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The role of 1,3-dithianes in natural product synthesis

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This review is dedicated to Professors E. J. Corey and D. Seebach for their seminal contributions to 2-lithio-1,3-dithianes

Contents

Keywords: carbanions; organolithium compounds; dithioacetal moiety.

Abbreviations: A-15E, Amberlyst 15E; 9-BBN, 9-borabicyclo[3.3.1]nonane; Bn, benzyl; Boc, *t*-butoxycarbonyl; BOM, benzyloxymethyl; Bz, benzoyl; 12-C-4, 12-crown-4; CSA, 10-camphorsulfonic acid; CIP, contact ion pairs; DEAD, diethyl azo dicarboxylate; DEIPS, diethylisopropylsilyl; DHP, dihydropyran; DIBALH, diisobutylaluminium hydride; DMB, 3,4-dimethoxyphenylmethyl; DMF, dimethylformamide; DMPU, *N*,*N*′-dimethylpropyleneurea; DMSO, dimethyl sulfoxide; DTBMS, di-*t*-butylmethylsilyl; EE, 1-ethoxyethyl; HMDS, hexamethyldisilazane; HMPA, hexamethylphosphoramide; LAH, lithium aluminium hydride; LDA, lithium diisopropylamide; LTB_4, leukotriene B_4; MCPBA, *m*-chloroperbenzoic acid; MEM, 2-methoxyethoxymethyl; MOE, 1-methoxyethyl; MOM, methoxymethyl; MTM, methylthiomethyl; Ms, methanesulfonyl (mesyl); Nap, 2-naphthylmethyl; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NMM, *N*-methylmorpholine; NMR, nuclear magnetic resonance; P, protecting group; PCC, pyridinium chlorochromate; Piv, pivaloyl (*t*-butylcarbonyl); PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; PPTS, pyridinium *p*-toluene sulfonate; Py, pyridine; RVC, reticulated vitreous carbon; SEM, 2-(trimethylsilyl)ethoxymethyl; SIP, separated ion pairs; TBAF, tetrabutylammonium fluoride; TBDPS, *t*-butyldiphenylsilyl; TBS, *t*-butyldimethylsilyl; TES, triethylsilyl; Tf, trifluoromethanesulfonyl (triflyl); TFA, trifluoroacetic acid; THC, tetrahydrocannabinol; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; TPS, triphenylsilyl; Tr, triphenylmethyl (trityl); Ts, *p*-methylbenzenesulfonyl (tosyl).

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1. Introduction

The normal reactivity of a carbonyl compound (**I**) is as an *a* ^{1}-reagent (**II**) and the temporary reversal of the characteristic pattern of reactivity of a functional group is described by the term umpolung which was introduced by Corey and Seebach and widely accepted in the scientific community. 2-Lithio-1,3-dithiane derivatives (**IV**) are the most successful sulfur-stabilised acyl anion equivalents (**V**), having been widely used as masked nucleophilic acylating agents (as well as carbanions **VI** by final sulfur–hydrogen exchange) since the pioneering work of Corey and Seebach.[1] These systems (also called *d* ^{1}-reagents following Seebach's nomenclature[2]) are easily prepared by deprotonation with alkyllithiums of the corresponding dithiane (**III**)[1] and show reverse reactivity of the carbonyl group. The dithioacetal moiety could be hydrolysed after reaction with an electrophile to provide the corresponding ketone (**VIII**) or it could be reductively removed to yield the compound **IX**. In the case of R=H, a second deprotonation of the dithiane **VII** would lead to a new 2-lithio-1,3-dithiane compound **X**, which, after reaction with a second electrophile and final hydrolysis or reduction of the dithiane unit, would give a difunctionalised ketone **XII** or a methylene derivative **XIII** (through dithiane **XI**), respectively. Through this strategy, the dithiane compound acted as an equivalent of the formaldehyde dianion (**XIV**) or the methylene dianion (**XV**) (Scheme 1).

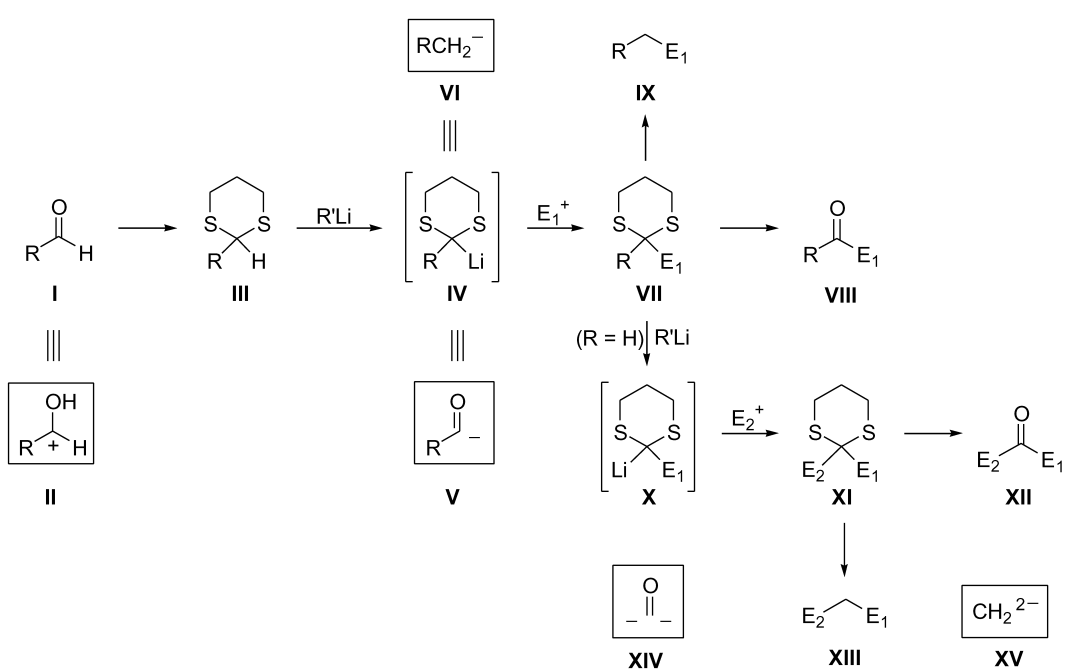
2-Lithio-1,3-dithiane derivatives are quite stable species, other intermediates containing different cations than lithium (for instance, sodium, potassium, magnesium[3] and copper) being less employed because of the lack of general methodologies for the introduction of the metal into the dithiane unit and their low reactivity. The stability of 2-lithio-1,3-dithiane is due to the effect of the sulfur atoms on adjacent carbanions[4] by electron back-donation into vacant sulfur d-orbitals.[5]

The 1,3-dithiane ring can be introduced in an organic molecule following two general approaches. The reaction of the anion of 1,3-dithiane, with or without substitution at the C(2) position, with different electrophilic reagents is the method most commonly used and thioacetalisation of a carbonyl group, using Lewis or Brönsted acid catalysis,[3,6] is the other methodology. The dithioacetal group is also suitable for the protection of carbonyl groups because it is stable towards acidic and basic conditions. When dithiane is used as an acyl anion equivalent, it must be hydrolysed at some stage during a synthesis to reveal the carbonyl group which was originally masked. Deprotection has often been extremely difficult to achieve, especially for complex and sensitive derivatives, and many procedures have therefore been developed[3,7–14] and there is not a single method that can be generally applied.

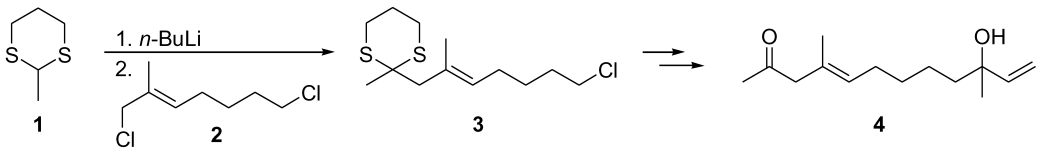
For all of the former reasons, synthetic organic chemists have found 1,3-dithianes to be versatile systems of great applicability, natural products being the main targets in organic synthesis. This review will try to survey and update published material on the use of 2-lithio-1,3-dithianes in the synthesis of natural products, paying special attention to the types of reaction in which they are involved. Other reviews regarding the synthetic uses of the 1,3-dithiane group have been reported earlier, covering the literature until 1990, and so in this review we will mainly consider total synthesis involving dithiane chemistry from 1990 up to now.[3,6,15,16]

2. C–C Bond-forming reactions

As mentioned above, 2-lithio-1,3-dithiane derivatives are usually prepared by deprotonation with *n*-BuLi in THF at low temperatures[2] and the anionic species obtained are able to react with many types of electrophiles. For 2-substituted-1,3-dithianes, however, deprotonation should sometimes be performed with *t*-BuLi and the reaction with electrophiles



Scheme 1.



Scheme 2.

should be done in the presence of HMPA or TMEDA, the most important processes probably involving C–C bond formation.

2.1. Reactions with alkyl halides, sulfonates and triflates

Alkylation reactions of 1,3-dithianes have been used in the total synthesis of a wide range of natural products. Primary alkyl iodides or bromides are the alkylating reagents more commonly used. For alkyl chlorides, however, this reaction is synthetically useful only in the case of allylic and benzylic derivatives. Regarding the mechanism of this reaction, Juaristi et al. reported that the reaction between 2-lithio-1,3-dithianes and optically active alkyl iodides was found to proceed with complete inversion of configuration. This result suggested that the S_N2 is the preferred pathway for the reaction with unhindered alkyl halides. In the case of sterically hindered optically active alkyl halides, however, complete racemisation took place, indicating that 2-lithio-1,3-dithianes can act as electron donors in reactions initiated by a single electron transfer (SET), at least with alkyl iodides.[17]

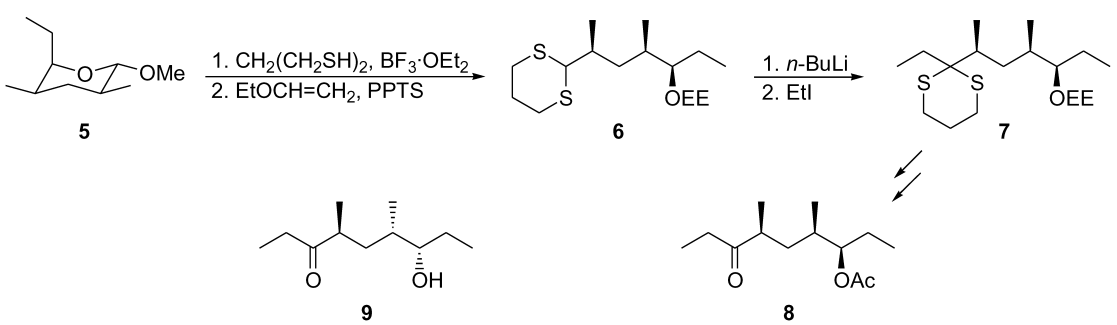
A total and stereoselective synthesis of racemic echinolone (**4**), a juvenile hormone mimic, was reported by Orsini and Pelizzoni.[18] In one step of the synthesis, alkylation of the anion resulting from deprotonation of 2-methyl-1,3-dithiane (**1**) with the dichloride **2** gave the adduct **3** in 75% yield. The reaction takes place at the more reactive allylic position, the last step of the synthesis being the conversion of the dithioacetal derivative to the parent ketone **4** (Scheme 2).

The absolute stereochemistry of serricornin (**9**), the sex pheromone of the cigarette beetle,[19] was determined to be (4*S*,6*S*,7*S*) by Mori et al. by the synthesis of the *O*-acetyl derivative of its (4*S*,6*R*,7*R*)-isomer **8**. The dithiane derivative **6** was prepared from the cyclic acetal **5** (obtained from D-glucose in 13 steps) through a transthioacetalisation and protection of the hydroxy group as the 1-ethoxyethyl acetal. Deprotonation of **6** with *n*-BuLi at temperatures ranging between −40 and −10°C in the presence of TMEDA, followed by reaction with ethyl iodide gave the product **7** in 94% yield, which, by hydrolysis and *O*-acetylation, led to the compound **8** (Scheme 3).[20]

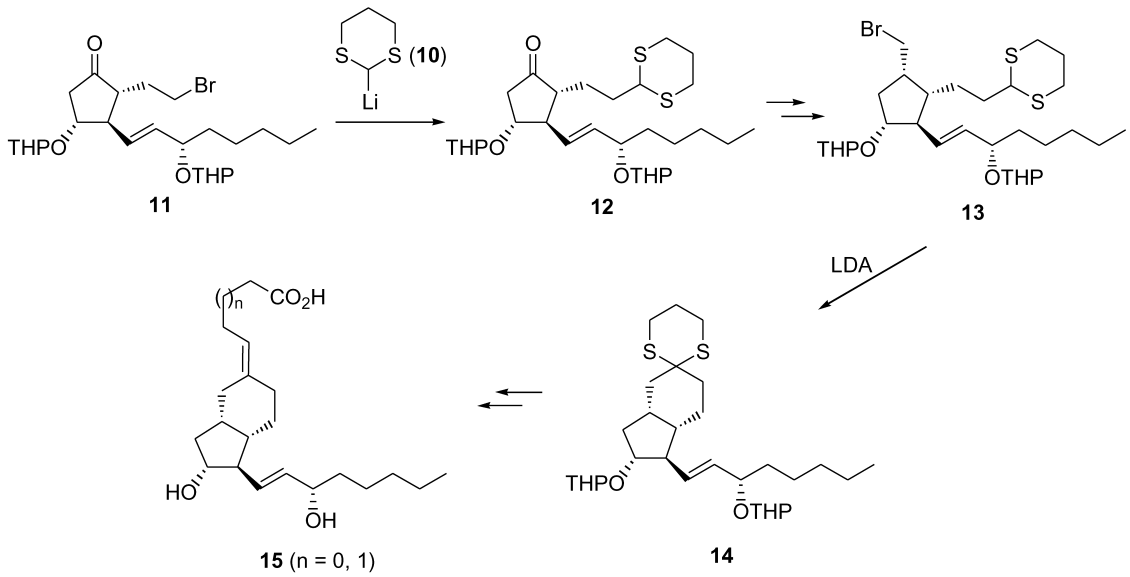
Sih has reported the synthesis of the 6-membered-ring analogues of 6α-carba-PGI_2 (carbacyclin) **15** in order to study the prostacyclin (PGI_2) structure–activity relationships.[21] The key cyclohexanone dithioacetal intermediate **14** was prepared in four steps from the bromide **11**. Alkylation of 2-lithio-1,3-dithiane (**10**, obtained by the deprotonation of 1,3-dithiane) with **11** afforded the dithiane derivative **12** in 95% yield, which was further converted to the bromide **13**. Next, intramolecular based-alkylation using LDA as the base at −20°C led to the thioacetal **14** in quantitative yield. Hydrolysis of the dithioacetal unit with methyl iodide and $CaCO_3$ in $MeCN–H_2O$, followed by Wittig olefination, yielded the compounds **15** as a separable mixture of *Z* and *E* diastereomers in 70% yield (Scheme 4).

Different dioxaspiro compounds **19** were prepared by Seebach et al. through a double sequential alkylation of 1,3-dithiane with the chlorides **16** and the bromoepoxide **17**, respectively, followed by oxirane cleavage with $LiBHEt_3$ or Me_2CuLi, to give the compounds **18** in 60–80% overall yields. Final hydrolysis of the acetals and the dithiane units gave diastereomeric mixtures of the dioxaspiro compounds **19**. Compound **19** (R=Me, *m*=1) is the aggregating pheromone of *Pityogenes chalcographus* (Scheme 5).[22]

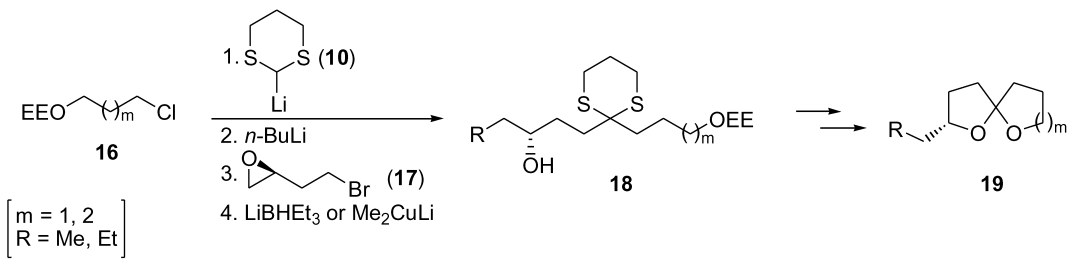
Seebach et al. reported on the total synthesis of the fungal germination self-inhibitor (−)-gloeosporone (**23**). The synthesis began with the coupling reaction of 2-lithio-1,3-dithiane (**10**) and the (*S*)-epoxy bromide **17** to give compound **20** in high yield.[23] The resulting epoxydithiane **20** was allowed to react with lithium butylcyanocuprate yielding, after protection of the hydroxy group, compound **21** in 83% overall yield. After a new deprotonation of the dithiane derivative **21** and reaction with the chiral epoxy bromide **17**, compound **22**, a direct precursor of (−)-gloeosporone (**23**), was obtained in 92% yield (Scheme 6).[24] This synthetic strategy was followed in the synthesis of



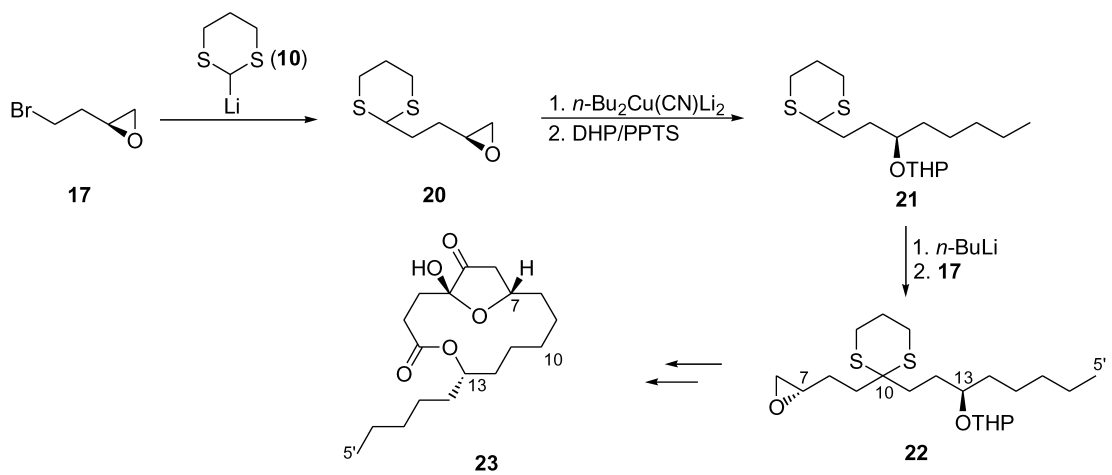
Scheme 3.



Scheme 4.



Scheme 5.

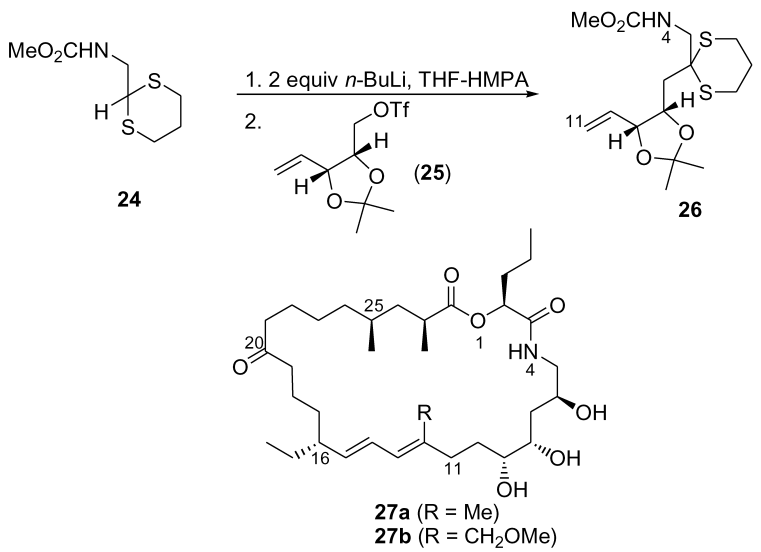


Scheme 6.

(+)-5′-oxagloeosporone, an analogue of (−)-gloeosporone with a 4-hydroxybutyl instead of a pentyl side chain, which shows promising biological activity.[25]

Myxovirescins are macrocyclic lactam–lactones with antibiotic activity isolated from a gliding bacteria.[26] Seebach et al. synthesised myxovirescins M_2 (**27a**),[27] A_1 (**27b**) and A_2 [C(25) epimer of A_1][28] following the same strategy. The N(4)–C(11) fragment of the target molecules was prepared by a coupling reaction between the dianion resulting from double deprotonation of the dithiane **24** (readily available from aminoacetaldehyde diethyl acetal) and the triflate **25** (obtained from D-ribose) to give the vinyl-substituted amide **26** in 72% yield (Scheme 7). The key steps of the synthesis are a Suzuki coupling between an alkylborane and a vinyl bromide, a Julia olefination and a final Yamaguchi macrolactonisation.

Compactin (**33**), an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, was isolated from the



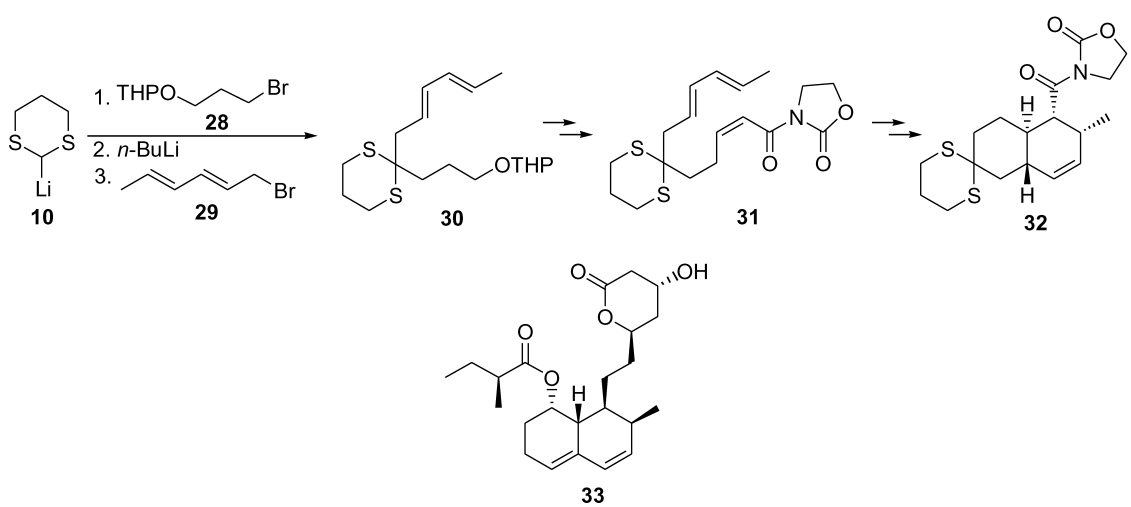
Scheme 7.

culture broth of the fungus *Penicillium brevicompactum* in 1976.[29] Since then, other compactin analogues (mevinic acids) have been isolated. Narasaka et al. reported the enantioselective synthesis of the hydronaphthalene moiety **32** of mevinic acids using an intramolecular Diels–Alder reaction of the dodecatrienoic acid derivative **31** catalysed by a chiral Lewis acid.[30] The assembly of the required carbon chain was based on double sequential alkylation reactions of 1,3-dithiane and, accordingly, the reaction of 2-lithio-1,3-dithiane (**10**) with the 3-bromo-1-propanol derivative **28**, followed by a new deprotonation with *n*-BuLi at −78°C and final reaction with 2,4-hexadienyl bromide **29**, gave compound **30** in 49% overall yield (Scheme 8).

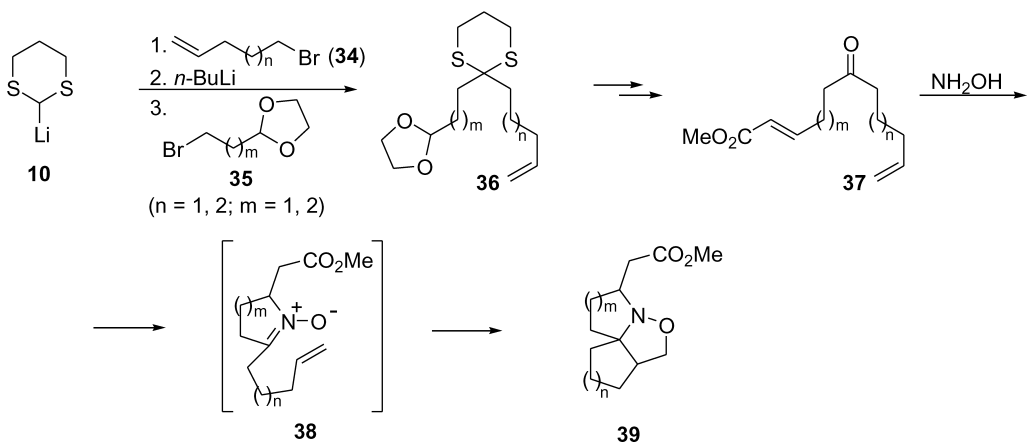
Aldoximes and ketoximes containing two alkenyl moieties in different side chains underwent thermal conversion to cyclic nitrones **38**, which, by stereospecific intramolecular cycloaddition, gave tricyclic spiro- and fused-ring systems **39**. Further synthetic manipulation of these spirocyclic-isoxazolidines affords a wide range of natural products. Thus, double alkylation of 1,3-dithiane [starting from 2-lithio-1,3-dithiane (**10**)] with the alkenyl bromide **34** and the appropriate bromoacetal **35** is achieved in high yields (70–90%) with *n*-BuLi in the presence of HMPA to give **36**. Selective hydrolysis of the acetal, followed by Wittig olefination and hydrolysis of the dithiane group with *N*-chlorosuccinimide and silver nitrate, led to the ketone **37** (Scheme 9).[31]

A formal total synthesis of the potent immunosuppressant FK-506 (**44**), isolated from *Streptomyces tsukubaensis*,[32] has been achieved via a concise construction of the advanced intermediate **43** by Smith et al.[33] A key feature of the convergent strategy includes an efficient coupling of the C(24)–C(34) dithiane **40** (which is deprotonated by *t*-BuLi at −78°C in the presence of HMPA) with the C(10)–C(23) primary iodide **41** to give the compound **42** in 74% yield (Scheme 10). Other approaches to the C(10)–C(34) segment of FK-506 have been reported by the same group using different methodologies.[34]

From the readily available dihydropyran (**45**), *cis*- and *trans*-1,7,9-trioxadispiro[5.1.5.3]hexadecanes **50** have been



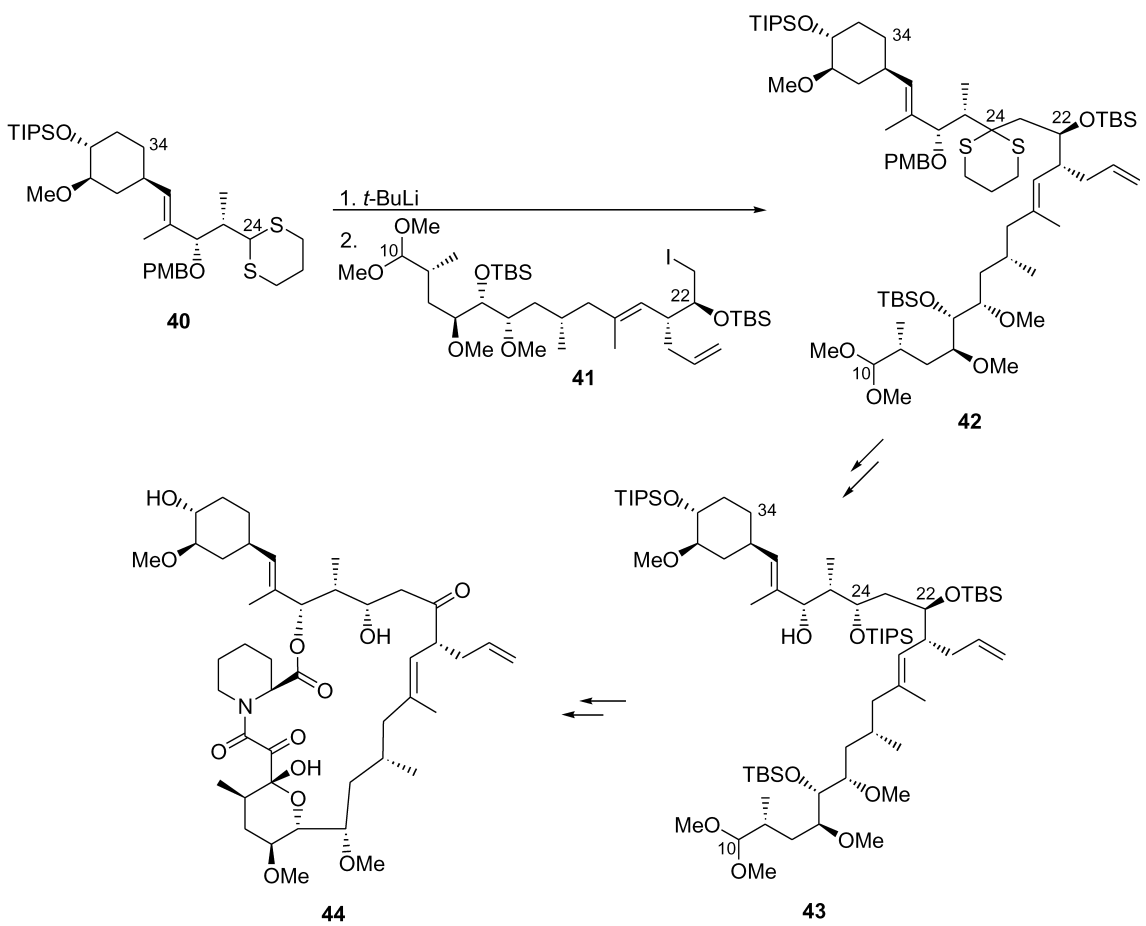
Scheme 8.



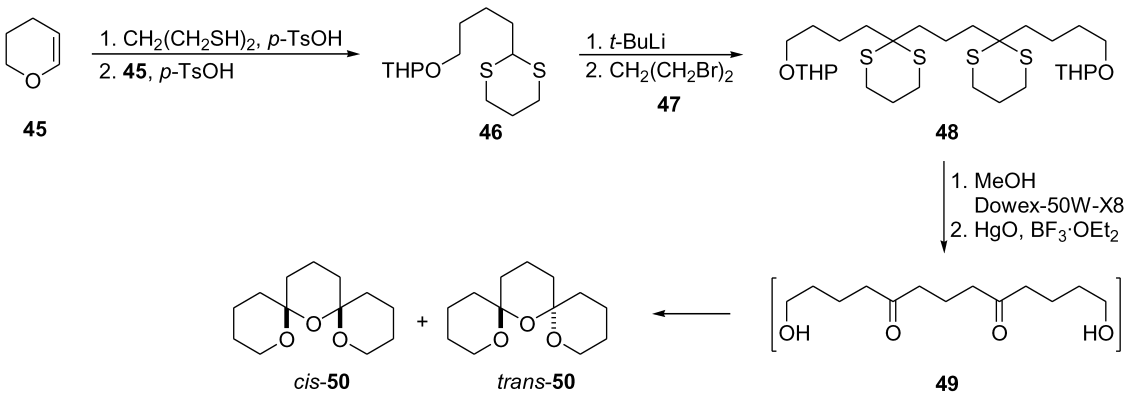
Scheme 9.

prepared by McGarvey and Stepanian in 28% overall yield.[35] Polycyclic spiroacetals are present in many natural products. Treatment of dihydropyran (**45**) with 1,3-propanedithiol in the presence of *p*-TsOH, followed by protection of the resulting hydroxyl group as a dihydropyranyl derivative, afforded the dithiane **46**. Alkylation of the anion resulting from the deprotonation of **46** with *t*-BuLi at −78°C with 1,3-dibromopropane (**47**) as a dielectrophile in the presence of HMPA, led to the intact carbon skeleton **48**. Finally, removal of the THP protecting groups and cleavage of the dithiane moiety led first to diketodiol **49**, which was converted into the trioxadispirodecanes **50** as a mixture of *cis* and *trans* isomers (Scheme 11).

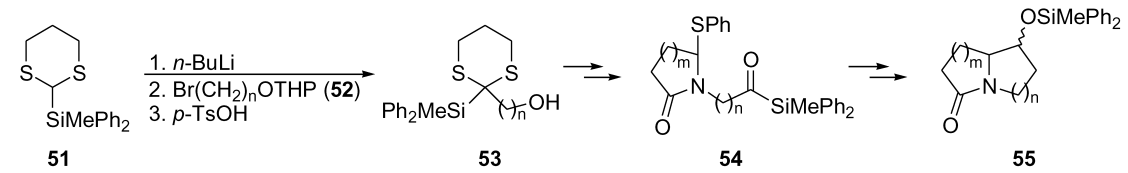
The silyloxy substituted pyrrolizidinones, indolizidinones and quinolizidinones **55** were synthesised from the acylsilanes **54** through an α-acylamino radical cyclisation. The compounds **53**, which are precursors of the acylsilanes **54**, were prepared by alkylation with bromoalkyl tetrahydropyranyl ethers **52** of the anion resulting from deprotonation of the 2-silyl-1,3-dithiane derivative **51** with *n*-BuLi (Scheme 12).[36]



Scheme 10.



Scheme 11.



Scheme 12.

Swinholide A (**59**), a C_2 symmetric 44-membered macrolide ring, is a marine natural product isolated from the sponge *Theonella swinhoei*[37] and displays antifungal activity and cytotoxicity against a number of tumour cells. Nicolaou et al. reported the total synthesis of this natural product in 1996.[38] One of the key reactions of this synthesis is the coupling of the lithio derivative of dithiane **56**,[39] generated at −78°C with *t*-BuLi, with the cyclic sulfate **57**[40] in the presence of HMPA to give the dithiane **58**, a direct precursor of the target compound **59**, in 72% overall yield (Scheme 13).

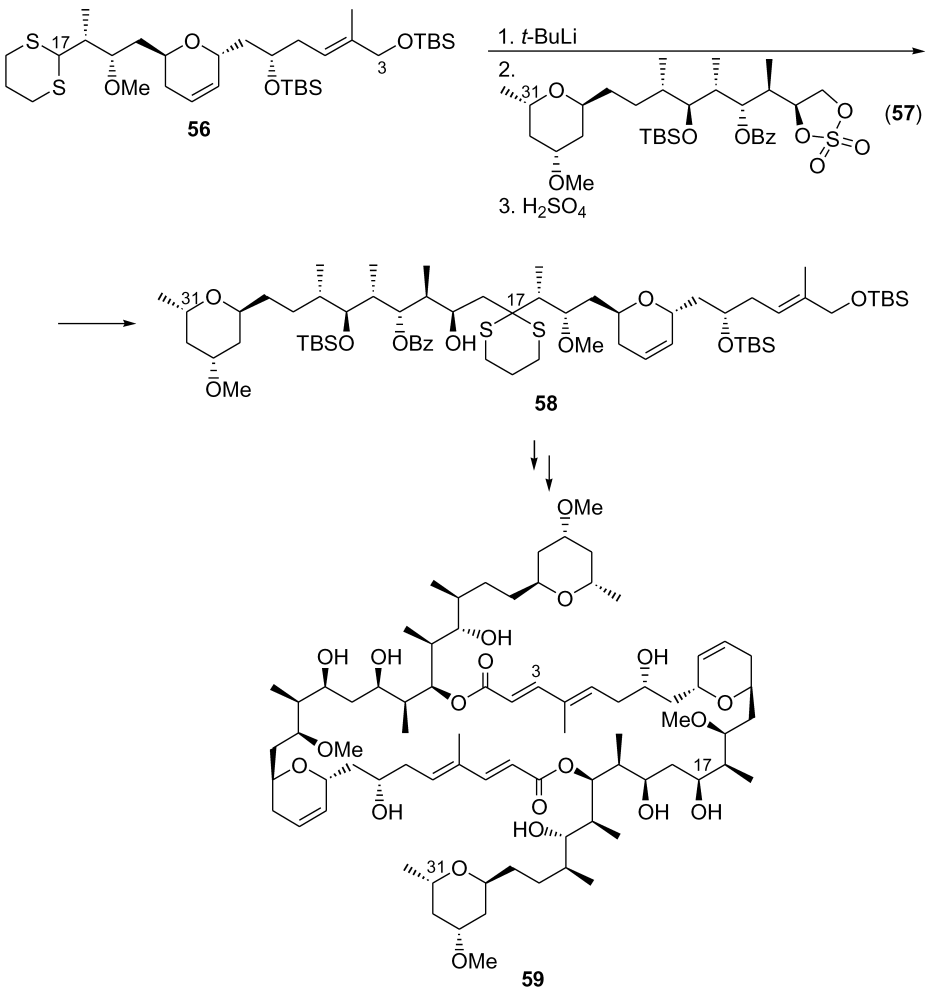
Kodama et al. have reported an efficient enantioselective synthesis of the C(1)–C(9) fragment **63** of octalactin A (**64**) starting from (−)-citronellol (**60**).[41] Octalactin A (**64**) was isolated from a marine bacterium *Streptomyces* sp. and exhibits a potent cytotoxic activity against some tumour cell lines.[42] In one of the steps of this synthesis, alkylation of 2-lithio-1,3-dithiane (**10**) with the alkyl bromide **61** gave the compound **62** in 65% yield (Scheme 14).

Smith et al. reported the synthesis of the naturally occurring immunomodulators (−)-rapamycin (**73**), produced by *Streptomyces hydroscopicus*, and (−)-27-demethoxyrapamycin (**74**).[43] They proposed a highly convergent strategy with common building blocks for both targets. In the final synthetic plan, two fragments were dithiane derivatives. The dithiane acetonide **66** [C(27–32) fragment] was prepared starting from (*R*)-3-hydroxy-2-methylpropionate **65**, the dithiane moiety being introduced by aldehyde protection with 1,3-propanedithiol. The synthesis of the subunit **68** [C(22–26) fragment] began with the enzymatic desymmetrisation of the *meso*-diester **67**, the dithiane moiety also being introduced by thioacetalisation of an aldehyde. Deprotonation of the compound **66** with *t*-BuLi at −78°C in the presence of HMPA (10% in THF), followed by reaction with the iodide **69** [C(33–42) fragment], gave the compound **70** in 78% yield.[44] Further transformations of compound **70** into the iodide **71** and reaction with the organolithium resulting from deprotonation of compound **68**, under the same reaction conditions used for the dithiane **66**, led to compound **72** in 42% yield (Scheme 15).

Perhydrohistrionicotoxin (**79**) is a non-natural alkaloid with a structure similar to that of (−)-histrionicotoxin, a spirocyclic alkaloid isolated from the poison dart frog *Dendrobates histrionicus*.[45] Both compounds exhibit important neurotoxic properties. Tanner and Hagberg reported a convergent enantioselective total synthesis of the compound **79**.[46] In one of the steps of this synthesis, compound **78** is prepared via an efficient one-pot three-component coupling of 2,2-bis[tri-(*n*-butyl)stannyl]dithiane (**75**) and the chiral iodides **76** and **77**. Tin/lithium transmetallation at the 2-position of the dithiane is a much faster process than the direct metallation and occurs within minutes at low temperatures, and so by sequential transmetallation it is possible to effectively introduce two electrophiles at that position.[47] Sequential treatment of compound **75** with *n*-BuLi, compound **76**, *n*-BuLi and, finally, compound **77** afforded the open-chain skeleton **78** of the target compound in 81% isolated yield (Scheme 16).

The first total synthesis of pinnatoxin A (**83**), a macrocycle containing a spiro-linked cyclic imine moiety isolated from shellfish *Pinna muricata*, was developed by Kishi et al. in 1998,[48] just 3 years after its isolation by Uemura et al.[49] Double sequential dithiane alkylation with the iodides **80** and **81** takes place in 92 and 71% yields, respectively, to afford the corresponding C(6)–C(32) fragment **82** (Scheme 17).

