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Review Paper

DIENONES AND ENYNONES IN THE SYNTHESIS OF DRUGS AND THEIR INTERMEDIATES

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Abstract: Eynones and dienones have been envisaged in recent years as intermediates for the synthesis of cytotoxic, antibiotic and other potential pharmacologically active compounds. The present review describes the various synthetic routes to Dienones and Enynones and their application in the synthesis of useful drugs, their intermediates and pharmacologically active compounds.

1. Introduction

Eynones and dienones have been envisaged in recent years as intermediates for the synthesis of cytotoxic, antibiotic and other potential pharmacologically active compounds such as Panaxytriol[46], Phomactin[52], Juncusol[41], Methylene Cyclopentenones[40], Spirocyclic Methylene Cyclopentenones[39], 14-β-hydroxy-androst-15-en-17-ones[53], 4-substituted-4-hydroxy-cyclohexa-2,5-dien-1-ones[54] and Androst-5-en-7-ones[50].

The present review describes the various synthetic routes to Dienones and Enynones and their application in the synthesis of useful drugs, their intermediates and pharmacologically active compounds.

2. SYNTHETIC ROUTE TO DIENONES

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2.1 From Phenol and its Derivatives

2.1.1 By Ipso-fluorination of 4-Alkylphenol

4-Fluorocyclohexa-2,5-dienones **2** have been synthesized from 4-substituted phenols **1** by hypervalent iodine reagent, phenyliodine bis (trifluoroacetate) [PIFA] and pyridiniumpolyhydrogenfluoride [PPHF] according to the procedure reported by Karam etal[1] (**Scheme1**).

The proposed mechanism shown in **Figure 1** employs reaction of the reagent PIFA with the phenolic OH of **1** resulting in the formation of intermediate **3**. The intermediate **3** is trapped by a nucleophile fluoride (F^-) resulting in elimination of trifluoroacetic acid and idobenzene to yield **2**.

It was observed by Karam etal[1] that Pummerer ketone **4** was obtained as a bi-product when *p*-cresol was used as starting material **1**. The formation of **4** has been

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accounted for an oxidative dimerization process shown in **Figure 2**.

2.1.2 By Ipso-Chlorination of 4-Alkylphenol Ethers

Mono and polycyclic 4-chloro-2,5-cyclohexadienones **6** were synthesized by ionic chlorination of methylethers of *p*-substituted phenols and related compounds **5** using $SbF_5/CH_2Cl_2(CHCl_3, CCl_4)$ at low temperature according to **Scheme 2**[2].

The proposed mechanism of Ipso chlorination exhibited in **Scheme 2** implies that chloromethyl cations liberate $Cl^{\oplus}$ ion and eliminate a carbene (**:**CH_2, **:**CHCl, **:**CCl_2, from $(ClCH_2)_2Cl^{\oplus}$, $CHCl_2^{\oplus}$ or CCl_3, respectively) which is trapped by HCl or HF under acidic conditions (**Figure 3**)

Previous method for synthesis of 4-chloro-2,5-cyclohexadienones by chlorination of *p*-alkylated phenols have employed chlorine[3-11], allayhypochlorites[6,12,13], sulfurylchloride[8], $SbCl_5$[14], *N*-chloro succinimide[15,16] and trichloroisocyanuric acid[16,17]. However, these methods lead to very low yield or formation of polychlorinated dienones as the major products and hence are unuseful.

2.1.3 By Nitration of 4-Halophenols:

Nitration of *p*-chlorophenol **7** with trifluoroacetylnitrate in ether led to formation of 4-chloro-4-nitrocyclohexa-2,5 dienone **8**. Similar reaction of *p*-chlorophenylacetate **9** with nitric acid in trifluoroacetic anhydride and acetic anhydride at –60°C gave 70% yield of **8** (**Scheme 3**)[18].

Ipso nitration to the halogen in *p*-halophenol and p-halophenylacetate occurs readily and in significant yield. The dienones have to be isolated at less than –40°C since the dienones rearranged to nitrophenols at room temperature as exhibited in **Scheme 4**[18].

2.1.4 Synthesis of Thiophenyl Substituted Cyclohexa-2,4-dien-1-one from 2,6-Xylenol:

The synthesis of various cyclohexa-2,4-dien-1-ones have earlier have been reported by Barton et.al.[19-21]. New cyclohexa 2,5-dienones having disulfide group **14** were prepared from commercially available 2,6-xylenol **10**. **10** on reaction with HCHO in NaOH solution gave **11** in 64% yield. **11** on treatment with $SOCl_2$ gave 4-chloromethyl 2,6-dimethyl phenol 12 in quantitative yield. Reaction of **12** with thiophenol in KOH gave thiophenyl substituted product **13**. **13** on further treatment with *N*-chlorosuccinimide and $(CH_3)_2S$ in presence of Et_3N gave **14** (**Scheme 5**)[22].

2.1.5 By Oxidative Dearomatization of Resorcinol Derivatives:

Mono protected resorcinol derivative **17** was subjected to oxidation by a variety of oxidants to yield cyclohexa-2,5-dienone **18**. **17** was synthesized from 2,4-hydroxy acetophenone **15** according to **Scheme 6**[23].

The best yield of 18 was obtained by use of $PhI(OCOCF_3)$ (Phenylidodiacetate) as an oxidant.

2.1.6 By Reaction of Cresols, Xylenols and 2-Naphthol With N_2O_4:

Reaction of *o*-cresol **19** with N_2O_4 gave 6-methyl-6-nitro-cyclohexa dien-2,4-one-1 **20** alongwith a mixture of 2-methyl-6-nitrophenol and 2-methyl 4-nitrophenol[24] (**Scheme 7**). The reaction of N_2O_4 with 2,3-dimethylphenol **22** resulted in the formation of 2,3-dimethyl 4-nitrocyclohexa dien-2,4-one-1 **21** as one of the major products **Scheme 7**[24].

2.1.7 Synthesis of 4-Diazocyclohexa-2,5-Dienones from *p*-Nitrophenol:

4-Diazocyclohexa-2,5-dienones **29** have been used as photoaffinity reagents for proteins in recent years. The synthesis of **29** was accomplished by Kessler et.al.[25]

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from 2-hydroxy-5-nitro-benzylbromide **23**. **23** was converted into 2-hydroxy-5-nitrobenzylcyanide **24** with LiCN. **24** was reduced with BH_3-THF complex to furnish 2-(2′-hydroxy-5′-nitro)-phenylethylamine hydrochloride **25**. Reductive amination of CH_3CHO by **25** and $NaBH_3CN$ yielded *N*,*N*-diethyl-2-(2′-hydroxy-5-nitro)-phenylethylamine hydrochloride **26**. Nitro of **26** was reduced by Pd-C/H_2. The resulting amine **27** was protected with $(CH_3)_3COCO$ group resulting in the formation of *N*,*N*-diethyl-2-(2′-hydroxy-5′-*t*-butloxycarbamate)-phenylethylamine hydrochloride **28**. Diazotization of **28** in HBF_4 afforded the protonated 2-(2′- *N*,*N*-diethylaminoethyl)-diazocyclohexa-2,5-dienone **29** (**Scheme 8**)[25].

2.2 CYCLOHEXENONE DERIVATIVES

2.2.1 From 2-(Acetoxymethyl)-cyclohex-2-en-1-one:

2-(Acetoxymethyl)-cyclohex-2-en-1-one **30** on nucleophilic substitution reaction with 1,3 diketones in presence of Et_3N and EtOH results in formation of triketone **31**. **31** on further treatment with K_2CO_3 and EtOH under refluxing condition resulted in the formation of 2-(3-oxoalkyl) cyclohexenones **32**. **32** is further cyclized by Robinson annulation procedure to form bicyclic dienone **33** (**Scheme 9**)[26].

2.2.2 By Oxidation With CrO_3/3,5-Dimethylpyrazole Reagent:

Enol diphenylphosphate ester **35** derived from 3-substituted-2,4,4-trimethyl-cyclohex-2-en-1-one **34** on oxidation by the CrO_3/3,5-dimethylpyrrazole reagent resulted in high yield of cross-conjugated dienone **36**. **36** was also obtained by oxidation of safranal derivative **37** by the reaction of CrO_3/3,5-dimethylpyrrazole reagent (**Scheme 10**)[27].

2.1.3 Organotin And Organomercury Reagents in the Synthesis of Dienones:

Conjugate addition of trimethyltinlithium to cyclohex-2-enone **38** followed by aq. workup afforded 3-trimethylstannyl cyclohexanone **39**. Treatment of the enolate with Grignard reagent resulted in the formation of 2-alkyl-3-stannylcyclohexanol derivative **40**. **40** on oxidation with $Pb(OAc)_4$ in benzene leads to fragmentation of cyclohexane ring which is triggered by trimethylstannyl leading to formation of dienone **41** (**Scheme 11**)[28].

2.3 By Diels Alder Reaction of 2-Bromo-2-Cycloalkenones:

2-Bromo-2-cycloalkenones **42** on Diels Alder reaction with dienes using stannicchloride as a catalyst gave high yields of cycloadducts **43**. Subsequent reaction of cycloadducts **43** with DBU gave the corresponding doubly cisoid fully conjugated dienones **44** and **45** (**Scheme 12**)[29].

2.4 Synthesis of Dienones By Knoevnagel Reaction:

2*E*, 4*E*-α,β : γ, δ-dienones **48** were prepared in good to excellent yields by the condensation of unsaturated aldehydes **46** with ketones **47** and ester lithiumenolate in the presence of trimethylchlorosilane[30] (**Scheme 13**).

2.5 By Grignard Reaction:

The dienone **52** was prepared by McClure et.al.[31] from *E*-hexadecenal **50**, which in turn was prepared from dioxalane **49**. Addition of vinylmagnisiumbromide on **50** led to the formation of dienol **51**. Further oxidation of **51** gave dienone **52** (**Scheme 14**)[31].

2.6 By Peterson Olefination Reaction:

The cross conjugated dienone **56** has been synthesized in two steps via a one-pot conjugate addition-Peterson Olefenation Reaction using *exo*-2-trimethylsilyl-3a,4,7,7a-tetrahydro-4-7-methanoinden-1-one **53** followed by a retero-diels Alder Reaction (**Scheme 15**)[32].

2.7 From Biphenyls:

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2- Methylbiphenyl **57** on anodic methoxylation under constant current intensity led to side chain substituted products **58** and **59**. In addition to these products the nuclear addition compound **60** was obtained. On acid hydrolysis of **59** and **60**, the cyclohexadienone **61** was obtained in quantitative yield (**Scheme 16**)[33]. Better yields of cyclohexadienones were obtained by using 4,4-di-*tert*-Butylbiphenyl **62** which on anodic methoxylation resulted in the formation of dienone derivative **63** (**Scheme 16**) [33].

2.8 From 1,4-Quinones:

1,4-Quinones **64** react with allyl indium halide to produce 4-allyl-4-hydroxycyclohexa-2,5-dienone derivatives **65** (**Scheme 17**)[34]. Thus 1,2-dihydroxy-9,10-anthraquinone **66** (alizarine) on treatment with allyl indium iodide generated *in situ* by reaction with indium metal and allyl bromide in the presence of NaI and DMF furnished 10-allyl-3,4,10-trihydroxy-10H-anthracen-9-one **67** (**Scheme 17**)[34].

The yields of cyclohexadienone derivatives were good at low temperature (≅-23°C). However, in some cases hydroquinone derivatives were obtained by reaction of 1,4-benzoquinones with allyl indium iodide. Thus 2,5-dimethyl-1,4-benzoquinone **68** under identical conditions produced hydroquinone derivative **69** at room temperature. The formation of **69** can be explain via rearrangement of **70** into **69** as shown in **Figure 4**[34].

