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Spiro[2.4]hepta-4,6-dienes: synthesis and application in organic synthesis

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This review integrates and describes systematically the data in the field of spiro[2.4]hepta-4,6-dienes published in the past 15 years. The changes in the development of studies that took place during this period are noted. The methods for the synthesis, the reactivity details and key chemical transformations of spiro[2.4]hepta-4,6-dienes are considered, with the emphasis on applications of these compounds in organic synthesis.
The bibliography includes 207 references.

Contents

I. Introduction 205
II. Methods of synthesis of spiro[2.4]hepta-4,6-dienes 206
III. Chemical transformations of spiro[2.4]hepta-4,6-dienes 210

I. Introduction

Chemical compounds of the spiro[2.4]hepta-4,6-diene (SHD) series, the first representatives of which were synthesized in 1955,[1] are currently attracting a great deal of research interest in various fields. The only review[2] devoted to SHDs has been published more than 20 years ago. During this period, a wealth of data on the methods of synthesis of spiro[2.4]hepta-4,6-dienes and their applications in targeted organic synthesis have been accumulated in the literature.

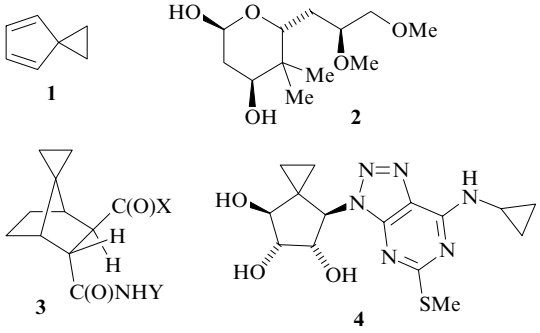
Spiro[2.4]hepta-4,6-diene has long been considered as a product exclusively of chemical synthesis. However, both unsubstituted spiro[2.4]hepta-4,6-diene (**1**) and its derivatives have been found in living nature in recent years.[3–13] It is noteworthy that spiro[2.4]hepta-4,6-diene is the main hydrocarbon in the wood of the Indian tree *Pamburus missionis* (Wigh) Swingle, the acetone stem extract containing >15% of SDH.[3] Spiro[2.4]hepta-4,6-diene was found even in foodstuff, in particular, in volatile fractions of the Muscat and Isabel wines[12] responsible for their odour, as well as in yoghurts based on fermented dairy bacteria of the genus *Lactococcus lactis* isolated from Tibetan Kefir grains.[13] Besides, SHD was found in the environment, including waste dumps and wastewaters.[14–16] However, it cannot be said with certainty that it is SHD that was detected in all of the cases taking into account the difficulties with the identification of this compound by GC/MS.[17]

The spiro[2.4]hepta-4,6-diene skeleton is a key moiety that is present in a number of drugs and insecticides.[2] This compound was used to synthesize natural and biologically active compounds: bisguanidine alkaloids,[18] glycosidase inhibitors,[19] pederol (**2**),[20] tricyclic sesquiterpenes,[21–25] prostaglandins,[26,27] anti-inflammatory agents (compounds **3**)[28–37] and agents for the treatment of cardiovascular diseases (compounds **4**),[38,39] immune system disorders,[40,41] smallpox[42] and malaria.[43] Besides, practically useful polymer materials[44–46] and active metal complex catalysts[2,47–60] were prepared based on SHD. The spiro[2.4]hepta-4,6-diene molecule is an interesting object for investigating the effect of spiroconjugation by means of different instrumental methods.[2,61]

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Structures 1 – 4



This review integrates and describes systematically the data on spiro[2.4]hepta-4,6-diene published in the past 15 years: key methods for the synthesis of SHD and its derivatives and some transformations of these compounds which are of most practical interest.

II. Methods of synthesis of spiro[2.4]hepta-4,6-dienes

Available methods for the synthesis of compounds of the SHD series can be arbitrarily divided into two groups.

One group includes methods based on the nucleophilic substitution (in particular, alkylation and cycloalkylation) and nucleophilic addition (addition of carbanions to Michael acceptors) of the intermediate cyclopentadienyl anion. These approaches are currently most commonly employed for the preparation of SHD.

Another group includes methods for the construction of the SHD skeleton through cyclomethylenation of the exocyclic double bond in fulvenes, as well as through cyclomethylenation of other double bonds (for example, by the reaction of diazocyclopentadiene and its derivatives with alkenes).

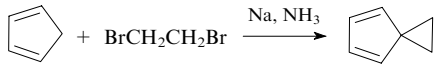
Besides, the formation of compounds of the SHD series, usually as minor products, was observed in some photochemical transformations and reactions involving carbenes.

II.1. Cycloalkylation of cyclopentadiene with 1,2-dihaloalkanes and other 1,2-difunctional compounds

II.1.a. Spiro[2.4]hepta-4,6-diene

Spiro[2.4]hepta-4,6-diene (**1**) was synthesized for the first time [1] by cycloalkylation of cyclopentadiene (CPD) with 1,2-dibromoethane in the presence of sodium in liquid ammonia (in 25% yield) (Scheme 1).

Scheme 1



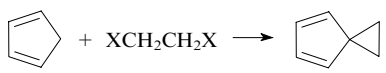
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The cycloalkylation of CPD with 1,2-dibromoethane remains the most convenient preparative procedure for the synthesis of SHD. The improvements of this approach are associated mainly with simplification of the procedure and an increase in the yield of the product.

Apart from dibromoethane, less expensive 1,2-dichloroethane and ethylene glycol bis(benzenesulfonate) are widely used for this purpose. The application of the latter compound in the synthesis of SHD is of particular interest because bis(benzenesulfonates) along with toluenesulfonates (tosylates, Ts) and dimethanesulfonates (mesylates, Ms) are often generated as intermediates in the synthesis of the corresponding dihalides.

In practice, NaH in THF (Table 1, Nos 1–3) and aqueous NaOH under phase-transfer catalysis (PTC) conditions in the absence of an organic solvent are most commonly employed as reagents instead of metallic sodium. These reagents substantially simplify the procedure and make the isolation of SHD easier (Scheme 2; Table 1, Nos 5 and 8–15).

Scheme 2



1

Table 1. Synthesis of spiro[2.4]hepta-4,6-diene (**1**) according to Scheme 2.

No.	X	Reagents and conditions	Yield (%)	Ref.
1	Br	NaH, THF	70	62
2	Br	NaH, THF, 20 °C	46	63
3	Br	NaH, THF, 0 °C	30	64
4	Br	NaOH, catalyst,[a] 20–50 °C	50–87	2
5	Br	KOH, TEBAC, 0–20 °C	80	2
6	Br	K_2CO_3, DMSO, 20 °C	70	2
7	Cl	NaH, THF, 20 °C	63	63
8	Cl	NaOH,[b] TEBAC, 50 °C	See [c]	29, 32–34
9	Cl	NaOH, TEBAC, 50 °C	50	65
10	Cl	NaOH, Bu^n_4NI, 20 °C	23	66
11	Cl	NaOH, TEBAC, 50 °C	51	20
12	Cl	NaOH, PEG	82	67
13	Cl	NaOH, $MeBu^n_3NCl$, 30 °C	59–78	68
14	Cl	NaOH, TEBAC, 50 °C	65	69
15	OSO_2Ph	NaOH, TEBAC, 30–40 °C	60	69, 70

Note. TEBAC is benzyltriethylammonium chloride, PEG is polyethylene glycol. [a] The catalyst is TEBAC, Bu^n_4NI or PEG; [b] in examples 8–15, a 50% aqueous NaOH solution was used; [c] the yield was not reported.

Kilcher *et al.*[68] developed a continuous process for the phase-transfer-catalyzed synthesis of SHD from cyclopentadiene and 1,2-dichloroethane in a flow microreactor. In this process, the product was obtained in a yield of up to 95% with a productivity of 15 g h^{-1}. The chart of one of such set-ups is shown in Fig. 1. Therefore, prerequisites were created for the implementation of the industrial production of SHD.

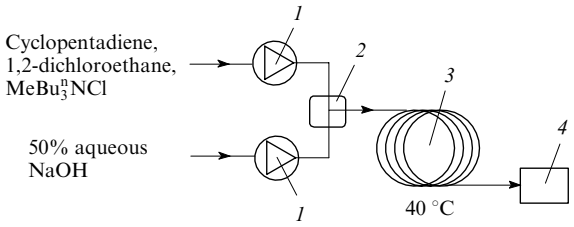
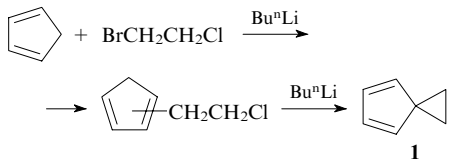


Figure 1. Chart of a flow set-up for continuous production of SHD.[68]
The reactants are fed by pumps (*1*) into a Raschig ring static mixer (*2*) and then into a homemade residence time unit (*3*) consisting of a Teflon (PFTE) tube filled with small pieces cut from the same PFTE. The reaction mixture containing SHD comes out through a tube (*4*).

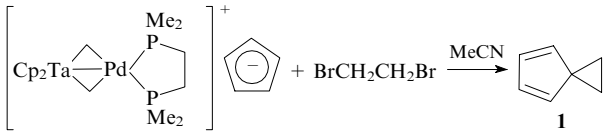
Some other examples of the synthesis of spiro[2.4]hepta-4,6-dienes were described in the literature; however, they have no preparative value. For instance, the scheme of the synthesis of SHD and its derivatives by the two-step alkylation of CPD was proposed.[71] In particular, the alkylation of CPD with 1-bromo-2-chloroethane in the presence of 1 equiv. of Bu^nLi affords monosubstituted CPD and the intramolecular cyclization of the latter gives SHD in high yield (Scheme 3).

Scheme 3



Another example is the reaction of 1,2-dibromoethane with two molecules of the heterobimetallic tantalum palladium complex, which proceeds at room temperature and produces SHD in a yield of up to 90% (Scheme 4).[72, 73]

Scheme 4

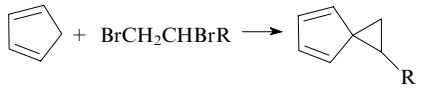


Cp is cyclopentadienyl

II.1.b. Spiro[2.4]hepta-4,6-diene derivatives

Apart from unsubstituted SHD, monosubstituted spiro[2.4]hepta-4,6-dienes were synthesized by the phase-transfer-catalyzed cycloalkylation of CPD with appropriate 1,2-dibromoethane derivatives.[2, 70, 74–76] The reactions with alkyl and cycloalkyl derivatives were performed in a 50% aqueous NaOH solution; functionalized SHDs were synthesized using a KOH powder in CH_2Cl_2, which excluded side reactions involving functional groups, for example, hydrolysis.[2, 70, 75] This method was applied to prepare SHD derivatives with the substituted cyclopropyl moiety in yields of up to 70%–95% (Scheme 5).

Scheme 5

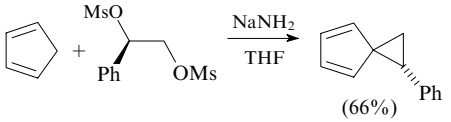


R = Alk, cyclo-C_nH_{2n-1}, Ar, Hal, CN, CO_2Me, Ac, CH_2OAc, *etc.*

It should be noted that the yields of the products largely depend on the electronic properties of the functional group R in the starting 1,2-dibromoethane. Thus, if the group R has electron-withdrawing properties (CO_2Me, Ac, CN, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$, Cl), the corresponding SHD derivatives are produced in high yields (70%–95%), whereas the reactions with 1,2-dibromoethane derivatives containing a functional group with pronounced electron-donating properties (R = OAc, OEt) afford SHD derivatives in substantially lower yields (25%–50%). However, if the functional group R is separated from the reaction centre by a methylene unit (R = CH_2OAc, CH_2OMe), the electronic properties of this group have only a slight effect on the yield of SHD derivatives, which are usually obtained 60%–80% yields.[2, 70]

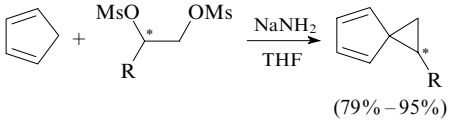
Since the cycloalkylation of CPD proceeds by the S_N2 mechanism,[2] this reaction provides a route to optically active isomers. Earlier, this has been exemplified by the synthesis of optically active 1-methyl-substituted SHD.[77] (*S*)-1-Phenylspiro[2.4]hepta-4,6-diene was synthesized in a similar way by the reaction with sodium amide in THF (Scheme 6).[51, 78, 79]

Scheme 6



More recently, similar procedures have been employed to prepare other chiral monosubstituted SHDs † in yields of 80%–95%, and these compounds were used for the synthesis of catalytically active metal complexes (Scheme 7).[80–82]

