H
Me
Me
MeO
Me
Me
O
O
H
MeO
Me
Me
NOH
H
O
N
O
Me
Me
1) O3
2) HIO4
3) CH2N2
MeO2C
H
NOH
CO2Me
MeO2C
MeO2C
H
O
N
H
H
MeO2C
1) NaOMe
2) HOMe
2) PhSH
MeOH
HCl
CO2Me
MeO2C
SPh
O3
MeO2C
H
O
MeO2C
NH
H
H
MeO2C
N
CHO
COSPh
vitamin B12

On the other hand, Eschenmoser and coworkers[75] used the pyrrolidone derivative in a synthesis of the corrin group of compounds as shown in Chart 52.

Chart 52

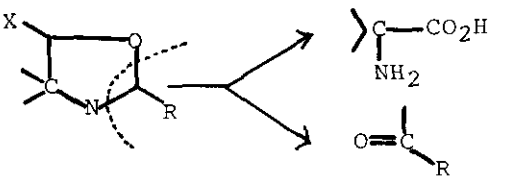


V Syntheses from Oxazoles[76]

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

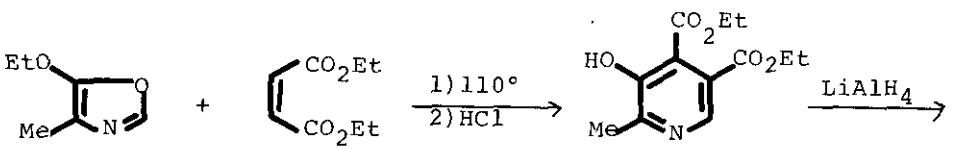
acid.[77] The latter reaction which utilizes the carbon at the 2 position in the oxazole ring as source for carbonyl or carboxyl functions was developed by Meyers.

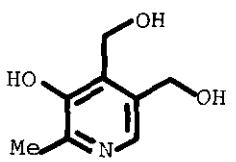
Chart 53



Total synthesis of natural products using all the atoms of the oxazole ring system is found in a simple synthesis of vitamin B_6 (42) via a Diels-Alder reaction of the appropriately substituted isoxazole with diethyl maleate.[78] Vitamin B_6 has also been prepared

Chart 54



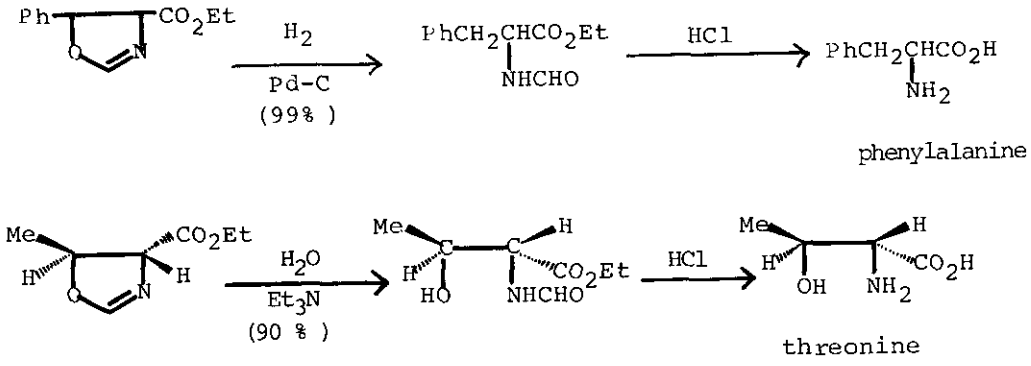


vitamin B_6 42

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 colleagues[79] who also examined the steric effect of dienophiles in the Diels-Alder reaction.

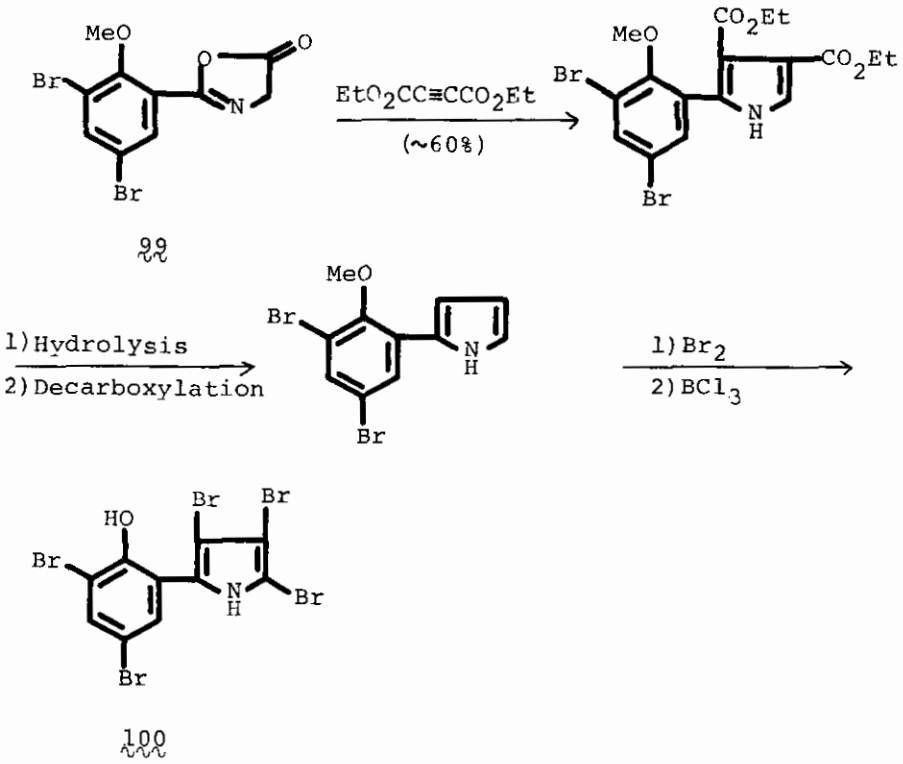
Schöllkopf and Hoppe[80] reported a synthesis of α-amino acids from oxazolines by hydrogenolysis of 5-phenyloxazoline-4-carboxylate and successive hydrolysis of the product to afforded phenylalanine. On the other hand, mild hydrolysis of 5-methyloxazoline-4-carboxylate in the presence of a catalytic 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 C_2-N-C_3 portion of oxazoline into the intermediate (100).[82]

