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Derivatives of 7-Oxabicyclo[2.2.1]heptane in Nature and as Useful Synthetic Intermediates

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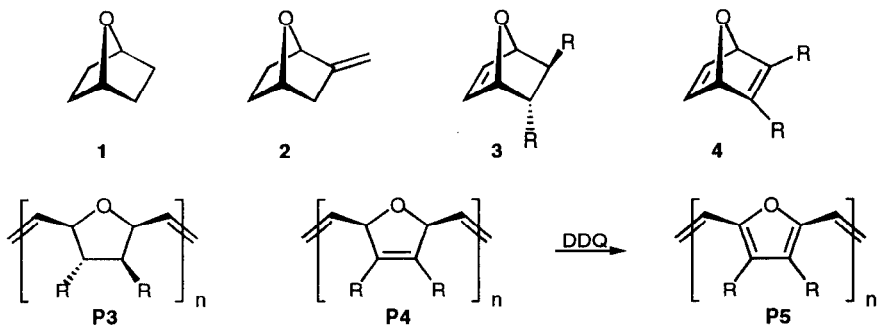
1. Introduction

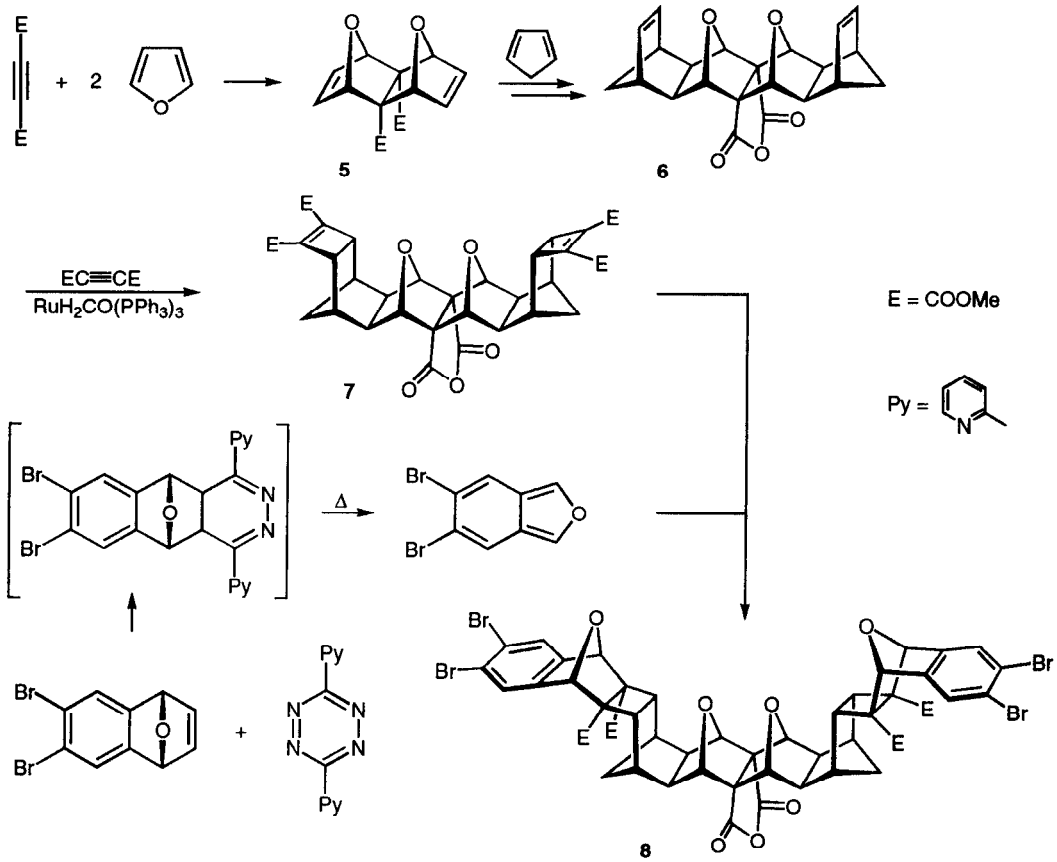
Derivatives of 7-oxabicyclo[2.2.1]heptanes (7-oxanorbornanes) are found in Nature, some of these having interesting biological activities. Analogues of these compounds have also been found to be bioactive. In the laboratory these bicyclic ethers are readily available through Diels-Alder addition of furans or other methods. The 7-oxanorbornanes and their unsaturated derivatives (7-oxabicyclo[2.2.1]hept-2-enes: 7-oxanorbornenes; 7-oxabicyclo[2.2.1]hepta-2,5-dienes: 7-oxanorbornadienes) undergo a variety of reactions making them quite useful synthetic intermediates in the total synthesis of natural products and analogues. Efficient procedures are now available that can provide enantiomerically pure 7-oxanorbornanes making them useful chirons. The chemistry of the 7-oxanorbornanes has already been reviewed several times during the last twelve years.[1-4] This report will therefore concentrate on the less known aspects of the 7-oxanorbornane chemistry and on the most recent developments without neglecting to review a number of principles that will guide the synthetic chemist in his own applications. Although we have chosen illustrations mostly from the field of natural product synthesis, it should not be forgotten that nowadays the 7-oxabicyclo[2.2.1]heptane systems are very valuable building blocks for polymers and material sciences. For instance, unsubstituted 7-oxanorbornane (**1**) undergoes cationic polymerization alone or mixed with other cyclic ethers,[5] 2-methylidene-7-oxanorbornane (**2**) has been used in radical induced alkene polymerizations,[6] 7-oxanorbornenes (**3**) and 7-oxanorbornadienes (**4**) undergo living ring-opening metathesis generating a variety of functional polymers (e.g. **P3**, **P4**)[7] and conjugated polyenes (e.g. **P5**).[8]



2. 7-Oxabicyclo[2.2.1]heptanes: pieces of a molecular "LEGO"®

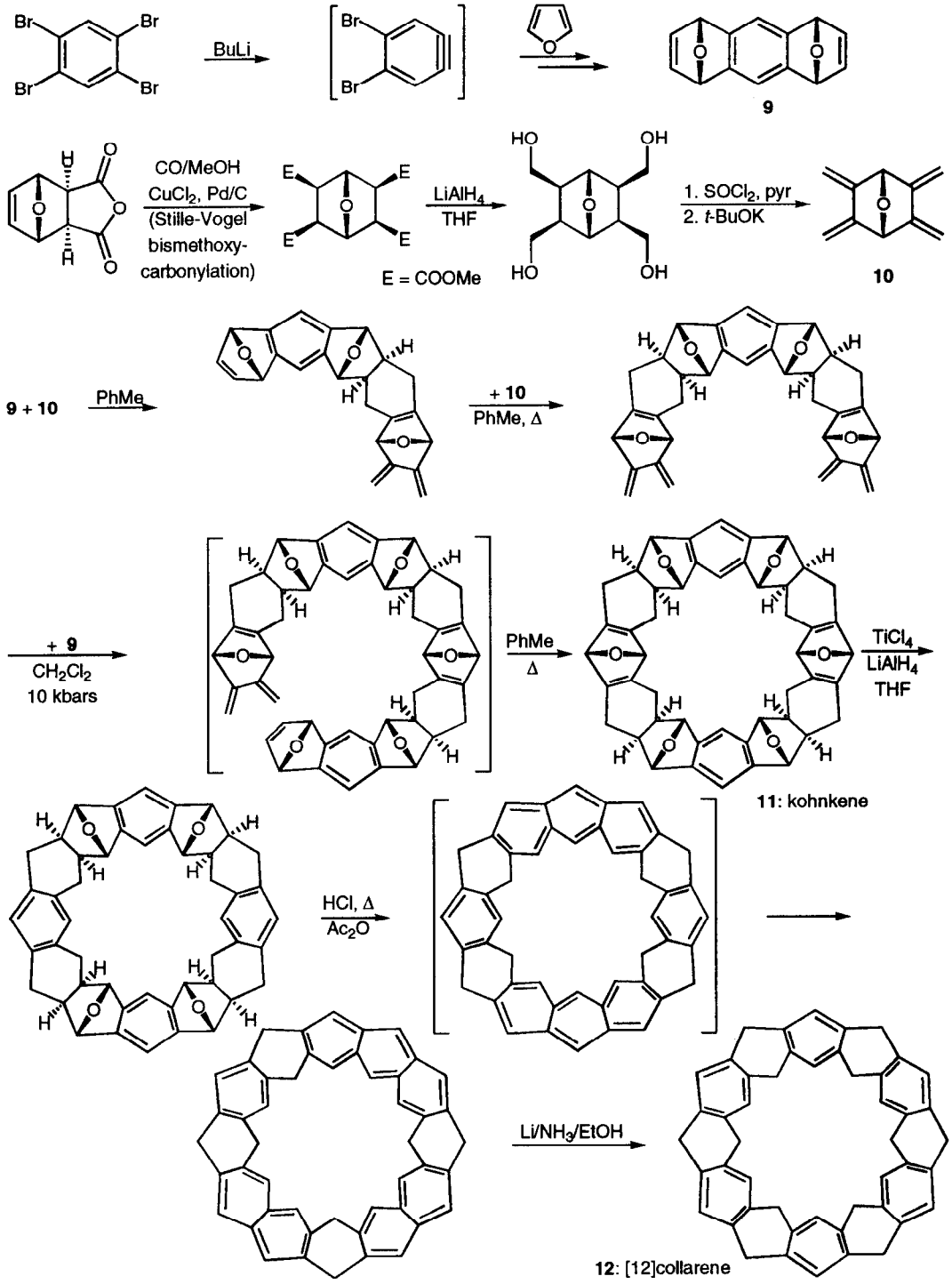
Semi-rigid U-shaped molecules with "inner-surface" functionality have been designed as hosts to provide enzyme-like pockets.[9,10] Such systems have been approached by Warrener, Wang and Russell[11] as shown in Scheme 1.

Scheme 1: Molecular LEGO® for the synthesis of U-shaped systems



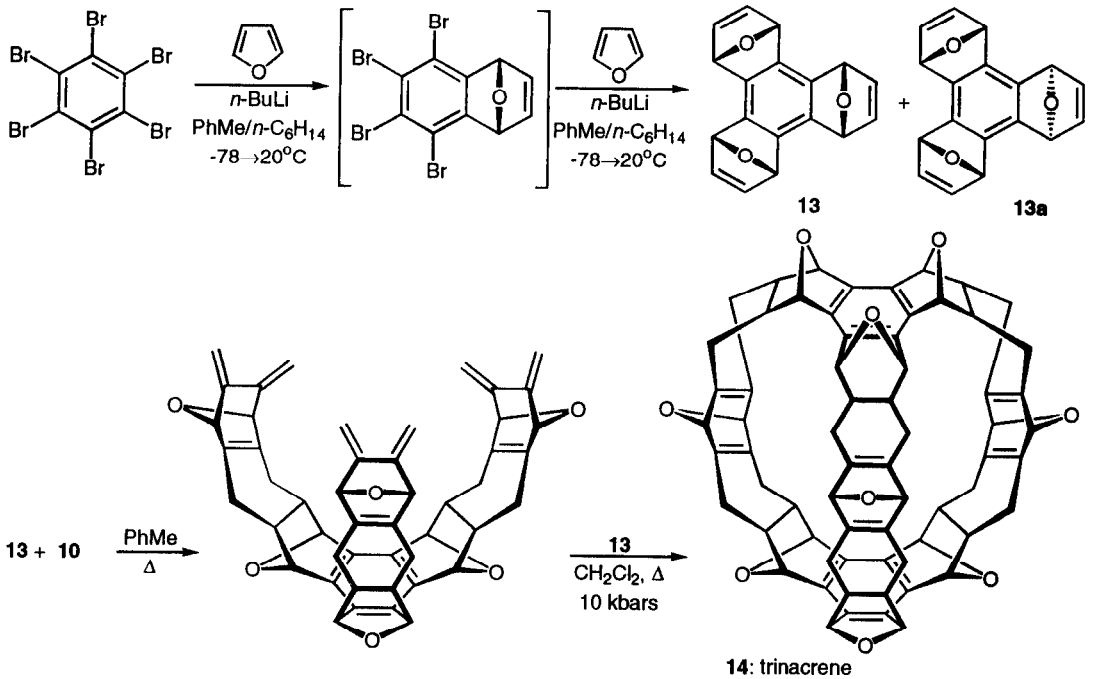
The 2:1 adduct **5** of furan to dimethyl acetylenedicarboxylate (see Chapter 5.4, Scheme 29B) is combined first with cyclopentadiene through two Diels-Alder additions giving **6**, then with dimethyl acetylenedicarboxylate through two ruthenium-catalyzed [2+2] cycloadditions (giving **7**), and finally with dibromoisobenzofuran to generate **8**.[12] Because of steric factors, the *exo* faces of the alkene moieties of 7-oxanorbornenes are favored in their cycloadditions. This facial selectivity makes these systems like pieces of LEGO® toys and thus can be used in a designed way to construct all kinds of molecular objects. Stoddart and co-workers[13] have prepared belt-like compounds such as **11** and **12** (Scheme 2A) by combining through Diels-Alder additions *cis*-1,4:5,8-diepoxy-1,4,5,8-tetrahydroanthracene (**9**) (obtained by reaction of furan with 1,2,4,5-tetrabromobenzene and *n*-BuLi)[14] and 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptene (**10**; obtained in 4 steps (64% overall yield) from the Diels-Alder adduct of furan and maleic anhydride).[15] Compound **11**, dubbed "kohnkene", has been converted into [12]collarene (**12**) through reduction of its two 7-oxanorbornadiene units, followed by acid-promoted elimination of water from the four 7-oxanorbornene moieties. This led to 1,4,7,10,14,17,21,24-octahydro-2,6:3,15-dimethyleneundecacene which underwent a selective Birch reduction into [12]collarene (**12**).

Scheme 2A: Molecular LEGO® set used for the synthesis of kohnkene (**11**) and [12]collarene (**12**)



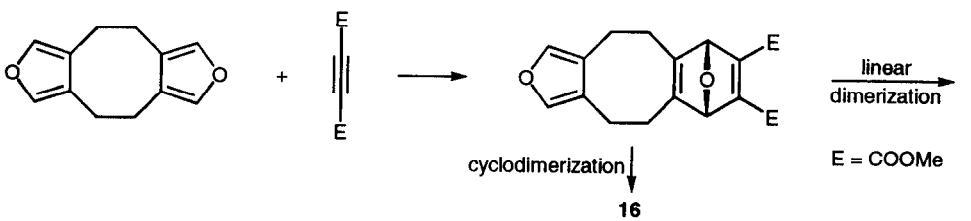
The all-*syn*-trisdienophile **13** was obtained in 0.6% yield, together with its isomer **13a** (1.8%) on treating hexabromobenzene with BuLi and an excess of furan. It reacted with tetraene **10** giving a trisadduct that reacted under high pressure with an equivalent of **13**, generating the cage compound trinacrene **14** (Scheme 2B).[16a] A better method for the generation of **13** + **13a** has been proposed. It features the double elimination of HBr from 6,7-dibromo-1,4-epoxy-1,4-dihydronaphthalene in the presence of $NaNH_2$ and furan.[16b]

Scheme 2B: Synthesis of a trinacrene

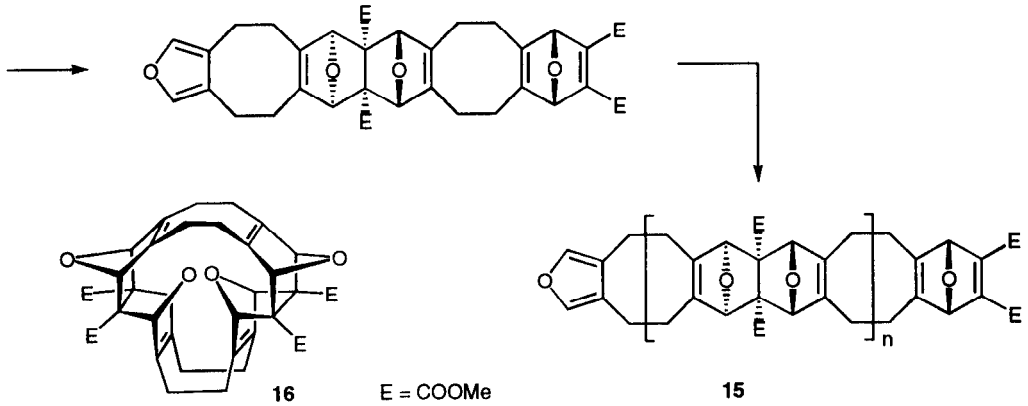


By using repetitive Diels-Alder reactions (Scheme 3), ribbon-type oligomers **15** have been prepared. Under high-pressure conditions, extended ribbon-type structures **15** with about 25 repeating units and the highly strained cage compound **16** have been obtained.[17]

Scheme 3: Semiflexible ribbon-type structures and cage-compounds by repetitive Diels-Alder additions



Scheme 3 (continued)

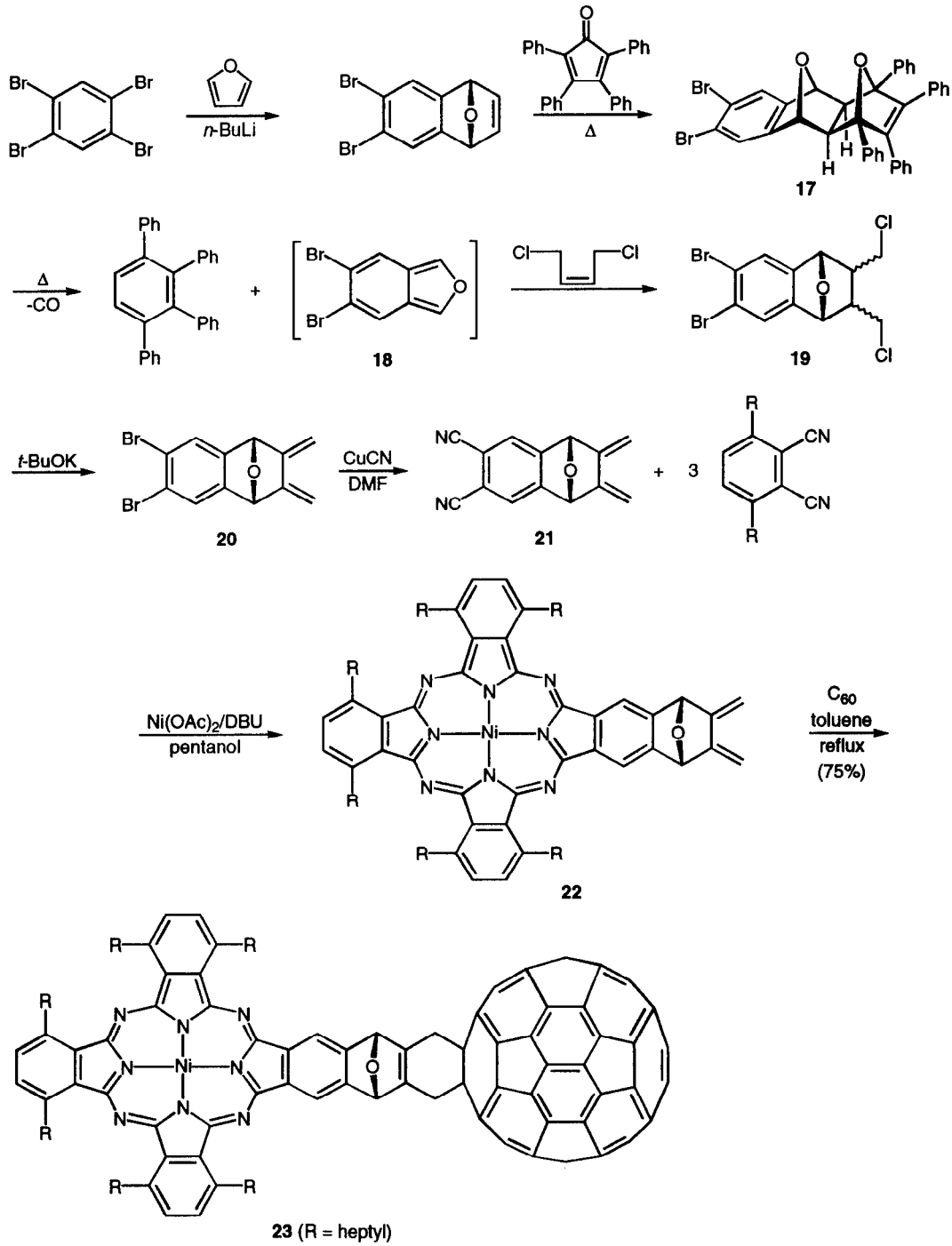


16 E = COOMe 15

3. 7-Oxabicyclo[2.2.1]heptanes for the synthesis of molecular devices

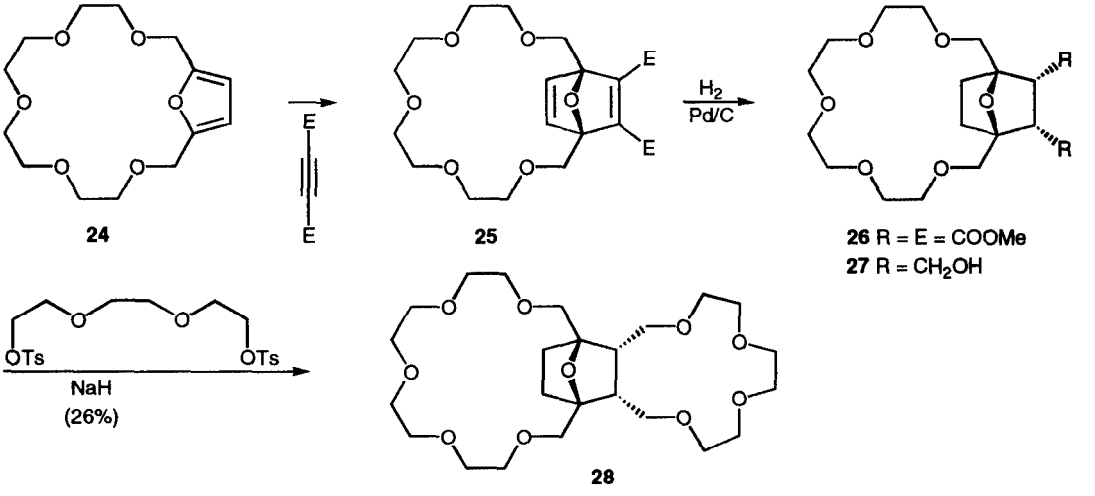
One of the most important properties of [60]fullerene is its ability to undergo multistage reductions with up to six electrons.[18] As a consequence, fulleride salts may find applications as materials for superconductivity,[19] or ferromagnetism.[20] Combining these features with other classes of compounds through Diels-Alder additions[21] opens the opportunity to design a variety of molecular devices. For instance Hirsch and coworkers[22] have found that the optical properties of the phthalocyanine moiety grafted onto [60]fullerene as in **23** change under reduction of the fullerene unit. Compound **23** was obtained as shown in Scheme 4 through a Diels-Alder addition of [60]fullerene to the nickel phthalocyanine **22** containing a 2,3-dimethylidene-7-oxanorbornane unit. This system was prepared by heating 3 equivalents of 3,6-diheptylphthalodinitrile and 1 equivalent of 1,2,3,4-tetrahydro-2,3-dimethylidene-1,4-epoxynaphthalene-6,7-dicarbonitrile (**21**) in the presence of $Ni(OAc)_2$ and of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pentanol. Diene **21** was prepared according to Luo and Hart[23] as shown in Scheme 4. Treatment of 1,2,4,5-tetrabromobenzene with *n*-butyllithium generates 4,5-dibromobenzyne which reacts with furan to generate a 4,5-dibromobenzo-7-oxanorbornadiene[24] that adds to tetraphenylcyclopentadienone giving the Diels-Alder adduct **17**. When reacted with (*Z*)-1,4-dichlorobut-2-ene under refluxing decalin, **17** undergoes a cheletropic elimination of CO, followed by a retro-Diels-Alder cycloreversion[25] with formation of 1,2,3,4-tetraphenylbenzene and dibromoisobenzofuran **18**, a highly reactive furan that adds to (*Z*)-1,4-dichlorobut-2-ene giving adduct **19**. Double HCl elimination (THF, *t*-BuOK) leads to diene **20**. Heating **20** with CuCN in DMF affords dinitrile **21**.[26]

Scheme 4: Synthesis of a molecular device



The bis-crown ether **28** containing the 18-crown-6 and the 17-crown-5 residues possesses a higher extractability towards Li^+, Na^+, K^+, Rb^+, Cs^+, Ag^+ (picrates; $CHCl_3$ extraction) than the parent 18-crown-6.[27] The bis-crown ether **28** was prepared as shown in Scheme 5 through a Diels-Alder addition of the furan **24** to dimethyl acetylenedicarboxylate giving the 7-oxanorbornadiene derivative **25** (71%) which was hydrogenated (H_2/Pd-C, MeOH) affording the diester **26**. Reduction of **26** with $LiAlH_4$ in THF furnished diol **27**. High dilution condensation of **27** with the ditosylate of triethyleneglycol (DMSO/DME, in the presence of NaH) provided **28**.[27]

Scheme 5: Synthesis of a bis-crown ether

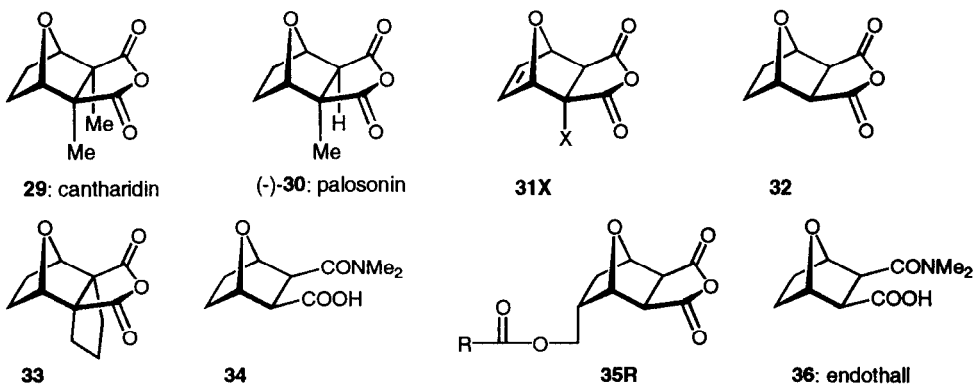


4. Natural 7-oxabicyclo[2.2.1]heptanes and bioactive analogues

4.1. Cantharidin and analogues

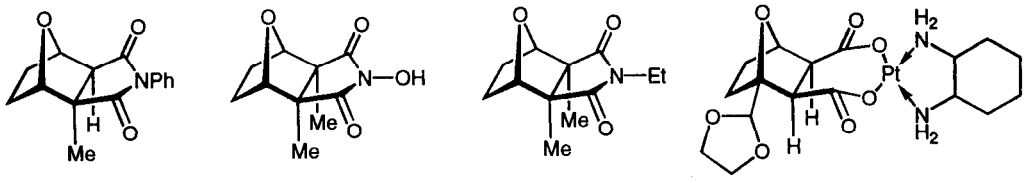
Cantharidin (**29**), the potent vessicant principle found in various species of cantharide beetles (e.g. the Spanish fly) was first obtained in the crystalline form by Robiquet in 1810.[28] This substance, believed to be an aphrodisiac, has stimulated extensive structural[29] and synthetic investigations,[30] the latter culminating in 1980 with the application of high-pressure Diels-Alder addition by Dauben and co-workers,[31] and more recently with the $LiClO_4$-promoted Diels-Alder addition (see Section 5.3) of furan to 2,5-dihydrothiophen-3,4-dicarboxylic anhydride by Grieco and co-workers.[32] Palasonin ((-)-**30**) was first isolated by Raj and Kurup[33] from the seeds of *Butea frondosa*. Its structure was established in 1968 by Bochis and Fischer.[34] Cantharidin, palasonin and simpler analogues such as **31X** (X = H) (obtained through Diels-Alder addition of furan to maleic anhydride, see Scheme 26) and **32** (obtained from **31X** (X = H) by catalytic hydrogenation) have been found to be inhibitors of the phosphorylation and dephosphorylation mediated by protein phosphatase 2A (PP2A) and

protein phosphatase 1 (PP1).[35] Both PP2A and PP1 are enzymes involved in dephosphorylation of serine and threonine residues of cellular phosphoproteins. Reversible phosphorylation of proteins is a major regulatory mechanism in signal transduction pathways that control cell proliferation, differentiation, and development.[36] These discoveries have recently stimulated the search for further derivatives of cantharidin such as the trimethylene anhydride **33**,[37] mono-amide **34**[38] and esters **35R**.[39] The studies suggested that both the 7-oxa ethereal bridge and the *exo*-dicarboxylic anhydride unit are necessary for a good inhibition of protein phosphatases. Compounds **34**[38] and **35R** are good inhibitors of calcineurin (protein phosphatase 2B [PP2B]) which is a calcium and calmodulin regulated enzyme composed of a 59-KDa catalytic subunit (CnA) and a 19-KDa calcium binding subunit (CnB).[40] This enzyme is a key signaling enzyme in T-lymphocyte activation. Its inhibition in T-lymphocytes prevents the formation of active transcription factors, such NF-AT and NF-IL2A, which are essential for interleukin-2 (IL2) gene expression.[41] Inhibition of calcineurin leads to the disruption of the cellular immune response since IL2 is necessary for T-cell proliferation.[42] Already in 1982, anhydride **31** was found to possess antitumor activity against Ehrlich ascites carcinoma cells.[43] Its dihydro derivative **32** was also found to have antitumor activity.[44] Inhibitors **35R** were prepared readily through the Diels-Alder additions of carboxylic esters of 3-(hydroxymethyl)furan to maleic anhydride, followed by catalytic hydrogenation of the 7-oxanorbornene olefin moieties. Derivative **35R** with R = 2-phenylcyclopropyl showed an inhibition constant K_i = 0.5 μM towards PP2B. This is a 23 fold enhancement compared with the inhibiting activity of endothall (**36**) toward calcineurin.[39]



Imide **37** has been isolated from the pod of *Butea monosperma*.[45] The *N*-hydroxycantharidinimide (**38**), an ingredient of *Mylabris phalerata* has an antitumor activity.[46] The synthetic analogue **39** was effective against mouse sarcoma 180.[47]

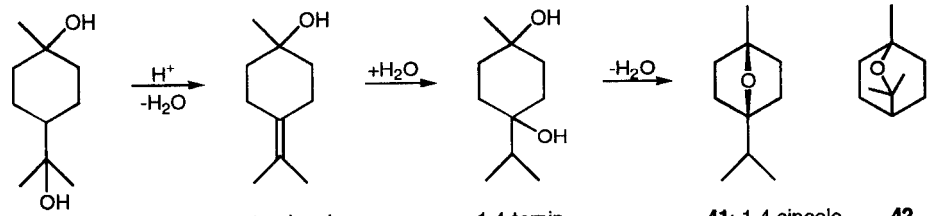
The diamineplatinium complex **40** has good antineoplastic activity against leukemia cells (P388) in mice.[48] This compound derives from the Diels-Alder adduct of maleic anhydride to the ethyleneglycol acetal of furfural.



37 38 39 40

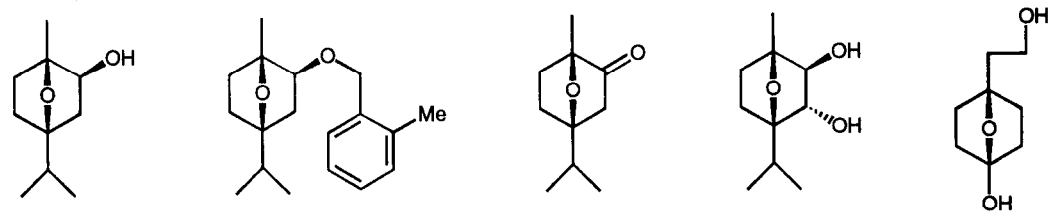
4.2. Cineole and derivatives

The bicyclic ether, cineole or 1,4-cineole (**41**: 1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane), was first described by Wallach in 1907.[49] It is formed by acid-promoted water elimination from 1,8-terpin (*p*-menthane-1,8-diol).[50] It is an isomer of 1,8-cineole (**42**).[51]



1,8-terpin γ-terpineol 1,4-terpin **41**: 1,4-cineole **42**

Cineole is present in many plants and in perfumes,[52] food or beverages derived from them. For instance, it is one of the 175 components already identified in the extract of tequila.[53] It is also found in the essential oils of leaves and flowers from *Bellis perennis*, the common daisy,[54] or in the essential oils of various lemon tree leaves.[55] Cineole is formed together with myrtenol and *trans*-pinocarveol by fermentation of β-pinene with basidiomycetes.[56]

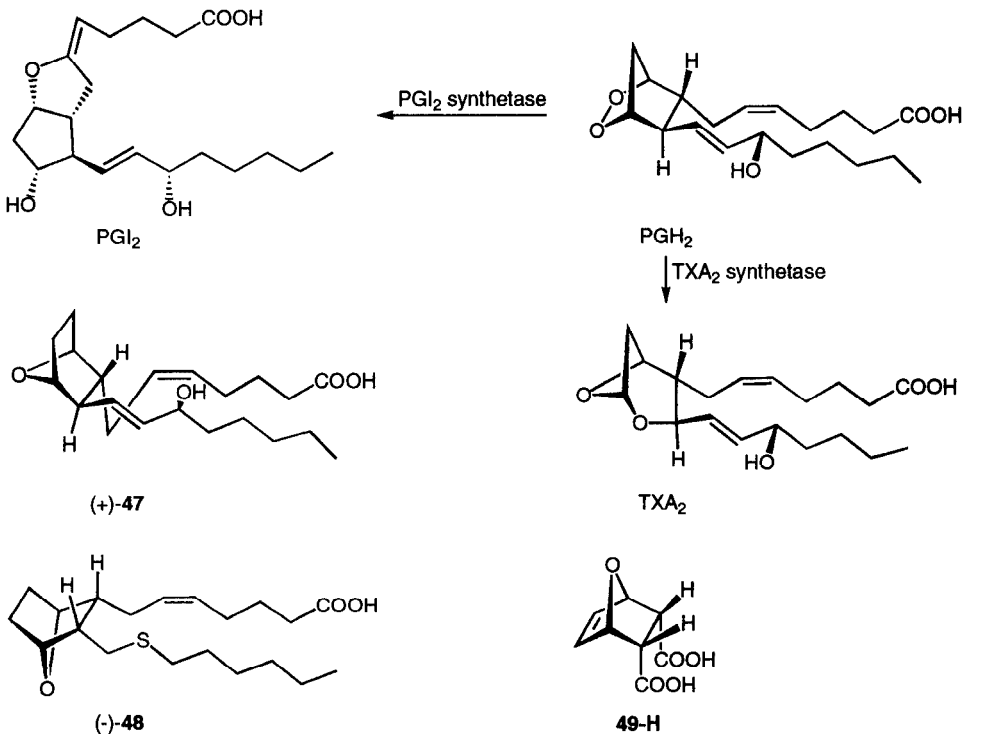


43 **44** **45** **46** rengyoxide

Cineole is a natural herbicide.[57] Its hydroxy derivative **43** (2-hydroxy-1,4-cineole; 1,4-epoxy-*p*-menthane-2-ol) is a constituent of the essential oil from rhizomes of *Ferula Jaeschkeana*.[58] Its 2'-methylbenzyl ether **44** (cinmethylin) is a pre-emergence grass herbicide.[59] Alcohol **43** can be prepared by microbial hydroxylation of 1,4-cineole.[60] Microbial transformation of 1,4-cineole also produced ketone **45** and its enantiomer.[61] Mullilam diol (**46**), a dihydroxy derivative of 1,4-cineole, has been isolated from *Zanthoxylum rhetsa*, a plant that exhibits antibiotic activity and is prescribed in dyspepsia and diarrhoea.[62a] The eight-carbon system rengyoxide has been found in *Forsythia suspensa* fruits.[62b]

4.3. Prostaglandin analogues

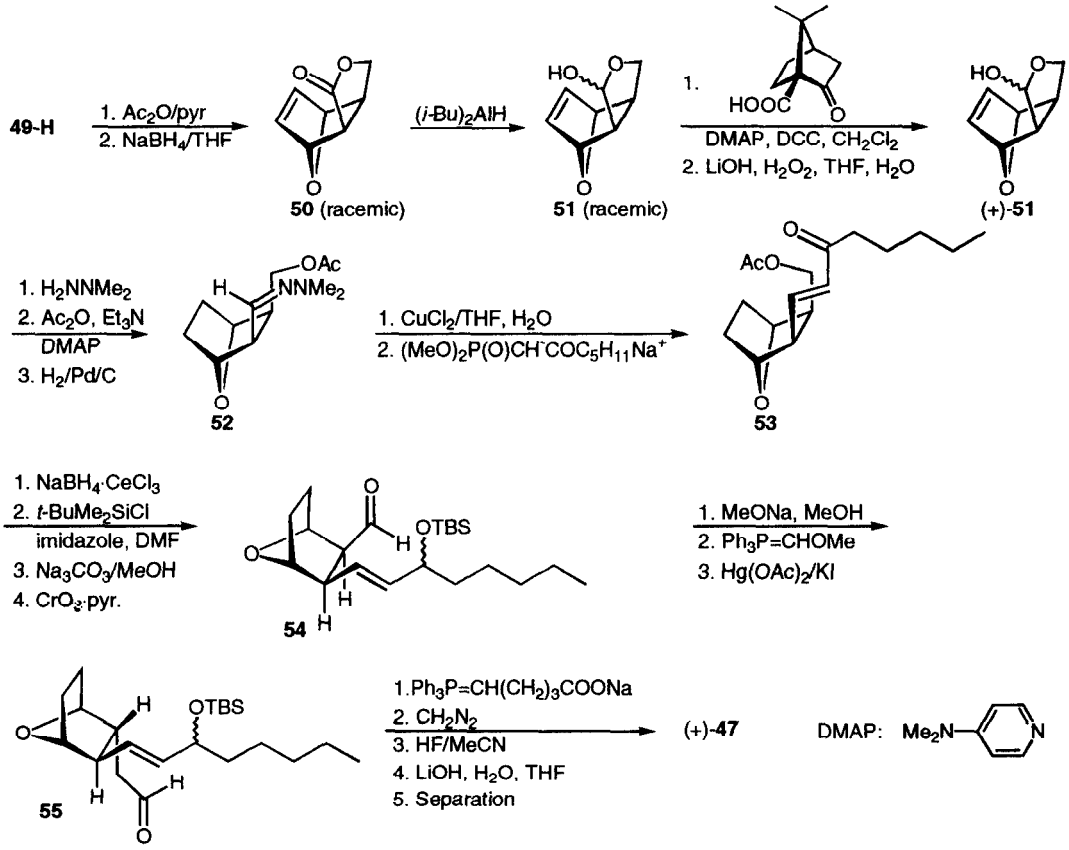
The adversary relationship between prostacyclin (PGI_2) and thromboxane-A_2 (TXA_2), which modulates coronary blood vessel caliber[63] and platelet aggregation,[64] presents opportunities for therapeutic intervention in cardiovascular desease. Substances that inhibit TXA_2 synthetase or interfere at the TXA_2 receptor have been sought for several years because they are expected to normalize pathological events caused by oversynthesis of TXA_2.[65] For instance, Hall and co-workers[66] have shown that the 7-oxanorbornane derivative (+)-**47** is a TXA_2/PGH_2 agonist. It was found also that (-)-**48** is a potent ligand for the PGH_2/TXA_2 receptor (K_d = 1.6±0.4 nM). All seven other stereoisomers were not active.[67] Compound (+)-**47** was obtained enantiomerically pure starting from the Diels-Alder adduct **49-H** of furan to maleic acid[68] (see Scheme 27) as shown in Scheme 6.[69]



Contrary to the reaction of furan to maleic anhydride which gives the *exo*-anhydride **31X** at room temperature (see however Chapter 5.3), the addition of furan to maleic acid (20 °C) follows the *endo* Alder rule and gives the *endo*-dicarboxylic acid **49-H**. Reduction of its mixed anhydride with acetic acid with $NaBH_4$ generates lactone (±)-**50**, the reduction of which with diisobutylaluminium hydride (DIBAH) produces lactol (±)-**51**. Its resolution was accomplished[69] through the esters derived from (+)-ketopinic acid. Ring opening of the lactol with Me_2NNH_2, followed by acetylation of the primary alcoholic moiety and hydrogenation of the 7-oxanorbornene double bond provided **52**. Copper(II)-promoted hydrolysis of the hydrazone liberated an

aldehyde that reacted (Wittig-Horner-Emmons) with $(MeO)_2POCHCOC_5H_{11}Na$ generating enone **53**. Under Luche's reduction conditions, **53** gave a mixture of two allylic alcohols and these were converted into silyl ethers **54**. Methanolysis of the acetate, followed by Collins oxidation, provided aldehyde **54** that was epimerized and then homologated to **55** through a Wittig olefination with Ph_3P=CHOMe. A second Wittig olefination, followed by esterification, desilylation, saponification and chromatographic separation provided (+)-**47**.

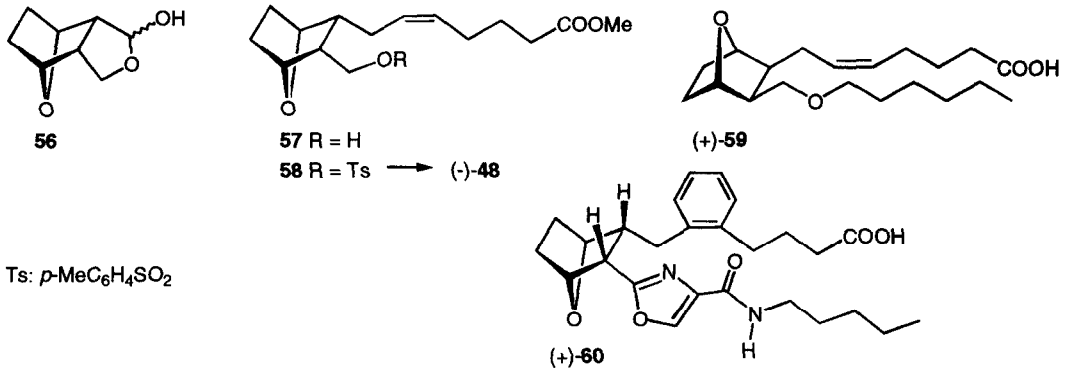
Scheme 6: Synthesis of thromboxane mimetics



The synthesis of (-)-**48** starts from **32** (which was converted following the technique described in Scheme 6 for **49** → (+)-**51**) into the racemic lactol **56**. Its optical resolution involved the separation of the corresponding (-)-ketopinic acid esters. Homologation of the lactol though a Wittig olefination, followed by installation of the (*Z*)-hept-5-enoic chain, led to intermediate **57** which was esterified into a *p*-toluenesulfonate **58**. Displacement with hexanethiol in the presence of *t*-BuOK in THF, followed by saponification (LiOH, H_2O/THF), provided (-)-**48**.