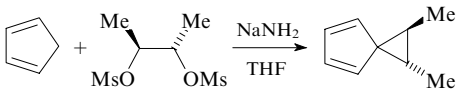
Scheme 7



R = α-Ph (81% yield), β-cyclo-C_6H_{11} (79%), α-$C_6H_2Me_3$-2,4,6 (87%), α-Bn (95%)

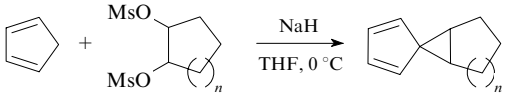
The cycloalkylation of CPD can be successfully applied to the synthesis of 1,2-disubstituted SHDs from appropriate 1,2-dibromides containing two bromine atoms at secondary carbon atoms. This reaction is stereospecific [2] and it enabled the synthesis of a number of optically active SHD derivatives.[2] For example, (*S*,*S*)-1,2-dimethylspiro[2.4]hepta-4,6-diene was prepared from (*R*,*R*)-butane-2,3-diol bis(methanesulfonate) by the reaction of the latter with sodium amide in THF (Scheme 8).[79]

Scheme 8



The cycloalkylation of CPD with cyclic dimesylates gave a number of polycyclic SHD derivatives (Scheme 9).[47, 48]

Scheme 9



n = 1 (50% yield), 2 (60%), 3 (50%), 4 (65%)

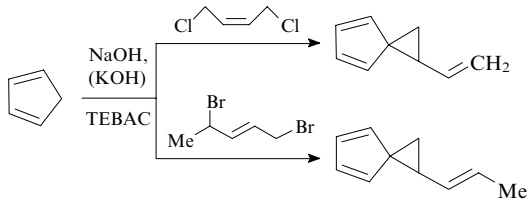
The formation of the only stereoisomer of mono- and 1,2-disubstituted spiro[2.4]heptadienes in the reaction of CPD with optically active dibromides is evidence for the S_N2 mechanism of the phase-transfer-catalyzed cycloalkylation.[2] It should be noted that the reaction proceeds only with 1,2-dibromoalkanes in which both bromine atoms are at the primary or secondary carbon atoms, and it is a convenient procedure for the synthesis of mono- and 1,2-disubstituted SHDs. Meanwhile, the phase-transfer-catalyzed reactions of 1,2-dibromoalkanes containing at least one bromine atom at the tertiary carbon atom do not produce SHD derivatives because of easy dehydrobromination.[2]

Among other alkylating agents used for the synthesis of SHD derivatives through cycloalkylation of cyclopentadiene, note 1,4-dihalobut-2-enes and epichlorohydrin.[2] The

† The symbols α and β refer to the down and up stereoconfigurations of substituents, respectively, by analogy with sugars.

reaction of CPD with 1,4-dihalobut-2-enes is accompanied by the allylic rearrangement giving 1-vinyl-substituted SHDs as the major products. For instance, the reaction with *cis*-1,4-dichlorobut-2-ene in the presence of solid KOH in CH_2Cl_2 affords 1-vinylspiro[2.4]hepta-4,6-diene in 60% yield.[2, 83] The cycloalkylation of CPD with *trans*-1,4-dibromopent-2-ene proceeds in a similar way and gives 1-(prop-1-en-1-yl)spiro[2.4]hepta-4,6-diene in 55% yield (Scheme 10).[2, 70, 83]

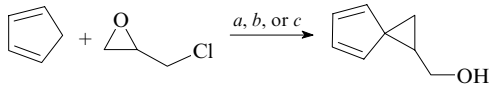
Scheme 10



The formation of vinyl-substituted SHDs in these reactions indicates that other 1,4-dihaloalk-2-enes are also suitable for the synthesis of alken-1-ylspiro[2.4]hepta-4,6-dienes.[2]

The cycloalkylation of cyclopentadiene with epichlorohydrin affords 1-hydroxymethylspiro[2.4]hepta-4,6-diene in 56%–77% yield (Scheme 11).[2, 19, 84]

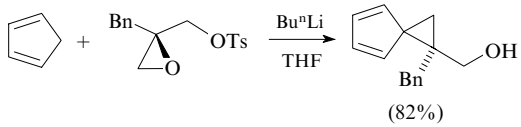
Scheme 11



(*a*) Na, THF, 10–40 °C (64%–77% yield);[2] (*b*) CpLi, NaH, THF, 0 °C (60% yield);[19] (*c*) Bu^nLi, THF, hexane, −20 °C, 0.5 h (56% yield).[84]

It should be noted that 1,1-disubstituted epoxide is also involved in this reaction (Scheme 12).[85]

Scheme 12



(82%)

Therefore, the cycloalkylation of CPD has a general character and provides the basis for the facile synthesis of SHD derivatives containing various functional groups in high yields. This method for the preparation of unsubstituted, mono- and 1,2-disubstituted spiro[2.4]hepta-4,6-dienes is the simplest and most efficient compared with alternative approaches. The cycloalkylation of CPD yielding compounds of the SHD series proceeds by the S_N2 mechanism[2, 70] and, in the case of chiral reagents, produces optically active derivatives. However, this method is not efficient in the synthesis of spiro[2.4]hepta-4,6-dienes containing electron-donating substituents and of *gem*-disubstituted SHDs.

II.2. Cyclomethylenation of the exocyclic double bond in fulvenes

A high polarity of fulvenes[2, 86] is responsible for substantial difference in the chemical properties of their double bonds. The exocyclic double bond in fulvene is electrophilic, whereas endocyclic bonds are nucleophilic (Scheme 13). For this reason, the exocyclic double bond in fulvenes can be cyclomethylenated only with nucleophilic species.

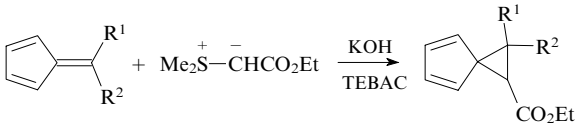
Scheme 13



Such methylenating agents include nucleophilic carbenes, which are involved in reactions to form SHD derivatives. However, the range of nucleophilic carbenes is limited to a small number of compounds with electron-donating substituents at the carbene centre (R = OAlk, OC(O)Alk),[2, 87] whereas the most commonly used electrophilic carbenes add to endocyclic nucleophilic double bonds.[2] Therefore, the addition of nucleophilic carbenes to the exocyclic double bond in fulvenes is an easy route to SHD derivatives containing electron-donating groups in the cyclopropane moiety.

Sulfur, nitrogen and phosphorus ylides bearing the X^+-C^- moiety (X = S, P, N) is another group of methylenating agents that also easily cyclopropanate the exocyclic double bond in fulvenes.[2] Sulfur ylides, which efficiently react with fulvenes,[2] are most widely employed for this purpose. For instance, the reaction of fulvenes with ethyl (dimethylsulfuranylidene)acetate, which was generated under PTC conditions from sulfonic acid in the presence of KOH, produced SHD derivatives in nearly quantitative yields (Scheme 14).[88]

Scheme 14

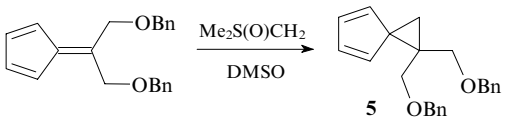


R^1, R^2 = Me, Et, cyclo-C_3H_5, 2-Fu, Ph; Fu is furyl

These compounds are of interest as potential highly efficient pyrethroid insecticides low-toxic to warm-blooded animals.[2]

The cyclopropanation of fulvene with methyl ylide that is generated from trimethylsulfoxonium iodide in the presence of NaH affords 1,1-disubstituted SHD **5** (78% yield) (Scheme 15).[89]

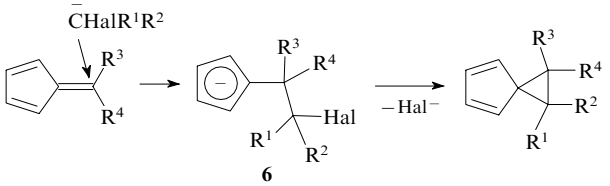
Scheme 15



5

Another known type of cyclomethylenation of the exocyclic double bond in fulvenes is the addition of carbanions followed by intramolecular cyclization yielding compounds of the SHD series. In particular, halogen-substituted carbanions ($^-CHalR^1R^2$) react with fulvene at the electrophilic exocyclic bond to form anion **6**, which undergoes intramolecular cyclization giving spiro[2.4]hepta-4,6-dienes (Scheme 16).

Scheme 16

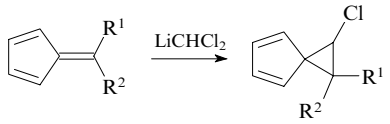


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The reaction of fulvenes with an equimolar amount of the organolithium derivative ($Li^+CHX_2^-$) generated in dif-

ferent ways proceeds *via* the same mechanism and affords, for example, chlorine derivatives of SHD in yields of up to 90% (Scheme 17).[2,90]

Scheme 17



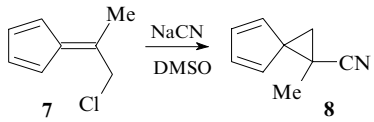
R^1, R^2 = H, Alk, Ar

Similarly, the reaction of dimethylfulvene with the carbanion generated from ethyl chloroacetate produced ethyl 2,2-dimethylspiro[2.4]hepta-4,6-diene-1-carboxylate, which is of interest for the synthesis of pyrethroid insecticides.[2]

The possible alternative mechanism for the preparation of SHD derivatives through the intermediate monohalocarbene or alkoxycarbonylcarbene is unlikely for the reactions of halogen-substituted carbanions with fulvenes because such carbenes are electrophilic and should react with the endocyclic (nucleophilic) double bond. Actually, monochlorocarbene adds to the endocyclic double bond in fulvene to form an unstable adduct, which undergoes isomerization to methylstyrene under the reaction conditions.[2]

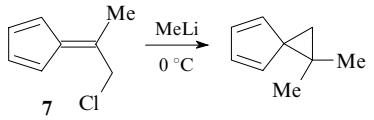
The reaction of chloromethyl-substituted fulvenes with simple carbanions is another known type of the addition of carbanions to fulvenes. For instance, 6-chloromethyl-6-methylfulvene (**7**) adds to the cyanide anion, thus forming 1-methylspiro[2.4]hepta-4,6-diene-l-carbonitrile (**8**) in 72% yield (Scheme 18).[91,92]

Scheme 18



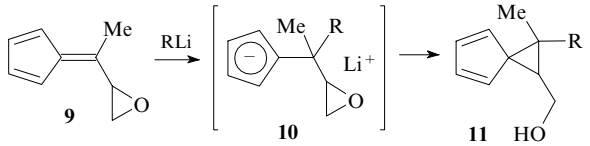
Similarly, fulvene **7** reacts with MeLi at 0 °C to give 1,1-dimethylspiro[2.4]hepta-4,6-diene in 62% yield (Scheme 19).[91,92]

Scheme 19



The reactions of oxiranylfulvene **9** with various organolithium compounds acting as nucleophiles were also described. These reactions proceed through the formation of intermediate anion **10**, which undergoes intramolecular cyclization to substituted SHDs **11** with different ratios of *Z* and *E* isomers (Scheme 20).[21,22,93]

Scheme 20

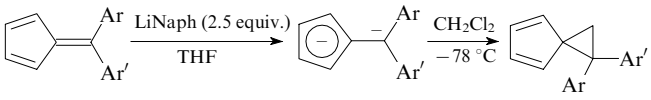


R = Me (55%–65% yield), Bu^n (52%, 1 : 1 isomer ratio), Bu^s (40%, 3 : 1), vinyl (46%), 1,3-dithian-2-yl (25%–31%)

An attempt to apply this scheme to the synthesis of nitro-substituted SHD (R = NO_2) using the $^-CH_2NO_2$ anion as the nucleophile failed because the reaction stops at the first step giving only substituted CPD.[21,22]

The cyclopropanation of the exocyclic double bond in 6,6-diarylfulvenes with dichloromethane in the presence of lithium naphthalide (LiNaph) produced 1,1-diaryl-substituted SHDs.[94] It is hypothesized that this reaction proceeds through the formation of the 6,6-diarylfulvene dianion, which undergoes nucleophilic substitution (Scheme 21).

Scheme 21



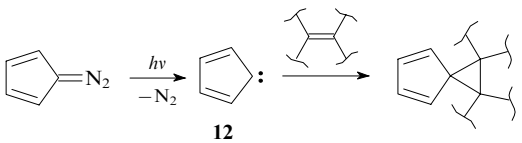
Ar = Ar′ = Ph (82% yield), 4-$MeOC_6H_4$ (95%), 4-ClC_6H_4 (53%); Ar = Ph: Ar′ = 4-$MeOC_6H_4$ (56%), 2-Py (20%); Py is pyridyl

Therefore, the above-considered methods for the synthesis of compounds of the SHD series through cyclomethylenation of the exocyclic double bond in fulvenes have specific features. It should be noted that the formation of SHD derivatives by carbene methods is typical only of a few nucleophilic carbenes, which are generated by procedures that are difficult to implement in common practice. Nevertheless, these methods are most efficient in the synthesis of SHDs with electron-donating groups. Such reactions are also typical of sulfur, nitrogen and phosphorus ylides. However, these ylides are few in number and the synthesis of SHD derivatives based on these compounds is a multistep process. Besides, it should be taken into account that highly reactive ylides easily form side products.[2] Nevertheless, ylides are successfully employed in the synthesis of aryl- and carboxy-substituted SHDs.