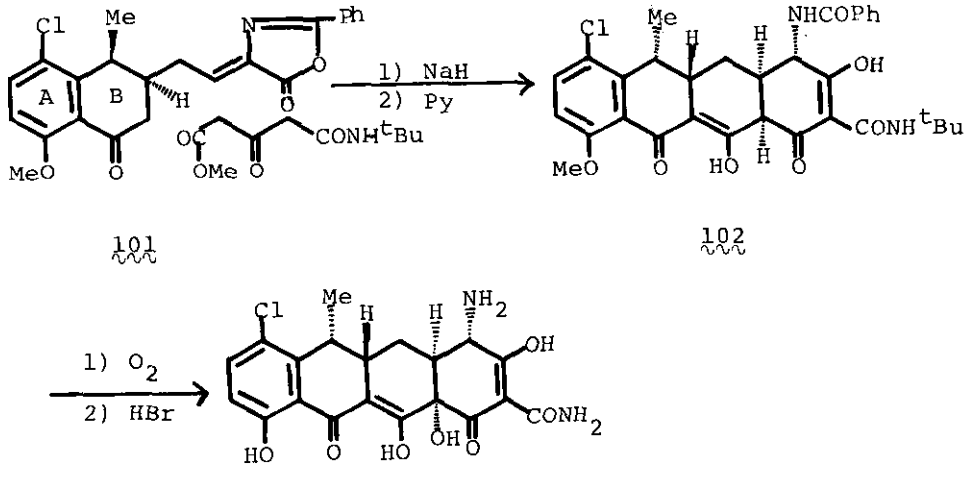
Chart 56



The C_4-C_5 unit in oxazolones has been utilized in forming the ring D in tetracycline. Martin and coworkers[83] treated the ring

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

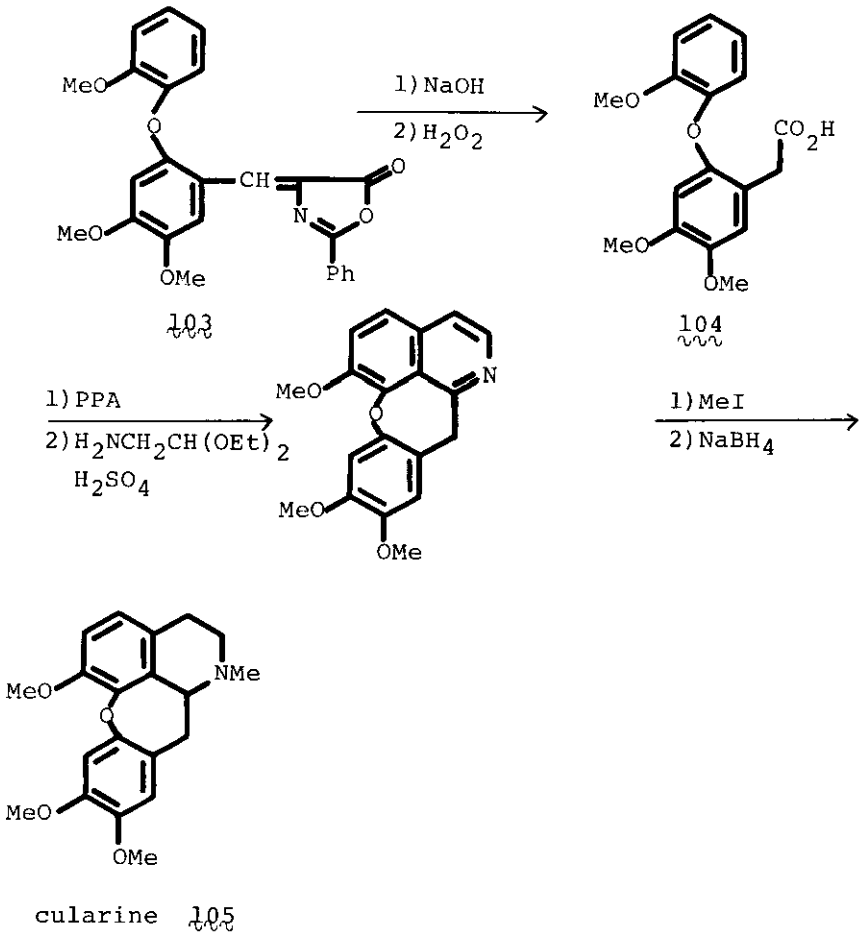
Chart 57



101 102

It is well known that oxazolones are useful precursors for α-amino acids[5,77]. Recently, Battersby and associates reported a stereospecific synthesis of C_3-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

