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

Miguel Yus, Carmen Nájera and Francisco Fouebo * 

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain 

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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

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Keywords: carbanions; organolithium compounds; dithiaocetal 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 azodicarboxylate; DEIPS, diethyliosopropylsilylethylidihydropyridin; DibalH, disobutylaluminium hydride; DMB, 3,4-dimethoxyphenylmethoxy; DMP, dimethylformamid; DMPU, N,N-dimethylpropyleneurea; DMSO, dimethyl sulfoxide; DTBMS, di-t-butyldimethylsilylethyl; EE, 1-ethoxyethyl; HMDS, hexamethyldisilazane; HMPA, hexamethylphosphoramide; LADH, lithium aluminium hydride; LDA, lithium diisopropylamide; LTB 4, leukotriene B 4; MCPBA, m-chloroperbenzoic acid; MEM, 2-methoxyethoxymethyl; MOE, 1-methoxyethyl; 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, tetraethylammonium fluoride; TBDPS, t-butyldiphenylsilylethyl; TBS, t-butyldimethylsilylethyl; TES, triethylsilyl; Tf, trifluoromethanesulfonyl (triflyl); TFA, trifluoroacetic acid; THC, tetrahydrocannabinol; THF, tetrahydrofuran; THP, tetrahydropyran; TIPS, triisopropylsilylethyl; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; TPS, triphenylsilyl; Tr, triphenylmethyl (trityl); Ts, p-methoxybenzenesulfonylethyl (tosy1).

Corresponding author. Tel.: +34-96-909672; fax: +34-96-903549; e-mail: fouebo@ua.es

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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.\(^2\) 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. 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.\(^5\)

![Scheme 1](image)

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 Brønsted 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\(^7–14\) 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 \(i\)-BuLi and the reaction with electrophiles...
The absolute stereochemistry of serricornin (9), the sex pheromone of the cigarette beetle, was determined to be (S)-diastereomer by Mori et al. by the synthesis of the O-acetyl derivative of its (S,R,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).

Sih has reported the synthesis of the 6-membered-ring analogues of 6α-carba-PGII2 (carbacyclin) 15 in order to study the prostacyclin (PGI2) structure–activity relationships. 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 thioacetal unit with methyl iodide and CaCO3 in MeCN–H2O, 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 LiBHEt3 or Me2CuLi, 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).

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. The resulting epoxydithiane 20 was allowed to react with lithium butylcyanocuprate yielding, after protection of the hydroxyl 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). This synthetic strategy was followed in the synthesis of...
(+)-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
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 \(-78^\circ C\) 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 \(-78^\circ C\) 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
prepared by McGarvey and Stepanian in 28% overall yield. 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).
Swinholide A (59), a $C_2$ symmetric 44-membered macrolide ring, is a marine natural product isolated from the sponge Theonella swinhoei 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. One of the key reactions of this synthesis is the coupling of the lithio derivative of dithiane 56, generated at $-78^\circ C$ with $t$-BuLi, with the cyclic sulfate 57 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). Octalactin A (64) was isolated from a marine bacterium Streptomyces sp. and exhibits a potent cytotoxic activity against some tumour cell lines. 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 hygroscopicus, and (−)-27-demethoxyrapamycin (74). 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 [C(27–32) fragment] was prepared starting from (−)-3-hydroxy-2-methylpropionate 65, the dithiane moiety being introduced by aldehyde protection with 1,3-propanedithiol. The synthesis of the subunit [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 $-78^\circ C$ 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. 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. Both compounds exhibit important neurotoxic properties. Tanner and Hagberg reported a convergent enantioselective total synthesis of the compound 79. 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. 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 macrocyclic containing a spiro-linked cyclic imine moiety isolated from shellfish Pinna muricata, was developed by Kishi et al. in 1998, just 3 years after its isolation by Uemura et al. 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)
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 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 13).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 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 14).53

Morimoto et al. have reported a total synthesis of (−)-stenine (95), an alkaloid isolated from the roots and
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). 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 17.

Scheme 18.

Scheme 19.

