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# Advances in the synthesis of natural butano- and butenolides

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**Abstract. A retrospective of modern approaches to the synthesis of natural butano- and butenolides based on the use of recent achievements of synthetic organic chemistry is given. For most of the considered compounds, natural sources and biological activities are indicated. The bibliography includes 131 references.**

## I. Introduction

Butano- and butenolides of various structures are widely represented among natural metabolites. During the last decades, studies of their synthesis have served as a unique testing ground for the development of new strategies for the construction of complex organic molecules. On the basis of this class of compounds, a new methodological arsenal is being vigorously developed in the chemistry of natural products and the scope of application of known advanced synthetic methods including metathesis reactions, the different versions of the enantioselective Sharpless, Jacobsen and other reactions is extended. The development of this field of fine organic synthesis is stimulated by the discovery of new natural compounds with different kind of practically useful activities. In particular, representatives of natural butenolides isolated from the plants of the family Annonaceae exhibit uniquely selective cytostatic activity with respect to human tumour cell cultures (see the review [1] and references cited therein). Many pest pheromone molecules contain butano- or butenolide fragments.[2]

This review covers the knowledge, mainly accumulated over the last 15 years, on the synthesis of natural butano- and butenolides and earlier data that have not been adequately covered in the published reviews [3–7] or monographs.[2,8] We considered only the methods for preparing compounds containing an isolated lactone ring in the molecule. The knowledge about the synthesis of other natural structures with a lactone ring in polycyclic molecules is fairly extensive and requires separate discussion.

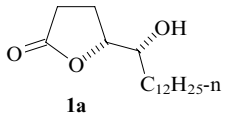
It is reasonable to present the material devoted to the synthesis of natural butanolides and butenolides, respectively, in two separate chapters. Each chapter is divided into sections according to the substitution pattern of the lactone ring, which largely determines the synthetic strategy and the choice of the key synthetic method and the starting compounds.

## II. Synthesis of natural butanolides

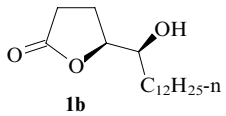
### 1. Synthesis of γ-substituted butyrolactones

During the last 15 year, muricatacin (**1**) has been the most popular γ-substituted butyrolactone among those that have attracted attention of synthetic chemists. This butanolide refers to acetogenin derivatives. It was isolated from seeds of the tree *Annona muricata*. Like other tropical plants of the Annonaceae family, this tree serves as the source of many acetogenins having antitumour, antimicrobial and pesticide action.[1] Natural muricatacin is a mixture of enantiomers where (4*R*,5*R*)-isomer **1a** predominates (isomer ratio ~63 : 37), both enantiomers exhibiting approximately equal cytotoxicity with respect to cultures of some tumour cells.

One of the first studies on the synthesis of enantiomers **1a** and **1b** was carried out by Wang *et al.*,[9] who used acrolein or tridecanal **2** as the starting compounds.



**1a**



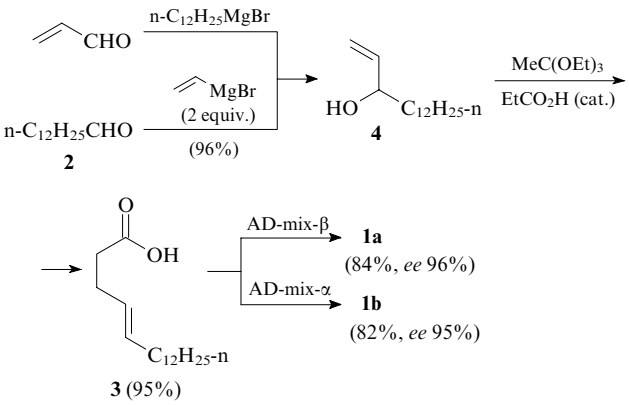
**1b**

The *E*-isomer **3** is formed as a result of the Johnson–Claisen rearrangement of allylic alcohol **4**.†

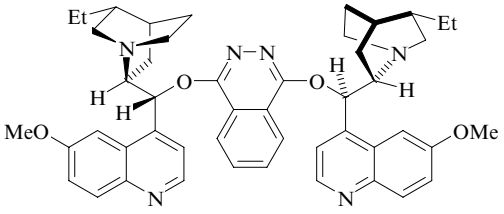
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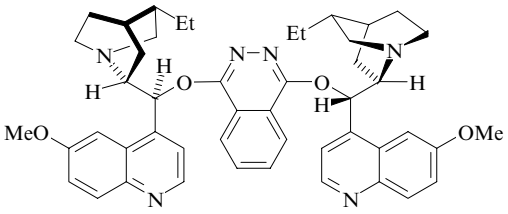
† Hereinafter, the conditions are given only for the key steps of the total synthetic scheme, the product yield and enantiomeric excess (*ee*) are given in parentheses.




The asymmertric dihydroxylation of compound (*E*)-**3** accompanied by lactonization is carried out in the presence of the catalyst AD-mix, which is a mixture of salts [$K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$ and $K_2CO_3$] with a chiral ligand **5a** (AD-mix-α) or **5b** (AD-mix-β).




**5a** [$(DHQ)_2PHAL$)]

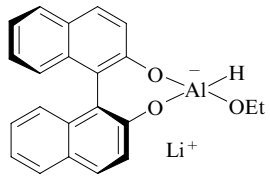



**5b** [$(DHQD)_2PHAL$]

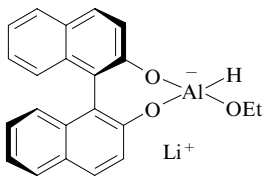
Depending on the type of the catalyst (AD-mix-β or AD-mix-α), the reaction gives isomer **1b** or **1a**. The enantiomeric purity of the products can be brought to 100% by recrystallization from a pentane–ether mixture.

Publications of the same year by American scientists [10, 11] describe the preparation of enantiomers **1a**,**b** through a larger number of steps (Scheme 1).

The stereochemistry of the final product depended on the form of the catalyst BINAL-H (*S*- or *R*-enantiomer) used for the reduction of the intermediate stannyl derivative **6**, which was obtained from available aldehyde **7**.




(*S*)-BINAL-H




(*R*)-BINAL-H

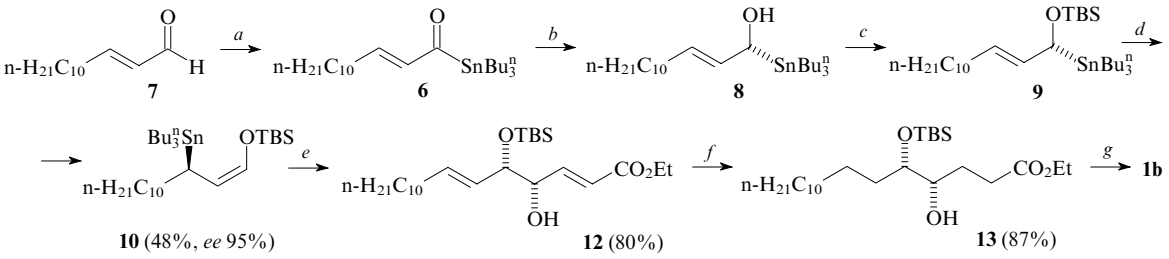
Thus under the action of (*S*)-BINAL-H, compound **6** is enantioselectively reduced to alcohol **8**, its hydroxy group is protected by converting the compound into TBS ether **9**. The latter rearranges in the presence of $F_3B \cdot OEt_2$ to give γ-silyloxystannane **10** with enantiomeric purity of 95%. Coupling of compound **10** with aldehyde **11** is stereoselective giving unsaturated ester **12**. Its subsequent hydrogenation and hydrolysis of hydroxy ester **13** afford butanolide **1b**. A similar route but using (*R*)-BINAL-H for the reduction of stannane **6** resulted in lactone **1a**.

The synthesis of muricatacin **1b** from L-(+)-tartaric acid is documented.[12] First, the acid is converted into glycol **14** by a known procedure;[13] then diacetylene derivative **15** is prepared *via* bisoxirane. In the key step of the synthesis, treatment of **15** with 2 equivalents of $W(CO)_5$ in THF leads to stable carbene complex **16**. The oxidative demetallation of **16** followed by coupling of the resulting butanolide with 1-iodoheptylacetylene (**17**) affords diyne **18**. The final step is hydrogenation of diyne **18** into target product **1b** (Scheme 2).

Yet another enantiospecific total synthesis of butanolide **1b** was performed [14] in eight steps in a 34% overall yield on the basis of available diethyl tartrate, which was easily converted into the initial homochiral compound **19**.[15]

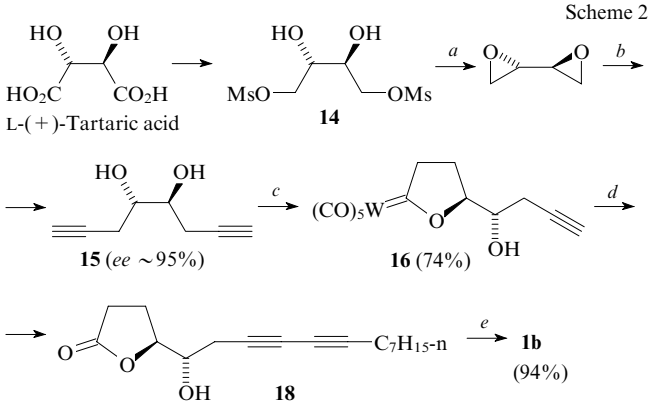
First, compound **19** was converted into diol **20** by conventional methods. The selective tosylation of its primary OH group followed by treatment of the tosylate with potash give epoxide **21**. The epoxide ring in compound **21** is opened by treatment with lithium ethoxyacetylenide. The intermediate acetylene derivative **22** is smoothly transformed on heating into lactone **23**, direct precursor of muricatacin **1b**.

Scheme 1

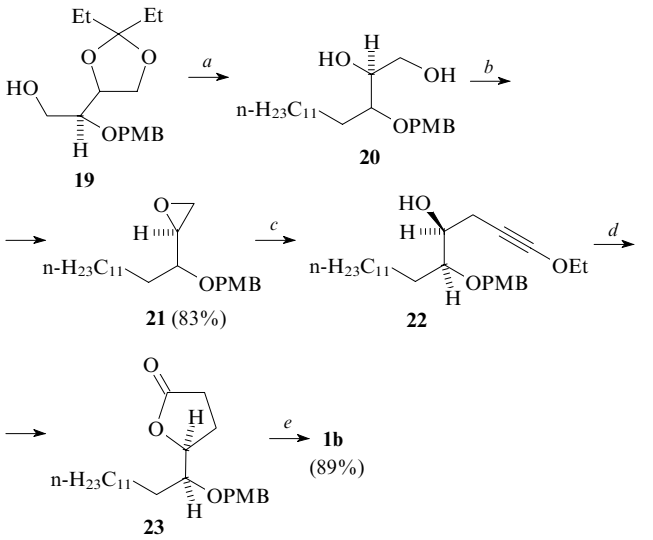



(*a*) $Bu^n_3SnLi$; (*b*) (*S*)-BINAL-H; (*c*) $Bu^tMe_2SiCl$ (TBSCl), imidazole, $CH_2Cl_2$; (*d*) $F_3B \cdot OEt_2$, −78 °C; (*e*) (*E*)-$EtO_2CCH{=}CHCHO$ (**11**), $F_3B \cdot OEt_2$, $CH_2Cl_2$; (*f*) $H_2$, Pd/C, EtOH; (*g*) 49% HF, THF–$H_2O$.

Scheme 2

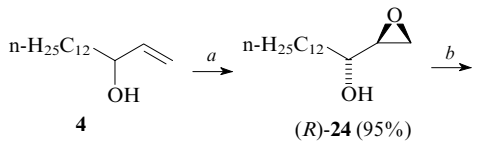


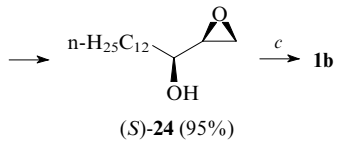
Ms is methylsulfonyl; (*a*) KOH (2.2 equiv.), $Et_2O$; (*b*) complex $LiC{\equiv}CH-H_2N(CH_2)_2NH_2$ (2.2 equiv.), THF–DMSO (1 : 10); (*c*) $W(CO)_5 \cdot$ THF (2 equiv.), THF, 20 °C; (*d*) (1) cerium ammonium nitrate (CAN), $Me_2CO$, 20 °C; (2) n-$C_7H_{15}C{\equiv}CI$ (**17**), $(Ph_3P)_2PdCl_2$ (3 mol.%), CuI (3 mol.%), diisopropylamine (DIPA), THF, 45 °C; (*e*) $H_2$, 10% Pd/C, EtOAc, 20 °C.



PMB is *p*-methoxybenzyl; (*a*) (1) TsCl (Ts is *p*-tolylsulfonyl), pyridine (Py), 0 °C; (2) n-$C_{11}H_{23}MgBr$, CuI, THF, −30 °C; (3) 2% $H_2SO_4$, MeOH; (*b*) (1) TsCl, Py, 0 °C; (2) $K_2CO_3$, MeOH; (*c*) $EtOC{\equiv}CH$, Bu$^n$Li, $F_3B \cdot OEt_2$, THF, −78 °C; (*d*) xylene, Δ; (*e*) 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), $CH_2Cl_2$, $H_2O$.

A shorter route to butanolide **1b** is based on regioselective cleavage of chiral epoxide (*S*)-**24** under the action of lithium lithioacetate.[16] Its enantiomer (*R*)-**24** was prepared from allylic alcohol **4** mentioned above by the successive asymmetric Sharpless epoxidation and the Mitsunobu epimerization. The optical purity of the butanolide **1b** synthesized in this way was ∼98%.

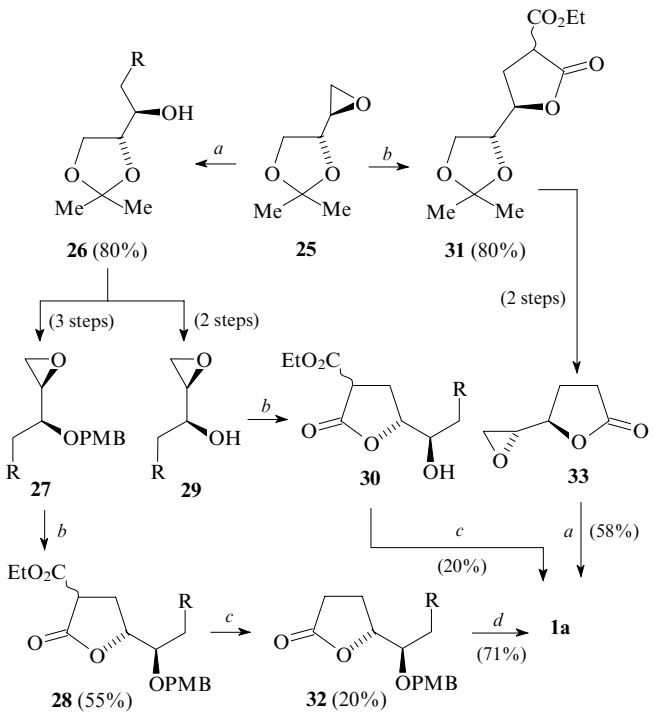




(*a*) Ti(OPr$^i$)$_4$, diisopropyl D-tartrate (D-DIPT), Bu$^t$OOH (TBHP), $CH_2Cl_2$, −20 °C; (*b*) (1) diethyl azodicarboxylate (DEAD), $Ph_3P$, $ClCH_2CO_2H$, PhH; (2) MeONa (1%), MeOH; (*c*) (1) $LiCH_2CO_2Li$, THF, Δ; (2) $H_2SO_4$, $H_2O$.

Even larger number of methods have been developed for the synthesis of lactone **1a**, three of these being described by French authors (Scheme 3).[17,18] They are all based on the same homochiral precursor **25** obtained from D-isoascorbic acid. According to the first method, coupling of epoxide **25** with a cuprate reagent gives alcohol **26**; this is converted into protected epoxy ether **27**, which reacts with diethyl malonate to give a mixture of diastereomeric lactones **28**. The coupling of diethyl malonate with epoxy alcohol **29** (second method) or epoxide **25** (third method) yields lactone **30** or **31**, respectively. Intermediate ethoxycarbonyl compounds **28**, **30** and **31** are further subjected to acid cleavage. These synthetic routes to lactone **1a** are completed by deprotection of *p*-methoxybenzyl derivative **32** and coupling of epoxy lactone **33** with undecyl cuprate.

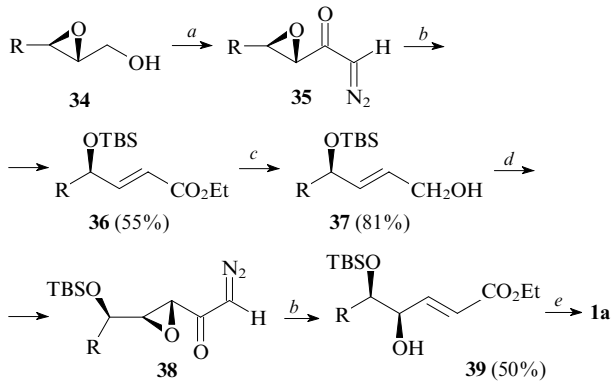
Scheme 3



R = n-$C_{11}H_{23}$; (*a*) n-$C_{11}H_{23}MgBr$, $Li_2CuCl_4$, THF, −40 → 80 °C; (*b*) $CH_2(CO_2Et)_2$, EtONa, EtOH, 60 °C; (*c*) $MgCl_2 \cdot 6H_2O$, $MeC(O)NMe_2$, Δ, 4 h; (*d*) DDQ, $CH_2Cl_2$, $H_2O$.

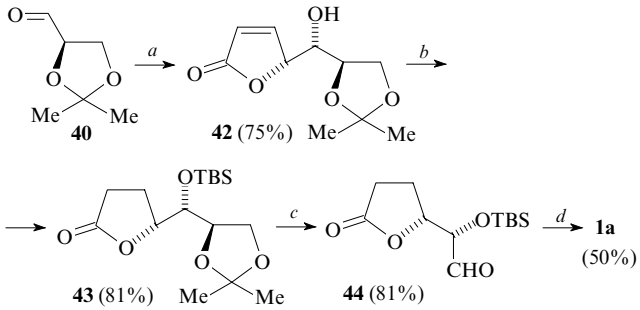
An original method for the synthesis of muricatacin **1a** was reported by van Aar *et al.*[19] The starting epoxy alcohol **34** obtained by the Sharpless epoxidation of the corresponding allyl alcohol was converted by conventional methods

into homochiral diazo derivative **35** photolysis of which gives α,β-unsaturated ester **36** of high enantiomeric purity. The iteration of this sequence of transformations for allylic alcohol **37** *via* diazo compound **38** gave unsaturated ester **39**, a precursor of butanolide **1a**.



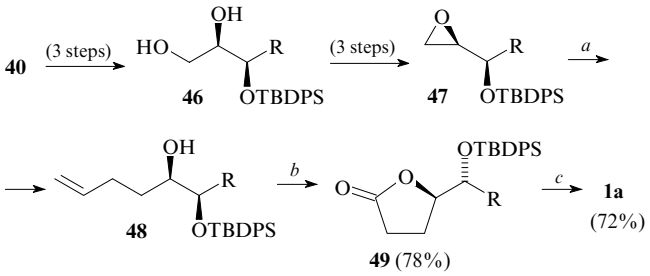
R = n-$C_{12}H_{25}$; (*a*) (1) DMSO, $(COCl)_2$, diisopropylethylamine (DIPEA); (2) $NaClO_2$, $NaH_2PO_4$; (3) $ClCO_2Bu^i$, $Et_3N$, $CH_2N_2$; (*b*) *hν*, TBSCl, EtOH; (*c*) diisobutylaluminium hydride (DIBAL-H); (*d*) (1) L-diethyl tartrate (L-DET), $Ti(OPr^i)_4$, TBHP; (2) $RuO_4$, $ClCO_2Bu^i$, $Et_3N$, $CH_2N_2$; (*e*) (1) $Ni(OAc)_2$, $NaBH_4$, TsOH; (2) tetrabutylammonium fluoride (TBAF).

Glyceraldehyde derivatives have also been used as the starting compounds for the synthesis of butanolides **1a** and **1b**. Thus diastereoselective coupling of (*R*)-(+)-aldehyde **40** with silyloxyfuran **41** yielded lactone **42**.[20] Using a standard route involving the formation of saturated lactone **43**, compound **42** was converted into aldehyde **44**, which was introduced in the Wittig reaction with phosphorane **45**. Hydrogenation of the unsaturated product thus formed and removal of the silyl protection completed the synthetic route to lactone **1a**. (*S*)-Glyceraldehyde was converted into enantiomer **1b** in a similar way.[20]



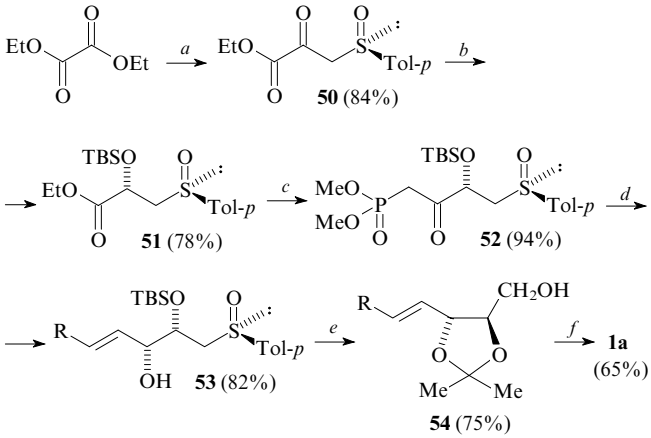
(*a*) 2-*tert*-butyldimethylsilyloxyfuran (**41**), $F_3B \cdot OEt_2$; (*b*) (1) $H_2$, Pd/C; (2) TBSCl, imidazole; (*c*) (1) 70% AcOH; (2) $NaIO_4$ (aq.), $CH_2Cl_2$; (*d*) (1) n-$C_{10}H_{21}CH{=}PPh_3$ (**45**), THF; (2) $H_2$, Pd/C; (3) $F_3B \cdot OEt_2$, $CH_2Cl_2$.

Another version of using (*R*)-(+)-glyceraldehyde derivative **40** in a rather simple synthesis of compound **1a** is based on the transformation of diol **46** obtained from aldehyde **40** into epoxide **47**. The regioselective coupling of epoxide **47** with allylmagnesium bromide affords alcohol **48**.[21] Ozonolysis of the latter and desilylation of product **49** lead to butanolide **1a**.



R = n-$C_{12}H_{25}$; TBDPS is *tert*-butyldiphenylsilyl; (*a*) AllMgBr, CuBr, −40 → 20 °C; (*b*) $O_3$, MeOH, NaOH, −15 °C; (*c*) TBAF, THF, 20 °C.

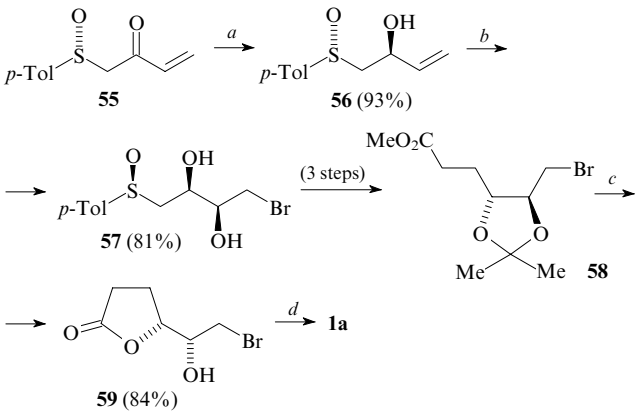
The synthesis of muricatacin **1a** proposed by Solladie *et al.*[22] is based on coupling of homochiral methyl (*R*)-*p*-tolyl sulfoxide with diethyl oxalate, resulting in sulfinyl derivative **50**. Diastereoselective reduction of the carbonyl group in **50** (*de* 92%) followed by protection of the OH group by silylation yields ether **51**, which is converted into phosphonate **52**. Compound **52** undergoes the Wittig reaction with undecanal. Treatment of the intermediate conjugated ketone with DIBAL-H results in diastereoselective formation of allylic alcohol **53**. The subsequent synthetic steps include transformation of the diol system into the acetonide, the Pummerer reaction of the *p*-toluenesulfinate group and hydride reduction of the product to give hydroxy ketal **54**. This was converted into muricatacin **1a** by conventional methods in 27% overall yield (in relation to diethyl oxalate).



R = n-$C_{10}H_{21}$; *p*-Tol = 4-$MeC_6H_4$; (*a*) (*R*)-*p*-TolS(O)Me, lithium diisopropylamide (LDA), THF, −78 °C; (*b*) (1) DIBAL-H, THF; (2) TBSCl, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), $CH_2Cl_2$; (*c*) $(MeO)_2P(O)Me$, $Bu^nLi$, THF; (*d*) (1) n-$C_{10}H_{21}CHO$, $Cs_2CO_3$, $Pr^iOH$; (2) DIBAL-H, $ZnI_2$, −78 °C; (*e*) (1) TBAF; (2) $(MeO)_2CMe_2$; (3) $Ac_2O$; (4) $LiAlH_4$; (*f*) (1) DMSO, $(COCl)_2$, $Et_3N$; (2) $Ph_3P{=}CHCO_2Me$; (3) $H_2$, Pd/C; (4) TsOH, THF, $H_2O$.

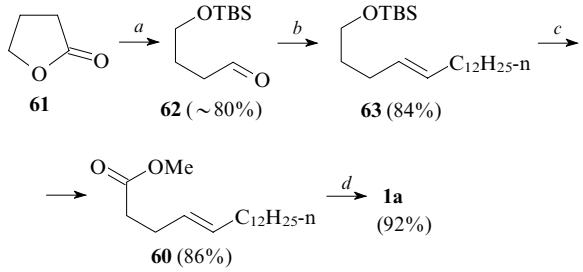
Yet another example of using optically active sulfoxide in the synthesis of muricatacin **1a** is known.[23] It is based on diastereoselective hydride reduction of available homochiral keto sulfoxide **55** and stereoselective bromohydroxylation of the allylic alcohol **56** obtained by treatment of **55** with *N*-bromosuccinimide (NBS). Dihydroxy sulfoxide **57** thus formed was converted into ester **58** using the

expedients similar to those described above. Acid hydrolysis of ester **58** was accompanied by deketalization to give bromohydrin **59**. By conventional procedure (*via* the corresponding epoxide), this product was converted into butyrolactone **1a**.



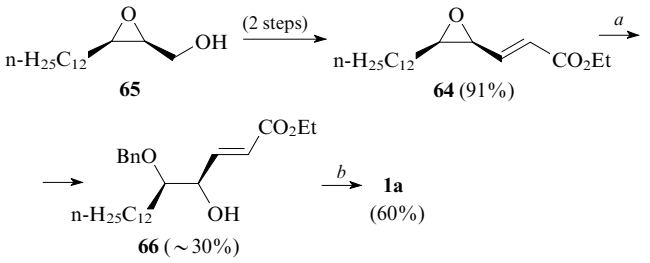

(*a*) DIBAL-H, THF, −78 °C; (*b*) NBS, $H_2O$, PhMe; (*c*) 10-camphorsulfonic acid (CSA), MeOH; (*d*) (1) $Ag_2O$, MeCN; (2) n-$C_{11}H_{23}MgBr$, $Li_2CuCl_4$, −78 → 20 °C, 36 h

A short route to muricatacin **1a** with the Sharpless asymmetric dihydroxylation of unsaturated ester **60** as the key step has been described.[24] First, butyrolactone **61** was converted by conventional procedures into silyloxybutyraldehyde (**62**), which was then olefinated according to Wittig–Schlosser with tridecylphosphorane. The process occurred stereoselectively and the product **63** was subjected to the Jones oxidation to give *trans*-configured unsaturated ester **60**, the key compound in the synthesis of butanolide **1a**. An obvious advantage of this method is small number of steps and high overall yield of the target product (43%).




(*a*) (1) DIBAL-H; (2) TBSCl, imidazole; (*b*) n-$C_{13}H_{27}Ph_3P^+Br^-$, $Bu^sLi$, −78 °C; (*c*) (1) $CrO_3$, $H_2SO_4$; (2) CSA, MeOH; (*d*) AD-mix-β.

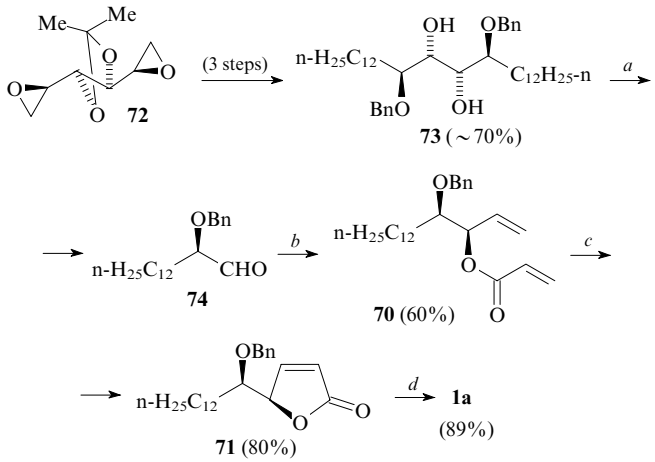
In yet another method for the synthesis of muricatacin **1a**, regio- and stereospecific opening of the oxirane ring of substituted epoxide **64** in the presence of a Lewis acid is the key step.[25] Epoxide **64** was prepared from propargyl alcohol *via* epoxy alcohol **65**. Unsaturated ester **66** was converted by conventional methods into the required butanolide **1a**.




(*a*) (1) 3,4-$(MeO)_2C_6H_3CH_2OH$, $F_3B\cdot OEt_2$, $Et_2O$; (2) NaH, BnBr, DMF; (3) DDQ, $CH_2Cl_2$, $H_2O$; (*b*) (1) $Ni(OAc)_2$, $NaBH_4$, EtOH; (2) TsOH, PhH; (3) $H_2$, Pd/C, EtOH.