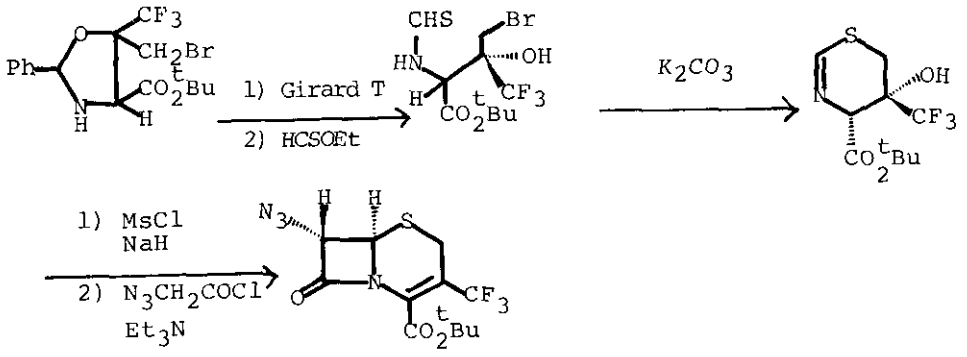


103 104

cularine 105

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



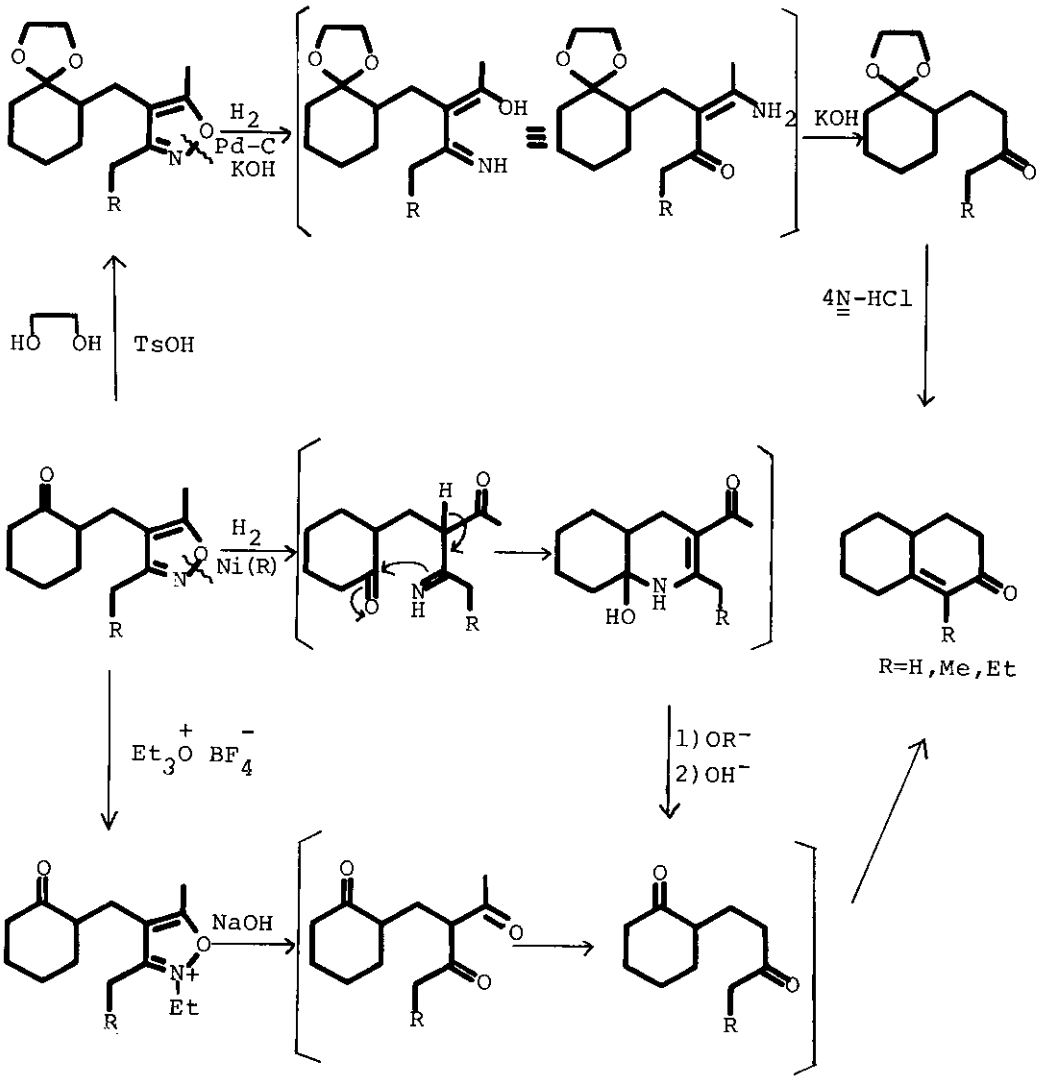
VI Syntheses from Isoxazoles

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 cleavege between the 1 and 2 positions.

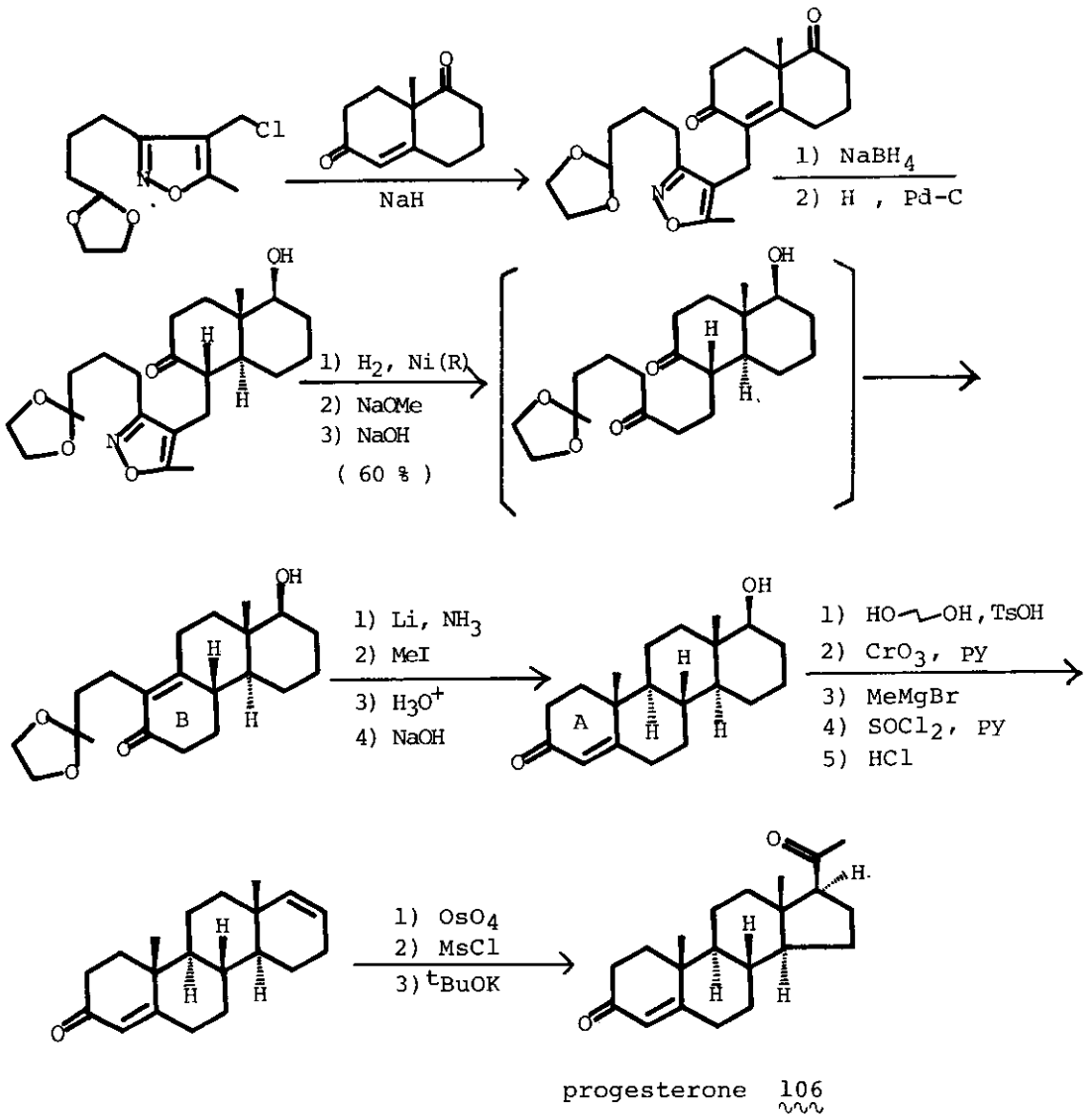
3-Methylisoxazoles with a halogenomethyl group at the 4-position condense easily with cyclohexanones followed by selective hydrogenolytic cleavage of the N-O bond and successive treatment with alcoholate and alkaline hydroxide to give 2-octalones[89,90]. Some modifications of this reaction have been reported. For example, 2-octalones are obtained by an alkaline treatment of the quaternary salts derived from the condensation product and triethyloxonium fluoroborate[88]. Moreover, hydrogenolyiss 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 reaction[21] has been developed by Stork, and the four-carbon unit consisting C_3, C_3-methyl, C_4 and C_4-methylene is utilized in this reaction.[87,90] Since 2-octalones