Scheme 20.
synthesised by Hoffmann et al.\textsuperscript{55} Lithiation of the sterically encumbered dithiane 97, prepared in 14 steps from 96 (27% overall yield),\textsuperscript{56} with \textit{t}-BuLi in the presence of 3 equiv. of HMPA at $-78\,^\circ\text{C}$, followed by addition of the triflate 98, afforded the compound 99 in 63% yield (Scheme 21).

Hatakeyama et al. have recently accomplished the enantio-controlled synthesis of (~)-mycestericin E (106),\textsuperscript{57} a potent immunosuppressant isolated from the culture broth of the fungus \textit{Mycelia sterilia} ATCC 20349.\textsuperscript{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\textsubscript{1} (110) was isolated from \textit{Streptomyces griseus} sp. sulfur and exhibits inhibitory activity against Gram-positive bacteria and fungi.\textsuperscript{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
treatment with HgCl₂ and CaCO₃ 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

Fabriás 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 NaBD₄, followed by tosylation of the formed alcohol and final treatment with LiAlD₄. 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

Pinelic acid (128) was isolated from a medicinal plant Pinelliae tuber and shows a potent adjuvant activity. ⁶⁶ Its absolute configuration of pinelic 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)
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

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

A double alkylation of 1,3-dithiane with (S)-(R)-2-methyl-1-iodooctane (131) led to the C2-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 Schüessler by an α-alkylation employing the SAMP/RAMP hydrazine method with a high asymmetric induction (Scheme 29).69

Burke et al. reported 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 C2 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
96% yield. The dithiane aldehyde 157 was prepared from 156 in two steps in 80% yield (Scheme 33). Smith et al. have recently reported the synthesis of 13-deoxytedanolide (164), which was isolated from a sea sponge and shows significant cytotoxic activity. In their synthetic strategy, two fragments were combined using a dithiane-based methodology, deprotonation of the compound 161 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).

### 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
dithiane anions to vinyl epoxides by exploiting the steric nature of the dithiane. Meanwhile, the ring-opening reaction of N-activated aziridines with anions derived from 1,3-dithianes has been studied by Sweeney et al., 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. and has been found to be active against herpes simplex virus type 1, also displaying peripheral analgesic activity. In the convergent synthetic strategy, the C(1)–C(5) unit was prepared via alkylation of 2-lithio-2-methyl-1,3-dithiane with (S)-epichlorohydrin (165), affording inversion of the configuration at C(4). 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 aplysia toxin (174), isolated from the digestive gland of the sea hare Stylocheilus longicauda, and debromoaplysia toxin (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). A formal total synthesis of aplysia toxin (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 32.](image)

![Scheme 33.](image)
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 thioacetelisation 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 MnO2 oxidation afforded pironetin in 72% overall yield (Scheme 38).90

A general strategy for the transformation of D-glucose into (2S)-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 E2 (187) (Scheme 39).

Benefice-Malouet et al. reported on the synthesis of methyl 3-deoxy-3-C-formyl-α-D-arabinofuranosides (191) and 2-deoxy-2-C-formyl-α-D-xylofuranosides (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
gave the carbohydrate derivatives 191 and 192 (Scheme 40).\textsuperscript{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-\(\alpha\)-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\(_3\)·OEt\(_2\) in THF–H\(_2\)O, followed by further transformations, led to the compounds 197 and 198 (Scheme 41).\textsuperscript{94}

Tautomycin (205) is a natural polyether isolated from Streptomyces spiroverticillatus\textsuperscript{65} with strong antifungal activity and also an inhibitor of protein phosphatases.
Isobe et al. reported a convergent synthesis of [205], in which retrosynthetic analysis they divided the target molecule into three segments (A, B, and C). In the synthesis of fragment B, [206] 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 took place by the reaction of the lithiated sulfone [203] (with a carbonyl group protected as the dithioacetal) [207] with the epoxide [202] to give the alcohol [204] in 81% yield (Scheme 42). [208]

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). [209]

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 Discoderma calyx. [202] 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). [203] A total synthesis of these natural
products using this strategy was reported by the same research group\textsuperscript{104}.