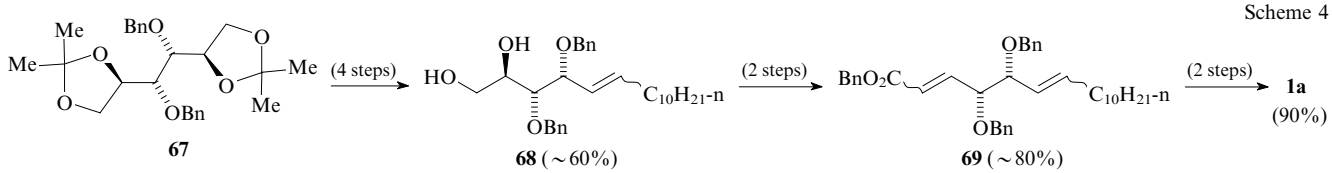
An enantioselective synthesis of butanolide **1a** from readily available D-mannitol has been described.[26] The starting compound was converted to diacetonide **67**, its selective hydrolysis followed by oxidative degradation of the resulting diol into aldehyde and olefination gave derivative **68**. A similar reaction sequence starting from diol **68** results in ester **69**, which is transformed into muricatacin **1a** in two steps (Scheme 4).

Spanish chemists[27] synthesized muricatacin **1a** using an intramolecular metathesis reaction. The key step is the transformation of allylic acrylate (**70**) into butenolide **71** in the presence of the Grubbs catalyst [benzylidenebis(tricyclohexylphosphine)dichlororuthenium]; the synthetic route is completed by hydrogenation of **71** into lactone **1a**. The homochiral diene **70** was synthesized from bis-oxirane **72**. By treatment with 2 equivalents of undecylmagnesium bromide in the presence of CuI and subsequent manipulations with the protective groups, bisoxirane **72** was transformed into diol **73**, which was subjected to oxidative degradation to aldehyde **74**. The diastereoselective reaction of compound **74** with vinylmagnesium bromide yielded intermediate allylic alcohol, which was then acylated with acryloyl chloride.

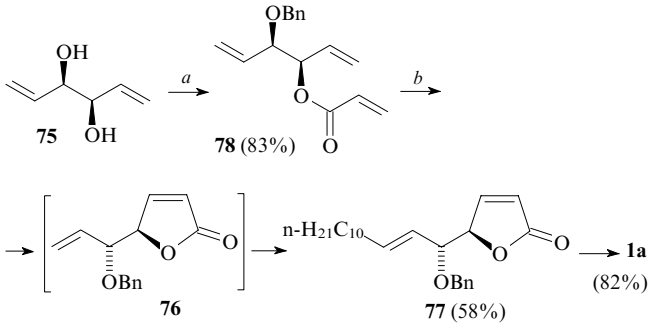



(*a*) $Pb(OAc)_4$, PhH; (*b*) (1) $CH_2{=}CHMgBr$, $MgBr_2$, $CH_2Cl_2$, $Et_2O$; (2) $CH_2{=}CHC(O)Cl$, 4-dimethylaminopyridine (DMAP), $CH_2Cl_2$; (*c*) the Grubbs catalyst, PhMe; (*d*) Pd/C, EtOH.

Scheme 4

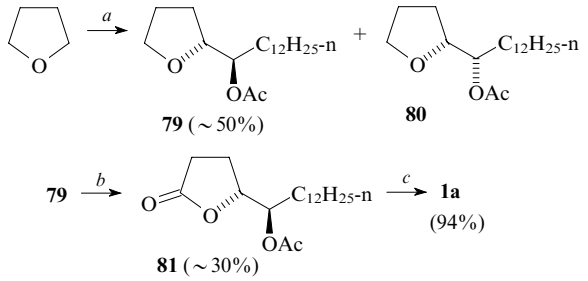


A similar approach was used by Quinn *et al.*[28] to prepare muricatacin **1a** from diol **75**.[29] A chemo- and stereoselective tandem intra- and intermolecular metathesis in which butenolides **76** and then **77** are formed from allylic acrylate **78** is the key issue in this sequence of transformations. This is an example of efficient one-pot process.



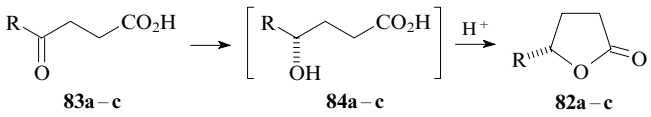

(*a*) (1) $Bu^n_2SnO$, $Bu^n_4NI$, PhH (aq.), BnBr; (2) $CH_2{=}CHC(O)Cl$, DMAP, $CH_2Cl_2$; (*b*) the Grubbs catalyst, PhMe.

An original approach to the synthesis of butanolide **1a** was proposed by Japanese chemists.[30] This is based on α-hydroxyalkylation of tetrahydrofuran with an aldehyde in the presence of the $Et_3B-Bu^tOOH$ system (a reaction discovered by the authors). Diastereoselective reaction of THF with tridecanal, which apparently followed a radical mechanism, gave a mixture of diastereomeric alcohols in 64% yield (*de* 30%), which were isolated as acetates **79** and **80**. Racemate **79** with the appropriate configuration was then subjected to enzymatic resolution into enantiomers. The scalemic product thus obtained (*ee* ~80%) was oxidized by a modified Sharpless procedure to lactone **81**, which is a direct precursor of the target butanolide **1a**.



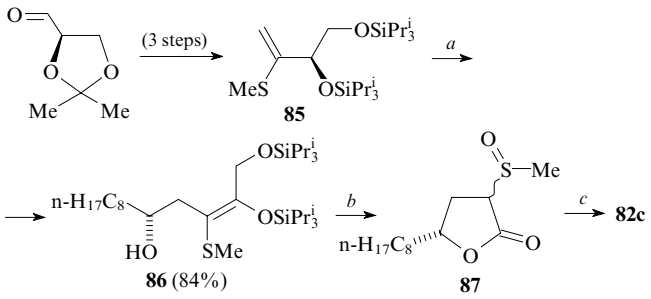

(*a*) (1) n-$C_{12}H_{25}CHO$, TBHP, $Et_3B$ (6 equiv.), $CH_2Cl_2$; (2) $Ac_2O$, $Et_3N$, $CH_2Cl_2$; (*b*) (1) porcine liver esterase (PLE), MeCN, phosphate buffer; (2) $RuCl_3 \cdot n\,H_2O$, $NaHCO_3$, $NaIO_4$, $CCl_4$, MeCN, $H_2O$; (*c*) (1) $K_2CO_3$, EtOH; (2) pyridinium *p*-toluenesulfonate (PPTS), PhH, Δ.

Three representatives of γ-substituted butyrolactones[31] differing in the side chain length, namely, pheromone of the beetle *Trogoderma glabrum* (**82a**), sex pheromone of the rice weevil *Sitophilus zeamais* (**82b**), defensive secretion of the rove beetle *Bledius mandibularis* (**82c**), were obtained by a common route. The key step was enantioselective reduction (*ee* > 98%) of keto acids **83a–c** to hydroxy acids **84a–c** under the action of baker's yeast (pH 6–7, 25–28 °C, 2 days).




R = Et (**a**), n-$C_5H_{11}$ (**b**), n-$C_8H_{17}$ (**c**).

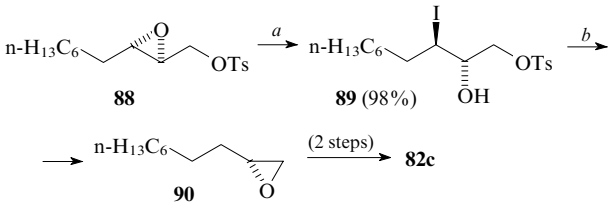
Lactone **82c** with high optical purity was also obtained in 68% yield using the enantioselective reaction of nonanal with homochiral vinyl sulfide **85** synthesized from an accessible D-glyceraldehyde acetonide.[32]




(*a*) n-$C_8H_{17}CHO$, $Me_2AlCl$; (*b*) (1) TBAF; (2) $NaIO_4$, THF, $H_2O$, MeOH; (*c*) Ni/Ra.

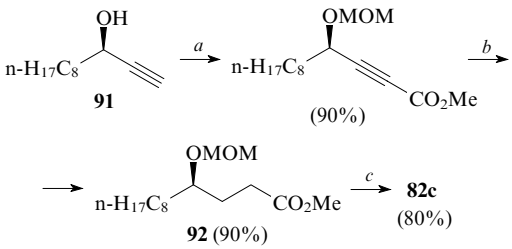
This Lewis acid-catalyzed reaction furnishes compound **86**, which was converted into the target product **82c** by conventional procedures *via* diastereomeric lactones **87**.

Another approach to the asymmetric synthesis of lactone **82c** is based on regio- and stereoselective opening of optically active tosyloxy epoxide **88** by treatment with lithium iodide in acetonitrile.[33] The resulting iodohydrin **89** was first converted into epoxide **90**, which then gave butanolide **82c**.[34]



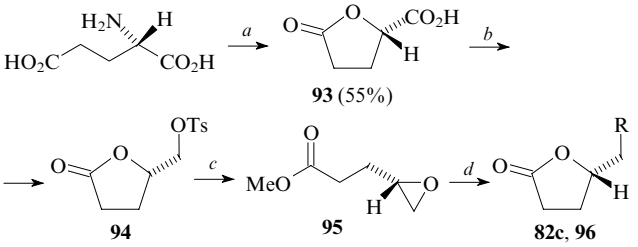

(*a*) LiI, MeCN; (*b*) (1) $Bu^n_3SnH$, azobis(isobutyronitrile) (AIBN), PhH; (2) $K_2CO_3$, MeOH.

Yet another short route to dodecanolide **82c**[35] consists of transformation of alkynol **91** with high enantiomeric purity obtained by a reported procedure[36] into ester **92**. Deprotection of the ester is accompanied by lactonization into the target butanolide **82c**.



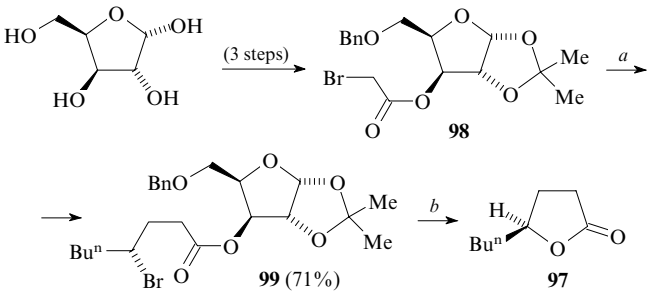

(*a*) (1) Methoxymethyl chloride (MOMCl), DIPEA, $CH_2Cl_2$; (2) $Bu^nLi$; (3) $ClCO_2Me$, THF; (*b*) $H_2$, Pd/C, EtOAc; (*c*) TsOH, MeOH.

The synthesis of butanolide **82c** from L-glutamic acid has been reported.[37] Diazotization of the acid smoothly yields lactone **93**,[38] which was converted in two steps into tosylate **94** without epimerization of the chiral centre. This product reacts with MeONa to give epoxy ester **95**, which is then coupled with heptylmagnesium bromide. The use of propylmagnesium bromide instead of heptylmagnesium bromide affords octanolide **96** representing a secretion of some parasite wasps considered as a tool for biological control of their population.



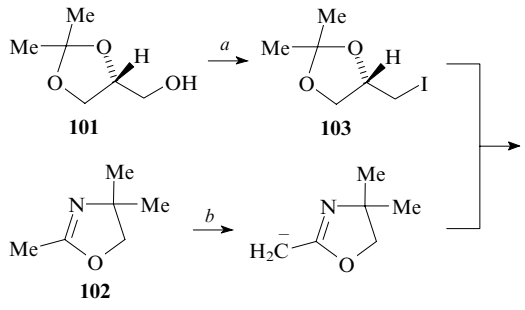

R = $Pr^n$ (**96**), n-$C_7H_{15}$ (**82c**); (*a*) $NaNO_2$, HCl (aq.); (*b*) (1) $H_3B{\cdot}SMe_2$; (2) TsCl, Py; (*c*) NaOMe, MeOH; (*d*) RMgBr.

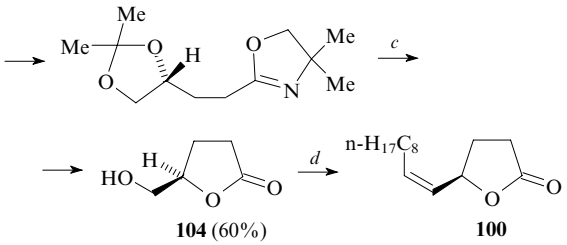
Note that the enantiomer of octanolide **96**, natural butanolide **97**, is responsible for the taste and odour of some fruits. This product was synthesized by asymmetric version of the Kharash reaction of homochiral bromoacetate **98**.[39] Although the induced centre is remote from the chiral inductor, D-xylose residue, the product **99** had a rather high diastereomeric purity (*de* 85%). γ-Brominated ester **99** was then converted into lactone **97** with optical purity of 74%.




(*a*) Hex-1-ene, $BEt_3$, $O_2$, $Eu(OTf)_3$, $CH_2Cl_2$; (*b*) (1) $H_2O_2$, LiOH; (2) $K_2CO_3$, THF (aq.).

Yet another representative of the considered family of γ-substituted natural butyrolactones is the sex pheromone of the beetle *Popillia japonica* (**100**) used in pest control traps. The synthesis of compound **100** from commercially available dioxolane **101** and oxazoline **102** has been described.[40] The former was coupled into iodide **103** and condensed with the oxazoline anion. Hydrolysis of the

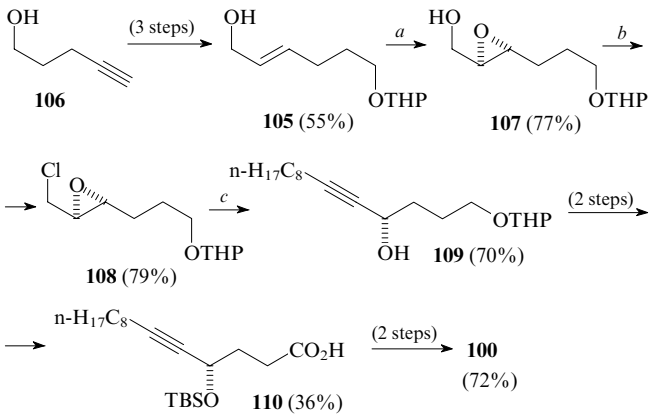



THP is tetrahydropyran-2-yl; (*a*) $I_2$, $Ph_3P$, imidazole, $Et_2O$; (*b*) $Bu^nLi$, THF; (*c*) $H^+$, MeOH; (*d*) (1) DMSO, $(COCl)_2$, $Et_3N$; (2) n-$C_8H_{17}CH{=}PPh_3$.

intermediate product thus obtained gave optically pure hydroxy lactone **104**, which was converted into the target butanolide **100** (overall yield 33%) by a reported procedure.[41]

The last of the published methods for the synthesis of butanolide **100** is based on asymmetric epoxidation of allylic alcohol **105** obtained from pent-4-ynol (**106**) in three steps.[42] Epoxide **107** was converted into chloroepoxide **108**, which was first treated with lithium in liquid ammonia and then (one-pot procedure) with bromooctane. The product **109** thus formed was subjected to conventional procedures including protection, oxidative transformation of the primary alcohol into acid **110** and partial hydrogenation of the triple bond to give the target butanolide **100**.

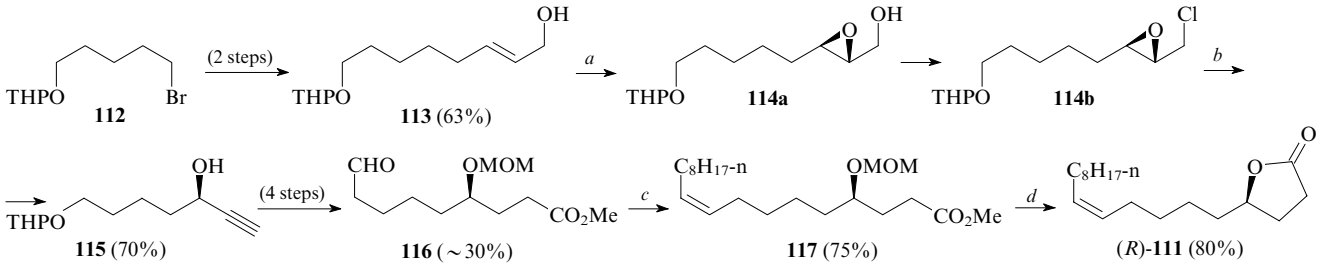



(*a*) (−)-DET, $Ti(OPr^i)_4$, cumene hydroperoxide, $CH_2Cl_2$; (*b*) $CCl_4$, $Ph_3P$, $NaHCO_3$; (*c*) (1) Li, $NH_3$, $Fe(NO_3)_2$ (cat.), THF; (2) n-$C_8H_{17}Br$.

The same authors used a similar strategy for the synthesis of butanolide **111**,[42] which is the sex pheromone of the female butterfly *Janus integer*, an orchard crop pest. The accessible bromide **112** and propargyl alcohol were used as the starting compounds (Scheme 5) to prepare allylic alcohol **113**, which was then subjected to the Sharpless asymmetric epoxidation to give optically active oxirane **114a**. The oxirane was converted into chloroepoxide **114b** and then into acetylenic alcohol **115**, which was used to prepare aldehyde **116** by conventional methods. The *Z*-stereoselective olefination of **116** with an appropriate phosphorane resulted in ester **117**, which gave the target butanolide (*R*)-**111** with high enantiomeric purity after deprotection.

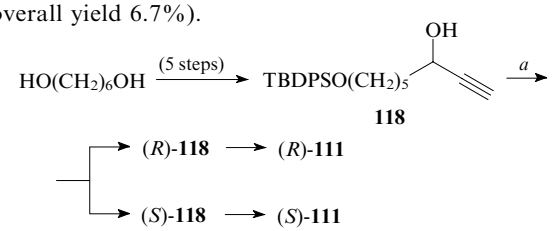
For the synthesis of both enantiomers of butanolide **111**, which allowed determining the absolute configuration of the natural pheromone, a chemo-enzymatic strategy was used.[43] In the key step of this transformation, racemic acetylenic alcohol (±)-**118** obtained from hexane-1,6-diol was subjected to AH-S lipase-catalyzed asymmetric acety-

Scheme 5



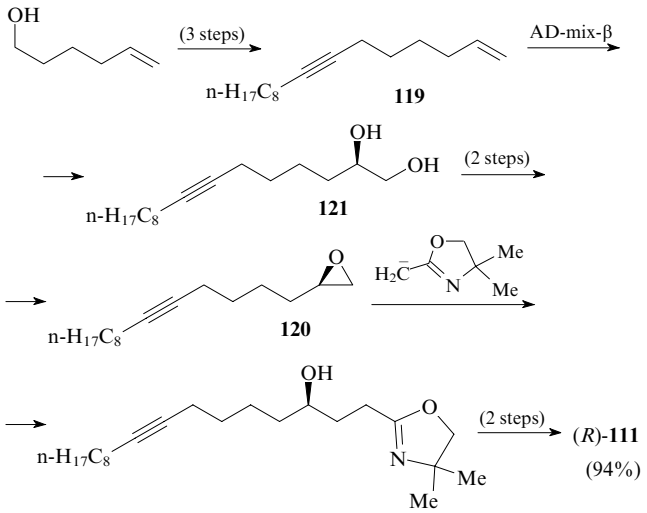

(*a*) (−)-DET, $Ti(OPr^i)_4$, cumene hydroperoxide, $CH_2Cl_2$; (*b*) Li, $NH_3$, $Fe(NO_3)_2$ (cat.), THF; (*c*) n-$C_9H_{19}P^+Ph_3Br^-$, THF, hexamethylphosphotriamide (HMPA); (*d*) TsOH, MeOH.

lation. This yielded enantiomers (*R*)- and (*S*)-**118** with *ee* 96% and 93%, respectively. The subsequent transformations of stereoisomers **118** using methods similar to those indicated in the previous scheme afforded natural butanolide (*R*)-**111** (overall yield 5.1%) and its antipode (*S*)-**111** (overall yield 6.7%).

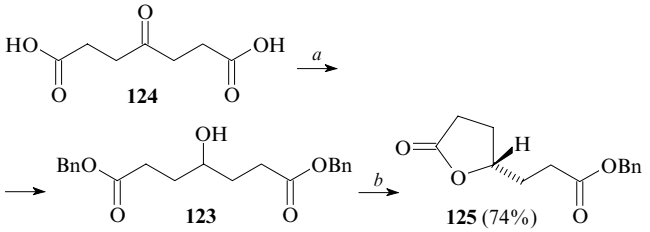



(*a*) (1) AH-S lipase, $CH_2{=}CHOAc$; (2) chromatography; (3) hydrolysis.

Yet another approach[44] to the synthesis of lactone **111** is based on the use of two asymmetric processes: the Sharpless dihydroxylation of terminal alkene **119** and the Jacobsen kinetic resolution of the products of hydrolysis of epoxide **120** that allowed increasing the insufficient optical purity of diol **121**. Scalemic diol **121**, which initially had 87% enantiomeric excess, was thus enriched to *ee* 96%. Epoxide **120** obtained from **121** was converted into target lactone (*R*)-**111** *via* the oxazoline precursor.

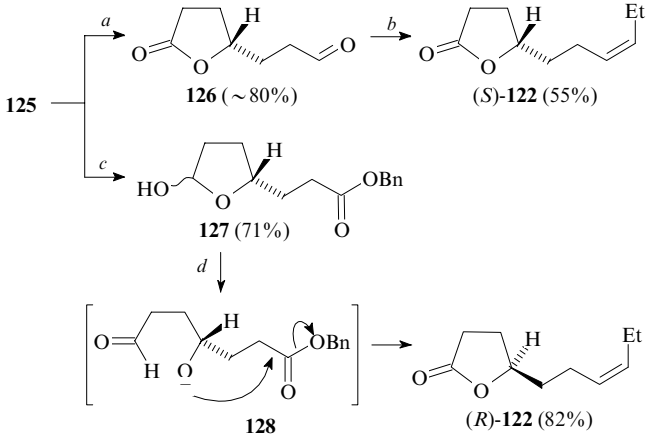



(*R*)-(+)-γ-Jasmolactone [(*R*)-**122**] and its enantiomer (*S*)-**122**, which is a minor component of the natural product, were synthesized using lipase-catalyzed desymmetrization of alcohol **123** as the key step.[45,46] Alcohol **123** was prepared from commercially available ketopimelic acid (**124**). Treatment of alcohol **123** with lipase gave lactone (*S*)-**125** (*ee* 95%) containing an ester group in the side chain.




(*a*) (1) BnBr, $Cs_2CO_3$, DMF–MeOH, pH 7; (2) $NaBH_4$, $Et_2O$, MeOH; (*b*) PPL (pig pancreatic lipase), $Et_2O$.

Lactone **125** was converted into aldehyde derivative **126** almost without epimerization**.** Olefination of the latter afforded a mixture of *Z*- and *E*-isomers (85 : 15 ratio); the desired *Z*-configured product, (*S*)-**122**, was isolated from the mixture by chromatography (*ee* 92%). Enantiomer (*R*)-**122** was synthesized by selective reduction of lactone (*S*)-**125** that did not affect the ester group.

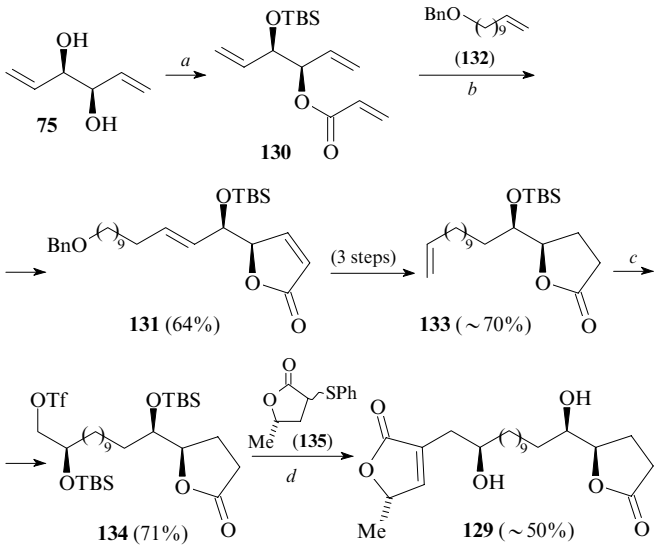



(*a*) (1) Pd/C, $H_2$; (2) $H_3B{\cdot}SMe_2$, THF, 20 °C; (3) pyridinium chlorochromate (PCC), $CH_2Cl_2$; (*b*) $Pr^nPh_3P^+Br^-$, lithium hexamethyldisilazide (LiHMDS), THF; (*c*) DIBAL-H, THF; (*d*) $Pr^nPh_3P^+Br^-$, NaH, DMSO.

In the presence of an excess of the alkylidenephosphorane as a base, lactonization accompanied by inversion of the chiral centre in compound **127** and olefination of intermediate **128** takes place; ultimately this afforded (*R*)-(+)-jasmolactone [(*R*)-**122**] containing 11% of *E*-isomer (overall yield 34%).

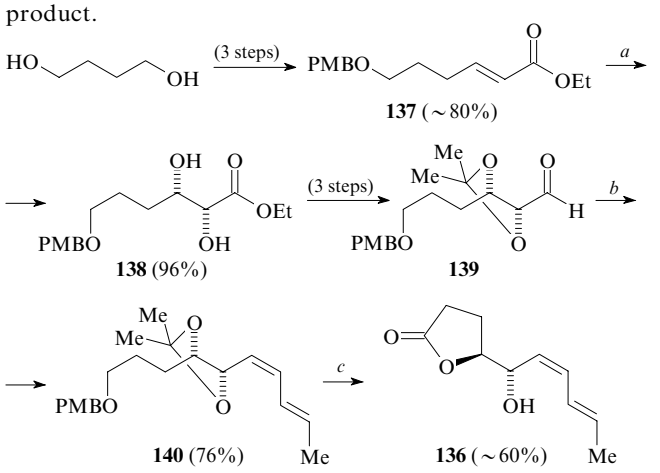
Rollicosin (**129**) containing two terminal γ-lactone fragments shows antitumour activity. It was recently synthesized in 12 steps in 9% overall yield.[47] The key step included tandem ring-closing cross metathesis (one-pot) reactions to transform unsaturated ester **130** into the butenolide fragment and the side chain of lactone **131** (reaction with alkene

**132**). Lactone **131** converted over three simple steps into butanolide **133**, which was subjected to asymmetric dihydroxylation. The coupling of triflate derivative **134** with sulfide **135** and subsequent conventional reactions of the resulting adduct produced the target product **129**.




(*a*) (1) TBSCl (1 equiv.), imidazole, $CH_2Cl_2$; (2) $CH_2{=}CHC(O)Cl$, DIPEA, $CH_2Cl_2$; (*b*) the Grubbs catalyst, PhH; (*c*) (1) AD-mix-β; (2) $Tf_2O$, 2,6-lutidine; (3) TBSOTf; (*d*) (1) KHMDS, THF; (2) *m*-chloroperoxybenzoic acid (mCPBA), $CH_2Cl_2$; (3) PhMe, Δ; (4) AcCl, MeOH.

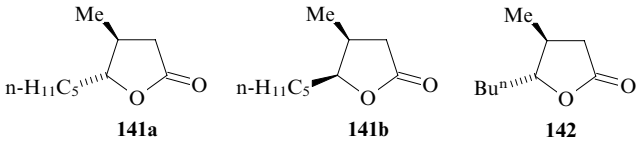
Recently, enantioselective synthesis of sapinofuranone B1 (**136**), previously unknown metabolite of the fungi *Acremonium strictum*, has been carried out.[48] Butanediol served as the starting compound being converted into ester **137** by conventional methods. On asymmetric hydroxylation of ester **137**, diol **138** was formed in high yield (*ee* 97%). This was converted into aldehyde **139** *via* the acetonide; olefination of **139** gave diene **140**. The removal of *p*-methoxybenzyl protection and the subsequent oxidative transformations of the resulting alcohol furnished the final product.



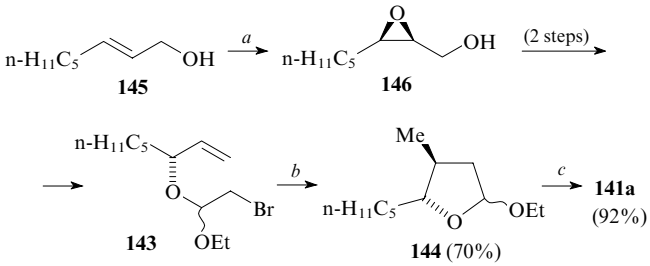

(*a*) $OsO_4$ (0.4 mol.%), **5a** (1 mol.%), $K_2CO_3$, $K_3Fe(CN)_6$, $MsNH_2$, $Bu^tOH$ (aq.); (*b*) $MeCH{=}CHCH_2Ph_3P^+Br^-$, LiHMDS, THF; (*c*) (1) DDQ, $CH_2Cl_2$ (aq.); (2) DMSO, $(COCl)_2$, $Et_3N$; (3) $NaClO_2$, DMSO, $NaH_2PO_4$; (4) HCl (cat.), MeOH.

## 2. Disubstituted butyrolactones

Compounds **141a**,**b** and **142** have been called cognac and whisky lactones, respectively, as they largely determine the taste and bouquet of these alcoholic beverages.

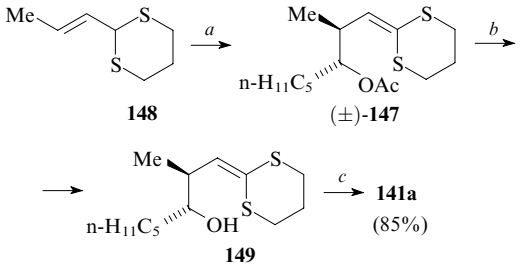



The enantioselective synthesis of natural (+)-(3*S*,4*R*)-lactone **141a** was carried out recently using radical cyclization of bromoacetal **143** to give acetal **144** as the key step.[49] Allylic alcohol **145** and chiral epoxide **146** served as precursors of bromoacetal **143**.



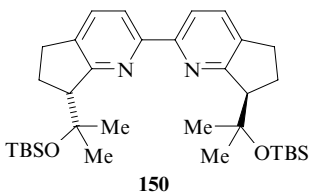

(*a*) (−)-DET, $Ti(OPr^i)_4$, cumene hydroperoxide, $CH_2Cl_2$; (*b*) $Bu^n_3SnH$, PhH, Δ; (*c*) (1) AcOH (aq.); (2) PCC, $CH_2Cl_2$.