In the synthesis of the C(10)–C(31) (BCDEF rings)

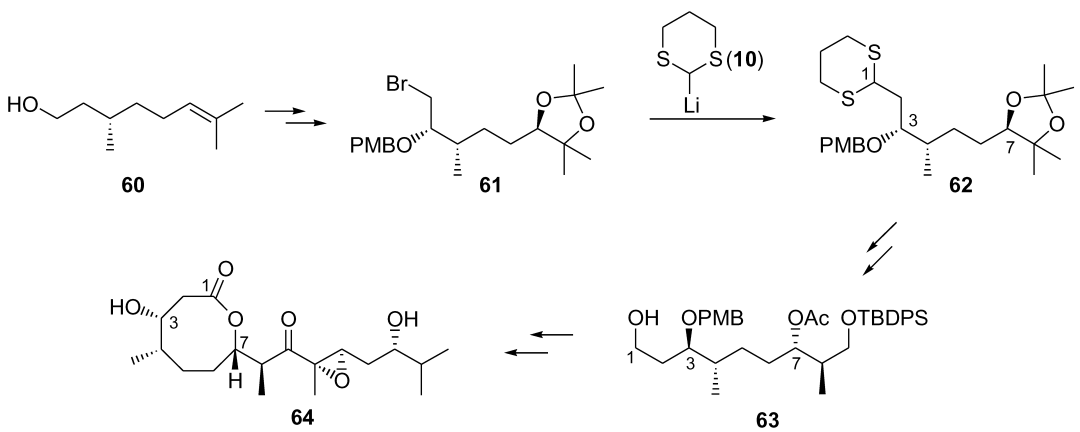


Scheme 13.

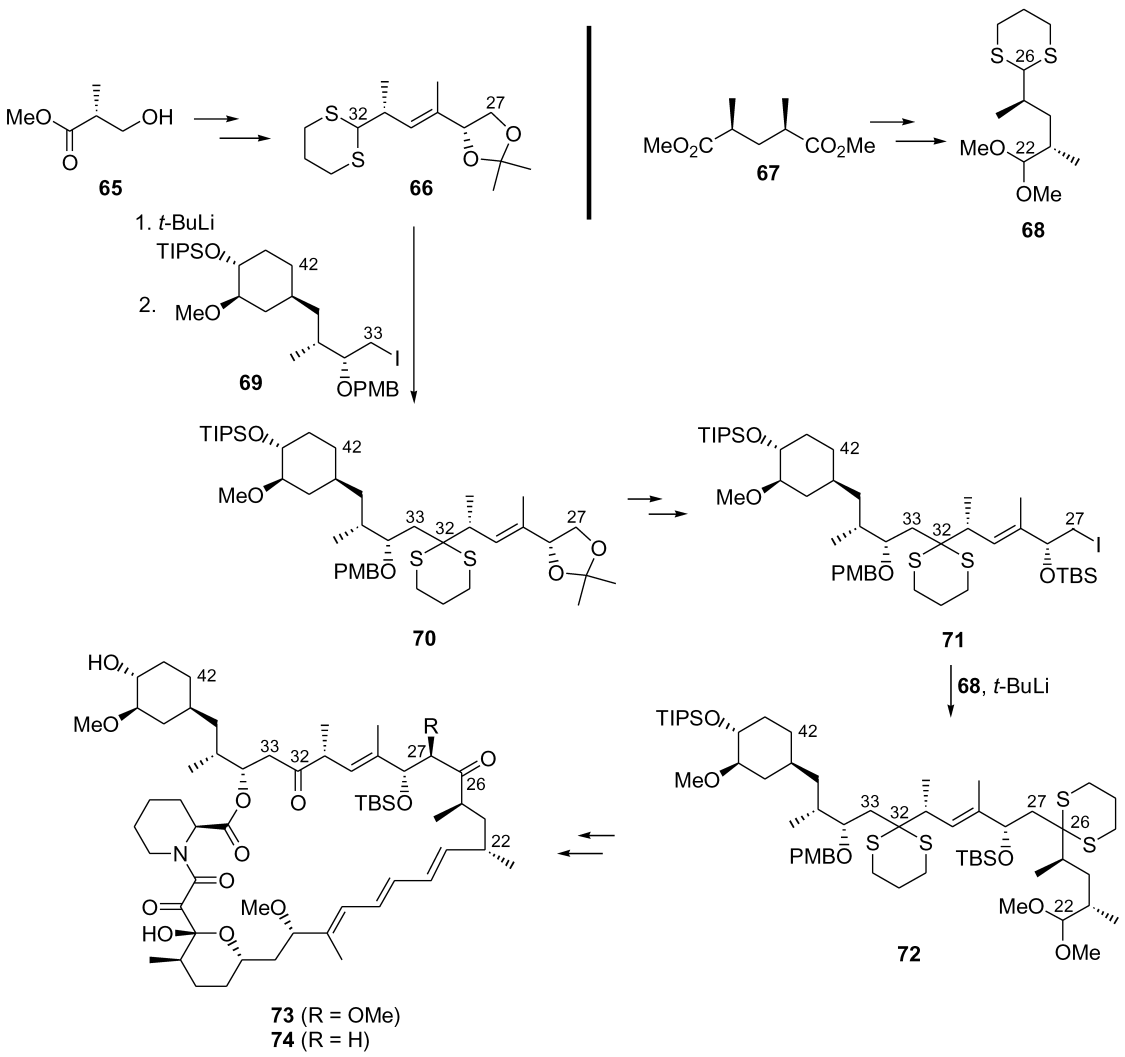
fragment **86** of pinnatoxin A (**83**), developed by Hashimoto et al., the C(15)–C(23) unit was prepared by lithiation of the dithiane **46**[35] with *n*-BuLi in THF–HMPA (10/1) at −78°C, followed by alkylation with the iodide **84**, to give the compound **85** in 95% yield (Scheme 18).[50]

The eight-carbon sugar, 3-deoxy-D-manno-2-octulosic acid (KDO),[51] is an integral component of lipopolysaccharides isolated from the cell walls of Gram-negative bacteria. The reaction of the anion resulting from the deprotonation of the benzyl glyoxylate dithioacetal **87** (prepared by transacetalisation of the corresponding diethyl acetal) with the cyclic sulfate **88**[52] gave after acidic workup the dithiane derivative **89** in 51% yield. Unmasking the dithioacetal group in **89** with NBS, led to the compound **90** in 74% yield as a mixture of anomers, which are KDO derivatives suitable for oligosaccharide synthesis (Scheme 19).[53]

Morimoto et al. have reported a total synthesis of (−)-stenine (**95**), an alkaloid isolated from the roots and



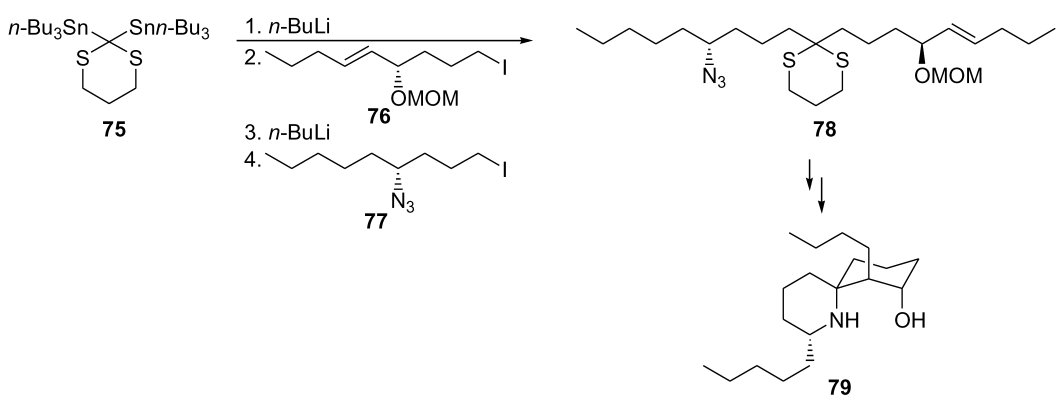
Scheme 14.



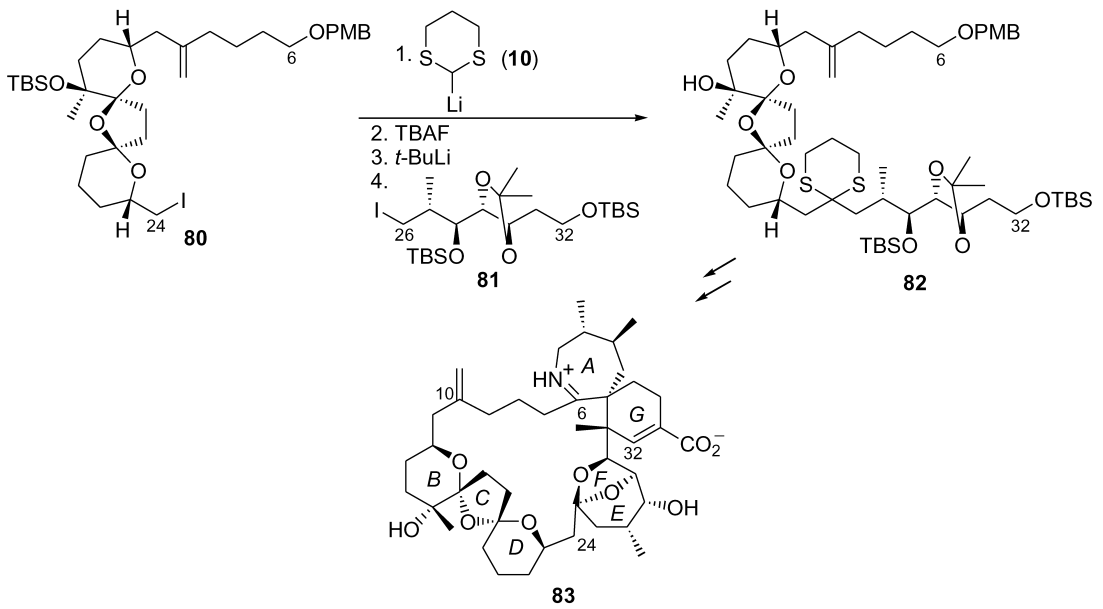
Scheme 15.

rhizomes of stemonaceous plants. In its convergent synthesis, alkylation of the anion of the dithiane **91** (prepared from 4-hydroxybutanal) with the dienyl chloride **92** gave the compound **93** in high yield. This compound was converted into the triene **94** by coupling its aldehyde derivative with a chiral phosphonate. The key reaction of this synthesis is the intramolecular asymmetric Diels–Alder reaction of **94**, which proceeded with a high stereoselectivity, forming the B ring of the target molecule with the correct configuration at the formed stereogenic centers (Scheme 20).[54] The dithiane unit is removed by treatment with *N*-chlorosuccinimide and silver nitrate to generate the corresponding carbonyl group in a later step.

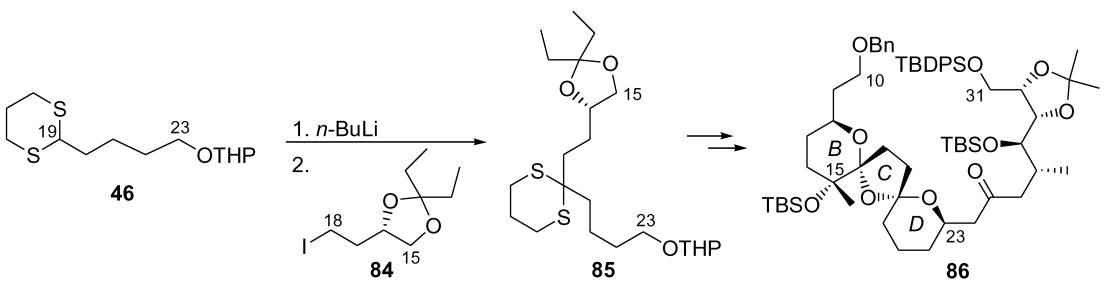
Starting from the bicyclic ketone **96**, the C(1)–C(16) segment **99** of bryostatin 1 (**100**), a bis-spiroacetal macrolide that displays extraordinary antitumour activities against a wide variety of human cancer cell lines, has been



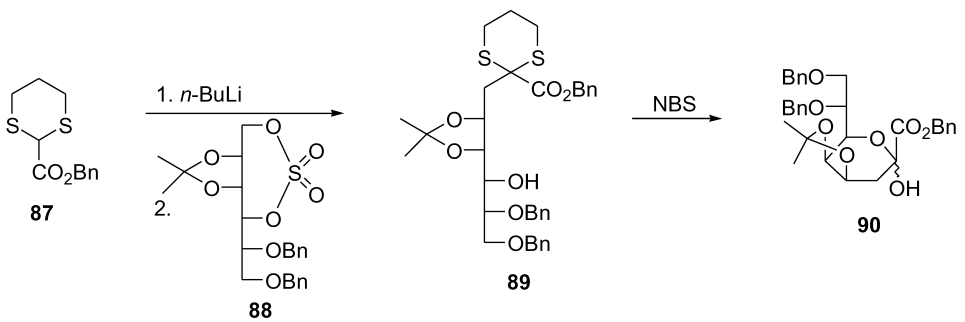
Scheme 16.



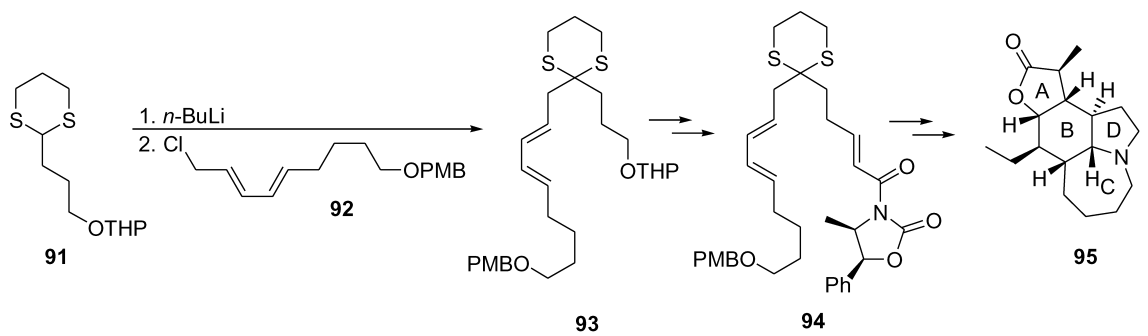
Scheme 17.



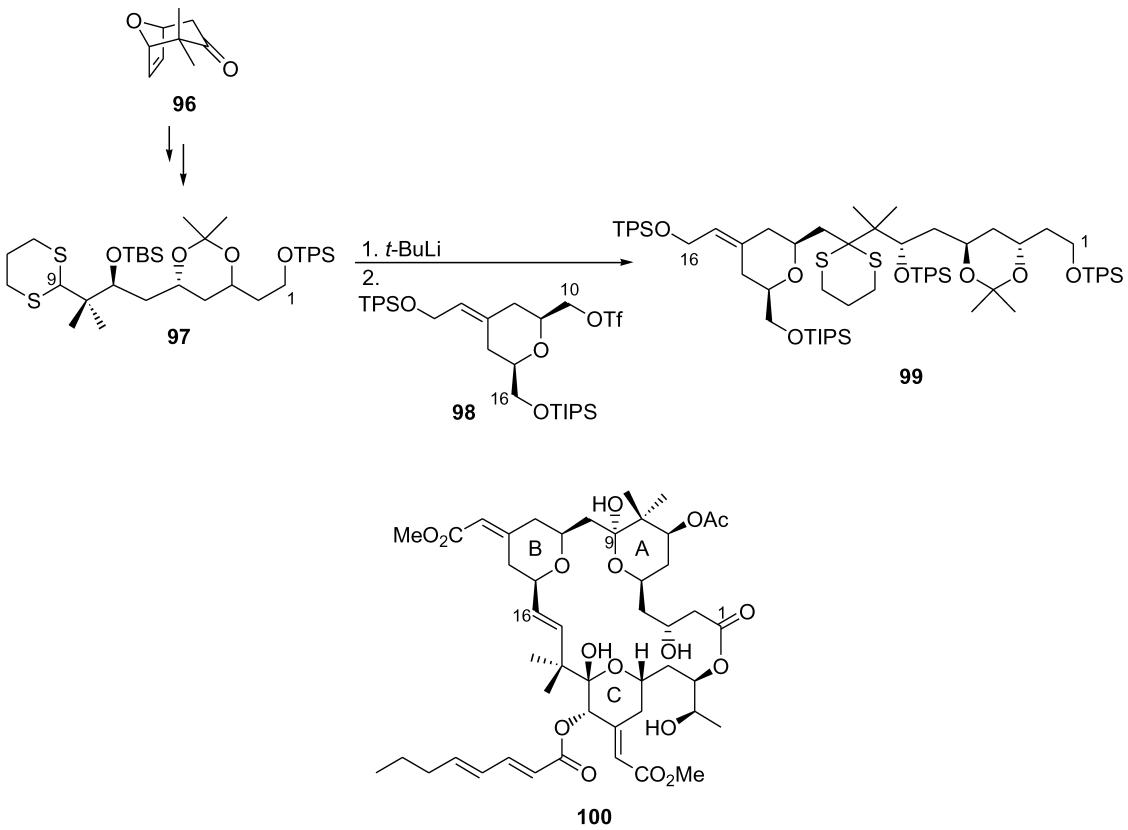
Scheme 18.



Scheme 19.



Scheme 20.

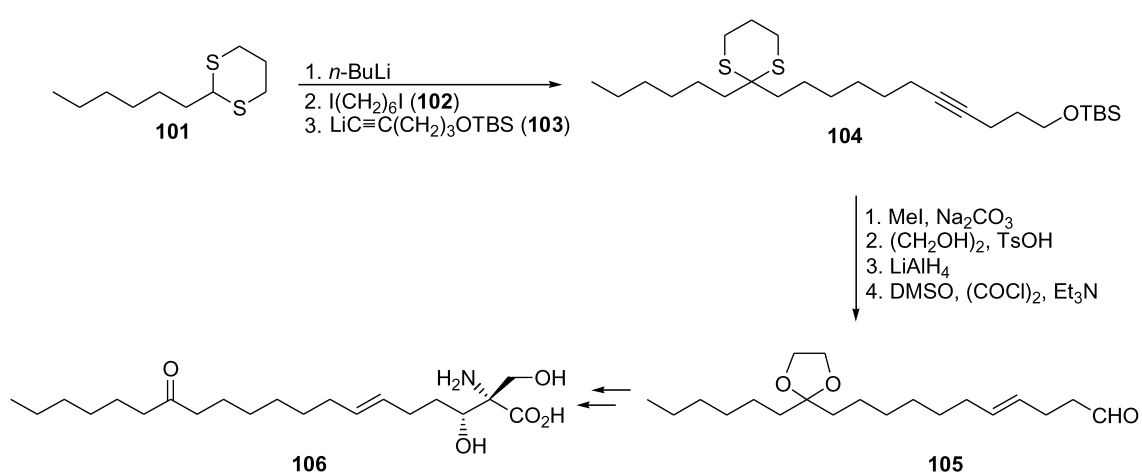


Scheme 21.

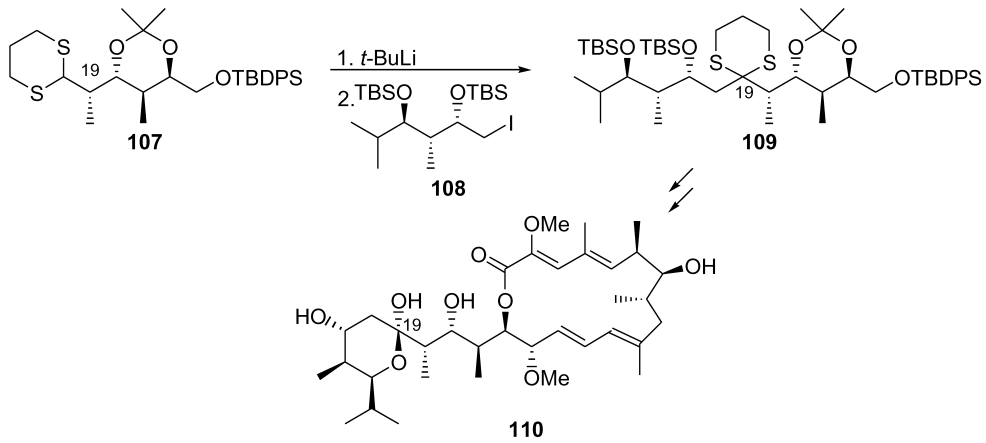
synthesised by Hoffmann et al.[55] Lithiation of the sterically encumbered dithiane **97**, prepared in 14 steps from **96** (27% overall yield),[56] with *t*-BuLi in the presence of 3 equiv. of HMPA at −78°C, followed by addition of the triflate **98**, afforded the compound **99** in 63% yield (Scheme 21).

Hatakeyama et al. have recently accomplished the enantiocontrolled synthesis of (−)-mycestericin E (**106**),[57] a potent immunosuppressant isolated from the culture broth of the fungus *Mycelia sterilia* ATCC 20349.[58] The required long-chain compound **104** was prepared from the dithiane **101**, 1,6-diiodohexane **102** and the pentynol derivative **103**, sequential substitution of both terminal carbon–iodine bonds of 1,6-diiodohexane (**102**) with lithiated **101** and **103** giving the compound **104** in 70% yield. Hydrolysis of the dithiane unit of compound **104**, followed by acetalisation, stereoselective reduction of the triple bond and Swern oxidation, led to the compound **105**, which is a precursor of (−)-mycestericin E (**106**) in 78% overall yield (Scheme 22).

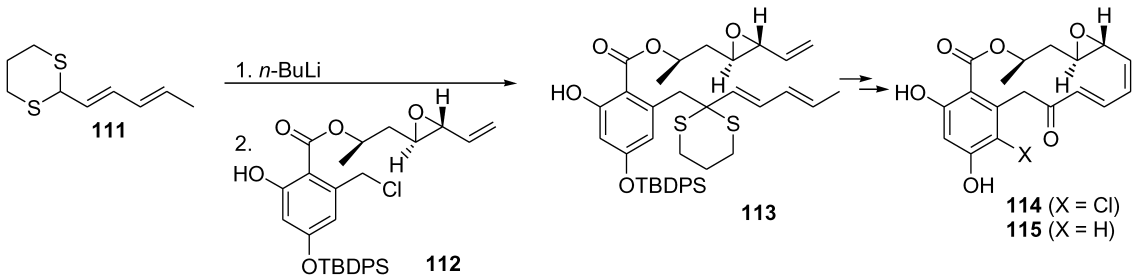
The macrolide bafilomycin A_1 (**110**) was isolated from *Streptomyces griseus* sp. sulfuru and exhibits inhibitory activity against Gram-positive bacteria and fungi.[59] The convergent synthesis reported by Hanessian et al. includes the coupling of the lithium derivative of the dithiane **107** and the alkyl iodide **108** to give the compound **109** in 84% yield. The dithiane unit is removed from C(19) at the end of the synthesis to generate the spiroacetal moiety in **110** by



Scheme 22.



Scheme 23.



Scheme 24.

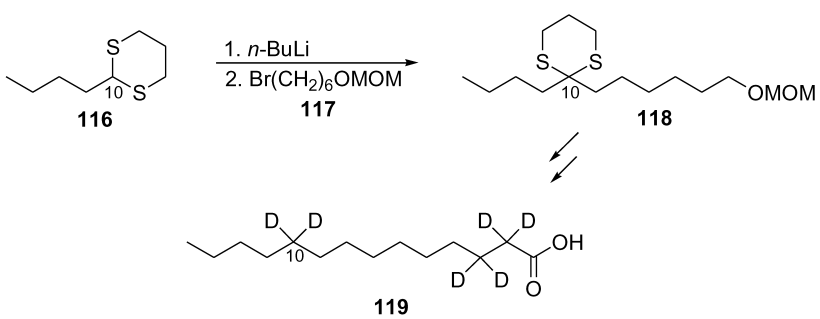
treatment with $HgCl_2$ and $CaCO_3$ in a mixture of acetonitrile and water (Scheme 23).[60]

Radicicol (**114**) and monocillin (**115**)[61,62] are resorcylic macrolides isolated from *Monocillium nordini* and exhibit a variety of antifungal and antibiotic properties. In their recent total synthesis provided by Danishefsky et al., alkylation of the dithiane derivative **111** with the benzylic chloride **112** gives the compound **113** in 50% yield. This intermediate plays an important role in the construction of the skeleton of the target molecule by a final ring-closing metathesis, providing the macrolide (Scheme 24).[63]

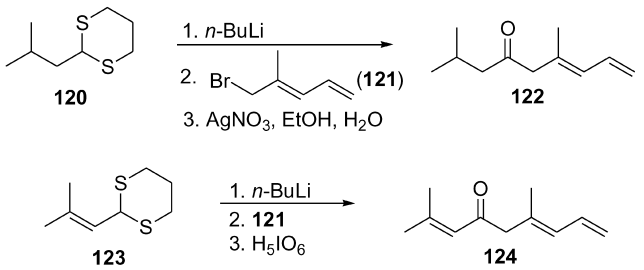
Fabriàs et al. prepared 2,2,3,3,10,10-hexadeuteriotetradecanoic acid (**119**) in order to investigate the mechanism of the enzymatic transformations of tetradecanoic acids. The synthesis of the target molecule started with the coupling reaction of the bromide **117** with the anion of the dithiane **116** (prepared from the corresponding aldehyde) to give the compound **118** in 81% yield. Introduction of the deuterium label at the 10-position was carried out in three steps: hydrolysis of the dithiane unit and reduction of the resulting ketone with $NaBD_4$, followed by tosylation of the formed alcohol and final treatment with $LiAlD_4$. Further reactions led to the desired product **119** (Scheme 25).[64]

The homoterpenoids **122** and **124** are volatiles emitted by elm plants and may be involved in attracting a parasitoid wasp of the elm leaf beetle. These compounds have been prepared by Schulz and Wegener first by alkylation of the deprotonated dithianes **120** and **123** with (*E*)-5-bromo-4-methylpenta-1,3-diene (**121**), followed by removal of the dithiane unit. The dithianes **120** and **123** were prepared from the corresponding aldehydes (Scheme 26).[65]

Pinellic acid (**128**) was isolated from a medicinal plant *Pinelliae tuber* and shows a potent adjuvant activity,[66] its absolute configuration of pinellic acid being assigned by comparison of the spectral data of the natural product with those of the synthetic compound. The synthesis of the C(18)

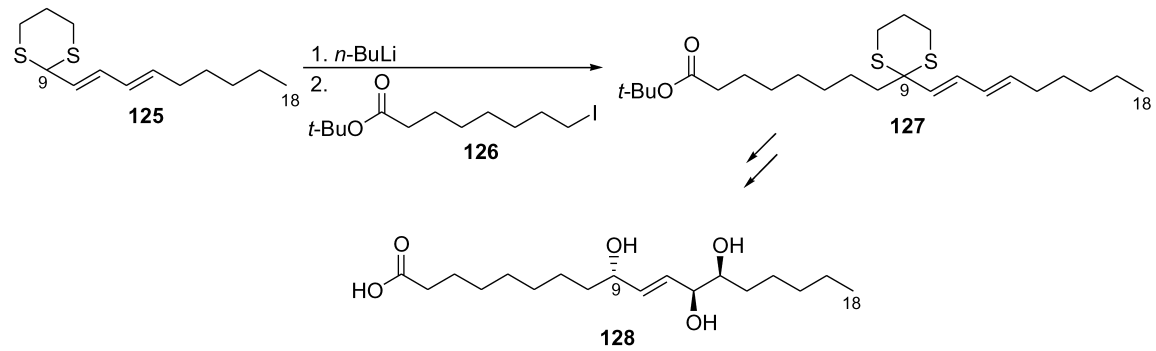


Scheme 25.



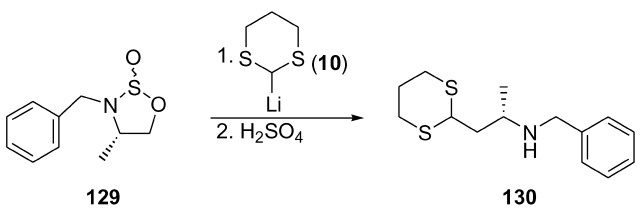
Scheme 26.

skeleton started with the coupling of the lithiated **125** (derived from the corresponding commercially available aldehyde) and the iodide **126** to give the diene **127** in 85% yield. Asymmetric dihydroxylation and selective functional group transformations led to the target molecule **128** (Scheme 27).[67]



Scheme 27.

The cyclic sulfamidate **129** undergoes ring-opening monosubstitution reactions with stabilised organolithium compounds. Using 2-lithio-1,3-dithiane (**10**) as the nucleophile, the corresponding amine dithiane **130** was obtained in 64% yield after acid–base workup (Scheme 28).[68]



Scheme 28.

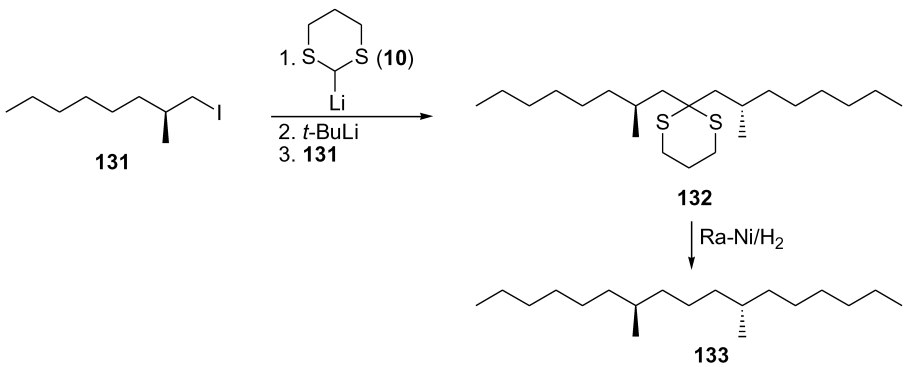
A double alkylation of 1,3-dithiane with (*S*)-2-methyl-1-iodooctane (**131**) led to the C_2-symmetrical dithiane **132** in 84% overall yield. Reduction of the dithiane derivative **132** with Raney nickel gave (*S*,*S*)-7,11-dimethylheptadecane (**133**),[69] a component of the female sex pheromone of the spring hemlock and the pitch pine looper moths.[70] The starting iodide **131** was prepared by Enders and Schüsseler by an α-alkylation employing the SAMP/RAMP hydrazone method with a high asymmetric induction (Scheme 29).[69]

Burke et al. reported the synthesis of the bicyclic acetal **139**, a precursor of several polyfunctionalised 1,7-dioxaspiro[5.5]undecane spiroacetal systems via an acid-catalysed rearrangement.[71] In one of the steps of the synthesis of the bicyclic acetal **139**, the dithiane **134** (prepared from the corresponding aldehyde) was alkylated with 1-bromo-3-chloropropane (**135**) to give the compound **136** in 74% yield. Deprotection of the ketone, acetalisation with the C_2 symmetric diene diol **137**, followed by dehydrochlorination, led to the acetal **138** in 30% yield. Desymmetrisation of the compound **138** by a ring-closing metathesis with Grubb's catalyst, afforded the compound **139** in 97% yield (Scheme 30).

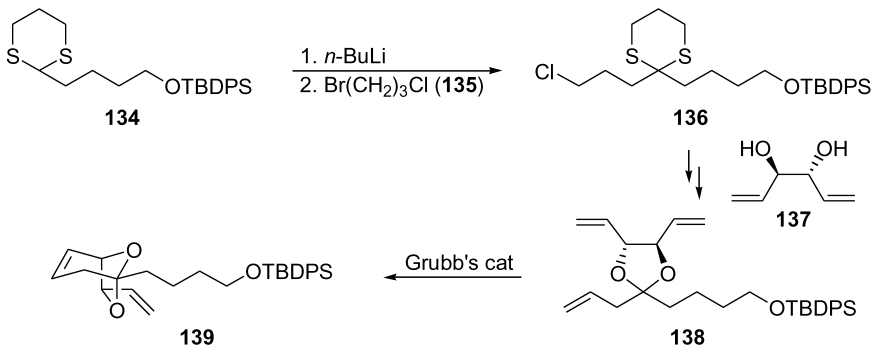
A convergent synthesis of the cyclic core of the marine macrolide leucascandrolide A (**144**) has been accomplished by Wipf and Reeves. In one step of the synthesis, the 1,3-dithiane derivative **141** is prepared in 64% yield through a transacetalisation process starting from the acetal **140**. Alkylation of the organolithium resulting from deprotonation of **141** with *t*-BuLi with the alkyl iodide **142**, followed by oxidative deprotection of the thioacetal moiety, gave the ketone **143** in 61% yield, which is a direct precursor of the cyclic core of leucascandrolide A (Scheme 31).[72]

Cushman et al. synthesised a series of 6-carboxyalkyl and 6-phosphonoxyalkyl derivatives of 7-oxo-8-D-ribityllumazine as inhibitors of both *Escherichia coli* riboflavin and *Bacillus subtilis* lumazine synthases.[73] Alkylation of the anion of ethyl glyoxylate dithioacetal **145** with ethyl 5-bromopentanoate (**146**) gave the diester dithioacetal **147**, which, after deprotection, led to the ketone diester **148**. Monoalkylation of the anion of **145** with 1,4-dibromobutane (**149**) gave the compound **150**. Displacement of the bromide with silver dibenzyl phosphate, hydrolysis and final debenzylation yielded the compound **151**. Reaction of the compounds **148** and **151** with the lumazine synthase substrate **152** gave the substituted lumazines **153** and **154**, respectively (Scheme 32).[73]

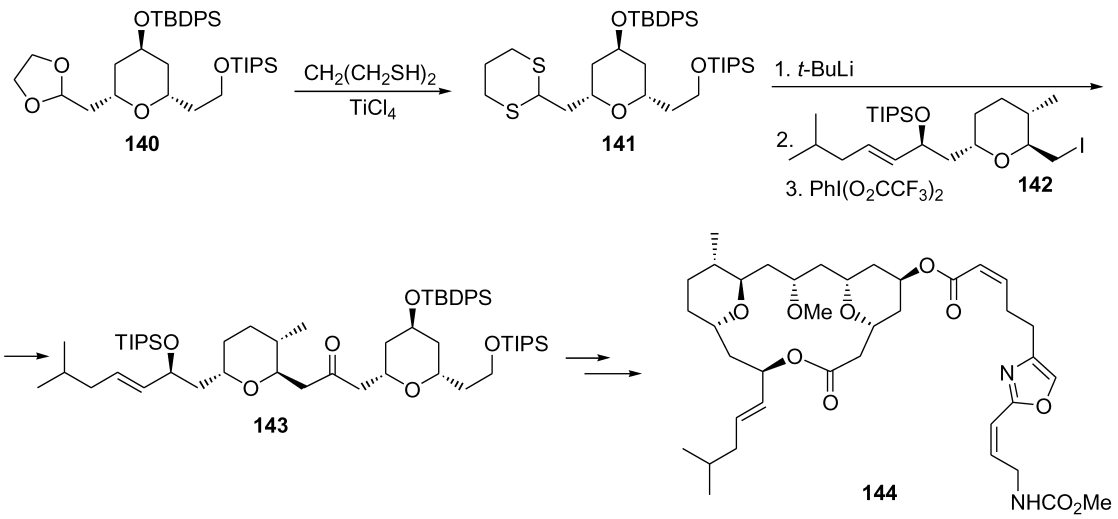
The alkaloid manzamine A (**160**) contains a complex pentacyclic ring system. It was first isolated from the marine sponge of the genus *Haliclona*[74] and has antitumour and antimalarial activity. In the synthesis of the ABC ring system of manzamine proposed by Coldham et al., the condensation of a dithiane aldehyde **157** and sarcosine ethyl ester hydrochloride salt gives an intermediate azomethine ylide **158**, which undergoes an intramolecular cycloaddition reaction to set up two new rings and three new chiral centers stereoselectively, giving the compound **159** in 50% yield. The starting dithiane **87** was deprotonated with *n*-BuLi and alkylated with the iodide **155**, giving the compound **156** in



Scheme 29.



Scheme 30.



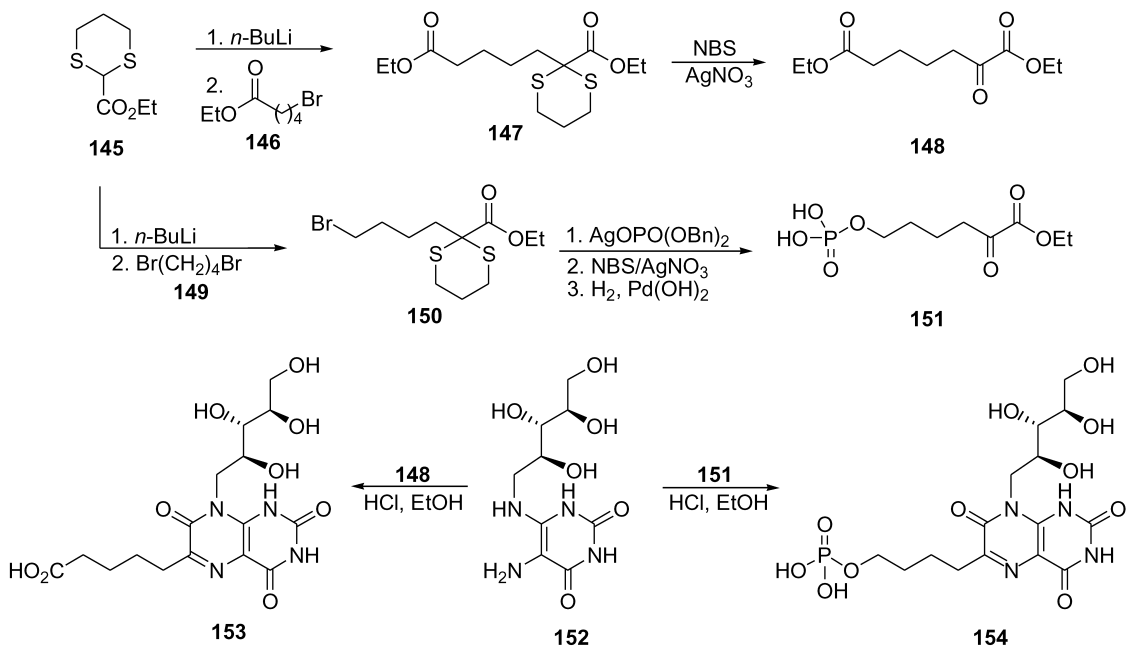
Scheme 31.

96% yield. The dithiane aldehyde **157** was prepared from **156** in two steps in 80% yield (Scheme 33).[75]

Smith et al. have recently reported the synthesis of 13-deoxytedanolide (**164**), which was isolated from a sea sponge[76] and shows significant cytotoxic activity. In their synthetic strategy, two fragments were combined using a dithiane-based methodology, deprotonation of the compound **161**[77] and reaction with the iodide **162** leading to the compound **163** in 75% yield. Further transformations, which include Evans–Tishchenko oxidation and Yamaguchi macrocyclisation, led to the compound **164** (Scheme 34).[78]

2.2. Reactions with epoxides

Epoxides react with nucleophiles at the less sterically hindered carbon of the heterocycle. Since epoxides are easily available in enantiomerically pure form, the reaction with nucleophiles would yield chiral alcohols. Especially interesting is the reaction of epoxides with 2-lithio-1,3-dithiane derivatives, because enantiomerically pure masked β-hydroxycarbonyl compounds are prepared in a single step, this strategy having been extensively used in natural product synthesis. Recently, Smith et al. have reported the highly chemoselective addition of this kind of lithium

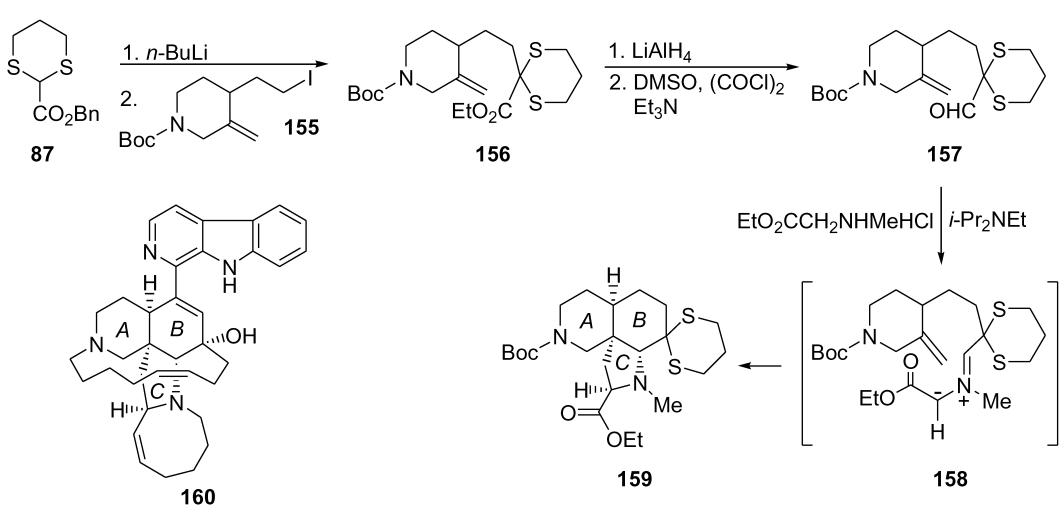


Scheme 32.

