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Sultones in Organic Synthesis

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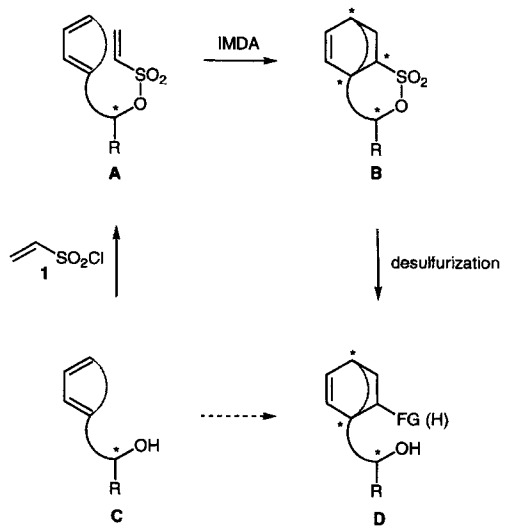
Abstract. Sultones are readily prepared by intramolecular Diels–Alder reaction of vinylsulfonates in an often highly stereoselective fashion. Various methods for the synthetic elaboration of these heterocycles have been developed and applied to the total synthesis of biologically active natural products.

1 Introduction
2 Preparation of Sultones *via* Intramolecular Diels–Alder Reaction of Vinylsulfonates
3 Synthetic Elaboration of Sultones
4 Application of Sultones towards the Synthesis of Natural Products
5 Conclusion and Perspectives

1 Introduction

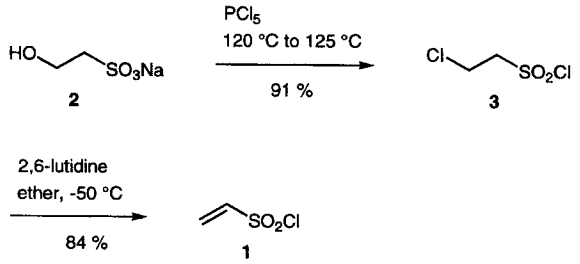
This article briefly outlines our recent synthetic work with sultones [1, 2]. Over the past several years, these cyclic sulfonic acid esters have emerged as valuable heterocyclic intermediates that offer interesting options for stereoselective synthesis. The basic concept which provided the major impetus for the studies described here is illustrated in Scheme 1. An intramolecular Diels–Alder reaction [3] of a vinylsulfonate **A** prepared by esterification of the corresponding alcohol **C** with vinylsulfonyl chloride (**1**) [4] was envisioned to generate a sultone **B** that is desulfurized by a suitable procedure to give a product **D** (FG = functional group) in a subsequent operation. This three-step sequence would be equivalent to an intermolecular [4+2] cycloaddition of 1,3-diene **C** with an olefinic dienophile; however, it might hold distinct advantages with respect to reactivity as well as regio- and diastereoselectivity. Complete regiocontrol is at hand through choosing an appropriate tether length which prevents formation of the isomeric bridged cycloadduct. Moreover, a defined stereochemical relationship between acyclic and cyclic stereogenic moieties within **D** is established if the cycloaddition step proceeds diastereoselectively with respect to the chiral center in the tether linking diene and dienophile. Both selectivities can hardly be efficiently achieved through an intermolecular [4+2] addition strategy [5].

The vinylsulfonate functionality appeared especially promising for the cycloaddition step because, next to the electron-withdrawing nature of the sulfonate unit [4, 6], it is unhampered by the unfavorable conformational preferences associated with acrylates [7] and thus, it was anticipated that rather mild cyclization conditions would ensue. On the other hand, desulfurizations of sultones [8] had not been investigated as thoroughly as corresponding processes for sulfones [9], and new methods would have to be developed.



Scheme 1

Vinylsulfonyl chloride (**1**) is readily available from isethionic acid sodium salt (**2**) according to published literature procedures. Chlorination of **2** to give 2-chloroethanesulfonyl chloride (**3**) [10] as well as dehydrohalogenation of **3** to **1** [11] proceed in high yield on a multi-gram scale (Scheme 2). Although **1** can be stored in a refrigerator for a longer period of time, redistillation shortly before use is recommended for best performance.



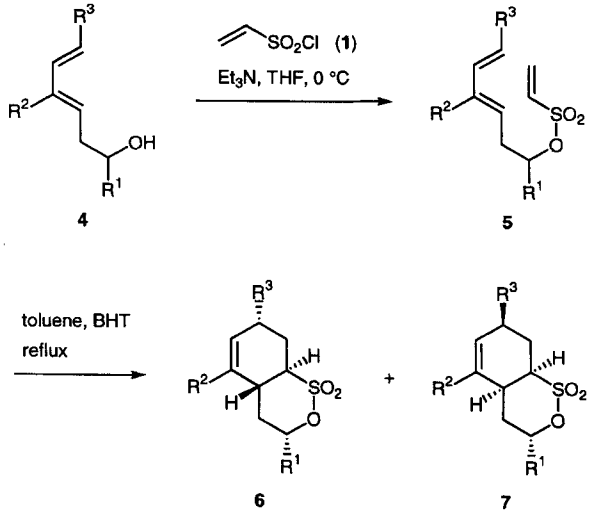
Scheme 2

2 Preparation of Sultones *via* Intramolecular Diels–Alder Reaction of Vinylsulfonates

Vinylsulfonates **5a–d** possessing an acyclic diene moiety were easily derived from the corresponding alcohols **4a–d** by esterification with vinylsulfonyl chloride (**1**). Upon heating of **5a–d** at reflux in toluene in the presence of a small amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT), a highly selective formation of the δ-sultones **6** and **7** out of four possible product diastereomers was observed. Sultones **6** and **7** presumably arise *via* chair-like transition states featuring an equatorial orientation of R^1. A substituent R^2 larger than hydrogen additionally causes a notable preference for the formation of the *exo* product **6** relative to **7** for R^2 = Me (**5c**) already, while virtually complete diastereoselectivity in favor of sultone **6** is achieved for the bulky R^2 = $SiMe_3$ (**5d**). A sterically unfavorable interaction between R^2 and the axial hydrogen at the carbinol center in the transition state is likely to be responsible for this enhanced *trans* selectivity (Scheme 3 [12, 13]).