A chemo-enzymatic strategy has also been used for enantioselective preparation of lactone **141a**.[50] First, lipase-catalyzed hydrolysis of racemic acetates (±)-**147** was carried out, which were obtained by coupling of dithioacetal **148** with hexanal and acetylation of the intermediate alcohols. The optically active product (3*S*,4*R*)-**149** (*ee* > 95%) thus obtained was smoothly converted into lactone **141a** on refluxing in aqueous methanol in the presence of mercuric chloride.

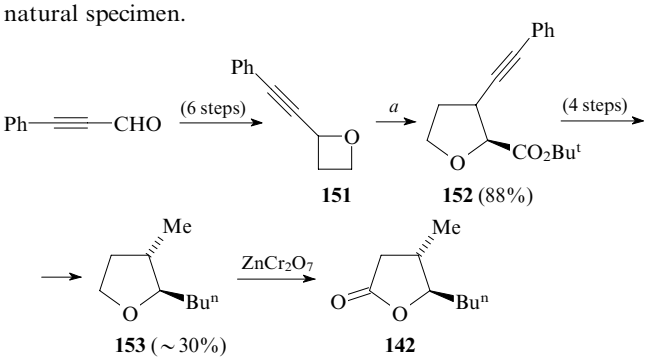



(*a*) (1) $Bu^nLi$, THF, n-$C_5H_{11}CHO$; (2) $Ac_2O$, $Et_3N$, DMAP (cat.), $CH_2Cl_2$; (*b*) lipase MY, DMF, phosphate buffer (pH 7.5); (*c*) $HgCl_2$, MeOH (aq.), Δ.

The enantioselective synthesis of *trans*-whisky lactone **142** having the same configuration as butanolide **141a** was accomplished by enantiospecific expansion of the oxetane ring in the presence of a catalyst based on a copper salt and chiral ligand **150**.[51]

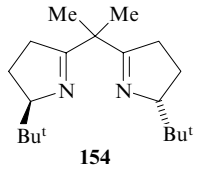


Substituted tetrahydrofuran **152** obtained from oxetane **151** by conventional methods including the formation of a methyl group from the alkynyl fragment was converted into compound **153**. This was oxidized to give target lactone **142**, which almost does not differ in the optical rotation from the natural specimen.

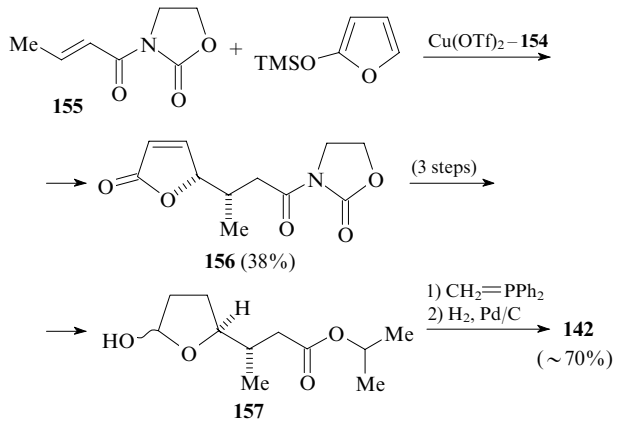



(*a*) $N_2CHCO_2Bu^t$, CuOTf – **150** (1 mol.%).

A shorter route to butanolide **142** is based on the enantioselective Michael reaction in the presence of a chiral catalyst based on ligand **154**.[52]

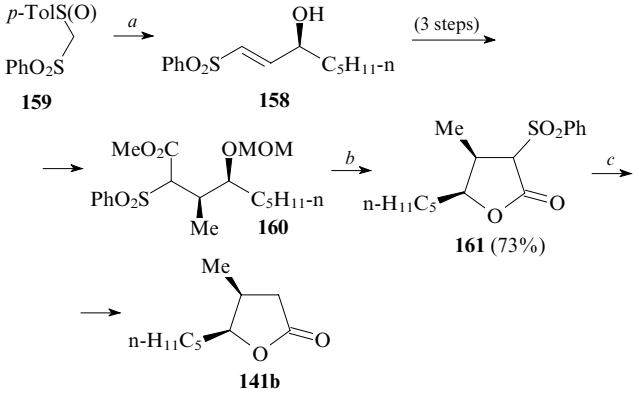



Under these conditions, α-trimethylsilyloxyfuran adds at the double bond of amide **155** to form butenolide **156** (*ee* 95%), which is subjected to traditional reactions involving the formation of lactol **157** being converted into the desired product **142** with a high enantiomeric purity.



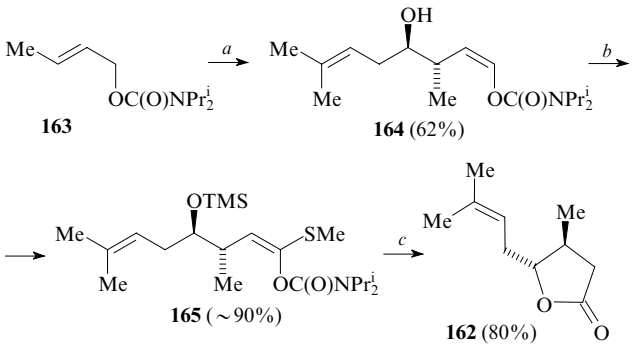

TMS is trimethylsilyl.

The synthesis of (3*S*,4*S*)-*cis*-lactone **141b** was performed using lipase-catalyzed enantioselective acetylation in order to increase the optical purity of alcohol **158** (*ee* 28%) resulting from coupling of homochiral sulfoxide **159** with heptanal.[53] The allyl alcohol **158** (*ee* ~98%) obtained in this reaction was converted by conventional methods into ester **160**, which lactonized on treatment with an acid giving rise to a sulfonyl derivative **161**. In the final step, compound **161** was desulfonylated under the action of sodium amalgam.



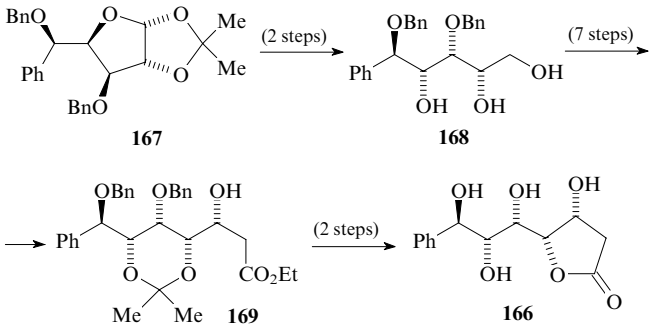

(*a*) (1) n-$C_6H_{13}CHO$, piperidine, MeCN; (2) PS lipase, $CH_2{=}CHOAc$, molecular sieves (MS), $Pr^i_2O$; (*b*) $H_2SO_4$, $Et_2O$, $H_2O$; (*c*) Na/Hg, $Na_2HPO_4$, MeOH.

A component of the pheromone of sugarcane pest *Eldana saccharina*, (3*R*,4*S*)-(+)-eldanolide (**162**), was prepared from carbamate **163**.[54] Product **164** (*ee* 92%) formed upon (−)-spartein-induced enantioselective coupling of compound **163** with 4-methylpent-3-enal was converted into vinyl sulfide **165**; its acid hydrolysis yielded the target butanolide **162**.

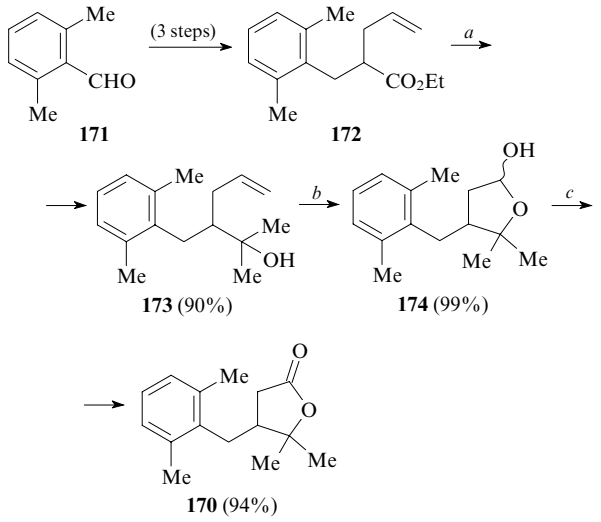



(*a*) (1) $Bu^nLi$, (−)-spartein, cyclohexane; (2) $Ti(OPr^i)_4$; (3) $Me_2C{=}CHCH_2CHO$, HCl (aq.); (*b*) (1) TMSCl, $Et_3N$, $CH_2Cl_2$; (2) $Bu^nLi$, tetramethylethylenediamine (TMEDA); (3) MeSSMe; (*c*) MsOH, MeOH.

(3*R*,4*R*)-(+)-Cardiobutanolide (**166**) isolated from plants *Goniothalamus cardiopetalus*[55] exhibits cytotoxic properties. This compound was synthesized from acetonide **167** obtained from D-glucose. Cleavage of acetonide **167** affords triol **168**; the introduction of a two-carbon fragment into this molecule by standard procedures results in ester **169**. After deprotection, the target butanolide **166** was obtained.



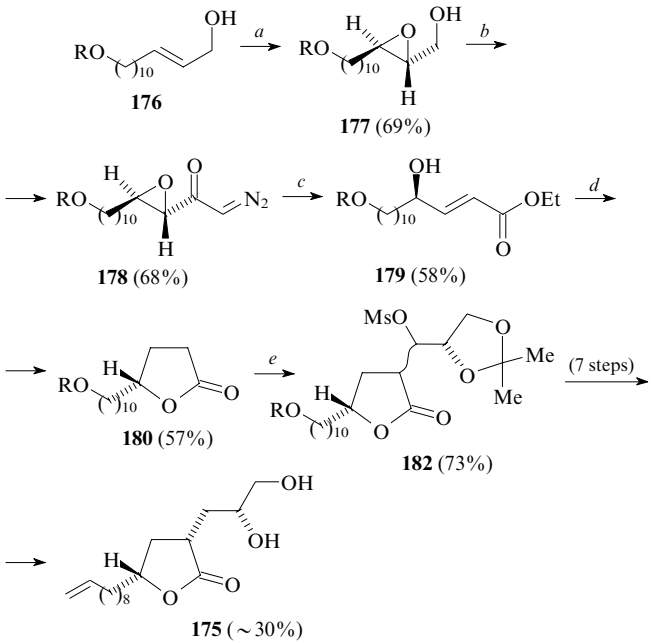
A natural butanolide, solafuranone (**170**), having 3*R*-configuration was isolated from a Taiwan plant used since ancient times in folk medicine to treat breast cancer and as an analgetic. Recently the first synthetic route to racemate (±)-**170** has been proposed [56]




(*a*) MeMgI, $Et_2O$; (*b*) (1) $O_3/O_2$, $CH_2Cl_2$, MeOH, −70 °C; (2) $Me_2S$; (*c*) PCC, $SiO_2$, $CH_2Cl_2$.

First, commercially available aldehyde **171** was converted into ester **172** by simple operations and **172** was further transformed into homoallylic alcohol **173** ozonolysis of which yielded lactol **174**. In the final step, lactol **174** was oxidized to butanolide **170**.

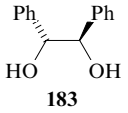
The molecule of natural α,γ-disubstituted butyrolactone rubrenolide (**175**) contains three asymmetric centres, their absolute configurations were determined by an independent synthesis.[57] The desired stereochemistry of the future centre was specified as a result of the Sharpless asymmetric epoxidation of available allylic alcohol **176**. The synthesized



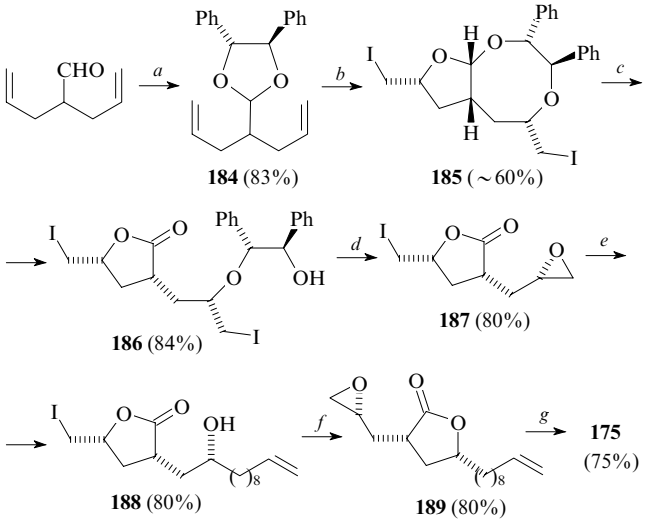

R = THP; (*a*) (−)-DET, $Ti(OPr^i)_4$, TBHP, $CH_2Cl_2$; (*b*) (1) DMSO, $(COCl)_2$, $Et_3N$; (2) $NaClO_2$; (3) $ClCO_2Bu^i$, $Et_3N$, $CH_2N_2$; (*c*) *hv*, EtOH; (*d*) $Ni(OAc)_2$, $NaBH_4$; (*e*) (1) LDA; (2) **181**, THF; (3) MsCl, Py.

epoxide **177** was then converted into diazo ketone **178**, which smoothly underwent photochemical rearrangement to afford unsaturated ester **179**. Hydrogenation of the latter is accompanied by lactonization yielding butanolide **180**. In the final step of the synthesis, butanolide **180** was coupled with (*S*)-glyceraldehyde acetonide (**181**), and the resulting disubstituted butyrolactone **182** was converted by conventional methods into the target product virtually identical to the natural compound in optical rotation.

The key step in another enantioselective synthetic route to butanolide **175** is desymmetrization of diallylacetaldehyde by acetalization with homochiral hydrobenzoin **183**.[58]




Double iodoetherification of acetal **184** obtained in this reaction with *N*-iodosuccinimide mainly resulted in stereoisomer **185**, which was purified from admixture of other isomers by chromatography. An oxidative transformation of compound **185** smoothly afforded butanolide **186**, which gave epoxide **187**. Coupling of epoxide **187** with an organocuprate reagent produced alkylation product **188**. On treatment with potash, the latter underwent translactonization accompanied by closure of the oxirane ring to give butanolide **189**, the immediate precursor of the target product.

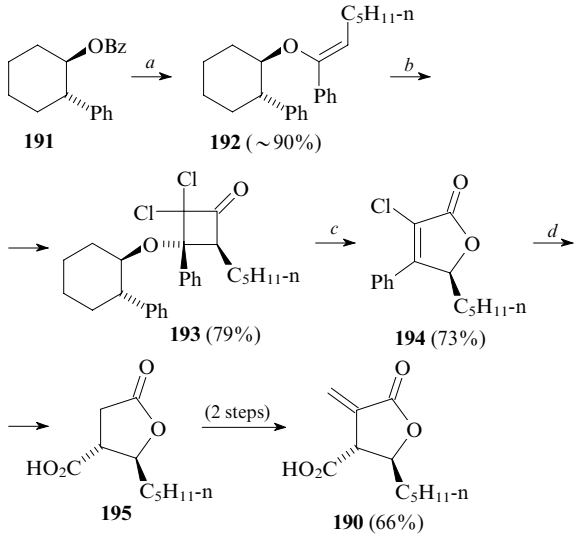



(*a*) **183**, TMSOTf, TMSOMe; (*b*) *N*-iodosuccinimide (NIS), $H_2O$; (*c*) (1) DDQ, MeCN (aq.), (2) $NaClO_2$; (*d*) (1) CAN, MeCN (aq.); (2) $K_2CO_3$; (*e*) $CH_2{=}CH(CH_2)_8MgBr$, CuI; (*f*) $K_2CO_3$, EtOAc; (*g*) $Bi(OTf)_3$, MeCN (aq.).

## 3. Trisubstituted butyrolactones

Paraconic acids are chiral trisubstituted γ-butyrolactones with a carboxyl group in the β-position. (−)-Methylenolactocin (**190**) isolated from the fungi of the *Penicillium* genus exhibits antibacterial activity with respect to gram-positive bacteria. The enantioselective synthesis of this compound was first performed starting from readily accessible homochiral (1*R*,2*S*)-phenylcyclohexanol benzoate (**191**), which stereoselectively reacted with a 1,1-dibromohexane–Zn–$TiCl_4$–TMEDA system to give *Z* enol ether **192** (Scheme 6).[59]

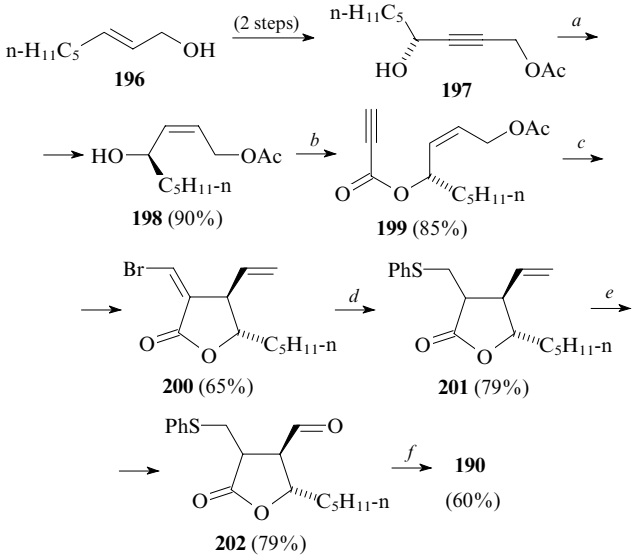
Scheme 6




(*a*) $Br_2CHC_5H_{11}$-n, Zn, $TiCl_4$, TMEDA, THF, $CH_2Cl_2$; (*b*) $Cl_3CCOCl$, Zn/Cu, $Et_2O$; (*c*) (1) mCPBA, $NaHCO_3$, $CH_2Cl_2$; (2) $Cr(ClO_4)_2$, $Me_2CO$; (*d*) (1) $H_2$, Pd/C, NaOAc, MeOH; (2) $RuCl_3$, $NaIO_4$, $CCl_4$, MeCN (aq.).

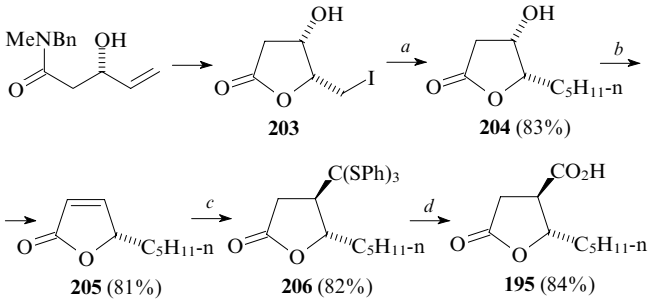
Treatment of compound **192** with dichloroketene led to crystalline cyclobutanone **193**, which was converted according to Baeyer–Villiger into α,α-dichlorolactone. Treatment of this product with chromium(II) perchlorate afforded butenolide **194**. Then lactone **194** was hydrogenated and the product was subjected to oxidative degradation to give carboxylic acid **195**. Methylenation of acid **195** afforded (−)-methylenolactocin (**190**) virtually identical to the natural compound in optical rotation.

In another enantioselective synthetic route to (−)-methylenolactocin (**190**), readily accessible allylic alcohol **196** was used as the starting compound.[60] It was converted into acetylenic alcohol **197** with high enantiomeric purity by a route similar to that shown in Scheme 5. Hydrogenation of alkyne **197** and Mitsunobu esterification of the resulting allylic alcohol **198** with propargylic acid accompanied by inversion of configuration at the asymmetric centre resulted in ester **199**, which gave butanolide **200** upon Pd(II)-catalyzed stereospecific cyclization. Using conventional methods, lactone **200** was converted *via* sulfide **201** and aldehyde **202**, into the target product **190** with nearly 100% optical purity.




(*a*) $H_2$, Ni/B, $(NH_2CH_2)_2$, EtOH; (*b*) $CH{\equiv}CCO_2H$, DEAD, $Ph_3P$, THF; (*c*) LiBr, $Pd(OAc)_2$, AcOH; (*d*) (1) Zn/Ag, MeOH; (2) $Et_3N$, PhSH THF; (*e*) $O_3$, MeOH, $CH_2Cl_2$; (*f*) (1) pyridinium dichromate (PDC), DMF; (2) $NaIO_4$, MeOH (aq.), PhH; (3) PhMe, Δ.

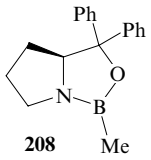
An enantioselective method for the synthesis of (−)-methylenolactocin (**190**) from accessible[61] disubstituted lactone **203** with high enantiomeric purity has been proposed.[62]




(*a*) $Bu^nMgBr$, CuBr–$Me_2S$, THF; (*b*) (1) BzCl, Py, PhH; (2) $NH_3$, MeOH; (*c*) $HC(SPh)_3$–$Bu^nLi$, THF; (*d*) HgO, $F_3B{\cdot}OEt_2$, THF (aq.).

Elongation of the side chain of lactone **203** and dehydration of product **204** obtained in these reactions yielded butenolide **205**, which was converted into acid **195** *via* trisulfenylmethyl derivative **206**. The possibility of transformation of **195** into (−)-methylenolactocin **190** has already been discussed above (see Scheme 6).

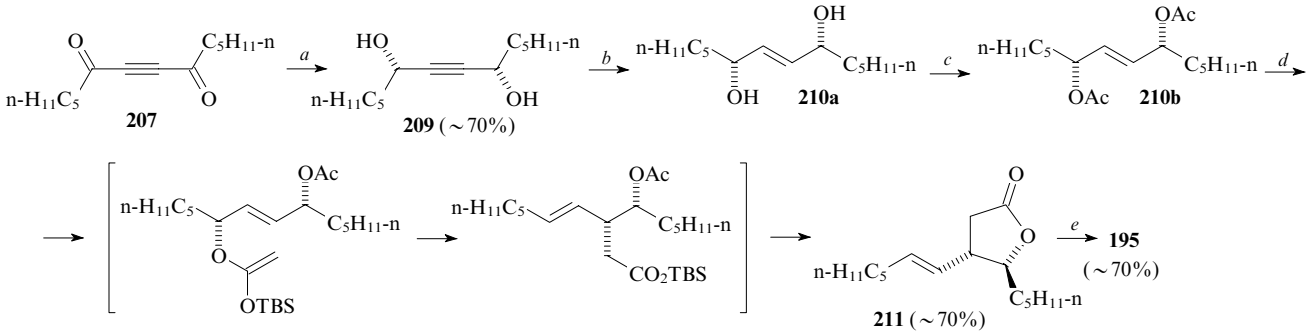
Readily accessible acetylenic diketone **207** has been recently used as the starting compound in yet another enantioselective synthesis of (−)-methylenolactocin (**190**) (Scheme 7).[63] Thus reduction of diketone **207** with borane in the presence of homochiral oxazaborolidine **208**



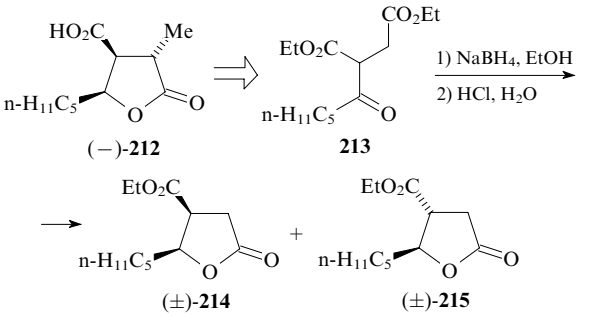

affords acetylenic diol **209** of high enantiomeric purity (*ee* >90%), which was subsequently reduced into allylic diol **210a**. The Ireland–Claisen rearrangement of diol diacetate (**210b**) smoothly furnishes butanolide **211**. By oxidative degradation of the side chain this product was converted into the immediate precursor of (−)-methylenolactocin (**190**), *viz*., carboxylic acid **195**.

(−)-Phaseolinic acid (**212**) related to (−)-methylenolactocin (**190**) is a metabolite of the fungi *Macrophomina phaseolina*. According to the scheme given below, it can be prepared by cyclization of keto ester **213** giving rise to a diastereomeric mixture (±)-**214** and (±)-**215** in a 4 : 1 ratio (overall yield 91%).[64]

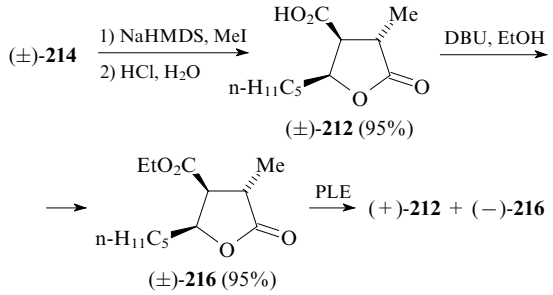
Scheme 7



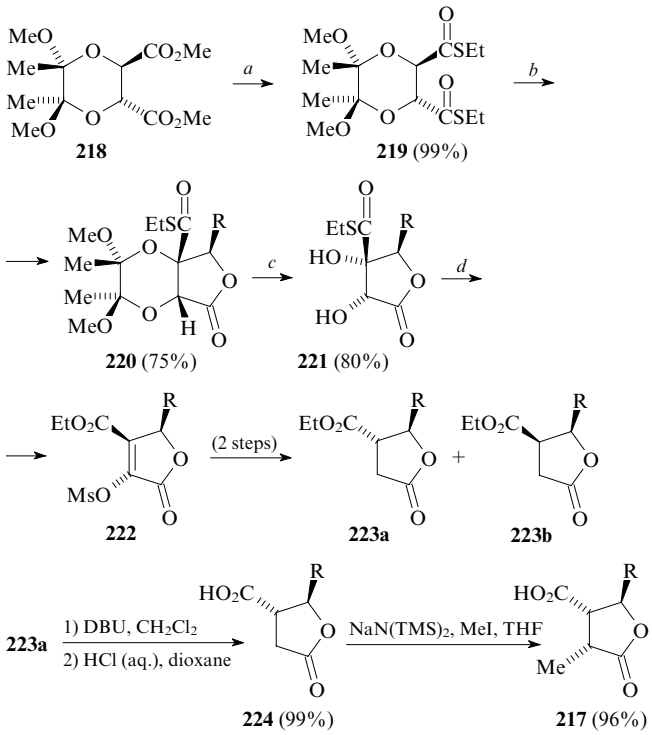
(*a*) $H_3B \cdot SMe_2$, **208**, THF; (*b*) $LiAlH_4$, THF; (*c*) $Ac_2O$, Py; (*d*) (1) KHMDS, TBSCl,THF; (2) PhMe, Δ; (*e*) $RuCl_3$, $NaIO_4$, $CCl_4$, MeCN (aq.).



The stereoselective α-methylation of the predominant stereoisomer **214** gives racemic acid (±)-**212**. This racemate was resolved into the antipodes by the chemo-enzymatic method *via* ester (±)-**216**. Selective hydrolysis of the latter in the presence of pig liver esterase (PLE) forms lactone (+)-**212**, which can easily be separated from unreacted ester (−)-**216**, which was then converted into product (−)-**212**.

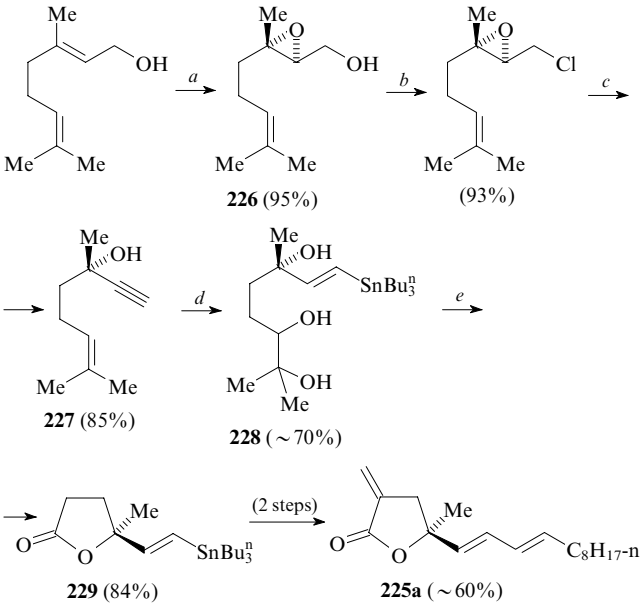


Yet another natural metabolite of this group, namely, (+)-nephrosteranic acid (**217**), isolated from various species of moss, lichen and fungi, has antitumour, antifungal and antibacterial activities. Its synthesis[65] was started from readily accessible homochiral dioxane **218** formed from L-tartaric acid.[66,67] It was found that the derived bis-thioester **219** can be smoothly converted into butanolide **220** by deprotonation with LDA and treatment of the lithium derivative with dodecanal. Then *cis*-diol **221** was obtained and converted, by conventional methods including hydrogenation of unsaturated ester **222**, into a mixture of isomeric lactones **223** (*cis* : *trans* ratio ~5 : 1). Treatment of this mixture with a base (DBU) yielded the equilibrium mixture (*cis* : *trans* ~1 : 5). The subsequent acid hydrolysis of the mixture resulted in acid **224** and recovered *cis*-ester **223b**, which was separated by chromatography. In the final step, the target product virtually identical to the natural lactone in properties was obtained by methylation of acid **224**.



R = n-$C_{11}H_{23}$; (*a*) EtSH, $CH_2Cl_2$, $Me_3Al$; (*b*) LDA, THF, n-$C_{11}H_{23}CHO$; (*c*) $F_3B \cdot OEt_2$, $HS(CH_2)_2SH$, $CH_2Cl_2$; (*d*) (1) NaOEt, EtOH, THF; (2) MsCl, DIPEA, $CH_2Cl_2$.

α-exo-Methylene-γ-disubstituted lactones isolated from sea sponges, (*S*)-(**225a**) and (*R*)-plakolides (**225b**), which also exhibit antitumour activity, can formally be classified as the trisubstituted butanolides considered here. Geraniol used as the starting compound for their synthesis was subjected to the Sharpless asymmetric epoxidation to give monoepoxide **226**.[68] The use of L-(+)-diisopropyl tartrate (this example is given below) finally results in butanolide **225a**, while the use of D-(−)-DIPT afforded its stereoisomer **225b**. The obtained epoxide **226** (*ee* > 95%) was transformed by simple operations first to acetylenic alcohol **227** and then to stannyl derivative **228**. The oxidative transformations of diol **228** yielded butanolide **229**, which was converted in two steps comprising stereoselective coupling with an appropriate vinyl iodide and the Corey α-methylenation of intermediate lactone[69] into (*S*)-plakolide (**225a**) of high enantiomeric purity.



