Reactivity features of cyclododecanone

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Abstract
Cyclododecanone is a highly important synthetic intermediate for macrocyclic systems. This review is the sole and comprehensive one that covers the different aspects of cyclododecanone chemistry over the period from 1950 to 2010.

Keywords: Cyclododecanone, muscone, fragrances, macrocylic ketones, ring enlargement and heterocycles

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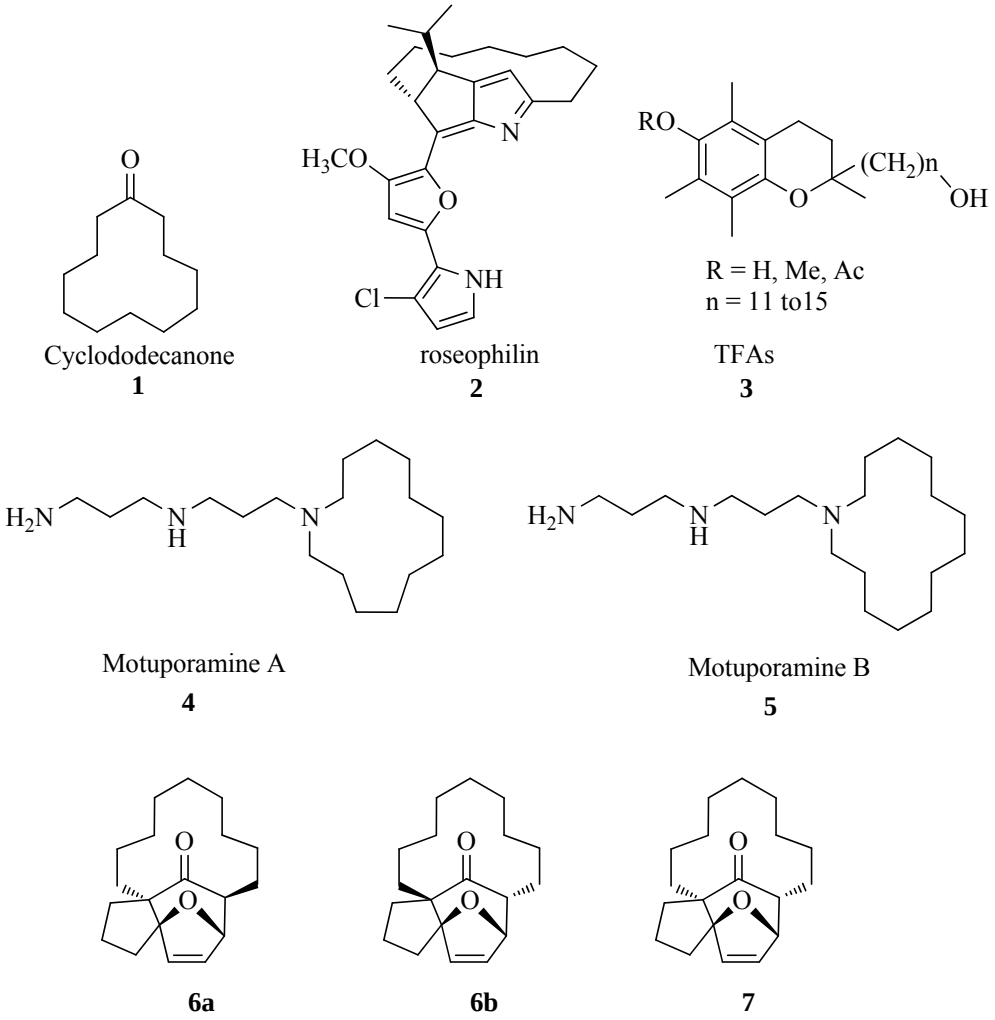
1. Introduction

Cyclododecanone **1** is a commercially available ketone, and important synthetic intermediate in the synthesis of natural products containing macrocyclic ring systems such as the anticancer rosphellin **2**,[1] the potent microglial activation modulators tocopherol fatty alcohols (TFAs) **3**,[2] cytotoxic sponge alkaloids motuporamine A **4**, motuporamine B **5**,[3] ingenes **6** and **7**,[4,5] (Scheme 1).



Cyclododecanone **1**

roseophilin **2**

TFAs **3**

Motuporamine A **4**

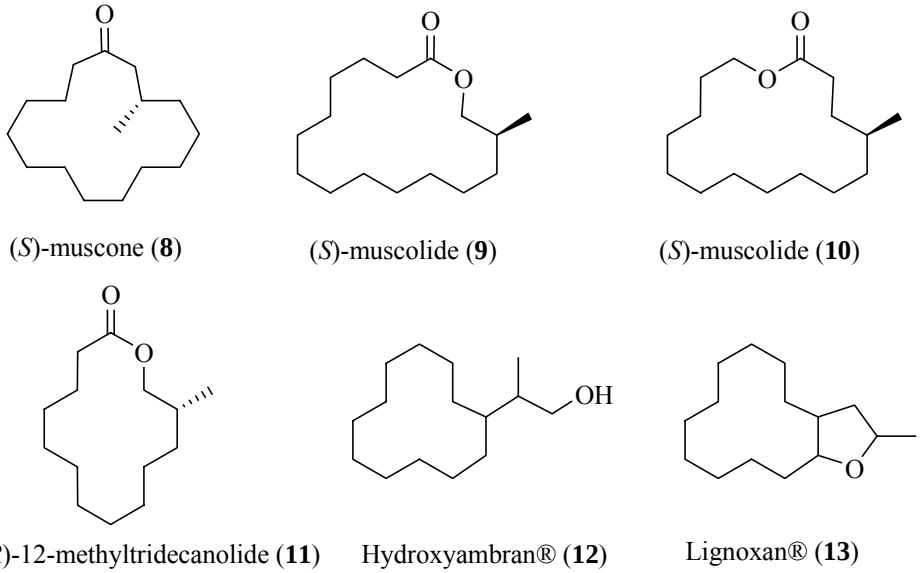
Motuporamine B **5**

6a **6b** **7**

Scheme 1

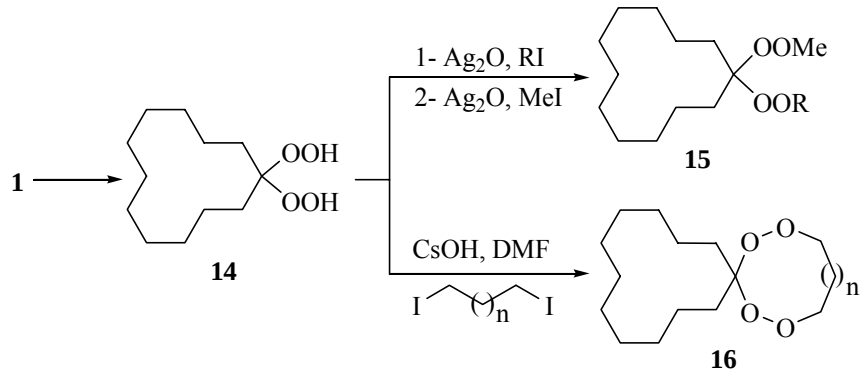
Cyclododecanone is also an important intermediate for synthesis of natural muscone **8** and macrocyclic fragrances of musk like odor *e.g.* (*S*)-muscolides: **9** and **10** as well as (*R*)-12-methyltridecanolide **11**.[6-10] In addition, it is also a starting material used for synthesis of the

expensive compounds having the greatly appreciated woody-amber odor,[11] such as Hydroxyambran® **12**,[12] and Lignoxan® **13**,[13] (Scheme 2).



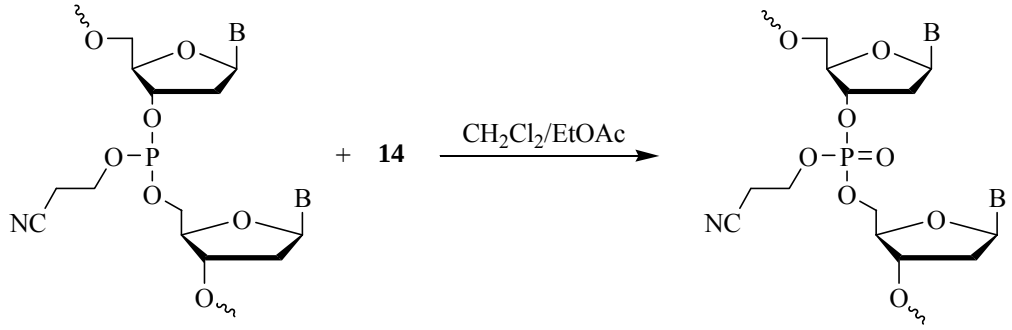
Scheme 2

Besides, it is served as a precursor for preparation of 1,1-dihydroperoxy-cyclododecane (DOD) **14** which in turn used as starting material for synthesis of a series of antimalarial agents such as **15** and **16** (Scheme 3).[14-18]

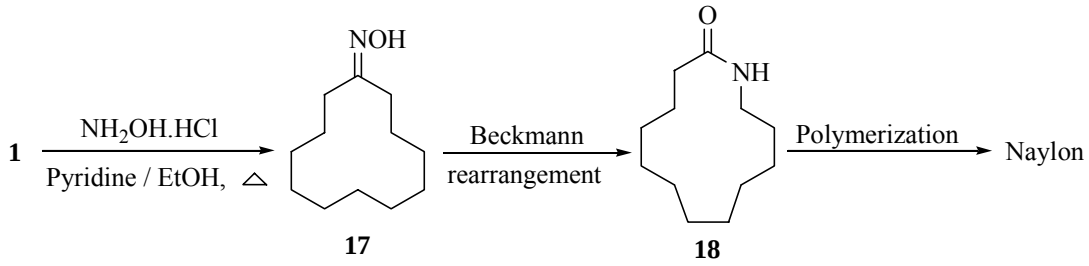


Scheme 3

1,1-Dihydroperoxy-cyclododecane (DOD) **14** is also proved to be a useful oxidizer applied in polynucleotide synthesis.[19]



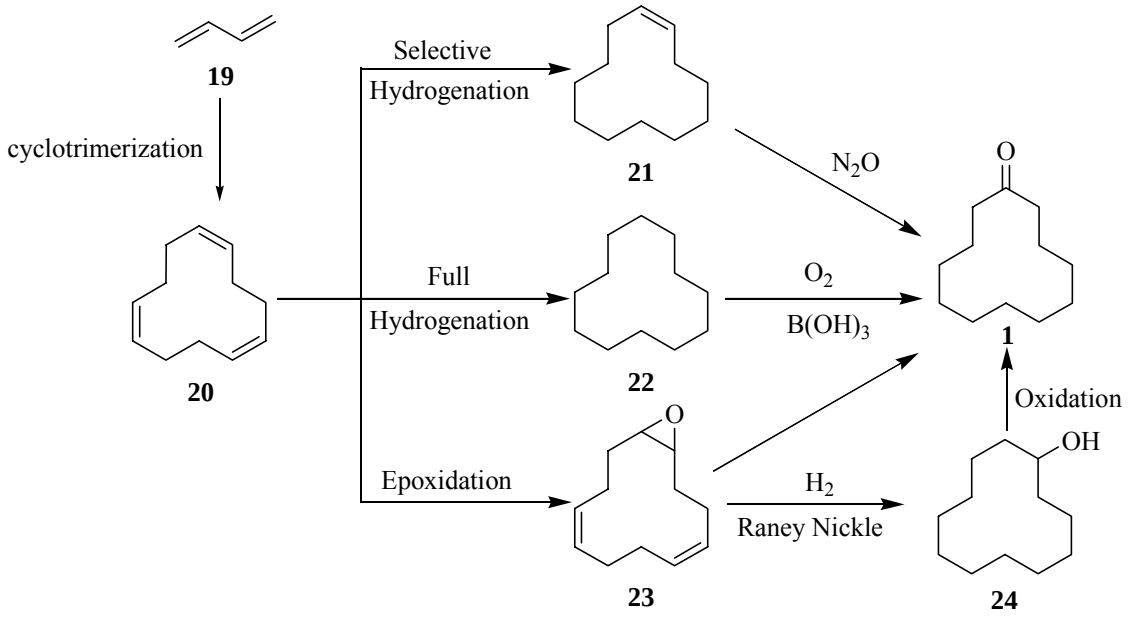
Once more, Beckmann rearrangement of cyclododecanone oxime **17** into laurolactam **18** is a highly important industrial process, where ring opening polymerization of lactam **18** is used industrially for production of Nylon and its copolymers (Scheme 4).[20]



Scheme 4

2. Synthesis of Cyclododecanone (1)

Generally speaking, the twelve-membered ring is easily assembled through cyclotrimerization of butadiene **19**. Butadiene cyclotrimerization process is performed in presence of various catalytic systems comprised transition metal compounds: Ti, Cr, Ni, Mn and organic compounds of aluminium.[21-24] The butadiene cyclotrimerization product 1,5,9-cyclododecatriene **20** is the key intermediate for production of various twelve-membered ring systems belonging to different classes of organic compounds. In this context, 1,5,9-cyclododecatriene is easily converted into **1** in several ways (Scheme 5).[25-35]

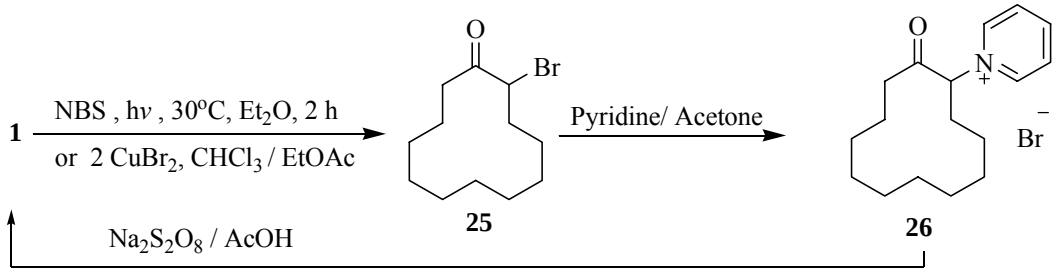


Scheme 5

3. Chemistry of Cyclododecanone

3.1 Halogenation

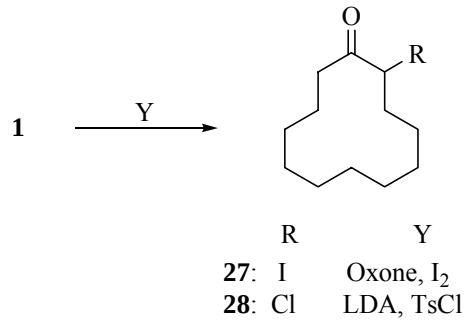
2-Bromocyclododecanone **25** can be obtained almost in quantitative yield by using *N*-bromosuccinimide (NBS) under photochemical conditions.[36] Bromoketone **25** is also prepared in an excellent yield using $CuBr_2$ in a mixture of chloroform and ethyl acetate under stream of nitrogen gas.[37] On the other hand, **1** can be regenerated by debromination of **25** through dithionite reduction of the pyridinium salt **26** (Scheme 6).[38]



Scheme 6

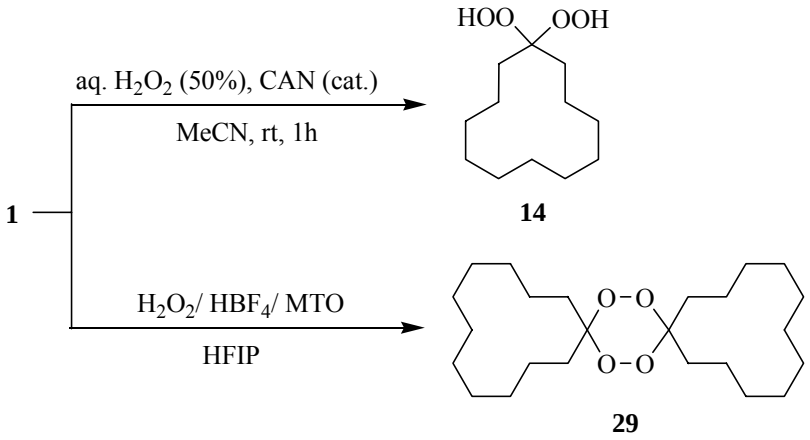
Selective *α*-iodination of **1** was accomplished in the solid state within a very short reaction time with excellent yield using elemental iodine and oxone as a catalyst, by grinding in a mortar to afford **27**.[39] Iodoketone **27** is also prepared efficiently using elemental Iodine and hydrogen peroxide.[40,41]

While, *α*-chlorocyclododecanone **28** was achieved in very good yield *via* treatment of cyclododecanone **1** with LDA followed by *p*-toluenesulfonyl chloride.[42]



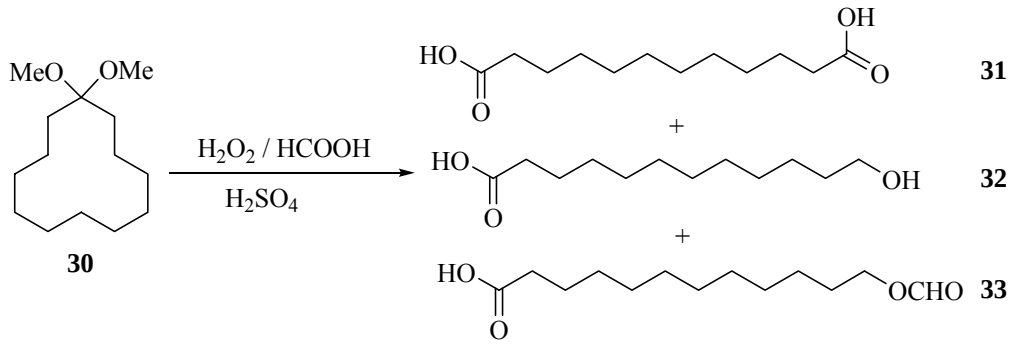
3.2 Oxidation

Cyclododecanone **1** was efficiently converted into the corresponding gem-dihydroperoxide **14** in high yield within a short period of time on treatment with aqueous H_2O_2 in the presence of catalytic amount of CAN in acetonitrile at room temperature.[43-45] While, treatment of **1** with H_2O_2 in fluorinated alcohol (HFIP) afforded the corresponding anti-malarial agent tetraoxane derivative **29** in 55% yield (Scheme 7).[46]

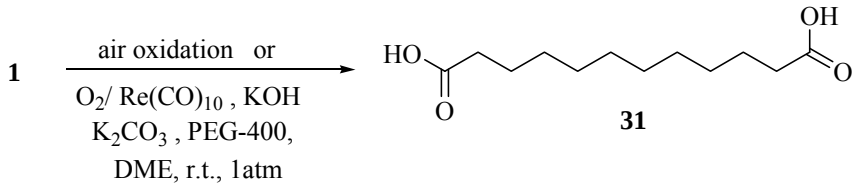


Scheme 7

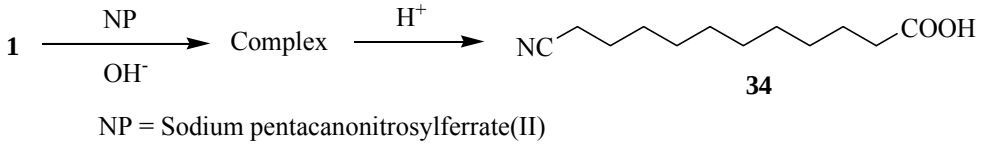
The industrially important 1,12-dodecanedioic acid **31** is the major oxidation product of cyclododecanone dimethyl acetal **30** by *in situ* generated performic acid, besides the minor products **32** and **33**.[47]



While Gauthard *et al*. reported that 1,12-dodecanedioic acid **31** can be obtained by air oxidation of **1** in presence of metal-free and platinum loaded carbon catalysts.[48] Alternatively, the diacid **31** is also obtained in 86% yield by oxidation of cyclododecanone **1** in presence of rhenium carbonyl and polyethylene glycol as phase transfer catalyst.[49] In addition, the dibutyl ester of **31** was achieved by oxidation of **1** with hydrogen peroxide in butanol.[50]

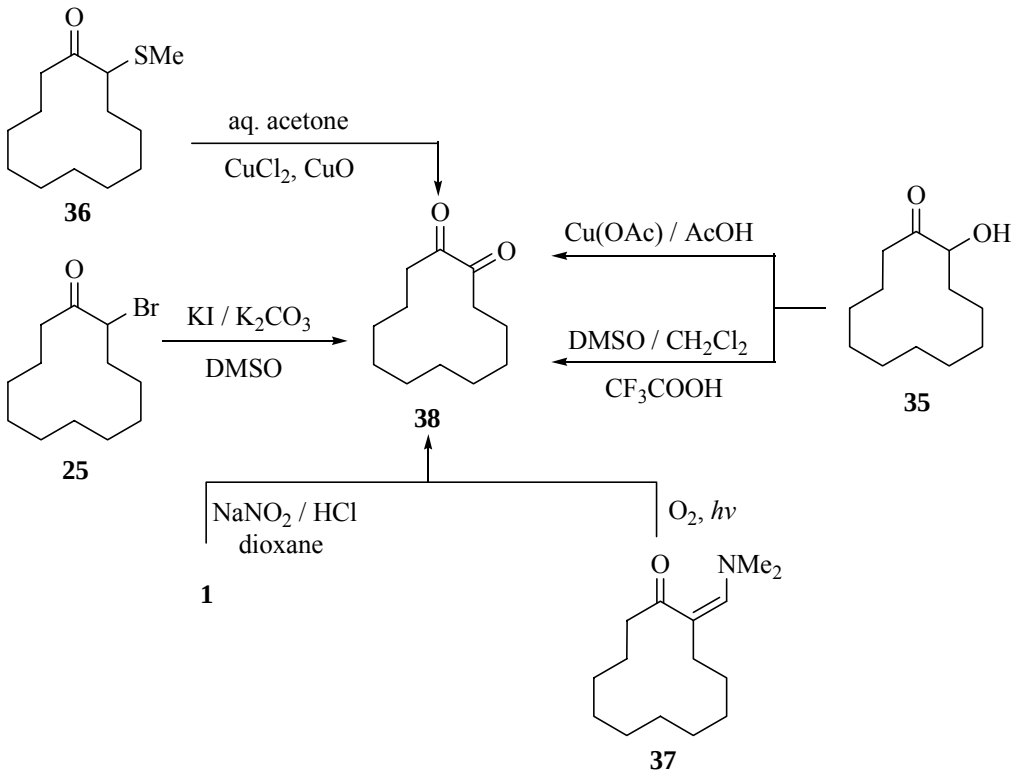


Alternatively, 11-cyanoundecanoic acid **34** was obtained by reaction of **1** with sodium pentacano nitrosyl ferrate(II) (NP) under basic conditions to give a colored complex which underwent acid hydrolysis to give **34**.[51]



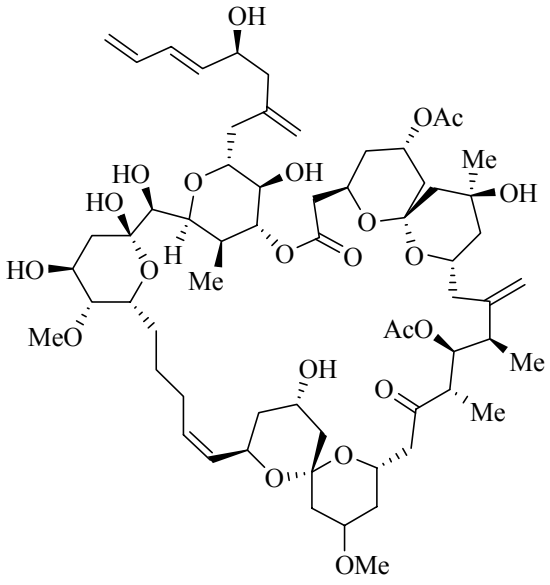
NP = Sodium pentacanonitrosylferrate(II)

1,2-Cyclododecanedione **38** was achieved in a good yield,[52-54] by a variety of oxidation methodologies (Scheme 5): (a) by treatment of **1** with excess sodium nitrite and aq. HCl,[55] (b) through treatment of 2-hydroxycyclododecanone **35** with either DMSO/CF_3COOH at -78 ^oC or Cu(OAc)/AcOH, (c) when 2-bromo-cyclododecanone **25** is oxidized using DMSO in presence of KI/K_2CO_3. Moreover, **38** was also obtained through chemical or photochemical oxidation of 2-(methylthio)cyclododecanone **36**,[56] and 2-((dimethylamino)methylene)cyclododecanone **37**,[57] respectively (Scheme 8).



Scheme 8

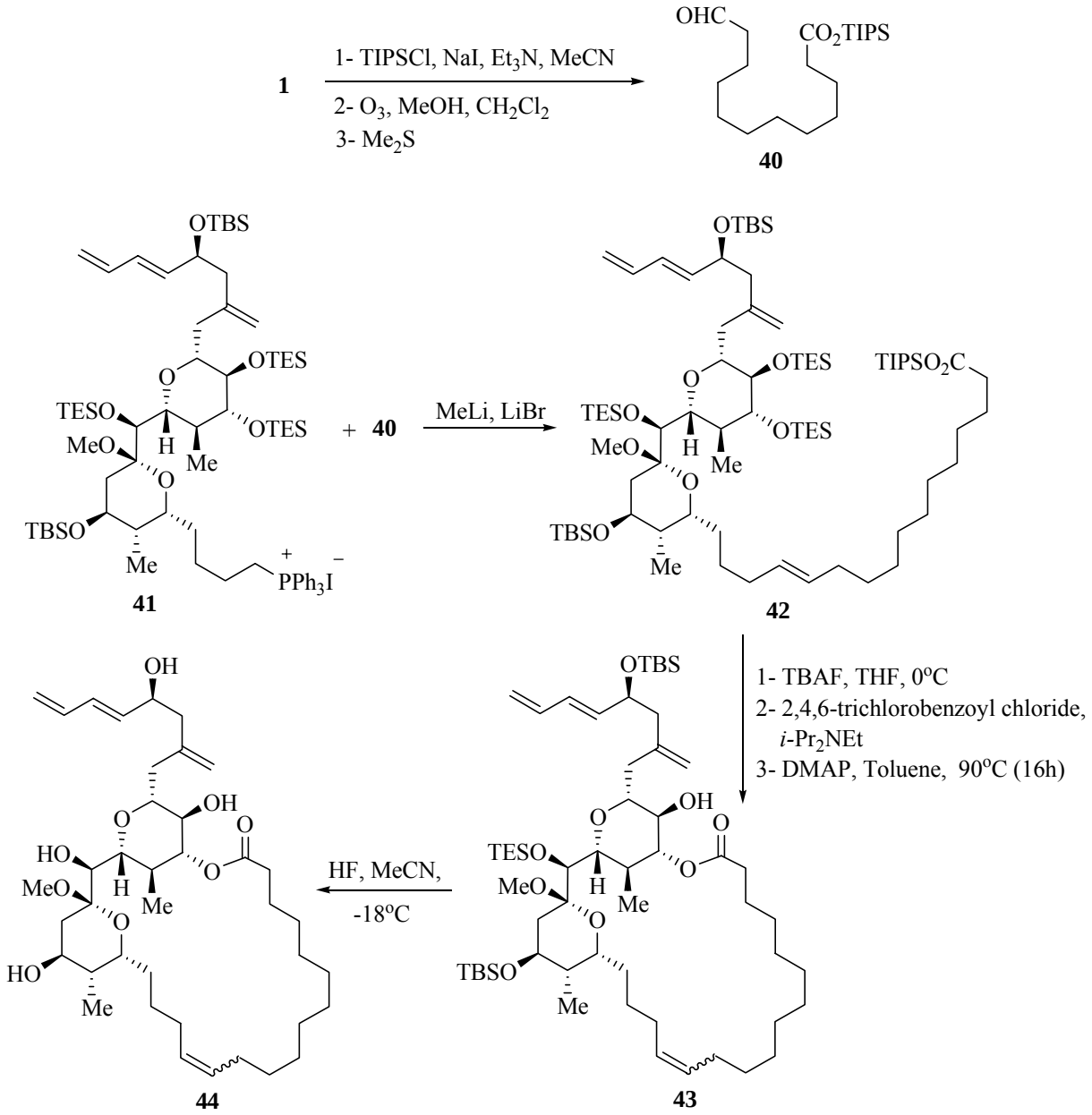
Altohyrtin C **39** was found to be exceedingly potent against human colon (HCT116) and ovarian (A2780) cell lines.[58]



(Altohyrtin C)

39

Cyclododecanone **1** is the source of **40** which is a main building block in the total synthesis of Altohyrtin C analogue **44** (Scheme 9).[58]