Whereas attempts to trigger cyclization of **5** at low temperature using different Lewis acids failed, the application of high pressure [2f] was effective. Thus, by applying a pressure of 12 kbar both **5b** and **5c** smoothly cyclized at room temperature in good yields. As anticipated, the more compact *endo* transition state leading to **7** is now favored for the cycloaddition of **5b**, while the steric effect mentioned above still predominates for the cyclization of **5c** [14].

Esterification of alcohols **8a,b** as equilibrium mixtures of diene isomers with vinylsulfonyl chloride (**1**) led after 2–3 h at 0° C directly to *exo* sultones **10a,b** with excellent diastereoselectivity (*ds* = 96 %) for both substrates. Only the depicted C-1 substituted diene isomers **9a,b** cyclize, while the other isomers are presumably converted to **9a,b** by 1,5-H shift during the reaction course. The cyclohexadiene homolog **9c** derived from alcohol **8c** required reflux in toluene for complete conversion, but again, the intramolecular Diels–Alder reaction proceeded with high diastereoselectivity (*ds* = 93 %). Interestingly, *endo* sultone **10c** was obtained predominantly (Scheme 4 [13, 15]). Since the alkyl substituent at the inducing stereogenic center occupies an equatorial position of a chair δ-sultone for all major products, a chair-like folded tether with minimized nonbonding interactions is probably the favored geometry in the transition state of these cycloadditions.



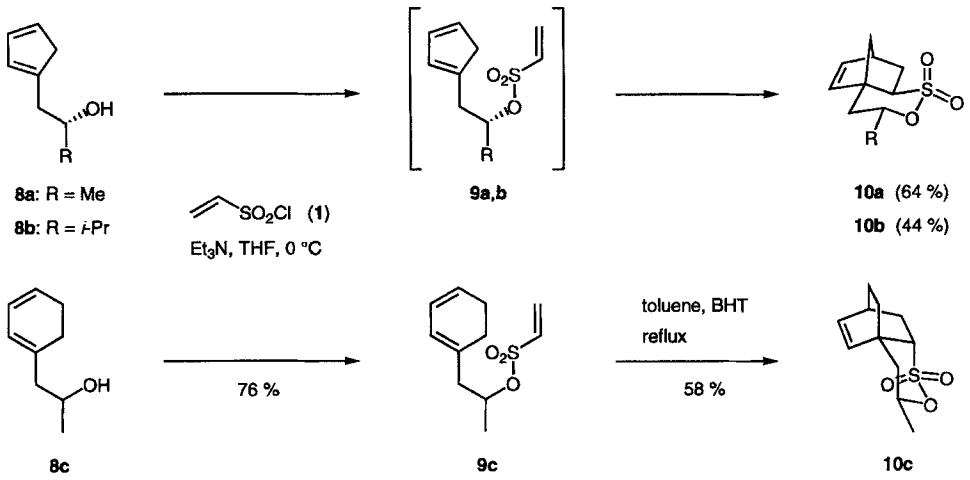
4–7	R^1	R^2	R^3	Yield **5** (%)	**6** : **7**	Yield **6**+**7** (%)
a	H	H	H	87	1 : 1	76
b	Me	H	Me	82	1.4 : 1	64
b [a]					1 : 2.0	64
c	*t*-Bu	Me	H	78	4.7 : 1	61
c [a]					3.6 : 1	70
d	Me	$SiMe_3$	H	86	>99 : 1	39

[a] Cycloaddition conditions: 12 kbar, CH_2Cl_2, 25 °C

Scheme 3

Furans are excellent 1,3-diene components for the intramolecular vinylsulfonate cycloaddition. Treatment of the hydroxyalkylfurans **11a–d** with vinylsulfonyl chloride (**1**) led within a few hours at room temperature to the *exo* adduct **12** featuring an equatorial alkyl group on a chair δ-sultone as the only stereoisomer (Scheme 5 [16, 17]). In contrast to these reactions of vinylsulfonates derived from **11a–d**, a second *exo* isomer was additionally formed from **11e** under these conditions, but a subsequent equilibration eventually afforded the thermodynamically more stable isomer **12e** in high diastereomeric excess [18].

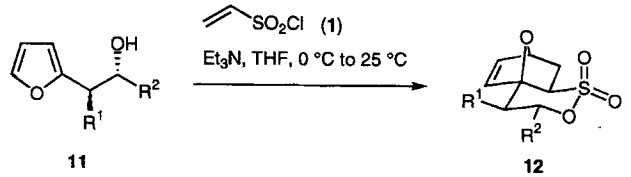
Recently, we found that vinylsulfonamides of aminoalkyl substituted furans undergo a facile cycloaddition as well. Thus, the δ-sultams **14a,b** were produced highly diastereoselectively (**14a**: *ds* = 94 %, **14b**: *ds* =



Scheme 4

92%) after treatment of the furan-containing *N*-benzylamines **13a,b** with vinylsulfonyl chloride (**1**) for several hours at room temperature. The pronounced stereoselectivity for the kinetically controlled [4+2] addition to **14b** is most probably due to a stereoelectronic effect that is also responsible for the axial orientation of the *N*-benzyl group on the chair δ-sultam moieties of **14a,b** (Scheme 6 [19]).