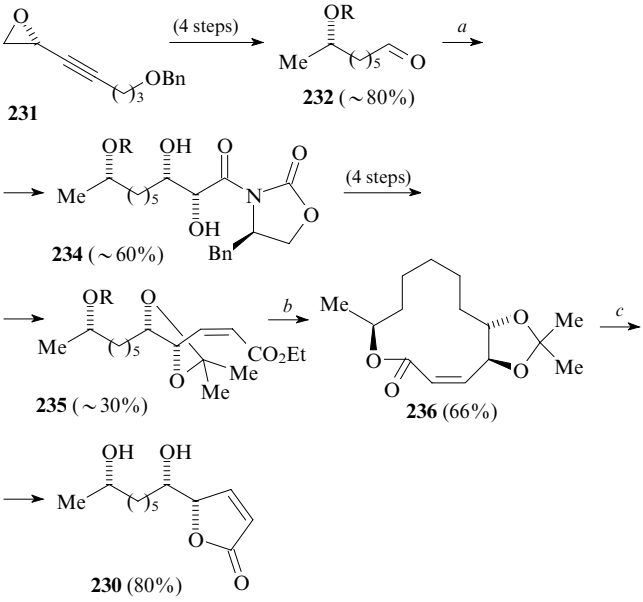

(*a*) L-(+)-DIPT, $Ti(OPr^i)_3$, TBHP, MS 4 Å, $CH_2Cl_2$; (*b*) $PPh_3$, $CCl_4$; (*c*) $Bu^nLi$, THF; (*d*) (1) $OsO_4$, *N*-methylmorpholine *N*-oxide (NMO), $Me_2CO$ (aq.); (2) $Bu_3^nSnH$, AIBN; (*e*) (1) $NaIO_4/SiO_2$, $CH_2Cl_2$; (2) PDC.

## III. Synthesis of natural butenolides

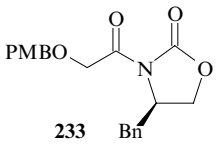
### 1. γ-Substituted butenolides

In the first enantioselective synthesis of isocladospolide B (**230**) isolated from sea microorganisms and exhibiting high herbicidal activity, the required stereochemistry was specified by the use of the Jacobsen asymmetric hydrolysis of the starting epoxide (±)-**231** (Scheme 8).[70] Homochiral *R*-oxirane (compound **231**) obtained in 43% yield was converted into aldehyde **232** by simple operations. The diastereoselective coupling of the aldehyde with chiral oxazolidinone **233**

Scheme 8



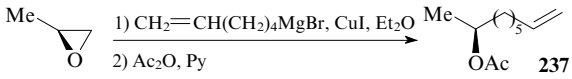

R = TBDPS; (*a*) (1) **233**, $Bu_2^nBOTf$, DIPEA, $CH_2Cl_2$; (2) $H_2$, Pd/C, MeOH; (*b*) 2,4,6-$Cl_3C_6H_2C(O)Cl$, $Et_3N$, DMAP, THF; (*c*) AcOH (aq.).

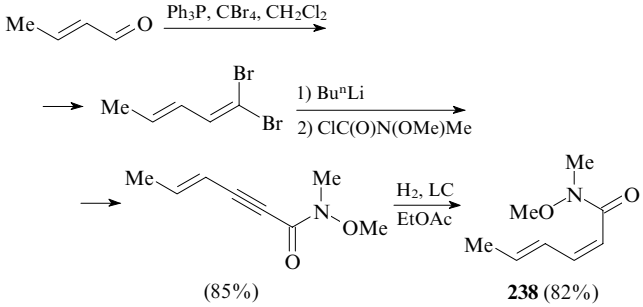



gave compound **234**. Several synthetic steps including the stereoselective Wittig reaction of an intermediate aldehyde gave unsaturated ester **235**.

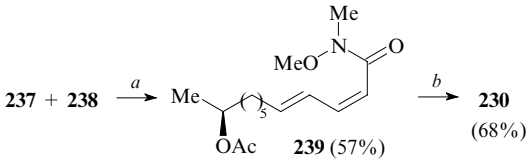
Macrolactonization of this hydroxy ester gave undecanolide **236** in which the removal of the acetonide protection was accompanied by translactonization to give product **230** with high enantiomeric purity.

Recently,[71] a shorter convergent synthetic route to isocladospolide B (**230**) has been proposed. This was based on intermolecular metathesis reaction of two structural blocks: homochiral unsaturated alcohol **237** and the Weinreb amide (**238**) containing a conjugated diene fragment. Compounds **237** and **238** were obtained by conventional methods starting from homochiral propylene oxide and crotonaldehyde, respectively. In the synthesis of amide **238,** the Lindlar catalyst (LC), *i.e.* palladium adsorbed on a neutral support ($BaSO_4$ or $CaCO_3$) and deactivated with quinoline, was used.




In the final step, the resulting dienamide **239** was subjected to the Sharpless asymmetric dyhydroxylation, which was accompanied, in this case, by stereoselective lactonization giving rise to butenolide **230**. This strategy was also used for enantioselective synthesis of muricatacin (**1**).

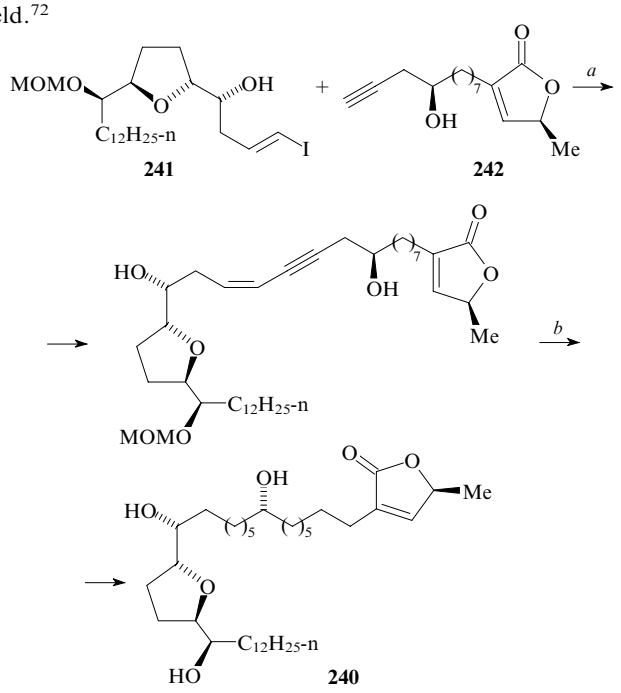



(*a*) the Grubbs catalyst (5 mol.%), $CH_2Cl_2$; (*b*) (1) LiOH, THF (aq.); (2) AD-mix-β.

### 2. α,γ-Disubstituted butenolides

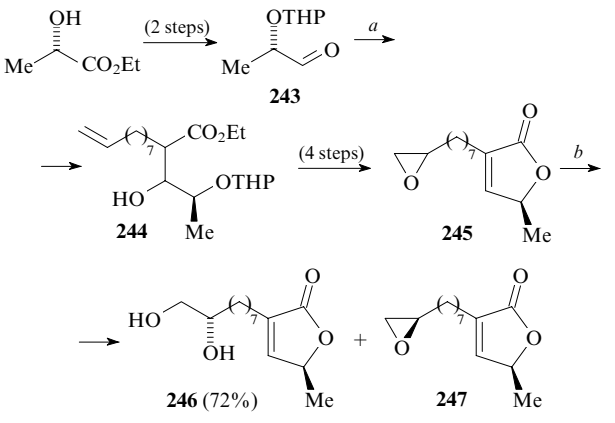
Butenolides with substituents in the α- and γ-positions are mainly represented by acetogenin derivatives. Compounds of this type containing one or two tetrahydrofuran fragments were isolated from the plants of the Annonaceae family.[1] They exhibit a broad spectrum of biological activities, which is of interest for pharmacology, and hence attract attention of synthetic chemists.

4-Deoxyannomontacin (**240**), which exhibits antitumour activity, is a representative of these butenolides with one THF fragment in the side chain. It was prepared by a 17-step enantioselective procedure in a ~15% overall yield.[72]



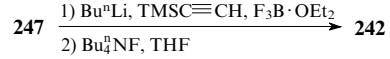

(*a*) $Pd(PPh_3)_4$, CuI, $Et_3N$; (*b*) (1) $TsNHNH_2$, NaOAc, dimethoxyethane (DME) (aq.); (2) $F_3B \cdot OEt_2$, DMSO.

The key step in this synthesis is Pd(0)–CuI-catalyzed coupling of two synthetic blocks, namely, vinyl iodide **241** and terminal acetylene **242**. The former was prepared in 12 steps starting from D-(+)-glucose. Lactone **242** with a terminal triple bond in the side chain was synthesized starting from ethyl (*S*)-(−)-lactate, which was easily converted into aldehyde **243** by a known procedure. For the formation of the lactone ring, the aldehyde was coupled with ethyl undec-10-enoate and product **244** thus formed was converted in four steps into diastereomeric lactones **245**. Treatment of this mixture with a chiral cobalt salen complex induces enantioselective opening of the oxirane ring in one of its component yielding diol **246**, which is separated by chromatography from epoxide **247** having the required stereochemistry. The latter was coupled with



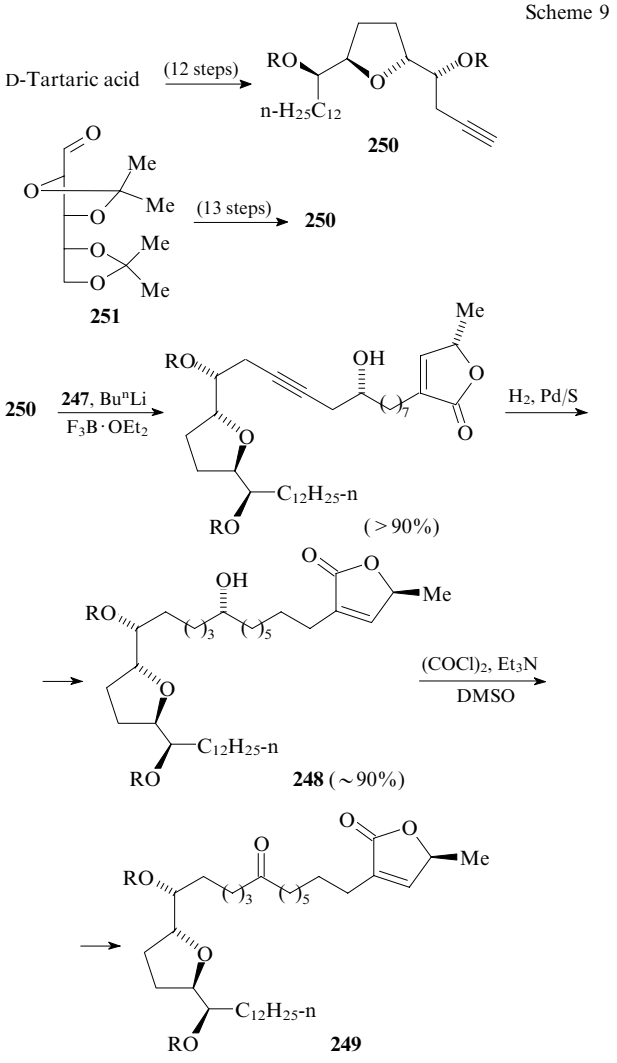

(*a*) $CH_2{=}CH(CH_2)_8CO_2Et$, LDA; (*b*) (*R*,*R*)-salenCo(OAc) (2 mol.%), $H_2O$.

trimethylsilylacetylene, the product was desilylated to give finally the target alkyne **242**.



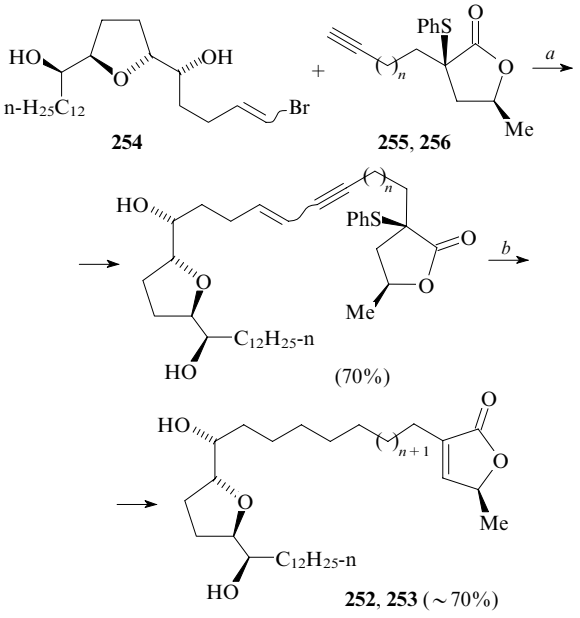

A similar strategy for enantioselective building of a lactone fragment has also been used in the synthesis of two more representatives of this class of natural butenolides — corrosolin (**248**, R = H) and corrosolone (**249**, R = H),[73,74] which exhibit cytostatic and antimicrobial activities (Scheme 9). In the key step of the synthesis, butenolide **247** containing a terminal epoxy group in the side chain was coupled with alkyne **250**. The THF fragment in compound **250** was created by multistep transformations of D-tartaric acid [73] or readily available diacetonide **251**.[74]

Scheme 9



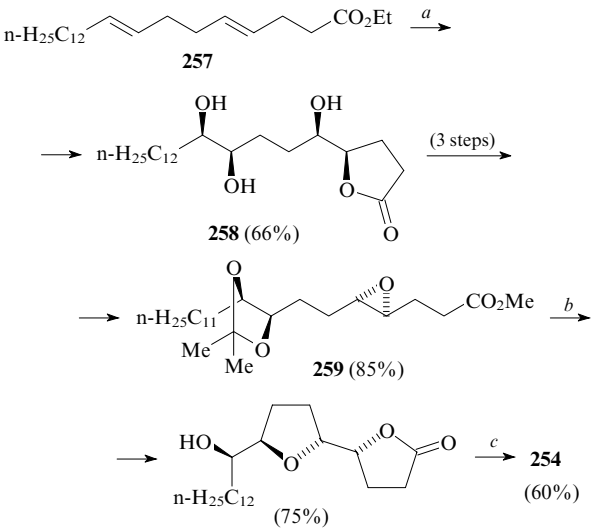

R = MOM or TBS, H.

Solamin (**252**) and reticulatacin (**253**), which have the same stereochemistry but differ in the side chain length, were prepared by a similar route. This is based on the coupling of substituted tetrahydrofuran **254** containing a vinyl halide fragment with butyrolactone derivative **255** or **256** with a terminal alkynyl group.[75]



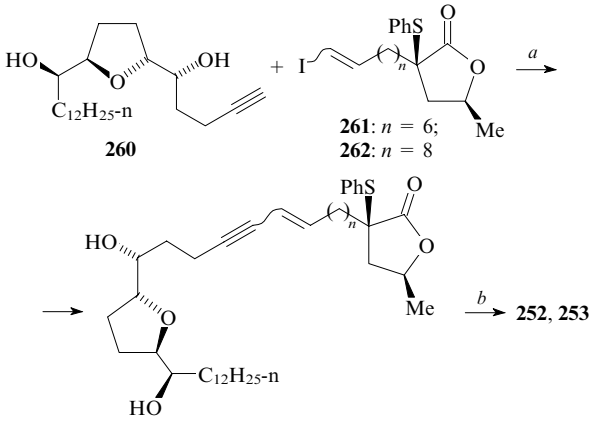

$n$ = 5 (**252**, **255**); 7 (**253**, **256**); (*a*) $Pd(PPh_3)_4$, CuI, $Et_3N$; (*b*) (1) $H_2$, $RhCl(PPh_3)_3$; (2) mCPBA; (3) PhMe, Δ.

Compounds **255** and **256** were prepared using a known procedure,[76] while compound **254** with a THF fragment was prepared from diene **257**. Its asymmetric dihydroxylation occurs stereoselectively and is accompanied by lactonization to give trihydroxylactone **258**. Protection of the vicinal diol system and opening of the lactone ring smoothly gave epoxide **259**, which was converted in three steps to a mixture of isomeric vinylic bromides **254**.



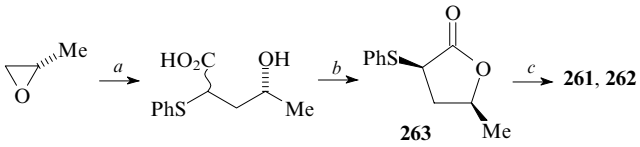

(*a*) AD-mix-β; (*b*) $F_3B \cdot OEt_2$, $CH_2Cl_2$; (*c*) DIBAL-H; $BrCH_2Ph_3P^+Br^-$, $Bu^tOK$.

Yet another version of enantioselective synthesis of butenolides **252** and **253** is also based on Pd(0)–CuI-catalyzed coupling of acetylenic and vinyl-halide components; however, in this case, the former is a substituted tetrahydrofuran **260**, while the latter is butyrolactone derivative **261** or **262**.[77]




(*a*) $Pd(PPh_3)_4$, CuI, $Et_3N$; (*b*) (1) $H_2$, $RhCl(PPh_3)_3$; (2) mCPBA; (3) PhMe, Δ.

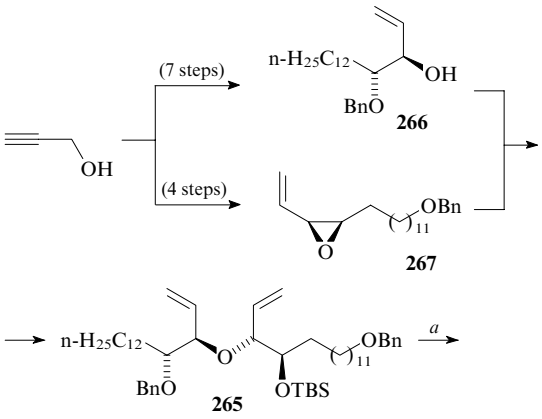
Tetrahydrofuran derivative **260** was obtained in 12 steps from a natural butanolide, (−)-muricatacin (**1a**), while lactones **261** and **262** were obtained from homochiral propylene oxide.[78] Coupling of propylene oxide with phenylthioacetic acid dianion afforded butanolide **263**, which was then alkylated with appropriate linear diiodides obtained from propargyl alcohol.

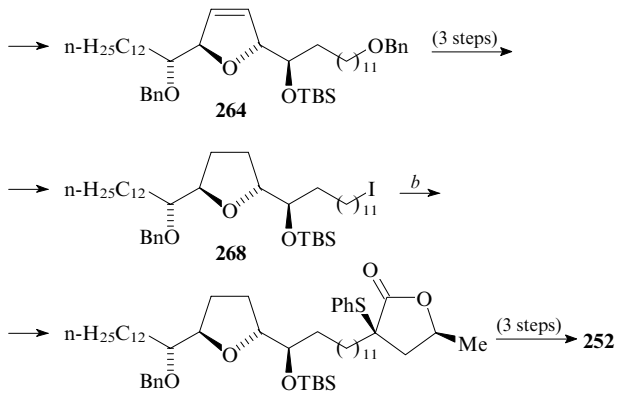



(*a*) $PhSCH_2CO_2H$, LDA; (*b*) chromatography; (*c*) $ICH{=}CH(CH_2)_nI$ ($n$ = 6, 8), NaHMDS.

Homochiral butanolide **263** was also used to construct the lactone fragment in an original synthesis of solamin (**252**) proposed by French authors.[79] The formation of a dihydrofuran fragment in compound **264** is based on intramolecular metathesis of homochiral diene **265**.

Diene **265** was prepared by coupling of allylic alcohol **266** with optically pure oxirane **267**. These were formed upon enantioselective transformations of propargyl alcohol, which included the Sharpless asymmetric epoxidation of intermediate allylic alcohols. Benzyl ether **264** was then converted into terminal iodide **268**, which was employed to alkylate α-phenylthiolactone **263**.

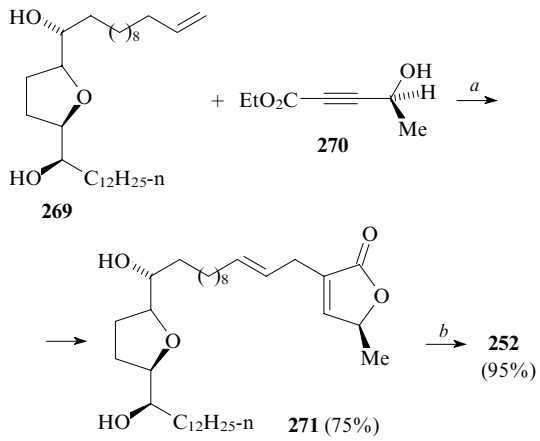





(*a*) The Grubbs catalyst; (*b*) **263**, NaHMDS.

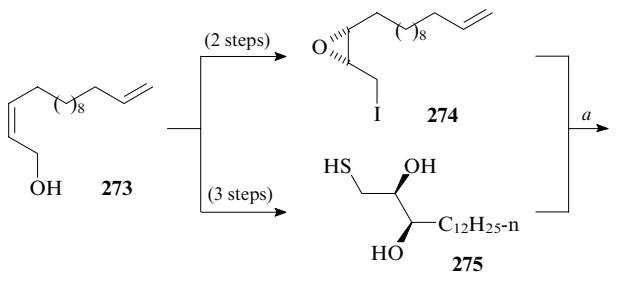
The conventional deprotection procedure and elimination of the phenylthio group through the formation of a phenylsulfinyl group completed the synthesis of the target product **252**.

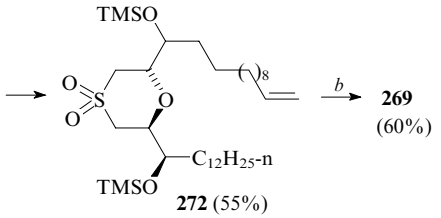
An extremely spectacular way of constructing a lactone fragment in the solamin molecule (**252**) was implemented by Trost *et al.*[80] They used annelation of the terminal olefin **269** by homochiral acetylenecarboxylic acid derivative **270** catalyzed by a ruthenium complex. Chemoselective hydrogenation of the product **271** thus formed completed this synthetic route.




(*a*) CpRu(cod)Cl (5 mol.%) (Cp = $\eta^5$-$C_5H_5$, cod is cycloocta-1,5-diene), MeOH, Δ; (*b*) $H_2$, $RhCl(PPh_3)_3$ (8 mol.%).

The formation of a THF fragment in compound **269** was accomplished by means of the Ramberg – Backlund reaction involving cyclic sulfone **272**. The latter was prepared from allylic alcohol **273** accessible from propargyl alcohol. Using the Sharpless asymmetric epoxidation, the required chiral centres in the intermediate iodoepoxide **274** and mercaptodiol **275** were formed.

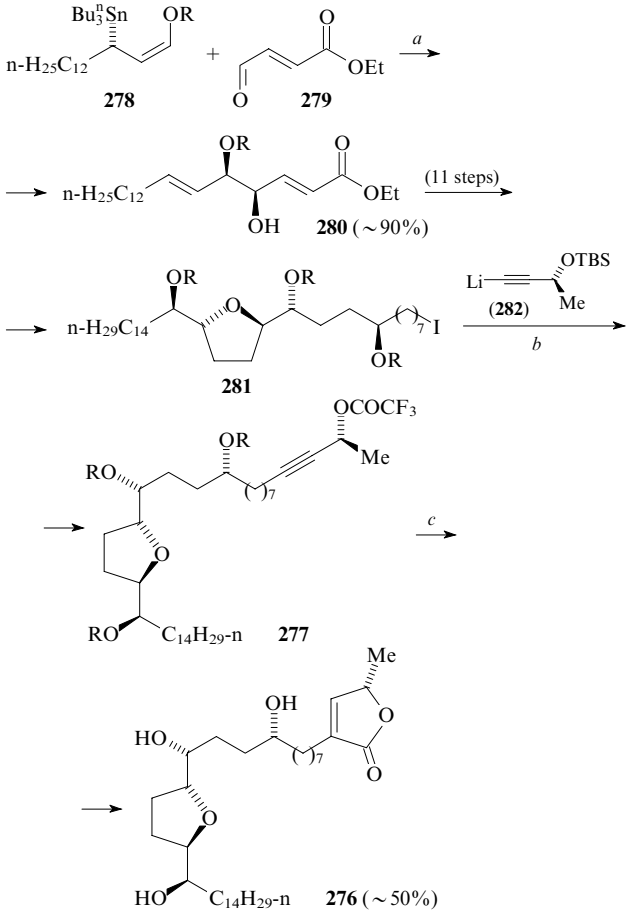



(*a*) (1) $Cs_2CO_3$, DMF; (2) KOH, $Bu^tOH$ (aq.); 3) mCPBA, PhH – hexane; (4) TMSCl, $Et_3N$; (*b*) (1) $Bu^tOK$, $CCl_4$, $Bu^tOH$; (2) TsOH, EtOH (aq.).

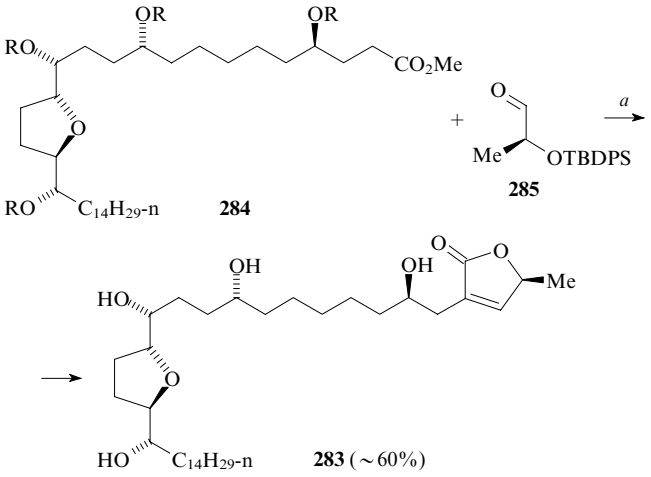
The acetogenin longifolicin (**276**) was synthesized using an original principle for the formation of the lactone fragment (Scheme 10).[81] The ring was constructed at later stages of the synthetic route by means of an original strategy, Pd(0)-catalyzed hydrocarbonylation of acetylenic derivative **277**. Compound **277** was obtained by a multistep synthesis with construction of stereogenic centres of the desired configuration on the basis of stereocontrolled condensation of homochiral stannyl derivative **278** and enal **279**. The reaction product (compound **280**) was converted in 11 steps into terminal iodide **281**, which was coupled with acetylenic synthon **282** to give compound **277**.

Scheme 10




R = MOM; (*a*) $F_3B \cdot OEt_2$, $CH_2Cl_2$; (*b*) (1) HMPA; (2) TBAF, THF; (3) trifluoroacetic anhydride (TFAA), Py; (*c*) (1) $Pd(PPh_3)_4$ (1 mol.%), CO, THF (aq.); (2) $AgNO_3$ (10 mol.%), HCl (aq.), MeOH – THF.

In the synthesis of the acetogenin (+)-longicin (**283**), the lactone fragment was also formed at a later stage using coupling of ester **284** with aldehyde **285** obtained from ethyl (*S*)-(−)-lactate.[82]



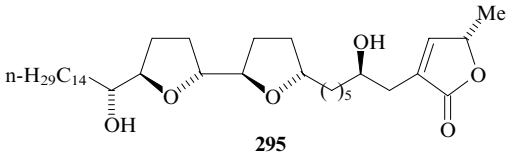

R = MOM; (*a*) (1) LDA, **285**, THF; (2) TBAF; (3) MsCl; (4) DBU.

The synthesis of substituted tetrahydrofuran **284** was started from homochiral lactone **286** accessible from D-glutamic acid, which was converted by conventional procedures to lactol acetate **287** (Scheme 11).

The condensation of compound **287** with α-trimethylsilyloxyfuran **288** afforded a mixture of *threo*- and *erythro*-isomers **289a**,**b**, the required isomer **289a** was isolated by chromatography and converted in several steps to amide **290**. Two alternative versions of using this synthon were proposed from which two different substrates (**291** and **292**) for intramolecular metathesis were prepared. By alcoholysis and the subsequent protection of the hydroxy group thus formed, the finally obtained macrocyclic lactones **293** and **294** were converted into compound **284**, the key compound in the synthesis of (+)-longicin (**283**).

The above approaches to the synthesis of butenolides with one THF fragment were used successfully for preparing acetogenins with two tetrahydrofuran rings in the molecule.