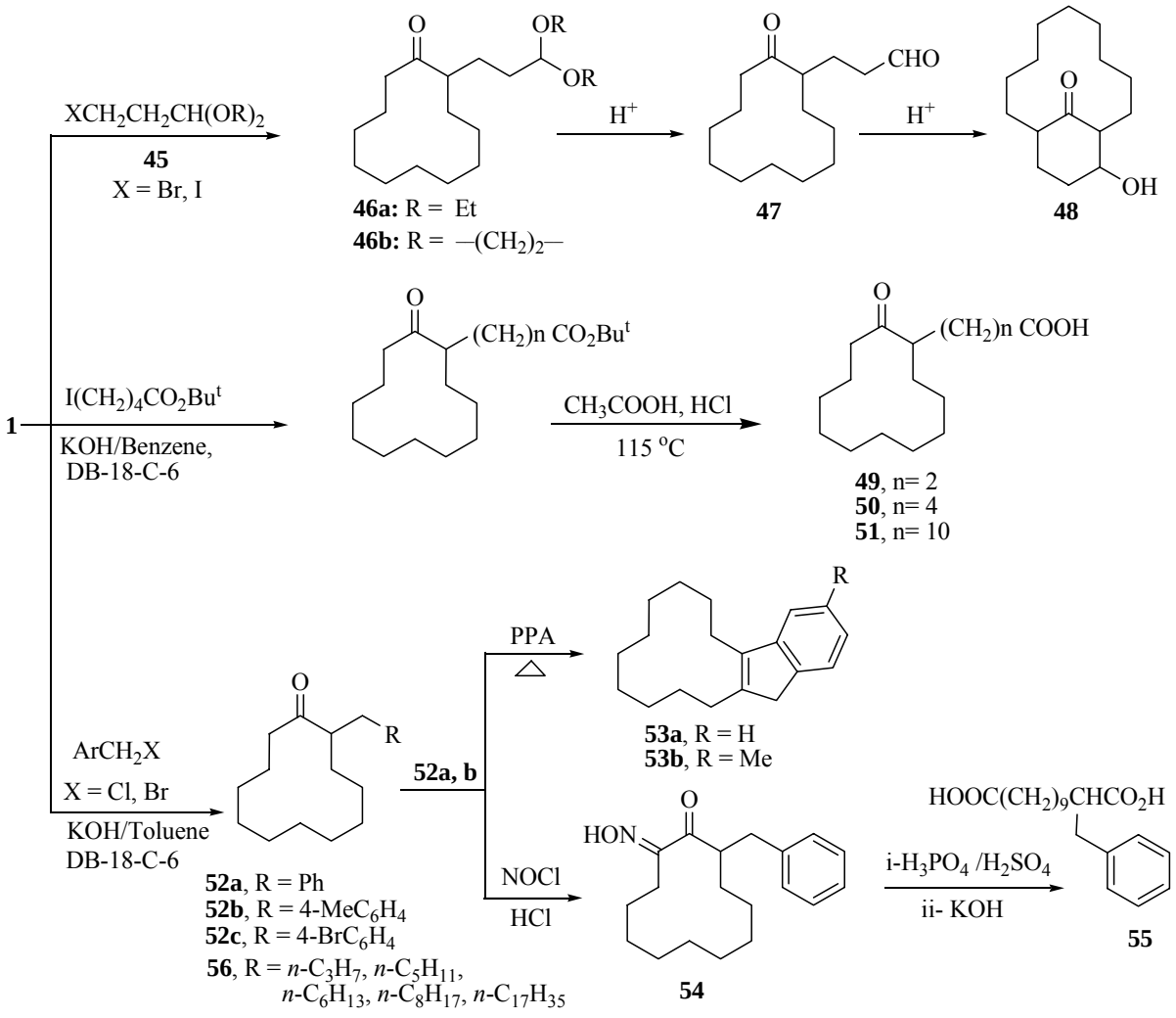


Scheme 9

3.3 Alkylation of cyclododecanone

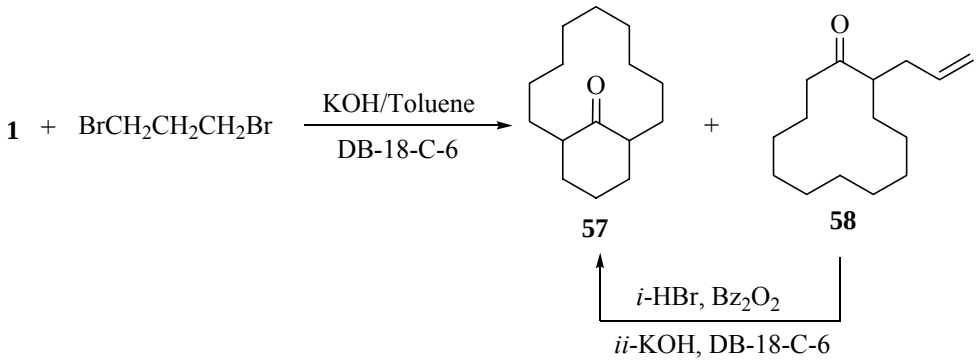
Cyclododecanone **1** easily undergoes alkylation on its α-carbon under phase-transfer catalysis (PTC). β-Halopropionic aldehyde acetals **45a**, **b** react readily with **1** to give the respective 2-(3-oxopropyl) cyclododecanone acetals **46a**, **b**. Acid hydrolysis of acetals **46** resulted in formation of 12-hydroxybicyclo[9.3.1]pentadecan-15-one **48** probably formed due to intramolecular aldol condensation of ketoaldehyde **47**.[59] 3-(2-Oxocyclododecyl)propionic acid and its esters are interesting starting materials for the synthesis of valuable aromatic substances such as decamethylene-8-valerolactone,[60] pentadecanolide (exaltolide),[61] and cyclopentadecanone (exaltone),[62] as well as macrocyclic ketoimides and *N*-acetylketolactams.[63] Accordingly, ω-(2-

oxocyclododecyl)alkanoic acids **49-51** were prepared based on alkylation of **1** with alkyl *ω*-haloalkanoates under conditions of phase-transfer catalysis (PTC) in a solid alkali-liquid system in the presence of crown-ethers (Scheme 14).[64] In addition, **1** is readily alkylated with benzyl halides ($ArCH_2X$) to give 2-benzylcyclododecanones **52a-c** under conditions of phase transfer catalysis. Then, polyphosphoric acid promotes cyclization of 2-benzylcyclododecanones **52a**,**b** into 1,2,3,4,5,6,7,8,9,10-decahydrocyclododeca[*b*]indenes **53a**,**b**. While, **52a** reacted with NOCl to give 12-hydroxyimino-2-benzylcyclododecanone **54**, which enters the Beckmann rearrangement followed by hydrolysis to afford 2-benzyl-1,12-dodecandioic acid **55**.[65] 2-Alkylcyclododecanones are starting compounds for the preparation of higher normal carboxylic and ketocarboxylic acids and alcohols. Unlike simple aliphatic ketones and lower cycloalkanones, **1** is smoothly alkylated by *n*-alkyl halides under phase-transfer catalysis conditions in the presence of solid potassium or sodium hydroxide in a medium of hydrocarbons with the formation of 2-alkylcyclododecanones **56** in high yield (75-85%) (Scheme 10).[66]

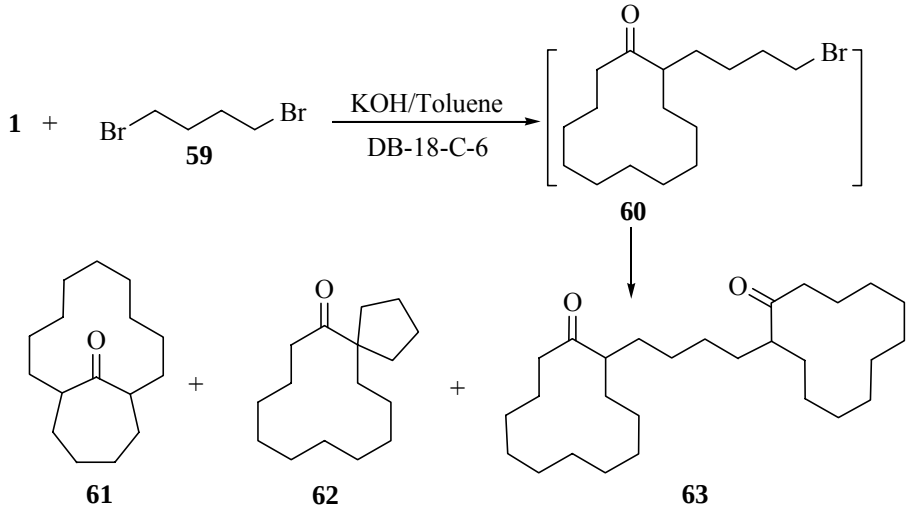


Scheme 10

Bicyclic ketones obtained from cyclododecanone, such as, bicycle[9.3.1]pentadecan-15-one and bicyclo[9.4.1]hexadecan-16-one, are highly important starting materials for syntheses of metacyclophanes,[67,68] and macrocyclic ketones, *viz*, cyclopentadecanone and muscone.[69] Alkylation of **1** with *α,ω*-dibromoalkanes under conditions of phase-transfer catalysis (PTC) was investigated in the aim of obtaining bicyclic ketones.[70] Thus, reaction of 1,3-dibromopropane with **1** in toluene at 80-100 °C in presence of KOH and crown ether (DB-18-C-6) as phase-transfer catalyst afforded *trans* bicycle[9.3.1]pentadecan-15-one **57** and 2-allylcyclododecanone **58** in 3:2 ratio with 67% total yield. Ketone **58** is formed as a mixture of cis- and trans-isomers if 2-ethoxycarbonylcyclododecanone is used as the starting material.[67]



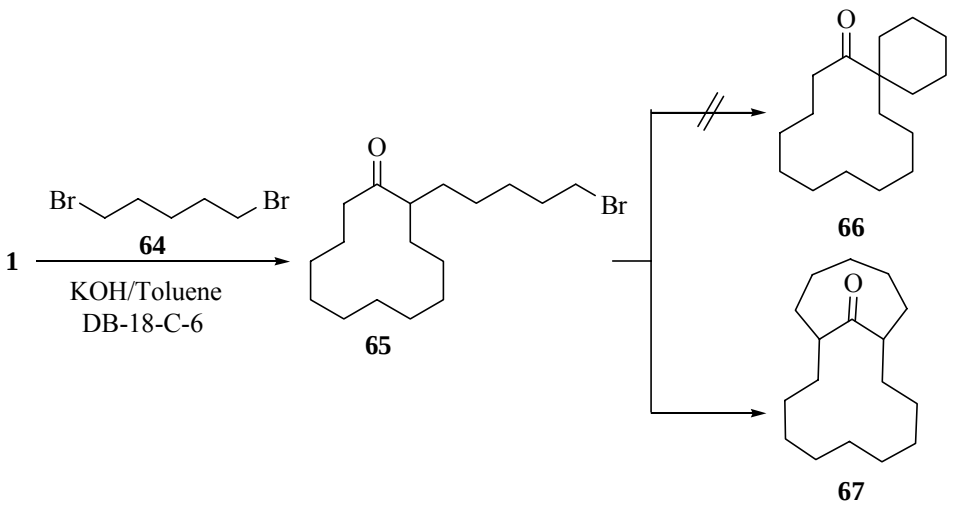
In the same manner, reaction of **1** with 1,4-dibromobutane **59** gives bicyclic ketone **61** and spirocyclic ketone **62** in 5:4 ratio in addition to small amount of 1,4-*bis*(2-oxocyclododecyl)butane **63** *via* cyclization of **60** (Scheme 11).[70]



Scheme 11

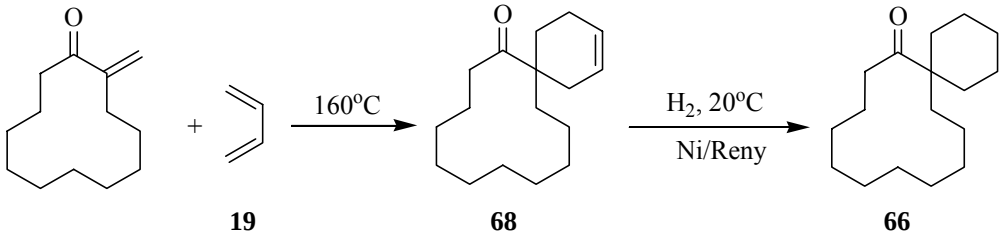
While alkylation of **1** with 1,5-dibromopentane **64** under the same conditions followed by cyclization of intermediate **65** didn t give the expected 7-oxospiro[5.11]heptadecane **66**, but

afforded bicyclo[9.5.l]hepta-decan-17-one **67** exclusively, the structure of which was established by ^{13}C NMR (Scheme 12).[70]



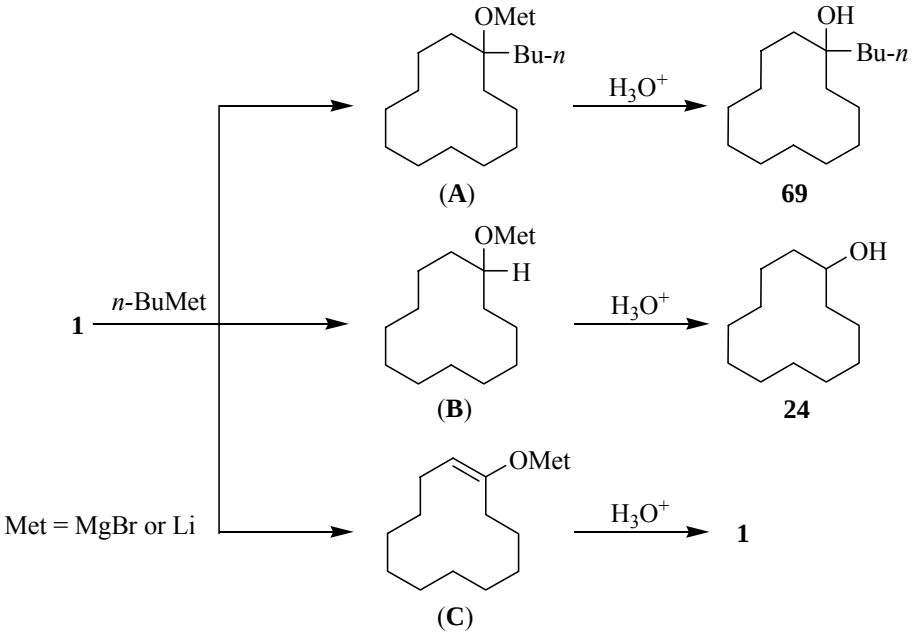
Scheme 12

The desired spirocyclic ketone **66** was alternatively achieved based on Diels-Alder reaction in a separate experiment (Scheme 13).[70]



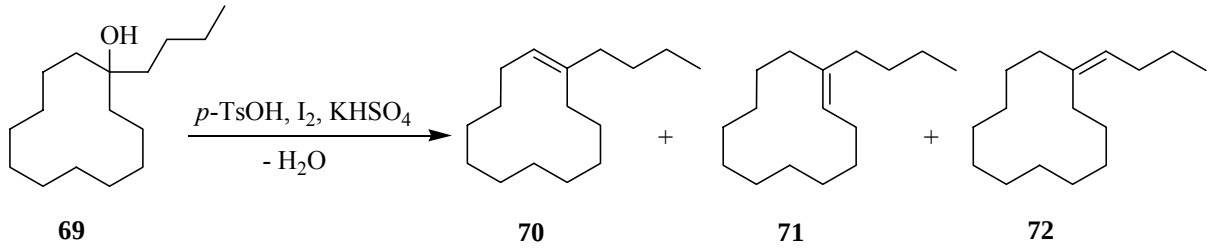
Scheme 13

Furthermore, interaction of *n*-BuMgBr and *n*-BuLi with **1** proceeds through three pathways (Scheme 14),[71] *i*. Addition to the carbonyl group to give the alcoholate of the tertiary alcohol (**A**). *ii*. Reduction of the ketone resulting in the alcoholate of cyclododecanol (**B**), and butene. *iii*. Deprotonation-enolization of the ketone with the formation of enolate (**C**) and liberation of butane. Hydrolysis of intermediates **A**, **B** and **C** afforded 1-butylcyclododecanol **69**, cyclododecanol **24**, and the original ketone **1**, respectively.

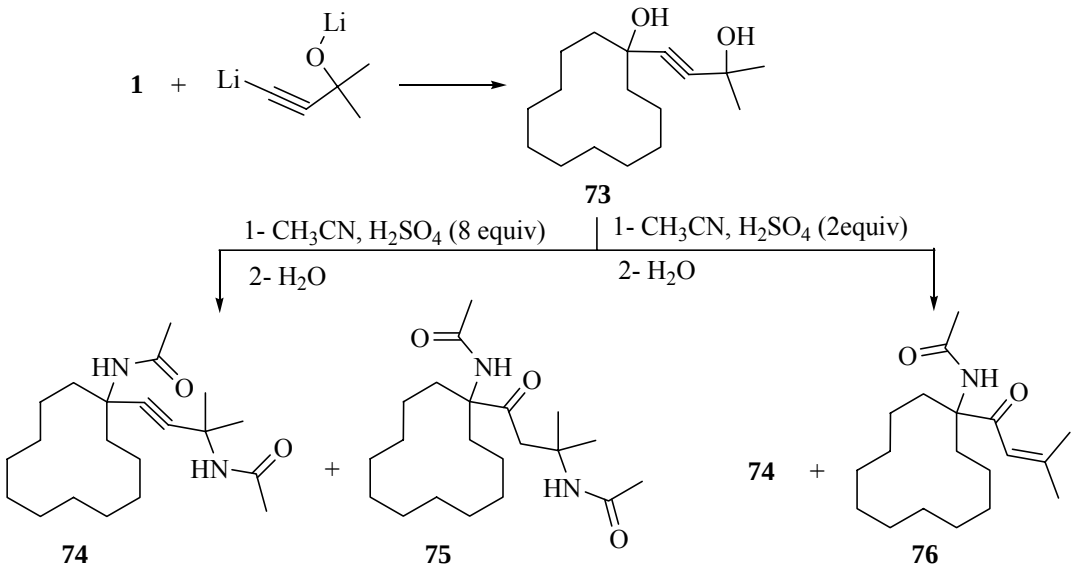


Scheme 14

Furthermore, dehydration of **69** gave a mixture of olefins, (*Z*)-1-butylcyclododec-1-ene **70**, (*E*)-1-butylcyclododec-1-ene **71** and butylidenecyclododecane **72**.

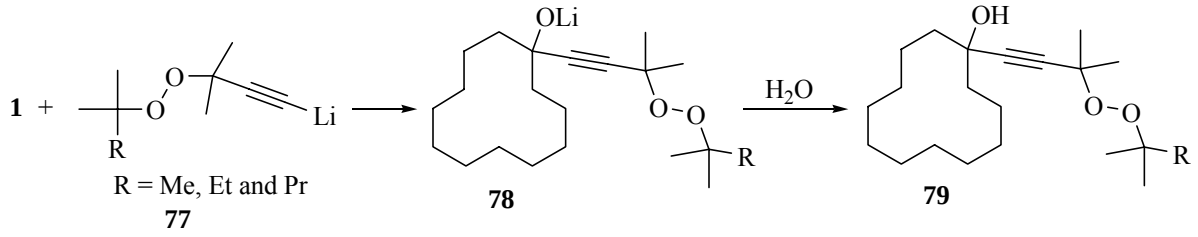


Acetylenic alcohols are widely used in organic synthesis owing to their high reactivity. In this context, 1-(3-hydroxy-3-methylbut-1-ynyl)-cyclododecanol **73** was prepared by the action of lithium (3-methyl-3-oxidobut-1-ynyl)lithium on **1**. The product reacts with acetonitile under Ritter reaction conditions. Therewith, in the presence of 8 g-equivalent of sulfuric acid, a (2:1) mixture of *N*-(1-(3-acetamido-3-methylbut-1-ynyl)-cyclododecyl)acetamide **74** and *N*-(1-(3-acetamido-3-methylbutanoyl)cyclododecyl)acetamide **75** is formed. Whereas, in the presence of 2 g-equivalent of the acid, a mixture of **74** and 1-acetylamino-1-(3-methyl-2-butenoyl)cyclododecanone **76** is formed (Scheme 15).[72]

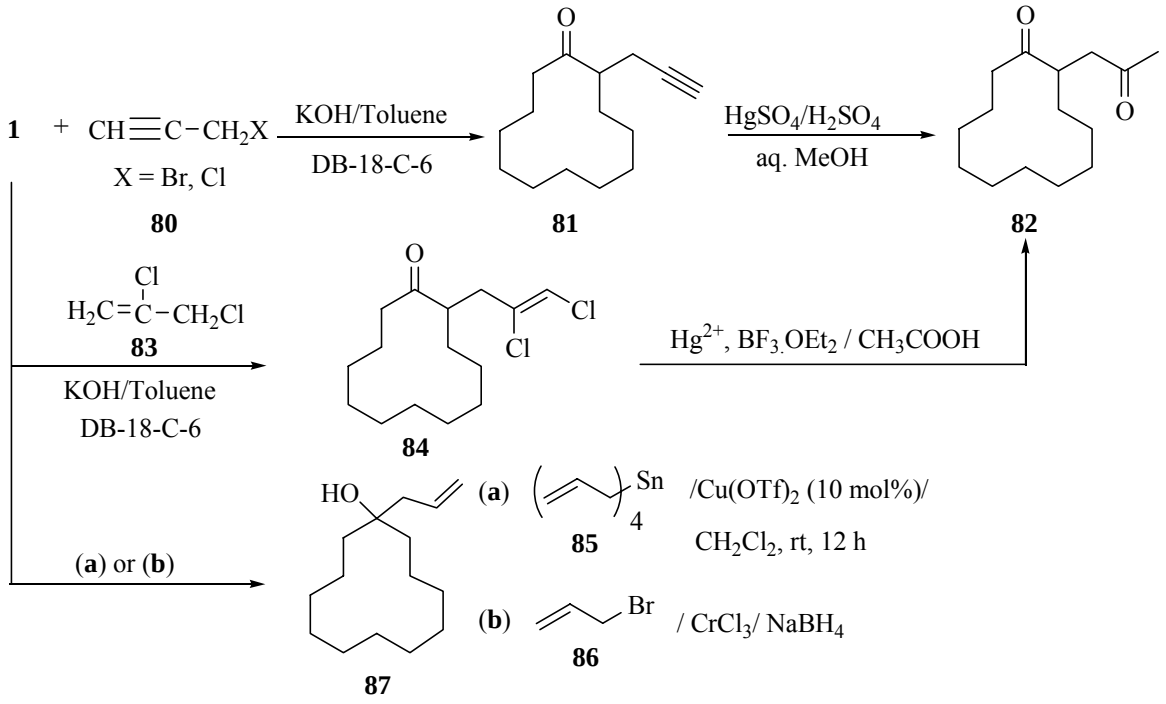


Scheme 15

In a similar manner, a series of peroxy containing tertiary acetylenic alcohols **79** were obtained through the intermediates **78** by reaction of lithium peroxyacetylides **77** with **1**.[73]

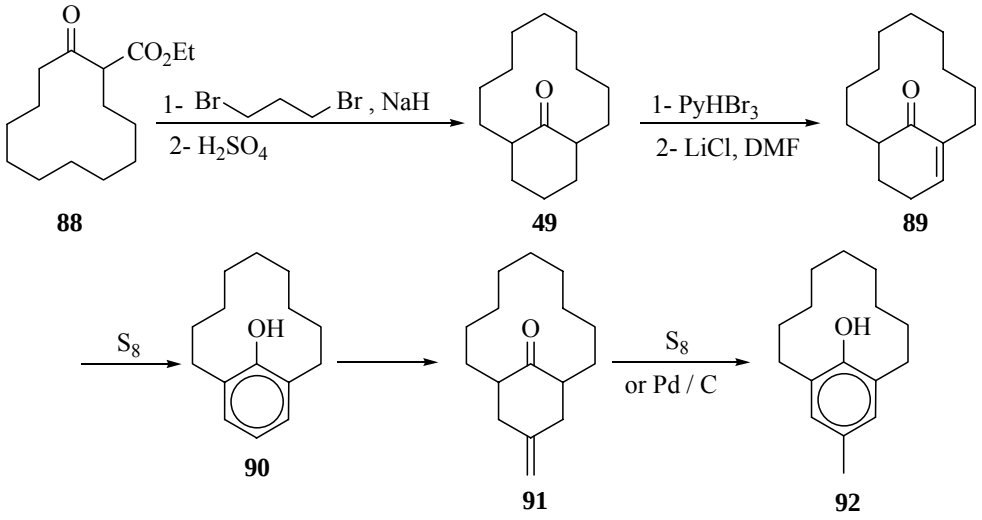


2-Acetonylcyclododecanone **82** is an important intermediate in the preparative synthesis of cyclopentadecanone (exaltone) and 3-methyl-cyclopenta-decanone (muscone) which are valuable fragrances.[70] Cyclododecanone **1** is readily alkylated by propargyl bromide or chloride **80** under phase transfer catalysis conditions with solid KOH, toluene, and dibenzo-18-crown-6 to give 2-propargylcyclododecanone **81** in high yield. The hydration of ketone **81** provides a simple approach to 2-Acetonylcyclododecanone **82**. Also, alkylation of **1** by 1,2-dichloropropene **83** under phase transfer catalysis conditions gave 2-(2-chloropropen-2-yl)cyclododecanone **84**, which, upon hydrolysis in acetic acid in presence of Hg^{2+} ions and $BF_3.OEt_2$ gave 2-acetonylcyclododecanone **82**.[74] Cyclododecanone **1** undergoes an allylation reaction with tetra-allyltin **85** in presence of a catalytic amount of $Cu(OTf)_2$ to afford 1-allyl-cyclododecanol **87** in 98% yield.[75,76] 1-Allylcyclododecanol **87** was alternatively obtained in 82% yield by reaction of **1** and allyl bromide **86** under the Influence of $CrCl_3/NaBH_4$ reagent (Scheme 16).[77]



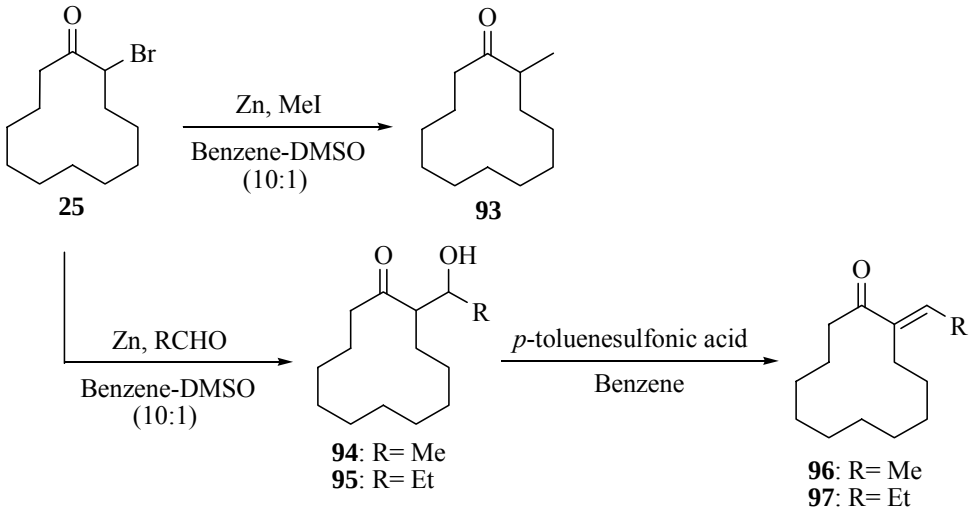
Scheme 16

Alkylation of 2-ethoxycarbonylcyclododecanone **88** with 1,3-dibromo-propane, followed by hydrolysis and decarboxylation, afforded the bicyclic ketone **49**, which on bromination with pyridinium hydrobromide ($PyHBr_3$) and subsequent dehydrobromination gave the bicyclic enone **89**. Dehydrogenative aromatization of **89** was accomplished by heating with sulfur to afford 15-hydroxy[9]metacyclophane **90**. Analogously, 12-methyl substituted derivative **92** was obtained from the enone **91** by simple dehydrogenation with sulfur or Pd/C (Scheme 17).[78]



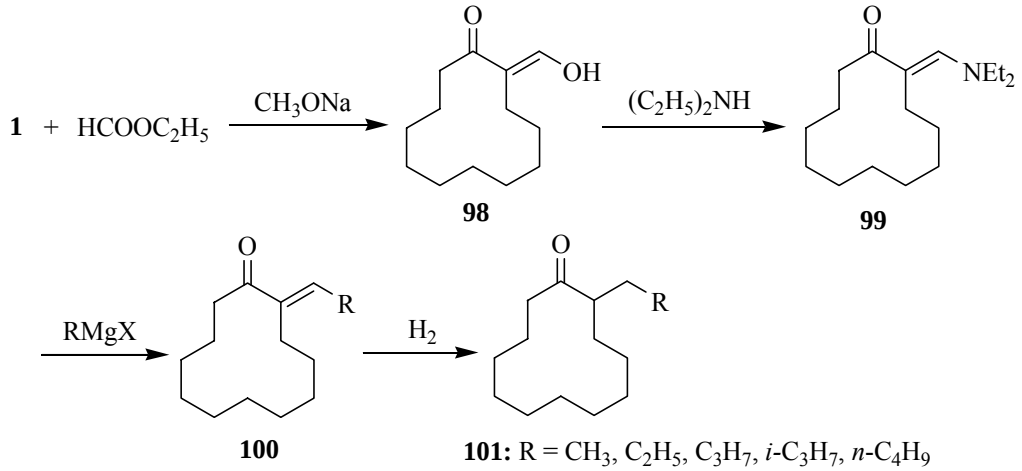
Scheme 17

Treatment of 2-bromocyclododecanone **25** with zinc powder and methyl iodide in benzene-DMSO mixture yielded 2-methylcyclododecanone **93** quantitatively. Also, the reaction of 2-bromocyclododecanone **25** with acetaldehyde and propionaldehyde under the same conditions afforded 2-(1-hydroxyethyl)cyclododecanone **94** and 2-(1-hydroxypropyl)cyclododecanone **95**, respectively. Dehydration of the aldols **94** and **95** furnished 2-ethylidenecyclododecanone **96** and 2-propylidenecyclododecanon **97**, respectively (Scheme 18).[79]