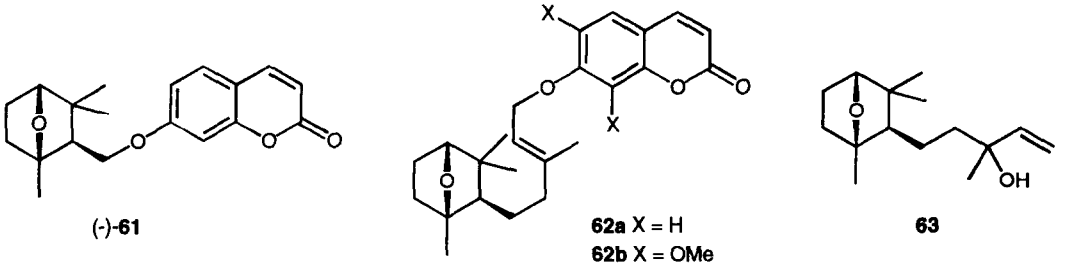
The prostaglandin analogue (+)-**59** was also derived from **56**. It is a potent inhibitor of fatty acid cyclooxygenase,[66] the enzyme catalyzing the formation of PGH_2 from arachidonic acid. Among a large number

of 7-oxanorbornane-like prostaglandin analogues prepared, compound (+)-**60** which incorporates an oxazolecarboxamide moiety was found to be a potent, selective, and orally-active TXA_2 antagonist with a long duration of action. It was also derived from **56**. In human platelet-rich plasma, (+)-**60** inhibits arachidonic acid-induced aggregation with an IC_{50} value of 7 nM.[70,71,72]



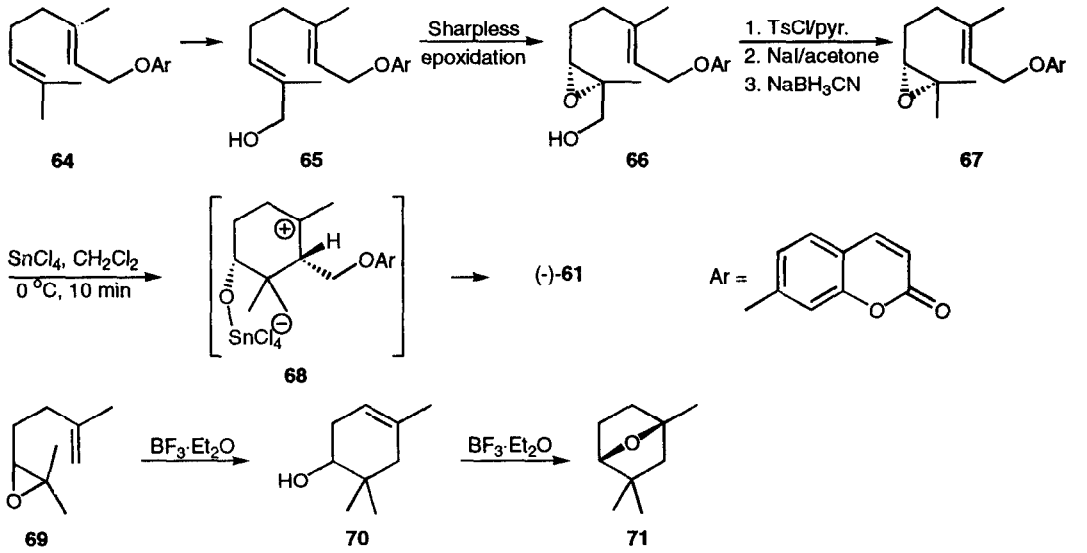
4.4. Further monoterpenoid and sesquiterpenoid 7-oxabicyclo[2.2.1]heptanes

3',6'-Epoxyauraptene (**61**)[73] and farnesiferol-C (**62a**)[74a] have been isolated from various plants. Creticacumarin (**62b**), an oxidized form of farnesiferol-C (**62a**), has been found in Turkish species of the genus *Anthemis*.[74b] Sesquiterpenol **63** has been isolated form *Arthemisia barrelieri*.[75]



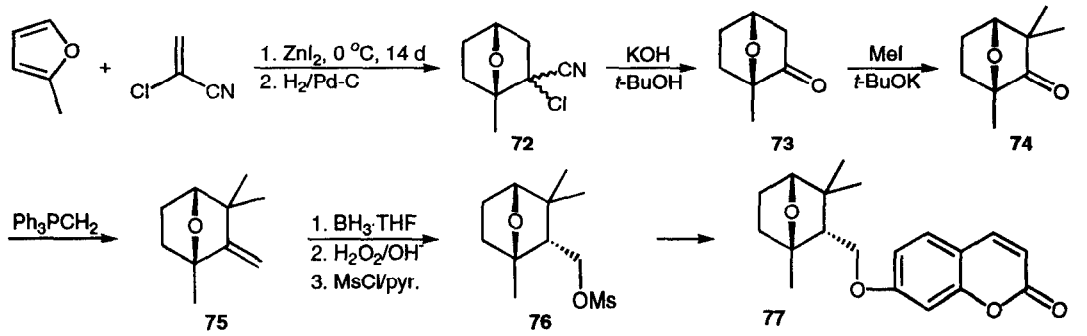
The synthesis of (-)-**61** has been achieved by Aziz and Rouessac[76] (Scheme 7) starting from product **64** (auraptene) resulting from the displacement of geranyl bromide with 7-hydroxycoumarin. Allylic oxidation with SeO_2 and *t*-BuOOH generates the allylic alcohol **65** which undergoes the asymmetric Sharpless epoxidation with (-)-diethyl D-tartrate/*t*-BuOOH/$(i\text{-PrO})_4$Ti into the epoxide **66**. Conversion of the hydroxymethyl group of **66** into a methyl group implies tosylation of the primary alcohol, followed by displacement by iodide (NaI, acetone) and subsequent hydride reduction with $NaBH_3CN$ into **67**. Treatment of **67** with $SnCl_4$ in CH_2Cl_2 led to (-)-**61**. The rearrangement probably involves intermediate **68**. This reaction has a precedent in work by Goldsmith[77] who had observed that geraniolene monoepoxide **69** isomerizes into the cyclohexenol **70** upon treatment with $BF_3{\cdot}Et_2O$. A longer reaction time induces the cyclization of **70** into 1,3,3-trimethyl-7-oxanorbornane (**71**).[78]

Scheme 7: Asymmetric synthesis of (-)-3',6'-epoxyauraptene

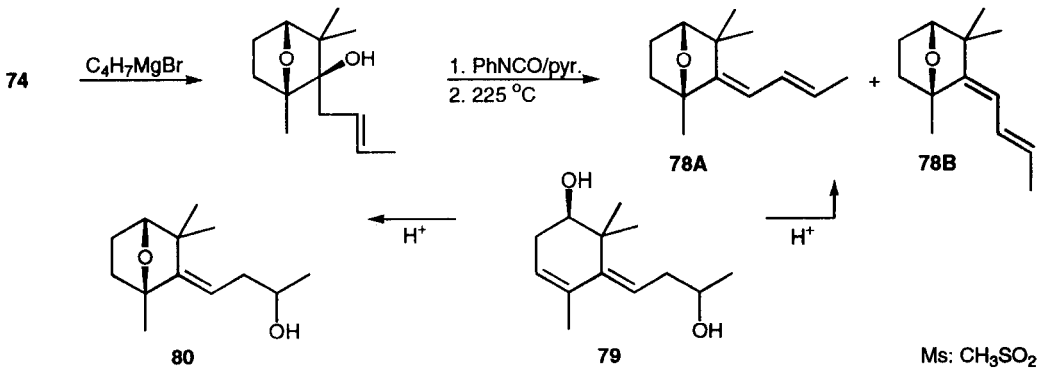


An alternative approach to the synthesis of 1,3,3-trimethyl-7-oxanorborn-2-yl derivatives has been proposed by Sneden[79] (Scheme 8). The Diels-Alder addition of 2-methylfuran (sylvan) to 2-chloroacrylonitrile gives a mixture of adducts **72** and these were hydrolyzed with KOH/*t*-BuOH to 1-methyl-7-oxanorbornan-2-one (**73**). Double methylation at C(3) gives **74** which reacted with Ph_3PCH_2 giving **75**. Oxidative hydroboration, followed by esterification with MsCl/pyridine, gave the 2-*endo*-mesyloxymethyl derivative **76** that was reacted with the potassium salt of 7-hydroxycoumarin to yield the 2-epimer of (±)-3',6'-epoxyauraptene (**77**). The bicyclic ketone **73** was also converted into (±)-2,5-epoxy-6(*E*),8(*E*)-megastigmadiene (**78A**). This compound and its 6(*Z*),8(*E*)-isomer **79B** were found in the extract (0.02%) of *Osmanthus*.[80] They can be obtained on acidic treatment of diol **79**, together with alcohol **80**,[81] also present in the *Osmanthus* extract, an important component in the perfume and fragrance industries.

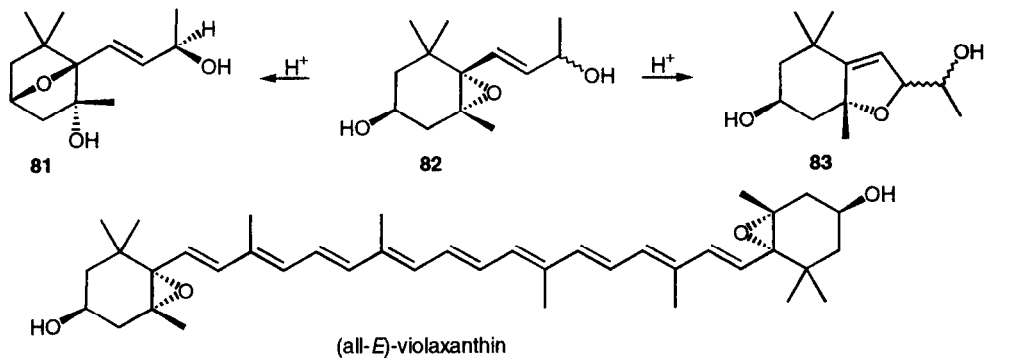
Scheme 8: Synthesis of the 2-epimer of (±)-3',6'-epoxyauraptene and of constituents of *Osmanthus* extract



Scheme 8 (continued):

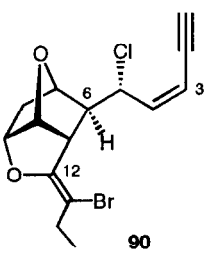


The 7-oxanorbornanol **81** was isolated from sun-cured Greek tobacco.[82] It is formed together with **83** on acidic treatment of **82**, a product of degradation of violaxanthin.[83]



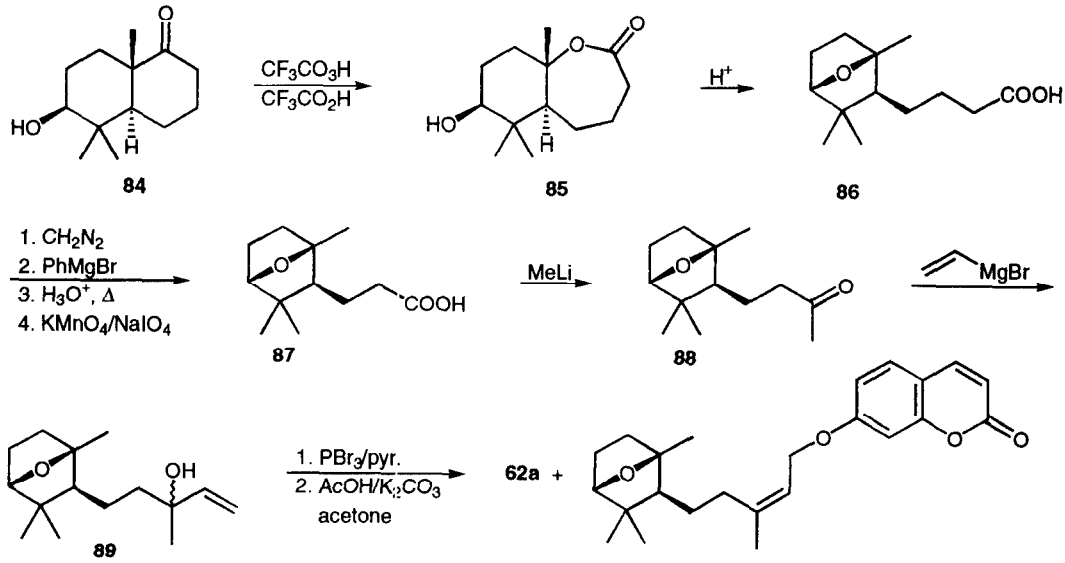
A synthesis of (±)-farnesiferol-C ((±)-**62a**) has been reported recently by Demnitz and co-workers[84] (Scheme 9). Baeyer-Villiger oxidation of the bicyclic ketone **84** with CF_3CO_3H/CF_3COOH in CH_2Cl_2 afforded the 7-oxanorbornane derivative **86** resulting from the rearrangement of the intermediate lactone **85**. Standard Barbier-Wieland degradation (CH_2N_2; PhMgBr; H_3O^+; $KMnO_4/NaIO_4$) of **86** gave the lower homologue **87**, treatment of which with 2 equivalents of MeLi afforded the methyl ketone **88**. Reaction of **88** with vinylmagnesium bromide provided the allylic alcohol **89** which was converted into the corresponding bromide on treatment with PBr_3 and pyridine. It was then displaced by 7-hydroxycoumarin to give a 3:1 mixture of (±)-**62a** and its (*Z*)-isomer.[84]

The maneonenes **90** are tricyclic diethers found in the marine alga *Laurencia nidifica*.[85]

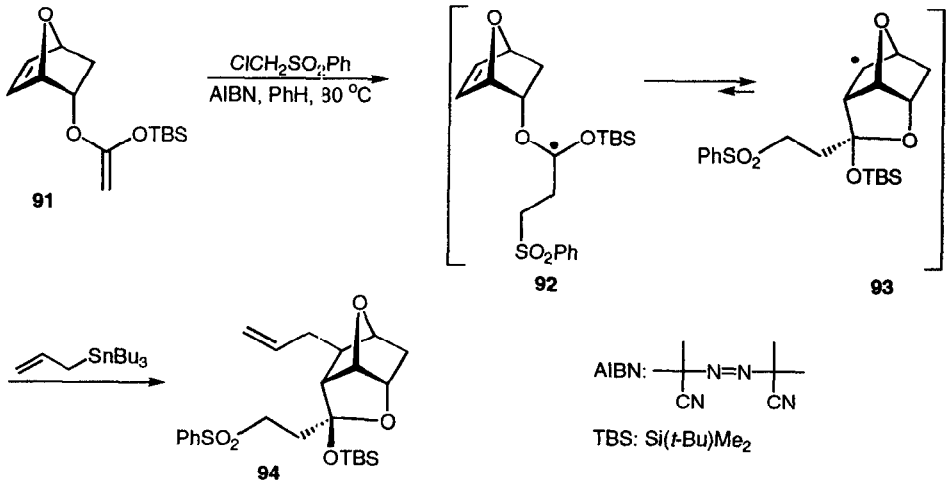


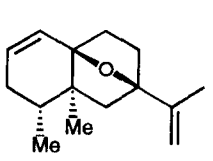
(3*Z*,6*S*,12*E*): maneonene A
(3*E*,6*S*,12*Z*): (*E*)-maneonene B
(3*Z*,6*S*,12*Z*): (*Z*)-maneonene B
(3*Z*,6*R*,12*E*): maneonene C

Scheme 9: Synthesis of (±)-farnesiferol-C

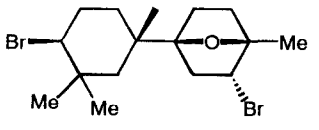


Synthetic analogues like **94** have been obtained by Renaud and Vionnet[86] through radical addition to the ketene acetal **91** and allyl quenching of the intermediate **93** with allyltributyltin. Vetiver oil contains small amounts of ether **95**.[87] The Mediterranean marine alga *Laurencia obtusa* has yielded 2-bromo-4-(4-bromo-3,3-dimethylcyclohexyl)-1-methyl-7-oxabicyclo[2.2.1]heptane (**96**)[88a] and 2,5-epoxy-1(6)-brasilen-9-ol (**97**).[88b] The terpenoid 1,4-epoxy-6-eudesmanol has been isolated from *Sideritis varoi*[88c] and from *Ambrosia artemisioides*.[88d] 1,4-Epoxycadinane is a constituent of *Dilophus fasciola*.[88e,89] Isomaneonene A has been found in extracts of *Laurencia nidifica*.[85] Shonachalin B is an eudesmanolide isolated from the aerial parts of *Artemisia caerulescens*.[88f]

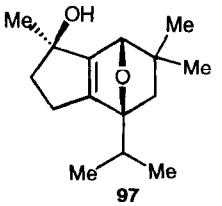




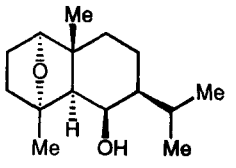
95



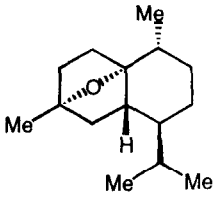
96



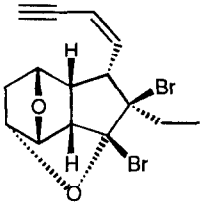
97



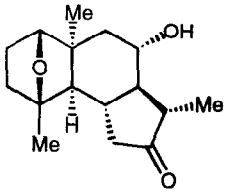
1,4-epoxy-6-eudesmanol



1,4-epoxycadinane



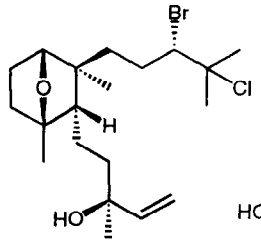
isomaneoene A



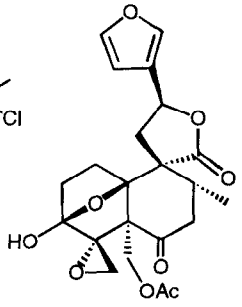
shonachalin B

4.5. Diterpenoid and triterpenoid 7-oxabicyclo[2.2.1]heptanes

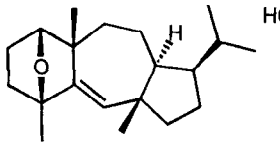
The bicyclic diterpene dactylomelol has been isolated from the shell-less mollusc *Aplysia dactylomela*.[90a] Teupestalin B is a constituent of *Teucrium pestalozzae*.[90b] 1,4-Epoxy-13-dolastene has been isolated from a *Dictyola* sp. brown alga.[90c] The secondary metabolite **98** (SCH 58450) that possesses the 6a,12a:7,12-diepoxybenzanthracene ring system has been isolated from a *Streptomyces* sp. by researchers at Schering. This compound inhibits farnesyl protein transferase with an IC_{50} = 29 μM.[91] Inhibitors of farnesyl protein transferase have shown considerable promise as antitumor agents based on their ability to inhibit cellular transformation induced by oncogenic Ras proteins.[92]



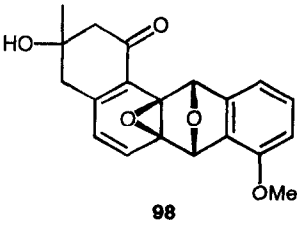
dactylomelol



teupestalin B



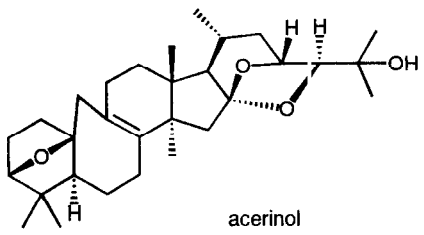
1,4-epoxy-13-dolastene



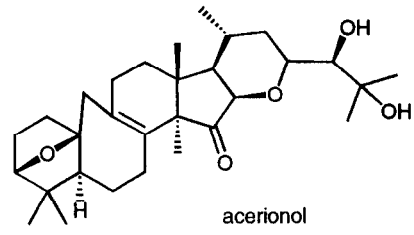
98

(SCH 58450)

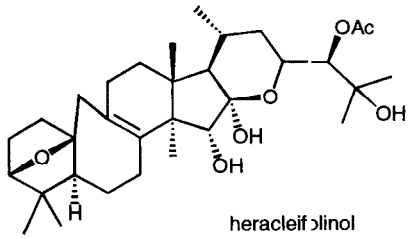
Acerinol and acerionol are constituents of *Cimicifuga* sp.[93a] Heracleifolinol has been isolated from *Cimicifuga heracleifolia*.[93b] Baccharis oxide is a constituent of *Baccharis halimifolia*.[93c] Campanulin, a 3,10-epoxyglutinane, is a constituent of *Rhododendron* sp. and *Dendropanax bifidus*.[93d] Subellinone, a polyisoprenylated phloroglucinol derivative, has been isolated from the wood of *Garcinia subelliptica*, a biologically active plant growing in the Yaeyama islands.[93e]



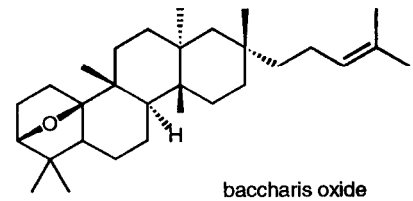
acerinol



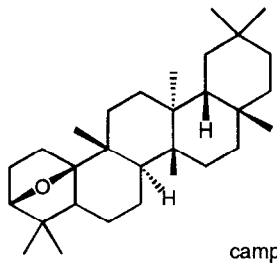
acerionol



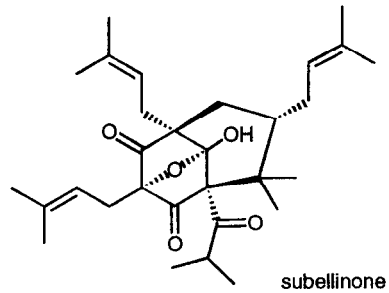
heracleifolinol



baccharis oxide

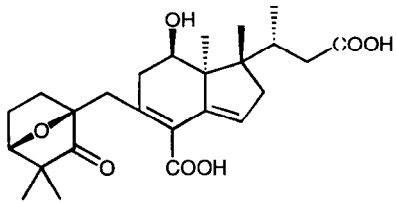


campanulin

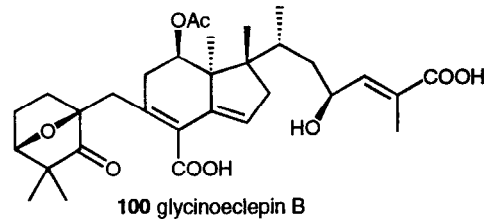


subellinone

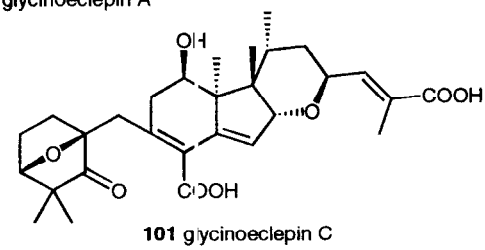
Cyst nematodes are serious pests of many crops. They generally have a limited host range and the specificity is thought to be based on a response to a chemical hatching stimulus secreted by the host plants. In 1985, Masamune and co-workers[94a] isolated glycinoeclepin A (**99**), a potent hatching stimulus for the soybean cyst nematode (*Heteropdera glycines* Ichinohe), from the dried root of the kidney bean (*Phaseolus vulgaris*). Glycinoeclepin B (**100**) and glycinoeclepin C (**101**) have also been isolated from the same root.[94b]



99 glycinoeclepin A



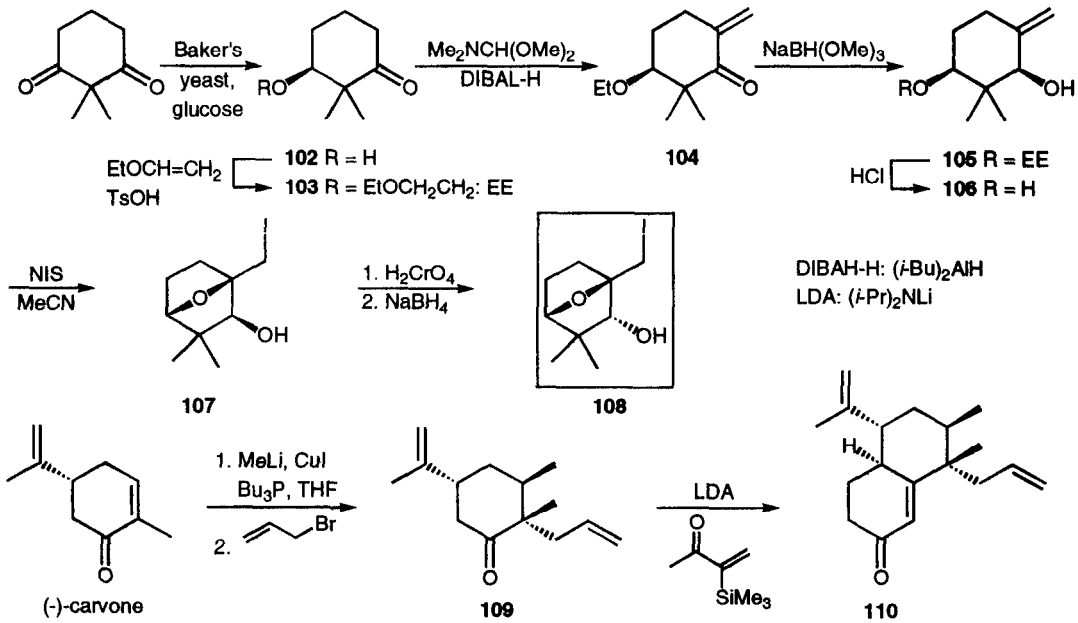
100 glycinoeclepin B



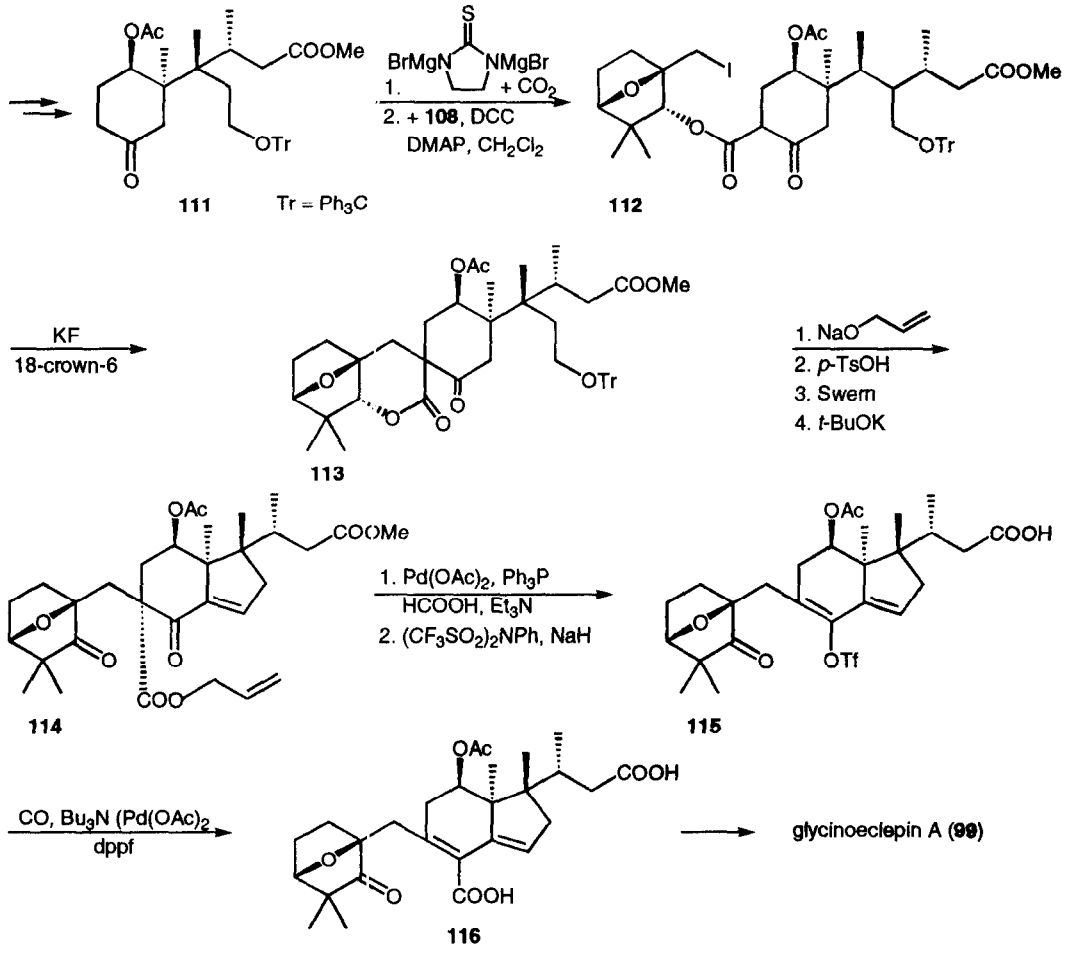
101 glycinoeclepin C

Three total syntheses of glycinoeclepin A (**99**) have been proposed. The first approach (Scheme 10) was reported by Murai and co-workers.[95] The enantiomerically pure 1-iodomethyl-3,3-dimethyl-7-oxanorbornan-2-*endo*-ol (**108**) was derived from 2,2-dimethylcyclohexa-1,3-dione via baker's yeast reduction into aldol **102**. After protection as an ethoxyethyl ether, treatment with Bredereck's reagent[96] ($Me_2NCH(OMe)_2$) and with $(i\text{-}Bu)_2AlH$ produced enone **104** that was reduced to the allylic alcohol **105** with $NaBH(OMe)_3$. Hydrolysis of the ethoxyethyl ether under acidic conditions generated diol **106**. Treatment of **106** with *N*-iodosuccinimide (NIS) in MeCN effected cyclization into iodide **107**. Jones oxidation, followed by reduction with $NaBH_4$ (*exo* face selective addition) provided the key synthetic intermediate **108** (8 steps, 27.6% overall yield). The synthesis of fragment **111** corresponding to the C and D ring moiety of **99** started from (*R*)-(-)-carvone which was converted into **109** via methylcuprate addition and allylic quenching. Robinson annelation yielded **110** which was further transformed into **111**. α-Carboxylation of ketone **111** with bromomagnesium thioureide-CO_2 complex[97] yielded the expected oxocarboxylic acid which was immediately reacted with **108** in the presence of dicyclohexylcarbodiimide giving ester **112**. Reaction of **112** with KF/MeCN/18-crown-6 effected the C-C coupling into **113**. Lactone **113** was treated with sodium allyloxide and then with *p*-toluenesulfonic acid (TsOH). A Swern oxidation followed giving an aldehyde that underwent intramolecular aldolisation generating **114**. Palladium-catalyzed hydrolysis of the allyl ester, enolisation and quenching of the enolate as a triflate led to **115** which underwent carboxylation ($CO/Pd(OAc)_2$) giving **116**. Saponification and purification provided glycinoeclepin A (**99**).

Scheme 10: Synthesis of glycinoeclepin A according to Murai

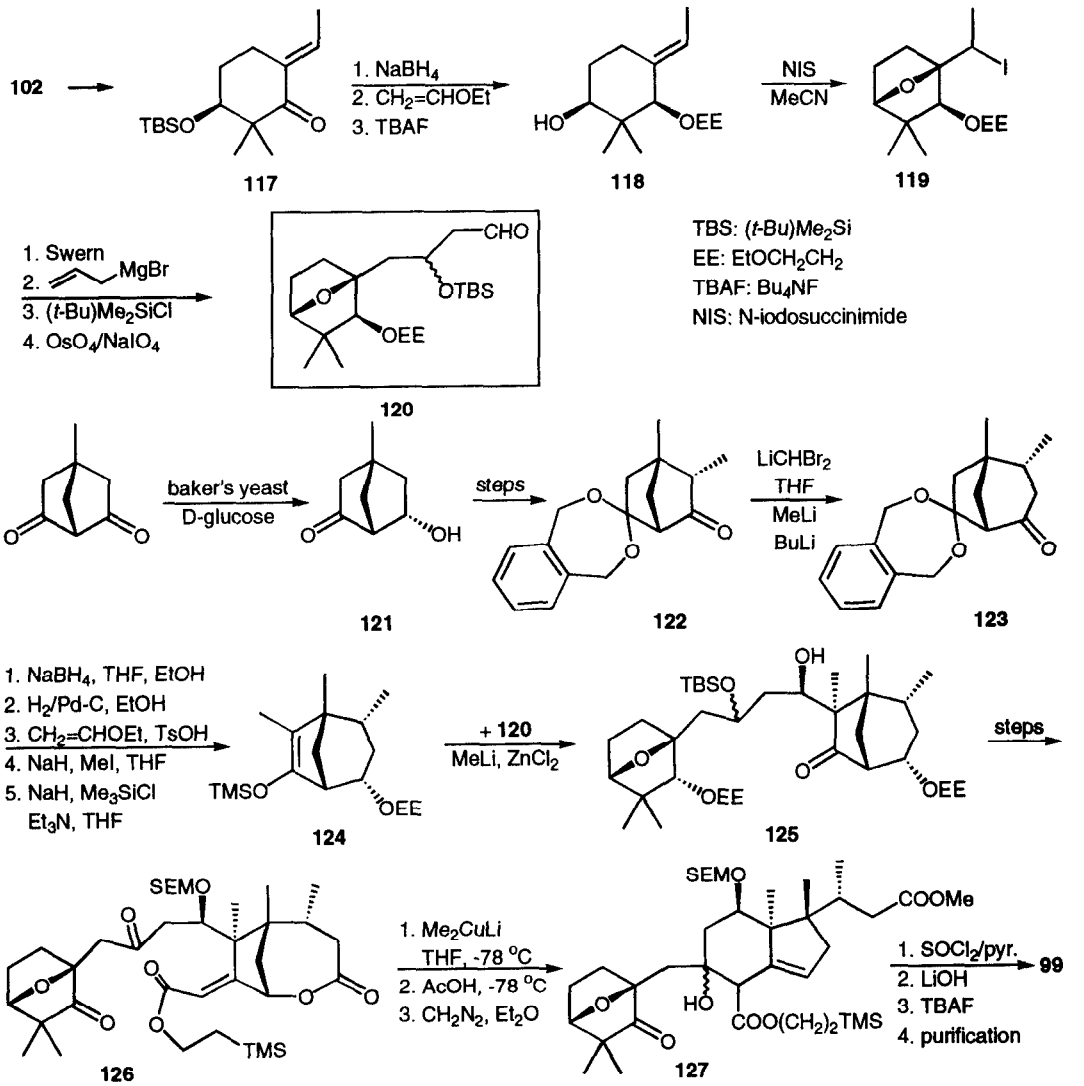


Scheme 10 (continued)



The second synthesis (Scheme 11) of **99** was reported by Mori and Watanabe.[98] The A-ring portion was also derived from 2,2-dimethylcyclohexa-1,3-dione. Aldol **102** was converted into enone **117**, and then into 7-oxanorbornane **119** via iodoetherification with NIS, as in the synthesis of Murai (Scheme 10). Further transformations led to the key intermediate **120**. The other key intermediate **124** was derived from 4-methylbicyclo[2.2.1]hepta-2,6-dione which was reduced into aldol **121** with baker's yeast. Aldol **121** was then converted into **122** which underwent ring enlargement with $LiCHBr_2$/MeLi/BuLi into **123**. Reduction, alcohol protection, deprotection of the ketone, α-methylation and enolization provided **124** which was condensed finally with aldehyde **120**. Several steps converted the resulting aldol **125** into **126**. Lactone **126** reacted with Me_2CuLi (reductive agent) generating an enolate intermediate that underwent intramolecular aldolisation, generating the C-ring of **127**. Water elimination from **127**, followed by deprotection, generated glycinoeclepin A (**99**).

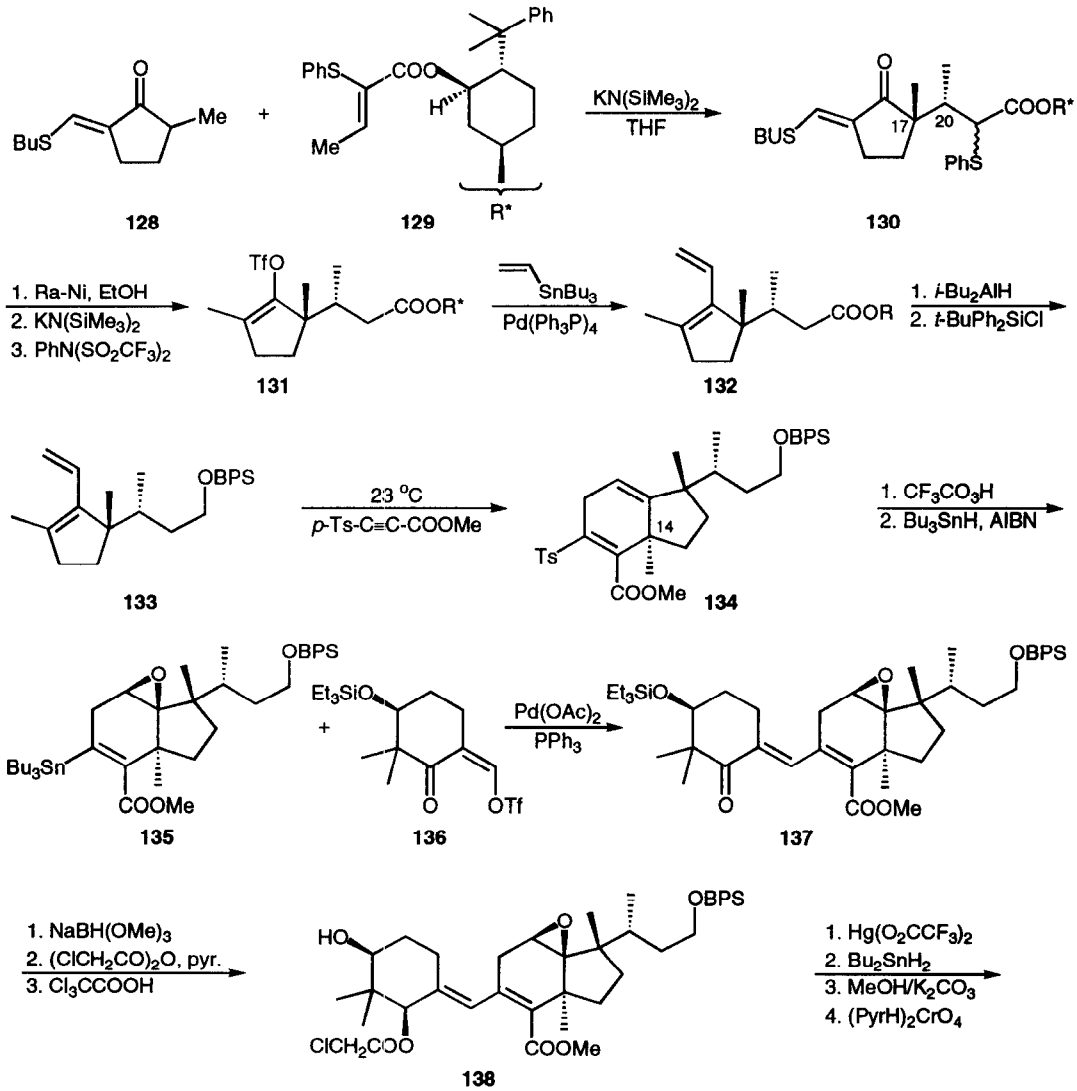
Scheme 11: Synthesis of glycinoeclepin A according to Mori



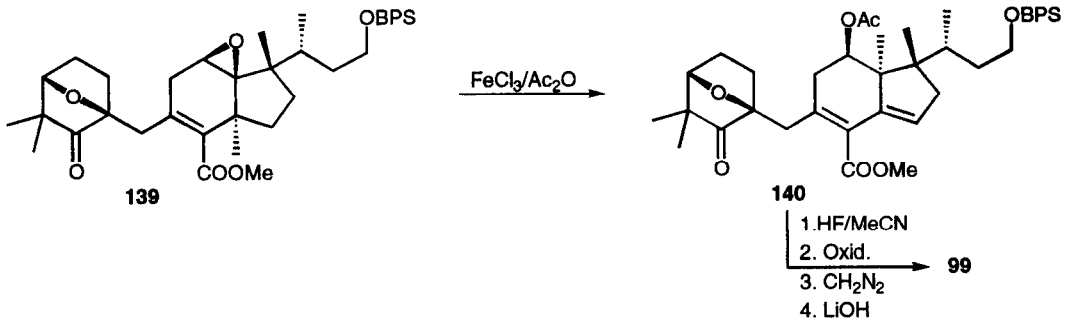
Corey and Houpis[99a] reported an approach to the synthesis of glycinoeclepin A starting from the cyclopentanone **128** (Scheme 12) and the (Z)-2-(phenylthio)crotonic ester of (-)-8-phenylmenthol (**129**). The potassium enolate of **128** reacted with **129** with 95:5 enantioselectivity and 5:1 C(17)-C(20) (steroid numbering) diastereoselectivity. The major adduct **130** was converted to the enol triflate **131**. Vinylation of **131** with vinyltributyltin-LiCl ($Pd(Ph_3P)_4$ cat.) afforded **132** which was reduced and protected to give the diene **133**. Diels-Alder addition of **133** with methyl 3-(*p*-toluenesulfonyl)propiolate generated the diene **134** and its C(14) diastereomer in a ratio of 3:1. Epoxidation, radical sulfonyl group reduction and coupling with $Bu_3Sn^{\bullet}$ gave **135**. Stille coupling of **135** with vinyl triflate **136** (derived from 2,2-dimethylcyclohexa-1,3-dione) provided

137. Carbonyl reduction, chloroacetylation and desilylation led to **138**. Reaction of **138** with mercuric trifluoroacetate and mercuric oxide in MeCN effected internal oxymercuration to give a single bridged ether chloromercurial intermediate that underwent demercuration with Bu_2SnH_2. Methanolysis to cleave the chloroacetate followed by oxidation provided ketone **139**. Epoxide ring opening of **139** was induced with anhydrous $FeCl_3$ in Ac_2O; this generated a tertiary cationic intermediate which underwent a 1,2-methyl shift and proton elimination with the formation of the acetate **140**. After deprotection of the primary alcohol, it was oxidized into the corresponding carboxylic acid that was then esterified with CH_2N_2. Selective saponification with LiOH (DME/H_2O) provided **99**.

Scheme 12: Synthesis of glycinoeclepin A according to Corey and Houpis

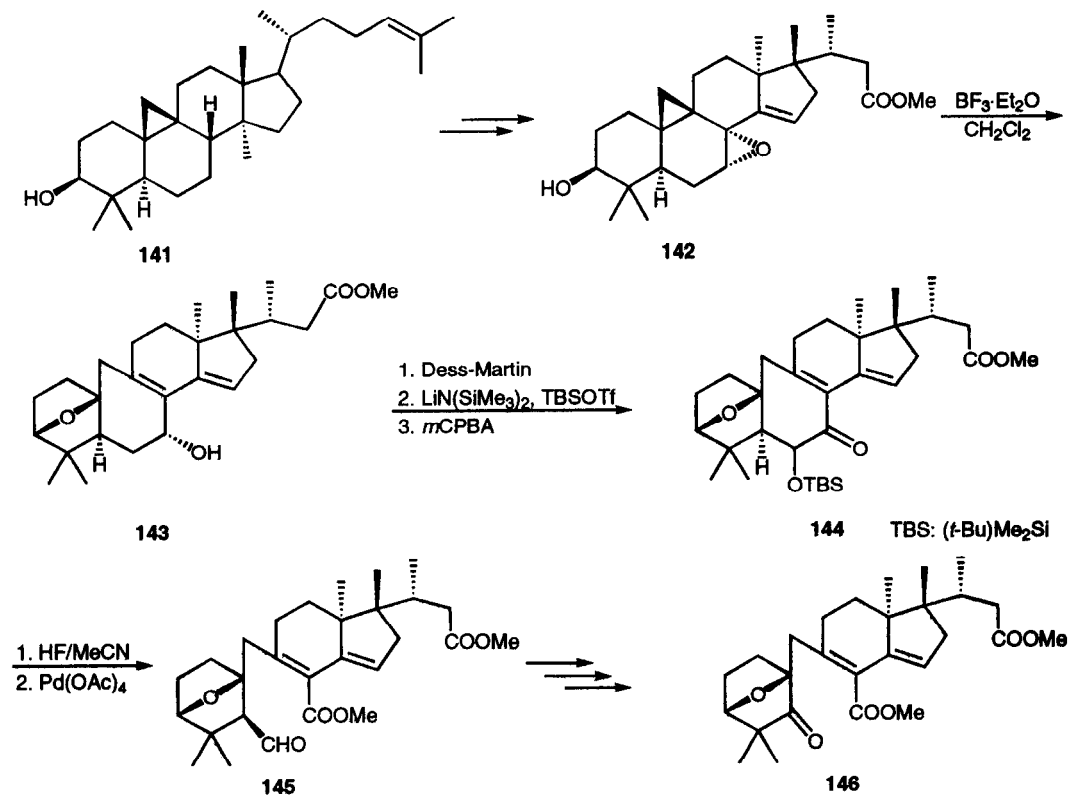


Scheme 12 (continued)



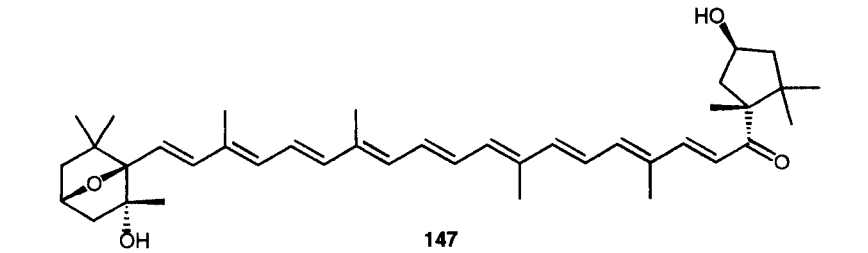
Corey and Hong[99b] (Scheme 13) have derived 12-deoxyglycinoeclepin dimethyl ester (**146**) from cycloartemol (**141**). A key step is the acid-promoted rearrangement of the epoxy-cyclopropyl-alcohol **142** which generates the 7-oxanorbornane system **143**. Oxidation of the alcohol **143** followed by silyl enolization and subsequent oxidation with *meta*-chloroperbenzoic acid (*m*CPBA) gave **144**. Desilylation of **144** and oxidation of the intermediate α-hydroxyketone with $Pb(OAc)_4$ furnished **145** which was further oxidized into **146**.[100]

Scheme 13: Synthesis of 12-deoxyglycinoeclepin according to Corey and Hong

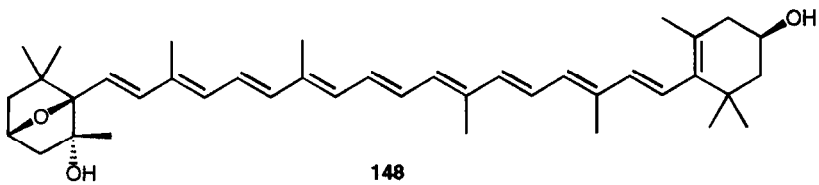


4.6. Carotenoids with 7-oxabicyclo[2.2.1]heptyl end groups

Red paprika, *Capsium annum*, contains a variety of carotenoid pigments among them capsanthin-5,6-epoxide (**147**) and cucurbitaxanthin A (**148**) that contain one 2-*endo*-hydroxy-3-*exo*,6,6-trimethyl-7-oxanorborn-1-yl end group.[101] Carotenoids **148** and **149** (cucurbitaxanthin B) were found in pumpkin, *cucurbita maxima*.[102] The 7-oxanorbornanone **150** (eutreptiellanone) was isolated from the alga *Eutreptiella gymnastica*.[103] The 7-oxanorbornyl derivatives probably derive biosynthetically from analogous carotenoids bearing a 4-hydroxy-1,2-epoxycyclohexyl moiety as in autheraoxanthin (**151**).