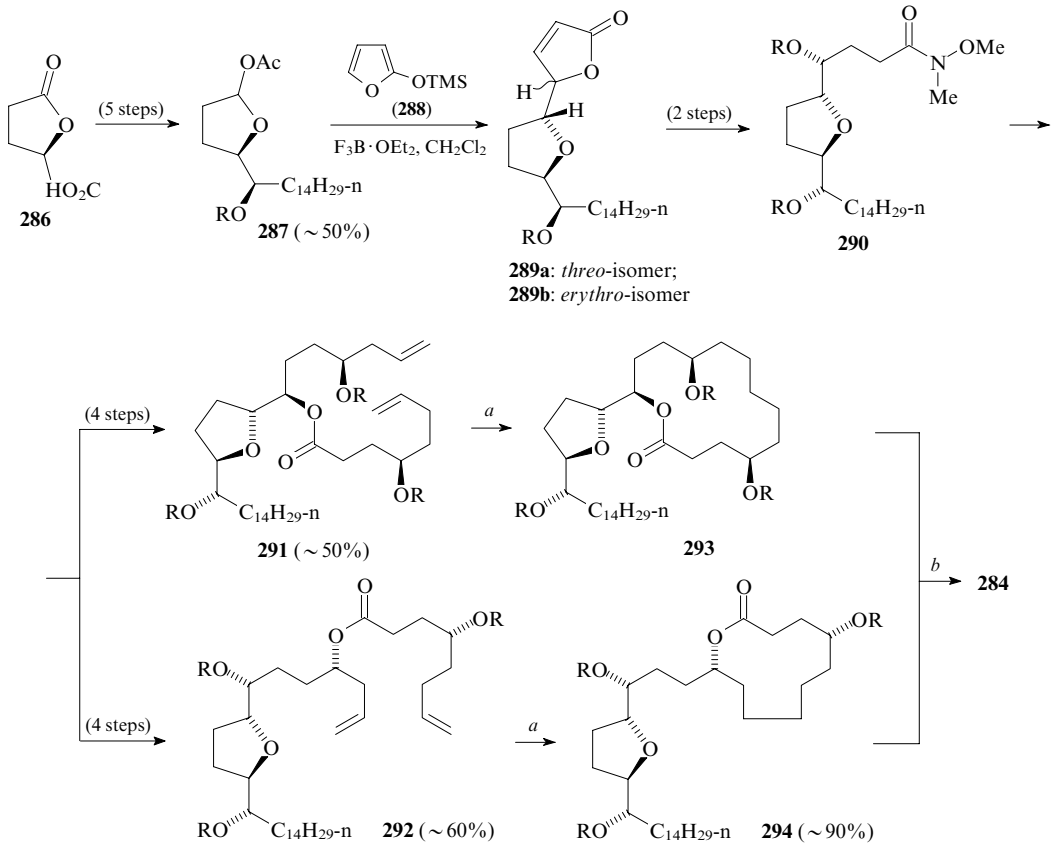
For example, enantioselective formation of the butenolide fragment of (+)-asimilobine (**295**)



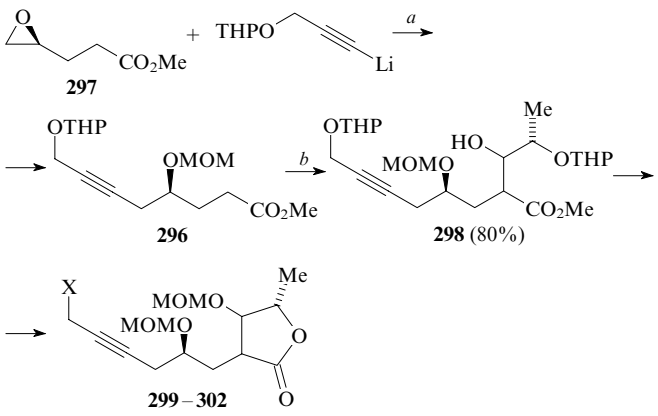

**295**

was based on the coupling of ester **296** prepared from propargyl alcohol and epoxide **297** with aldehyde **243** prepared from ethyl (*S*)-(−)-lactate.[83]

Scheme 11



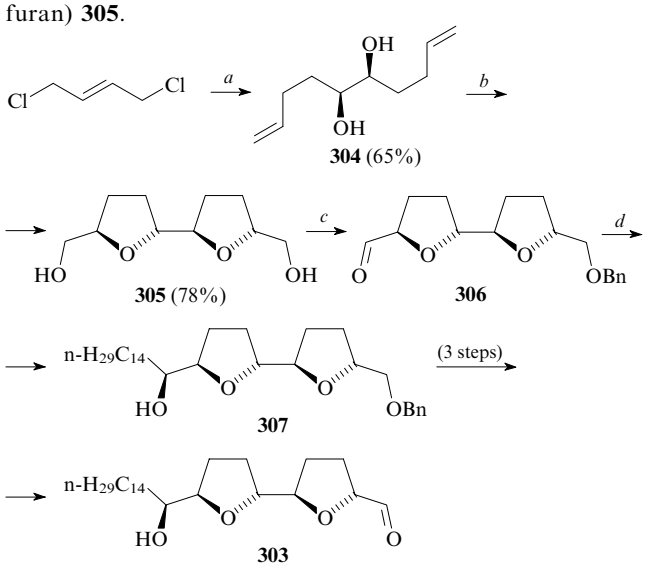

R = MOM; (*a*) (1) the Grubbs catalyst; (2) $H_2$, Pd/C; (*b*) (1) NaOMe, MeOH; (2) MOMCl, DIPEA.



X = THPO (**299**), HO (**300**), Br (**301**), $Ph_3P^+Br^-$ (**302**);
(*a*) (1) $F_3B \cdot OEt_2$, THF; (2) MOMCl, DIPEA; (*b*) LDA, **243**, THF.

This study provided reliable determination of the absolute configuration of compound **295**, while earlier results, in particular, concerning the configuration of its bis(tetrahydrofuryl) fragment were contradictory. The adduct **298** formed upon coupling gave, after conventional protection manipulations, lactone **299**. After two intermediate steps (leading to compounds **300** and **301**), **299** was converted into phosphonium salt **302**.

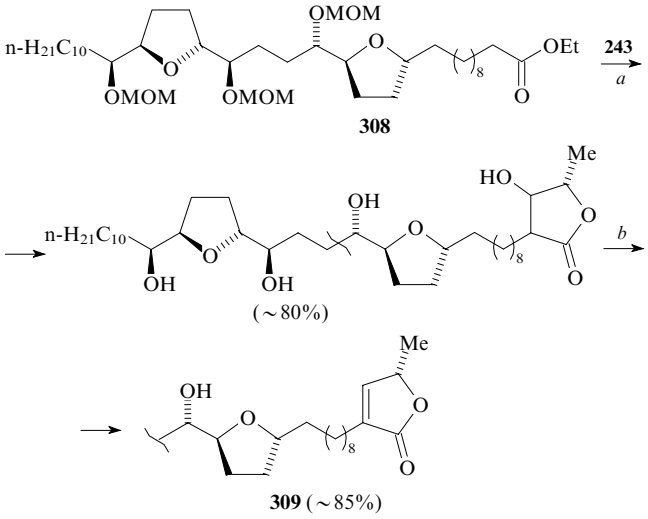
Aldehyde **303** containing two THF fragments was prepared starting from *trans*-1,4-dichlorobut-2-ene the Sharpless dihydroxylation of which yields intermediate diol (*ee* 94%), which was converted into dienol **304**. This product smoothly cyclized on oxidation to give bis(tetrahydrofuran) **305**.



(*a*) (1) AD-mix-α, $MsNH_2$, $Bu^tOH$ (aq.); (2) NaH; (3) AllMgBr, CuI, THF; (*b*) $Co(modp)_2$ (modp is 1-morpholinocarbonyl-4,4-dimethylpenta-1,3-dionate), TBHP, $O_2$, $Pr^iOH$; (*c*) (1) NaH, BnCl, THF; (2) DMSO, $(COCl)_2$, $Et_3N$; (*d*) $n\text{-}C_{14}H_{29}MgCl$, $CuBr \cdot SMe_2$, $Et_2O$.

The coupling of aldehyde **306** with tetradecylmagnesium chloride occurs diastereoselectively giving rise to the desired stereoisomer **307**, which was purified by chromatography and then converted into aldehyde **303** by the Swern oxidation. Olefination of aldehyde **303** containing two THF fragments having the configuration shown with the phosphorane obtained from salt **302**, hydrogenation of the resulting enyne and deprotection gave finally a product differing from natural butenolide **295** in the sign of optical rotation. This fact provided grounds for revision of the absolute configuration of the natural compound accepted at that time.

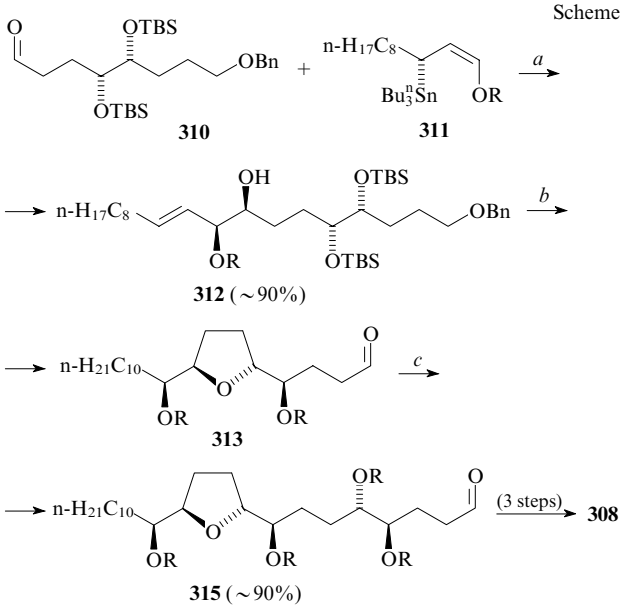
The coupling of ester **308** with aldehyde **243** was used for the construction of the butenolide fragment of the acetogenin (+)-squamostatin D (**309**) having unusual structure (unlike most compounds of this class, in this compound, the tetrahydrofuran rings are separated by a four-carbon chain).[84]



(*a*) (1) LDA, THF; (2) TBAF, THF; (*b*) (1) TFAA, $Et_3N$; (2) HCl, THF, MeOH.

For constructing the skeleton of butenolide **309**, homochiral aldehyde **310** was used as the starting compound (Scheme 12), which was prepared by the Sharpless asymmetric dihydroxylation of the readily accessible unsaturated precursor.

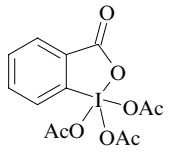
Scheme 12



R = MOM; (*a*) $F_3B \cdot OEt_2$; (*b*) (1) TBAF, THF; (2) MOMCl, DIPEA; (3) $H_2$, Pd/C, EtOH; (4) **314**; (*c*) (1) *trans*-(*S*)-$Bu^n_3SnCH(OMOM)CH{=}CH.CH_2OTBS$, $InCl_3$, EtOAc; (2) $H_2$, $Rh/Al_2O_3$, EtOAc; (3) TBAF, THF; (4) **314**.

The coupling of aldehyde **310** with stannyl derivative **311** occurs diastereoselectively to give only *syn*-adduct **312**. By a

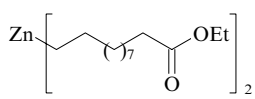
sequence of conventional manipulations including the use of a mild oxidant, the Dess–Martin reagent (**314**), this product was converted into substituted tetrahydrofuran **313**.



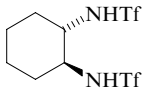
**314**

The latter was coupled with the allylindium reagent generated *in situ* from the appropriate stannane; the condensation was no less selective than the previous one. The coupling product was desilylated and the intermediate terminal alcohol was oxidized by the Dess–Martin reagent into aldehyde **315** (see Scheme 12).

In several steps including stereoselective coupling with organozinc compound **316** in the presence of a chiral catalyst ligand **317**–$Ti(OPr^i)_4$, aldehyde **315** was converted into ester **308**, which is the key compound in the synthesis of (+)-squamostatin D (**309**).

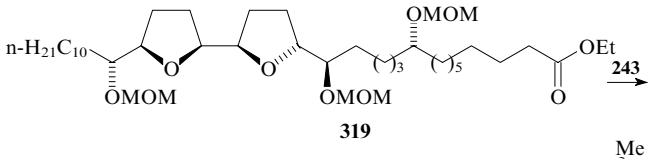


**316**

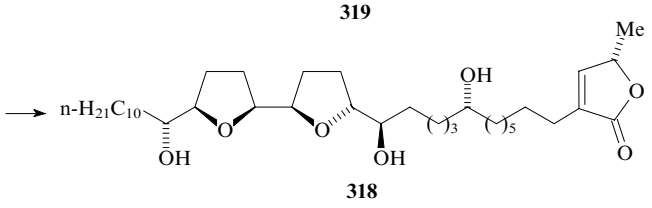


**317**

The same strategy was used in the synthesis of (+)-trilobin (**318**) in which the lactone fragment was formed upon coupling of the above-mentioned homochiral aldehyde **243** with ester **319**.[85]

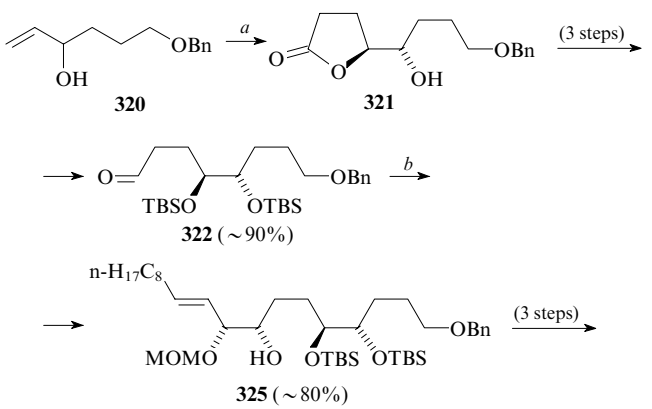


**319**

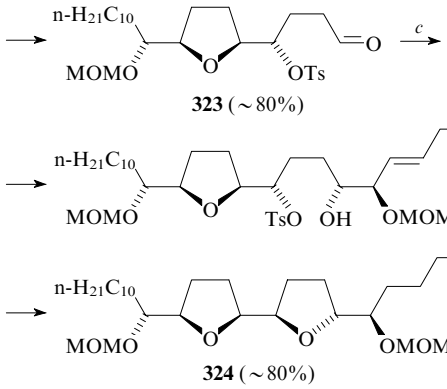


**318**

Ester **319** containing two THF fragments was prepared starting from allylic alcohol **320**, which was converted into lactone **321** (*ee* 95%) by the Claisen orthoester rearrangement and asymmetric dihydroxylation.



**325** (~80%)

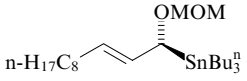


**323** (~80%)

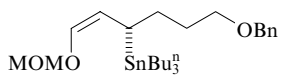
**324** (~80%)

(*a*) (1) $(MeO)_3CMe$, $EtCO_2H$, Δ; (2) AD-mix-β; (*b*) **326**, $InCl_3$, EtOAc; (*c*) **327**, $F_3B\cdot OEt_2$, $CH_2Cl_2$; (*d*) (1) $Bu^n_4NOH$, THF; (2) $H_2$, Pd/C, EtOH; (3) **314**.

As in the above-described example (see Scheme 12), the subsequent transformations included the reactions of intermediate aldehydes **322**, **323** and **324**. Elongation of the chain of aldehyde **322** to give adduct **325** was attained by reaction with an allylindium reagent generated *in situ* from stannane **326**. Compound **323** was coupled with allylstannane **327**, and aldehyde **324** was coupled with organozinc reagent **316** in the presence of the chiral catalyst ligand **317**–$Ti(OPr^i)_4$, which finally resulted in ester **319** (*ee* > 95%).



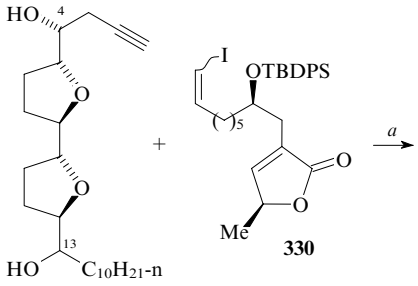
**326**



**327**

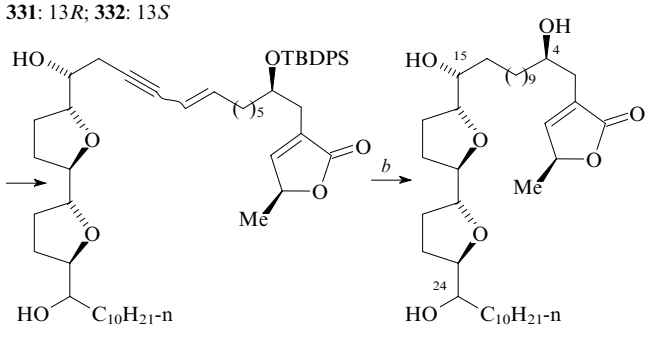
The synthetic routes to the epimers (+)-asimicin (**328**) and (+)-bullatacin (**329**) are based on Pd(0)–CuI-catalyzed coupling of butenolide **330** containing a iodovinyl fragment with terminal acetylenes, compounds **331** and **332** with the appropriate configuration (Scheme 13).[86]

Scheme 13



**330**

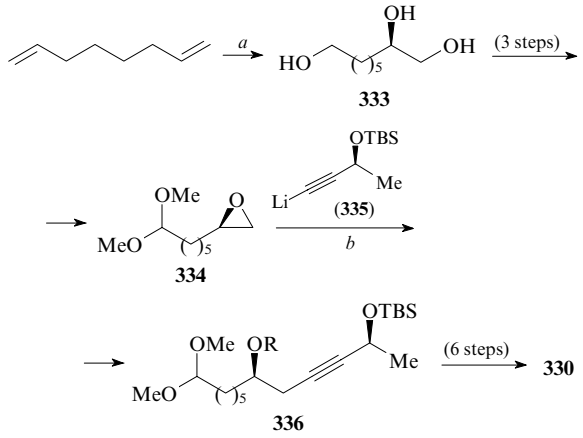
**331**: 13*R*; **332**: 13*S*



**328**: 24*R*; **329**: 24*S*

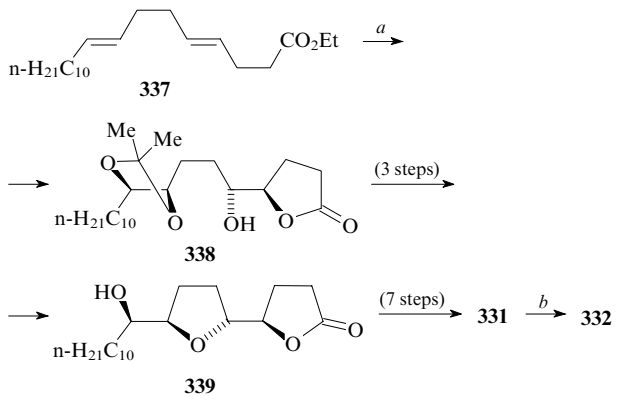
(*a*) $Pd(PPh_3)_2Cl_2$–CuI, $Et_3N$; (*b*) (1) $H_2$, $RhCl(PPh_3)_3$; (2) AcCl, MeOH.

Lactone **330** was prepared from octa-1,7-diene, which was converted into homochiral triol **333** by partial hydroboration of one of the double bonds, which resulted in asymmetric dihydroxylation. Three-step transformation of compound **333** to terminal epoxide **334** and coupling of **334** with lithium acetylenide **335** gave ultimately compound **336**, which is the key product in the synthesis of butenolide **330**.



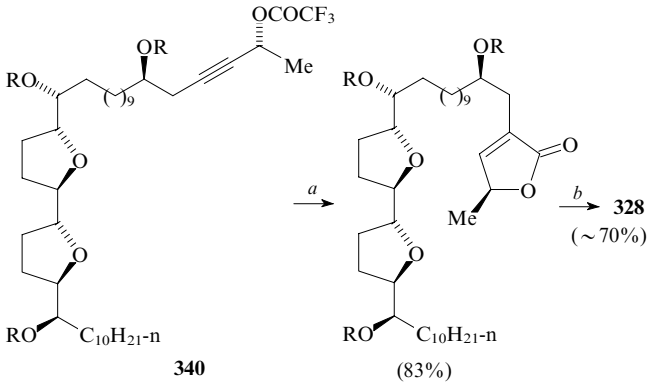

R = TBDPS; (*a*) (1) 9-borobicyclo[3.3.1]nonane (9-BBN); (2) AD-mix-β; (*b*) (1) $F_3B \cdot OEt_2$; (2) TBDPSCl.

The THF-containing compounds **331** and **332** were prepared starting from ethyl dienoate **337**, which was twice asymmetrically dihydroxylated. By conventional manipulations, the homochiral product **338** thus formed was converted into lactone **339**, which is the key compound in the synthesis of the 13*R*-isomer **331**. The Mitsunobu epimerization of the 13*R*-isomer **331** resulted in the (+)-bullatacin precursor — 13*S*-isomer **332**.



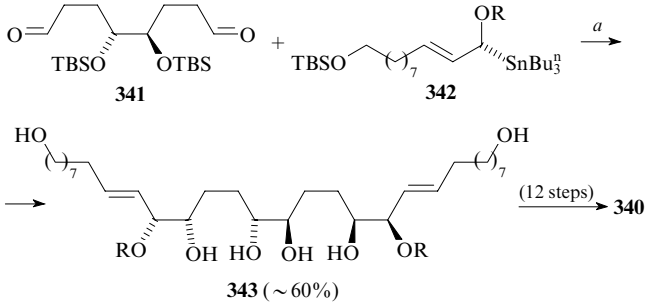

(*a*) (1) AD-mix-β; (2) 2,2-dimethoxypropane (DMP), TsOH; (*b*) DEAD, $Ph_3P$, 4-$NO_2C_6H_4CO_2H$.

In another synthetic route to (+)-asimicin (**328**), the above-mentioned (see Scheme 10) Pd(0)-catalyzed hydrocarbonylation of acetylenic derivative **340** was used to form the butenolide fragment.[87]



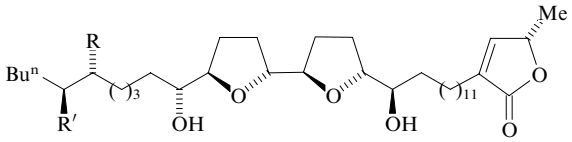

R = $TMSCH_2CH_2OCH_2$; (*a*) (1) $Pd(PPh_3)_4$ (1 mol.%), CO, THF (aq.); (2) $AgNO_3/SiO_2$; (*b*) PPTS, EtOH.

The stereochemistry of the bis(tetrahydrofuran) system in compound **340** was specified by using dialdehyde **341**, obtained from D-tartaric acid, as the starting compound. The coupling of **341** with homochiral stannyl derivative **342** was stereoselective, giving rise (after selective removal of the TBS protective groups) to polyol **343**, which served as the basis for the construction of tetrahydrofuran fragments of molecule **340**.



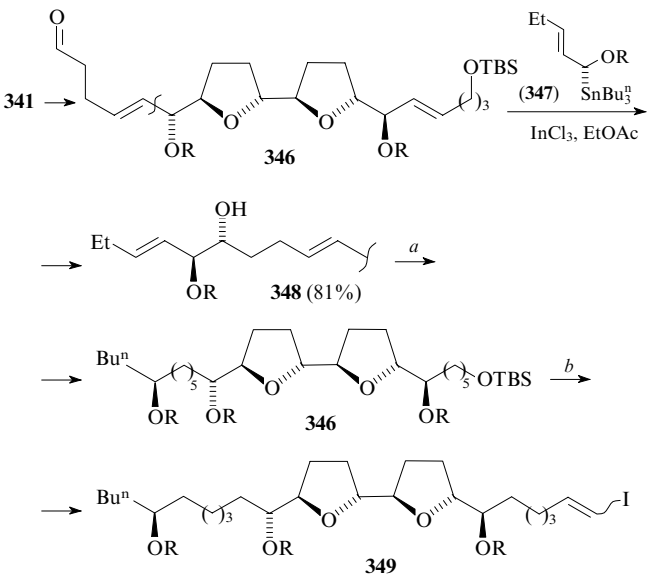

R = $TMSCH_2CH_2OCH_2$; (*a*) (1) $InCl_3$, EtOAc; (2) TBAF, THF.

Homochiral dialdehyde **341** was also used in the synthesis of two more representatives of acetogenin butenolides, (+)-asiminocin (**344**) and (+)-asiminecin (**345**),[88] which demonstrate exceptionally high cytotoxicity with respect to some human tumour cell lines.



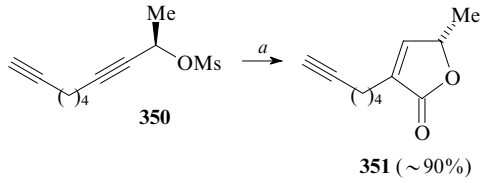

**344**: R = OH, R′ = H;
**345**: R = H, R′ = OH

Using the above-described reactions, dialdehyde **341** was first converted into a polyol analogous to compound **343** and then into bis(tetrahydrofuran) **346**. Treatment of aldehyde **346** with stannyl derivative **347** in the presence of $InCl_3$ resulted, as in the previous case, in the *anti*-isomer **348** in a nearly quantitative yield. This was followed by reductive elimination of the hydroxy group, hydrogenation of the double bonds, removal of the TBS protection group and formation of a iodovinyl group in the product, which was used to form terminal iodoalkene **349**.




R = $TMSCH_2CH_2OCH_2$; (*a*) (1) TsCl, Py;(2) $LiBEt_3H$; (3) $H_2$, $Rh/Al_2O_3$; (*b*) (1) TBAF, THF; (2) $(COCl)_2$, $Et_3N$, DMSO; (3) $CrCl_2$, $CHI_3$.

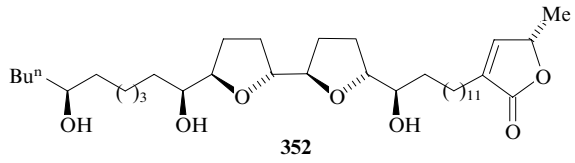
The butenolide fragment of the target acetogenins **344** and **345** was formed by Pd(0)-catalyzed hydrocarbonylation of diynoic alcohol derivative **350**.



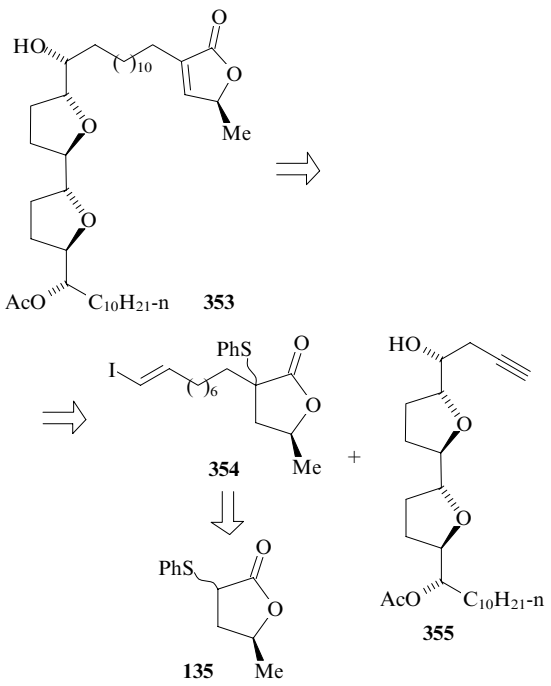

(*a*) (1) $Pd_2(dba)_3$ (1 mol.%) (dba is dibenzylideneacetone), $Ph_3P$, CO, THF (aq.); (2) $AgNO_3/SiO_2$.

The resulting homochiral butenolide **351** containing a terminal alkynyl group in the side chain was coupled with iodovinyl derivative **349**. The subsequent transformations of the intermediate enyne thus obtained were similar to those described above (see, for example, Scheme 13) and finally yielded (+)-asiminocin **344**. (+)-Asimenicin (**345**) isomeric to butenolide **344** was synthesized in the same way.

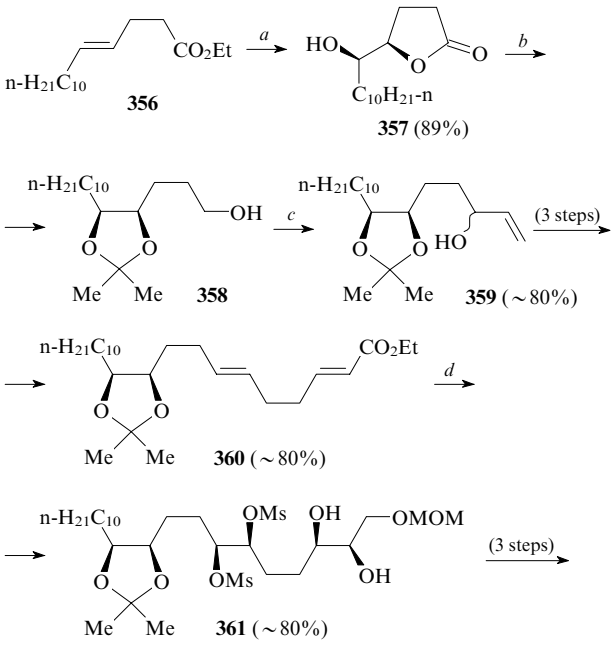
This strategy was also used to synthesize (+)-bullanin (**352**).[89] The final stage was the coupling of butenolide **351** having a terminal alkynyl substituent with appropriate derivative containing two THF rings and a iodovinyl group in the side chain.

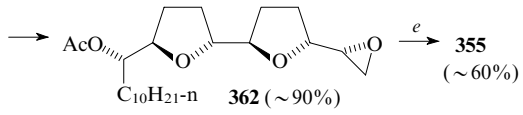



A convergent strategy was employed to prepare the butenolide (+)-uvaricin (**353**).[90] Retrosynthetic analysis has shown that Pd(0)–CuI-catalyzed coupling of lactone building block **354** containing a iodovinyl side chain substituent with compound **355** containing a terminal alkyne group and having a bis-THF skeleton can serve as the key step. Compound **354** can in turn be prepared by alkylation of the above-mentioned substituted butanolide **135**.



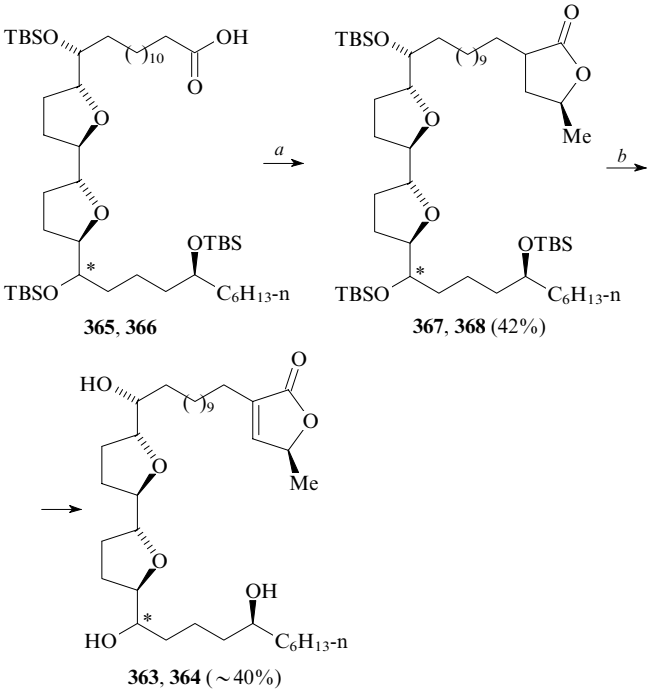

The synthesis of the bis-THF building block in **355** was performed using accessible ester **356** as the starting compound. This was converted into lactone **357** (*ee* > 95%) upon asymmetric dihydroxyation. Using conventional procedures including preliminary epimerization of the chiral centre at C(5), lactone **357** was converted into hydroxyacetonide **358**, from which allylic alcohol **359** was synthesized. The subsequent reactions included the Claisen orthoester rearrangement, the Horner–Emmons olefination and double dihydroxylation of the intermediate unsaturated ester **360** resulting in polyol derivative **361**. The preliminary acetonide deprotection of this compound and successive manipulations with the hydroxy groups finally yielded bis-THF-containing epoxide **362**, which is a direct precursor of the terminal acetylene **355**.





