ANNELATION REACTION BY USING HETEROCYCLIC COMPOUNDS

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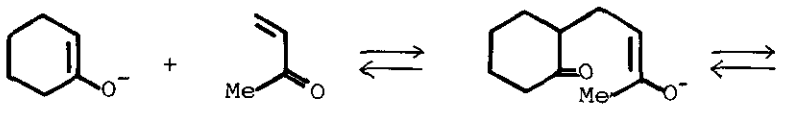
This review deals with the recent advances in the use of heterocyclic compounds as annelating reagents, especially as applied to the synthesis of natural products.

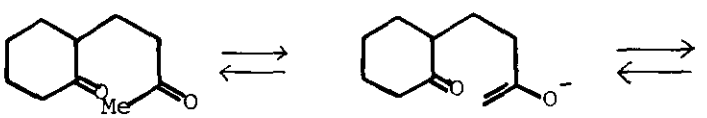
I. INTRODUCTION

Annelations related to the Robinson reaction[1,2] have been one of the most widely used synthetic methods in organic chemistry.[3-10] This reaction has proven to be invaluable to the organic chemist for the synthesis of such complex natural products as steroids, terpenes, and alkaloids. The original procedure involved a nucleophilic attack of a ketone or ketoester enolate, in a Michael reaction, on a vinyl ketone to produce the intermediate 1, which undergoes subsequent aldol-type ring closure to keto alcohol 2, followed by dehydration to the annelation product 3 (Scheme 1).

Although the process is very valuable, the Robinson annelation is unsuited for ordinary carbonyl substances since strongly basic enolates initiate polymerization of the vinyl ketone. A variety of modifications to overcome this restriction has been reporated

Scheme 1





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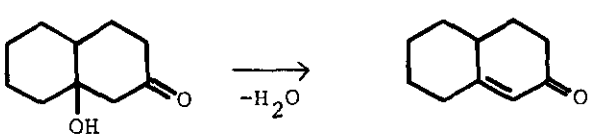


2 3

and includes the use of Mannich base and methiodide[11], β-halo ketone[12-15], enamine[16], α-silyl enone[17], and α-methylene cyclanone[18]. Another kind of modifications is the use of alkyl halides[19-23] (and sulfonates) and allylic[24-32] (or benzylic) halides. These reagents have potential since they may be able to trap regiospecifically enolate ions generated under aprotic, nonequilibrating conditions.

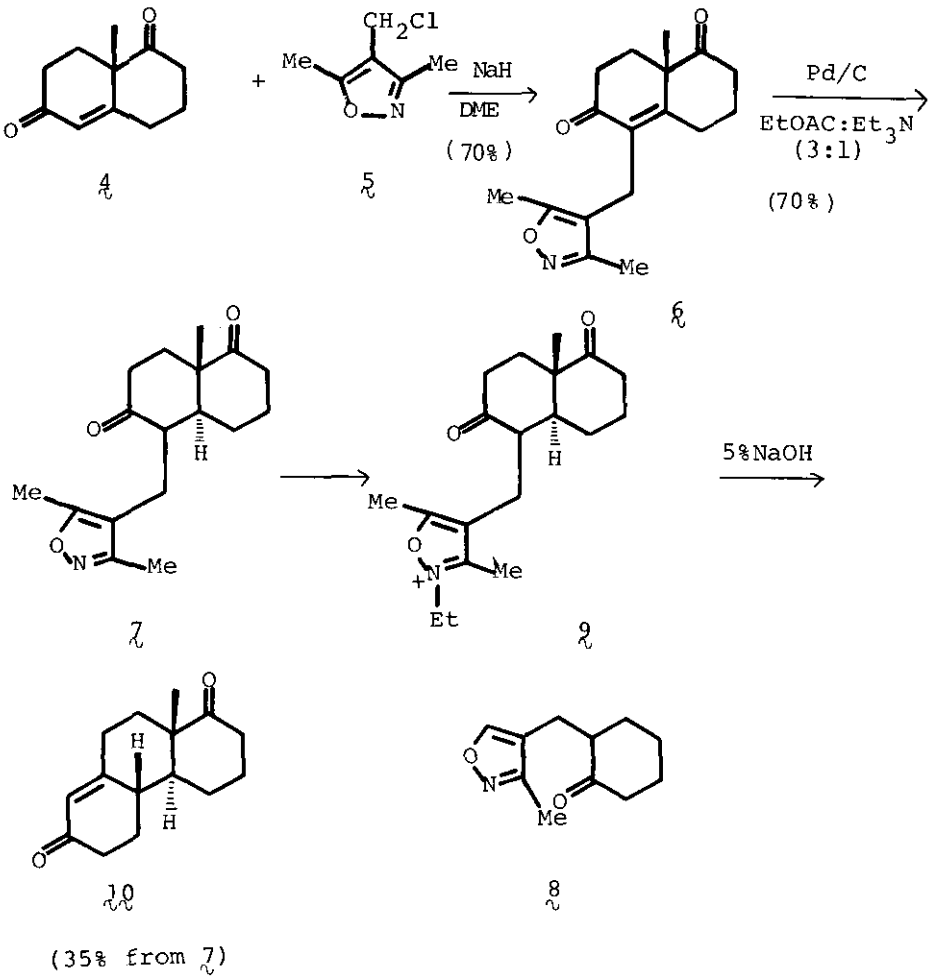
In this reviews we wish to summarize annelation reactions by means of heterocyclic compounds as annelating reagents and discuss their application to the synthesis of natural products.

II. THE ISOXAZOLE ANNELATION

The isoxazole annelation which uses 4-halomethylisoxazole derivatives as the reagent are at first introduced by Stork and coworkers[33]. They alkylated the sodium enolate of 10-methyl-$\Delta^{1,9}$-octalin-2,5-dione (4) with 4-chloromethyl-3,4-dimethylisoxazole (5) to give 6 in 70 % yield. Selective hydrogenation of 6 where the oxazole ring survived was carried out with palladium-charcoal by using ethyl acetate-triethylamine (3 : 1) to afford the compound 7 in 70 % yield. The rate of hydrogenolysis of the isoxazole ring was shown to be pH dependent since compound 8 was completely hydrogenolyzed with palladium-charcoal for 3 hr in ethyl acetate-triethylamine (1 : 1) but unaffected in ethyl acetate-acetic acid (5 : 1) for 20 hr. Based on this observation, quaternization of 7 with triethyloxonium fluoroborate followed by treatment with 5 % sodium hydroxide, gave via 9 the cyclized compound 10 in about 35 % yield. In more satisfactory transformation of the isoxazole

ring, compounds 11 and 12 were reduced with palladium-charcoal in ethyl acetate-triethylamine (1 : 1) to give the carbinolamides 13 and 14, respectively, followed by treatment with 10 % potassium hydroxide to afford an equilibrium mixture of $\Delta^{1,9}$-and $\Delta^{9,10}$-2-octalone 15 in high yield (Scheme 2a and 2b.)

Scheme 2a



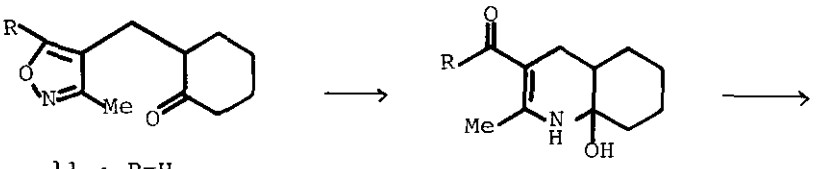
4 5 6

7 9

10 8

(35% from 7)

Scheme 2b

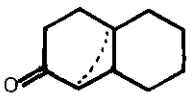


11 : R=H

12 : R=Me

13 : R=H

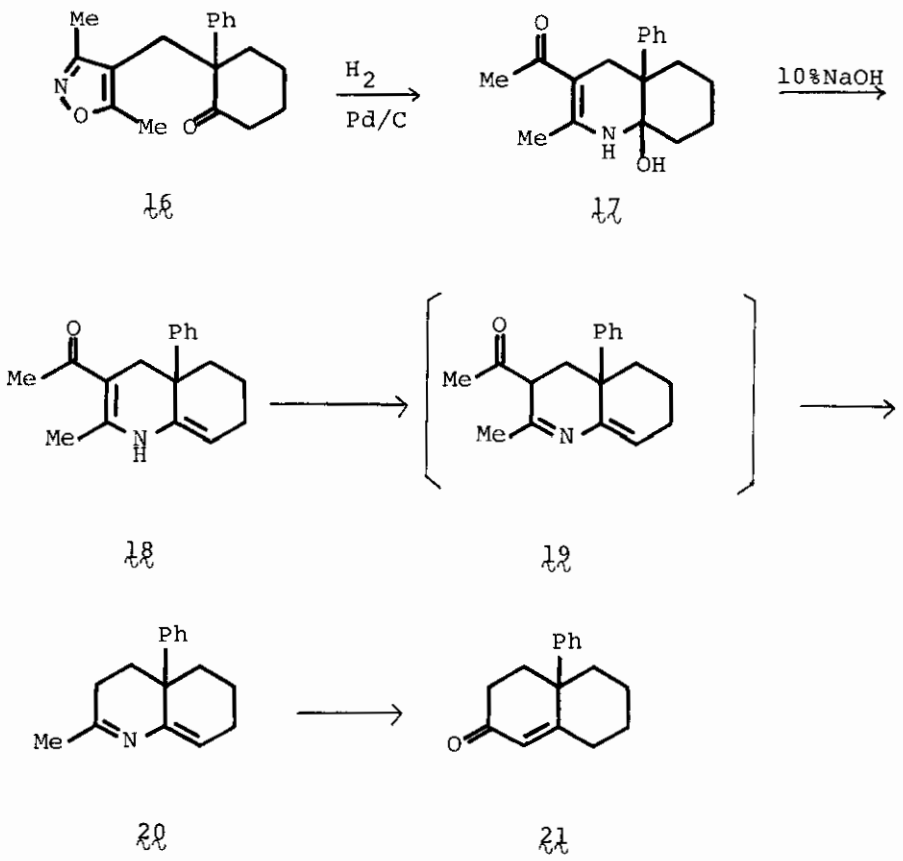
14 : R=Me



15

The mechanism of isoxazole conversion suggests that it is the alkyl group next to nitrogen which is retained in the final 3-ketoalkyl chain. Evidence for this mechanism was obtained as follows[34]. Dehydration of the cyclic carbinolamine 17 obtained from the hydrogenolysis of isoxazole 16, took place with 10 % sodium hydroxide to give the hexahydroquinoline 18. Refluxing 18 with 20 % ethanolic potassium hydroxide afforded 20, which was transformed into 10-phenyl-$\Delta^{1,9}$-2-octalone (21) on prolonged heating with aqueous base or by hydrolysis with acetate buffer to the diketone followed by cyclization with hot 5 % ethanolic potassium hydroxide (Scheme 3).