3. SYNTHETIC ROUTE TO EN-YNE-ONES

3.1 *R*-Carvone:

During the synthesis of both enantiomers of 1α, 25-dihydroxy Vitamin D_3 one of the precursor used was en-yne-one **74.** En-yne-one **74** was synthesized from *R*-Carvone **72**. **72** on sonochemical irradiation with H-C≡C-Li-ethylenediamine complex in THF yielded the *tert.* alcohol **73**. **73** on oxidation with PCC (Pyridinium Chlorochromate) and silica gel in CH_2Cl_2 gave en-yne-one **74 (Scheme 18)**[35]**.**

3.2 From Crotonaldehyde:

Enynone **79** was required during the synthesis of pumiliotoxins isolated from skin secretions of Dendrobatid frogs[36]. Enynone **79** was synthesized from crotonaldehyde **75** by fI.R.st reaction with CBr_4 and Ph_3P according to the procedure of Corey-Fuchs. The dibromoolefin **76** thus obtained was reacted with chiral ketone **77** in presence of *n*-BuLi and HMPA leading to the formation of eynyne **78**. The diastereomeric mixture of alcohols **78** on oxidation under Swern condition gave Enynone **79** in 70% yield **(Scheme 19)**[36]**.**

3.3 From Acetamide Derivatives:

During the synthesis of Amythiamicin, a thiopeptide belonging to a group of thiopeptide antibiotics, enynone **85** was needed as starting material. The synthesis of enynone **85** was carried out in five steps according to **Scheme 20** from 2,2-diethoxyacetamide **80**. Thionation of **80** was carried out with P_2S_5 to give thione **81**. Hantzsh thiazole synthesis of **81** with ethyl bromo pyruvate in EtOH was carried out in presence of 4Å molecular sieves to give thiazole derivative **82**. Deprotection of acetal in **82** was carried out in presence of acid to give aldehyde **83**. Addition of ethynylmagnesiumbromide on **83** resulted in the formation of Propargylic alcohol **84**. **84** on oxidation with MnO_2 afforded enynone [1-(2-thiazoyl)propyn-1-one] **85** in more than 98% yield **(Scheme 20)**[37]**.**

3.4 From Bromomethylethyl Ketone:

During the total synthesis of 3-Deoxy-3-thio-1α, 25-dihydroxy Vitamin D_3 for its biological evaluation, the synthesis of ring fragment containing sulfur atom was desired. The synthesis of ring fragment

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containing sulfur atom was accomplished by coupling of bromomethylethyl ketone **86** with thioglycolate **87** to afford ketoester **88** in 94% yield **(Scheme 21)**[38]**.** **88** underwent an intramolecular cyclization by using NaH to produce enolate **89**. Treatment of **89** with Ph_3P, I_2 and Et_3N produced Iodoenone **90**. **90** on further coupling with Me_3Si-≡-H using $(Ph_3P)_4Pd$ [0], CuI and *n*-butylamine gave enynone **91 (Scheme 21)**[38]**.**

3.5 From bis-Acetylenic Alcohols

Spirocyclic Methylenecyclopentenones have been known to possess anticancer activity. Enynone **95-*Z*** were required as starting material for synthesis of Spirocyclic methylenecyclopentenones. Bis-acetylenic alcohols **94** were synthesized by the reaction of 2-cycloalkenyl carboxylates **92** with lithium acetlides **93**. Bis-acetylenic alcohols **94** gave mixture of enynones **95 (*E*)** and **95 (*Z*)** on heating by oxy-Cope rearrangement **(Scheme 22)**[39]. Enynone 95 (*Z)* on further electrocyclic ring closure gave Spirocyclic ethylenecyclopentenones.

4. APPLICATION OF ENYNONES AND DIENONES IN THE SYNTHESIS OF DRUGS AND THEIR INTERMEDIATES

4.1 α-Tocopherol (Vitamin E) - Catalyzed Cyclization of Enynones to Methylenecyclopentenones

Enynones **96** on reaction with α-Tocopherol (1.10 eq.) alongwith 5eq. quantities of 1,2-epoxyoctane (as Scavenger) resulted in the formation of α-methylenecyclopentenones **97 (Scheme 23)**[40]**.**

4.2 Synthesis of cyclopentenone derivatives:

The acid catalyzed pyrolysis of Enynones **98** leads to two different pathways. The ring-closure according to Path A leads to 5-*exo* reaction leading to the formation of α-methylenecyclopentenones **100**. The Pathway B of ring closing reaction is 6-*endo* ring closing reaction resulting in the formation of phenolic derivative **101 (Scheme 24)**[41]**.**

4.3 Addition of Organocopper Reagents to Enynones:

Enynone **102** undergoes facile 1,6-addition of organocopper reagents to yield allenyl enols **103**. **103** isomerises stereoselectively to *Z*-dienones **104 (Scheme 25)**[42]**.**

4.4 Eynones in the Synthesis of Antibiotic Juncusol:

Antibiotic **Juncusol 110a** has been synthesized by electrocyclization of enynones **109.** The starting material for the synthesis of **110a** was the β-tetralone derivative **105.** Monoalkylation of **105** with allylbromide through intermediate pyrrolidine enamine formation afforded the mono alkylated product **106. 106** was directly converted to the unsaturated amide **108** by reaction with the Wittig reagent **107**[43] by employing the general condition of Masamune et.al.[44] Pure *endo* amide **108a** afforded *endo* enynone **109** on condensation with Lithium acetylide. The reaction of pure *exo* amide **108b** also gave predominantly *endo* enynone **109a** under identical conditions. Furthermore both *endo* and *exo* enynone **109** undergo electroclyclization to give the product **Juncusol 110a (Scheme 26)**[45]**.**

4.5 Synthesis of Panaxytriol: The Active Component of Red Ginseng

Total synthesis of (3*R*, 9*R*, 10*R*)-Panaxytriol **120** was achieved enantioselectively from enynone **111** by Danishefsky et.al.[46] Out of the two fragments of retero synthetic pathways of Panaxytriol **120**, one of the building block **113** was synthesized from enynone **111**. **111** on reduction by commercially available (*R*)-Me-CBS reducing agent afforded **112** with high enantioselectivity. **112** on deprotection of C-silyl function and bromination of terminal alkyne using

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NBS and $AgNO_3$ gave building block **113** in excellent yield **(Scheme 27)**[46]**.**

The synthetic route to other building block containing the vicinal diol **119** commenced with the commercially available *trans*-2-decen-1-ol **114**. **114** on protection with TBSCl gave the protected *tert*-butyldimethylsilyl ether **115**. Sharpless asymmetric dihydroxylation of **115** with AD-mix-β afforded **116** in excellent yield. Diol **116** was protected as isopropylidine derivative **117**. Acid induced cleavage followed by treatment of diol bromide with K_2CO_3 afforded **118**. The building block **119** was obtained by the epoxide cleavage with Lithium acetylide **(Scheme 28)** [46]**.**

Cadiot-Chodkiewicz cross-coupling reaction between key building block **113** and **119** resulted in the formation of Panaxytriol **120** in overall 40% yield **(Scheme 29)**[46]**.**

4.6 Synthesis of Methylenomycin B from Enynones:

Methylenomycin B **127** has been synthesized in 55% yield by single electron transfer catalyzed cyclization (SET) of enynone **125** according to **Scheme 30**[47]. The synthesis of enynone **125** was carried out from the ketone **121** by Wittig reaction with the commercially available Wittig reagent **122**. The crotonate ester **123** thus obtained was converted to the corresponding aldehyde **124** by a two-step sequence involving LAH reduction and oxidation of resulting allylic alcohol with Swern's reagent. Condensation of **124** with lithio acetlide followed by oxidation with MnO_2 afforded enynone **125**. **125** on heating with vitamin E at 200°C under conditions of SET or by photolysis in the presence of 4-*tert*-butylcatechol (TBC) afforded Methylenomycin B **127** via intermediate formation of dienynol **126 (Scheme 30)**[47]**.**

4.7 Synthesis of (±) - Gunacastepene A, A Novel Diterpine Antibiotic Used As Antibactrical Drug:

(±)-Gunacastepene **136** was synthesized by B. B. Snider et.al.[48] from 2-methylcyclopentenone **128** in 17 steps in 4% overall yield. The key intermediates have been shown in **(Scheme 31)** [48]**.**

4.8 Synthesis of (±) – Epoxysorbicillinol From Cyclohexa-2,5-Dienone Derivative:

(±) –Epoxysorbicillinol **144**, a, natural product has a wide range of biological activities. It has been synthesized from dienone derivative 138 according to **Scheme 32**[49]**.**

4.9 The Synthesis of Androsta-3,5-dien-7-ones as Aromatase Inhibitors in Human Placental Microsomes:

Androsta-3,5-dien-7-ones **149** has been synthesized from 3β, 19-dihydroxy-5-ene-7,17-dione derivative **145** which has a tosyl group at C-3 and a *tert*-Butyldimethylsylil (TBDMS) group at C-19. **145** on treatment with *N*-methylpyrrolidone at 80°C gave 19-hydroxy-3,5-dien-7,17-dione **147** alongwith 19-TBDMS derivative **146**. **146** was also converted into **147** by treatment with $(n\text{-Bu})_4NF$. The 19-ol **147** was converted into 19-al **148** by oxidation with pyridiniumdichromate (PDC) oxidation. Treatment of steroid **148** with KOH in aq. MeOH gave 19-nor-3,5-dien-7-one **149** as outlined in **Scheme 33**[50].

4.9.1 Application of Cyclohexadienones in the Synthesis of NF-κB Inhibitors, (-)-Cycloepoxydon:

NF-κB, an inducible transcription factor that regulates the expression of various cellular genes is involved in immune and inflammatory responses. The natural product Cycloepoxydon **160** has been shown to inhibit activation of NF-κB. The total synthesis of (-)-Cycloepoxydon **160** was accomplished from phenol derivative

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150. **150** on hypervalent iodine oxidation afforded dimethoxy ketal 151. Transketalization of **151** with 2,2-dimethyl-1,3-propane diol afforded 1,3-dioxane **152**. Epoxidation of **152** was accomplished by treatment with Ph_3COOH, (L)-Dipt and toluene to provide monoepoxide **153** (68% e.e.). Using similar epoxidation condition for the epoxidation of **152** at –50°C resulted in the formation of *opposite* enantiomer **154** (96% e.e.). The absolute configuration of **154** was assigned by correlation of compound produced by epoxidation of chiral quinone monoketal. Stille coupling of **154** with (E)-tributyl-1-pentenyl-stannane afforded **155**. **155** on reduction with DIBAL-H in THF gave *anti*-epoxy alcohol **156**. **156** on further reaction with HF in CH_3CN resulted in acetyl hydrolysis to provide epoxy quinol **157 (Scheme 34)**[51]**.**

Epoxy quinol **157** on treatment with *m*-CPBA afforded γ, δ- epoxynone **158**. **158** on treatment with HF in acetonitrile resulted in *endo*-epoxide ring opening to give (-)-cycloepoxydon **160** alongwith *exo*-epoxide ring opening product **159 (Scheme 35)**[51]**.**

4.9.2 Application of TosMIC in the synthesis of precursors of sex Pheromones

Both disodio- and dilitho- TosMIC[55-57] react with pyridine *N*-Oxide to form an unstable product **161**, which could not be isolated[55]. The stable dialkylated TosMIC derivative **162** was obtained by reaction of benzyl bromide with disodio or dilitho salt of TosMIC and pyridine *N*-oxide. **162** on dehydration with Tosyl chloride in pyridine at 0°C yields 1-cyano-5-isocyano-6-phenyl-5-tosylhexadiene-1,3 **163**. **163** on hydrolysis with aq. HCl in THF resulted in the formation of 1-cyano-6-phenyl-4-tosylhex-ene-1-one-5 **164**.**164** on rapid filtration through neutral Al_2O_3 in CH_2Cl_2 gave dienone **165**[58] (Scheme 36).

Analogous reaction of dilitho and disodio salt of TosMIC with pyridazine *N*-Oxide in presence of benzyl bromide and further hydrolysis led to formation of diazonium hydroxide **166**. Diazonium hydroxide **166** on prolonged standing at room temperature or heating forms enyne **167**. **167** on hydrolysis with aq. HCl and further chromatography over Al_2O_3 in CH_2Cl_2 yielded eynone **168**[58] **(Scheme 37)**.

Monosodium and disodium salts of TosMIC have been used for the synthesis of sex pheromones of common housefly[59].

Conclusion:

In conclusion several significant routes have been described for the synthesis of dienones and enynones which are useful intermediates for the synthesis of several drug intermediates and pharmaceutically useful agents.