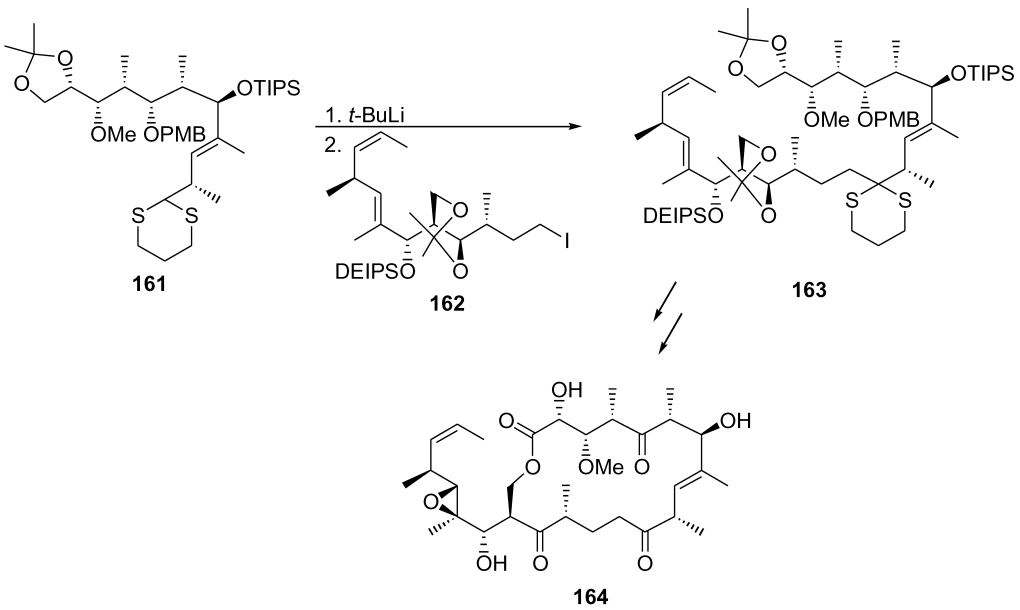
dithiane anions to vinyl epoxides by exploiting the steric nature of the dithiane.[79] Meanwhile, the ring-opening reaction of N-activated aziridines with anions derived from 1,3-dithianes has been studied by Sweeney et al.,[80] the reaction also proceeding regioselectively at the less substituted carbon.

Williams et al. reported a total synthesis of (−)-hennoxazole A (**168**), which was isolated from the marine sponge *Polyfibrospongia* sp.[81] and has been found to be active against herpes simplex virus type 1, also displaying peripheral analgesic activity. In the convergent synthetic strategy,[82] the C(1)–C(5) unit **166** was prepared via alkylation of 2-lithio-2-methyl-1,3-dithiane with (*S*)-epichlorohydrin (**165**), affording inversion of the configuration at C(4).[83] The dithiane unit was removed in a further step through a transacetalisation process by treatment with bis(trifluoroacetoxy)iodobenzene in the presence of 2,2-dimethyl-1,3-propanediol to give the intermediate **167** (Scheme 35).

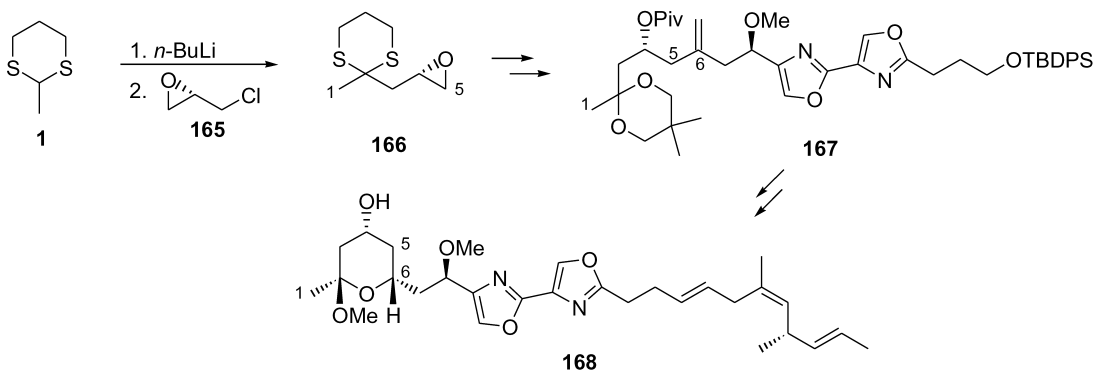
Kishi et al. proposed a convergent synthesis of the strong cancer promoter aplysiatoxin (**174**), isolated from the digestive gland of the sea hare *Stylocheilus longicauda*,[84] and debromoaplysiatoxin (**175**). Coupling of two of the fragments proposed in the synthetic strategy was achieved by nucleophilic addition of the anion resulting from deprotonation of the dithiane derivative **169** (prepared by dithioacetalisation of the corresponding aldehyde) to the chiral epoxide **170** and the alcohol derivative **171**, containing the C(3)–C(26) unit of the target molecules, was obtained in almost quantitative yield (Scheme 36).[85] A formal total synthesis of aplysiatoxin (**174**) was accomplished later by Katsuki et al. by assembling a different fragment to that proposed in the first approach, the anion resulting from deprotonation of the dithiane **172** (prepared



Scheme 33.



Scheme 34.



Scheme 35.

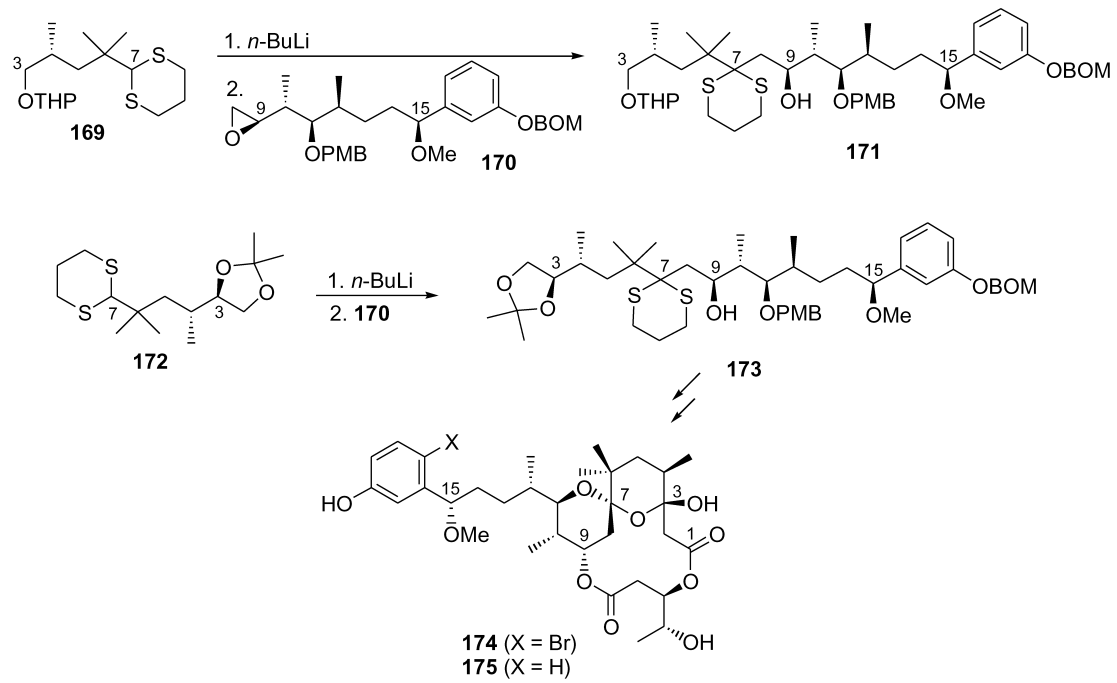
from the corresponding aldehyde) being reacted with the chiral epoxide **170** to give compound **173**, a precursor of aplysiatoxin, in 64% yield (Scheme 36).[86]

One of the fragments of the synthetic strategy proposed by Katsuki et al. for the synthesis of aplysiatoxin (**174**, Scheme 36) is the acid **178**, which was prepared in a two-step process comprising nucleophilic ring opening of the epoxide **176** (obtained from crotyl alcohol by titanium-mediated asymmetric epoxidation) with intermediate **10** to give the alcohol **177** in 90% yield and transformation of the compound **177** into the desired carboxylic acid **178** by selective protection of the hydroxy group, removal of the dithioacetal moiety and final oxidation of the resulting aldehyde, in 55% overall yield (Scheme 37).[87]

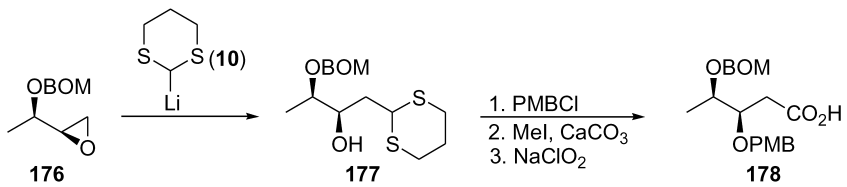
One of the key steps of the synthesis of pironetin (**183**), a natural product isolated from the fermentation broths of *Streptomyces* which shows plant growth regulatory activity,[88,89] reported by Chida et al. involves the alkylation of the anion of the dithiane derivative **179** (obtained by thioacetalisation of the corresponding aldehyde) with the chiral epoxide **180** to give the compound **181** in 56% yield. Deprotection of the dithioacetal moiety and reduction of the resulting ketone led to the *anti*-diol **182** as the major product, in 65% yield. Finally, removal of the *O*-silyl protecting group and MnO_2 oxidation afforded pironetin in 72% overall yield (Scheme 38).[90]

A general strategy for the transformation of D-glucose into (*R*)-2-[(1,3-dithian-2-yl)methyl]-4-hydroxycyclopent-2-enone (**186**) was described by Das and Achab.[91] In this strategy, nucleophilic addition of 2-lithio-1,3-dithiane (**10**) to the epoxide **184**, easily prepared from D-glucose,[92] gave the compound **185** in 93% yield. Further transformations led to the target molecule **186**, a potential chiral synthon for prostaglandin E_2 (**187**) (Scheme 39).

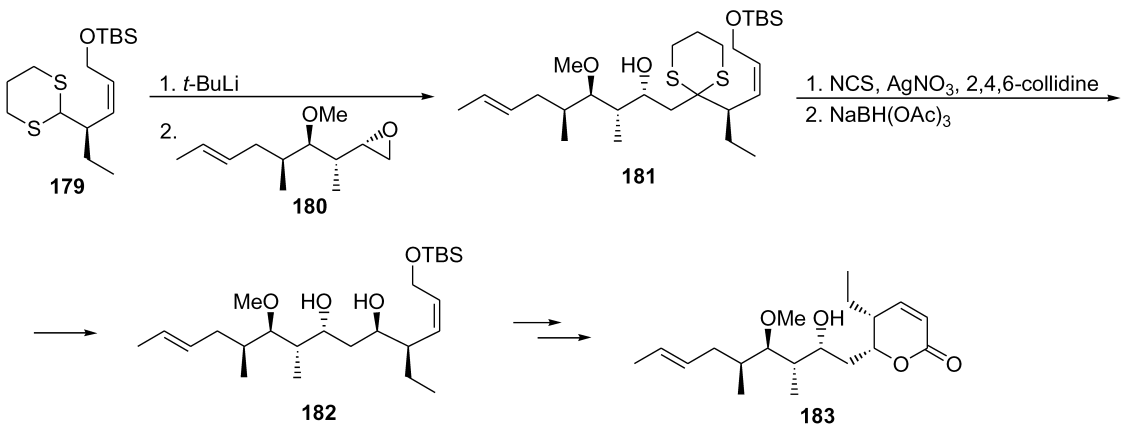
Benefice-Malouet et al. reported on the synthesis of methyl 3-deoxy-3-*C*-formyl-α-D-arabinopentofuranosides (**191**) and 2-deoxy-2-*C*-formyl-α-D-xylopentofuranosides (**192**) by the reaction of 2-lithio-1,3-dithiane (**10**) with methyl 2,3-anhydro-α-D-lyxofuranosides (**188**) at both positions of the epoxide ring, the process giving mainly attack at C(3). The ratio of the adducts **189** and **190** is affected by the nature of the 5-substituent. Hydrolysis of the dithiane unit



Scheme 36.



Scheme 37.

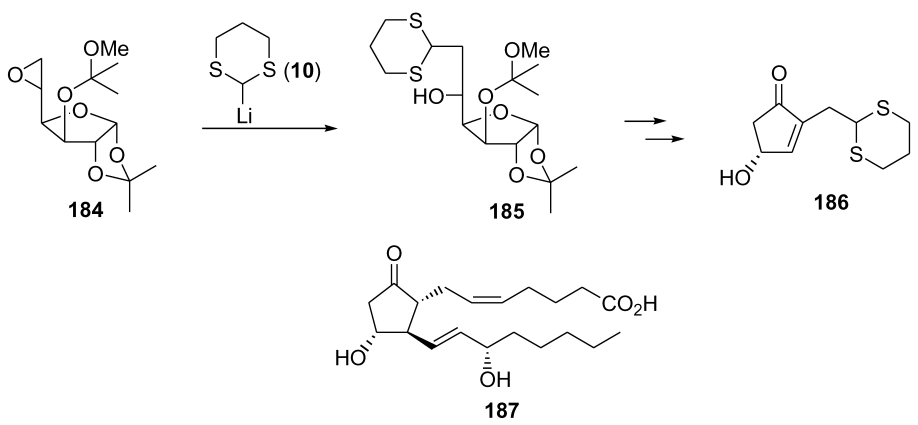


Scheme 38.

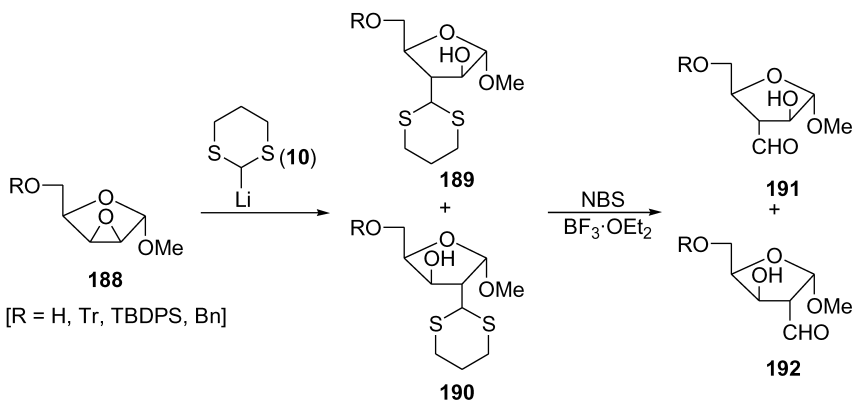
gave the carbohydrate derivatives **191** and **192** (Scheme 40).[93]

Vandewalle et al. studied the applications of the enzymatically prepared homochiral cyclohexane building block **193** to the synthesis of both the unnatural shikimic acid derivative **197** and pseudo-α-D-mannopyranose (**198**). The epoxide **195** was prepared in enantiomerically pure form from the compound **194** (a derivative of the compound **193**) by epoxidation with MCPBA in 83% yield. Introduction of the functionalised one-carbon unit was carried out by the addition of 2-lithio-1,3-dithiane (**10**) to give the compound **196** as the sole product in 91% yield. Hydrolysis of the dithioacetal with HgO in the presence of $BF_3{\cdot}OEt_2$ in THF–H_2O, followed by further transformations, led to the compounds **197** and **198** (Scheme 41).[94]

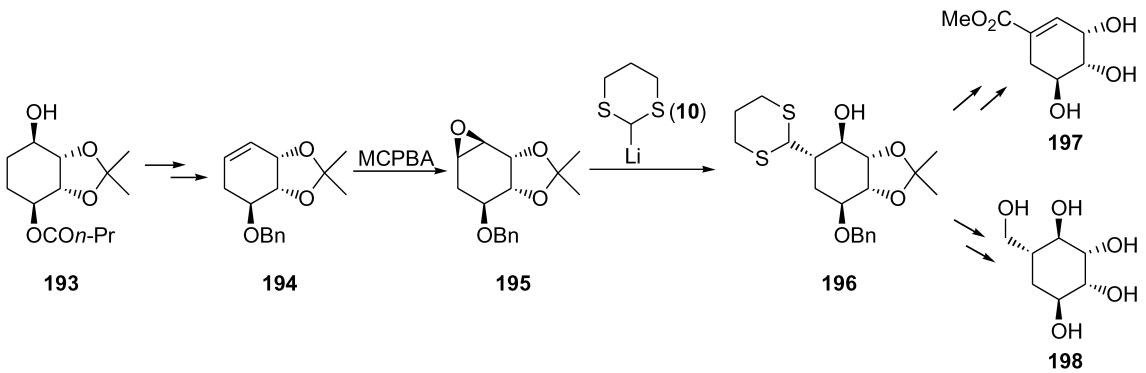
Tautomycin (**205**) is a natural polyether isolated from *Streptomyces spiroverticillatus*[95] with strong antifungal activity and also an inhibitor of protein phosphatases.



Scheme 39.



Scheme 40.

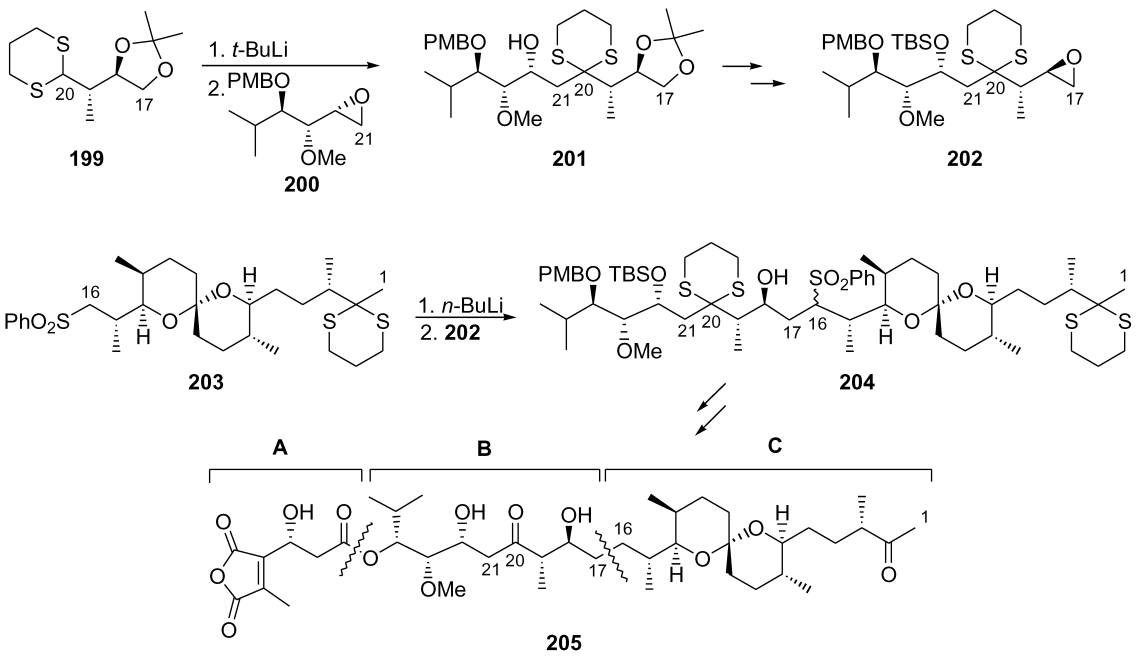


Scheme 41.

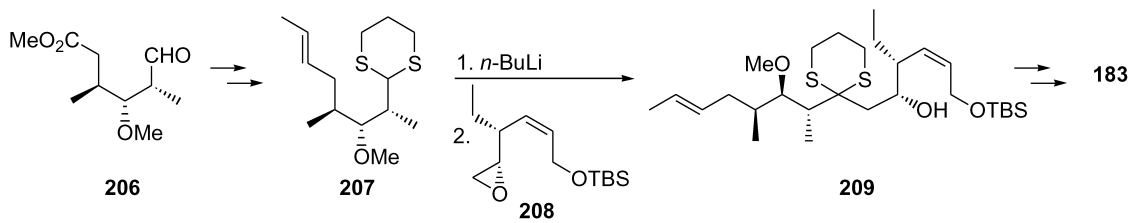
Isobe et al. reported a convergent synthesis of **205**, in which retrosynthetic analysis[96] they divided the target molecule into three segments (**A**, **B**, and **C**). In the synthesis of fragment **B**,[97] the lithiated dithioacetal **199** (prepared from the corresponding aldehyde) reacted with the epoxide **200** to give the alcohol **201**, which is a precursor of the epoxide **202**, in 47% yield. The connection of fragments **B** and **C**[98] took place by the reaction of the lithiated sulfone **203** (with a carbonyl group protected as the dithioacetal)[99] with the epoxide **202** to give the alcohol **204** in 81% yield (Scheme 42).[100]

Kitahara et al. reported on the total synthesis of pironetin (**183**) (Scheme 38). In this synthesis, one of the key steps is the reaction of the anion resulting from deprotonation of the dithiane **207** (which was obtained by transacetalisation of the corresponding dioxolane **206** in 97% yield) with the chiral epoxide **208** to give the compound **209** in 91% yield (Scheme 43).[101]

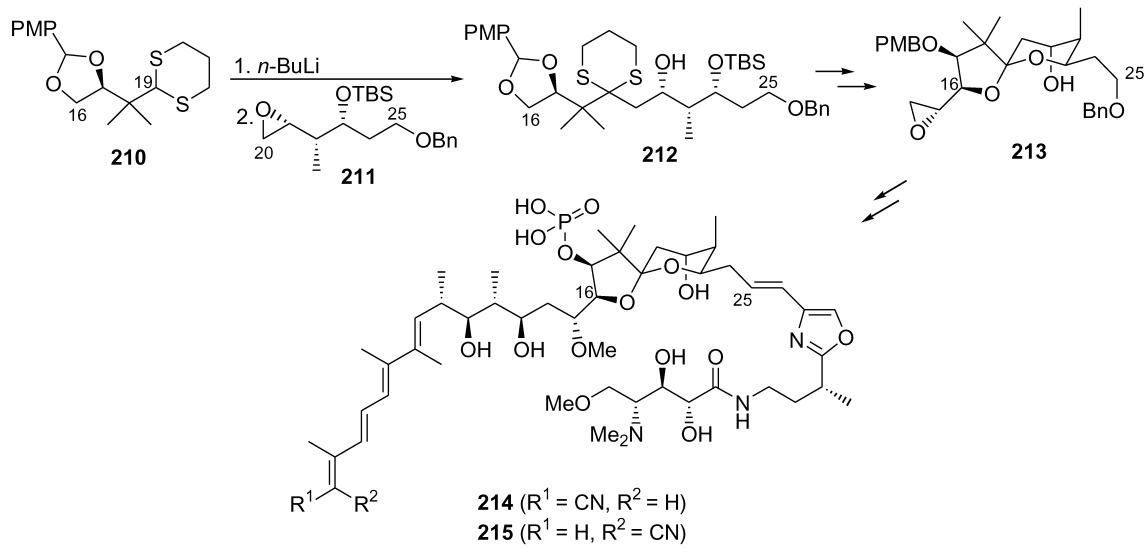
The asymmetric synthesis of the spiroacetal fragment of the calyculins A (**214**) and B (**215**) was described by Smith et al. Calyculin A (**214**) was isolated from the Pacific sponge *Discodermia calyx*.[102] One of the steps of the synthesis of the spiroacetal fragment **213** is based on the coupling of the epoxide **211** and the dithiane **210** to afford the alcohol **212** in 81% yield (Scheme 44).[103] A total synthesis of these natural



Scheme 42.



Scheme 43.



Scheme 44.

products using this strategy was reported by the same research group.[104]

An efficient, highly convergent, stereocontrolled total synthesis of the antimitotic agent (+)-discodermolide (**221**), derived from the deep-water marine sponge *Discodermia dissoluta*,[105] has been achieved on a g scale by Smith et al.[106] Three advanced fragments were prepared from the common precursor **216**. The C(1)–C(8) unit was prepared by alkylation of the anion resulting from deprotonation of the dithiane **217** with the chiral epoxide (*S*)-**218**, to the give alcohol **219** in 79% yield. This alcohol is

a precursor of compound **220**, which was directly used to prepare the final product **221** (Scheme 45).[107]

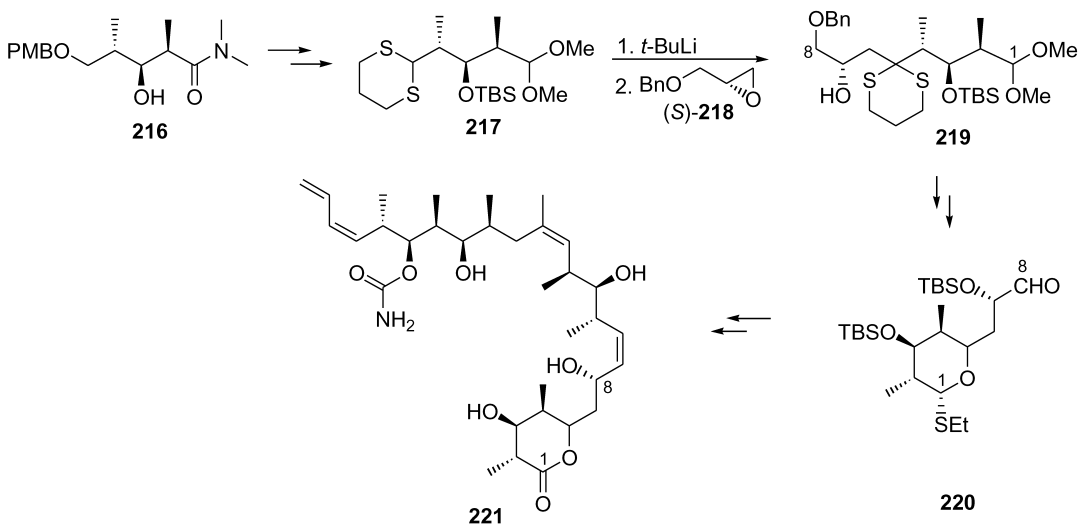
In the synthesis of (−)-hennoxazole A (**168**) (Scheme 35) reported by Yokokawa et al., the C(1)–C(6) fragment is prepared from the commercially available (*R*)-glycidyl tosylate [(*R*)-**222**]. Addition of 2-lithio-1,3-dithiane (**10**) to (*R*)-**222**, followed by a copper-catalysed coupling reaction with vinylmagnesium bromide, led to the alcohol **223** in 63% yield (Scheme 46).[108]

Jiang and Chen synthesised kurzilactone (**227**),[109] which was isolated from the leaves of the Malaysian plant *Cryptocarya kurzii* and has a close structural relationship with the statin family.[110] Coupling of the anion resulting from the deprotonation of the cinamaldehyde 1,3-dithiane derivative **224** and the chiral epoxide **225** gave the alcohol **226** in 58% yield. Further reactions leading to chain elongation, lactonisation and final hydrolysis of the dithiane moiety, to regenerate the carbonyl group, led to kurzilactone (**227**) (Scheme 47).[111]

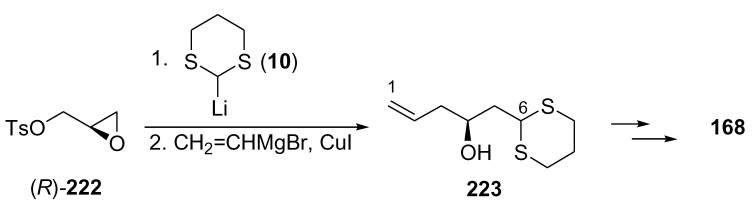
Fostriecin (CI-920, **231**) is an antitumour agent and is one of the most selective protein phosphatase inhibitory identified to date.[112] In one of the steps of the convergent total synthesis reported by Jacobsen and Chavez, the nucleophilic addition of the anion resulting from the deprotonation of the 2-alkynyl-1,3-dithiane derivative **228** (obtained from the corresponding aldehyde through a dithioacetalisation process)[113] to the chiral epoxide **229** gave the alcohol **230** in 89% yield. Hydrolysis of the dithiane, followed by asymmetric hydrogenation, gave a precursor compound **231** having the hydroxy group at C(11) with the correct stereochemistry (Scheme 48).[114]

The stereochemistry (6*R**,9*S**,11*S**) of the tetrahydropyranyl moiety in bistramide A (**235**), a potent antitumour agent in vitro (from *Didemnid ascidians*), has been established by stereoselective synthesis and high field NMR comparison by Kitching et al. They synthesised the tetrahydropyran derivative **234** starting from 2-lithio-1,3-dithiane (**10**) and the chiral epoxide **232**, to give the compound **233** in 70% yield (Scheme 49).[115]

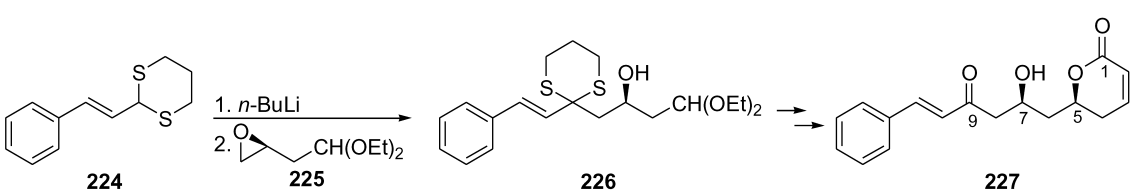
Apicularen A (**240**) also shows potent antitumour activity.[116] Maier and Kühnert reported a synthesis of the macrocyclic core (**239**) of **240**, one of the building blocks being constructed by connecting two fragments via the



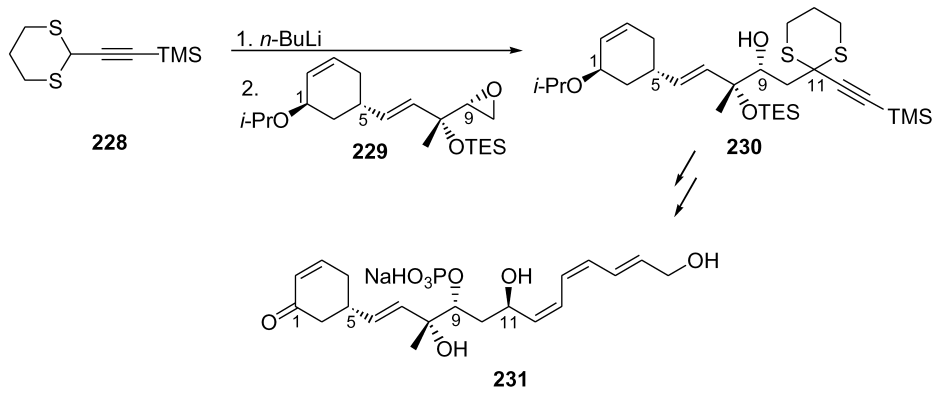
Scheme 45.



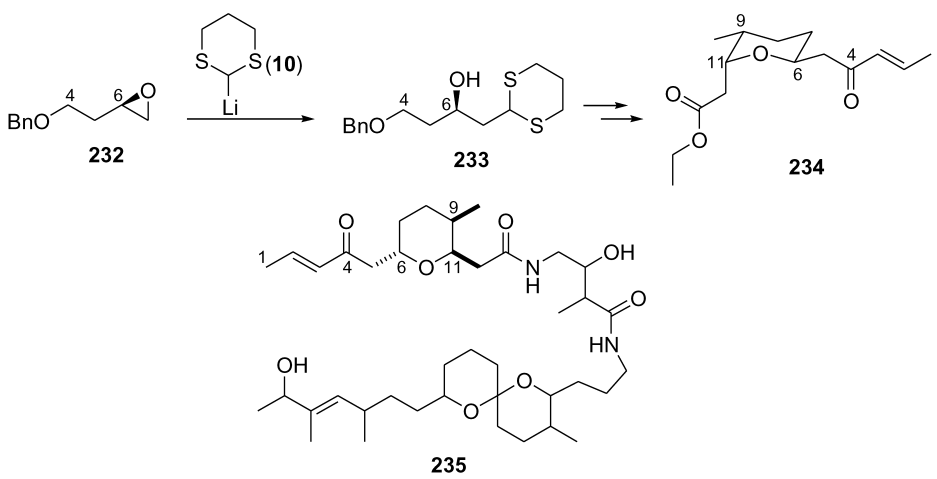
Scheme 46.



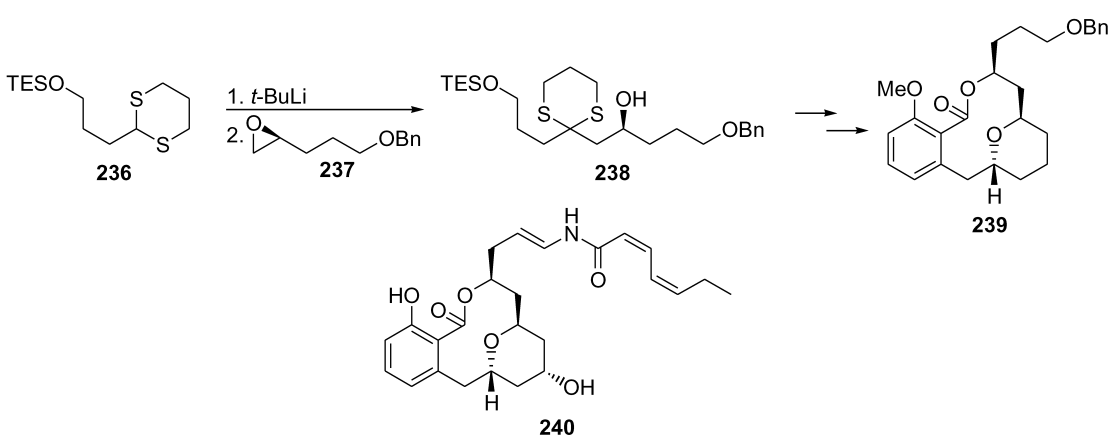
Scheme 47.



Scheme 48.



Scheme 49.

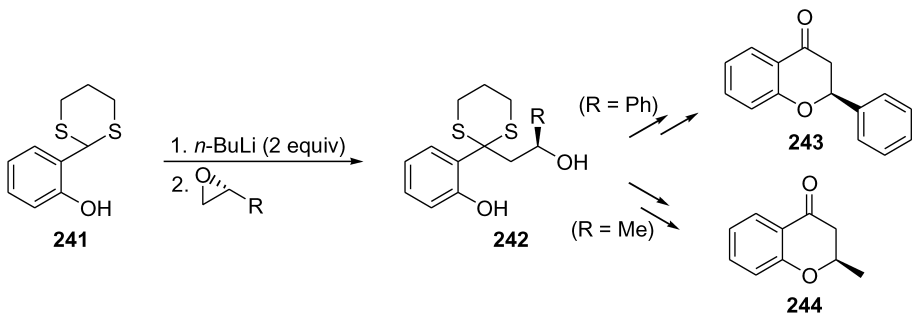


Scheme 50.

dithiane coupling. Alkylation of the anion resulting from deprotonation of the dithiane **236** with the chiral epoxide **237**, led to the alcohol derivative **238** in 89% yield. Cleavage of the dithiane group, stereoselective reduction of the resulting ketone and other transformations led to the desired compound **239** (Scheme 50).[117]

Noda and Watanabe developed a general and efficient synthesis of the optically active flavanone (**243**) and 2-methylchromanone (**244**) in high enantiomeric purity from readily available starting materials. Thioacetalisation of salicylaldehyde gave compound **241**, which, by deprotonation and reaction with chiral epoxides, led to the products **242**. Cyclisation under Mitsunobu reaction conditions and final hydrolysis yielded the expected products **243** and **244** (Scheme 51).[118]

A carbohydrate derivative with C_2-symmetry, such as the diol **246**, has been prepared by Takano et al. through a double alkylation of two equiv of (*R*)-*O*-benzylglycidol



Scheme 51.

[(*R*)-**218**] with 1,3-dithiane in high yield through the compound **245** (Scheme 52).[119]

Kishi et al. reported the total synthesis of spongistatin 1 (**253a**, named in this work altohyrtin A), a macrolide (together withe spongistatin 2, **253b**) derived from a marine sponge. In the retrosynthetic analysis, **253a** was dissected into two segments (**A** and **B**).[120] In the synthesis of segment **A** [C(1)–C(28)],[121] different carbon–carbon bonds were formed by reacting 2-lithio-1,3-dithiane derivatives with enantiomerically pure epoxides, the reaction of the epoxide **247** with 2-lithio-1,3-dithiane (**10**), *O*-silyl protection, new deprotonation of the remaining acidic hydrogen of the dithiane moiety and reaction with the second chiral epoxide **248** giving compound **249** [C(1)–C(12)] in 50% yield. A similar strategy was employed for the construction of the C(18)–C(28) unit **252**, deprotonation of the dithiane derivative **250** [obtained from (*S*)-glycidyl tosylate (*S*)-**222** and 2-lithio-1,3-dithiane (**10**)] with Lochman's base, followed by alkylation with the epoxide **251**, giving the compound **252** in 54% yield (Scheme 53).

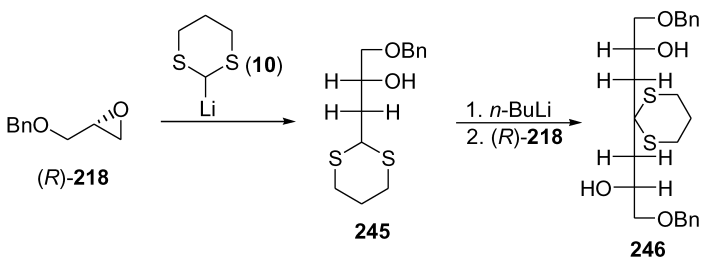
A one-flask multicomponent lynchpin coupling of 2-silylated-1,3-dithianes[122] with epoxides, based on the work of Tietze[123] and Oshima et al.,[124] exploiting a solvent-controlled Brook rearrangement, has been widely used by Smith et al. in the synthesis of 1,3-polyol compounds in a stereoselective manner. Deprotonation of 2-(*t*-butyldimethylsilyl)-1,3-dithiane (**254**), followed by reaction with an epoxide in Et_2O at low temperature, gave the alcoholate **255**. After introduction of HMPA, Brook rearrangement occurs within minutes to give the compound **256**, which by reaction with a second epoxide afforded the unsymmetrical bisalkylated products **257** in good yields (Scheme 54).[125]

The synthesis of the trisacetonide **260** using the silylated dithiane **254**, the Schreiber C(16)–C(28) subtarget for the macrolide antibiotics, mycoticins A (**261**) and B (**262**),[126] has been reported by Smith and Pitram. The key synthetic transformation entails a one-flask five-component lynchpin-coupling tactic. Treatment of the silylated dithiane **254** with *t*-BuLi, followed by the addition first of the epoxide (*R*)-**218** (almost in a 1:1 ratio) and then the diepoxide **258** (in a 1:0.5 ratio), led to the diol **259** in 59% overall yield, a precursor of the compound **260** (Scheme 55).[127]

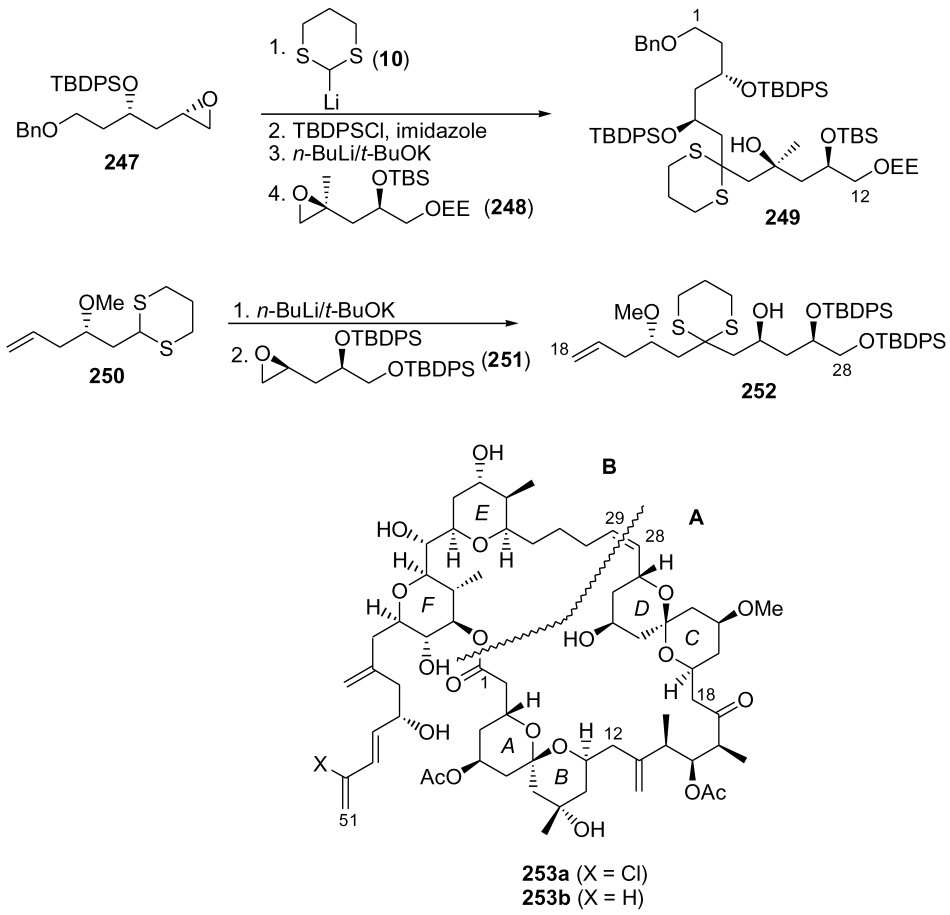
The previously mentioned methodology has been applied to the preparation of different fragments of the convergent route to spongistatin 1 and 2 (**253**) (Scheme 53). The C(18)–C(28) CD-ring spiroacetal **267** subunit of spongistatins has been generated via a highly convergent and completely stereocontrolled sequence. Smith et al. evaluated two approaches to the assembly of the compound **266**, a stepwise lithiation of the dithiane **263** (obtained from the corresponding aldehyde) and reaction with the epoxide **264** (20% yield) or a one-pot unsymmetrical bisalkylation of the silylated dithiane **254** with the epoxides **264** and **265**. The second method is more concise and, in this case, an efficient conversion took place with 72% yield. Final hydrolysis of the dithiane unit and metal-assisted spiroacetal equilibration gave the spiroacetal subunit **267** (Scheme 56).[128]

The same methodology was used in the construction of the C(1)–C(12) spiroacetal fragment **271** of spongistatins (**253**, Scheme 53), bisalkylation of the 2-silylated-1,3-dithiane **254** with the epoxides **268** and **269** giving the desired product **270**, a precursor of the spiroacetal **271**, in 65% yield (Scheme 57).[129] A formal synthesis of spongistatin 1 (**253a**) by the construction of an advanced ABCD fragment[130] and a total synthesis of spongistatin 2 (**253b**)[131] have been reported by Smith et al.