147



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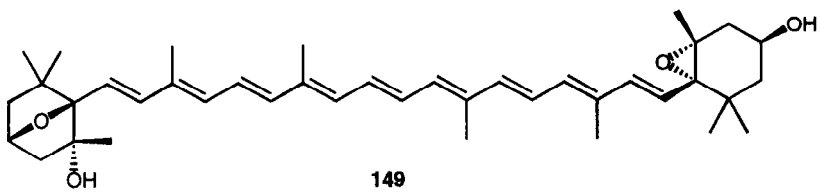
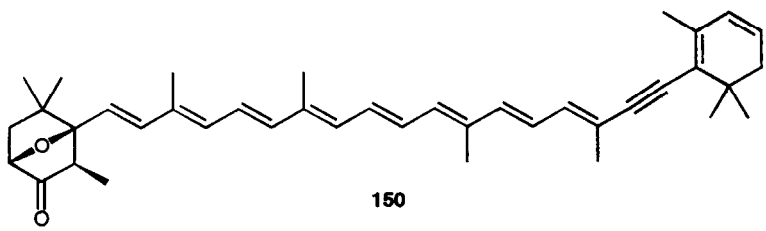
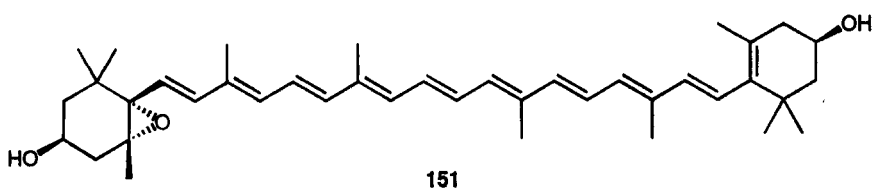


149



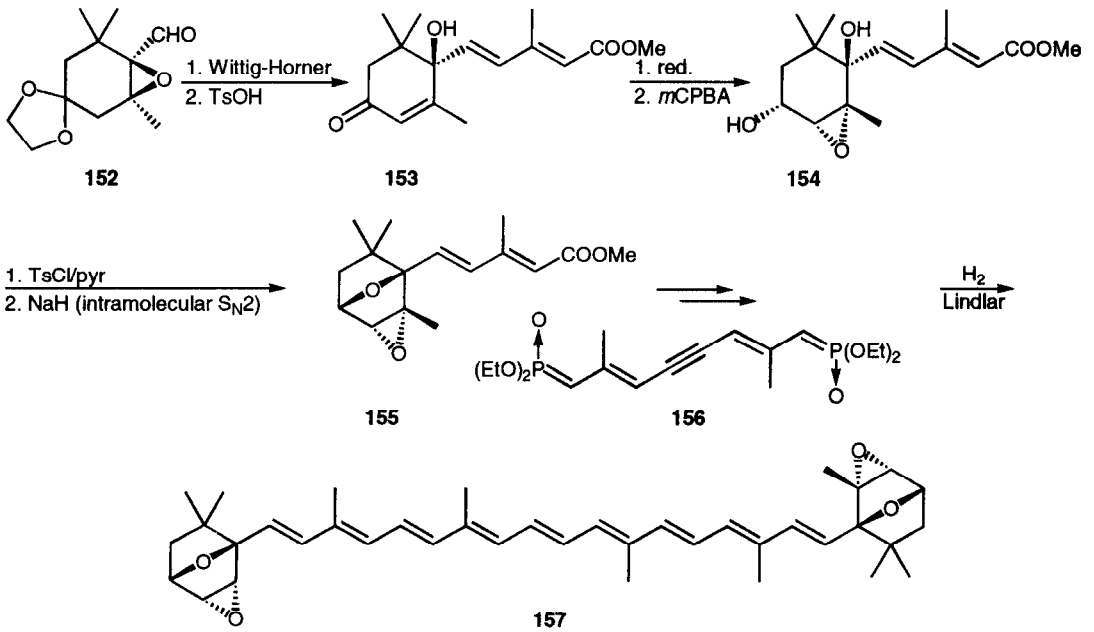
150



151

Synthetic analogues of **147-150** have been prepared by Gmünder and Eugster[83] starting from the aldehyde **152**. A first Wittig-Horner reaction with a C_5-phosphonate, followed by acidic treatment provided enone **153** (Scheme 14). Reduction of **153** with 9-borabicyclo[3.3.1]nonane gave an allylic alcohol which was epoxidized into **154**. Tosylation of the secondary alcohol of **154**, followed by formation of the sodium tertiary alcoholate with NaH engendered the 2,3-*endo*-epoxy-7-oxanorbornyl system **155**. Conversion of the methyl ester of **155** into a carbaldehyde group, then double Wittig-Horner condensation with **156**, provided the 15,15'-didehydrocarotenoid, the selective hydrogenation of which led to **157**.[104]

Scheme 14: Synthesis of a 3,6:3',6'-diepoxy-5,6,5',6'-tetrahydro-β,β-carotin analogue



152 **153** **154** **155** **156** **157**

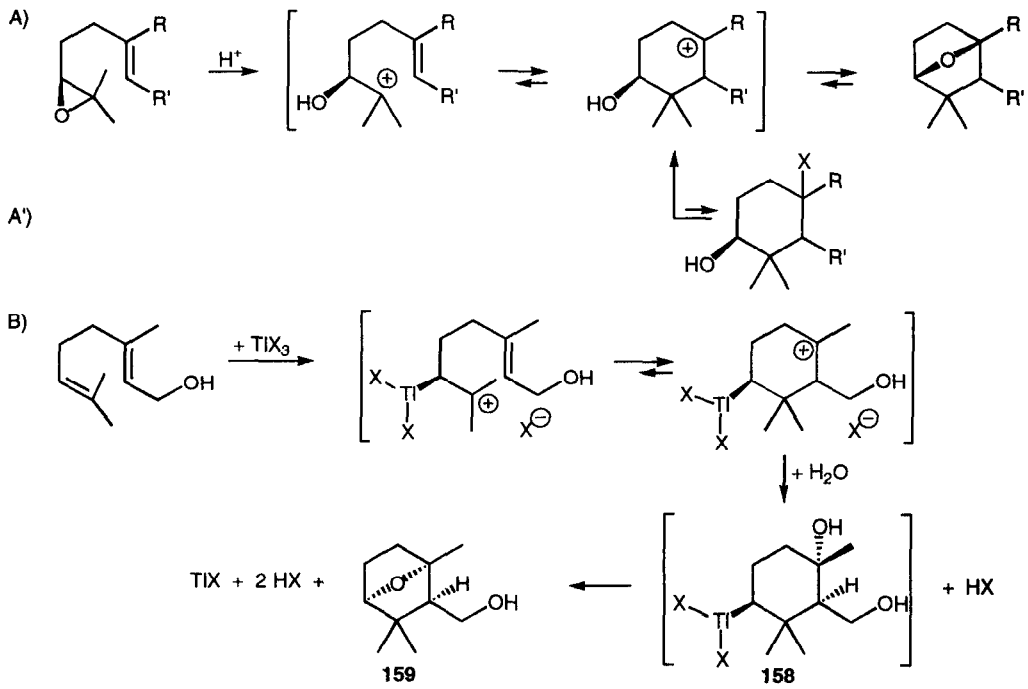
5. Syntheses of 7-oxabicyclo[2.2.1]heptanes

5.1. Non-cycloaddition approaches

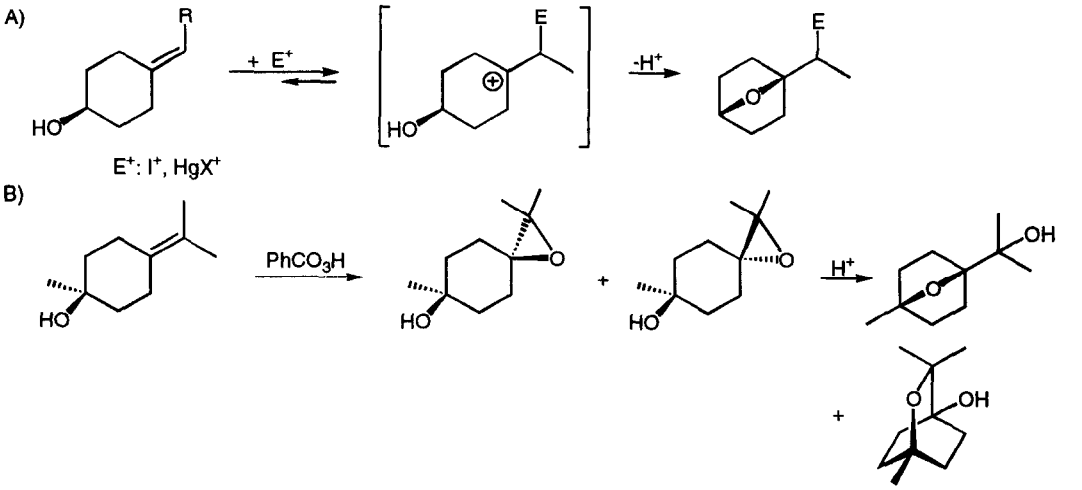
The syntheses of (-)-3',6'-epoxyauraptene (Scheme 7), (±)-farnesiferol C (Scheme 9), glycinoeclepin A (Schemes 10, 11, 12) and 12-deoxyglycinoeclepin (Scheme 13) illustrate methods for the synthesis of 7-oxa-norbornane systems that do not rely on the Diels-Alder additions of furans (Section 5.3). Four different methods were applied which convert acyclic or monocyclic systems to the bicyclic ethers: the first one, acid-promoted ring opening of monoepoxides of hexa-1,5-dienes, generates carbenium intermediates that undergo intramolecular additions to the alkene moiety with the formation of 4-hydroxycyclohexyl cationic intermediates that are quenched intramolecularly by the δ-hydroxy group (Scheme 15A). Related to that process is the

oxidative cyclization of geraniol induced by thallium tris(perchlorate). The reaction (Scheme 15B)[105] generates the 7-oxanorbornane **159** together with other compounds. The process implies probably the heterolysis of a 4-hydroxycyclohexylthallium intermediate of type **158**, a reaction analogous to that involved in the synthesis of (±)-farnesiferol C shown in Scheme 9 (part A' of Scheme 15).[106]

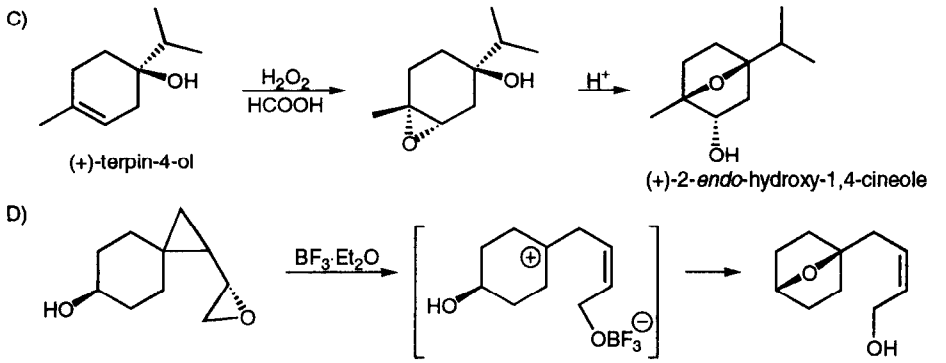
Scheme 15: Acid-promoted isomerization of δ,ε-unsaturated epoxides and related reactions



Scheme 16: Electrophile-induced etherification reactions

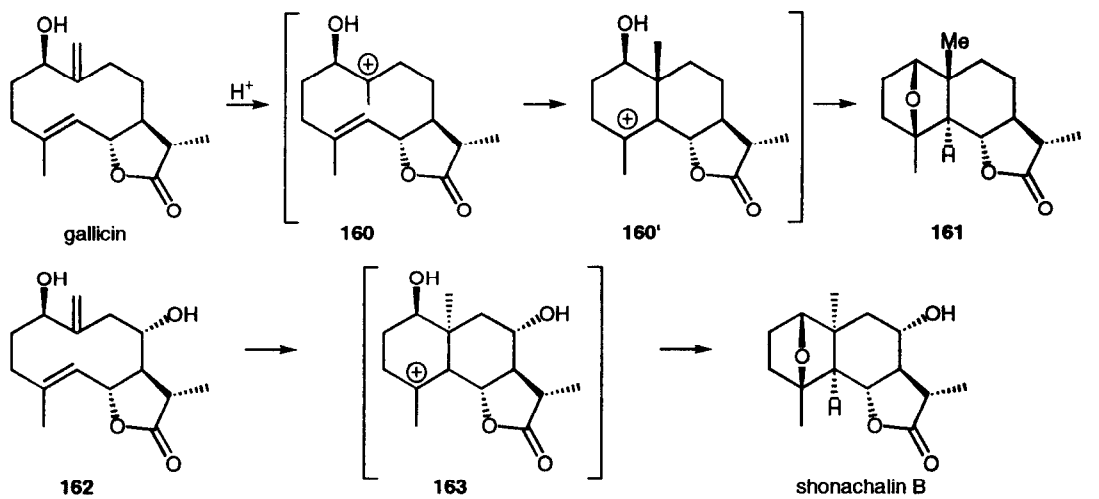


Scheme16 (continued)



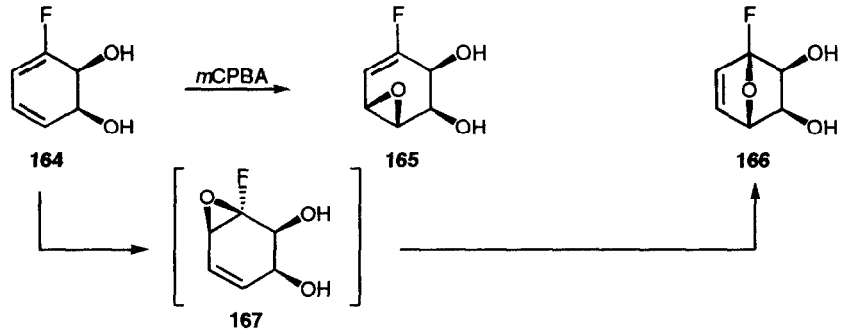
A second type of reaction leading to the formation of 7-oxanorbornane derivatives implies the generation of 4-hydroxycyclohexyl cationic intermediates through the electrophilic addition of 4-alkylidenecyclohexanols (Scheme 16A). The electrophile can be I^+ (see e.g. Schemes 10, 11) or a mercurial salt (see e.g. Scheme 12). Alternatively, the epoxides derived from the epoxidation of 4-alkylidenecyclohexanols can undergo ring opening under acidic conditions with the formation of 7-oxanorbornanols (Scheme 16B).[107] Related to this method, the epoxidation of (+)-terpin-4-ol under acidic conditions is found to lead to the formation of (+)-2-*endo*-hydroxy-1,4-cineole (Scheme 16C).[108] Other 4-hydroxycyclohexyl cations can be generated through the cyclopropylcarbinyl/homoallyl cationic rearrangement (Scheme 16D). An example applying this method was shown in Scheme 13 with the synthesis of 12-deoxyglycinoeclepin by Corey and Hong.

Scheme 17: Acid-catalyzed cyclizations of germacranolides



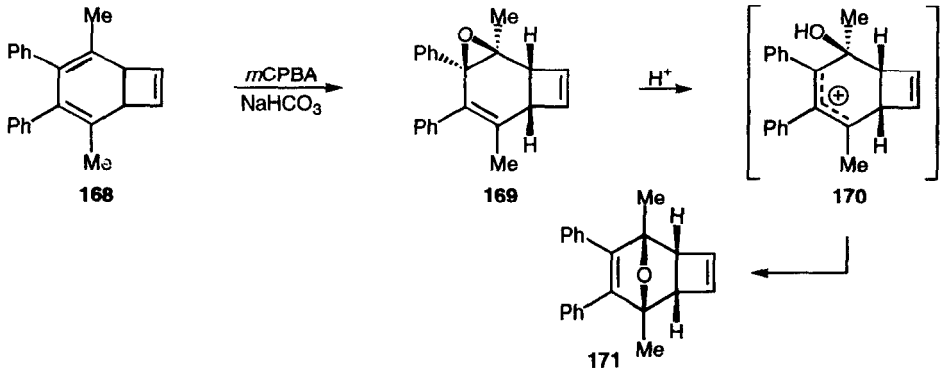
Acid-catalyzed cyclization of the natural germacranolide gallicin yielded, among other products, the 1,4-epoxyeudesmanolide **161**, which has a *trans*-fused decalin system (Scheme 17). Under the same conditions the closely related germacranolide 8α-hydroxygallicin (**162**) cyclized into shonachalin B with a *cis*-fused decalin system. These reactions proceed probably through the cationic intermediates **160**, **160'** and **163** shown in Scheme 17.[109]

Scheme 18: Vinyl epoxide isomerization



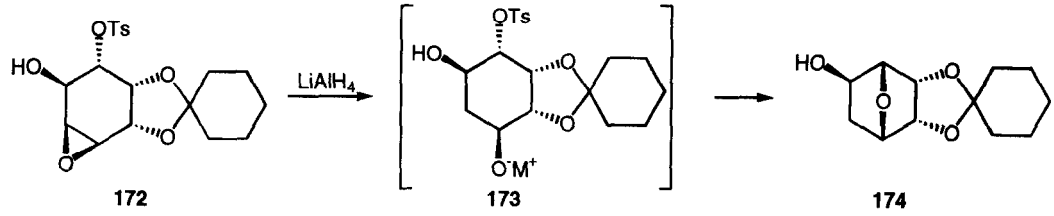
Epoxidation of (1*S*,2*S*)-3-fluorocyclohexa-3,5-diene-1,2-diol (**164**) with *meta*-chloroperbenzoic acid gives a 2:1 mixture of the epoxide **165** and 7-oxanorbornanediol **166** (Scheme 18). The isomeric epoxide **167** was not observed. It is proposed to be unstable under the reaction conditions and to be isomerized quickly into the 7-oxanorbornane **166**.[110] Related to this synthesis is the epoxidation of the bicyclo[4.2.0]octa-2,4,7-triene derivative **168** with *m*CPBA/$NaHCO_3$ which provides the epoxide **169** (Scheme 19). In the presence of a trace of acid in $CDCl_3$, **169** is isomerized into 7-oxanorbornene **171** probably via the intermediacy of the hydroxy-allylic cation **170**.[111]

Scheme 19: Acid-induced vinyl epoxide isomerization



Intramolecular displacement reactions have also been applied to generate 7-oxanorbornane systems (Scheme 20). For instance, the reduction of epoxide **172** with $LiAlH_4$ in THF, expected to give alcoholate **173**, furnished the 7-oxanorbornanol derivative **174** in 53% yield.[112]

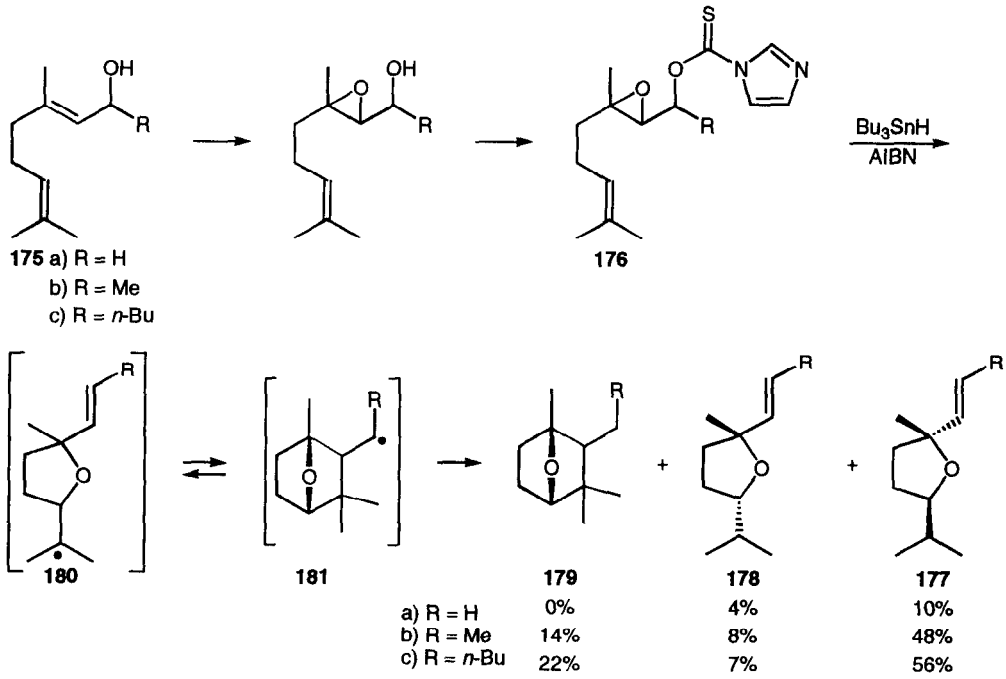
Scheme 20: Intramolecular nucleophilic displacement



172 **173** **174**

Radical cyclization is an alternative method for preparing 7-oxanorbornane derivatives (Scheme 21). Geraniol (**175a**) and the products **175b** and **175c** derived from addition of methyl lithium and *n*-butyl lithium to citral were epoxidized using the Sharpless vanadium technology.[113] Reaction with thiocarbonyl diimidazole in CH_2Cl_2 gave rise to **176** that underwent reactions with Bu_3SnH and AIBN to generate mixtures of the tetrahydrofurans **177**, **178** and 7-oxanorbornanes **179**. The bicyclic compounds **179** resulted from further reactions of radical intermediates **180**, a process generating the corresponding bicyclic radicals **181**. The proportion of **179a** was very low compared to **179b** and **179c**. This is explained by a greater relative stability of the secondary radicals **181b,c** compared to that of the primary radical **181a**.[114]

Scheme 21: Radical isomerization



175 a) R = H
b) R = Me
c) R = *n*-Bu

176

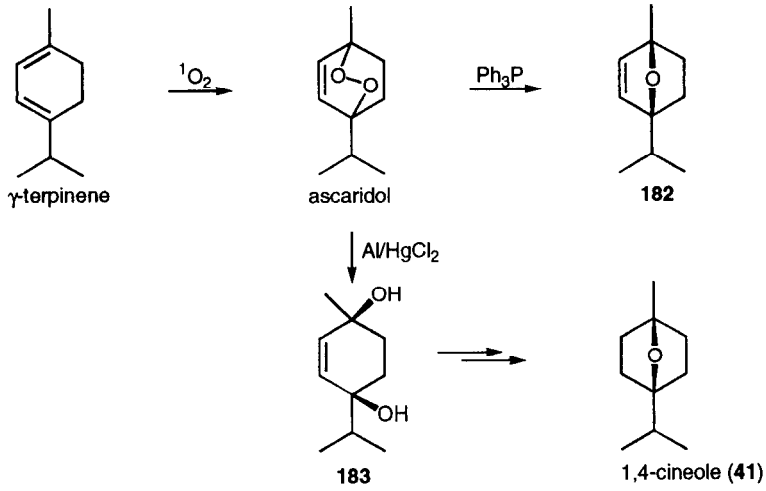
180 **181**

	179	**178**	**177**
a) R = H	0%	4%	10%
b) R = Me	14%	8%	48%
c) R = *n*-Bu	22%	7%	56%

Schenk et al.[115] have reported that ascaridol, the product of singlet oxygen [4+2] addition to γ-terpinene, can be reduced with triphenylphosphine into 1,4-oxido-*p*-menthene **182**. Reduction of ascaridol with aluminum

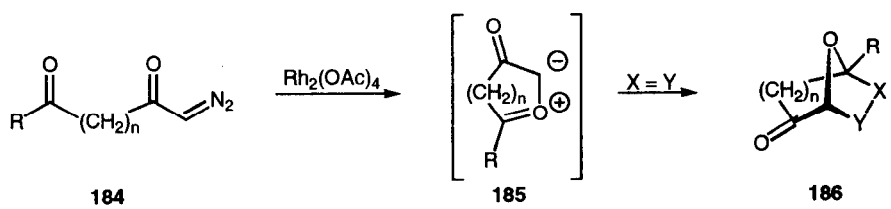
powder and $HgCl_2$ generated the diol **183** which, after hydrogenation and water elimination, provided 1,4-cineole (Scheme 22).

Scheme 22: Singlet oxygen addition to cyclohexa-1,4-dienes

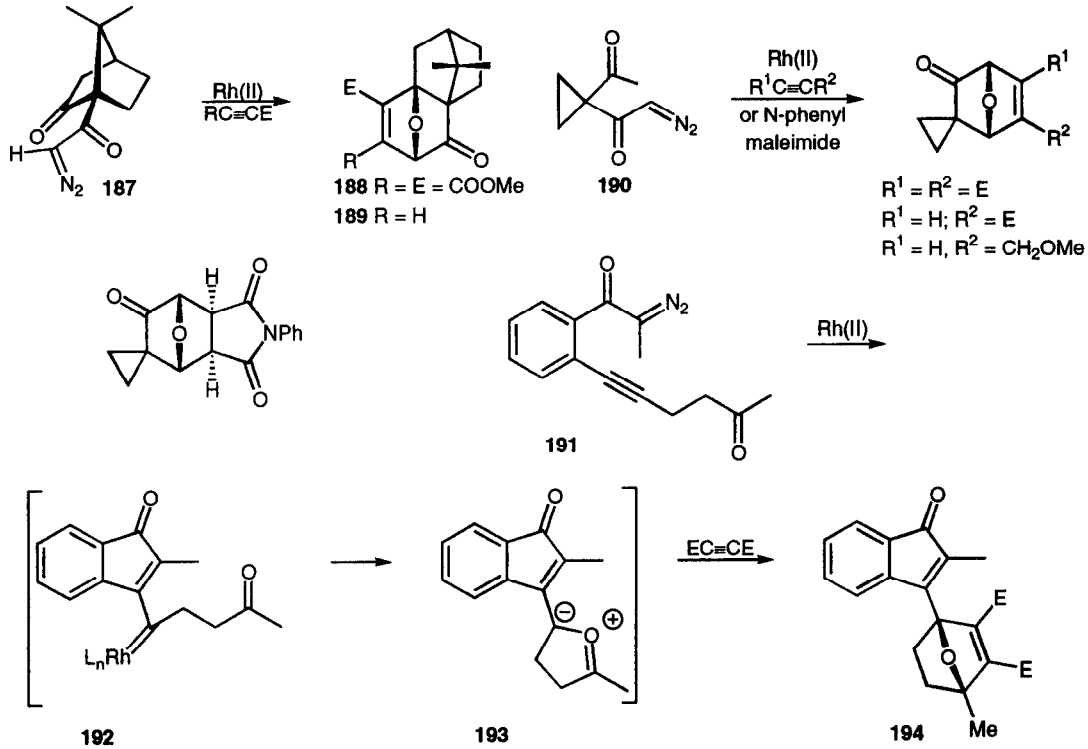


5.2. Cyclic carbonyl ylide cycloadditions

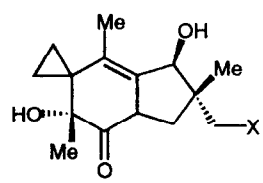
Treatment of 1-diazoalkanediones **184** with rhodium(II) acetate generates cyclic carbonyl ylides **185** that can undergo 1,3-dipolar cycloadditions with all types of dipolarophiles[116] giving adducts **186**. Padwa et al.[117] derived 6-diazoketo-7,7-dimethylbicyclo[2.2.1]heptane **187** from ketopinic acid. Treatment of **187** with $Rh_2(OAc)_4$ in benzene at 25 °C in the presence of dimethyl acetylenedicarboxylate provided the cycloadduct **188** in 85% yield. The cycloaddition proceeded with complete diastereofacial selectivity. In the presence of methyl propynoate, adduct **189** was obtained in 72% yield, showing the high degree of regioselectivity in the 1,3-dipolar cycloaddition. Similarly, the cyclopropyl substituted diazoketone **190** was reacted with $Rh_2(OAc)_4$ in the presence of various dipolarophiles giving the bicyclic adducts shown in Scheme 23.[118] A rhodium carbenoid intermediate may result from the carbenoid additions into an alkyne moiety as shown with **191**→**192**. If the carbenoid finds a γ-keto group it reacts with it to generate a five-membered cyclic carbonyl ylide, e.g. **193**, which can add to a dipolarophile such as dimethyl acetylenedicarboxylate with the formation of a 7-oxa-norbornene derivative, e.g. **194**.



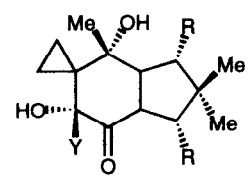
Scheme 23: Tandem carbonyl ylide formation and 1,3-dipolar cycloadditions



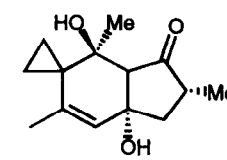
Padwa et al.[119] have used the carbonyl ylide cycloaddition approach to generate 7-oxanorbornanones that may be converted into illudins and ptaquilosin analogues. The key reaction involves the reaction of **190** with $Rh_2(OAc)_4$ in the presence of cyclopentenones leading to 7-oxanorbornanones **195**.[120] One illudin analogue, the acylfulvene **196**, was prepared by McMorris and al.[121] following (Scheme 24) Padwa's approach and was found to have similar *in vivo* activity to that of mitomycin C in mice implanted with MV522 cells (cancer cells). Compound **195** has also been converted into several members of the pterosin family of sesquiterpenes.[122]



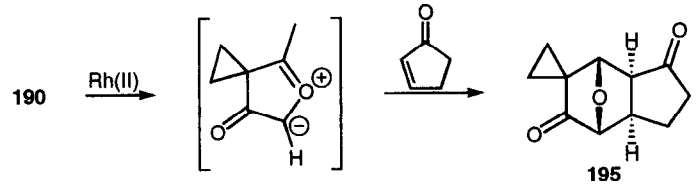
illudin M (X = H)
illudin S (X = OH)



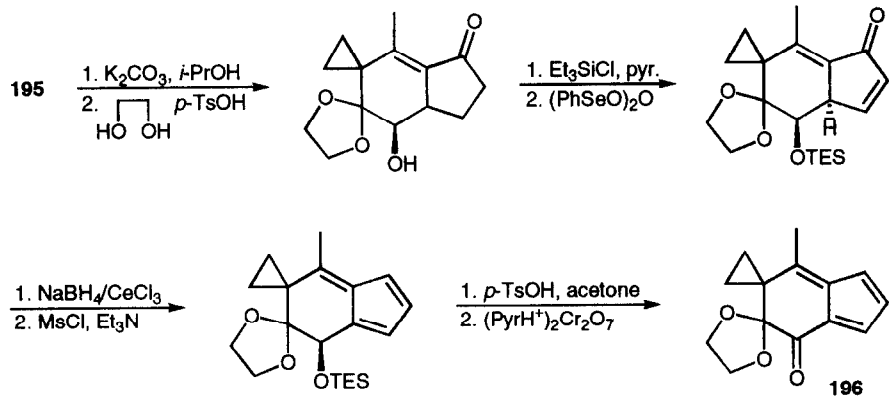
illudin A (R = H, X = OH, Y = Me)
illudin B (R = OH, X = Me, Y = OH)



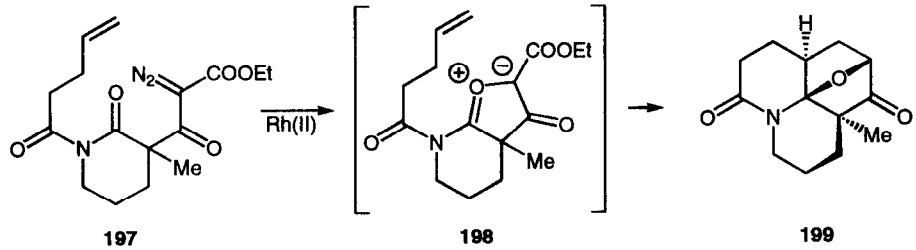
ptaquilosin



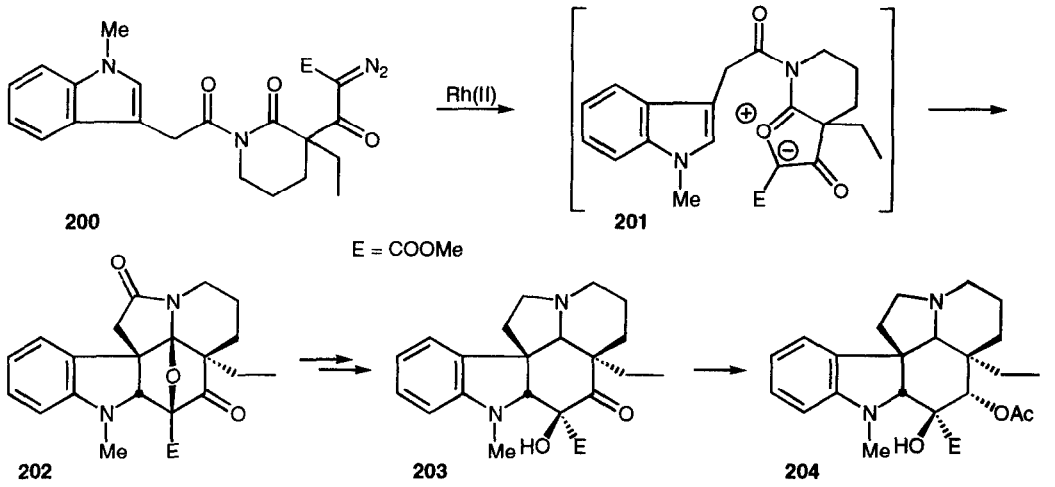
Scheme 24: Synthesis of an antitumor acylfulvene (**196**)



An intramolecular version of the carbonyl ylide cycloaddition has been developed by Padwa and co-workers.[123] For instance, the rhodium(II)-catalyzed formation of the carbonyl ylide intermediate **198** derived from cyclic diazo-amide **197** furnished tetracyclic **199** in good yield. The method has been applied by Padwa and Price[124] to generate the pentacyclic skeleton of the aspidosperma alkaloids. The key step in this synthesis involves the Rh(II)-induced formation of carbonyl ylide **201** from **200** and its intramolecular 1,3-dipolar cycloaddition across the indole moiety giving **202**. A few steps converted **202** into the vindoline analogues **203** and **204**.

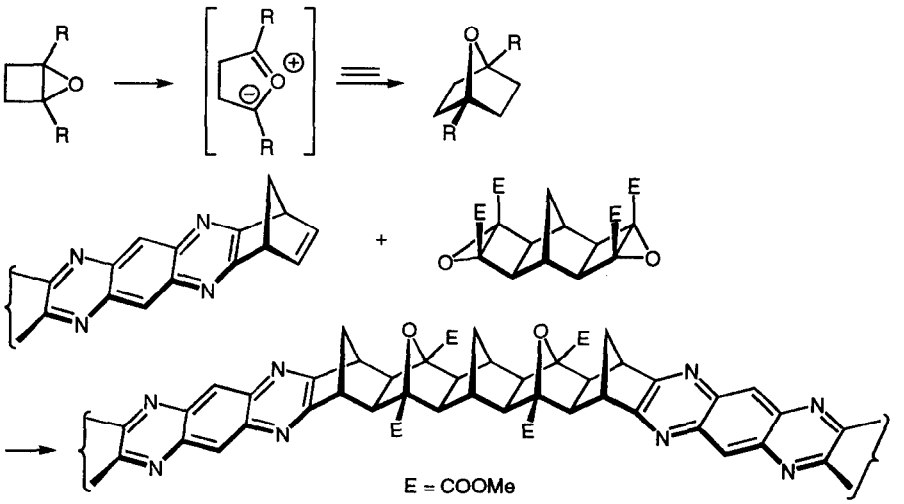


197 **198** **199**



Warrener and co-workers[125] have shown that cyclobutene epoxides can undergo ring opening to generate cyclic carbonyl ylides prone to undergo 1,3-dipolar cycloaddition (Scheme 25). The method has been applied to construct polynorbornanes.

Scheme 25: Warrener's 7-oxanorbornane synthesis

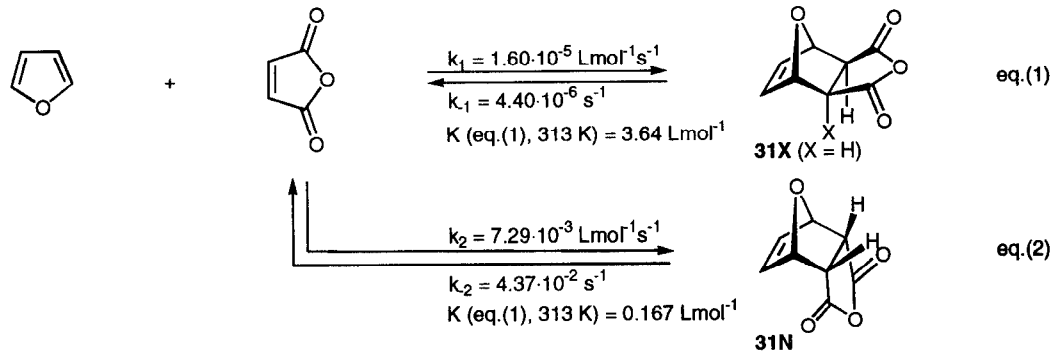


5.3. Intermolecular Diels-Alder additions of furans

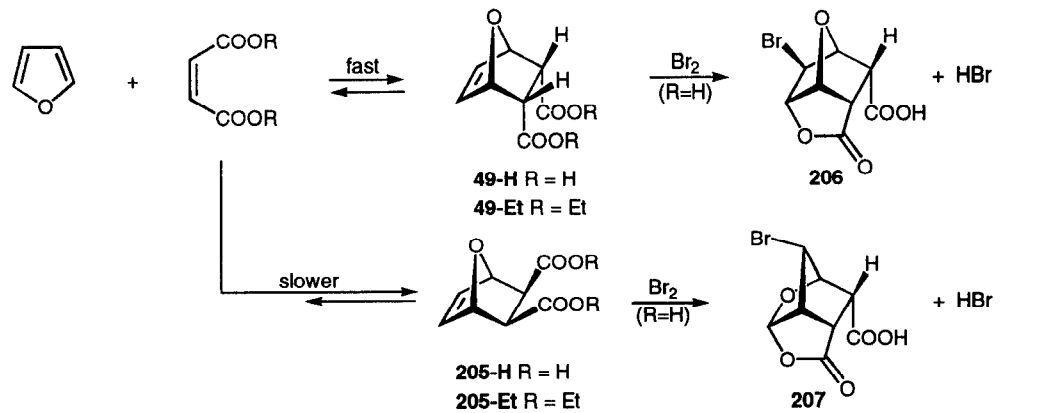
The shortest method to generate 7-oxabicyclo[2.2.1]hept-2-ene derivatives is the Diels-Alder addition of furans to alkenes. The shortest method to generate 7-oxabicyclo[2.2.1]hepta-2,5-dienes is the cycloaddition of furans to alkynes. The reaction between furan and maleic anhydride was first investigated by Diels and Alder in 1929.[126a] At room temperature it gives rise to the *exo*-adduct **31X** (X = H), the structure of which was first demonstrated by Woodward and Baer[127] in 1948. In 1962, Anet[128] found that at low temperature, the *endo*-

adduct **31N** was formed concurrently with **31X** (X = H), but after a while, only the thermodynamically favored *exo*-adduct **31X** (X = H) was present in the reaction mixture (Scheme 26). The *endo*-adduct **31N** corresponds to the *endo* Alder rule which states that the preferred transition state implies a maximum accumulation of unsaturation and makes the formation of the less stable stereomer **31N** faster than that of the more stable adduct **31X** (X = H),[126b] as a deviation from the Dimroth principle.[129] Lee and Herndon[130] have measured, for equilibrium (1) and (2) in MeCN, the rate constants, k_1, k_{-1}, k_2 and k_{-2} shown in Scheme 26 and have established the stability difference ΔH_r(**31X** (X = H) = **31N**) = 1.9 kcal/mol.

Scheme 26: Kinetic and thermodynamic data for the Diels-Alder additions of furan and maleic anhydride



Scheme 27: Endo Alder rule



Berson and Swidler[131] showed that the Diels-Alder reaction of furan with maleic acid in water gives first the *endo*-adduct **49-H**, but this gradually isomerizes to the stable *exo*-adduct **205-H**. With bromine **49-H** gives the bromolactone **206** and HBr, whereas with **205-H**, it generates the rearranged bromolactone **207** and HBr (Scheme 27). The *endo* dicarboxylic acid **49-H** can be converted to the *endo*-anhydride **31N** on treatment with Ac_2O/pyridine at 0 °C.[68] The reaction of furan with diethyl maleate is much slower[132] than with maleic acid or maleic anhydride. Without solvent and at 20 °C, 33% of the *endo*-adduct **49-Et** is formed after three

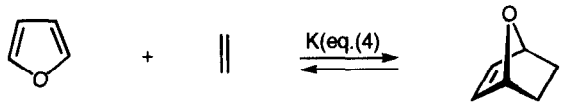
months,[133] together with 2% of the *exo*-adduct **205-Et**. Short path distillation of **49-Et** *in vacuo* causes fragmentation into furan and diethyl maleate. The reaction of furan with fumaric acid in DMSO-d_6 (20 °C) gives adduct **208-H**, a reaction slower than equilibrium (1). The addition of furan to diethyl fumarate giving adduct **208-Et** is also very slow at 20 °C. Equilibrium (3) is reached after one month leading to ca. 40% conversion (neat furan, no solvent), which leads to an estimate for the equilibrium constant K(eq. (3), R = Et, 293 K) = 0.044 $Lmol^{-1}$.

eq.(3)

208-H R = H
208-Et R = Et

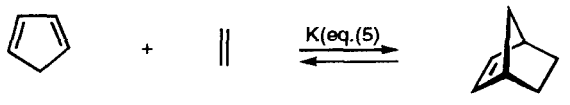
Because of the aromaticity of furan,[134] the 7-oxabicyclo[2.2.1]hept-2-enes are rather sensitive thermally and revert to the starting cycloadducts. It is often suggested that only with the use of very reactive dienophiles such as maleic anhydride or dimethyl acetylenedicarboxylate (see below) can respectable yields of cycloadducts be attained, provided that the reactions are carried out in concentrated solutions at or below room temperature. Application of high pressure (10-20 kbar) at 20 °C can overcome the difficult Diels-Alder additions of furans[135,136] or the use of Lewis acid promoters (catalysts) that activate the dienophile whithout polymerizing the furan or decomposing the cycloadducts formed (see below). The relatively small equilibrium constants K(eq.(1)), K(eq.(2)) and K(eq.(3)) reported for equilibria (1), (2) and (3), respectively, are not exclusively due to the loss of aromaticity of furan when forming the oxanorbornene systems. Other factors intervene as will seen. Very importantly, non-activated dienophiles may add to furan if the thermodynamics are favorable.

In 1944, Nudenberg and Butz[137] reported that when a mixture of furan and ethylene was heated in an autoclave to 428 K, the pressure gradually decreased until a stable value was reached after ca. 16 h. This led to a 5-8% yield of 7-oxabicyclo[2.2.1]hept-2-ene (**209**). It corresponds to a minimal equilibrium constant K(eq.(4), 428 K) = [**209**]/[C_2H_4][furan] of 0.02 $Lmol^{-1}$. For reaction in the gas phase and assuming that laws for ideal gas apply, most of the entropy of reaction ΔS_r(eq.(4)) is due to the change of entropy of translation (S_{tr}= 6.86 logM(g) + 11.44 logT – 2.31 e.u.) between adduct and cycloaddents. One thus calculates ΔS_r(eq.(4), 428 K) = -36.7 e.u., which leads to a higher estimate for the heat of reaction furan + C_2H_4 = **209** of ΔH_r(eq.(4), 428 K) = 3327-428(-36.7) kcal/mol = -12.4 kcal/mol. Thermochemical data for the gas phase[138] give a heat of formation of –11 kcal/mol for **209**; this allows one to calculate ΔH_f°(eq.(4), 298 K, gas) = -15.2 kcal/mol. For the cycloaddition of cyclopentadiene to ethylene giving bicyclo[2.2.1]hept-2-ene (**210**, eq.(5)), a value for ΔH_f°(eq.(5), 298 K) = -23 kcal/mol is determined. The difference of ca. 8 kcal/mol between ΔH_f°(eq.(4)) and ΔH_f°(eq.(5)) is due, in part, to the furan aromaticity (ca. –15 kcal/mol), and additionally to a ring strain difference (ca. –7 kcal/mol) between 7-oxabicyclo[2.2.1]heptane (+8.5 kcal/mol) and bicyclo[2.2.1]heptane (+16.2 kcal/mol).[139]



eq.(4)

$K(eq.(4),313K)_{est}$ = 920 $Lmol^{-1}$ **209** ΔH_r°(eq.(4), gas) = -15.2 kcal/mol

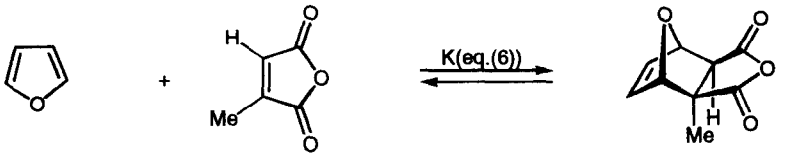


eq.(5)

210 ΔH_r°(eq.(5), gas) = -23 kcal/mol

The larger stability of *exo*-adducts (e.g. **31X**) compared with that of *endo* isomers (e.g. **31N**) can be attributed to steric repulsions between the substituents at C(5), C(6) and the 7-oxabicyclo[2.2.1]hept-2-ene skeleton. These repulsions are not present in **209** and can thus explain, in part, the higher K(eq.(4)) value compared with those of K(eq.(1)), K(eq.(2)) and K(eq.(3)) at the same temperature. Assuming ΔS_r(eq.(4)) = -35 e.u. at 313 K, one calculates K(eq.(4), 313 K) = 920 $Lmol^{-1}$, which is 255 times greater than K(eq.(1), 313 K). The heat of hydrogenation of maleic anhydride amounts to –30 kcal/mol in the gas phase.[138] This may be compared with the heat of hydrogenation of 2,5-dihydrofuran into tetrahydrofuran (-28±2 kcal/mol) and that of cyclopentene into cyclopentane (-27.3±0.4 kcal/mol). These values demonstrate that the hypothetical π-conjugation energy in maleic anhydride does not exist. It cannot be said that the smaller equilibrium constant K(eq.(1)) compared with K(eq.(4)) at 313 K is due to loss of π-conjugation in the dienophile going from cycloaddents to Diels-Alder adducts!

Dauben et al.[140] have shown recently that citraconic anhydride equilibrates in pure furan with *exo*-adduct **31X** (X = Me) with equilibrium constants K(eq.(6), 293 K) = 0.0011 and K(eq.(6), 313 K) = 0.0008 $Lmol^{-1}$. Applying the Van't Hoff method for ideal solutions leads to ΔH_r(eq.(6)) = -2.9 kcal/mol and ΔS_r(eq.(6)) = -23.4 e.u. Both ΔH_r(eq.(6)) and ΔS_r(eq.(6)) so-obtained are too large (not negative enough) compared with the values expected for the gas phase (see: ΔH_r(eq.(4) = -15.2 kcal/mol, ΔS_r(eq.(4)) = -35 e.u.). This analysis demonstrates that solvation and other solute/solute associations (activities ≠ concentrations) affect both the heat and the entropy of the Diels-Alder additions of furan. Furthermore, it is found that equilibrium constants depend on the medium (solvent and additives). For instance, equilibrium constant K(eq.(6)) is ca. 9 times larger at 293 K in 5 M $LiClO_4/Et_2O$ than in pure furan (4.41 molar initial furan concentration, 0.4 molar in citraconic anhydride).



eq.(6)

citraconic anhydride **31X** (X = Me)

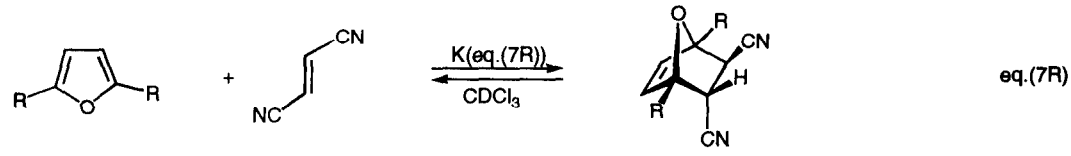
in furan: K (eq.(6), 313 K) = 0.0008 $Lmol^{-1}$

K (eq.(6), 293 K) = 0.0011 $Lmol^{-1}$

in 5 M $LiClO_4/Et_2O$: K (eq.(6), 293 K) = 0.01 $Lmol^{-1}$

Lee and Herndon[130] observed that their equilibrium constant measured for the cycloaddition of furan to maleic anhydride in MeCN varied with the initial concentration of the reactants (at 1.50 M initial concentration of furan and maleic anhydride (K(eq.(1), 313 K) = 3.46 $Lmol^{-1}$, at 0.12 M initial concentration K(eq.(1), 313 K) = 3.90 $Lmol^{-1}$, K giving as [**31**]/[furan][maleic anhydride], in agreement with the hypothesis that solvation and autoassociation of reactants play a significant role on the equilibrium constants of the Diels-Alder additions of furan to polar dienophiles. Applying the Van't Hoff method to the equilibrium constants (measured as concentration ratios) of the cycloaddition of fumarodinitrile to furan and 2,5-disubstituted furans **211R** giving adducts **212R**,[141] Cook and Cracknell[142] obtained the thermodynamic parameters shown in Table 1.