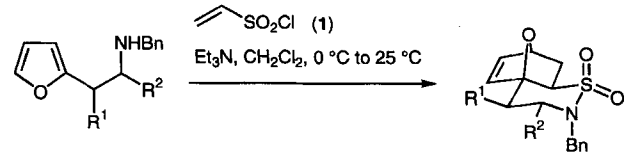
Vinylsulfonamides **15** featuring a three atom tether connecting the furan and the dienophile units did not undergo ring closure during preparation or workup.



11,12	R^1	R^2	Yield **12** (%)
a	H	Me	90
b	H	Et	91
c	H	*i*-Pr	87
d	H	*n*-Pr	81
e	Me	H	86 [a]

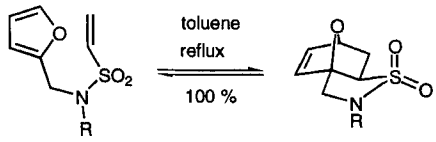
[a] After equilibration of 2 diastereomeric *exo* adducts formed at 0 °C (*dr* = 1.4 : 1) in refluxing tolouene (→ *dr* = 9.5 : 1)

Scheme 5



Scheme 6

Whereas heating at reflux in toluene was ineffective for **15a** and caused only a modest conversion of **15b**, equilibrium was largely shifted to the *exo* γ-sultam **16** for the *N*-benzyl analog **15c** at this elevated temperature. Remarkably, a quantitative yield of crystalline γ-sultam **16b** was isolated upon slow evaporation of a chloroform solution of the equilibrium mixture of **15b/16b** (71 : 29) at room temperature (Scheme 7 [19]).



	15	**16**
a: R = H	100	0
b: R = Me	71	29
c: R = Bn	9	91

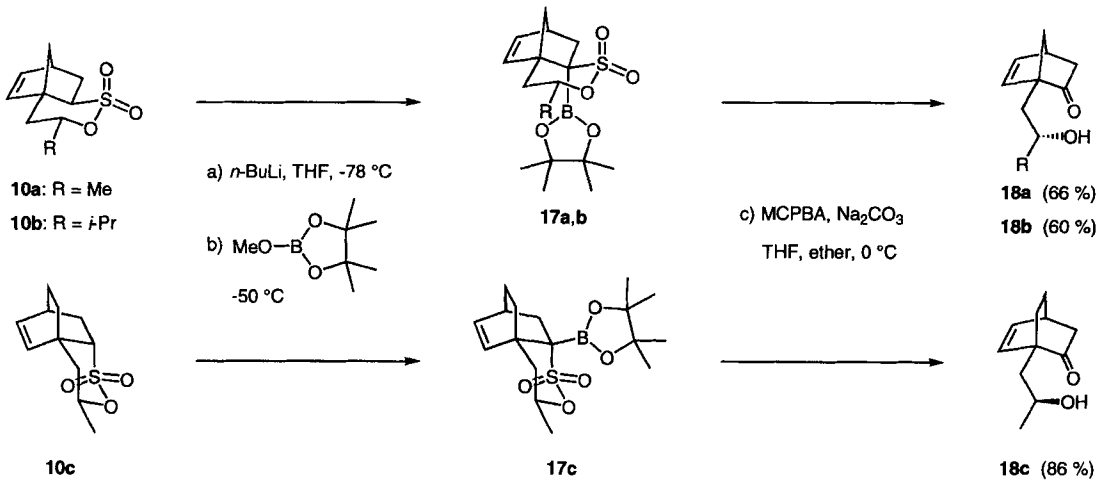
Scheme 7

3 Synthetic Elaboration of Sultones

According to the concept illustrated in the introduction, different methods for the desulfurization of sultones were investigated.

An efficient oxidative desulfurization of sultones **10a–c** to hydroxy ketones **18a–c** was accomplished by borylation of the α-lithiated sultones with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and subsequent oxidation of the resulting boronates **17a–c** using *m*-chloroperbenzoic acid in the presence of sodium carbonate (Scheme 8 [13, 15]). The alkene moiety of **17** is completely unaffected by the peracid under these conditions. Only the boron atom is attacked to give an intermediate α-oxygenated sultone which, as anticipated, breaks down to the desired hydroxy ketone **18**. Though isolation of the intermediates **17** is easily