Scheme 18

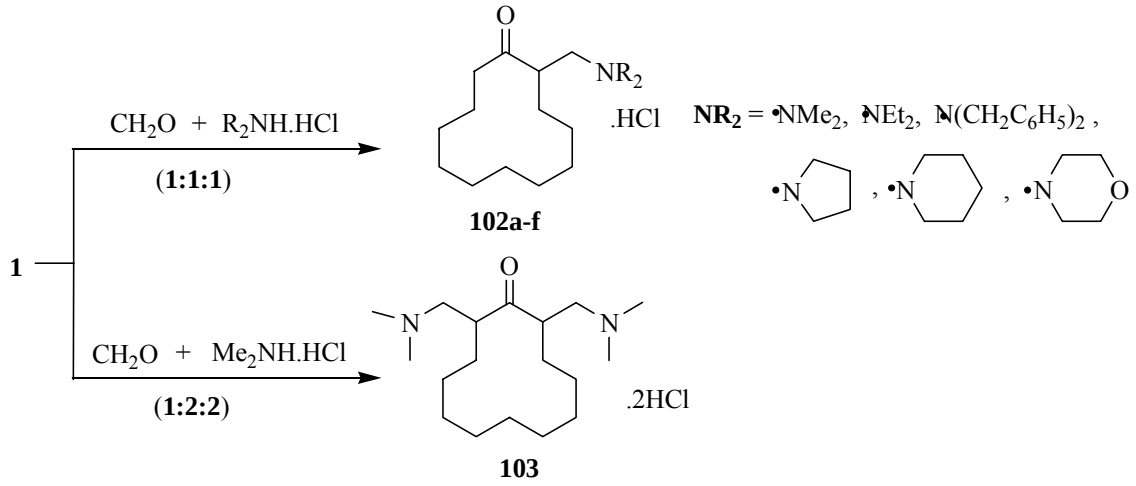
Ynthesis of molecules having musk odor is a very attractive topic. Hence, Zakharkin *et al*. reported the synthesis of 2-alkylidene-and 2-alkylcyclododecanones which had a very delicate musk odor. In this context, **1** was treated with ethylformate in the presence of sodium methoxide to give 2-hydroxymethylene cyclododecanone **98** in a high yield. Its treatment with diethylamine yielded 2-*N*-diethylaminomethylenecyclododecanone **99**. Treatment of **99** with alkyl magnesium halides afforded 2-alkylidenocyclododecanones **100** which upon catalytic hydrogenation gave 2-alkylcyclododecanones **101** (Scheme 19).[80]



Scheme 19

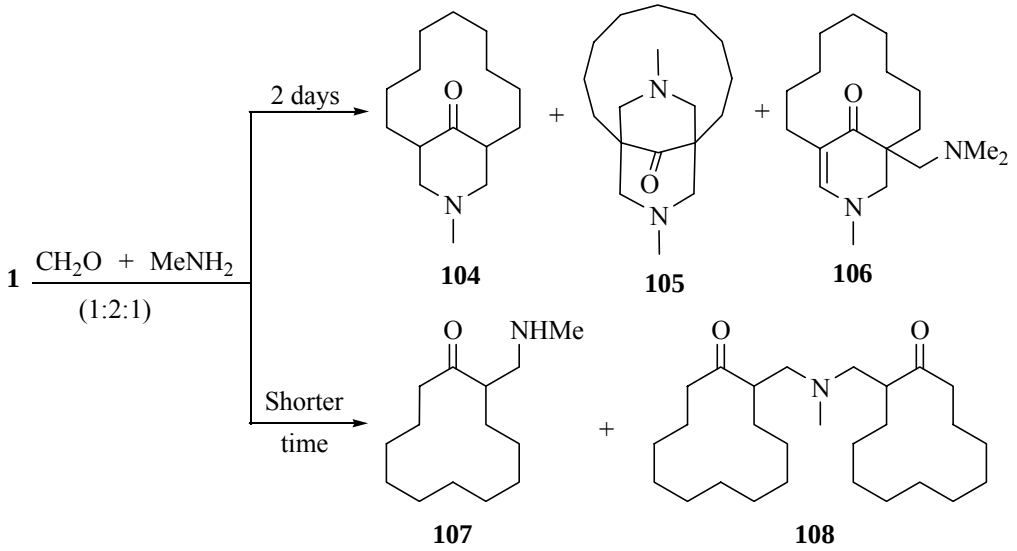
3.4 Mannich reaction

A series of mono Mannich bases of cyclododecanones **102a-f** were synthesized and their cytotoxicity was evaluated. Also, the double Mannich base **103** was synthesized for the same purpose (Scheme 20).[81,82]



Scheme 20

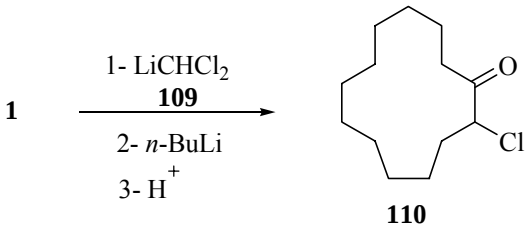
In the same context, when **1** was heated under reflux for 2 days with aqueous ethanolic formaldehyde (2.0 mol equiv.) and methylamine (1.0 mol. equiv.) a complex products mixture was obtained. Consequently, three compounds were isolated from the basic fraction by column chromatography on silica-gel and crystallization. In addition to the expected azabicyclopentadecanone **104**, there was found the *bis*-pidone, (the diazatricyclooctadecanone) **105**. The major component isolated from the reaction mixture was the dihydropyridin-4-one **106** (20%). Similar condensations carried out with shorter reaction times have allowed the isolation of the simpler bases **107** and **108** (Scheme 21).[83]



Scheme 21

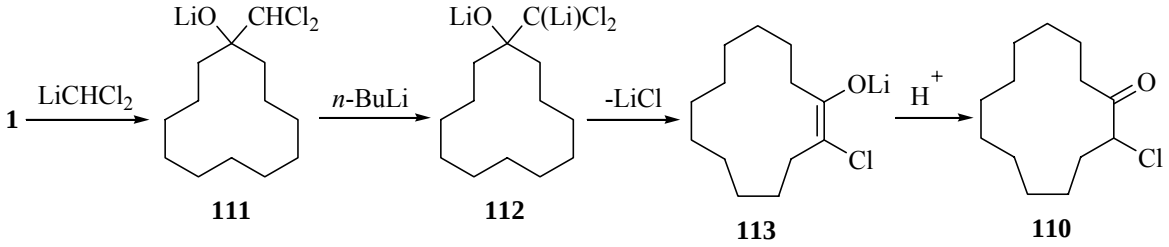
3.5 Ring enlargement

3.5.1 Macrocyclic ketones and esters. Cyclododecanone **1** was transformed into its next higher ring homologue,[84] chlorinated at the α-carbon **110** under the influence of (dichloromethyl)lithium **109** and butyl lithium.[85]



110

The proposed mechanism for transformation of **1** into 2-chlorocyclotridecanone **110** was illustrated by the following reaction sequences compounds **111-113** (Scheme 22).

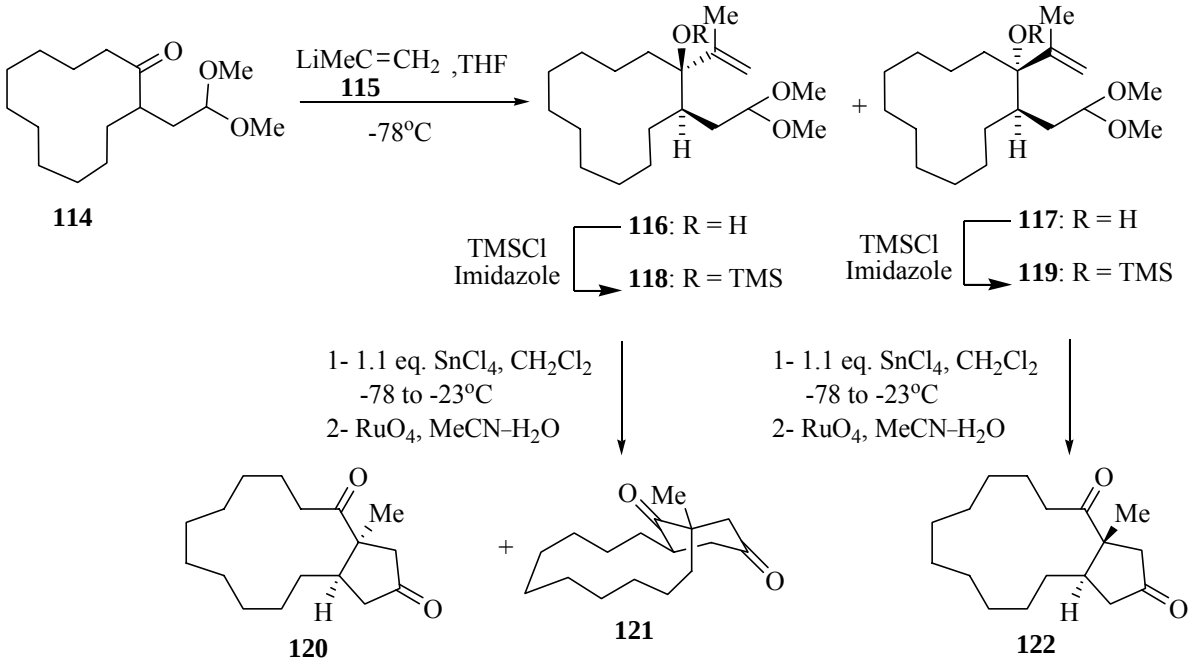


111 **112** **113** **110**

Scheme 22

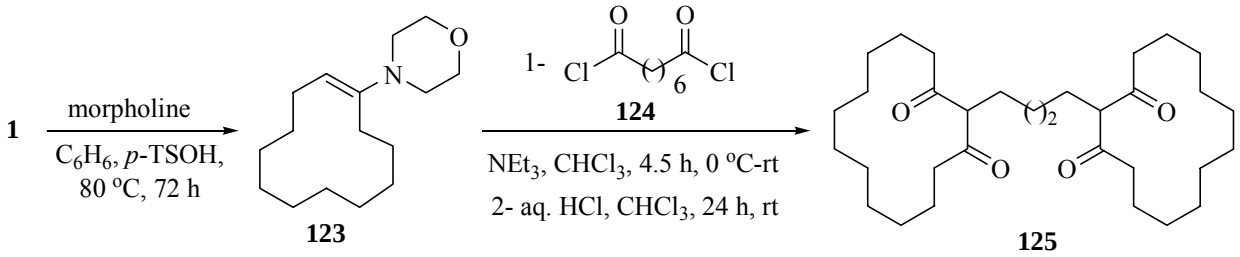
Condensation of 2-(2,2-dimethoxyethyl)cyclododecanone **114** with 2-propenyllithium **115** at -78 ^{o}C gave the two epimeric alcohols **116** and silylated **117**. Both alcohols are silylated to give **118** and **119**, respectively. Prins-Pinacol reaction of **118** gave cis-bicyclo[11.3.0]hexadecandione **120** as the major product (55%), besides the unusual inside-outside bicyclic dione **121** in 13% yield. Identical treatment of epimeric alkenyl acetal **119** produced neither **120** nor **121**, but rather trans-bicyclo[11.3.0]hexadecandione **122** in 61% yield (Scheme 23).[86]

The morpholino enamine of cyclododecanone **123** was synthesized by the acid-catalyzed condensation of morpholine and cyclododecanone. A [2+2] cycloaddition of the enamine **123** and suberoyl chloride **124** produced the macrocyclic tetraketone **125** (Scheme 24).[87]



114 **120** **121** **122**

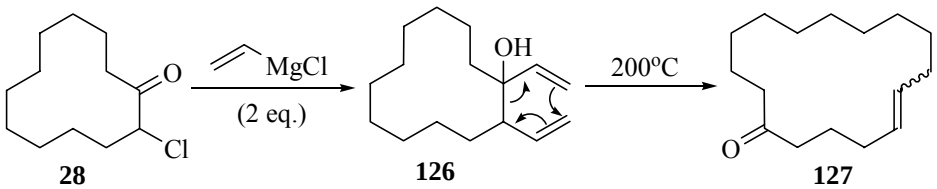
Scheme 23



123 **125**

Scheme 24

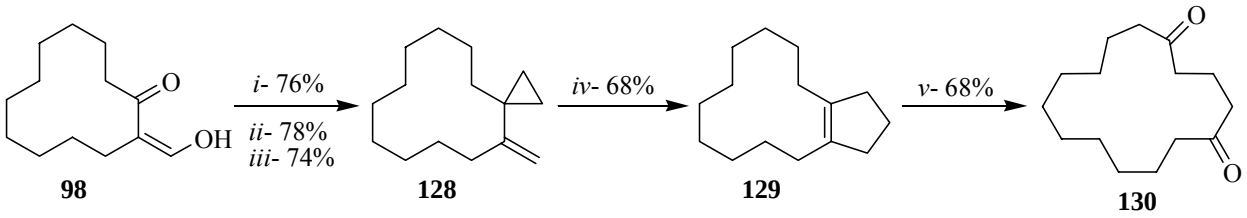
An efficient ring enlargement with four carbon atoms using the oxy-Cope rearrangement transforms **1** into cyclohexadec-5-ene-1-one **127**,[88,89] which is a valuable musky compound known under the trade name Ambretone® and musk TM II® (Scheme 25).[90]



28 **126** **127**

Scheme 25

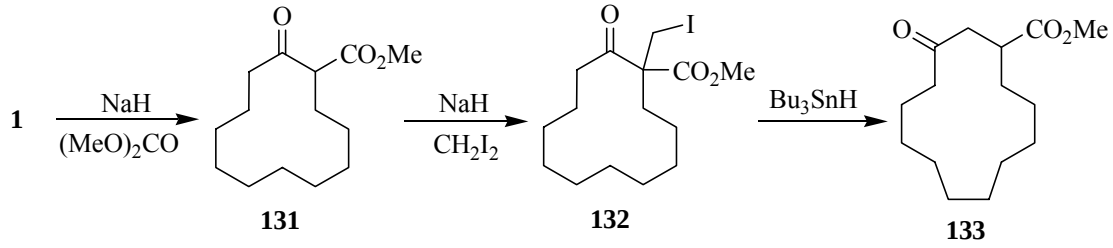
The diketone **130** is a key synthetic intermediate for muscone,[91] it was synthesized from 2-hydroxymethelenecyclododecanone **98** *via* thermal rearrangement of spirocyclicvinylcyclo-propane **128** into 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-cyclopenta[12]annulene **129**. Then periodate oxidation of **129** furnished the target dione **130** (Scheme 26).[92]



i- Mannich/CH_3I; *ii*- $(Me)_3S^+=OI^-$/NaH; *iii*- $Zn/TiCl_4/CH_2Br_2$;
iv- 500°C; *v*- $RuCl_3/NaIO_4$,CCl_4, MeCN, H_2O

Scheme 26

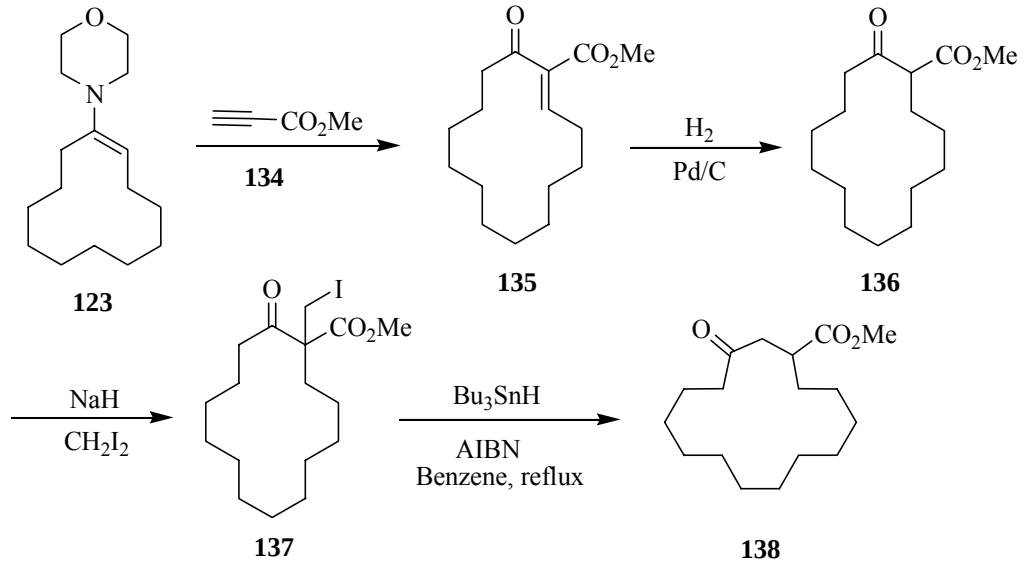
The thirteen-membered ring *γ*-ketoester **133** was achieved through free radical one carbon ring expansion of the iodomethylene derivative **132** which was prepared by alkylation of *β*-ketoester **131** with methylene iodide as illustrated by the following equation (Scheme 27).[93]



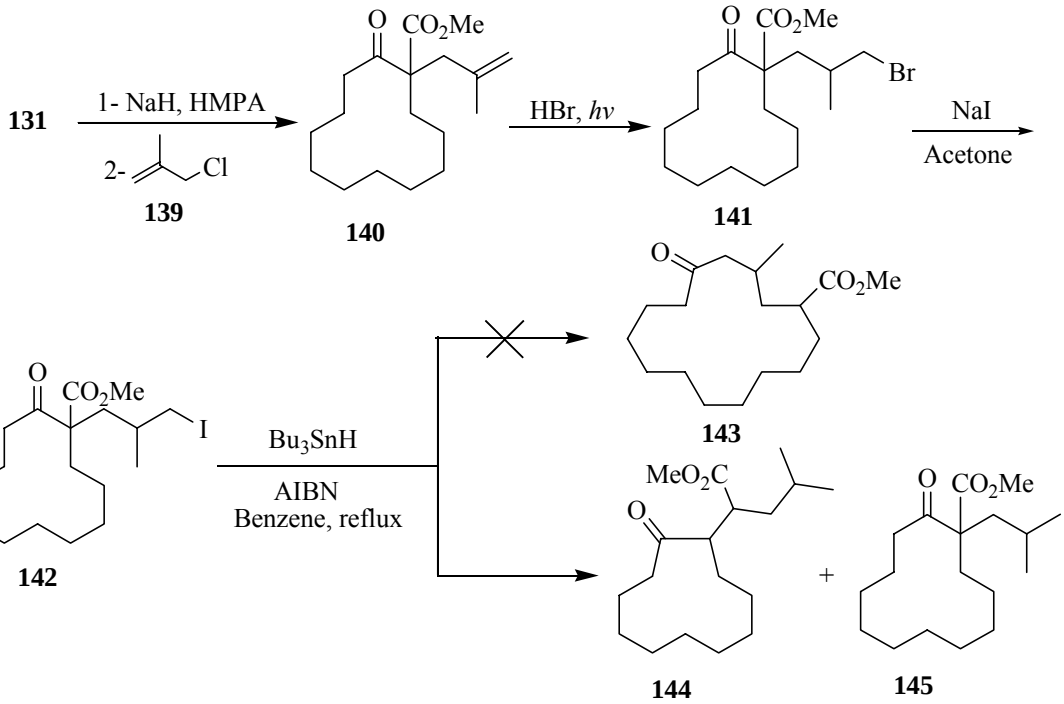
Scheme 27

The fourteen-membered ring *β*-ketoester **136** was prepared by cycloaddition of methyl propiolate **134** to the morpholino enamine of cyclododecanone **123**,[94] followed by catalytic hydrogenation of the adduct **135**. Alkylation of *β*-ketoester **136** with methylene iodide yielded **137**. Tri-*n*-butyltin hydride (Bu_3SnH) promoted ring expansion of **137** into the desired fifteen-membered ring *γ*-ketoester **138** (Scheme 28).[93]

The three-carbon ring expansion of a twelve to a fifteen-membered ring was used to explore the extension of preceeding method to larger increments. For this purpose, muscone was chosen as a target molecule. First, methyl cyclododecanone-2-carboxylate **131** was alkylated with 3-chloro-2-methylpropene **139**. The resulting adduct **140** was then hydrobrominated under free radical conditions yielding the terminal bromide **141**, which was then converted to the iodide **142** in a Finklestein displacement reaction. The iodide **142** when treated with tri-*n*-butyltin hydride did not yield the desired fifteen-membered ketoester **143**. Instead, ring contraction occurred yielding the eleven-membered ketoester **144** together with the product of direct reduction **145** (Scheme 29).[93]

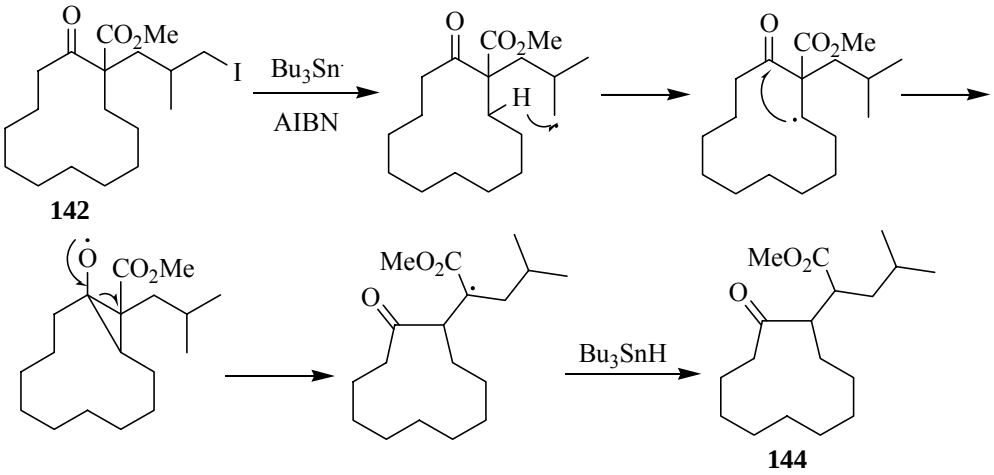


Scheme 28



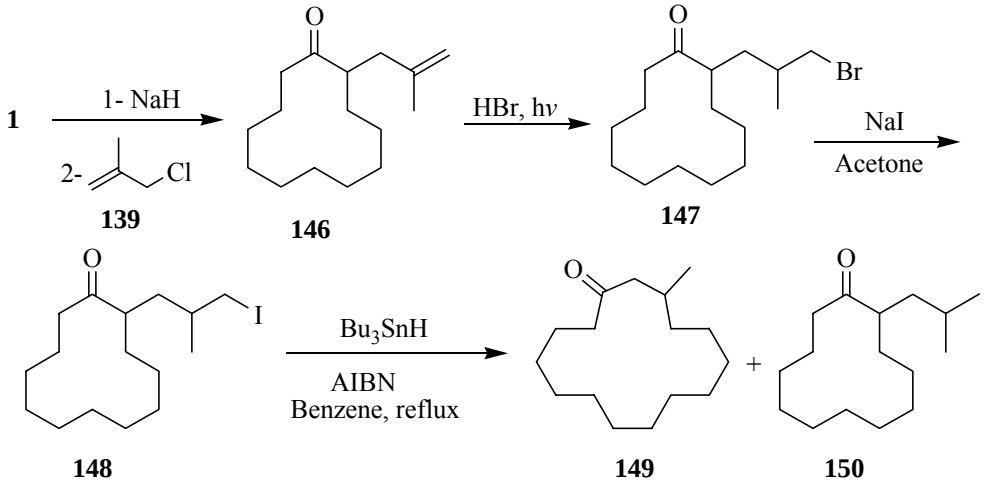
Scheme 29

A plausible mechanism for formation of **144** is presented in the Scheme 30.[93]



Scheme 30

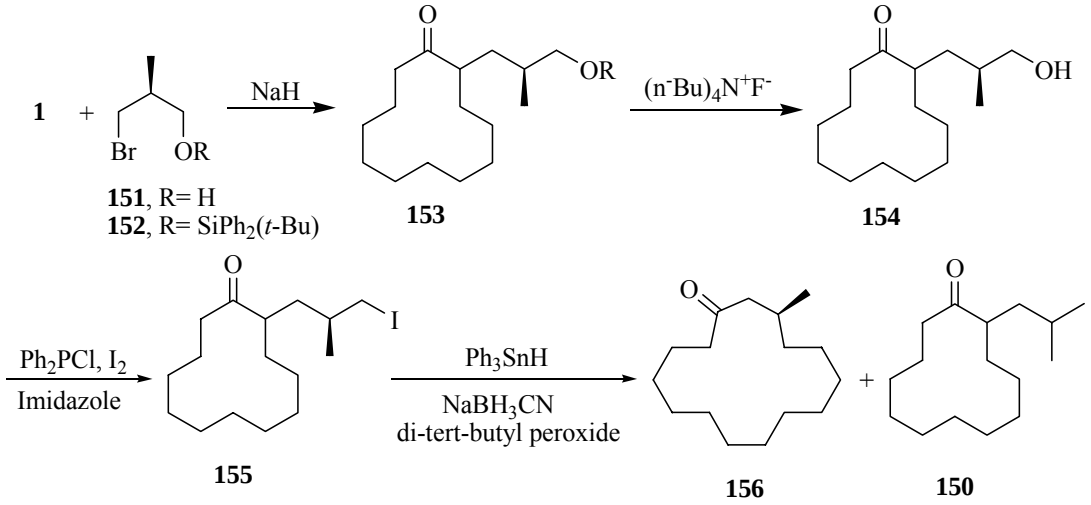
So this strategy failed to achieve muscone, and to achieve that target another trial was carried out where the enolate anion of **1** was alkylated with 3-chloro-2-methylpropene **139** in the presence of iodide ion to yield the adduct **146** (54%). Hydrogen bromide was added to the double bond of **146** under free radical conditions leading to **147**. The primary bromide in **147** was displaced by iodide ion in a Finkelstein reaction. The resulting iodide **148** was treated with tri-*n*-butyltin hydride and rearranged to (±)-muscone **149** (15%) together with the product of direct reduction **150** (Scheme 31).[93]



Scheme 31

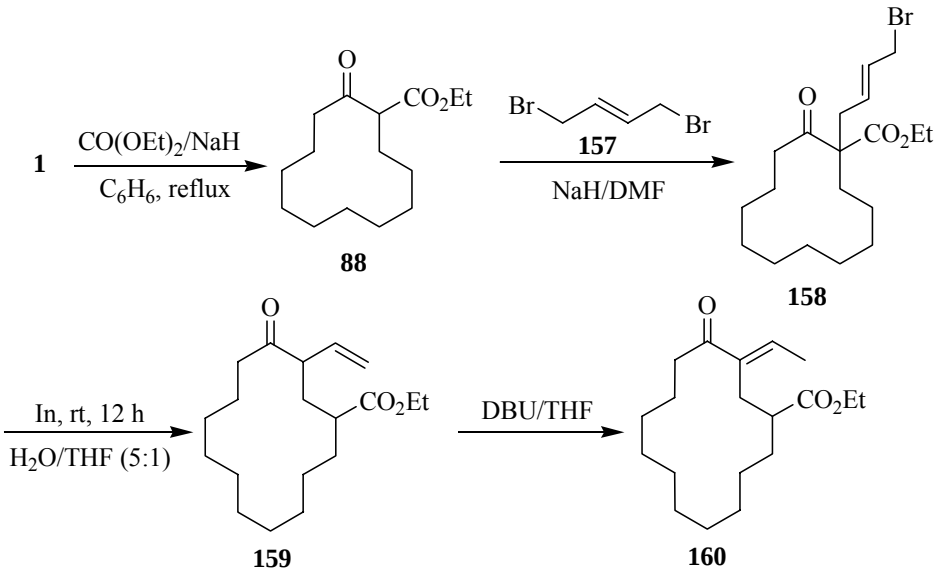
Success of the preceeding methodology promoted the synthesis of the naturally occurring levorotatory enantiomer of muscone. Thus, the readily available (*S*)-(+)-3-bromo-2-methylpropanol **151** was protected as its *t*-butyldiphenylsilyl ether **152**, and the latter was used to alkylate **1** yielding **153**. The silyl group was removed with fluoride ion and the resulting alcohol **154** was converted to

the iodide **155** with chlorodiphenylphospine and iodine. The iodide **155** was treated with triphenyltin hydride under modified conditions,[95] which yielded, after workup and chromatographic separation, pure (*R*)-(-)-muscone **156** in addition to **150** (Scheme 32).[93]



