NATURAL CYCLIC α,β-ENONE MONOTERPENOIDS IN NUCLEOPHILIC ADDITION REACTIONS

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The literature on transformations of natural cyclic α,β*-enone monoterpenoids into compounds of more complicated structure via 1,2- and 1,4-addition reactions was reviewed. The data were systematized according to the effects of the conditions and nature of the starting substrates on the selectivity of the 1,2- and 1,4-addition reactions.*

Key words: organometallic reagents, natural cyclic α,β-enone monoterpenoids, Michael reaction, 1,2- and 1,4-addition reactions.

Carvone (**1**), pulegone (**2**), piperitone (**3**), menthenone (**4**), carenone (**5**), and verbenone (**6**) are the most common natural monoterpenoids that contain both a double bond and a carbonyl group conjugated to it and are interesting with respect to directed synthesis.

The portion of these molecules that includes the vinyl and carbonyl groups acts as a unified system for which both 1,2- and 1,4-nucleophilic addition reactions are characteristic. It is rather difficult to predict accurately how a process will occur in an actual situation because each molecule has its own peculiarities. Nevertheless, definite generalizations can be made based on existing data, which are reviewed herein [1].

ADDITION OF ORGANOMETLLIC REAGENTS. GENERAL CONCEPTS

The ability of nucleophiles to add to α,β-enones is very significant because the modifications of reagents and the reaction conditions can direct a reaction preferentially to one of two possible pathways.

Grignard reagents and organolithium and -copper compounds are used most frequently for this in practice. Recently reports of studies using organozinc and -manganese reagents [2-5] have appeared. However, they have not yet been widely applied.

Depending on the reaction conditions, a Grignard reagent may give both the 1,2- and 1,4-adducts. Kinetically controlled addition of an organomagnesium reagent at low temperatures favors formation of the 1,2-adduct whereas increasing the reaction temperature leads primarily to formation of the thermodynamically more favorable 1,4-addition product. The reactions of Grignard reagents can be illustrated using (*R*)-pulegone (*R*-**2**) as an example. Addition of allyl-, crotyl-, and 3-methyl-2-enyl derivatives **7a-d** at -15°C leads exclusively to formation of allyl alcohols **8a-d**, the 1,2-addition products. Increasing the temperature to 0°C for the reaction with 3,3-dimethylallyl Grignard reagent (**9**) gives a mixture (2:1) of the 1,2- (**10** and **11**) and 1,4- (**12** and **13**) adducts [6]. The reaction with secondary 3-pentenylmagnesium chloride (**14**) at 20°C gave the 1,4-addition product **15** as the dominant one.

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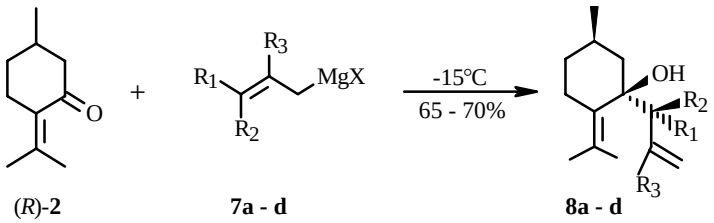
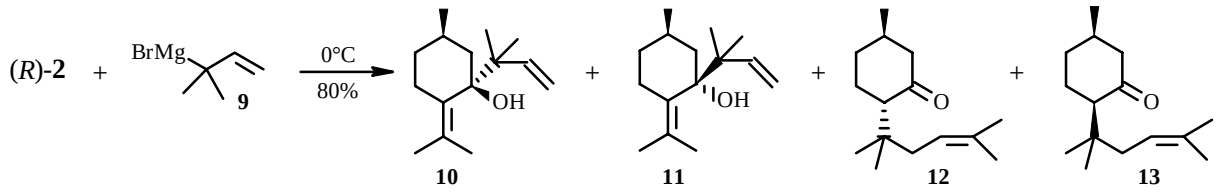


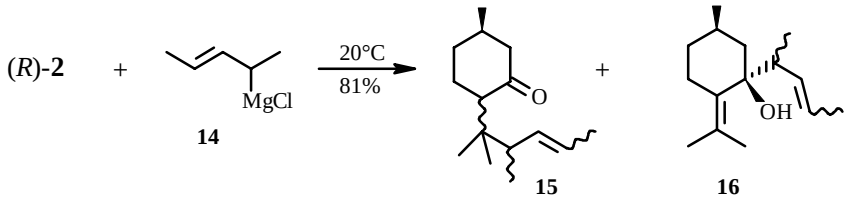
(*R*)-**2** **7a - d** **8a - d**

a: $R_1 = R_2 = R_3 = H$, X = Cl; **b:** $R_1 = CH_3$, $R_2 = R_3 = H$; X = Cl;
c: $R_1 = R_2 = H$, $R_3 = CH_3$, X = Cl; **d:** $R_1 = R_3 = CH_3$, $R_2 = H$, X = Br



10 **11** **12** **13**

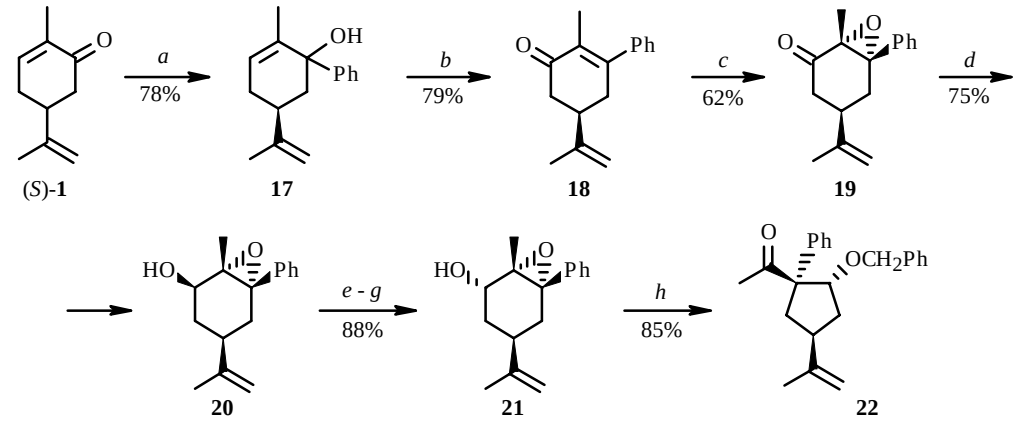
10 : **11** : **12** : **13** = 4 : 2 : 2 :1



15 **16**

15 : **16** = 1.2 : 1

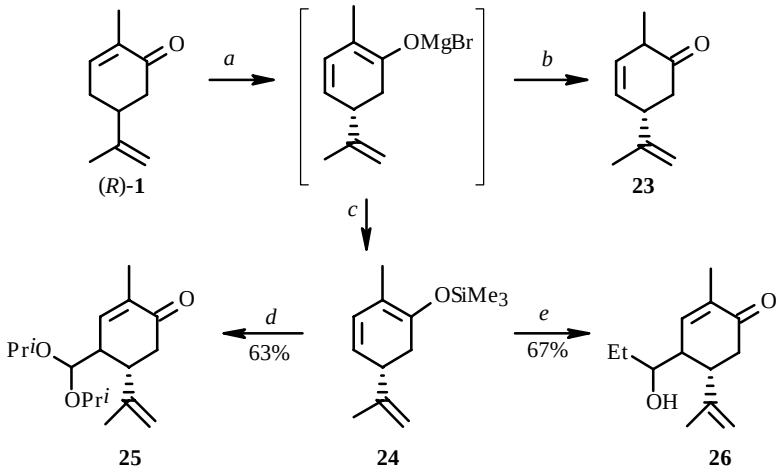
Regioselective 1,2-addition of organometallic reagents enables the preparation of tertiary allyl alcohols, oxidation of which by Cr(VI) is accompanied by rearrangement to form β-substituted conjugated enones. For example, mild oxidation of alcohol **17**, the reaction product of (*S*)-carvone (**1**) and a phenyl Grignard reagent, gave enone **18**, which was then transformed through epoxides **19** and **20** into key compound **21**, rearrangement of which in the presence of a Lewis acid gave ketoether **22** [7].



(*S*)-**1** **17** **18** **19** **20** **21** **22**

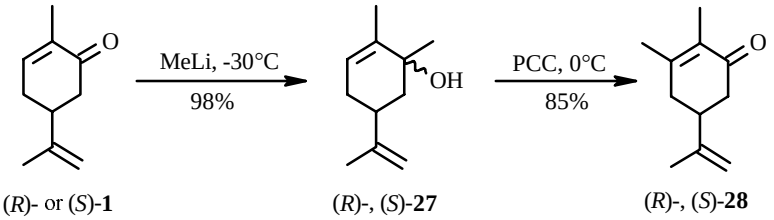
a. PhMgBr; *b.* PCC; *c.* H_2O_2, Triton B; *d.* $Li(Bu^tO)_3AlH$; *e.* Ph_3P, DIAD, $PhCO_2H$;
f. KOH, MeOH; *g.* $PhCH_2Br$, NaH, DMF; *h.* $BF_3 \cdot Et_2O$, -78°C

α,β-Enones react smoothly with Grignard reagents. However, side reactions caused by steric factors or reaction conditions, namely temperature and the presence in the reaction mixture of reagents that can form products through enol formation or reduction, have been reported. Japanese researchers [8] demonstrated that the oxo group of **1** formed an enol in the presence of catalytic amounts of ferric chloride and an excess of Grignard reagent. This shifted the double bond to the β,γ-position. Subsequent hydrolysis of the mixture produced β,γ-enone **23**. Stabilization of the enol form as silyl ether **24** enabled an aldol reaction to be carried out to form oxoacetal **25** or hydroxyketone **26**.

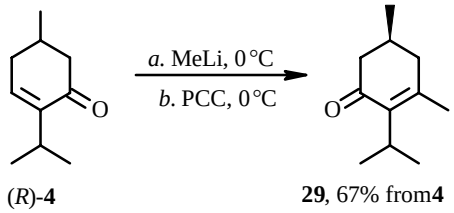


a. MeMgBr, $FeCl_3$, -20°C; *b.* H_2O; *c.* TMSCl, Et_3N, HMPA; *d.* $CH(OPr^i)_3$, $BF_3{\cdot}OEt_2$; *e.* EtCHO, $BF_3{\cdot}OEt_2$

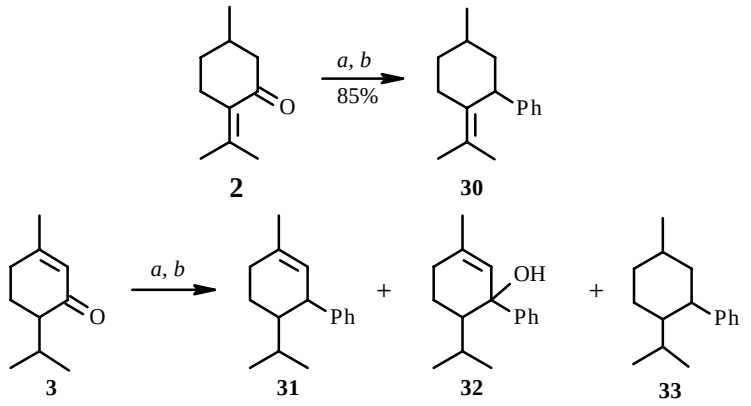
As a rule, alkyllithium reagents, which are sources of unstable carbanions [9, 10], are highly reactive and react with enones to give exclusively the 1,2-adducts. Thus, **1** reacted with methyllithium at -30°C to give tertiary alcohol **27**, which was oxidized further to methylcarvone (**28**).



Although alkyllithium reagents are usually reacted with enones at low temperatures (from -78 to -30°C), (*R*)-4-menthenone (**4**) was successfully reacted with methyllithium at 0°C, which undoubtedly makes the process more attractive to industry [11]. This produced methylated menthenone (**29**) with inversion of the configuration of the asymmetric center.

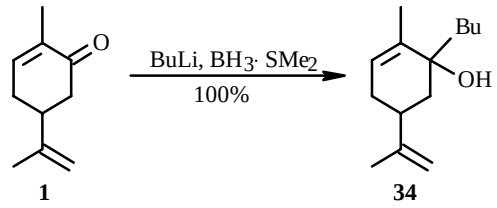


Treatment with Li in ammonia of the reaction mixture from 1,2-addition of PhLi to enone **2** gave a deoxygenated product, phenylated dihydroterpenoline (**30**) [12]. Under these same conditions, piperitone (**3**) gave deoxygenated derivative **31**, tertiary alcohol **32**, and phenylmenthane (**33**).