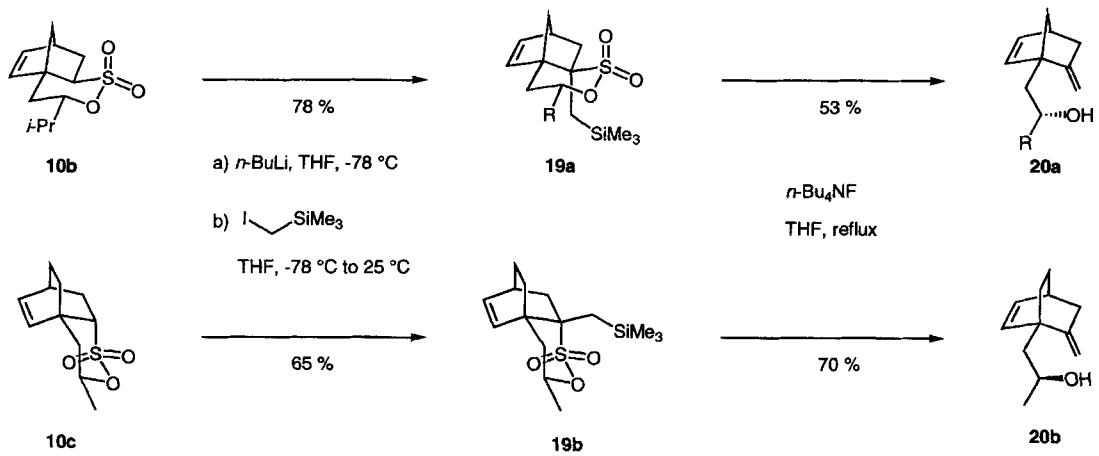
achieved, and conversion to **18** can be performed in a separate operation, best results were obtained when borylation was immediately followed by cannulating the resultant solution of **17** to a suspension of the oxidizing agent at low temperature. Since the hydroxy ketones **18a–c** are formal [4+2] adducts of ketene with the hydroxyalkyl substituted dienes **8a–c** from which sultones **10a–c** were prepared, vinylsulfonyl chloride (**1**) can be used as a ketene equivalent for the intramolecular Diels–Alder reaction both in a completely regioselective as well as highly diastereoselective fashion.



Scheme 8

A mechanistically similar sultone cleavage allows the use of vinylsulfonyl chloride (**1**) as a regio- and stereoselectively reacting allene equivalent for the intramolecular Diels-Alder reaction as well without resorting to an olefination of hydroxy ketones **18**. Thus, a desulfurization of sultones **10b,c** with simultaneous methylenation to give the bishomoallylic alcohols **20** was achieved by alkylation with (iodomethyl)trimethylsilane followed by fluoride-induced elimination of the resultant silanes **19a,b** using tetra-*n*-butylammonium fluoride (Scheme 9 [20]).

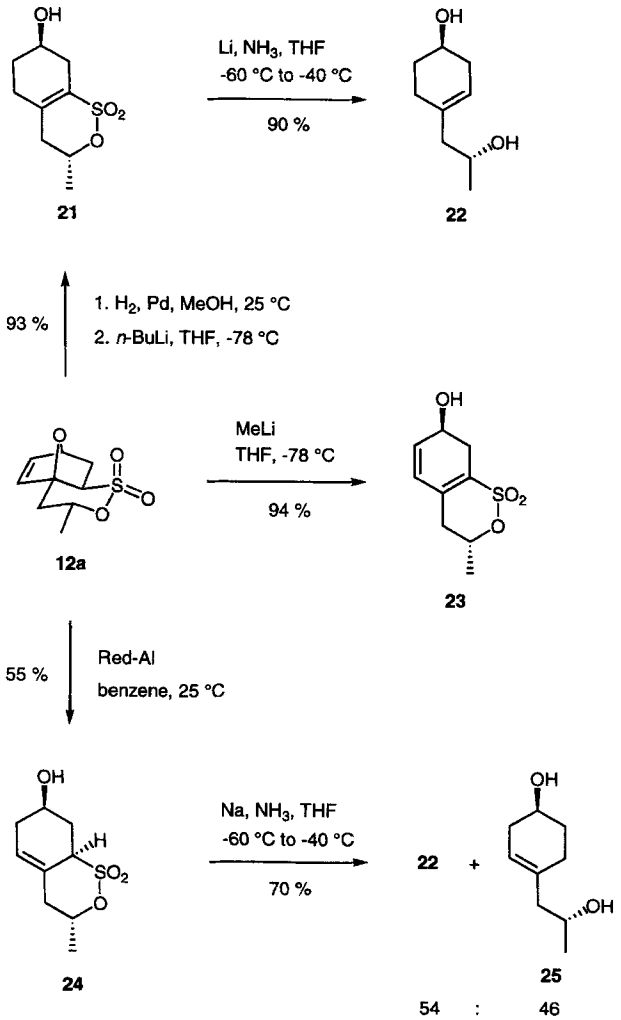
Due to the presence of a heteroatom β to sulfur, sultones derived from furan 1,3-dienes offer special options for further synthetic elaboration. Treatment of sultone **12a** with strong bases such as methyllithium [21, 22] caused a cleavage of the oxygen bridge to give the dienol **23** in high yield, although a subsequent dehydration would produce a benzene derivative. Likewise, deprotonation of the saturated analog of **12a** with *n*-butyllithium afforded the cyclohexenol **21**. Unexpectedly, sultone **24** featuring an allylic C–S bond was formed upon reaction of **12a** with one equivalent of sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al). Since **24** was also obtained from **23** under identical conditions, the latter process is probably again initiated by an elimination with one hydride from Red-Al acting as a base. The resultant aluminate of **23** in turn is converted to **24** *via* intramolecular 1,6-addition of the second hydride followed by a regio- and stereo-