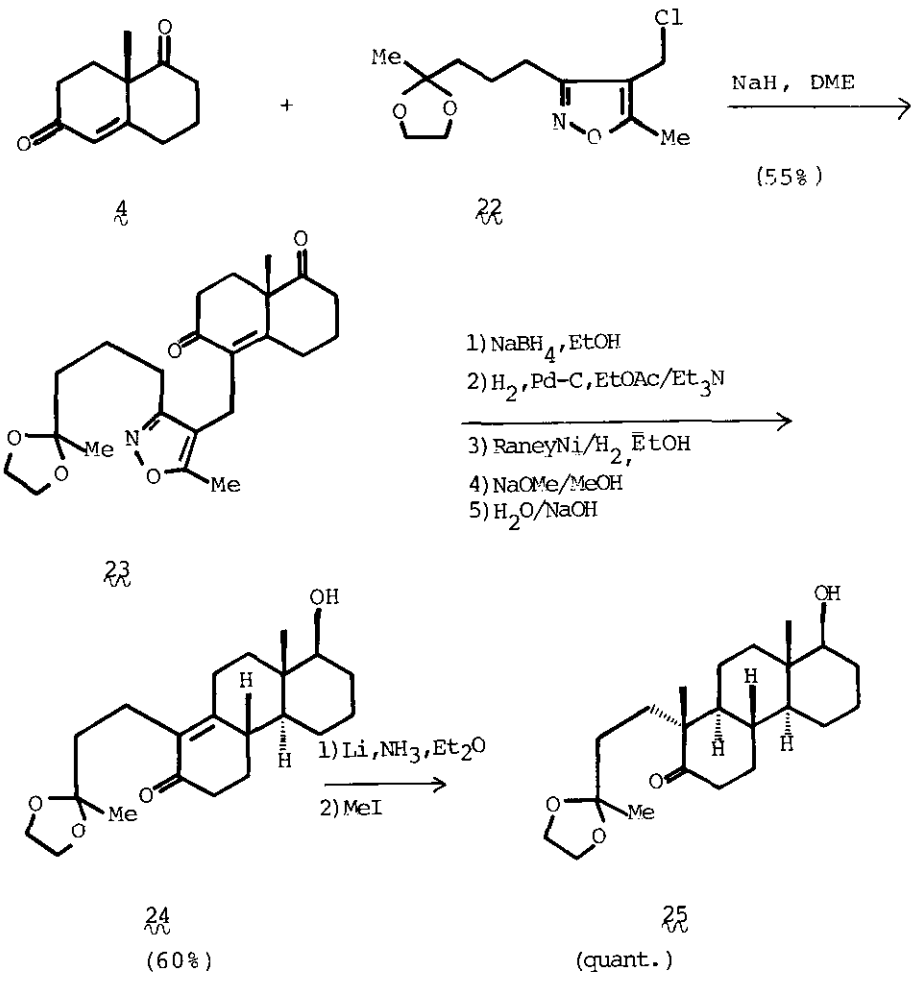
Scheme 3



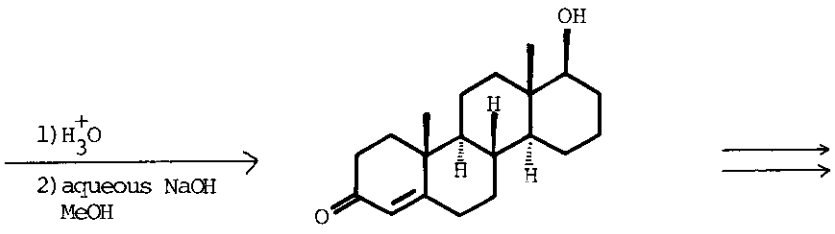
This observation led to the use of the isoxazole 22 as bis-annelation reagent in the synthesis of D-homotestosterone (26) and progesterone (27)[35]. Alkylation of the enolate derived from the octalone 4 with 22 gave in moderate yield the isoxazole 23 which was converted by the usual reaction sequences to the tricyclic enone 24 in 60 % overall yield. Initially the C_{18}-methyl group was introduced via sodium tert-amylate or sodium hydride, and

methyl iodide to afford the usual mixture of $\Delta^{9,11}$-10β 28 and 10α-epimers 29. Subsequently it was observed that the alkylation-trapping method directly converts 24 into a single isomer (25) in almost quantitative yield. Transformation of 25 into D-homotestosterone (26) and progesterone (27) was achieved by the usual multi-step sequences (Scheme 4a and 4b).

Scheme 4a

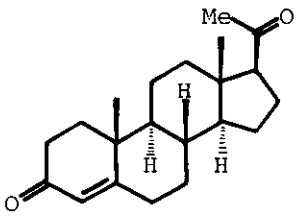


Scheme 4b



26

(80%)



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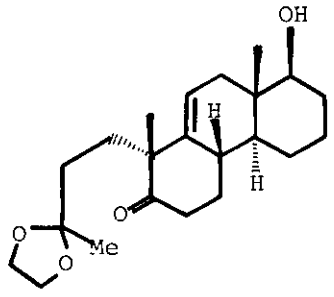

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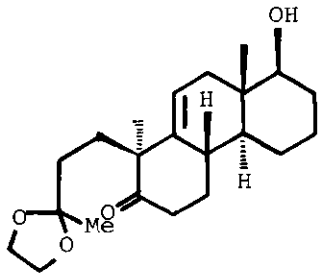
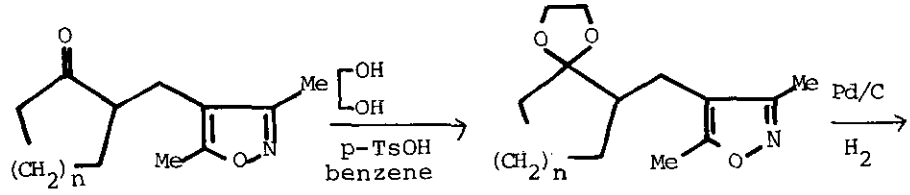


29

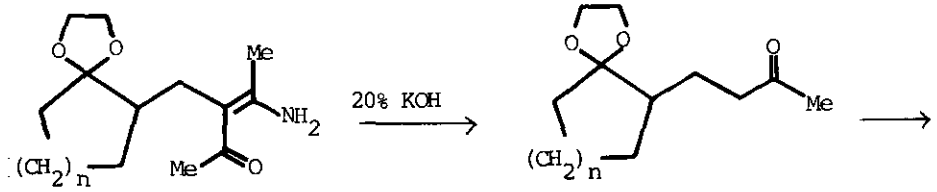
In contrast to the finding [34] that the carbinolamine 17, upon treatment with base, is rapidly dehydrated to the dihydropyridines 18 and 20 which are susceptible to oxidation and/or disproportionation, Saucy and coworkers[36] improved the isoxazole annelation reaction as follows. The ketals 31 and 32, obtained in 85 % and 86 % yield by the usual ketalization, were hydrogenated over palladium-charcoal in 3 ∿ 4 % ethanolic potassium hydroxide solution. The

Scheme 5



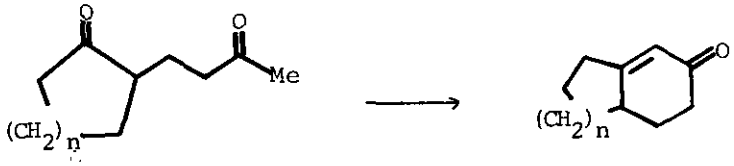
30 : n=1
12 : n=2

31 : n=1(85%)
32 : n=2(86%)



33 : n=1
34 : n=2

35 : n=1(83% from31)
36 : n=2(84% from32)



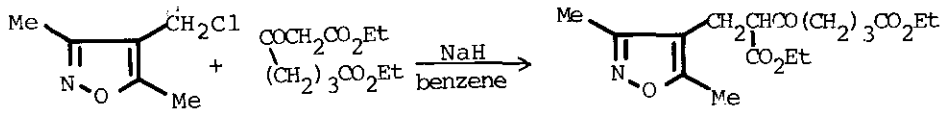
37 : n=1

38 : n=1 (57% from31)
39 : n=2 (76% from32)

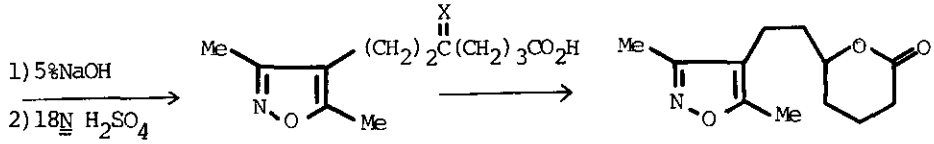
resulting vinylogous amides 33 and 34 were heated in 20 % aqueous potassium hydroxide solution to give the keto ketals 35 and 36 in 83 % and 84 % yields from 31 and 32, respectively. The keto ketal 36 was heated with methanolic hydrochloric acid to afford directly in 76 % yield from the isoxazole 32 the octalone 39, which contains about 20 % of the isomeric β,γ-unsaturated ketone. These yields compare favorably with the 50 % yield previously reported[33] for the conversion of 12 into 39. However, treatment of the keto ketal 35 with methanolic hydrochloric acid caused deketalization to 37 which was not cyclized under these conditions but was converted with methanolic sodium hydroxide into the indenone 38 (57 % yield from the ketal 31) (Scheme 5).

Scott and Saucy[37] applied isoxazole annelation for the synthesis of (±)-estr-4-ene-3,17-dione and (±)-13β-ethylgon-4-ene-3,17-dione. The desired lactone 44 was synthesized by two different routes. Initially, the anion of diethyl β-oxopimelate (40) was alkylated with 4-chloromethyl-3,5-dimethylisoxazole (5) and the crude alkylated diester 41 was saponified with dilute sodium hydroxide followed by acid treatment to obtain the acid 42 which was subsequently reduced with sodium borohydride to give the lactone 44 in 32 % yield. Alternatively, the chloride 5 was converted into the phosphonium salt 45, followed by reaction with acrolein dimer (46) to furnish 47 which was then treated with dilute sulfuric acid in dioxane to give the hemiacetal 48. After oxidation of 48 with manganese dioxide, the resulting lactone 49 was hydrogenated over palladium-charcoal to afford the isoxazole lactone 44, in 76 % yield (Scheme 6a and 6b).

Scheme 6a



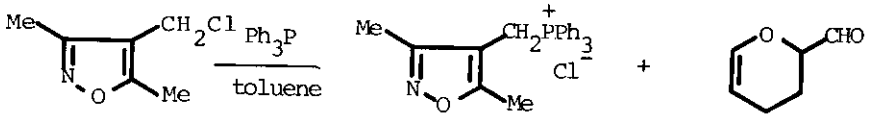
5 40 41



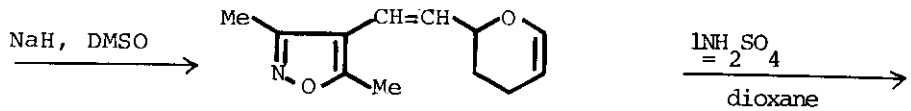
42 : X=O
43 : X=H,OH

44
(32% from 40)

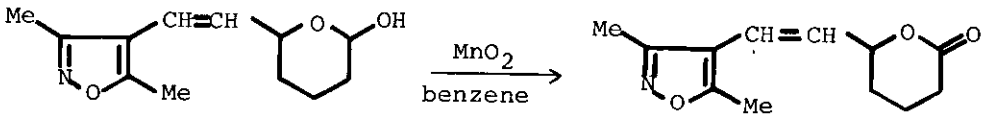
Scheme 6b



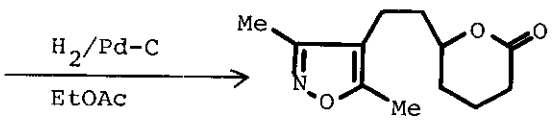
5 45 (91%) 46



47 (82%)