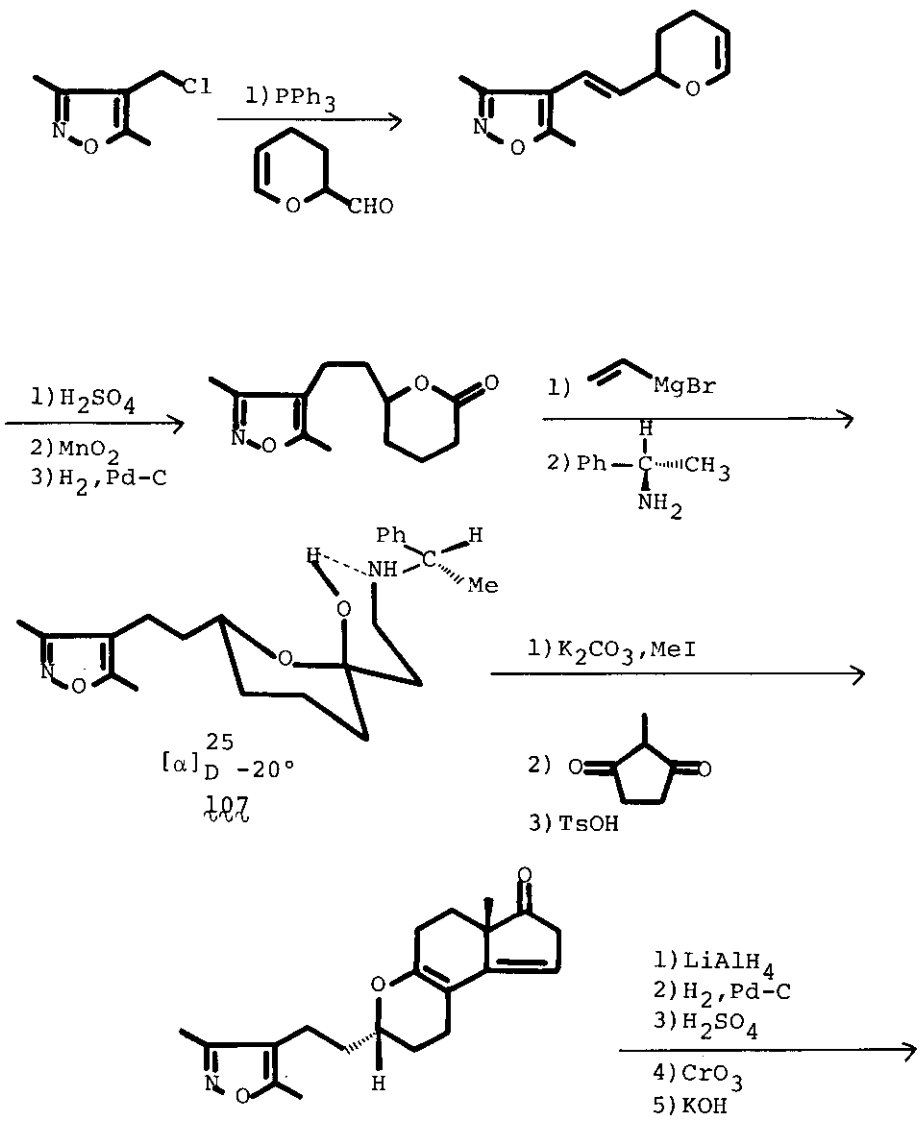


progesterone 106

are obtained in good yield by an annelation reaction between 3-alkyl-4-chloromethylisoxazoles and cyclic ketones[91], 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 McMurry[92]. 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 C_3-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 aminoethyllactol 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

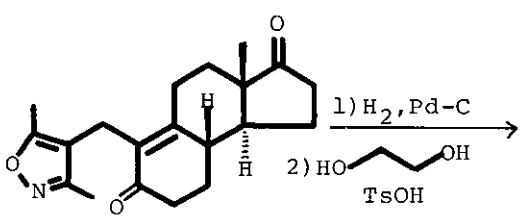
Chart 62



$[\alpha]_D^{25}$ -20°

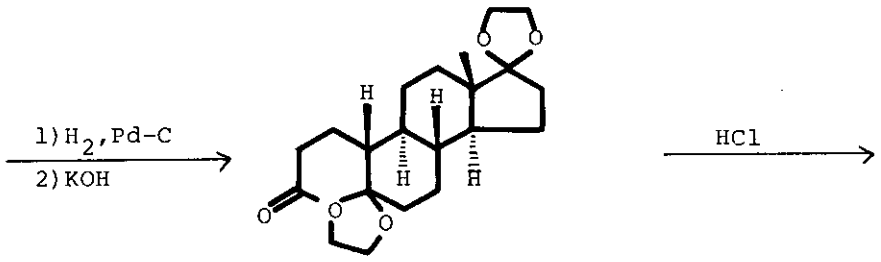
107

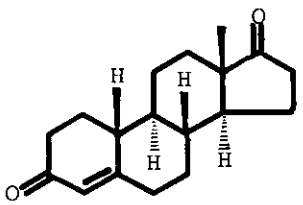
continued



$[\alpha]_D^{25}$ +98.32°

108





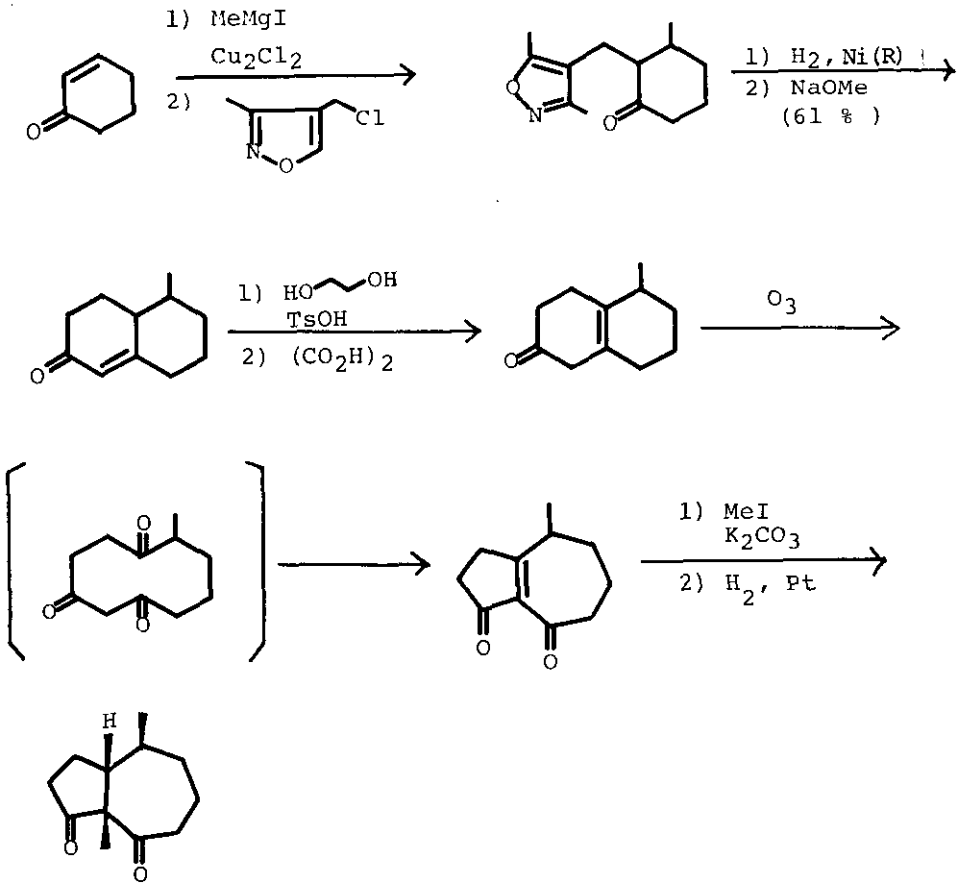
$[\alpha]_D^{25}$ +139.5°

109

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.