II.3. Other methods for the synthesis of spiro[2.4]hepta-4,6-dienes

The reaction of cyclopentadienylidene (CPDI, **12**) with unsaturated compounds[2] has long been one of the methods most commonly used for the synthesis of SHD. In these transformations, CPDI generated by photolysis of diazocyclopentadiene enters into reactions typical of carbenes, in particular, adds to double bonds of alkenes resulting in the formation of SHD derivatives in yields from 10% to 60% (Scheme 22).[2,87]

Scheme 22



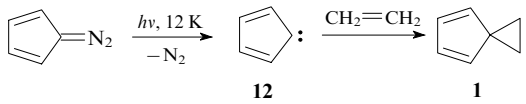
This method is quite versatile,[2] although it has a number of significant limitations. Firstly, spiro[2.4]hepta-4,6-dienes are produced in low yields. Besides, this method generates a considerable number of side products (in particular, products of the insertion into single bonds) typical of reactions with carbenes.

Since CPDI is an electrophilic carbene, the rate of its addition to multiple bonds decreases if the alkene contains electron-withdrawing substituents, resulting in an increase in the amount of side products. Therefore, this method is not suitable for the synthesis of most of functionally

substituted SHDs. Moreover, this approach is experimentally difficult to implement because diazocyclopentadiene and its derivatives are highly explosive.[2] For these reasons, this method is used very rarely, mainly for physicochemical studies and the synthesis of complex SHD derivatives.

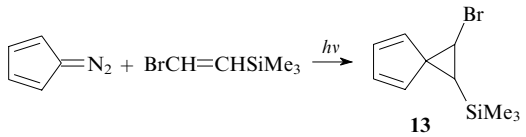
Free CPDI and its reaction with ethylene yielding compound **1** were detected in the $Ar-N_2O$ matrix (Scheme 23) at low temperatures (from 12 to 45 K).[95,96]

Scheme 23



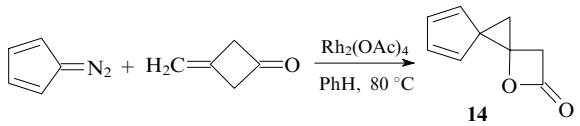
The reaction of diazocyclopentadiene with 2-(bromovinyl)trimethylsilane afforded disubstituted SHD **13** (in 5.7% yield),[97,98] which is difficult to synthesize by other methods. This compound was used in the synthesis of spiro[2.4]hepta-1,4,6-triene essential for investigation of the effect of spiroconjugation (Scheme 24).

Scheme 24



The reaction of diazocyclopentadiene with diketene gives cyclopropane **14** spiro-fused to cyclopentadiene and β-lactone (31% yield) (Scheme 25).[99]

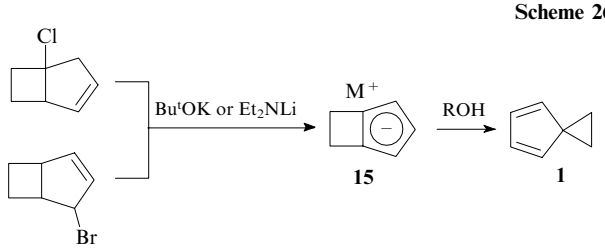
Scheme 25



Apart from the reaction of diazocyclopentadiene with alkenes, other examples of the construction of the SHD system were documented. However, they are random and have no importance for preparative applications. Most of these examples are related to various intramolecular rearrangements.

For instance, the dehydrohalogenation of halogen-substituted bicyclo[3.2.0]hept-2-enes affords bicyclo[3.2.0]-hepta-1,3-dienyl carbanion **15**, which binds a proton and is rearranged into compound **1** (Scheme 26).[100,101]

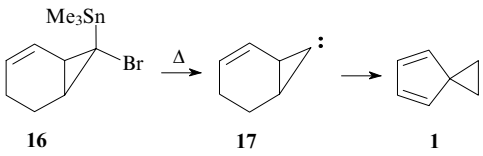
Scheme 26



M = K, Li; R = H, Alk

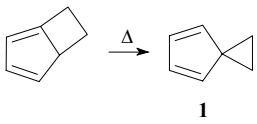
The thermal decomposition of substituted norcarene **16** produces carbene **17**, which undergoes intramolecular rearrangement giving spiro[2.4]hepta-4,6-diene in 76%–86% yield.[102] The reaction proceeds at 101–162 °C; the conversion of the starting compound is 75%–85% (Scheme 27).

Scheme 27



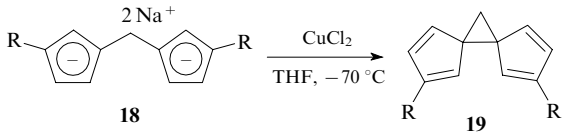
The thermal decomposition of bicyclo[3.2.0]hepta-1,3-diene is accompanied by isomerization and also affords compound **1** (Scheme 28).[84]

Scheme 28



Note also the oxidation of compounds **18** — salts of methylenedicyclopentadiene and its *tert*-butyl derivative — with $CuCl_2$ giving dispiro[4.0.4.1]undeca-1,3,7,9-tetraenes (homopentafulvalenes, **19**) in 24% yield (Scheme 29).[103]

Scheme 29



R = H, Bu^t

Besides, the formation of SHDs in some other transformations involving carbenes was also documented.[2]

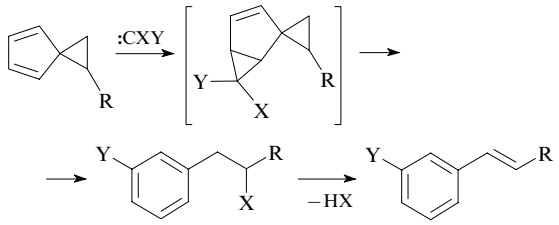
III. Chemical transformations of spiro[2.4]hepta-4,6-dienes

This section is devoted to cycloaddition reactions and some other transformations involving compounds of the SHD series, as well as their applications in targeted organic synthesis. It should be noted that numerous well-studied complexation[63,104–106] and polymerization reactions[2] are beyond the scope of this review.

III.1. [2 + 1]-Cycloaddition reactions

[2 + 1]-Cycloaddition reactions, *i.e.*, reactions of SHD with carbenes, yield both mono- and dicyclopropanation products. Thus, the Simmons–Smith reaction affords a product of cyclopropanation at both multiple bonds of SHD.[2] Meanwhile, in the case of dihalocarbenes generated under phase-transfer catalysis conditions, intermediates produced through dichlorocyclomethylenation at one double bond in SHD are unstable and are transformed into 3-(2-haloethyl)-halobenzenes under the reaction conditions.[2,107] The latter compounds easily undergo dehydrohalogenation giving 3-halogen-substituted styrenes. The reactions of 1-aryl-substituted SHDs with dihalocarbenes afford 3-halogen-substituted stilbenes (Scheme 30).[107]

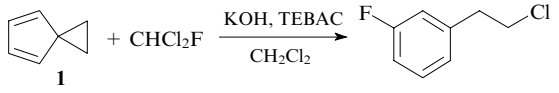
Scheme 30



R = H, Alk, Ar; X = Y = Br, Cl; X = Br, Y = F

Similarly, the reaction of SHDs with chlorofluorocarbene generated under PTC conditions produces 3-(2-chloroethyl)fluorobenzene in 59% yield (Scheme 31).[108]

Scheme 31

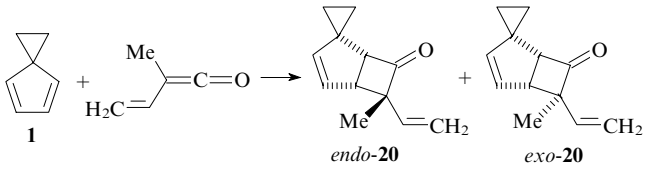


The fact that these reactions form exclusively *meta*-substituted benzenes provides the basis for the facile one-step method for the synthesis of these compounds. This is an additional piece of evidence that SHD derivatives are promising synthons in organic synthesis.

III.2. [2 + 2]-Cycloaddition reactions

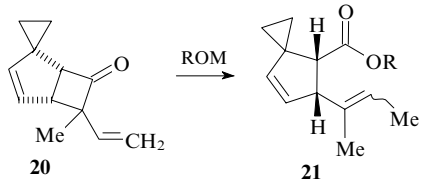
[2 + 2]-Cycloaddition reactions of SHDs with ketenes produce cyclobutanones.[2, 109] For example, the reaction of methyl vinyl ketene with SHD affords a mixture of *endo*- and *exo*-isomers **20** in a ratio of 25 : 75 in a total yield of 40% (Scheme 32).[109]

Scheme 32



In the presence of Bu^{t}OK or MeONa, the resulting cyclobutanones **20** undergo the opening of the four-membered carbon ring, resulting in the formation of vicinal disubstituted spiro[2.4]heptenes **21**.[109] It should be noted that the cyclobutane ring opening occurs regioselectively and produces carboxylates **21**, which are convenient intermediates for organic synthesis (Scheme 33).[2, 109]

Scheme 33



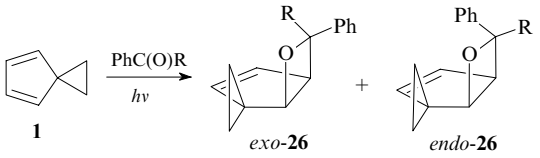
ROM = MeONa (18% yield, $E:Z = 67:33$), Bu^{t}OK (43%, $E:Z = 80:20$)

As another example of [2 + 2]-cycloaddition reactions, noteworthy is the use of SHD as a trapping agent for cyclic allene **22**, which is generated from bromide **23** in the reaction with Bu^{t}OK in THF in the presence of 18-crown-6. This reaction affords allene isomerization products **22** along with compounds **24**, as well as *syn*- and *anti*-isomers **25** in 9%, 4% and 7% yields, respectively (Scheme 34).[110]

The [2 + 2]-cycloaddition of SHD to a carbonyl group (Paternò – Büchi reaction) proceeds under photochemical conditions and gives oxetanes **26**.[111] It should be noted that this structure is convenient for studying the problem of spiroannulation because the *endo* side of product **26** is additionally shielded by the spirocyclopropane moiety (Scheme 35).

As a result, the reaction is regioselective (the conversion is 20%), and the diastereoselectivity substantially depends on the bulkiness of the substituent in the starting carbonyl compound.

Scheme 35



R = H (*exo* : *endo* = 3.5 : 1), CO_2Me (*exo* : *endo* = < 1 : 19)

III.3. [4 + 2]-Cycloaddition reactions

Most of the known processes with the involvement of SHDs are [4 + 2]-cycloaddition reactions, in which spiro[2.4]hepta-4,6-diene and its derivatives serve as a diene component, thus giving spiro(bicyclo[2.2.1]hept-2-ene-7,1′-cyclopropane) derivatives. The transformations, in which SHD acts as a dienophile, are much more rare. Most of these processes were performed with compound **1** and its 1-hydroxymethyl derivative. The Diels – Alder reactions with SHDs can take place under both thermal and catalytic conditions.[2]

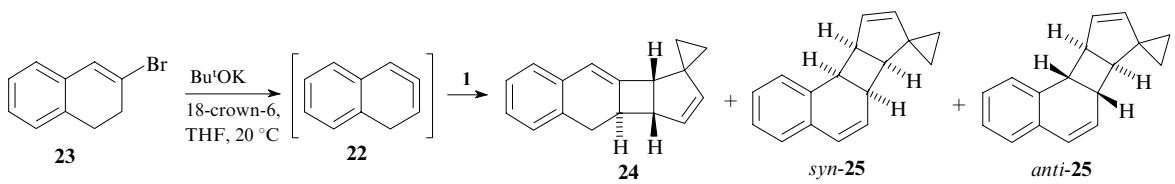
III.3.a. Synthesis of cage structures

The literature data provide evidence of high reactivity of unsubstituted spiro[2.4]hepta-4,6-diene in the [4 + 2]-cycloaddition reaction.[2] Therefore, SHD holds great promise for the synthesis of cage structures.