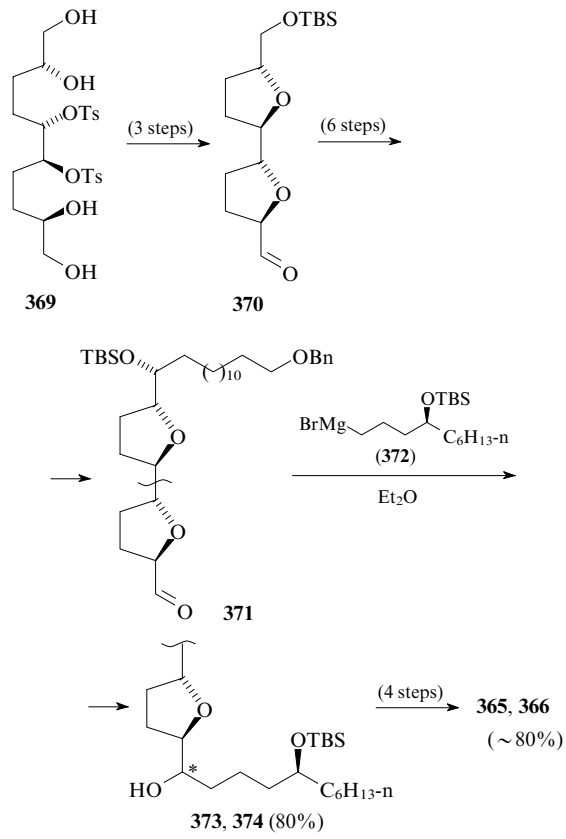

(*a*) (1) AD-mix-β, $MsNH_2$; (2) KOH, $H_2O$; (3) TsOH, $CH_2Cl_2$; (4) 4-$NO_2C_6H_4CO_2H$, DEAD, $Ph_3P$, PhH; (*b*) (1) $LiAlH_4$, THF; (2) $Me_2CO$, TsOH, hexane; (*c*) (1) PCC, $CH_2Cl_2$; (2) $H_2C{=}CHMgBr$; (*d*) (1) DIBAL-H, THF; (2) MOMCl, DIPEA, $CH_2Cl_2$; (3) AD-mix-β, $MsNH_2$, $Bu^nOH$ (aq.); (4) MsCl, $Et_3N$; (*e*) (1) HC≡CTMS, $Bu^nLi$; (2) $F_3B\cdot OEt_2$, THF; (3) TBAF.

The enantioselective construction of the butenolide residue of squamocin A (**363**) and squamocin D (**364**), which are epimers, was carried out in a different way.[91] In the final step, dianions of the carboxylic acids **365** and **366** were coupled with homochiral propylene oxide. The resulting epimeric saturated lactones **367** and **368** were subjected to conventional selenenation–elimination procedure to give the corresponding butenolides and the removal of TBS groups gave the target lactones **363** and **364**.



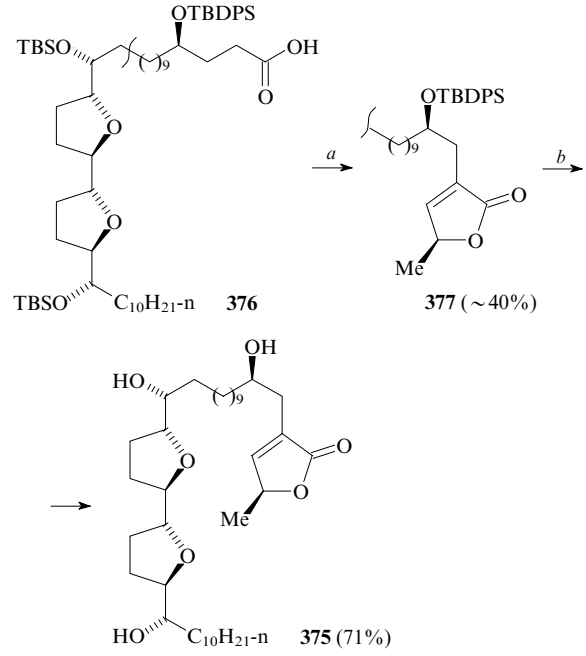

*S*-Isomers (**363**, **365**, **367**); *R*-isomers (**364**, **366**, **368**); (*a*) (1) LDA, (*S*)-propylene oxide, THF; (2) $Bu^tCO_2Cl$, $Et_3N$; (*b*) (1) KHMDS, PhSeCl; (2) magnesium monoperoxyphthalate, THF–MeOH; (3) TBAF, THF.

For the synthesis of the bis-THF fragment, the authors used enantiomerically pure ditosylate **369** obtained from D-tartaric acid; using the Williamson reaction, compound **369** was transformed into product **370** containing two THF rings. Elongation of the side chain in this product gave aldehyde **371**. The coupling of this aldehyde with homochiral organomagnesium compound **372** led to a mixture of epimers **373** and **374**, which were separated by chromatography, debenzylated and oxidized to carboxylic acids **365** and **366**, respectively.




*S*-Isomers (**365**, **373**); *R*-isomers (**366**, **374**).

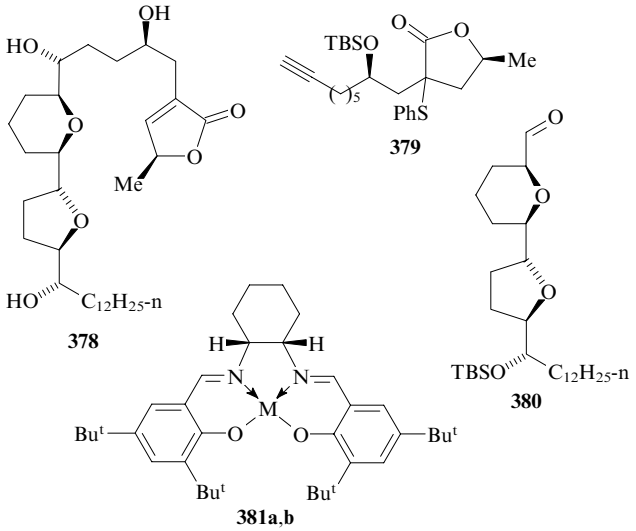
This rather efficient approach to the construction of a lactone fragment was also used in the enantioselective synthesis of (+)-rollinastatin (**375**).[92] At the final step of the synthesis, the bis-THF derivative **376** containing a carboxylic acid residue was deprotonated and the bis-anion thus formed was treated with diphenyl disulfide. The repeated




(*a*) (1) LDA, PhSSPh, THF; (2) LDA, (*S*)-propylene oxide, THF; (3) TsOH; (*b*) (1) magnesium monoperoxyphthalate, THF–MeOH; (2) TBAF, THF.

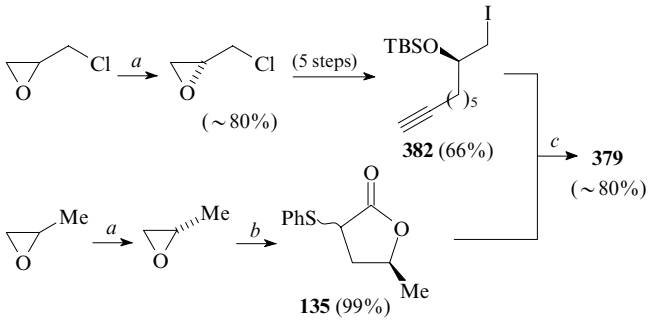
deprotonation of the intermediate α-phenylthio compound and addition of homochiral propylene oxide followed by acidification of the reaction mixture gave unsaturated lactone **377**, which was transformed by conventional procedures into the target butenolide **375**.

(−)-Muconin (**378**) is the acetogenin butenolide with an unusual structure containing a tetrahydropyran ring instead of one tetrahydrofuran fragment. The enantioselective synthesis of this butenolide was performed by a convergent route where the key step was coupling of the lithium butanolide derivative **379** containing a terminal alkynyl residue in the side chain with aldehyde **380** containing tetrahydropyran and tetrahydrofuran rings.[93] Hydrolytic kinetic resolution of the terminal epoxides in the presence of chiral cobalt complex **381a** (the Jacobsen reaction) was employed for the formation of asymmetric centres in molecule **378**.




M = Co(OAc) (**a**), Cr($BF_4$) (**b**).

This catalyst was used in the synthesis of butanolide **379** for preparing the starting homochiral epichlorohydrin (*ee* > 99%) and optically pure propylene oxide and for kinetic resolution of epoxide **383**. Epichlorohydrin was then converted using simple operations into iodoalkyne **382**, while propylene oxide was converted into a mixture of diastereomeric lactones **135**. The coupling of these two synthons gave butanolide **379** in a reasonable yield.

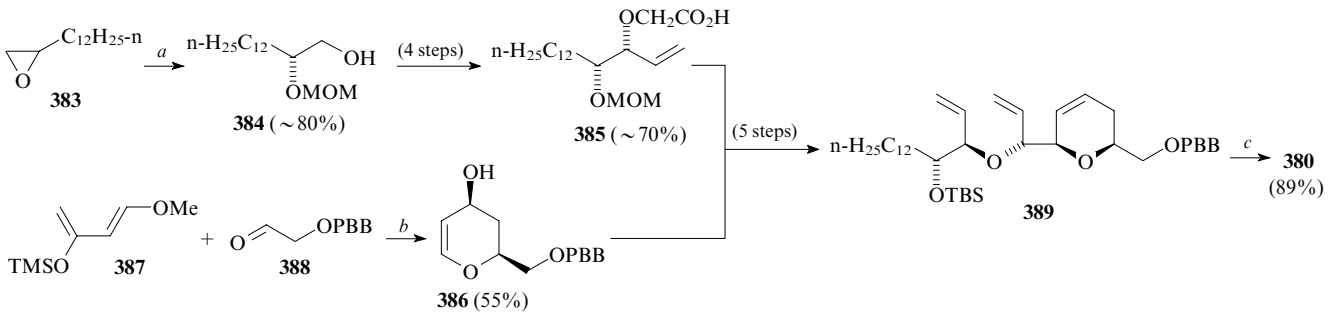



(*a*) **381a** (0.5 mol.%), $H_2O$; (*b*) (1) LDA, THF, $PhSCH_2CO_2H$; (2) TsOH, PhH; (*c*) LDA, HMPA, THF.

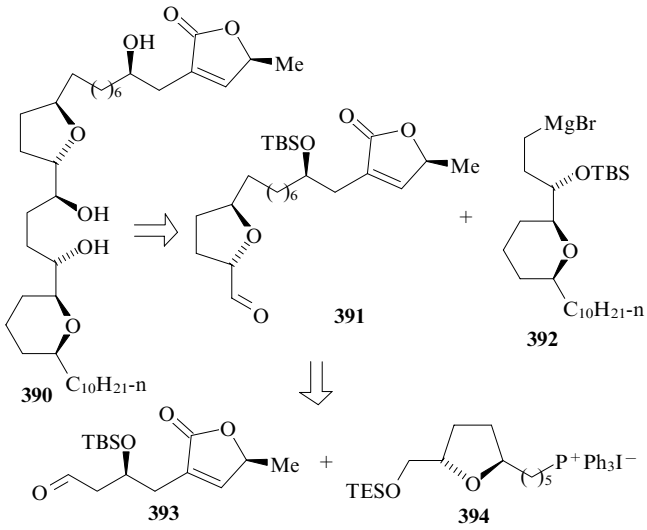
The homochiral product obtained by resolution of racemic epoxide **383** was converted into alcohol **384**, which was then transformed into carboxylic acid **385** (Scheme 14). The second component, pyranol **386**, was obtained by the enantioselective hetero-Diels–Alder reaction of the Danishefsky diene (**387**) and aldehyde **388** catalyzed by chiral chromium complex (**381b**) and subsequent diastereoselective hydride reduction of the intermediate cyclic ketone. The scalemic alcohol **386** thus obtained (*ee* 80%) gave virtually pure enantiomer upon recrystallization. This product was esterified with acid **385** and the resulting ester was converted into diene **389** by a sequence of reactions including the Ireland–Claisen rearrangement.[94] In this case, the rearrangement occurred diastereoselectively to give the *threo*-stereoisomer. In the final step of the synthesis of aldehyde **380**, diene **389** underwent metathesis.

Yet another acetogenin lactone, (−)-mucocin (**390**), also contains both tetrahydrofuran and tetrahydropyran rings in the molecule, but the rings are separated by a four-carbon chain. This compound has an exceptionally high cytostatic activity and selectivity with respect to human pancreatic and lung tumour cells. The convergent scheme of enantioselective synthesis of this compound is based on coupling of aldehyde **391** containing butenolide and tetrahydrofuran fragments with the Grignard reagent **392** containing a tetrahydropyran ring in the molecule.[95] In turn, aldehyde **391** was prepared from aldehyde **393** and phosphonium salt **394**.

Scheme 14

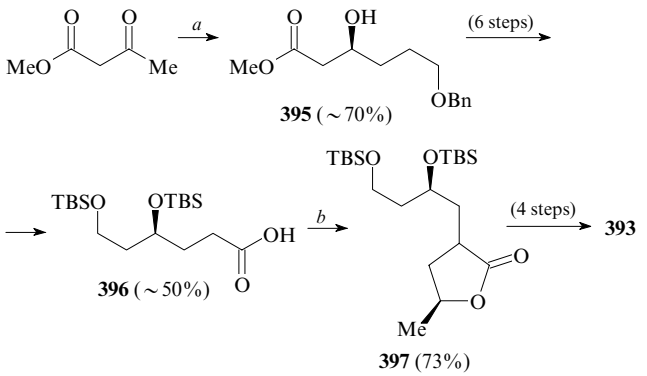



PBB is *p*-bromobenzyl; (*a*) (1) **381a** (0.5 mol.%), $H_2O$; (2) $CH(OMe)_3$, CSA, $CH_2Cl_2$; (3) DIBAL-H, $CH_2Cl_2$; (*b*) (1) **381b** (2 mol.%), $MeOBu^t$, MS 4 Å; (2) trifluoroacetic acid (TFA); (3) $NaBH_4$, $CeCl_3 \cdot H_2O$, EtOH; (*c*) (1) $Mo(CHMe_2Ph)(NC_6H_2Me_3\text{-}2,4,6)[OCMe(CF_3)_2]_2$ (5 mol.%), PhH; (2) $H_2$, Pd/C, $NaHCO_3$, EtOH; (3) **314**, Py, $CH_2Cl_2$.



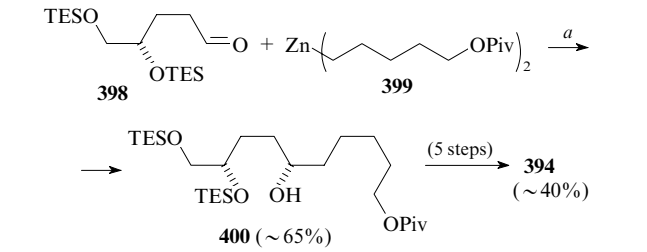
TES is triethylsilyl.

The stereogenic centres of butenolide **393** were formed using the Noyori enantioselective reduction of the alkylation product of methyl acetoacetate into hydroxy ester **395** (*ee* 97%), multistep transformation of ester **395** into acid **396** and coupling of the acid with homochiral propylene oxide. Butyrolactone **397** formed in this sequence of transformations was then converted into butenolide **393**.



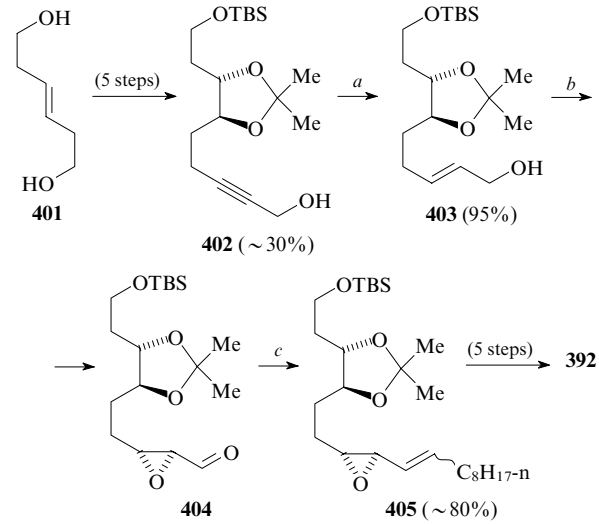
(*a*) (1) NaH, $Bu^nLi$, THF; (2) $Br(CH_2)_2OBn$; (3) $H_2$, Ru(II)–(*S*)-(−)-BINAP [BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]; (*b*) (1) LDA, THF; (2) (*S*)-propylene oxide; (3) $Bu^tCO_2Cl$ (PivCl), $Et_3N$, $CH_2Cl_2$.

For the synthesis of THF-containing structural block **394**, the authors made use of diastereoselective coupling of readily accessible homochiral aldehyde **398** with dialkylzinc reagent **399** in the presence of chiral ligand **317**. Diastereomer **400** thus formed (*de* 95%) was purified by chromatography and converted into phosphonium salt **394** using standard procedures.



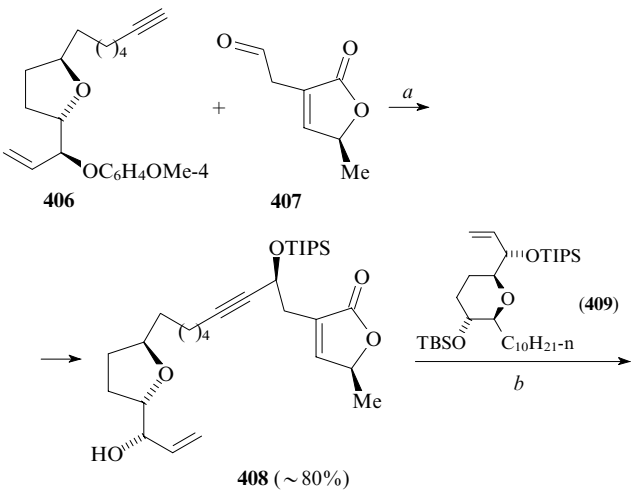
(*a*) **317** (10 mol.%), xylene.

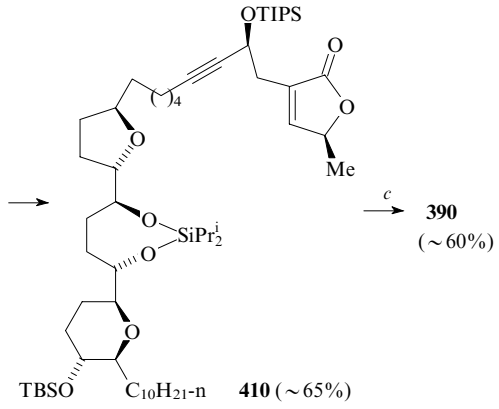
Substituted tetrahydropyran **392** was synthesized using unsaturated alcohol **401** as the starting compound By standard function separation methods, asymmetric dihydroxylation and homologization, alcohol **401** was converted into acetylenic alcohol **402**. The hydride reduction of alcohol **402** gave allylic alcohol **403** and the subsequent sequence of oxidative transformations including the Sharpless asymmetric epoxidation and the Dess–Martin oxidation afforded epoxy aldehyde **404**, which was then introduced into the Wittig reaction with nonylidenephosphorane. The resulting product **405** contained functional groups necessary for the formation of the tetrahydropyran ring in organomagnesium derivative **392**.



(*a*) $NaAlH_2(OC_2H_4OMe)_2$ (Red-Al), THF; (*b*) (1) TBHP, (−)-DIPT (12 mol.%), $Ti(OPr^i)_4$, $CH_2Cl_2$; (2) **314**, Py, $CH_2Cl_2$; (*c*) (1) n-$C_9H_{19}Ph_3P^+Br^-$, NaHMDS, THF; (2) CSA, $CH_2Cl_2$, $Pr^iOH$.

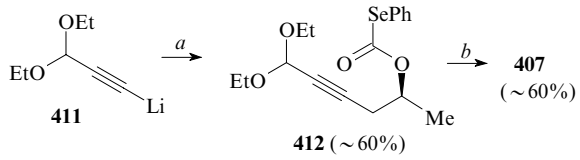
Recently, one more convergent scheme for the synthesis of (−)-mucocin (**390**) has been proposed.[96] This is based on three successive reactions. The first one is diastereoselective (*de* > 90%) coupling of organozinc derivative of alkyne **406** with aldehyde **407** to give compound **408**. This undergoes metathesis with substituted tetrahydropyran **409**. The intermediate unsymmetric dialkoxysilane **410** was converted into (−)-mucocin by standard procedures.





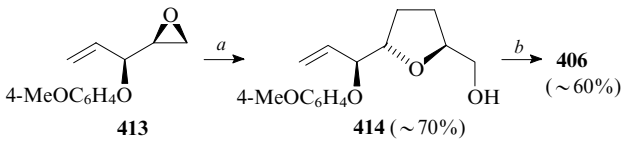

TIPS is triisopropylsilyl; (*a*) (1) $Et_2Zn$, PhMe; (2) (*R*)-BINOL, $Ti(OPr^i)_4$, THF; (3) TIPSOTf, Py, DMAP, THF; (4) CAN, MeCN (aq.); (*b*) (1) $Pr^i_2SiCl_2$, imidazole, $CH_2Cl_2$; (2) the Grubbs catalyst, $(CH_2Cl)_2$; (*c*) (1) HF, MeCN, $CH_2Cl_2$; (2) $TsNHNH_2$, NaOAc, DME (aq.).

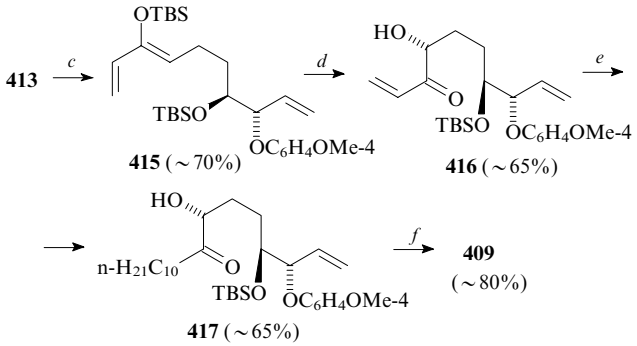
The homochiral butenolide **407** needed in this synthetic route was synthesized by coupling of lithium derivative **411** with optically pure propylene oxide and subsequent preparation of selenocarbonate **412**, which is smoothly converted into the desired product by a free-radical mechanism.




(*a*) (1) (*S*)-Propylene oxide, Bu$^n$Li, THF; (2) $COCl_2$, $Et_3N$, PhH; (3) PhSeH, Py; (*b*) (1) $Bu^n_3SnH$, AIBN, PhH; (2) $RhH(CO)(Ph_3P)_3$, PhH; (3) $HCO_2H$, pentane.

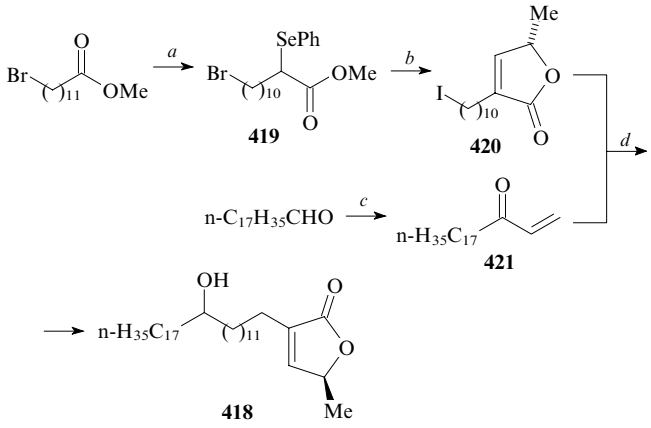
The starting compounds **406** and **409** were prepared by a common precursor, readily accessible homochiral epoxide **413**. In the synthesis of the former, this was coupled with allylmagnesium halide and the intermediate secondary alcohol thus formed was subjected to cobalt complex-promoted oxidative cyclization to tetrahydrofuran **414**, which was converted into alkyne **406** by standard procedures. In the synthesis of the latter, epoxide **413** was first opened on treatment with an equivalent amount of the homoenolate generated from the penta-1,4-dien-3-ol TBS derivative. The obtained diene **415** was subjected to the selective Sharpless dihydroxylation, which resulted in conjugated ketone **416** with high enantiomeric purity. The subsequent CuCN-catalyzed conjugate addition of octylmagnesium bromide to ketone **416** yields compound **417**, which is the immediate precursor of tetrahydropyran **409**.



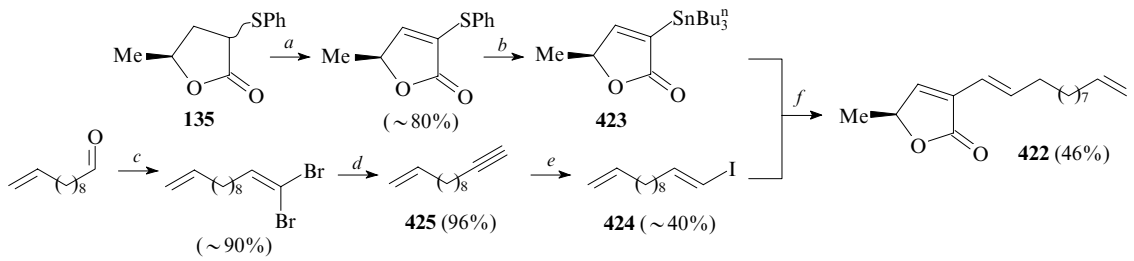

(*a*) (1) AllMgBr, CuCN, $Et_2O$; (2) TBHP, $O_2$, $Co(modp)_2$, $Pr^iOH$; (*b*) (1) $Tf_2O$, $Et_3N$, $CH_2Cl_2$; 2) $TMSC{\equiv}C(CH_2)_4MgBr$, CuI, THF; (3) TBAF, MeOH; (*c*) (1) $(CH_2{=}CH)_2CHOTBS$, Bu$^n$Li, THF; (2) TBSOTf, 2,6-lutidine; (*d*) AD-mix-β, Bu$^n$OH (aq.), $MsNH_2$; (*e*) n-$C_8H_{17}MgBr$, CuCN, THF; (*f*) (1) $BiBr_3$, TBSH, MeCN; (2) TBSOTf, 2,6-lutidine; (3) CAN, MeCN (aq.).

Mention should be made of one more representative of acetogenin butenolides discovered in plants of the Annonaceae family, (+)-reticulatamol (**418**). This compound differs from the above-considered compounds of this class in the absence of oxygen-containing rings in its molecule. (+)-Reticulatamol was isolated from the custard apple *A. reticulata* and its structure was confirmed by total synthesis.[97] The key element of this structure, the substituted butenolide fragment, was formed by coupling of the appropriate functionalized methyl carboxylate **419** containing a phenylselenenyl group in the α-position with homochiral propylene oxide. The subsequent transformations of the condensation product gave iodide **420** in ~45% overall yield with respect to the starting compound, commercially available methyl 12-bromododecanoate. Simultaneously, octadecanal was converted by conventional methods into conjugated ketone **421**. The coupling of the latter with iodide **420** under free-radical reaction conditions and the subsequent hydride reduction of the reaction product afforded a mixture of diastereomers, (+)-reticulatamol (**418**) and its non-natural 15-*epi*-stereoisomer.




(*a*) (1) LDA; (2) PhSeCl, THF; (*b*) (1) LDA; (2) (*S*)-propylene oxide, THF; (3) $H_2O_2$, AcOH; (4) NaI, $Me_2CO$; (*c*) (1) $CH_2{=}CHMgBr$, THF; (2) $MnO_2$,$CH_2Cl_2$; (*d*) (1) $Bu^n_3SnH$, AIBN, PhMe; (2) $Bu^n_3SnH$, $SiO_2$, $CH_2Cl_2$.

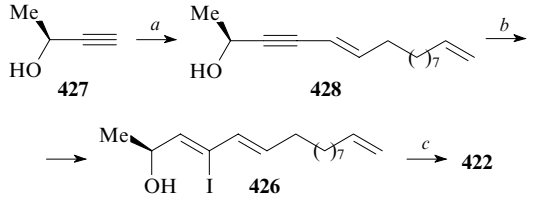
Scheme 15



(*a*) 1) $SO_2Cl_2$, $CCl_4$; 2) $Li_2CO_3$, LiBr, THF; (*b*) $Bu^n_3SnH$, 1,1′-azobis(cyclohexanecarbonitrile), PhMe; (*c*) $CBr_4$, $PPh_3$, Zn, $CH_2Cl_2$; (*d*) $Bu^nLi$, THF; (*e*) 1) DIBAL-H, PhMe; 2) $I_2$; (*f*) $Pd(dba)_2$ (0.25 mol.%), $Ph_3As$, CuI, DMF.

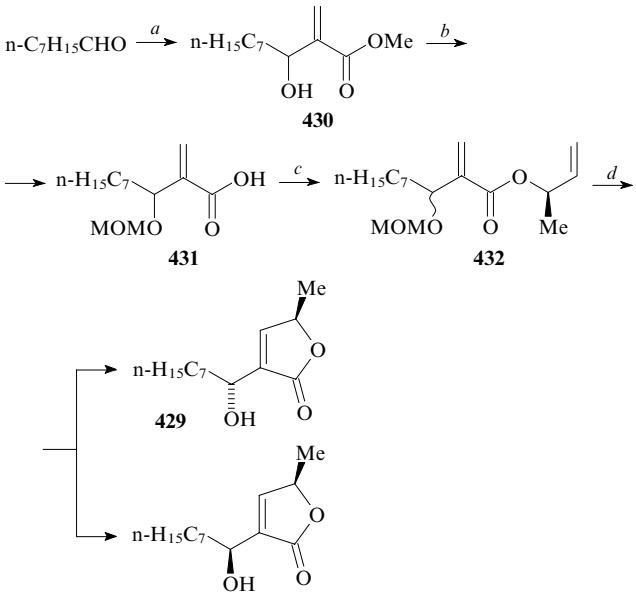
Among derivatives of 5-(*S*)-methylfuran-2(5*H*)-one, the plant metabolite (+)-hamabiwalactone B (**422**) is also known. The enantioselective synthesis of this compound was performed using the above-mentioned mixture of diastereomeric lactones **135** (see above). The key step of the synthesis is Pd(0)-catalyzed cross-coupling of homochiral stannyl derivative **423** (obtained from the mixture of lactones **135**) with vinylic iodide **424**.[98] The latter was synthesized from undec-10-enal using the Corey–Fuchs homologization procedure followed by *cis*-hydroalumination of the resulting enyne **425** with diisobutylaluminium hydride and iodination of the corresponding vinylalane (Scheme 15).