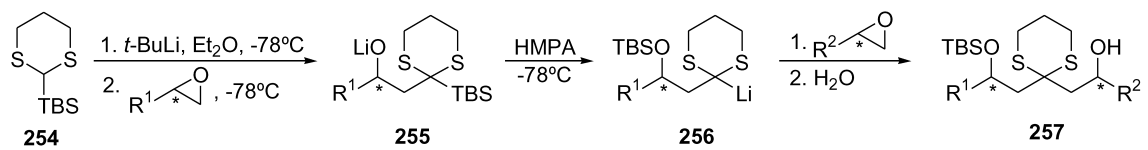
A short, efficient and stereocontrolled synthesis of the compound (−)-**279**, an advanced ABCD subunit of the spongistatins (**253**) (Scheme 53), has been achieved recently by Smith et al. Central to their synthetic strategy is the multicomponent lynchpin union of 2-silyldithianes with



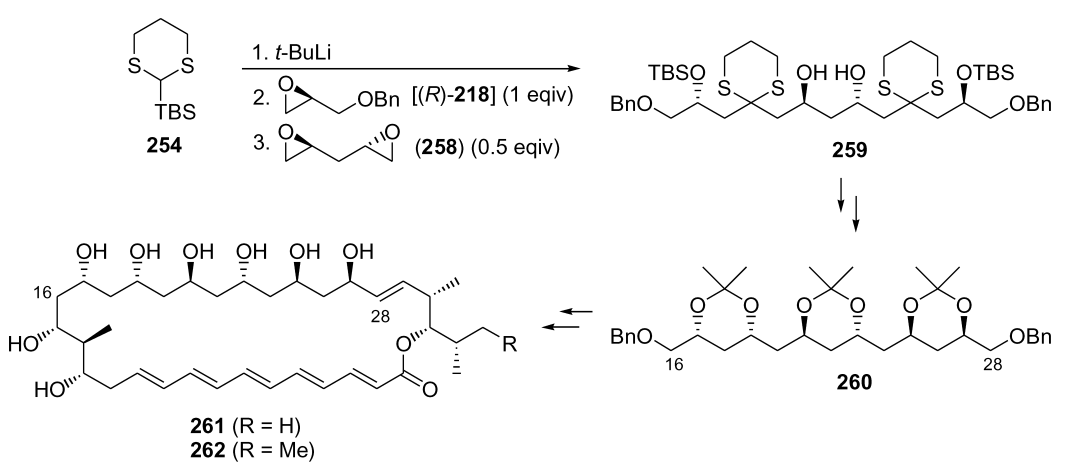
Scheme 52.



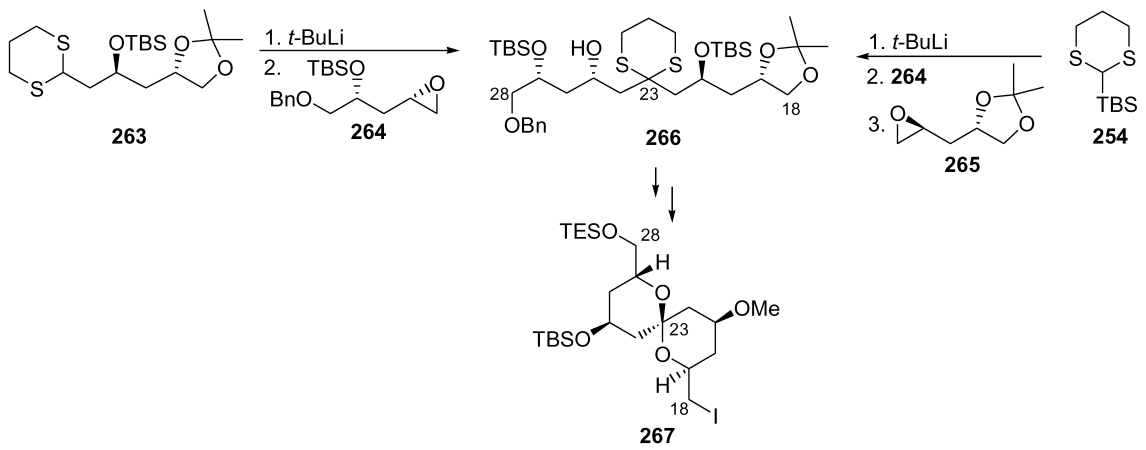
Scheme 53.



Scheme 54.



Scheme 55.



Scheme 56.

epoxides to access both the AB (**274**) and CD (**277**) fragments. Compound **274** was obtained from the epoxides **272** and **273** in 58% yield and compound **277** from the epoxides **264** and **276** in 69% yield. Fragment coupling was then achieved via an efficient stereoselective aldol reaction of the aldehyde **275** and the ketone **278** to give the compound **279** as a 9:1 mixture of diastereomers in 64% yield (Scheme 58).[132]

When the former process was carried out starting from the 2-silyl-1,3-dithiane derivative **254** in the presence of C_2-symmetrical bisepoxides derived from D-mannitol **280**, a one-pot tandem alkylation–cyclisation gave the polyhydroxycycloheptane derivative **281**, in the case of *O*-benzyl protected compound **280a**, or the polyhydroxycyclohexane derivative **282** for the isopropylidene derivative **280b**.[133] For the compound **281**, the aminocyclitols **283** can be prepared by reductive amination of the ketone resulting from hydrolysis of the dithiane moiety with different amines and are able to act as pseudo-azadisaccharide candidates for glycosidase inhibition (Scheme 59).[134]

Bryostatin 1 (**100**) (Scheme 21) is a natural antitumour macrolide[135] that has shown considerable clinical promise for the treatment of various human cancers. Hale et al. reported the stereocontrolled asymmetric synthesis of the B-ring fragment (**286**) of bryostatin 1 (**100**). A noteworthy feature of this synthesis includes the Smith–Tietze bisalkylation reaction between the silyl dithiane **254** and 2 equiv. of the epoxide **284** to give the C_2-symmetrical dithiane **285** in 87% yield (Scheme 60).[136]

2.3. Reactions with carbonyl compounds

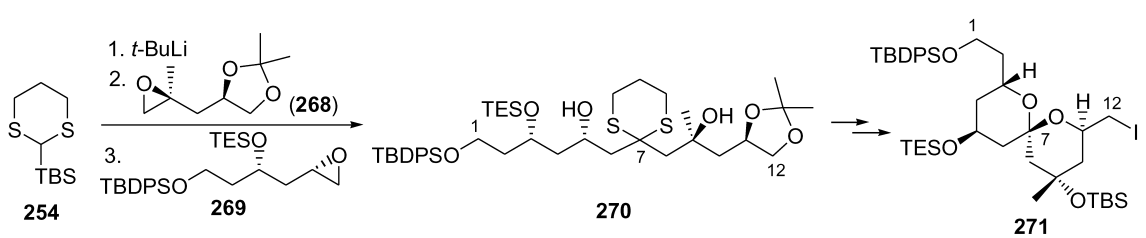
The addition of 2-lithio-1,3-dithianes to the unprotected carbonyl functionality of partially blocked compounds can be highly diastereoselective, depending on the structure of these compounds.[137] α-Hydroxy carbonyl compounds can be prepared by this method, sugar derivatives being available through these chain extension reactions, the reaction of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**287**) with the 2-lithio-1,3-dithiane (**10**) giving stereoselectively the D-glycero-α-D-galactoheptose derivative **288** (Scheme 61).[138]

The reaction of the aldehyde **289**, derived from D-glucose, with the carbanion of the 1,3-dithiane (**10**) gave a diastereomeric mixture of alcohols (4.6:1) in 86% yield, mainly consisting of the Cram adduct **290**, which, by further reactions, led to 9-dehydroerythronolide (**291**, Scheme 62).[139]

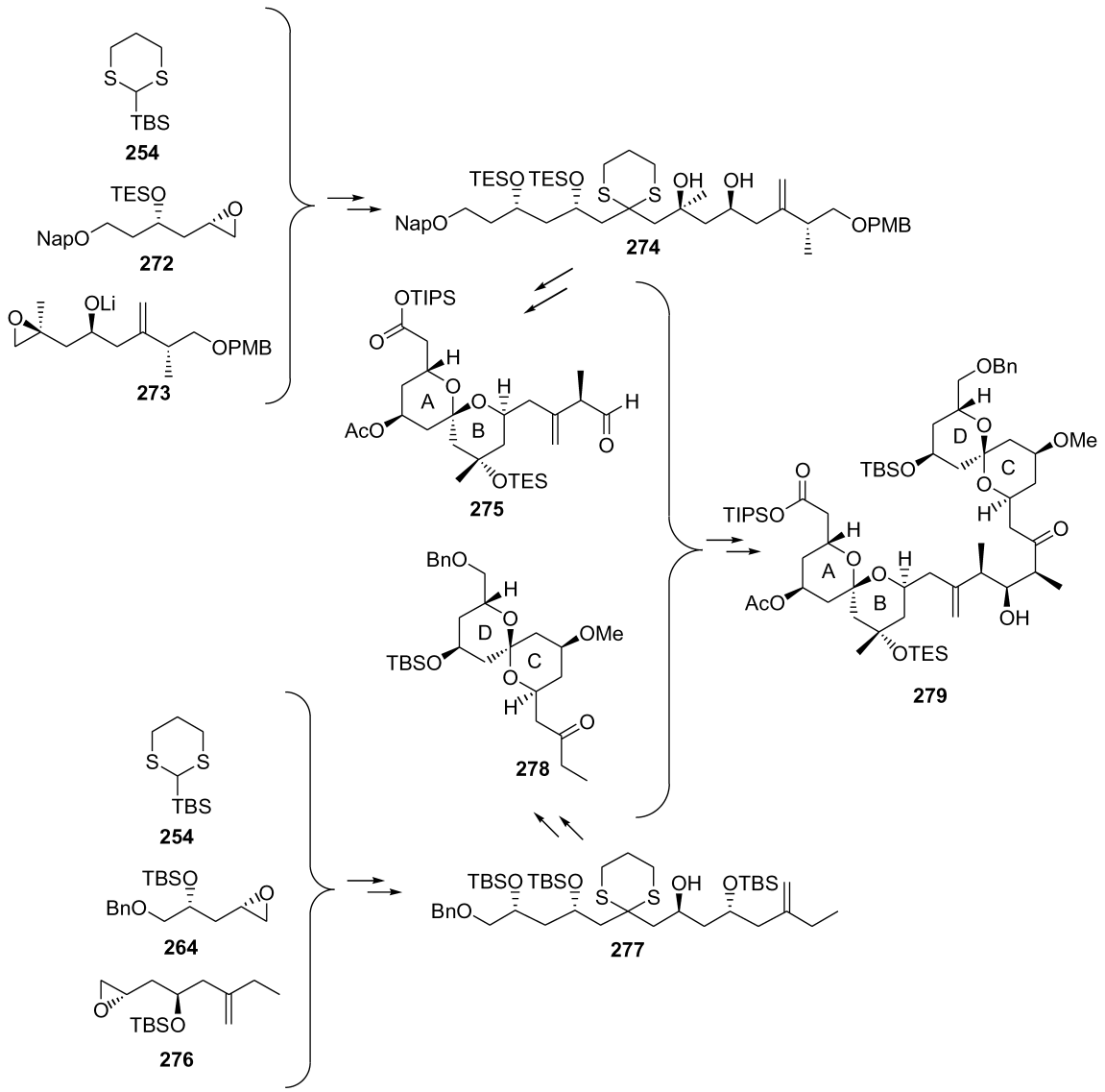
Nakata et al. prepared a 1,3-*syn*-polyol derivative such as the all-*syn*-nonamethoxy-1-pentacosene **295** from the compound **294**, which was obtained through a successive double alkylation of 1,3-dithiane with the chiral aldehydes **292** and **293**, respectively (Scheme 63).[140]

A synthesis of the C(10)–C(19) moiety **301** of FK-506 (**44**) (Scheme 10) has been proposed by Gu and Sih. The synthesis started from racemic ethyl 2-methyl-4-pentenoate (**296**), which, by oxidation and thioacetalisation, gave the compound **297** in 77% yield. Enzymatic hydrolysis of **297** and further transformations gave the enantiomerically pure dithiane derivative **298**. Double deprotonation of **298**, followed by reaction with the aldehyde **299**, gave the adduct **300** as a mixture of diastereomers in 66% yield (Scheme 64).[141]

Starting from (+)-nopinone (**302**) [or (−)-nopinone],

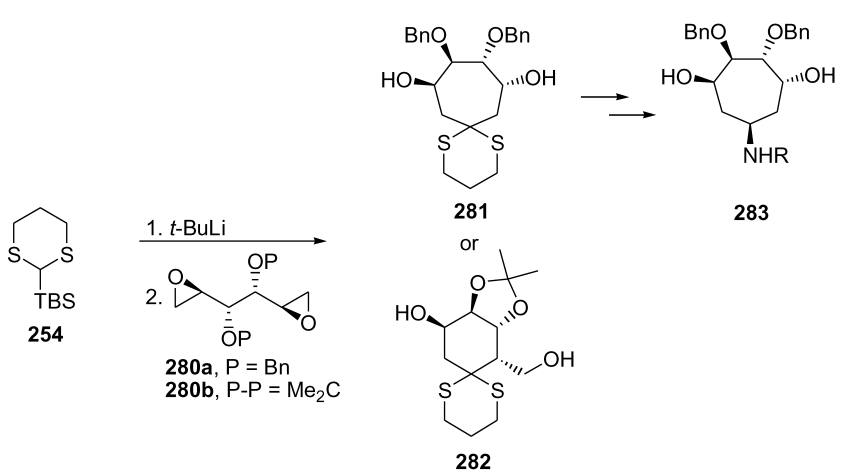


Scheme 57.

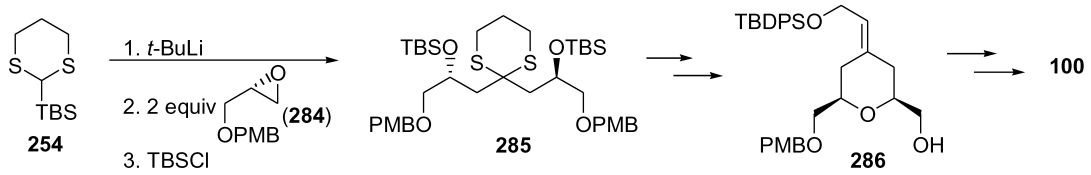


Scheme 58.

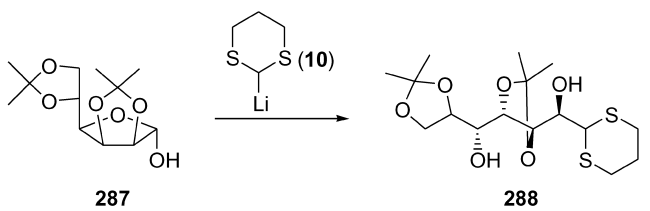
Razdan et al. synthesised the enantiomeric cannabinoid terpene intermediate **305**.[142] Transformation of nopinone into the enol ether **303** first and then to the enone **304**,[143] followed by reaction with 2-lithio-1,3-dithiane (**10**) and reduction with LAH, led to the expected compound **305** in 59% overall yield. Compound **305** was transformed into (+)-11-hydroxy-5-norpentyl-5-(1′,1′-dimethylheptyl)-THC (THC=tetrahydrocannabinol) **306**, without any loss



Scheme 59.



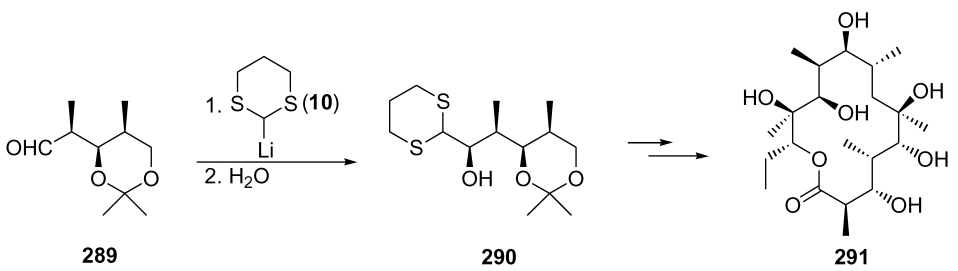
Scheme 60.



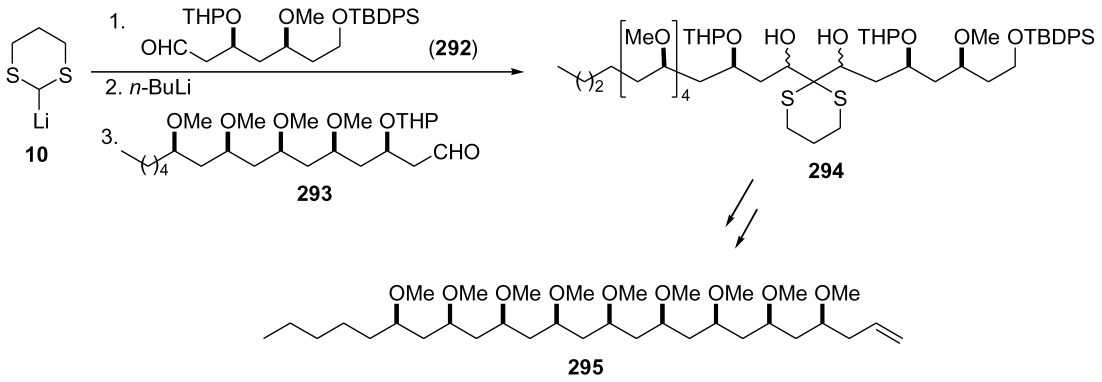
Scheme 61.

in optical purity from the starting nopinone (Scheme 65).[144]

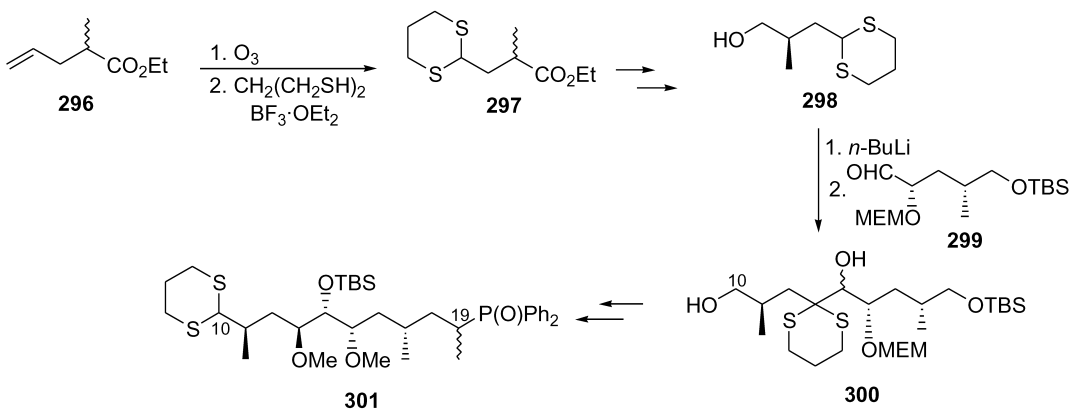
Zaragozic acid A (**310**), which was isolated from a fungus, is a competitive inhibitor of squalene synthase and also shows antifungal activity. In its convergent synthesis reported by Nicolaou et al., the dithiane **307**, prepared by transthioacetalisation of the corresponding dioxolan, is one of the building blocks. It reacted after deprotonation with



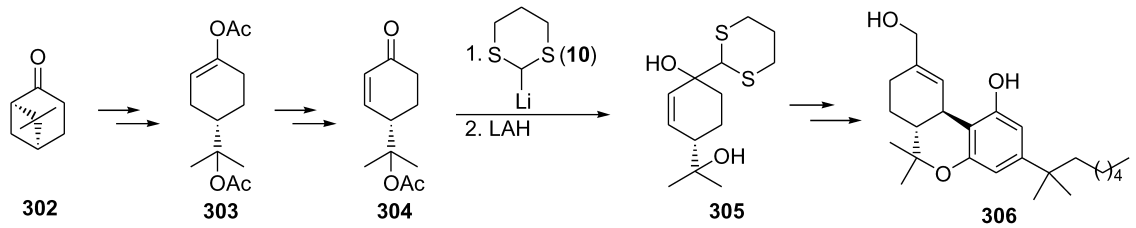
Scheme 62.



Scheme 63.



Scheme 64.



Scheme 65.

the aldehyde **308** to give the compound **309** as a 1:1 mixture of diastereomers in 75% yield (Scheme 66).[145]

In the synthesis of spongistatins (**253**) (Scheme 53) reported by Smith et al. that was commented on Section 2.2,[130,131] the unit containing the E and F rings was prepared by coupling the anion resulting from deprotonation of the dithiane derivative **311** and the aldehyde **312** to give the compound **313** in 63% yield as an 8:1 mixture of diastereomers (Scheme 67).[146] More recently, a different approach to this subunit of the spongistatins has been reported by the same group. In this case, the union of the cerium anion generated from the dithiane **311** with a premixed solution of the aldehyde **314** and zinc chloride gave the alcohol derivative **315** with high stereoselectivity (>20:1) and reasonable yield (51%) (Scheme 67).[147]

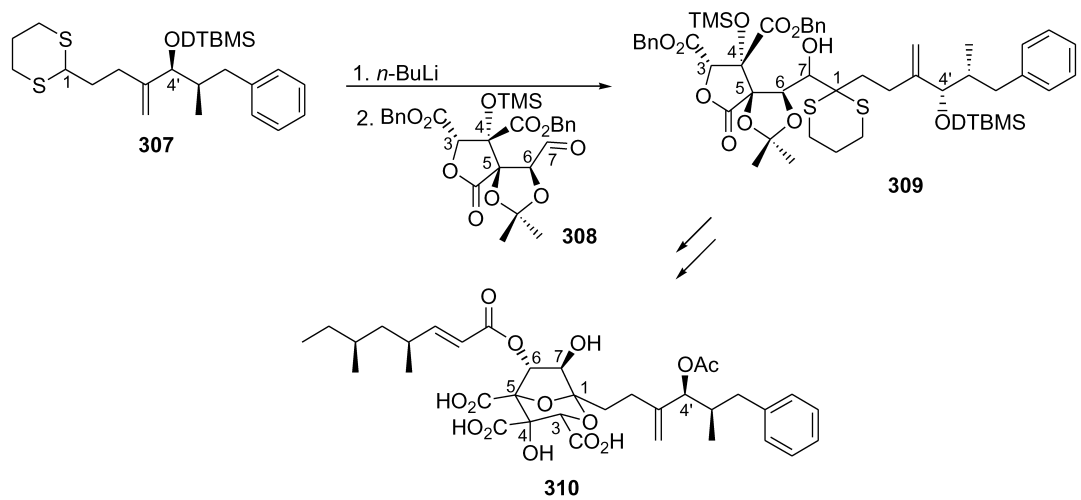
Galbonolides are macrolides which exhibit a broad range of antifungal activity.[148] Thomas and Smith reported on the synthesis of the C(7)–C(15) fragment **317** of galbonolide B (**318**). In the very early steps of the synthesis, the reaction of the organolithium derived from 2-methyl-1,3-dithiane (**1**) (obtained by deprotonation with *s*-BuLi) with propanal, followed by protection of hydroxy group and final hydrolysis of the dithiane unit, gave the ketone **316** in 43% overall yield (Scheme 68).[149]

A total synthesis of (+)-zaragozic acid C (**322**) was reported by Armstrong et al. The key features of the synthesis are, among others, the introduction of the C(1)-side chain by reaction between the anion derived from the dithiane monosulfoxide **319** and the core aldehyde **320** to give, after reduction with P_2I_4, the dithiane derivative **321** as an almost 1:1 mixture of diastereomers in ca. 60% yield. In a further step, acid-mediated simultaneous acetonide deprotection, dithiane removal and acetalisation yielded the dioxabicyclooctane core of **322** (Scheme 69).[150]

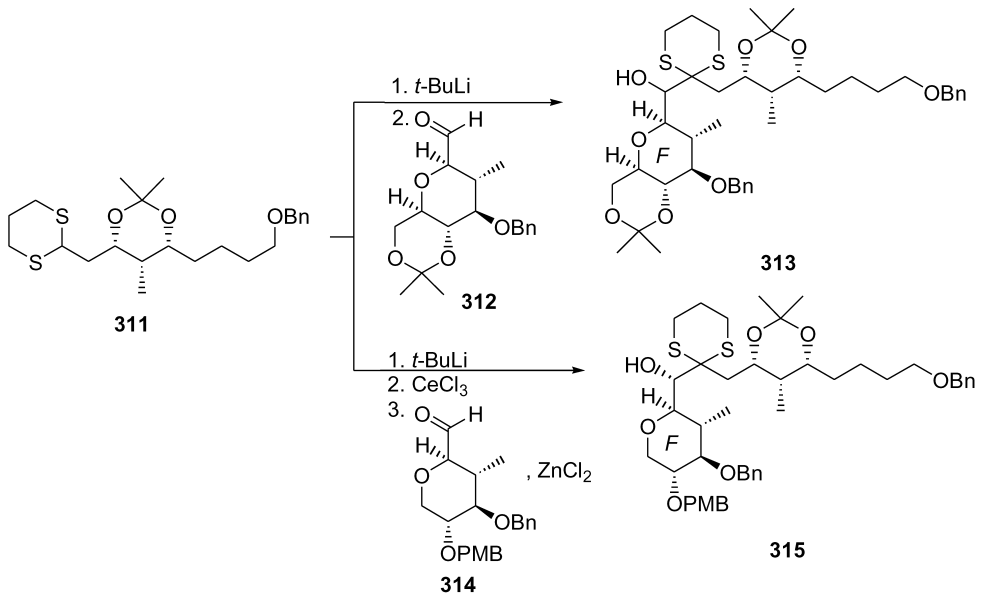
More recently, and taking advantage of the previously mentioned methodology, Armstrong et al. reported the synthesis of the 1,3-dithiane **324** corresponding to the C(1)-side chain of zaragozic acid D (**325**). The stereochemistry of the C(1)-side chain has not yet been unambiguously assigned, probably being the same as that for the analogues **310** and **322**. In this case, reaction of the anion resulting from deprotonation of the dithiane monosulfoxide **323** with the aldehyde **320** in a 3:1 ratio gave, after reduction with P_2I_4, the dithiane derivative **324** as an almost 1:1.5 mixture of diastereomers in ca. 30% yield (Scheme 70).[151]

The synthesis of CP-263,114 (**332**) and CP-225,917 (**333**), two fungal metabolites extracted from juniper twigs (in Texas) which act as inhibitors of Ras farnesyl transferase and squalene synthase, has been reported by both Danishefsky's[152] and Nicolaou's[153] groups. In both synthetic approaches, the addition of a 2-alkyl-2-lithiodithiane **327** [generated in situ from its tri-(*n*-butyl)stannyl derivative **326**] to either the aldehyde **328**[152] or **329**[153] is involved in the process, the corresponding alcohols **330** (70% yield, 10:1 diastereomeric mixture)[152] and **331** (80% yield, 11:1 diastereomeric mixture)[153] being obtained, respectively (Scheme 71).

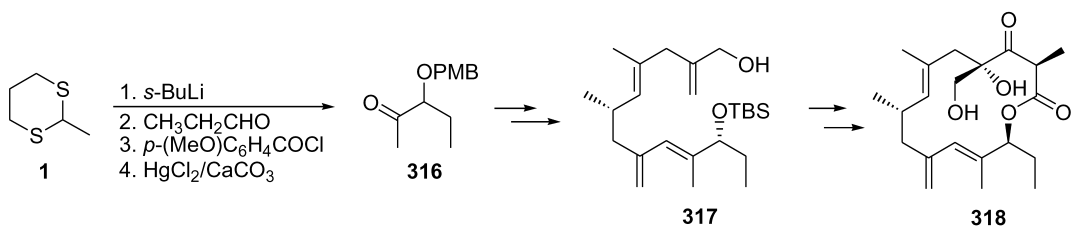
Ciguatoxin 1B (**337**), one of the principal toxins causing ciguatera fish poisoning, was first isolated from the moray eel, *Gymnothorax javanicus*.[154] Isobe et al. studied the synthesis of the BC-ring segment of this natural product, lithiation of the dithiane **334** and addition of the resulting



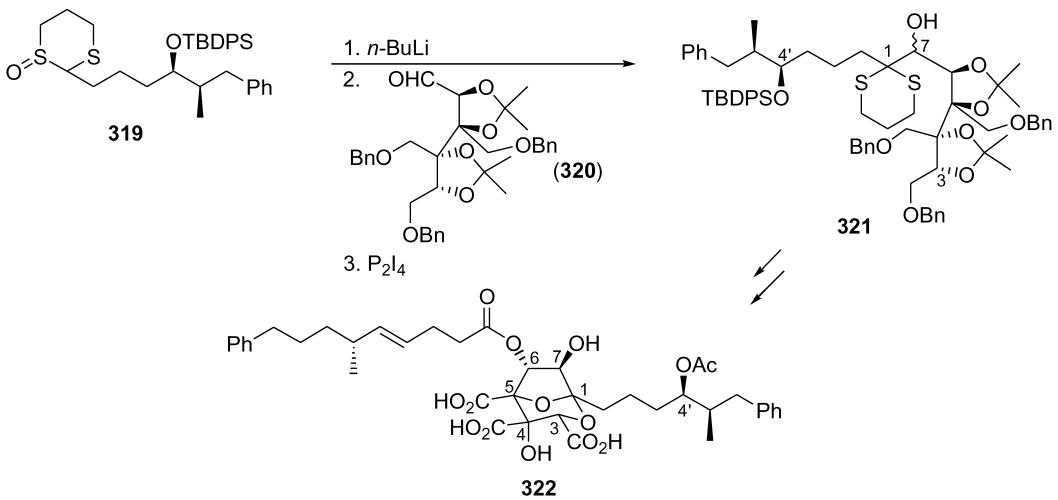
Scheme 66.



Scheme 67.



Scheme 68.

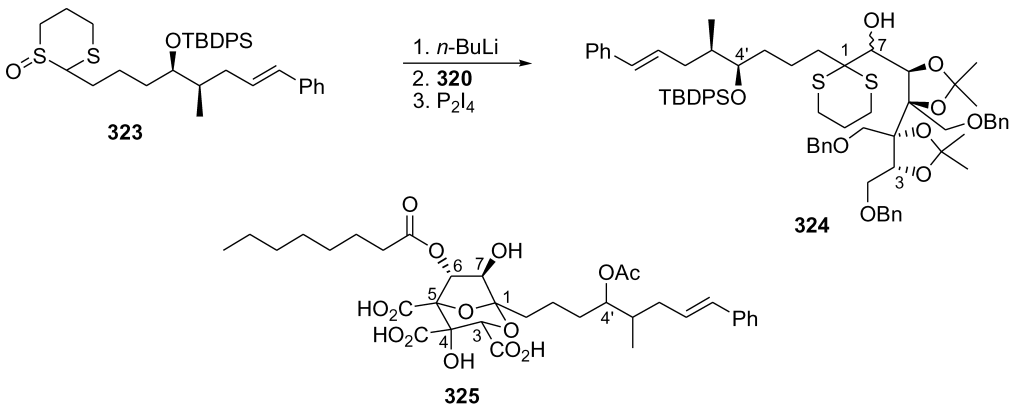


Scheme 69.

anion to the aldehyde **335** giving a coupling adduct with all the carbons needed to construct the BC-ring skeleton, which after selective protection–deprotection provided the compound **336** in 70% overall yield (Scheme 72).[155]

2.4. Reactions with acylating reagents

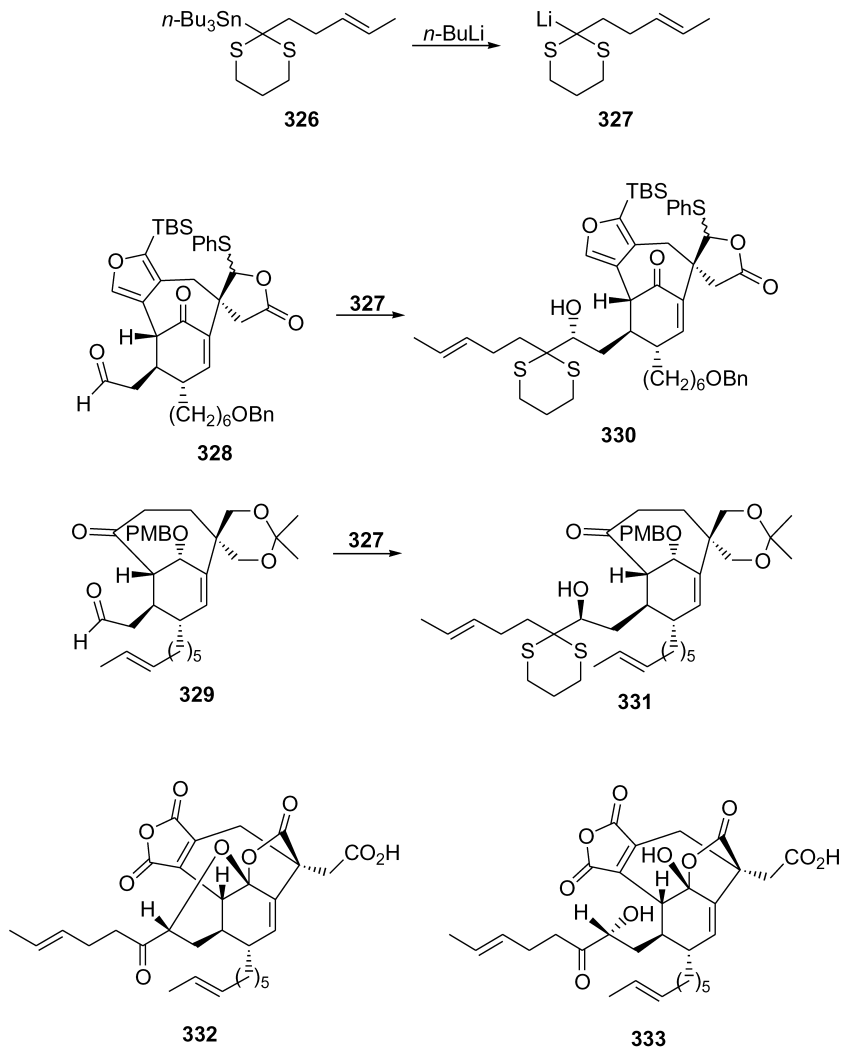
Anions derived from 1,3-dithianes and 2-silylated-1,3-dithianes react with acylating reagents to give masked β-ketocarbonyl compound derivatives. In the case of using simple nitriles as electrophiles, primary aminoketene thioacetals are obtained as the reaction products. These aminoketene thioacetals react with appropriate substrates allowing the preparation of different carbo- and heterocyclic compounds.[156] Examples of reactions involving acylation processes of dithiane anions in natural product synthesis will now be described.



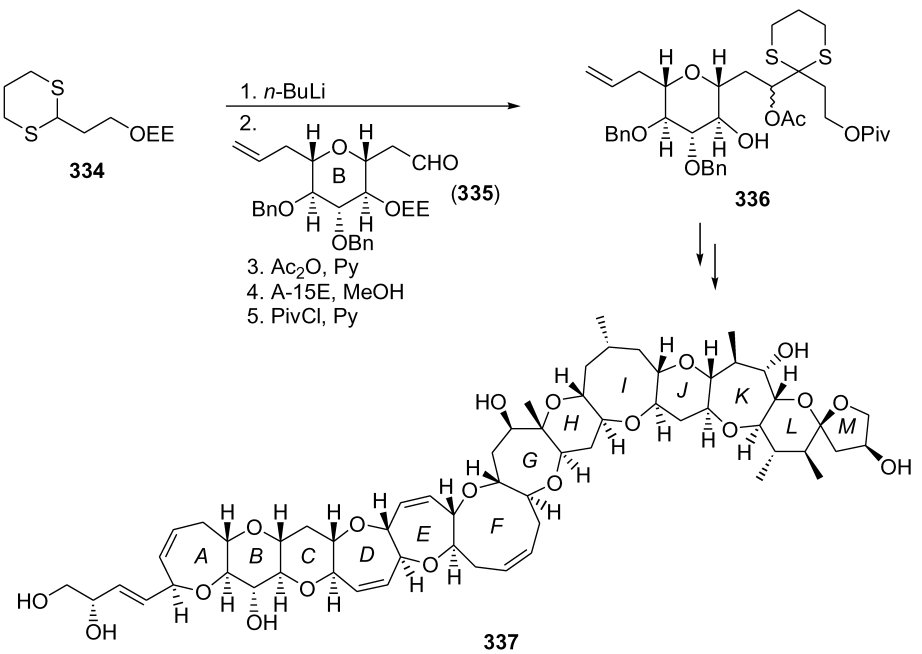
Scheme 70.

Seebach and Meyer reported the synthesis of some fungal metabolites with a 4-methoxy-5,6-dihydro-2-pyrone structure, such as (−)-pestalotin (**341**), which was isolated from *Pestalotia cryptomeriaecola*.[157] Reaction of the aldehyde **338**, obtained by acylation of the anion resulting from deprotonation of the dithiane derivative **116** with DMF in 95% yield, with 2 equiv. of the dianion of ethyl acetylacetate (**339**) gave the compound **340** in 80% yield. Further steps in the route to (−)-pestalotin (**341**) include *O*-methylation, hydrolysis of the dithiane unit and final stereoselective reduction of the resulting ketone (Scheme 73).[158]

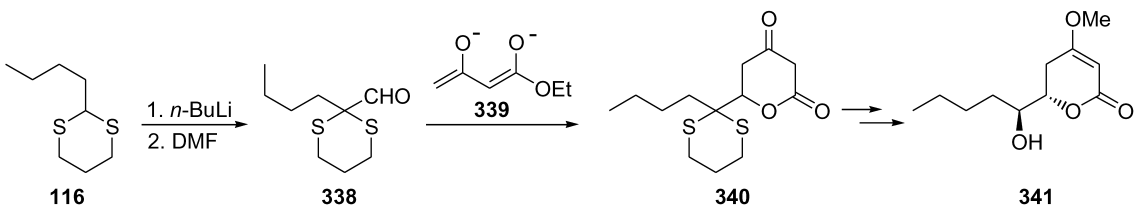
The methyl benzoyl formate derivative **343** was prepared by Pattenden and Knight from the dithiane **342** by successive metallation, carboxylation, esterification and final removal of the dithiane group in 60% overall yield. Compound **343** had been used in the synthesis of *O*-methylisopinastric acid (**344**) and permethylated gomphidic acid (**345**), which have



Scheme 71.



Scheme 72.