Table 1: Thermochemical data for the Diels-Alder additions of fumarodinitrile to furans



211R **212R**

	ΔH_r[kcal/mol]	ΔS_r[e.u.]	K(at 296 K)[a]	[$Lmol^{-1}$]	
R = H	-1.8±0.2	-15.5±0.5	0.0087	0.0058[b])	0.004[c])
R = Me	-4.0±0.1	-18.4±0.5	0.0926	0.0587	0.023
R = *n*-Bu	-3.2±0.1	-17.2±0.5	0.0384		
R = *n*-Hex	-2.7±0.2	-16.0±0.5	0.0161		

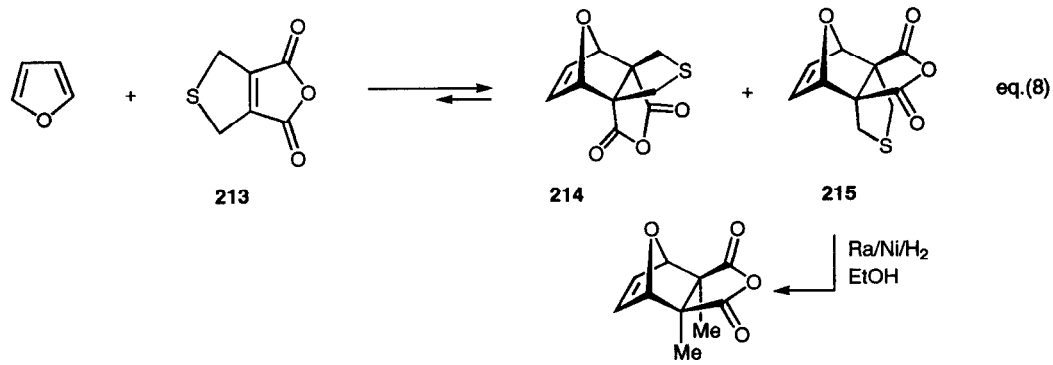
[a]) at 0.004 M initial concentrations of cycloaddents in $CDCl_3$

[b]) in CD_3OH; [c]) in CD_3COCD_3

The data deviate significantly from those estimated for the gas phase (ΔH_r(eq.(4)), ΔS_r(eq.(4))). This shows again the importance of differential solvation and autoassociation effects on cycloaddents and adducts, and thus on the Diels-Alder equilibrium constants. The introduction of alkyl substituents at the bridgehead centers C(1), C(4) of adducts **212R** is expected to destabilize them because of gauche interactions between these alkyl groups and the carbonitrile functions. If this were the unique factor affecting the equilibrium constants K (eq.(7R), it would have been expected that K(eq.(7,R≠H) < K(eq.(7,R=H), contrary to observation (Table 1). Similar observations have been reported by Schuda and Bennett[143] for the cycloadditions of furan, 2-methylfuran and 2,5-dimethylfuran to α-chloroacrylonitrile. These authors found that the highest yields of adducts were obtained with the most substituted furan under conditions that were close to equilibrium conditions. The fact that the heat of reaction ΔH_r(eq.(7,R=Me) = -4.0 kcal/mol is more negative than ΔH_r(eq.(7,R=H) = -1.8 kcal/mol suggests that non-substituted furan (**211R**, R=H) is more solvated or associated with the dienophile or/and itself than the 2,5-dimethylfuran (**211R**, R=Me). This hypothesis is

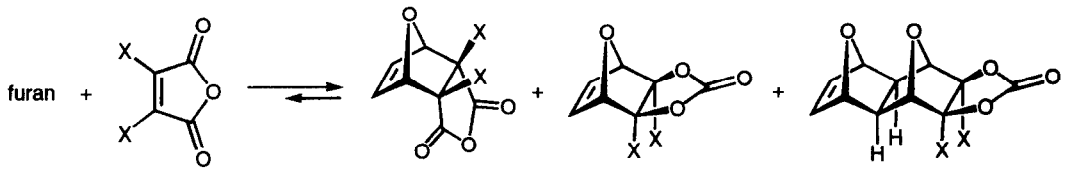
consistent with the observation that the ΔS_r(eq.(7)) values are less negative than expected for condensation reactions in the gas phase or as ideal solutions (see: ΔS_r(eq.(8)) = -35 u.e.). This confirms that aggregation of the reactants is larger for unsubstituted furans than for the disubstituted furans. The importance of differential solvent effects between adducts and cycloaddents is manifested also by the observation of significant solvent effects on equilibrium constants K(eq.(7,R=H) and K(eq.(7,R=Me) at 296 K (Table 1). Dewar and Pierini[144] have reported that substitution of furans at C(2) and C(5) destabilizes slightly the corresponding Diels-Alder adducts with maleic anhydride as they found equilibrium constants K = 1.237, 0.967 and 0.683 dm^3mol^{-1} for the addition of maleic anhydride to furan, 2-methylfuran and 2,5-dimethylfuran, respectively, in MeCN at 49.5 °C.

Scheme 28: Synthesis of cantharidin according to Dauben



29 (cantharidin)

Dauben and co-workers[31,145] have developed a two step synthesis of cantharidin (**29**) (Scheme 28). The first step involves the Diels-Alder addition of furan to 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**213**) which leads to a 1:4 mixture of adducts **214** and **215**. The reaction initially required a very high pressure (7 kbar) at 20 °C. After desulfurization and alkene hydrogenation with hydrogen and Raney nickel, a mixture of cantharidin and *epi*-cantharidin was obtained from which pure cantharidin (**29**) was isolated in 51% yield after selective recrystallization from EtOAc. Recently, Dauben et al.[140] found that the cycloaddition (eq. (8)) can be carried out at 20 °C under atmospheric pressure using Grieco's reagent (5 M $LiClO_4$ in Et_2O).[146] Under these conditions, an equilibrium constant K(eq.(8), 293 K) = 3 $Lmol^{-1}$ was evaluated. It is ca. 300 times as large as K(eq.(6), 293 K) = 0.01 $Lmol^{-1}$ found for the cycloaddition of furan to citraconic anhydride under the same conditions. Here again, one cannot attribute this difference to steric factors in the adducts. Other factors such as differential solvation effects and cycloaddents aggregation can be invoked to interpret the results.



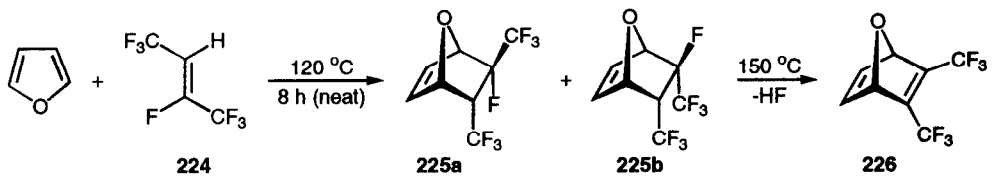
216 X = H
220 X = Cl

217 X = H
221 X = Cl

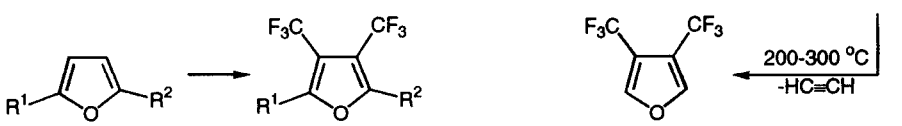
218 X = H
222 X = Cl

219 X = H
223 X = Cl

If the thermodynamic factors are favorable, furan can undergo cycloaddition with dienophiles that are not electron-poor, as already seen with the reaction furan + ethylene = **209**. Newman and Addor[147] have shown that the vinylene carbonate (**216**) adds to furan when heated in a sealed tube to 123-127 °C for 21 h, giving a 34% yield of a mixture of *endo* and *exo*-adducts (**217**, **218**) and of the 1:2 adduct **219**. Similar results were reported by Scharf[148] for the reaction of furan with dichlorovinylene carbonate (**220**). A 67% yield of adducts **221** + **223** (1:2.15), together with 1.5% of **223** was obtained on heating furan with **220** in *ortho*-dichlorobenzene to 180 °C. These experiments show that the equilibrium constants for these cycloadditions must be much larger than those measured for the Diels-Alder additions of furan to electron-poor dienophiles (K(eq.(1)), K(eq.(3)), K(eq.(7R))). Adducts **217** and **218** have been converted to *myo*-, *allo*-, *neo*- and *epi*-inositols.[149]



224 **225a** **225b** **226**



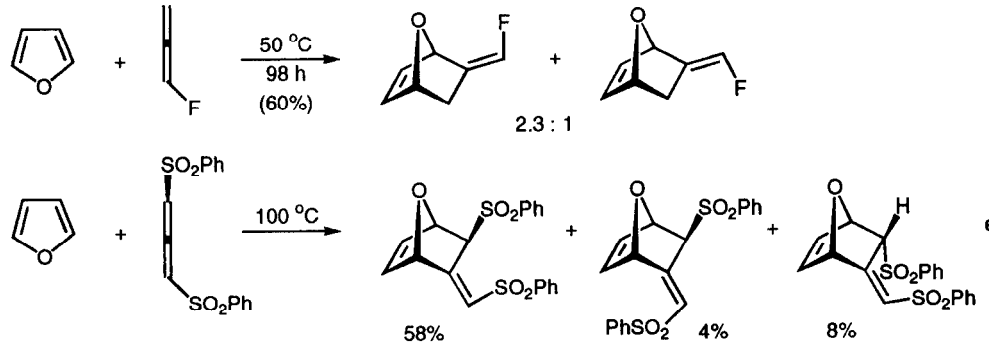
228 **229** **227**

R^1, R^2 = H, Me, CN, CHO, COOR

Chambers and coworkers[150] have found that the readily accessible heptafluorobut-2-ene (**224**)[151] participates readily in Diels-Alder additions to furans at temperatures under which simpler olefinic dienophiles would not form stable adducts because the cycloreversion is favored thermodynamically. For instance, furan adds to **224** at 120 °C giving a 1:1 mixture of adducts **225a** and **225b** in 78% yield. Heating to 150 °C induced HF elimination with formation of the diene **226**. Above 200 °C, cycloreversion with formation of 3,4-bis(trifluoromethyl)furan (**227**) and acetylene occurs. The method applied to substituted furans **228** allows the preparation of a large variety of substituted furans **229** in a one pot operation on heating furans **228** with **224** at 250-300 °C.[152]

The cycloreversion of 7-oxabicyclo[2.2.1]hepta-2,5-diene derivatives to generate substituted furans has been used before.[153] Traditionally, selective hydrogenation of the less-substituted alkene moiety of the 7-oxabicyclo[2.2.1]hepta-2,5-diene system, leading to the corresponding 7-oxabicyclo[2.2.1]hept-2-ene derivative, precedes the pyrolysis that, in the latter case, generates ethylene, instead of acetylene, and the substituted furan.[154]

Monosubstituted alkenes are often good dienophiles for Diels-Alder additions with furan and alkyl-substituted derivatives. With acrylonitrile[155] or phenyl ethylenesulfonate[156] good conversions are reached at 20 °C with the use of a Lewis acid promoter or high pressure conditions.[135,136] All dienophiles that can be coordinated to a Lewis acid will undergo accelerated Diels-Alder cycloadditions.[157] For instance, ZnI_2 has been found to be a catalyst of choice for the reaction of furan with acrylonitrile, methyl acrylate, α-chloroacrylonitrile or methyl methylidenemalonate[158] and $ZnCl_2$ for the additions of furan to 2-vinylpyridine and 4-vinylpyridine.[159]



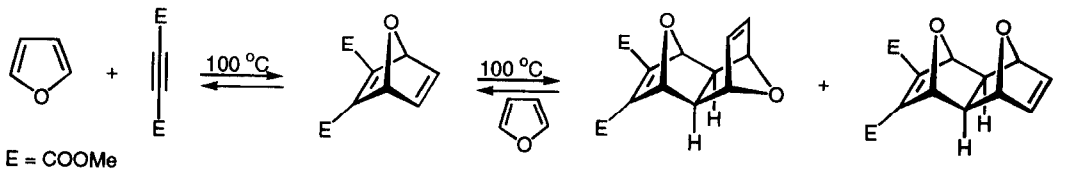
Since the heat of hydrogenation of an allene nearly equals the heat of hydrogenation of an acetylenic compound,[138] and since the ring strain of a 5-alkylidene-7-oxabicyclo[2.2.1]hept-2-ene (3 sp^2 carbon centers) is lower than that of an isomeric 7-oxabicyclo[2.2.1]hepta-2,5-diene (4 sp^2 carbon centers in the bicyclic system), the heat of the Diels-Alder additions of allenic dienophiles to furans is expected to be more negative than those of the cycloadditions of furan to ethylenic and acetylenic dienophiles. Thus, good yields can be expected for the Diels-Alder additions of allenic dienophiles to furans[160] (see e.g. eq.(9),[161] eq.(10)[162]), even if the reactions require a relatively high temperature (up to 100 °C).[163] Further aspects of intermolecular and intramolecular Diels-Alder additions of furans have been discussed recently.[1c,164]

5.4. Tandem Diels-Alder additions of furans

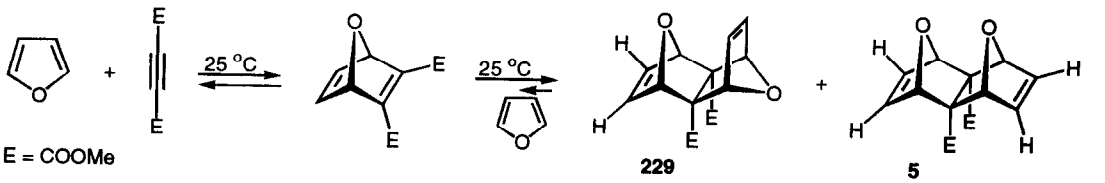
In 1931, Diels and Alder[165] observed that the reaction of furan with dimethyl acetylenedicarboxylate at 100 °C generates 2:1 adducts in which the C(5)-C(6) olefinic moiety of the 1:1 adduct has reacted with furan (Scheme 29A), a process referred as "domino" tandem Diels-Alder addition,[166] and a newly created double bond is involved in a successive cycloaddition. Later, Diels and Olsen found that, at 25 °C, other types of 2:1

adducts **229** and **5** are formed (conditions of kinetic control) following a process called "pincer" tandem Diels-Alder addition (Scheme 29B).[167] The 2:1 adduct **5** has become an important building block for the construction of U-shape systems (see Scheme 1).[11]

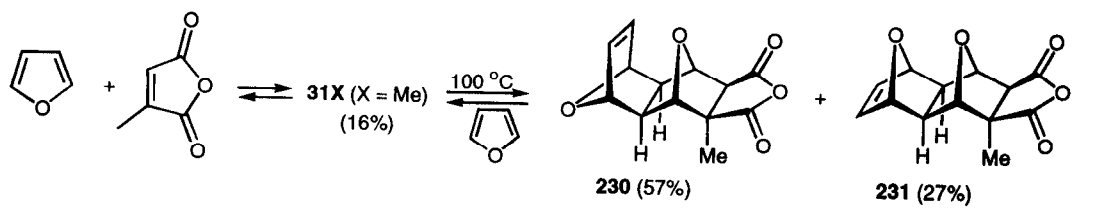
Scheme 29A: "Domino" tandem Diels-Alder addition

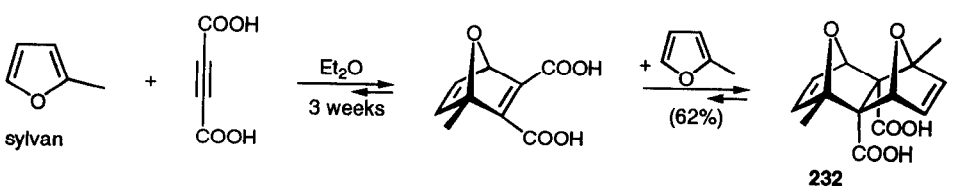


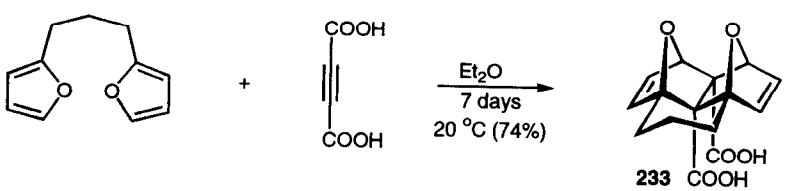
Scheme 29B: "Pincer" tandem Diels-Alder addition



The reaction of furan with 2-methylmaleic anhydride (citraconic anhydride) giving the 1:1 adduct **31X** (X = Me) (eq.(6)) is accompanied by the formation of 2:1 adducts **230** and **231** when using 1.1 equivalents of furan.[140]



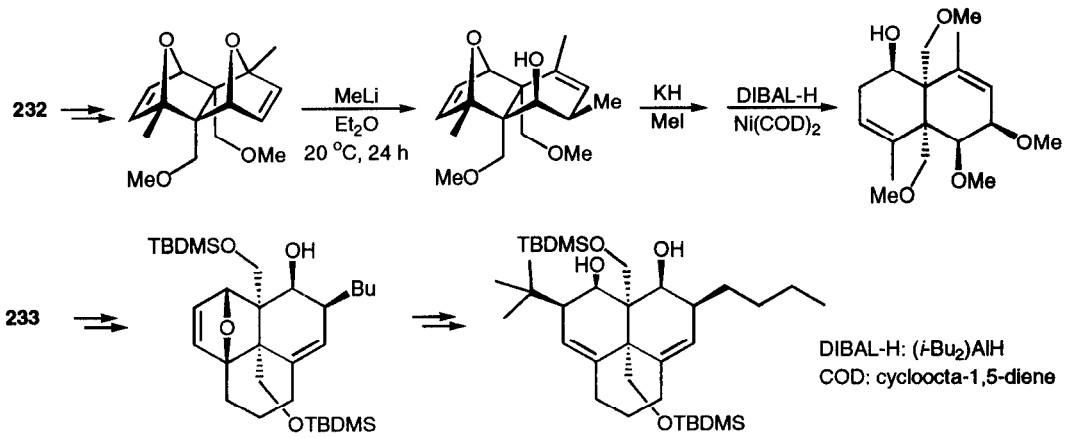




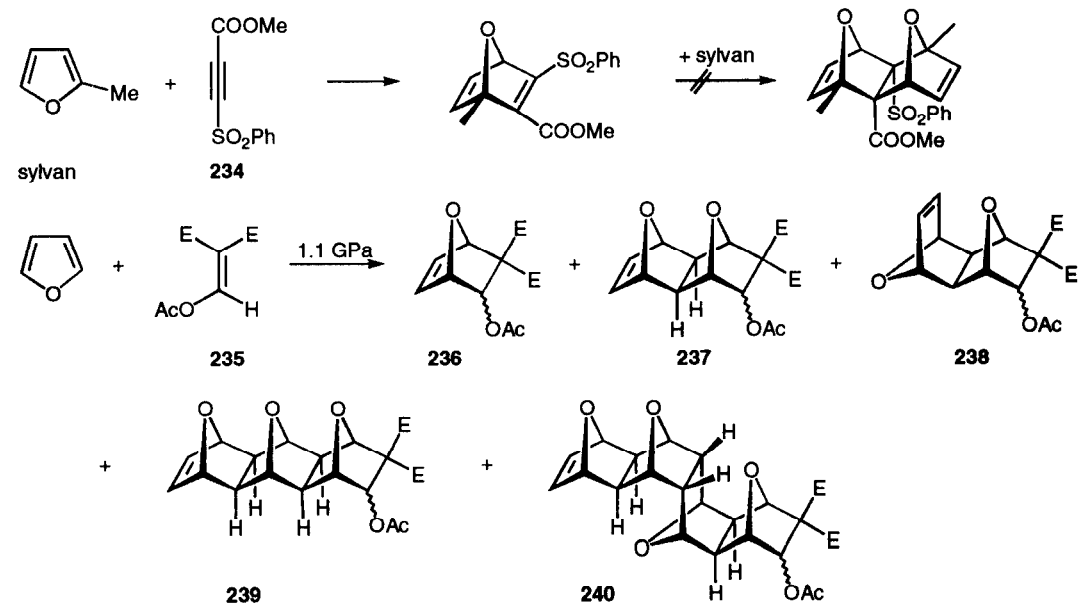
With sylvan (2-methylfuran), Lautens and Fillion[168] found that its reaction with acetylenedicarboxylic acid in ether gives a single 2:1 adduct **232** in 62% yield. The high stereo- and regioselectivity of this "pincer" tandem Diels-Alder addition was attributed to steric factors. With 1,3-bis(α-furyl)propane, its reaction with

acetylenedicarboxylic acid gave **233** in 74% yield.[168] Adducts **232** and **233** have been converted into polysubstituted decalins, via selective 7-oxanorbornene ring openings induced by S_N2' reactions with alkyllithium reagents (Scheme 30) or/and diisobutylaluminium hydride/Ni(COD)$_2$. The "pincer" tandem Diels-Alder addition could not be observed with the reaction of sylvan with the dienophile **234**.[169]

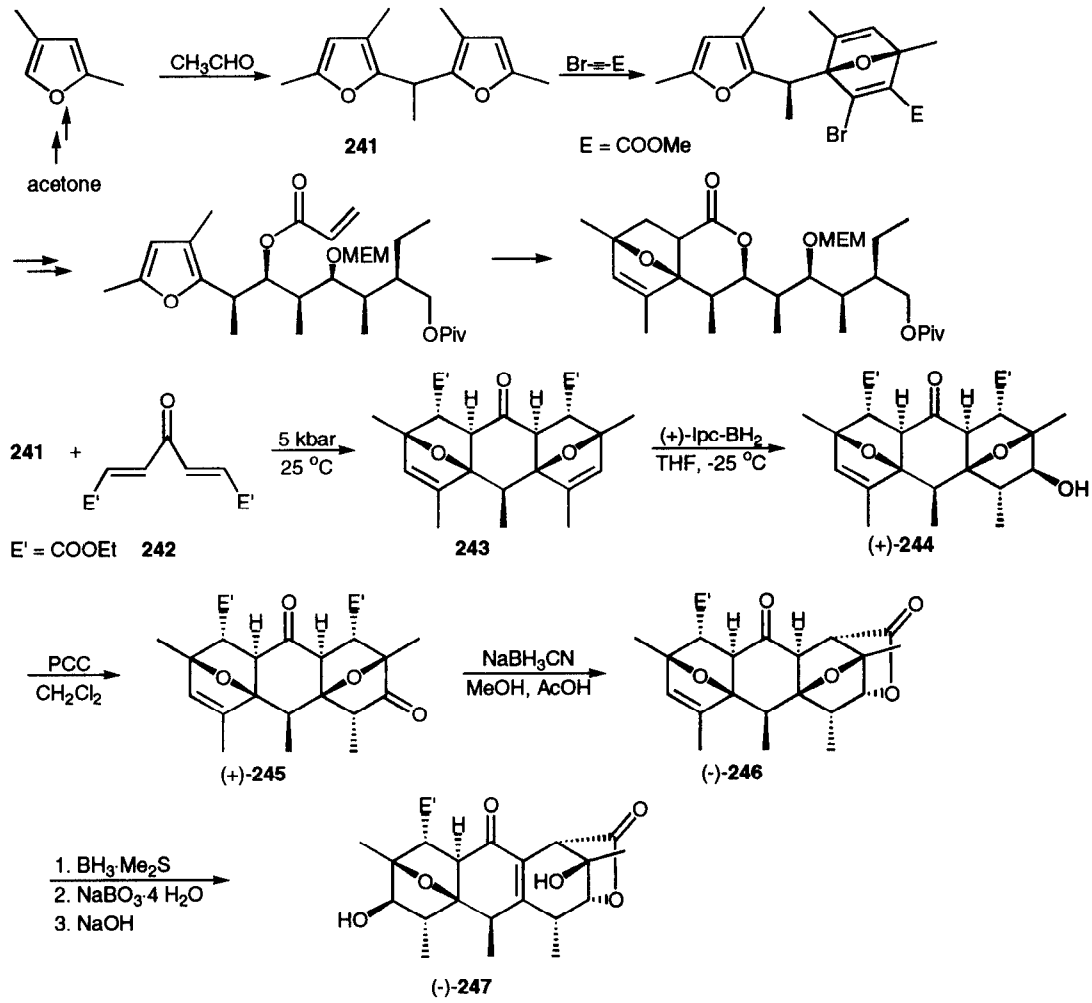
Scheme 30: Sequential 7-oxanorbornene S_N2' reactions and synthesis of decalins



The Diels-Alder addition of dienophile **235** to furan does not occur under thermal conditions, even in the presence of Lewis acid catalysts. However, under high pressure (1.1 GPa) the expected 1:1 adduct **236** were formed, together with the "domino" 2:1 adducts **237** and **238**, the "domino" 3:1 adduct **239** and the "domino" 4:1 adduct **240**.[170]



Scheme 31: Double Diels-Alder additions of a bis-furyl system and synthesis of long-chain polypropionates

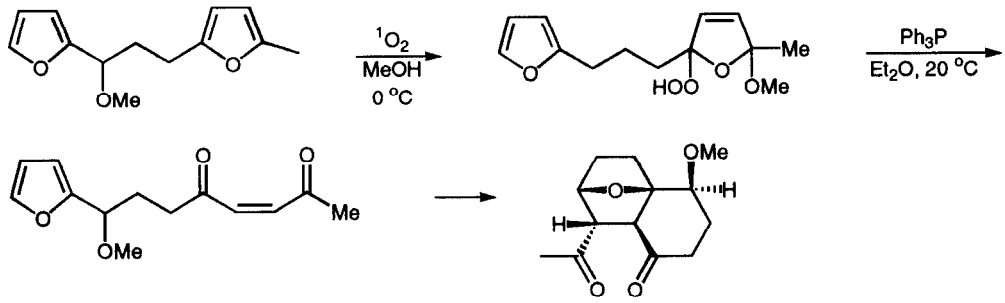


The double furan **241** (1,1-bis(3,5-dimethylfur-2-yl)ethane), obtained in one step by condensation of 2,4-dimethylfuran with acetaldehyde; 2,4-dimethylfuran is derived in 3 steps from acetone), can be converted into a variety of polypropionate fragments with high stereoselectivity through a sequence of reactions implying two Diels-Alder additions (Scheme 31).[171] When an equimolar mixture of **241** and diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate (**242**) (25% in $CHCl_3$) was pressurized for 5 h at 5 kbar (25 °C), a single adduct **243** was obtained in 95% yield. Using 1.1 equivalents of monoisopinocampheylborane ((+)-$IpcBH_2$) in THF provided (+)-**244** (59% yield, e.e. 78%). Thus, in two synthetic steps, the two planar cycloadducts **241** + **242** were converted into an enantiomerically enriched polycyclic system (+)-**244** containing eleven stereogenic centers! Differentiation of the chemistry of the two 7-oxanorbornane moieties of (+)-**244** was achieved in the following way. Oxidation of (+)-**244** with pyridinium chlorochromate (PCC) gave the ketone (+)-**245** that was reduced to

the corresponding *endo* alcohol (which was not isolated), and this underwent lactonisation giving (-)-**246**. Hydroboration of the remaining 7-oxanorbornene unit followed by oxidative and alkaline work-up provided (-)-**247** in which the most strained 7-oxanorbornene moiety has undergone chemoselective 7-oxa-bridge opening (E_{1cb}-type of elimination, see Section 7.6).[172]

The tandem photooxidation and Diels-Alder addition of 1,3-bis(α-furyl)propane derivatives generates first enedione intermediates (reductive work-up with Ph_3P) that undergo intramolecular Diels-Alder additions providing polysubstituted decalins with complete control of the stereoselectivity.[173] An example is shown in Scheme 32.

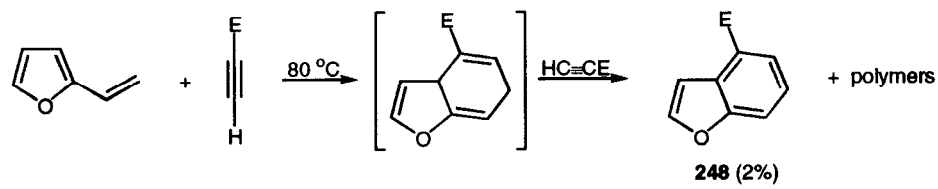
Scheme 32: Tandem photooxidation and Diels-Alder addition; synthesis of decalins



5.5. Site selectivity of the Diels-Alder additions of vinylfurans

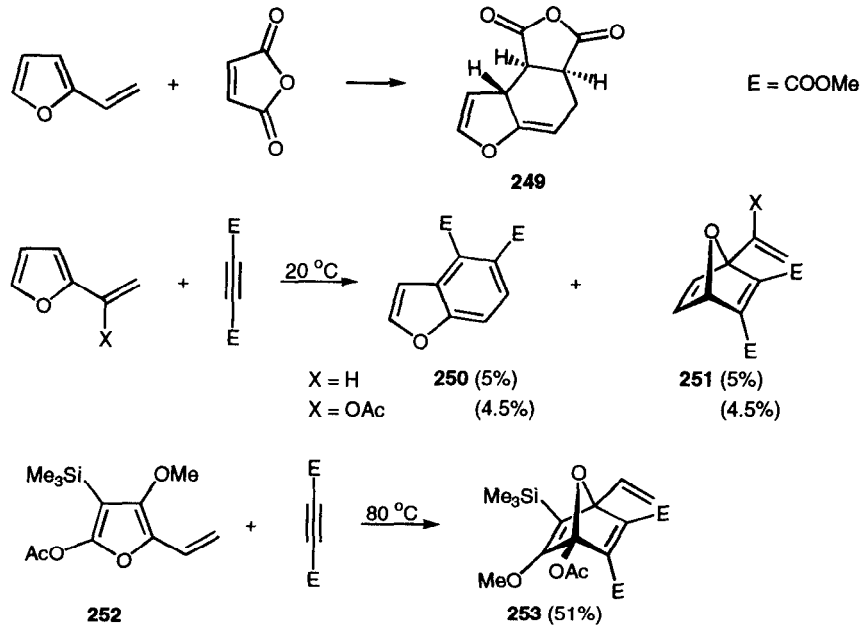
Methyl propynoate adds to 2-vinylfuran after prolonged heating at 80 °C and gives 2% of **248** together with polymeric material. With maleic anhydride, adduct **249** arising from an extraannular mode of cycloaddition, was obtained.[174a] Dimethyl acetylenedicarboxylate adds to 2-vinylfuran at 20 °C and this leads to a 1:1 mixture (10%) of the benzofuran derivative **250** (extraannular mode of cycloaddition) and the 7-oxanorbornadiene system **251** (intraannular mode of cycloaddition).[174a] Similar results were obtained with the reaction of dimethyl acetylenedicarboxylate with 1-(α-furyl)vinyl acetate (Scheme 33). In contrast, the persubstituted furan **252** reacted with dimethyl acetylenedicarboxylate giving a major adduct **253** (51%) arising from the intraannular mode of cycloaddition.[174b]

Scheme 33: Extra- vs. intraannular mode of cycloaddition



248 (2%)

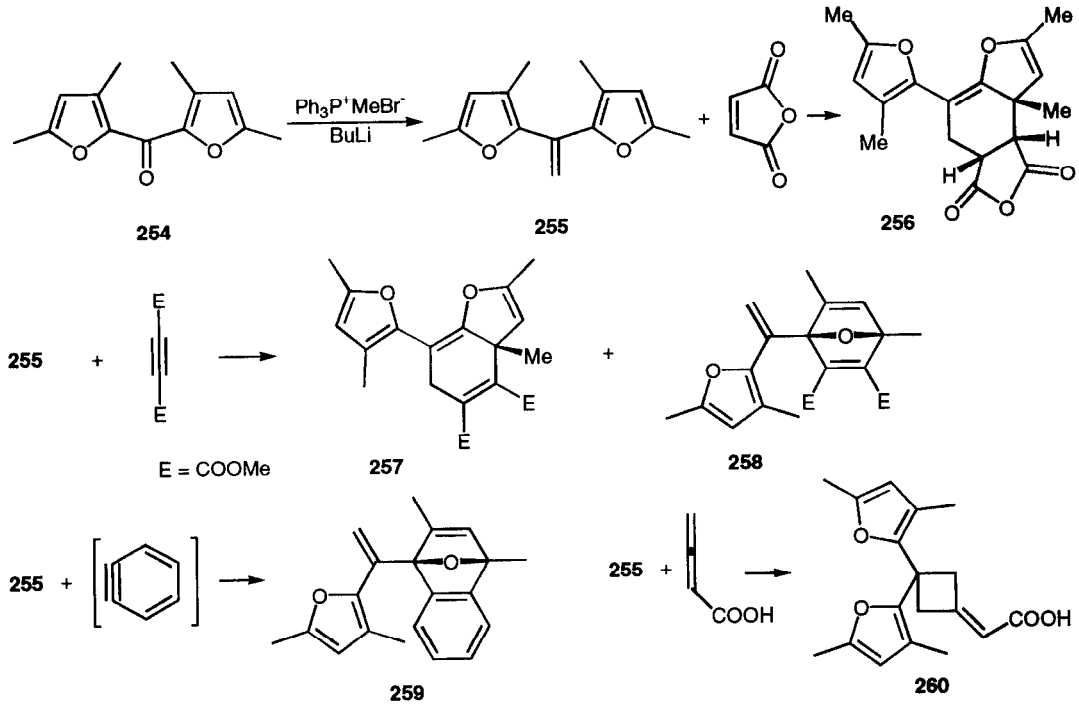
Scheme 33 (continued)



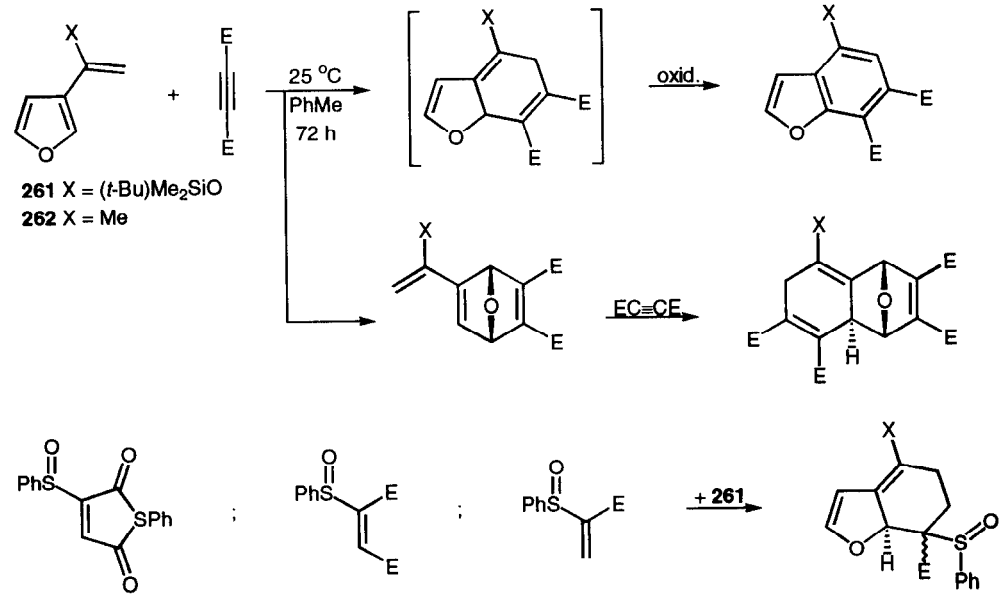
Treatment of 3,5-dimethylfuran[175] with BuLi generated the corresponding 2-furyllithium derivative, the reaction of which with methyl N,N-dimethylcarbamate provided the ketone **254** (61%). Wittig methylenation of **254** furnished 1,1-bis(3,5-dimethyl-2-furyl)ethene (**255**).[176] It adds to maleic anhydride giving a single adduct **256** (80%) arising from an extraannular Diels-Alder addition.[176] Similar cycloadditions were observed with benzoquinone and 1-cyanovinyl acetate as dienophiles. With dimethyl acetylenedicarboxylate, neat **255** led to a 4:1 mixture of 1:1 adducts **257** and **258**. No trace of a double adduct resulting from the reaction of the two dimethylfuryl moieties could be seen. The proportion of adducts **257** and **258** depended on the solvent, this being 2.4:1 for the reaction in MeCN and 6:1 in benzene containing Et_3Al (Scheme 34). The reaction of **255** with benzyne generated by decomposition of anthranilic acid with isopentyl nitrite gave a low yield (10%) of a single adduct **259**. Surprisingly, buta-2,3-dienoic acid (Et_2O, 20 °C, 3 d) did not undergo Diels-Alder addition with **255** but gave a [2+2]-cycloadduct **260** involving exclusively the exocyclic double bond of **255**.[176]

The 3-vinylfuran **261** (derived from 3-acetylfuran) and **262** added to dimethyl acetylenedicarboxylate, N-phenylmaleimide, and dimethyl maleate giving 1:1 adducts derived both from the intraannular mode of cycloaddition and from the extraannular mode of cycloaddition (Scheme 35). In contrast, dienophiles containing a phenylsulfinyl group gave products derived exclusively from the extraannular mode of cycloaddition. These products are useful precursors of 4-substituted benzofurans.[177]

Scheme 34: Site and chemoselectivity of the cycloadditions of 1,1-bis(3,5-dimethyl-2-furyl)ethene



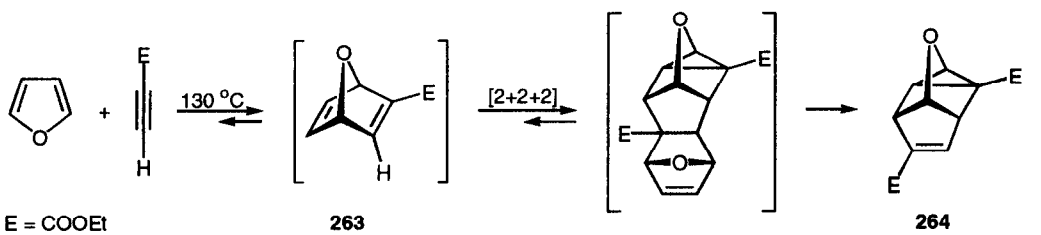
Scheme 35: Tandem Diels-Alder reactions with 3-vinylfurans



5.6. Side-reactions of furan Diels-Alder additions

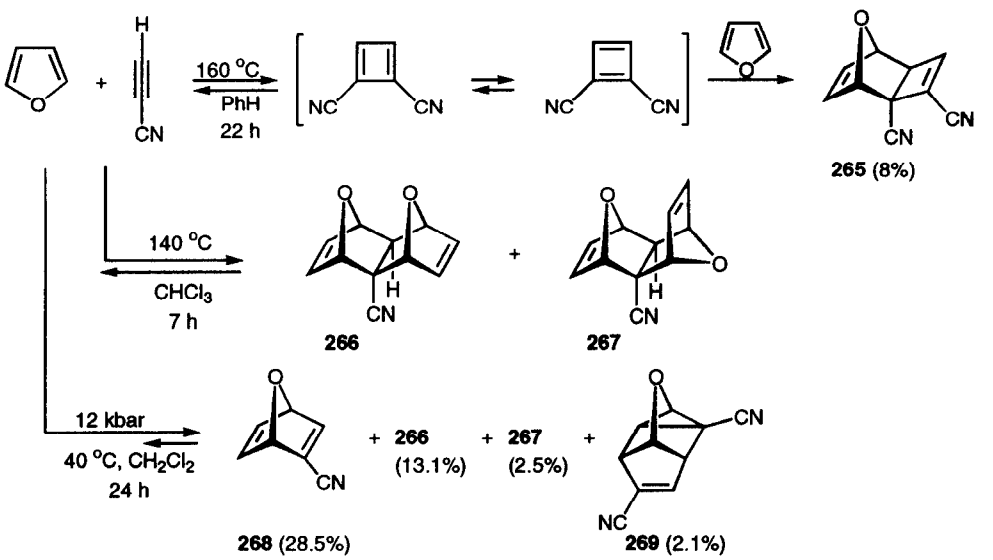
Apart from the "pincer" and "domino" tandem Diels-Alder cycloadditions (Section 5.4) and dehydrogenation of the adducts formed (see e.g. Scheme 33), [2+2] (see Scheme 34), [2+2+2]-cycloadditions, [4+2]-cycloreversions (see e.g. **226**→**227** + HC≡CH), Michael additions, as well as water elimination from the 7-oxanorbornenes formed or their isomerisation may compete with the Diels-Alder additions of furans. For instance, heating furan and ethyl propynoate to 130 °C generates the 1:2 adduct **264** in low yield (9%).[178] This adduct might arise from the [2+2+2]-cyclodimerization of the 1:1 Diels-Alder adduct **263**, followed by a [4+2]-cycloreversion as shown in Scheme 36.[178]

Scheme 36: [2+2+2]-cycloaddition

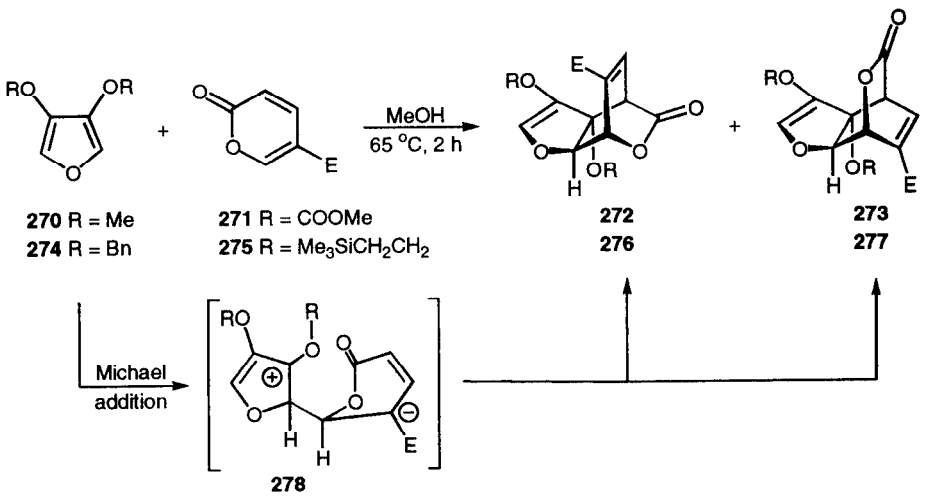


Heating furan and ethynecarbonitrile in benzene at 160 °C produces 8% of the 1:2 adduct **265** arising probably from the [2+2]-cyclodimerisation of the dienophile into cyclobutadiene-1,2-dicarbonitrile (Scheme 37). In $CHCl_3$ and at 140 °C, a 1:3 mixture of furan and ethynecarbonitrile gives mostly the expected "pincer" 2:1 adducts **266** + **267**. At 40 °C under high pressure (12 kbar), a mixture of the 1:1 adduct **268** (28.5%), 2:1 adducts **266** and **267** (13.1% and 2.5%) and the 1:2 adduct **269** (2.1%) is obtained[179] (Scheme 37).

Scheme 37: Competing [4+2], [2+2] and [2+2+2]-cycloadditions



The electron-rich 3,4-dimethoxyfuran **270** adds to methyl coumalate (**271**) giving a 1:1 mixture of the corresponding *endo* and *exo*-[2+2]-cycloadducts **272** and **273** (52%). Similarly, derivatives **274** + **275** give a 1:1 mixture of adducts **276** and **277** (86% yield). These results can be interpreted in terms of a non-concerted process involving zwitterionic intermediates of type **278** the stability of which arises, in part, from the electron-releasing substituents of the furans.[180]



270 R = Me
274 R = Bn

271 R = COOMe
275 R = $Me_3SiCH_2CH_2$

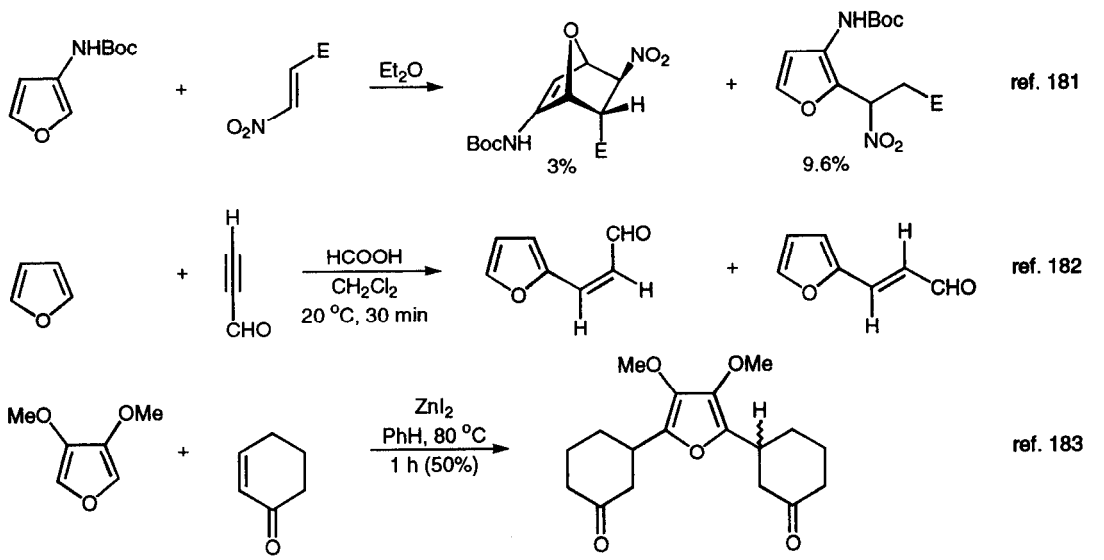
272
276

273
277

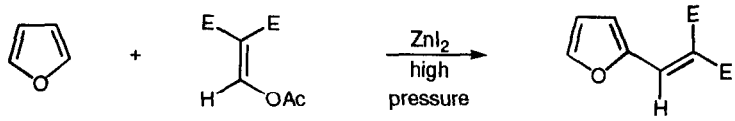
278

With electron-rich furans or in the presence of protic or Lewis acids, the Diels-Alder additions can be accompanied by products of Michael additions (Scheme 38).[170,181-183]

Scheme 38: Examples of Michael additions of furans



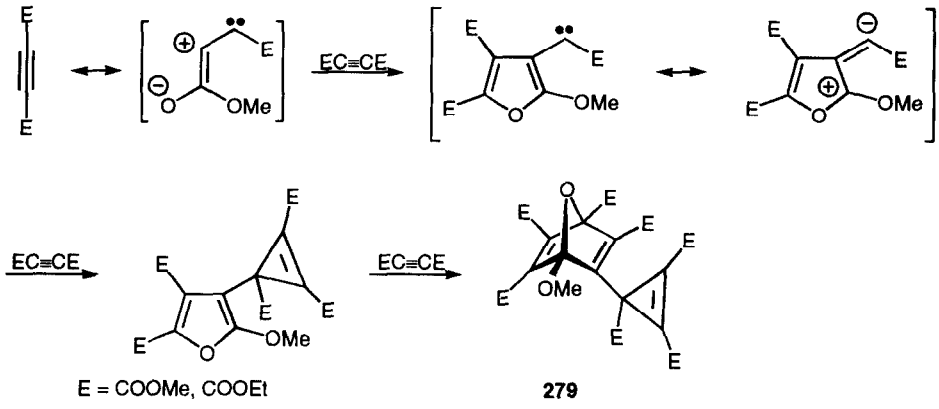
Scheme 38 (continued)



ref. 170

Prolonged heating of solutions containing dimethyl or diethyl acetylenedicarboxylate generates tetrameric compounds of type **279**, the formation of which can be interpreted in terms of dipolar cyclodimerization, followed by cyclopropanation giving a furan intermediate that undergoes Diels-Alder addition with a fourth equivalent of the acetylenic dienophile (Scheme 39).[184]

Scheme 39: Tetramerization of dialkyl acetylenedicarboxylate



E = COOMe, COOEt

279

6. Enantiomerically and diastereomerically enriched 7-oxanorbornyl derivatives

Because of their high utility as synthetic intermediates, a large variety of 7-oxanorbornyl derivatives have been obtained, some of them with high diastereomeric or enantiomeric purity. All of the possible methods of asymmetric synthesis have been applied for obtaining these derivatives as illustrated in Table 2. The most important 7-oxanorbornyl synthetic intermediates have been classified according to their number of carbon atoms and indications are given of their mode of preparation.