An efficient, highly convergent, stereocontrolled total synthesis of the antimitotic agent \((\pm \)-discodermolide \((221)\), derived from the deep-water marine sponge \textit{Dis-}

codermia dissoluta\textsuperscript{105} has been achieved on a g scale by Smith et al.\textsuperscript{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 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 vinylnMagnesium 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

Fostriecein (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 (6R *,9S *,11S *) 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 tetrahydropyrany 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

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Scheme 45.

Scheme 46.

Scheme 47.
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).  

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).  

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...
Kishi et al. reported the total synthesis of spongistatin 1 \((253a, \text{named in this work altohyrtin A}), \) a macrolide (together with spongistatin 2, \(253b\)) derived from a marine sponge. In the retrosynthetic analysis, \(253a\) was dissected into two segments (A and B). In the synthesis of segment A [C(1)–C(28)], 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), Osilyl 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).

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 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). 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). 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 1,3-dithiane in high yield through the compound 245 (Scheme 52). \(^{119}\)

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). \(^{127}\)

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 Et2O 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 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 1,3-dithiane in high yield through the compound 245 (Scheme 52). \(^{119}\)
Scheme 53.

Scheme 54.

Scheme 55.
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 C₂-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 macrolide135 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 C₂-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 α-D-galactoheptose derivative 288 (Scheme 61).138

The reaction of the aldehyde 289, derived from d-glucose, with the carbanon 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
Razdan et al. synthesised the enantiomeric cannabinoid terpene intermediate 305. Transformation of nopine into the enol ether 303 first and then to the enone 304, 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.
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
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 hydroxyl 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 2I4, 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 P2I4, 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’s152 and Nicolaou’s153 groups. In both synthetic approaches, the addition of a 2-alkyl-2-lithiodithiane [generated in situ from its tri-(n-butyl)stannyl derivative 326] to either the aldehyde 328152 or 329153 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 65.

Scheme 66.
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 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 67.

Scheme 68.

Scheme 69.
Seebach and Meyer reported the synthesis of some fungal metabolites with a 4-methoxy-5,6-dihydro-2-pyrene structure, such as (−)-pestalotin (341), which was isolated from *Pestalotia cryptomeriaecola*. 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).

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 70.

Scheme 71.
long been recognised as the pigments responsible for the striking yellow and orange colour of lichens (Scheme 74). Nicolaou et al. reported the synthesis of the saturated lactone 349, a potential intermediate in the synthesis of prostaglandin A2. From a readily available cyclopentene derivative 346, 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).

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...
Aplasmomycin (359), a boron-containing antibiotic isolated from a marine-derived strain of *S. griseus* that exhibits activity against Gram-positive bacteria, was synthesised by Corey et al. following a convergent strategy. The precursor corresponding to the C(11)–C(17) fragment (the dithiane unit was introduced in the molecule from the corresponding aldehyde) from the inexpensive (+)-pulegone. Thus, reaction of the vinylstannane with *n*-BuLi and addition of the dithiane epoxide 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. Metallation of with *n*-BuLi and reaction with dimethyl oxalate gave the *a*-ketoester 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 (Scheme 77).164

In an approach to the synthesis of the alkaloid lycorenine (364), Confalone et al. synthesised the azomethine ylide, which, upon [3+2] intramolecular cycloaddition, led to the desired octahydroindole ring system. Formylation of the dithiane derivative by lithiation with *n*-BuLi and reaction with DMF led to the aldehyde in 32% yield. Condensation of the aldehyde with ethyl *N*-methylglycinate at high temperatures led to the octahydroindole 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. 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 with 2-lithio-1,3-dithiane (10) afforded the alkylation product in 60% yield (Scheme 79).167