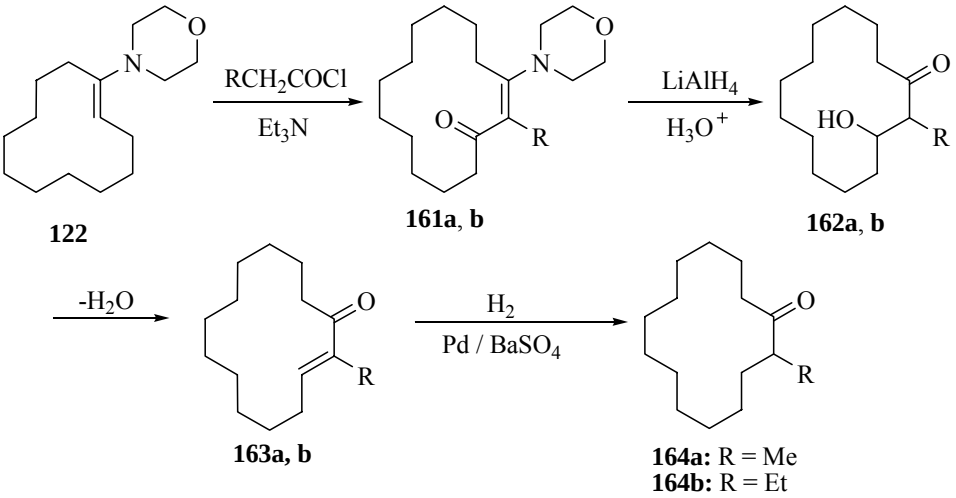
Scheme 32

Cyclododecanone **1** was enlarged by two carbon atoms into the fourteen-membered ring derivative **160**. The ring expansion takes place in water in presence of indium as a metal mediator (Scheme 33).[96]



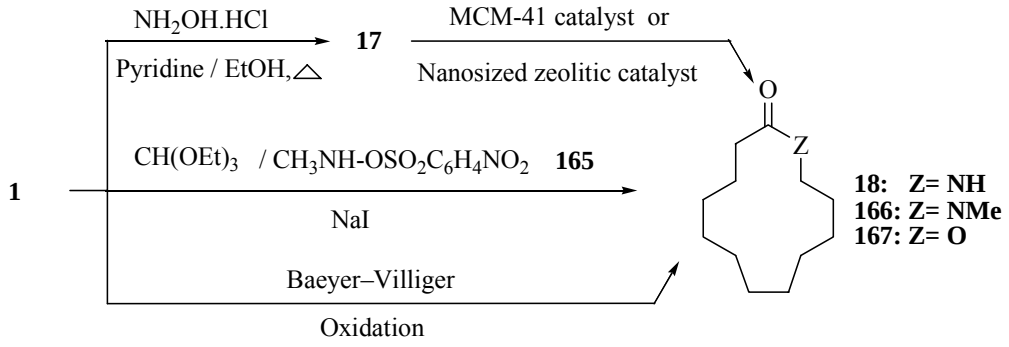
Scheme 33

The reaction of 1-morpholinocyclododecene **122** with either propionyl chloride or butyryl chloride in the presence of triethylamine gives the 1-morpholino-2-alkyl-l-cyclotetradecen-3-one **161a**,**b** in 70-75% yield. After separating the triethylamine hydrochloride, the crude ketones **161a**,**b** are smoothly reduced by complex aluminium hydrides [$LiAlH_4$, $NaAlH_4$, $NaAlH_2(OCH_2CH_2OCH_3)_2$] and forms the 2-alkyl-3-hydroxy-cyclotetradecanone **162a**,**b** on subsequent hydrolysis. Ketols **162a**,**b** easily leaves water when refluxed in toluene in presence of catalytic amounts of *p*-toluenesulfonic acid to give a mixture of the cis- and trans-2-alkyl-2-cyclotetradecen-1-one **163a**,**b** in high yield. Hydrogenation of the unsaturated ketones **163a**,**b** over Pd catalyst gives the 2-methyl- and 2-ethylcyclotetradecanones **164a**,**b** in quantitative yield (Scheme 34).[97]



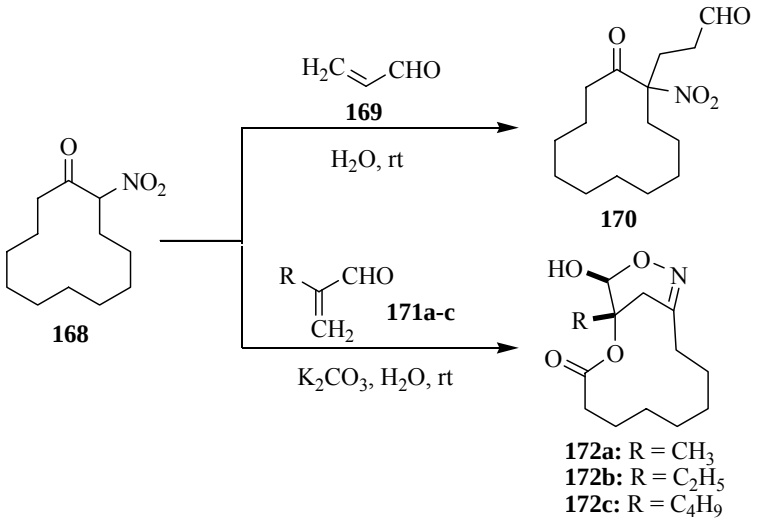
Scheme 34

3.5.2 Macrocyclic lactams and lactones. Thirteen-membered ring lactam **18** was prepared by Beckmann rearrangement of ketoxime **17** under the influence of wide variety of catalysts such as mesoporous silicoaluminophosphates,[98] nanosized and delayer zeolitic catalyst,[99] and many other catalytic systems.[100-106] Lactam **18** can be also accessed from cyclododecanone *via* Schmidt reaction under microwave irradiation using P_2O_5/SiO_2,[107] or silica-sulfuric acid as catalyst,[108] and $TMSN_3$ in presence of $FeCl_3$.[109] While, *N*-methyl azacyclotridecan-2-one **166** was produced simply in 69% yield in a one-pot reaction of **1**, triethylorthoformate and *N*-((*p*-nitrobenzene)sulfonyl)oxymethylamine ($CH_3NH\text{-}OSO_2C_6H_4NO_2$) **165** in presence of sodium iodide.[110] Baeyer-Villiger oxidation of **1** resulted in formation of oxacyclotridecan-2-one **167**. The oxidation process is achieved using chemical and biochemical catalysts (Scheme 35).[111-113]



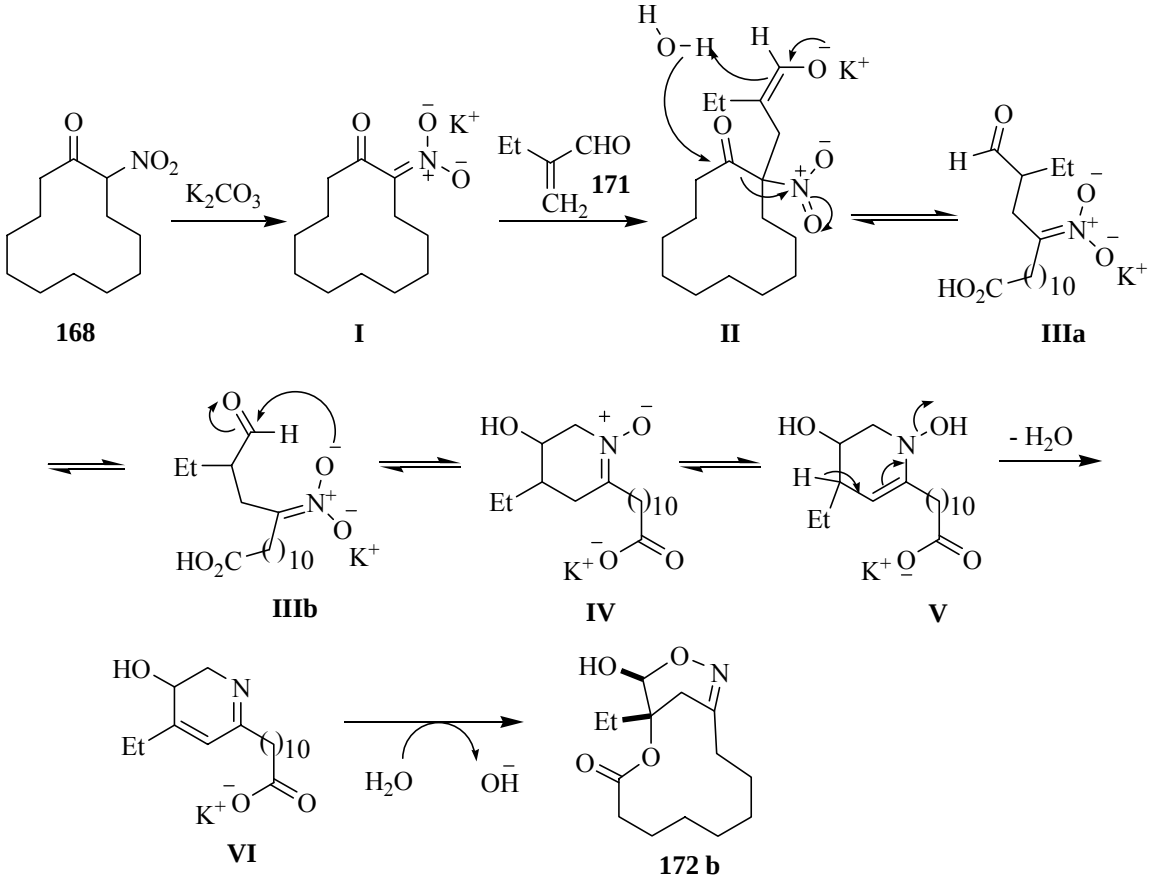
Scheme 35

α-Nitrocyclododecanone **168** reacts with acrolein **169** in water at room temperature giving the expected Michael adduct **170**. However, in the case of the more hindered *α,β*-unsaturated aldehydes bearing an alkyl group at their α position **171a-c**, the reaction did not take place in the absence of catalyst, and addition of base led to an abrupt change in the course of the reaction, since the product was bridged bicyclic lactone **172a-c** bearing an unusual 6-hydroxy-1,2-oxazine ring (Scheme 36).[114]



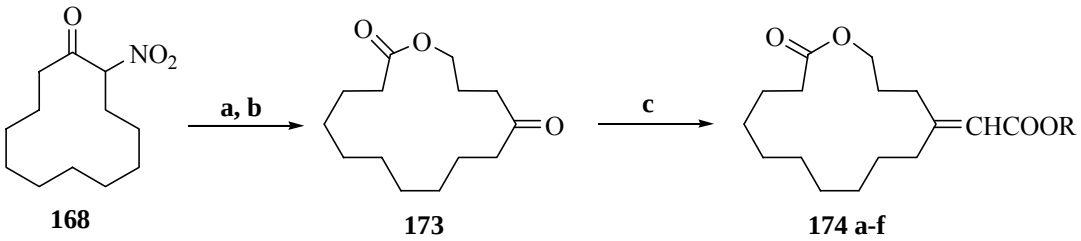
Scheme 36

A mechanism that accounts for the isolation of compounds **172a-c** is summarized in Scheme 36 and involves a unique anionic domino transformation including up to six different reactions in a one-pot process. It was proposed that anion **II** from the initial Michael addition evolves to **III** through a retro Claisen-type reaction. Cyclization of **III** by attack of the nitronate oxygen onto the aldehyde group requires the existence of conformation **IIIb**, which would be favored by repulsive interactions between the nitronate and ethyl groups in **IIIa** and would lead to the *N*-oxide **IV**. Elimination of water from its tautomer **V** would give 1,2-oxazine **VI**, and a final intramolecular conjugate addition of the carboxylate group in **VI** onto the *α,β*-unsaturated imine system contained in the oxazine ring would lead to the observed products **172a-c** (Scheme 37).[114]



Scheme 37

Six novel 12-alkoxycarbonylmethylene-1,15-pentadecanolides **174** were synthesized from 2-nitrocyclododecanone **168**, by the Michael addition with acrolein followed by ring enlargement, Nef and Wittig-Horner reactions (Scheme 38).[115]



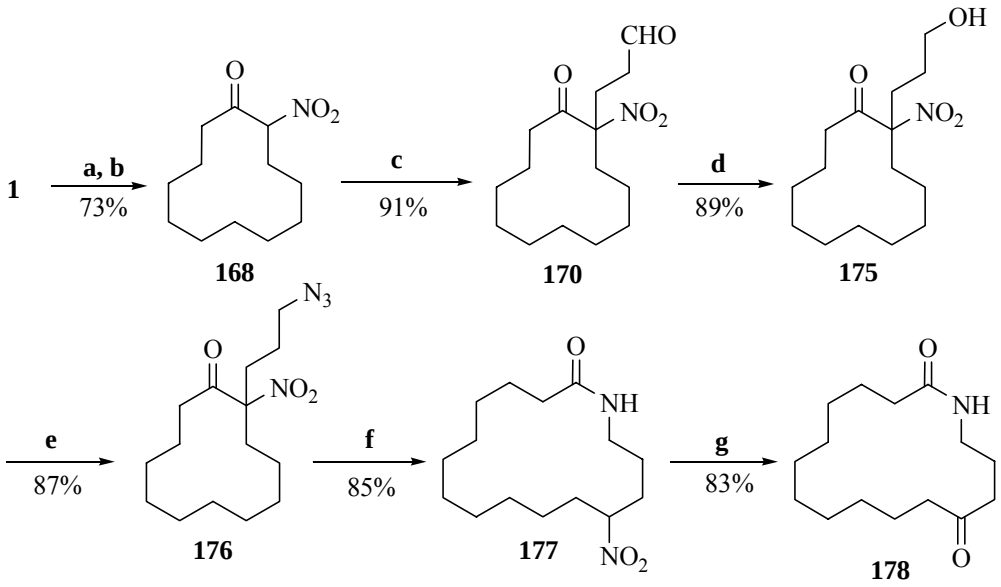
a: acrolein, THF, Et_3N, 0 ^oC; **b**: (*i*)$NaBH_4$, NaOH, CH_3OH (*ii*) HCl;

c: $(EtO)_2P(O)CH_2COOR$, $KOBu^t$, THF, reflux

R; **a**:CH_3, **b**:C_2H_5, **c**:$(CH_2)_4CH_3$, **d**:$(CH_2)_2CH(CH_3)_2$, **e**:$(CH_2)_7CH_3$, **f**:cyclohexyl

Scheme 38

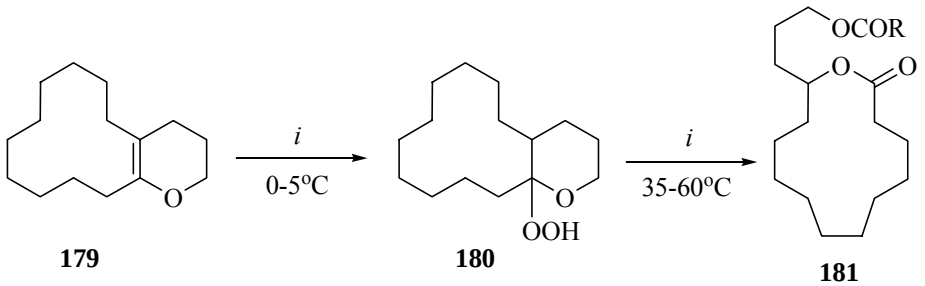
12-Oxo-1,15-pentadecanlactam **178** was synthesized from **1** with a total yield of 36% in seven steps. Conversion of the azide **176** to 12-nitro-1,15-pentadecanlactam **177** is the key step featured by direct ring expansion (Scheme 39).[116]



a) Ac_2O, TsOH, reflux; **b**) Ac_2O , CCl_4, concentrated H_2SO_4, concentrated HNO_3, AcOH; **c**) CH_2=CHCHO, Et_3N, THF; **d**) $NaBH_4$, MeOH, 0°C, 40 min; **e**) $MeSO_2Cl$, Et_3N, toluene, 0°C, 40 min then NaN_3, Bu_4NBr, H_2O, 60 °C; **f**) H_2/Lindlar catalyst, EtOH, r.t; **g**) NaOMe, MeOH then 4 mol/L HCl.

Scheme 39

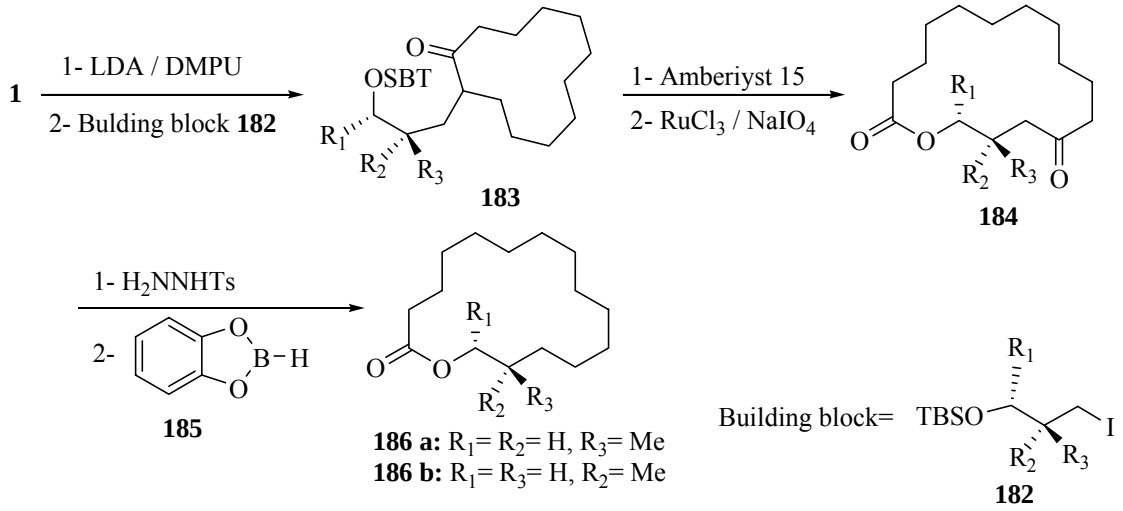
Oxabicycloalkene **179**,[117] was transformed into the 13-membered ring lactone **181**, by gradual addition of excess hydrogen peroxide and 0.1 equiv. H_2SO_4 to a solution of **181** in formic or acetic acid (Scheme 40).[118,119]



i. HCO_2H or CH_3COOH, H_2O_2 (3.4 equiv.), H_2SO_4 (0.1 equiv.)

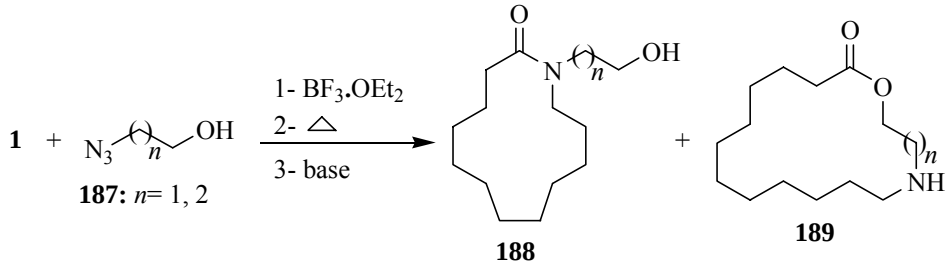
Scheme 40

The (*R*)-enantiomer of muscolide **186a**, related to naturally occurring (*R*)-muscone the principal odorous constituent of the male musk deer (Moschus moschiferus L., Ungulata), was prepared in 23% overall yield from chiral building block **182a** and **1**, (Scheme 41).[120]

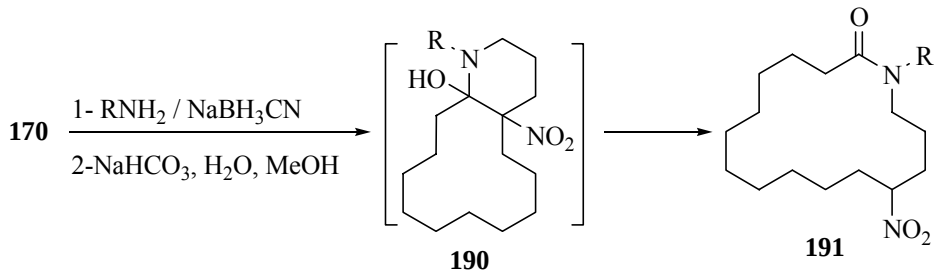


Scheme 41

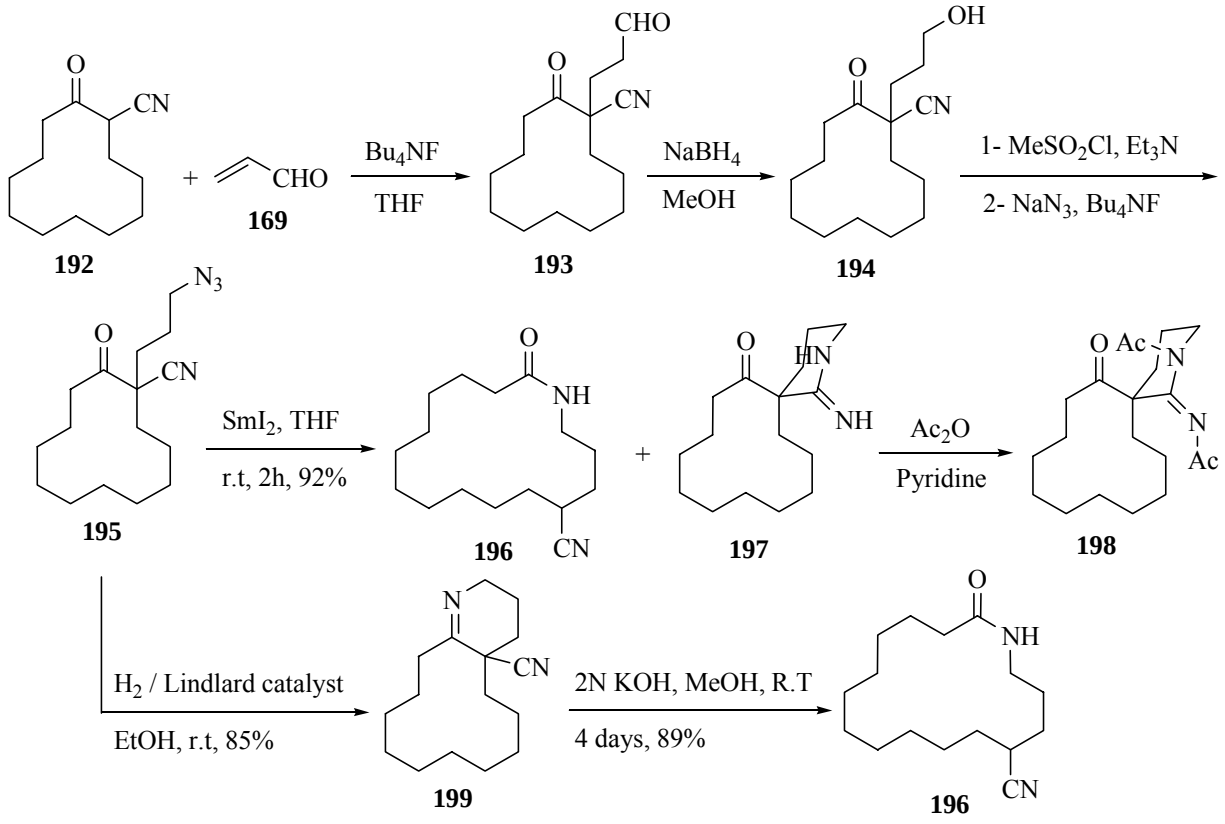
Acid catalyzed reaction of **1** with the azido alcohols **187** followed by base catalyzed hydrolysis of iminium ether intermediate produced the macrocyclic lactam **188** and lactone **189**.[121]



Goulaouic-Dubois *et al*, reported the retro Aldol type ring enlargement of 2-nitrocycloalkanones in basic medium as a methodology for synthesis of macrocyclic lactams. Reductive amination of the aldehyde **170** allows the nitrogen atom to react with the carbonyl group to give a bicyclic intermediate **190** which give the desired lactam **191**.[122]

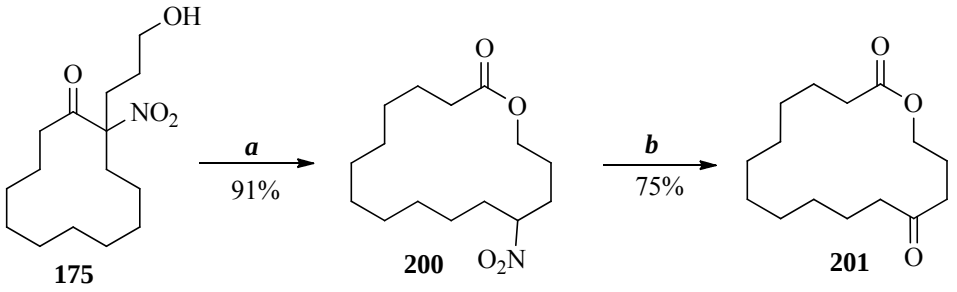


The alcohol **194** was obtained in two steps by Michael addition of 2-cyanocyclododecanone **192**,[123,124] to acrylaldehyde **169** followed by selective reduction of the aldehydic group of the adduct **193** by $NaBH_4$ in methanol.[125,126] Alcohol **194** was then converted into the azide **195** *via* reaction of the corresponding mesylate with NaN_3 under phase-transfer catalysis.[127] Treatment of the azide **195** with samarium iodide (SmI_2),[128] (3.3 equiv.) in THF at room temperature for 2 hours promoted a smooth transformation into the 16-membered ring lactam **196** and the unexpected amidine **197** which was then acetylated to afford **198**.[122] Alternatively, the 16-membered ring lactam **196** was prepared from **195** in two steps by another route for direct comparison. Catalytic hydrogenation of azide **195** with Lindlar catalyst,[129] afforded the bicyclic imine **199** which was hydrolyzed to the desired lactam **196** (Scheme 42).[122]



Scheme 42

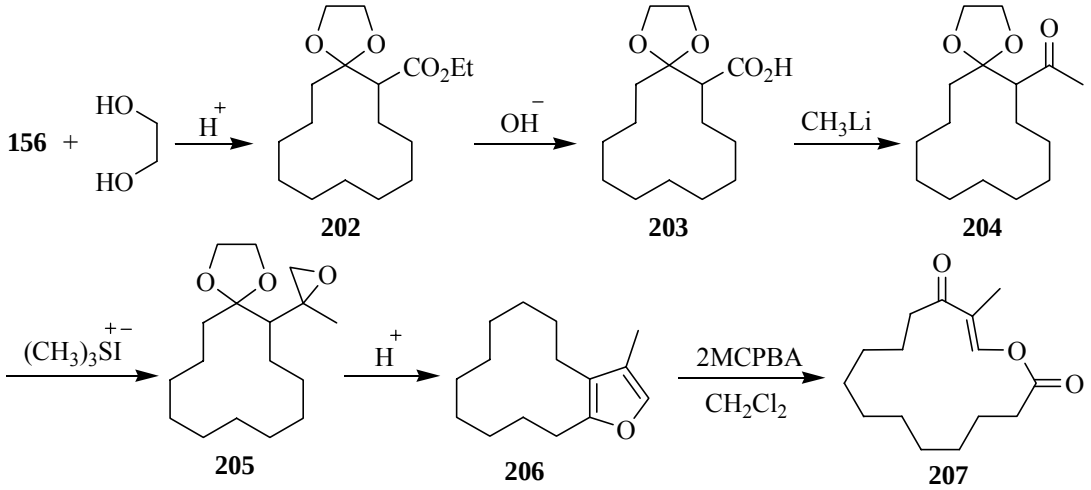
Lactonization of keto-alcohol **175** proceeded smoothly in DME in presence of catalytic amount of sodium hydride. Then, the nitro-lactone **200** was converted to the keto-lactone **201** in 75% (Scheme 43).[130]



a: NaH, DME; ***b***: $(C_2H_5)_3N$ (3 equivs.), CH_3CN, aq. $(NH_4)_2$ $[Ce(N0_3)_6]$ (3 equivs.), reflux, 2 days