In a later study,[99] homochiral (+)-hamabiwalactone B (**422**) was prepared using the Pd(II)-catalyzed Stille type carbonylation of (*Z*)-iodoalkenol **426**. In the synthesis of **426**, commercially available acetylenic alcohol **427** was used as the starting compound to form the stereogenic centre of the desired configuration. Its palladium(0)-catalyzed cross-coupling with the above-mentioned vinylic iodide **424** afforded enyne **428**, which was converted into compound **426** by means of a hydroalumination–iodinolysis reaction sequence; this product was then carbonylated to complete the synthesis of the target butenolide **422**.



(*a*) **424**, $Pd(PPh_3)_4$, pyrrolidine; (*b*) (1) $LiAlH_4$, THF; (2) $I_2$; (*c*) CO (35 atm), $PdCl_2(PPh_3)_2$ (4 mol.%), $Et_3N$.

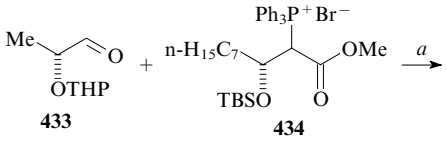
A metabolite of the bacteria *Pseudomonas sp*. A92, (−)-acaterin (**429**), a 5-(*R*)-methylfuran-2(5*H*)-one derivative, acting as acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitor, is promising as a therapeutic agent for treating atherosclerosis. A simple synthesis of this compound was proposed by Indian chemists, who used the Baylis–Hillman reaction of octanal with methyl acrylate.[100] Product **430** formed in this reaction was converted, by conventional methods, into carboxylic acid **431**, which was esterified with commercially available (*R*)-but-3-en-2-ol.

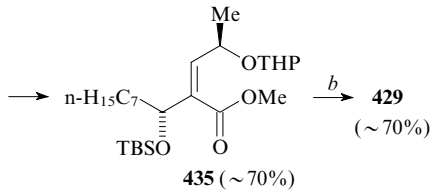


(*a*) $CH_2{=}CHCO_2Me$, quinuclidine; (*b*) (1) MOMCl, DIPEA, $CH_2Cl_2$; (2) 1N LiOH (aq.), THF; (*c*) (*R*)-but-3-en-2-ol, dicyclohexylcarbodiimide (DCC), DMAP, $CH_2Cl_2$; (*d*) (1) the Grubbs catalyst (30 mol.%), $CH_2Cl_2$; (2) chromatography; (3) $TiCl_4$, $CH_2Cl_2$.

The intramolecular metathesis of the mixture of diastereomeric diene esters **432** thus formed (1 : 1 ratio) induced by the Grubbs catalyst furnished the corresponding cyclic stereoisomers, which were separated by chromatography. The isomer with the required stereochemistry was converted into target butenolide **429** upon deprotection.

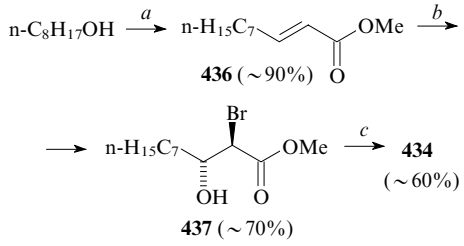
In another enantioselective synthesis of (−)-acaterin (**429**), olefination of known aldehyde **433** prepared from methyl (*R*)-lactate with homochiral phosphonium salt **434** was used as the key step.[101] The synthesis was completed by acid hydrolysis of product **435**.





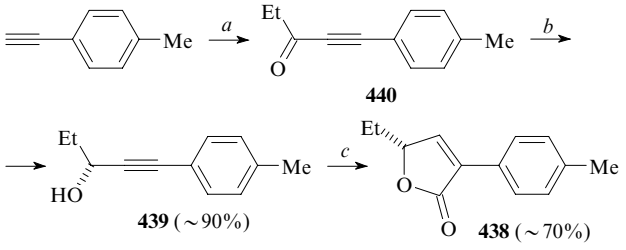

(*a*) LiHMDS, THF; (*b*) TsOH, MeOH.

The starting phosphonium salt **434** was prepared from acrylate **436** obtained from octanol. The asymmetric dihydroxylation of ester **436** followed by chemoselective transformation, using the Sharpless procedure,[102] of the intermediate dihydroxy ester into α-bromo ester **437**, which was converted into phosphonium salt **434** after protection of the hydroxy group.



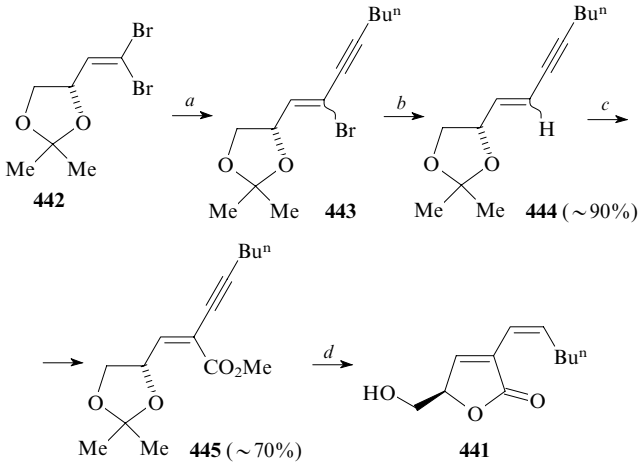

(*a*) (1) $P_2O_5$, $Et_3N$, DMSO, $CH_2Cl_2$; (2) $Ph_3P{=}CHCO_2Me$, THF; (*b*) (1) $OsO_4$, **5a**,[103] $MsNH_2$, $K_3Fe(CN)_6$, $Bu^tOH$; (2) HBr, AcOH, MeOH; (*c*) (1) TBSCl, imidazole, DMAP, $CH_2Cl_2$; (2) $PPh_3$, MeCN.

(−)-Incrustoporin (**438**) is produced by the fungi *Incrustoporia carneola* and exhibits clear-cut antimycotic activity. Its enantioselective synthesis is based on Pd(0)-catalyzed cyclocarbonylation of acetylenic alcohol **439** (*ee* 97%).[104] In the synthesis of alcohol **439**, the reduction of ketone **440** accessible from tolylacetylene was accomplished by asymmetric hydride transfer developed by Noyori and co-workers.[105]




(*a*) (1) EtMgBr, THF; (2) $ZnBr_2$; (3) EtCOCl, $Pd(PPh_3)_4$; (*b*) $Pr^iOH$, $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, (1*R*,2*R*)-*N*-(4-tolylsulfonyl)-1,2-diphenylethylenediamine; (*c*) CO, $H_2$, $Pd(dba)_2$, 1,4-bis(diphenylphosphino)butane, $CH_2Cl_2$.

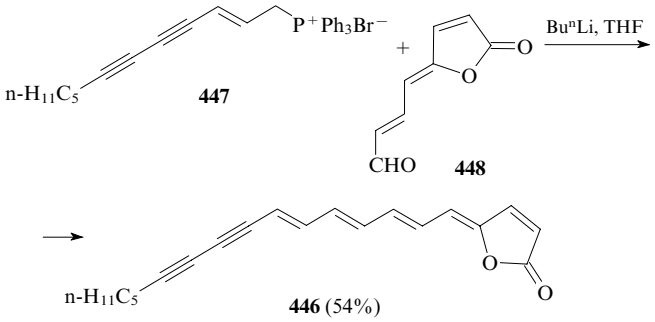
Yet another representative of α,γ-disubstituted butenolides, (−)-fugomycin (**441**), produced by the bacteria *Pseudomonas aureofaciens* also exhibits high antifungal activity. The enantioselective synthesis of this lactone that allowed determining its absolute configuration is based on the transformations of dioxolane **442** derivatied from D-glyceraldehyde.[106] The Pd(0)-catalyzed reaction of compound **442** with hexynylmagnesium bromide proved to be insufficiently stereoselective giving a mixture of monobromo derivatives **443** in a 4 : 1 ratio. However, the isomeric composition of formal hydrodebromination products (**444**) obtained from this mixture was different (96 : 4). Probably, this can be attributed to favourable isomerization of intermediate vinyllithium derivatives formed upon metallation of bromides **443**, which were then subjected to methanolysis. Enynes **444** were converted into esters **445**; subsequent conventional transformations completed the synthesis of the target product **441**.



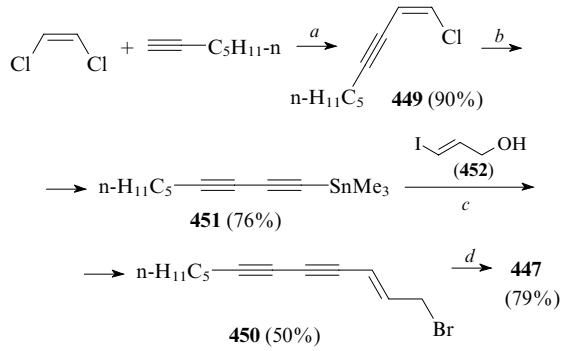

(*a*) $Bu^nC{\equiv}CMgBr$, $Pd(PPh_3)_4$ (2.5 mol.%), PhH, $Et_2O$; (*b*) (1) $Bu^sLi$, $Et_2O$; (2) MeOH; (*c*) (1) $Bu^sLi$, $Et_2O$; (2) $ClCO_2Me$; (*d*) (1) $H_2$, $Pd/CaCO_3$, MeOH; (2) $H_2SO_4$, MeOH.

### 3. γ-Alkylidenebutenolides

Some representatives of natural γ-alkylidenebutenolides comprise extended systems of conjugated multiple bonds. For example, dihydroxerulin (**446**) comprises a chain of four conjugated double bonds and a diyne fragment. This compound attracts attention for its ability to serve as an inhibitor of cholesterol biosynthesis being non-cytotoxic. The final step in the multistep convergent synthesis of butenolide **446** is the Wittig coupling of two intermediates, a phosphorate derived from salt **447** and aldehydolactone **448**.[107]

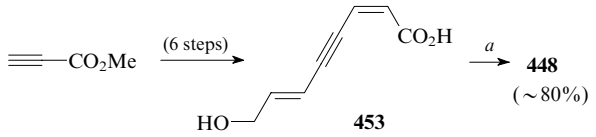



1,2-Dichloroethene and pent-1-yne served as the starting compounds in the preparation of phosphonium salt **447**. Their coupling catalyzed by a Pd(0) complex gave compound **449**, which was then converted into isomerically pure bromide **450**. The reaction sequence included coupling of stannyl derivative **451** with *trans*-iodoprop-2-en-1-ol (**452**) accessible from propargyl alcohol.



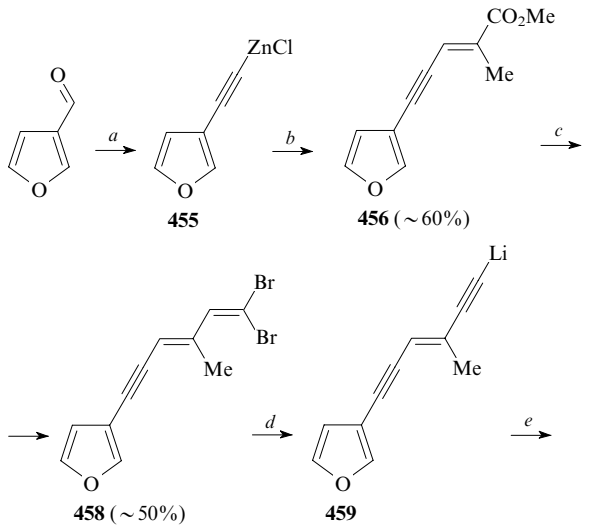
(*a*) $Bu^nNH_2$, CuI, $Pd(PPh_3)_4$, PhH; (*b*) (1) LDA, $Et_2O$; (2) $Me_3SnCl$; (*c*) 1) $PdCl_2(PhCN)_2$, DMF; (2) NBS, $PPh_3$, $CH_2Cl_2$; (*d*) $PPh_3$, PhH.

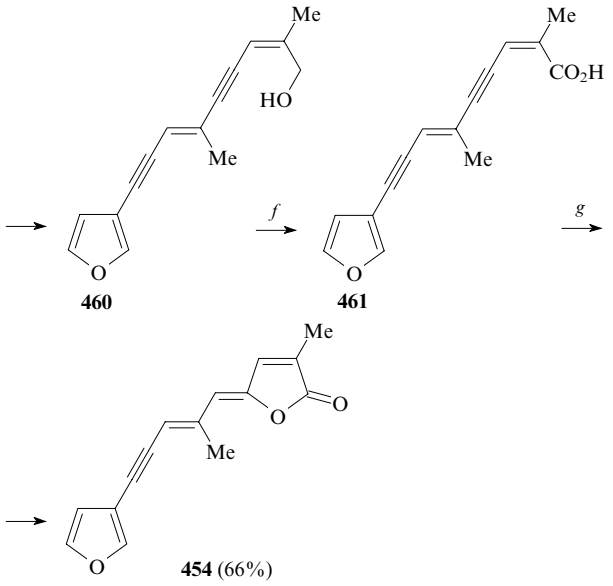
Butenolide **448** was obtained from acid **453**, which was prepared in a reaction sequence including coupling of acetylenic derivatives with vinyl halides in the presence of palladium catalyst.



(*a*) (1) $AgNO_3$, $Me_2CO$; (2) tetra-n-propylammonium perruthenate (TPAP), NMO, $CH_2Cl_2$.

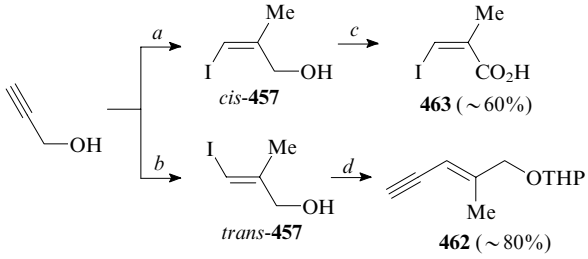
The molecule of the butenolide freelingyne (**454**) contains an acetylene group at a furan ring conjugated with a triene system. It is obvious that the main challenge in the synthesis of this compound is the stereocontrolled formation of trisubstituted double bonds of the required configuration. Japanese chemists[108] successfully solved this problem by using stereoselective palladium-catalyzed reactions. One of them involved cross-coupling of organozinc compound **455** obtained from furan-3-carbaldehyde with methyl β-bromomethacrylate to give adduct **456**. The second reaction was coupling of vinyl iodide **457** with enediyne **459** obtained from diene **458**. The reaction product was dienediyne **460**. The third reaction that completed the synthesis of the target product was *Z*-stereospecific lactonization of carboxylic acid **461** containing a 4,5-triple bond.





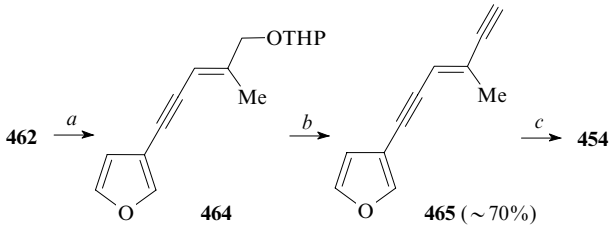
(*a*) (1) $CBr_4$, $Ph_3P$; (2) $Bu^nLi$; 3) $ZnCl_2$; (*b*) (*E*)-BrCH=C(Me)$CO_2Me$, $Pd(PPh_3)_4$; (*c*) (1) $LiAlH_4$; (2) $MnO_2$; (3) $CBr_4$, $Ph_3P$; (*d*) $Bu^nLi$; (*e*) (*Z*)-ICH=C(Me)$CH_2OH$ (**457**), $Pd(PPh_3)_4$, piperidine; (*f*) (1) $MnO_2$; (2) $NaClO_2$; (*g*) $PdCl_2(MeCN)_2$, $Et_3N$, dppe.

This methodology was used in an alternative synthesis of freelingyne (**454**).[109] Propargyl alcohol was used as the starting compound, which was converted into iodoalkenes *cis*-**457** and *trans*-**457** with >99% stereoselectivities. Cross-coupling of the *trans*-isomer (after protection of the hydroxy group) with the commercially available Iotsich reagent afforded enyne **462**. The *cis*-isomer was oxidized to acid **463**.



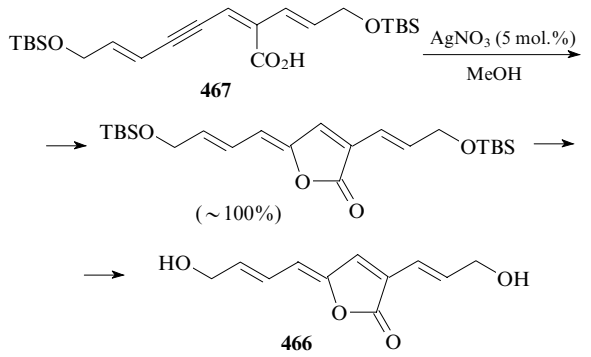
(*a*) (1) MeMgBr, CuI; (2) $I_2$; (*b*) (1) $Me_3Al$, $Cp_2ZrCl_2$; (2) $I_2$; (*c*) (1) PCC, zeolite, $CH_2Cl_2$; (2) $NaClO_2$, $H_2O_2$, $NaH_2PO_3$, MeCN; (*d*) (1) 3,4-dihydro-2*H*-pyran (DHP), TsOH; (2) HC≡CMgCl, $Pd(PPh_3)_4$ (5 mol.%).

The organozinc compound generated *in situ* from compound **462** was coupled with 3-iodofuran in the presence of a Pd(0) complex. The product **464** was converted into enediyne **465** by conventional methods; Pd(0) – CuI – $Et_3N$-catalyzed coupling of **465** with carboxylic acid **463** afforded freelingyne (**454**) in ~60% yield.

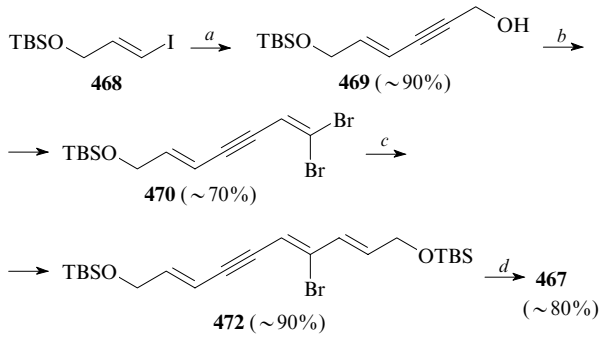


(*a*) (1) $Bu^nLi$; (2) $ZnBr_2$; (3) 3-iodofuran, $Pd(PPh_3)_4$ (5 mol.%); (*b*) (1) TsOH, MeOH; (2) **314**, Py, $CH_2Cl_2$; (3) $CBr_4$, $Ph_3P$, $K_2CO_3$; (4) NaHMDS; (5) $Bu^nLi$; (6) MeOH; (*c*) **463**, $Pd(PPh_3)_4$ (5 mol.%), CuI, $Et_3N$.

Palladium-catalyzed stereocontrolled cross-coupling of vinyl derivatives was also efficiently used to prepare yet another representative of γ-alkylidenebutenolides — lissoclinolide (**466**).[110] The key step was $AgNO_3$-catalyzed lactonization of enynoic acid **467**.

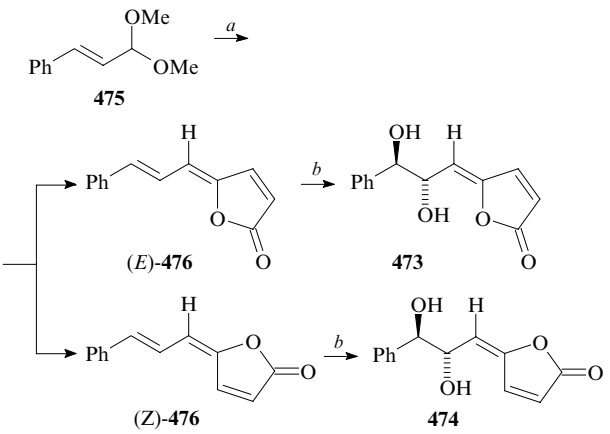



The synthesis of acid **467** started from propargyl alcohol, which was coupled with vinyl iodide **468** (obtained from propargyl alcohol) to give acetylenic alcohol **469**. Using conventional procedures, this product was converted into dibromide **470**, which underwent Pd(II)-catalyzed stereoselective (>98%) cross-coupling with vinylzirconium derivative **471** (also obtained from propargyl alcohol). Vinyl bromide **472** thus formed was further converted into acid **467** using a conventional procedure.



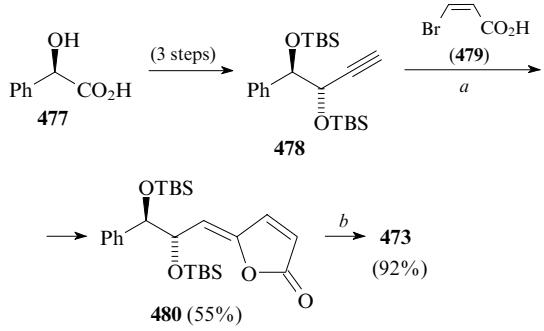

(*a*) $HC{\equiv}CCH_2OH$, $Pd(PPh_3)_4$ (5 mol.%), pyrrolidine;
(*b*) (1) DMSO, $(COCl)_2$, $Et_3N$; (2) $CBr_4$, $Ph_3P$, $K_2CO_3$;
(*c*) (*E*)-$TBSOCH_2CH{=}CHZrCp_2Cl$ (**471**), $PdCl_2(PPh_3)_2$ (5 mol.%);
(*d*) (1) $Bu^nLi$; (2) $CO_2$.

Stereoisomeric lactones, (+)-goniobutenolide A (**473**) and (−)-goniobutenolide B (**474**), isolated from the bark of an endemic Thailand plant, are cytotoxic with respect to human tumour cells. In the simplest synthesis of butenolides **473** and **474** characterized by a high overall yield (60%),[111] cinnamaldehyde dimethyl acetal (**475**) was used as the starting compound. Its condensation with α-trimethylsilyloxyfuran (**288**) gave a mixture of isomers (*E*)-**476** and (*Z*)-**476** in a 1 : 1 ratio. The isomers were separated by column chromatography and subjected to chemoselective asymmetric dihydroxylation to give butenolides **473** and **474**, respectively (the enantiomeric excess was 99% for each isomer).



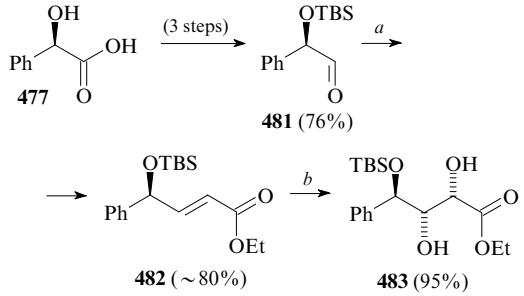

(*a*) **288**, $TiCl_4$, KOAc, AcOH; (*b*) AD-mix-β.

The enantioselective synthesis of (+)-goniobutenolide A (**473**) was also accomplished using mandelic acid (**477**).[112] Acetylene **478** obtained from this acid was subjected to Pd(II)-catalyzed stereoselective coupling with (*Z*)-3-bromoacrylic acid (**479**), which was accompanied by lactonization. Deprotection of silylated lactone **480** completed the synthesis.




(*a*) $PdCl_2(PPh_3)_2$ (0.05 equiv.), CuI (0.05 equiv.), $Et_3N$, MeCN;
(*b*) THF, 3 M HCl.

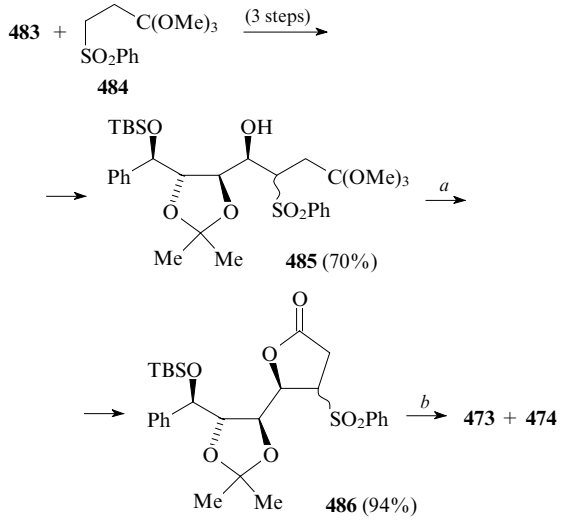
Another method for the synthesis of butenolides **473** and **474** from the same precursor **477** involved preparation of aldehyde **481**,[113] which was converted into unsaturated ester **482** by the Wittig stereoselective olefination. The $OsO_4$-catalyzed dihydroxylation of the latter mainly resulted in stereoisomer **483** from which admixtures were removed by chromatography.




(*a*) $Ph_3P{=}CHCO_2Et$, PhMe; (*b*) $OsO_4$, NMO, $Me_2CO$ (aq.).

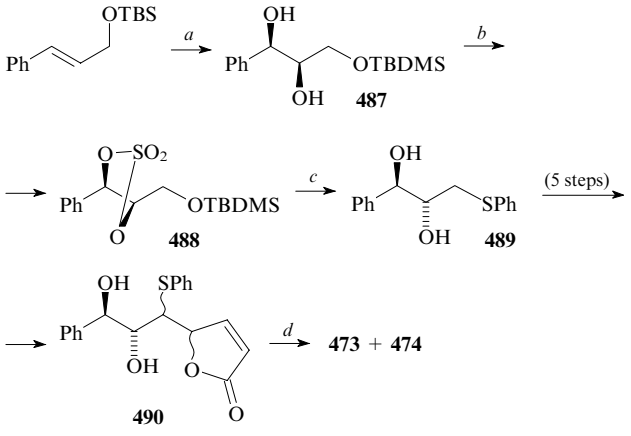
Then conventional reactions of diol **483** including coupling with 3-phenylsulfonylorthopropionate (**484**) afforded

sulfonyl derivative **485**, which was smoothly converted into butanolide **486** in acidic medium. Dehydrosulfonylation and desilylation of the latter product resulted in a mixture of lactones **473** and **474** in a 3 : 1, ratio which were readily separated by chromatography (overall yield 75%).



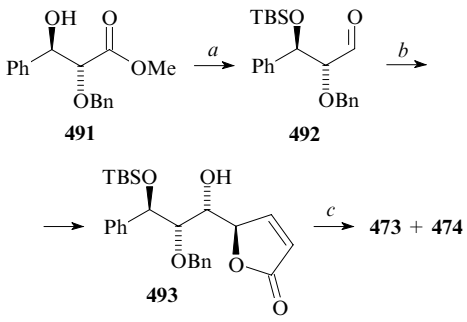

(*a*) CSA, PhMe; (*b*) (1) DBU, $CH_2Cl_2$; (2) AcOH (aq.), THF.

The chiral centres in butenolides **473** and **474** were constructed using asymmetric dihydroxylation of silyl derivative of cinnamyl alcohol to give *threo*-diol **487** (*ee* ~95%); this was converted into cyclic sulfate **488**, which underwent rearrangement–opening using $PhS^-$ as the nucleophile.[114] The *erythro*-diol **489** was then converted into a mixture of diastereomeric butenolides **490**, their treatment with AgF in pyridine resulted in elimination of benzenethiol. The ratio of isomers **473** and **474** in the mixture was 1.6 : 1 and the overall yield was 68%. The individual compounds were isolated by column chromatography.



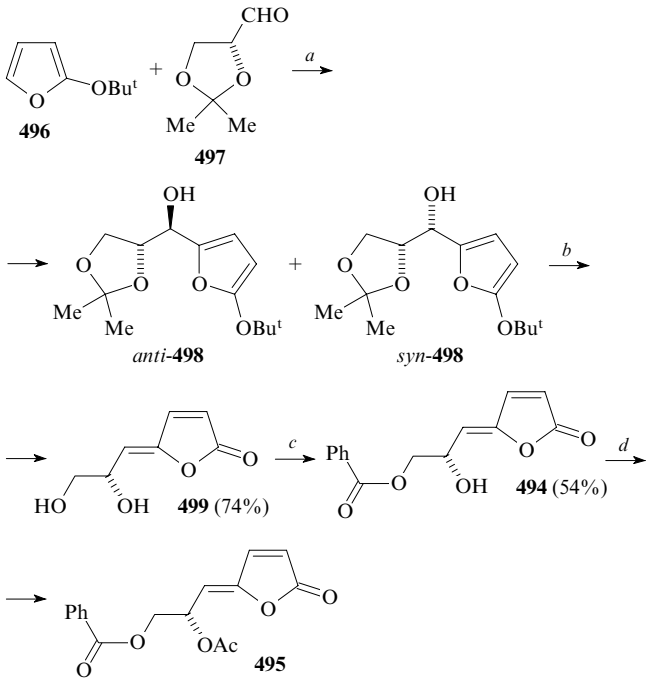

(*a*) AD-mix-β; (*b*) (1) $SOCl_2$, $NEt_3$; (2) $RuCl_3$, $NaIO_4$; (*c*) TBAF, PhSNa, $H_2SO_4$; (*d*) AgF, Py.

The enantioselective synthesis of butenolides **473** and **474** was also based[115] on ester **491** with high enantiomeric purity.[116] The key step of this approach is diastereoselective aldol condensation of aldehyde **492** obtained from ester **491** with α-trimethylsilyloxyfuran (**288**). Deprotection of butenolide **493** and dehydration resulted in a separable mixture of isomers **473** and **474**.



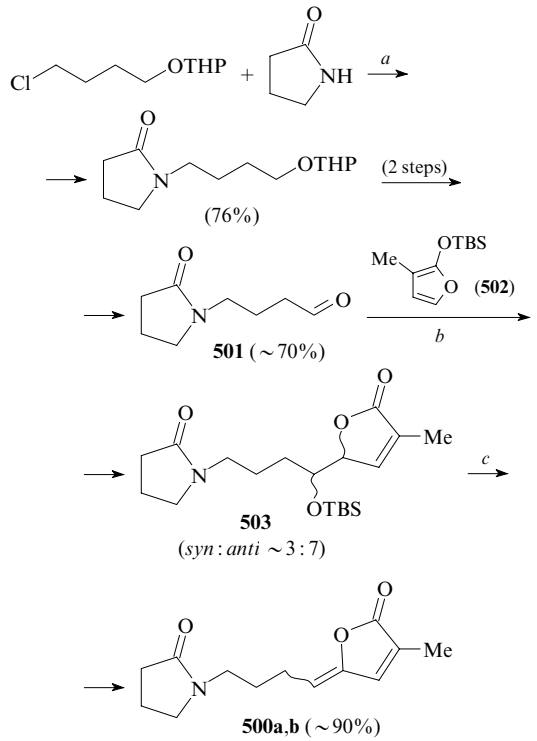

(*a*) (1) TBSOTf, DMAP, $CH_2Cl_2$; (2) DIBAL-H, PhH; (*b*) **288**, $Ti(OPr^i)_2Cl_2$, $CH_2Cl_2$; (*c*) (1) TBAF, THF; (2) $TiCl_4$, $CH_2Cl_2$.