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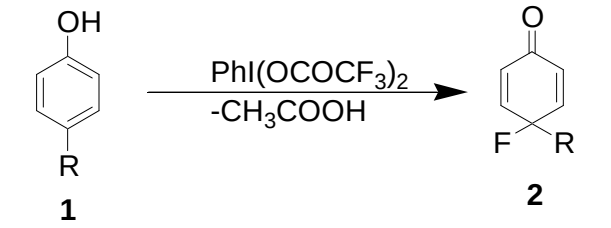
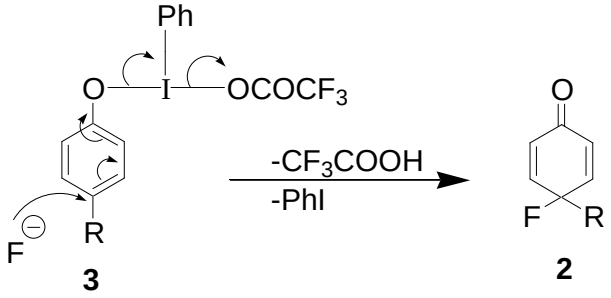


1 **2**

R= Me, Et etc. (42-77%)

Scheme 1



3 **2**

Figure 1

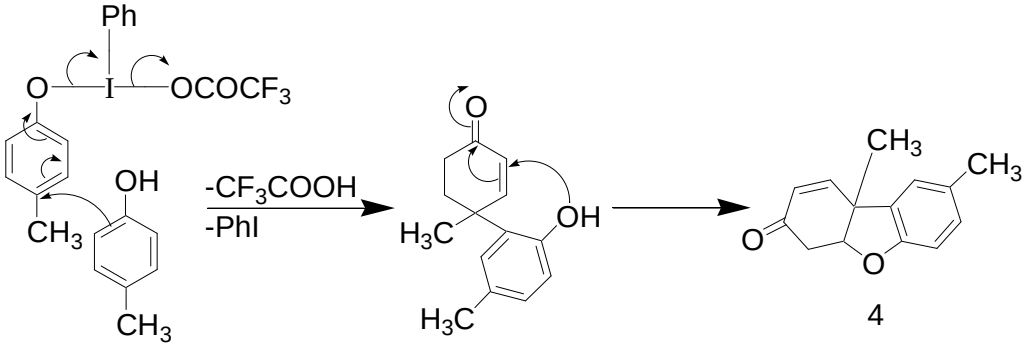


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Figure 2

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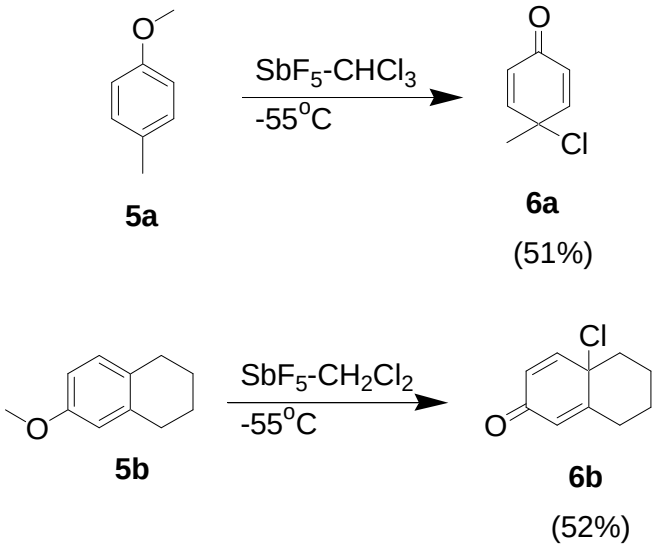

Scheme 2

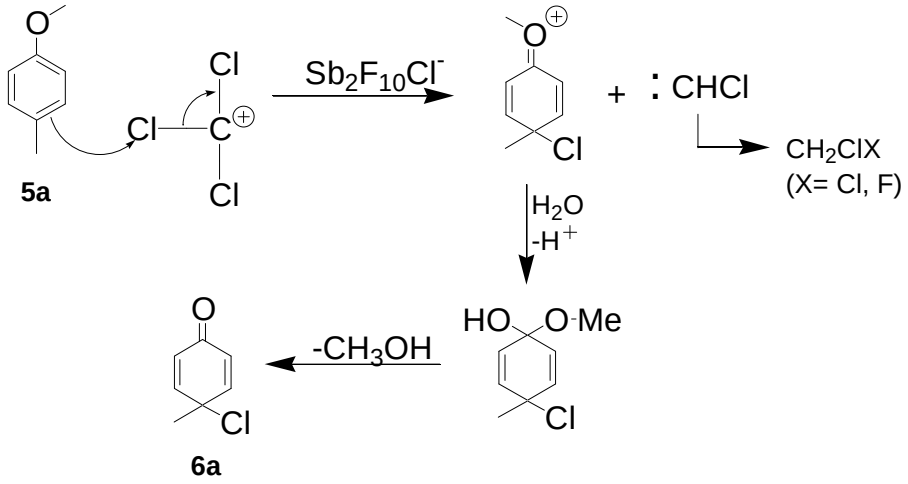

Figure 3

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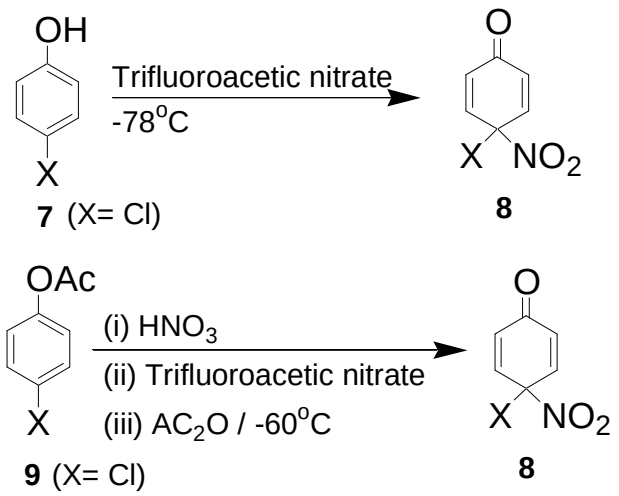
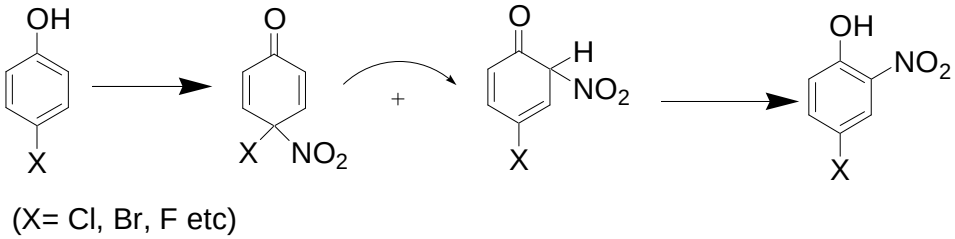


Scheme 3



(X= Cl, Br, F etc)

Scheme 4

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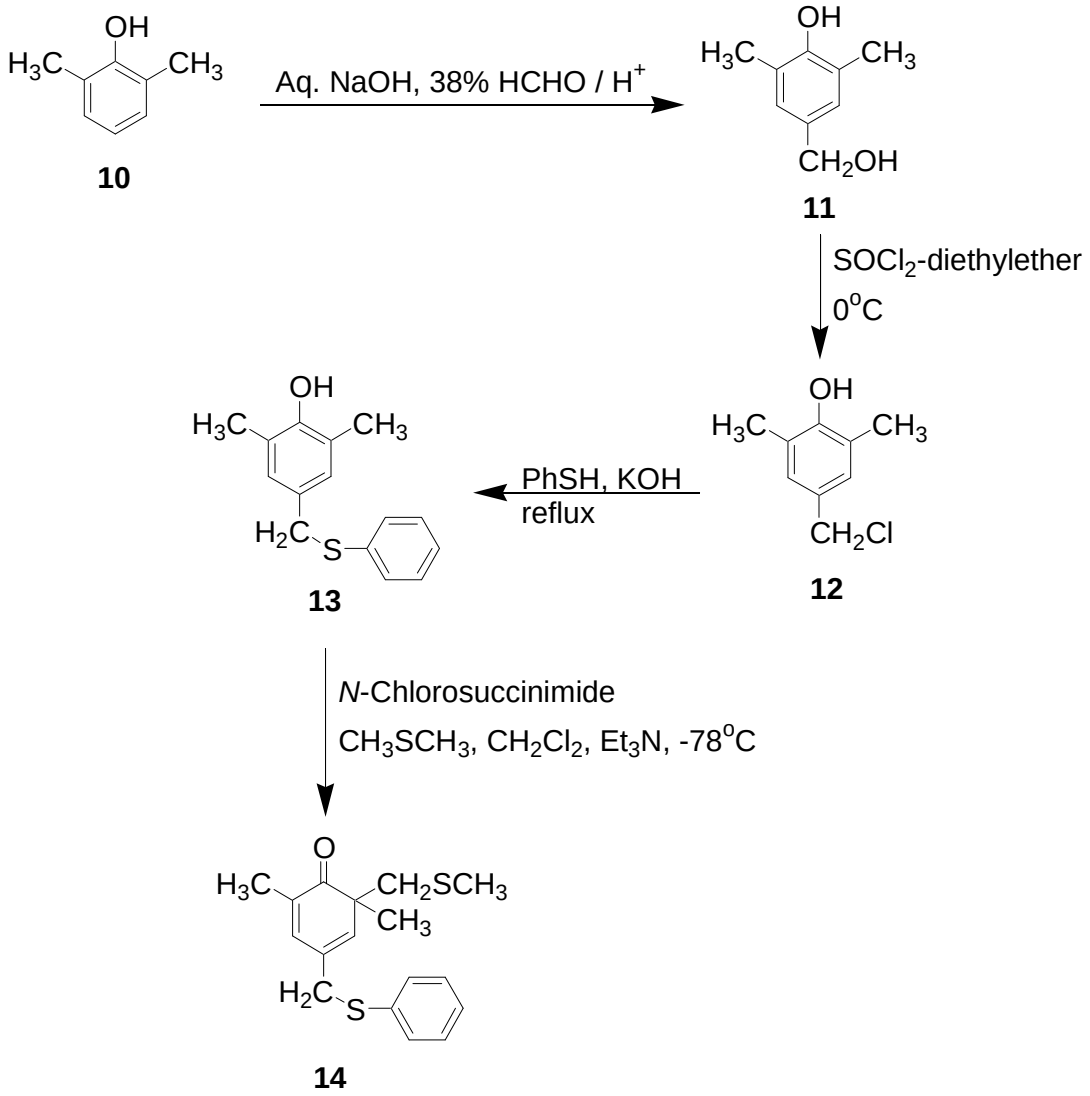

Scheme 5

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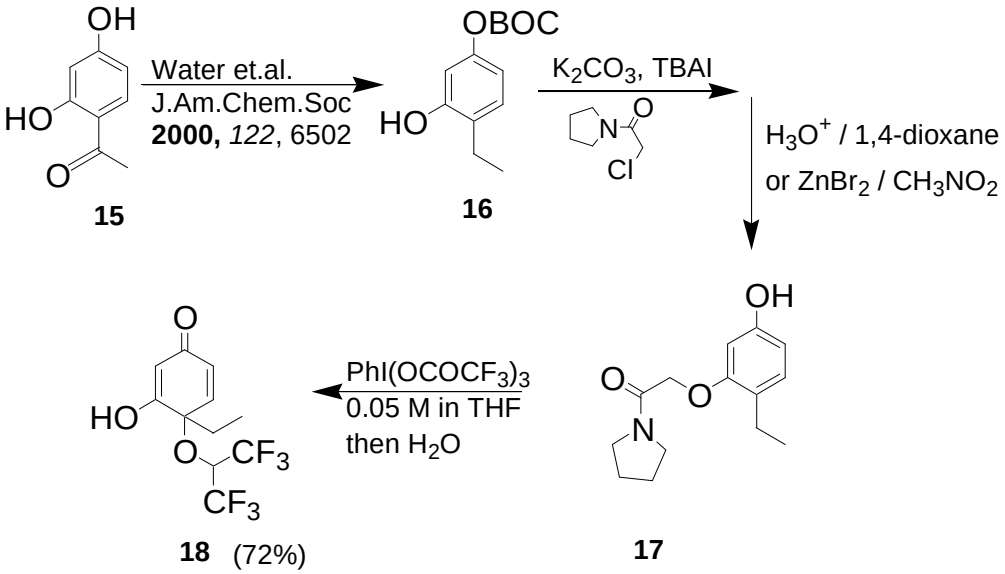
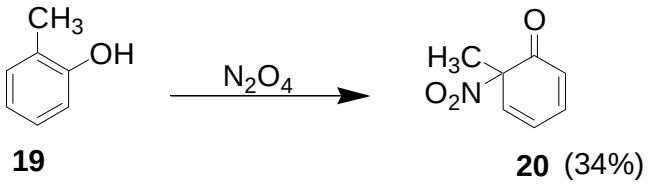
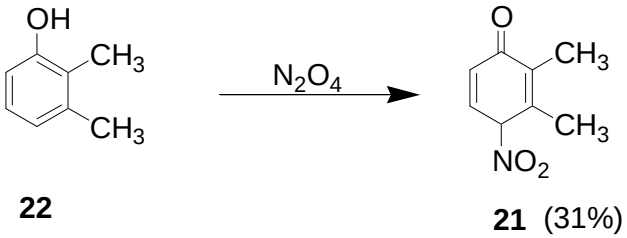