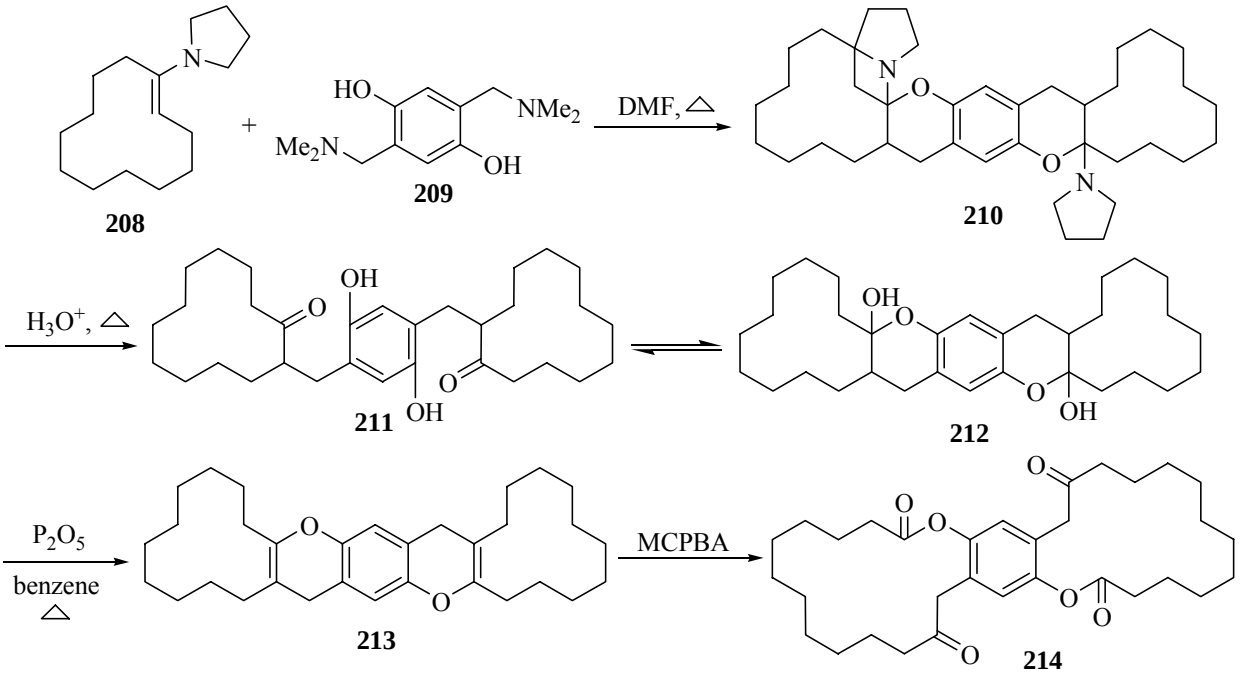
Scheme 43

Manfredi *et al*. reported the synthesis of the furan derivative **206** from **156**, and explored its oxidation with two equivalents of *m*-chloroperbenzoic acid (MCPA) in methylene chloride which resulted in formation of 15-membered ring keolactone **207** in 70% yield as a result of oxidative ring opening (Scheme 44).[131]



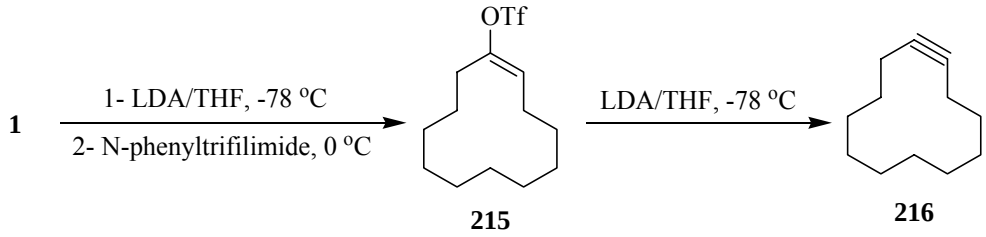
Scheme 44

Alkylation of the pyrrolidine enamine derivative **208** with 2,5-*bis*(dimethylaminomethyl)hydroquinone **209** in DMF afforded the benzodipyran derivative **210** as a coarse powder in 57% yield. Hydrolysis of **210** furnished **211** which recyclized to **212**. Dehydration of **212** with P_2O_5 afforded the benzodipyran derivative **213**, which transformed into the macrocyclic benzodilactone **214** under the influence of *m*-chloroperbenzoic acid (Scheme 45).[132]



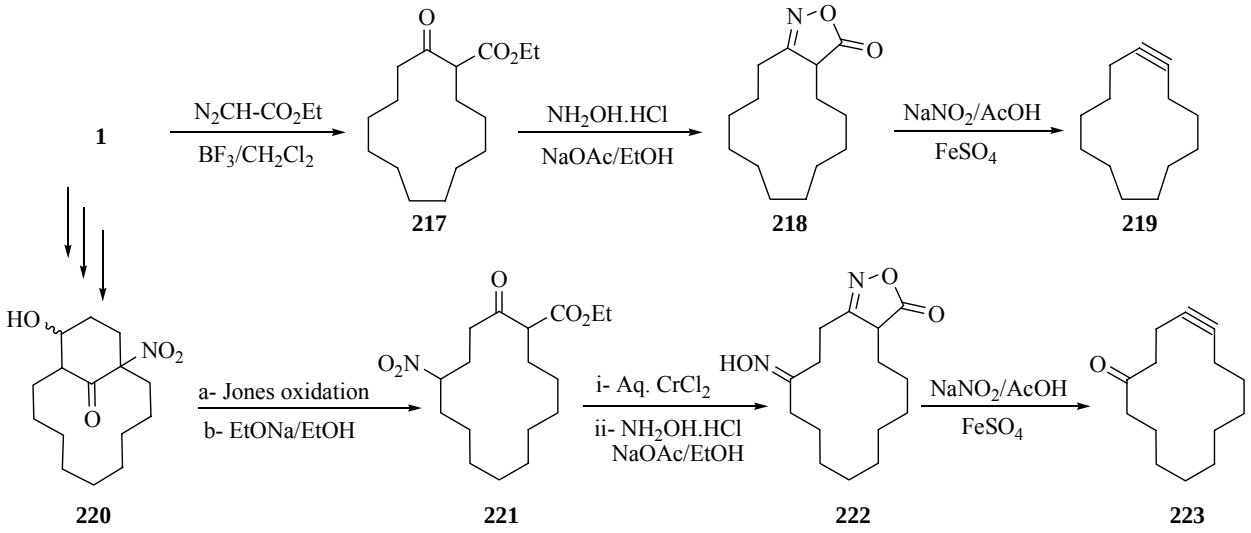
Scheme 45

3.5.3 Macrocyclic acetylenes. Treatment of cyclododecenyl trifluoromethanesulfonate **215** with LDA resulted in formation of the twelve-membered ring acetylenecyclododecyne **216** in 95% yield (Scheme 46).[133]



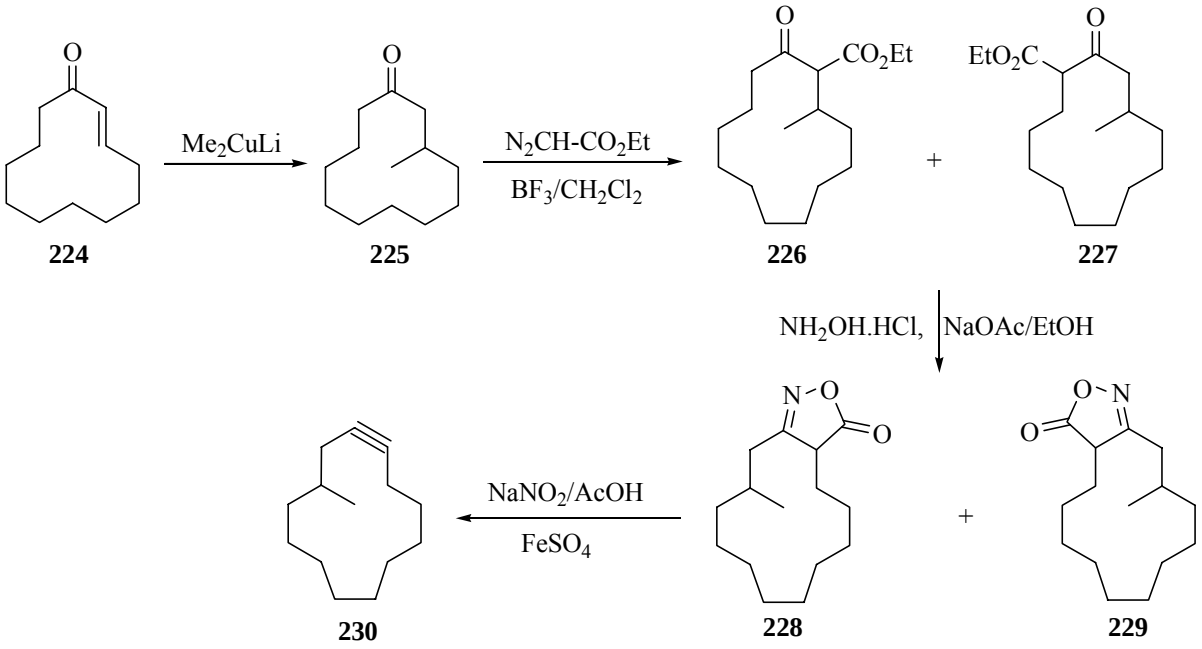
Scheme 46

Furthermore, thirteen and fourteen membered ring acytelenes **219** and **223** are accessed through nitrosation of isoxazolones **218** and **222**, respectively. They are prepared through reaction of macrocyclic *β*-ketoesters **217** and **221** with hydroxyl amine hydrochloride (Scheme 47).[134]



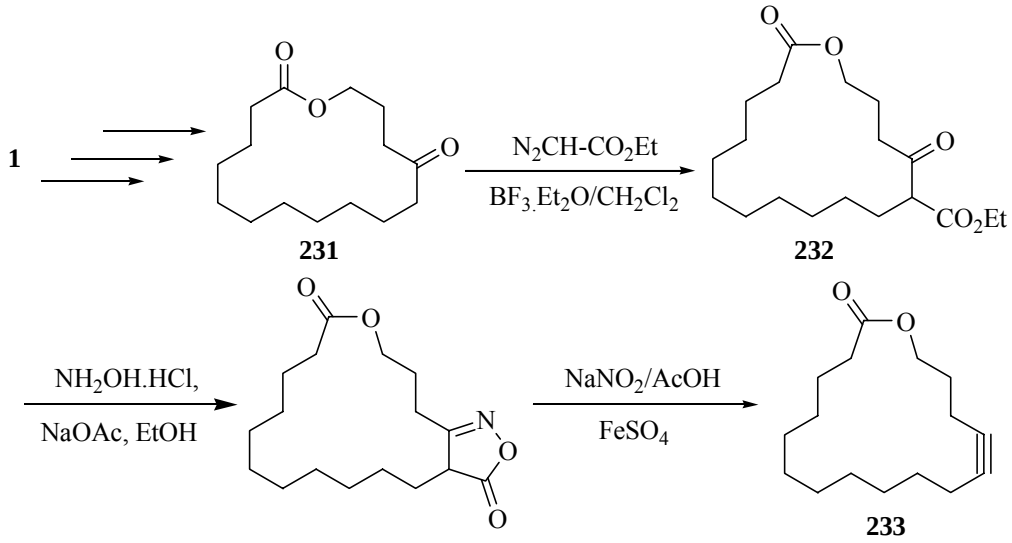
Scheme 47

In the same manner both regioisomeric *β*-ketoesters **226** and **227** gave 4-methylcyclotridecyne **230** in 87% yield from the corresponding isoxazolones **228** and **229** (Scheme 48).[134]



Scheme 48

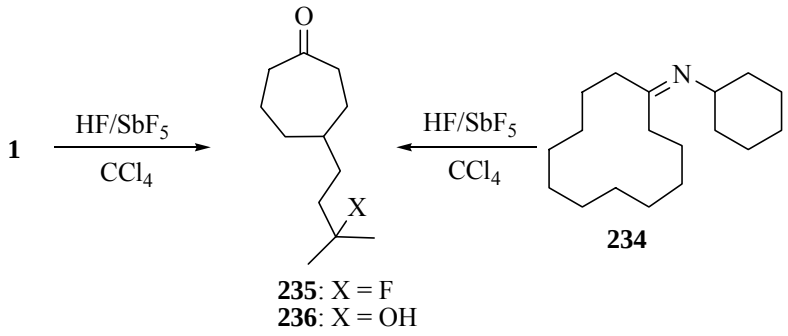
Also, the macrocyclic lactone **231** was converted to 17-membered ring acetylene **233** following the same methodology (Scheme 49).[134]



Scheme 49

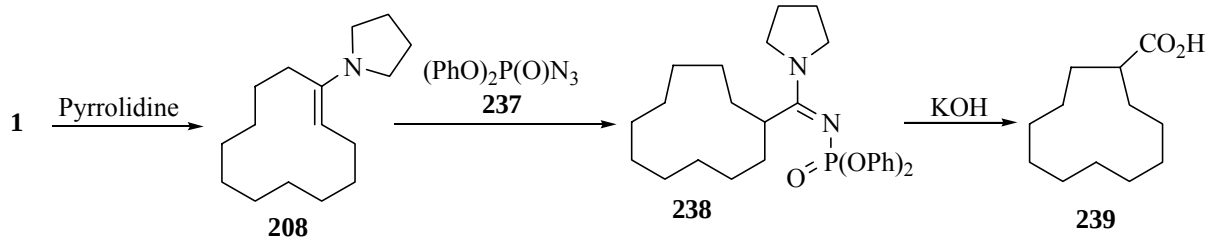
3.6 Ring contraction

Cyclododecanone **1** and its imine derivative **234** react with HF/SbF_5 in presence of CCl_4 whereby ring contraction takes place to produce a mixture of fluoro and hydroxy cycloheptanone derivatives **235** and **236**, respectively. The ratio of **235**/**236** is about 3 when starting from **1** while it is about 0.5 when starting with imine **234** (Scheme 50).[135]



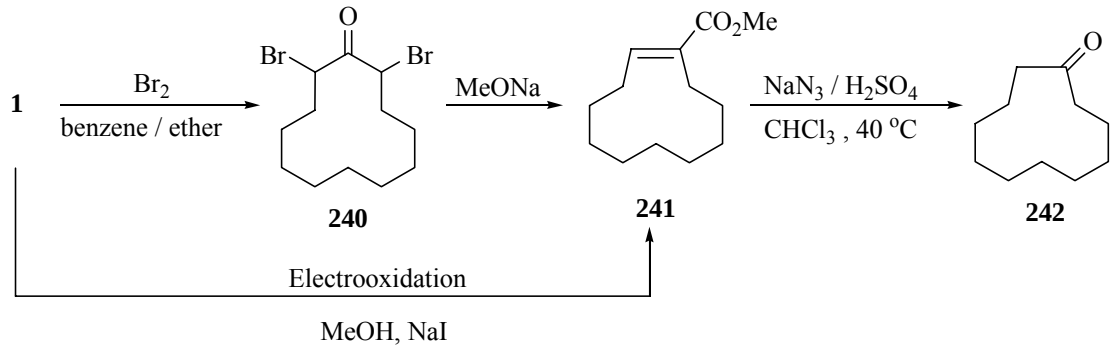
Scheme 50

Cycloundecanecarboxylic acid **239** has been prepared from **1** in three steps. The first step is the usual procedure for the preparation of enamines. The second step involves 1,3-dipolar cycloaddition of diphenyl phosphorazidate **237** to the pyrrolidine enamine **208** followed by ring contraction with evolution of nitrogen. The third step is hydrolysis of the *N*-phosphorylated amidines **238** to the desired acid (Scheme 51).[136]



Scheme 51

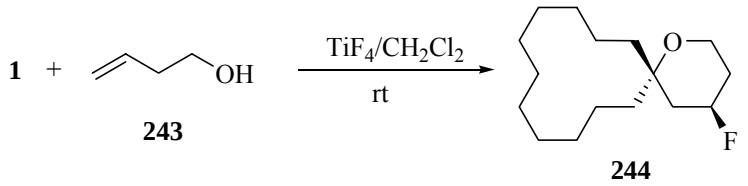
Favorskii-type rearrangement of 2,12-dibromocyclododecanone **240** afforded methyl 1-cycloundecenecarboxylate **241** which in turn underwent Schmidt degradation yielding cyclo-undecanone **242** (Scheme 52).[137,138]



Scheme 52

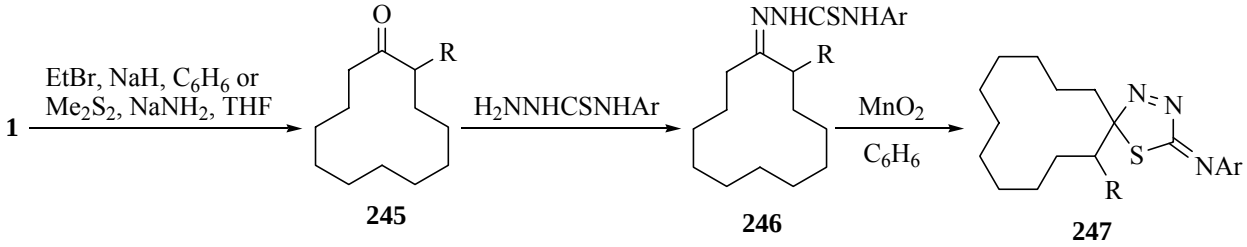
3.7 Construction of spiro and fused heterocyclic systems

3.7.1 Spiro heterocyclic systems. Titanium tetrafluoride can efficiently be used for the stereoselective synthesis of 4-fluorotetrahydropyrans *via* Prins cyclization. By applying this methodology 4-fluorotetrahydropyran derivative **244** was achieved *via* reaction of **1** with but-3-en-1-ol **243** in 50% yield.[139]



4-Iodo analogue of **244** was synthesized in analogous manner, but using TMSCl/NaI in acetonitrile instead of TiF_4 in methylene chloride.[140] A series of novel 2-(1-substituted-1,11-undecylidene)-5-arylimino-Δ^3-1,3,4-thiadiazolines **247a-f** were synthesized and their structures

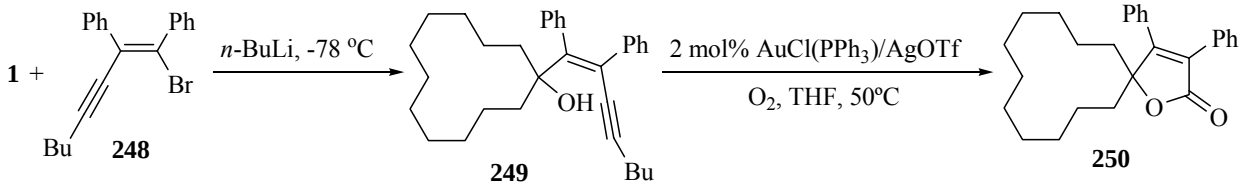
were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis. Their solubility and fungicidal activity was also investigated (Scheme 53).[141]



247a: R = Et, Ar = C_6H_5; **247b**: R = Et, Ar = 4-FC_6H_4; **247c**: R = Et, Ar =2-ClC_6H_4;
247d: R = Et, Ar = 4-MeC_6H_4; **247e**: R = Et, Ar = 2,4-$Me_2C_6H_3$; **247f**: R = MeS, Ar = 4-ClC_6H_4;
247g: R = MeS, Ar = 4-MeC_6H_4;

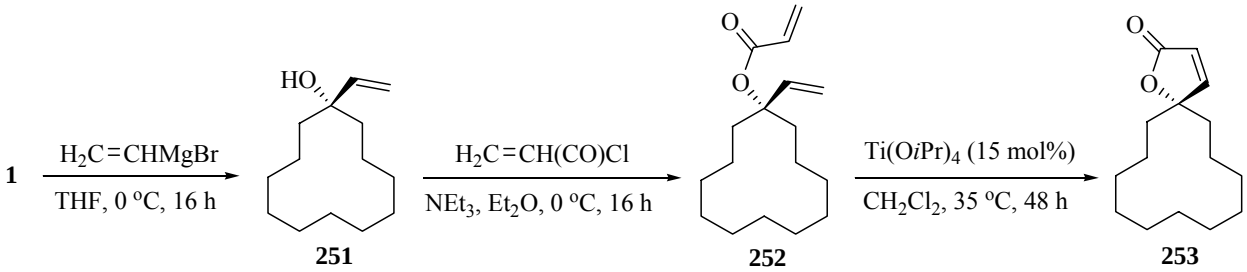
Scheme 53

A facile approach for the synthesis of spirocyclic butenolides through cascade oxidative/cleavage reaction of (*Z*)-enynols bearing cyclic substituents at the C-1 position catalyzed by gold under oxygen atmosphere has been developed and applied on transformation of **1** into the butenolide **250** through the enynol **249** in a good overall yield (Scheme 54).[142]



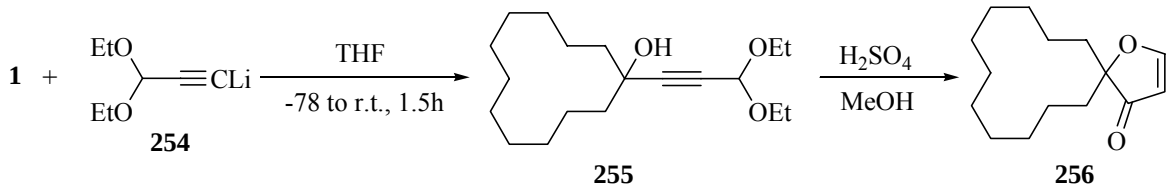
Scheme 54

Spirocyclic butenolide **253** was also achieved stereoselectively by ring closing metathesis strategy (Scheme 55).[143]



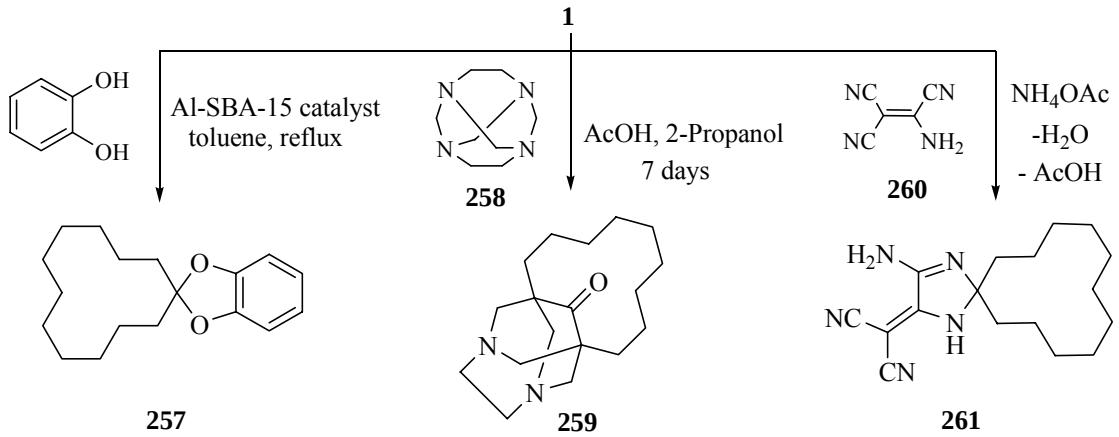
Scheme 55

While, spirocyclic furanone **256** was achieved in good yield through reaction of **1** with the lithium salt of propynal diethyl acetal **254**, followed by treatment of the resulting 1-(3,3-diethoxyprop-1-ynyl)cyclododecanol **255** with sulfuric acid in methanol (Scheme 56).[144]



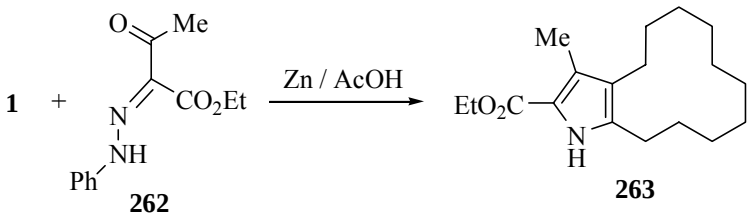
Scheme 56

A novel application of Al-SBA-15 catalyst in the protection of ketones was reported and applied on transformation of **1** into spiro[1,3-benzodioxole-2,1-cyclododecane] **257** through reaction with catechol.[145] 1,8-Nonamethylene-3,6-diazahomoadamantan-9-one **259** was synthesized by condensation of tetramethylenediethylenetetramine **258** with cyclododecanone **1**.[146] Furthermore, **1** reacted with 2-aminoethene-1,1,2-tricarbonitrile **260** in presence of ammonium acetate in dioxane at room temperature to give the spiro derivative **261** (Scheme 57).[147,148]

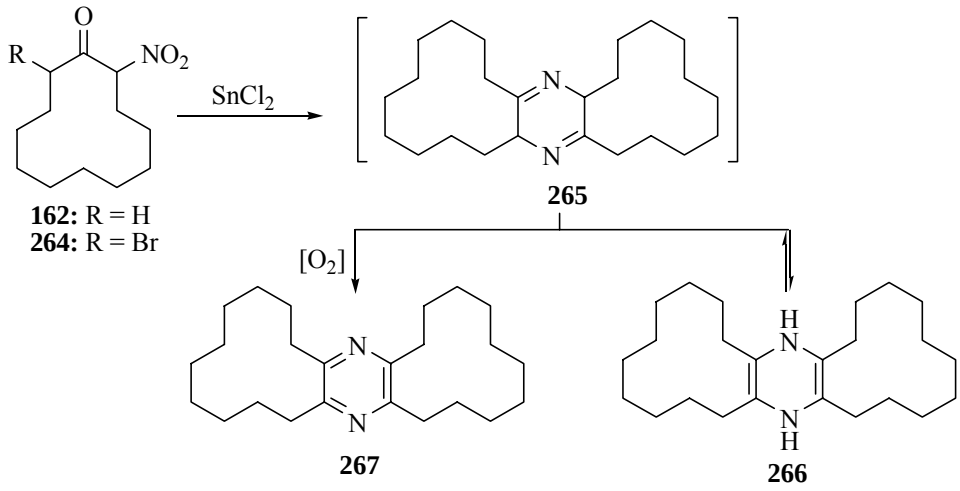


Scheme 57

3.7.2 Fused heterocyclic systems. Cyclododeca[*b*]pyrrole derivative **263** was synthesized *via* modified Knorr-pyrrole condensation between **1** and phenyl-hydrazone **262** under reducing conditions (Zn/AcOH).[149]

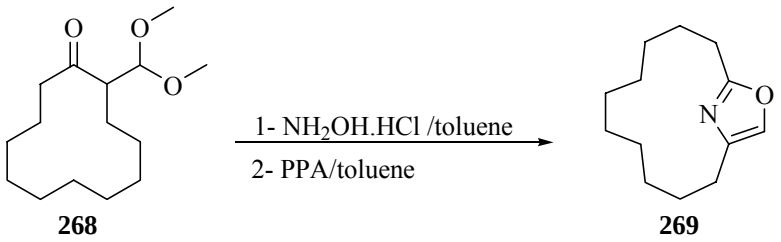


The $SnCl_2$ reduction of 2-nitrocyclododecanone **162** or 2-bromo-12-nitrocyclododecanone **264** gave a colorless compound 2,3,5,6-*bis*-(ortho-1,10-decylidene)dihydropyrazine **266**,[150,151] X-ray studies showed that the product exists in the 1,4-dihydropyrazine form **266** and not in diimino form **265**. Compound **265** can be transformed to the pyrazine form **267** by the effect of oxygen (Scheme 58).