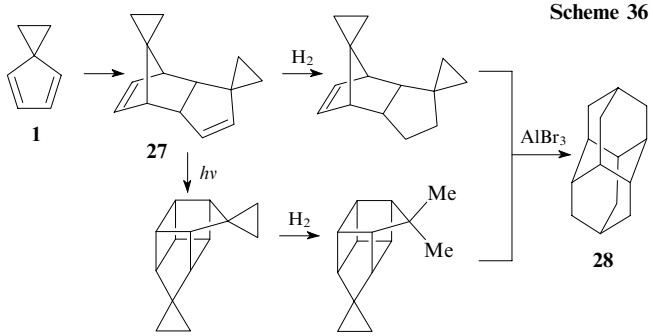
Compound **1** undergoes [4 + 2]-cycloaddition giving spiroheptadiene dimer **27**, *i.e.*, it serves simultaneously as a diene and a dienophile.[112] The resulting dimer **27** was used in the synthesis of cage compounds, in particular, of diamantane **28** (9% – 13% yield) (Scheme 36).[113]

A number of other polycyclic hydrocarbons were synthesized by the Diels – Alder reaction of SHD with *p*-benzoquinone. This reaction affords adducts that are generated through the addition of quinone to one (**29**) or two (**30**) SHD molecules (Scheme 37).[114 – 116]

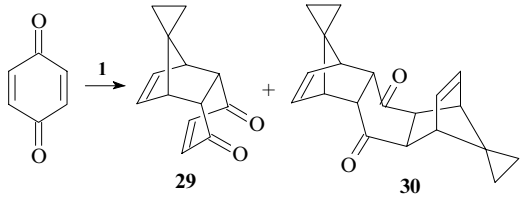
Scheme 34



Scheme 36



Scheme 37



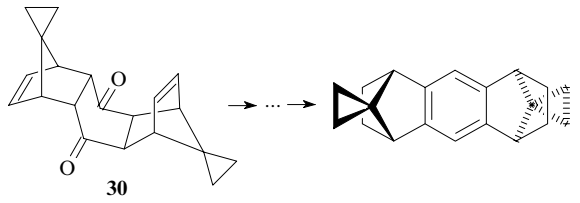
When exposed to radiation, monoadduct **29** underwent intramolecular cyclization yielding polycyclic dione **31**,[115,116] which was used, for example, in the synthesis of cage-type spiroannulated hydrocarbons **32a–d** (Scheme 38).[116]

The transformation of diadduct **30** produces dimethanoanthracene containing two norbornane moieties annulated with the aromatic core.[117] These products are employed in supramolecular chemistry, in particular, as molecular tweezers and molecular clips (Scheme 39).[117]

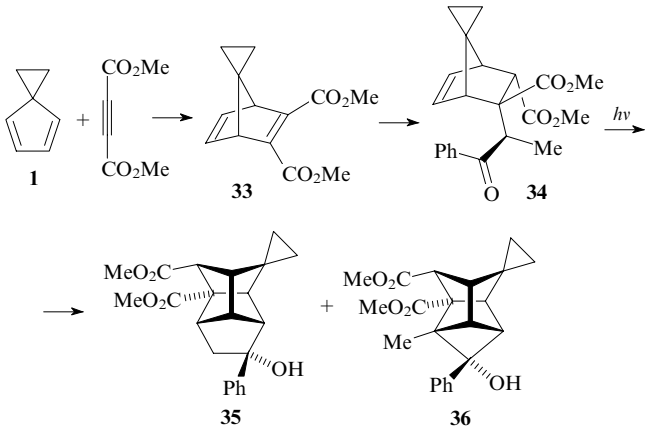
The Diels–Alder reaction of SHD with acetylenic dienophiles affords adducts **33**, and the Michael reaction of these compounds with aromatic ketones produces derivatives **34**. The latter undergo photoinduced intramolecular cyclization thus providing a facile route to new polycyclic cage compounds **35** (77% yield) and **36** (20% yield) (Scheme 40).[118]

A series of other polycyclic cage compounds were synthesized in a similar manner.[118]

Scheme 39



Scheme 40

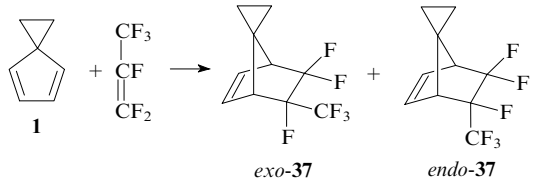


III.3.b. Reactions with alkenes and alkynes

Apart from cage structures, [4+2]-cycloaddition reactions of SHD were applied to synthesize a wide range of various compounds serving as convenient synthons for further transformations.

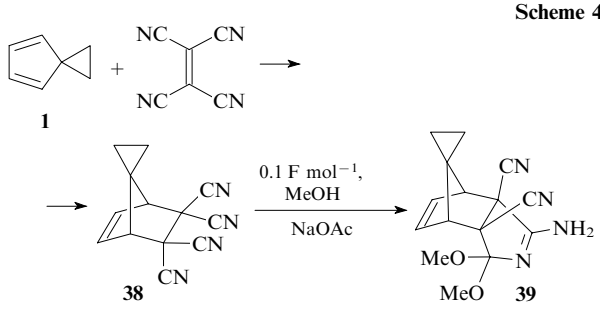
For instance, the Diels–Alder reaction of spiro[2.4]-hepta-4,6-diene (**1**) with hexafluoropropene produced adducts **37** in nearly quantitative yield (isomer ratio *exo* : *endo* = 48 : 52).[46] Products **37** were polymerized by the metathesis reaction, in which the *exo*- and *endo*-isomers exhibited different selectivity (Scheme 41).[46]

Scheme 41

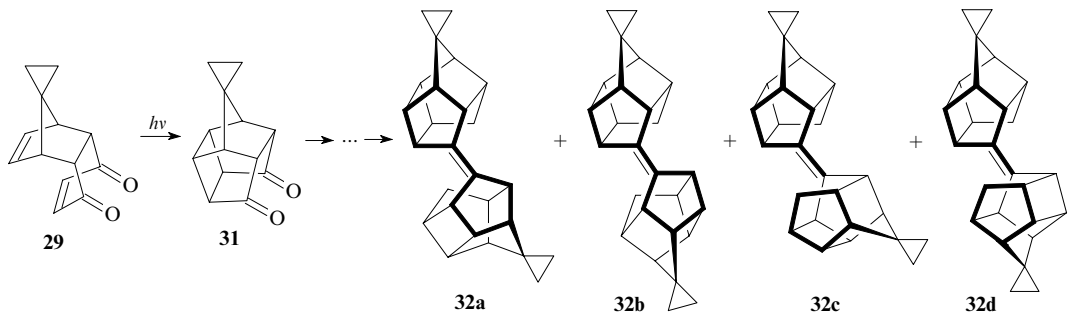


The reaction of SHD with tetracyanoethylene affords adduct **38** in 78%–90% yield,[119–121] and the electrochemical cyclization of the latter produces fused pyrroline **39** in 88% yield (Scheme 42).[121]

Scheme 42

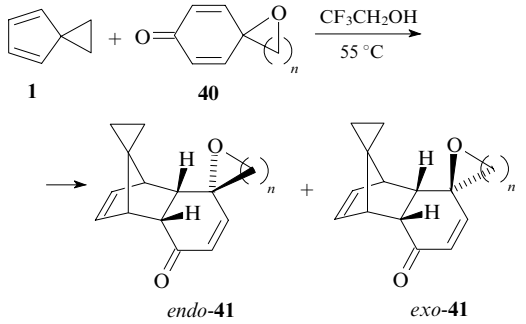


Scheme 38



The SHD structure is responsible for unique stereo- and regioselectivity of many [4 + 2]-cycloaddition reactions with this compound. For example, the Diels–Alder reaction of spirocyclic cross-conjugated cyclohexadienones **40** with SHD is diastereoselective and gives *endo*-isomers of oxaspiran ring products (*endo*-**41**) as the major products. Both products **41** are *endo*-isomers with respect to the cyclohexadienone moiety (Scheme 43).[122, 123]

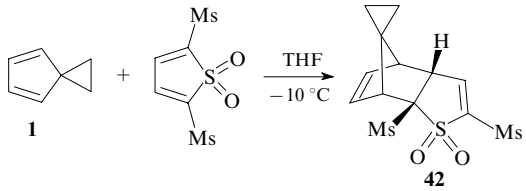
Scheme 43



n = 1 (59% yield, *endo* : *exo* = 66 : 34),
2 (67%–83%, *endo* : *exo* = 65 : 35), 3 (86%, *endo* : *exo* = 77 : 23)

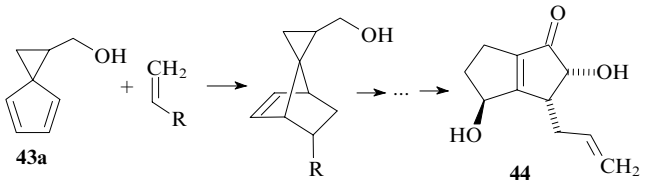
The Diels–Alder reaction of compound **1** with 2,5-dimesylthiophene 1,1-dioxide is also chemo-, regio- and stereoselective and gives tetrahydrobenzothiophene 1,1-dioxide **42** in 74% yield (Scheme 44).[124, 125]

Scheme 44



Among SHD derivatives, spiro[2.4]hepta-4,6-dien-1-ylmethanol (**43a**) is most widely used in the targeted organic synthesis. The [4 + 2]-cycloaddition reactions with alcohol **43a** and its derivatives are suitable for the synthesis of various complex structures. For example, the reactions of compound **43a** with acrylonitrile and acrylates are selective and give products in quantitative yields (> 95%).[126] The latter compounds served as the basis for the synthesis of xialenone A (**44**) produced by cultures of the genus *Streptomyces* (Scheme 45).[126]

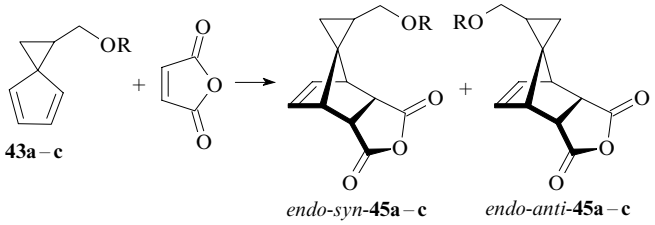
Scheme 45



R = CN, CO_2Alk

The [4 + 2]-cycloaddition of maleic anhydride to spiro[2.4]hepta-4,6-dien-1-ylmethanol (**43a**) and its ethers **43b**,**c** affords exclusively *endo*-isomers **45** containing a side substituent in the *syn* and *anti* configuration, which can be separated by chromatography (Scheme 46).[84]

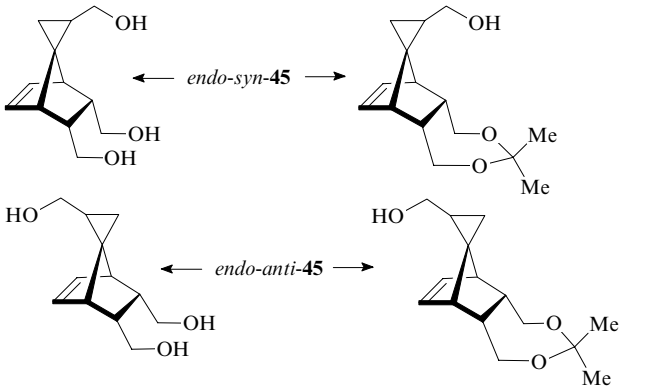
Scheme 46



R = H (**a**, yield of the *endo-syn*-isomer is 29%; *endo-anti*, 39%), Ts (**b**, *endo-syn*, 22%; *endo-anti*, 52%), $(CH_2)_5$OTBDMS (**c**, *endo-syn*, 34%; *endo-anti*, 28%); TBDMS is *tert*-butyldimethylsilyl

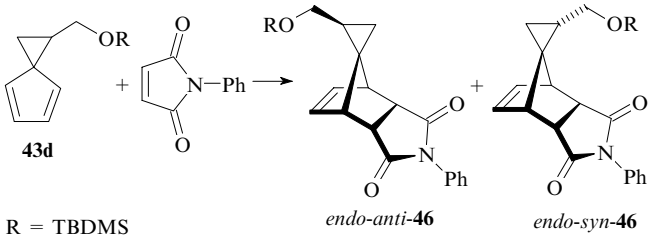
Compounds **45** were used to synthesize various individual isomers of oxygen-containing polycyclic compounds, which are of interest as intermediates for organic synthesis (Scheme 47).[84]

Scheme 47



The [4 + 2]-cycloaddition of derivative **43d** to *N*-phenylmaleimide also affords exclusively *endo*-isomers **46** with the ratio *syn* : *anti* = 1 : 1 (Scheme 48).[18]

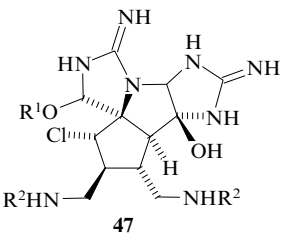
Scheme 48



R = TBDMS

Compound *endo-anti*-**46** was isolated and used in the enantioselective synthesis of natural bisguanidine alkaloids — axinellamines **47** exhibiting bactericidal activity against *Helicobacter pylori*, which is considered as a cause of gastric ulcer diseases and gastric cancer.[18]