Annelation utilizing oxazoles has been applied to the synthesis

Chart 63

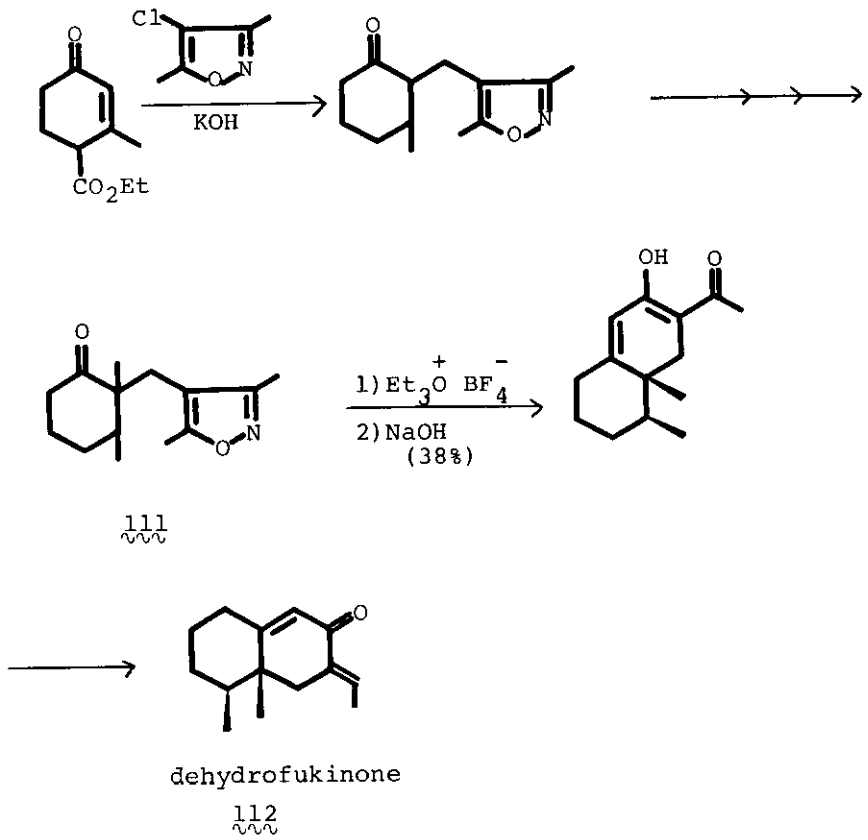


110

of terpenes. Kretchmer and Shafer[95] 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. Ohashi[96] employed oxazoles as a synthon for β-diketones in a synthesis of sesqui- and diterpenes. Thus,

Chart 64



111

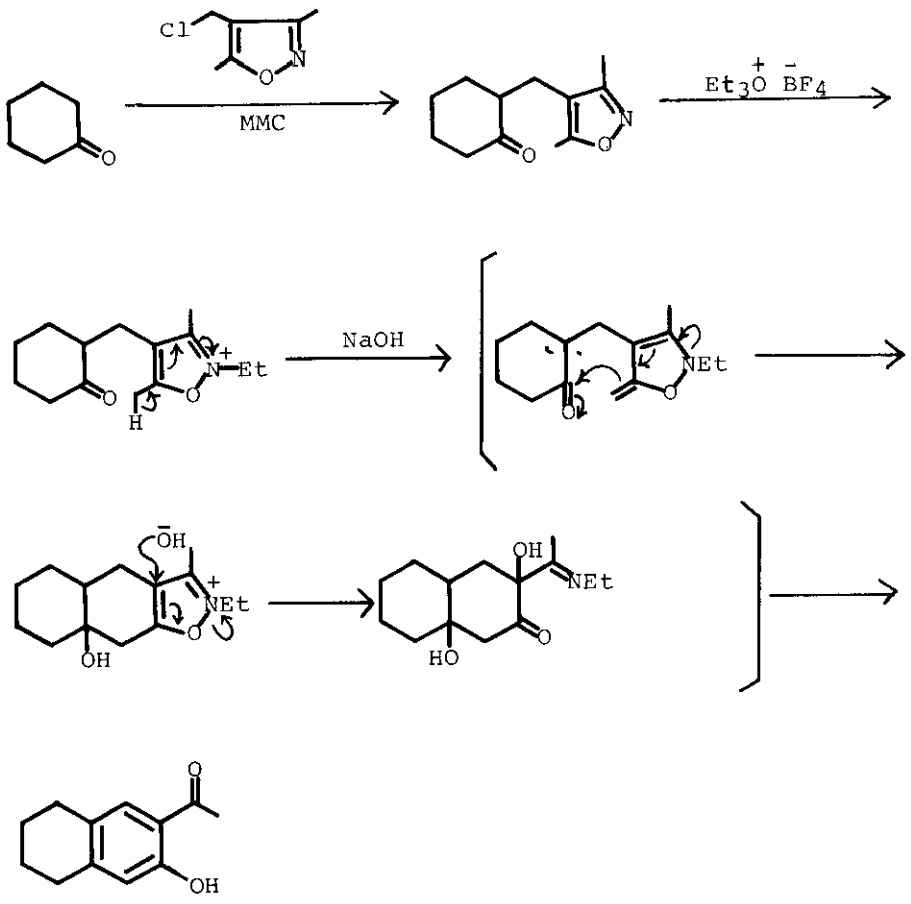
dehydrofukinone

112

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 contruction of the aromatic ring.[97] 4-Chloromethyl-3,5-dimethylisoxazole was

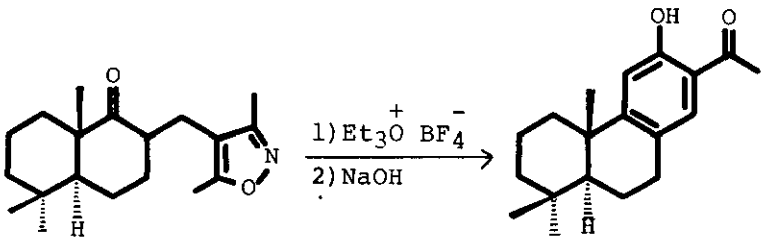
Chart 65

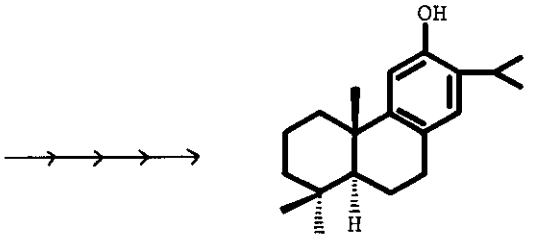


condensed with cyclohexanone and converted to the quaternary salt in the usual manner. Treatment with sodium hydroxide afforded the acylphenol in 40 - 50 % yield as shown in Chart 65.