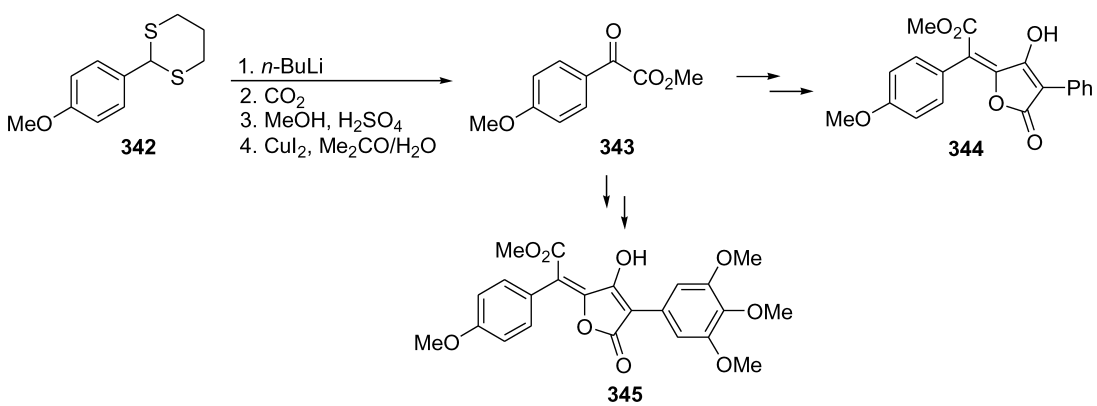


Scheme 73.

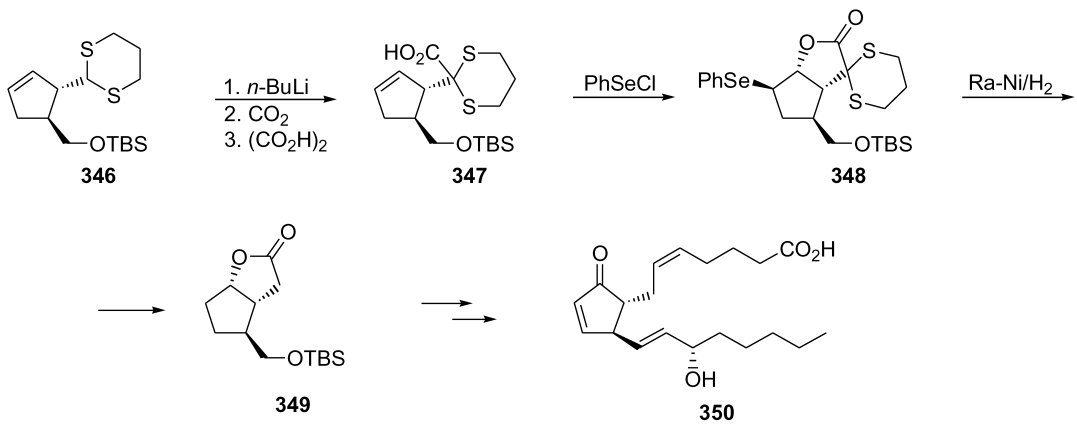
long been recognised as the pigments responsible for the striking yellow and orange colour of lichens (Scheme 74).[159]

Nicolaou et al. reported the synthesis of the saturated lactone **349**, a potential intermediate in the synthesis of prostaglandin A_2 (**350**). From a readily available cyclopentene derivative **346**,[160] the corresponding acid **347** was prepared in 85% yield after lithiation and carboxylation. Phenylselenolactonisation of this material gave the compound **348** in 92% yield and Raney nickel reduction resulted in removal of both the phenylseleno and the dithiane groups to give the compound **349** in almost quantitative yield (Scheme 75).[161]

Horton and Priebe reported on the synthesis of higher-carbon sugars, the reaction of 2-lithio-1,3-dithiane (**10**) with the per(trimethylsilyl) ether derived from D-glucono-1,5-lactone (**351**) giving, after removal of the protecting groups, a 62% yield of 1-*C*-(1,3-dithian-2-yl)-α-D-glucopyranose (**352**) as a single diastereomer (formally a derivative of a 7-carbon, 1,2-dicarbonyl sugar). The crystalline 2,3,4,6-tetraacetate **353** was readily obtained also as a single diastereomer, its desulfuration with Raney nickel giving



Scheme 74.



Scheme 75.

1-deoxy-D-gluco-heptulose as its α-pyranose 3,4,5,7-tetra-acetate **354** (Scheme 76).[162]

Aplasmomycin (**359**), a boron-containing antibiotic isolated from a marine-derived strain of *S. griseus* that exhibits activity against Gram-positive bacteria,[163] was synthesised by Corey et al. following a convergent strategy. The precursor corresponding to the C(11)–C(17) fragment **355** was prepared from D-mannose and the C(3)–C(10) fragment **356** (the dithiane unit was introduced in the molecule from the corresponding aldehyde) from the inexpensive (+)-pulegone. Thus, reaction of the vinylstannane **355** with *n*-BuLi and addition of the dithiane epoxide **356** to the solution containing the resulting vinyl lithium derivative afforded, after hydrolysis, the corresponding alcohol in 75% yield, which was converted into the trisilylated compound **357**. Metallation of **357** with *n*-BuLi and reaction with dimethyl oxalate gave the α-ketoester **358** in 96% yield. Hydrolysis of the ester unit, desilylation, macrolactonisation, reduction of the ketone units and final hydrolysis of the dithiane groups led to the desired product **359** (Scheme 77).[164]

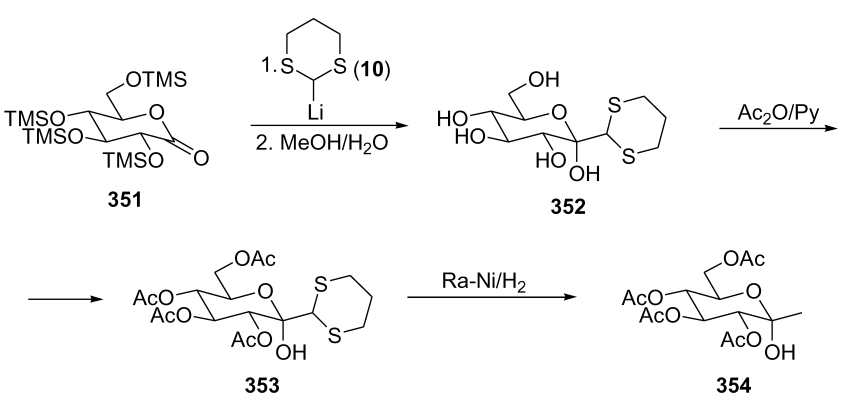
In an approach to the synthesis of the alkaloid lycorenine (**364**), Confalone et al. synthesised the azomethine ylide **362**, which, upon [3+2] intramolecular cycloaddition, led to the desired octahydroindole ring system **363**. Formylation of the dithiane derivative **360** by lithiation with *n*-BuLi and reaction with DMF led to the aldehyde **361** in 32% yield. Condensation of the aldehyde **361** with ethyl *N*-methylglycinate at high temperatures led to the octahydroindole **363** in 51% yield (Scheme 78).[165] More recently, Coldham et al. reported the optimisation, scope and stereoselectivity of this methodology.[166]

Murai and Feng have described the synthesis of the racemic hemibrevetoxin B (**368**) C- and D-ring-containing aldehyde **367**. The natural toxin is a polycyclic ether isolated from cultured cells of the red tide with cytotoxic activity at low concentrations. In its synthesis, the reaction of the enol triflate derived from the lactone **365** with 2-lithio-1,3-dithiane (**10**) afforded the alkylated product **366** in 60% yield (Scheme 79).[167]

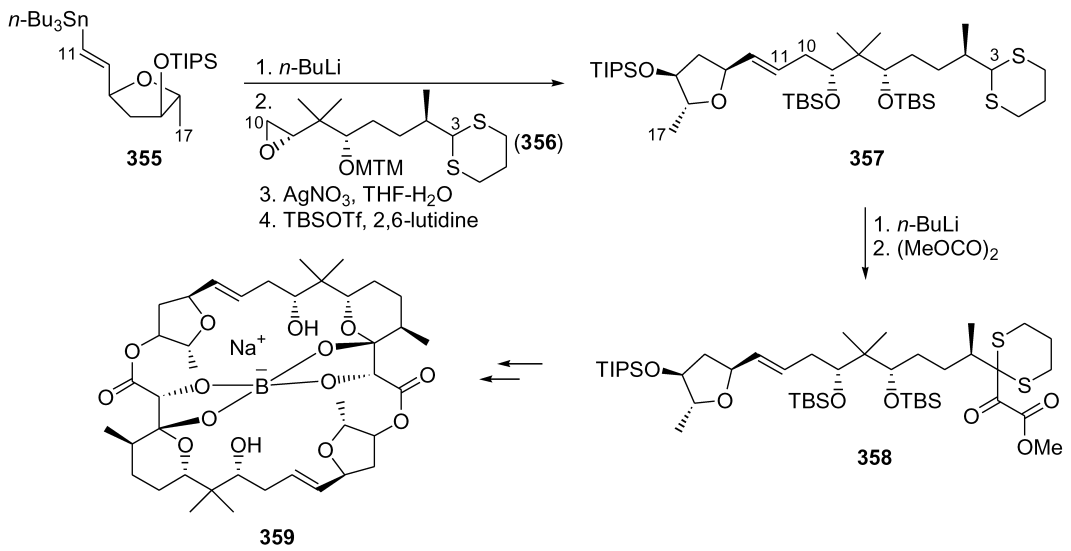
Ezquerra et al. found that ethyl *N*-Boc L-pyroglutamate (**369**) reacted with 2-lithio-1,3-dithiane (**10**) at the amide functionality in a chemoselective manner to give the highly functionalised α-amino acid derivative **370** in 72% yield (Scheme 80).[168]

The dianion derived from the dithioacetal **371** (prepared by thioacetalisation of the corresponding aldehyde) has been used in the synthesis of difluorinated [6]-gingerol **374** by Kitazume et al. Acylation of the corresponding organolithium intermediate with the protected 2,2-difluoro-3-hydroxy ester **372** gave the ketone **373** in 65% yield, which was easily converted into the gingerol derivative **374** (Scheme 81).[169]

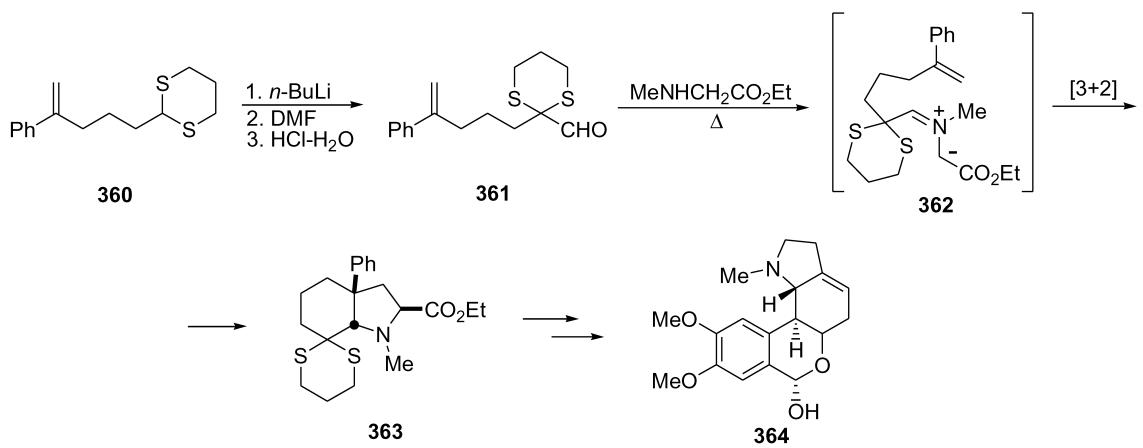
The first total synthesis of the very unstable biochemical intermediate 12-oxo-LTB$_4$ (**378**), a key pivotal intermediate in LTB$_4$ metabolism, was accomplished by Rokach et al., an



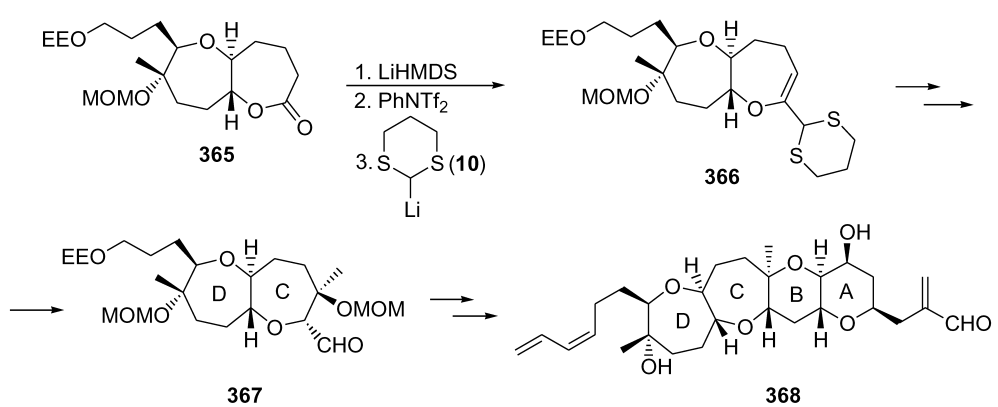
Scheme 76.



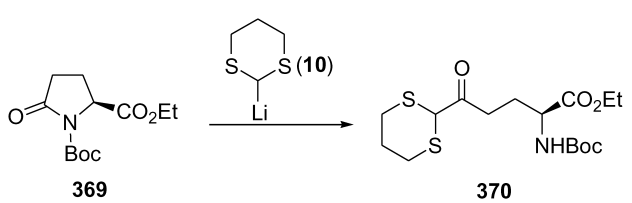
Scheme 77.



Scheme 78.

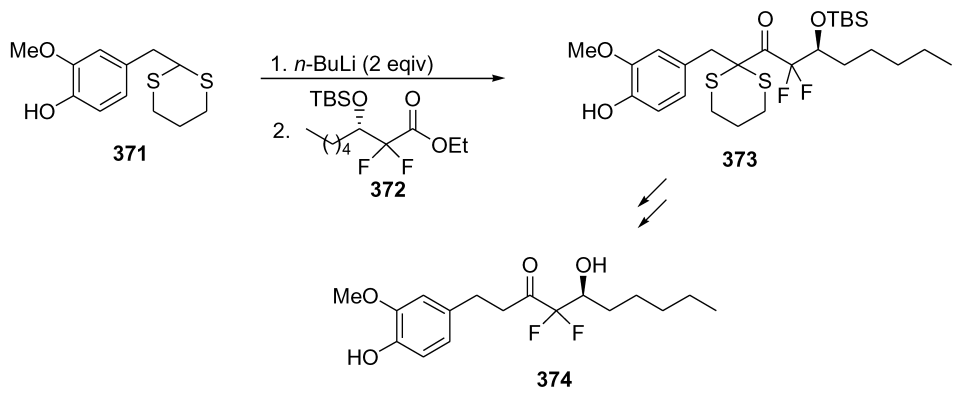


Scheme 79.

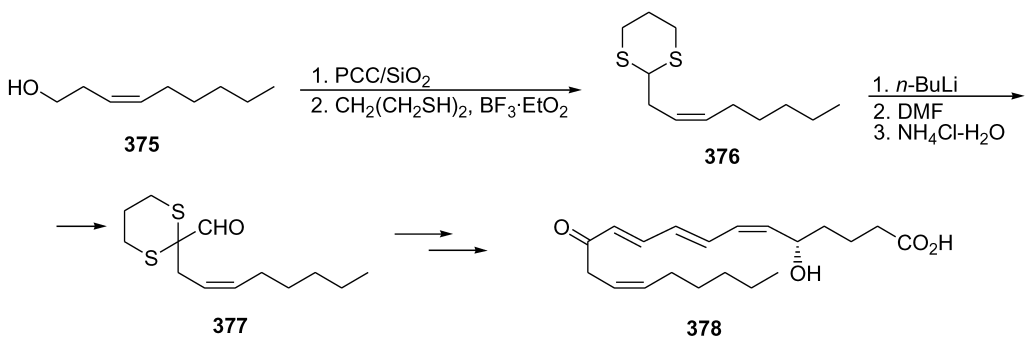


Scheme 80.

acylation of a 1,3-dithiane derivative being involved in the synthetic strategy. The octenyl dithiane **376** was prepared in a two-step, one-pot procedure from the commercially available alcohol **375** in 60% yield. Lithiation of the compound **376** and further reaction with DMF of the resulting lithium derivative gave, after acidic hydrolysis, the aldehyde **377** in 76% yield, which was further transformed into 12-oxo-LTB$_4$ (**378**) (Scheme 82).[170]



Scheme 81.



Scheme 82.

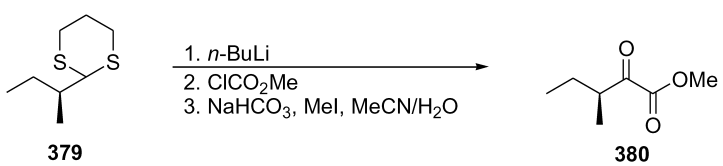
A number of chiral dithianes were synthesised by Tyrrell et al. from the corresponding chiral aldehydes. The lithiation of the dithiane **379** with *n*-BuLi, followed by reaction with methyl chloroformate and final hydrolysis of the dithiane functionality, leading to the formation of the chiral α-oxoester **380** in 54% yield and high enantiomeric purity. This methodology can be applied to the preparation of other β-alkyl-α-oxoesters (Scheme 83).[171]

2.5. Reactions with electron poor-olefins

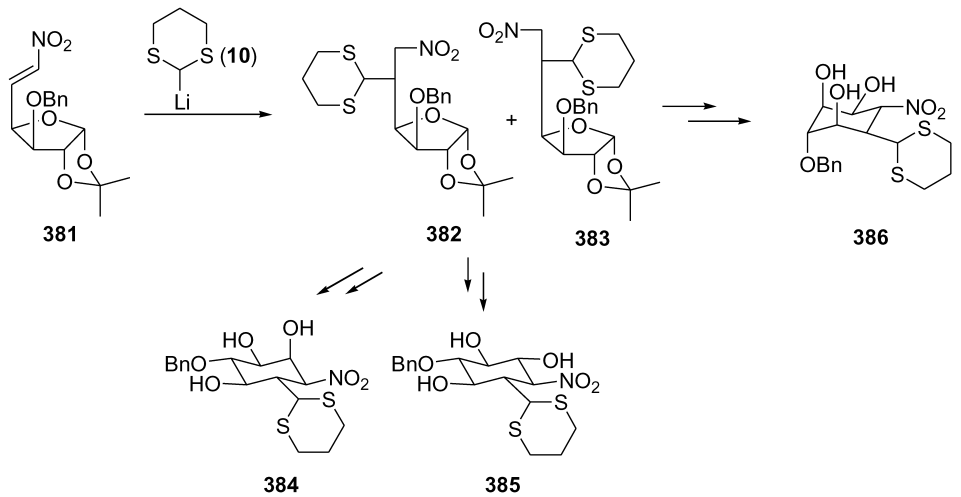
Reich et al. studied the role of polar solvents in controlling the ratio of 1,2- to 1,4-addition of sulfur-substituted organolithium reagents to cyclohexenones by means of multinuclear NMR. In the case of contact ion pairs (CIP), and using THF as the solvent, only the 1,2-addition products are observed. Solvent-separated ion pairs (SIP), however, which are formed by the addition of HMPA, reacted to give predominantly 1,4-addition.[172] The influence of different chiral compounds derived from *N*,*N*′-dimethylpropyleneurea (DMPU) on the regio- and enantioselectivity of the addition of 2-lithio-1,3-dithiane to cyclohex-2-en-1-one was studied by Juaristi et al.[173] These organolithium compounds added smoothly to aliphatic and aromatic nitroolefins between −70 and −110°C.[174,175] Funabashi and Yoshimura studied the Michael addition of 2-lithio-1,3-dithiane (**10**) to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose (**381**).[176] They obtained a mixture of β-L-idofuranose **382** and α-D-glucofuranose **383** derivatives in a ratio of 4:3, respectively. Removal of the isopropylidene group and intramolecular cyclisation under mildly basic conditions gave branched-chain cyclitols having a *myo*- (**384**) or *scyllo*-configuration (**385**) from **382** and a *muco*-configuration (**386**) from **383** (Scheme 84).

Michael addition of 2-lithio-1,3-dithiane (**10**) to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*ribo*-hex-5-enofuranose (**387**)[177] gave a mixture of β-L-talofuranose (**388**) and α-D-allofuranose (**389**) derivatives in a ratio of 1:1 and in 59% yield. Intramolecular cyclisation under mildly basic conditions gave branched-chain cyclitols having an *epi*- (**390**) and *allo*-configuration (**391**) from **389** and a *myo*-configuration (**392**) from **388** (Scheme 85).[177]

The same group observed that the Michael addition of 2-lithio-1,3-dithiane (**10**) to the α-D-*xylo*-hex-5-enofuranose derivative **393** gave α-D-glucofuranose (**394**) and β-L-idofuranose (**395**) derivatives in a ratio of 4:3, respectively, and in ca. 60% yield. In the case of the glucofuranose derivative **394**, intramolecular cyclisation after removal of

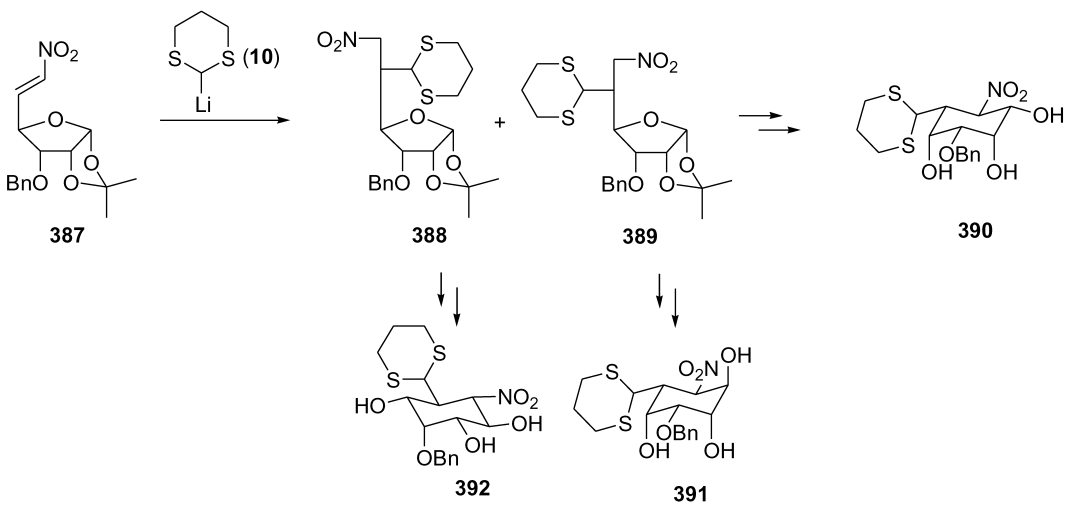


Scheme 83.



381 382 383 386 384 385

Scheme 84.

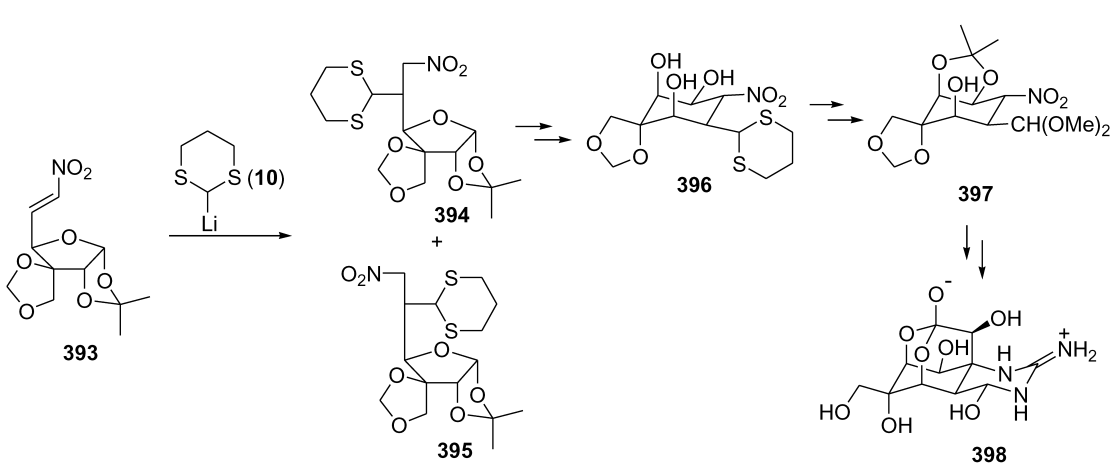


387 388 389 390 392 391

Scheme 85.

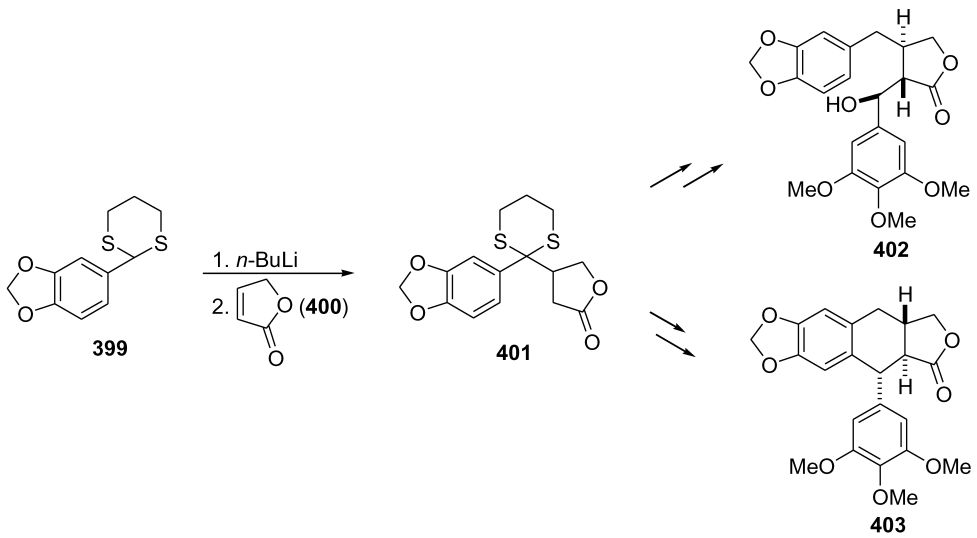
the isopropylidene group gave the branched-chain cyclitol **396** with a *muco*-configuration, which was easily converted into the compound **397**, a potential key precursor for the total synthesis of optically active tetrodotoxin (**398**) (Scheme 86).[178]

The conjugate addition of the aryl dithiane anion derived from the compound **399** to 2-butenolide (**400**) gave the corresponding enolate, which, by low-temperature protonation, led to the compound **401** in 88% yield. The reaction of the enolate resulting from the deprotonation of **401** with an



393 394 395 396 397 398

Scheme 86.



Scheme 87.

appropriate aryl halide or an aromatic aldehyde gave products which were transformed into the lignan lactones (±)-podorhizol (**402**) and (±)-isopodophyllotoxone (**403**) (Scheme 87).[179]

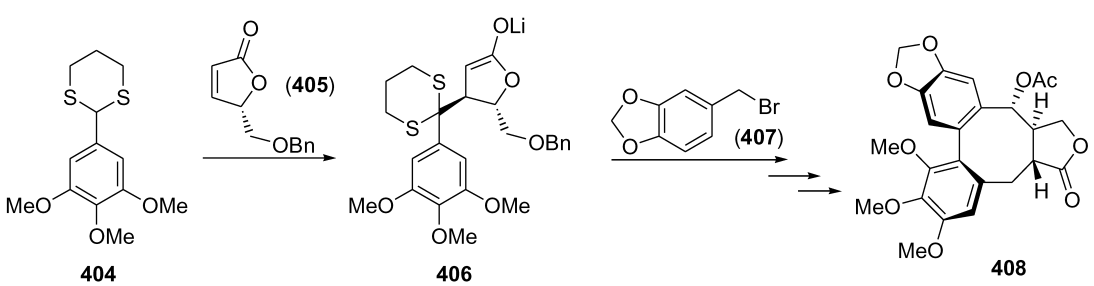
A similar strategy was applied by Koga et al. to the synthesis of the natural lignan (−)-steganacin (**408**), a benzocyclooctadiene lactone with significant antileukemic activity. Stereoselective addition of the aryl-stabilised 2-lithio-1,3-dithiane obtained by the deprotonation of compound **404** to the optically active butenolide **405** gave the enolate **406** in almost quantitative yield, which was trapped with the benzyl bromide **407**. Further transformations including an Ullmann coupling reaction led to (−)-steganacin (**408**) (Scheme 88).[180]

The 1,4-addition of 2-lithio-1,3-dithianes to unsaturated amides, followed by α-alkylation, also constituted a general and efficient synthetic procedure for the formation of two carbon–carbon bonds in a one-pot process. Snieckus and Mpango applied this strategy to the synthesis of the lignans galcatin (**412a**) and isogalcatin (**412b**).[181,182] In this case, sequential reaction of *N*,*N*-dimethylcrotonamide with the anions of the dithianes **409** and the aromatic aldehydes **410** gave the alcohols **411** in ca. 80% yield as a 7:1 mixture of diastereomers, which were efficiently converted into the lignans **412** (Scheme 89).

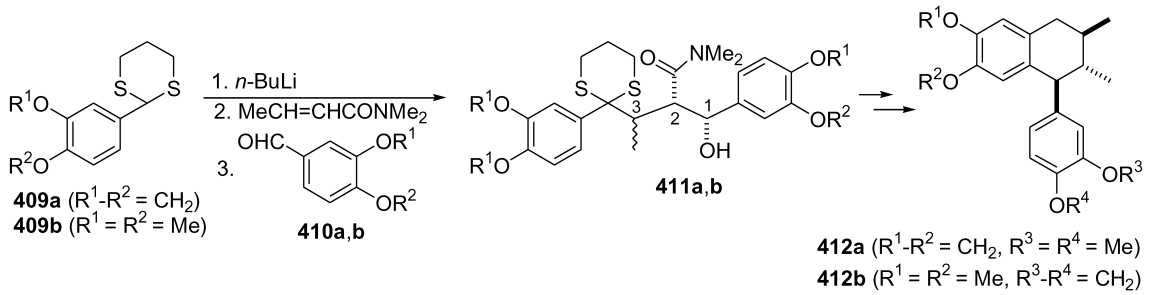
The lithium anion derived from the dithiane of (*E*)-2-methyl-2-butenal (**413**) has been shown to undergo a highly regioselective Michael addition to 2-cyclopentenone (**414**), reacting at the γ-position. Ziegler and Fang reported that the reaction of the resulting enolate with allyl bromide gave the ketone **415** in 87% yield. Subsequent stereoselective transformations of **415** have culminated in the synthesis of the pseudoguaianolide sesquiterpenes (±)-aromatin (**416**) and (±)-confertin (**417**) (Scheme 90).[183]

Fuchs and Saddler have reported on the enantiospecific synthesis of γ-substituted enones such as **421** directed to the synthesis of lathrane-type diterpenes such as jolkinol C (**422**). The dithiane **418** (prepared from the corresponding aldehyde) suffered deprotonation, followed by addition to the vinyl sulfone alcoholate **419**, giving the sulfonyl alcohol **420** in 65% yield, which, by further Swern oxidation and β-elimination of benzenesulfinic acid, led to the chiral enone **421**, a direct precursor of jolkinol C (**422**) (Scheme 91).[184]

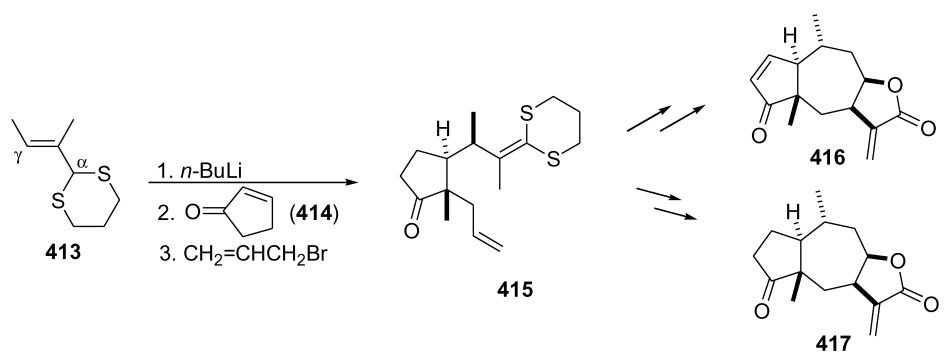
Cameron et al. reported that the addition of the 2-sodium-1,3-dithiane derived from the compound **423** to the phosphonium salt **424** led to the cyclopentenone derivative **425**,[185] which was later converted to dihydrojasmone (**426**) and dihydrojasmolone (**427**) (Scheme 92).[186] On the other hand, the addition of 2-lithio-1,3-dithiane (**10**) to cycloalkenylphosphonium salts has allowed the preparation of chiral *trans*-phosphinocarboxylic acids.[187] These compounds were effective as ligands for the palladium-catalysed asymmetric allylic alkylation of different allylic substrates with soft nucleophiles, to give high yields of the alkylation products with high stereoselectivity. This methodology has



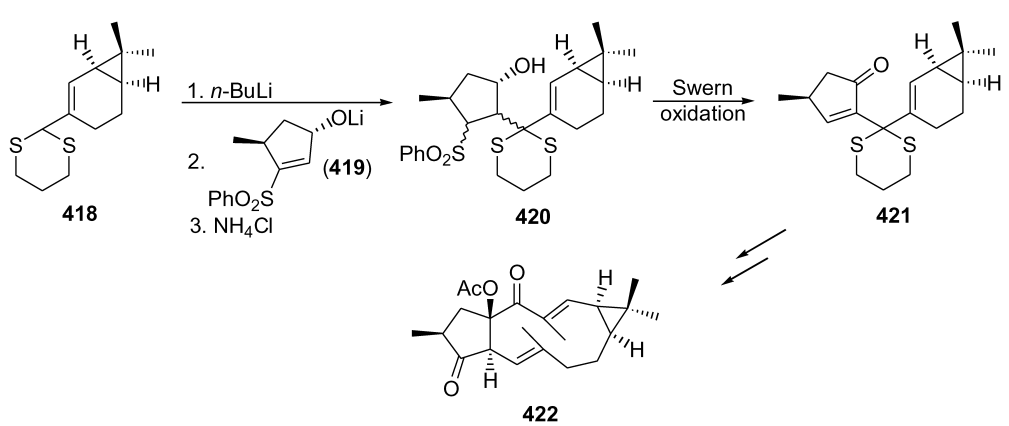
Scheme 88.



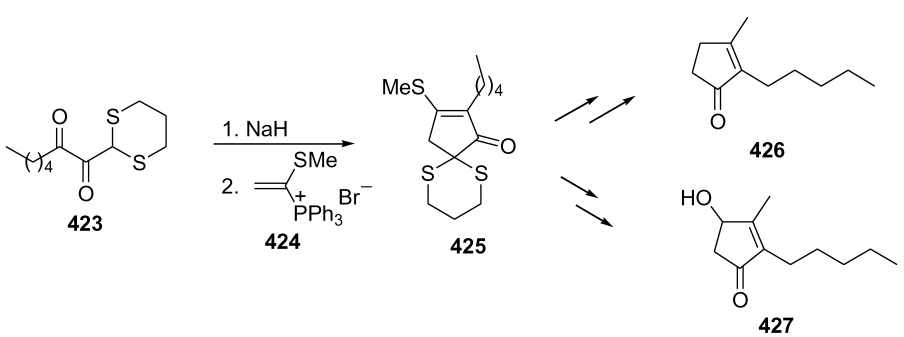
Scheme 89.



Scheme 90.



Scheme 91.



Scheme 92.

been applied to the synthesis of optically active α-methylene-γ-lactones and other α-methylene macrolide derivatives.[188]

The dianion **429**, derived from 2-(1,3-dithian-2-yl)indole (**428**), has found a wide applicability in the synthesis of different strychnos alkaloids developed by the groups of Husson and Rubiralta. The reaction of the compound **429** with allylic amino nitriles **430** or α,β-unsaturated lactams **431** allowed the preparation of 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indoles **432**, with the ABED ring system of strychnos alkaloids, through a conjugate addition.[189–194] Using an optically active lactam **431** [R=2-hydroxy-1-phenylethyl with (*R*)-configuration, prepared by nucleophilic attack of the nitrogen on the benzylic position of (*S*)-styrene oxide], it is possible to prepare the compounds **432** in an enantioselective form (Scheme 93).[195] It is also known that conjugate addition occurs in the reaction of lithiated 1,3-dithianes with 1-methyl-4-quinolone.[196]

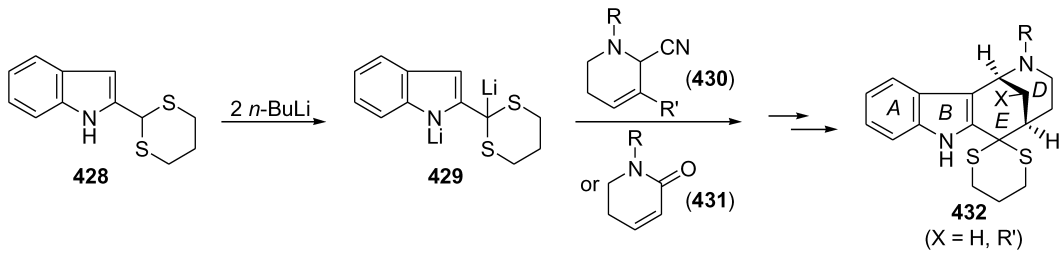
The previously mentioned methodology has been applied to the synthesis of 20-epidasycarpidone (**434**) and 20-epiuleine (**435**), using the 2-ethyl-substituted α,β-unsaturated lactam **433** as the electrophile (Scheme 94).[197]

A tandem conjugate addition–alkylation reaction starting from the indolyldithiane **428**, the methylenelactam **436** and ethyl iodide yielded the adduct **437**. Treatment of the lactam **437** with DIBALH led to a pyridocarbazole with the ABCD ring structure of the alkaloid aspidospermidine (**438**). The remaining ring E was constructed at the end of the synthesis (Scheme 95).[198]

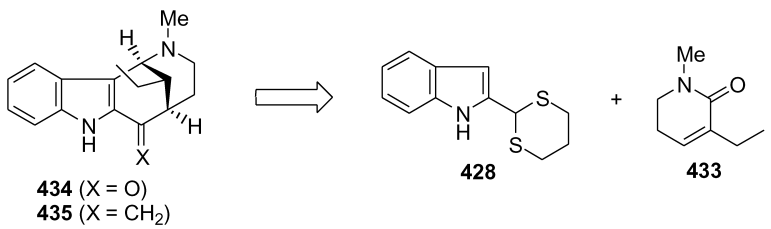
Goto et al. reported the synthesis of the compounds **441** having a bicyclo[7.3.1]tridec-4-ene-2,6-diyne system which is present in dynemicin A,[199] a potent antitumour antibiotic. The synthesis started from 3-ethoxy-2-cyclohexen-1-one (**439**), acting as a β-acylvinyl cationic equivalent,[200] which was homologated to give the compound **440** in ca. 60% yield with 2-lithio-1,3-dithiane (**10**), through nucleophilic vinylic substitution of the intermediate **10**, followed by transacetalisation (Scheme 96).[201]

Harrowven reported a concise regioselective total synthesis of the lignans taiwanin E (**444a**) and chinensinaphthol (**444b**). This approach features a Michael-initiated ring closure (MIRC) sequence to access the key lignan intermediates **443**. The reaction of the organolithium compound initially formed by the deprotonation of the starting material **442** with 2-butenolide (**400**) led to the compounds **443a** and **443b** in 79 and 53% yield, respectively. Final hydrolysis afforded the products **444** after smooth aromatisation (Scheme 97).[202]

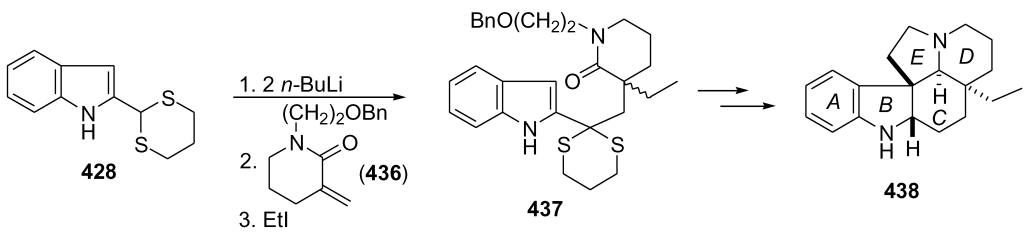
The 1,4-addition of 2-lithio-1,3-dithiane (**10**) to α,β-unsaturated nitriles was initially investigated by DeBernardis et al.[203] The intramolecular version of this process has been used for the construction of the quinolizidine ring **446**, which is potentially an excellent alkaloid precursor, using



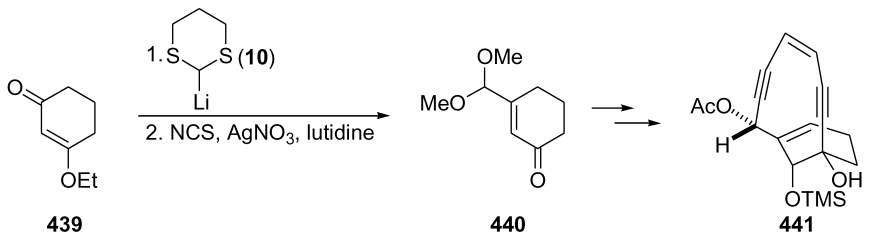
Scheme 93.