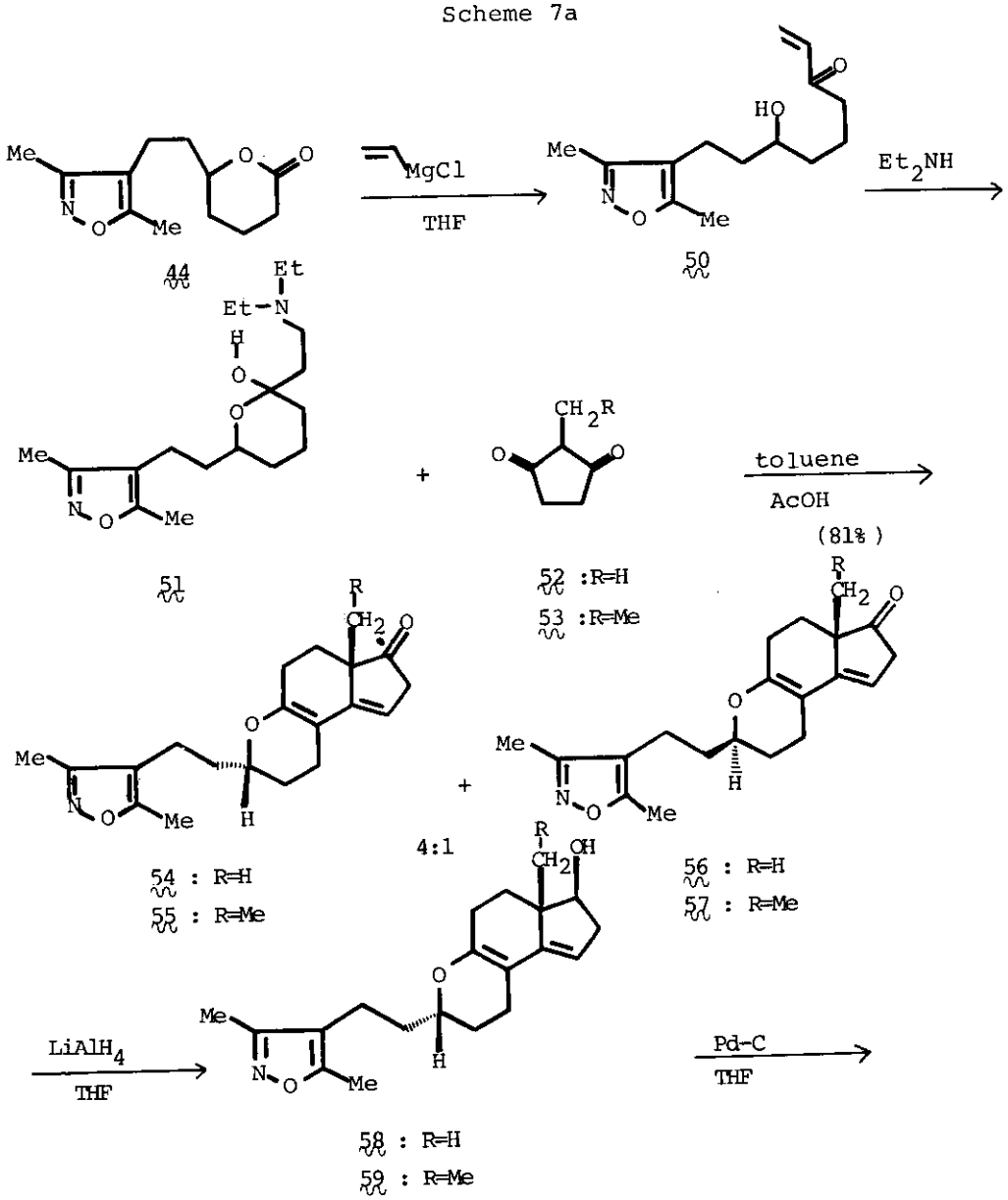
48 49 (40% from 47)



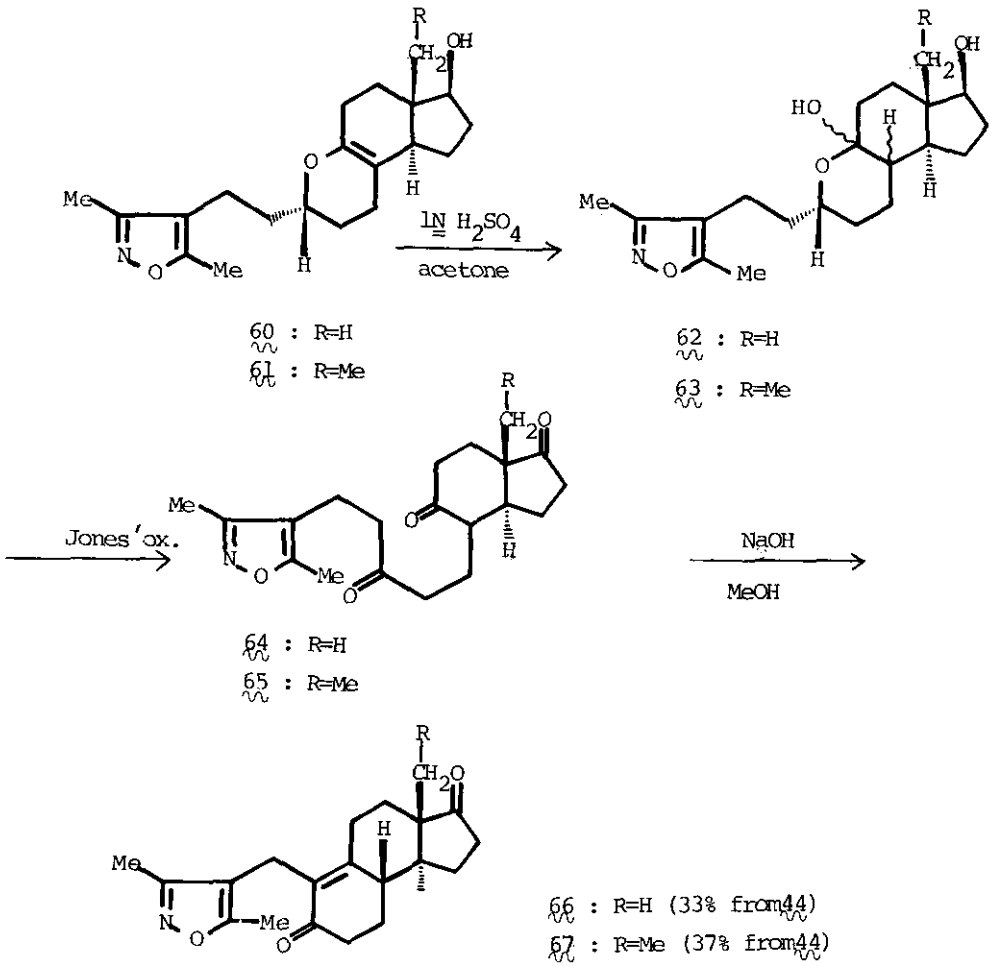
44 (76%)

Reaction of this lactone 44 with vinylmagnesium chloride gave the vinyl ketone 50 which was treated with diethylamine to afford the corresponding Mannich base 51 in 80 - 85 % overall yield. Con-

Scheme 7a



Scheme 7b



densation of the Mannich base (51) with 2-methylcyclopentane-1,3-dione (52) in toluene-acetic acid provided in 81 % yield a mixture of trans and cis dienol ethers 54 and 56. Reduction of this mixture with lithium aluminum hydride gave the trans and cis dienol ether alcohols 58 which were hydrogenated over palladium to afford 60. Hydration of 60 with 1N sulfuric acid in acetone gave the

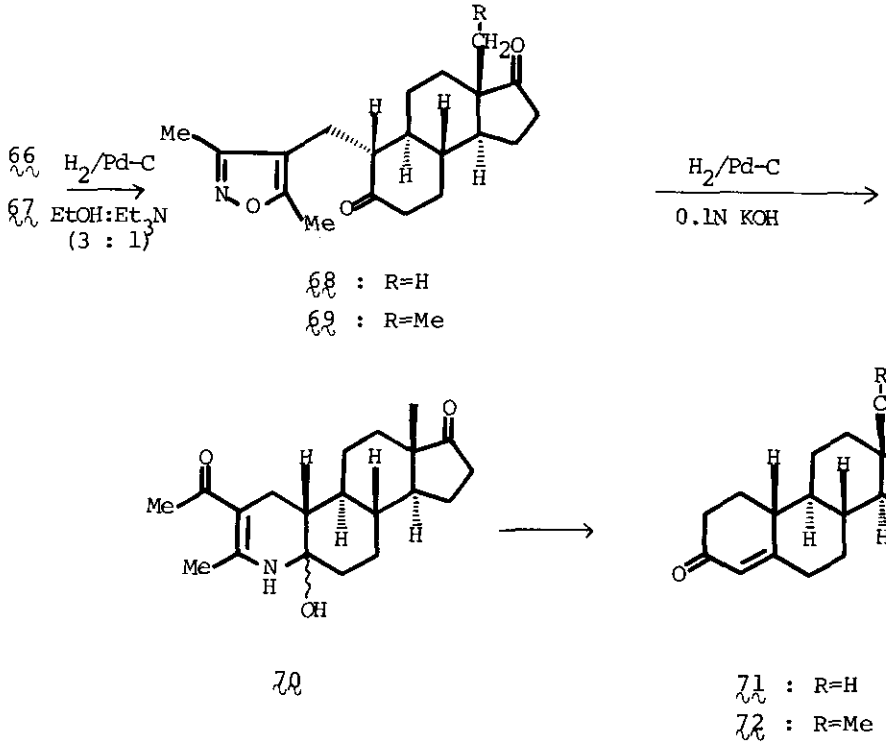
hemiketal 62 as a mixture of compounds with unknown configuration at C-3a and C-9b. Without isolation, hemiketal 62 was directly oxidized with Jones reagent to give the trione 64 which was again directly cyclized with methanolic sodium hydroxide solution to give the racemic tricyclic dione 66, in 33 % overall yield. Similarly the dione 67 was obtained in 37 % yield from the lactone (44) (Scheme 7a and 7b).

To complete the synthesis of the steroids 71 and 72, it was necessary to saturate the Δ^9 double bond in compounds 66 and 67 stereoselectively and to elaborate ring A. Hydrogenation of the enones 66 and 67 over palladium-charcoal in an ethanol-triethylamine mixture (3 : 1) gave the diones 68 and 69. When the hydrogenation mixture containing the dione 68 was made alkaline with 0.1 N in potassium hydroxide, a second equivalent of hydrogen was rapidly taken up to yield the vinylogous amide 70 which was converted upon heating with aqueous base into 71 in 45 % yield from 66. Based on the previous work[36], it was theorized that if the cyclization of the initial ixosazole hydrogenolysis product to the carbinolamine from 70 was prevented, the overall yield might be significantly higher. In fact, this proved to be the case. The crude dione 68 was ketalized to give the bis-ketal 73. Hydrogenolysis of this bis-ketal 73 over palladium-charcoalin 4 % ethanolic potassium hydroxide solution proceeded smoothly. Addition of 20 % aqueous potassium hydroxide solution to the hydrogenated solution, followed by heating, gave the keto bis-ketal 77. Heating 77 with methanolic hydrochloric acid caused deketalization and cyclization to give the steroid 71 in 80 - 85 % yield

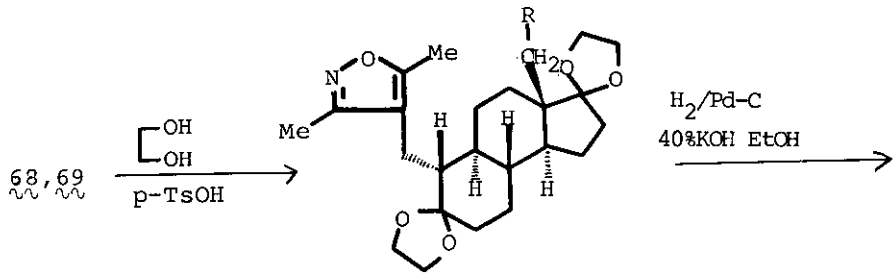
from 68. In a similar manner, 72 was obtained via 74, 76, and 78 from 69 in 70 % yield.

This multi-step synthesis of steroids proved that the isoxazole ring is very stable to most reagents but is readily opened by hydrogenation under the proper conditions (Scheme 8a and 8b).