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

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

The first total synthesis of the very unstable biochemical intermediate 12-oxo-LTB4 (378), a key pivotal intermediate in LTB4 metabolism, was accomplished by Rokach et al., an
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-LTB₄ (378) (Scheme 82).
A number of chiral dithianes were synthesised by Tyrrell et al. from the corresponding chiral aldehydes. The lithiation of the dithiane $\text{379}$ with $n$-BuLi, followed by reaction with methyl chloroformate and final hydrolysis of the dithiane functionality, leading to the formation of the chiral $\alpha$-oxoester $\text{380}$ in 54% yield and high enantiomeric purity. This methodology can be applied to the preparation of other $\beta$-alkyl-/$\alpha$-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 $-110^\circ\text{C}$.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-$\alpha$-D-xylo-hex-5-enofuranose (381).176 They obtained a mixture of $\beta$-1-idofuranose 382 and $\alpha$-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 $\text{myo}$- (384) or $\text{scylo}$-configuration (385) from 382 and a $\text{muco}$-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-$\alpha$-D-ribo-hex-5-enofuranose (387) gave a mixture of $\beta$-1-talofuranose (388) and $\alpha$-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 $\text{epi}$- (390) and $\text{allo}$-configuration (391) from 389 and a $\text{myo}$-configuration (392) from 388 (Scheme 85).177

The same group observed that the Michael addition of 2-lithio-1,3-dithiane (10) to the $\alpha$-D-xypo-hex-5-enofuranose derivative 393 gave $\alpha$-D-glucofuranose (394) and $\beta$-1-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
the isopropylidene group gave the branched-chain cyclitol 396 with a \textit{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).\textsuperscript{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
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 dihydrojasmon (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 87.](image1)

![Scheme 88.](image2)
Scheme 89.

Scheme 90.

Scheme 91.

Scheme 92.
been applied to the synthesis of optically active \(\alpha\)-methylene-\(\gamma\)-lactones and other \(\alpha\)-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 \(\alpha,\beta\)-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 \([R=\text{2-hydroxy-1-phenylethyl} \text{ with } (R)-\text{configuration}]\), it is possible to prepare the compounds 432 in an enantioselective form (Scheme 93).\(^{195}\)

The previously mentioned methodology has been applied to the synthesis of 20-epidasycarpidone (434) and 20-epiuleine (435), using the 2-ethyl-substituted \(\alpha,\beta\)-unsaturated lactam 433 as the electrophile (Scheme 94).\(^{197}\)

A tandem conjugate addition–alkylation reaction starting from the indolyldithiane 428, the methylene lactam 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 \(\beta\)-acylvinylic 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 chinensinaphtol (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 \(\alpha,\beta\)-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
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 SbCl₅ – Me₂S₂, but in this case the reaction product is not the anticipated ketone 448, but the vinyl sulfide 447. Bis(trifluoroacetoxy)iodobenzene, however, led to the formation of the expected ketone 448 in 85% yield, further purification not being necessary (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).

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 products. 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(η⁵-cyclohexadienyl)manganese, nucleophilic addition took place at the terminus of the π-system and, after oxidation, 5-[2-(1,3-dithianyl]-1,3-cyclohexadiene was obtained in good yield. Similarly, an example of the addition of dithiane anions to an arene molybdenum tricarbonyl complex has been reported by Kündig et al.
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-methoxy-naphthalene–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 Ph₃P-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,
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).

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-erythulose, 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
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
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

Roflamycoin (520) (Scheme 111) is a polyene macrolide with potent antifungal activity.226 Its synthesis and structural elucidation227 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 525 in almost 80% yield. The chiral building block 522 was prepared by microbial reduction of 2-(3-oxopropyl)-1,3-dithiane with baker’s yeast233 and has been used in the synthesis of the macrocyclic lactone (S)-curvularin234 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.

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 theobromae230 with significant antileukemic activity231 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 yeast233 and has been used in the synthesis of the macrocyclic lactone (S)-curvularin234 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 attenuata236 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
of the dithiane \( \text{525} \) gave a hydroxyketone, which was reduced stereoselectively to the anti-diol \( \text{526} \) in 88% yield, along with the syn-diol (10% yield) (Scheme 113).\(^{237}\)

Molander et al. have reported the synthesis of pinidinol (\( \text{532} \)).\(^{238}\) 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 (\( \text{529} \)) to give the alcohol \( \text{530} \), which, without purification, was converted to the compound \( \text{531} \) by protecting the alcohol with TBDPSCI, removing the dithiane unit with HgCl\(_2\) and stereoselectively reducing the siloxyketone with NaBH\(_4\). A
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 iodoacetamide 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 Jenkins242 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
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–BF₃·OEt₂, 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 reduction233 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
(+)-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 rocaclamide (563), an antileukemic benzofuran derivative.252 The requisite alkylating agent 559 was easily prepared in 50% overall yield by
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).