Scheme 94.

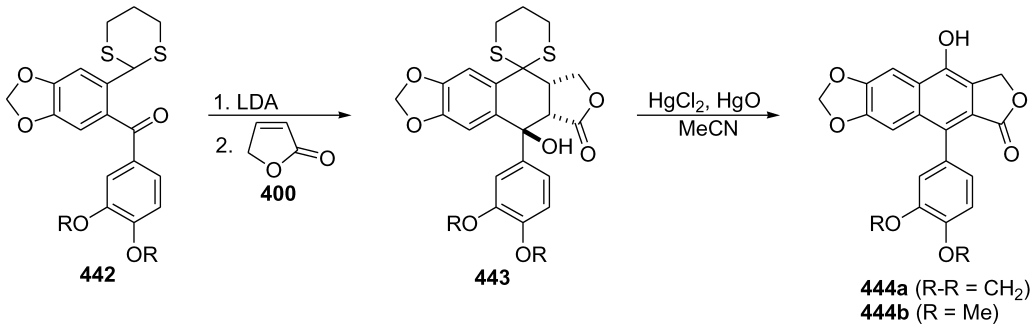


Scheme 95.



439 440 441

Scheme 96.

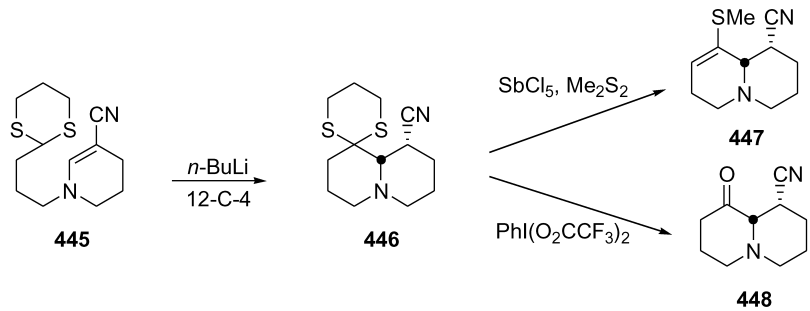


442 443 **444a** (R-R = CH_2) **444b** (R = Me)

Scheme 97.

the 1,3-dithiane derivative **445** as the starting material. The process takes place with good diastereoselectivity (90% yield, 4:1 mixture of diastereomers). Only a few reagents can be used in deprotecting dithiane-containing alkaloids, including the combination $SbCl_5$–Me_2S_2, but in this case the reaction product is not the anticipated ketone **448**, but the vinyl sulfide **447**.[204,205] Bis(trifluoroacetoxy)iodobenzene, however, led to the formation of the expected ketone **448** in 85% yield, further purification not being necessary (Scheme 98).[206,207]

products.[209] Using 2-lithio-1,3-dithianes as nucleophiles, these metal tricarbonyl complexes act as alkylation reagents at the 2-position of the dithiane unit. This methodology has been used extensively in synthesis and, more recently, examples of nucleophilic addition of anionic dithiane derivatives to other metal tricarbonyl complexes different to iron and chromium have been reported. With tricarbonyl(η^5-cyclohexadienyl)manganese, nucleophilic addition took place at the terminus of the π-system and, after oxidation, 5-[2-(1,3-dithianyl)]-



445 446 447 448

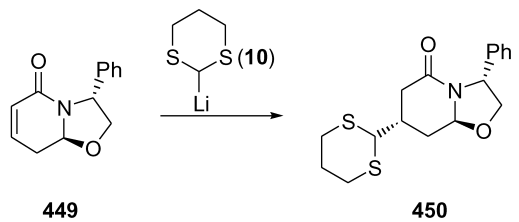
Scheme 98.

In the stereodivergent synthesis of enantiopure *cis*- and *trans*-3-ethyl-4-piperidine acetates, Amat et al. reported that the conjugate addition of stabilised anions such as 2-lithio-1,3-dithiane (**10**) to the α,β-unsaturated ketone **449** takes place with total stereoselectivity, to give the dithioacetal **450** in 71% yield (Scheme 99).[208]

2.6. Reactions with metal–arene complexes

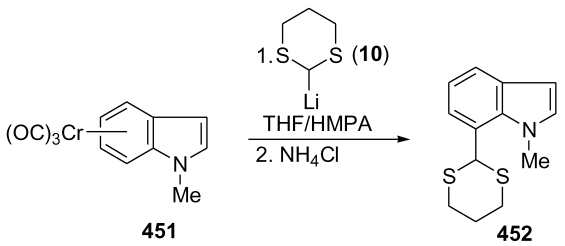
Attachment of a metal tricarbonyl fragment to a diene for iron derivatives or to an arene for chromium derivatives induces a strong polarisability in the carbon π-bond systems. Nucleophilic addition can occur to give anionic intermediates which can be manipulated into useful organic

1,3-cyclohexadiene was obtained in good yield.[210] Similarly, an example of the addition of dithiane anions to an arene molybdenum tricarbonyl complex has been reported by Kündig et al.[211]



449 450

Scheme 99.



Scheme 100.

The tricarbonylchromium complex of *N*-methylindole **451** underwent a nucleophilic substitution reaction with 2-lithio-1,3-dithiane (**10**) to give the 7-substituted indol **452** in 41% yield (Scheme 100).[212]

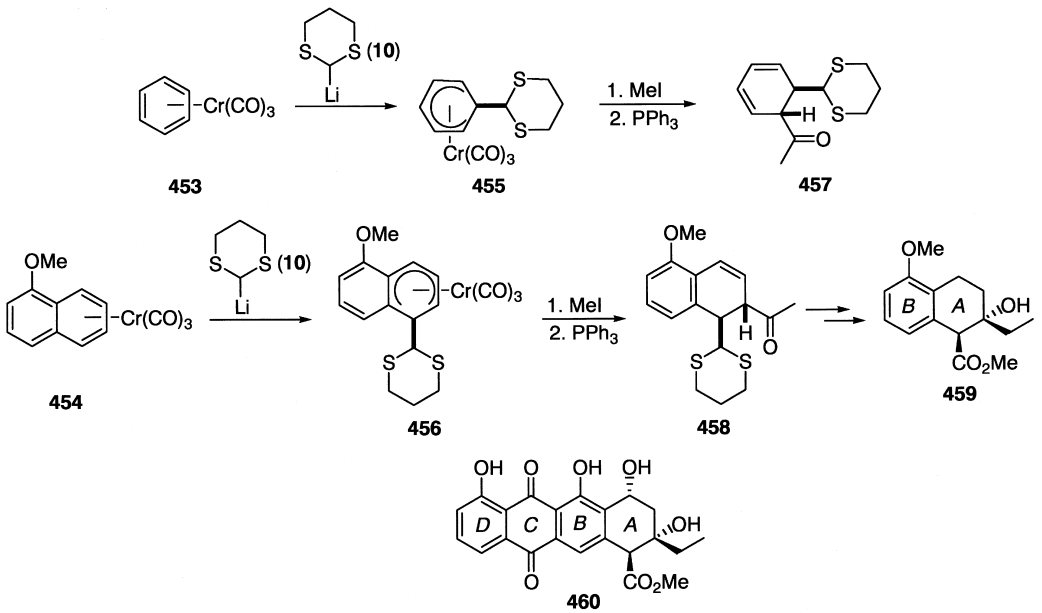
Kündig et al. also reported that the addition of 2-lithio-1,3-dithiane (**10**) to benzene–$Cr(CO)_3$ (**453**) and 1-methoxynaphthalene–$Cr(CO)_3$ (**454**) led to the anionic cyclohexadienyl-$Cr(CO)_3$ complexes **455** and **456**, respectively, which, by reaction with methyl iodide, led, after Ph_3P-induced carbonylation, to the disubstituted cyclohexadiene **457** and dihydronaphthalene **458**, in 54 and 72% overall yield, respectively (Scheme 101).[213] This methodology has been applied to a formal synthesis of the aklavinone AB ring (**459**). Aklavinone (**460**) is the aglycone of aclacynomycine A, an antibiotic of the anthracyclinone family (Scheme 101).[214]

Woodgate et al. studied the nucleophilic substitution in the methyl podocarpa-8,11,13-trien-19-oate tricarbonylchromium complex (**461**) with 2-lithio-2-methyl-1,3-dithiane (**462**). Regioselective attack took place to give, after treatment with iodine, compound **463** in 39% yield and its C(14) regioisomer in a lesser extension (Scheme 102).[215]

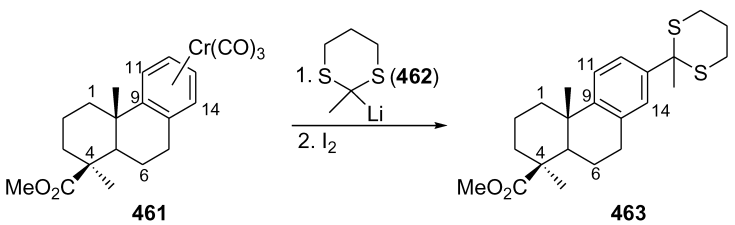
The enantioselective total synthesis of the marine natural product (+)-ptilocaulin, a highly antimicrobial and cytotoxic active metabolite which was first isolated from a Caribbean sponge in 1981 as its nitrate **467**,[216] was accomplished by Schmalz et al.[217] The key step of the synthesis is the nucleophilic addition of 2-lithio-1,3-dithiane (**10**) to the enantiomerically pure arene–$Cr(CO)_3$ complex **464**,[218] followed by treatment with TMSCl, light-induced decomplexation and final acidic hydrolysis, to give the desired enone **465** in 45–53% yield and >99% optical purity. This compound was transformed into the hydroindenone **466** by a 4-step sequence, which, by reaction with guanidine and protonation with dilute nitric acid, gave a crude product consisting mainly of the desired product **467** and an epimer in a ratio of ca. 4:1 (Scheme 103).

2.7. Combined methods

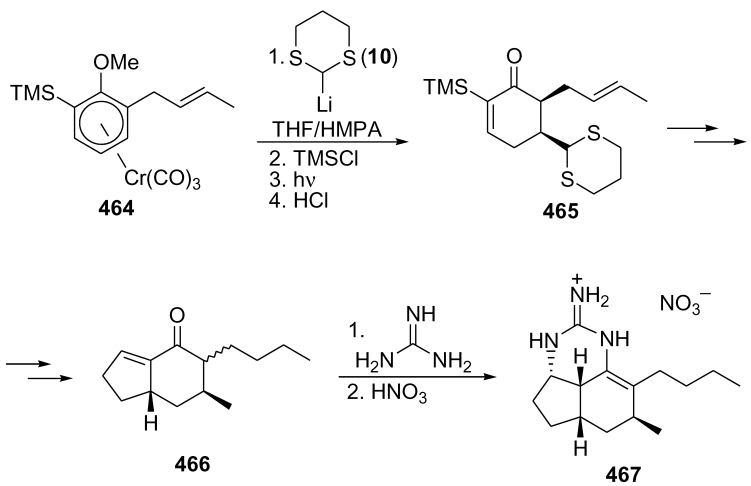
In this section, processes in which 1,3-dithianes are involved in reactions with different types of electrophiles,



Scheme 101.



Scheme 102.



Scheme 103.

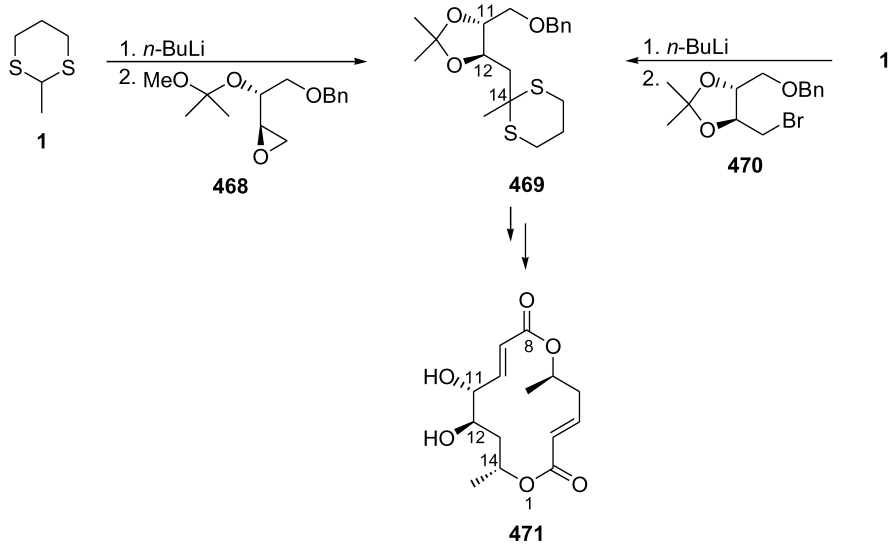
either acting as formyl dianion or multiple acyl anion equivalents, will be considered.

2.7.1. Reactions with alkyl halides or sulfonates and epoxides. The methoxyisopropyloxy derivative **468** reacted with 2-lithio-2-methyl-1,3-dithiane [2-Li-(**1**)] to form the acetonide **469**, in 89% yield, a key intermediate in the synthesis of the macrodiolide antibiotic (+)-colletodiol (**471**) reported by Seebach et al. The compound **469** could also be prepared in high yield from the bromide **470** by reaction with the same lithio dithiane derivative (Scheme 104).[219]

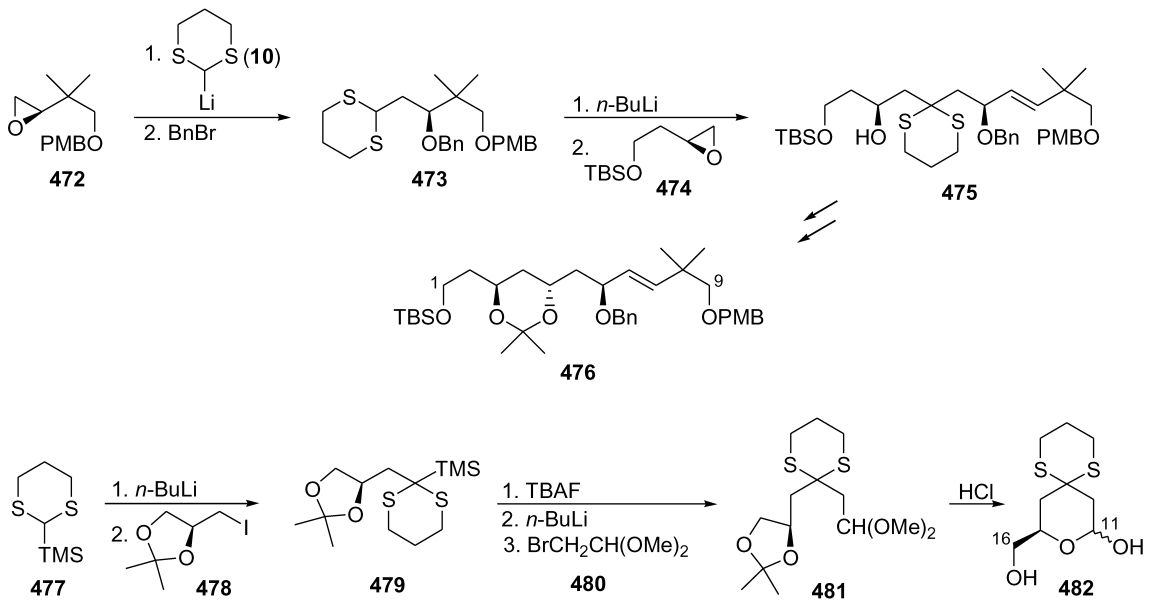
The fragments C(1)–C(9) **476** and C(11)–C(16) **482** of bryostatin 1 (**100**) (Scheme 21) were constructed by Vandewalle et al. in an enantioselective and highly diastereoselective fashion from different chiral templates. For the synthesis of the compound **476**, the epoxide **472** reacted with 2-lithio-1,3-dithiane (**10**) to give the dithiane **473** in 84% yield, after formation of the corresponding benzyl ether. Deprotonation of the dithiane derivative **473** and further reaction with the chiral epoxide **474**, led to the expected product **475** in only 21% yield, this being a convenient precursor of the target compound **476**. For the construction of the fragment C(11)–C(16) **482**, the iodide **478**, derived from L-erythrulose, reacted with the anion resulting from the deprotonation of the 2-silyl-1,3-dithiane derivative **477** to give the dithiane **479** in 82% yield. Desilylation, deprotonation and reaction with 2-bromoacetaldehyde dimethyl acetal (**480**) gave the compound **481** in 80% yield, which was subsequently hydrolysed, affording the compound **482** as the corresponding anomeric mixture (Scheme 105).[220]

A 14-membered lactone was synthesised by Weiler and Spracklin by a double alkylation of 1,3-dithiane, the reaction of 2-lithio-1,3-dithiane (**10**) with the alkyl bromide **483**, followed by a new deprotonation and reaction with propylene oxide (**484**), affording the corresponding compound **485** in 67% overall yield. Convenient functional group transformations including lactonisation led to the expected macrocyclic lactone **486** (Scheme 106).[221]

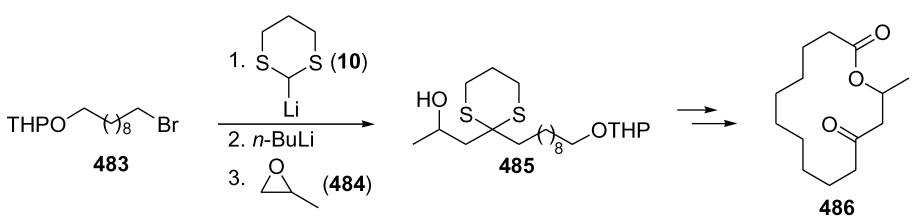
Krohn and Börner reported the synthesis of several carbocyclic rings starting from the dithioacetal **488** by intramolecular nucleophilic displacement reactions. The



Scheme 104.



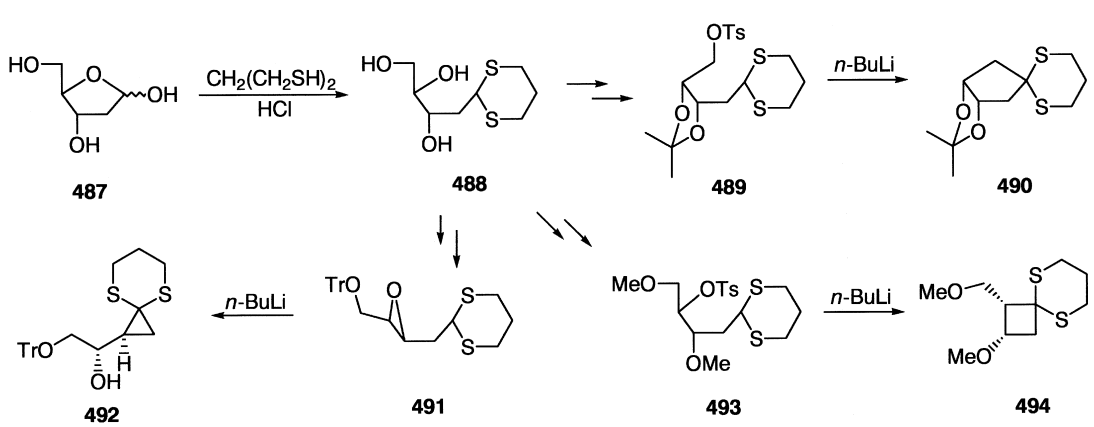
Scheme 105.



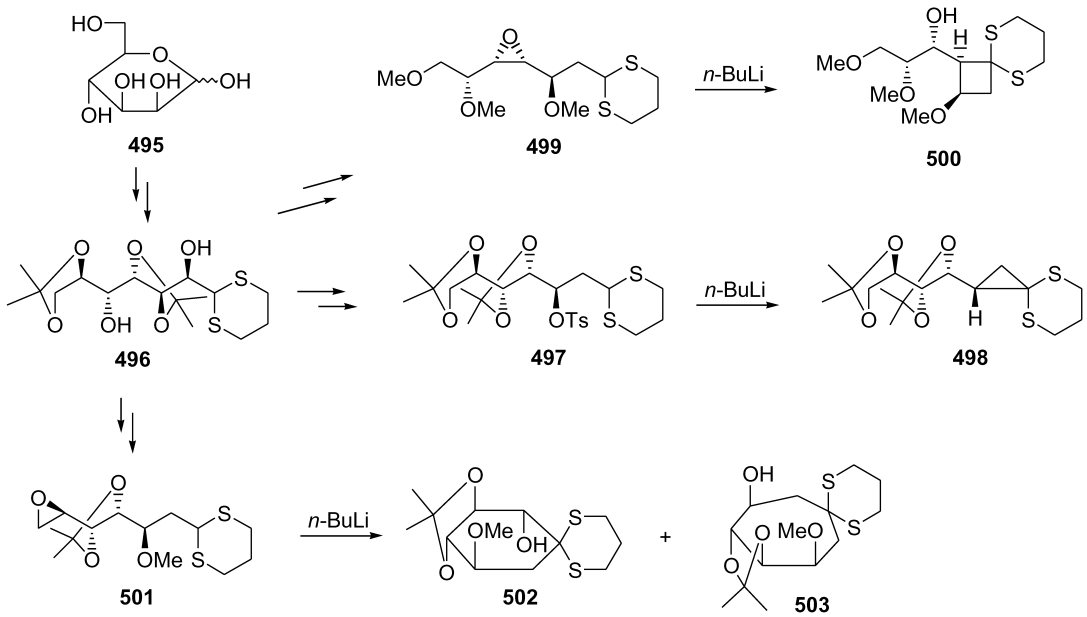
Scheme 106.

dithioacetal **488** was prepared from 2-deoxy-D-ribose (**487**) in 90% yield and the conversion of the aldehyde functionality into a dithiane provided the sugar in a fixed open-chain form that is advantageous for selective functional group transformations, treatment of the tosylate acetonide **489** with *n*-BuLi giving the cyclopentane derivative **490** in 71% yield. Although, in the case of the epoxide **491**, the cyclopropane **492** was obtained in 70% yield, in the case of the tosylate **493**, intramolecular nucleophilic displacement gave the cyclobutane **494** in only 18% yield (Scheme 107).[222]

The same authors have reported the synthesis of other carbocycles starting from the dithiane derivative **496**, which was prepared from D-mannose (**495**).[223] Appropriate activation (tosylate, epoxide) and protection (acetonide, methyl ether) yielded the compounds **497**, **499** and **501**, the starting materials for carbocyclisation. These were converted by intramolecular nucleophilic displacement to the optically active cyclopropane **498** (34% yield), the cyclobutane **500** (77% yield) and a mixture of the cyclohexane **502** (55% yield) and the cycloheptane **503** (12% yield), respectively (Scheme 108).[224]

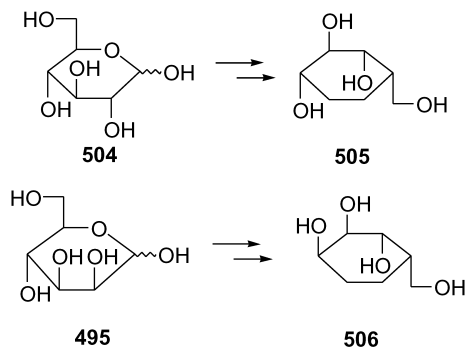


Scheme 107.



Scheme 108.

Through intramolecular nucleophilic displacement reactions, valitol (**505**) and 4-*epi*-valitol (**506**) have also been synthesised, starting from D-glucose (**504**) and D-mannose (**495**), respectively (Scheme 109).[225]



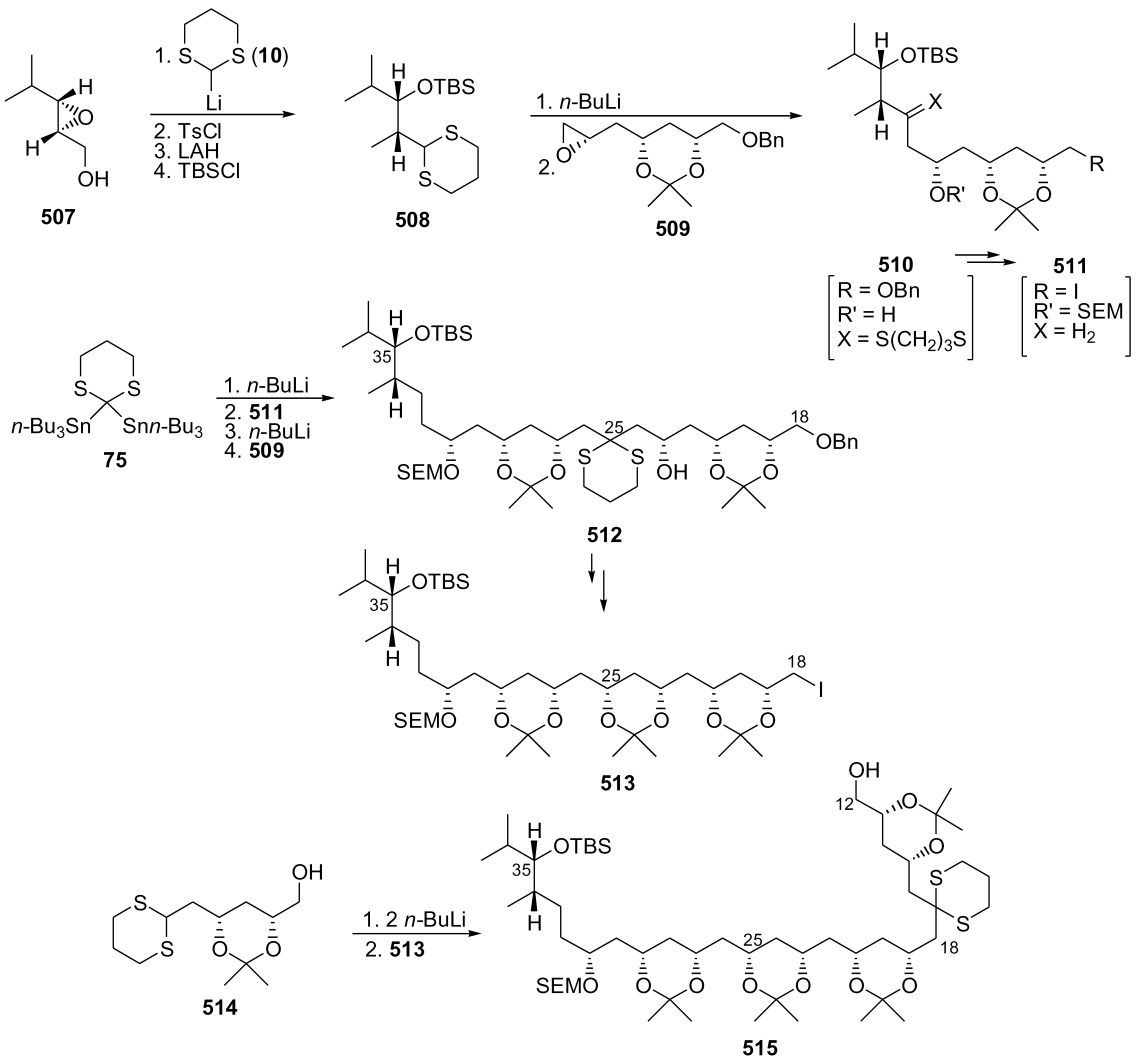
Scheme 109.

Roflamycoin (**520**) (Scheme 111) is a polyene macrolide with potent antifungal activity.[226] Its synthesis and structural elucidation[227] have received much attention in recent years. A partial synthesis of roflamycoin has been developed by Lipshutz et al. involving dithiane anion derivatives.[228] Treatment of the epoxy alcohol **507** with 2 equiv. of 2-lithio-1,3-dithiane (**10**) gave the corresponding diol in 79% yield, which was transformed into the dithiane derivative **508** after three reaction steps. Deprotonation of the compound **508** and reaction with the epoxide **509** gave the alcohol **510**, in 80% yield, a precursor of the iodide **511**. On the other hand, the distannylated dithiane **75** was used as a one-carbon lynchpin in the connection of the fragments **511** and **509**, through a double sequential tin–lithium exchange and reaction with the corresponding electrophile to give the compound **512**, which is a precursor of the iodide **513**. Finally, reaction of the lithiodithiane derived from **514** with the iodide **513** gave the alcohol **515** in 93% yield, and the Southern hemisphere corresponding to the C(12)–C(35) fragment of the target molecule was therefore accessible (Scheme 110).

A similar strategy has been developed by Rychnovsky et al. in the total synthesis of roflamycoin (**520**). Transmetallation of the distannane **75** with *n*-BuLi and reaction with the epoxide **516** gave the *anti*-diol **517** in 56% yield. Acetonide protection, transmetallation and alkylation with an excess of the dibromide **518** gave the dithiane **519** in 60% overall yield. This compound was further transformed into roflamycoin (**520**) (Scheme 111).[229]

Lasiodiplodin 1 (**524**) is a constituent of the fungus *Lasiodiplodia theobromae*[230] with significant antileukemic activity[231] for which Bracher and Schulte have reported a straightforward approach. Double alkylation of 1,3-dithiane with 5-bromopent-1-ene (**34**) and (*S*)-propylene oxide [(*S*)-**484**] gave the alcohol **521** in 86% yield, an advanced precursor of the target molecule **524**. The compound **521** could also be prepared in 85% yield by double deprotonation of the dithiane derivative **522** and reaction with the bromide **34** (Scheme 112).[232] The chiral building block **522** was prepared by microbial reduction of 2-(3-oxopropyl)-1,3-dithiane with baker's yeast[233] and has been used in the synthesis of the macrocyclic lactone (*S*)-curvularin[234] and the pheromone (*S*)-tridecanol acetate.[235] Hydroboration of the compound **521**, followed by palladium-catalysed coupling with the triflate **523**, basic hydrolysis of the ester unit, macrolactonisation under Mitsunobu reaction conditions and final reduction of the dithiane unit with Raney nickel, gave lasiodiplodin 1 (**524**) in 26% overall yield.

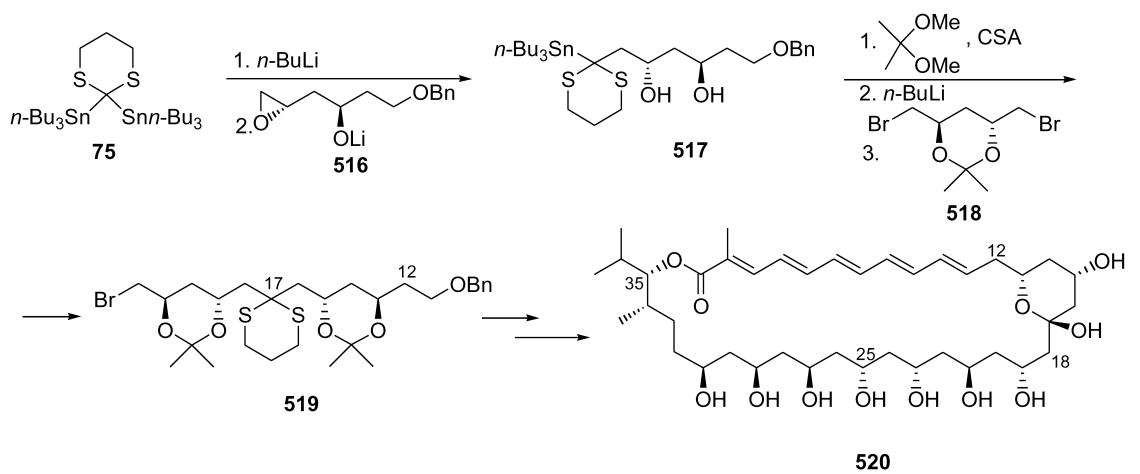
The bicyclic ethers attenol A (**527**) and B (**528**) were isolated from the Chinese bivalve *Pinna attenuata*[236] and exhibit cytotoxic activity against different cells. In the synthesis of the left-hand segment proposed by Suenaga et al., double alkylation of 1,3-dithiane with 5-bromo-1-pentene (**34**) and (*R*)-benzylglycidyl ether [(*R*)-**218**] afforded the compound **525** in almost 80% yield. Hydrolysis



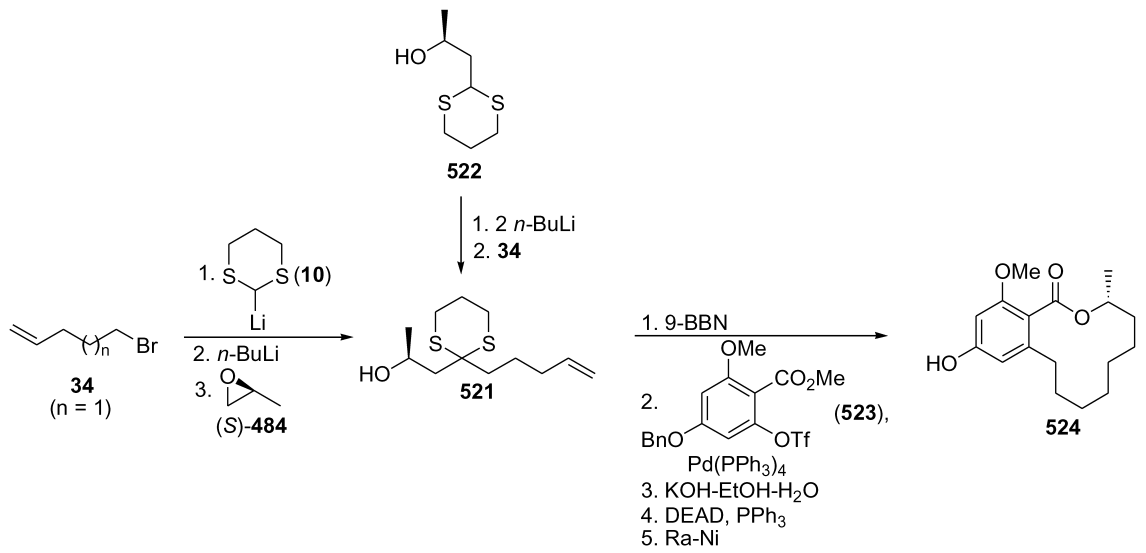
Scheme 110.

of the dithiane **525** gave a hydroxyketone, which was reduced stereoselectively to the *anti*-diol **526** in 88% yield, along with the *syn*-diol (10% yield) (Scheme 113).[237]

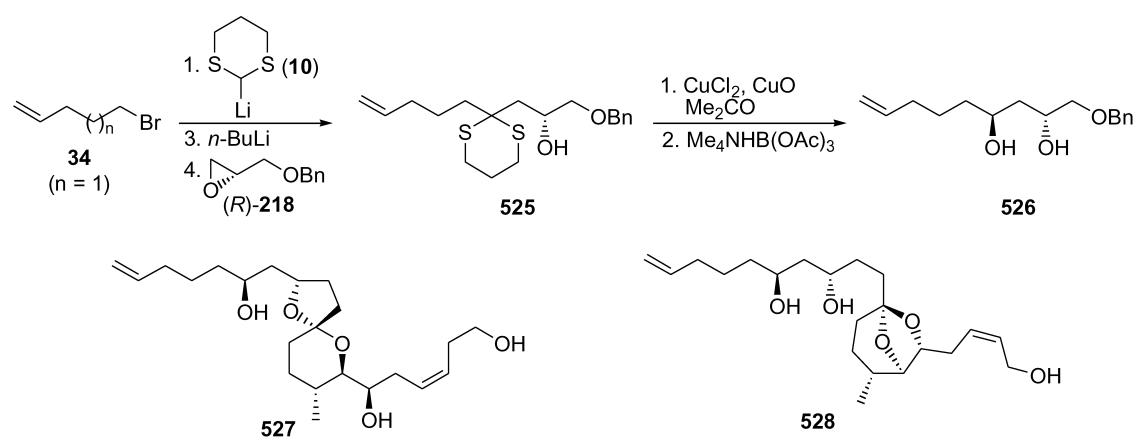
Molander et al. have reported the synthesis of pinidinol (**532**).[238] The starting material in this synthesis was prepared by a one-pot alkylation of 1,3-dithiane with (*R*)-propylene oxide [(*R*)-**484**] and 1-iodo-4-pentene (**529**) to give the alcohol **530**, which, without purification, was converted to the compound **531** by protecting the alcohol with TBDPSCl, removing the dithiane unit with $HgCl_2$ and stereoselectively reducing the siloxyketone with $NaBH_4$. A



Scheme 111.



Scheme 112.

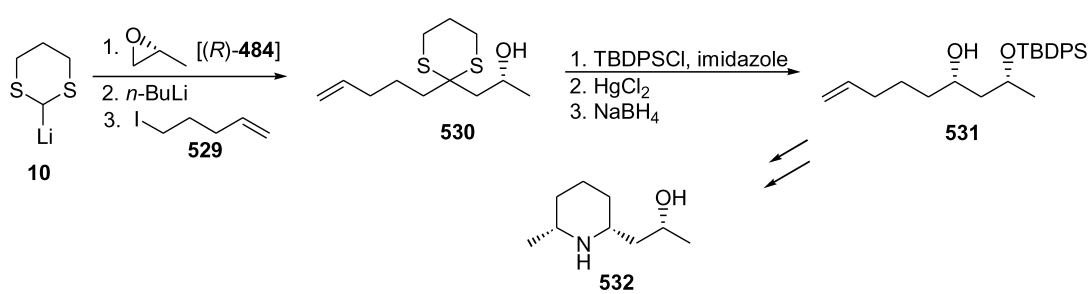


Scheme 113.

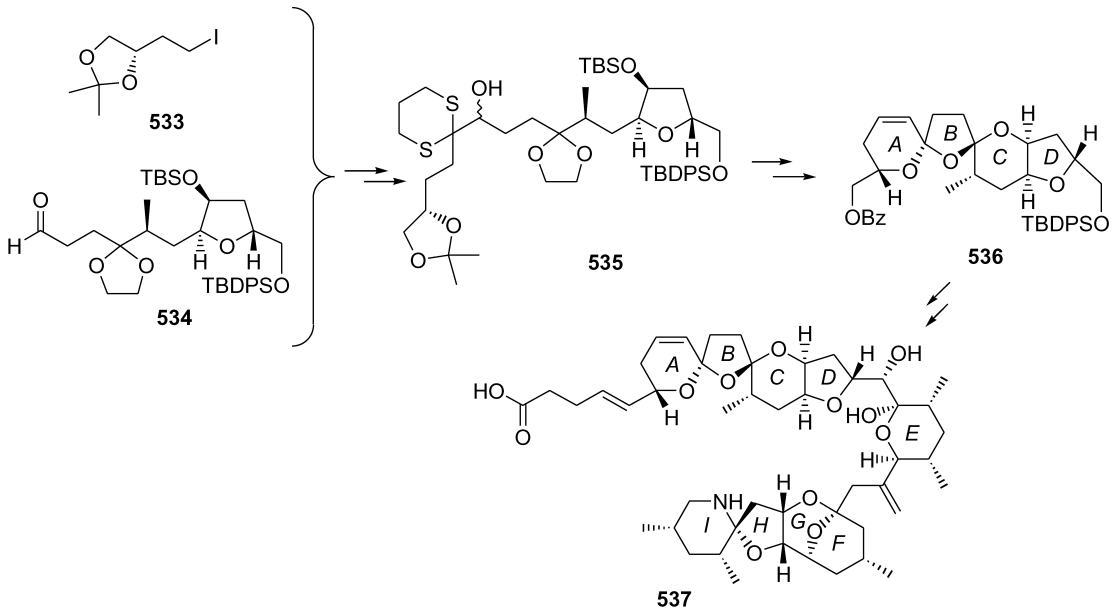
3.7:1 ratio of chromatographically separable diastereomers was obtained in 74% overall yield, the major isomer being the *syn*-diol derivative **531**. Another key step of the synthesis is the formation of the piperidine ring by a lanthanide-promoted heterocyclisation (Scheme 114).[239]

2.7.2. Reactions with alkyl halides and carbonyl compounds. Azaspiracid (**537**) is a marine biotoxin.[240] In the synthesis of the ABCD ring framework **536** reported by Nicolaou et al., a sequential double alkylation of 1,3-dithiane first with the iodoacetonide **533** and then with the chiral aldehyde **534** led to a 1:1 mixture of diastereomeric alcohols **535** in 88% yield (Scheme 115).[241] The nule stereoselectivity in this kind of reaction had previously been observed by Jenkins[242] and Chikashita et al.[243]

2.7.3. Reactions with alkyl halides and acylating reagents. In order to investigate the antibiotic activities of different diolides against numerous microorganisms, Seebach et al. synthesised (−)-pyrenophorin (**541a**)[23,244] and norpyrenophorin (**541b**)[23] following a common strategy. Alkylation of 2-lithio-1,3-dithiane (**10**) with the alkyl halides **538**, followed by a second lithiation of the resulting 2-substituted-1,3-dithiane and reaction with DMF, gave the



Scheme 114.