Scheme 6





Scheme 7

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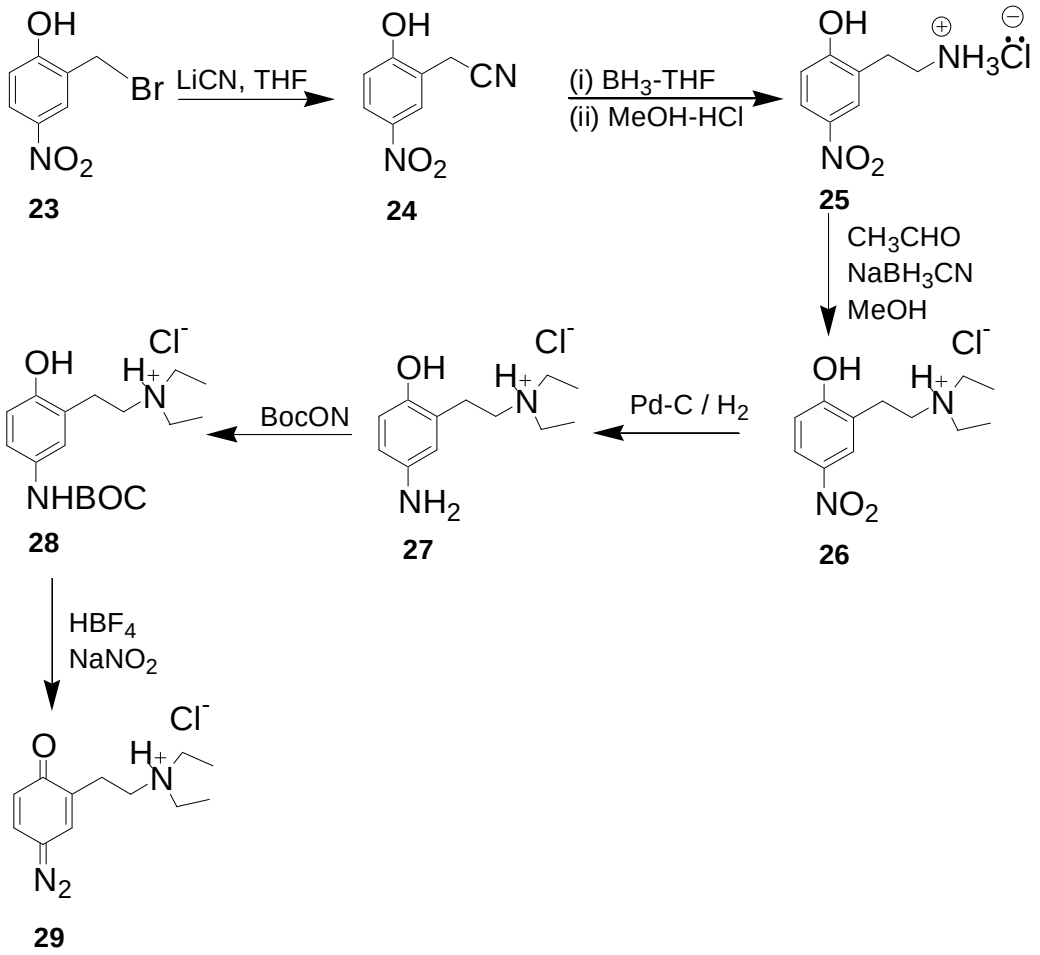
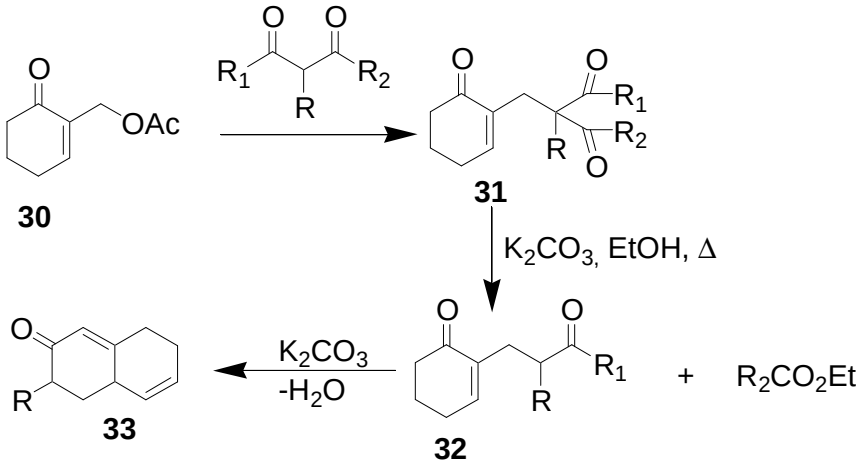


Scheme 8



Scheme 9

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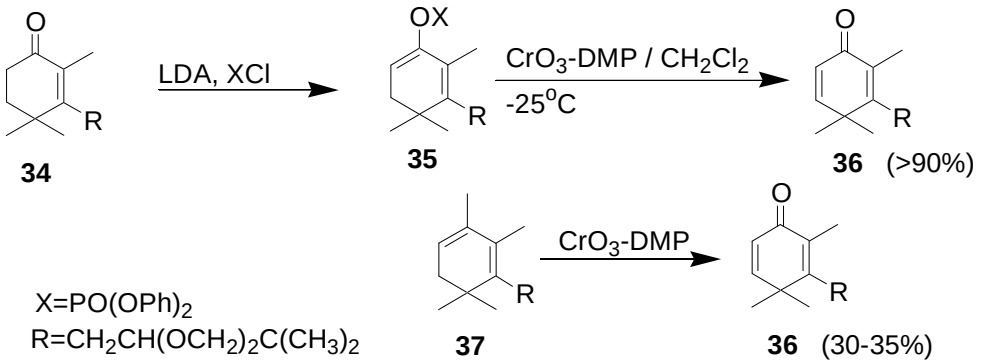
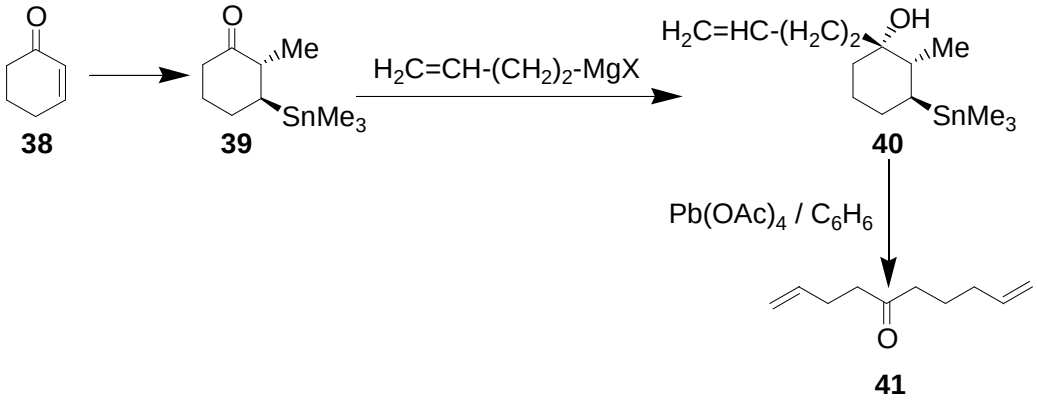
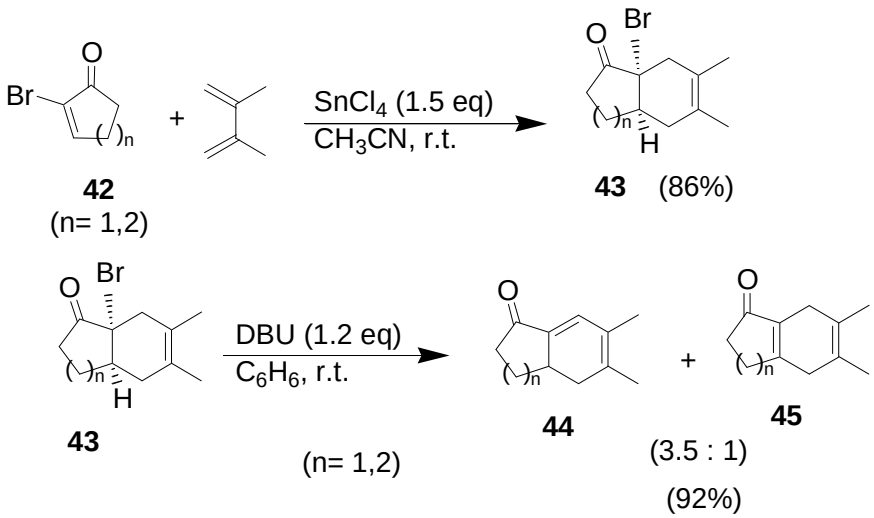


Scheme 10



Scheme 11



Scheme 12

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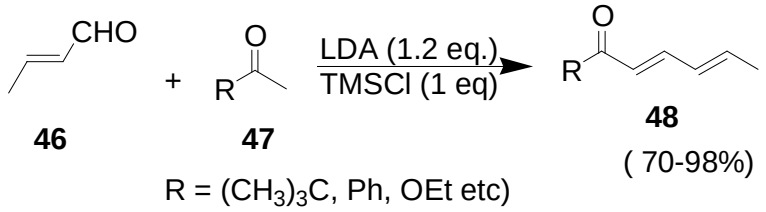
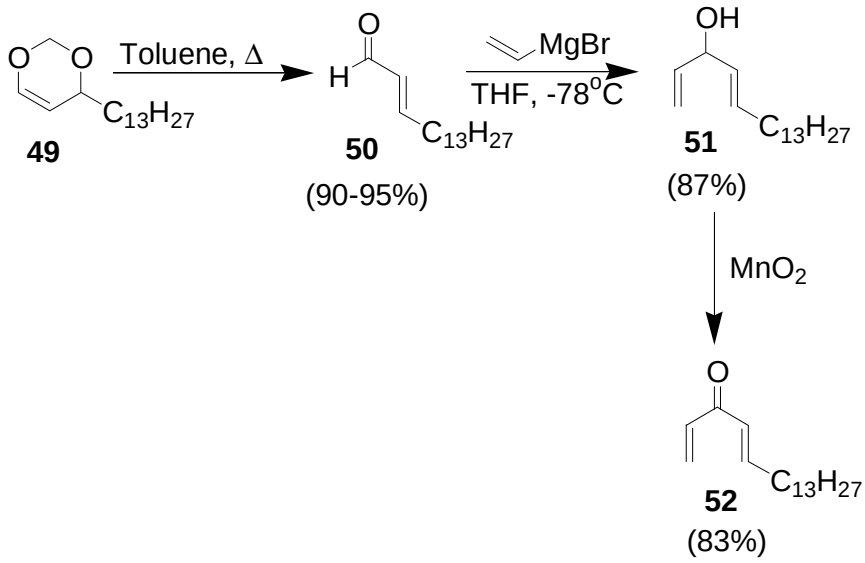
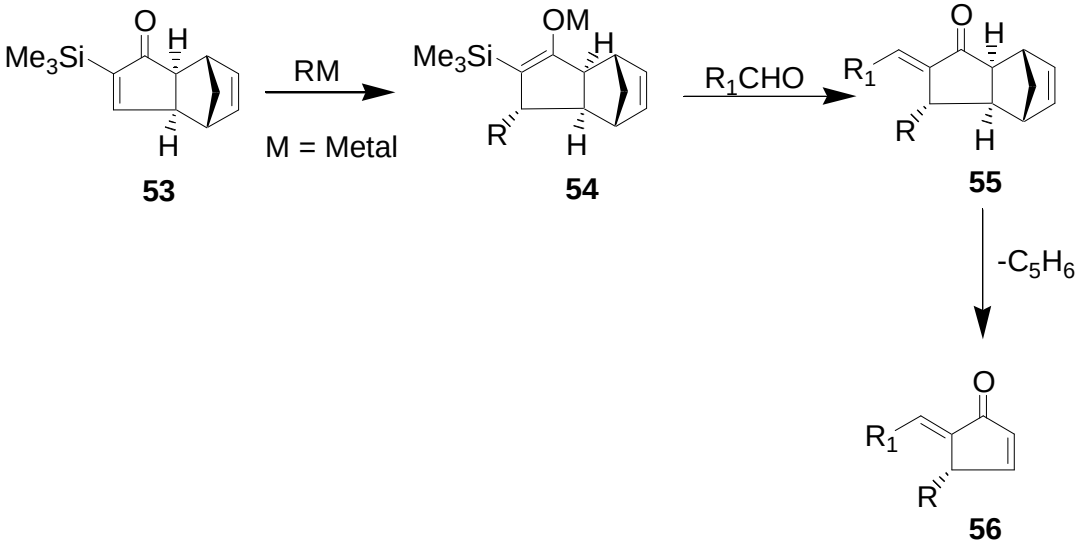