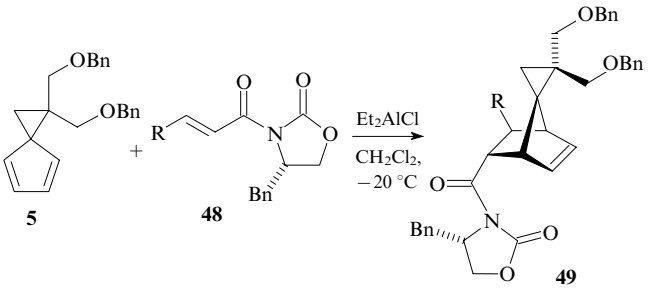
Structures 47



R^1 = H, Me; R^2 = 4,5-dibromopyrrol-2-ylcarbonyl

The [4+2]-cycloaddition reaction of SHD derivative **5** with dienophile **48** affords only isomer **49** in 84% yield (Scheme 49).[89]

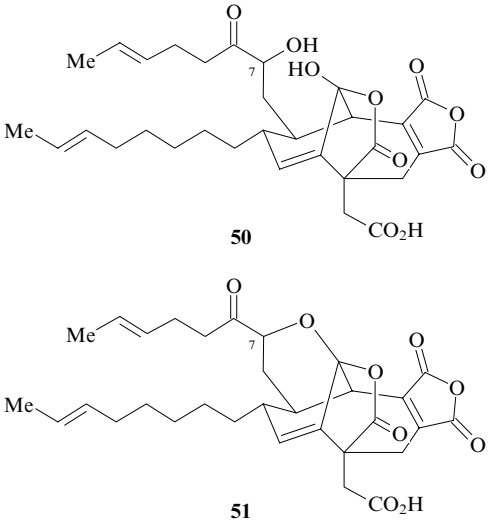
Scheme 49



R = (*E*)-MeCH=CH(CH$_2$)$_5$

Adduct **49** is a convenient starting compound for the synthesis of natural phomoidrides A [(7*S*)-**50**], B [(7*S*)-**51**], C [(7*R*)-**50**] and D [(7*R*)-**51**] exhibiting diverse biological activities, including antimicrobial and fungicidal.[89]

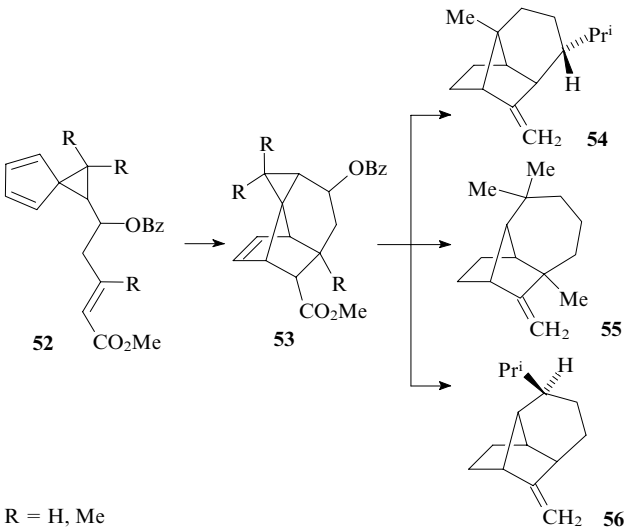
Structures 50, 51



Apart from intermolecular [4+2]-cycloaddition reactions, SHD derivatives containing double bonds in a peripheral substituent can be subjected to intramolecular Diels–Alder reactions. This results in the selective formation of unique isomers, which are not accessible by other methods and which are valuable synthons for the synthesis of complex natural compounds.

Thus, the intramolecular [4+2]-cycloaddition reaction using SHD derivatives **52** produced adducts **53**. The process is stereospecific and gives products in quantitative yields (up to 97%) (Scheme 50).[23,24]

Scheme 50

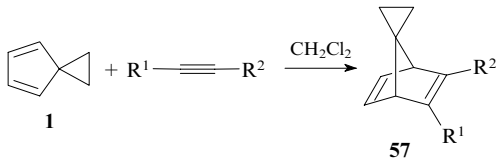


R = H, Me

Adducts **53** served as intermediates in the synthesis of the sesquiterpenes sinularene (**54**), longifolene (**55**) and sativene (**56**).[23,24]

The [4+2]-cycloaddition reactions of SHD with acetylenes, in particular, with 1-trimethylstannyl-2-trifluoroacetyl- and 1-bromo-2-trifluoroacetylacetylenes give adducts **57** in good yields (Scheme 51).[127–131]

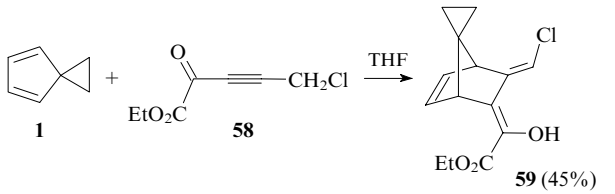
Scheme 51



R^1 = C(O)CF$_3$: R^2 = SnMe$_3$ (69% yield), Br (83%),[127] Ph (97%–98%);[131] R^1 = Cl, R^2 = C(O)CO$_2$Et (78%)[129]

By contrast, the adduct generated by the reaction of SHD with ethyl 5-chloro-2-oxopent-3-ynoate (**58**) is stable in enol form **59** (Scheme 52).[130]

Scheme 52



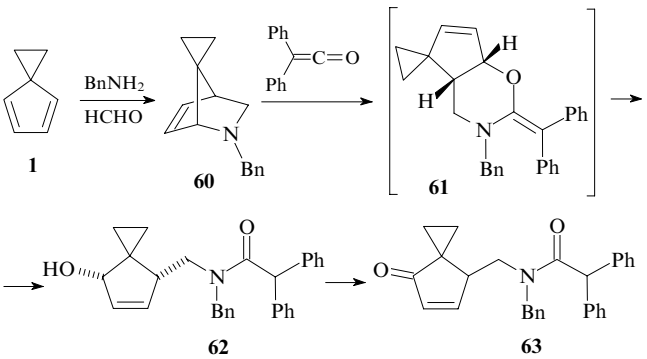
Therefore, compounds of the SHD act as highly reactive dienes in [4+2]-cycloaddition reactions and easily form polycyclic adducts with diverse structures.

III.3.c. Reactions with heteroalkenes

Spiro[2.4]hepta-4,6-diene and its derivatives are involved as dienes in reactions with heteroalkenes.

For instance, the aza-Diels–Alder reaction of compound **1** with imine generated from benzylimine and formaldehyde gave adduct **60** in 62% yield.[132] The latter was introduced in the reaction with diphenyl ketene accompa-

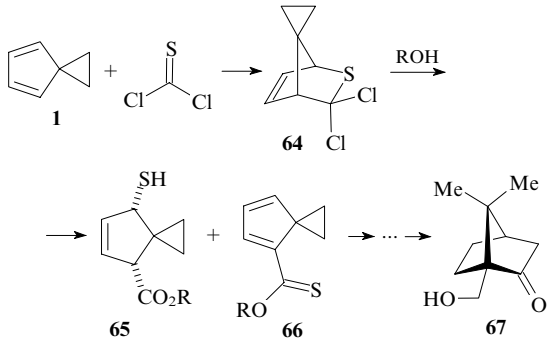
Scheme 53



nied by aza-Claisen rearrangement. However, this reaction gave unstable product **61**, which underwent the cleavage of the heterocycle giving spirohept-5-ene **62**. The oxidation of the latter with pyridinium chlorochromate produced final ketone **63** in 83% yield [132] (Scheme 53).

The [4 + 2]-cycloaddition of SHD to thiophosgene gave sulfur-containing tricyclic product **64** in a yield of 74%–91%. The treatment of compound **64** with methanol (or ethanol) resulted in the formation of a mixture of esters **65** and **66**, which were used in the synthesis of substituted bornane structures **67** (Scheme 54).[120]

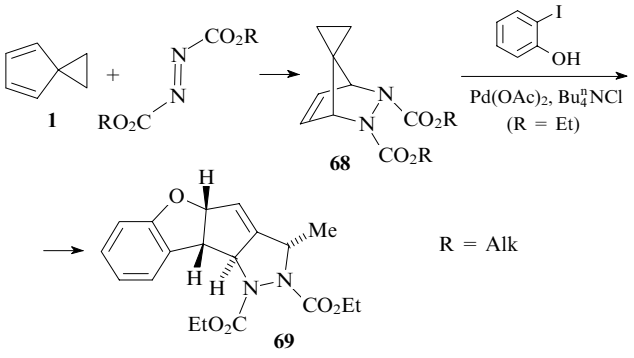
Scheme 54



R = Me (**65**, 34% yield; **66**, 41%), Et (**65**, 17%; **66**, 69%)

The reaction of SHD with dialkyl azodicarboxylates affords spirotricyclic compounds **68**, and the tandem reaction of the latter with 2-iodophenol gives tetracyclic compound **69** (for R = Et) containing multiple stereocentres (Scheme 55).[133]

Scheme 55

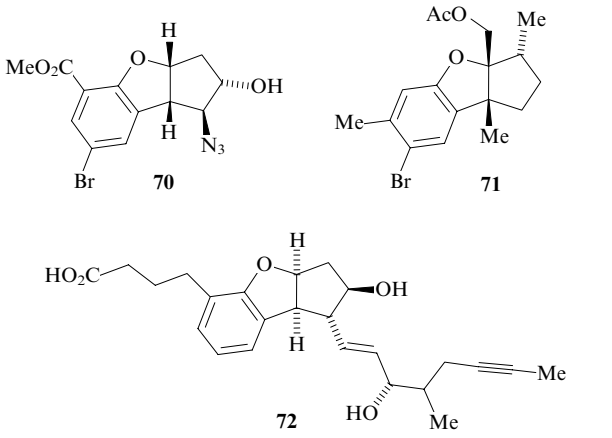


Compound **69** and its analogues are convenient intermediates in the synthesis of a number of natural and biologically active compounds, for example, the thromboxane A2 inhibitor (azide **70**), the antioxidant aplysinol acetate (**71**) and the prostacyclin receptor agonist‡ — beraprost (**72**).[133]

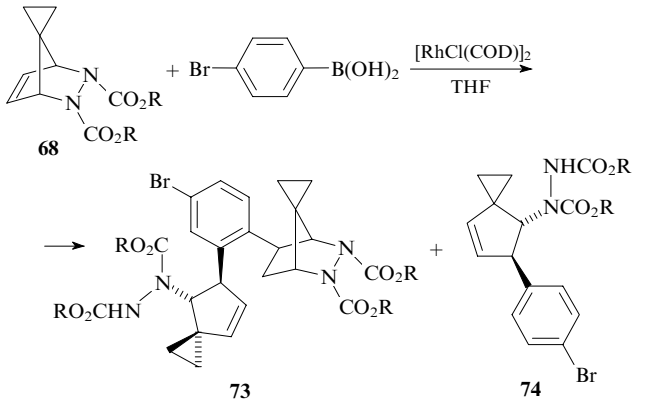
The treatment of spirotricyclic compounds **68** with 4-bromophenylboronic acid in the presence of a rhodium catalyst (THF, 60 °C, 12 h) resulted in the stereoselective formation of functionalized arenes **73** in high yields, in some cases in a mixture with minor spiro[2.4]heptaenes **74** (Scheme 56).[134]

‡ An agonist is a chemical compound (ligand) that binds to a receptor and changes its state to produce a biological response. Direct agonists enhance the response of the receptor, inverse agonists cause an opposite action, and antagonists block the action of agonists.