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).

Apoptolidin (572), isolated from *Nocardiopsis* sp., has recently been synthesised by Nicolaou et al. This compound exhibits selective induction of apoptosis in transformed rat glia cells in the presence of normal cells. 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).

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 hexanolate 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 BF₃·OEt₂ and the resulting carbonyl group was reduced with NaBH₄ to give the final diol 576 (Scheme 123).

$$\text{Scheme 120.}$$

$$\text{Scheme 121.}$$
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. 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. 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).

2.7.6. Reactions with alkyl triflates, epoxides, carbonyl compounds and acylating reagents. (−)-Vermiculin is a natural diolide with antibiotic activity. 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 (5)-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,
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).$^{23,24}$

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),$^{26}$ a polyene macrolide with antifungal properties, reported by Solladie 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).$^{26}$

3. Other reactions

3.1. Reactions involving ketene dithioacetals

Ketene dithioacetals show a versatile reactivity since they can be easily converted into thietones, 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$_2$SiSiMe$_3$, 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
anions derived from the trimethylsilyl derivative 477 and the dithiane phosphonate 594. 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), an intermediate in Fleming’s synthesis of 599. Furaquinocins 603 constitute a new class of antibiotics.
which show cytotoxic activity against some melanoma cells, but no antimicrobial activity.\textsuperscript{271} In the total synthesis of these compounds reported by Suzuki et al., the lithio anion of \(594\)\textsuperscript{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).\textsuperscript{272}

The mevinolin homologue \(606\)\textsuperscript{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.\textsuperscript{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 (\(609\)).\textsuperscript{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).\textsuperscript{275} These cyclic ketones are useful precursors in steroid synthesis.

Ketene dithioacetals have also been used as terminators in electrophilic cyclisations promoted by carbocations.\textsuperscript{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 (\(\pm\))-heliotridine (\(619\)) (Scheme 132).

Ketene dithioacetals can also act as heterodienophiles in
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 \(\gamma\)-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 \(\gamma\)-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 \(\alpha\)-position.

The anion of 2-(2-phenylthioethylidene)-1,3-dithiane (632) (prepared from 2-bromoacrolein) reacted with alkyl halides and aldehydes preferentially at the \(\alpha\)-position. With open-chain aliphatic ketones, however, it reacts at the \(\gamma\)-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 noremoenic acid (639), the Northern portion of the macropyrrolizidine alkaloid noremoensine (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 trimethylaluminium and 1,3-propanedithiol, gave the ketene dithioacetal\(^{286}\) 636 in 70% yield, which, after four reaction steps, led

\[\text{Scheme 131.}\]

\[\text{Scheme 132.}\]

\[\text{Scheme 133.}\]
to the desired substrate 637. Anodic oxidation of the compound 637 yielded the tetrahydrofuran derivative 638 in 71% yield, a direct precursor (three reaction steps, 65% overall yield) of nmorensic acid (639) (Scheme 137).

3.2. 1,3-Dithiane as a protecting group

As noted previously, thioacetalisation of a carbonyl group, using Lewis or Brønsted acid catalysis, 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. For the same reasons, however, deprotection often proved to be problematic, many methods having been reported in the literature. The most common methods are acidic hydrolysis, transition metal-induced hydrolysis and oxidative or alkylative hydrolysis. It is important to note that the corresponding sulfoxides undergo hydrolysis much more readily, because the oxidised sulphur 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.

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). Deprotonation of the phosphine oxide 644 and reaction with the aldehyde 645 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).

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).

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 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), 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. A total synthesis of FK-506 (44) had already been reported from compound 648 by other authors 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), a powerful cardiotonic constituent isolated from the marine sponge Xestospongia sapra. The first total synthesis of this compound has been achieved by Harada et al. 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). Here, the dithiane moiety has been introduced for the carbonyl protection of the ketone group.

Scheme 138.

Scheme 139.

Scheme 140.