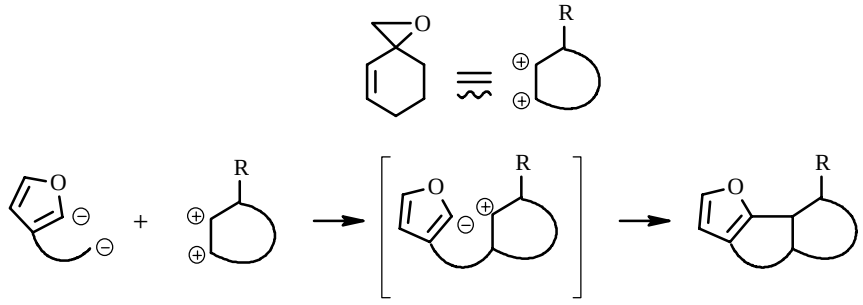


a. PhLi, -78°C; *b.* Li-NH_3, NH_4Cl

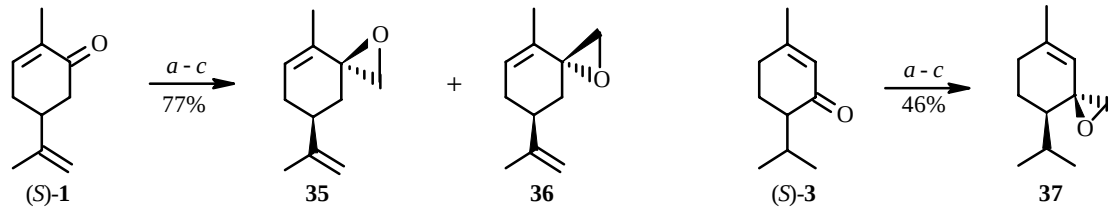
Using borane-dimethylsulfide complex produced in quantitative yield alcohol **34**, the 1,2-addition product of butyllithium and **1** [13].



Reacting *bis*-electrophiles with *bis*-nucleophiles is an interesting approach to tricyclic compounds.

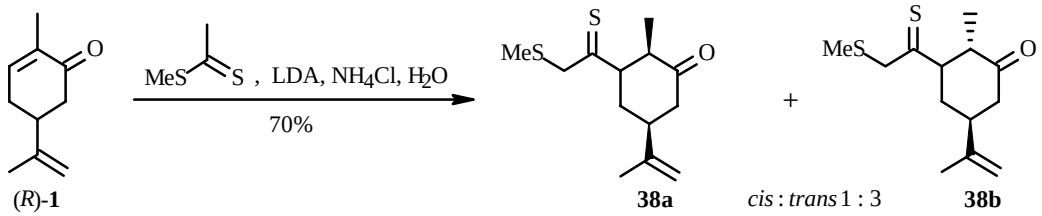


α,β-Unsaturated epoxides are electron acceptors of this class. Tanis et al. investigated their synthesis based on 1,2-addition of a S-containing compound as its Li derivative to an unsaturated ketone [14]. Thus, its reaction with (*S*)-**1** led to a mixture (4.5:1) of epoxides **35** and **36** whereas (*S*)-(+)-**3** gave a single isomer of **37** in 90% yield.



a. $MeSCH_2Li$; *b.* MeI; *c.* $KOBu^t$-THF

Although ordinary RLi reagents (where R = alkyl or aryl) give primarily 1,2-addition products, CH_2=C(SMe)SLi, which is prepared using methyldithioacetate, afforded 1,4-addition products **38a** and **38b**, which in turn are precursors of bicyclics [15].



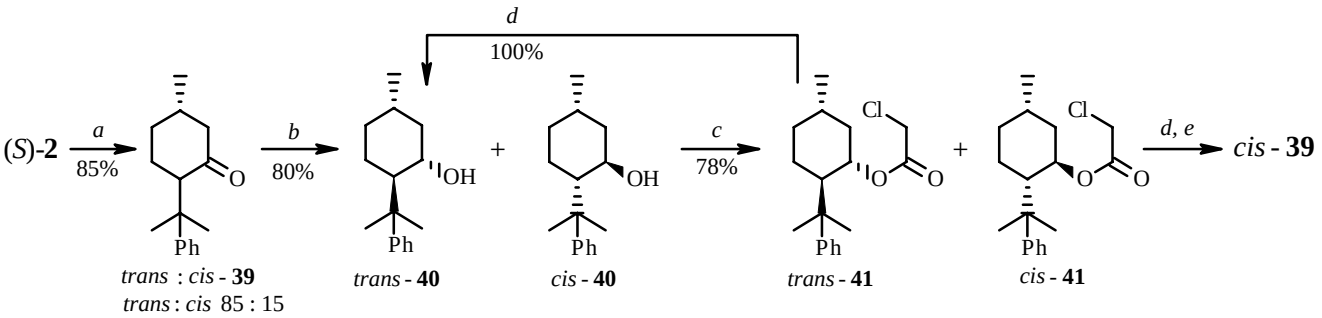
(*R*)-**1** **38a** **38b**

Lithium dialkyl- or diarylcuprates (LiR_2Cu), their mixed analogs (LiRR′Cu and LiRXCu), and organocopper compounds (RCu) in the presence of lithium halides are used in that order of frequency as reagents that undergo selective 1,4-addition [16, 17]. The symmetric organic cuprates are the best organometallic compounds for 1,4-alkylation of conjugated cyclic enones. Thus, the products of reacting two equivalents of an organolithium compound (or Grignard reagent) with one equivalent of anhydrous CuI are used most often to add methyl, ethyl, propyl, allyl, and vinyl groups [18].

A consensus on the mechanism of reactions using lithium organocuprates has not been reached. Some researchers propose that the conjugated addition occurs through electron transfer; others, by direct nucleophilic addition [19]. However, there is more experimental evidence that agrees with the electron-transfer mechanism [20-22].

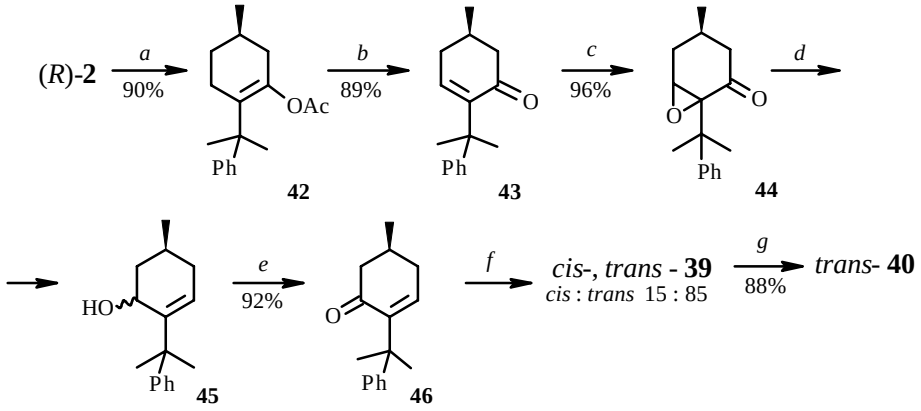
Kharasch demonstrated that catalytic amounts of Cu ions direct a reaction toward the 1,4-addition mechanism [23]. House et al. proposed that alkylcopper reagents formed from a Grignard reagent and Cu^+ are in fact the attacking particles in this instance [24].

This property of Cu salts to direct a reaction toward the 1,4-addition mechanism has subsequently been widely used in organic synthesis. Thus, reaction of **2** with PhMgBr in the presence of CuI and subsequent treatment of the reaction mixture with alcoholic potash produced 8-phenylmenthone (**39**) primarily as the *trans*-isomer [25]. The resulting ketone **39** was reduced to give diastereomeric alcohols *trans*-**40** and *cis*-**40**, which were separated chromatographically as esters *trans*-**41** and *cis*-**41**, respectively [26]. (+)-8-Phenylmenthol (*trans*-**40**) has found use in the synthesis of optically active prostaglandins [25].



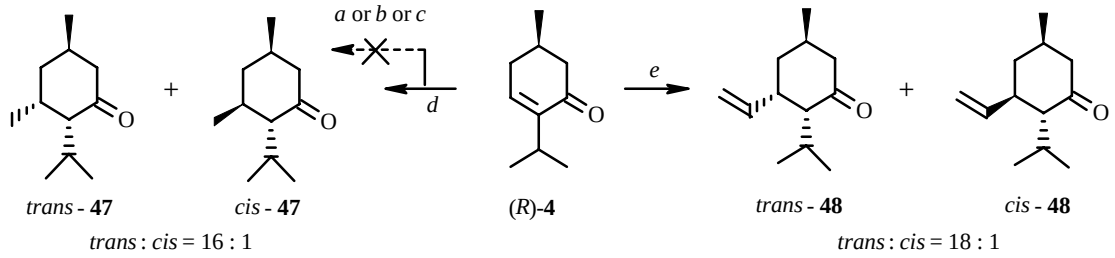
a. PhMgBr, CuI, -15°C; K_2CO_3-EtOH; *b*. Na-PhMe, Δ; *c*. $ClCH_2CO_2H$, $(COCl)_2$, DMF; *d*. KOH - EtOH; *e*. $Na_2Cr_2O_7$ - H_2SO_4

A longer synthetic pathway to *trans*-**40** beginning with (*R*)-pulegone (**2**) has been proposed [27]. Thus, 1,4-addition of PhMgBr to enone (*R*)-**2** and stabilization of the intermediate enolate as acetate **42** followed by bromination—dehydrobromination produced the conjugated 8-phenylmenthenone system (**43**). The configuration of epoxyketone **44** was inverted by Barton reduction, which effected simultaneously allylic rearrangement to form a mixture of epimeric alcohols **45** that was oxidized further to enone (+)-**46**. Birch reduction gave an equal mixture of diastereomeric ketone **39**, storage of which in alcoholic base increased the amount of *trans*-**39**. Final reduction of the oxo group and chromatography gave the target alcohol *trans*-**40**.



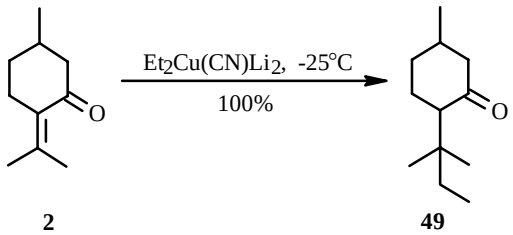
a. PhMgBr, CuI, -20°C; AcCl; *b*. Br_2; LiBr; Na_2CO_3, DMF; *c*. H_2O_2, NaOH;
d. $N_2H_4 \cdot H_2O$, AcOH; *e*. PCC; *f*. Li-NH_3; NaOH - EtOH; *g*. Na-PhMe, Pr^iOH

Conjugated 1,4-addition of organometallic reagents to (*R*)-4-menthenone (**4**) was unsuccessful even if traditional cuprates were used [28]. Adducts **47** and **48** could be prepared only if the reaction was carried out at higher temperatures and with the use of organocopper catalysts with stronger complexing properties.

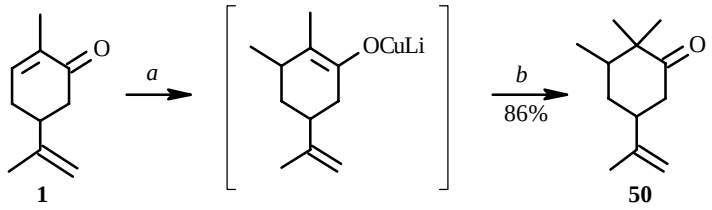


a. C_2H_5MgBr, Li_2CuCl_4, -78°C; *b*. CH_3Li, CuI, -78°C; *c*. C_2H_5MgBr, $Me_2S \cdot CuBr$, -30°C;
d. CH_3Li, $CuBr \cdot Me_2S$, 20°C; *e*. $CH_2=CHMgBr$, CuI, $BF_3 \cdot OEt_2$, -70°C

It should be noted that symmetric organocuprates have certain drawbacks. First, they are unstable and are used in a large excess (3- to 5-fold) Furthermore, these reagents transfer only one of two radicals into the substrate. This is also inefficient because the radicals are sometimes difficulty accessible. These drawbacks can be overcome by using heterocuprates R(Z)CuM (where Z = OR′, SR′, CN, Cl, Br; M = Li, MgX) [29, 30]. Lipshutz et al. demonstrated that use of $R_2Cu(CN)Li_2$ was more effective than use of R_2CuLi [30]. Thus, **2** reacted with $Et_2Cu(CN)Li_2$ to give practically quantitative yield of **49**.