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

Chart 66

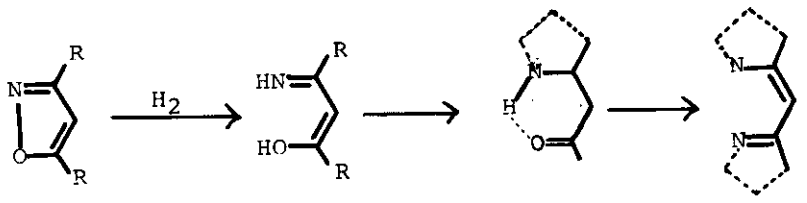




ferruginol 113

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

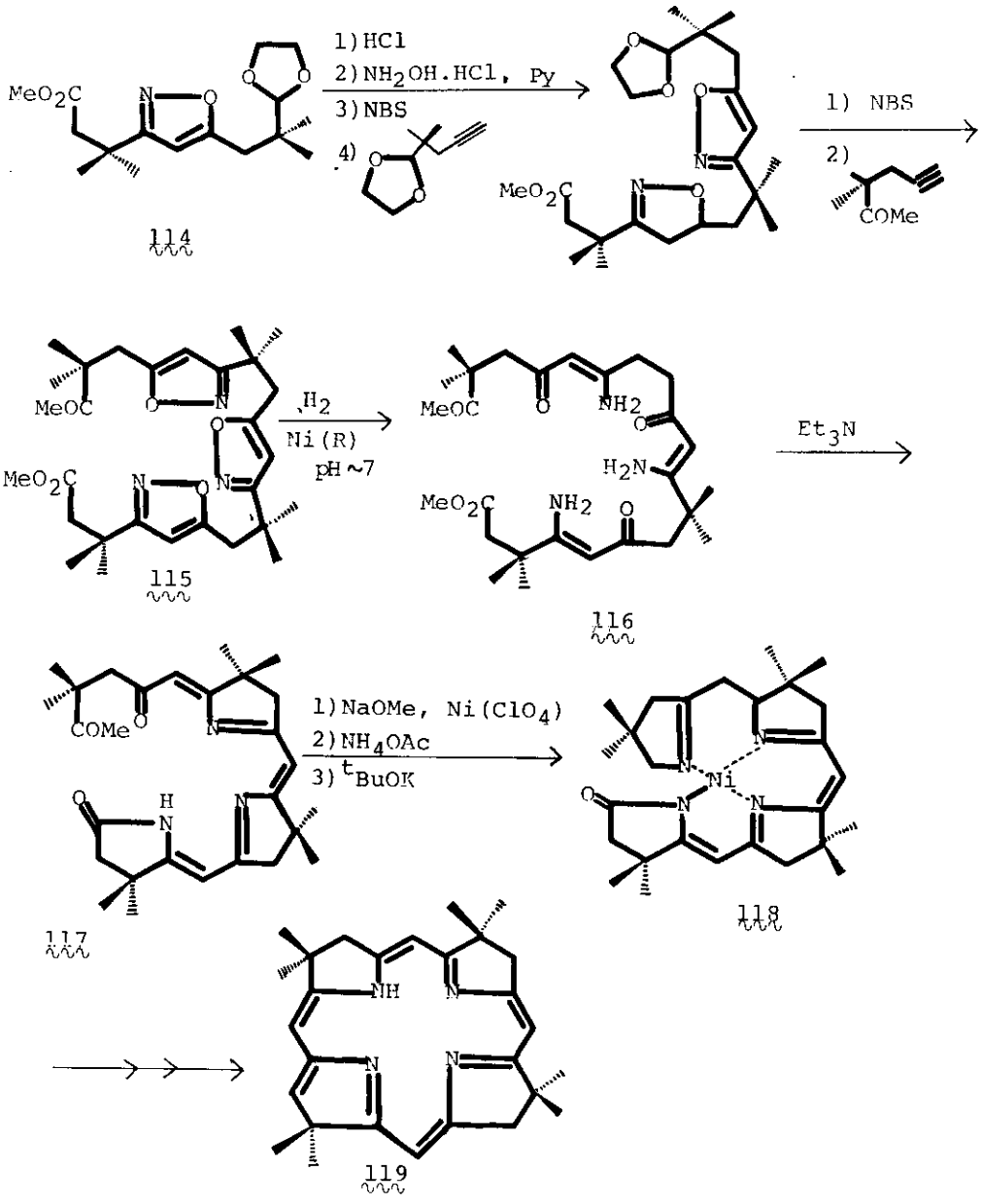
Chart 67



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 associates[101] achieved a synthesis of semicorrin from isoxazole derivatives via reductive ring opening and ammonolysis.