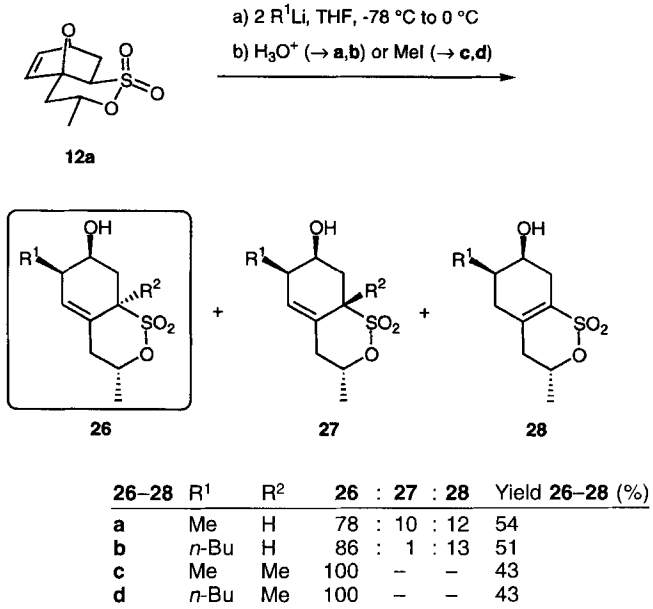
Scheme 9

selective protonation of an allylsodium species during aqueous workup (Scheme 10 [23]). Sultones **21** and **24** were efficiently desulfurized by metal/ammonia reduction. While a mixture of cyclohexenes **22** and **25** was produced from allylic sultone **24**, the vinylic sultone **21** reacted with complete regioselectivity to yield only **22** [21].

A tandem elimination/alkoxide-directed 1,6-addition leading to alkylated products was accomplished by treatment of sultone **12a** with two equivalents of an alkyllithium reagent (Scheme 11 [24–26]). The first equivalent of R^1Li deprotonates **12a** with concomitant ring opening to a lithium alkoxide at –78 °C. This electron-deficient diene in turn serves as an extended conjugate acceptor toward the second equivalent R^1Li. Since only an addition adjacent and *cis* to the hydroxyl group was noted, the alkyllithium reagent probably coordinates to the alkoxide moiety prior to C–C coupling. Protonation of the resultant allyllithium intermediate led to mixtures of isomeric sultones **26a,b–28a,b**, but a subsequent equilibration with catalytic amounts of potassium *t*-butoxide resulted in complete conversion of the minor isomers to the thermodynamically most stable allylic sultone **26a** (77 %) and **26b** (91 %), respectively. Trapping of the allyllithium species with methyl iodide instead of aqueous workup allowed formation of a second C–C bond in a one-pot procedure. In contrast to protonation, methylation of these intermediates occurred in a completely regio- and stereoselective fashion to yield only **26c,d**.



Scheme 10



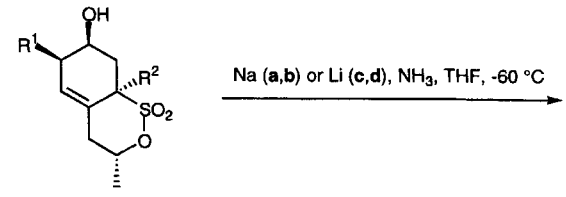
26–28	R^1	R^2	26 : 27 : 28	Yield 26–28 (%)
a	Me	H	78 : 10 : 12	54
b	*n*-Bu	H	86 : 1 : 13	51
c	Me	Me	100 – –	43
d	*n*-Bu	Me	100 – –	43

Scheme 11

Sodium or lithium in liquid ammonia again effected a smooth reductive desulfurization of allylic sultones **26** to substituted cyclohexenols possessing a defined stereochemical relationship between acyclic and cyclic stereogenic moieties. Due to conformational reasons, the double bond isomers **29a,b** were preferentially formed from **26a,b**, whereas sultones **26c** and **26d** exclusively provided the tetrasubstituted olefins **29** *via* protonation of the intermediate allylmetal species at the less substituted terminus (Scheme 12 [24–26]).

4 Application of Sultones towards the Synthesis of Natural Products

The macrotetrolides **31**, also known as actins or nactins, have been isolated from various *Streptomyces* cultures (Figure 1 [27]). These neutral ionophores display pronounced antibacterial [28], insecticidal [29], and in part immunosuppressive activities [30] as well. Whereas efficient methods for macrocyclization of suitable linear precursors have been reported [31], a short and general access to the monomeric hydroxy acids was still highly desirable in view of the biological activities associated with the actins.



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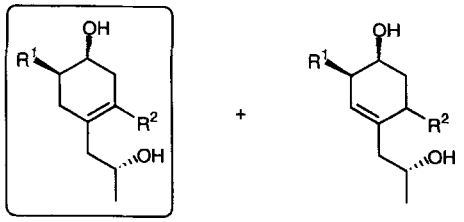


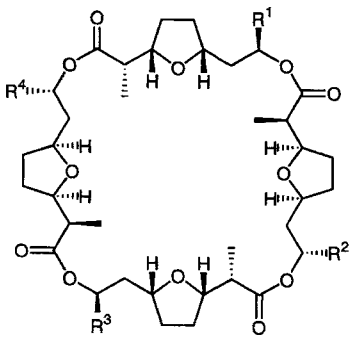
29 30

26,29,30	R^1	R^2	29 : 30	Yield 29+30 (%)
a	Me	H	70 : 30	95
b	*n*-Bu	H	64 : 36	96
c	Me	Me	100 –	95
d	*n*-Bu	Me	100 –	98

Scheme 12

Using the sultone chemistry described above, we have recently developed a highly stereoselective and flexible synthesis of actic acids **32** that is not only applicable to the naturally occurring compounds with R^1 = Me, Et, *i*-Pr and R^2 = Me, but allows a further variation of the substituents R^1 and R^2 in a straightforward manner. Figure 2 illustrates how the hydroxy acids **32** can be assembled from four simple building blocks: furan, an epoxide, vinylsulfonyl chloride (**1**), and an organolithium reagent. Moreover, an enantioselective synthesis is at hand, since a large variety of the requisite enantiomerically pure epoxides is readily available in both enantiomeric forms, *e.g.* from α-amino acids [32].