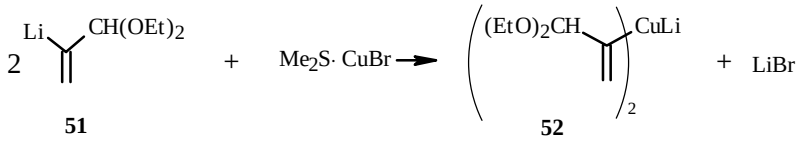


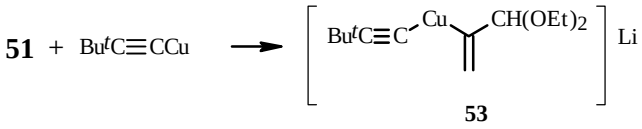
Treatment of Cu—Li enolates formed by conjugated addition of dialkylcuprates to enones with alkyl halides enabled yet another substituent to be added but in the α-position to the oxo group. It should be noted that the reaction in dimethoxyethane occurs approximately 10 times faster than in Et_2O [31]. Thus, application of this method to **1** gave 2,2,3-trimethylcyclohexanone (**50**) in high yield.



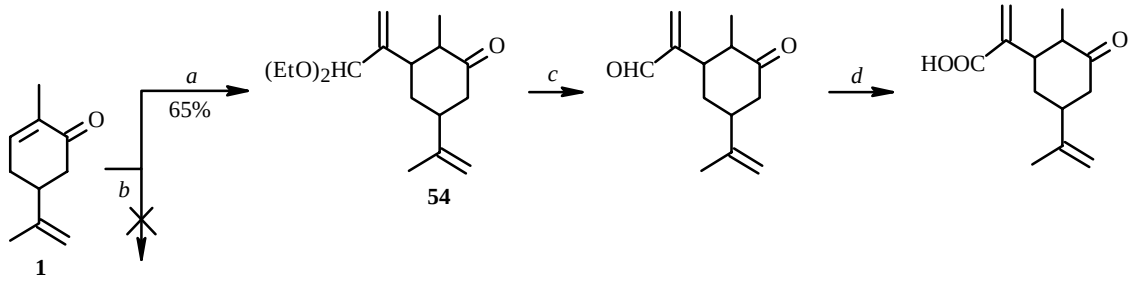
a. MeLi, CuI, 0°C; *b*. MeI, DME

Two new cuprates **52** and **53**, which were prepared from organolithium derivative **51**, were used to synthesize acrylic acid derivatives from enones [32].



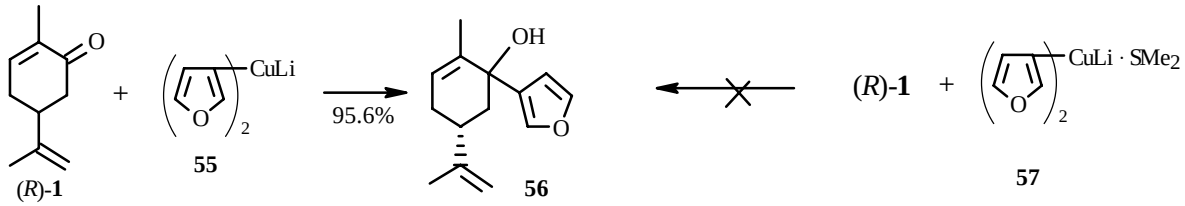


However, acetylenide **53** did not react with enone **1** due apparently to steric hindrance from the organometallic reagent.



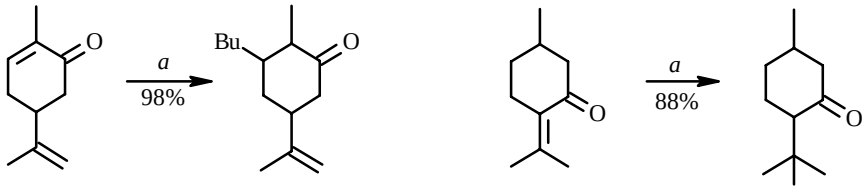
a. **52**, -70°C; *b*. **53**, -40°C; *c*. AcOH, H_2O; *d*. Ag_2O

Although dialkylcuprates usually add to the 1,4-position of the starting enone, lithium di(3-furyl)cuprates (**55** and **57**) undergo 1,2-addition [33].



Carvone (*R*)-**1** in this instance exhibited specific properties. Whereas it gave the 1,2-adduct **56** in greater than 95% yield with the first cuprate prepared in Et_2O, a reaction was not observed in the second instance and only the starting substrate was isolated. This can be explained by the milder activity of the cuprate in dimethylsulfide. Furthermore, there is also steric hindrance in (*R*)-**1** due to the isopropenyl group, which interferes with the approach of the bulkier dimethylsulfide complex. The overall effect of these factors prevents the reaction.

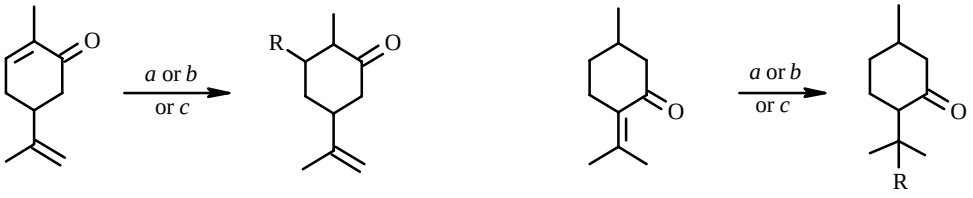
1,4-Addition gave high product yields also if an organomanganese reagent was used in combination with a copper catalyst [3, 34]. Use of optimized conditions and natural monoterpenoids **1** and **2** produced **58** and **59**, respectively.



1 **58** **2** **59**

a. BuMnCl, 5% CuCl, 0°C

Studies of the reaction of **1** and **2** with R_3ZnLi ($R_3ZnMgBr$), which were prepared by reaction of $ZnCl_2$ with three equivalents of RLi (or RMgCl) or R_2Zn with one equivalent of RLi (or RMgCl) [35], showed that they were less effective reagents for 1,4-addition than those examined in prior instances [31, 32, 34]. The yields of **60**-**63** were less than 21%.

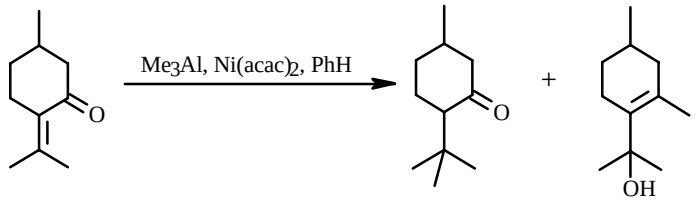


1 **60, 61** **2** **62, 63**

60, 62: R = Me; **61, 63:** R = Et

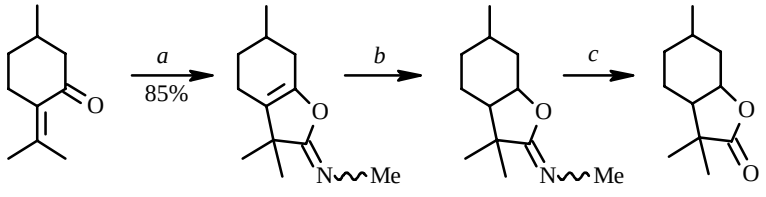
a. Me_3ZnLi, $Co(acac)_2$; *b*. Me_3ZnLi, $CoCl_2(PPh_3)_2$; *c*. $Et_3ZnMgBr$

Bagnell et al. established that $Ni(acac)_2$ catalyzes conjugated addition of Me_3Al to cyclic α,β-enones [36]. For **2**, the product of allylic rearrangement of the 1,2-adduct, alcohol **65**, was obtained in addition to the expected 8-methylmenthone (**64**).



2 **64** *cis* : *trans* 3 : 7 **65**

Whereas in the previous instance the organoaluminum compound was used as a reagent, Ito et al. used Et_2AlCl as a catalyst for addition of an isonitrile to an α,β-enone [37]. Thus, the reaction with **2** gave bicyclic **66**, reduction of the double bond of which and subsequent hydrolysis of **67** gave lactone **68**. The last can be used to synthesize vitamins E and K [38].



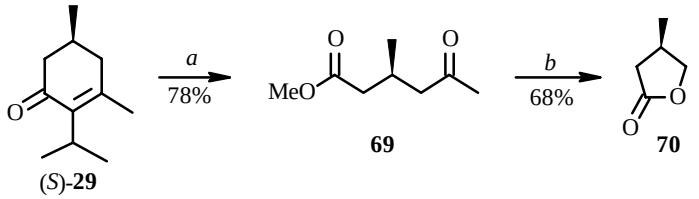
2 **66** **67** **68**

a. MeNC, Et_2AlCl; *b*. H_2, Pd-C; *c*. H^+

USE OF 1,2-ADDUCTS OF CYCLIC α,β-ENONE MONOTERPENOIDS AND ORGANOMETALLIC REAGENTS

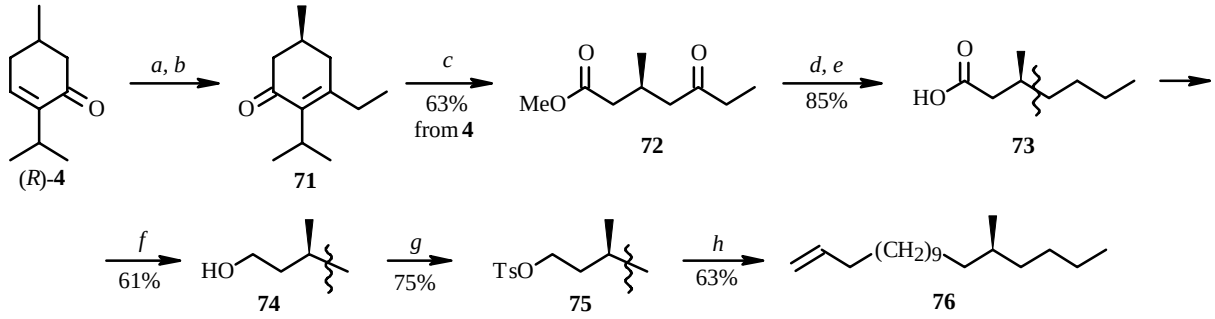
As shown above, 1,2-addition of organometallic reagents to α,β-enones forms an unstable tertiary allylic alcohol, the oxidation of which is accompanied by allylic rearrangement and produces the inverted β-substituted enone. This expands the synthetic potential of α,β-enones of natural origin. Research showed that the most effective oxidant in this instance is Cr(VI) [39].

Thus, treatment of the product from reaction of (*R*)-4-menthenone (**4**) and methyllithium [11] with pyridinium chlorochromate gave methylated menthenone (*S*)-**29** and inverted the configuration of the asymmetric center. We demonstrated the synthetic versatility of the resulting menthenone derivative using the synthesis of (*R*)-3-methyl-γ-butyrolactone (**70**), a synthon for optically active vitamins E and K, the terpene dolichol and its analogs, and (14*S*)-methyloctadec-1-ene (**76**), a sex pheromone of the peach leafminer (*Lyonetia clerkella*) as examples [11, 40]. The preparation of lactone **70** necessitated transformations consisting of ozonolytic cleavage of enone (*S*)-**29** with subsequent methanolysis of the peroxide products. Although a many-fold excess of ozone is usually used to cleave conjugated ketones, an equimolar amount was sufficient for complete transformation of (*S*)-**29**. A single-pot sequential process of Baeyer—Villager oxidation of ketoester **69** and alkaline saponification of the reaction mixture and its acidolysis to give optically pure lactone **70** completed the synthesis.



a. 1 eq. O_3, MeOH-CH_2Cl_2, MeOH-TsOH; *b.* MCPBA, KOH-MeOH, HCl

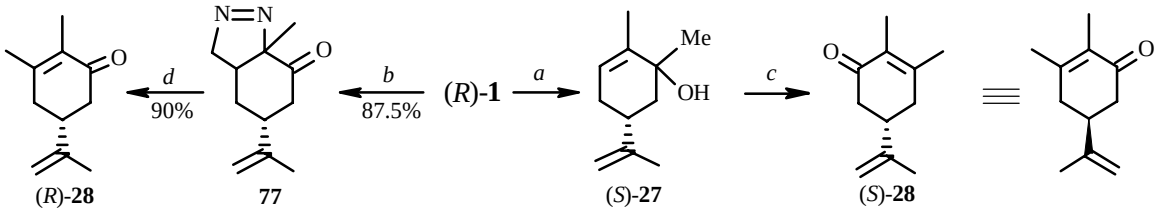
Ethylmenthenone (**71**) that was prepared by oxidation of the ethylation product of methenone (*R*)-**4** was converted by ozonolytic cleavage into the methyl ester of (*S*)-3-methyl-5-oxoheptanoic acid (**72**) in the synthesis of the sex pheromone of the peach leafminer (**76**).