Structures 70–72



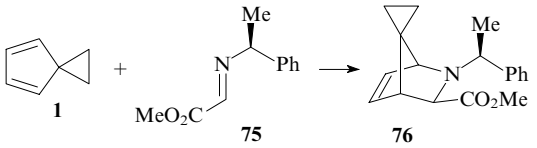
Scheme 56



R = Et, Pr^i, Bu^t, Bn; COD is cycloocta-1,5-diene

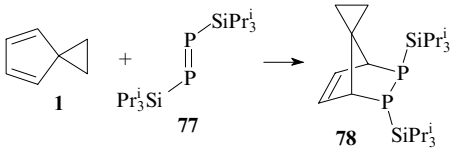
Unstable imine — methyl (*S*)-1-ethyl(phenyl)iminoacetate (**75**) — was introduced in the Diels–Alder reaction with SHD giving product **76** with the *exo* configuration of the ester group in 32% yield (Scheme 57).[66]

Scheme 57



Besides, compounds of the SHD series can serve as convenient trapping agents for unstable compounds with the P=P double bond — phosphenes **77**. These reactions give Diels–Alder adducts — spirotricyclic phosphorus-containing compounds **78** (Scheme 58).[135, 136]

Scheme 58

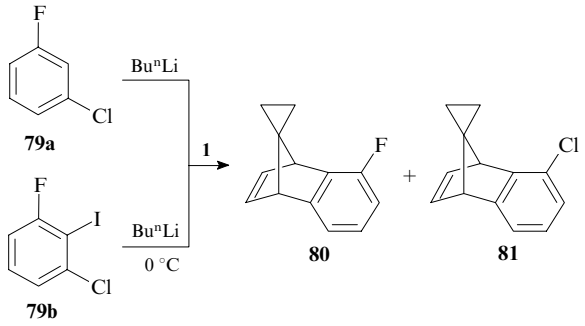


III.3.d. Use of spiro[2.4]hepta-4,6-diene as a trapping agent for unstable molecules

Compounds of the spiro[2.4]hepta-4,6-diene series are often used as convenient trapping agents (Diels–Alder reaction) for various unstable compounds containing a reactive

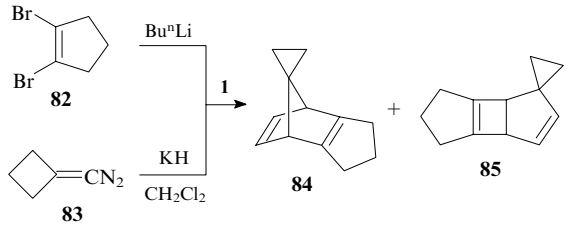
highly strained double (triple) carbon–carbon bond, for example, of benzyne and its derivatives generated *in situ* from arenes **79a**,**b** (Scheme 59).[137, 138] The ratio of halides **80** and **81** depends on the nature of the solvent and is relevant to the conclusion about the ratio of the halogen-substituted dehydrobenzenes formed. Thus, the ratio of the products **80** : **81** in THF is 97 : 3; in pentane, 3 : 97.[137]

Scheme 59



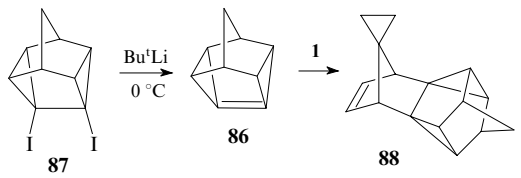
Spiro[2.4]hepta-4,6-diene also traps highly strained cyclic acetylene — cyclopentyne (generated from compound **82** or **83**) — resulting in the formation of a mixture of [2 + 2]- and [4 + 2]-cycloaddition products.[139, 140] In the case of dibromide **82** as a source of cyclopentyne, products **84** and **85** were obtained in a ratio of 3 : 1, *i.e.*, the [4 + 2]-cycloaddition is the main reaction. By contrast, in the case of cyclobutane **83**, the ratio of the products was 1 : (10–60), *i.e.*, the main reaction was [2 + 2]-cycloaddition (Scheme 60).

Scheme 60



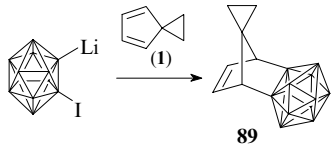
Another highly strained alkene, *viz.*, pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]non-4-ene (**86**), generated from appropriate diiodide **87**, is also easily trapped by SHD giving cycloadduct **88** in 13% yield (Scheme 61).[141]

Scheme 61



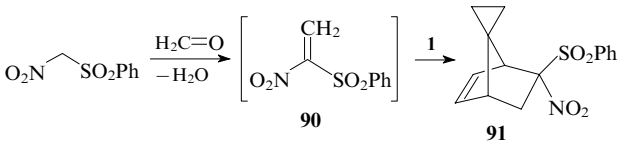
Spiro[2.4]hepta-4,6-diene readily forms [4 + 2]-cycloadducts **89** with *ortho*-carboryne (1,2-dehydro-*ortho*-carborane), which is generated *in situ* from 1-iodo-2-lithio-*ortho*-carborane. The reaction is regioselective and provides an access to polycyclic compounds containing a carborane moiety, which may be used in medicine and materials science (Scheme 62).[142]

Scheme 62



Let us mention also nitroethylenes as unstable alkenes, which are good trapping agents for spiro[2.4]hepta-4,6-diene (**1**) as well. Thus, the reaction of nitroethylene **90** with SHD produces adducts **91** in 93% yield, the *endo*-nitro isomer being the major product (*endo* : *exo* = > 97 : 3) (Scheme 63).[143]

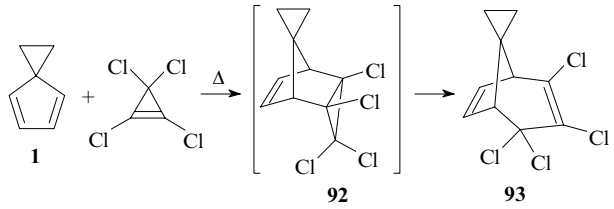
Scheme 63



Spiro[2.4]hepta-4,6-diene serves as a good trapping agent for highly reactive unstable unsaturated molecules such as cyclopropenes. In this case, intermediate unstable strained molecules containing a double bond easily form [4 + 2]-cycloadducts with SHD. Similar products are generated in reactions with stable cyclopropenes.

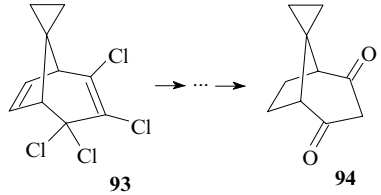
For instance, the reaction of SHD with tetrachlorocyclopropene gives unstable adduct **92**, which, under the reaction conditions, undergoes isomerization accompanied by the ring opening to form bicyclo[3.2.1]octadiene derivative **93** in 54%–84% yield (Scheme 64).[144–146]

Scheme 64



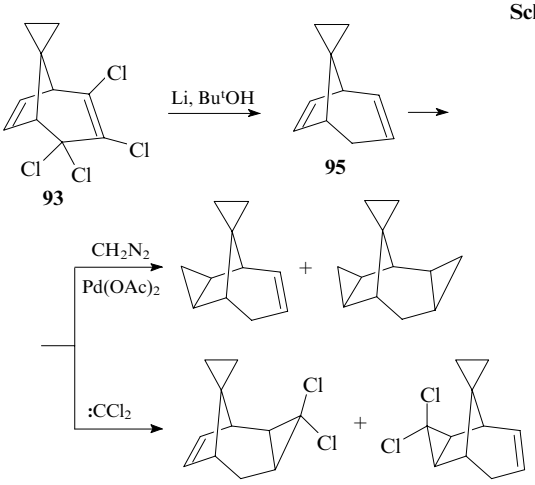
A number of transformations were developed based on the reaction of SHD with tetrachlorocyclopropene. Thus, product **93** was then used to synthesize bicyclo[3.2.1]octane-2,4-dione derivative **94**, which is a promising 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor — a representative of a new class of herbicides (Scheme 65).[144]

Scheme 65



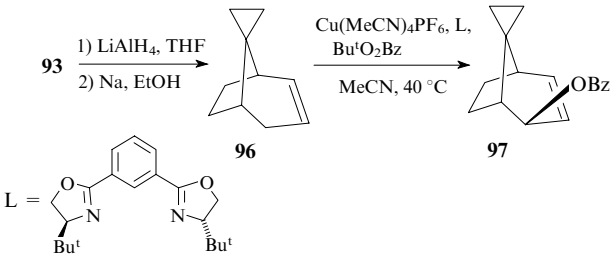
Another strategy for further transformations of compound **93** involves the reduction to hydrocarbon **95** (62% yield) and the reactions of the latter with carbenes giving various polycyclic compounds (Scheme 66).[145]

Scheme 66



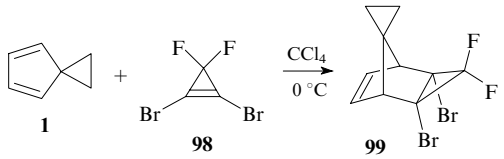
The reduction of bicyclo[3.2.1]octadiene derivative **93** to hydrocarbon **96** (47% yield) followed by the Kharasch–Sosnovsky reaction produced optically active compound **97** in high yield (80%–84%) with good enantiomeric excess (*ee* up to 70%) (Scheme 67).[146]

Scheme 67



The reaction of SHD with 1,2-dibromo-3,3-difluorocyclopropene (**98**) affords stable adduct **99** in 49% yield (Scheme 68).[147]

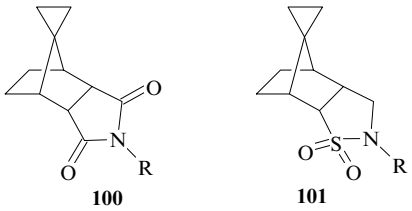
Scheme 68



Therefore, compounds of the spiro[2.4]hepta-4,6-diene series exhibit high activity as the diene components in [4+2]-cycloaddition reactions. The Diels–Alder adducts thus formed are interesting valuable intermediates for organic synthesis (in particular, for the synthesis of various sesquiterpenes[21,22,148]). Some of these compounds are of practical value by themselves. Thus, adducts of SHD with fumaric acid derivatives (compounds **3**) are of industrial importance[149] and are proposed as ALX/FPR2 receptor agonists.[29–32]

Related compounds of another class — phthalimide analogues **100** — exhibit activity against the receptors FPRL-1.[35] These derivatives can be used for the prevention and therapy of inflammatory, allergic, immune system and other diseases. Compounds **101** (like polycyclic compounds **100**) are suggested as modulators of nuclear hormone receptor function in order to use them as anticancer agents and drugs for the treatment of immune system diseases.[40,41]

Structures 100, 101



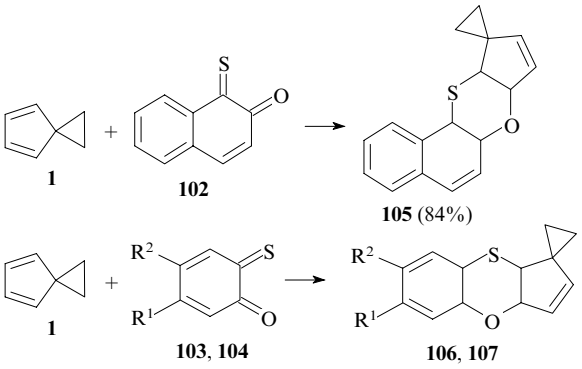
A number of other practically valuable products were prepared based on [4+2]-cycloaddition adducts of SHD.[2]

III.3.e. Reactions with spiro[2.4]hepta-4,6-diene as a dienophile

In [4+2]-cycloaddition reactions, spiro[2.4]hepta-4,6-diene and its derivatives can serve not only as dienes but also as dienophiles, particularly in tandem with highly reactive dienes.[2]

Thus, SHD serves as a dienophile in the reaction with *o*-thioquinones **102**–**104**, resulting in the regioselective formation of benzoxathiynes **105**–**107** (Scheme 69).[150]

Scheme 69



R^1 = OMe, R^2 = H (**103**; **106**, 58% yield);
R^1 = H, R^2 = Me (**104**; **107**, 74% yield)

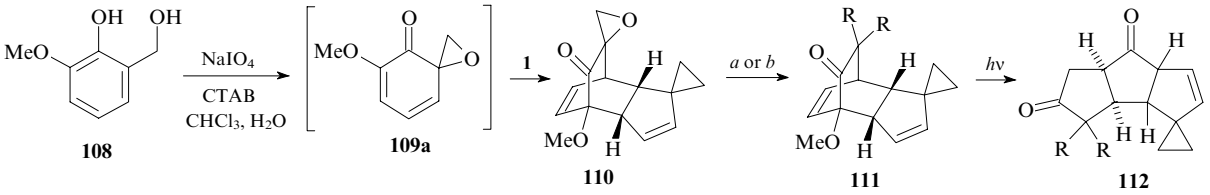
Besides, SHD acts as a dienophile in the reaction with cyclohexa-2,4-dienones. These transformations were employed as the basis for the development of a versatile and efficient route to polyquinane natural compounds.[151–155]

For example, the oxidation of *o*-vanillyl alcohol **108** with potassium periodate in the presence of trimethylcetylammonium bromide (CTAB) in a two-phase system followed by the trapping of intermediate spiro oxirane derivative **109a** with spiro[2.4]hepta-4,6-diene produces adduct **110** in 46% yield. The latter is reduced to polycyclic compound **111** (47%–54% yields), which undergoes rearrangement into functionalized triquinanes **112** in 48% yield (Scheme 70).[151,152,155]

The proposed strategy is suitable for the synthesis of various natural triquinanes with a broad spectrum of biological activities. For example, this group of compounds includes coriolin (**113**) having antitumour and antibacterial activities and the antibiotic hirsutic acid (**114**).[151,152]

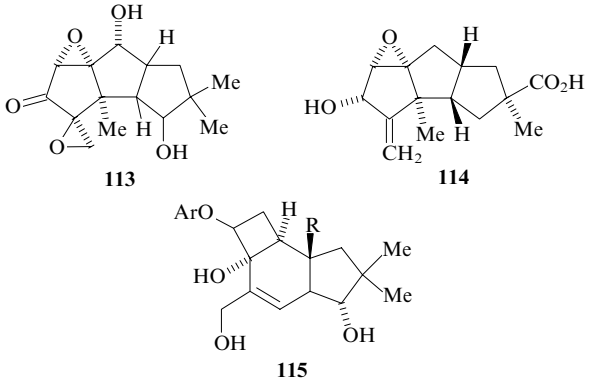
This approach was also employed to synthesize compounds **115** — protoilludane-type sesquiterpenes exhibiting anticancer and antimicrobial activities.[153–155]

Scheme 70



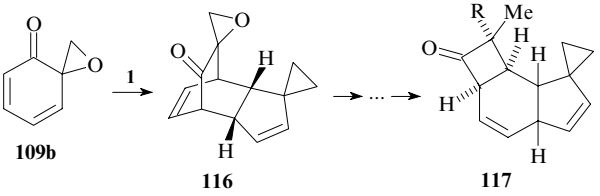
R = H, Me; (*a*) for R = H: Zn, NH_4Cl, dioxane, Δ; (*b*) for R = Me: NaH, THF, MeI

Structures 113–115



The reaction of SHD with 1-oxaspiro[2.5]octa-5,7-dien-4-one (**109b**) generated *in situ* by oxidation of salicylic alcohol produced adduct **116**. The reduction of compound **116** followed by photoisomerization gave target products **117** in 50%–90% yield (Scheme 71).