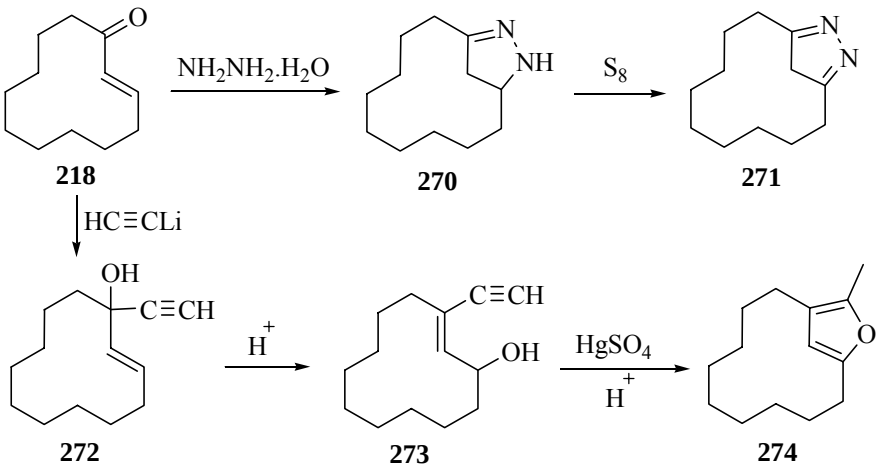


Scheme 58

Reaction of 2-(dimethoxymethyl)cyclododecanone **268** with hydroxylamine hydrochloride in toluene under reflux for **24** hours then treating the solution with polyphosphoric acid in toluene under reflux gave oxazole **269** in 46% yield.[152]



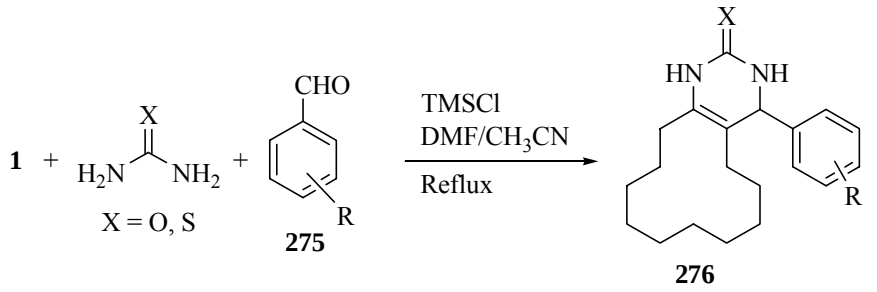
While, [9](3,5)pyrazolophane **271** and 11-methyl[9](2,4)furanophane **274** were prepared from 2-cyclododecenone **218**,[153] and their spectral properties were discussed (Scheme 59).[154]



Scheme 59

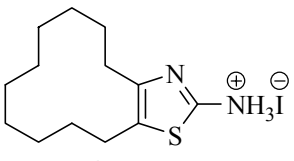
Utilization of trimethylsilyl chloride (TMSCl) as a Lewis acid allowed one-pot chemoselective multicomponent Biginelli reaction between **1**, urea or thiourea and aldehydes to afford fused heterobicyclic compounds **276a-g**.[155]

Table 1



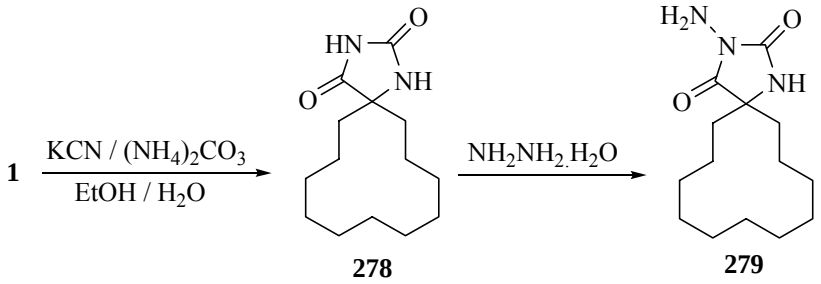
Product	X	R	Yield%	Product	X	R	Yield%
276a	O	4-Cl	87	**276e**	O	2-Br	85
276b	O	2-OCH_3	96	**276f**	S	4-OCH_3	89
276c	O	2-F	93	**276g**	S	2-F	83
276d	O	2-Cl	90				

The aminothiazolium salt **277** was obtained in 72% yield by heating **1**, thiourea and iodine in a one pot reaction.[156]



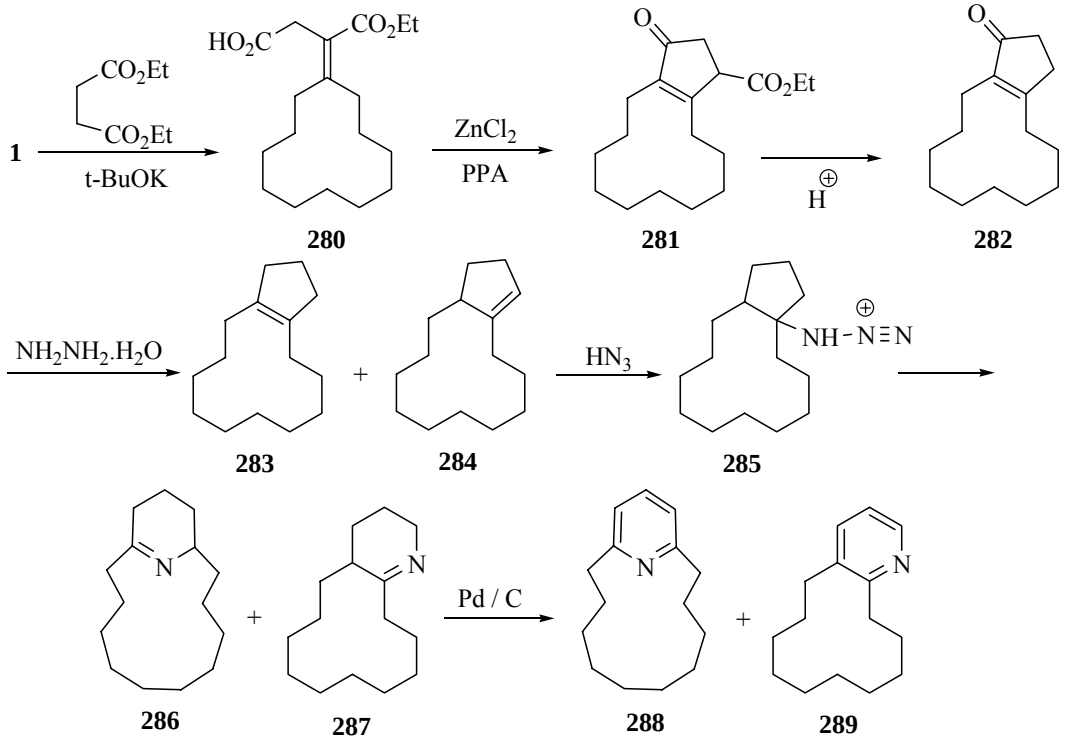
277

Spirohydantoin **278** and its amino derivative **279** were synthesized and their biological activity was studied. The synthesis of **278** was achieved by refluxing a mixture of **1**, potassium cyanide and ammonium carbonate in aqueous ethanol. Treatment of the resulting spirohydantoine with hydrazine hydrate furnished the 3-amino derivative **279** (Scheme 60).[157]



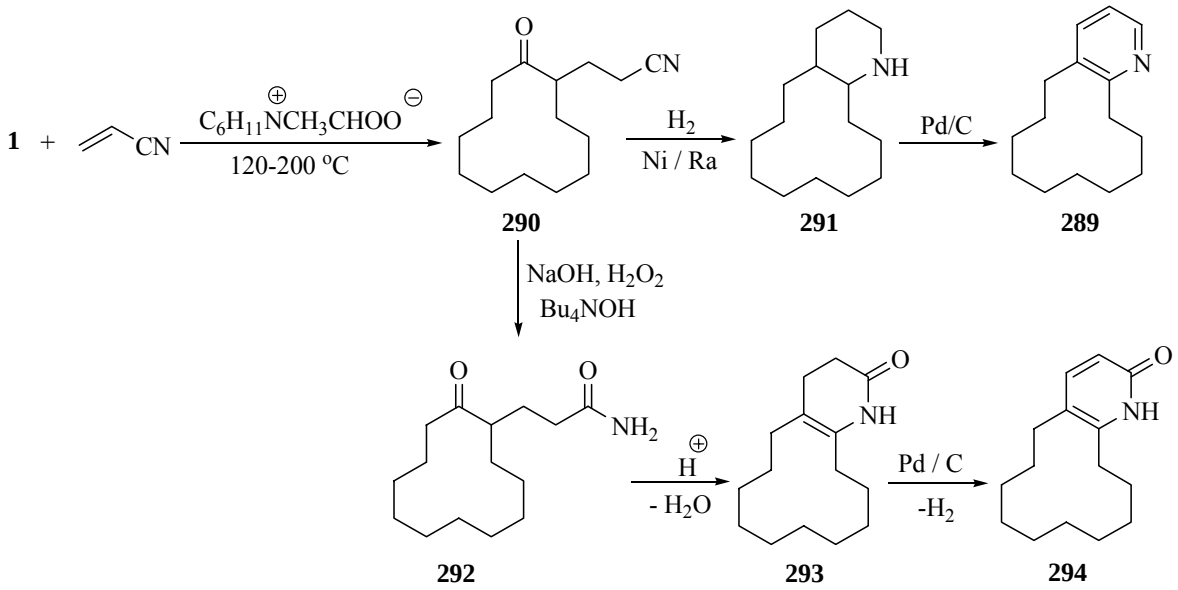
Scheme 60

The Stobbe condensation of cyclododecanone **1** with diethyl succinate gave the exocyclic carboxylic acid **280** which then underwent cyclization with zinc chloride in polyphosphoric acid to the *δ*-keto *β,γ*-unsaturated ester **281**. Acid hydrolysis of **281** with simultaneous decarboxylation gave the *α,β*-unsaturated ketone **282**. Wolff-Kizhner reduction of the obtained bicyclo[10.3.0]-l(12)-pentadecen-13-one **282** gave the two isomeric olefins **283** and **284**, from which the trisubstituted olefin **284** is formed with a 70% yield. The Schmidt reaction for compound **284** and dehydrogenation over Pd/C gave 2,6-pyridinophane **288** and its 2,3 isomer **289** (Scheme 61).[158]



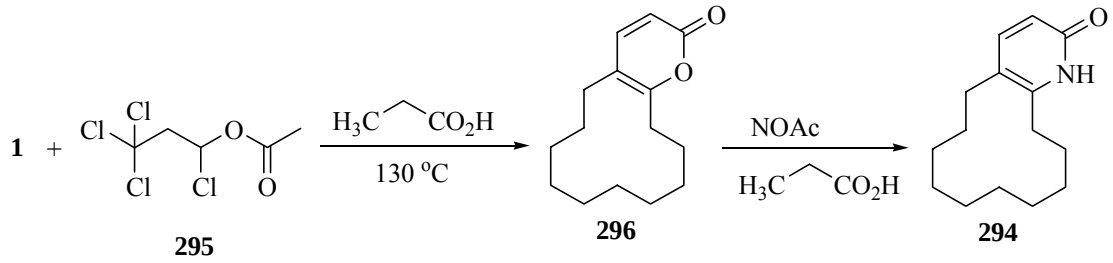
Scheme 61

Cyclododeca[*b*]pyridine **289** was also synthesized from **1** *via* hydrogenation of the oxonitrile **290** into **291** which on dehydrogenation over Pd/C furnished **289**.[158] The oxonitrile **290** proved to be a valuable intermediate where it was also used as a key precursor in the synthesis of dihydropyridone **293** and pyridone **294** (Scheme 62).[158]



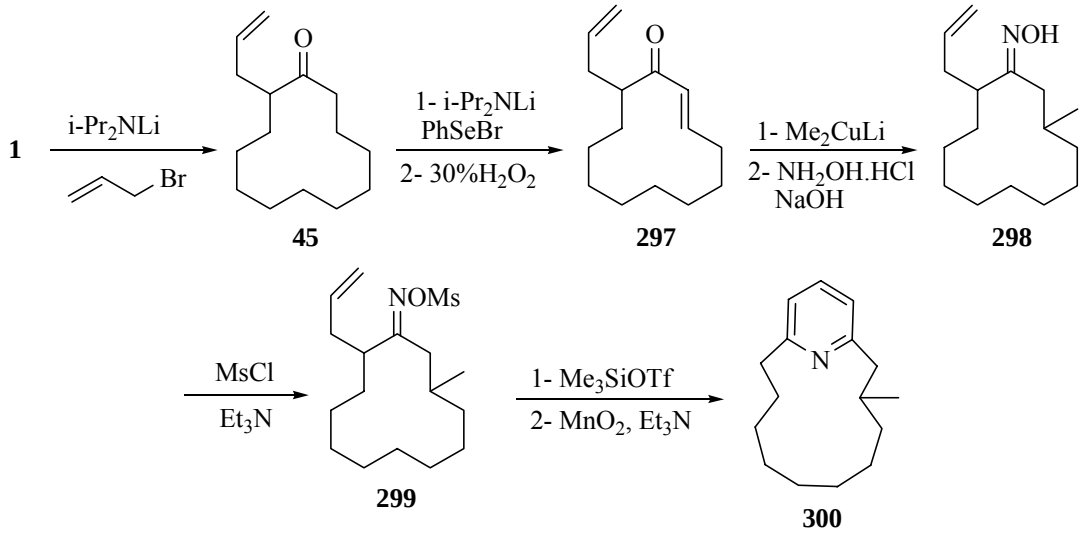
Scheme 62

A second approach to the synthesis of the pyridone **294** involves the reaction of **1** with 1,1,1,3-tetrachloro-3-acetoxypropane **295** with the formation of the α-pyrone **296**. Its transformation by the action of ammonium acetate gave the (2,3)pyridinophane **294** (Scheme 63).[158]



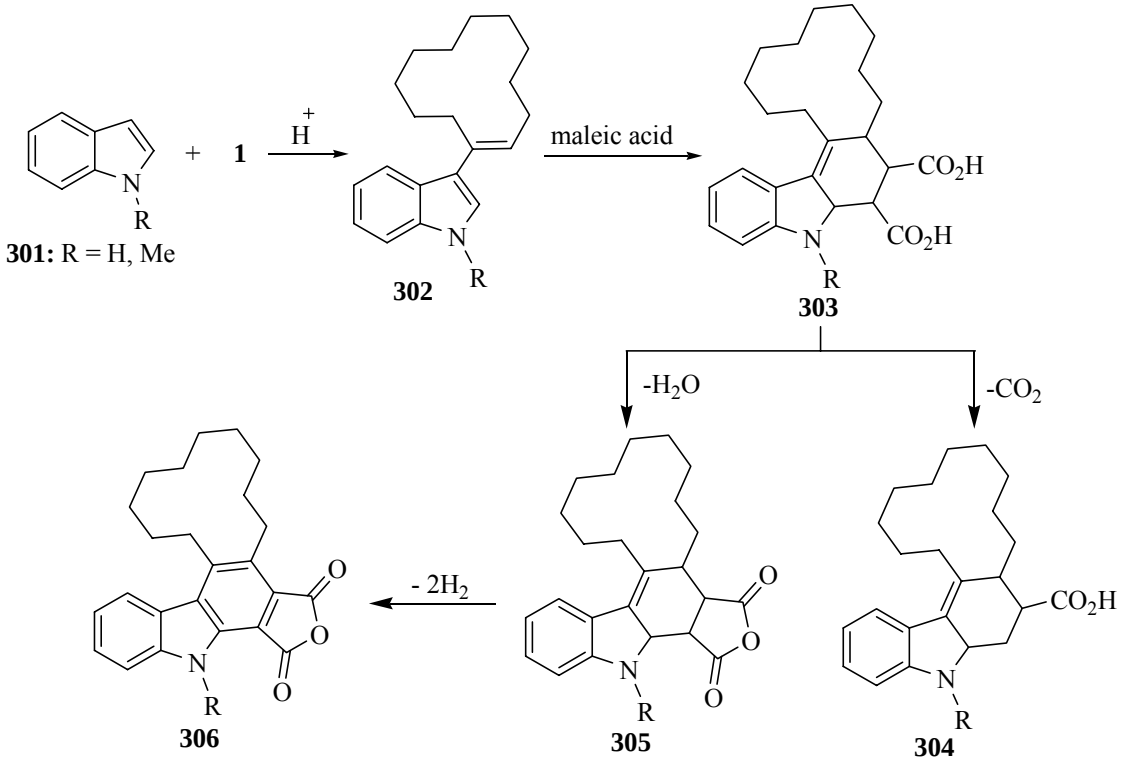
Scheme 63

Significant successes by Japanese chemists in the use of new reagents for the Beckmann rearrangement made it possible to realize an original and effective approach to the synthesis of muscopyridines. So, muscopyridine **300** was synthesized from **1** in five steps as presented in Scheme 64.[158]



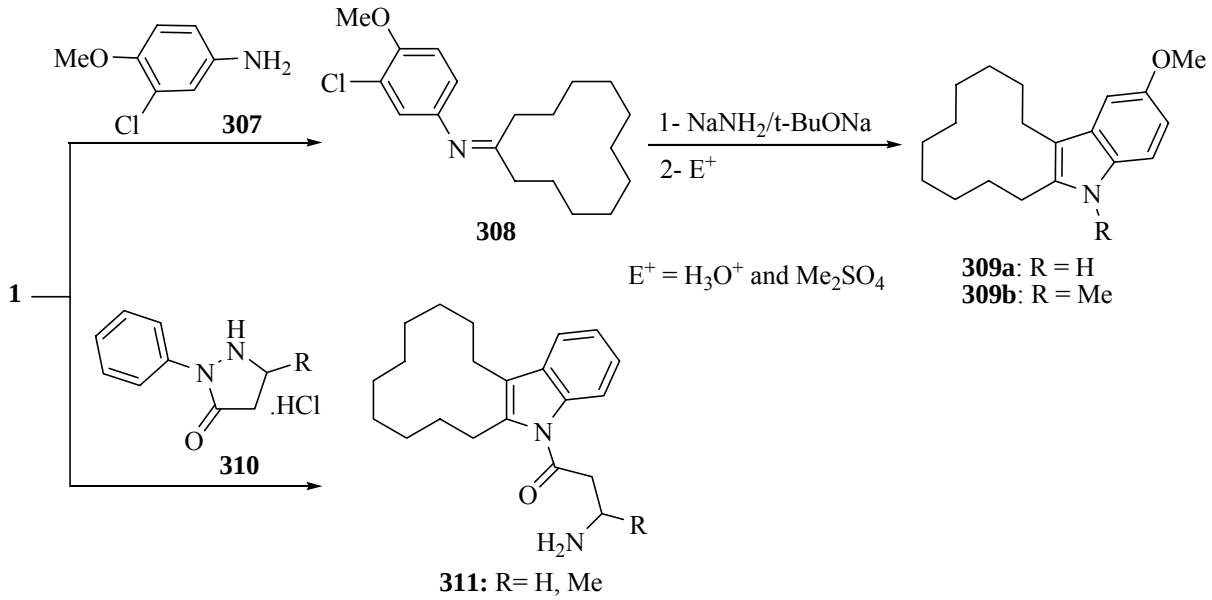
Scheme 64

Tetrahydrocarbazole derivatives **303** have been prepared in one flask from indols **301**, **1** and maleic acid with acid catalysis. The reaction involves a condensation of the indol with the ketone followed by an *in situ* trapping of the vinylindol **302** in a Diels-Alder reaction with maleic acid.[159] Also, hydrolysis of **303** followed by dehydrogenation afforded the anhydrides **305** and **306**, respectively (Scheme 65).



Scheme 65

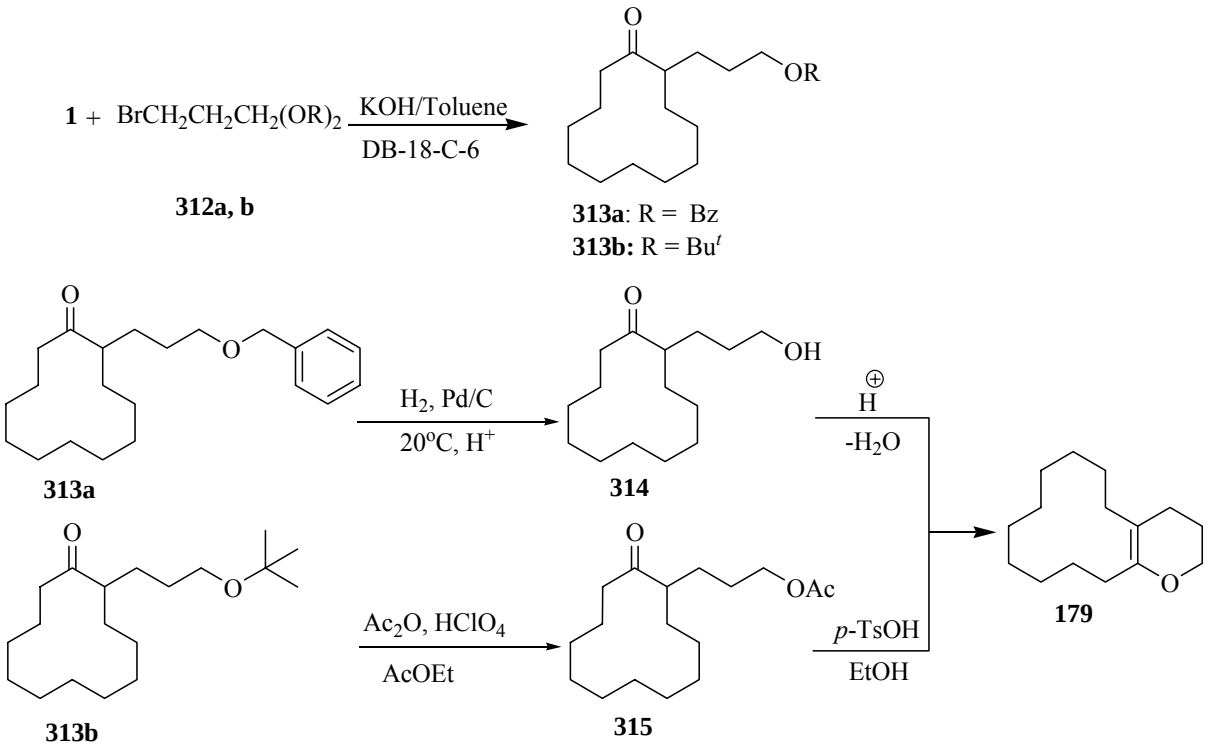
The complex base $NaNH_2$-*t*-BuONa allowed expeditious syntheses of indoles **309a**, **b** by arynic cyclization of cyclododecanone imine derivative **308** which prepared from chloroaniline derivative **307** and **1**.[160] Furthermore, the indol derivatives **311** are obtained *via* the reaction of **1** with pyrazolone derivatives **310** in refluxing glacial acetic acid (Scheme 66).[161]



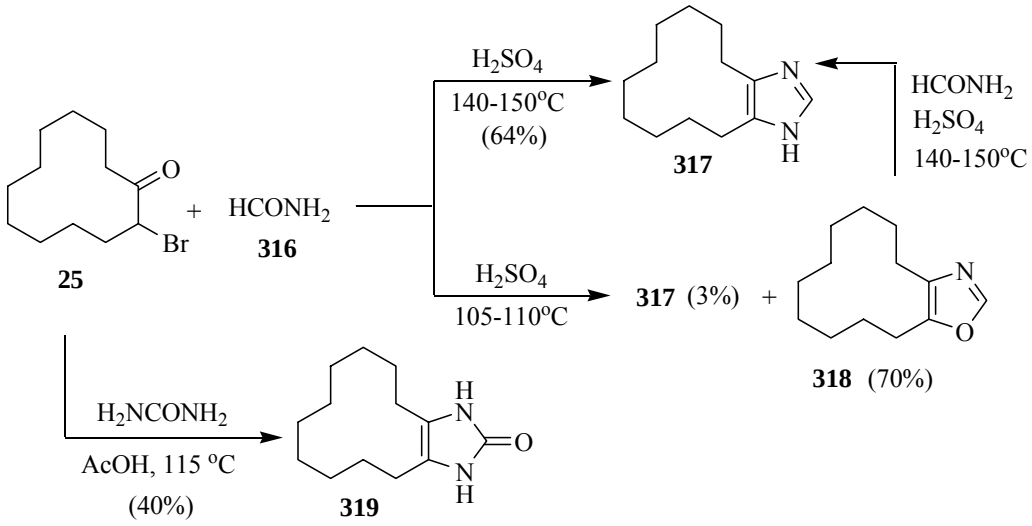
Scheme 66

The synthesis of 2-oxabicyclo[4.10.0]hexadec-l(6)-ene **179**, which is the key material in the production of pentadecanolide (tibetolide), a valuable fragrant macrocycliclactone with a fine musk odor was achieved by alkylation of **1** with 3-*tert*-butoxy- and 3-benzyloxy-propyl bromides **312a**, **b** under phase-transfer catalysis conditions in the presence of an alkali, to obtain 2-(3-alkoxypropyl)cyclododecanones **313a**, **b** which then transformed into **179** according to Scheme 67.[162]

4,5-Decamethyleneimidazole **317**, 4,5-decamethyleneoxazole **318**, and 4,5-decamethylene-imidazolone **319** were synthesized by reactions of 2-bromocyclododecanone **25** with formamide and urea, respectively (Scheme 68).[163]

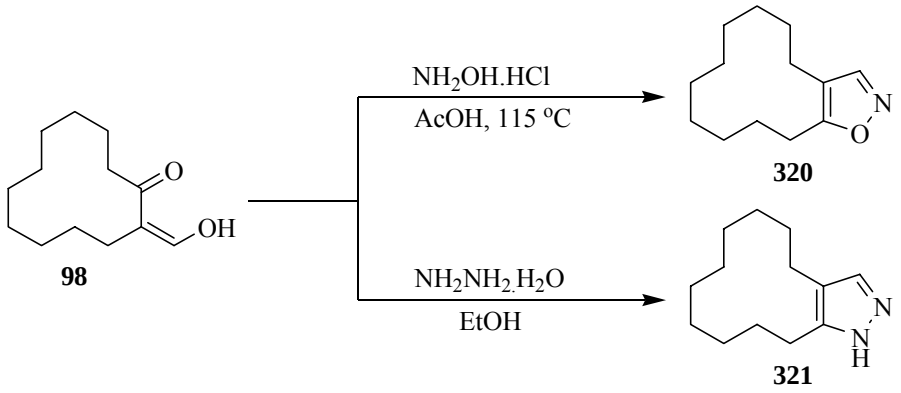


Scheme 67



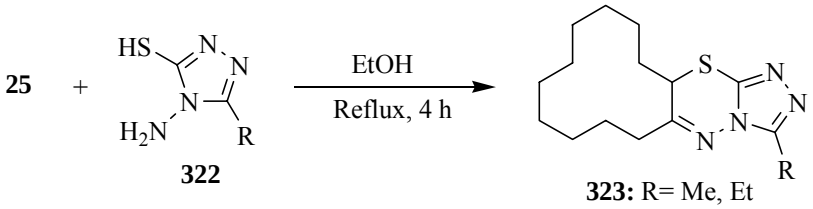
Scheme 68

While, condensation of 2-hydroxymethylenecyclododecanone **98** with hydroxylamine hydrochloride and hydrazine hydrate resulted in formation of 4,5-decamethyleneisoxazole **320** and 4,5-decamethylene-pyrazole **321**, respectively (Scheme 69).[163]

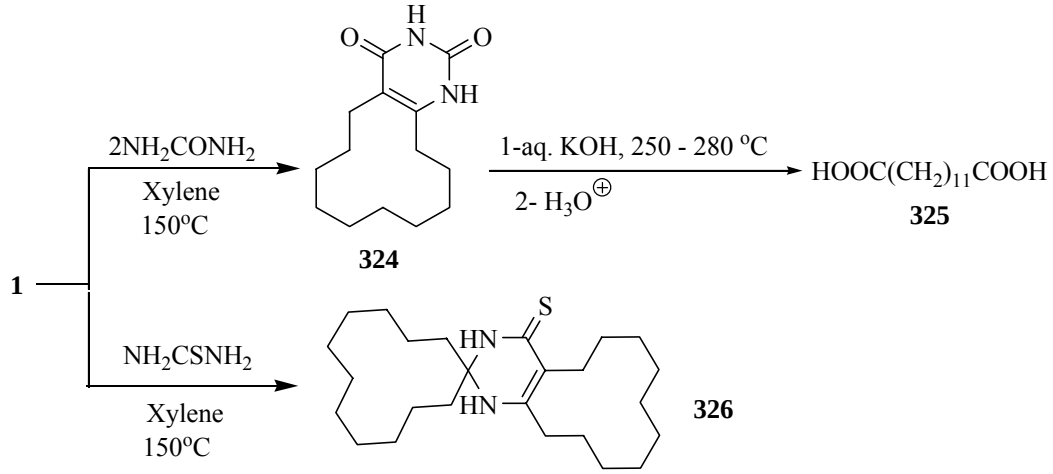


Scheme 69

The triazolothiadiazine derivatives **323** were obtained in low yield *via* direct condensation of 2-bromocyclododecanone **25** with the aminotriazole derivatives **322**.[164]

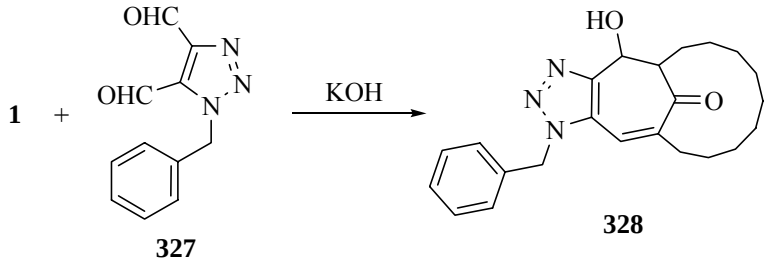


Brassylic acid **325** is used in the perfume industry for the preparation of the valuable fragrance, ethylenebrassylate, which has a musk odor. A simple method is proposed for the preparation of brassylic acid by the alkaline hydrolysis of 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca-[l,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione **324**, which is the product of the condensation of **1** with urea or biuret. On the other hand, condensation of the cyclododecanone with thiourea proceeds differently, leading to 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[l,2-*d*]pyrimidine(1*H*,3*H*)-spirocyclo-dodecane-2-thione **326** (Scheme 70).[165]