a. EtLi; *b.* PCC; *c.* O_3, MeOH-CH_2Cl_2, MeOH-TsOH; *d.* $N_2H_4 \cdot H_2SO_4$, KOH;
e. KOH; *f.* $LiAlH_4$; *g.* TsCl, Py; *h.* $H_2C{=}CH(CH_2)_9MgBr$, Li_2CuCl_4

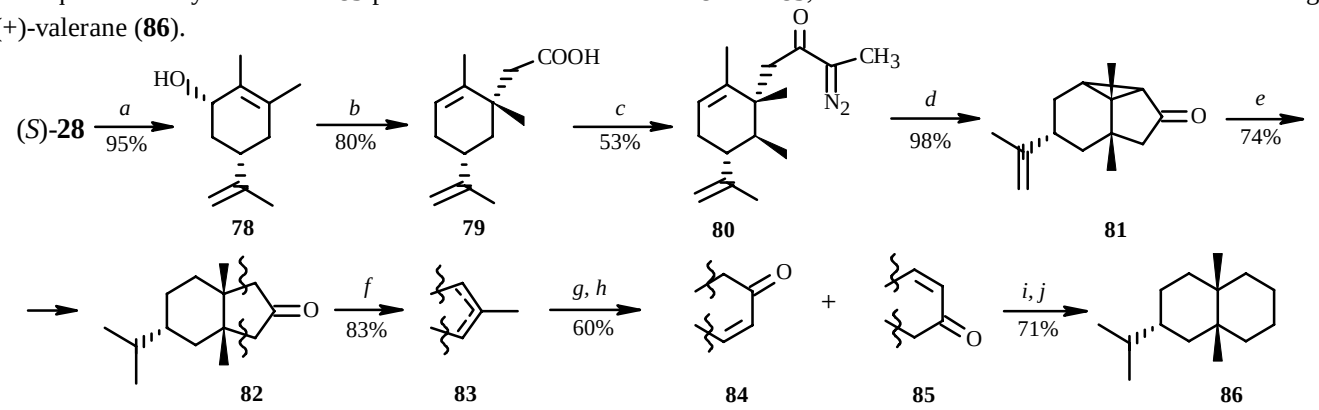
Huang—Minlon deoxygenation of **72** was accompanied by saponification of the ester to give (3*S*)-methylheptanoic acid (**73**), which was converted as usual to the target **76** through alcohol **74** and tosylate **75**.

The series of experiments of Srikrishna et al. on 1,2-addition of organometallic reagents to carvone (**1**) to give chiral synthons used to synthesize natural compounds vitamin D, taxanes, thapsanes, pinguisinol, and certain compounds used in medicine are interesting [41-49]. The ability to synthesize methylcarvone was demonstrated beforehand. Whereas (*S*)-**28** was the oxidation product of 1,2-adduct **27**, which was prepared by reacting enone (*R*)-**1** with MeMgI; (*R*)-**28** was prepared using methylation of pyrazoline derivative **77** [50].



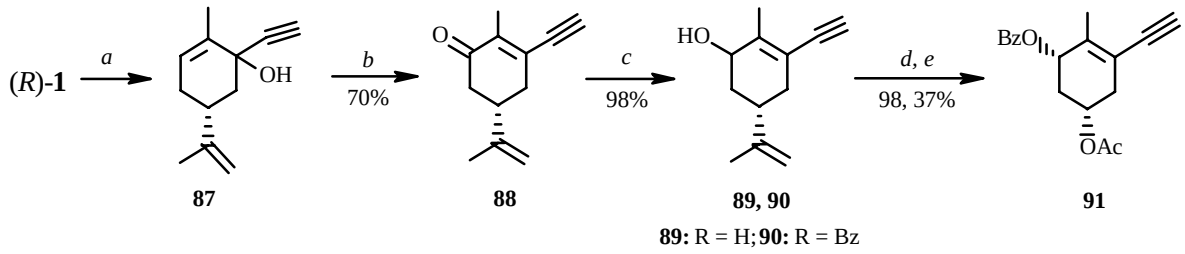
a. MeMgI; *b.* CH_2N_2; *c.* PCC; *d.* Δ

This same β-methylcarvone (*S*)-**28** was used to synthesize the medicinal sesquiterpene (+)-valerane (**86**), which was isolated from valerian rhizomes [41]. For this, (*S*)-**28** was transformed into substituted cyclohexeneacetic acid **79** using Claisen rearrangement of the condensation product of alcohol **78** and orthoacetate. Then, cyclopropanation of diazoketone **80** produced tricyclic **81**, reduction of which gave the key bicyclic **82**. Cross conjugation of ketone **82** with methylmagnesium iodide and subsequent ozonolysis of olefin **83** produced a mixture of enones **84** and **85**, which were then transformed into the target (+)-valerane (**86**).



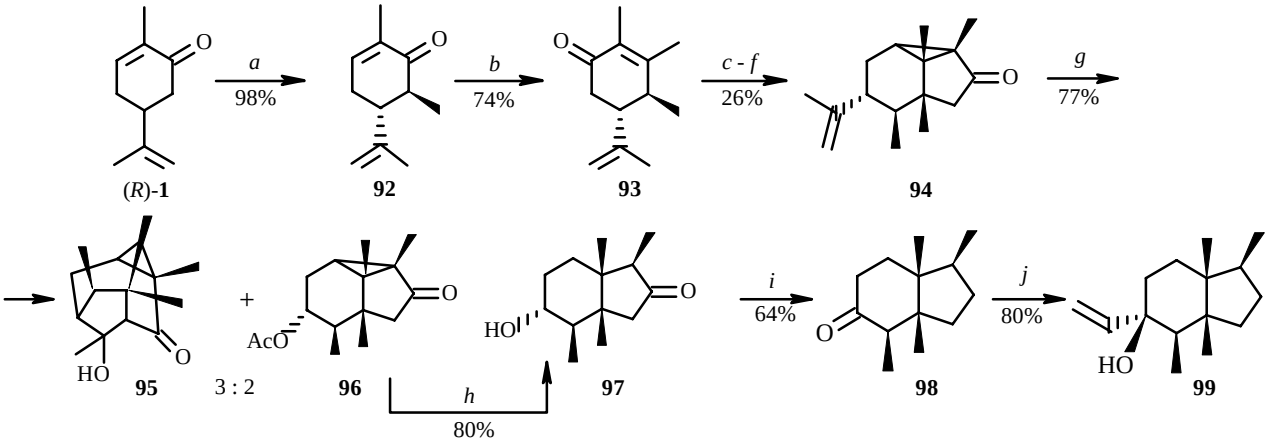
a. $LiAlH_4$; *b.* $Me_3CC(OEt)_3$, $EtCO_2H$, 10% NaOH, MeOH; *c.* $(COCl)_2$, CH_3CHN_2; *d.* $CuSO_4$, *e.* Li-NH_3, H_2, 10% Pd-C; *f.* MeMgI, TsOH; *g.* O_3, CH_2Cl_2-MeOH, PPh_3; *h.* KOH-MeOH; *i.* $Na(CN)BH_3$, BF_3OEt_2; *j.* H_2, 10% Pd-C

Carvone (*R*)-**1** was acetylenated in the synthesis of substituted cyclohexene **91**, which was used to prepare vitamin D [42]. The isolated propargyl alcohol **87** was converted through enone **88** and alcohol **89** into benzoate **90**, partial ozonolysis of which gave the required compound **91**.

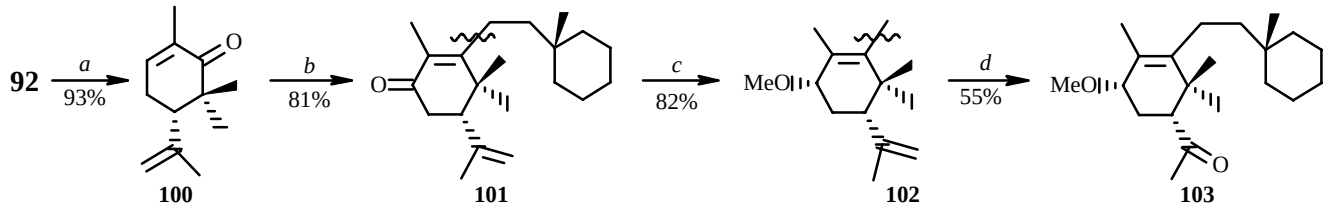


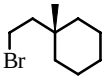
a. HC≡CLi·$(CH_2NH_2)_2$; *b.* PCC; *c.* $LiAlH_4$, -40C; *d.* BzCl, Py, DMAP; *e.* O_3, CH_2Cl_2-MeOH, $NaHCO_3$, -70°C; Ac_2O, Et_3N, DMAP

Enone (*R*)-**1** was also used in the synthesis of (+)-pinguisenol (**99**), the optical antimer of a natural sesquiterpene that was isolated from the liverworts *Porella vernicosa* and *P. densifiola* and possesses antitumor activity [43, 44]. A methyl was introduced preliminarily into the α′-position of (*R*)-**1** by alkylation of the corresponding lithium enolate in the presence of DBU. This gave a mixture of epimers of methylcarvone in a *trans*:*cis* ratio of 3:2, from which the *trans*-isomer **92** was isolated by crystallization [45]. Transformation of **92** through enone **93** gave tricyclic ketone **94**, as described above for the synthesis of (+)-valerane (**87**) [41], ozonolysis of the double bond in which gave a mixture of **95** and **96** in a 3:2 ratio. Treatment of acetoxyketone **96**, which was isolated by chromatography, with Li in ammonia led to partial ring opening to form bicyclic hydroxyketone **97**, which was then transformed through ketone **98** into the target sesquiterpene **99**.

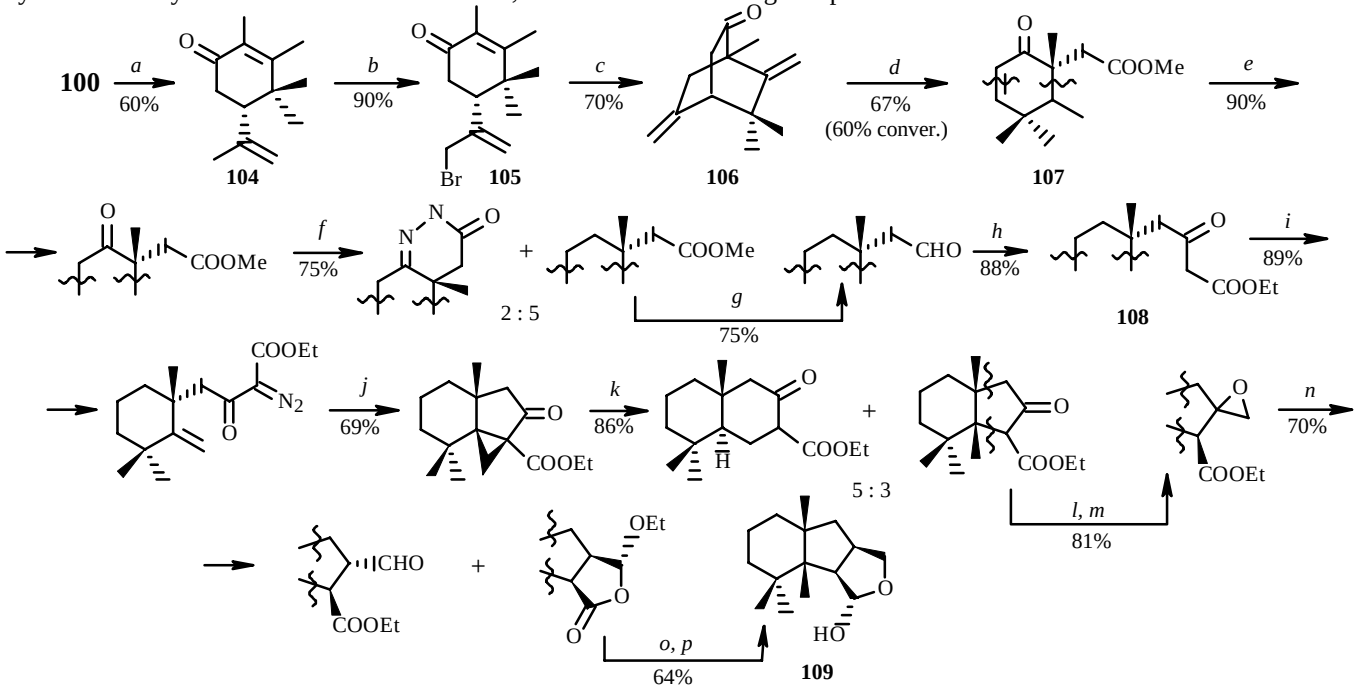


a. LDA, MeI, -10°C; DBU; *b.* MeMgI, PCC; *c.* $LiAlH_4$; *d.* $MeC(OEt)_3$, $EtCO_2H$, 10% NaOH, MeOH; *e.* $(COCl)_2$, CH_3CHN_2; *f.* $CuSO_4$; *g.* O_3, MeOH-CH_2Cl_2; Ac_2O, DMAP; *h.* Li-NH_3; *i.* N_2H_4, NaOH, PCC; *j.* CH_2=CHMgBr



a. MeI, LDA, -10°C; *b.*  , Li, THF, PCC; *c.* $LiAlH_4$, MeI, NaH, Bu_4NI; *d.* O_3, MeOH-CH_2Cl_2, Me_2S