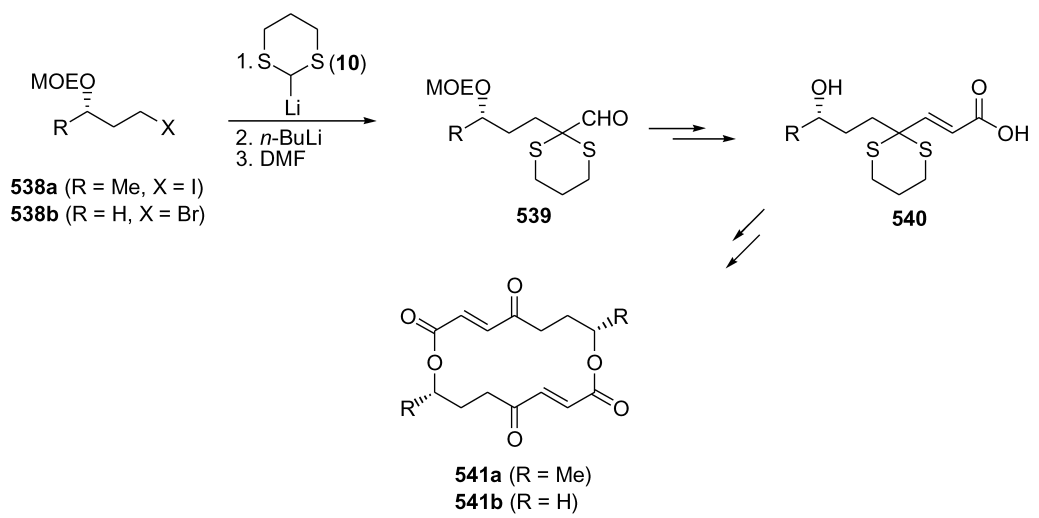
Scheme 115.

corresponding aldehydes **539**. Olefination and deprotection of the hydroxy group gave the half-protected *seco*-acid derivatives **540** in 60% overall yields in both cases, which, after Mitsunobu macrocyclisation and hydrolytic cleavage of the dithiane with $HgO–BF_3·OEt_2$, led to (−)-pyrenophorin (**541a**) and norpyrenophorin (**541b**) in 27 and 17% overall yields, respectively (Scheme 116). This methodology was used to prepare also in an enantiomerically pure form, (+)-pyrenophorin and a hexafluoro (+)-pyrenophorin derivative,[245] by changing the starting alkyl halide **538**.

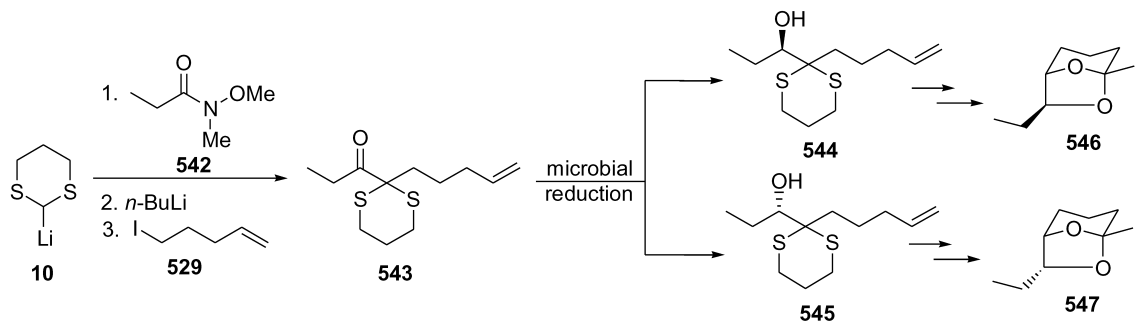
Microbial reduction[233] of the α-ketothioacetal **543**, prepared from 2-lithio-1,3-dithiane (**10**) by successive acylation with the Weinreb amide **542** and alkylation with the iodide **529**, gave the enantiopure alcohols **544** and **545**. These compounds have been used as precursors in the synthesis of natural insect pheromones such as (−)-*exo*-(**546**) and (−)-*endo*-brevicomine (**547**) (Scheme 117).[246]

2.7.4. Reactions with epoxides and carbonyl compounds. In 1980, Corey et al. reported the first total synthesis of maytansine (**552**), a natural product with antitumour activity. The acetal thioacetal **549** was prepared in 86% overall yield by alkylation of 2-lithio-1,3-dithiane (**10**) with the chiral epoxide **548**, followed by protection of the resulting hydroxy group.[247] Lithiation of the compound **549**, followed by reaction with the aldehyde **550**,[248] led in ca. 90% yield to a 1:1 mixture of compound **551** and its C(10) epimer. These epimers were readily separated to give **551** in 44% yield and an equal amount of the C(10) epimer, which was efficiently converted into compound **551** by oxidation to the corresponding ketone and final reduction. The compound **551**, which is an advanced key intermediate in the synthesis of maytansine (**552**), was obtained in 80% overall yield from **549** (Scheme 118).[249]

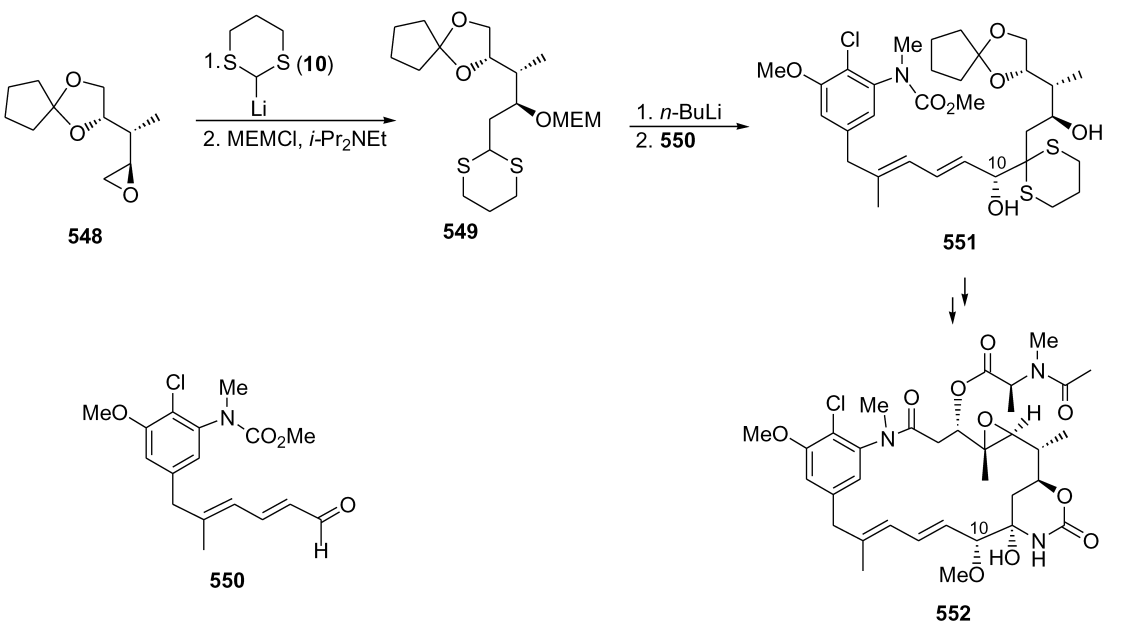
Williams and Sit have reported the total synthesis of



Scheme 116.



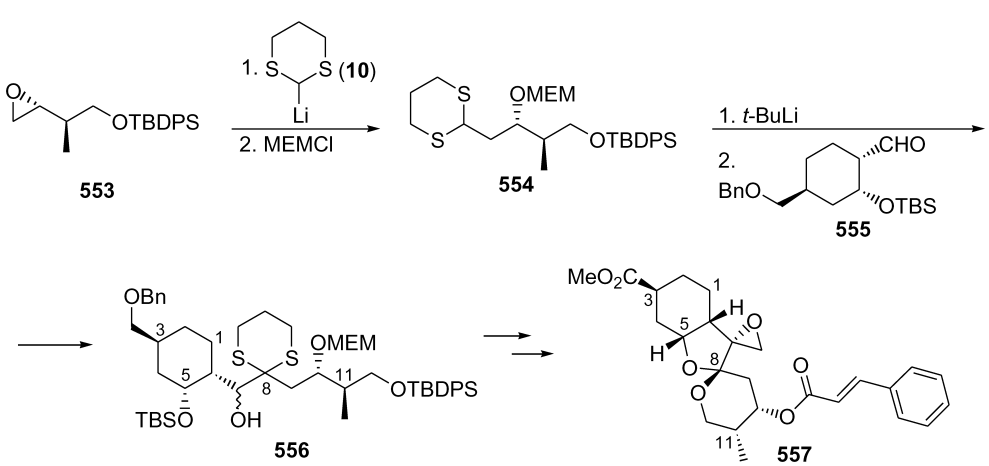
Scheme 117.



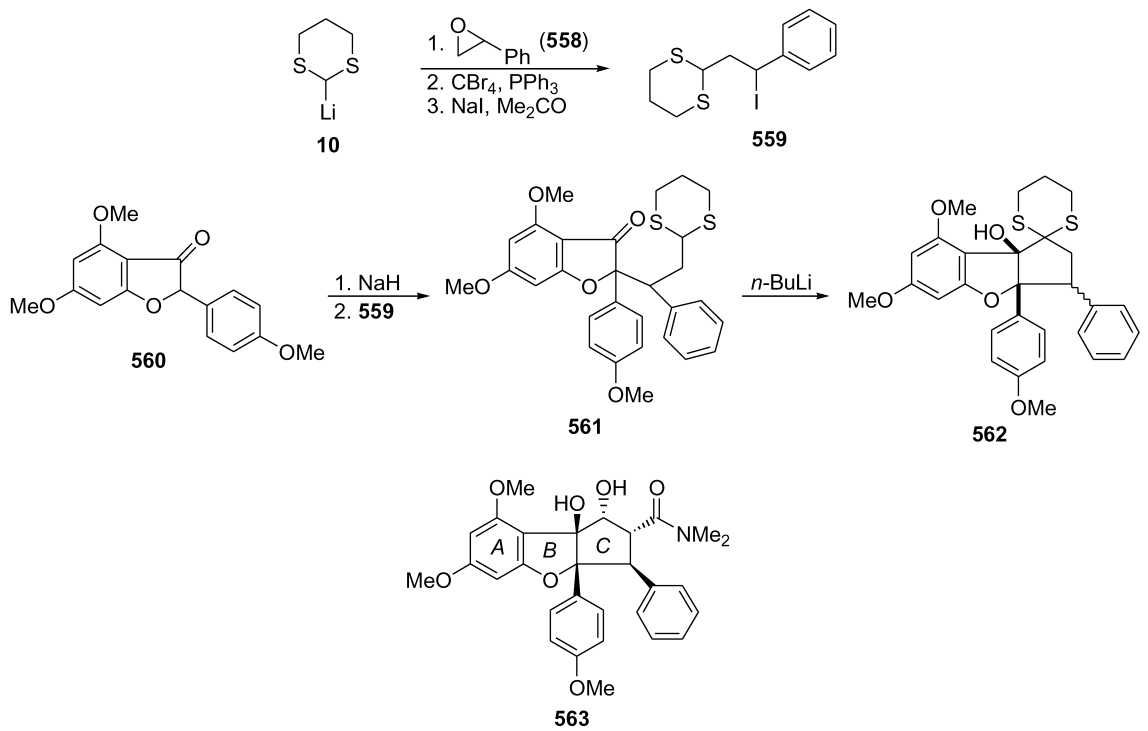
Scheme 118.

(+)-phyllanthocin (**557**), the aglycon of (+)-phyllanthoside,[250] an antileukemic glycoside. In this convergent synthesis, the substituted dithiane **554** was prepared in 90% overall yield by the addition of 2-lithio-1,3-dithiane (**10**) to the epoxide **553**, followed by protection of the hydroxy group. Deprotonation of the compound **554** and addition to the aldehyde **555** gave the compound **556** as a 3.5:1 mixture of diastereomers in 80% yield, which could be separated. Further transformations led to the desired product **557** (Scheme 119).[251]

A three-carbon cyclopentanone annelation procedure has been employed by Davey and Taylor in the construction of ring C in a synthetic approach to rocaglamide (**563**), an antileukemic benzofuran derivative.[252] The requisite alkylating agent **559** was easily prepared in 50% overall yield by



Scheme 119.



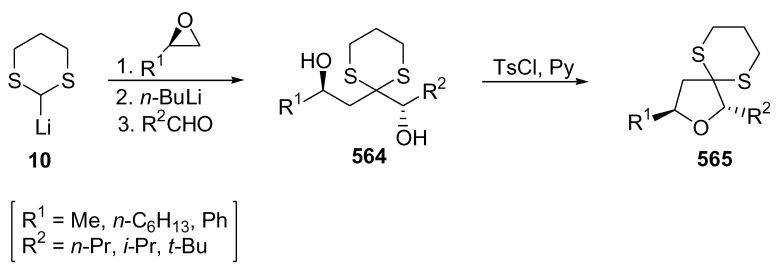
Scheme 120.

the reaction of styrene oxide (**558**) with 2-lithio-1,3-dithiane (**10**), followed by iodination of the resulting benzylic alcohol. Treatment of the benzofuranone **560** with sodium hydride and the alkyl iodide **559** afforded the compound **561** in 61% yield. Deprotonation of this compound with *n*-BuLi in the presence of HMPA at low temperature gave the expected cyclisation product **562** in 64% yield (Scheme 120).[253]

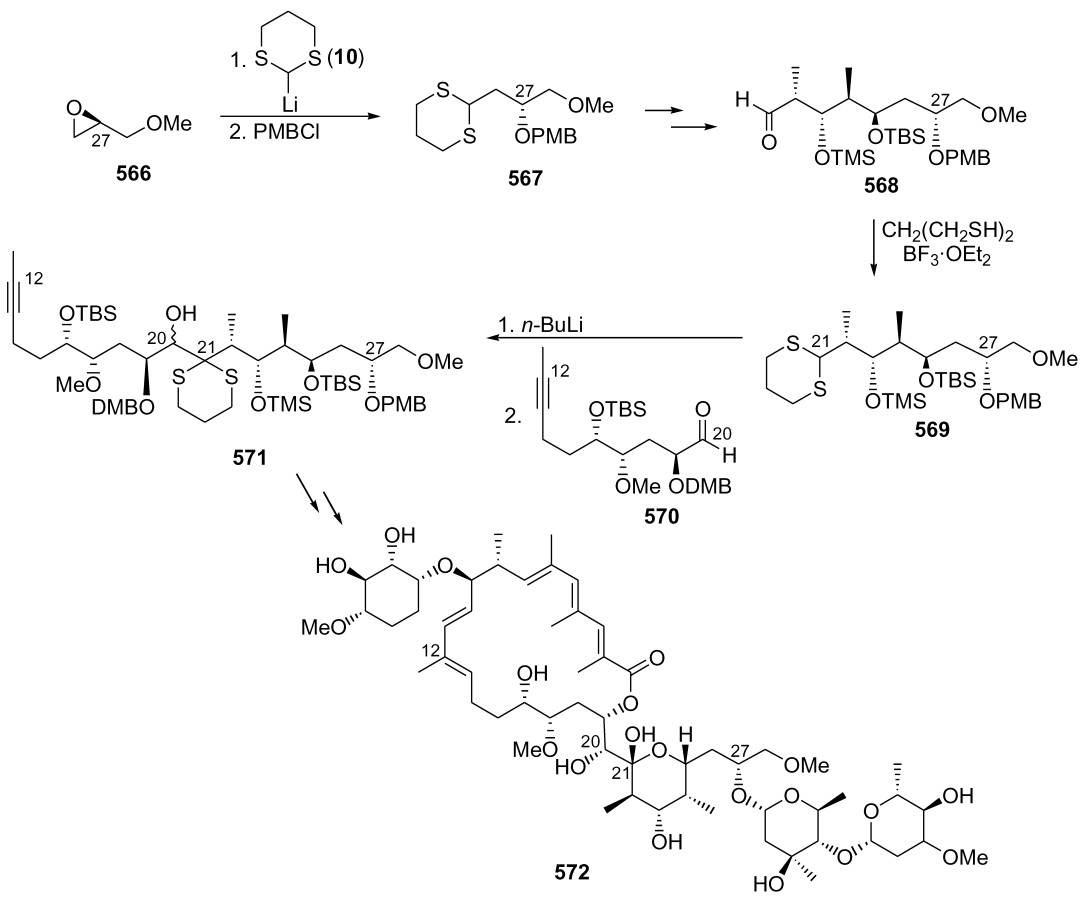
An effective new route for the stereocontrolled synthesis of the *trans*-2,5-disubstituted tetrahydrofurans **565** was described by Chikashita et al. and involves a new type of 1,4-asymmetric induction based on the addition of chiral 2-lithio-1,3-dithiane derivatives (obtained by the reaction of the intermediate **10** with enantiomerically pure epoxides) to the prostereogenic carbonyl group of aldehydes, the major reaction products being the *anti*-diols **564** (Scheme 121).[254]

Apoptolidin (**572**), isolated from *Nocardiopsis* sp.,[255] has recently been synthesised by Nicolaou et al.[256] This compound exhibits selective induction of apoptosis in transformed rat glia cells in the presence of normal cells.[257] One of the building blocks planned in the synthetic strategy is the dithiane **571**. (−)-Glycidyl methyl ether **566** was treated with 2-lithio-1,3-dithiane (**10**) to afford a secondary alcohol, the protection with PMBCl led to the PMB ether **567** in 90% overall yield. Deprotection of the dithiane yielded the corresponding aldehyde, which, after further transformations, gave the compound **568**. Finally, conversion of the aldehyde functionality of **568** to the dithiane moiety (78% yield) furnished the compound **569**. Generation of the anion from **569**, followed by addition to the aldehyde **570**, resulted in the formation of the coupling product **571** as a ca. 1.5:1 mixture of diastereomers (Scheme 122).[258]

2.7.5. Reactions with epoxides and acylating reagents. The asymmetric total synthesis of the lipidic diol **576** (a component of the brown alga, *Notheia anomala*) proposed by Chikashita et al. starts with the reaction of 2 equiv. of 2-lithio-1,3-dithiane (**10**) with (*S*)-glycidol (**573**) to give a dihydroxypropyldithiane, which was selectively protected to afford the alcohol **574** in 70% overall yield. The dianion derived from the dithiane **574** was acylated with methyl hexanoate in the presence of HMPA to give the cyclic hemiacetal **575** in 82% yield. In the last two steps of this synthesis, the dithiane group was removed by hydrolysis with HgO and $BF_3{\cdot}OEt_2$ and the resulting carbonyl group was reduced with $NaBH_4$ to give the final diol **576** (Scheme 123).[259]



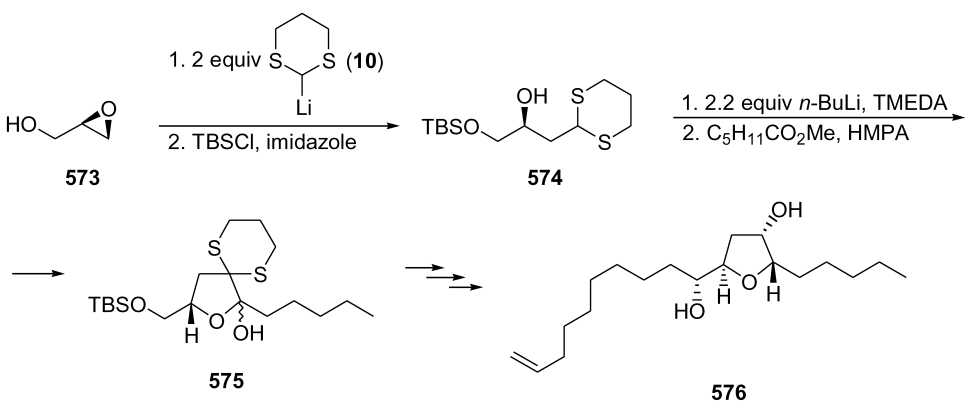
Scheme 121.



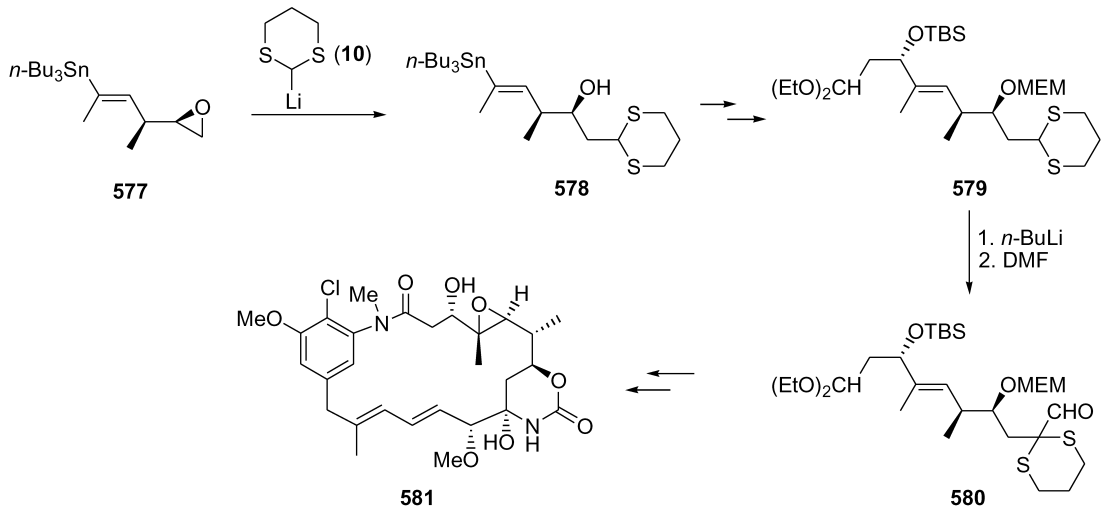
Scheme 122.

The total synthesis of (−)-maytansinol (**581**), a maytansinoid with a potentially interesting biological activity which could replace maytansine (**552**) (Scheme 118) in order to overcome its toxicity in clinical use, was achieved by Bénéchie and Khuong-Huu in a convergent route, the aldehyde **580** being one of the two main fragments.[260] Nucleophilic opening of the epoxide **577** with 2-lithio-1,3-dithiane (**10**) gave the compound **578** in 81% yield, which, after further transformations, led to the compound **579**.[261] Formylation of the dithiane **579** by treatment with *n*-BuLi and DMF gave, after hydrolysis, the aldehyde **580** in 97% yield, a precursor of (−)-maytansinol (**581**) (Scheme 124).[262]

2.7.6. Reactions with alkyl triflates, epoxides, carbonyl compounds and acylating reagents. (−)-Vermiculin is a natural diolide with antibiotic activity.[263] In order to investigate the biological activity of (+)-vermiculin (**584**), Seebach et al. prepared it in an enantiomerically pure form in a similar manner as for (−)-pyrenophorin (**541a**) (Scheme 116). The compound **20** was prepared first in high yield through a coupling reaction of 2-lithio-1,3-dithiane (**10**) and (*S*)-epoxy bromide **17** (Scheme 6). A second coupling reaction between the anion resulting from the deprotonation of 2-methyl-1,3-dithiane (**1**) and the epoxide **20**, followed by a new deprotonation and reaction with DMF, gave the corresponding aldehyde **582**, which,



Scheme 123.



Scheme 124.

after olefination, led to the acid derivative **583**. Finally, Mitsunobu macrocyclisation and hydrolytic cleavage of the dithiane unit with $HgO–BF_3·OEt_2$ led to (+)-vermiculin (**584**) in 8% overall yield (Scheme 125).[23,244]

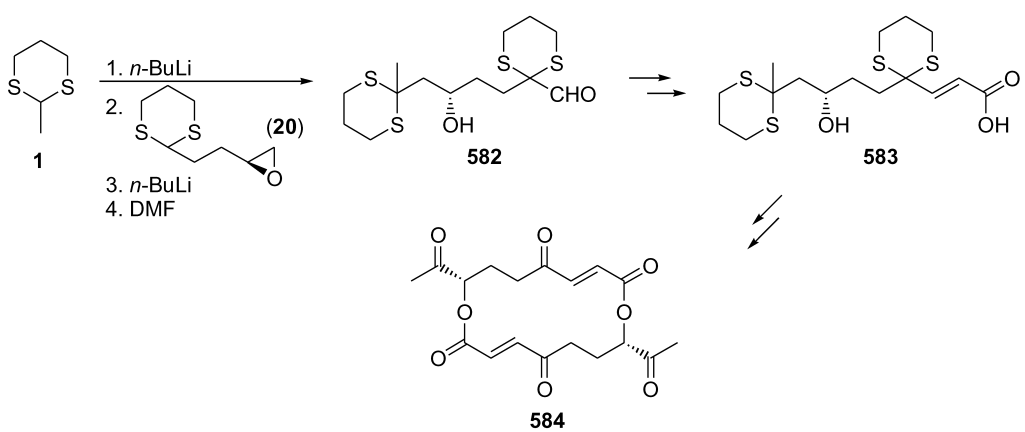
The 1,3-dithiane functionality is involved in different steps of the highly stereoselective synthesis of the C(1)–C(12) unit (**592**) of amphotericin B (**593**),[264] a polyene macrolide with antifungal properties, reported by Solladié and Hutt. First, alkylation of 2-lithio-1,3-dithiane (**10**) with the glycidol derivative (*S*)-**218** gave the alcohol **585** in 87% yield, which was then protected and the dithiane unit hydrolysed to give the aldehyde **586** (81% yield). Further addition of 2-bromomagnesio-1,3-dithiane (**587**) led to the (*S*,*S*)-diastereomer **588** in a distereoselective manner (70% yield), the stereochemistry of the addition being explained by considering Cram's chelated model. The aldehyde **589**, which is easily obtained from **588**, reacts again with 2-bromomagnesio-1,3-dithiane (**587**) to give the *syn* adduct **590** in 90% yield, the corresponding reaction with 2-lithio-1,3-dithiane giving the adducts in a 3:2 *anti*–*syn* ratio. Deprotonation of the compound **590**, followed by alkylation with the triflate **591**, afforded the target compound **592** in 50% yield (Scheme 126).[265]

3. Other reactions

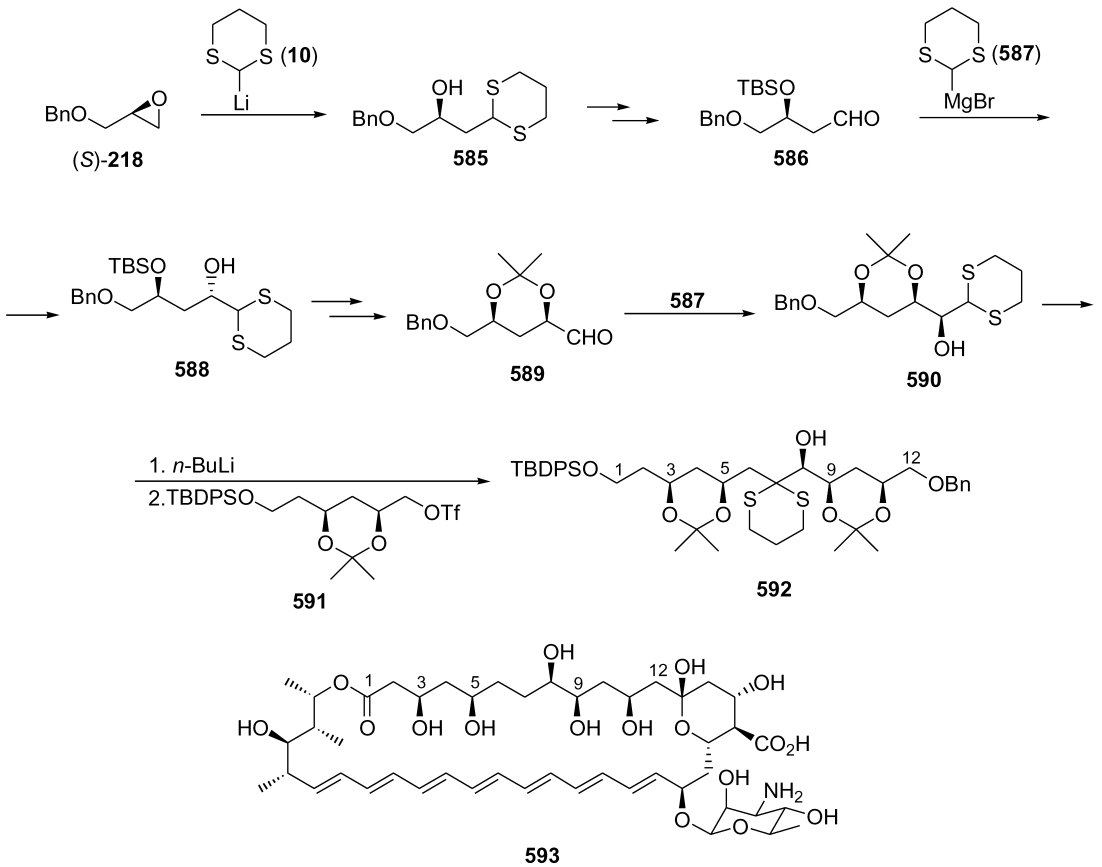
3.1. Reactions involving ketene dithioacetals

Ketene dithioacetals show a versatile reactivity since they can be easily converted into thioketenes, carboxylic acids or carboxylic acid derivatives.[15] Their most general pattern of reactivity includes nucleophilic attack at the non-sulfur-substituted carbon atom of the double bond combined with the introduction of an electrophile at C(1). The most general method for the preparation of ketene dithioacetals includes the olefination of a carbonyl compound using the anions derived from the 2-trimethylsilyl derivative **477**[266] or the dithiane phosphonate **594**[267] (Scheme 127). In the case of the silyl derivative, treatment of 1,3-dithiane with *n*-BuLi, HMPA and $Me_3SiSiMe_3$, followed by the addition of a carbonyl compound, allows the preparation of ketene dithioacetals in a one-pot process.[268]

On the other hand, the iridoid glucoside loganin (**599**) is a widely distributed biosynthetic intermediate in the plant world which has attracted considerable attention as a synthetic target.[269] The assays for the synthesis of this product by Hewson and MacPherson included the use of



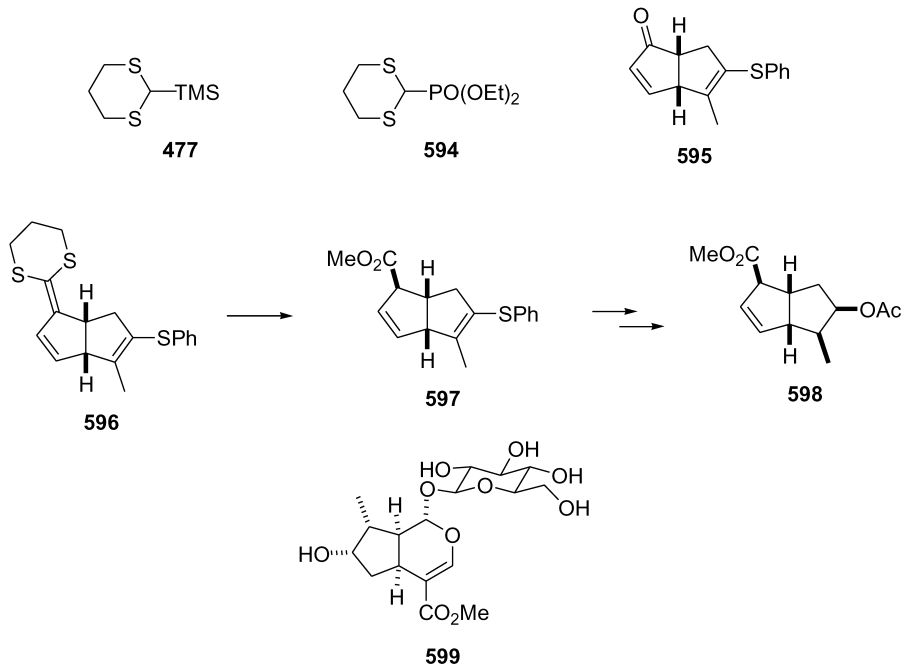
Scheme 125.



Scheme 126.

anions derived from the trimethylsilyl derivative **477**[266] and the dithiane phosphonate **594**.[267] The addition of these anions to the enone **595** gave the 1,4-addition product, in the case of the phosphonate derivative **594**, and a mixture of 1,2- and 1,4-addition for the silyl derivative **477**. This last reaction in the mixed solvent hexane–THF, however, gave the desired 1,2- adduct **596** in 58% yield. Hydrolysis of **596** would give the desired intermediate **597**, which could easily be transformed into the compound **598** (Scheme 127),[270] an intermediate in Fleming's synthesis of **599**.[269c]

Furaquinocins **603** constitute a new class of antibiotics



Scheme 127.

which show cytotoxic activity against some melanoma cells, but no antimicrobial activity.[271] In the total synthesis of these compounds reported by Suzuki et al., the lithio anion of **594**[267] is involved, the reaction of this intermediate with the iodoaldehyde **600** giving the corresponding ketene dithioacetal **601**, which was solvolysed under Ag(I)-promoted conditions to give the methyl ester **602** in 95% overall yield, a convenient precursor of the compound **603** (Scheme 128).[272]

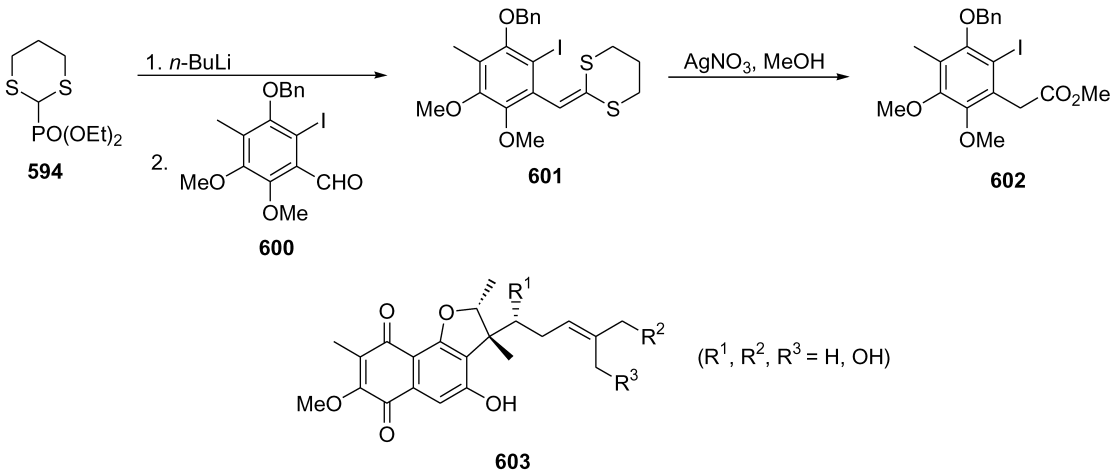
The mevinolin homologue **606**[273] was synthesised starting from the natural product mevinolin (**604**), which was reduced to the corresponding lactol and converted into the ketene dithioacetal **605** in 92% yield by treatment with an appropriate phosphonate carbanion.[267] Acid-catalysed cyclisation, followed by hydrolysis of the dithioacetal, gave the compound **606** (Scheme 129), the whole process representing a lactone homologation.

The same type of cyclisation process was used in one of the steps in the stereocontrolled synthesis of the macrocycle protomycinolide IV (**609**).[274] Treatment of the ketene dithioacetal **607** with hydrochloric acid afforded the lactone dithioacetal **608** in 92% yield, a precursor of the natural product **609** (Scheme 130).

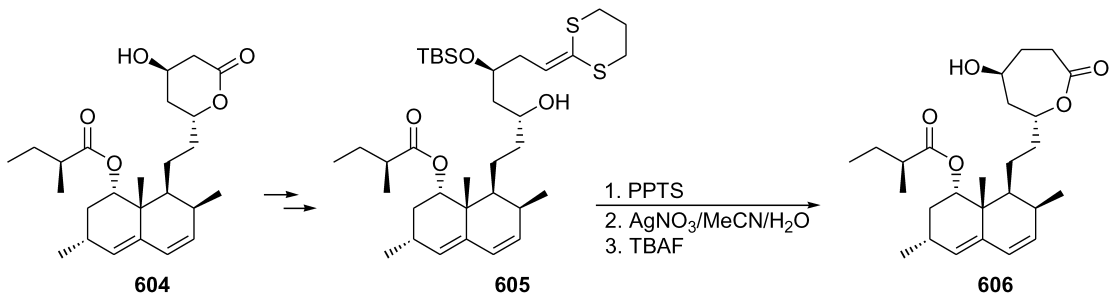
Ketene dithioacetals have also been used as initiators in electrophilic cyclisation reactions due to the adjacent-cation-stabilising property of the sulfur. Thus, the cyclic ketones **612** and **613** have been prepared by the trifluoroacetic acid-promoted electrophilic cyclisation of the 2-alkylidene-1,3-dithianes **610** and **611** in 55 and 76% yield, respectively (Scheme 131).[275] These cyclic ketones are useful precursors in steroid synthesis.

Ketene dithioacetals have also been used as terminators in electrophilic cyclisations promoted by carbocations.[276–278] Treatment of the hydroxylactams **614** with methanesulfonyl chloride in the presence of triethylamine afforded the compounds **615**. This methodology was employed in the synthesis of different alkaloids such as supinidine (**616**), trachelanthanidine (**617**), epilupinine (**618**) and (+)-heliotridine (**619**) (Scheme 132).

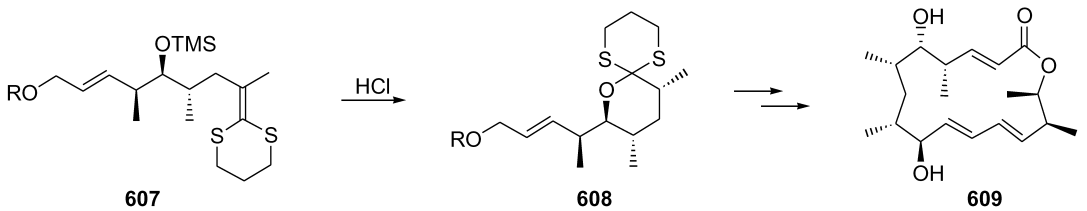
Ketene dithioacetals can also act as heterodienophiles in



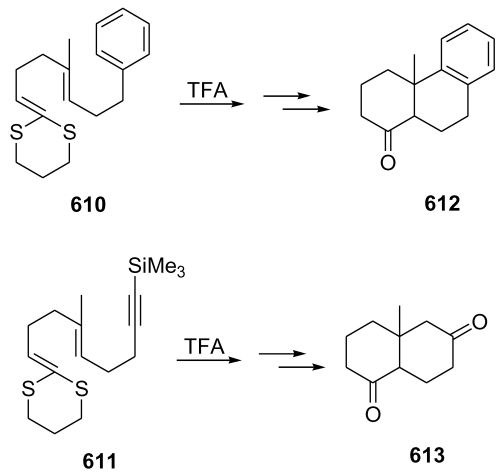
Scheme 128.



Scheme 129.



Scheme 130.



Scheme 131.

Diels–Alder reactions. In the stereospecific total synthesis of (+)-nepetalactone (**623**) reported by Denmark and Sternberg, the ketene dithioacetal **621** afforded the dithioortholactone **622** in 55% yield through an intramolecular hetero Diels–Alder reaction.[279] The ketene **621** was prepared in ten steps from 5-hydroxypentanal (**620**). Finally, mercuric oxide hydrolysis of the compound **622** gave (+)-nepetalactone (**623**) in 76% yield (Scheme 133).