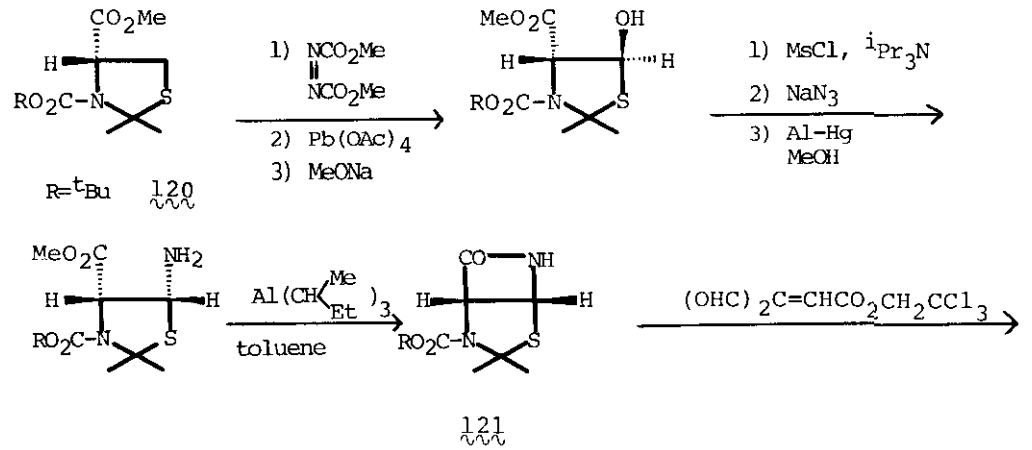
Chart 68

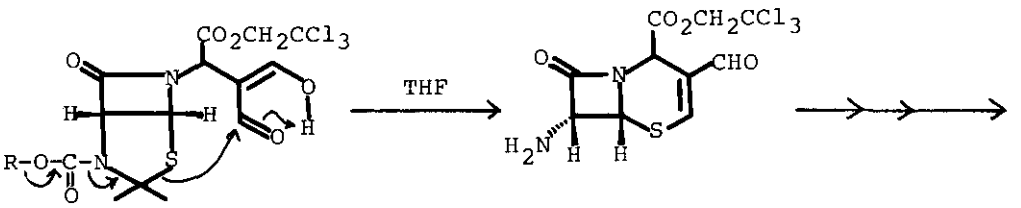

1) HCl
2) NH2OH.HCl, Py
3) NBS
4)
1) NBS
2)
COMe
MeO2C
MeOC
H2
Ni(R)
pH ~7
Et3N
NH2
H2N
1) NaOMe, Ni(ClO4)
2) NH4OAc
3) tBuOK
Ni
NH
114
115
116
117
118
119

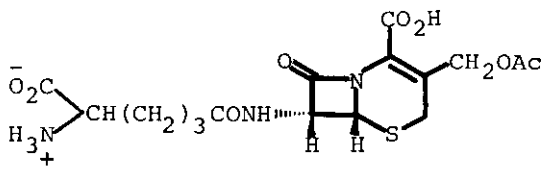
VII Syntheses from Thiazoles and Isothiazoles

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







cephalosporin C

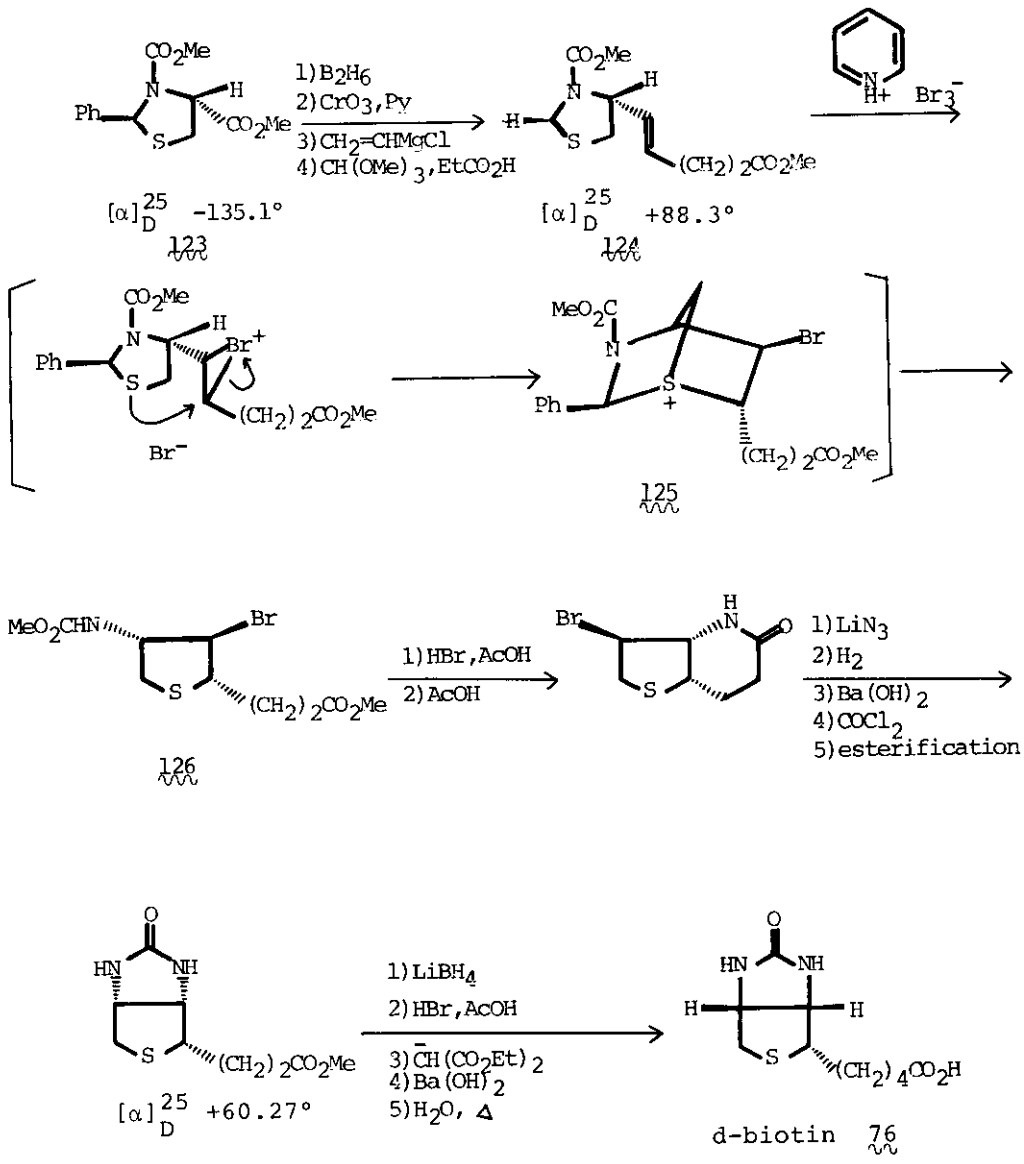
122

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

Woodward and coworkers[102] 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).

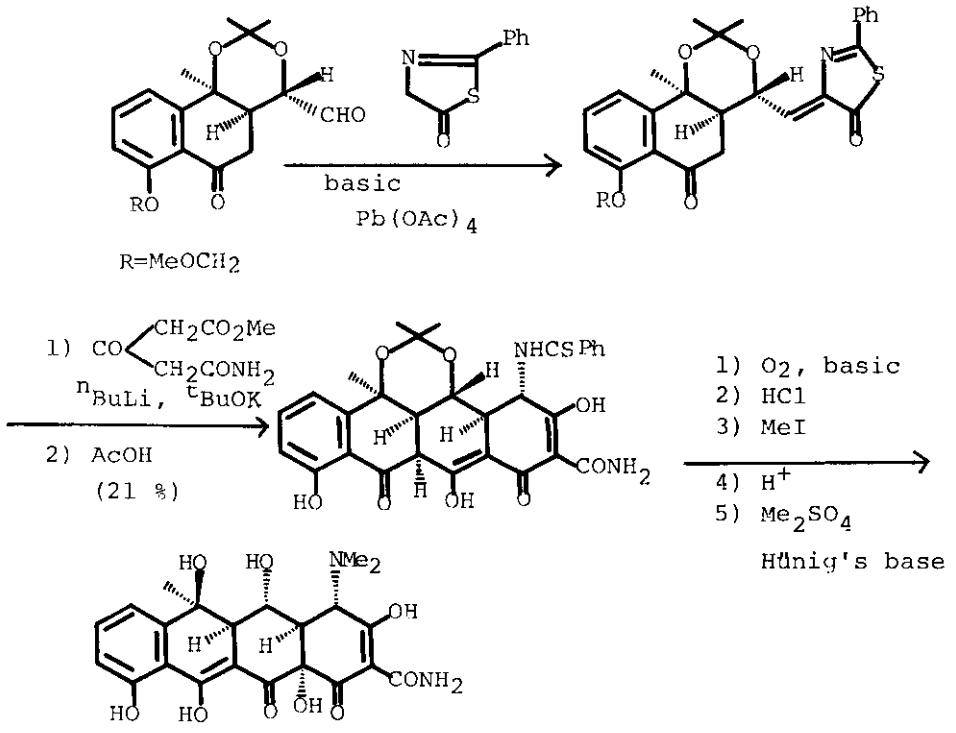
Moreover, many cephams and penams have been prepared by cleavage of the thiazoline ring followed by recyclisation due to the nucleophilicity of the sulphur thus formed.[103] Stereospecific synthesis of d-biotin (76) from L-(+)-cystein *via* the thiazoline-4-carboxylate 123 has been reported by Uskokovic 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.