Our sultone route to **32** was first exemplified for nonactic acid (R^1 = R^2 = Me). Due to the extensive applica-



31

(R^1 - R^4 = Me, Et, *i*-Pr)

Fig. 1

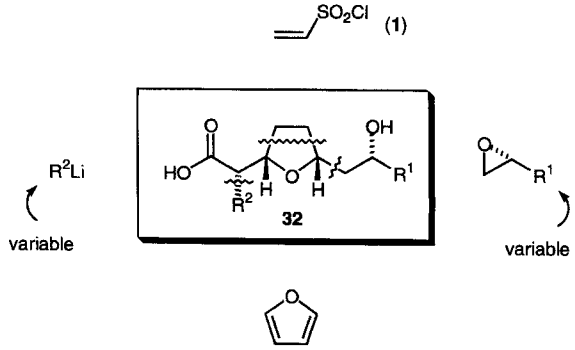


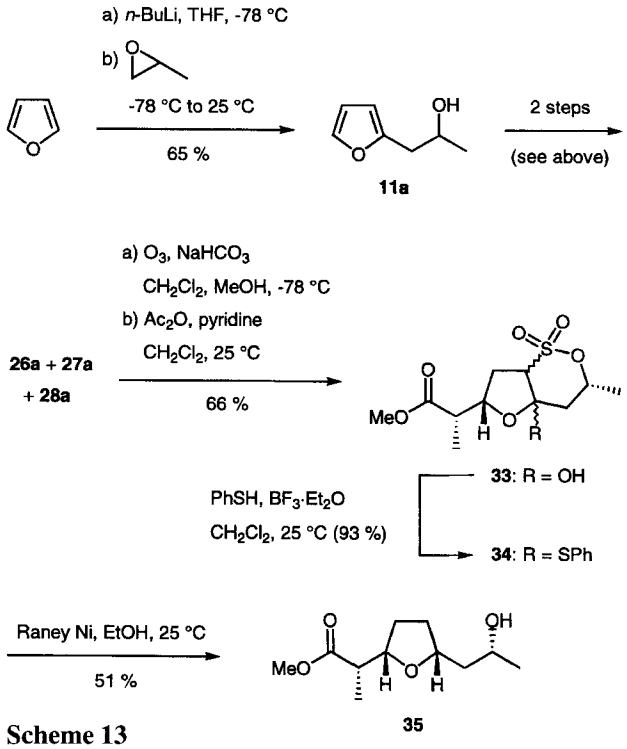
Fig. 2

tion of sequential transformations [33], only six steps were needed to secure methyl nonactate (**35**) from furan (Scheme 13 [34–36]).

Lithiation of furan followed by alkylation with epoxypropane yielded alcohol **11a** that was transformed to a mixture of sultones **26a**, **27a**, and **28a** by intramolecular Diels–Alder reaction of the derived vinylsulfonate (see Scheme 5) and subsequent tandem elimination/alkoxide-directed 1,6-addition (see Scheme 11). Ozonolysis of this mixture caused only a conversion of the trisubstituted olefins **26a** and **27a**, while **28a** could easily be separated later on. Due to a regioselective cycloreversion of the primary ozonides from **26a** and **27a**, eliminative workup involving a chemoselective acetylation eventually gave rise to two diastereomeric hemiacetals **33**. A Lewis acid-catalyzed exchange of the hydroxyl group in **33** against a phenylthio group in **34** set the stage for a chemoselective reductive cleavage of both C–S bonds in one operation. Gratifyingly, upon treatment of **34** with Raney nickel, methyl nonactate (**35**) was directly obtained. Presumably, first a reductive elimination occurs to give a single 2,3-dihydrofuran which in turn is immediately hydrogenated by the hydrogen adsorbed within the Raney nickel highly diastereoselectively (**35** : 6-*epi*-**35** = 96 : 4) from the sterically less hindered π-face. Saponification of **35** to nonactic acid is known and thus, the reaction sequence from furan to **35** also constitutes the shortest synthesis of nonactic acid with excellent stereocontrol.

In a similar fashion, hydroxyalkyl substituted furan *ent*-**11d** (see Scheme 5) was converted to an enantiomerically pure *n*-propyl homolog of **35** [17] that serves as an intermediate for the synthesis of the macrodiolide antibiotic pamamycin-607 (**36**) (Figure 3 [37]).

The bicyclic sesquiterpene lactones ivangulin (**37**) [38], 1,6-diacetylbritannilactone (**38**) [39], eriolanin (**39**), and eriolangin (**40**) [40] belong to the class of the 1,10-*seco*-eudesmanolides, the highly oxygenated members of which, **39** and **40**, display a significant antileukemic activity in vivo [40]. A central problem associated with the diastereoselective synthesis of **37**–**40** is con-



Scheme 13

trol of the relative configuration of the exocyclic stereogenic center (Figure 4).

A short and highly stereoselective synthesis of the 1,10-*seco*-eudesmanolide ivangulin (**37**) was achieved by means of a thermodynamically controlled intramolecular Diels–Alder reaction of a furan-derived vinylsulfonate, a radical cyclization onto a dienylsultone, and a reductive sultone cleavage as the key steps (Schemes 14, 15 [18, 26]).