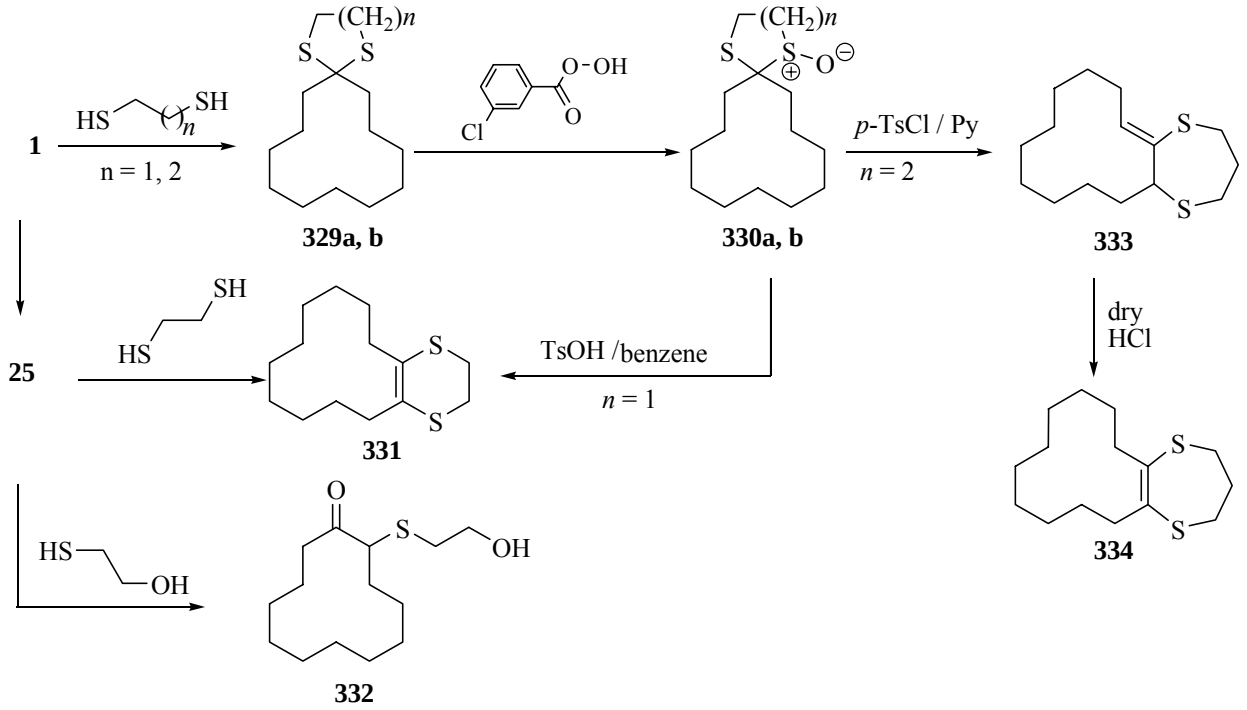


Scheme 70

The condensation reaction of 1-benzyl-1*H*-1,2,3-triazole-4,5-dicarboxaldehyde **327** with **1** under aldol condensation conditions resulted in formation of the hydroxyl cycloheptatriazolone derivative **328**.[166]

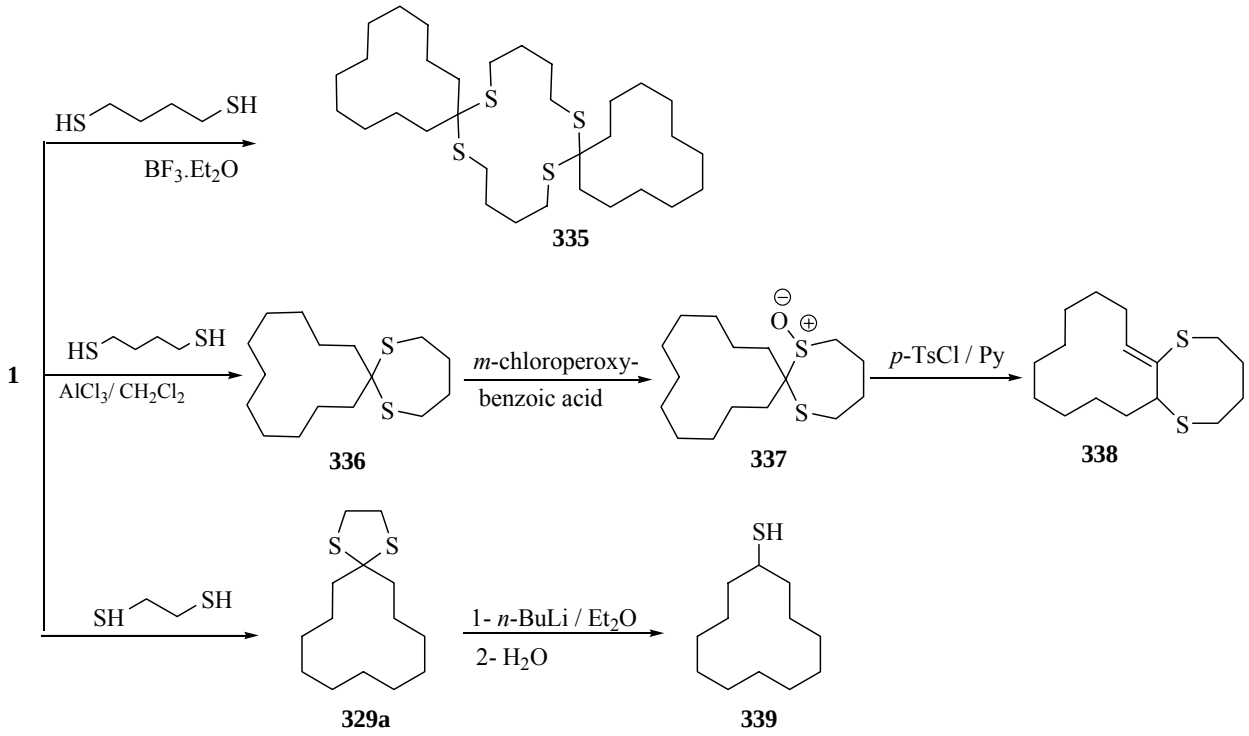


Cyclododecanone **1** was converted conventionally to the dithioketals **329a**, **b** and then to monosulfoxides **330a**, **b**.[167] Action of *p*-toluenesulfonic acid mono hydrate converted **330a** to the corresponding l,4-dithiine **331**. Compound **331** was also obtained by a different route, through the action of 1,2-ethanedithiol on 2-bromocyclododecanone **25** in 67% yield. However this condensation reaction was modeled on an analogous behavior of acyclic α-haloketones reported by Rubinstein and Wuerthele.[168] Also, treatment of 2-bromocyclododecanone **25** with the monoanion from 2-mercaptoethanol gave the sulfide **332** as illustrated by IR and ^{1}H NMR. *p*-Toluenesulfonylchloride in dry pyridine converted sulfoxide **330b** almost quantitatively to the liquid trisubstituted alkene **333** which isomerized to the crystalline tetra-substituted alkene **334** by action of dry hydrogen chloride (Scheme 71).[169]



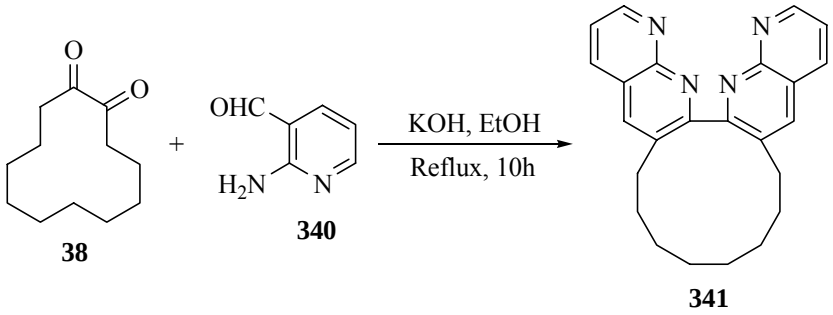
Scheme 71

This effective route for preparation of compound **334** as fused bicyclic 12/7 ring system, encourage Ong,[170] to apply the same methodology whereby fused bicyclic 12/8 ring system represented by **338** was synthesized. Accordingly, attempted preparation of dithioketal of cyclododecanone **336** by reaction of **1** with 1,4-butanedithiol and $BF_3.Et_2O$ resulted in formation of the dimmer **335**. However, repeating the reaction, but using $AlCl_3/CH_2Cl_2$, in lieu of $BF_3.Et_2O$ converted **1** to the desired dithioketal **336** in good yield (67%) which then converted to the monosulfoxide **337** which in turn gave the desired compound **338** under the influence of TsCl/Py system.[169] The secondary mercaptan cyclododecanethiol **339** was synthesized in 90% yield by butyl lithium reduction of thioketal **329a** (Scheme 72).[171]



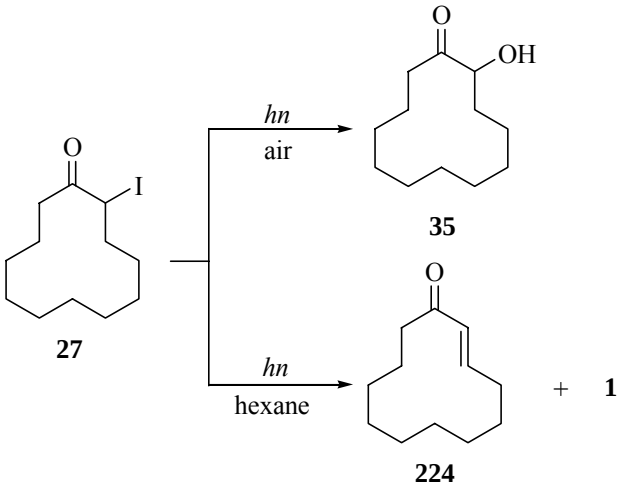
Scheme 72

Base catalyzed condensation of 1,2-cyclododecanedione **38** and 2-aminonicotinaldehyde **340** afforded 3,3'-octamethylene-2,2'-bi-1,8-naphthyridin **341** in 70% yield.[172]



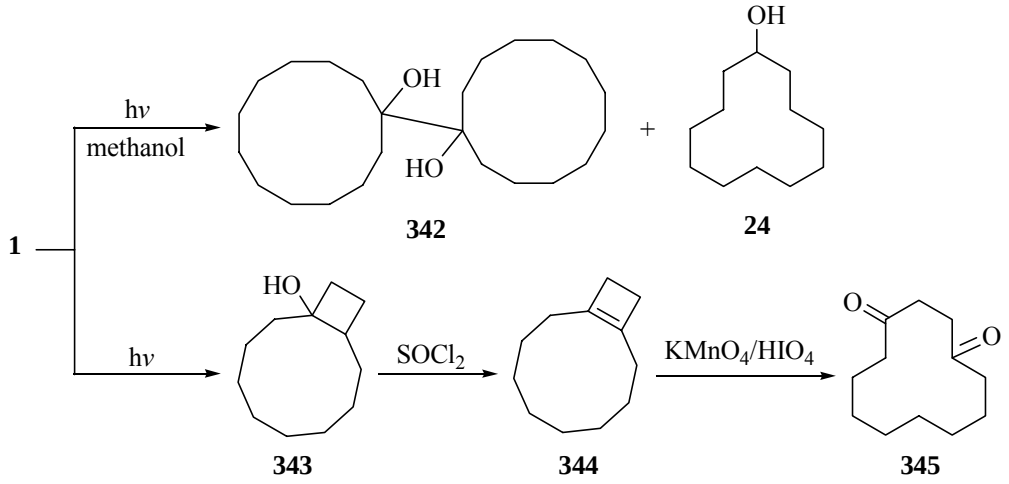
3.8 Photochemistry

Irradiation of 2-iodocyclododecanone **27** under high pressure mercury lamp gave 2-hydroxycyclododecanone **35** in a good yield.[173] Also, the reaction of 2-iodocyclododecanone **27** in hexane containing triethylamine (molar equivalent) at room temperature under nitrogen atmosphere with a 400 W mercury lamp for 2 hours gave cyclododec-2-enone **224** (70%) and **1** (30%) (Scheme 73).[174]



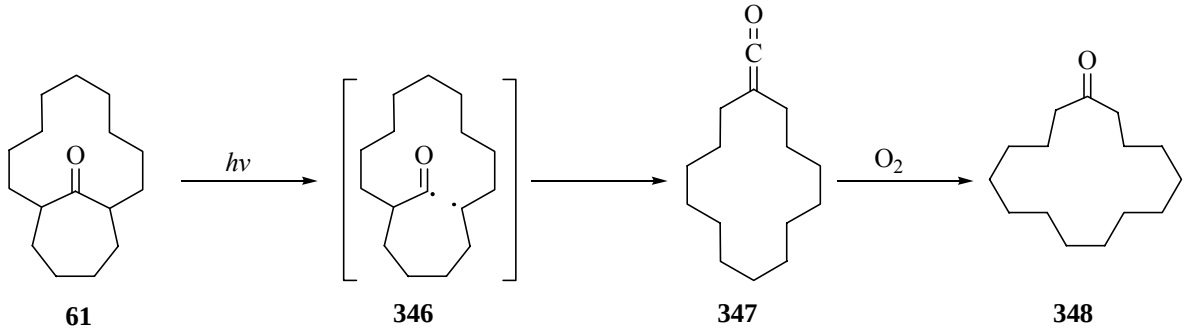
Scheme 73

While irradiation of **1** in methanol at room temperature under a nitrogen atmosphere with a 400 W mercury lamp for 4 hours gave 1,1-bicyclododecanol **342** and cyclododecanol **24**.[175] On the other hand, irradiation of **1** in *n*-hexane with high-pressure mercury lamp in atmosphere of nitrogen for 2.5 hours afforded bicyclo[8.2.0]dodecan-1-ol **343** which on dehydration with thionyl chloride afforded bicyclo[8.2.0]dodec-1(10)-ene **344**. Oxidation of the bicyclic olefin **344** resulted in formation of cyclododecane-1,4-dione **345** (Scheme 74).[176,177]



Scheme 74

A solution of bicyclo[9.4.1]-hexadecan-16-one **61** in CCl_4 was irradiated with a high pressure mercury arc lamp under oxygen stream to afford 20-30% yields of cyclopentadecanone **348** (Scheme 75).[178]

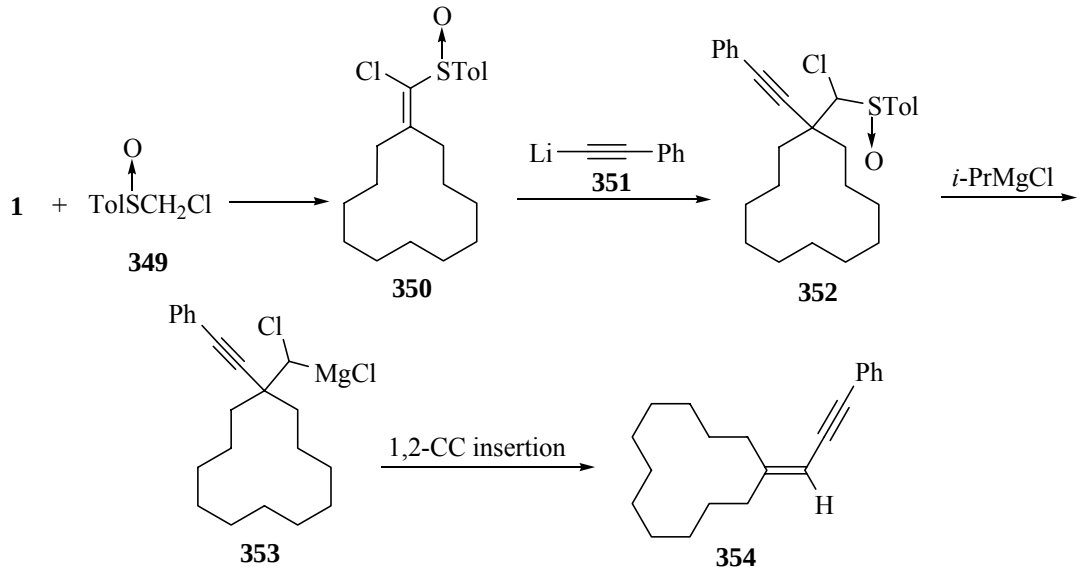


61 **346** **347** **348**

Scheme 75

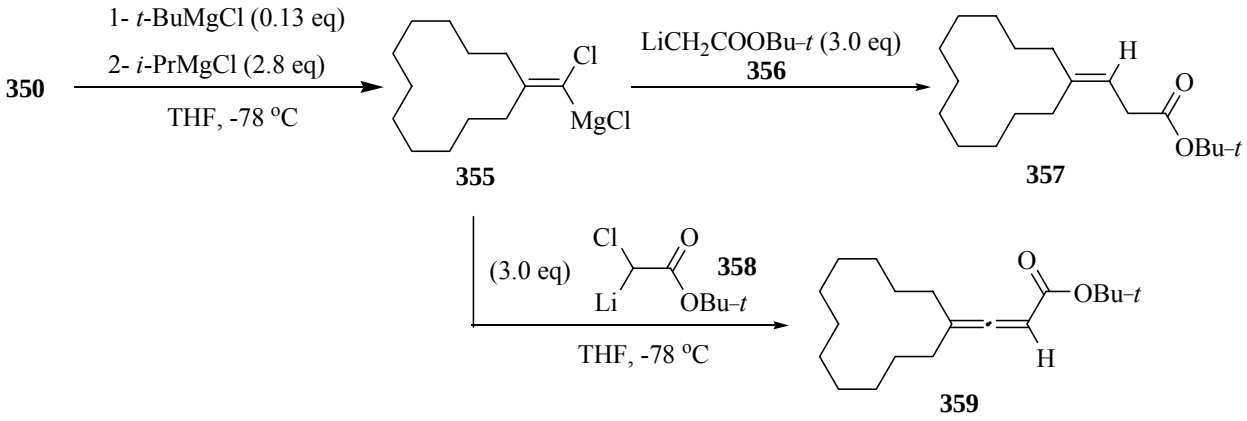
3.9 Miscellaneous reactions

The reaction of 1-chlorovinyl *p*-tolylsulfoxide derivative **350**, which is derived from cyclododecanone **1** and chloromethyl *p*-tolyl sulfoxide **349**, with lithium acetylide **351** gave the adduct **352** in moderate yield. Treatment of **352** with Grignard reagent (*i*-PrMgCl) resulted in the formation of magnesium carbenoid **353** by the sulfoxide-magnesium exchange reaction. 1,2-Carbon-carbon insertion (1,2 CC insertion) reaction of the generated magnesium carbenoid **353** took place to afford the conjugated enyne **354** in high yield (Scheme 76).[179]



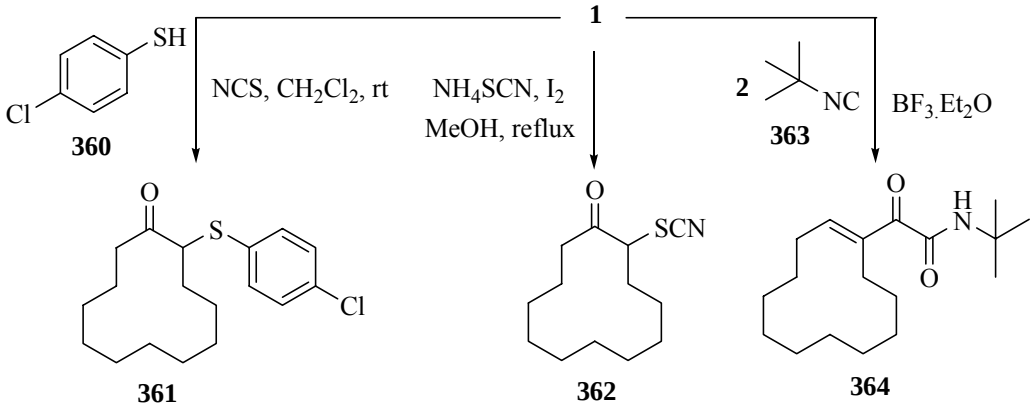
Scheme 76

Also, treatment of **350** with *t*-BuMgCl and *i*-PrMgCl in THF afforded magnesium alkylidene carbenoid **355** which then treated with lithium ester enolate **356** to give the *β,γ*-unsaturated carboxylic acid ester **357** in a good yield. When this reaction was conducted with lithium enolate of *α*-chlorocarboxylic ester **358**, allenic ester **359** was obtained (Scheme 77).[180]



Scheme 77

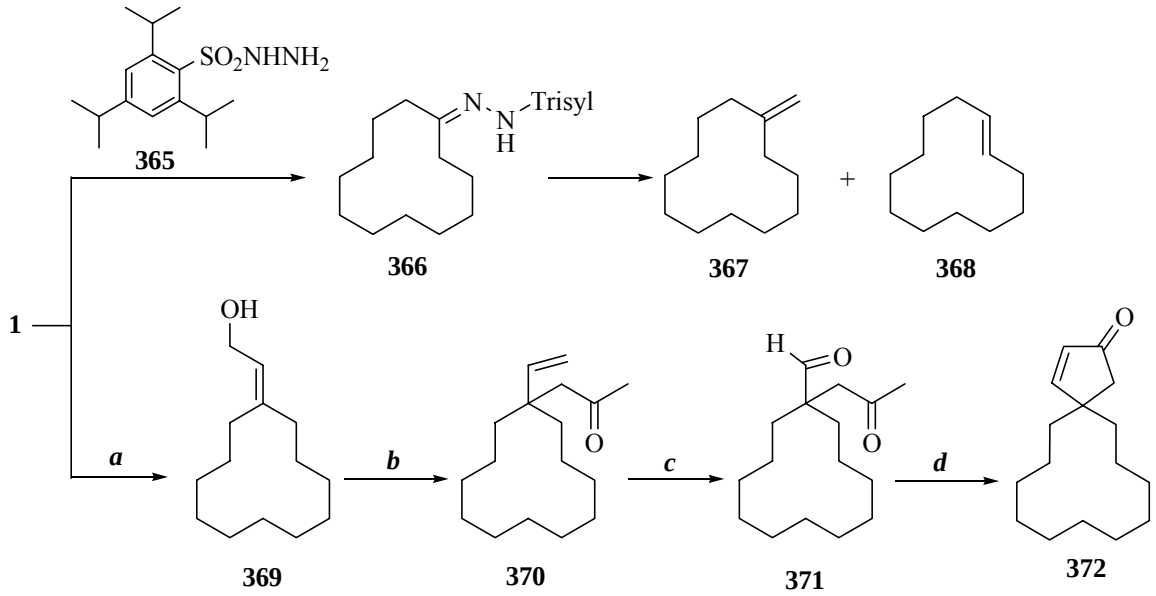
The sulfenylation of **1** has been achieved using *N*-chlorosuccinimide (NCS) under mild conditions to afford **361** in good yield.[181] Cyclododecanone **1** undergoes smooth thiocyanation with ammonium thiocyanate in the presence of molecular iodine in refluxing methanol to produce the corresponding *α*-ketothiocyanate **362** in a very good yield.[182] Treatment of **1** with two equivalents of *t*-butyl isonitrile **363** in presence of $BF_3.OEt_2$ in nonpolar solvent afforded the *β,γ*-unsaturated *α*-oxocarboxylic amide **364**. One equivalent of the isocyanide is the source of the *α*-carbon atom in this reaction (Scheme 78).[183]



Scheme 78

Reaction of the 2,4,6-triisopropylbenzenesulfonylhydrazone of cyclododecanone **366** with *α*-magnesio methyl phenyl sulfone afforded the methylidene derivative **367** contaminated with the

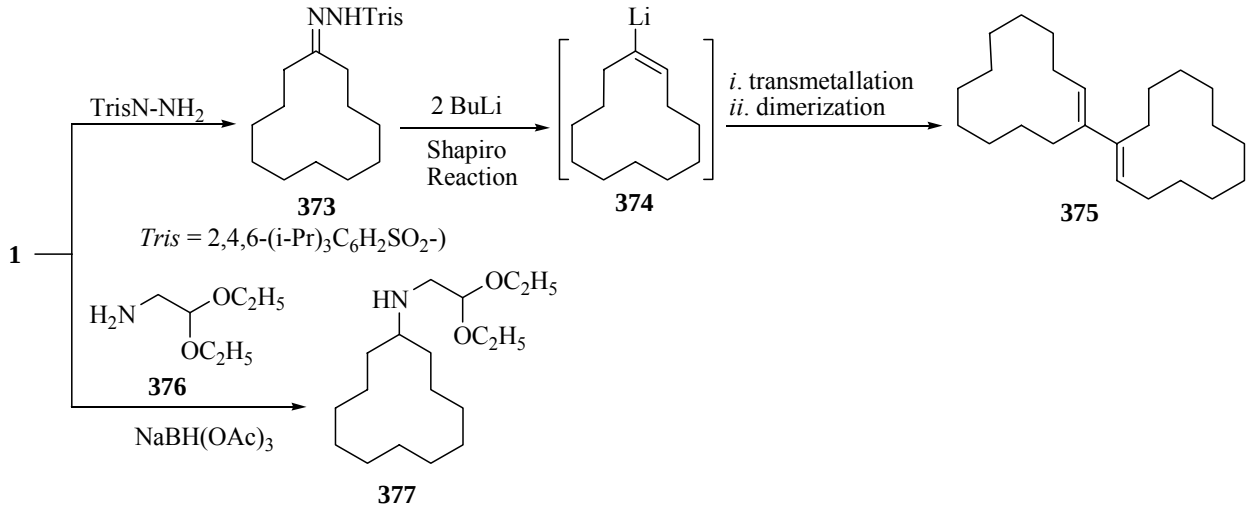
Shapiro product **368**.[184] The spiroenone **372** was synthesized from **1** in four steps sequence in a good yield (Scheme 79).[185]



Reagents: (***a***) (i) NaH, $(EtO)_2POCH_2COOEt$; (ii) $LiAlH_4$; (***b***) CH_2vC(Me)OMe, $Hg(OAc)_2$; (***c***) (i) O_3/O_2; (ii) PPh_3;(***d***) KOH.