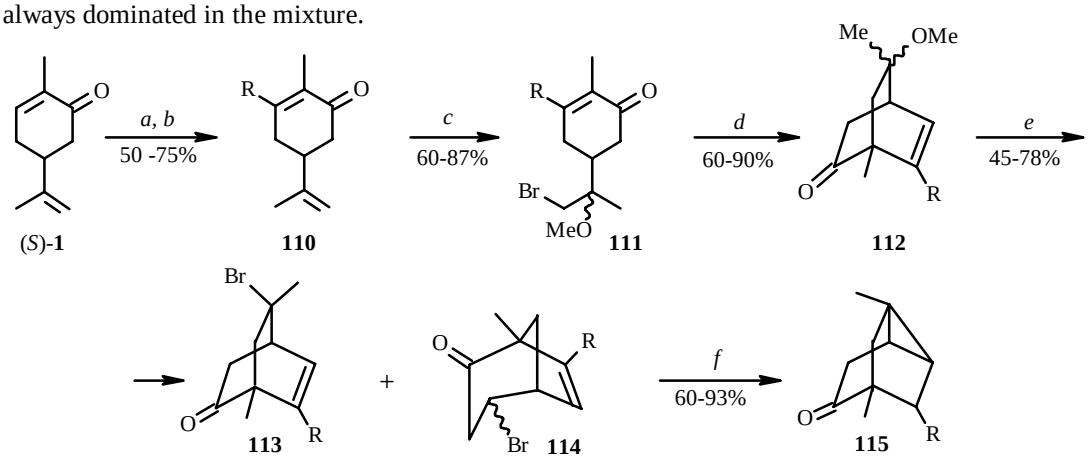
Methylcarvone (**92**) was used to synthesize seconortaxenone (**103**), a precursor of taxol, a known antitumor compound [46]. For this, a second methyl was introduced into the α'-position. Then, the required carbon skeleton of **103** was constructed by a second alkylation of enone **100** but via a 1,2-mechanism and using compounds **101** and **102**.



a. MeMgI, 0°C, PCC; *b.* NBS, CH_2Cl_2-MeOH; *c.* Bu^tOK, Bu^tOH-THF; *d.* O_3, MeOH-CH_2Cl_2, $NaHCO_3$, Ac_2O, Et_3N, DMAP; *e.* 5% Pd-C, H_2; *f.* $N_2H_4 \cdot H_2O$, KOH, CH_2N_2; *g.* $LiAlH_4$, PCC; *h.* N_2CHCO_2Et, $SnCl_2 \cdot 2H_2O$; *i.* TsN_3, Et_3N, CH_3CN; *j.* $Rh_2(OAc)_4$, r.t.; *k.* Li-NH_3; *l.* $Ph_3P^+MeBr^-$, Am^tOK; *m.* MMPPA; *n.* $BF_3 \cdot Et_2O$; *o.* Et_3SiH, CF_3CO_2H; *p.* DIBAH

The structure of (*R*)-**1** was ideal for preparing β-ketoester **108**, which is a key intermediate in the synthesis of thapsane sesquiterpene **109**, which was isolated from the mediterrean plant *Thapsia villosa* [47, 48]. Trimethylcarvone (**104**) underwent intramolecular cyclization through bromide **105**. Ozonolytic cleavage of the resulting bicyclic compound **106** occurred at the less strically hindered double bond and furnished ketoester **107** due to Crigee cleavage. The stereochemistry of the last compound was determined by further structural transformations that gave the target **109**.

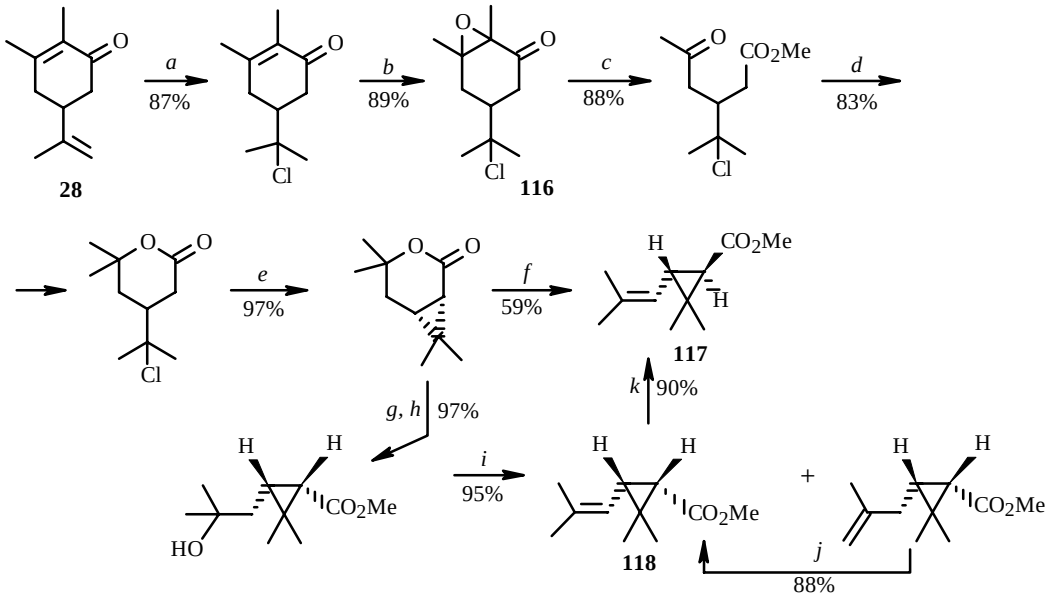
Srikrishna et al. used β-substituted carvones **110** to study the stereochemistry of radical cyclization of enonebromides **113** and **114**. Both compounds were synthesized using a mixture of **111** and **112** and were transformed into the single tricyclic product **115** [49, 50]. In this instance, the cyclization was shown to be possible using only norbornenylbromide as an example. The ratio of isomers of **113** and **114** and the yield depended on the nature of the substituent introduced in the first step but isomer **113** always dominated in the mixture.



R = Ph, *p*-tolyl. *p*-anisyl, *o*-anisyl, -C≡C-Ph

a. RMgBr, 0°C or RLi, -78C; *b.* PCC; *c.* NBS, MeOH-CH_2Cl_2; *d.* Bu^{t}OK, Bu^{t}OH-THF; *e.* BBr_3; *f.* Bu$^n{}_3$SnH, AIBN

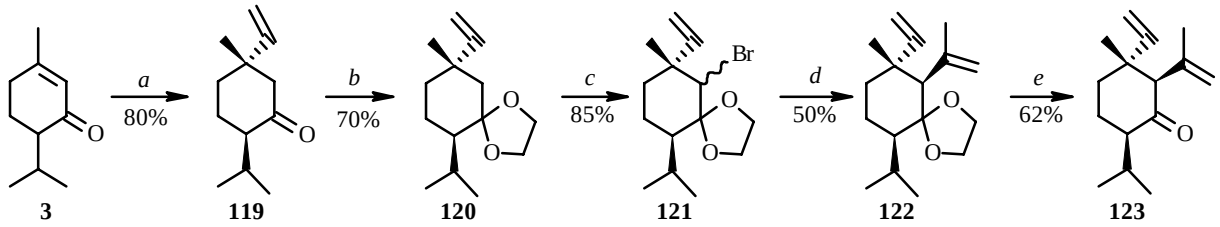
Available (*S*)- and (*R*)-**1** were used as starting materials to synthesize chiral *trans*- (**117**) and *cis*-chrysanthemates (**118**), on which pyrethrins are based. Hydrochlorination of the isopropenyl group followed by epoxidation of the remaining double bond furnished the key chlorinated α,β-epoxycyclohexanone **116**, which was then converted to the target esters [9].



a. HCl; *b.* H_2O_2-NaOH; *c.* e^-; *d.* MeMgI; *e.* LDA; *f.* NaOH, $O(CH_2CH_2OH)_2$, 230–235°C; CH_2N_2;
g. KOH-H_2O; *h.* CH_2N_2; *i.* $POCl_3$; *j.* $RhCl_3 \cdot 3H_2O$; *k.* MeONa-MeOH

1,4-ADDUCTS OF CYCLIC α,β-ENONE MONOTERPENOIDS AND ORGANOMETALLIC REAGENTS

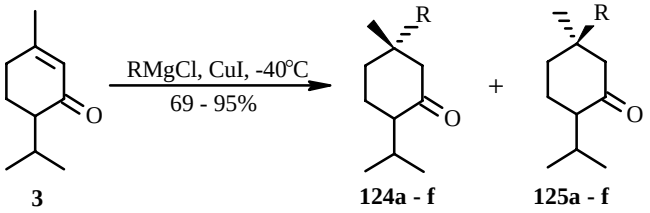
The first reaction in multi-step syntheses where natural cyclic enone monoterpenoids are used as the starting material is 1,4-addition of organometallic compounds. Symmetric organic cuprates that were formed by reacting two equivalents of an organolithium compound (or Grignard reagent) with one equivalent of CuI (the chloride or bromide can also be used) turned out to be the best reagents for 1,4-alkylation of conjugated enones. This formed enols that were converted by hydrolysis into the corresponding ketones.



a. CH_2=CHMgBr, CuI, 0°C; *b.* $(CH_2OH)_2$, TsOH; *c.* $PhNMe_3^+Br^-_3$; *d.* Pr^i_2LiCu; *e.* TsOH, H_2O, Me_2CO

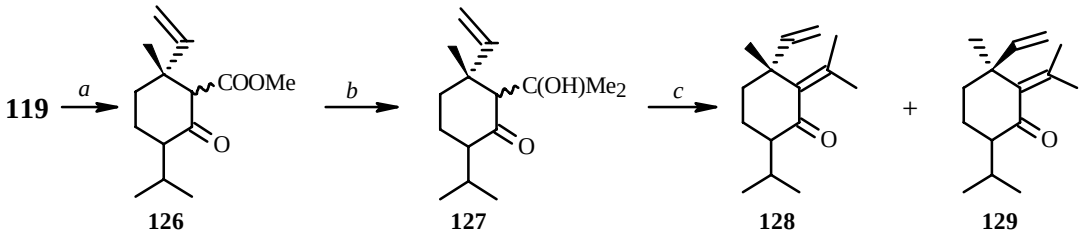
Thus, the first step in the preparation of *dl*-shyobunone (**123**), which was isolated from sweet flag *Acorus calamus* L. and was used in the production of fragrances, was addition to piperitone (**3**) of divinyllithiumcuprate [51]. Ethyleneketal **120** could be brominated regioselectively at the less alkylated α-C atom if the oxo group was protected in the resulting ketone **119**. Bromide **121** was transformed into the target **123** through alkylation product **122**.

Weyerstahl et al. performed a series of experiments on 1,4-addition of various Grignard reagents to enone **3** to produce **124** and **125** in order to synthesize shyobunone derivatives and study their organoleptic properties [52]. The structure of the resulting asymmetric center was not always clear.