Scheme 13



Scheme 14



Scheme 15

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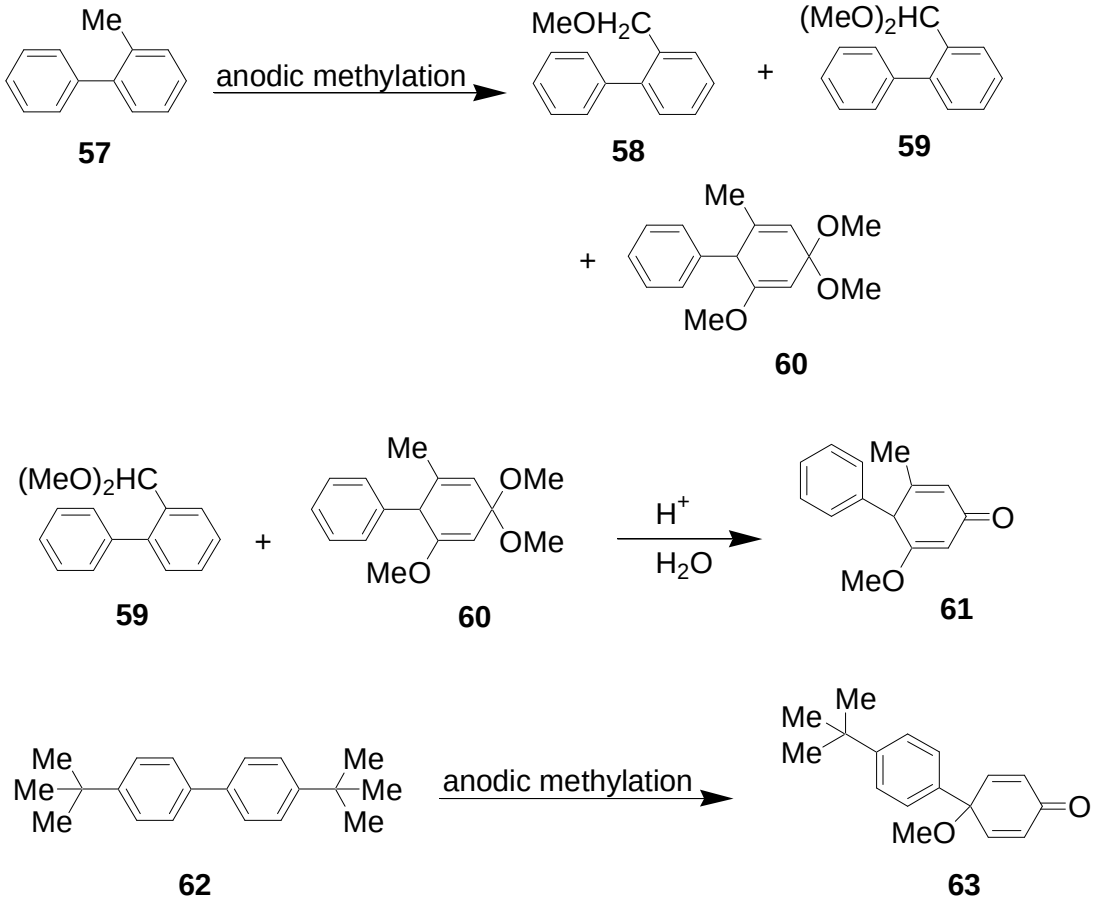
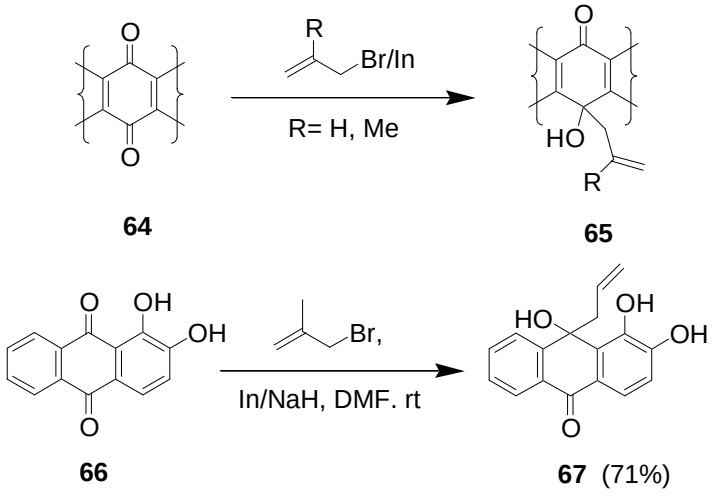


Scheme 16



Scheme 17

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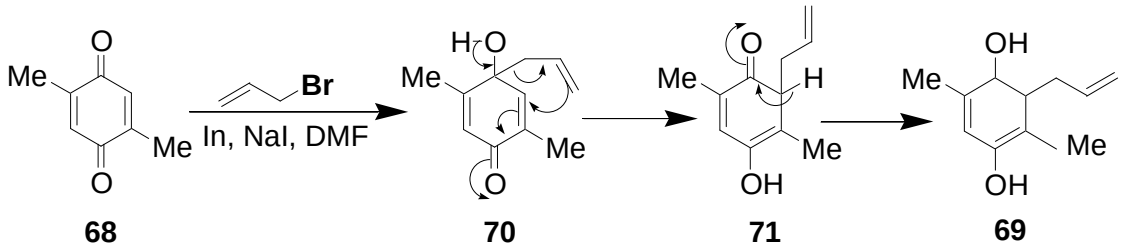
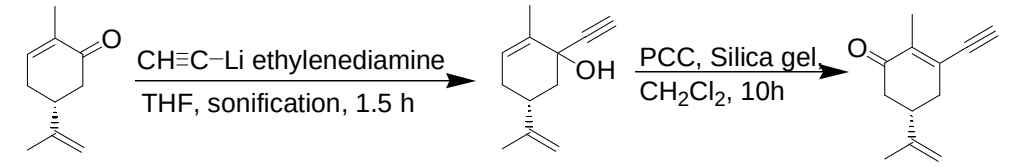


68 **70** **71** **69**

Figure 4

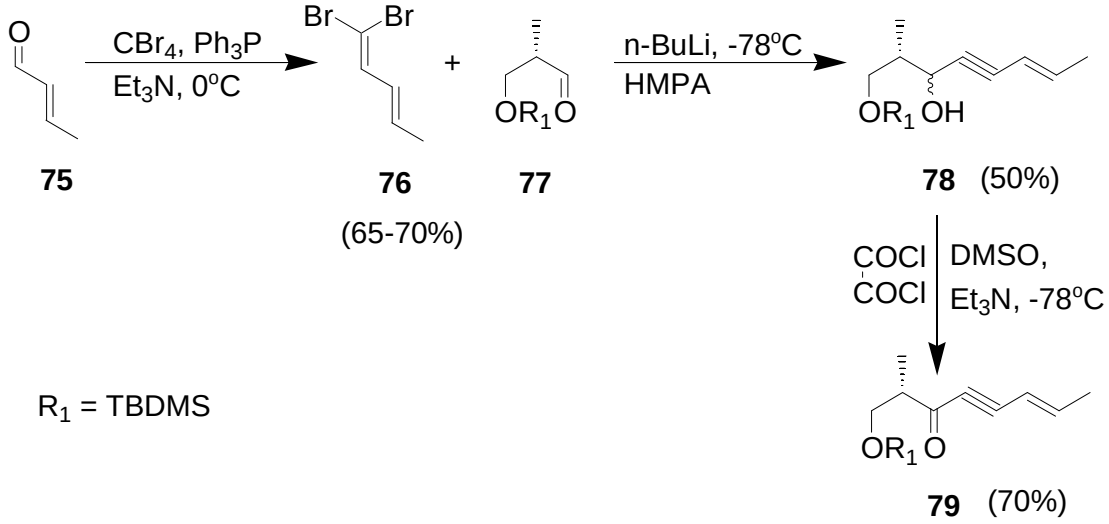


72
R-Carvone

73

74 (70%)

Scheme 18



75 **76** (65-70%) **77** **78** (50%)

79 (70%)

R_1 = TBDMS

Scheme 19

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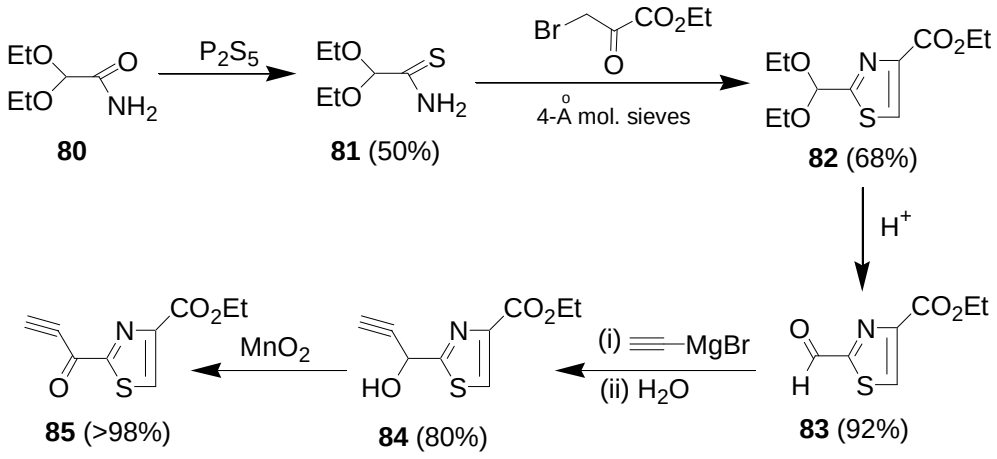
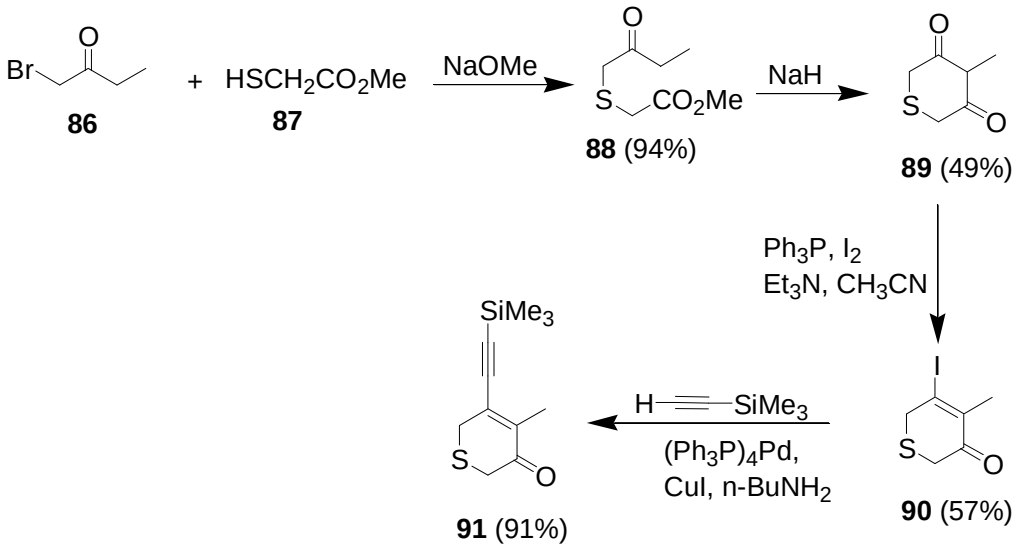


Scheme 20



Scheme 21

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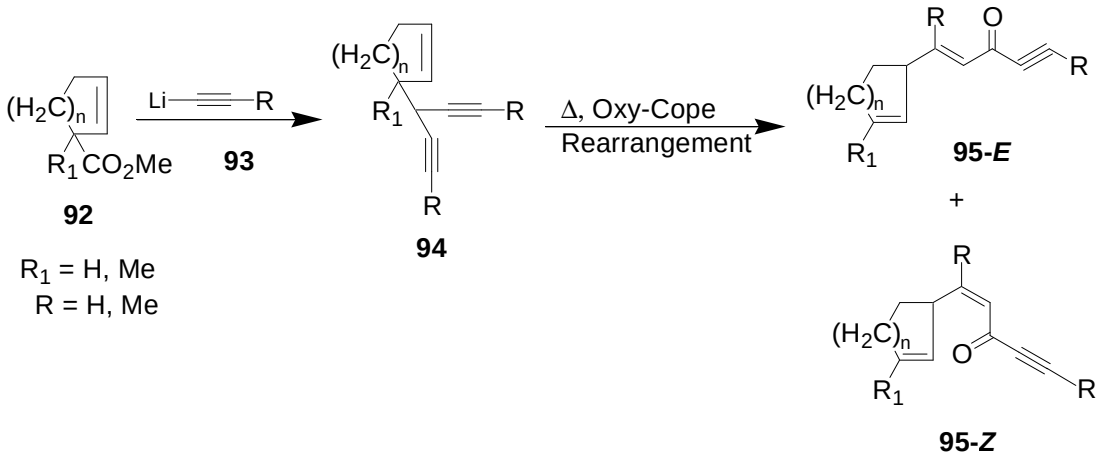
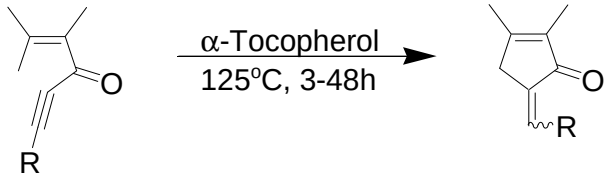
Chemistry & Biology Interface, 2012, 2, 2, 76-106