Alcohol **11e** prepared by Wittig olefination and subsequent hydroboration/oxidation from 2-acetylfuran (**41**) was efficiently transformed to sultone **12e** (see Scheme 5). After cleavage of the oxygen bridge in **12e** *via* eliminaton [41] to give dienol **42**, the γ-lactone of the target molecule **37** was constructed in masked form by a chromium(II)-induced cyclization of the mixed bromoacetal epimers **43**. Methylation of the resultant mixture of diastereomeric allyl sultones **44**, all of which already possess the correct relative configuration of the three stereogenic centers present in **37**, occurred only

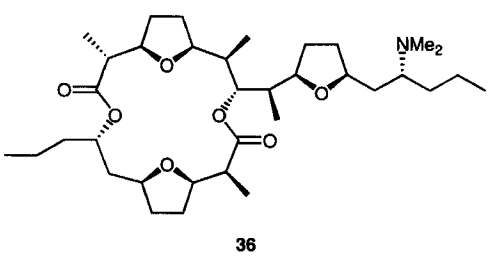


Fig. 3

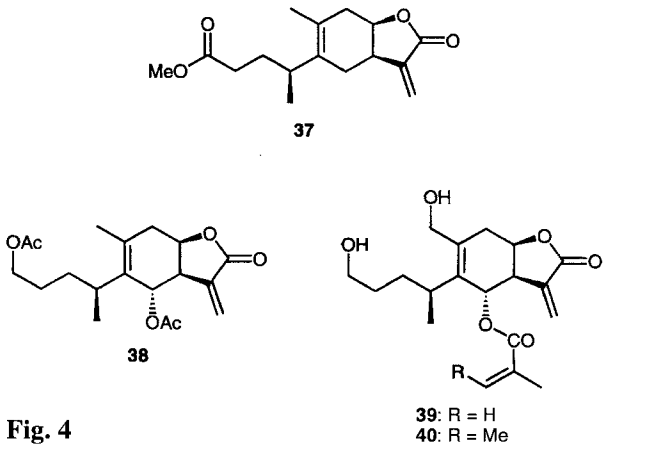
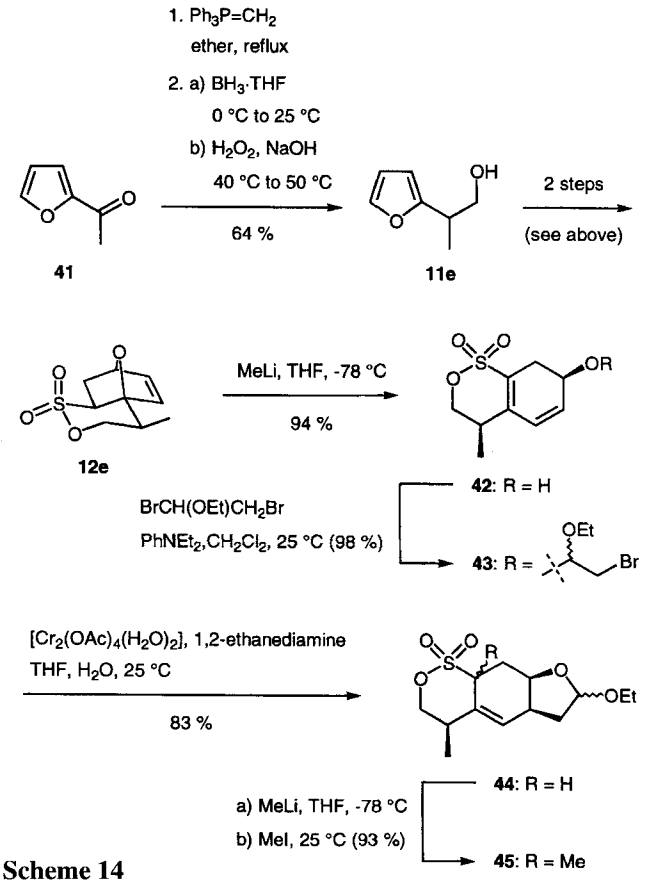


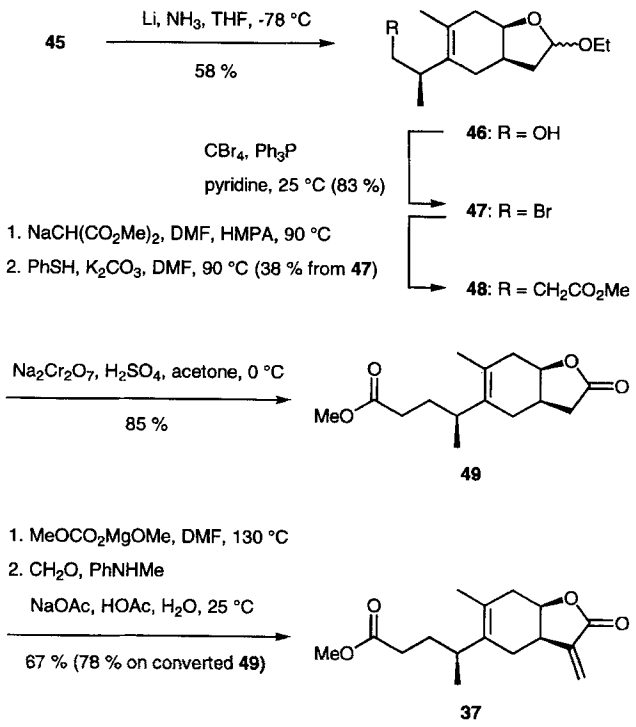
Fig. 4

in α-position to sulfur with formation of the diastereomeric alkylation products **45**.