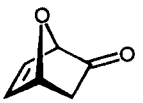
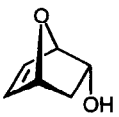
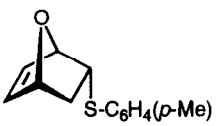
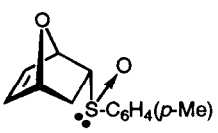
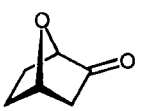
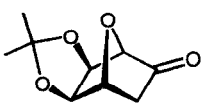
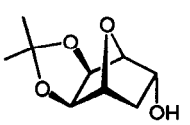
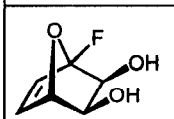
Table 2.	Enantiomerically and diastereomerically enriched 7-oxanorbornyl derivatives and their mode of preparation (e.e. and d.e. given for purified products)
 (+)-**280**[a,b] (>99% e.e.)[190]	Saponification of Diels-Alder adducts of furan to 1-cyanovinyl esters with recovery of the chiral auxiliaries;[185,186] oxidation of (+)-**281**;[187] 3 steps from **298**;[188] treatment of (+)-**282** with NCS, then with $CuCl_2$;[189] resolution of (±)-**280** with (*R*,*R*)-1,2-diphenylenediamine.[190a]
 (+)-**281**[a] (>99% e.e.)[190]	Synthesis of (±)-**280**,[190b] and lipase-catalyzed hydrolysis of racemic butyrate;[187] $NaBH_4$ reduction of (+)-**280**.[2b]
 (+)-**282** (>99% e.e.)[189]	Treatment of (+)-**283** with pyridine and 2-chloro-1,3,2-benzodioxaphosphole.[189]
 (+)-**283** (>99% d.e.)[189]	Diels-Alder addition of furan to (*S*)-(-)-ethoxy *p*-tolyl vinyl sulfonium tetrafluoroborate, and chromatography.[189]
 (+)-**284**[a] (>99% e.e.)	Hydrogenation (H_2, Pd/C) of (+)-**280**; resolution of (±)-**284** applying Zeller-Johnson's method[191] ((+)-(*S*)-N,S-dimethyl-S-phenylsulfoximide).[186b]
 (+)-**285**[a] (>99% e.e.)	Via double hydroxylation of (+)-**290** or (+)-**291**, protection and saponification;[2b] resolution of (±)-**285** by the Zeller-Johnson method;[192] (-)-**285** by treatment of menthyl esters **304** (mixture of epimers) with LiF/DMF.[193]
 (-)-**286** (>97% e.e.)[187]	Double hydroxylation of (+)-**281**, and acetonide formation;[187] $NaBH_4$ reduction of (+)-**285**.[2b]
 **166**[c,e]	Microbial oxidation of fluorobenzene giving (1*S*,2*S*)-6-fluorocyclohexa-3,5-diene-1,2-diol followed by epoxidation (see Scheme 18, 20% yield).[110]

Table 2. (continued)

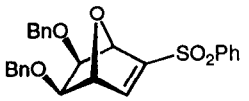
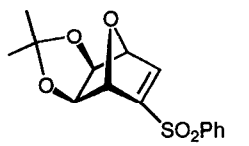
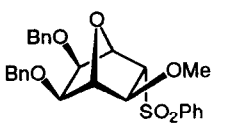
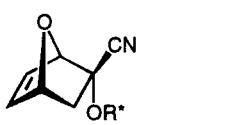
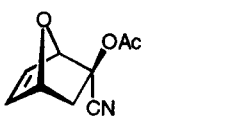
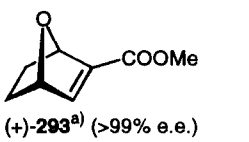
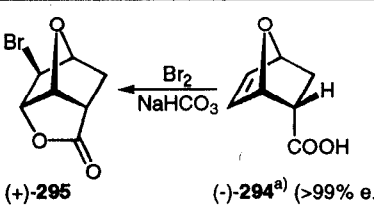
 (+)-**287**[a] (>95% e.e.)[194]	The Diels-Alder adduct of furan with (*E*)-$PhSO_2CH{=}CHSO_2Ph$ is converted into (±)-5,6-*exo*-bis(benzyloxy)-3-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptan-2-*exo*-ol, with resolution by the chromatographic separation of the camphanates.[194]
 (+)-**288**[a] (>95% e.e.)[314]	(-)-**287** + $EtSH/BF_3{\cdot}Et_2O$; $(MeO)_2CMe_2/TsOH$.[195,314]
 (+)-**289** (>95% e.e.)[194]	(+)-**287** + MeONa/MeOH.[194]
 (+)-**290**[a] R* = (-)-camphanoyl (+)-**291**[a] R* = (-)-RADO(Et) (>99% d.e.)[f]	ZnI_2 or $ZnBr_2$-catalyzed Diels-Alder addition of furan to (-)-1-cyanovinyl camphanate[185a] or (-)-1-cyanovinyl ((1*R*,5*S*,7*S*)-3-ethyl-2-oxo-6,8-dioxa-3-azabicylco[3.2.1]octane-7-*exo*-carboxylate, and recrystallization.[186b] Other diastereomeric adducts are recycled into (+)-**290** or (+)-**291** via a retro-Diels-Alder reaction on heating.
 (+)-**292**[a] (>99% e.e.)[b]	Cycloaddition of furan to 1-cyanovinyl acetate, saponification and resolution of the (±)-cyanhydrine with brucine, and acetylation.[186]
 (+)-**293**[a] (>99% e.e.)	Resolution of the (±)-3-*endo*-nitro-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylic acid[195] derived from furan and ethyl β-nitroacrylate.[196]
 (+)-**295** (-)-**294**[a] (>99% e.e.)	Resolution of the adduct of furan and acrylic acid using (+)-(*R*)-α-methylbenzylamine;[197] asymmetric Diels-Alder addition of furan to (1*R*,2*S*,5*R*)-8-phenylmethyl acrylate in the presence of $ZnCl_2/SiO_2$ or $TiCl_4/SiO_2$ (e.e. 76%).[198]

Table 2. (continued)

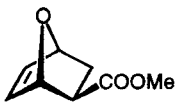
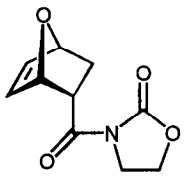
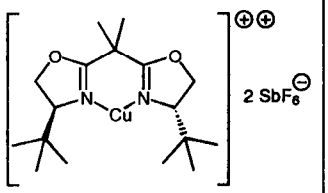
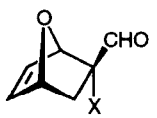
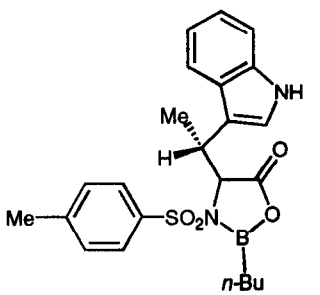
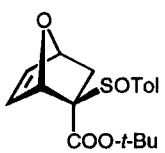
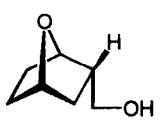
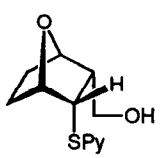
 (+)-**296** (92% e.e.)	Kinetic resolution by lipase-catalyzed (*Candida rugosa*) hydrolysis of (±)-**296**.[199]
 (+)-**297** (97% e.e.)[200]	Enantioselective Diels-Alder addition of furan catalyzed by 
 **298** X = Br (92% e.e.)[e] **299** X = Cl (90% e.e.)[e]	Enantioselective Diels-Alder additions of furan to α-bromo- or α-chloro-acrolein[188] catalyzed by 
 (+)-**300**[f] (>99% d.e.)	Furan Diels-Alder addition to *t*-butyl-2-*p*-tolylsulfinylpropenoate (4-13 kbar, 25 °C), and chromatographic separation of diastereomeric adducts.[201]
 (+)-**301**[a] (>99% e.e.)	By hydrogenolysis (Ra-Ni, EtOH) of (+)-**302**.[202]
 (+)-**302**[a] (>99% e.e.) Py = 2-pyridyl	Diastereoselective addition of furan to menthyl (*S*)$_S$-3-(2-pyridylsulfinyl)acrylate, followed by reduction with $TiCl_3$/EtOH, then with $LiAlH_4/Et_2O$.[202]

Table 2. (continued)

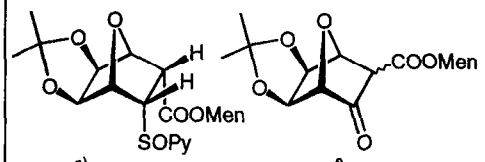
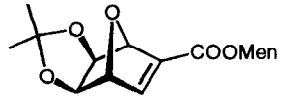
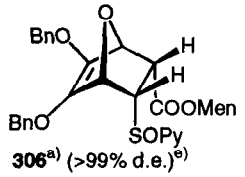
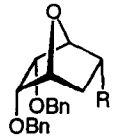
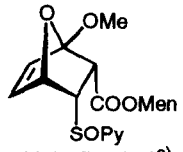
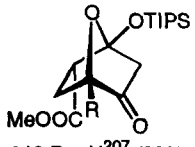
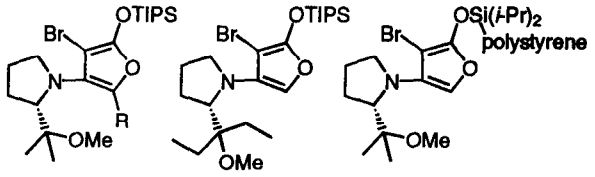
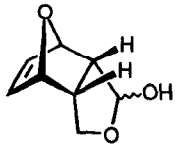
 (-)-**303**[a] (>99% d.e.) **304**[f]	Diastereoselective addition of furan to menthyl $(S)_S$-3-(2-pyridylsulfinyl)acrylate, followed by double hydroxylation of the Diels-Alder adduct, and acetonide formation →(-)-**303**; Pummerer rearr.[193]→ **304** (Men = (-)-menthyl)
 **305** (>99% e.e.)[e]	Derived from (-)-**303**.[203]
 **306**[a] (>99% d.e.)[e]	Diastereoselective addition of 3,4-dibenzyloxyfuran.[204]
 **307** R = CH_2OH (>99% e.e.)[205] **308** R = COOMe (>99% e.e.)[205]	Hydrogenation and further transformations of **306**.[204,205]
 **309** (>95% d.e.)[e]	Diastereoselective Diels-Alder addition of 2-methoxyfuran to menthyl $(S)_S$-3-(2-pyridylsulinyl)acrylate.[206] (Men = (-)-menthyl)
 **310** R = H[207] (99% e.e.)[e] **311** R = Me[208] (99% e.e.)[e] and derivatives thereof[207]	Via the diastereoselective addition of methyl acrylate to L-proline-derived furans:[207-209] 
 (+)-**51** (>99% e.e.)	Resolution of (±)-**51** with (+)-ketopinic acid (see Scheme 6).[68]

Table 2. (continued)

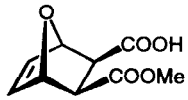
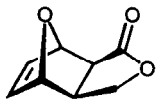
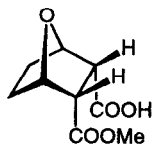
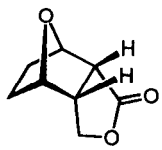
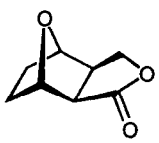
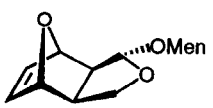
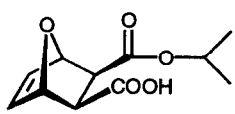
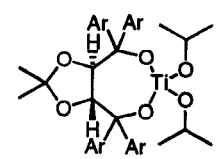
 (-)-**312** (>98% e.e)	Pig liver esterase (PLE)-catalyzed hydrolysis of the Diels-Alder adduct of furan to dimethyl maleate.[210]
 (-)-**313**[a)] (>98% e.e)	(-)-**312** + *n*-BuLi/$LiBH_4$/THF;[210a,b] (-)-**312** + $ClCO_2Et/NEt_3$ then $NaBH_4$/MeOH → (+)-**313**;[210] reduction of (+)-**318** with $LiBEt_3H$;[211] via microbiol oxidation;[212] enantioselective reduction of **31X**.[213]
 (-)-**314** (>97% e.e.)	PLE-catalyzed hydrolysis of the dimethyl diester obtained by hydrogenation of the adduct of furan to dimethyl acetylenedicarboxylate.[210]
 (+)-**315** (>98% e.e.)[214]	Horse liver alcohol dehydrogenase-catalyzed oxidation of 7-oxabicyclo[2.2.1]heptane-2,3-*endo*-dimethanol;[214] from (-)-**314** by treatment with *n*-BuLi/$LiBH_4$/THF.[210]
 (+)-**316**[a)] (>98% e.e)[214]	As above from the Diels-Alder adduct of furan to maleic anhydride;[210,214] hydrogenation of (+)-**313**;[214] reduction of (+)-**319** with $LiBEt_3H$;[211] enantioselective reduction of **32**;[213] Horse liver alcohol dehydrogenase-catalyzed oxidation of 7-oxabicyclo[2.2.1]heptane-2,3-*exo*-dimethanol under indirect electrochemical cofactor (NADH) regeneration using *N*-methylphenanthrolinedione$^+BF_4^-$; method can be applied to prepare (+)-**313** (>98% e.e).[215]
 (-)-**317A** (>99% d.e) (+)-**317B** (>99% d.e)	Chromatographic separation of diastereomeric acetals derived from (-)-menthol[216] (Men = (-)-menthyl).
 (+)-**318**[a)] (98% e.e.)[211]	Addition of a titanium TADDOLate to the adduct of furan to maleic anhydride (**31X**). (Ar = β-naphthyl).  TADDOLate

Table 2. (continued)

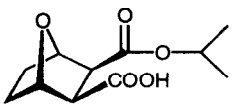
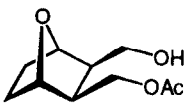
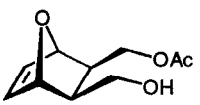
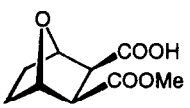
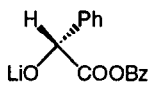
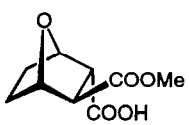
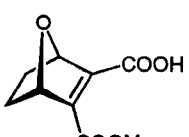
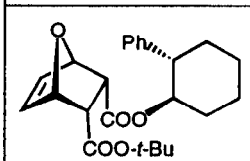
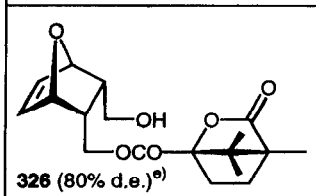
 (+)-**319**[a] (96% e.e.)	Addition of titanium TADDOLate to **32**, the product of hydrogenation of **31X**.[211]
 (+)-**320**[a] (99% e.e.)	Hydrogenation of **31X**, $LiAlH_4$ reduction, and pancreatic pig lipase-catalyzed transesterification with vinyl acetate; (-)-**320** (96.5% e.e) with lipase of *Candida cyclindracea* and isopropenyl acetate.[217]
 (+)-**321**[a] (>98% e.e.)	Transesterification of the corresponding *meso* diol with vinyl acetate catalyzed with lipase of *Pseudomonas cepacia* (Amano);[217b] (-)-**321** (>98% e.e.) obtained by lipase PS (Amano)-catalyzed transesterification of *meso* diol.[217b]
 (-)-**322**[a] (>97% e.e.)	Diastereoselective addition of  to **32**, MeOH/TsOH, H_2/Pd-C.[218]
 (+)-**323**[a] (96% e.e.)	Diastereoselective addition as above, and treatment with MeONa/MeOH.[218]
 (-)-**324** (>95% e.e.)	Selective hydrogenation of the Diels-Alder adduct of furan to dimethyl acetylenedicarboxylate, and pig liver esterase-catalyzed hydrolysis.[219]
 (+)-**325** (98% d.e.)	Et_2AlCl-promoted Diels-Alder addition of furan (-20 °C) to the corresponding maleate.[220]
 **326** (80% d.e.)[e]	Acylation of *meso*-diol obtained by reduction of furan adduct to dimethyl acetylenedicarboxylate with (1*S*,4*R*)-(-)-camphanoyl iodide. Similar diastereoselectivity with the 2,3-*exo*-dimethanol stereomer.[221]

Table 2. (continued)

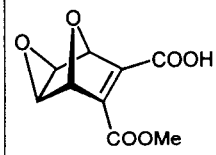
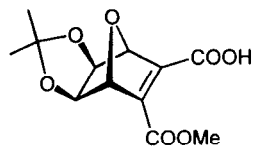
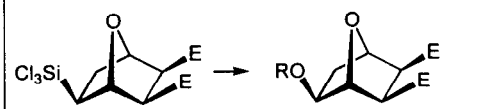
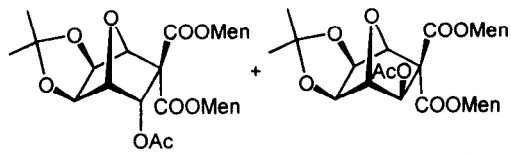
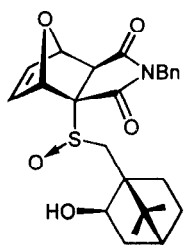
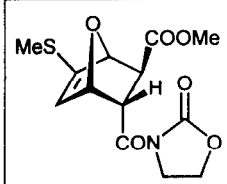
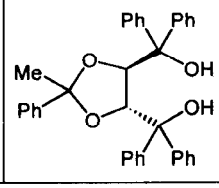
 (-)-**327** (77% e.e.)	Selective epoxidation of the adduct of furan to dimethyl acetylenedicarboxylate, and pig liver esterase (PLE)-catalyzed hydrolysis.[214b]
 (+)-**328** (77% e.e.)	Dihydroxylation of the adduct of furan to dimethyl acetylenedicarboxylate, protection as an acetonide, and PLE-catalyzed hydrolysis.[222]
 **329** (E = COOMe, CH_2OMe) **330** (R = H, 95% e.e.)[e] (-)-**331** (R = CONHPh)	Enantioselective hydrosilylation ($HSiCl_3$) catalyzed by (*R*)-2-methoxy-2'-diphenylphosphino-1,1'-binaphthyl ((*R*)-MOP) and $[PdCl(\pi\text{-}C_3H_5)_2)]$.[223]
 **332N** (54% d.e.)[e] **332X** (61% d.e.)[e]	Furan + di-*l*-menthyl acetoxymethylenemalonate (11 kbar, 5d).[224]
 **333**[e,f]	Furan addition ($ZnCl_2$, 10 °C) to N-benzyl-α-(2-*exo*-hydroxy-10-bronylsulfinyl)maleimide.[225]
 **334**[e] (86% e.e.)	Diels-Alder addition of 3-methylthiofuran to 3-[3-(methoxycarbonyl)propenoyl]-1,3-oxazolidin-2-one[226] catalyzed by  + $TiCl_2(O\text{-}i\text{-}Pr)_2$

Table 2. (continued)

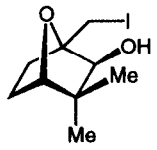
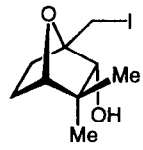
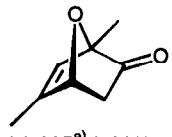
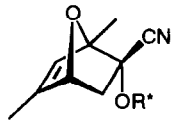
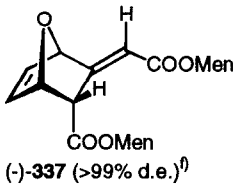
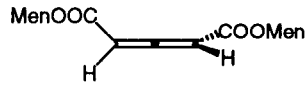
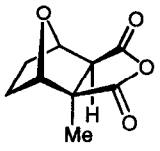
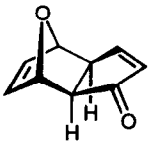
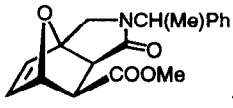
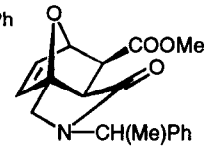
 **107** (>99% e.e.)[e]  **107'** (>99% e.e.)[e]	Derived from 2,2-dimethylcyclohexane-1,3-dione (see Scheme 10).[95] Jones oxidation of **107**, followed by $NaBH_4$ reduction afforded the *endo* isomeric alcohol.
 (+)-**335**[a] (>99% e.e.)[g]	Saponification of (+)-**336**, then treatment with formalin.[227]
 (+)-**336** (>99% d.e.)[g] R* = (1*R*)-camphanoyl	ZnI_2-catalyzed reversible Diels-Alder addition of 2,4-dimethylfuran to 1-cyanovinyl (1'*R*)-camphanate; under equilibrium conditions (+)-**336** precipitates diastereoselectively.[227]
 (-)-**337** (>99% d.e.)[f]	Lewis-acid-catalyzed cycloaddition[228] of furan to  Structure established by single crystal X-ray diffraction. Men = (-)-menthyl
 (-)-**30**	Palasonin: resolution of (±)-**30** (eq.(6)) with (*S*)-(-)-α-methylbenzylamine.[140]
 (-)-**338** (53% e.e)	$ZnCl_2$-catalyzed cycloaddition of furan to (*R*)-(+)-4-acetoxycyclopent-2-en-1-one (12 kbar, 3 d) derived from cyclopentadiene (35% yield).[229]
 **339** (>95% d.e.)[e]  **340** (>95% d.e.)[e]	Reaction of maleic anhydride with (*S*)-N-(α-furyl)-1-phenylethylamine, followed by esterification with CH_2N_2 and chromatography; 2:1 **339/340**.[230] Absolute configuration established by single crystal X-ray diffraction of **339**.

Table 2. (continued)

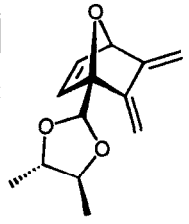
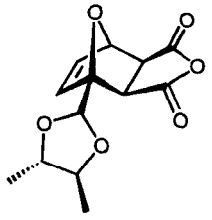
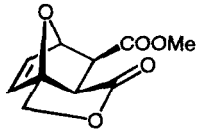
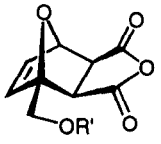
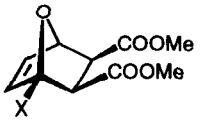
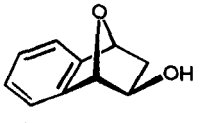
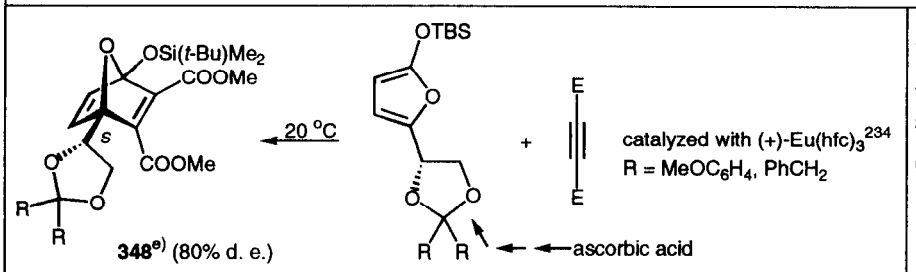
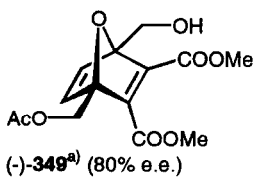
 (+)-**341** (>99% d.e.)	By $LiAlH_4$ reduction of (+)-**342**, followed by double mesylation and double elimination of MsOH.[231]
 (+)-**342** (>99% d.e.)	The acetal of (2*S*,3*S*)-butane-2,3-diol and furfural is equilibrated in molten maleic anhydride with one major crystalline 1:1 complex of maleic anhydride and (+)-**342**.[231]
 (-)-**343**[a] (>98% e.e.)	Saponification of (+)-**344**, acidic treatment, with recovery of (1*S*)-camphanic acid, the chiral auxiliary.[232]
 (+)-**344** R' = (1'*S*)-camphanoyl (>99% d.e.)	(*S*)-camphanate of furfuryl alcohol in molten maleic anhydride gives one major crystalline adduct (+)-**344**.[232]
 (+)-**345**[a] X = CH_2OH (+)-**346**[a] X = CHO	Saponification of (+)-**344**, esterification with CH_2N_2 → (+)-**345**; Dess-Martin periodinane oxidation → (+)-**346**.[232]
 (+)-**347** (>99% e.e.)	Reaction of 7-oxabenzonorbornadiene (obtained by cycloaddition of furan to 1,2-didehydrobenzene) with (-)-diisopinocampheylborane, work-up with CH_3CHO, then with H_2O_2/NaOH.[233]

Table 2. (continued)

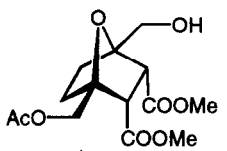


Absolute configuration by X-ray analysis of **348** (R = CH_2Ph).

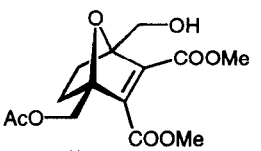


(-)-**349**[a] (80% e.e.)

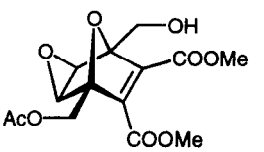
Diels-Alder addition of 1,4-bis(hydroxymethyl)furan to dimethyl acetylenedicarboxylate, *Candida rugosa* lipase-catalyzed acylation with vinyl acetate; similar asymmetric monoacylation of *meso*-diols generated (+)-**350**, (+)-**351**, (+)-**352**.[235]



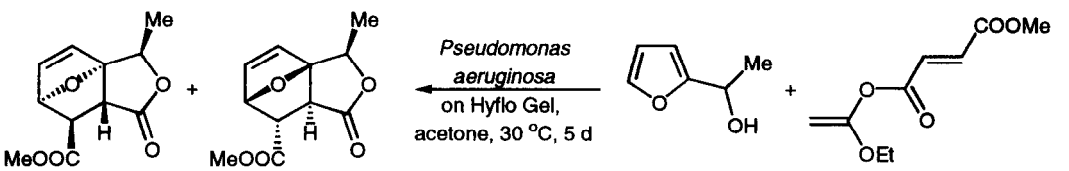
(+)-**350**[a] (95% e.e.)



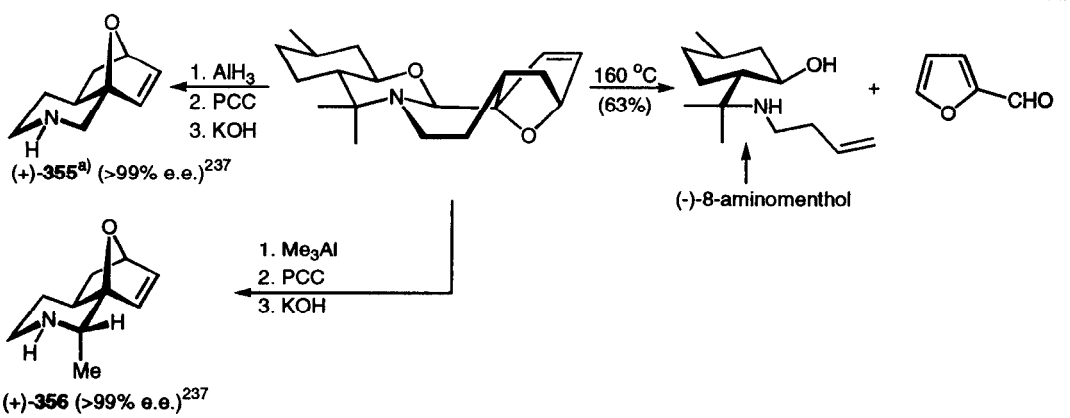
(+)-**351**[b] (80% e.e.)



(+)-**352** (82% e.e.)



(+)-**353**[c] (86% e.e.) (+)-**354**[e] (93% e.e.)[236] racemic

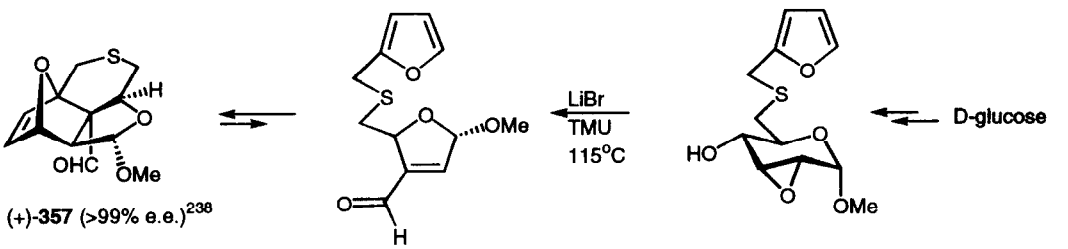


(+)-**355**[a] (>99% e.e.)[237]

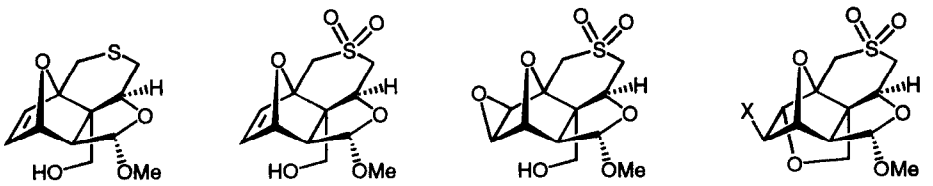
(-)-8-aminomenthol

(+)-**356** (>99% e.e.)[237]

Table 2. (continued)



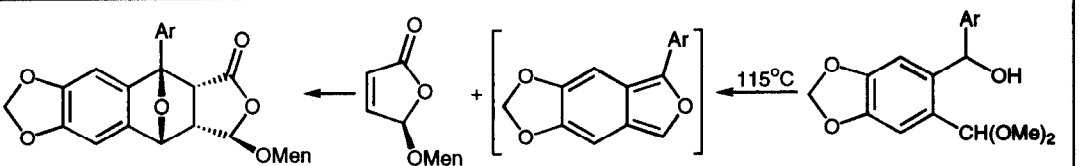
(+)-**357** (>99% e.e.)[238]



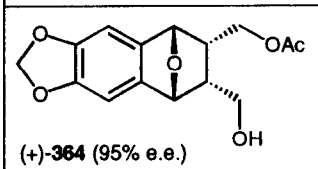
(+)-**358** (+)-**359** (+)-**360** (+)-**361** R = OH

(+)-**358** - (+)-**362** all derived from (+)-**357**[238]

(+)-**362** R = Cl

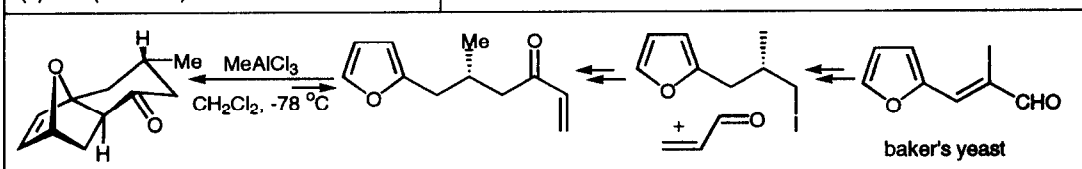


363[e),239]

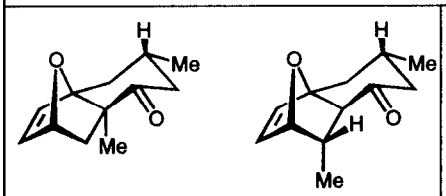


(+)-**364** (95% e.e.)

By porcine pancreatic lipase-catalyzed hydrolysis of the corresponding *meso*-diacetate.[240]



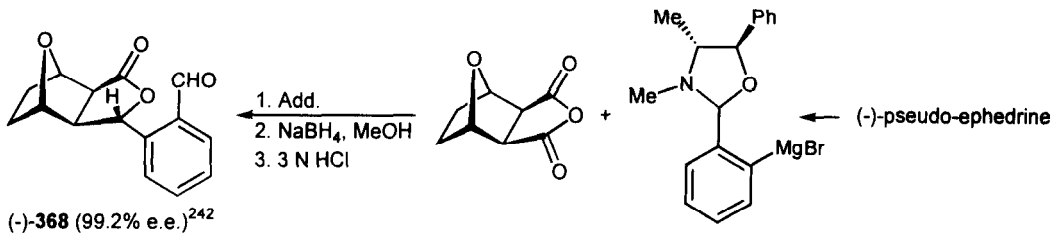
(-)-**365** (>99% e.e) + 5% of other diastereomer[241]



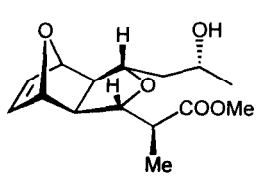
(-)-**366** (>99% e.e.) (-)-**367** (>99% e.e.)

Similar intramolecular Diels-Alder addition under thermodynamically controlled conditions, with $MeAlCl_2$ at –78 °C.[241]

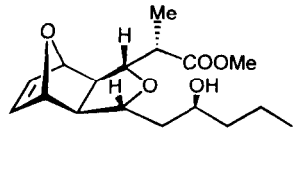
Table 2. (continued)



(-)-**368** (99.2% e.e.)[242]

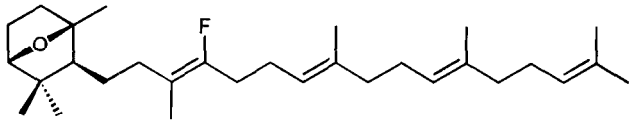


(-)-**369** (>95% e.e.)[243]



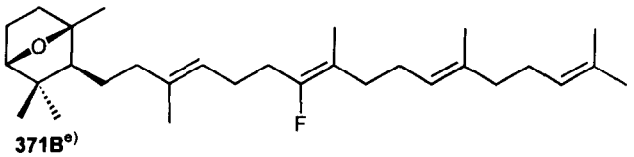
(+)-**370** (>95% e.e.)[244]

Both derived from (-)-**321**.



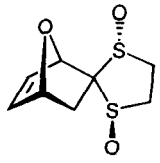
371A[e)]

Cyclization of (3*S*)-11-fluoro-2,3-oxidosqualene catalyzed by recombinant *Alicyclobacillus acidoraldarius* SHC (27% yield).[245a]

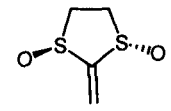


371B[e)]

As above, starting from (3*S*)-14-fluoro-2,3-oxidosqualene (33% yield).[245b]



(+)-**372** (>97% e.e.)[246]

Diels-Alder addition of furan to  catalyzed by $SnCl_4$.[246]

a) can be obtained in both enantiomeric forms

b) "a naked sugar of the first generation"[2]

c) unstable compound, isolated in low yield by chromatography

d) RADO(Et)-OH derived from (*R*,*R*)-tartaric acid and N-ethylaminoethanal[185b]
(SADO(Et)-OH derived from (*S*,*S*)-tartaric acid and N-ethylaminoethanal)[185b]

e) $[\alpha]_D^{25}$ values not reported

f) other diastereomers also isolated

g) "a naked sugar of the second generation"[227]

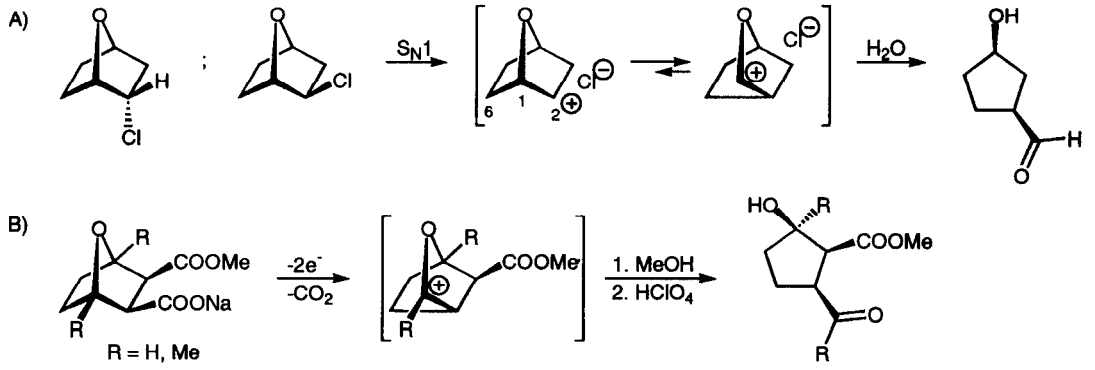
7. Reactions and synthetic applications of the 7-oxabicyclo[2.2.1]heptyl derivatives

Various synthetic applications of the 7-oxabicyclo[2.2.1]heptyl derivatives have been reviewed.[1-4] We shall therefore limit ourselves to the presentation of some fundamental principles and concentrate on the most recent applications.

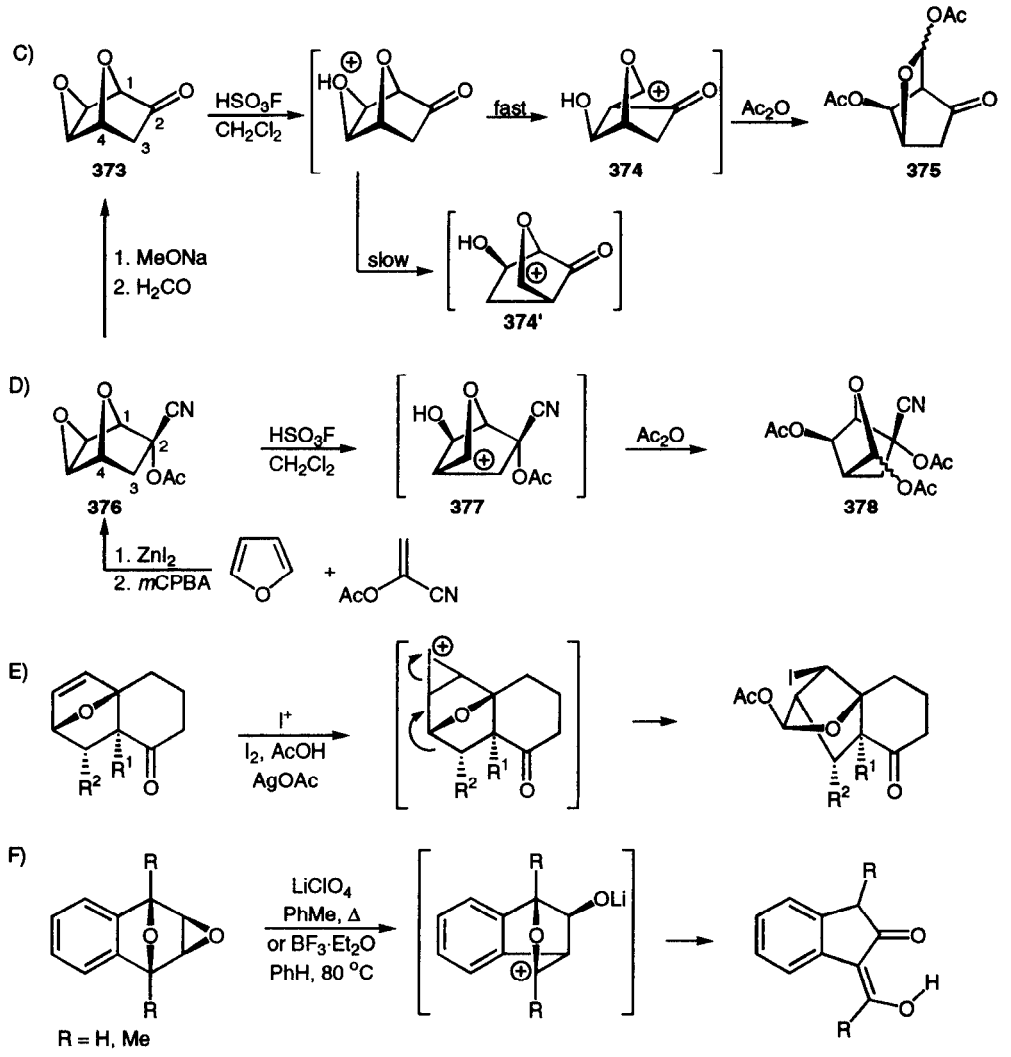
7.1. Cyclopentanes from 7-oxabicyclo[2.2.1]hept-2-yl derivatives

In 1957, Martin and Bartlett[247] showed that the S_N1 hydrolysis of 2-*exo* and 2-*endo*-chloro-7-oxabicyclo[2.2.1]heptane implies the formation of a 7-oxabicyclo[2.2.1]hept-2-yl cationic intermediate that undergoes an irreversible σ(C(1)-C(6)) bond shift (Wagner-Meerwein or pinacolic rearrangement) leading to a 2-oxabicyclo[2.2.1]hept-3-yl cationic intermediate that reacts with water to generate *cis*-3-hydroxycyclopentanecarbaldehyde (Scheme 40A). Under the Kolbe decarboxylation conditions (electrolysis), sodium salts of 3-*exo*-methoxycarbonyl-7-oxanorbornane-2-*exo*-carboxylate generate 7-oxanorborn-2-yl cationic intermediates that undergo pinacolic rearrangements and give the corresponding cyclopentanol derivatives (Scheme 40B).[248] Under strongly acidic conditions ($HSO_3F/CH_2Cl_2/Ac_2O$), Le Drian et al.[249a] have found that the epoxy-ketone **373** (Scheme 40C) undergoes selective acyl group migration to generate intermediate **374** that reacts with Ac_2O to give the trisubstituted cyclopentanones **375**. In this case, the acyl shift occurs 50 times faster than the migration of the non-substituted σ(C(3),C(4)) bond, in agreement with calculations[250] suggesting that the electron-releasing ability of the carbonyl group[251] makes the acyl group have a greater migrating ability than an unsubstituted alkyl group in Wagner-Meerwein and pinacolic rearrangements.[250] In contrast, the corresponding cyano-acetate **376** undergoes acid-promoted epoxide ring opening with selective migration of the σ(C(3),C(4)) bond, generating intermediate **377** that reacts with Ac_2O to give products **378**. In this latter case (Scheme 40D), the bond substituted by the electron-withdrawing acetoxy and cyano groups, bond σ(C(2),C(1)), migrates more slowly than bond σ(C(3),C(4)).[249a]

Scheme 40: Wagner-Meerwein (pinacolic) rearrangements of 7-oxabicyclo[2.2.1]hept-2-yl derivatives



Scheme 40 (continued)



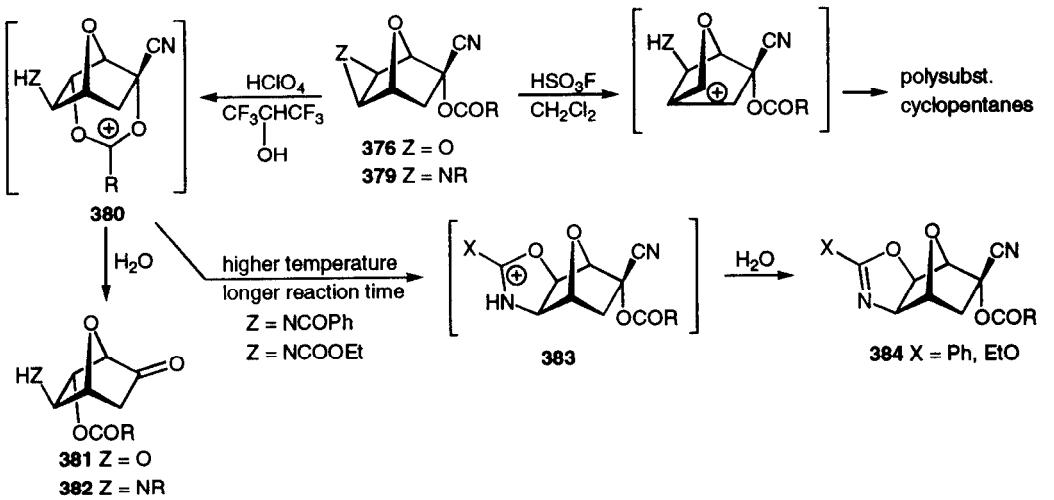
Iodination (Prévost conditions) of 7-oxanorbornenes can be accompanied by pinacolic rearrangements (Scheme 40E).[249b] Epoxides of benzo-7-oxabicyclo[2.2.1]hepta-2,5-dienes are much more reactive than epoxides of type **373** or **376** towards acids. They are rearranged with $LiClO_4$ in boiling toluene, or with $BF_3{\cdot}Et_2O$ in benzene at 8 °C, giving indanone derivatives (Scheme 40F).[253]

7.1.1. Pinacolic rearrangement vs. ester group participation

Depending on the solvent and the acid, the pinacolic rearrangement of **376** can be retarded in favor of the participation of the *endo* acetoxy group, leading to the selective formation of 5-*exo*,6-*endo*-dihydroxy-7-

oxabicyclo[2.2.1]hepta-2-one derivatives (e.g. **381**, Scheme 41).[254] The treatment of aziridines **379** with HSO_3F/CH_2Cl_2 generates aminocyclopentanone derivatives (Scheme 41). With a weaker acid ($HClO_4/CF_3CH(OH)CF_3$), *endo*-acyloxy group migration generates cationic intermediates of the type **380**. Depending on the conditions, *trans* amino-hydroxyketones **382** are obtained, or protected *exo-cis*-derivatives **384** are generated.[254]

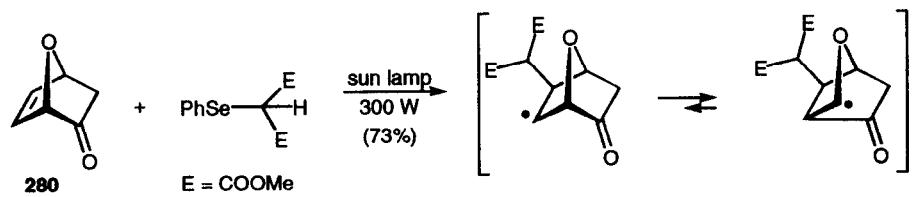
Scheme 41: Competition between pinacolic rearrangement and *endo*-acyloxy group migration



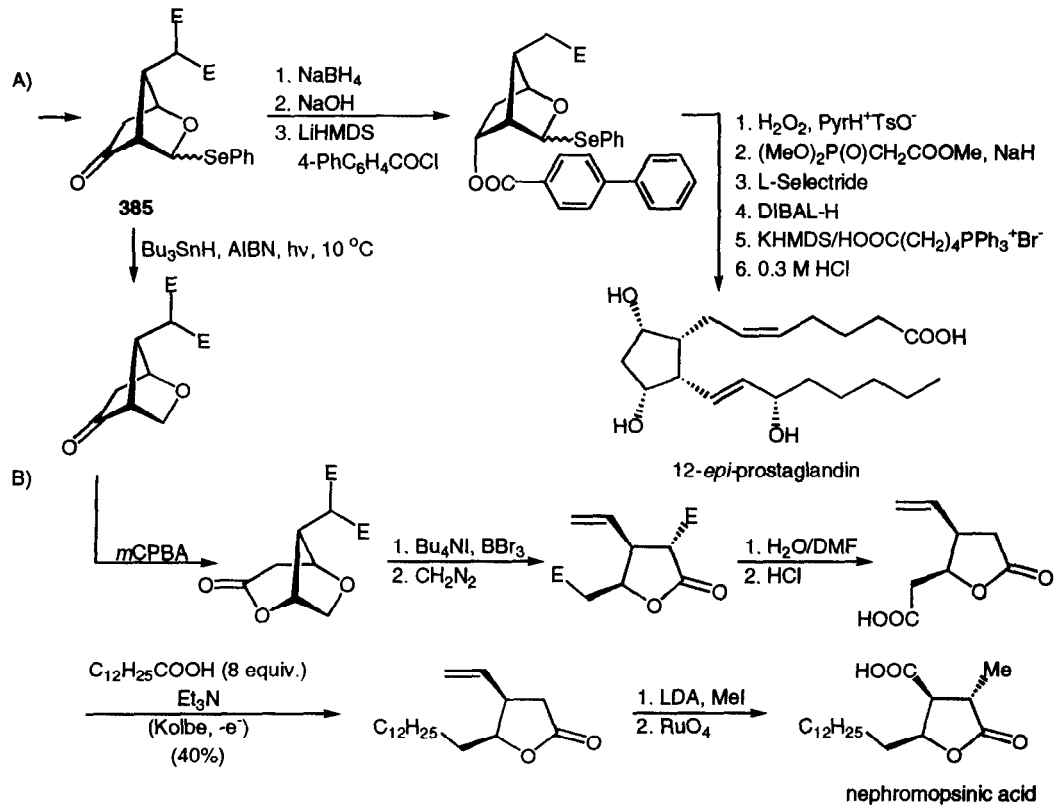
7.1.2. *Acyl shift in 6-oxo-7-oxabicyclo[2.2.1]hept-2-yl radicals*

Renaud and Vionnet[255] have found that the addition of a dimethyl malonyl radical to enone (±)-**280** is not only highly *exo* face selective, but regioselective and accompanied by a skeletal rearrangement analogous to a Wagner-Meerwein rearrangement (as in Scheme 40B) involving a 1,2-acyl shift. The selenides **385** so obtained have been converted into (±)-12-*epi*-prostaglandins (Scheme 42A)[256] and into (±)-nephromopsinic acid (Scheme 42B).[257] These compounds can be obtained optically pure in both their enantiomeric forms using the "naked sugars" (+)-**280** and (-)-**280** (Table 2).