Scheme 22



96 **97**

R = Ph, *p*-MeOH, *p*-NO_2Ph, SPh,
OMe, TMS, CO_2Et, $CO_2{}^t$-Bu

Scheme 23

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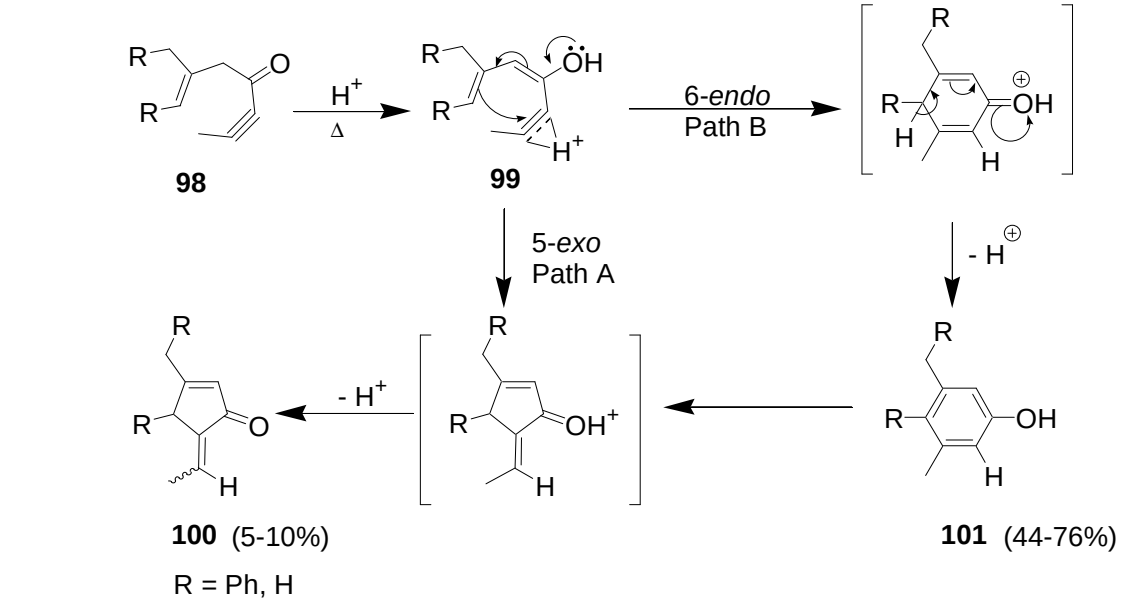
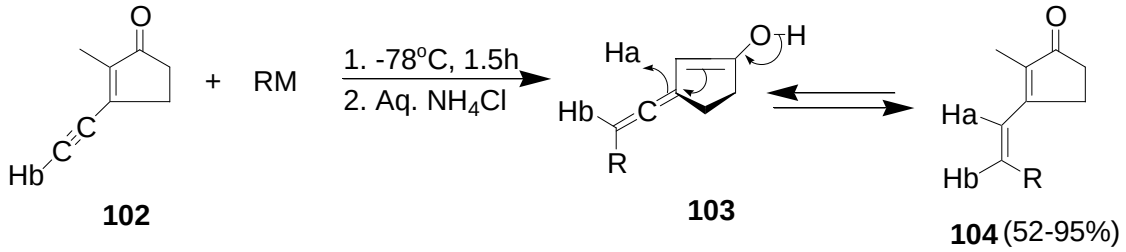


Scheme 24



RM = $(CH_3)_2CuLi$, $CH_3Cu(CN)Li$, $(i\text{-}Pr)_2Cu(CN)(MgCl_2)$, PhSLi

R = CH_3, *i*-Pr, PhS

Scheme 25

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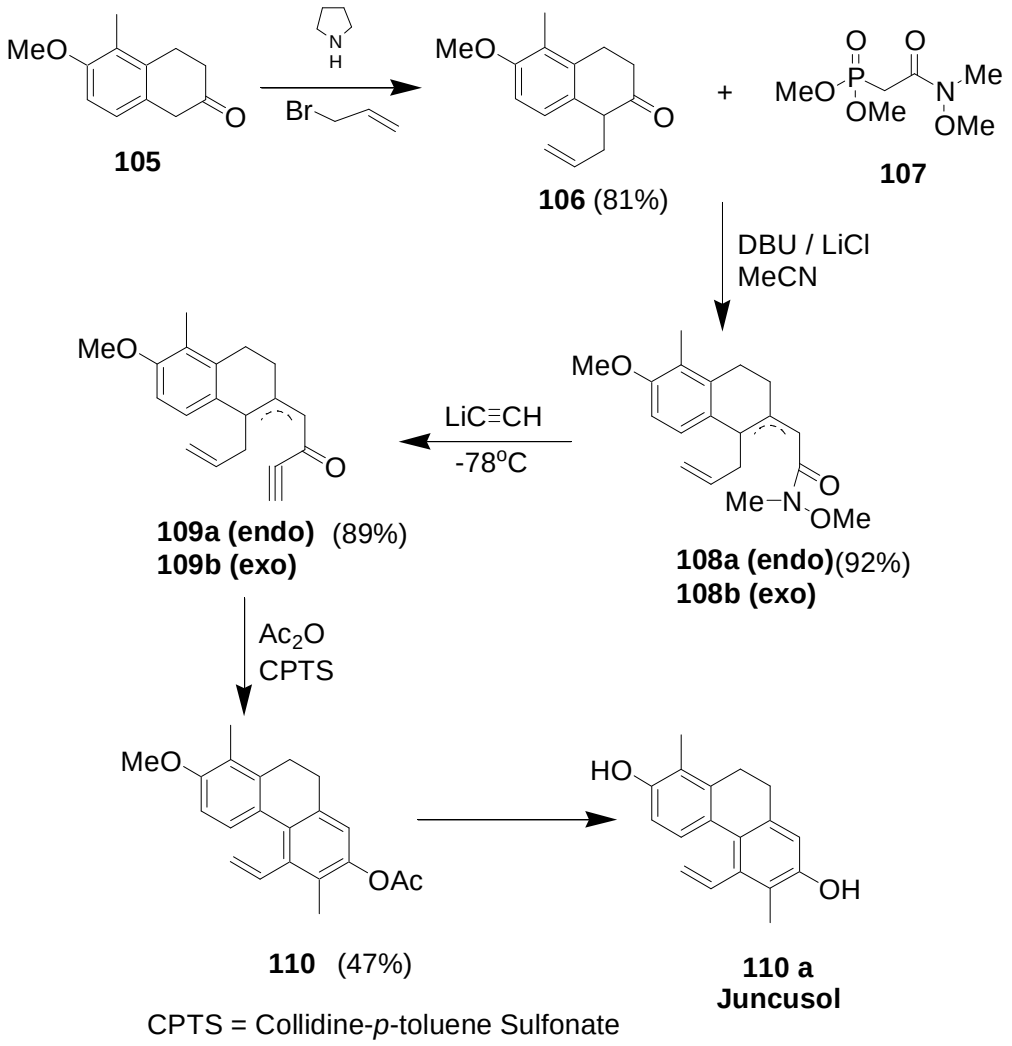
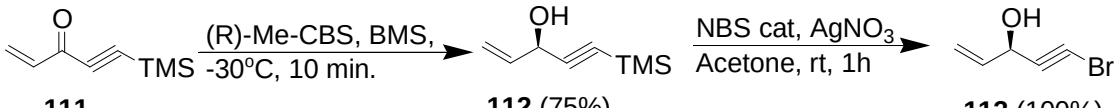


CPTS = Collidine-*p*-toluene Sulfonate

Scheme 26



Scheme 27

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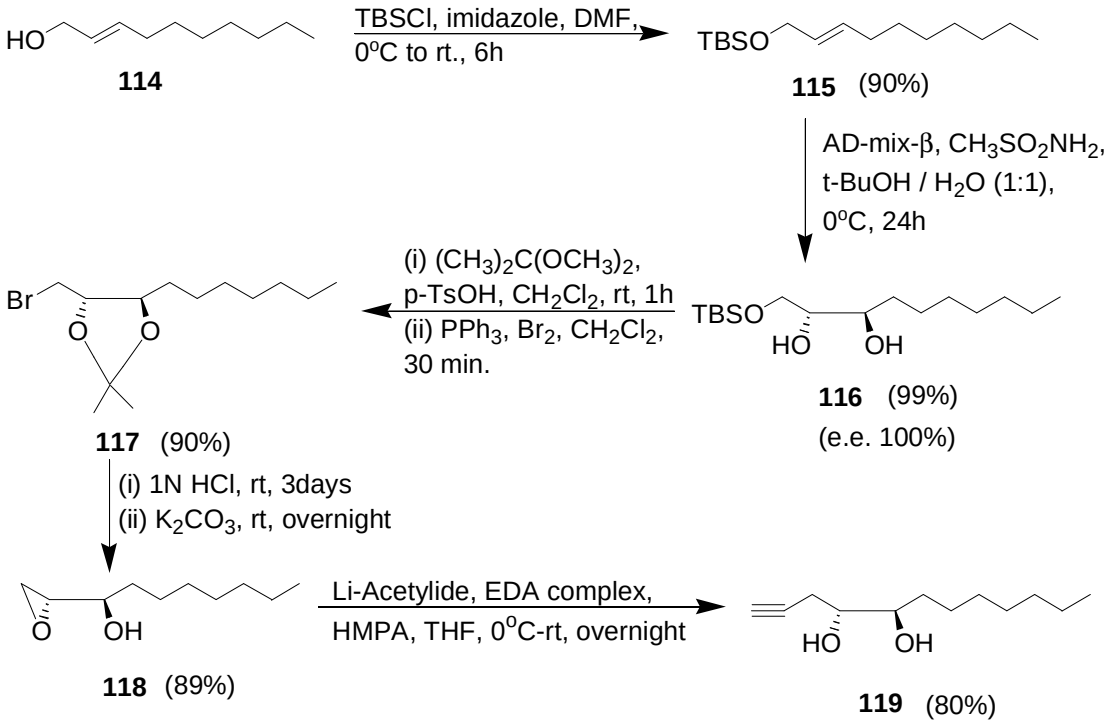
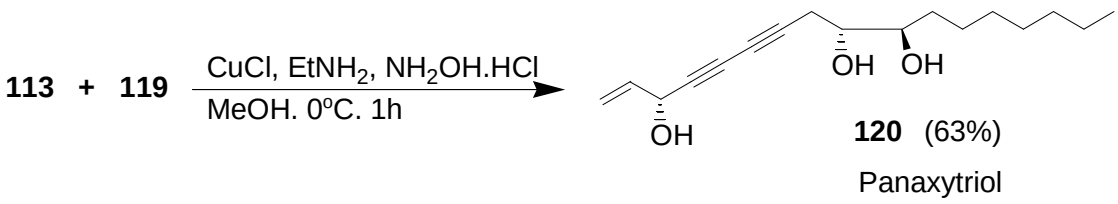


Scheme 28



Scheme 29

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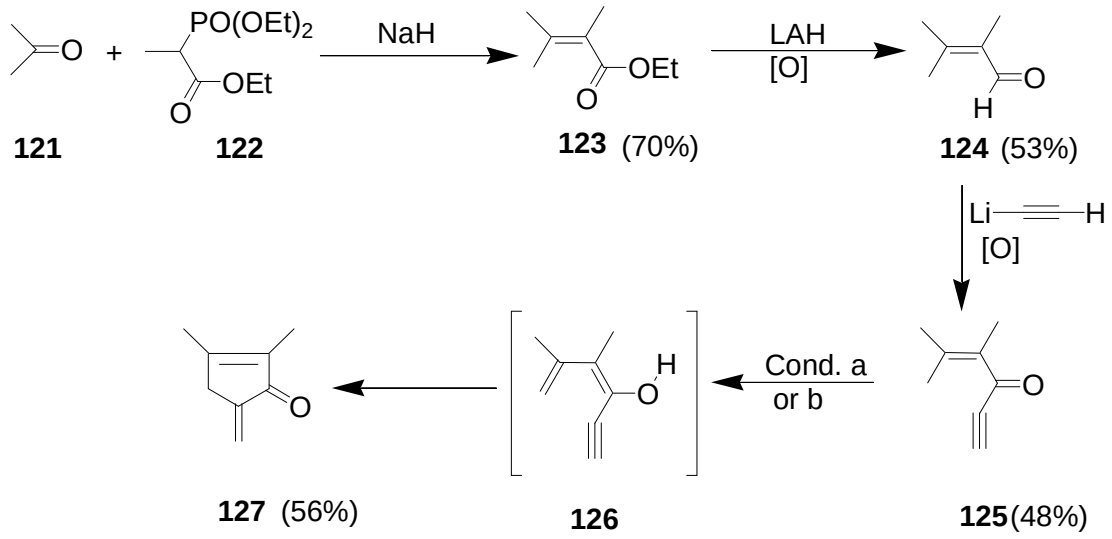

121 **122** **123** (70%) **124** (53%)

127 (56%) **126** **125**(48%)

Cond. a: 1.1 eq. vitamin E, 1,2-epoxyoctane, 1,2-dicholorohexane, 200^{o}C, 12h.
b: 1.1 eq. TBC, hν(300nm) 1,2-epoxyoctane, 1,2-dicholorohexane, 200^{o}C, 12h.