(+)-Melodorinol (**494**) and (+)-acetylmelodorinol (**495**) isolated from the plant *Melodorum fruticosum* (Annonaceae) exhibit cytotoxicity with respect to some human tumour cell lines. The condensation of a metallated α-alkoxyfuran **496** with D-glyceraldehyde derivative **497** served as the key step in the total synthesis of lactones **494** and **495**.[117] The stereoisomeric mixture **498** thus formed was hydrolyzed to give stereochemically homogeneous butenolide **499** (for an alternative route to butenolide **499**, see Ref. 118); its chemoselective benzoylation with benzoyl cyanide gave (+)-melodorinol (**494**); acetylmelodorinol (**495**) was obtained by acetylation of melodorinol.




(*a*) $Bu^nLi$, THF; (*b*) TsOH, THF (aq.); (*c*) BzCN, $Et_3N$, THF; (*d*) $Ac_2O$, Py, $CH_2Cl_2$.

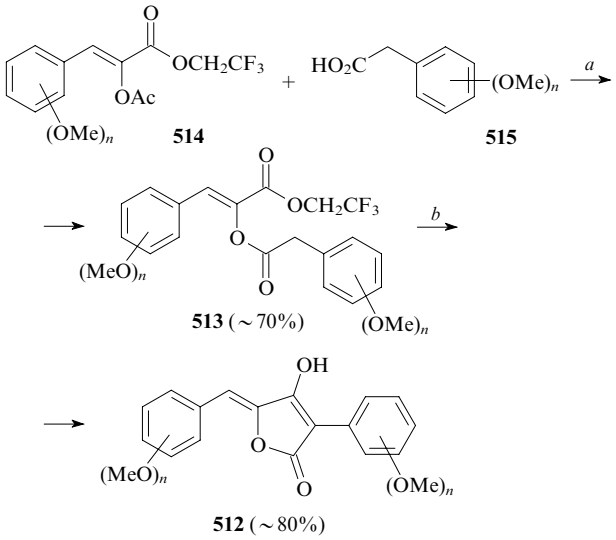
The alkaloids pandamarilactams 3Y (**500a**) and 3X (**500b**) with unique structures isolated from the medical plant *Pandanus amaryllifolius* contain a γ-alkylidenebutenolide fragment. The synthesis of these compounds includes aldol type coupling of aldehyde **501** and silyloxyfuran **502**.[119] On treatment with DBU, the resulting aldol mixture **503** (*syn* : *anti* ~3 : 7) gives alkylidenebutenolides **500a** and **500b** (~9 : 1), the individual components being isolated by HPLC.




Isomers: *Z* (**a**), *E* (**b**); (*a*) $KF/Al_2O_3$, KI (cat.), DMF; (*b*) TBSOTf, TBAF, THF; (*c*) (1) DBU, THF; (2) HPLC.

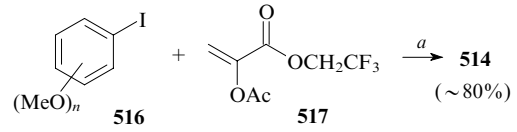
Metabolites of cyanobacteria, nostoclides I (**504a**) and II (**504b**), containing aromatic substituents in the side chain, which are promising as herbicides, were synthesized from commercially available phosphoramidate **505** and substituted benzoic acids **506a**,**b** (Scheme 16).[120] Compounds **506a**,**b** were converted by conventional methods into benzaldehydes **507a**,**b**, which were introduced in the final stage of the synthesis in the TBSOTf-catalyzed coupling with α-silyloxyfuran **508**. The latter compound was prepared from phosphoramidate **505** as the starting compound. The regioselective introduction of the isopropyl group into the benzylbutenolide molecule **509** was accomplished by 1,3-dipolar cycloaddition of 2-diazopropane. The subsequent thermolysis of the resulting pyrazolinolactone **510** yielded butenolide **511**, which was converted into α-silyloxyfuran **508** by standard reactions.

A different approach was needed for stereocontrolled synthesis of a series of metabolites of some fungi species, pulvinones, generally described by formula **512**, which possess antibacterial properties.[121, 122] This was based on stereoselective cyclization of 3-aryl-2-(arylacetoxy)acrylates **513** obtained by transesterification of the corresponding acetyl cinnamates **514** with arylacetic acids **515**.



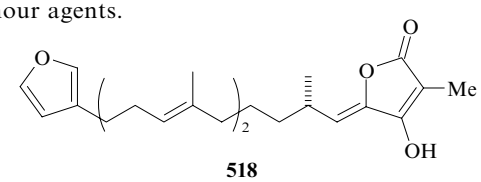

**514**, **515**: 4-, 2,4- and 3,4-isomers; (*a*) (1) $CF_3CH_2OLi$, THF; (2) Dowex XW-50; (3) DCC, DMAP, $CH_2Cl_2$; (*b*) $Bu^tOK$, DMF.

Compounds **514** are the Heck coupling products of aryl iodides **516** with 2-acetoxyacrylate **517**.

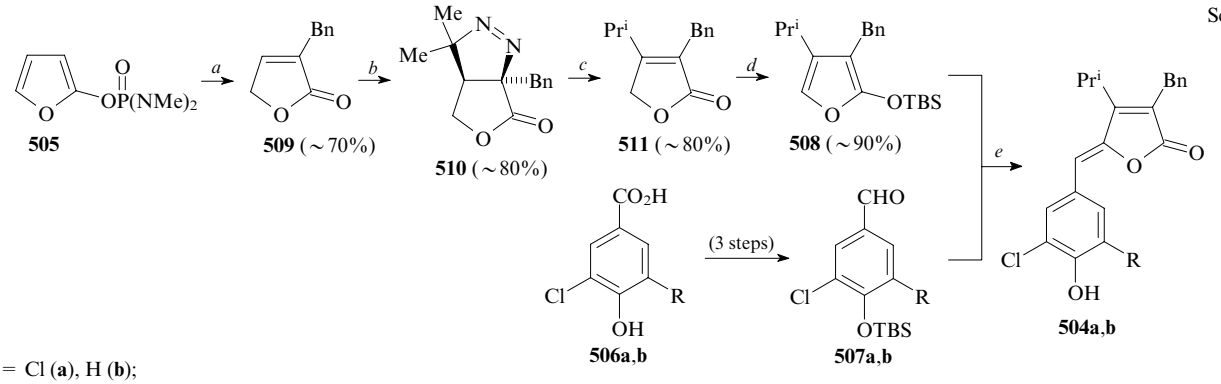



**516**: 4-, 2,4- and 3,4-isomers; (*a*) $Pd(OAc)_2$ (5 mol.%), NaOAc, $Bu^n_4PBr$, DMF.

Yet another representative of alkylidene-β-hydroxybutenolides (derivatives of so-called tetronic acid), variabilin (**518**), solated from marine sponges in research for iantitumour agents.



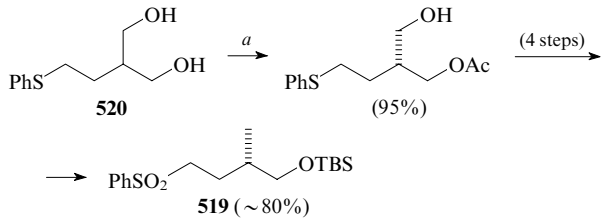

Scheme 16




R = Cl (**a**), H (**b**);

(*a*) (1) $Bu^nLi$, THF; (2) BnBr; (*b*) $Me_2C{=}N_2$, $Et_2O$; (*c*) PhH, Δ; (*d*) TBSOTf, $Et_3N$, $CH_2CCl_2$; (*e*) (1) TBSOTf, $CH_2Cl_2$; (2) DBU, $CHCl_3$; (3) 3 M HCl.

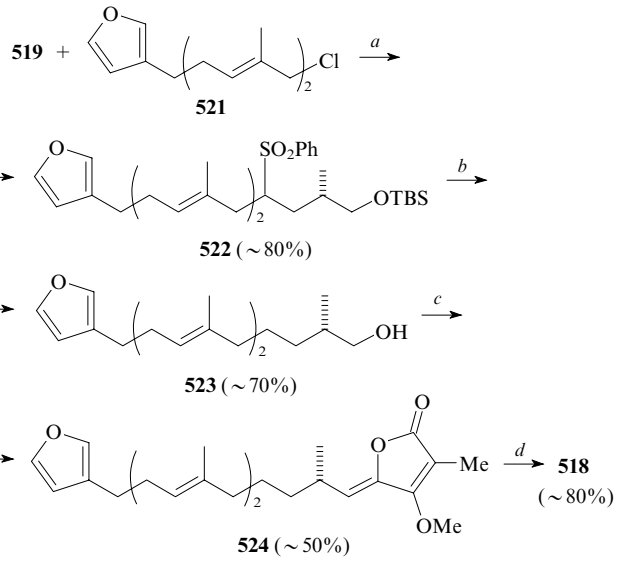
The principal problem to be solved for enantioselective synthesis of this compound was to construct a fragment containing a branched asymmetric centre.[123] To this end, the authors applied a chemico-enzymatic strategy for the preparation of key chiral sulfone **519**. Thus desymmetrization of the preceding 1,3-diol **520** was performed using lipase-catalyzed asymmetric acetylation.




**520** (95%) **519** (~80%)

(*a*) Lipase PS, $CH_2{=}CHOAc$, $Et_2O$.

The alkylation of sulfone **519** with allylic chloride **521** accessible from geraniol and desulfonylation of derivative **522** furnished terminal alcohol **523**, which was oxidized to the transient aldehyde; its coupling with methyl tetronate finally yielded compound **524**, an immediate precursor of variabilin (**518**).

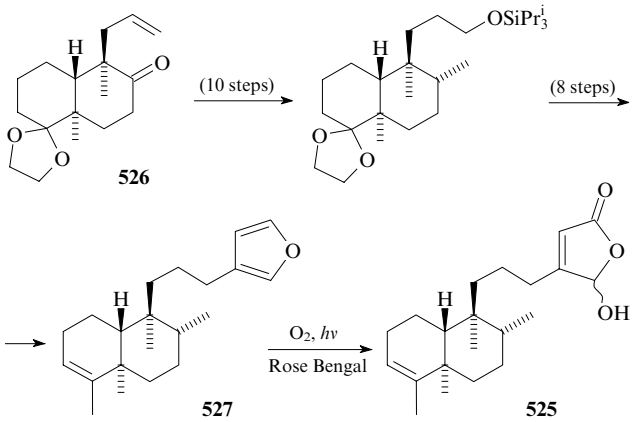



**521** **522** (~80%) **523** (~70%) **524** (~50%) **518** (~80%)

(*a*) $Bu^nLi$, HMPA, THF; (*b*) Na, $Pr^iOH$, THF; (*c*) (1) TPAP, NMO, $CH_2Cl_2$; (2) LDA, methyl tetronate, THF; (*d*) $Pr^nSLi$, HMPA.

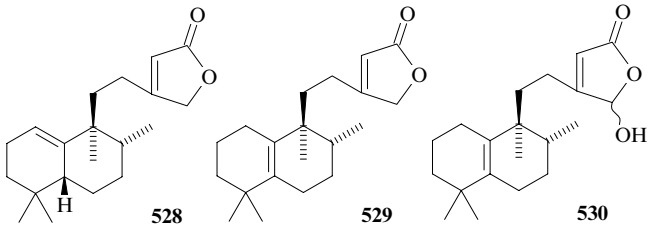
## 4. γ-Hydroxybutenolides

In recent years, substituted isoprenoid butenolides containing a hydroxy group in the γ-position of the lactone ring have been isolated from various sources. The biological activity of these compounds is of practical interest. Thus butenolide **525** with a clerodane-type isoprenoid framework possesses bactericidal activity, comparable with that of streptomycin, against gram-positive bacteria (see Ref. 124 and references cited therein). The total synthesis of this compound (overall yield ~3%) is based on a multistep route starting from accessible perhydronaphthalene **526** of high enantiomeric purity having the required configuration of three chiral centres.[124,125] In the final step of this synthesis, the formation of the butenolide fragment in molecule **525** was performed by photochemical oxidation of substituted furan **527** in the presence of a dye Rose Bengal.



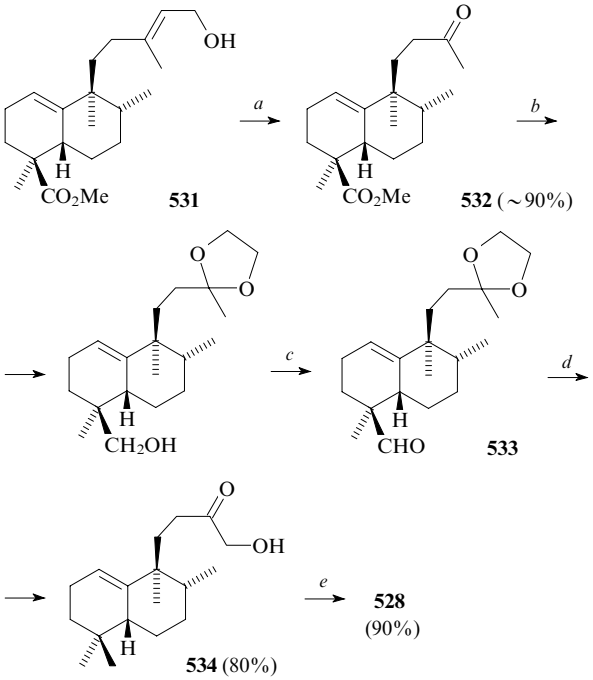

**526** **527** **525**

Halimanolides **528**, **529** and **530** with a carbon framework isomeric to that of butenolide **525** were also isolated from a plant of the Annonaceae family. Their partial synthesis was started from accessible halimic acid.[126]




**528** **529** **530**

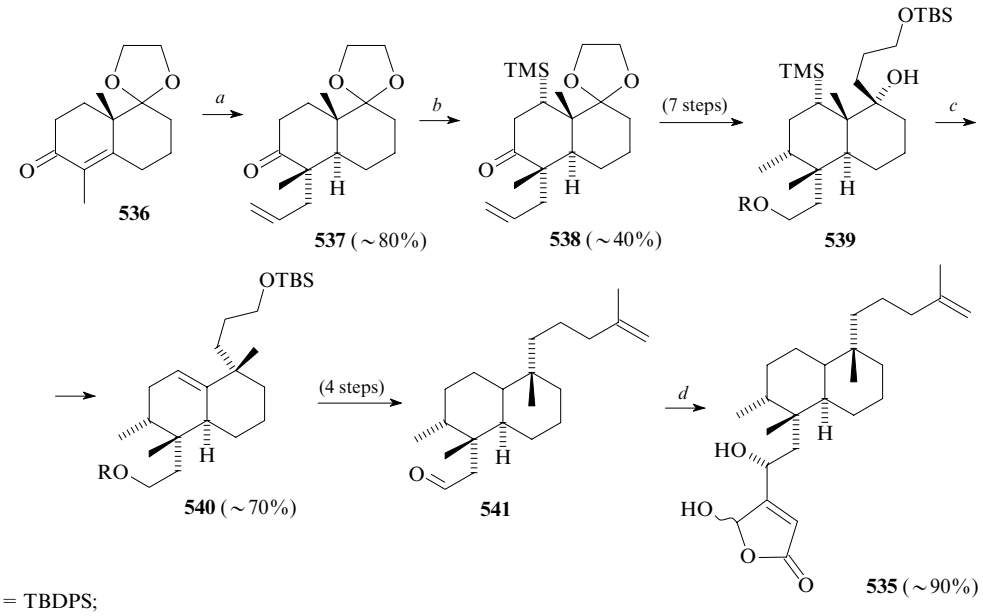
Thus oxidative degradation of halimic acid ester (**531**) gives ketone **532**, which was converted into keto aldehyde ketal **533** and then to hydroxy ketone **534** using conventional methods. The latter reacted with ketenephosphorane smoothly giving butenolide **528**.




**531** **532** (~90%) **533** **534** (80%) **528** (90%)

(*a*) (1) $OsO_4$, NMO, THF, $Bu^tOH$ (aq.); (2) $Pb(OAc)_4$, PhH; (*b*) (1) ethylene glycol, TsOH, PhH; (2) LAH, $Et_2O$; (*c*) TPAP, NMO, $CH_2Cl_2$; (*d*) (1) $NH_2NH_2 \cdot H_2O$, KOH; (2) TsOH, $Me_2CO$; (3) LDA, TMSCl, THF; (4) $OsO_4$, NMO, $Bu^tOH$ (aq.); (*e*) $Ph_3P{=}C{=}C{=}O$, PhH.

Scheme 17



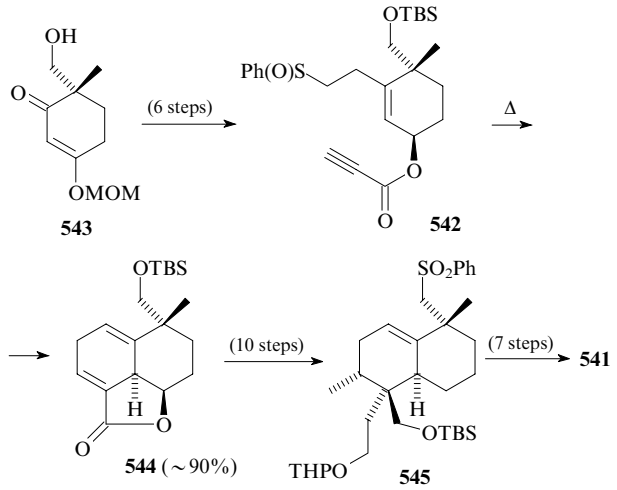

R = TBDPS;

(*a*) (1) $Li/NH_3$, THF; (2) isoprene; (3) AllBr; (*b*) (1) LDA, PhSSPh, THF, HMPA; (2) mCPBA, $CH_2Cl_2$; (3) $(MeO)_3P$, PhH; (4) TMSLi, HMPA, $Et_2O$; (*c*) (1) $BF_3$, $CH_2Cl_2$; (2) TsOH · Py, EtOH; (*d*) 1) $Bu^nLi$, THF; (2) 3-bromofuran; (3) $O_2$, *hv*, Rose Bengal, DIPEA, $CH_2Cl_2$.

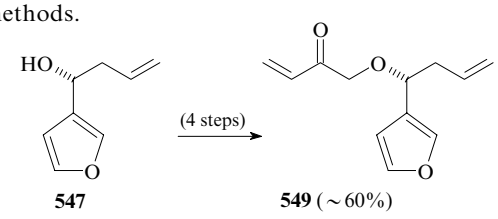
Iodine-induced isomerization of this compound in benzene afforded butenolide **529**, while γ-hydroxylation of lactone **528** and double bond migration when applying the reaction sequence (1st step: LDA, TBSOTf, THF; 2nd step: mCPBA, $CH_2Cl_2$; 3rd step: HI, PhH) gave finally hydroxybutenolide **530**.

Yet another representative of this group, dysidiolide (**535**), the cdc25A protein phosphatase inhibitor, exhibiting clear-cut antitumour activity, was isolates from a Caribbean sponge. The first synthesis of this compound was performed by Corey *et al.*[127] starting from accessible homochiral enedione monoketal **536** (Scheme 17). This synthetic route comprises several key steps. The reduction of enone **536** with lithium in liquid ammonia and the treatment of the enolate thus formed with allyl bromide result in diastereoselective formation of allyl derivative **537**. Following introduction of the TMS group into the β-position relative to the carbonyl group of ketone **537**, the intermediate **538** was converted into derivative **539**, which could be subjected to a skeletal rearrangement. The carbon skeleton and the stereochemistry of compound **540** formed upon the rearrangement were fully identical to those in butenolide **535**. The subsequent transformations included the formation of aldehyde **541**, which was converted into the target product.

The intramolecular Diels–Alder-type reaction involving the ethynyl group and the diene system resulting from elimination of the sulfinyl group from sulfoxide **542** was the key step in another synthetic route to dysidiolide (**535**).[128] The substrate **542** needed for this reaction was obtained from accessible homochiral cyclohexenone derivative **543**. Using conventional methods, the tricyclic compound **544** formed upon thermolysis of **542** was converted, *via* intermediate sulfone **545**, into aldehyde **541**, the immediate precursor of dysidiolide (**535**).

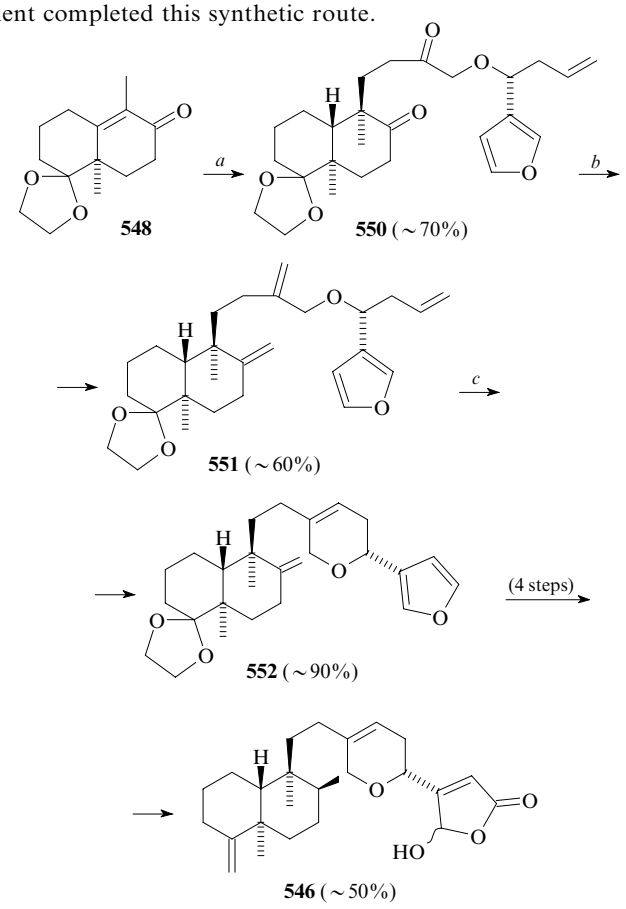



The first synthesis of (−)-cacospongionolide B (**546**),[129] isolated from a marine sponge and possessing antimicrobial, cytostatic and antiinflammatory activities, was based on the use of accessible synthons: homoallylic alcohol **547** (*ee* 94%) and enantiomerically pure enone **548**. In the first step, the alcohol was converted into enone **549** by standard methods.



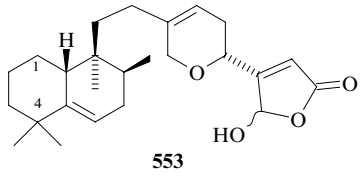

Compound **549** was subjected to the Michael condensation with the enolate generated by reduction of enone **548** with lithium in liquid ammonia. Bis-olefination of the dicarbonyl compound **550** obtained in this diastereoselective reaction afforded triene **551**. The ring-closing metathesis of triene **551** produced dihydropyran **552**. The stereo-

selective hydrogenation of the *exo*-methylene group in compound **552**, deketalization and methylenation of the carbonyl group thus formed and the subsequent photooxidation of the furan ring to a hydroxybutenolide fragment completed this synthetic route.



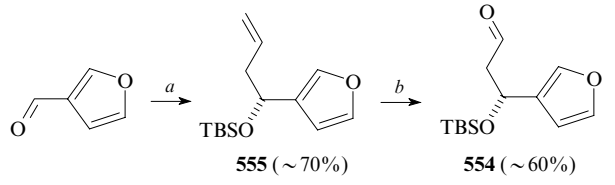

(*a*) (1) Li/$NH_3$, Bu$^t$OH, $Et_2O$; 2) **549**; (*b*) $Ph_3P{=}CH_2$, DMSO; (*c*) the Grubbs catalyst, $CH_2Cl_2$.

Yet another representative of this series of natural butenolides, (−)-cacospongionolide F (**553**), was also synthesized by a convergent scheme.[130]



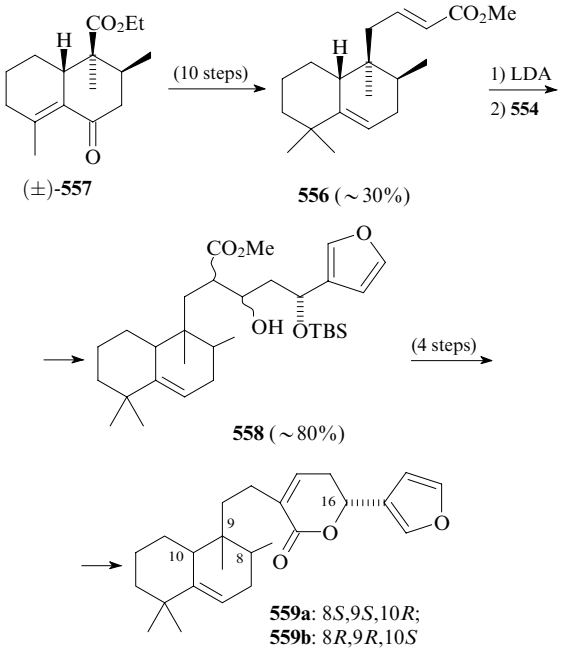
**553**

In the crucial step of this synthesis, optically active aldehyde **554** (*ee* 93%) obtained upon asymmetric allylation of furan-3-carboxaldehyde followed by oxidative degradation of the terminal double bond of the allyl derivative **555**

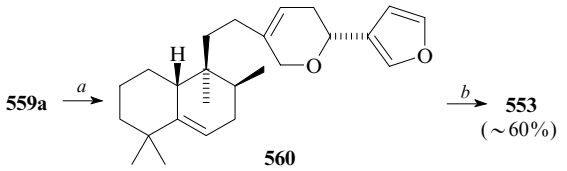



(*a*) (1) AllMgBr, (−)-DIPCl (DIPCl is diisopinocampheyl chloroborane); (2) TBSOTf, 2,6-lutidine; (*b*) $OsO_4$, NMO, $NaIO_4$.

was coupled with racemic bicyclic ether **556**. The latter was synthesized using standard methods from known keto ester (±)-**557**. Treatment of the enolate generated from ester **556** with aldehyde **554** yielded a mixture of diastereomers **558**, which were then converted by simple operations into a mixture of isomeric dihydropyranones **559a**,**b** (overall yield ~40%).

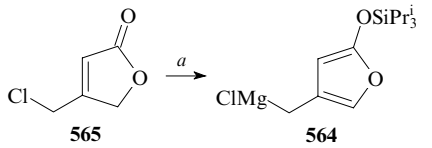



The stereoisomer **559a** with appropriate configuration established by X-ray diffraction analysis was isolated by chromatography. This was converted into substituted dihydropyran **560** and, after photooxidation of the furan fragment, into butenolide **553**.



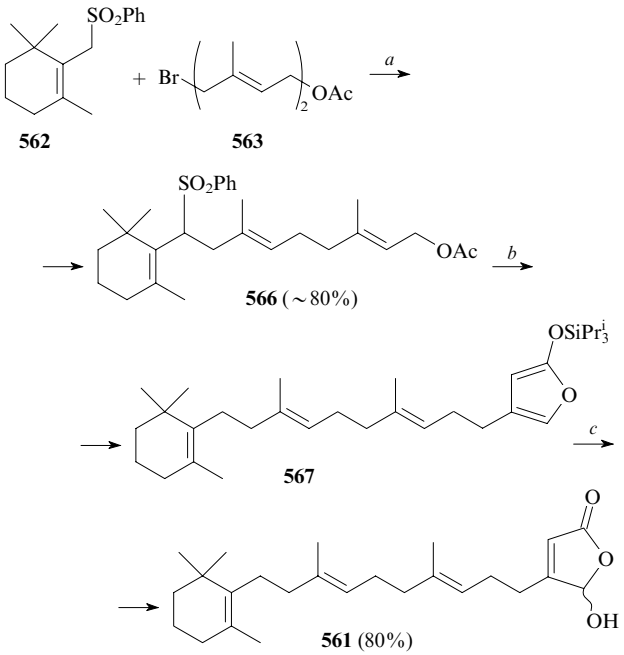

(*a*) (1) DIBAL-H, $CH_2Cl_2$; (2) $Et_3SiH$, $F_3B{\cdot}OEt_2$; (*b*) $O_2$, *hv*, Rose Bengal, DIPEA, $CH_2Cl_2$.

Yet another representative of γ-hydroxybutenolides from the marine sponge is luffariellolide (**561**). Unlike the compounds considered above, this compound contains a monocyclic fragment connected to the lactone ring by a chain of two *trans*-isoprene units.[131] This has determined the strategy of its synthesis. The scheme was based on coupling of three synthons: known derivatives of commercially available cyclogeraniol sulfone (**562**), bromide **563** and the Grignard reagent **564**. The Grignard reagent **564** was synthesized in two steps from readily accessible lactone **565**.




(*a*) (1) TIPSOTf, $Et_3N$, $CH_2Cl_2$; (2) Mg, THF.

The condensation of bromide **563** with the metallated sulfone **562** smoothly yielded compound **566**, which was desulfonylated, the terminal acetoxy group was replaced by a chlorine atom and the product was coupled with the Grignard reagent **564**. The resulting furyl derivative **567** was oxidized to produce the target compound **561**.




(*a*) (1) Bu$^n$Li, THF, HMPA; (2) MeONa, MeOH; (*b*) (1) Li, $EtNH_2$, $Et_2O$; (2) *N*-chlorosuccinimide (NCS), $Me_2S$; (3) **564**, $Li_2CuCl_4$, THF; (*c*) (1) dimethyldioxirane; (2) $H_2O$.

* * *

The material presented in this review demonstrates the application of almost the whole range of modern synthetic methods of organic chemistry for the preparation of natural butano- and butenolides. Solving the problems faced by total syntheses of these compounds appreciably enriches the theoretical and applied potential of fine organic synthesis, results in advancing and development of a large number of methods and expedients that open up efficient routes to complex molecules.

The topicality of further development of this area of research is due to not only the fundamental aspect but also the demand for efficient methods for the synthesis of compounds of this class, as they possess unique practically useful properties.

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