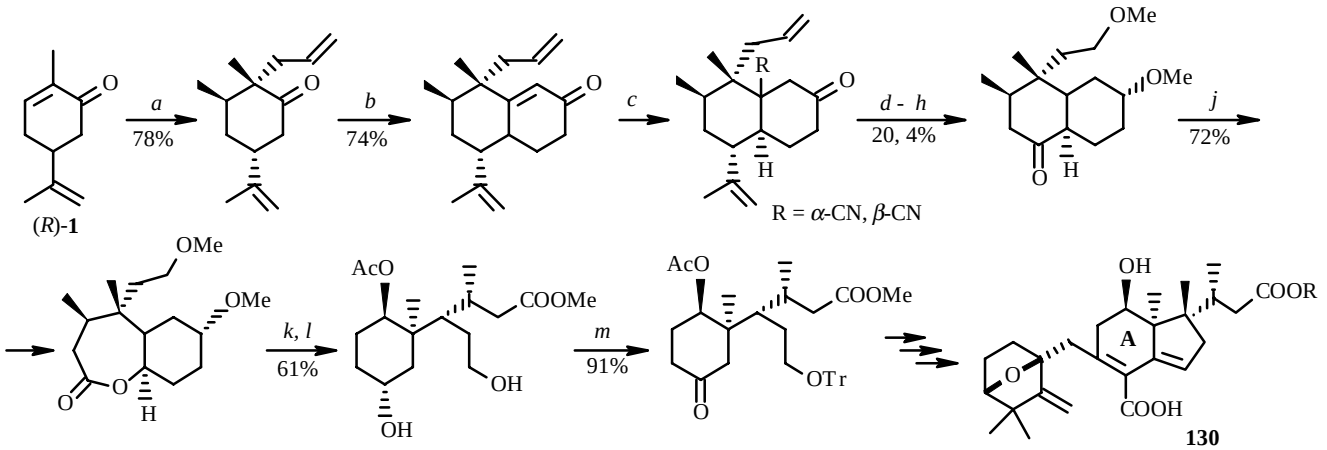
R = Me, Et, Pr^i, Bu^i, Am, $CH_2(Me)C=CH_2$

Ketone **119** was also used to synthesize isoshyobunone (**128**) and its epimer **129** [53]. Successive condensations of the sodium enolate to form **126** and methylation in the presence of sodium hydride effected dialkylation of the ester. Dehydration of the resulting ketol **127** led to a mixture of diene ketones **128** and **129**.



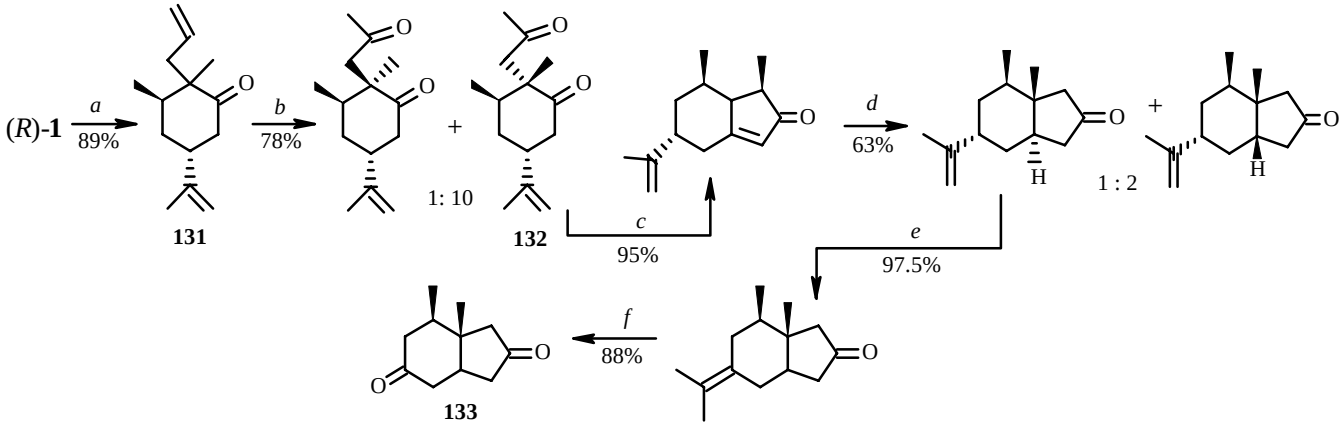
a. $(MeO)_2CO$, NaH; *b.* NaH, MeLi; *c.* 1% HCl, MeOH

A synthesis of fragment A of glycinoeclepin A (**130**), which possesses emetic activity [54], was proposed based on 1,4-addition of lithium dimethylcuprate to (*R*)-**1**. The initial step was one-pot methylation of enone (*R*)-**1** with subsequent annelation of the enol intermediate. Apparently the first reaction occurred exclusively stereoselectively because the formation of two diastereomers was not observed.



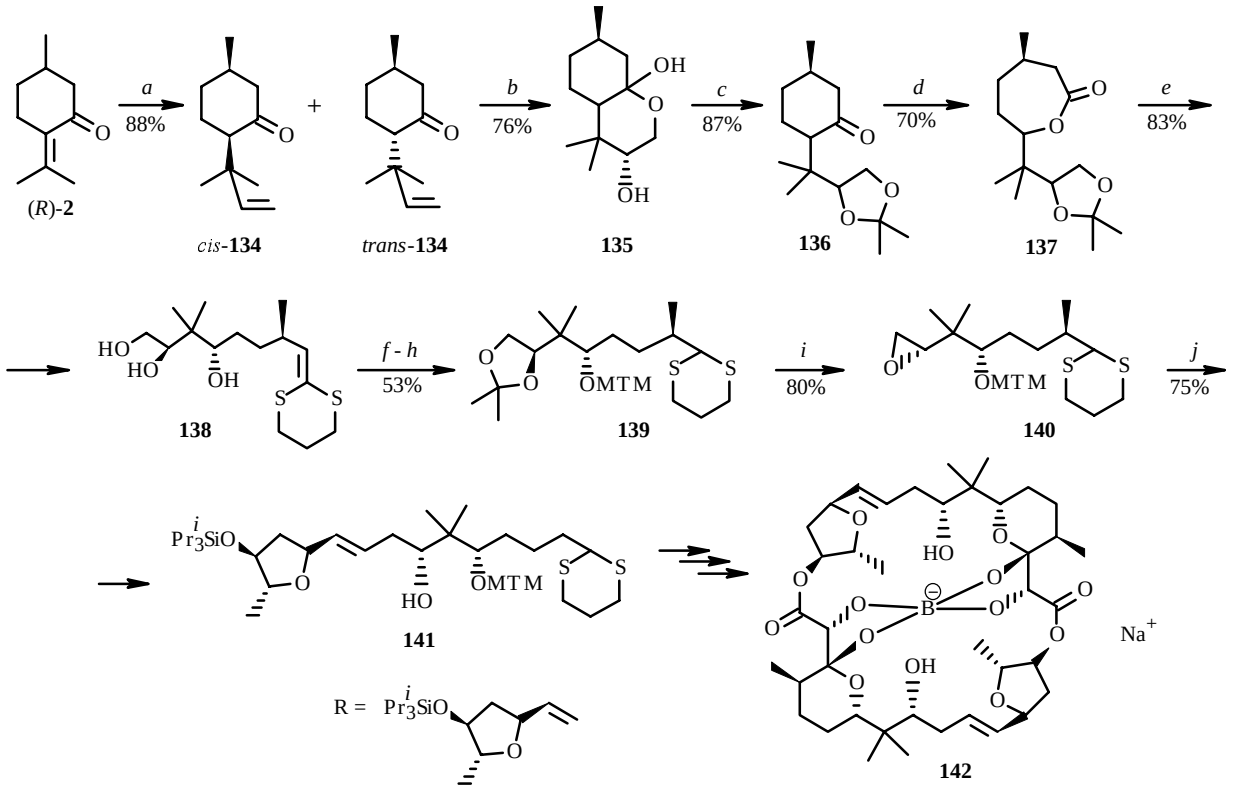
a. MeLi, CuI, Bu_3P, CH_2=$CHCH_2Br$, HMPA; *b.* AcC(TMSi)=CH_2, LDA, NaOMe; *c.* HCN, Et_2Al; *d.* OsO_4, NMO; *e.* $NaIO_4$, $NaBH_4$, MeI, NaH; *f.* DIBAH, N_2H_4·2HCl, KOH; *g.* O_3, Me_2S, CF_3CO_3H; *h.* $LiAlH_4$, $K_2Cr_2O_7$-H_2SO_4; *j.* CF_3CO_3H; *k.* KOH, CH_2N_2, Ac_2O, Et_3N, DMAP; CH_2N_2; *l.* $AlCl_3$, MeCN, NaI; *m.* TrCl, Et_3N, DMAP, PDC

However, the formation of a mixture (1:10) of diastereomeric diketones prepared by Wacker oxidation of the double bond in oxodiene **131** was observed [55, 56]. Diketone **132** was used to synthesize bicyclo[4.3.0]nonan-3,8-dione (**133**), which is the structural framework of such compounds as picrotoxinin, bakkenolide, homogynolide, palmosalide, zizaene, and neopupukeane [55, 56]. The second ring was constructed by intramolecular Robinson annelation.



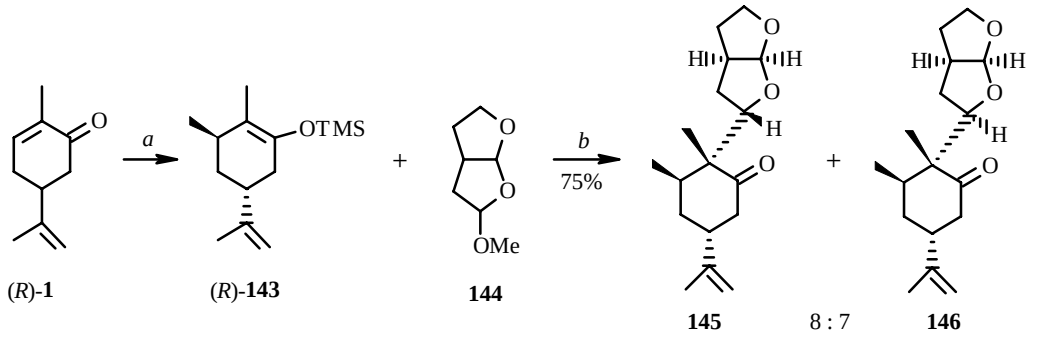
a. Me_2CuLi; CH_2=$CHCH_2Br$, HMPA; *b.* O_2, $PdCl_2$, Cu_2Cl_2, DMF-H_2O; *c.* KOH, H_2O-MeOH; *d.* Li-NH_3; *e.* HBr; DBU; *f.* O_3; Me_2S

Several examples of the use of **2** to synthesize chiral structural units are based on 1,4-addition [26, 27, 57]. Thus, **2** was used to synthesize the antibiotic aplasmomycin (**142**), which was isolated from a culture of the actinomycete *Streptomyces griseus* and is the sodium salt with empirical formula $C_{40}H_{60}O_{14}BNa$ (**142**) [57]. An equilibrium mixture of *cis*- and *trans*-8-vinylmenthones (**134**) was prepared in order to synthesize key synthon **141** by cross conjugation of (*R*)-**2** with vinylmagnesiumbromide in the presence of a cuprate catalyst. Treatment of **134** with Na_2CO_3—MeOH shifted the equilibrium to a 15:85 ratio with the *trans*-product dominating. The *trans*-isomer of **134** that was isolated by chromatography was transformed into tetrahydropyranol **135**, which was converted to triol **138** through ketone **136** and lactone **137**. Triol **138** was transformed into acetonide **139** and then into epoxide **140**. Condensation of **140** and the stannate formed from D-mannose gave the required synthon **141**.

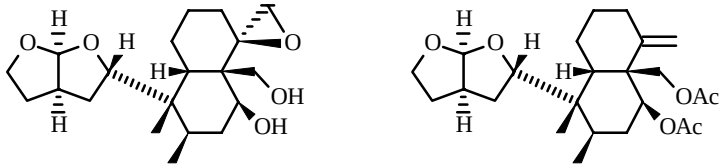


a. CH_2=CHMgBr, CuI; Na_2CO_3-MeOH; *b.* OsO_4, NMO, AcOH; *c.* $LiAlH_4$; Me_2CO, TsOH; PCC; *d.* MCPBA; *e.* $CH_2(CH_2SH)_2$, Me_3Al; *f.* O_3; Me_2S; *g.* $CH_2(CH_2SH)_2$, $BF_3 \cdot OEt_2$; *h.* DMSO-Ac_2O-AcOH, AcONa; *i.* AcOH-H_2O; BzCN, Et_3N; $MeSO_2Cl$, Et_3N; $Bu^t_4N^+OH^-$-MeOH; *j.* Bu^n_3SnR, Bu^nLi, CuCN

The enol form of the product of 1,4-addition of an organometallic reagent could be isolated if it was stabilized. This broadened the synthetic potential of the process. Thus, treatment with trimethylsilylchloride of the reaction mixture obtained from addition of MeMgBr to conjugated enone (*R*)-**1** in the presence of Cu(I) gave the stable silyl ether (*R*)-**143**. This enabled a second substituent to be introduced into this system via the Mukayama aldol reaction. Use of (±)-2-methoxy-hexahydrofuro[2,3-*b*]furan (**144**) as the second alkylating agent led to a mixture of substituted cyclohexanones **145** and **146**, which were separated by chromatography. Ketone **145** was used as a substrate in the synthesis of optically pure natural compounds [58-63], for example, to prepare clerodanes, namely dihydroclerodane (**147**) and lupulin C (**148**), diterpenoids with broad spectra of biological activity (antiviral, antiseptic, antitumor, antiulcer, etc.) [58, 59].