Scheme 8a

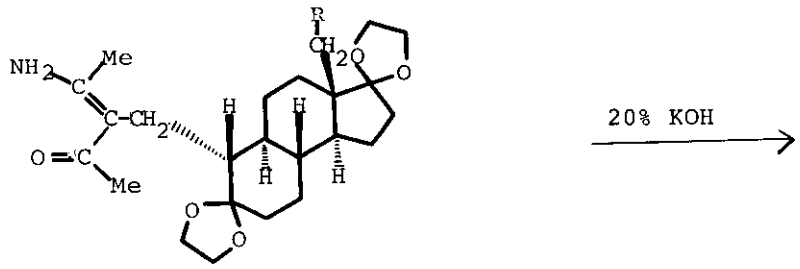


Scheme 8b



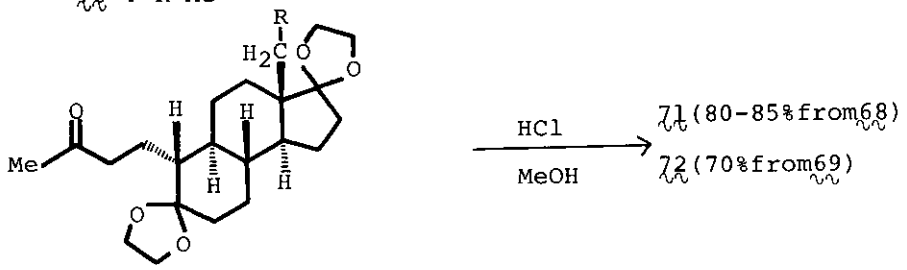
73 : R=H

74 : R=Me



75 : R=H

76 : R=Me

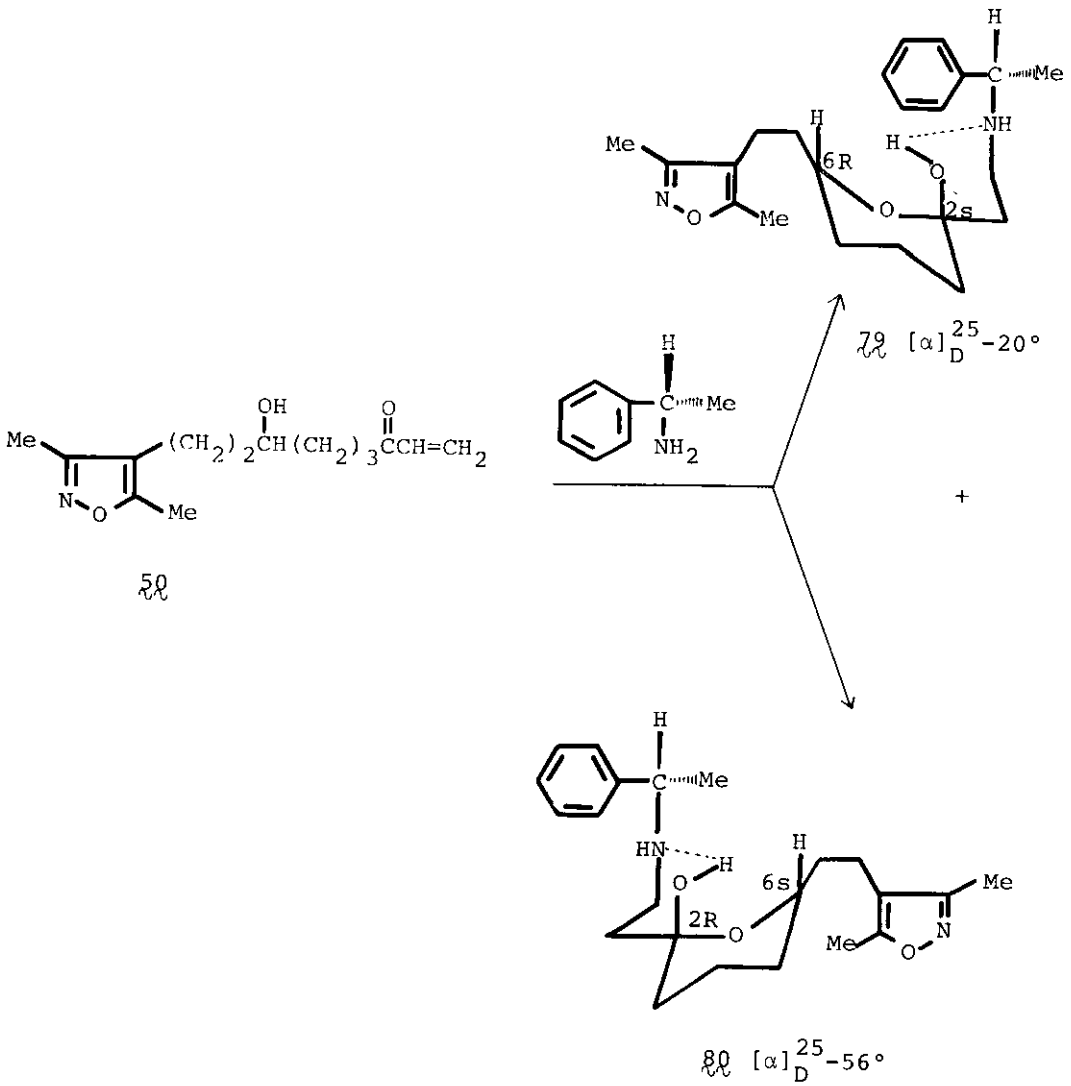


77 : R=H

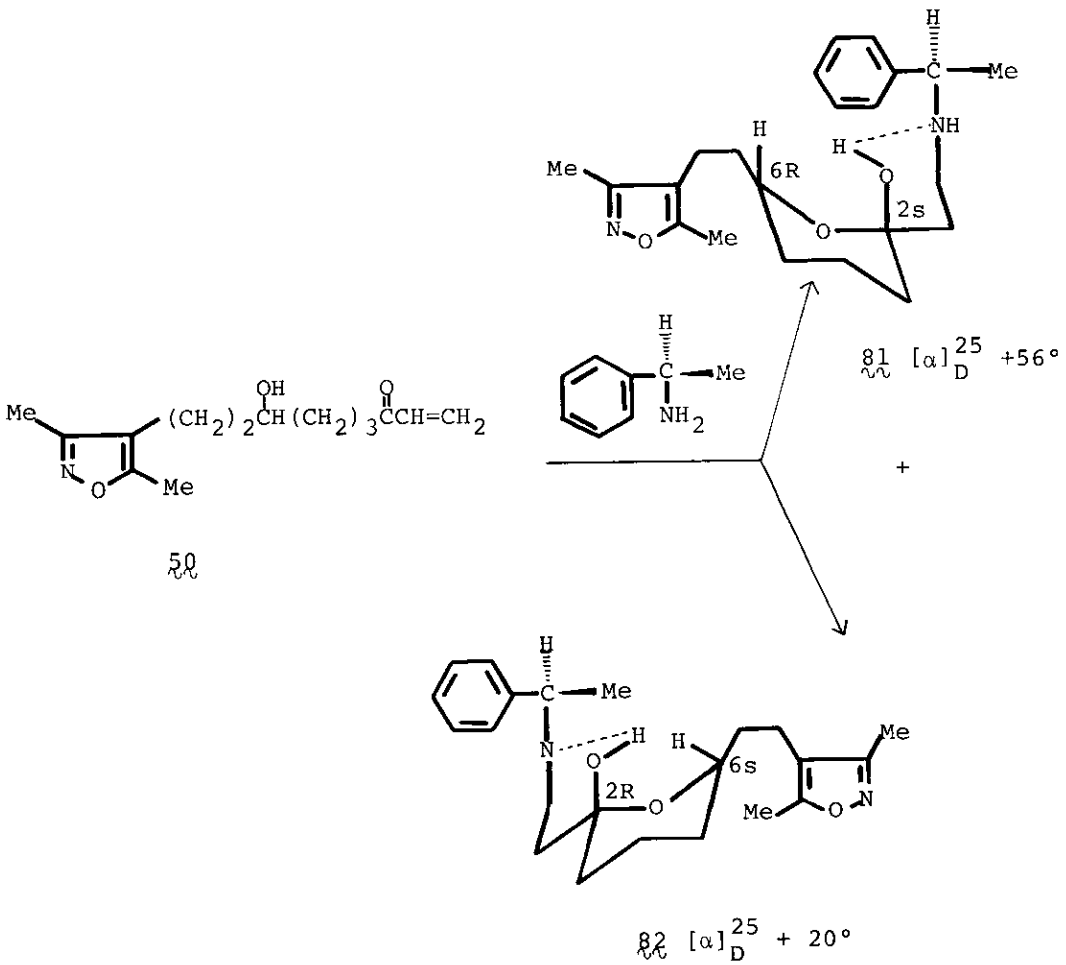
78 : R=Me

As an extension of the study described above, Saucy and co-workers[38] succeeded in synthesizing (+)-estr-4-ene-3,17-dione (97) from the optically active Mannich base 79. Reaction of the

Scheme 9a



Scheme 9b

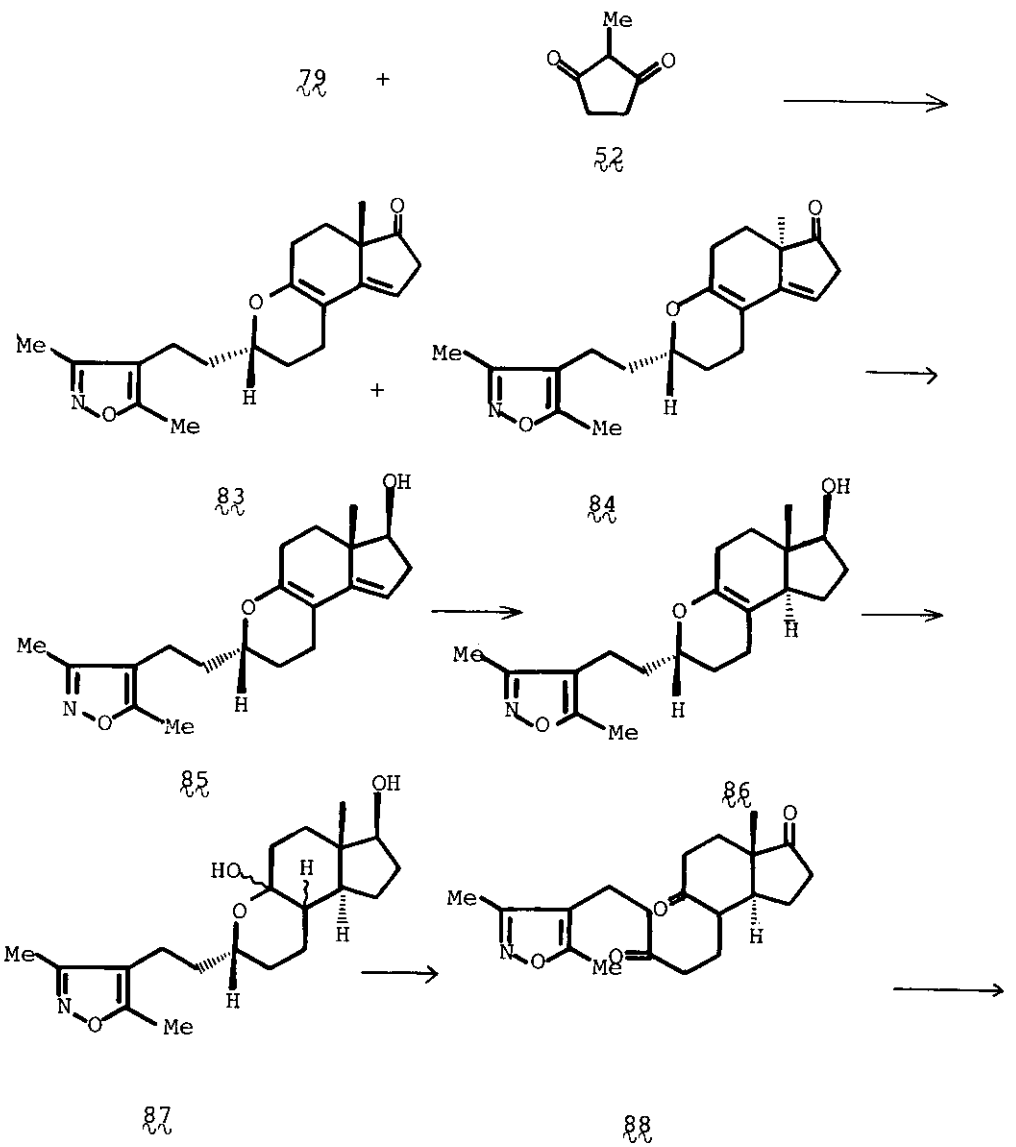


racemic vinyl ketone 50 with (-)-α-phenethylamine gave the diastereomeric Mannich base 79 and 80. Similar reaction with (+)-α-phenethylamine gave the antipodal Mannich bases 81 and 82 (Scheme 9a and 9b).