Scheme 42: Facial and regioselective addition of radicals to a "naked sugar" followed by a 1,2-acyl shift: synthesis of *epi*-prostaglandins and nephromopsinic acid

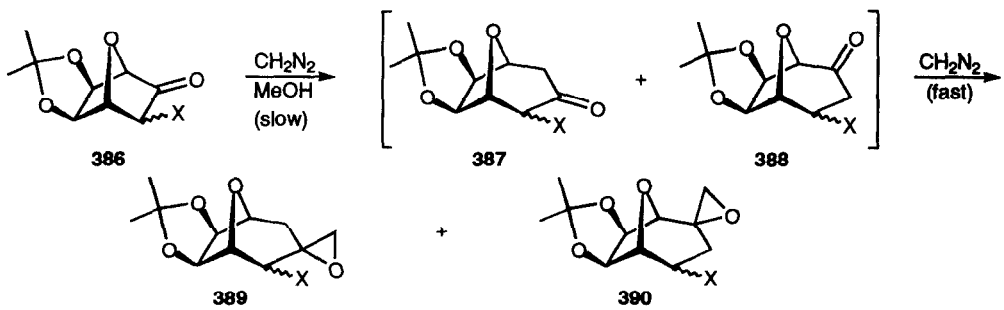


Scheme 42 (continued)



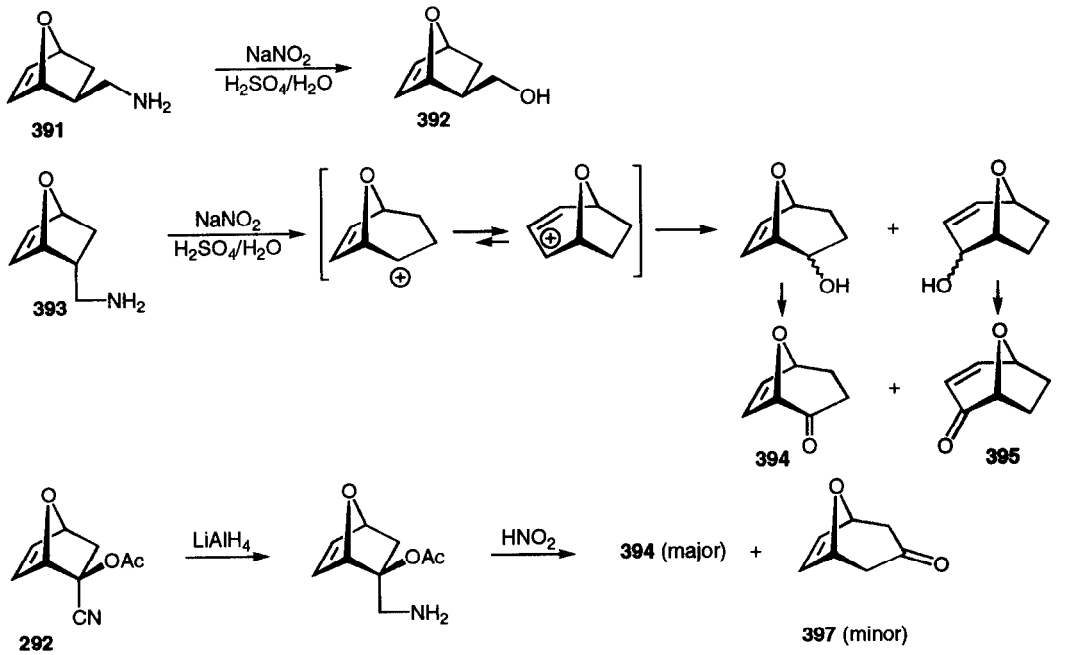
7.2. Ring-enlargement reactions

Addition of diazomethane to 7-oxanorbornanones **386** gives the corresponding products of one-carbon ring enlargement with a regioselectivity (ratio of products **387/388**) dependent on the nature of the 3-substituent X. Ketones **387** and **388** are very reactive towards CH_2N_2 and only products **389** and **390** are isolated.[258]

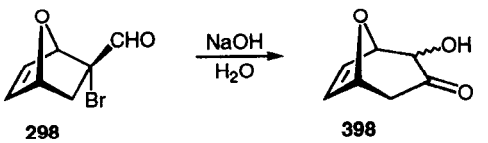


Treatment of the *exo*-amine **391** (obtained by $LiAlH_4$ reduction of the *exo*-adduct of furan to acrylonitrile) with nitrous acid generates the unrearranged alcohol **392**. In contrast, the *endo* isomer **393** reacts with HNO_2 leading to a mixture of alcohols resulting from a Demjanov rearrangement. These alcohols were oxidized to a 1:1 mixture of enones **394** and **395**. With the amino-alcohol **396** obtained by $LiAlH_4$ reduction of (±)-**292**, a 12:1 mixture of enones **394** and **397** was obtained (Scheme 43) upon treatment with HNO_2.[259]

Scheme 43: Demjanov and Tiffeneau-Demjanov rearrangements



Aqueous NaOH hydrolyses and rearranges (pinacolic rearrangement) the Diels-Alder adduct of furan to α-bromoacrolein (**298**, Table 2) giving a mixture of the α-hydroxyketones **398**.[188]

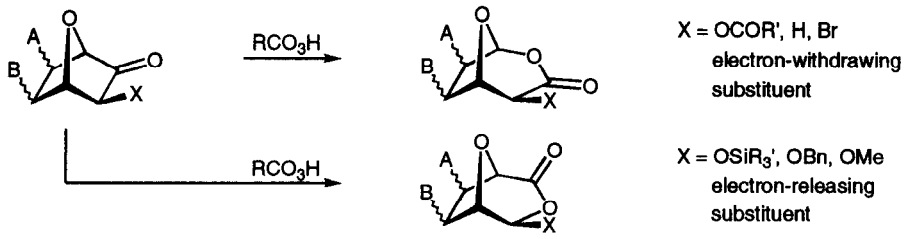


7.3. Cleavage of carbon-carbon bonds of 7-oxanorbornyl derivatives

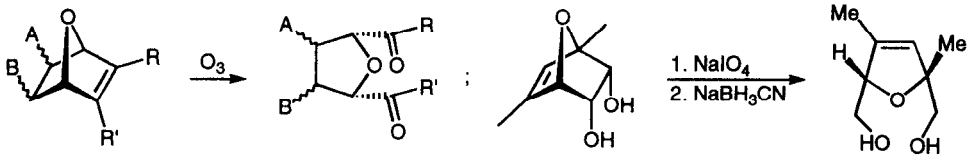
The most important methods (Scheme 44) used to cleave the C-C bonds of 7-oxabicyclo[2.2.1]heptyl systems have been reviewed recently by Chiu and Lautens[3b] and will not be discussed further. Cycloreversions of 7-oxanorbornenes have been used to generate polysubstituted furans[265] (see also Section 5.3) or to liberate complicated alkene systems. In this latter case, the 7-oxanorbornenes represent protected forms of the C=C moieties of alkenes.[266]

Scheme 44: Methods to cleave C-C bonds of 7-oxabicyclo[2.2.1]heptyl derivatives.[3b]

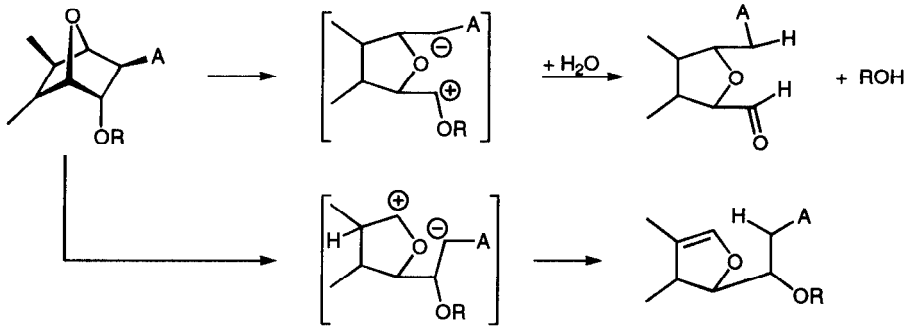
A) Baeyer-Villiger lactonisation[2,260]



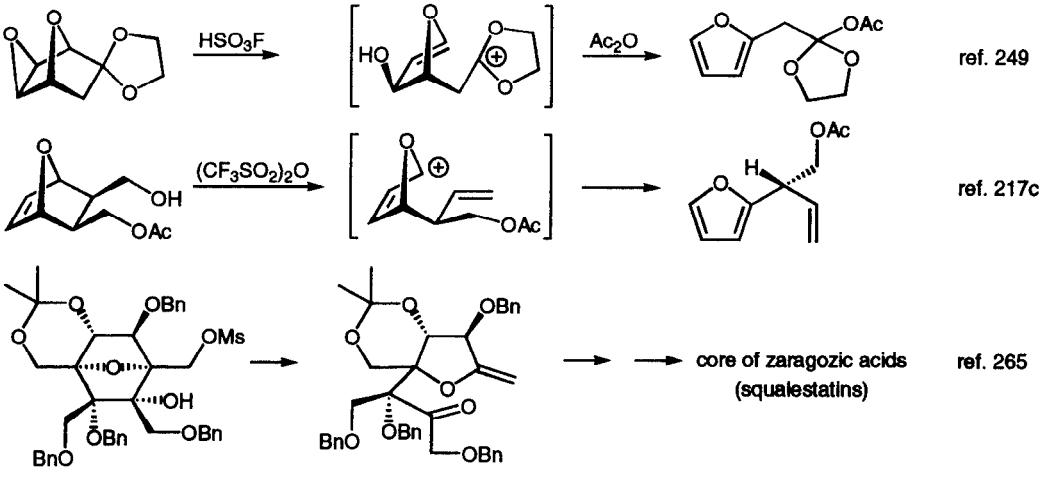
B) Oxidative cleavage of alkenes,[261] of *cis*-1,2-diols[262]



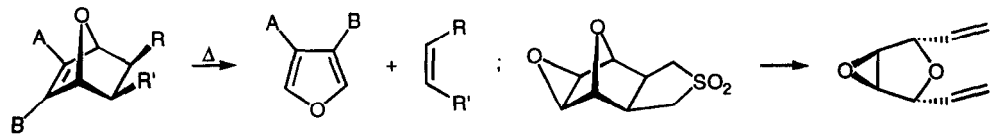
C) Retro-Claisen, retro-Dieckmann, etc.[263,264]



D) Grob fragmentations[217c,249,265]



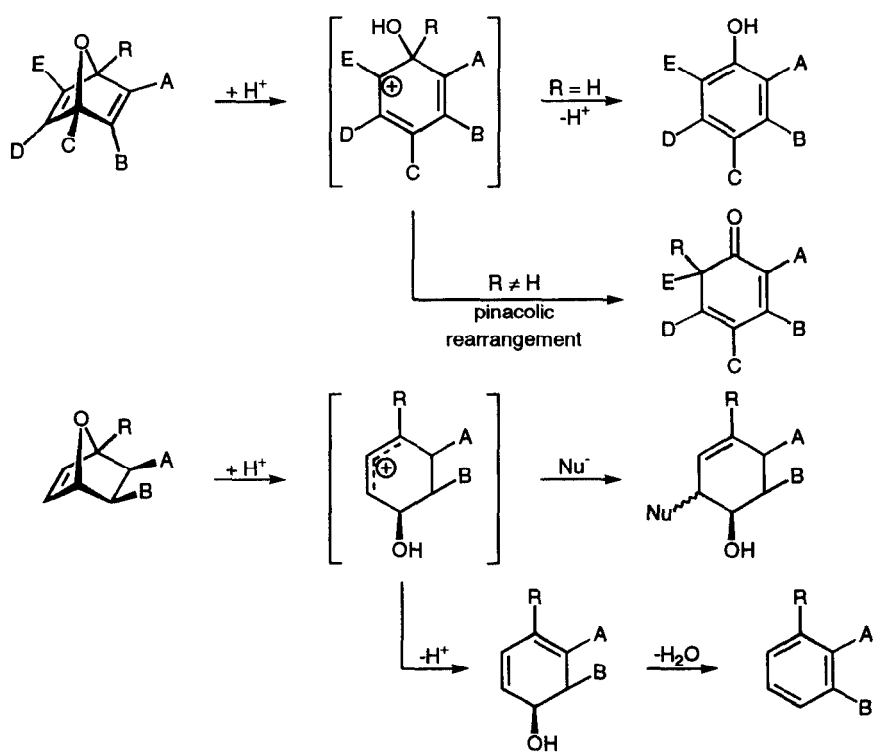
E) Cycloreversions[266-267]



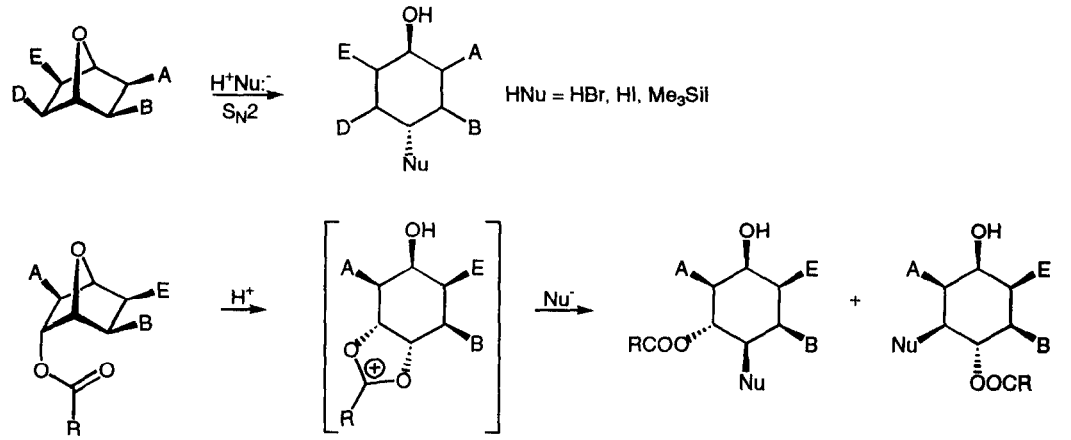
7.4. Acid-induced ethereal bridge openings of 7-oxabicyclo[2.2.1]heptyl derivatives

In general, 7-oxanorbornadienes are isomerized into the corresponding phenols or cyclohexa-2,4-dienones under acidic conditions.[151c] The 7-oxanorbornenes may undergo S_N1 ethereal heterolyses with generation of γ-hydroxycyclohexenyl cationic intermediates that can either react with a nucleophile to give cyclohexenol derivatives or eliminate a proton and water to generate substituted benzenes[268] (Scheme 45). The 7-oxa ring opening can be assisted by *endo*-substituents. The 7-oxanorbornanes are less reactive than the 7-oxanorbornenes under acidic conditions. Ethereal cleavage can be induced by acids such as HBr, HI or $(CH_3)_3SiI$ which are both oxyphilic (activate the oxa bridge) and nucleophilic (S_N2 displacement of the ethereal moiety). If an *endo*-carboxylic ester is present, the oxa bridge cleavage can be assisted by it (S_N1 process) leading to products with retention of configuration or acyloxy group migration.

Scheme 45: Most common reactions of 7-oxanorbornyl systems under acidic conditions



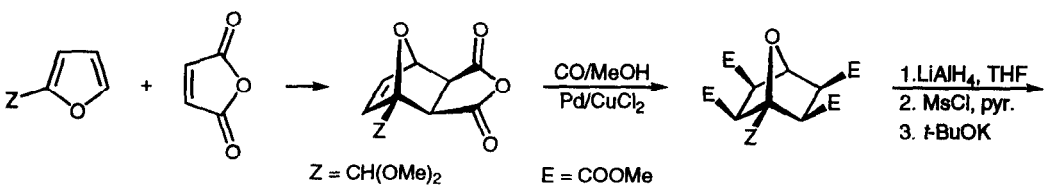
Scheme 45 (continued)



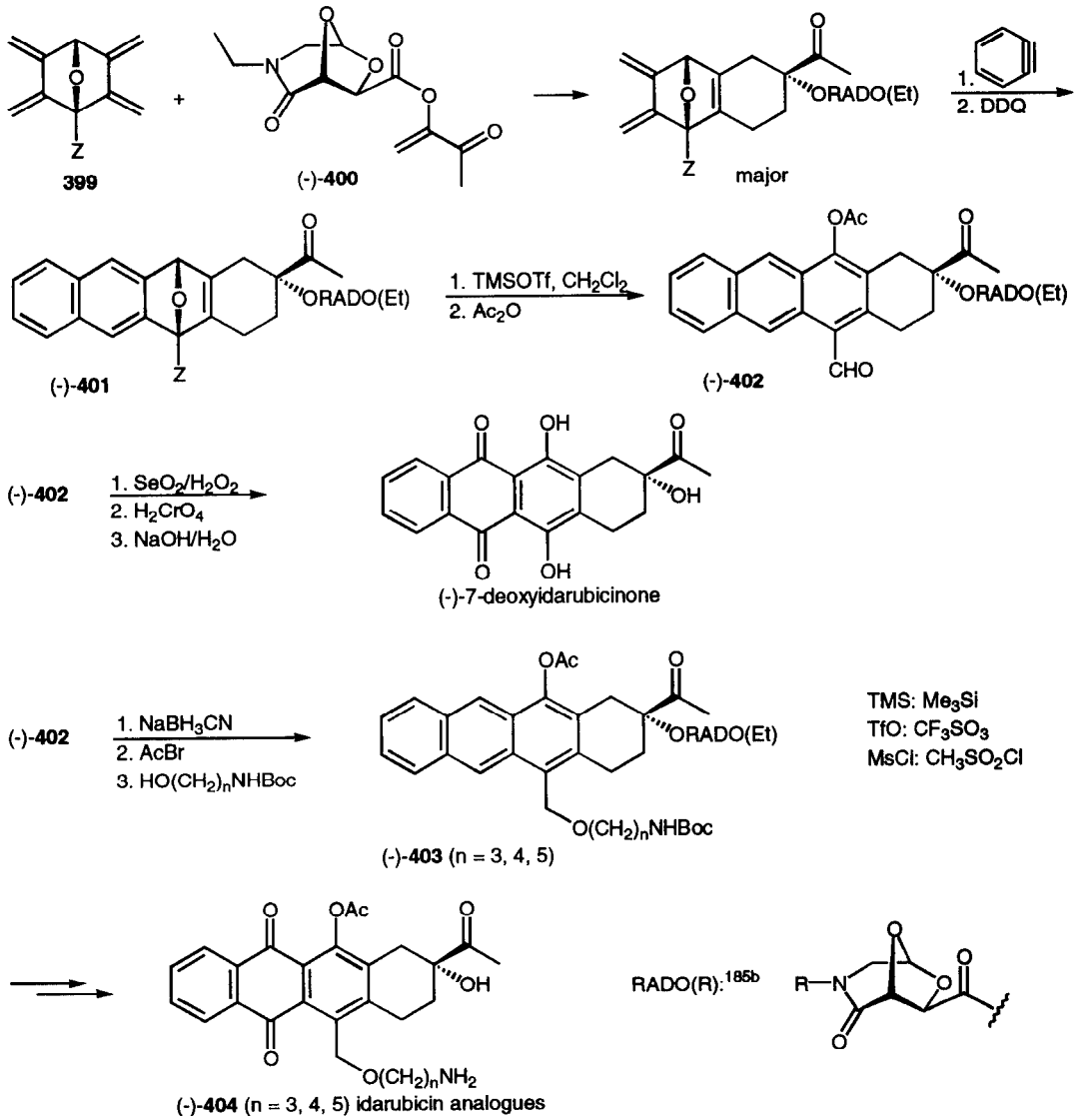
7.4.1. Phenols by acid-induced isomerization of 7-oxabicyclo[2.2.1]hepta-2,5-dienes: synthesis of anthracyclines

The combinatorial Diels-Alder approach of Vogel to the synthesis of antitumor anthracyclines[269] has been applied to generate enantiomerically pure (-)-4-demethoxy-7-deoxydaunomycinone ((-)-7-deoxyidarubicinone) and daunomycine mimetics (-)-**404** that intercalate calf thymus DNA (Scheme 46). The $BF_3{\cdot}Et_2O$-promoted Diels-Alder addition of 1-acetylvinyl RADO(Et)-ate ((-)-**400**) to 1-(dimethoxymethyl)-2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane (**399**, obtained by Diels-Alder addition of the dimethyl acetal of furfural to maleic anhydride, followed by Stille-Vogel dimethoxycarbonylation, reduction of the tetraester, mesylation and quadruple elimination of mesylic acid[270a]) gave a 87:13 mixture of diastereomeric adducts which added to 1,2-didehydrobenzene generating (-)-**401** after DDQ oxidation. Treatment of (-)-**401** with $Me_3SiOSO_2CF_3$ in CH_2Cl_2 led to aromatization of the 7-oxanorbornadiene giving (-)-**402** after acetylation. Oxidation of (-)-**402** with SeO_2/H_2O_2, first, then with 4 N Jones reagent, followed by saponification, afforded (-)-7-deoxyidarubicinone. Aldehyde (-)-**402** was also reduced with $NaBH_3CN$ giving a *para*-hydroxybenzyl alcohol that was acetylated and activated with AcBr for substitution by various nucleophiles including semi-protected aminoalcohols leading to benzyl ethers (-)-**403** that were transformed into the idarubicin analogues (-)-**404** (Scheme 46).[270b,271]

Scheme 46: The combinatorial Diels-Alder approach to the synthesis of anthracyclinones and analogues

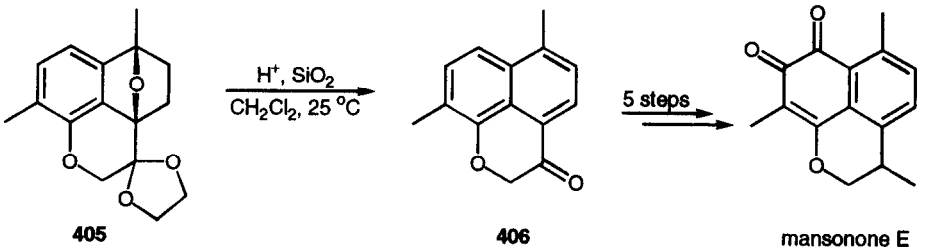


Scheme 46 (continued)

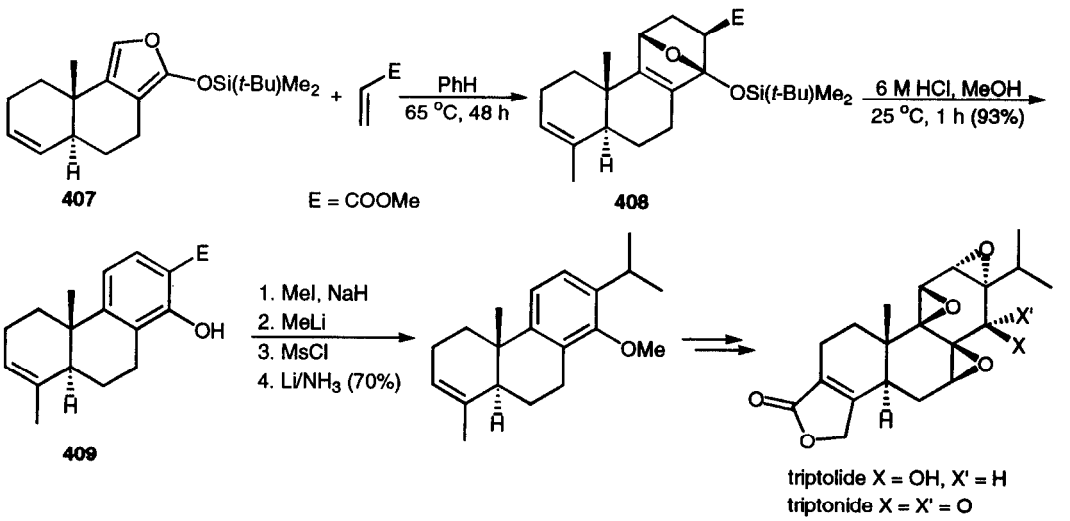


7.4.2. *Water elimination from 7-oxabicyclo[2.2.1]hept-2-enes: synthesis of substituted benzenes*

The naturally occurring *o*-naphthoquinone, mansonone E, has been derived in its racemic form from the benzo-7-oxanorbornene derivative (±)-**405** via a water elimination step generating the naphthalene derivative **406**.[272]

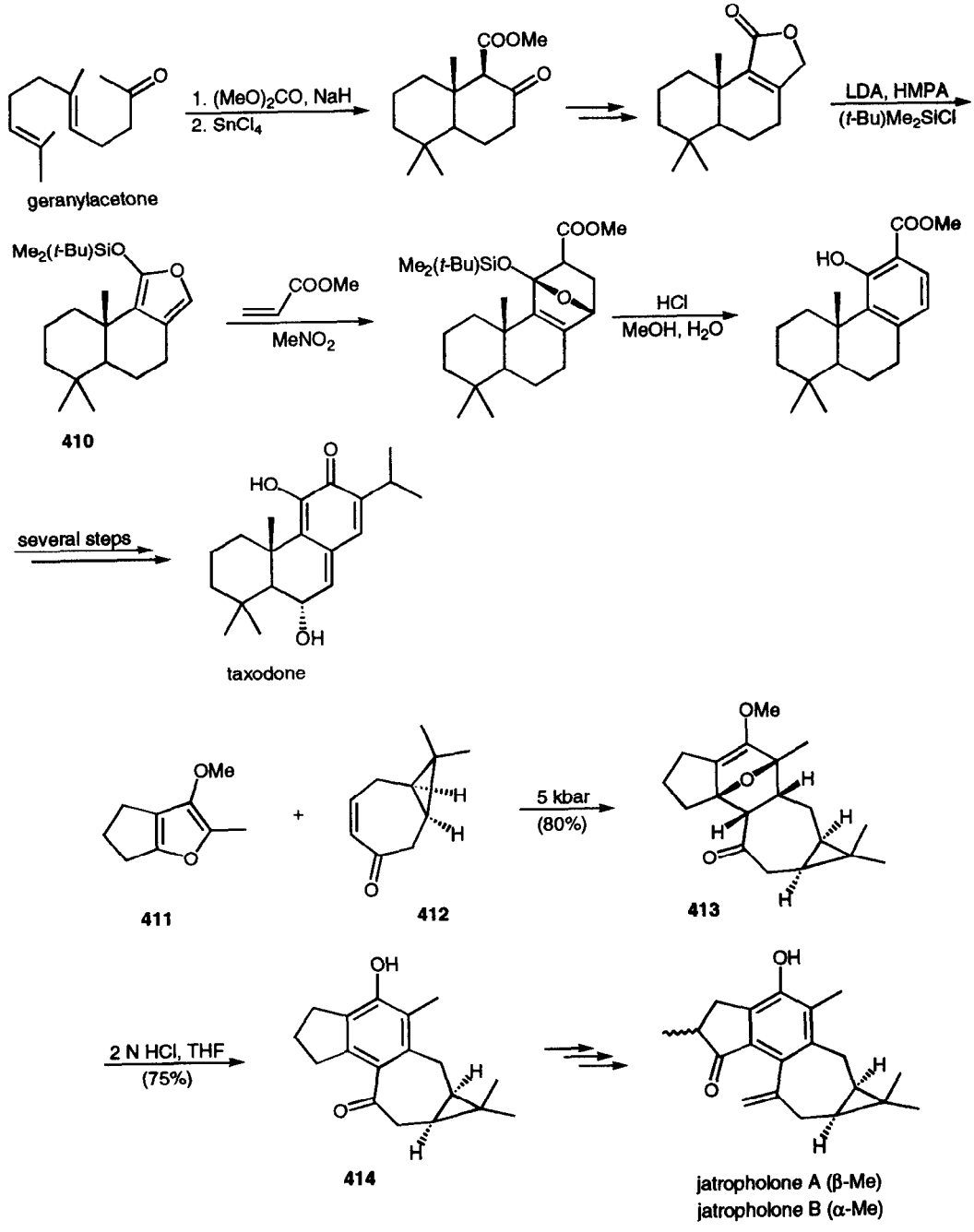


A total synthesis of (±)-triptonide and (±)-triptolide proposed by Garver and Van Tamelen uses the Diels-Alder addition of the 2-silyloxyfuran derivative (±)-**407** to methyl acrylate giving adduct **408** with high "ortho" regioselectivity. Treatment of **408** with HCl/MeOH induces a facile S_N1 heterolysis of the ethereal bridge with the formation of a relatively stable silyloxycyclohexenyl cationic intermediate that eliminates one equivalent of H_2O and liberates the phenol **409**. After phenol methylation and further transformations, (±)-triptolide and (±)-triptonide have been obtained.[273]



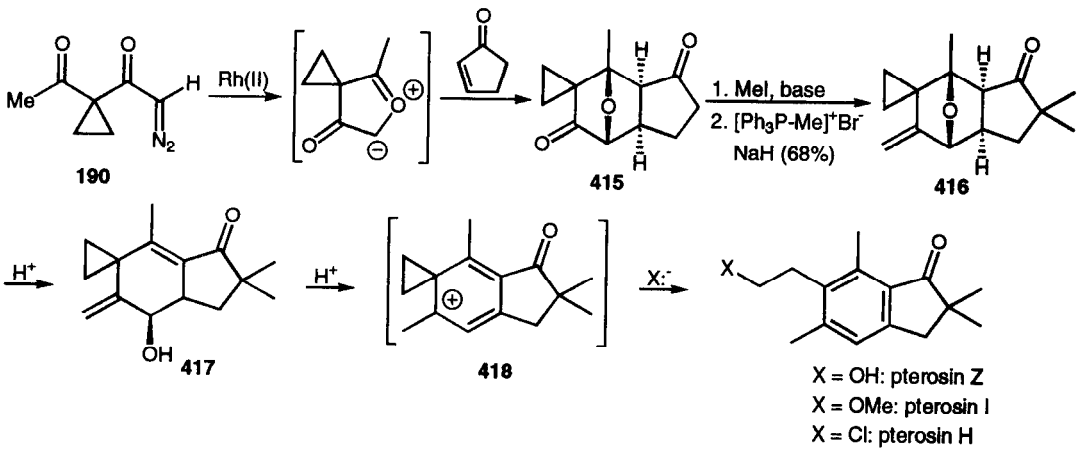
The same strategy was used to convert the furan derivative (±)-**410** into (±)-taxodone as shown below.[274]

Water elimination from a 7-oxanorbornene system has also been used as the key step in a total synthesis of (±)-jatropholone A and B by Smith and co-workers.[275] Cyclic enones are usually less reactive than acyclic derivatives as dienophiles.[276] The Diels-Alder addition of furan **411** to cyclohept-2-en-1-one (±)-**412** this required high-pressure conditions, giving adduct **413**. Treatment of **413** under acidic conditions generated the phenol **414** (H_2O elimination, phenoxymethyl hydrolysis) that was converted, after several steps, into (±)-jatropholone A and B.[275]


1. (MeO)2CO, NaH
2. SnCl4
COOMe
LDA, HMPA
(t-Bu)Me2SiCl
geranylacetone
Me2(t-Bu)SiO
COOMe
MeNO2
HCl
MeOH, H2O
HO
410
several steps
taxodone
OMe
5 kbar
(80%)
411
412
413
2 N HCl, THF
(75%)
OH
414
jatropholone A (β-Me)
jatropholone B (α-Me)

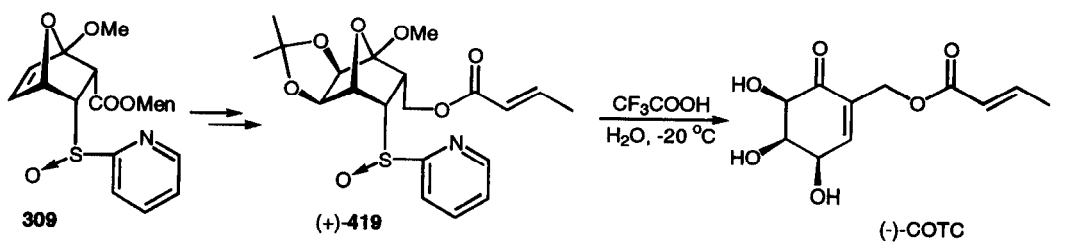
7.4.3. *Water elimination from 2-methylidene-7-oxabicyclo[2.2.1]heptanes*

Several members of the pterosin family have been prepared by Padwa and co-workers using acid-induced heterolysis of the 2-methylidene-7-oxanorbornane derivative **416**.[277] This compound was obtained via a tandem carbonyl ylide formation and the 1,3-dipolar cycloaddition method (Scheme 23) using **190** and cyclopent-2-enone as starting materials. The diketone **415** so obtained was then α-methylated and subjected to a Wittig methylenation to provide **416**. Under acidic conditions, the allylic ether is isomerized into the allylic alcohol **417**. The latter is ionized into the hypothetical cyclohexadienyl cationic intermediate **418** which reacts with the nucleophile X^- to give the pterosins.

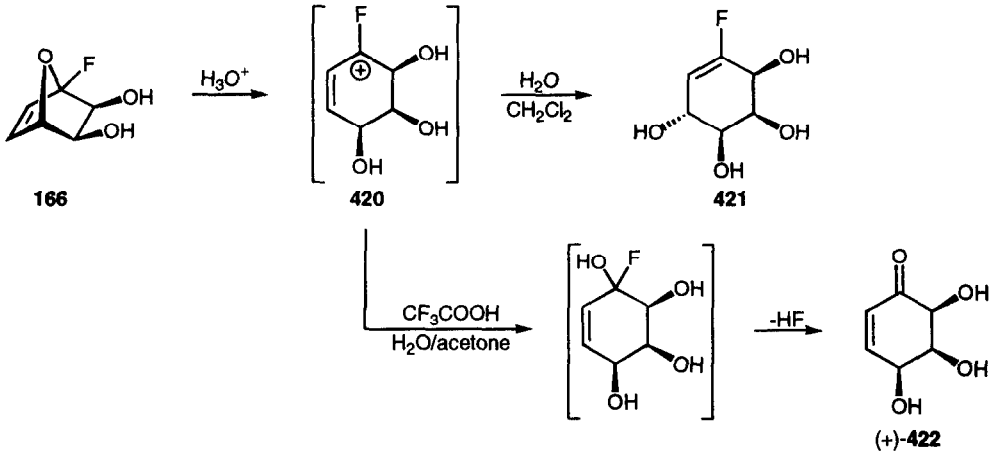


7.4.4. *Acid-induced isomerizations of 7-oxabicyclo[2.2.1]hept-2-enes without loss of water*

Derivatives of 7-oxanorborn-2-enes with an electron-releasing substituent at one of the bridgehead centers undergo a S_N1-type of ethereal cleavage under relatively weak acidic conditions, generating relatively stable substituted cyclohexenyl cationic intermediates that can be quenched with water or another nucleophile (Nu) giving cyclohexenyl derivatives. The latter do not eliminate water or H-Nu because of the weakly acidic medium. This principle has been exploited by Koizumi and co-workers[278] in a total, asymmetric synthesis of (-)-COTC, a glyoxalase I inhibitor. The diastereomerically pure adduct **309** obtained by cycloaddition of 2-methoxyfuran to *l*-menthyl (*S*)$_S$-3-(2-pyridylsulfinyl)acrylate (Table 2) was converted in 6 steps into (+)-**419**. Treatment of (+)-**419** with 80% aqueous CF_3COOH at –20 °C provided (-)-COTC.[278]



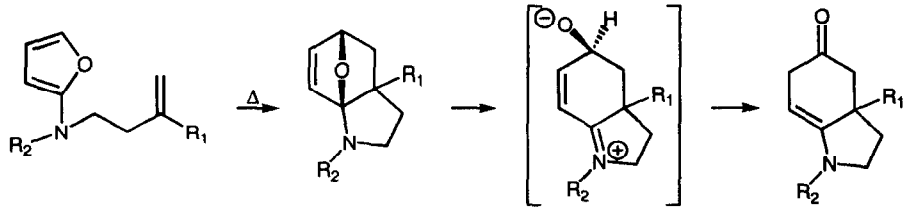
Under acidic conditions (*meta*-chlorobenzoic acid, CH_2Cl_2, H_2O), the 1-fluoro-7-oxanorbornene **166** (see Scheme 18 and Table 2) undergoes hydrolysis with the formation of 6-fluoroconduritol C (**421**). The latter arises from the quenching of water by the fluorocyclohexenyl cationic intermediate **420** on its less sterically hindered face.[110] Treatment of **166** with CF_3COOH in acetone and H_2O generates the crystalline trihydroxycyclohexenone (+)-**422**.[110]



166 420 421 (+)-422

One of the key features of the synthetic approach to the octahydroindole-based alkaloids proposed by Padwa and co-workers[279] uses intramolecular Diels-Alder additions of N-homoallyl-2-aminofurans **423** (Scheme 47). The electron-rich 7-oxanorbornenes **424** so obtained undergo facile C-O heterolysis with the formation of zwitterions of type **425** that are isomerized into the corresponding eneamines **426**.

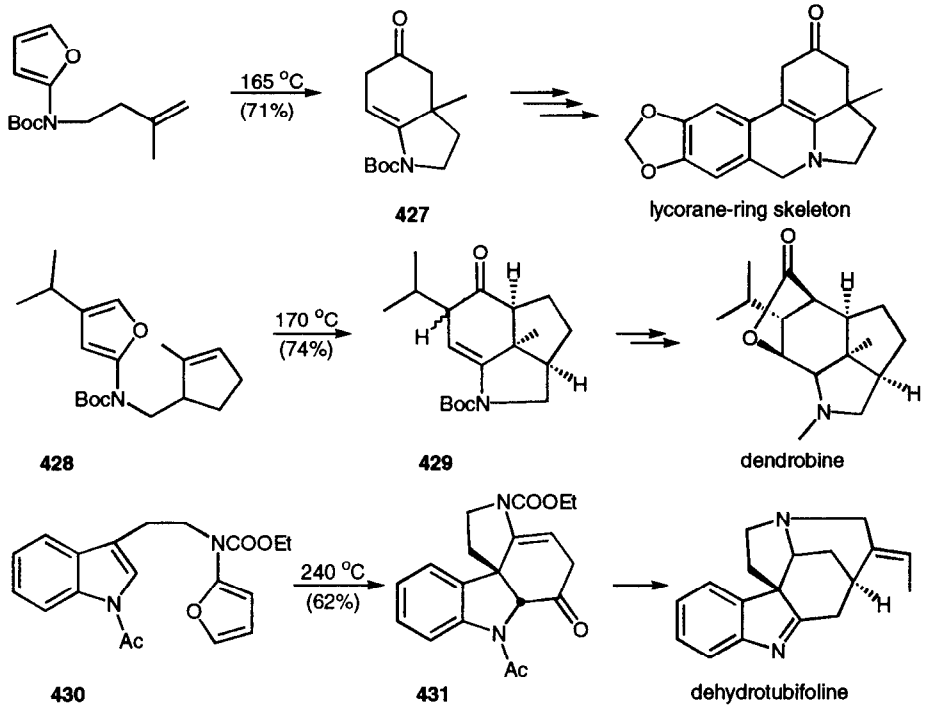
Scheme 47: Padwa's approach to bicyclic enamines



423 424 425 426

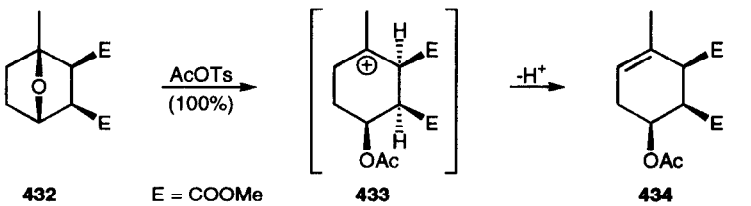
Using enamine **427**, the lycorane ring skeleton was constructed readily (Scheme 48). Thermolysis of **428** generated a 2:1 mixture of diastereomers **429** that has been converted into (±)-dendrobine.[279] This alkaloid is a component of the Chinese folk medicine "Chin-Shih-Hu" shown to exhibit antipyretic and hypotensive activities.[280] In a similar way, the tandem intramolecular Diels-Alder addition and aminal/enamine rearrangement of **430** generated **431** that could be converted into (±)-dehydrotubifoline.

Scheme 48: Padwa's alkaloid syntheses



7.4.5. Acid-induced isomerization of 7-oxabicyclo[2.2.1]heptanes into cyclohexenols

Treatment of **432** with acetic *p*-toluenesulfonic anhydride led to cyclohexenyl acetate **434** in quantitative yield.[281] This is surprising as facile deprotonation of the hypothetical cyclohexyl cationic intermediate **433** involving the α-proton of a carboxylate moiety is expected to be an easy process. Furthermore, a facile elimination of AcOH from the β-acetoxycarboxylic system is expected.

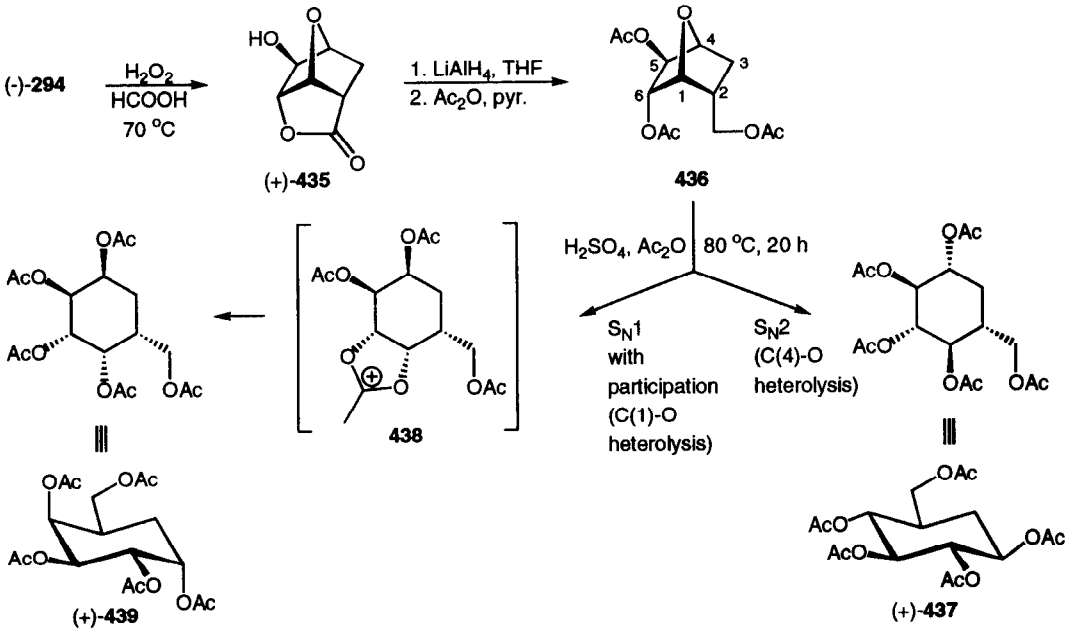


7.4.6. Substitution of 7-oxabicyclo[2.2.1]heptanes with ethereal bridge heterolysis

Ogawa and co-workers[197] have prepared the carba analogues of α-D-galactopyranose and β-D-glucopyranose by H_2SO_4-induced acetolysis of 7-oxanorbornane **436** derived from the enantiomerically pure 7-oxanorbornene (-)-**294** (see Table 2). Under these conditions S_N2 displacement of the less sterically hindered C-O

bond (Ac_2O attacks the bridgehead center C(4) of **436**) leading to the β-D-carba-glucopyranose derivative (+)-**437** competes with a S_N1 heterolysis of the 7-oxa-bridge that is assisted by the *endo*-6-acetoxy group. This generates the hypothetical cationic intermediate **438** that reacts with Ac_2O/AcOH giving the α-D-carba-galactopyranose derivative (+)-**439** (Scheme 49). With 20% HBr in AcOH, products of S_N1 heterolysis are not observed, probably because the bromide anion which is a better nucleophile than AcOH/Ac_2O favors the S_N2 mode of heterolysis leading to the dibromide (+)-**440** (arising from Br^- attack of C(4) and S_N2 displacement of the primary acetate). Displacement of the primary bromide moiety of (+)-**440** with AcONa, followed by S_N2 displacement of the secondary bromide with NaN_3 in DMF, provided (+)-**441** that was converted into penta-*N,O*-acetate of validamine (Scheme 50).[197,282] Owaga and co-workers have also prepared the (±)-valiolamine and (±)-valienamine analogues using the HBr S_N2 heterolysis of the tricyclic diether (±)-**442** (Scheme 50).[283]

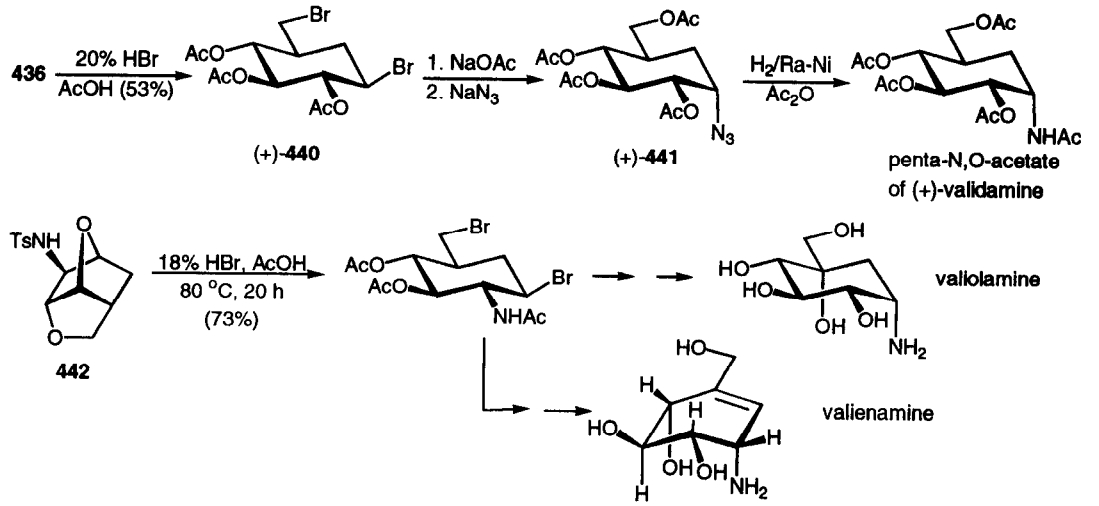
Scheme 49: Competition between S_N2 and S_N1 heterolyses of the ethereal bridge of 7-oxanorbornanes



A total synthesis of the glucosidase inhibitor cyclophellitol applying the "naked sugar" methodology relies on a S_N2 heterolysis of the 7-oxanorbornane **447** by HBr/AcOH that produces the bromide **448** (Scheme 51).[284] Since (+)-**280** and (-)-**280** are both readily available, the method described in Scheme 51 can generate optically pure cyclophellitol in both its enantiomeric forms. It is interesting to note that the acid-induced epoxide-ring opening of **442** does not lead to a pinacolic rearrangement (see Scheme 40) but is assisted by the *endo*-benzyloxy group of the dibenzyl acetal. This generates an intermediate or transition state **443** that is hydrolyzed (aqueous work-up) into **444** (see Scheme 41). After silylation into **446**, Mukaiyama cross-

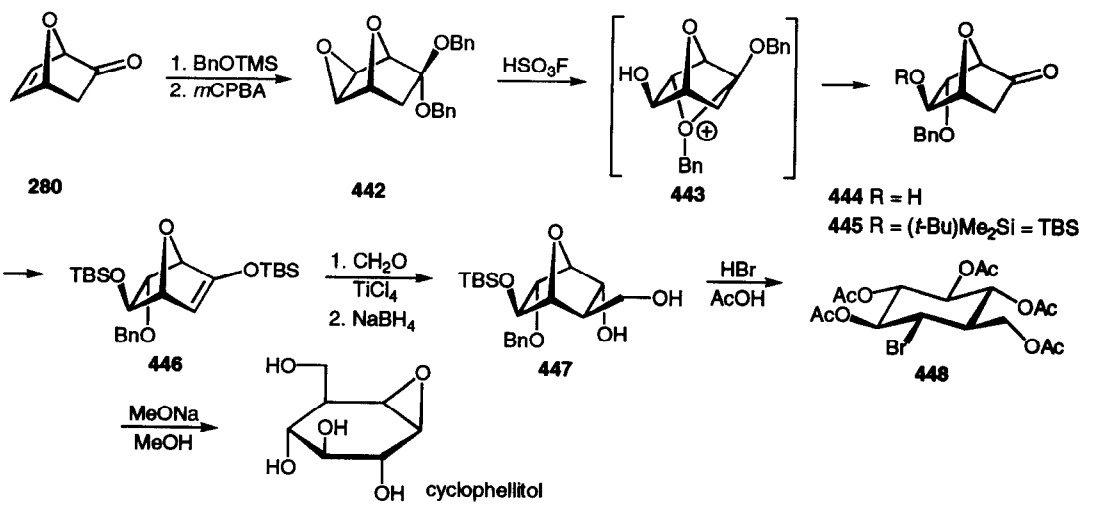
aldolisation with CH_2O followed by reduction provides **447** that reacts with HBr with high regio- and stereoselectivity giving **448**. Treatment of **448** with MeONa/MeOH provides cyclophellitol.