Scheme 71



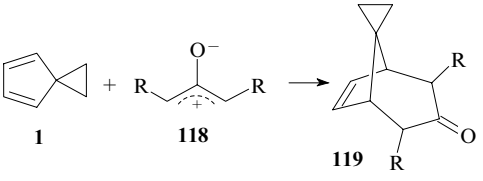
R = Me, All; All is allyl

The method for the synthesis of polyquinane natural compounds based on cyclohexa-2,4-dienones has been considered in detail.[155]

III.4. [4 + 3]-Cycloaddition reactions

The [4 + 3]-cycloaddition reactions of spiro[2.4]hepta-4,6-diene are also known. Thus, the dipolar cycloaddition of *in situ* generated propen-2-olates **118** to SHD affords adducts **119** (Scheme 72).[2, 156–163]

Scheme 72

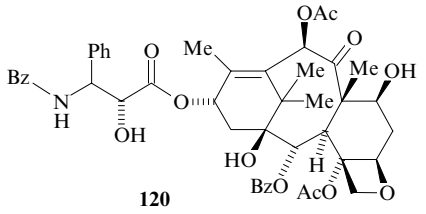


R = Cl, Me; R–R = $(CH_2)_2$

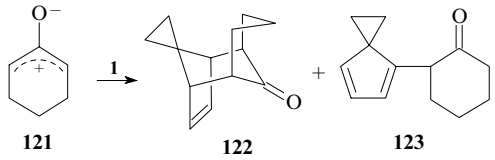
Polycyclic compounds **119** are convenient intermediates in the synthesis of various natural compounds, in particular, of taxane diterpenes. Taxol (**120**) having high antitumour activity is of particular interest.[159–161]

Cyclic oxyallyl intermediate **121**, which is generated from 2-chlorocyclohexanone and related compounds, reacts with SHD to give polycyclic [4 + 3]-cycloaddition adducts **122** in 13%–57% yields. In this case, side products, in particular addition products at the double bond of SHD (**123**), were detected (Scheme 73).[163]

Structure 120

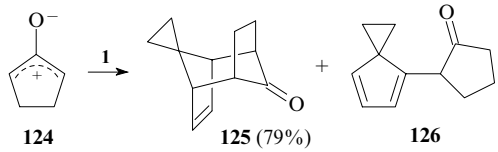


Scheme 73



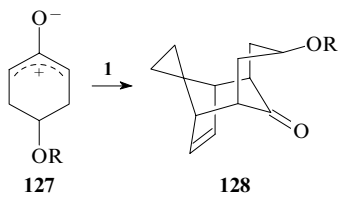
The reaction of the five-membered cyclic intermediate — 2-oxidocyclopent-2-en-1-ylium (**124**) — with SHD proceeds in a similar manner and gives [4 + 3]-cycloaddition products **125** along with addition product **126** as a side product (Scheme 74).[158, 164]

Scheme 74



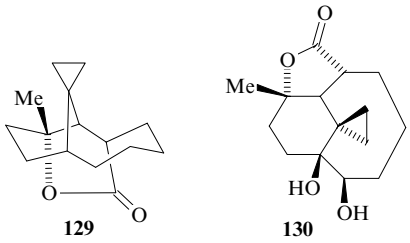
The [4 + 3]-cycloaddition of SHD to six-membered cyclic intermediates **127** affords adducts **128** in 44% yield (Scheme 75).[162]

Scheme 75



Adduct **128** served as the basis for the development of a strategy for the synthesis of various polycyclic compounds (in particular, polycyclic compounds **129** and **130**) containing medium-sized carbocycles.[162]

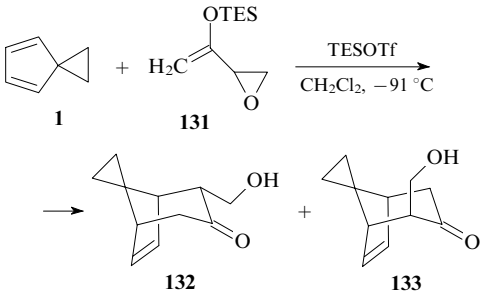
Structures 129, 130



129 **130**

The reaction of SHD with oxiranylvinyloxysilanes is another type of [4 + 3]-cycloaddition reactions. For example, the reaction of epoxy enol silane **131** (TES is triethylsilyl) with SHD is promoted by triethylsilyl trifluoromethanesulfonate (TESOTf) and gives a mixture of α- and β-epimers **132** and **133** in a total yield of 47% in a 77 : 23 ratio (Scheme 76).[165]

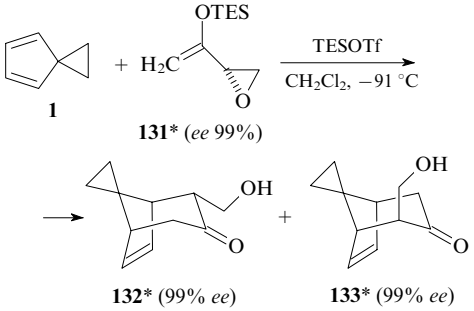
Scheme 76



1 **131** **132** **133**

The reaction of SHD with chiral epoxide **131*** affords a mixture of optically active products in 40% yield (**132*** : **133*** = 73 : 27) (Scheme 77).[166]

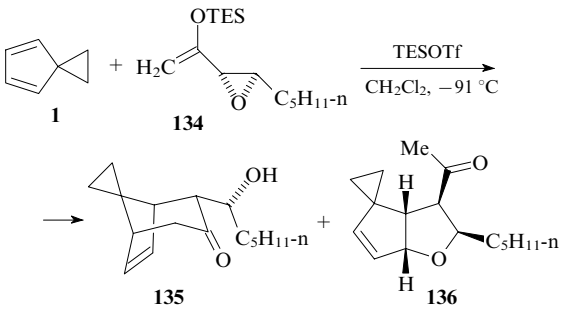
Scheme 77



1 **131*** (*ee* 99%) **132*** (99% *ee*) **133*** (99% *ee*)

The reaction of SHD with optically active epoxide **134** produces exclusively chiral α-isomer **135** in 57% – 67% yield and a minor amount (3.7%) of [3 + 2]-cycloaddition adduct **136** (Scheme 78).[165, 167]

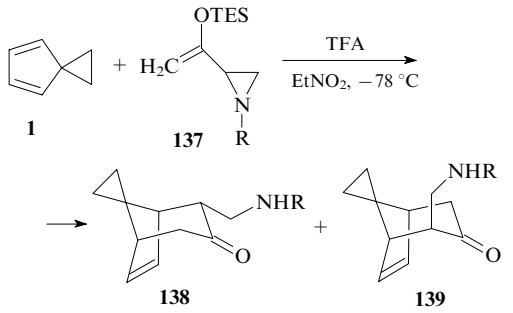
Scheme 78



1 **134** **135** **136**

Aziridinyl(vinyloxy)silanes **137** react with SHD similarly to epoxy enol silanes. The [4 + 3]-cycloaddition reaction with compounds **137** is promoted by trifluoroacetic acid (TFA) and produces a mixture of α- and β-epimers **138** and **139** in 69% yield in a 83 : 17 ratio (Scheme 79).[168]

Scheme 79

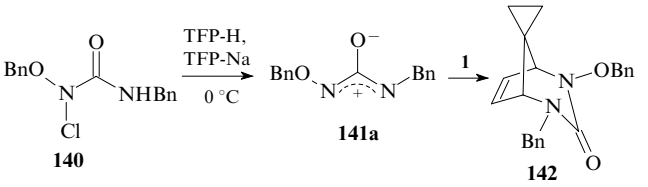


1 **137** **138** **139**

R = CO_2Bu^t, CO_2Bn

The 1,4-diamination of dienes with diaza oxyallyl cations[169, 170] also belongs to [4 + 3]-cycloaddition reactions of SHD. Thus, cation **141a** generated from chloramine **140** undergoes [4 + 3]-cycloaddition with SHD to form adduct **142** in high yield (82% – 88%) (Scheme 80).[169]

Scheme 80

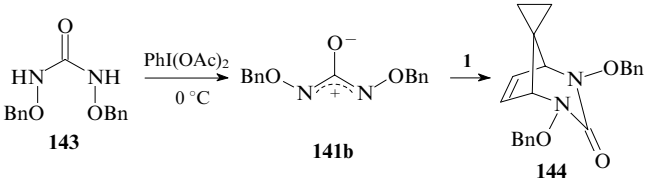


140 **141a** **142**

TFP = $OCH_2CF_2CHF_2$

The oxidative 1,4-diamination proceeds *via* a similar mechanism. Adduct **144** can be easily prepared in high yield (82% – 84%) by the addition of an oxidant to a mixture of SHD and diamine **143**.[170] This reaction is of particular interest because the diamination of alkenes and dienes is widely used in the synthesis of biologically active target molecules (Scheme 81).[170]

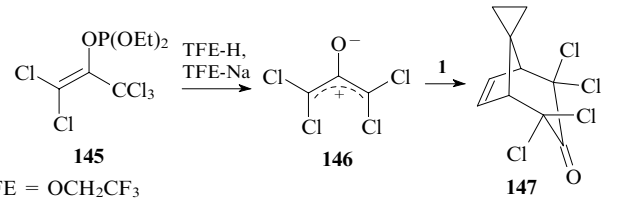
Scheme 81



143 **141b** **144**

Yet another example is the [4 + 3]-cycloaddition reaction of SHD with tetrachloro-substituted oxyallyl cation **146**, which is generated in the reaction of enol phosphate **145** with sodium trifluoroethoxide in trifluoroethanol. This reaction affords substituted [3.2.1]bicyclic ketone **147** in 45% – 49% yield (Scheme 82).[171]

Scheme 82



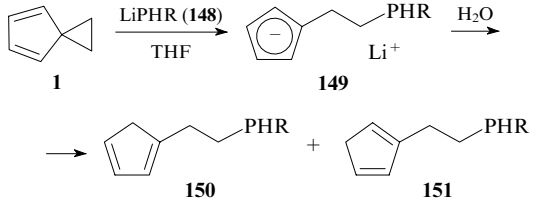
145 **146** **147**

TFE = OCH_2CF_3

III.5. Nucleophilic opening of the three-membered ring in spiro[2,4]hepta-4,6-diene

The treatment of spiro[2,4]hepta-4,6-diene with lithium phosphides **148** in THF leads to the nucleophilic opening of the three-membered ring giving cyclopentadienyl lithium salt **149**. Hydrolysis of the latter affords a mixture of isomeric phosphines **150** and **151** in a total yield of 69%–80% (Scheme 83).[172–174] Cyclopentadienyl salt **149** is also alkylated by different halides to form disubstituted CPDs.[174]

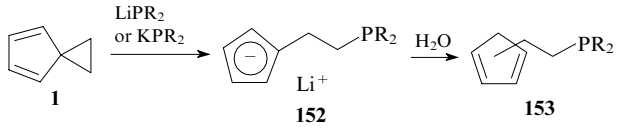
Scheme 83



R = Bu^t, Ph, Ar

A similar reaction of SHD with lithium or potassium dialkyl(aryl)phosphides in THF produces salts **152** in high yields through the cyclopropane ring opening. The hydrolysis of salts **152** gives a mixture of substituted CPDs, and salts **152** by themselves can be used, in particular, as ligands in various metal complexes (Scheme 84).[175–183]

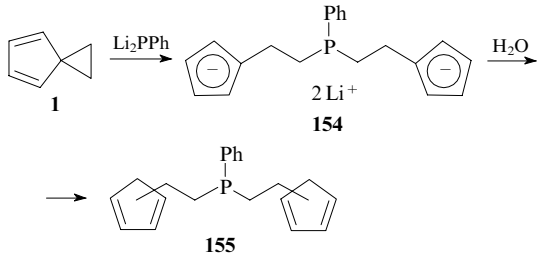
Scheme 84



R = Me, Et, Pr^i, Bu^t, Ph

A similar reaction with dilithiophenylphosphide, which is generated from phenylphosphine and n-butyllithium, occurs with the involvement of two SHD molecules and gives salt **154** (Scheme 85).[183, 184]

Scheme 85



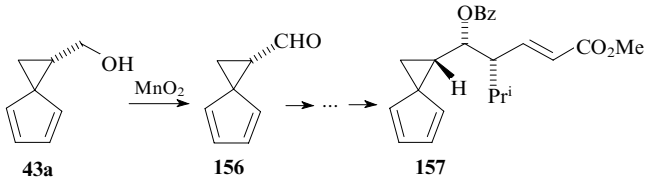
The hydrolysis of salt **154** produces a mixture of phenylbis(2-cyclopentadienylethyl)phosphines **155** in 50% yield.[183, 184]

III.6. Transformations, in which the spiro[2.4]hepta-4,6-diene system remains intact

There is a large group of reactions with SHD, in which only substituents in the cyclopropane moiety are subjected to transformations, while the spiro[2.4]hepta-4,6-diene skeleton remains intact. Spiro[2.4]hepta-4,6-dien-1-ylmethanol (**43a**) most often serves as the starting compound in these reactions.