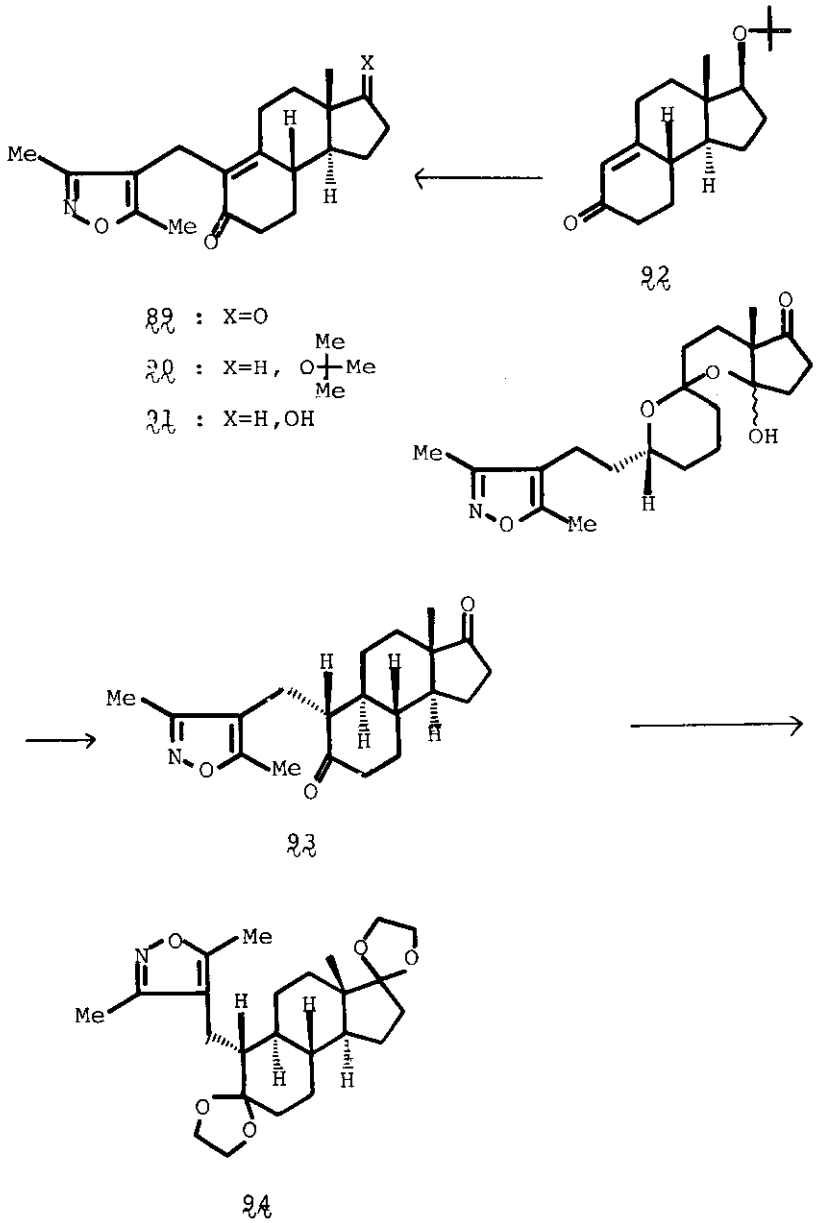
Reaction of the base 79 with the dione 52 in a toluene-pyridine-acetic acid mixture gave a mixture of trans 83 and cis 84 dienol

ethers which were converted into the dione 89 by using the same reaction sequences described for the racemic series[37]. The optical purity of the dione (89) was determined to be 44 % by com-

Scheme 10a



Scheme 10b



89 : X=O

90 : X=H, O(Me)(Me)Me

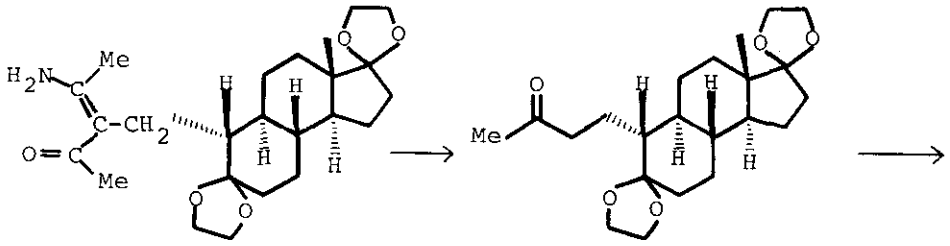
91 : X=H,OH

92

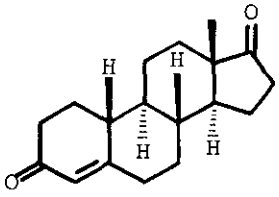
93

94

Scheme 10c



95 96



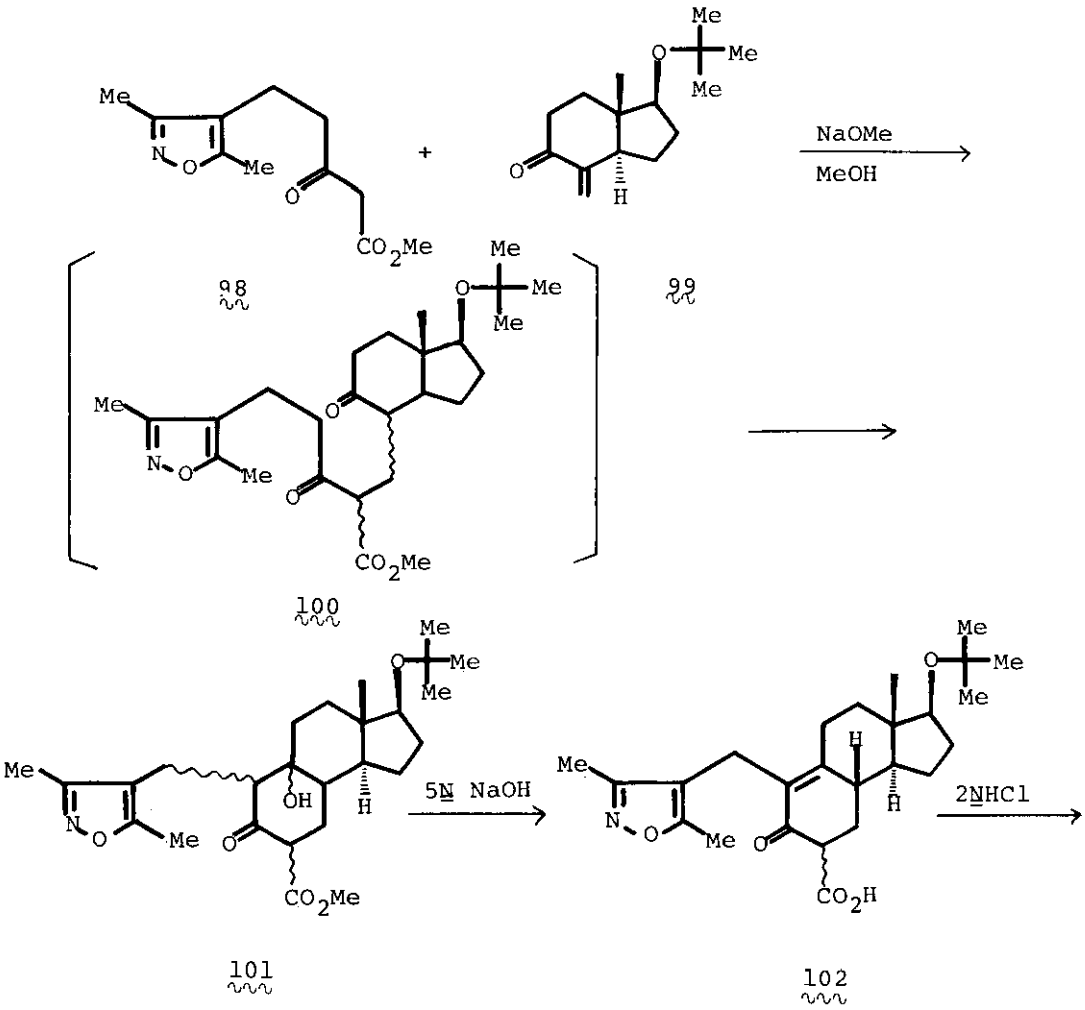
97

parison with an authentic sample synthesized by alkylation of the enone 92 with 4-chloromethyl-3,5-dimethylisoxazole (5) followed by acid-catalyzed cleavage of the ether group and oxidation of the resulting alcohol 91. Alternatively the Mannich base 79 was quaternized with methyl iodide in the presence of potassium carbonate and the crude salt was then treated with 52 in aqueous tert-butyl alcohol to give a mixture of compounds which is in accord with the general structure 98. Treatment of this mixture with p-toluenesulfonic acid gave the dienol ethers 83 and 84 in 46 % yield from the Mannich base 79. The enone 89 prepared from this mixture was fractionally crystallized to give optically pure (+)-19-(3,5-dimethyl-4-isoxazolyl)-de-A-androst-9-ene-5,17-dione from the dienol

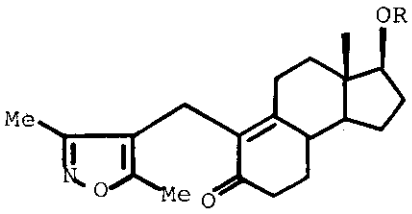
ether mixture 83 and 84 in 31 % yield. Conversion of the optically pure enedione (89) to (+)-estr-4-ene-3,17-dione (97) was carried out as previously described for the racemic series[37] (Scheme 10a, 10b and 10c).

Optically active $\Delta^{9(11)}$-dehydrotestosterone (113), a potential

Scheme 11a



Scheme 11b



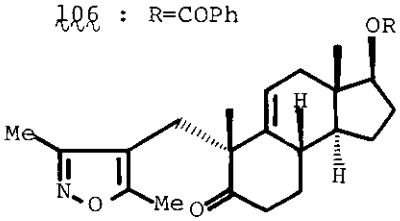
NaH, MeI
glyme

103 : R=CMe_3 (65%)

104 : R=H

105 : R=COMe

106 : R=COPh



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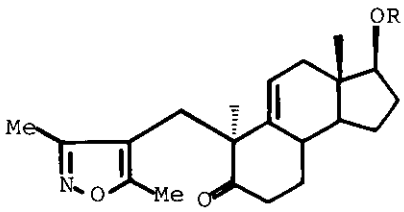


107 : R=CMe_3

108 : R=COMe

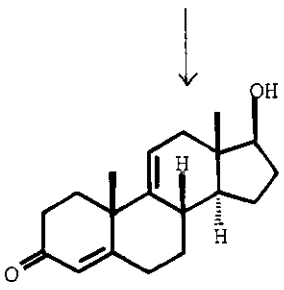
109 : R=COPh

(82.8 : 17.8)