Scheme 30

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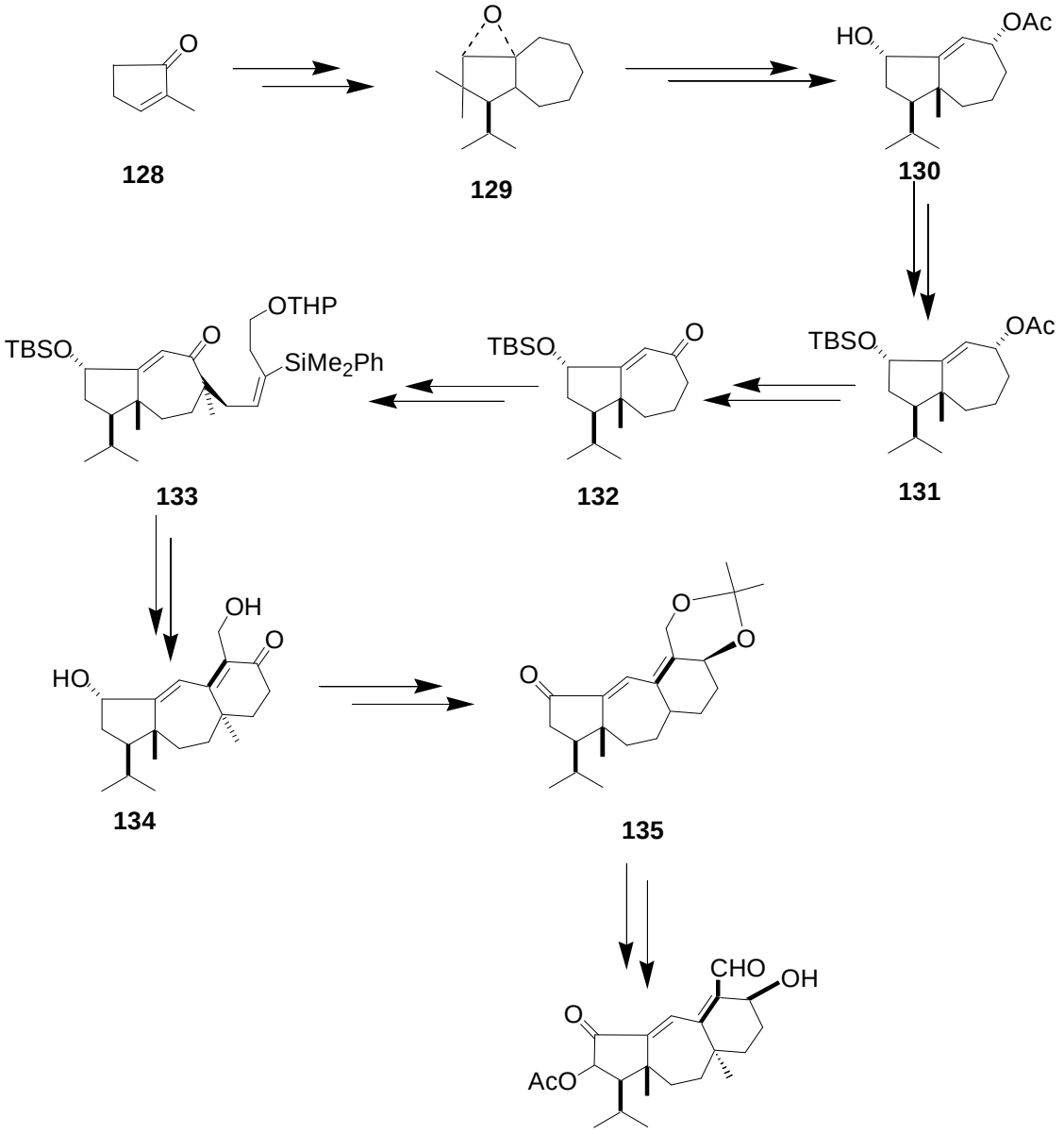

128 **129** **130** **131** **132** **133** **134** **135** **136**

(±)- Guanacastepene A

Scheme 31

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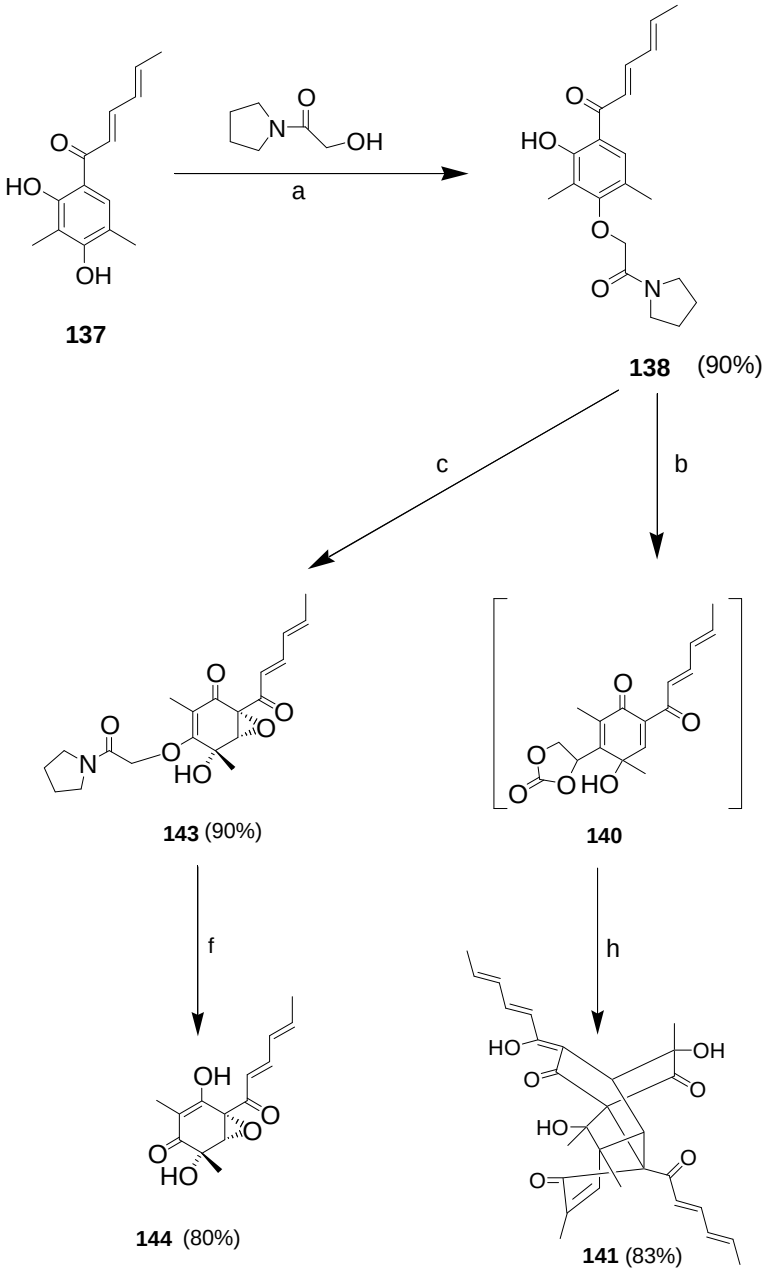

a: DEAD, PPh_3, CH_2Cl_2
b: 1.0 eq. of $PhI(OCOCF_3)$ in CH_2Cl_2 / CH_3NO_2 (3:1)
c: 2.2 eq. of $PhI(OCOCF_3)$ in CH_2Cl_2 / CH_3NO_2 (3:1)
d: 1.1 eq. of $PhI(OCOCF_3)$ in CH_2Cl_2
e: Di methyl aluminium amide, CH_2Cl_2
f: $SnCl_4$, CH_2Cl_2
g: 8.0 eq. of Conc. HCl in THF
h: 1.5 eq. of KOH in H_2O

Scheme 32

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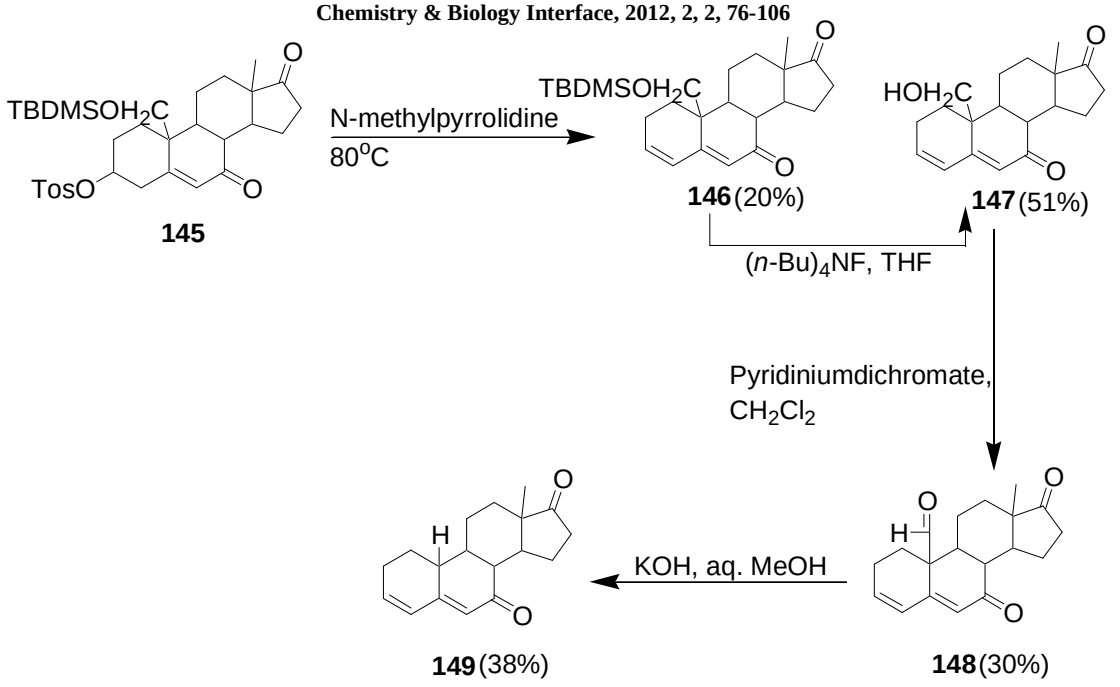
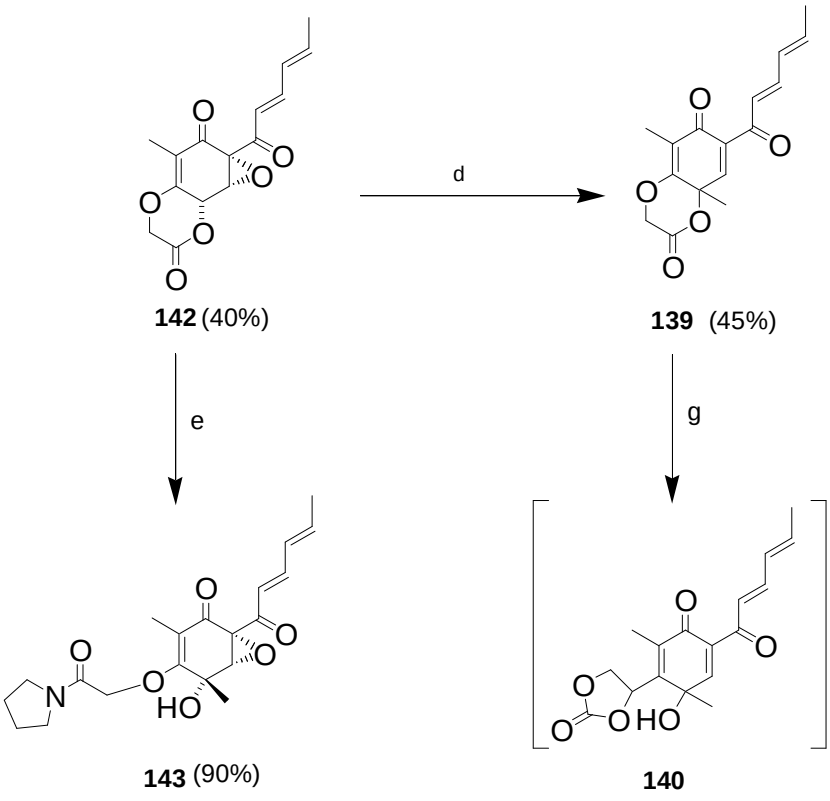