Chart 70


CO2Me
Ph
CO2Me
1)B2H6
2)CrO3,Py
3)CH2=CHMgCl
4)CH(OMe)3,EtCO2H
(CH2)2CO2Me
Br3-
[α]D25 -135.1°
123
[α]D25 +88.3°
124
Br+
Br-
MeO2C
Br
125
MeO2CHN
1)HBr,AcOH
2)AcOH
126
1)LiN3
2)H2
3)Ba(OH)2
4)COCl2
5)esterification
HN
NH
1)LiBH4
2)HBr,AcOH
3)CH(CO2Et)2
4)Ba(OH)2
5)H2O, Δ
[α]D25 +60.27°
(CH2)4CO2H
d-biotin 76

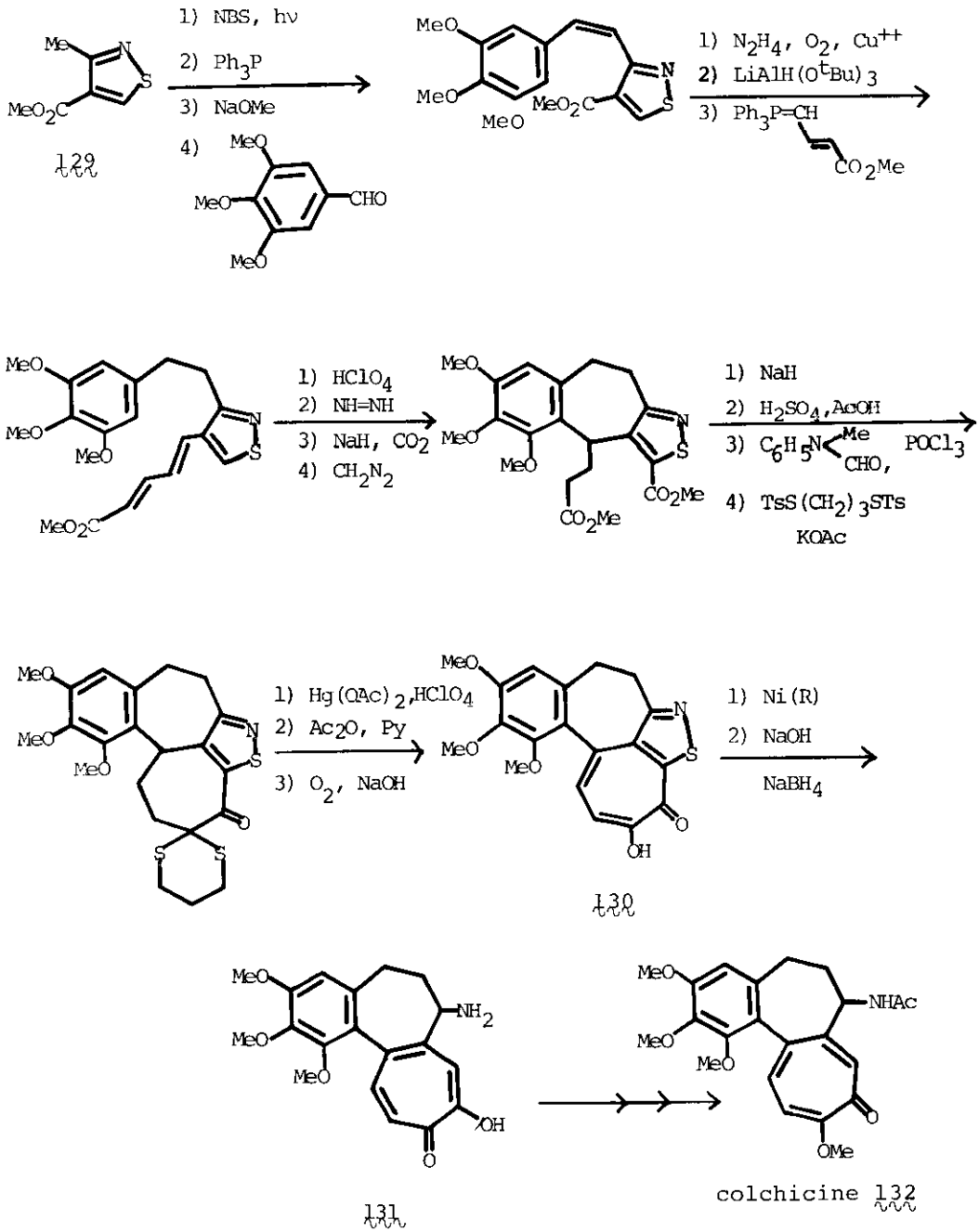
Muxfeldt and associates[105] achieved a total synthesis of terramycin (128) from a thiazolone derivative which was used to form ring D.

Chart 71



Isothiazole has been utilized by Woodward[106] in a total synthesis of colchicine (132). In this synthesis the nitrogen

Chart 72


1) NBS, hν
2) Ph3P
3) NaOMe
4)
MeO
MeO
MeO
CHO
129
MeO
MeO
MeO
MeO2C
1) N2H4, O2, Cu++
2) LiAlH(OtBu)3
3) Ph3P=CH
CO2Me
1) HClO4
2) NH=NH
3) NaH, CO2
4) CH2N2
1) NaH
2) H2SO4, AcOH
3) C6H5N(Me)CHO, POCl3
4) TsS(CH2)3STs
KOAc
CO2Me
1) Hg(OAc)2, HClO4
2) Ac2O, Py
3) O2, NaOH
1) Ni(R)
2) NaOH
NaBH4
OH
130
NH2
OH
131
NHAc
OMe
colchicine 132

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 descolchiceine (131) which had previously been converted into the target compound colchicine (132).

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