Scheme 50: Ogawa's syntheses of (+)-validamine, (±)-valiolamine and (±)-valienamine analogues

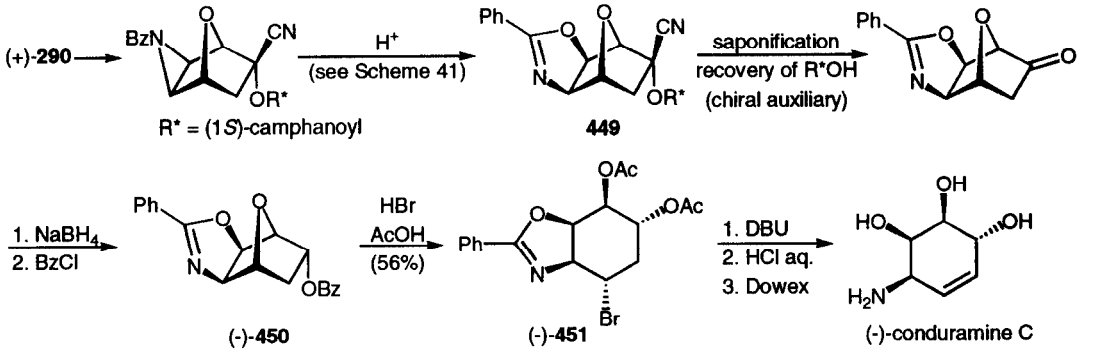


Enantiomerically pure (-)-conduramine C has been prepared by HBr-induced heterolysis of (-)-**450** derived from "naked sugar" (+)-**290** via double bond aziridination and ester-assisted aziridine ring opening (see Scheme 52). This produces the *endo*-camphanate **449** that is converted into the *endo*-benzoate (-)-**450**. Treatment of (-)-**450** with HBr/AcOH is highly stereo- and regioselective and implies attack at the less sterically hindered bridgehead center by the bromide anion giving (-)-**451**. The latter eliminates HBr on treatment with DBU in boiling toluene (Scheme 52). Acidic hydrolysis liberates (-)-conduramine C.[285]

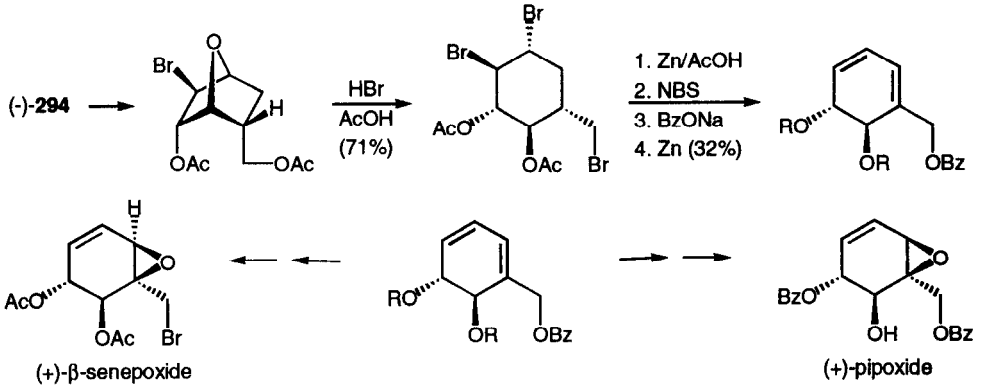
Scheme 51: Synthesis of cyclophellitol



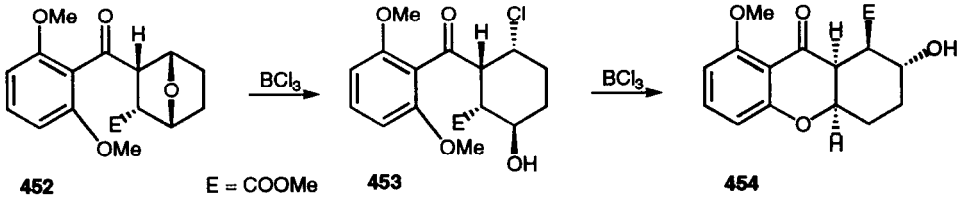
Scheme 52: Synthesis of (-)-conduramine C



Another example of HBr heterolysis of 7-oxanorbornane derivatives is given by the syntheses of (+)-β-senepoxide and of (+)-pipoxide proposed by Ogawa and Takagahi[286] as shown below.

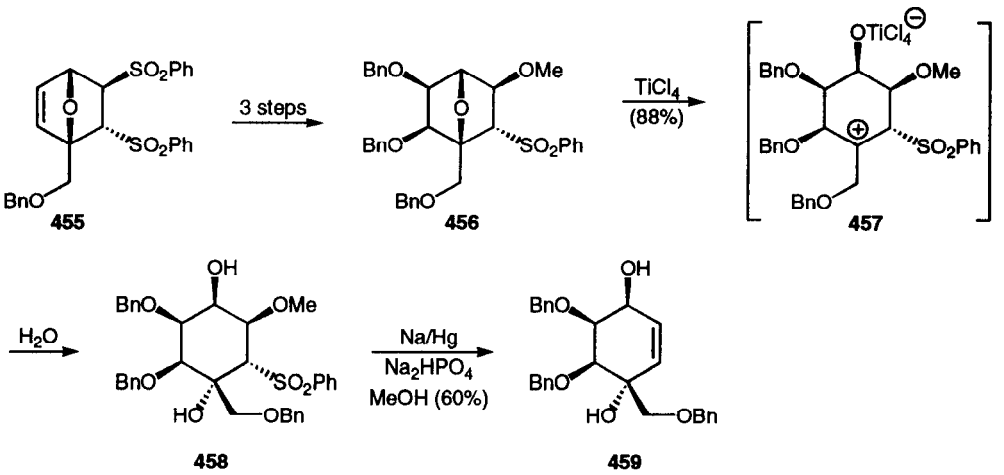


Lewis acids can also induce heterolytic cleavage of the ethereal bridge of 7-oxanorbornanes. For example, treatment of **452** with BCl_3 generates **453** arising from the S_N2 attack by chloride anion at the less sterically hindered bridgehead center. It is of interest to note that H_2O is not eliminated from **453** or **454** (*syn*-eliminations). Heterolysis of the anisole moiety may be followed by the formation of xanthone (±)-**454**.[287]



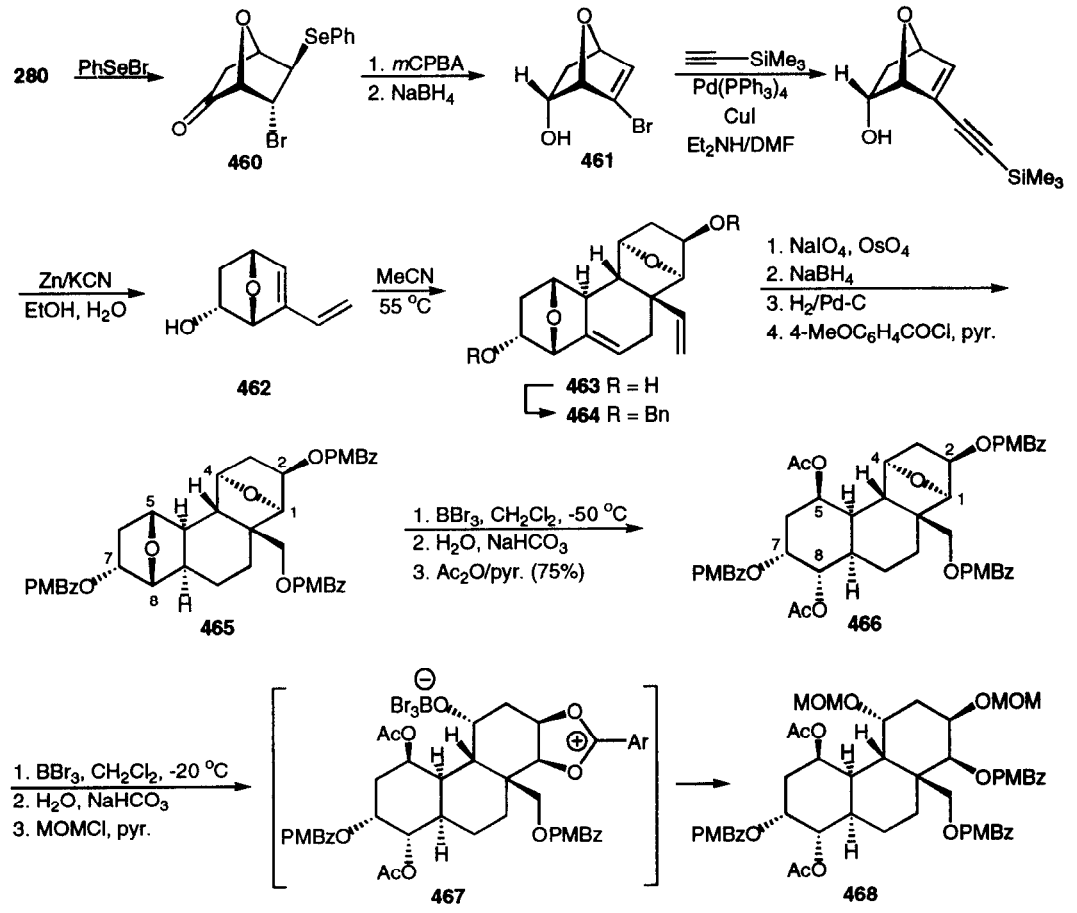
A short and highly stereoselective synthesis of a protected form of (±)-1-(hydroxymethyl)conduritol C ((±)-**459**) uses a $TiCl_4$-induced cleavage of 7-oxanorbornyl sulfone (±)-**456**. This compound was obtained in three steps from the Diels-Alder adduct ((±)-**455**) of 2-(benzyloxymethyl)furan to (*E*)-1,2-diphenylsulfonylethene.[288] $TiCl_4$ produces from **456** a tertiary carbenium intermediate of type **457** which reacts with traces of

water on its less sterically hindered face giving **458**. Reductive elimination of the phenylsulfone group with sodium amalgam produces (±)-**459**.[289]

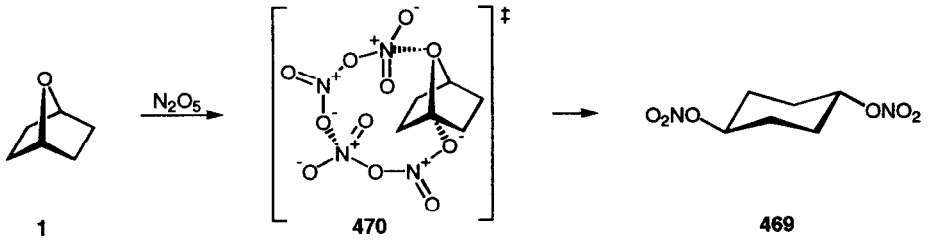


An interesting application of Lewis acid-induced heterolysis of 7-oxabicyclo[2.2.1]heptane systems is the highly stereoselective synthesis of perhydro-8a-(hydroxymethyl)-phenanthrene-1,2,4,5,7,8-hexols starting from (±)-**280** (Scheme 53).[290a] Regiospecific and stereospecific addition of PhSeBr to (±)-**280** (*exo* face selectivity, the homoconjugated carbonyl group acting as an electron-releasing group due to its frangomeric effect[251,252]) gives adduct **460** that undergoes oxidative deselenation with mCPBA. $NaBH_4$ reduction of the ketone gives **461** which undergoes a Sonogashira coupling with ethynyltrimethylsilane. Zinc reduction provides the semi-cyclic diene **462** which is cyclodimerized into a *single* adduct **463** with homochiral matching. Chemoselective oxidation of the vinyl moiety and hydrogenation of the trisubstituted alkene unit generates, after esterification of the alcoholic moieties, the tri-*p*-methoxybenzoate **465**. On treating **465** with BBr_3 in CH_2Cl_2 at −50 °C, and then with an aqueous solution of $NaHCO_3$, a diol was obtained that was acetylated into the diacetate **466**. This chemo- and regioselective heterolysis implies the participation of the *p*-methoxybenzoyloxy group at C(7) giving the intermediate **467**. Its quenching with H_2O does not lead to products in which the ester group has migrated from C(7) to C(8). Apparently the 7-(*p*-methoxybenzoyloxy) group is more prone to participate than the 2-(*p*-methoxybenzoyloxy) group, probably for steric reasons (the *endo* face of the less reactive 7-oxa-norbornane unit is substituted with the (*p*-methoxybenzoyloxy)methyl group). Treatment of **466** with BBr_3 in CH_2Cl_2 at −20 °C induces heterolysis of the second 7-oxanorbornane system, giving a diol after work-up with $NaHCO_3/H_2O$ that was protected as a diMOM derivative **468**.[290a] Under these somewhat more severe conditions, the 2-(*p*-methoxybenzoyloxy) substituent assists the 7-oxa bridge heterolysis. For reasons that are not obvious, the process leads to migration of the *p*-methoxybenzoyloxy group from C(2) to C(1).[290b]

Scheme 53: Selective 7-oxanorbornane heterolyses with BBr_3

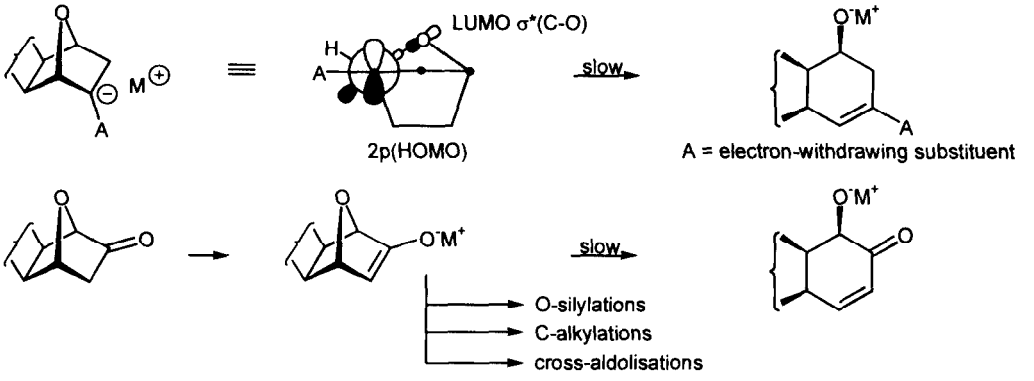


Unsubstituted 7-oxanorbornane (**1**) reacts with dinitrogen pentoxide in CH_2Cl_2 giving exclusively *trans*-cyclohexa-1,4-diyl dinitrate (**469**). Kinetic measurements suggested a transition state such as **470** in which two molecules of N_2O_5 are involved ($\Delta H^{\ddagger}$ = 7±1 kcal/mol; $\Delta S^{\ddagger}$ = -52±5 $calK^{-1}mol^{-1}$).[291]



7.5. Base-induced ethereal bridge openings of 7-oxabicyclo[2.2.1]heptyl derivatives

Scheme 54: Stereoelectronic factors retarding E_{1cb}-like 7-oxa ring openings



When a carbanionic center is generated β to an ethereal bond, β-elimination follows (E_{1cb} type of elimination). In the case of 7-oxanorbornanes, their conjugate bases (anionic center at C(2)) do not undergo fast β-eliminations for stereoelectronic reasons (Scheme 54). Indeed, for geometrical reasons, the 2p orbital (HOMO) of the carbanionic center at C(2) is poorly aligned with the LUMO of the σ(C(1)-O(7)) bond. For the electrons from C(2) to flow into σ*(C(1)-O(7)), severe deformations of the bicyclic ether are required, thus retarding the β-elimination. The more the carbanionic moiety is delocalized (stabilized), the slower the 7-oxa ring opening. The property is fundamental to the successful chemistry of the "naked sugars". Because enolates of 7-oxanorbornanones do not undergo fast isomerization into the corresponding cyclohex-3-enolates (Scheme 54), they can be used in intermolecular condensations including O-silylations, C-alkylations, and cross-aldolisations.[2,284,292]

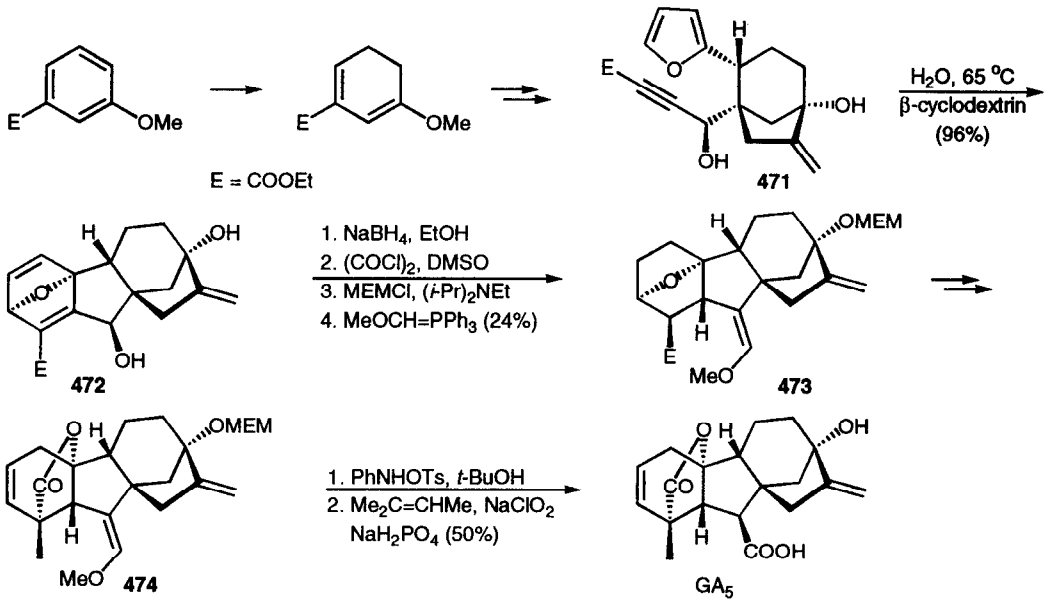
7.5.1. *Isomerization of 7-oxabicyclo[2.2.1]heptane-2-carboxylic esters*

In the absence of electrophilic reagents, enolates derived from 7-oxanorbornane-2-carboxylates or from 7-oxanorborn-5-ene-2-carboxylates undergo facile 7-oxa ring openings with the formation of the corresponding cyclohex-3-en-1-ols. These reactions have been applied to the total synthesis of shikimic acid and its analogues as reviewed recently by Jiang and Singh.[4]

Racemic gibberellin (±)-GA_5 has been obtained from *m*-methoxybenzoic acid in 16 steps by Grootaert and Declerq[293] (Scheme 55). The synthesis involves the intramolecular Diels-Alder addition of (±)-**471** in water containing β-cyclodextrin which gives **472** in high yield. In four steps **472** was converted into the 7-oxa-norbornane-2-carboxylic ester **473**. Treatment of **473** with 6 equivalents of lithium isopropylcyclohexylamide (-78 to 20 °C), followed by the addition of MeI provided lactone **474** (52% yield). The reaction involves the formation of the lithium enolate of **473** that isomerizes into the corresponding cyclohex-3-enolate. The latter is

enolized a second time and is α-methylated by MeI, the alcoholate adding intramolecularly to the methyl ester with the formation of the lactone **474**. Two further steps transform **474** into (±)-GA_5.

Scheme 55: Total synthesis of gibberellin (±)-GA_5



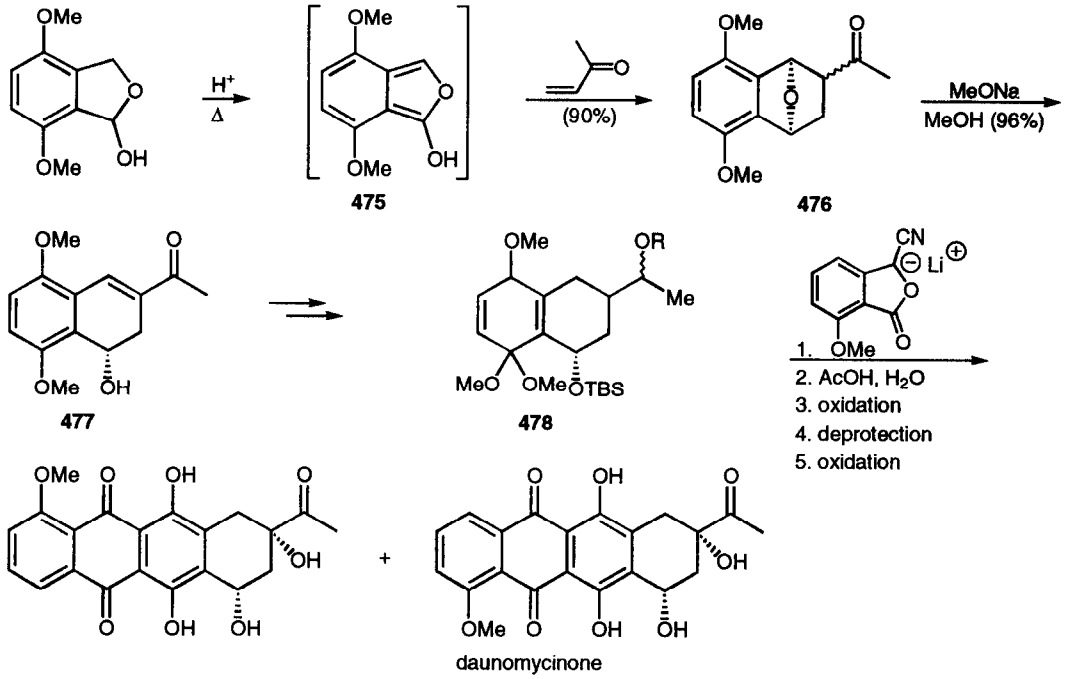
7.5.2. *Isomerization of 7-oxabicyclo[2.2.1]hept-2-yl alkyl ketones*

Keay and Rodrigo[294] have developed a short synthesis of (±)-daunomycinone (Scheme 56) based on the MeONa-induced isomerization of the Diels-Alder adduct **476** of methyl vinyl ketone to isobenzofuran **475**. This generates the hydroxy-enone **477** which is converted into **478**. Annelation using the Kraus' technique[295] provides a mixture of products that are then oxidized into (±)-daunomycinone and its 4-demethoxy-1-methoxy isomer.

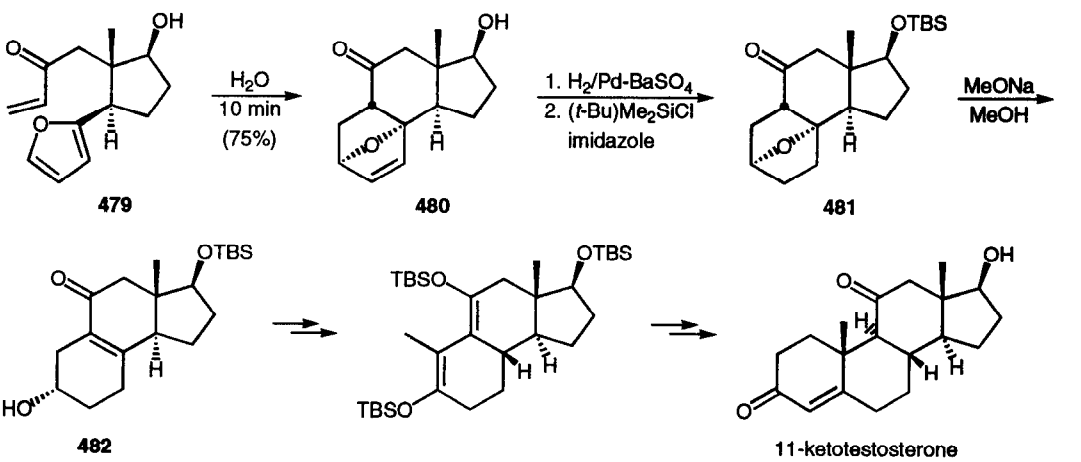
De Clercq and co-workers[296] have prepared (±)-11-ketotestosterone applying an intramolecular Diels-Alder addition of the furan derivative (±)-**479** producing 7-oxanorbornene **480** (Scheme 57). Hydrogenation, then alcohol silylation provides **481** that is isomerized into the hydroxy-enone **482** on treatment with MeONa in MeOH. Further synthetic steps[297] convert **482** into (±)-11-ketotestosterone.

Illudin M shows *in vitro* selective toxicity toward tumor cells.[298a] Racemic (±)-illudin M has been derived from the product (±)-**483** of reaction of diazoketone **190** with 4-bromo-5,5-dimethylcyclopent-2-enone in the presence of $Rh_2(OAc)_4$ as catalyst (see Scheme 23). Addition of MeMgCl to (±)-**483** is chemo- and *exo* face selective giving **484**. Methanolysis of **484** with KOH/MeOH leads to **485** that is converted into (±)-illudin M (Scheme 58).

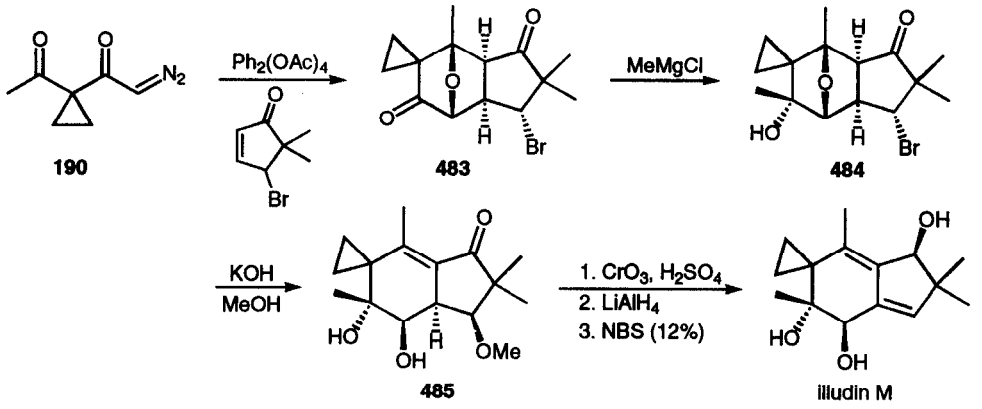
Scheme 56: Synthesis of (±)-daunomycinone



Scheme 57: Synthesis of (±)-11-ketotestosterone



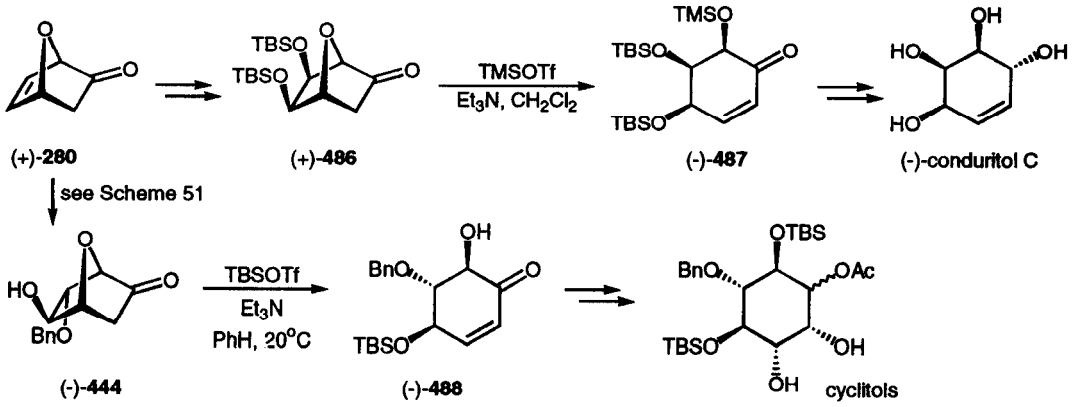
Scheme 58: Synthesis of (±)-illudin M



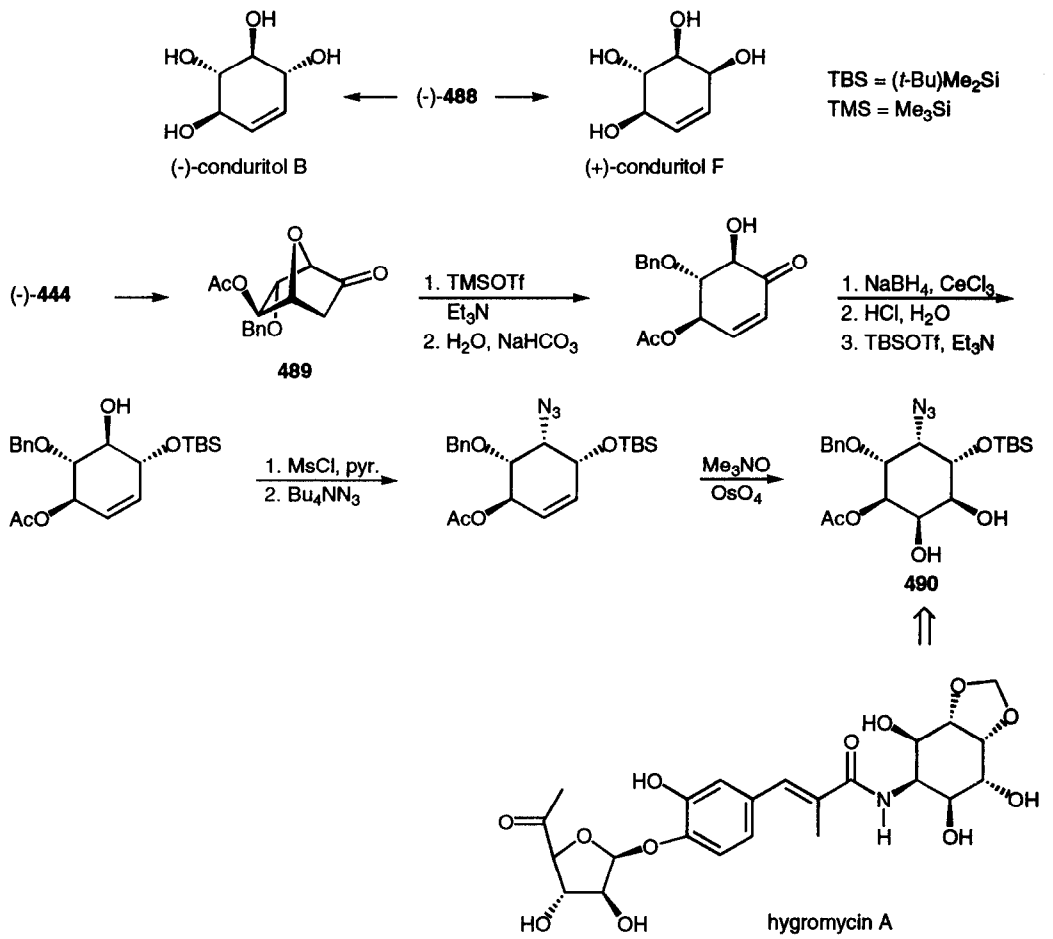
7.5.3. *Isomerization of 7-oxabicyclo[2.2.1]heptan-2-ones*

As already discussed (Scheme 54), 7-oxanorbornanones are not isomerized readily into the corresponding 6-hydroxycyclohex-2-en-1-ones when treated under basic conditions.[299] To assist this isomerization, oxyphilic Lewis acids can be added to the reaction mixture as illustrated by the first total, asymmetric synthesis of (-)-conduritol C reported by Le Drian and co-workers.[300] The 7-oxanorbornanone (+)-**486** undergoes a slow aldol/crotonalisation in the presence of a base such Et_3N, without 7-oxa ring opening. When $Me_3SiOSO_2CF_3$ and Et_3N are added to the ketone, isomerization into enone (-)-**487** occurs. Stereoselective reduction of the ketone, followed by deprotection of the polyol liberates (-)-conduritol C (Scheme 59). The same method has been applied to the 7-oxanorbornanone (-)-**444** to prepare (-)-conduritol B, (+)-conduritol F[301] and semi-protected *myo*-inositols[302] (Scheme 59). Aminocyclitols can also be prepared in the same way as illustrated (Scheme 59) with the synthesis of **490**, a precursor of the antibiotic hygromycin A.[303]

Scheme 59: Syntheses of conduritols, cyclitols and aminocyclitols starting from "naked sugars"



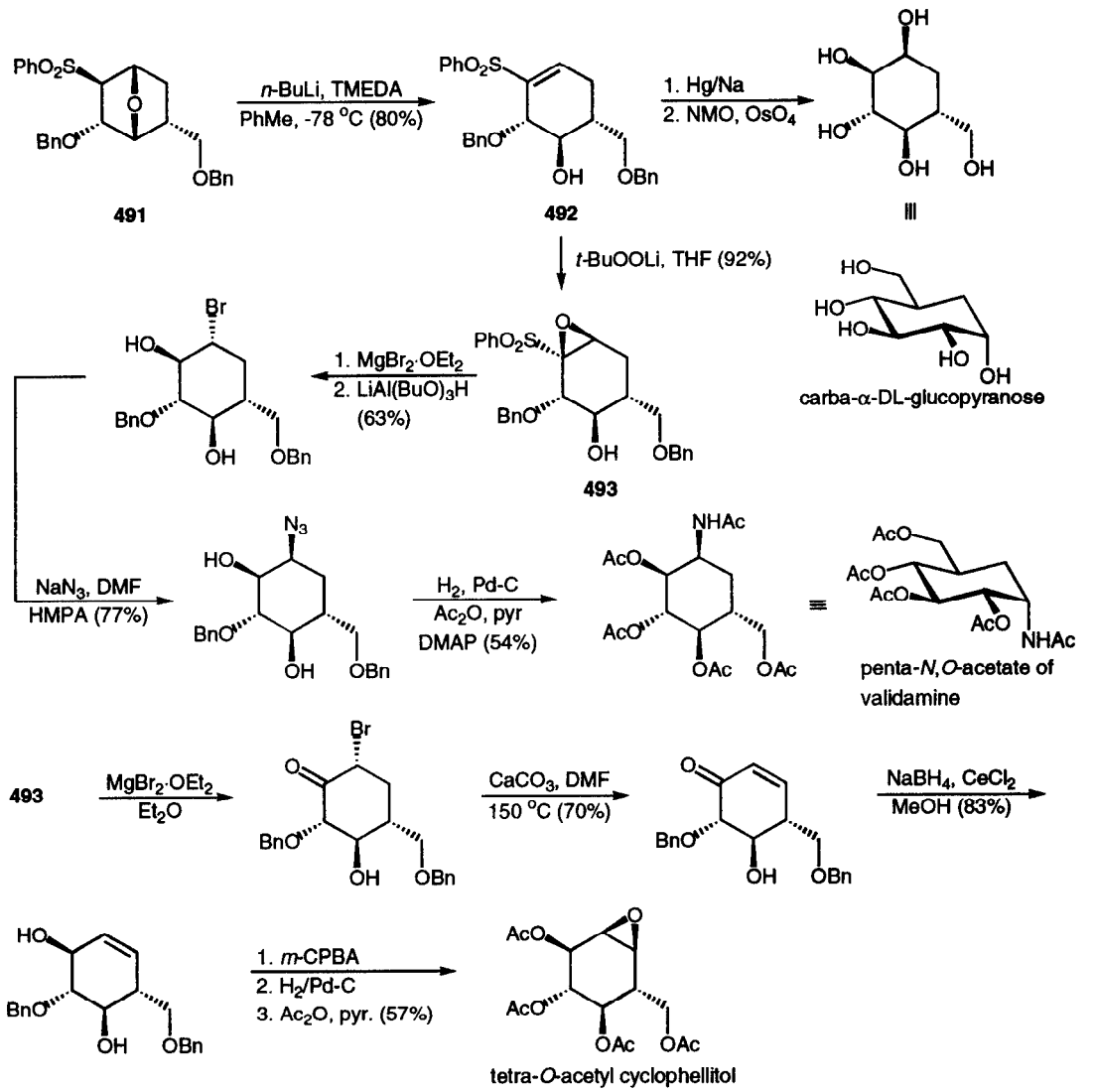
Scheme 59 (continued)



7.5.4. Isomerization of 7-oxabicyclo[2.2.1]hept-2-yl sulfones

Racemic carba-α-DL-glucopyranose (see also Scheme 49) has been obtained from (±)-**491** via deprotonation with *n*-BuLi. This induces an E_{1cb}-type of 7-oxa ring opening[304] with formation of cyclohex-3-enol **492** after aqueous work-up. Reductive desulfonylation, followed by dihydroxylation provides carba-α-DL-glucopyranose.[305] Epoxidation of **492** generates **493** that was converted into penta-*N*,*O*-acetyl (±)-validamine as shown in Scheme 60[306a] (see also Scheme 50). Epoxide **493** has also been converted into (±)-cyclophellitol[306b] (see also Scheme 51).

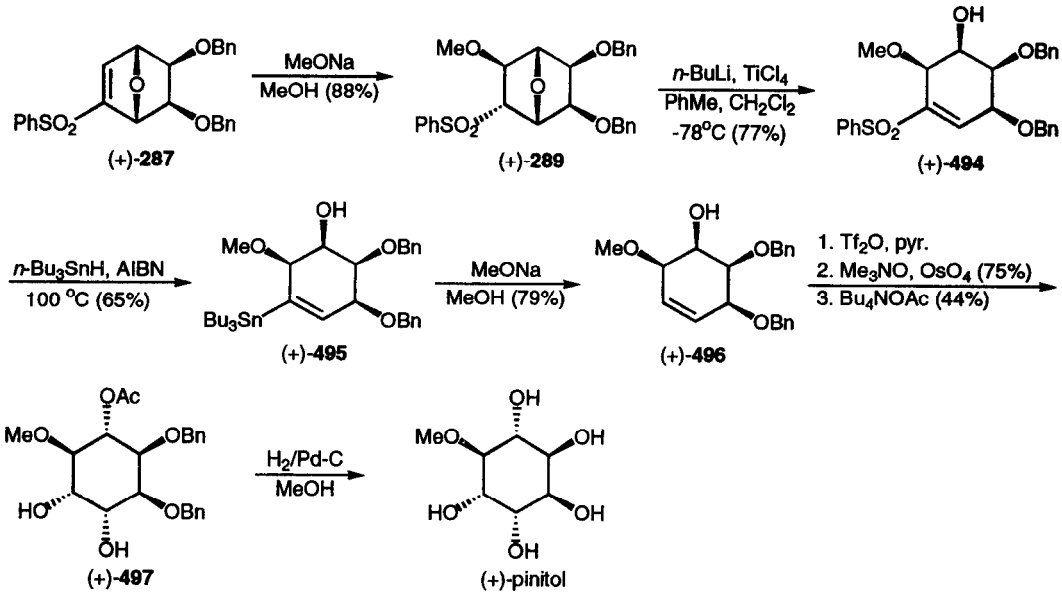
Scheme 60: Syntheses of (±)-carba-α-DL-glucopyranose, (±)-validamine, and (±)-cyclophellitol



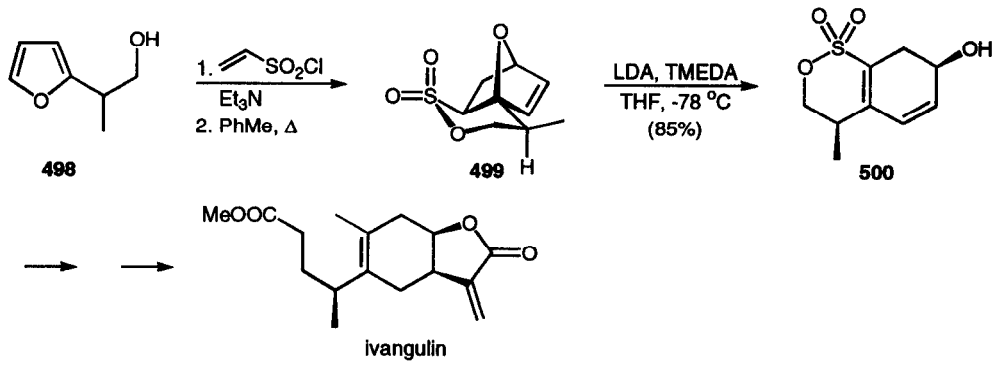
A new synthesis of (+)-pinitol (Scheme 61) has been developed using the enantiomerically pure 7-oxa-norborn-2-en-2-yl sulfone (+)-**287** (Table 2).[194] Addition of MeOH (MeONa/MeOH) to (+)-**287** provided (+)-**289** that underwent 7-oxa bridge opening rather than MeO^- elimination when treated with *n*-BuLi and $TiCl_4$ giving (+)-**494**. Desulfonylation of (+)-**494** could not be carried out by the usual reductive methods due to competitive double bond migrations and allylic deoxygenations. However, this problem was circumvented using a two-step procedure, namely formation of the tributylstannane (+)-**495** and subsequent NaOMe-mediated destannylation leading to the conduritol D derivative (+)-**496**. Esterification of (+)-**496** with triflic

anhydride, dihydroxylation and S_N2 displacement of the triflate with Bu_4NOAc provided (+)-**497** that was hydrogenolyzed to (+)-pinitol.[194]

Scheme 61: Synthesis of (+)-pinitol



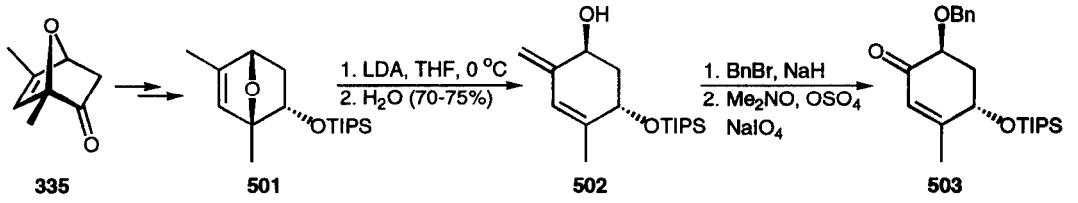
The sulfone (±)-**499** (resulting from a thermodynamically controlled intramolecular Diels-Alder addition of the vinyl sulfonate generated by esterification of alcohol **498** with ethenesulfonyl chloride) was isomerized into the cyclohexadienol **500** on treatment with lithium diisopropylamide (LDA) and tetramethylethylenediamine (TMEDA) at low temperature. Compound **500** is a synthetic precursor of (±)-ivangulin.[307]



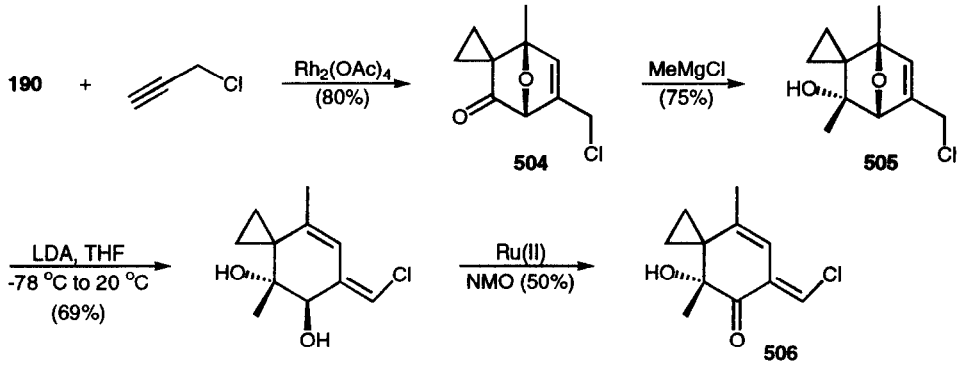
Base-induced isomerizations of 7-oxanorbornenes giving cyclohexa-2,4-dienols may be accompanied by aromatization due to H_2O elimination.[308]

7.5.5. *Isomerization of 2-alkyl-7-oxabicyclo[2.2.1]hept-2-enes*

Strong bases can deprotonate alkyl substituted alkenes into allylic carbanions. In the case of 2-alkyl-7-oxanorborn-2-enes, the resulting carbanions are isomerized into the corresponding dienolates. For instance, treatment of **501** with LDA in THF at 0 °C leads to the dienol **502** after aqueous work-up.[309] Benzylation of the alcohol **502** followed by selective oxidative cleavage of the exocyclic alkene moiety generates **503**, which is a precursor of taxol analogues.[310]



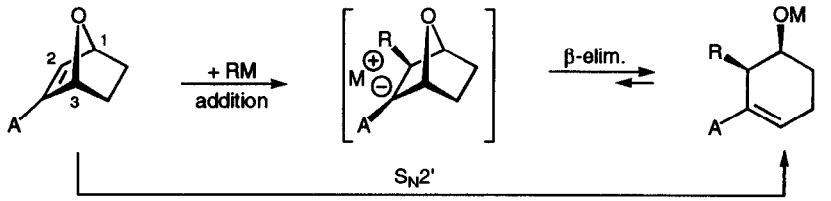
The bicyclic analogue of illudin M (±)-**506** has been derived from **504**. Methylmagnesium chloride addition to **504** gives the *endo* alcohol **505**, treatment of which with LDA leads to a dienediol which is oxidized into **506**.[311]



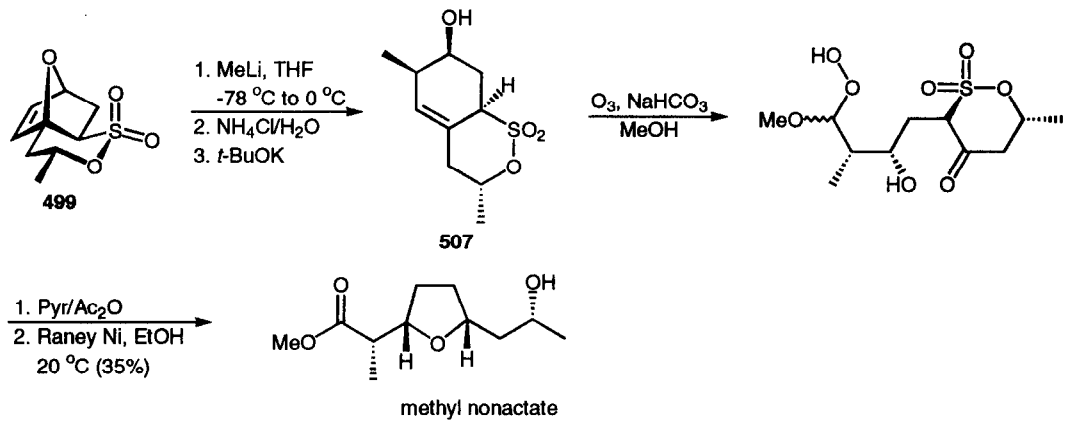
7.6. Nucleophilic additions of 7-oxabicyclo[2.2.1]hept-2-enes with ethereal bridge openings

Organolithium reagents may add to the alkene moiety of an 7-oxanorborn-2-ene with opening of the ethereal bridge and formation of substituted cyclohex-3-enols (Scheme 62). Depending on the substitution at C(3), the reaction can follow a concerted, one-step S_N2' process or a two step mechanism with the formation of carbanionic intermediates.[311] The latter mechanism may prevail when electron-withdrawing 3-substituents are present such as phenylsulfonyl groups. To complete recent reviews,[3] some further applications of this mode of 7-oxa bridge opening are described below (see also Scheme 30).