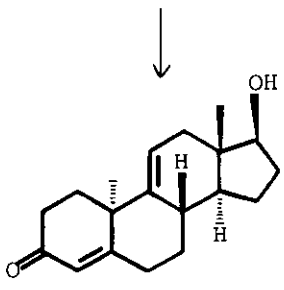
110 : R=CMe_3

111 : R=COMe

112 : R=COPh

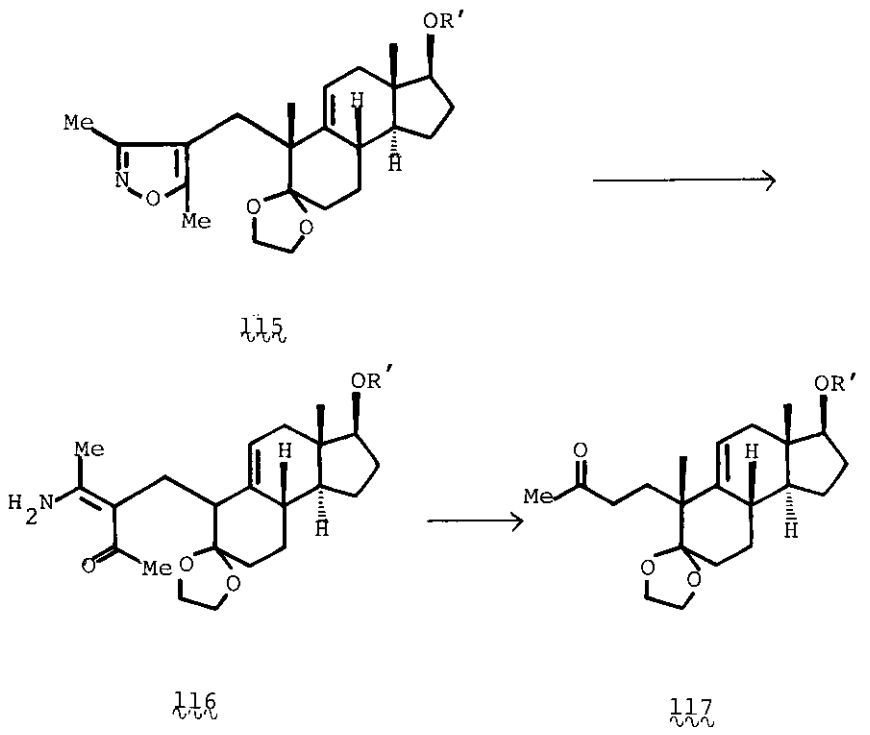


113



114

Scheme 11c



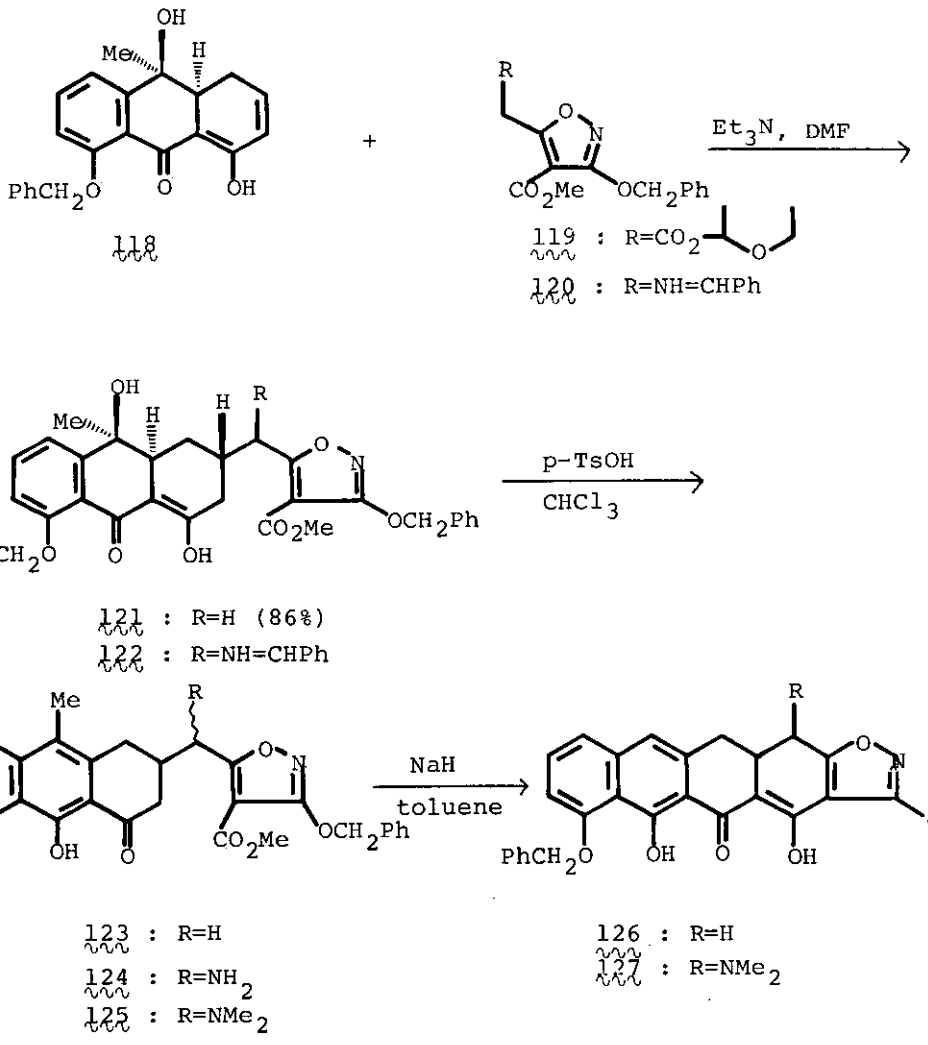
intermediate for the synthesis of 11-oxygenated steroids has been synthesized by isoxazole annelation, starting from the optically active methylene ketone 99 and the isoxazole 98[39]. Condensation of 98 and 99 in the presence of base led, via intermediates 100 and 101, to the acid 102, which readily decarboxylated on warming to give the tricyclic enone 103 in an overall yield of 65 %. Acetylation and benzoylation of 104, prepared by hydrolysis of 103, gave esters 105 and 106. The reaction conditions for the stereospecific introduction of the C_{19}-methyl group in compound 103 were investigated and methylation of the enolate, derived by treatment of 103 with sodium hydride in glyme, with methyl iodide at low tem-

perature gave 107 in 78 % yield. Conversion of the tricyclic compounds 107 and 110 into 113 and 114 via acetal 115, vinylogous amide 116, and keto acetal 117 was achieved by the same reaction sequences described above in 53 % and 37 % yields from 107 and 110, respectively (Scheme 11a, 11b and 11c).

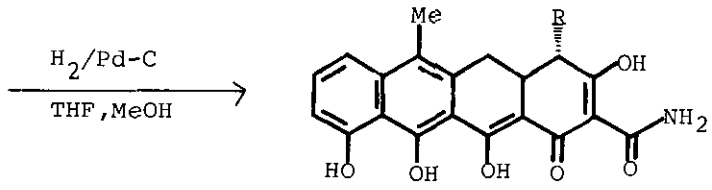
Dedimethylamino-12a-deoxyanhydrotetracycline (128) and 12a-deoxyanhydrotetracycline (129) have been synthesized by using 3-benzyloxyisoxazole system for the purpose of introducing the β-keto amide system[40]. Michael addition of the isoxazole 119 to the tricyclic dienolone 118 followed by deesterification-decarboxylation afforded 121 in 86 % yield. Compound 121 was dehydrated to give 123 which was then cyclized to 126 in 85 % yield. Finally, (±)-dedimethylamino-12a-deoxyanhydrotetracycline (128) was obtained in more than 90 % yield by the hydrogenolysis of 126 over palladium-charcoal. Similarly, for the synthesis of 129, Michael addition of 118 to the Schiff base 120 gave a mixture of epimers 122 which was dehydrated (with hydrolysis of the Schiff base) to 124 by warming with diluted hydrochloric acid. The resulting crude product was reductively methylated giving 125 in 40 % yield. Cyclization of 125 furnished in 74 % yield the tetracyclic 127 whose hydrogenolysis then afforded (±)-12a-deoxyanhydrotetracycline (129).

Thus, annelation sequences involving isoxazole rings have proven useful in the synthesis of a number of steroids and tetracyclines (Scheme 12a and 12b).

Scheme 12a


OH
Me
H
PhCH2O
O
OH
118
+
R
O
N
CO2Me
OCH2Ph
Et3N, DMF
119 : R=CO2
120 : R=NH=CHPh
OH
Me
H
H
R
O
N
CO2Me
OCH2Ph
PhCH2O
O
OH
p-TsOH
CHCl3
121 : R=H (86%)
122 : R=NH=CHPh
Me
R
O
N
CO2Me
OCH2Ph
PhCH2O
OH
O
NaH
toluene
123 : R=H
124 : R=NH2
125 : R=NMe2
126 : R=H
127 : R=NMe2

Scheme 12b



128 : R=H

129 : R=NMe_2

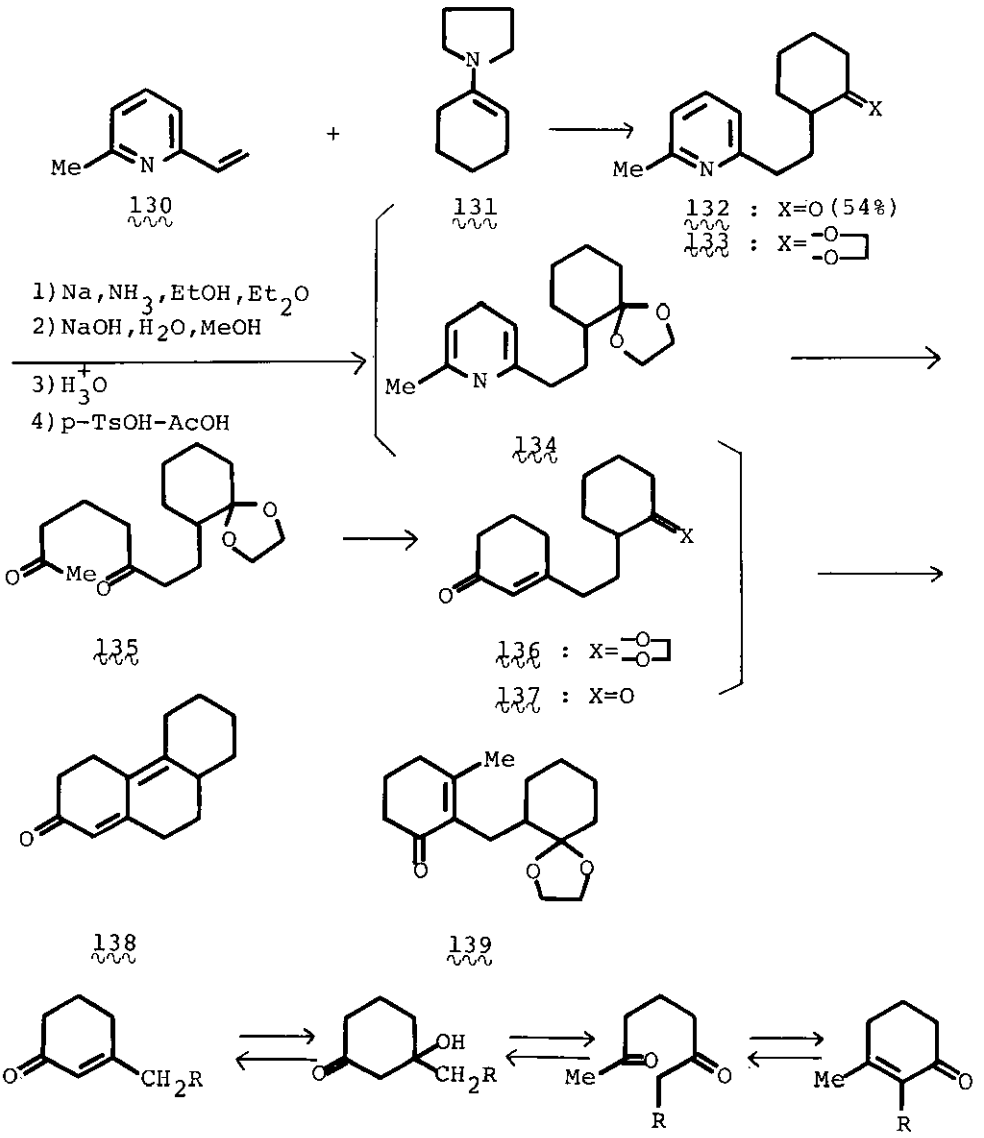
III PYRIDINE ANNELATION

The successful introduction of 6-vinyl-2-picoline (130) as an eight-carbon fragment for bis-annelation has been achieved by Danishefsky and coworkers[41-44]. For example in the transformation of cyclohexanone into tricyclic compounds 138, reaction of the pyrrolidine enamine of cyclohexanone (131) with 130 gave the picolylethylated ketone 132 in 54 % yield which was converted to the ketal 133. Compound 133 was subjected to the successive reaction sequences shown in Scheme 13a to give the tricyclic dienone 138 in 40 % yield. Alternatively, when the precurser enedione 137 was isolated (42 % yield) and treated with 10 % p-toluenesulfonic acid in acetic acid, a near-quantitative yield of 138 was obtained. Although the 1,4-dihydropyridine 134 was not identified, 1,4-dihydropyridine derived from 2,6-lutidine through Birch reduction was shown to be hydrolyzed with great facility to give 2,6-heptanedione in 72 % yield. The predominant cyclization of the presumed intermediate 135 into the compound 138 was attributed to the avoidance of the serious steric repulsion which arises

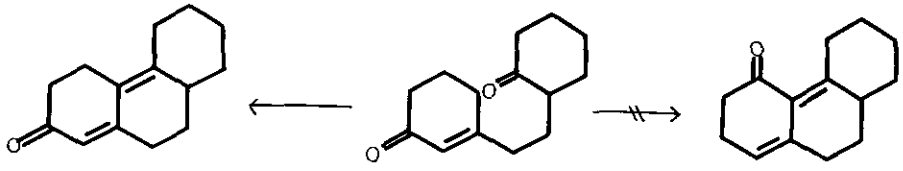
from cyclization in the alternate sense to give the compound 139.