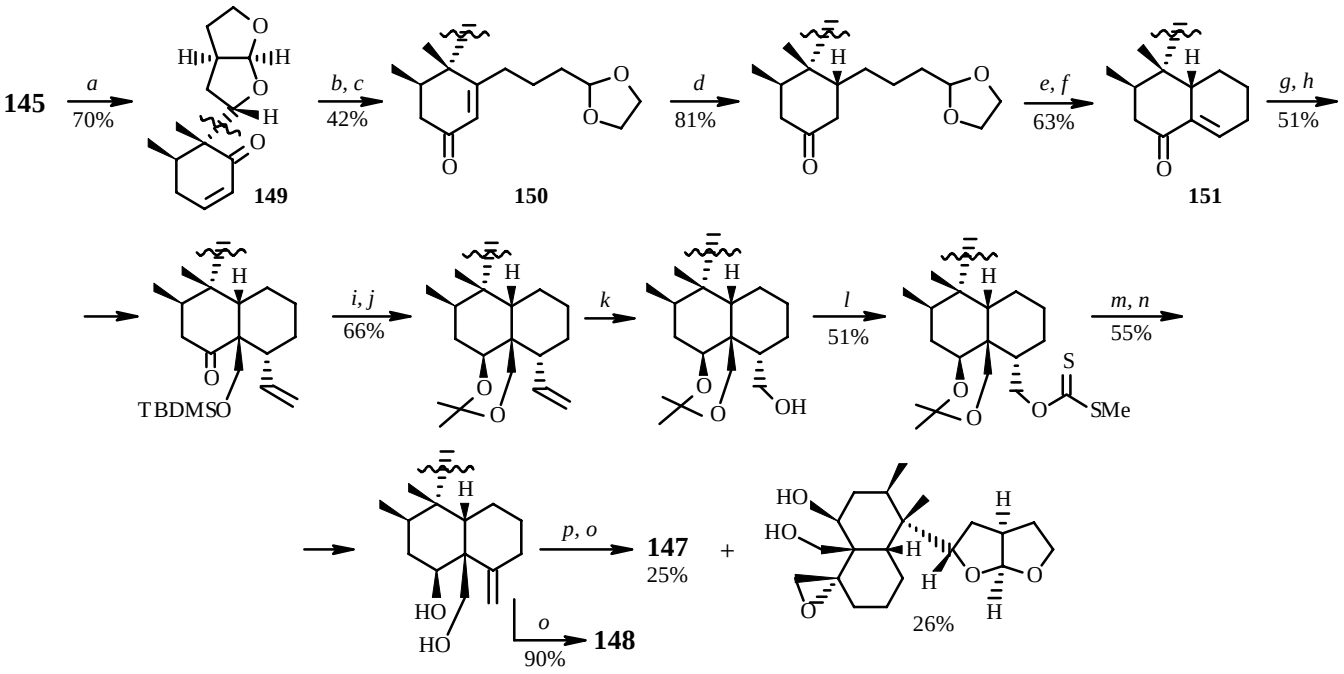


a. MeMgI, CuBr·Me_2S, TMSCl, HMPA; *b.* $TrClO_4$



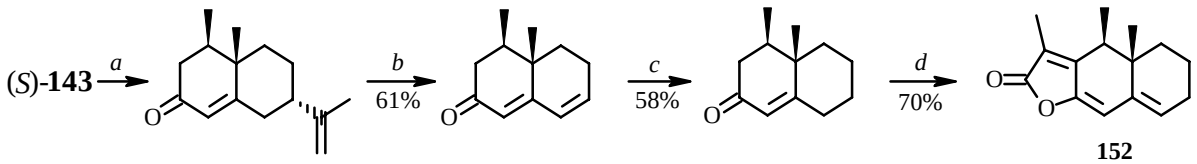
147 **148**

For this, ozonolytic cleavage of the isopropenyl substituent in unsaturated cyclohexanone **145** was used, which occurred with introduction of an *endo*-cyclic double bond conjugated with the carbonyl. Subsequent 1,4-addition of 3-(1,3-dioxolan-2-yl)-propyllithium to the resulting enone **149** and oxidation led to β-substituted enone **150**. Hydrogenation and deprotection of the latter enabled the annelation to be performed. Here it should be mentioned that the approach in which the intermediate 1,4-adduct of bicyclic enone **151** with vinylmagnesiumbromide was used without isolation in the reaction with formaldehyde was successful. This enabled a hydroxymethylene group to be introduced into the structure.



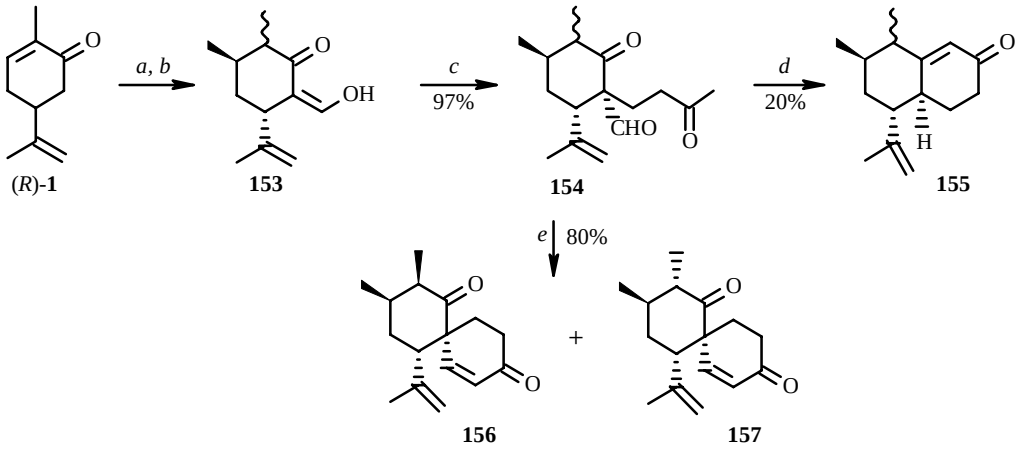
a. O_3, $Cu(OAc)_2$, $FeSO_4$; *b*. 3-(1,3-dioxolan-2-yl)propyllithium; *c*. PCC; *d*. H_2, Pd-C; *e*. PPTS, H_2O; *f*. Δ, PPTS; *g*. CH_2=CHMgBr, CuBr·Me_2S; CH_2O; *h*. TBDMSCl, imidazole; *i*. $LiAlH_4$; *j*. 2,2-dimethoxypropan, PPTS; *k*. O_3; $NaBH_4$; *l*. MeI, CS_2, NaH; *m*. 216°C; *n*. CF_3CO_2H; *o*. Ac_2O, DMAP; *p*. MCPBA

Annelation of enol silyl ether (*S*)-**143** was used to synthesize *R*-(−)-ligularenolide (**152**), which is the principal part of microbiological metabolites (−)-PF1092A, -B, and -C [60, 61].



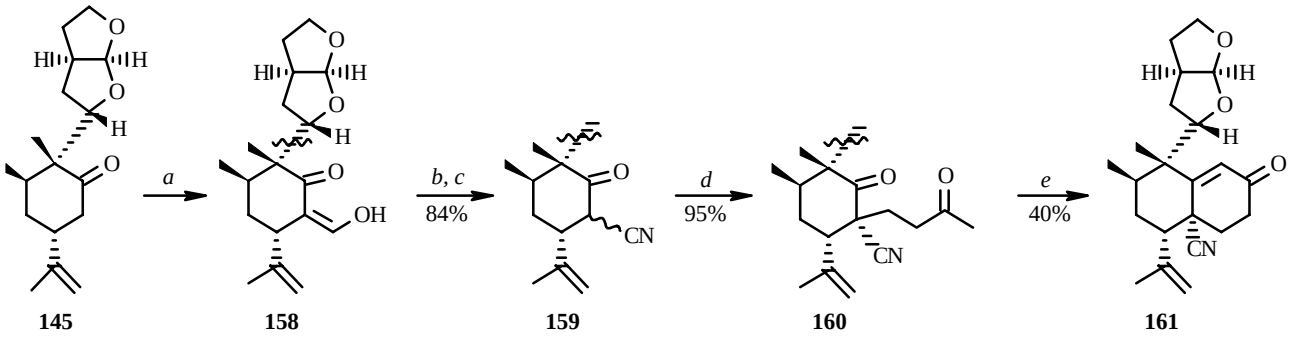
a. MVK, BF_3·OEt_2; MeONa; *b*. O_3, MeOH; Ac_2O, Et_3N, DMAP; MeONa; *c*. L-Selectride, DMPU, MeONa; *d*. LDA; ethyl pyruvate, $ZnCl_2$; TsOH, PhMe, Δ

The synthetic potential of (*R*)-**1** was expanded based on an approach proposed for the synthesis of bicyclic **155** and spiro-compounds **156** and **157**, which were used to synthesize enantiomerically pure clerodanes, which possess psychoactive properties, and drimane and lactarane sesquiterpenes, which are used in medicine [62, 63]. Vinyl alcohol **153** and aldehyde **154** were prepared as intermediates.



a. MeMgI, CuBr·Me_2S; *b*. HCO_2Et, NaH; *c*. MVK, Et_3N, KOH; *d*. KOH-MeOH; *e*. pyrrolidine, AcOH

In an analogous approach, cyclohexanone **145** was used to synthesize decalone **161**, which was also used to synthesize clerodanes.

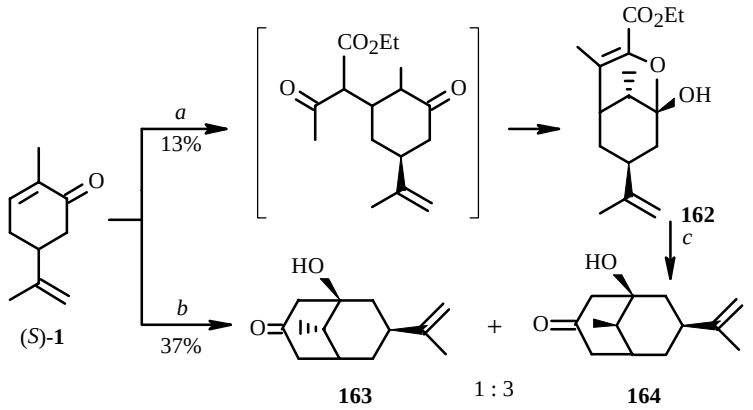


a. HCO_2Et, NaH; *b*. NH_2OH, AcONa; *c*. MeONa-MeOH; *d*. MVK, MeONa; *e*. pyrrolidine, AcOH

MICHAEL REACTIONS

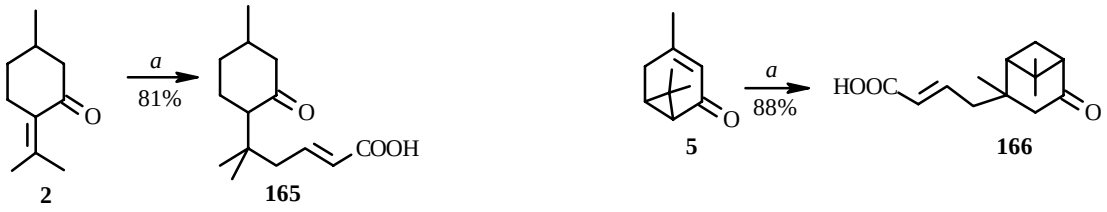
Monoterpenoids with an enone system in their structure have been recommended as good Michael acceptors that bind nucleophiles in the β-position relative to the carbonyl [64-82]. The Michael reaction is a rather common method of forming C–C bonds. The process often proceeds beyond the first step to further condensation. This can significantly complicate the substrate structure for a "single addition." Base is necessary to initiate the Michael reaction. Sodium ethoxide, diisopropylamide, and lithium hexamethyldisilazide are usually used for this.

Thus, the reaction of (*S*)-**1** and acetoacetic ester in the presence of catalytic amounts of EtONa at 20°C produced enol monoacetal **162**, treatment of which with aqueous base gave the aldol condensation product, which was a mixture of isomeric bicyclic hydroxyketones **163** and **164** [64]. If the Michael reaction was carried out at 80°C in the presence of stoichiometric amounts of base, these were formed in one step.