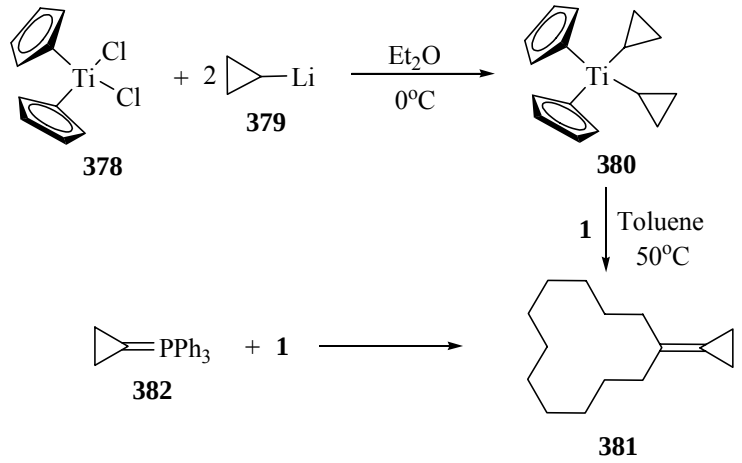
Scheme 79

The diene **375** was prepared from **1** in a two steps procedure involving organolithium-induced Shapiro reaction to produce the corresponding vinyl lithium species **374**.[186] Treatment of **1** with 2,2-diethoxyethanamine **376** under reductive amination conditions affords the secondary amine **377** in 88% yield (Scheme 80).[187]



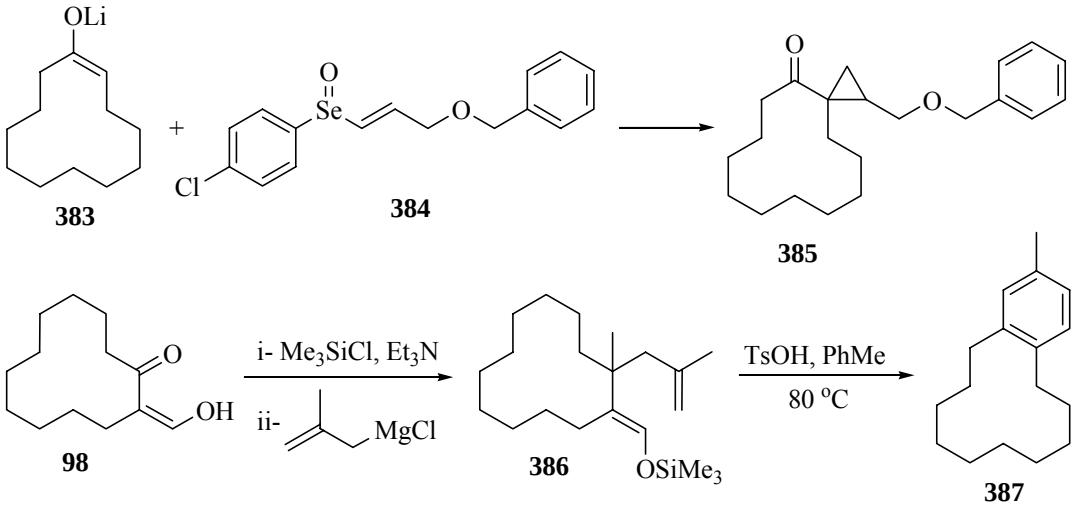
Scheme 80

Cyclopropylidenecyclododecane **381** was obtained by reaction of *bis*cyclopropyltitanocene **380** with cyclododecanone.[188] Alternatively, cyclopropylidenecyclododecane **381** was also obtained *via* Wittig reaction between **1** and cyclopropylidenetriphenyl-phosphorane **382** in 54% yield (Scheme 81).[189]



Scheme 81

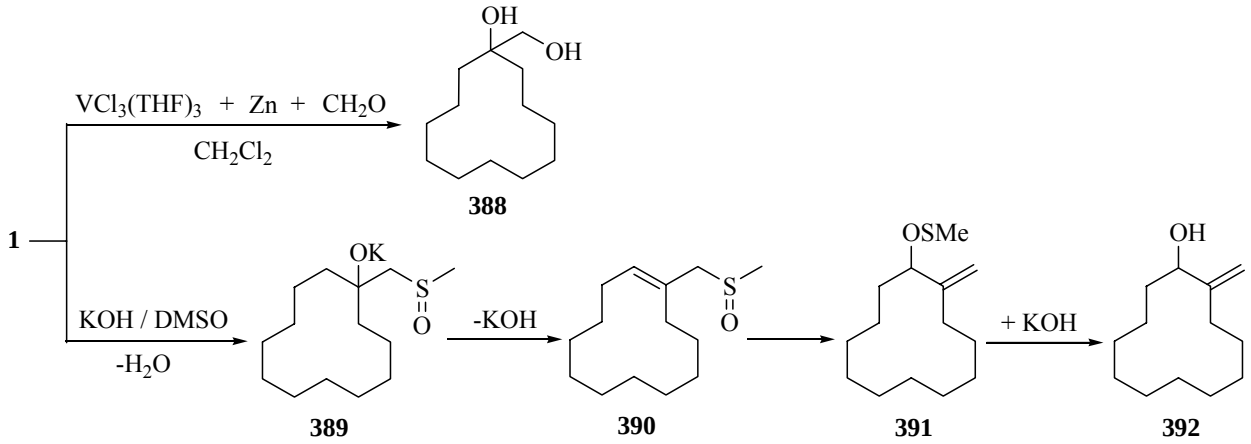
Reaction of lithium enolate of cyclododecanone **383** with aryl vinyl selenoxide **384** afforded the corresponding cyclopropyl ketone derivative **385**.[190] Besides, 5,6,7,8,9,10,11,12,13,14-Decahydro-2-methylbenzo[12]annulene **387** was synthesized from 2-hydroxymethylene-cyclododecanone **98** in two steps in 86% overall yield (Scheme 82).[191]



Scheme 82

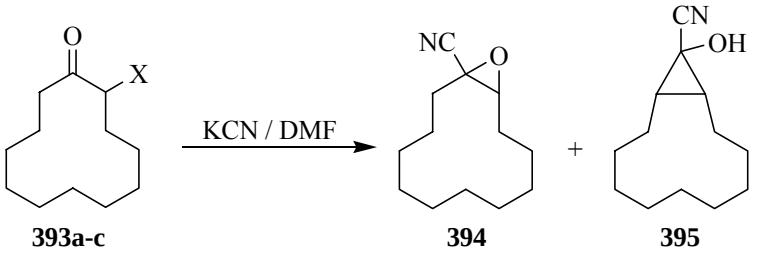
Hydroxymethylation of aldehydes or ketones, leading to terminal 1,2-diols, represents a potentially useful strategy for the one carbon extension of carbonyls. Cyclododecanone **1** was

hydroxymethylated by a simple and direct approach which involve the pinacole cross coupling with formaldehyde catalyzed by vanadium(III)chloride in presence of Zn to produce 1-(hydroxylmethyl)cyclododecanol **388**.[192] Cyclododecanone **1** was converted to 2-methylenecyclododecanol **392** under the influence of KOH-DMSO system in a poor yield (11%) (Scheme 83).[193]



Scheme 83

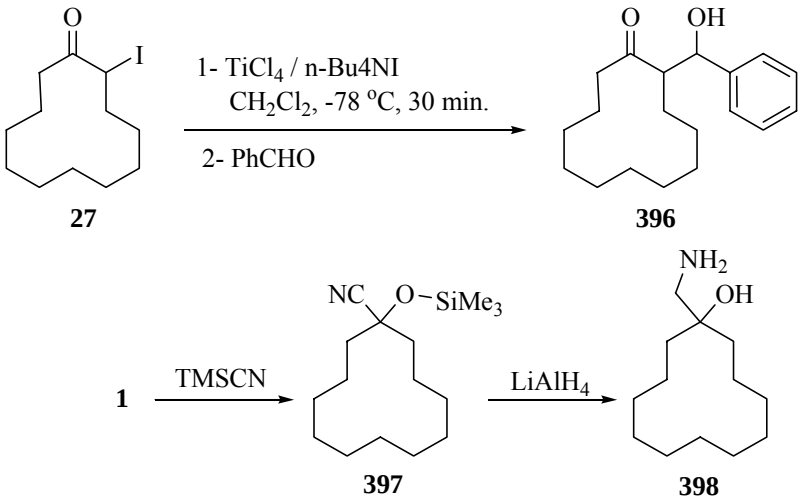
α-Substituted-cyclododecanones **393a-c** react with KCN in DMF to afford 13-oxabicyclo[10.1.0]tridecane-1-carbonitrile **394** and 12-hydroxybicyclo[9.1.0]dodecane-12-carbonitrile **395** the products ratio depends on the nature of *α*-substituent.[194]



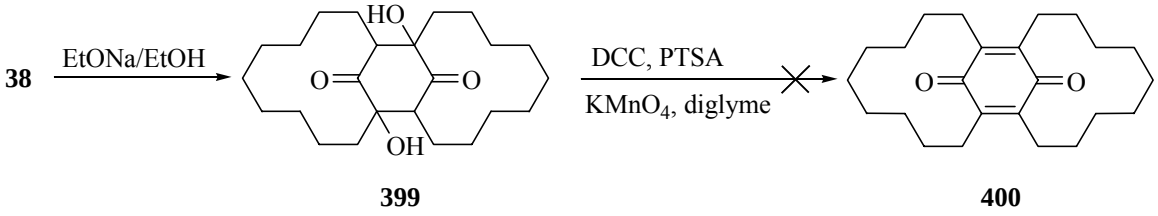
X	yield%	
	394	**395**
a:OMe	0	92
b: Cl	11	72
c: Br	56	35

The Aldol **396** was obtained from the reaction 2-iodocyclododecan-one **27** and benzaldehyde under the influence of $TiCl_4$–*n*-Bu_4NI system.[195] Moreover, trimethylsilyl cyanide (TMSCN) is used for the direct formation of trimethylsilyl cyanohydrine ether of cyclododecanone **397** in excellent yield which on reduction with $LiAlH_4$ afforded 1-(aminomethyl)cyclododecanol **398** in 59.4% yield (Scheme 84).[196]

The base catalyzed self condensation of cyclododecane-1,2-dione **38** afforded the tricyclic macrolide **399** as a highly insoluble, high melting colorless crystalline material. The dehydration of **399** failed to produce the benzoquinone derivative **400** and only **399** was recovered unchanged (Scheme 85).[197]

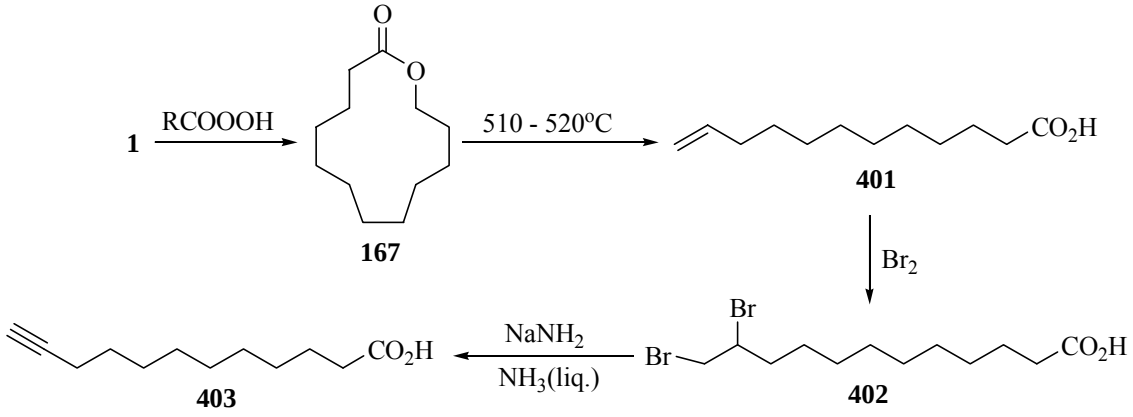


Scheme 84



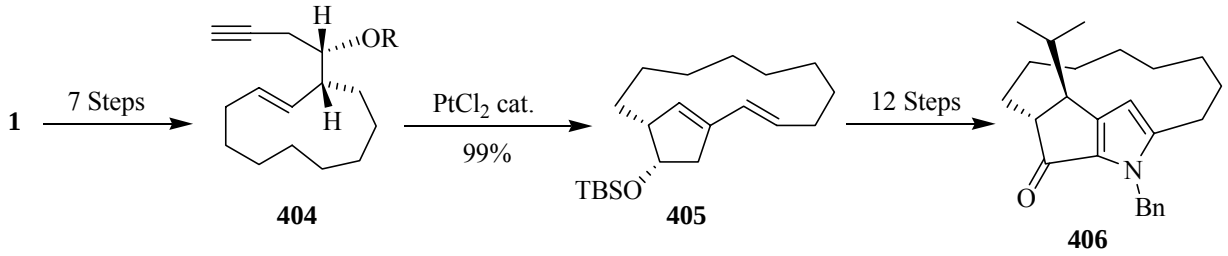
Scheme 85

Finally, dodec-11-ynoic acid **403** may serve as a basic intermediate in the synthesis of *Z*-11- and *E*-11-alkenals, alken-l-ols and their acetates which are insect pheromones.[198] This acid **403** can be obtained from **1** through the macrocyclic lactone **167** (Scheme 86).[199]



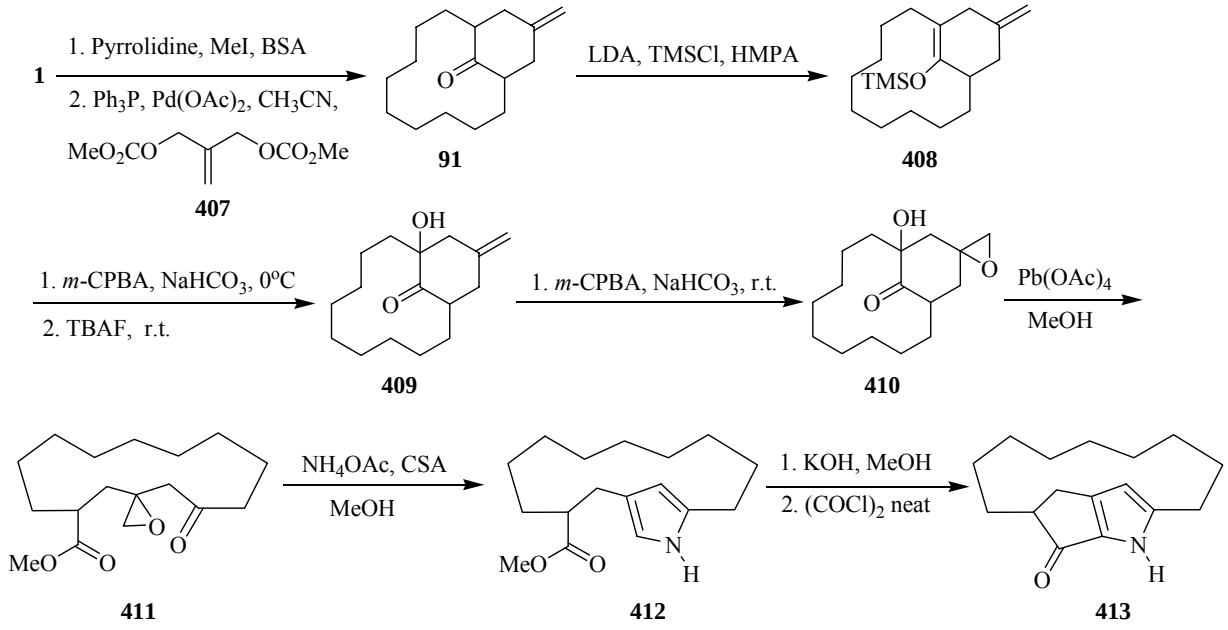
Scheme 86

Trost *et al*,[200] were the first group achieved the construction of Roseophilin tricyclic core **406** without using macrocyclization reactions. They go through a ring contraction of **1** followed by elaboration of a fused bicycle using enyne metathesis, to obtain the tricyclic core in 20 steps and less than 2% overall yield (Scheme 87).



Scheme 87

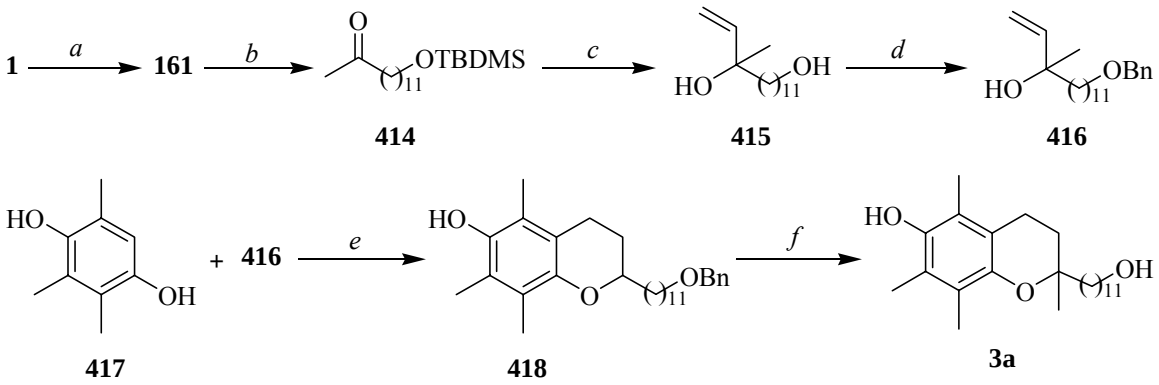
Furthermore, compound **413** which serve as a model for the tricyclic core of roseophilin **2** is described in Scheme 88. The synthetic scheme features a palladium-catalyzed annulation and oxidative cleavage sequence to provide a macrocyclic ketoester **411**. Modified Paal-Knorr pyrrole synthesis and Friedel-Crafts acylation complete the pyrrolophane model system **413** (Scheme 88).[201]



Scheme 88

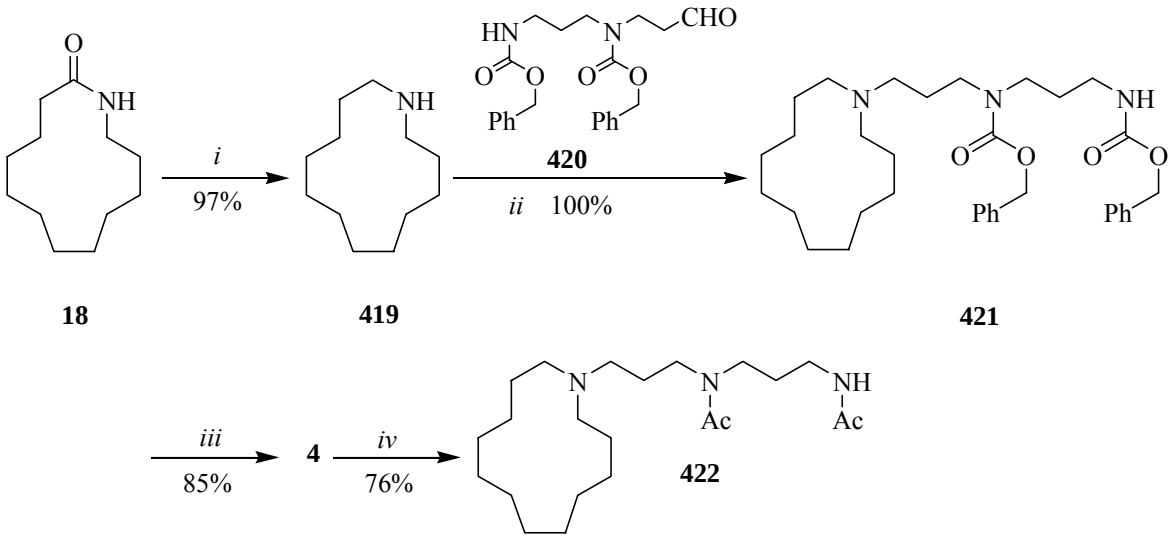
Tocopherol fatty alcohols (TFAs) **3** were first synthesized through *C*-alkylation of trimethylhydroquinone **417** (THQ) using *ω*-benzyloxy allylic alcohols. Cyclododecanone **1** serves

as a source of the *ω*-benzyloxy allylic alcohol **416** which was used in the synthesis of TFAs member **3a**,[2] as outlined in Scheme 89.



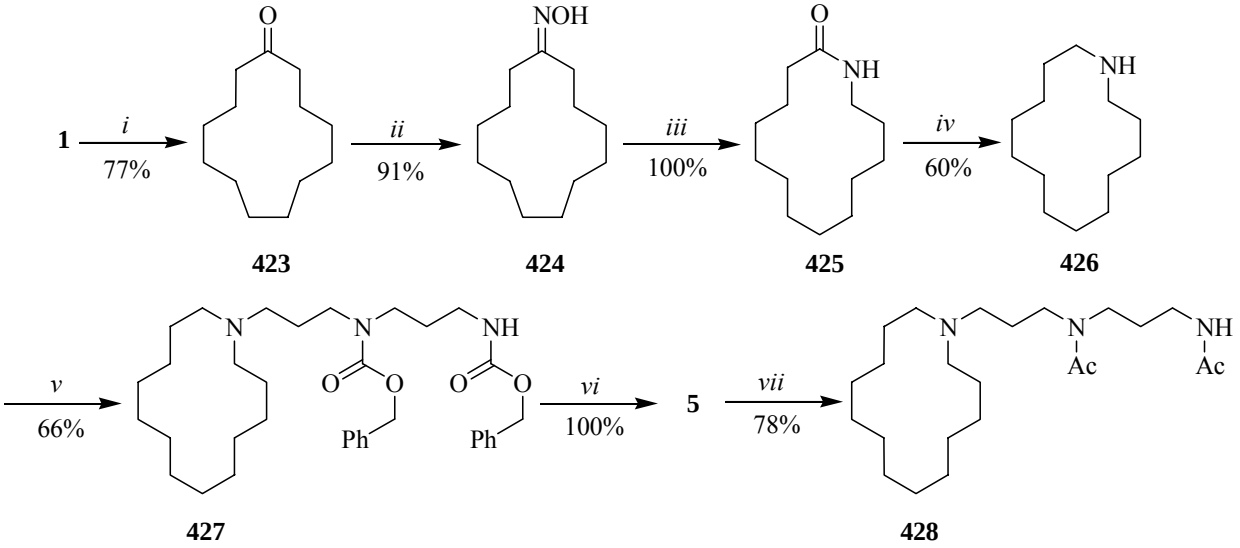
Scheme 89. Reagents and conditions: (*a*) *m*-CPBA, CF_3CO_2H, CH_2Cl_2, reflux (80-85%), (*b*) (*i*) NHMeOMe.HCl, MeLi, (*ii*) MeLi, (*iii*) TBDMSCl, imidazole, THF, 0 °C to rt (68-76%), (*c*) (*i*) $CH_2CHMgBr$, THF, 0 °C to rt, (*ii*) TBAF (66-88%), (*d*) NaH, BnBr, THF, reflux (73-81%). (*e*) $ZnCl_2$, HCl, EtOAc, rt (68-76%), (f) H_2, Pd/C 5%, EtOH, rt (82-96%).

The sponge alkaloids motuporamine A **4** was synthesized starting from the commercially available laurolactam **18** which upon reduction with $LiAlH_4$ afforded azacyclotridecane **419**. Reductive amination of **419** with aldehyde **420** using sodium triacetoxyborohydride in 1,2-dichloroethane gave protected triamine **421** in quantitative yield. Deprotection of **421** by hydrogenolysis gave **4** in 85% yield (Scheme 90).[3]



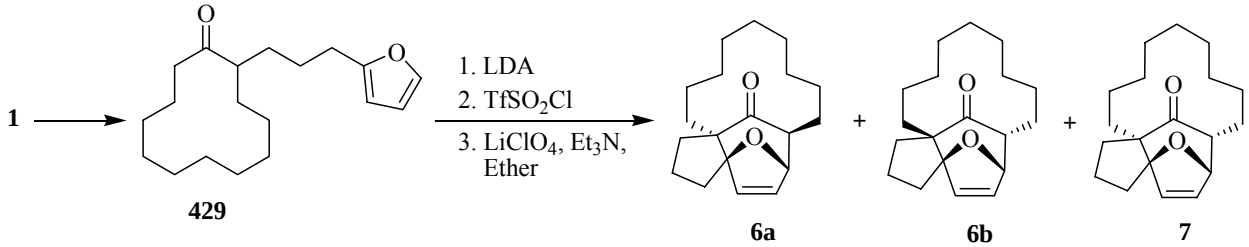
Scheme 90. Reagents and conditions: (*i*) $LiAlH_4$, THF, reflux, (*ii*) $NaBH(OAc)_3$, 1,2-dichloroethane, (*iii*) H_2, Pd/C, MeOH, (*iv*) Ac_2O, Et_3N.

In the same context, synthesis of motuporamine B **5** begin with ring expansion of **1** with trimethylsilyldiazomethane to give cyclotridecanone **423**, which then smoothly transformed into the macrocyclic lactam **425** *via* Beckmann rearrangement of keto-oxime **424**. The target molecule **5** was then obtained by applying reduction/ reductive amination/ deprotection protocol cited above (Scheme 91).[3]



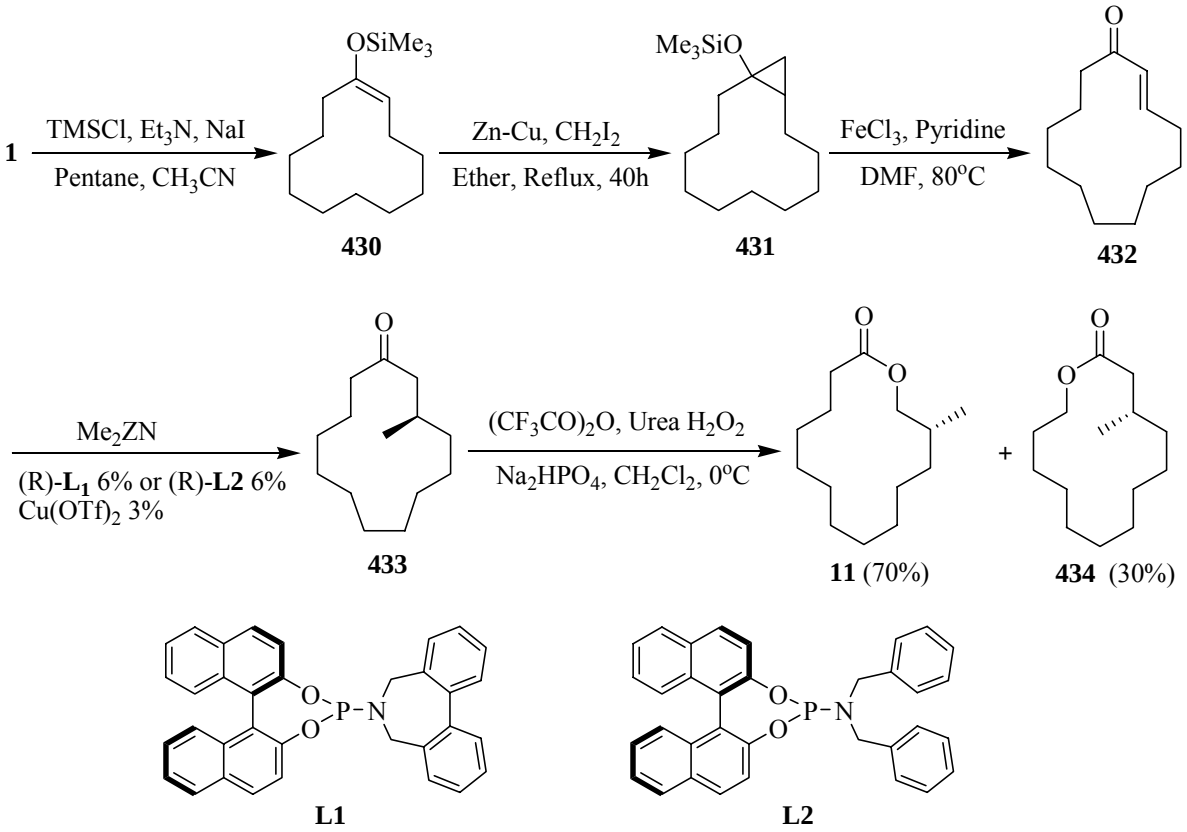
Scheme 91. Reagents and conditions: (*i*) Me_3SiCHN_2, $BF_3.Et_2O$, CH_2Cl_2; (*ii*) $NH_2OH.HCl$, $NaHCO_3$, MeOH; (*iii*) P_2O_5, CH_3SO_3H; (*iv*) $LiAlH_4$, THF, reflux; (*v*) **420**, $NaBH(OAc)_3$, 1,2-dichloroethane; (*vi*) H_2, Pd/C, MeOH; (*vii*) Ac_2O, Et_3N, Pyridine.

The isomeric cyclo adducts **6** and **7** were obtained in 71% yield from ketone **429** through enolate formation and chlorination followed immediately by cyclization under Fohlish conditions. Cyclododecanone derivative **429** underwent smooth cycloaddition to give **6a**, **6b** and **7** in 72% overall yield in a ratio of 7.3:1:1, respectively. The reaction course includes enolate formation and chlorination followed immediately by cyclization (Scheme 92).[3,]



Scheme 92

(*R*)-12-Methyltridecanolide **11** was efficiently prepared by a sequence of reactions consisting of a catalytic asymmetric conjugated addition of dimethylzinc to cyclotridec-2-enone **432** followed by a Baeyer–Villiger oxidation (Scheme 93).[6]



Scheme 93

4. Conformational Characteristics of Cyclododecanone

Knowledge of the conformation and conformational processes of 12-membered rings constitute the first step in the elucidation of the substantially unknown conformational features of large ring compounds. Some structural information is available on a rather limited number of synthetically valuable 12-membered carbocyclic compounds. For cyclododecanone **1** X-ray diffraction studies showed that it exists as a square [3333]-2-one conformation. This same conformation is also adopted by 2,12-dibromocyclododecanone and cyclododecanone oxime. Anet has reported that the low temperature ^{13}C-NMR spectrum of **1** is consistent with a [3333]-2-one conformation. However, the low temperature ^{1}H-NMR spectrum of **1** is complex and it cannot be fully analyzed nor can be various chemical shifts and coupling constants is determined. Furthermore, the iterative force-field calculations of **1** showed that two distinct conformational processes are needed to achieve pseudo rotation of the lowest energy [3333]-2-one conformation,[202,203] (Figures 1 and 2).

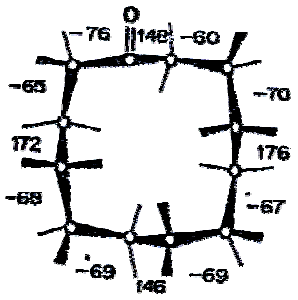


Figure 1. Lowest energy conformation of cyclododecanone, [3333]-2-one and its calculated torsional angles

Moreover, indications for the existence of preferred, distinction orientations of the carbonyl group in 5-12-membered cycloalcanones was found by Ledaal.[204] The orientation of the carbonyl group seemed to change in an irregular way within the series indicating a preferred orientation for each ring size. Consequently, the result of the study indicates that in the 5-ring ketones the carbonyl group is pointing outward with an angle of 0^{o} between its dipole and the ring plane. This angle is steadily increasing for the larger ring ketones, reaching a maximum value for the 11- and 12-ring ketones, which then may have true " inside-carbonyl"-conformations,[205] (Figure 2).

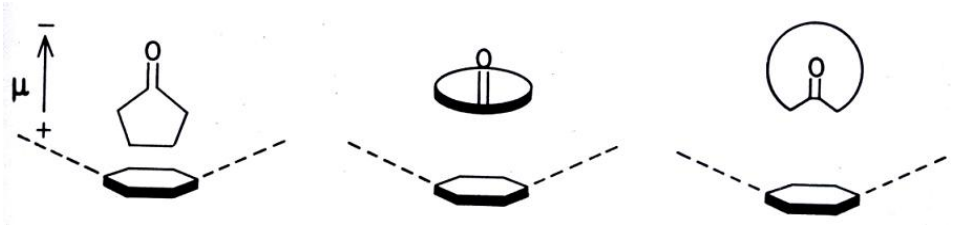


Figure 2. The angle between the carbonyl group dipole and the ring plane for cycloalkanones.

5. Conclusions

The present review has illuminated different aspects of cyclododecanone chemistry, the progress of some reactions of cyclododecanone and its conformational features has outlined the importance of cyclododecanone as a valuable synthetic building block for synthesis of wide range of organic classes including natural products, macrocyclic lactams and lactones and various heterocyclic systems. The vast majority of these important compounds still require further exploration and application, especially as macrocyclic fragrances, drugs, photochemistry and highly important in industrial process.

6. Appendix: Abbreviations and Acronyms

AIBN	Azobisisobutyronitrile
DB-18-C-6	Dibenzo-18-crown-6
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DMPA	4-Dimethylaminopyridine
DME	Dimethoxyethane
DOD	1,1-Dihydroperoxycyclododecane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
LDA	Lithiumdiisopropylamide
MCPA	*m*-Chloroperbenzoic acid
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
PTSA	*p*-Toluenesulfonic acid
TBAF	Tetrabutylammonium fluoride
TIPSCl	Triisopropylsilyl chloride
TMSCl	Trimethylsilyl chloride
TsCl	Toluenesulfonyl chloride

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