Due to faster protonation at the less substituted terminus of the allyllithium intermediate, a reductive desulfurization of **45** with lithium in liquid ammonia led with good selectivity to the tetrasubstituted olefin **46** which was converted to bromide **47**. The side chain of **37** was completed by reaction of **47** with sodium dimethylmalonate followed by demethoxycarbonylation of the resultant substituted malonate, and Jones oxidation of the epimeric acetals **48** unmasked the γ-lactone **49**. For



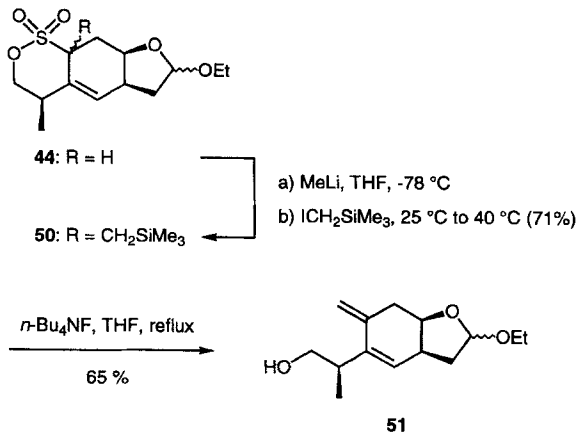
Scheme 14



Scheme 15

α-methylenation to ivangulin (**37**), a two-step sequence consisting of carboxylation of **49** with methyl methoxymagnesium carbonate and a subsequent Mannich reaction with decarboxylation was used which succeeded with complete chemoselectivity.

Starting from 2-acetylfuran (**41**), this sultone route featuring excellent control of the relative configuration of the stereogenic center located on the side chain requires only 15 steps, and thus halves the number of steps needed in the previously published synthesis of **37** [42].

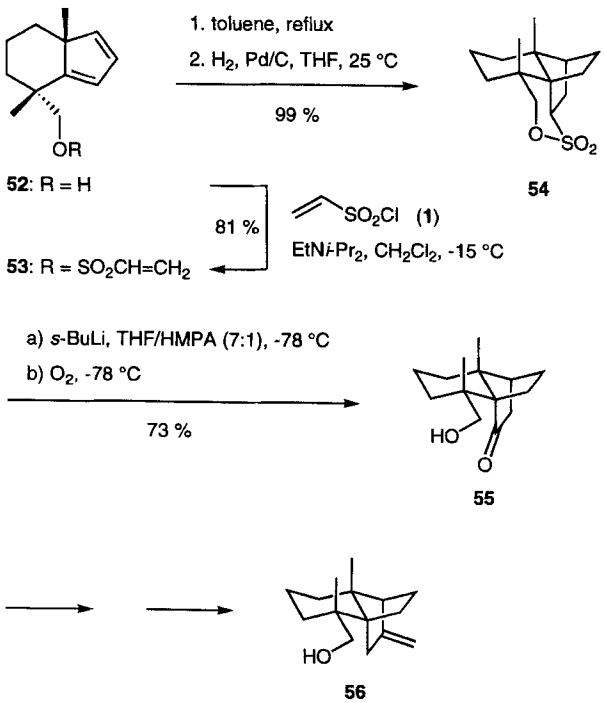


Scheme 16

In a recent study [43], a highly enantioselective preparation of (*S*)-**11e** was developed using Oppolzer's sultam methodology [44] to enable a practical synthesis of naturally occuring (+)–**37** as well.

After some minor modifications, the two-step procedure for desulfurization of sultones with simultaneous methylenation described in chapter 3 was successfully applied to the ivangulin (**37**) precursor **44** (Scheme 16 [20, 35]). Since both termini of the 1,3-diene unit in the resultant alcohol **51** are activated towards an oxygenation, this compound represents a promising intermediate for the total synthesis of the more highly oxygenated 1,10-*seco*-eudesmanolides **38–40** by a route similar to the one that led to ivangulin (**37**).

Recently, Winterfeldt and coworkers utilized the regio- and stereoselective formal [4+2] addition of ketene to hydroxyalkyl substituted dienes *via* intramolecular Diels–Alder reaction of the derived vinylsulfonate and subsequent oxidative desulfurization (cf. Scheme 8) as a key sequence in an enantioselective synthesis of the unusual sesquiterpenoid alcohol (–)-myltaylenol (**56**) (Scheme 17 [2h]). Due to the steric hindrance around the carbon α to sulfur in lithiated **54**, the original borylation/oxidation protocol had to be replaced by an oxidative sultone scission with molecular oxygen. The resultant hydroxy ketone **55** was elaborated to the target **56** in a straightforward fashion.



Scheme 17

5 Conclusion and Perspectives

The efficient and often highly stereoselective intramolecular Diels–Alder reaction of vinylsulfonates followed by the flexible elaboration with cleavage of the resultant heterocycles has evolved as a powerful sequence for organic synthesis. Variation of the tether length, the use of nitrogen for attachment of the sulfur functionality, and discovery of novel methods for desulfurization remain topics that will be addressed to further enhance the versatility of cyclic sulfonic acid derivatives. Moreover, since tethering of a vinylsulfonyl unit to another reactive moiety surely is not limited to [4+2] cycloadditions, many new applications based on such a temporary „sulfur connection" are foreseeable.

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