The cyclization of 135 to 136 was further investigated as follows. For this purpose, compound 133 was treated with sodium-

Scheme 13a



Scheme 13b



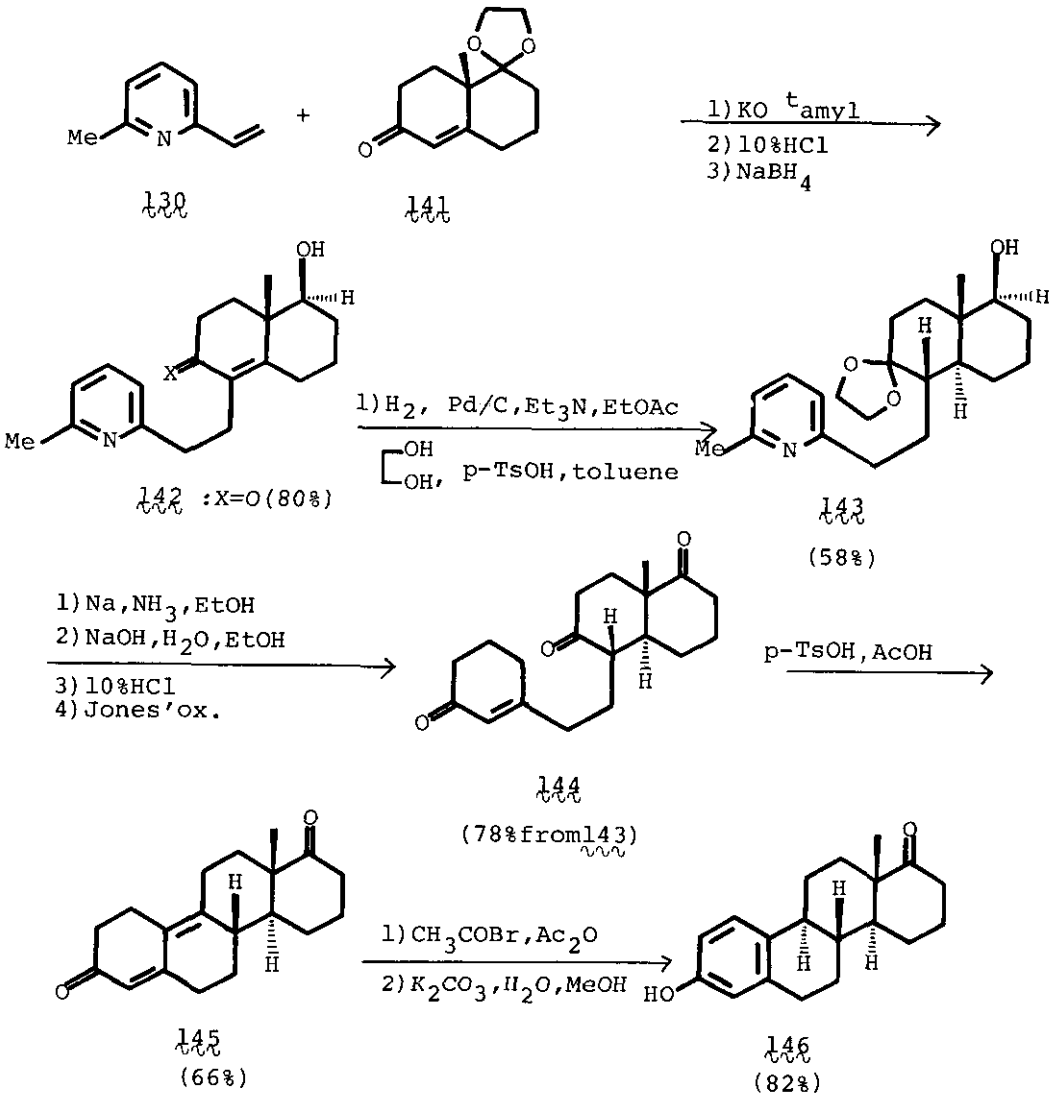
138 137 140

ammonia-ethanol and the dihydropyridine, assumed to be present, was hydrolysed under nearly neutral conditions in order to avoid premature aldolization and deketalization. The diketone 135 was isolated in substantially lower yield than was realized for enone 136. Treatment of 135 with aqueous ethanolic sodium hydroxide at room temperature gave, in 95 % combined yield, a 3.8 : 1 ratio of 136 : 139. This finding is significant since it is the first demonstration of the preferential formation of a trisubstituted cyclenone relative to its tetrasubstituted isomer from an internal aldolization reaction. However, when the diketone 135 was heated under reflux for 50 hr, ketalenones 136 and 139 were now isolated in a ratio of 1 : 3.4. This result was interpreted by invoking the well-known reversibility of the aldol condensation and this transformation was also demonstrated more convincingly by starting with pure ketalenone 136. When 136 was heated under the same conditions in aqueous ethanolic alkali, a mixture (1 : 3.4) of 136 : 139 was isolated. The vinylogous aldolization was also studied. By using 137, the extended dienone 138, not the cross-conjugated dienone 140, was the sole com-

pound isolated (Scheme 13a and 13b).

The successful bis-annelation of cyclohexanone was used for the synthesis of (±)-D-homoestrone. Michael addition of 141 to

Scheme 14

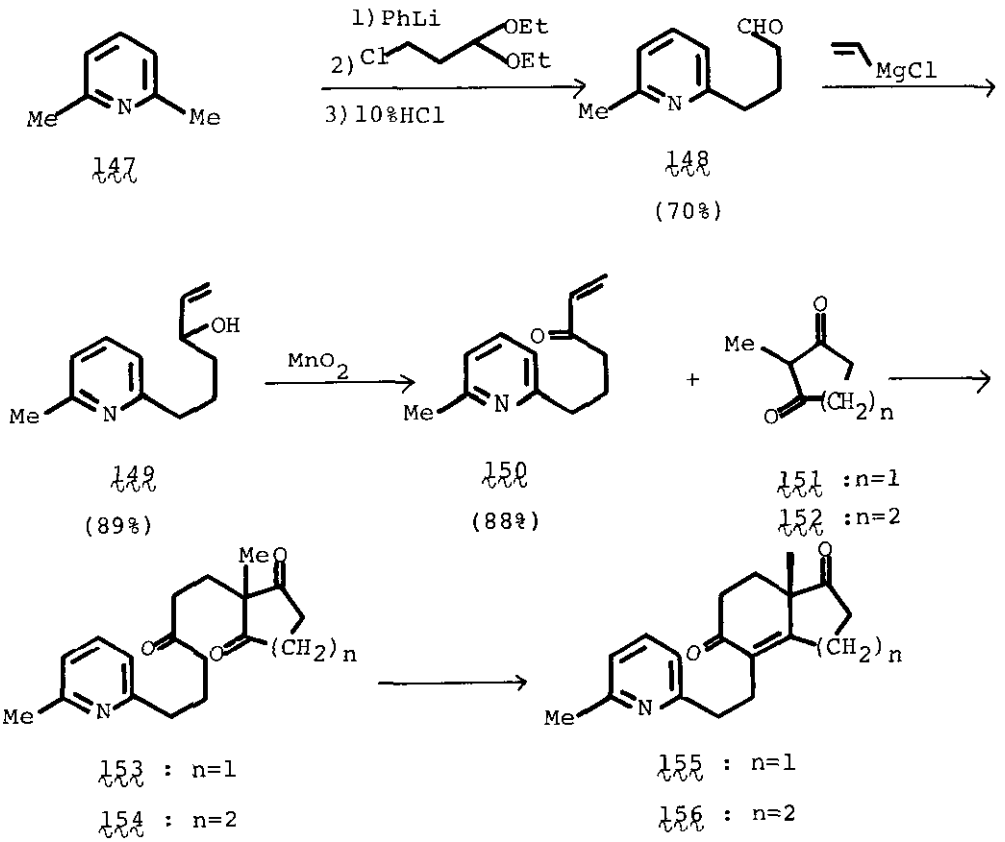


methyl vinyl pyridine 130 followed by selective reduction of the saturated ketone resulting from acid treatment of the Michael adduct afforded the enone alcohol 142 in 80 % yield. After stereoselective hydrogenation of 142, the saturated ketone was ketalized to give the hydroxyketal 143 in 58 % yield. Successive treatment of 143 involving Birch-type reduction of the pyridine ring, base-catalyzed cyclization, deketalization, and Jones oxidation of the alcohol, afforded 144 in 78 % yield. The dienedione 145, derived from the acid-catalyzed cyclization of 144, was converted to (±)-D-homoestrone 146 via the action of acetyl bromide-acetic anhydride followed by saponification of the intermediate phenolic acetate in 82 % yield (Scheme 14).

The same authors reported[45] the novel and improved synthesis of 155 and 156 via the tris-annelating agent 150. The vinylpicoline 130 was obtained in low yield via hydroxymethylation of 2,6-lutidine. Treatment of 2,6-lutidine (147) with phenyllithium followed by alkylation of the resultant anion with 3-chloropropionaldehyde diethyl acetal and hydrolysis gave 148 in 70 % yield. Addition of vinylmagensium chloride to 148 gave the alcohol 149 in 89 % yield which underwent oxidation by manganese dioxide to afford the desired tris-annelating agent 150 in 88 % yield. Under the influence of sodium hydride, enone 150 coupled smoothly with 152 to give 154. Cyclization of 154 in the presence of 3-aminopropionic acid afforded 156 in 75 % yield. In addition, the one-step condensation of 151 with 150 in aqueous acid gave the enedione 155 in 92 % yield. Alternatively, 151 and 150 could be coupled in the presence of triethylamine to give the trione 153, which could be cyclized via

3-aminopropionic acid to give 155 (Scheme 15).

Scheme 15



147

148 (70%)

149 (89%)

150 (88%)

151 : n=1
152 : n=2

153 : n=1
154 : n=2

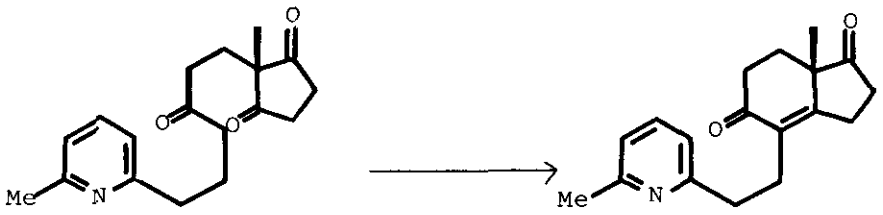
155 : n=1
156 : n=2

The advantage of using symmetrical intermediates such as 153 and 154 for the preparation of 155 and 156 has been utilized in the synthesis of optically active estrone[46].

A wide variety of amino acid have been tested to effect the chirally specific cylization of 153. The results of this study indicate that the optimal optical purity of 86 % for 155 was obtained by using 1 equiv. of 153 to 1.2 equiv. of L-phenylalanine

to 0.5 equiv. of perchloric acid in refluxing acetonitrile (2.7 ml/mmol of 153) (Table 1).