Scheme 62: Addition of organometals to 7-oxanorbornenyl systems

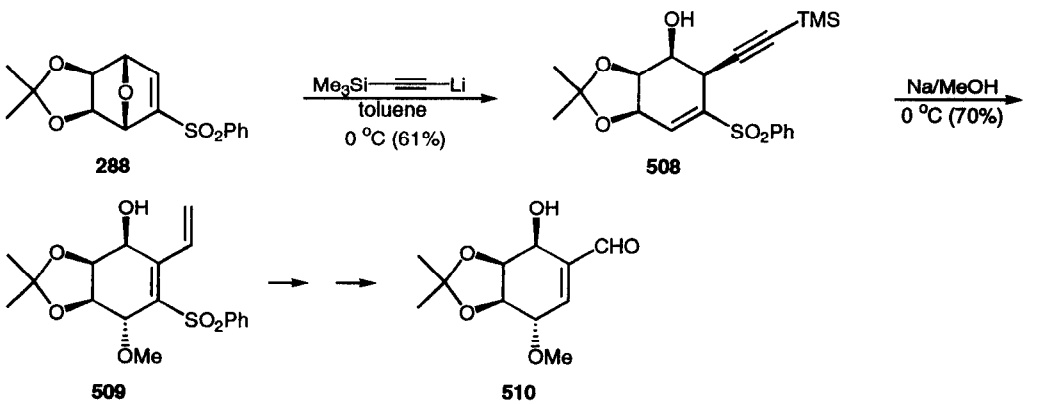


Metz and co-workers have shown recently[312] that the reaction of their sultone (±)-**499** with methyllithium generates the cyclohexenol **507**. After ozonolysis of the alkene moiety of **507**, treatment with Ac_2O/pyridine and reductive desulfonylation with Raney nickel and EtOH led to methyl (±)-nonactate.

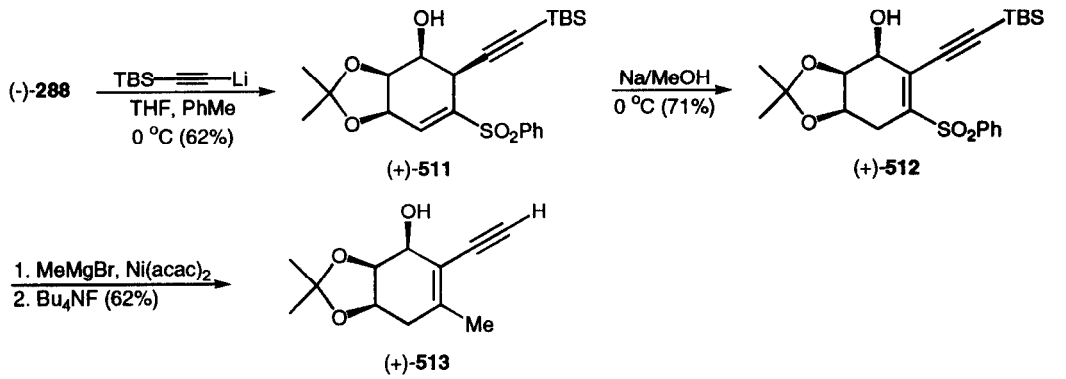


499 **507** methyl nonactate

A new synthetic approach to carba-pyranoses has been proposed[313] which starts with the reaction of lithium trimethylsilylacetylide to (±)-**288** (Table 2) that gives the cyclohexenol **508**. Reduction of **508** with sodium in methanol produces the dienol **509** which can be converted into (±)-**510**.

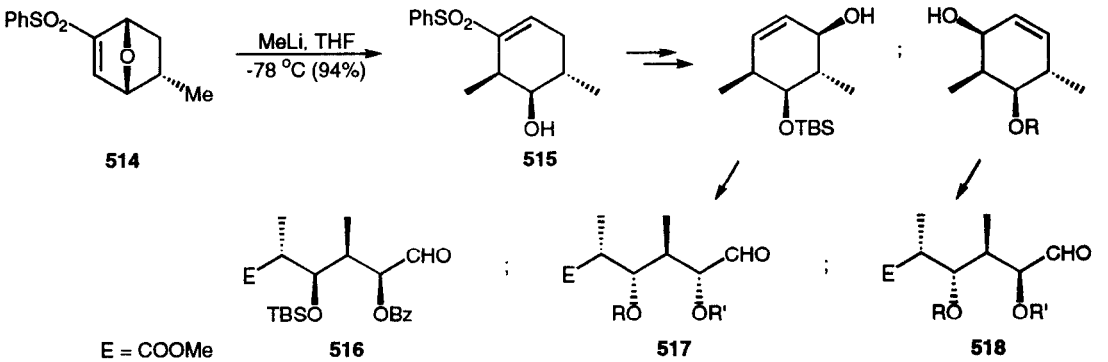


288 **508** **509** **510**



A highly stereoselective synthesis of (+)-**513**, an analogue of the A ring fragment of Vitamin D_3, has been described starting from enantiomerically pure (-)-**288**. Addition of lithium (*tert*-butyl)dimethylsilylacetylide to (-)-**288** gives (+)-**511** that is reduced into (+)-**512**. Reaction of (+)-**512** with methylmagnesium bromide leads to substitution of the benzenesulfonyl group. Desilylation produces (+)-**513**.[314]

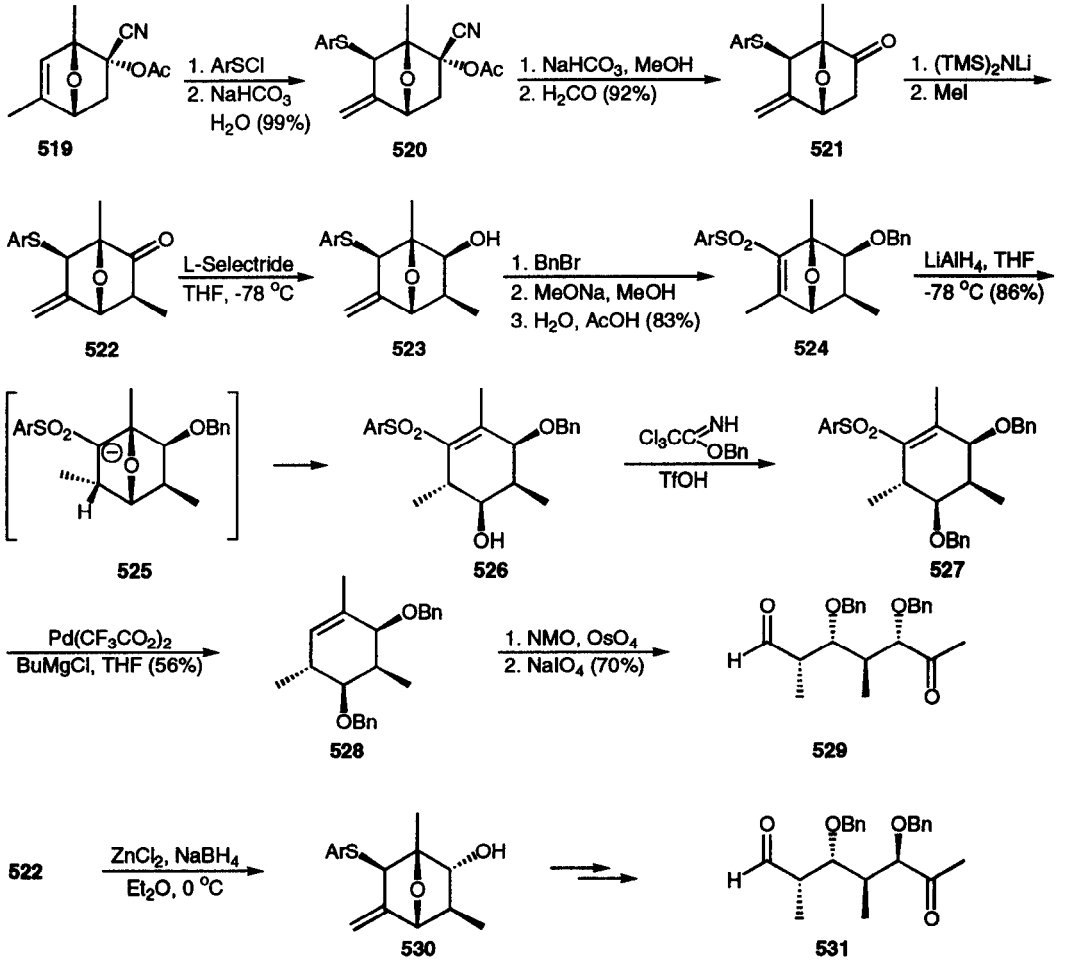
Polypropionate fragments can be obtained starting from 7-oxanorbornenes.[227] For instance, addition of methyllithium to the sulfone (±)-**514** gives a high yield of the cyclohexenol **515** that is converted into the stereotetrads (±)-**516**, (±)-**517** and (±)-**518**.[315]



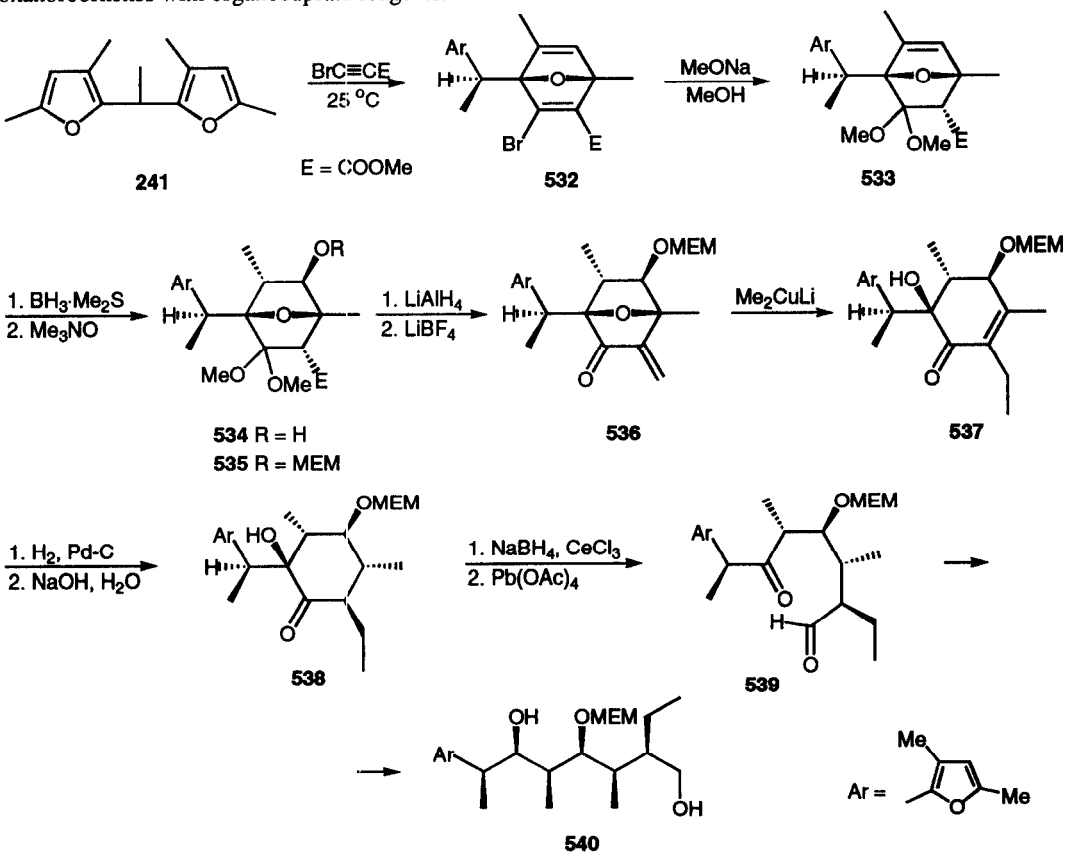
Analogous stereoselective syntheses of 2,4,6-trimethylcyclohex-4-ene-1,3-diols and of polypropionate fragments with four contiguous stereogenic centers have been developed using the "naked sugars of the second generation" such as (+)-**336** (Table 2). The study was carried out with (±)-**519**, the Diels-Alder adduct of 2,4-dimethylfuran to 1-cyanovinyl acetate (Scheme 63).[316a] The reaction of (±)-**519** with *p*-chlorobenzenesulfenyl chloride, followed by work-up with aqueous $NaHCO_3$ generates **520**. Saponification under mild conditions, followed by treatment with formalin liberates enone **521**. Treatment of **521** with $(Me_3Si)_2NLi$ at -78 °C generates the corresponding enolate that does not undergo 7-oxa bridge opening (see Scheme 54) and can be quenched with MeI to generate exclusively the product of *exo*-α-methylation **522**. Reduction of the ketone **522** with L-selectride ($LiB[CH(Me)Et]_3$) is *endo* selective,[316] giving the *exo* alcohol **523**. After benzylation, treatment with MeONa in MeOH induces migration of the exocyclic double bond into the

corresponding 7-oxanorbornene derivative that is oxidized with H_2O_2 into the sulfone **524**. Reaction of **524** with $LiAlH_4$ generates the product of reduction and ethereal bridge heterolysis **526**. The process probably involves the formation of the carbanionic intermediate **525** arising from hydride addition to the α,β-unsaturated sulfone **524**. Benzylation of the alcohol **526** provides **527** which is desulfonylated under reductive conditions to give the alkene **528**. Oxidative cleavage of the C=C double bond gives the polypropionate fragment **529**. Reduction of the bicyclic ketone **522** with $NaBH_4/ZnCl_2$ is *exo* face selective giving the *endo* alcohol **530**. This has been converted as above into the polypropionate fragment **531**.[316a] Repeating the chemistry of Scheme 63 with optically pure (+)-**336** or with its diastereomer-derived form (1*S*)-camphanic acid (see Table 2), these polypropionate fragments can be obtained optically pure in both their enantiomeric forms.

Scheme 63: Hydride addition to α,β-unsaturated sulfones; synthesis of polypropionate fragments

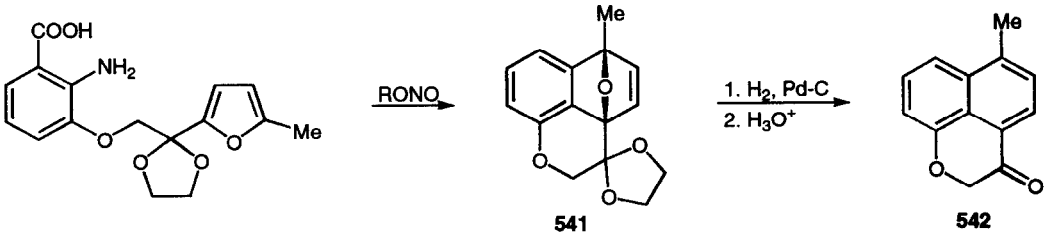


We have shown that hydrides as well as organolithium reagents can induce S_N2'-type reactions with 7-oxanorbornenes. We present a case in which a methyl cuprate has been used to cleave the ethereal bridge of a 3-methylidene-7-oxanorbornan-2-one derivative. The 1,4-addition of the methyl cuprate to the exocyclic enone was accompanied by a 7-oxa bridge opening. Reaction of 2,2'-ethylidenebis[3,5-dimethylfuran] (**241**) with methyl bromopropynoate (see Scheme 31) gives a major monoadduct (±)-**532**. Methanolysis of (±)-**532** with MeONa/MeOH produces the acetal **533**. Hydroboration of **533** is highly *exo* face selective and regioselective giving the alcohol **534** that is protected as **535**. Ester reduction with $LiAlH_4$ gives the corresponding primary alcohol which, on treatment with $LiBF_4$, generates the exocyclic enone **536**. Addition of Me_2CuLi to **536** produces **537** arising from 1,4-addition of the cuprate with concomitant 7-oxa ring opening. Hydrogenation of the alkene moiety, followed by basic treatment leads to the ketone **538** which is reduced and cleaved oxidatively into **539**. The latter compound is then converted into the long-chain polypropionate fragment (±)-**540**.[171] The review by Chiu and Lautens[3b] presents the most important examples of S_N2' reactions of 7-oxanorbornenes with organocuprate reagents.[317]



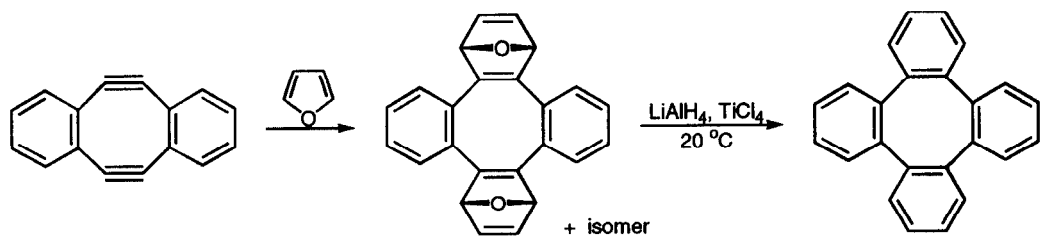
7.7. Reductive ethereal cleavage

Brown has shown that the complex from lithium tri(*tert*-butoxy)aluminum hydride and triethylborane reduces 7-oxanorbornane (**1**) into cyclohexanol.[317] Similarly, Rickborn[318] reported that benzo-7-oxanorbornadiene is reduced into 1-hydroxy-1,4-dihydronaphthalene by S_N2 delivery of hydride (deuteride). Probably because of the benzylic character of the C-O bond to cleave, the latter S_N2 hydride attack is faster than an alternative S_N2' process. Other 7-oxanorbornenes that are not substituted at the olefinic centers by electron-withdrawing groups are usually reduced into the corresponding cyclohex-3-enol following an S_N2' mechanism.[307b,319] Catalytic hydrogenolysis of benzo-7-oxanorbornenes to generate 1-hydroxy-1,2,3,4-tetrahydronaphthalene derivatives has also been reported.[320] In the case of benzo-7-oxanorbornadiene, catalytic hydrogenolysis may generate the corresponding naphthalene derivative arising from the loss of one equivalent of water as illustrated with reaction **541** → **542**.[321] Deoxygenation of **541** can also be achieved with $Fe_2(CO)_9$.[322] Benzo-7-oxanorbornadiene has been reduced into naphthalene under photochemical conditions with triethylamine.[323]



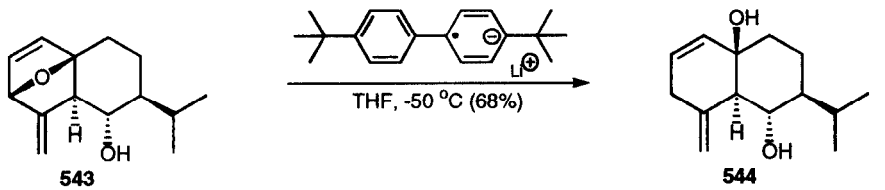
541 **542**

Deoxygenation of 7-oxanorbornadienes can be carried out with *n*-BuLi and transition metal chlorides such as $FeCl_3$, WCl_6 or $TiCl_4$[324] or with $LiAlH_4$ and $TiCl_4$ (e.g.: see Scheme 2A) as illustrated by the synthesis of tetraphenylene.[325] Alternatively, mixtures of $LiAlH_4$ and cyclopentadienyltitanium trichloride or of $LiAlH_4$ and di(cyclopentadienyl)titanium dichloride can be used to deoxygenate 7-oxanorbornadienes into the corresponding benzene derivatives.[326] Grignard reagents in excess are also capable of reducing benzo-7-oxanorbornadienes into the corresponding naphthalenes.[327]



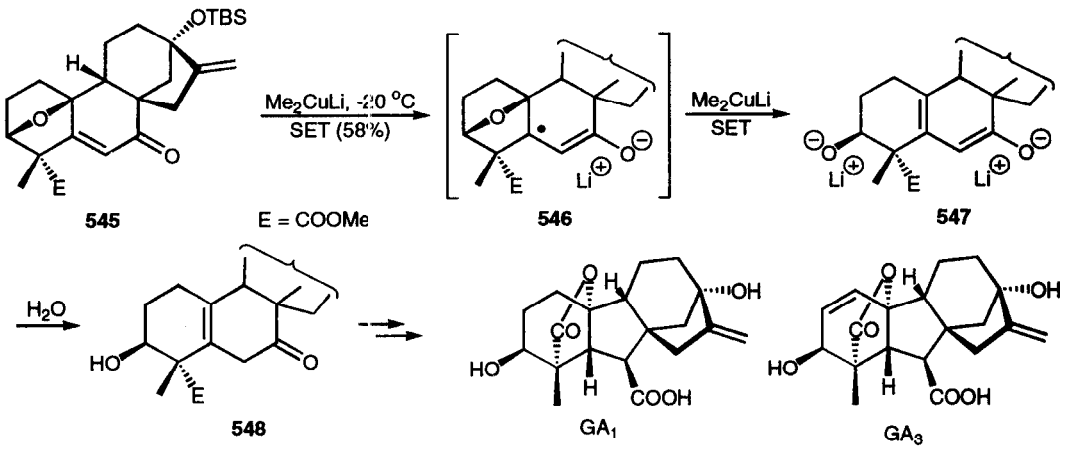
Single electron transfer to 7-oxanorbornanes having a high electron affinity because of their adequate substitution generates radical-anions that may lead to ethereal bond cleavage. De Clercq and co-workers[328]

have prepared (±)-periplanone B starting from the 6-methylidene-7-oxanorborn-2-ene derivative (±)-**543**. This homoconjugated diene reacts with lithium di-*tert*-butylbiphenyl radical anion (2 equivalents) to produce an alcoholate that is neutralized into dienol (±)-**544**.[3b]



543 **544**

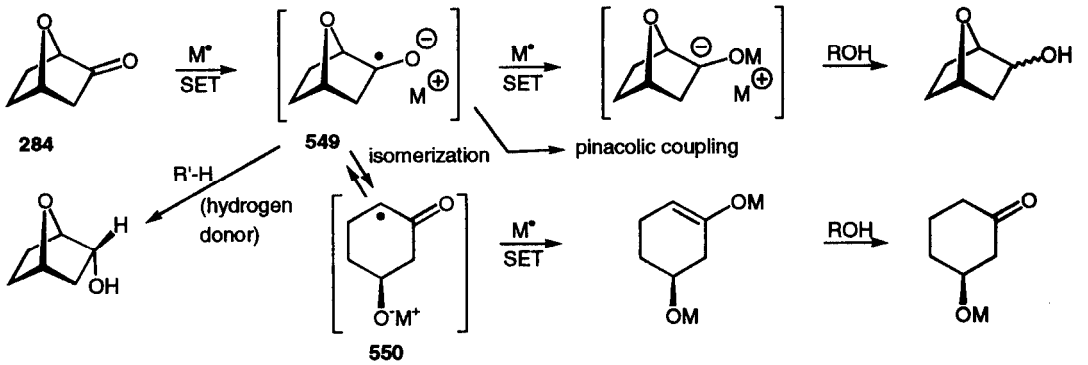
Applying a method similar to that presented in Scheme 55, De Clercq and co-workers[329] have proposed a new approach to the total syntheses of gibberellins (±)-GA_1 and (±)-GA_3 that uses the reductive oxa ring opening of 7-oxanorbornane **545** into **548**. In the presence of Me_2CuLi, enone **545** takes an electron (single electron transfer: SET) to generate the hypothetical radical-anion **546**. The latter then takes a second electron or undergoes 7-oxa ring opening giving an intermediate of type **547** that generates **548** after aqueous neutralization. Further synthetic steps convert **548** into (±)-GA_3 and (±)-GA_1.



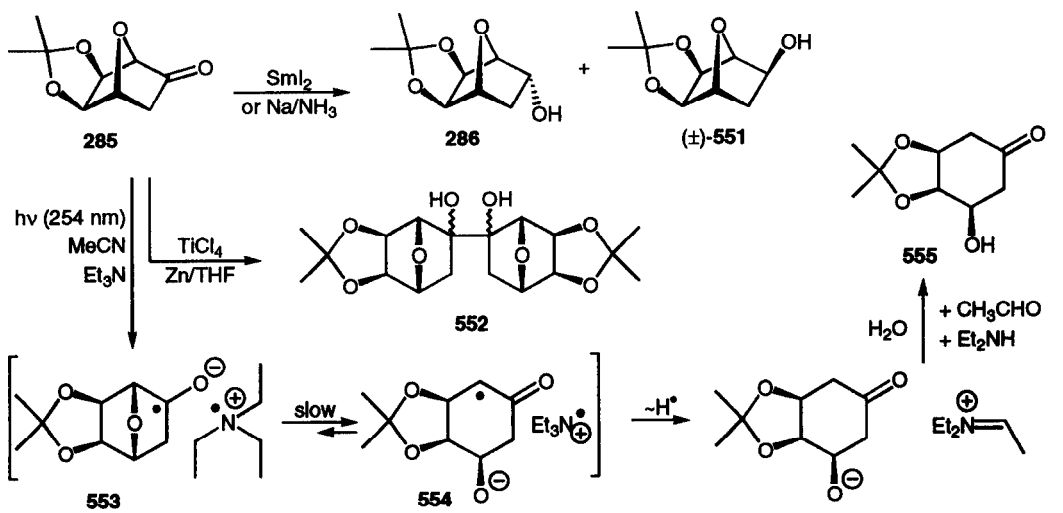
7.7.1. Ketyl radical-anions from 7-oxabicyclo[2.2.1]heptanones

Single electron transfer to 7-oxanorbornanones generates the corresponding ketyl radical-anions that may be reduced further and quenched by the solvent to generate the corresponding 7-oxanorbornanols. Alternatively, the ketyl radical-anions may lead to a pinacolic coupling or undergo 7-oxa ring opening before a second electron is transferred to them (Scheme 64). For stereoelectronic reasons (Scheme 54) the isomerizations of the 7-oxanorbornanone ketyl anion-radicals (**549**) into the corresponding γ-oxy-β-oxocyclohexyl radicals (**550**) are not rapid processes. Thus competition between oxa ring openings and reductions or pinacolic couplings will depend on the nature of the reducing agent (nature of the counter-ion M^+), on the substitution of the 7-oxanorbornanone and on the solvent (radical hydrogen source, protic solvent).

Scheme 64: Principal reactions of ketyl radical-anions derived from 7-oxanorbornan-2-one

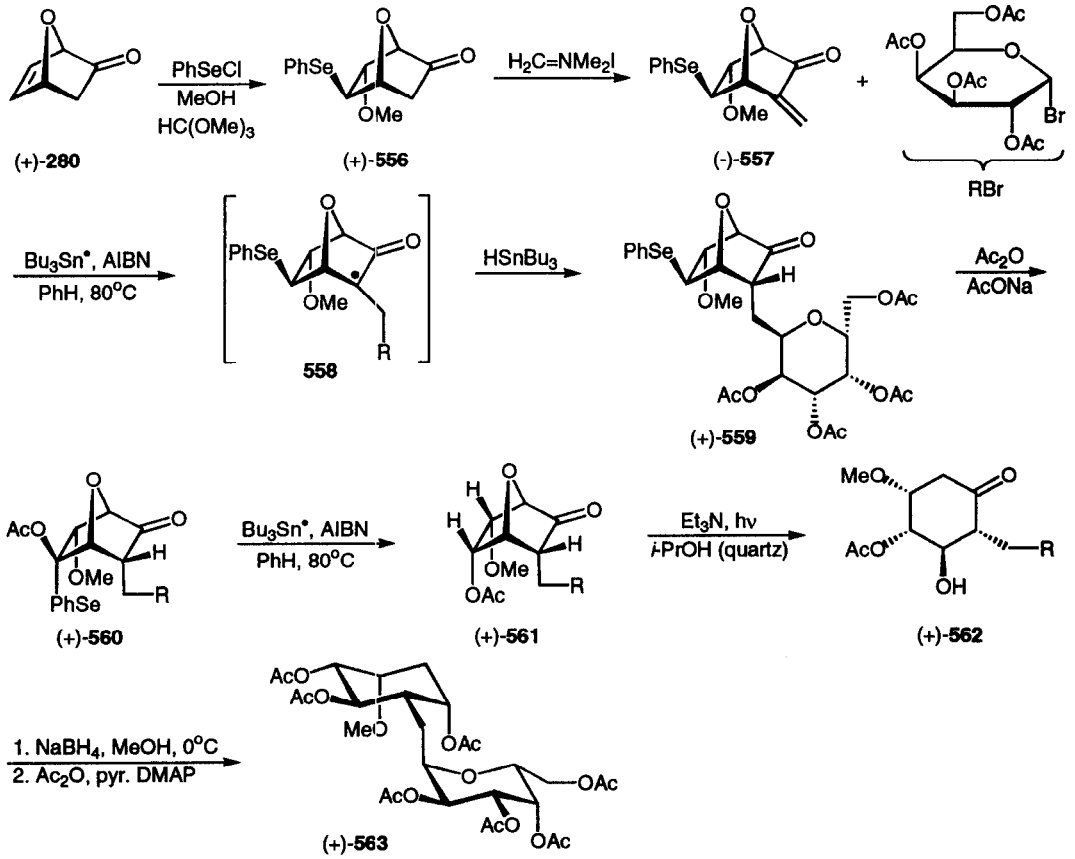


De Clercq[330] and Padwa[119] have used SmI_2[331] to induce the reductive oxa bridge opening of 7-oxanorbornanones.[3b] In the case of **285**, a 45% yield of the *endo* alcohol **286** was obtained (50% conversion) when this was treated with 3 equivalents of SmI_2 in THF. No trace of product **555** was detected in the crude reaction mixture. Similarly, treatment of **285** with Na in liquid NH_3 at –78 °C gave a 10:1 mixture of the *endo* and *exo* alcohols **286** and **551**, respectively. Low-valent titanium salts are known to induce single electron transfers to ketones.[332] With mixtures of $TiCl_4$ and activated zinc powder in THF, **285** was transformed into a 11:2:1:7 mixture (27% yield) of the stereoisomeric pinacols **552**, with no trace of the β-hydroxyketone **555** or of its products of pinacolic coupling. Several examples of reactions involving 7-oxanorborn-2-yl radical intermediates have shown that the latter are not able to undergo ethereal bond cleavages although the processes would liberate ca. 6 kcal/mol of ring strain[139] (see Section 5.3); the cyclohexyloxy radicals that would arise from such isomerizations are expected to be less stable than the corresponding 7-oxabicyclo[2.2.1]hept-2-yl radicals ($DH°(Me_2CHO•/H•)$ = 104.5 kcal/mol, $DH°(Me_2CH•/H•)$ = 96.5 kcal/mol[333]). Finally it was found



that **285** could be isomerized reductively into **555** by irradiation in MeCN (low-pressure Hg lamp, quartz vessel) in the presence of Et_3N. This method[334] implies an electron transfer from Et_3N to the excited state of the ketone with formation of a ketyl radical-anion of type **553**, the counter-ion of which is the triethylaminium radical-cation, a voluminous species that, contrary to SmI_2^+ or Na^+, is not tightly bound to the radical-anion. This enhances the electron density at center C(2) which can transfer to the LUMO of the σ(C(1)-O(7)) bond (see Scheme 54) and forces the 7-oxa ring opening into **554**. Thus, in the case of the reduction with SmI_2, Na or Ti(III) species, the intermediates are more like 7-oxanorborn-2-yl radicals than ketyl radical-anions of type **549** or **553**.[335]

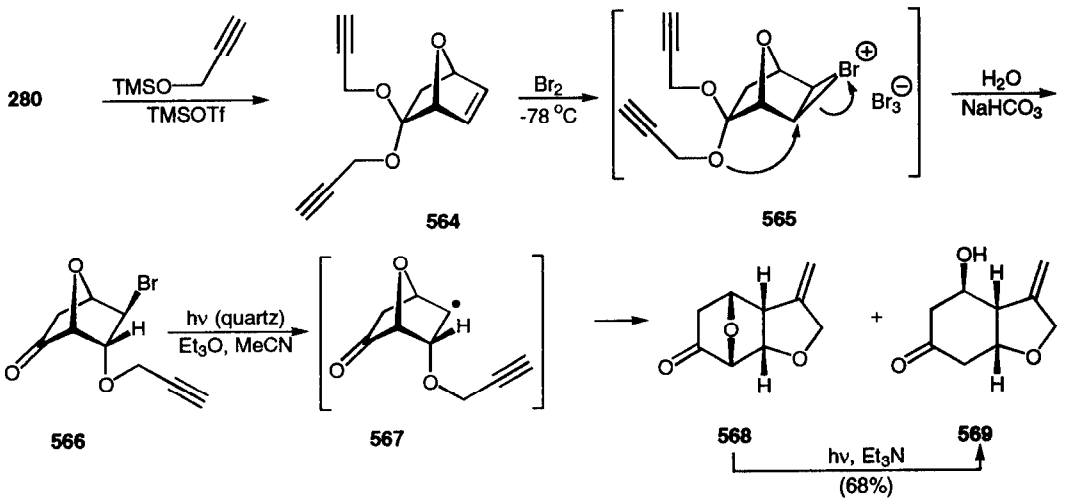
Scheme 65: Synthesis of an α-C-galactopyranoside of a carbapentopyranose



The photoinduced single electron transfer from Et_3N onto 7-oxabicyclo[2.2.1]heptan-2-ones has the advantage of being highly tolerant in terms of polyfunctionalities. It has been applied to the synthesis of a new class of disaccharide mimics that are C-pyranosides of carbapentopyranoses (Scheme 65). The synthesis starts from the "naked sugar" (+)-**280** (Table 2) that adds to PhSeCl in the presence of $HC(OMe)_2$/MeOH to give (+)-**556**. Treatment of the lithium enolate of (+)-**556** with the Eschenmoser's salt (CH_2=NMe_2I) affords the

enone (-)-**557**. Radical glycosidation of (-)-**557** with acetobromogalactose generates the 7-oxanorbon-2-yl radical intermediate **558** which does not undergo 7-oxa ring cleavage but reacts intermolecularly with Bu_3SnH exclusively onto its *exo* face to give the *endo*-C-galactoside (+)-**559**. Treatment of (+)-**559** with Ac_2O/AcONa induces a seleno-Pummerer rearrangement that gives a mixture of products from which (+)-**560** is isolated in 82% yield. Radical reduction of (+)-**560** gives the 2-*endo*-acetoxy-3-*endo*-methoxy-7-oxanorbornan-2-one (+)-**561**. Attemps to ring open (+)-**561** with excess SmI_2 led to only a 7% yield of the 3-hydroxycyclohexanone (+)-**562**. Irradiation of (+)-**561** in isopropanol with Et_3N generates (+)-**562** in 35% yield (60% conversion). Reduction of (+)-**562** with $NaBH_4$, followed by acetylation, provides the α-C-galactoside (+)-**563** (Scheme 65).[335]

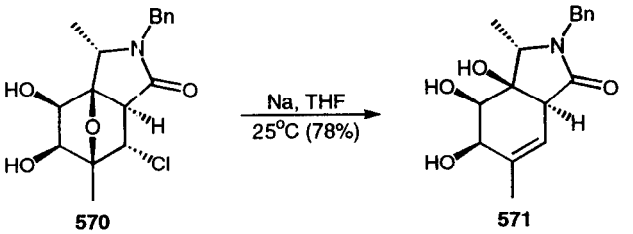
Scheme 66: Approach to the skeleton of eriolanin



The skeleton of eriolanin has also been obtained by following a similar approach (Scheme 66).[336] Acetalization of (±)-**280** with propargyl alcohol gives **564**. Addition of bromine to **564** was chemoselective, the electrophile preferring the reactive bicyclic alkene to the propargyl ethers. Intermediate **565** is formed which undergoes migration of the *endo* propargyloxy group to produce **566**, the process being analogous to that described in Scheme 51 for the acid-promoted epoxide ring opening of **442** (a similar process is also involved during reaction (+)-**280** + PhSeCl/MeOH → (+)-**556**, Scheme 65). Irradiation of **566** in MeCN in the presence of Et_3N leads to a mixture of **568** (40%) and **569** (37%). On further irradiation in the presence of Et_3N, **568** is converted into **569**. The reaction involves first the formation of radical **567** which undergoes an *exo*-trig cyclization and reduction (hydrogen transfer from triethylaminium radical-cation) into **568**. Photo-induced electron transfer to **568** generates **569**.

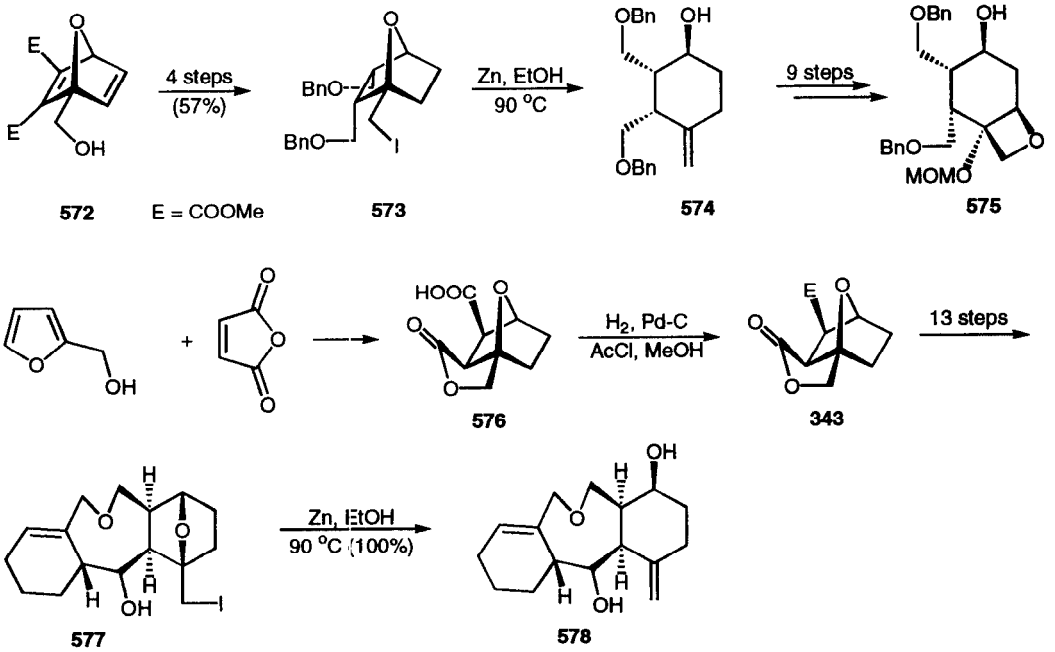
7.7.2. Metal reduction of halides

Halides and sulfones β to the 7-oxa bridge of 7-oxanorbornanes are reduced with metals with ethereal bond cleavage.[337] It their study of the synthesis of avermectin, Jung and Street[338] have employed the sodium reduction of the chloride (±)-**570** that gives (±)-**571**.



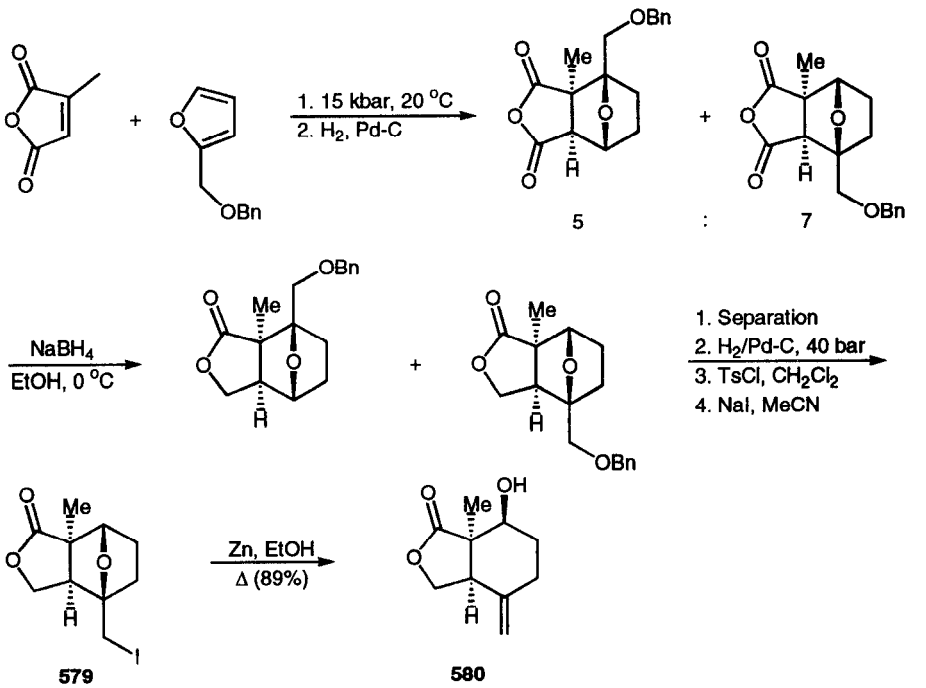
570 **571**

Taxol CD rings have been constructed using a similar reductive 7-oxa ring opening.[339] The Diels-Alder adduct (±)-**572** of furfuryl alcohol to dimethyl acetylenedicarboxylate has been converted into the 1-iodomethyl-7-oxanorbornane **573**. On treatment with zinc dust in EtOH, **573** was reduced quantitatively into the 4-methylidenecyclohexanol **574**. After 9 further synthetic steps, system **575** was obtained.[339] A similar approach was used to generate skeletons of analogues of Taxol. Diels-Alder addition of maleic anhydride to furfuryl alcohol gives **576**. After 15 synthetic steps, the iodomethyl-7-oxanorbornane **577** was obtained. Its reduction with zinc generates (±)-**578**.[340]



Potential precursors for the CD-ring fragments of Taxol and analogues have been derived from the Diels-Alder adducts of citraconic anhydride to the benzyl ether of furfuryl alcohol. The method relies on a reductive

7-oxa bridge opening of the 1-iodomethyl-7-oxanorbornane (±)-**579** into the corresponding 4-methylidene-cyclohexanol derivative (±)-**580**.[341]



8. Conclusion

This report completes the recent reviews of Padwa,[1c] Hudlicky,[1b] Keay,[3a] Lautens[3b] and Jiang[4] on the chemistry and the applications of 7-oxabicyclo[2.2.1]heptane derivatives. We have emphasized their importance in Nature, and as biologically active compounds. We have sketched their potential in materials sciences. The 7-oxabicyclo[2.2.1]heptanes can be prepared by methods other than Diels-Alder cycloadditions of furans following various approaches that imply either cationic or radical intermediates. However, the intermolecular and intramolecular Diels-Alder additions of furans remain the most general and simple approach to obtain 7-oxabicyclo[2.2.1]heptane systems with various degree of complexity. Kinetic and thermodynamic aspects of these cycloadditions are discussed critically. It is found that solvation and aggregation of cycloaddents and adducts affect their equilibrium constants in significant ways. We have also shown that various types of side-reactions can compete with the Diels-Alder additions of furans. Table 2 lists the most important 7-oxabicyclo[2.2.1]heptanes as chirons (enantiomerically or diastereomerically enriched systems) and this should help the synthetic chemist in his design of synthetic plans. Finally, the most recent synthetic applications of the 7-oxabicyclo[2.2.1]heptanes are reviewed in a way that stresses the fundamental principles of their reactivity. The reader will have no doubt about the huge potential of the 7-oxabicyclo[2.2.1]heptanes in materials sciences and in the synthesis of complicated structures, whether these be natural compounds or analogues of biological interest.

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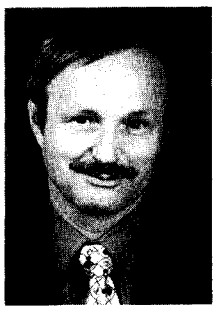
Biographical sketch



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