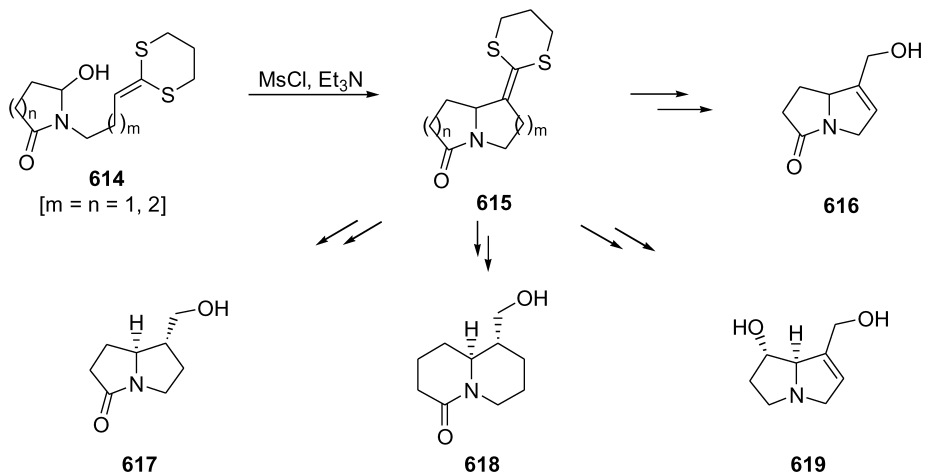
Deprotonation of 2-vinyl-1,3-dithianes and reaction with electrophiles at the γ-position leads to ketene dithioacetals (Scheme 90),[183] the reaction of the crotyllithium compound **625**, generated from 2-(1-propen-1-yl)-1,3-dithiane (**624**) (prepared from crotonaldehyde and 1,3-propanedithiol), with aldehydes giving the corresponding γ-products **626**.[280]

Subsequent hydrolysis culminated in expedient syntheses of (±)-*trans*-quercus lactone (**627**)[281] and (±)-eldanolide (**628**),[282] the latter compound being an insect pheromone (Scheme 134).

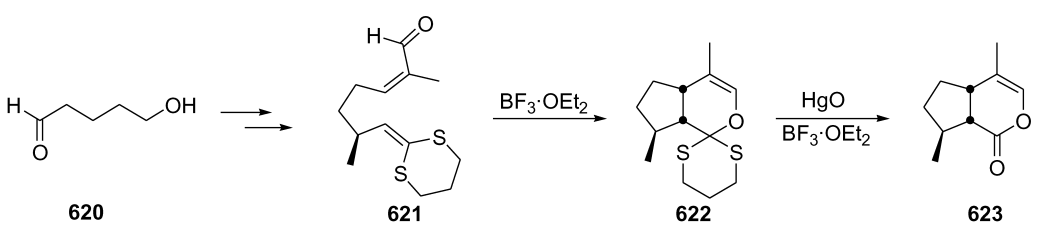
Deprotonation of ketene dithioacetals leads to allylic metallated systems with two non-equivalent reactive positions, the regiochemistry of the reaction with electrophiles being dependent on many factors. In the synthesis of racemic anatoxin A (**631**), deprotonation of the compound **629**, followed by alkylation with methyl iodide, gave the dithiane **630** in 85% yield (Scheme 135),[283] in which the alkylation took place at the α-position.

The anion of 2-(2-phenylthioethylidene)-1,3-dithiane (**632**) (prepared from 2-bromoacrolein) reacted with alkyl halides and aldehydes preferentially at the α-position. With open-chain aliphatic ketones, however, it reacts at the γ-position to give the compounds **633**, the intermediate acting, in this case, as an umpolung reagent (homoenolate). Hydrolysis of the dithioacetal in **633** gave the butenolides **634** in high yields (Scheme 136).[284]

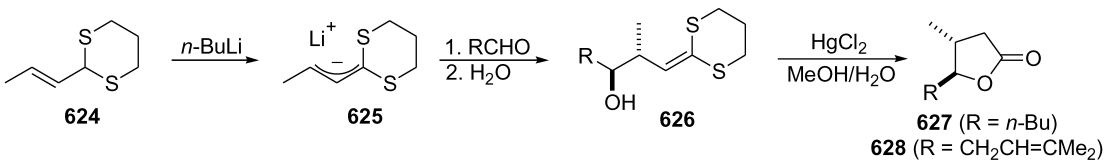
Tetrahydrofurans are available through the electrochemical oxidative cyclisation of the appropriate hydroxyketene dithioacetals. In this context, Moeller et al. reported the synthesis of nemorensic acid (**639**), the Northern portion of the macropyrrolizidine alkaloid nemorensine (**640**).[285] In this synthesis, the oxidative cyclisation of the ketene dithioacetal **637** gave the tetrahydrofuran ring with high stereoselectivity. The lactone **635** was prepared from methyl (+)-3-methylglutarate and, by treatment with trimethylaluminum and 1,3-propanedithiol, gave the ketene dithioacetal[286] **636** in 70% yield, which, after four reaction steps, led



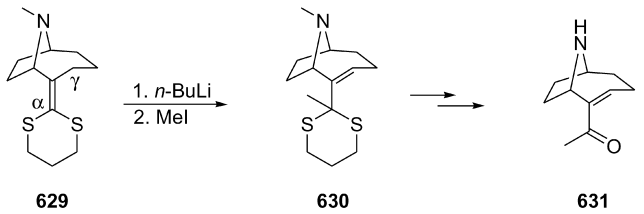
Scheme 132.



Scheme 133.

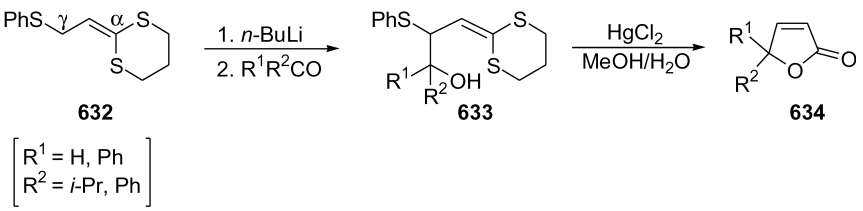


Scheme 134.



Scheme 135.

the corresponding sulfoxides undergo hydrolysis much more readily, because the oxidised sulfur moiety is a better leaving group and oxidative methods will, in some cases, facilitate the hydrolysis processes. There are many examples reported in which the role of the dithiane unit is simply to mask a carbonyl group, which will be revealed one stage later in the synthetic route to the target molecule. Some recent examples of this process will now be discussed.



Scheme 136.

to the desired substrate **637**. Anodic oxidation of the compound **637** yielded the tetrahydrofuran derivative **638** in 71% yield,[287] a direct precursor (three reaction steps, 65% overall yield) of nemorensic acid (**639**) (Scheme 137).

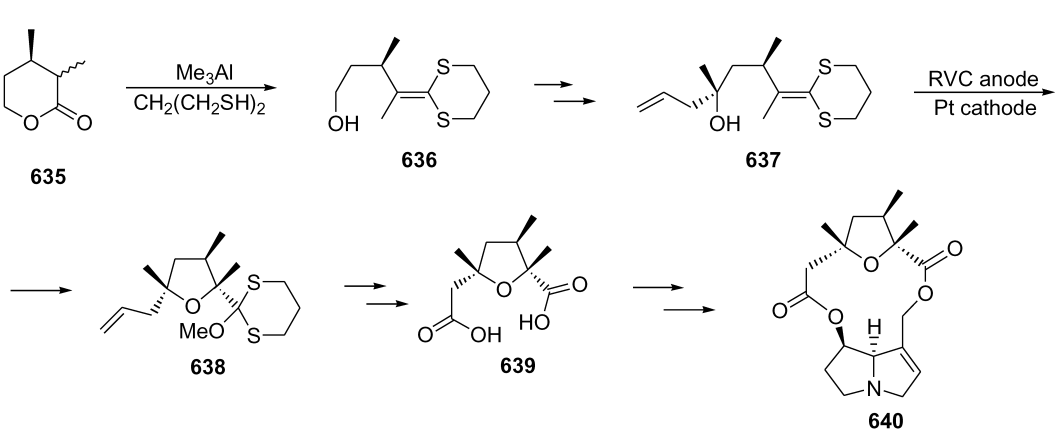
3.2. 1,3-Dithiane as a protecting group

As noted previously, thioacetalisation of a carbonyl group, using Lewis or Brönsted acid catalysis,[2,3,6] is one of the most utilised methods for the introduction of the 1,3-dithiane unit in an organic molecule. Due to the stability of this group towards acidic and basic conditions, it is suitable for the protection of carbonyl groups.[288] For the same reasons, however, deprotection often proved to be problematic, many methods having been reported in the literature.[6d,289] The most common methods are acidic hydrolysis, transition metal-induced hydrolysis and oxidative or alkylative hydrolysis. It is important to note that

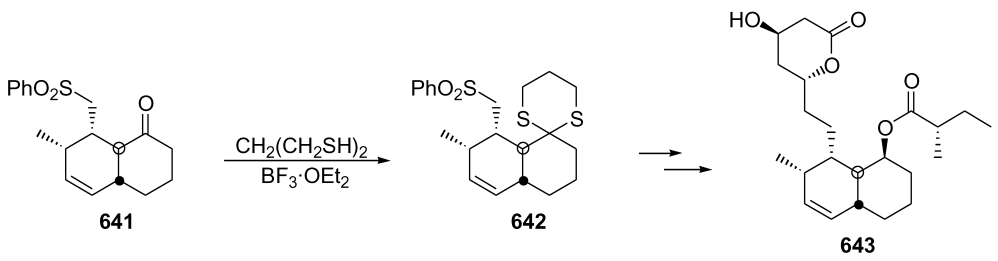
Dihydrocompactin **643** is a fungal metabolite with potent hypocholesterolemic activity. Falck et al. reported a synthesis of this natural product, the sulfone dithioacetal **642** (prepared by dithioacetalisation of the ketone **641**) being a key intermediate in the synthesis (Scheme 138).[290]

The dithiane unit acts as a protecting group in the phosphine oxide **644** [C(10)–C(19) unit] used in the synthesis of FK-506 (**44**) (Scheme 10) as reported by Jones et al. Deprotonation of the phosphine oxide **644** and reaction with the aldehyde **645** [C(20)–C(34) unit] gave the olefin **646** with an (*E*)-configuration at C(19) in 82% yield. Hydrolysis of the dithiane unit regenerates the aldehyde at C(10) (Scheme 139).[291]

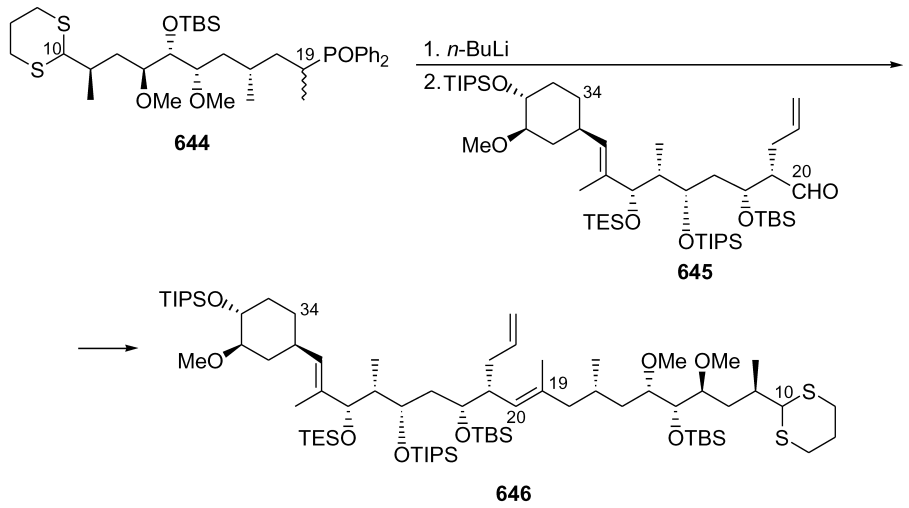
Compound **648** with a 1,3-dithiane moiety in its structure has been envisioned by Danishefsky's group to be an important building block in the synthesis of FK-506 (**44**)



Scheme 137.



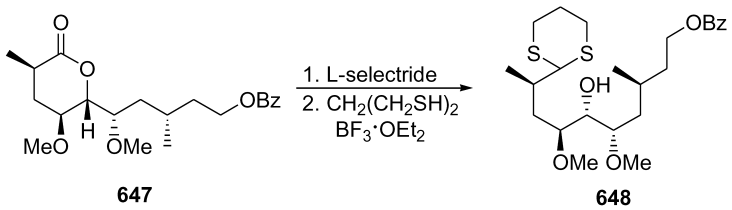
Scheme 138.



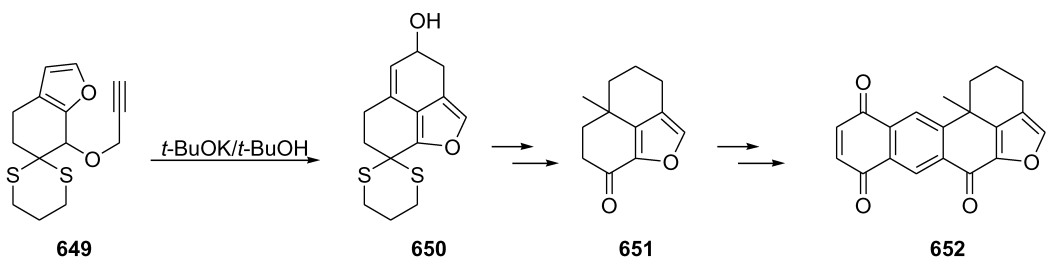
Scheme 139.

(Scheme 10). Reduction of the lactone group in compound **647**, followed by dithioacetalisation of the resulting aldehyde, led to the dithiane derivative **648** in 80% yield (Scheme 140),[292] the dithiane group acting as a protecting group of the aldehyde which is later regenerated. The synthesis of other fragments leading to FK-506 has been reported by the same authors.[293] A total synthesis of FK-506 (**44**) had already been reported from compound **648** by other authors[291] and this work therefore represents a formal total synthesis of the target compound **44**.

Kanematsu et al. have reported a formal total synthesis of the natural fused furan xestoquinone (**652**),[294] a powerful cardiotonic constituent isolated from the marine sponge *Xestospongia sapra*.[295] The first total synthesis of this compound has been achieved by Harada et al.[296] The tricyclic furan **651** is a key intermediate in this synthesis, having been prepared from the dithiane derivative **649**, which underwent a furan ring transfer reaction to give the compound **650** in 92% yield (Scheme 141).[297] Here, the dithiane moiety has been introduced for the carbonyl protection of the ketone group.



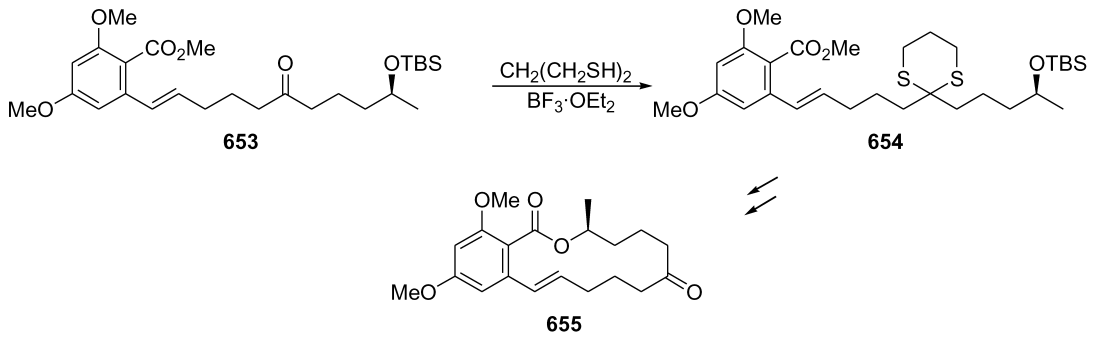
Scheme 140.



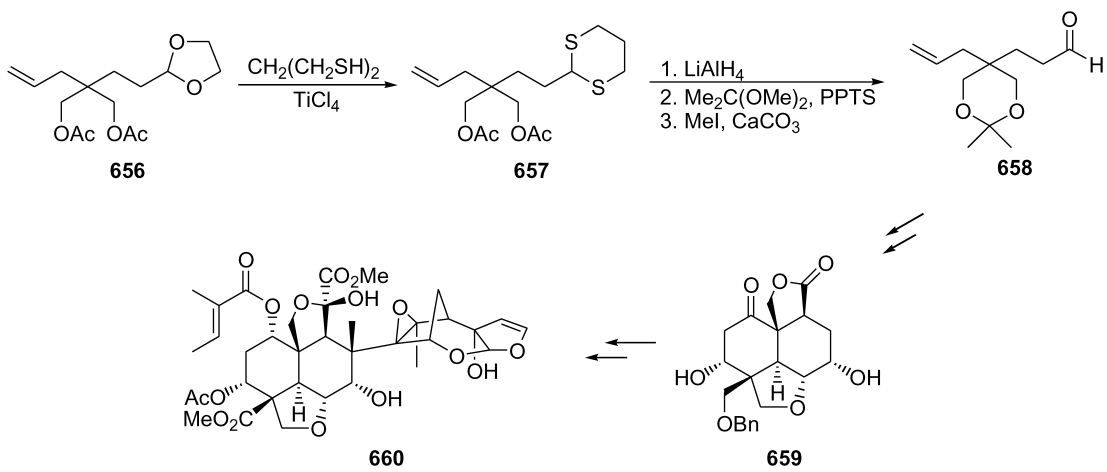
Scheme 141.

A synthesis of (*S*)-zearalenone dimethyl ether (**655**), a naturally occurring 14-membered orsellinic acid-type macrolide with anabolic and uterotropic activity, was described by Solladié et al.[298] In the last steps of this synthesis, protection of the carbonyl group of compound **653** with 1,3-propanedithiol to give the compound **654** (78% yield) was necessary before macrolactonisation, suffering final deprotection with HgO and $BF_3{\cdot}OEt_2$ in $THF-H_2O$ (Scheme 142).[299]

Murai et al. described a stereocontrolled enantioselective synthesis of the decalin **659**,[300,301] which embodies the Western part of azadirachtin **660**,[302] isolated from the seeds of an Indian Neem tree, with strong antifeedant, insect growth regulatory and reproductive effects. In the synthesis, a dithiane derivative **657** is prepared from the dioxolane **656**, through a transacetalisation process, in 98% yield, which is further transformed into the aldehyde **658** by an alkylative deprotection procedure in ca. 50% yield from **657** (Scheme 143).[303]



Scheme 142.

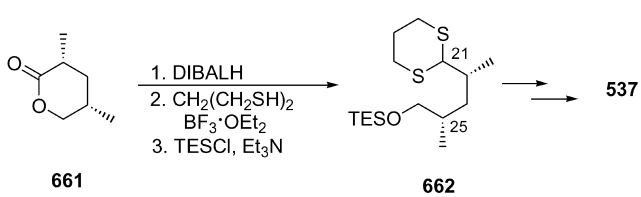


Scheme 143.

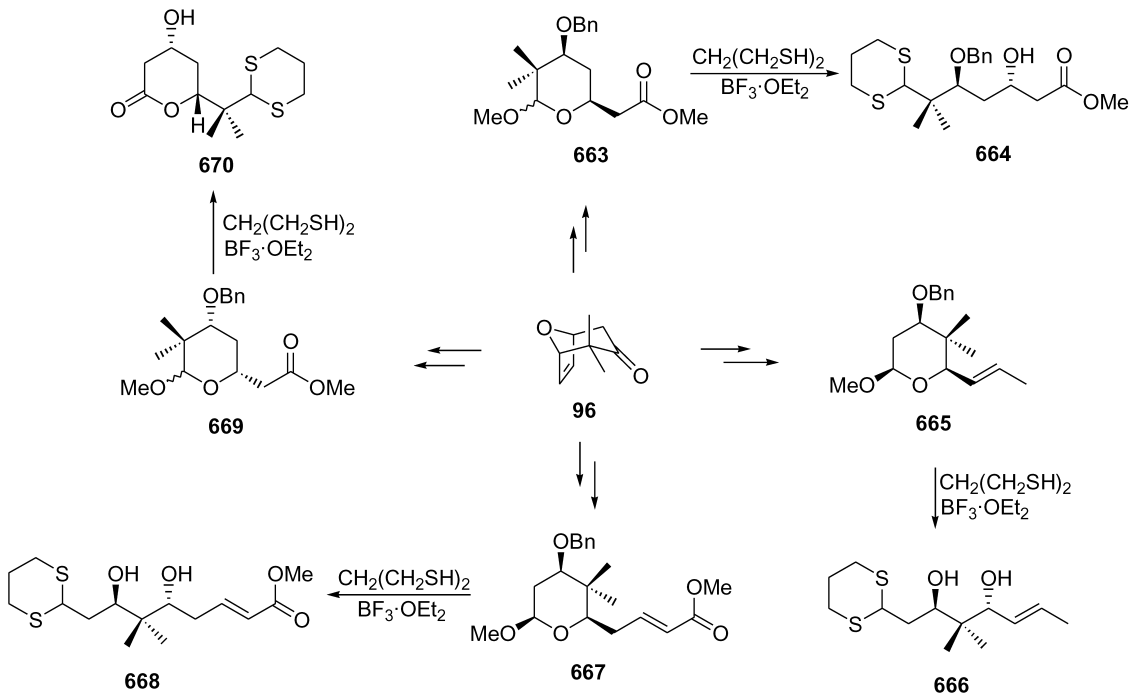
In the synthetic strategy for the preparation of azaspiracid (**537**) (Scheme 115), Carter and Graves proposed the participation of a 1,3-dithiane **662**, which contains the C(21)–C(25) skeleton of the desired product. Starting from the known lactone **661**, the corresponding dithiane derivative **662** was prepared in three steps in 57% overall yield (Scheme 144).[304]

A methodology for the opening of (±)-2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**96**) (Scheme 21), a 6-membered ring ether containing *gem*-dimethyl groups, to give δ-hydroxy-1,3-dithianes has been developed by Hoffmann et al.[305] Treatment of the compounds **663**, **665**, **667** and **669**, derived from the compound **96**, with 1,3-propanedithiol in the presence of boron trifluoride etherate led to the dithiane derivatives **664**, **666**, **668** and **670**, respectively. These compounds are segments of different natural products, being carbonyl groups masked by dithiane units (Scheme 145). Compound **664**, for example, is the C3–C9 segment of bryostatin 1 (**100**) (Scheme 21).

Through a transacetalisation of the compound **671**, derived from (+)-pulegone, followed by the protection of two hydroxy groups and then dehydroxylation of the tertiary hydroxyl group, Tu et al. prepared the compound **672** in 24% yield. Dethioacetalisation of the compound **672** with $HgCl_2$ and $CaCO_3$ in aqueous acetonitrile gave the corresponding aldehyde, which, by alkylation and further



Scheme 144.



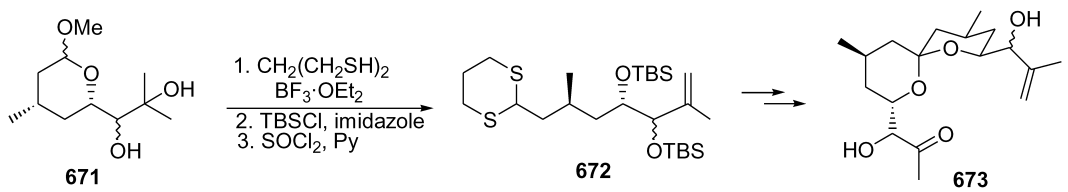
Scheme 145.

transformations, led to a mixture (5:1) of the spiroacetals **673** (Scheme 146),[306] the key mother spiroacetals of some natural products from the ascidian *Didemnum* sp. which have a highly inhibitory activity against HIV-1 protease.[307]

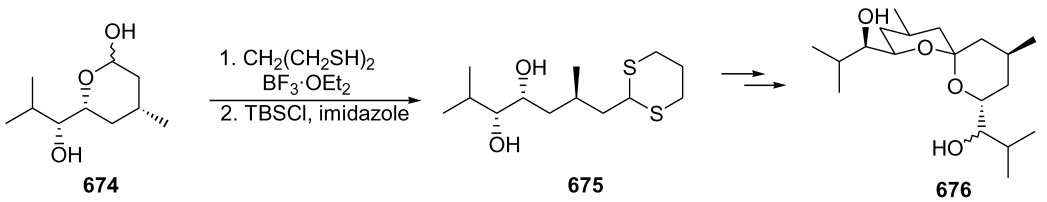
Tu et al. have also reported a stereocontrolled and efficient synthesis of the spiroacetal compound **676** and its C(1″)-epimer, the core of the HIV-1 protease inhibitor. The starting compound **674** was prepared in an enantiomerically pure form from L-(−)-menthone and converted into the dithiane derivative **675** in 64% yield (Scheme 147).[308]

Nakata et al. reported the stereoselective synthesis of cyclic ethers by SmI_2-induced intramolecular cyclisation, a 1,3-dithiane being involved as a protecting group. Reduction of the lactones **677** with DIBALH, followed by dithioacetalisation with 1,3-propanedithiol, gave the hydroxy dithiane derivatives **678** in almost quantitative yields. Treatment of the compound **678** with ethyl propiolate in the presence of NMM gave the β-alkoxyacrylates **679**. Deprotection of the thioacetal with methyl iodide in aqueous acetonitrile and treatment of the resulting aldehyde with SmI_2 led, after radical reductive cyclisation, to the hydroxyester **680** with complete stereoselectivity (Scheme 148).[309]

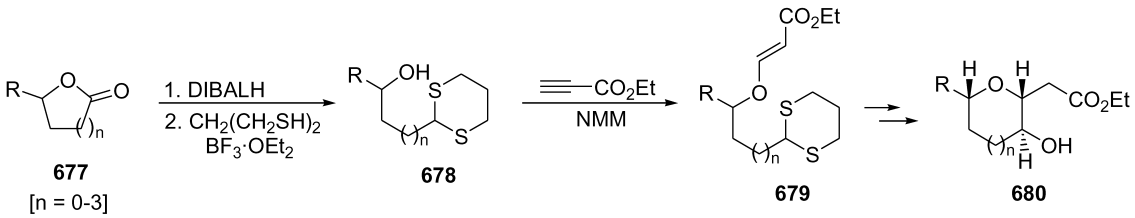
Some natural and unnatural polyhydroxylated pyrrolidines and piperidines have inhibitory activities. Among these azasugars, 1,4-dideoxy-1,4-imino-D-galactiol (**684**) is an inhibitor of mycobacterial galactan biosynthesis.[310] BeMiller et al. reported a synthesis of compound **684**, in which the dithioacetal precursor **681** was prepared from D-glucose and 1,3-propanedithiol in 90% yield. Acetonation of the compound **681** with an excess of 2,2-dimethoxypropane gave the compound **682** in 66% yield. Further transformations,



Scheme 146.



Scheme 147.



Scheme 148.

including substitution of the hydroxy group by an azido moiety, led first to the compound **683** and, finally, to the desired product **684** (Scheme 149).[311]

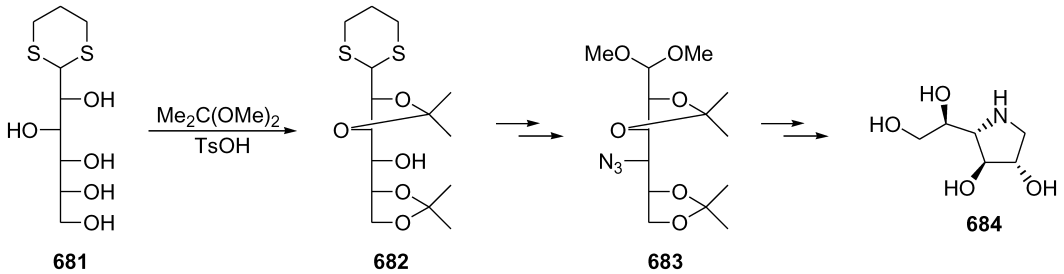
Enders and Schüsseler have reported the synthesis of (*S*)-7-methylheptadecane **687**,[69] a component of the sex pheromone of the spring hemlock and the pitch pine looper moths.[70] The hydrazone derivative **685** was prepared by α-alkylation with high asymmetric induction employing the SAMP/RAMP hydrazone method. Cleavage of the hydrazone with a Lewis acid in the presence of 1,3-propanedithiol afforded the dithiane derivative **686**, which, after treatment with Raney nickel, led to the compound **687** in 83% overall yield (Scheme 150).

Taking advantage of the methodology developed by Uenishi et al. (for the simultaneous activation of an ethyl enol ether and deprotection of a 1,3-dithiane to form substituted cyclohexenones[312]) by using bis(trifluoroacetoxy)iodobenzene, Wong reported the first synthesis of two new antiprotozoal agents from *Amomum aculeatum* rhizomes,[313] aculeatins A (**691**) and B (**692**). Deprotection of the phenol derivative **688**, followed by protection of the ketone, gave the β-1,3-dithiane ester **689**. After selective transformations into the 1,3-diol **690** and final hydrolysis of the dithiane unit with bis(trifluoroacetoxy)iodobenzene, a mixture of (±)-aculeatin A (**691**) and B (**692**) was obtained in 44 and 15% yield, respectively (Scheme 151).[314]

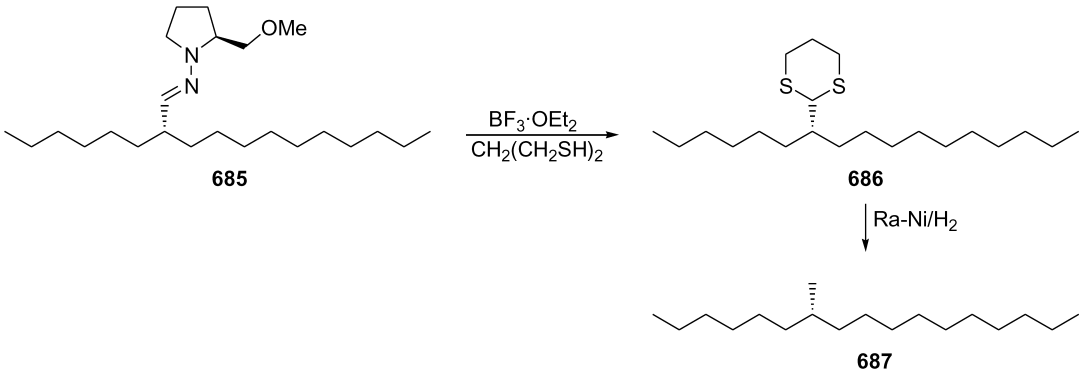
Isobe et al. in their studies on the synthesis of ciguatoxin 1B (**337**) (Scheme 72) protected the ketone moiety at C(7) in compound **693** to give **694** in ca. 80% yield, a precursor of the acetylene derivative **695**. The carbonyl functionality is regenerated in a further step by treatment with bis(trifluoroacetoxy)iodobenzene (Scheme 152).[154]

Mucocin (**699**) is a representative annonaceous acetogenin, which shows antitumour activity.[315] In the synthesis proposed by Nakata et al., the bis(thioacetal) **697** is formed from the bistetrahydrofuran derivative **696** in 86% yield using zinc triflate as the Lewis acid. Hetero-Michael addition of the compound **697** to ethyl propiolate, followed by alkylative dethioacetalisation, afforded the key intermediate **698** in 73% yield, a precursor of mucocin (Scheme 153).[316]

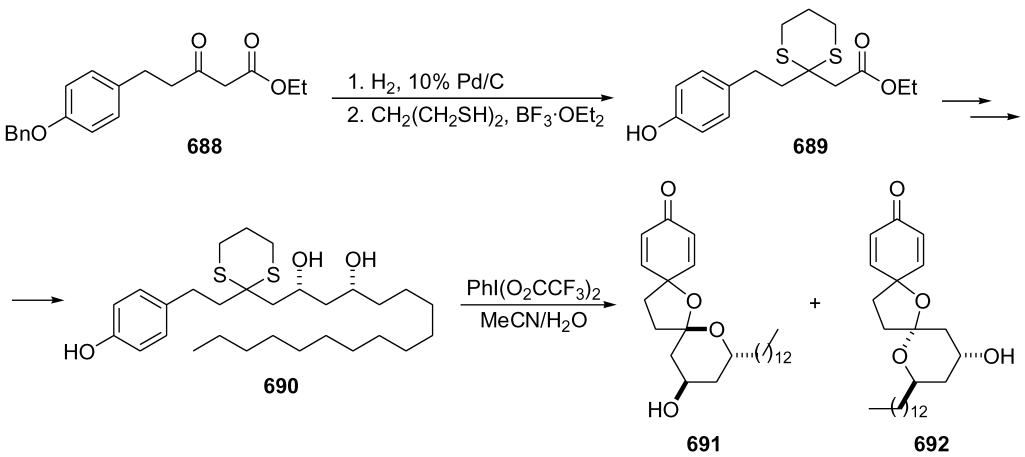
Ley et al. have recently reported the preparation of 3-keto 1,3-dithianes by a double conjugate addition of 1,3-propanedithiol to propargylic ketones, esters and aldehydes, the process taking place with excellent yields. As masked 1,3-dicarbonyl systems, these substrates can be converted to a range of functionalised oxygen-containing heterocycles,



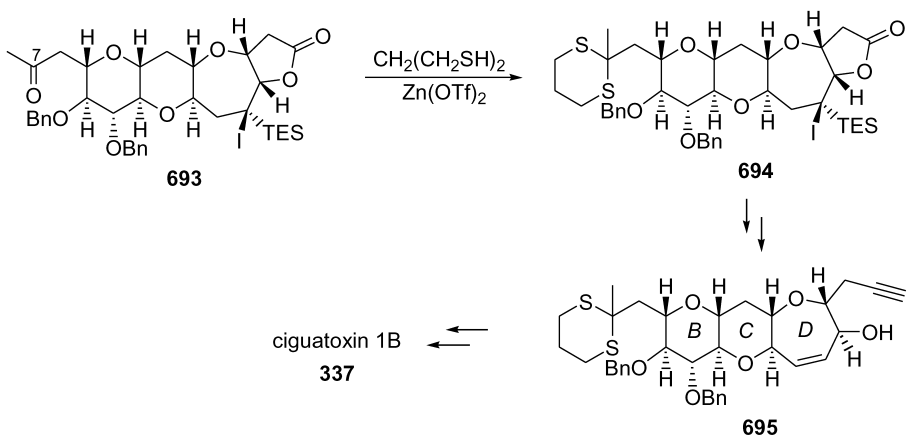
Scheme 149.



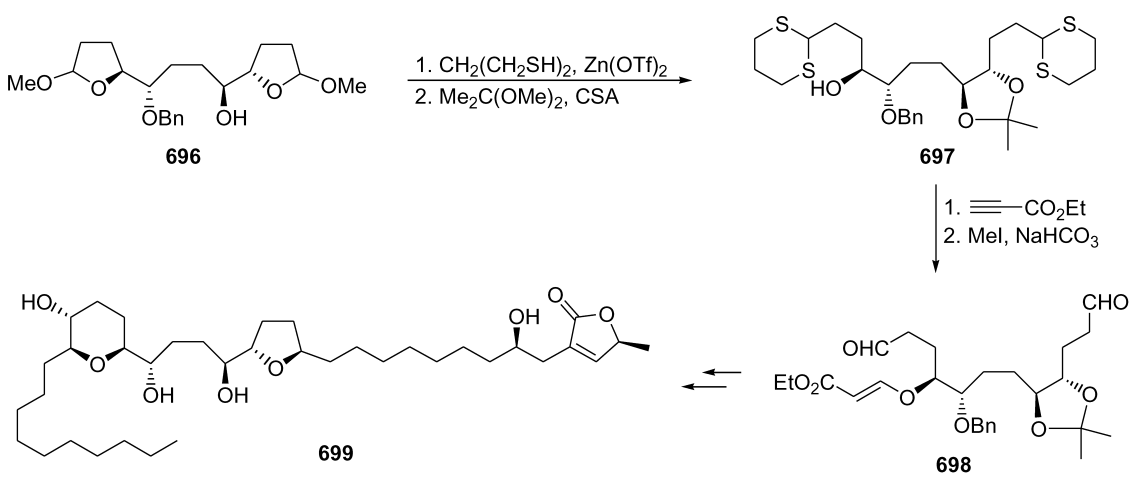
Scheme 150.



Scheme 151.



Scheme 152.

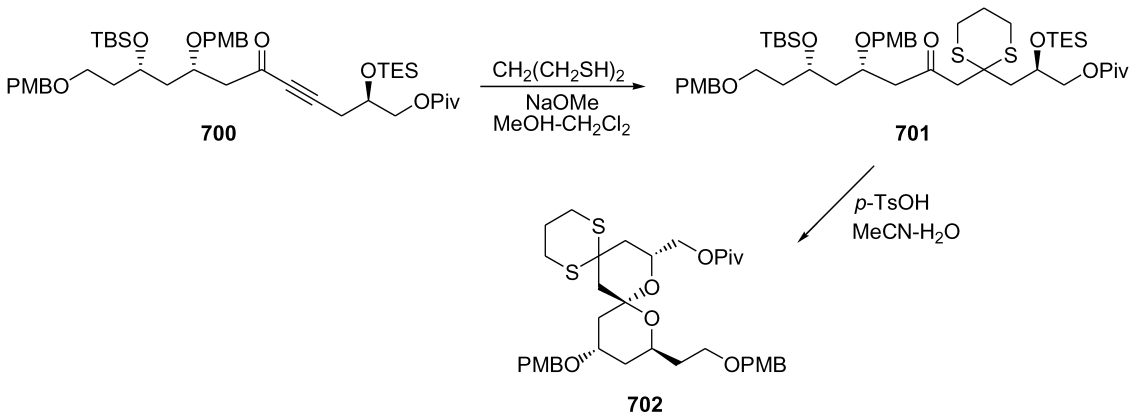


Scheme 153.

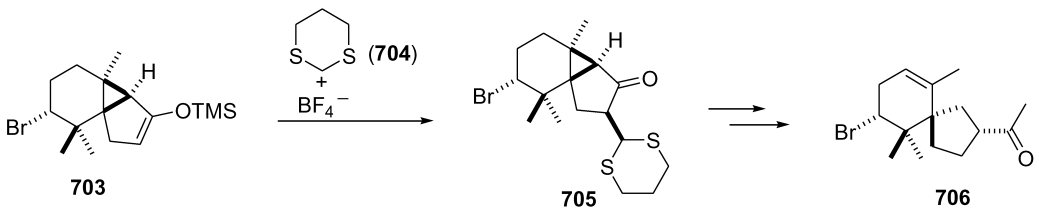
which can be used in natural product synthesis, complex substrates also being amenable to this reaction. In one example, successive treatment of the propargyl ketone **700** with NaOMe and 1,3-propanedithiol in MeOH–CH_2Cl_2 at temperatures ranging between −10 and 0°C gave, through a double conjugate addition, the dithiane derivative **701** in 90% yield. In this reaction, the rigid acetylene unit is removed from the molecule, permitting a range of cyclisation reactions. A model compound **702** for the synthesis of the AB spiroacetal unit of the spongistatins (**253**) (Scheme 53) is obtained in 95% yield after removing the two silicon groups from compound **701** under acidic conditions and subsequent cyclisation (Scheme 154).[317]

3.3. 2-(1,3-Dithianyl) cation as an electrophile

(±)-Spirolaurenone (**706**), an antifungal compound isolated from the red alga *Laurencia glandulifera*, was synthesised



Scheme 154.



Scheme 155.

for the first time by Masamune et al. In this synthesis, an electrophilic addition of the 1,3-dithienium tetrafluoroborate **704**[318] to the silyl enol ether **703** took place to give the ketone **705** in 94% yield. This ketone **705** underwent cleavage of the cyclopropyl ring under acidic conditions and, after further transformations, gave (±)-spirolaurenone (**706**) (Scheme 155).[319]

4. Conclusions

From the chemistry described in this report we can conclude that the 1,3-dithiane unit is very useful in synthetic organic chemistry, both as an acyl anion synthetic equivalent and as protecting group for carbonyl functionalities. In the first case, functionalisation of the masked carbonyl group allows different transformations, which have been widely used in the total synthesis of complex polyfunctionalised natural compounds, as shown in this review article.

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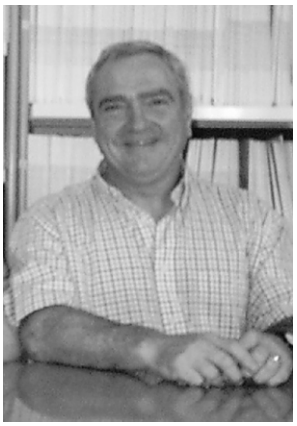
Biographical sketch



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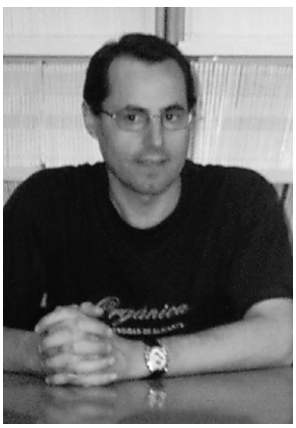

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