Table 1



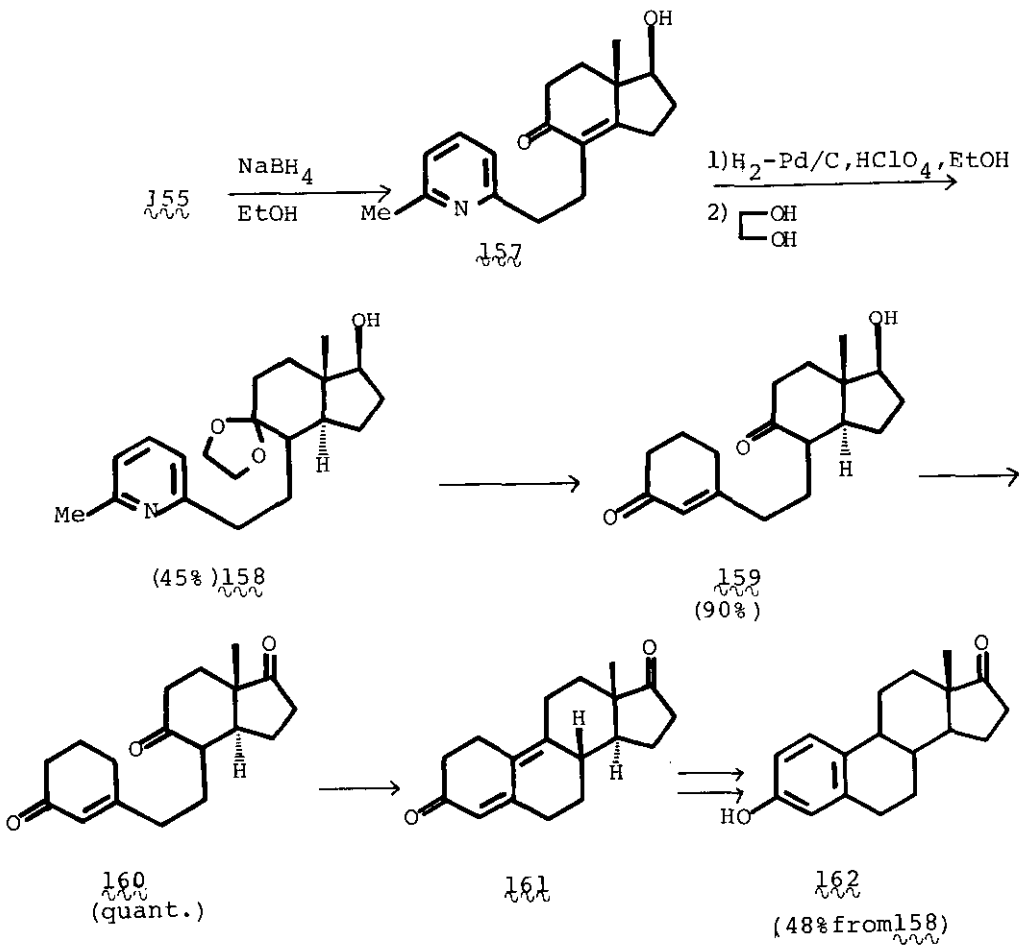
153 155

Amino acid (1.2 equiv.)	$HClO_4$ equiv.	$[\alpha]_D$ deg.	Optical purity of 155, %	%yield of 155
L-Phenylalanine	0.5	173.6	86	82
L-Phenylalanine	0.25	172.1	85	82
L-Phenylalanine	1.0	162.3	80	80
L-Tyrosine o-methyl ether	0.25	169.5	84	82
D-Tryptophan	0.25	-156.0	78	70
L-Serine	0.25	70.2	35	77
L-Proline	0.25	53.0	26	67
D-Valine	0.25	-41.7	21	72

The optically enriched 155 so obtained was converted to alcohol 157, hydrogenated over palladium-charcoal in acidic media, and ketalized to afford 158 in 45 % yield. The conversion of 158 into estrone *via* 159, 160, and 161 was achieved by the same reaction sequences shown in Scheme 14. Thus, the overall yield of estrone

from 158 was 48 % (Scheme 16).

Scheme 16

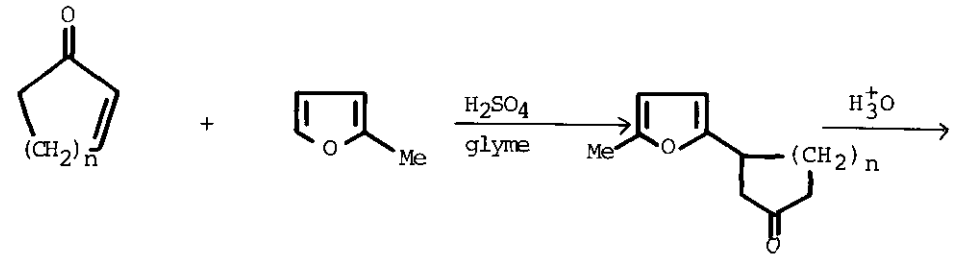


IV FURAN ANNELATION

Furan derivatives have also been used for the synthesis of condensed ring systems[47] although this method has not been applied to the synthesis of natural products. Reaction of the α,β-unsatu-

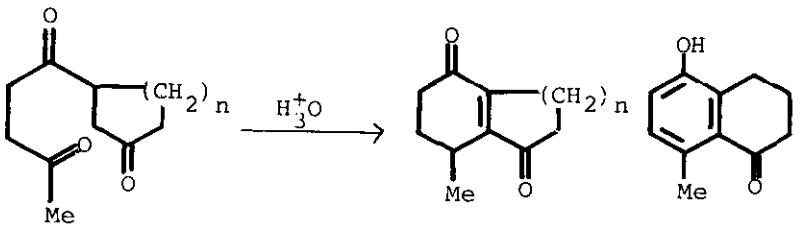
rated ketones 163, 164, and 165 with 2-methylfuran in refluxing glyme containing a catalytic amount of sulfuric acid afforded 166, 167, and 168 in the yields of 36, 40, and 32 % respectively. Preparation of the dionenes 172 (47 %) and 173 (35 %) was best accomplished by refluxing 166 and 167 for 48 hr in aqueous acetic acid containing a trace of sulfuric acid. In contrast, although extended treatment (72 hr) of 168 under the same conditions yielded the triketone 171, no bicyclic dionene 174 could be iso-

Scheme 17



163 : n=1
164 : n=2
165 : n=3

166 : n=1(36%)
167 : n=2(40%)
168 : n=3(32%)



169 : n=1
170 : n=2
171 : n=3

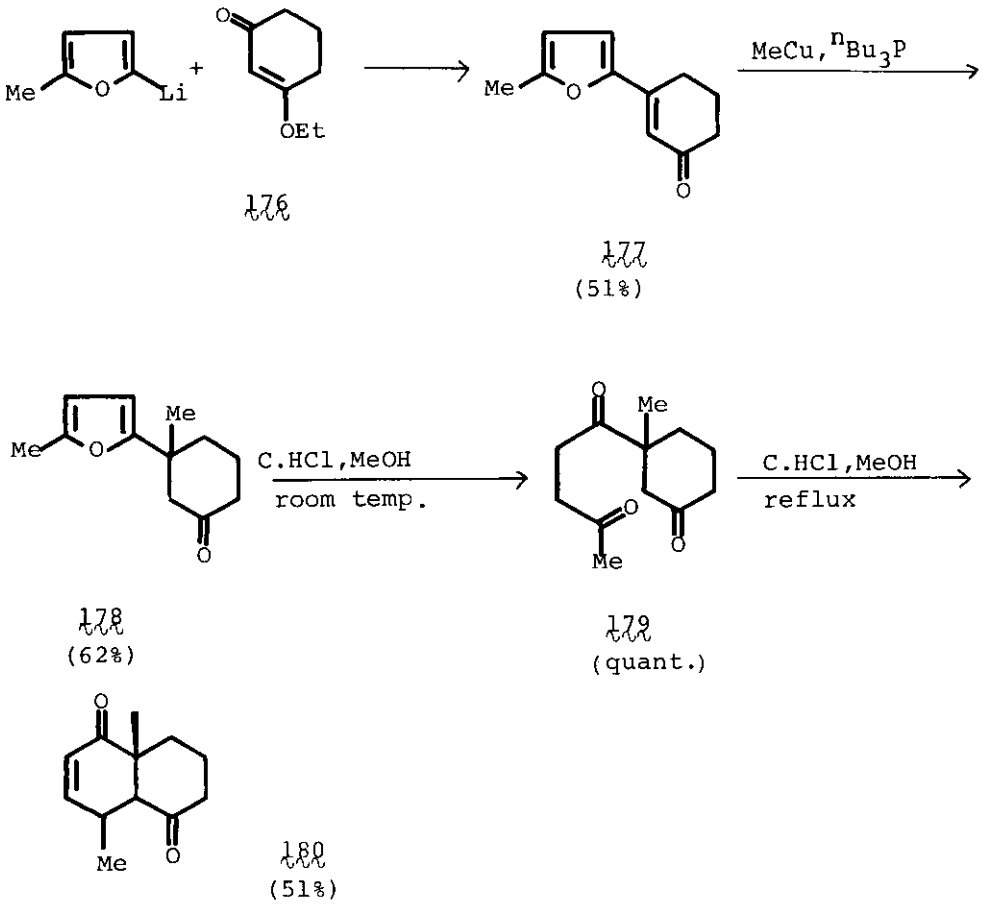
172 : n=1(47%)
173 : n=2(35%)
174 : n=3

175

lated from this reaction. When 167 was subjected to variations in the amount of time that it was heated under these acidic conditions, significant changes in the product composition from this reaction occurred. Thus, while treatment for 24 hr yielded almost equal amounts of 170 and 173, refluxing for 72 hr afforded both 173 and 175. Heating 167 for 96 hr produced a tarry reaction mixture, from which only traces of 170 and 173 could be isolated, but a 20 % yield of 175 was obtained (Scheme 17).

The low yield in opening the furan ring, the successive cycli-

Scheme 18



176

177 (51%)

178 (62%)

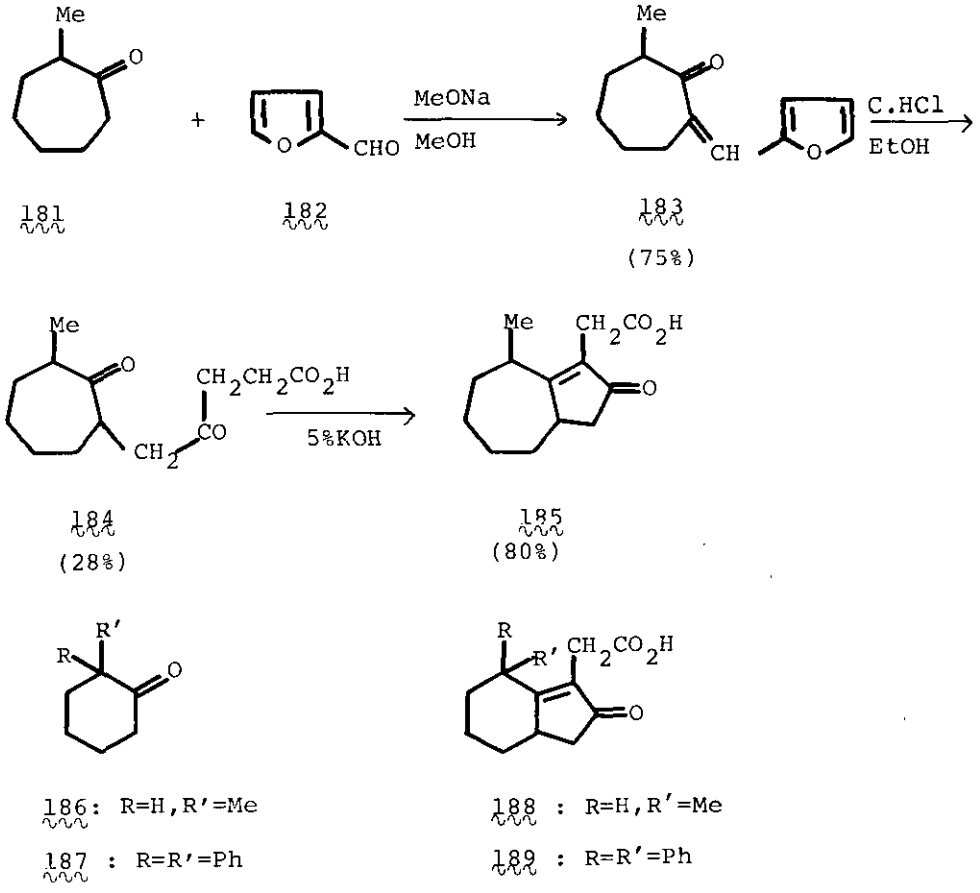
179 (quant.)

180 (51%)

zation of compounds 166 and 167 to 172 and 173, and the difficulty of setting the reaction conditions was avoided in the synthesis of compound 178[48,49] (Scheme 18).

Reaction of 2-lithio-5-methylfuran, derived from the lithiation of 5-methylfuran, with enone 176 gave the furan enone 177 followed by 1,4-addition of the methyl group to afford the saturated ketone

Scheme 19



178. Opening of one furan ring in compound 178, followed by the cyclization of the resulting triketone 179 gave the bicyclic compound 180, a potential intermediate for the eudesman type of sesquiterpenes.

A new synthesis of the bicyclo[5.3.0]decane and bicyclo[4.3.0]-nonane systems via furan annelation has also been reported[50]. Condensation of 2-methylcycloheptanone (181) with furfural afforded the furfurylidene 183 in 75 % yield. Opening of the furan ring in 183 (28 %), followed by cyclizaiton (80 %) of the resulting keto acid 184 gave the bicyclic acid 185. In a similar manner, compounds 188 and 189 have been prepared (Scheme 19).

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