Scheme 141.
A synthesis of (S)-zearealenone dimethyl ether (655), a naturally occurring 14-membered orsellinic acid-type macrolide with anabolic and uterotropic activity, was described by Solladie 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 BF3·OEt2 in THF–H2O (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

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 8-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 HgCl2 and CaCO3 in aqueous acetonitrile gave the corresponding aldehyde, which, by alkylation and further
transformations, led to a mixture (5:1) of the spiroacetals 673 (Scheme 146), 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)<sup>00</sup>-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<sub>2</sub>-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<sub>2</sub> 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,
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).\textsuperscript{311}

Enders and Schüssele have reported the synthesis of (S)-7-methylheptadecane 687,\textsuperscript{69} a component of the sex pheromone of the spring hemlock and the pitch pine looper moths.\textsuperscript{70} The hydrazone derivative 685 was prepared by $\alpha$-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\textsuperscript{312}) by using bis(trifluoroacetoxy)iodobenzene, Wong reported the first synthesis of two new antiprotozoal agents from Amomum aculeatum rhizomes,\textsuperscript{313} aculeatins A (691) and B (692). Deprotection of the phenol derivative 688, followed by protection of the ketone, gave the $\beta$-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).\textsuperscript{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).\textsuperscript{154}

Mucocin (699) is a representative annonaceous acetogenin, which shows antitumour activity.\textsuperscript{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).\textsuperscript{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 148.](image)

![Scheme 149.](image)

![Scheme 150.](image)
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\(_2\)Cl\(_2\) at temperatures ranging between \(-10 \) and \(0^\circ\text{C}\) 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

\((\pm)\)-Spirolaurenone (706), an antifungal compound isolated from the red alga Laurencia glandulifera, was synthesised
for the first time by Masamune et al. In this synthesis, an electrophilic addition of the 1,3-dithienium tetrafluoroborate $\text{704}^3$ to the silyl enol ether $\text{703}$ took place to give the ketone $\text{705}$ in 94% yield. This ketone $\text{705}$ underwent cleavage of the cyclopropyl ring under acidic conditions and, after further transformations, gave (±)-spirolaurenone ($\text{706}$) (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.

References

3. For a review, see: Gröbel, B.-T.; Seebach, D. Synthesis 1977, 357.


Miguel Yus was born in Zaragoza in 1947. He received the BSc (1969), MSc (1971), and PhD (1973) degrees from the University of Zaragoza. After spending 2 years as a postdoc at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo where he became Associate Professor in 1977, being promoted to Full Professor in 1987 at the same university. In 1988, he moved to a chair in Organic Chemistry at the University of Alicante. Professor Yus has been visiting Professor at different institutions such as ETH-Zürich and the universities of Oxford, Harvard, Uppsala, Marseille, Okayama and Paris VI. He is a member or fellow of the Chemical Societies of Argentina, England, Germany, Japan, Spain, Switzerland, and United States. He is the co-author of more than 300 papers mainly in the field of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry. Among others, he has recently received the Spanish–French Prize (1999), the Japan Society for the Promotion of Science Prize (2000) and the Stiefvater Memorial Lectureship Award (2001).

Carmen Nájera was born in Nájera (La Rioja) and graduated from the University of Zaragoza in 1973, obtaining her doctorate in Chemistry from the University of Oviedo in 1979. She spent postdoctoral stays at the ETH (Zurich), at the Dyson Perrins Laboratory (Oxford), at Harvard University and at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante, where she is currently the Head of the Organic Chemistry Department. She is the co-author of more than 160 papers and her current research interest is focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis and peptide coupling reagents.

Francisco Foubelo was born in Carreña-Cabrales (Asturias) in 1961. He received his BSc (1984), MSc (1986), and PhD (1989) degrees in Chemistry from the University of Oviedo. After a postdoctoral stay (1989–1991) as a Fulbright fellow at Princeton University, he moved to the University of Alicante and joined the research group of Professor M. Yus where he became Associate Professor in 1995 and Full Professor in 2002. He has published more than 60 papers. His research interest has focused on the development of new synthetic methodologies for the preparation of functionalised organolithium compounds from different precursors and the application of these organometallic intermediates in organic synthesis.