Scheme 33



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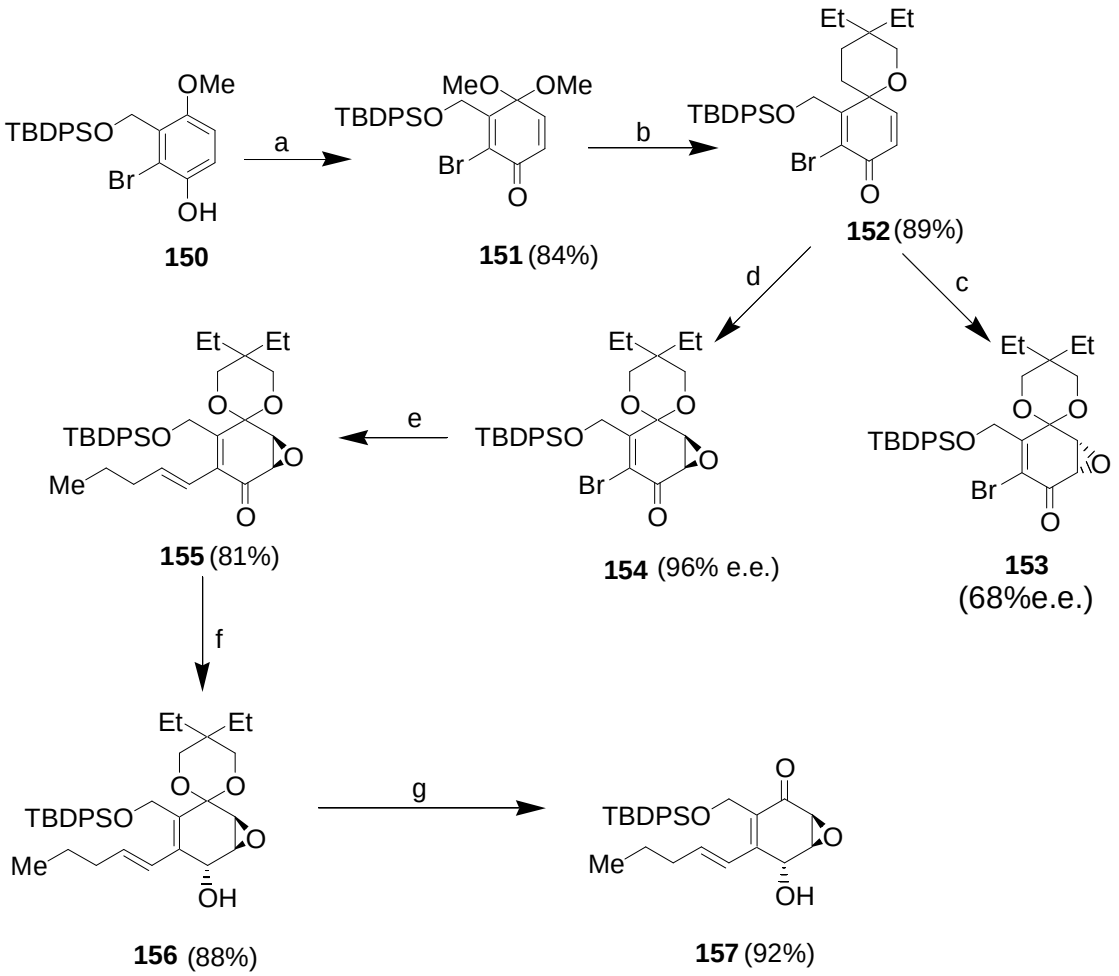
Chemistry & Biology Interface, 2012, 2, 2, 76-106



150

151 (84%)

152 (89%)

154 (96% e.e.)

153 (68%e.e.)

155 (81%)

156 (88%)

157 (92%)

(a); $PhI(OAc)_2$, MeOH, rt, 30min (b); 2,2-diethyl-1,3-propanediol, PPTS, benzene, 70^oC, 80min (c); *n*-BuLi, L-DIPT, Ph_3CO_3H, $PhCH_3$, rt, 24h (d); NaHMDS,L-DIPT, Ph_3CO_3H, $PhCH_3$(20%THF), -50^oC, 30h (e): (*E*)-tributyl-1-pentenyl-stannane, Pd_2dba_3, $CHCl_3$, $ClCH_2CH_2Cl$, 60^oC, 40h (f):DIBAL-H, THF, 78^oC,15min (g): 48%HF, CH_3CN, 0^oC, 5min

Scheme 34

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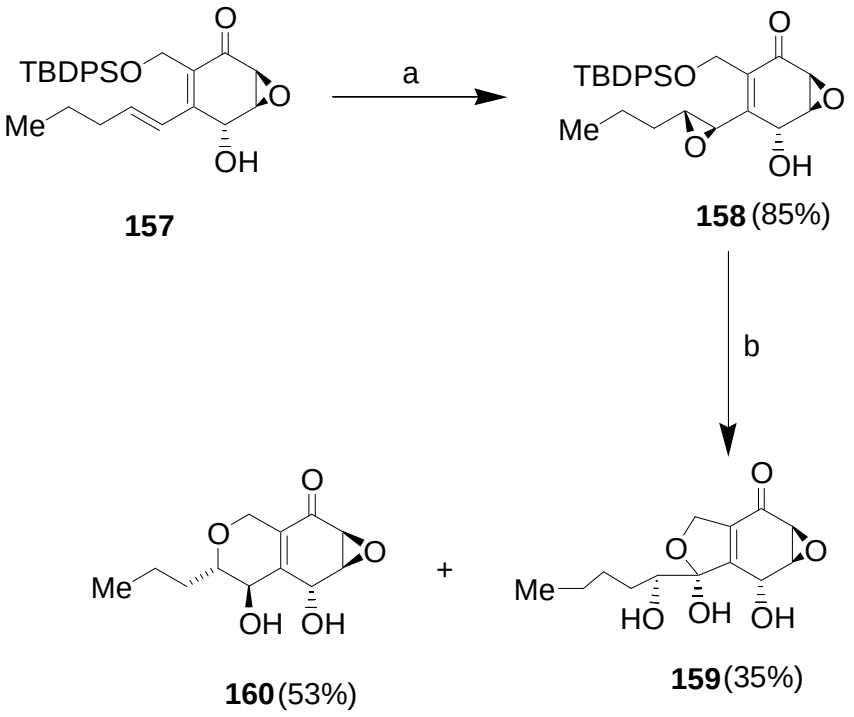

157

158 (85%)

160 (53%)

159 (35%)

(a): *m*-CPBA, CH_2Cl_2, rt, 4h
(b): 48% HF, CH_3CN, rt, 2h

Scheme 35

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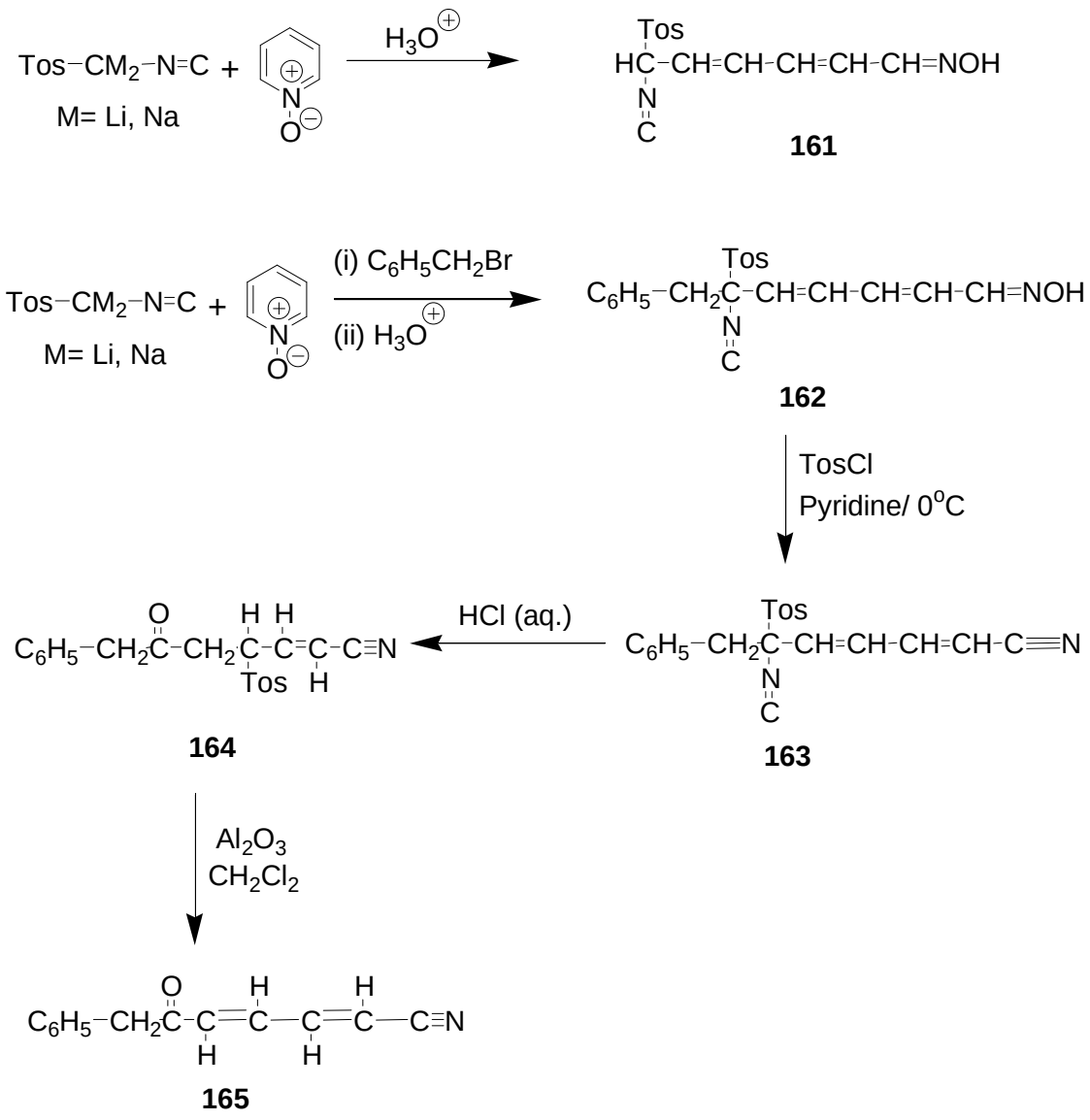

Scheme 36

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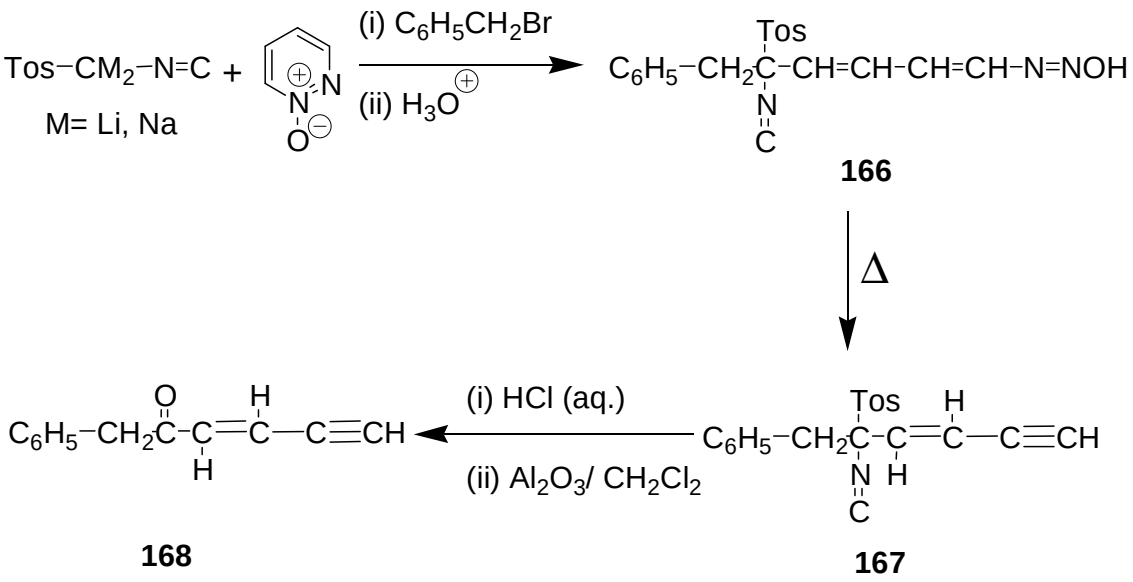

Scheme 37

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