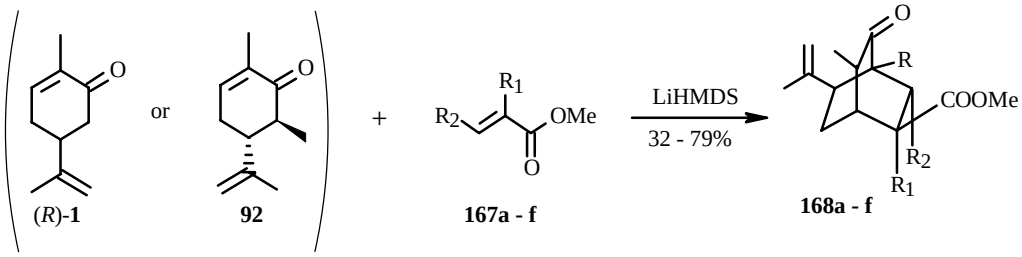
a. $AcCH_2CO_2Et$, EtONa, 20°C; *b*. $AcCH_2CO_2Et$, EtONa, 80°C, *c*. KOH-H_2O

Research on the regioselectivity of the conjugated addition reaction of crotonic acid and α,β-unsaturated ketones showed that although aliphatic enones formed a mixture of 1,4-α- and 1,4-γ-adducts, cyclic ketones gave exclusively the γ-adducts in high yields [65]. It was considered that the reaction in the first instance occurred through a tandem process that included 1,2-addition and Coupe oxo-rearrangement; in the second, 1,2-addition through a successive retroaldol process and Michael addition. Thus, the condensation products of **2** and **5** were conjugated 7-oxoacids **165** and **166**, respectively.

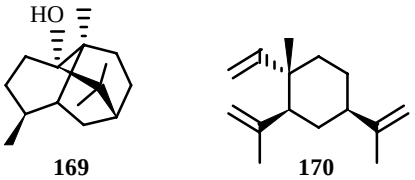


a. $MeCH{=}CHCO_2H$, Et_2NLi

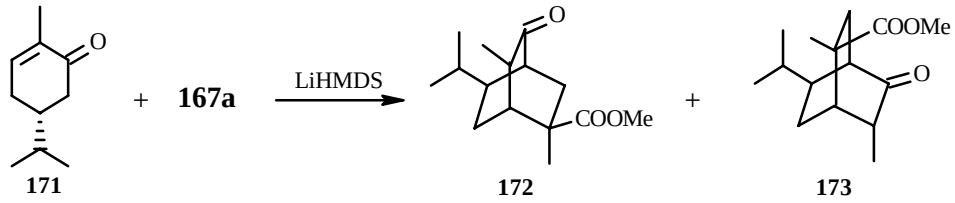
Two successive Michael reactions are an effective pathway for constructing cyclic and polycyclic compounds because the second addition often concludes with ring closing. This strategy was used to synthesize derivatives of bicyclo[2.2.2]octane **168a-f**, which are the structural base of many natural compounds or their precursors, in particular to prepare (–)-patchouli (**169**), which is used in perfumes [66], (+)-curdione and β-elemene (**170**), an analog of elemene [67].



168a: R = H, R_1 = H, R_2 = Me; **168b:** R = H, R_1 = Me, R_2 = H; **168c:** R = H, R_1 = H, R_2 = H,
168d: R = Me, R_1 = H, R_2 = Me; **168e:** R = Me, R_1 = Me, R_2 = H; **168f:** R = Me, R_1 = H, R_2 = H

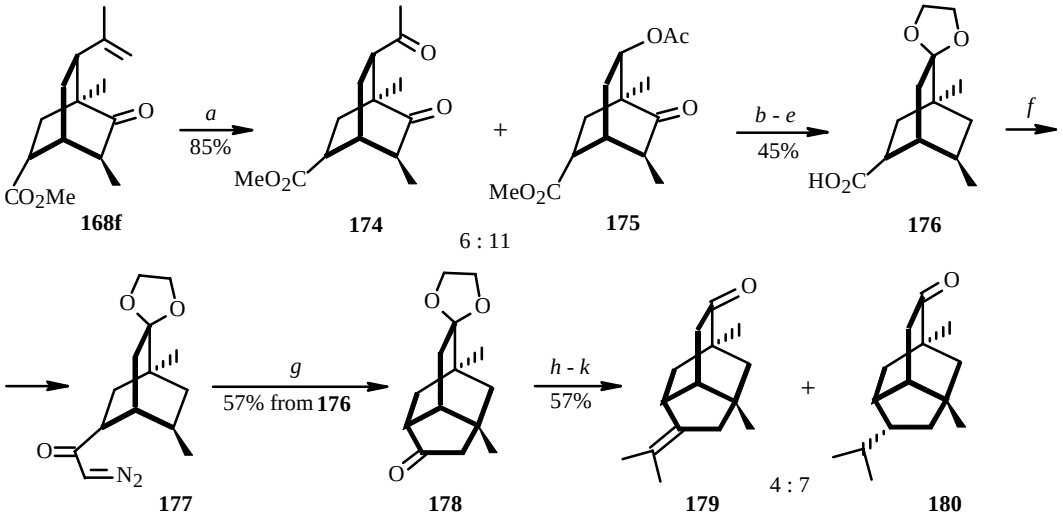


Carvotanacetone (**171**) reacted with methylcrotonate to give **172** as the main product in addition to **173**, the addition adduct of the nucleophile at the α'-position of enone **171**.



171 **172** **173**

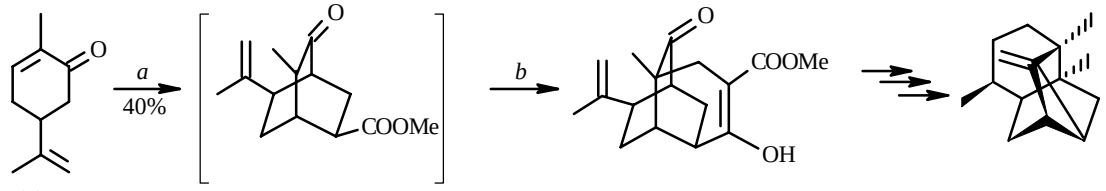
Another example of the use of bicyclics prepared by two successive Michael reactions is the synthesis of sesquiterpene (–)-9-pupukeanone (**180**), the secretion of nudibranch sea slug *Phyllidia varicosa* Lamark, and its derivatives [68-71]. Ozonolysis of the double bond in **168f** with subsequent treatment of the methoxyhydroperoxide with acetic anhydride produced the usual ozonolysis product **174** and acetate **175**. Acetoxyketone **175** was isolated by column chromatography and converted in several steps to acid **176**, which was transformed into diazoketone **177**, cyclized to form ketone **178**, and then transformed through enone **179** into (–)-9-pupukeanone (**180**).



168f **174** **175** **176** **177** **178** **179** **180**

a. O_3, MeOH, Ac_2O, Et_3N, DMAP; *b*. $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$; *c*. Ni-Ra, EtOH; *d*. K_2CO_3, MeOH; PCC; *e*. $(CH_2OH)_2$, TsOH, NaOH-H_2O-MeOH; *f*. $(COCl)_2$ CH_2N_2; *g*. $Rh_2(tfa)_4$; *h*. CH_2=C(Me)Li; *j*. TsOH; *k*. H_2, PtO_2, MeOH

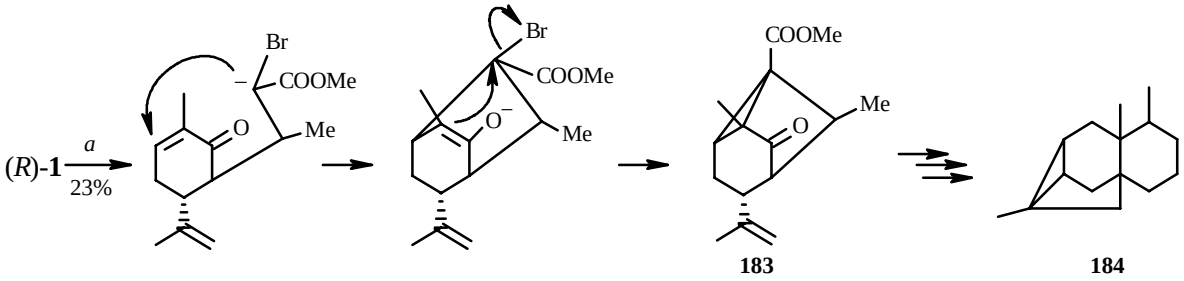
Involvement of (*R*)-**1** in three tandem successive Michael reactions and Dieckmann cyclization involving methylacrylate led to the preparation of optically pure tricyclo[5.3.1.$0^{3,8}$]undecenes **181**, structural frameworks of seychellene (**182**) [72].



(*R*)-**1** **168c** **181** **182**

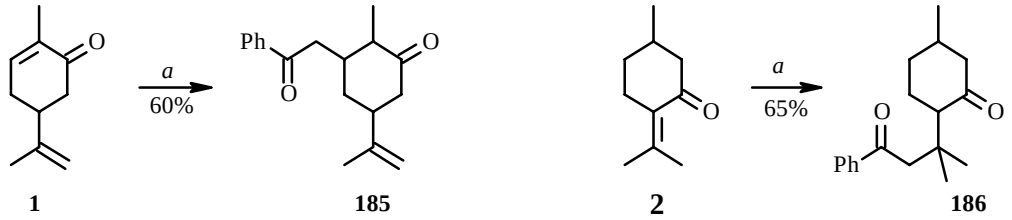
a. CH_2=$CHCO_2Me$, LDA-HMPA; *b*. CH_2=$CHCO_2Me$

An intramolecular tandem process for synthesizing tricyclic ketoester **183**, from which the tetracyclic framework of ishwarane **184** can be formed, began with α'-addition to (*R*)-**1** of α-bromomethylcrotonate [73].



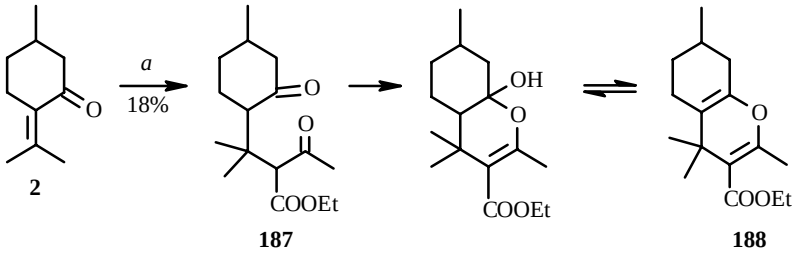
a. MeCH=CBrCO$_2$Me, LDA

Michael reactions performed under basic conditions were described above. However, Lewis acids have recently been used as catalysts. These include $ZnCl_2$ [75], Fe(III) [76-78], titanium [79, 80], CsF [81], and lanthanide salts [82]. The Michael reaction of **1** and **2** with acetophenone catalyzed by CsF gave 1,5-dicarbonyl compounds **185** and **186**, respectively, in good yields (compared with the use of $ZnCl_2$ and $FeCl_3$).



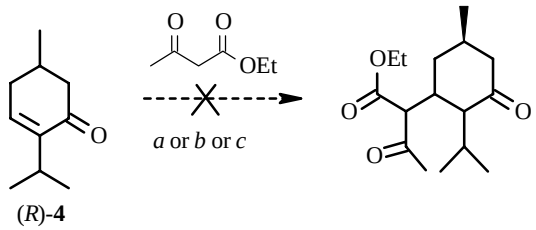
a. PhCOMe, CsF, Si(OEt)$_4$

The reaction of **2** and acetoacetic ester afforded 1,5-dicarbonyl compound **187**, subsequent intromolecular condensation of which produced carbethoxypyran **188**, which was used to study the effect of substituents on chemical shifts in PMR spectra [75].



a. AcCH$_2$CO$_2$Et, $ZnCl_2$

Attempts to effect a Michael reaction of **4** with acetoacetic ester using sodium hydride, hydrated crystalline iron chloride, and boron trifluoride etherate were unsuccessful [74]. The results confirmed that the conjugated system of menthenone (**4**) was unusually passive, as noted previously [28].



a. $FeCl_3 \cdot 6H_2O$; *b*. NaH, THF; *c*. $BF_3 \cdot OEt_2$

Thus, the review of the literature showed that conjugated 1,2- and 1,4-addition of organometallic reagents and the Michael reaction as a special case of 1,4-addition are widely used in the synthesis of optically pure natural compounds and their analogs. In fact, namely this step often determines the overall synthetic strategy.

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