Alcohol **43a** is most commonly used in the synthesis of natural compounds. Thus, the oxidation of compound **43a** affords aldehyde **156** (83% yield), and transformations of the latter with the involvement of the aldehyde group give triene **157** (Scheme 86).[23, 24]

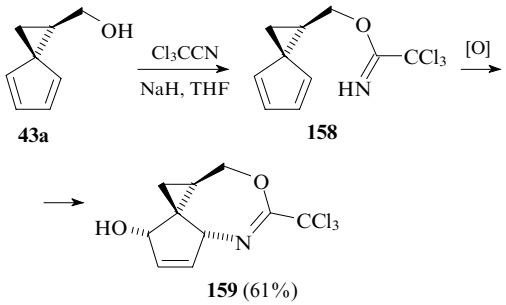
Scheme 86



The triene **157** was introduced into the intramolecular Diels–Alder reaction. The product of the latter served as basis for the synthesis of the above-mentioned sesquiterpenes sinularene (**54**), longifolene (**55**) and sativene (**56**) (see Section III.3.b).[23, 24]

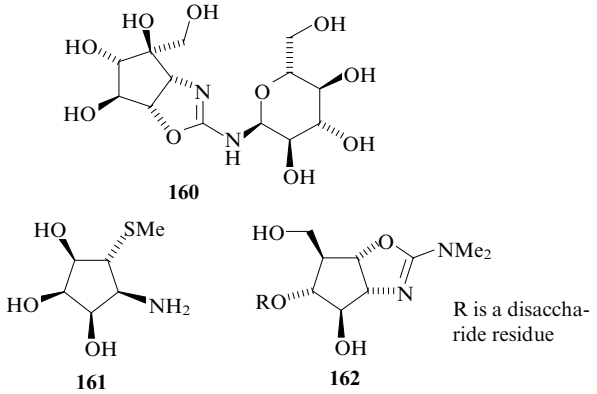
Some other natural products were synthesized by transforming alcohol **43a** into trichloroacetimidate **158** (60% yield) followed by oxidation of the latter with iodonium di-*sym*-collidine perchlorate to compound **159** (Scheme 87).[19]

Scheme 87



Compound **159** served as the basis for the preparation of aminocyclopentitol-derived (aminoxylitol-derived) natural products such as trehazolin (**160**), mannostatin A (**161**) and allosamidins **162**, which are efficient glycosidase inhibitors.[19] These compounds are employed in immunology, virology and oncology.

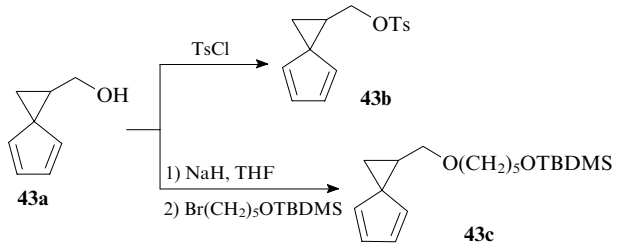
Structures 160–162



Reactions involving the OH group of compound **43a** produced esters, in particular, tosylate **43b** (95% yield) and 5-(*tert*-butyldimethylsilyloxy)pentyloxy derivative **43c** (55% yield), which were employed in the stereoselective synthesis of spirotricyclic compounds (Scheme 88).[84]

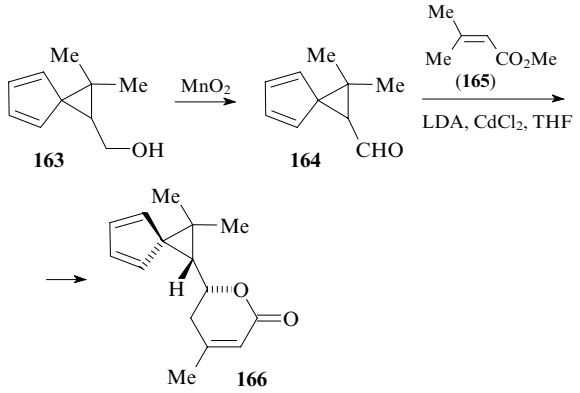
A strategy for the synthesis of a number of sesquiterpenes was developed based on SHD derivative **163**. For example, the oxidation of compound **163** to aldehyde **164** (81% yield) followed by the condensation of the latter with

Scheme 88



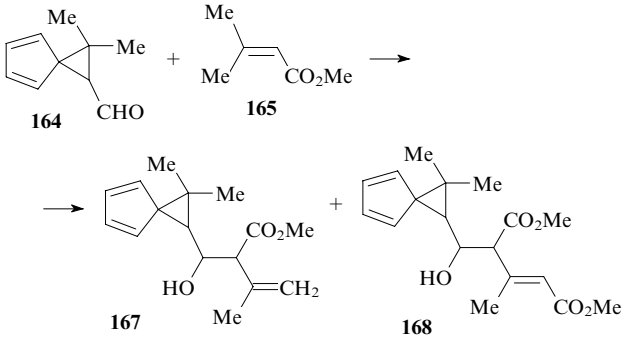
the anion, which is generated from methyl crotonate (**165**) in the presence of lithium diisopropylamide (LDA), produced lactone **166** in 73% yield (Scheme 89).[93]

Scheme 89



The condensation of compound **164** with methyl crotonate mediated by some other reagents affords the kinetically controlled product (**167**), the thermodynamically controlled product (**168**) or their mixture (Scheme 90). The reaction is regioselective and gives the final products in yields of up to 90%.[185, 186] Similar compounds are generated by the condensation of aldehyde **164** with other allylic anions.

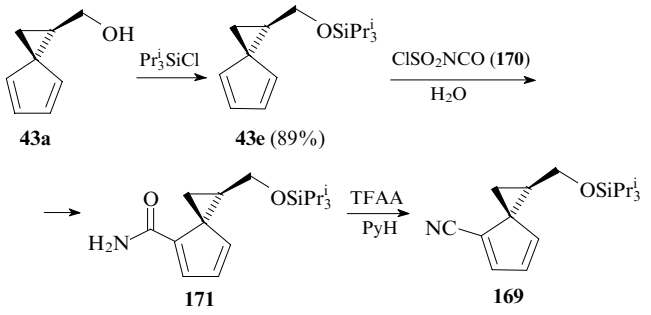
Scheme 90



Another interesting example of transformations involving side substituents is the synthesis of 4-cyano-substituted SHD **169**. The OH group of alcohol **43a** is first protected by a silyl protecting group, ether **43e** thus formed is treated with chlorosulfonyl isocyanate (**170**) to prepare amide **171**, and the reaction of the latter with trifluoroacetic anhydride (TFAA) in pyridine (PyH) gives the final product (Scheme 91).[187]

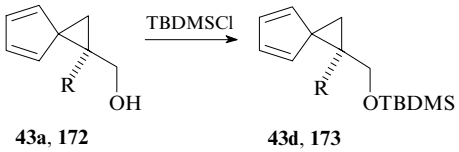
Besides, examples of the silyl protection of the OH group in SHD derivatives **43a** and **172** (Scheme 92) were documented.[85] Silyl ethers **43d** and **173** were isolated in

Scheme 91



yields of up to 97% and were then used in the synthesis of chiral ruthenium complexes.

Scheme 92



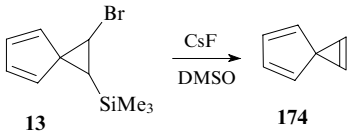
R = H (**43a**, **43d**), Bn (**172**, **173**)

III.7. Other reactions of spiro[2.4]hepta-4,6-diene

Data on other reactions with spiro[2.4]hepta-4,6-diene are, as a rule, fragmentary because these transformations are employed to solve highly specific problems.

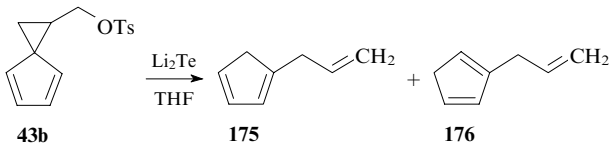
For example, spiro[2.4]hepta-1,4,6-triene **174** synthesized from bromo-substituted SHD **13** is of interest in the context of the examination of the effect of spiroconjugation (Scheme 93).[97, 98] The double bond in the three-membered ring in compound **174** is arranged perpendicular to the pentadiene ring, and the molecule is stabilized by through-space interactions between π-systems (effect of spiroconjugation).

Scheme 93



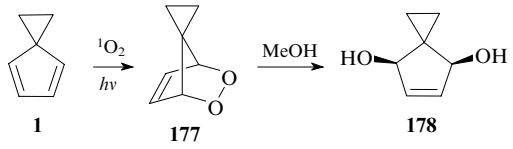
When treated with lithium telluride, substituted SHD **43b** undergoes nucleophilic reduction accompanied by cyclopropane ring opening to form a mixture of allyl-substituted cyclopentadienes **175** and **176** (Scheme 94).[188]

Scheme 94



Spiro[2.4]hepta-4,6-diene can be oxidized at double bonds with various reagents.[2] For instance, the oxidation with singlet oxygen initially leads to the 1,4-addition of oxygen to the diene system of SHD giving endoperoxide **177**. Under the reaction conditions, the latter undergoes further transformations. In particular endoperoxide **177** is transformed into product **178** in 24% yield under the action of methanol (Scheme 95).[2, 20, 189]

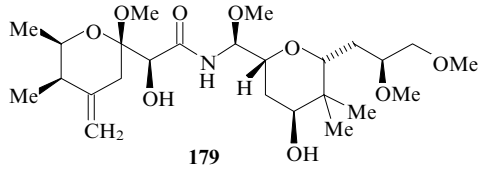
Scheme 95



1 **177** **178**

Similar reactions are employed in the total synthesis of natural pederol (**2**) and its derivatives, for example, pederin (**179**).[20]

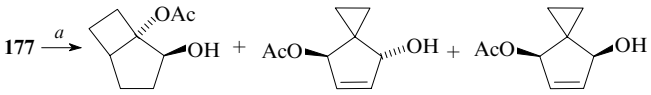
Structure 179



179

Endoperoxide **177**, which is produced *via* the oxidation of SHD with singlet oxygen,[189] can give reduction (**180**) and nucleophilic rearrangement (**181**) products after the treatment with triphenylphosphine (Scheme 96).[190]

Scheme 96

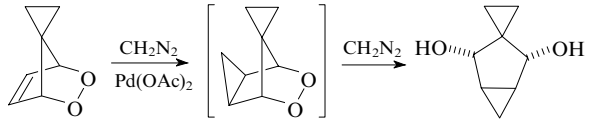


180 (13%) *trans*-**181** (28%) *cis*-**181** (27%)

(*a*) PPh_3, AcOH, CH_2Cl_2

Endoperoxide **177** is efficiently cyclopropanated with diazomethane and then reduced, under the reaction conditions, with an excess of diazomethane to diol **182** (Scheme 97).[191]

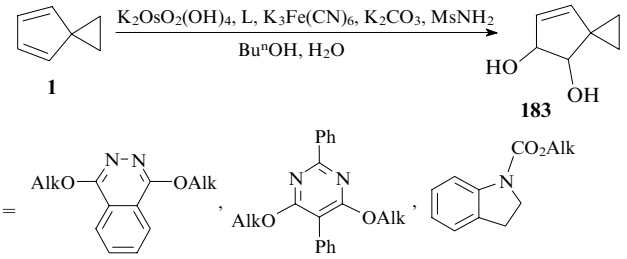
Scheme 97



177 **182**

The oxidation of SHD with some other reagents was also documented. Thus, the asymmetric dihydroxylation of SHD in the presence of various osmium catalysts affords one optically active 3*S*,4*R*-derivative **183** in 50%–55% yields (Scheme 98).[192]

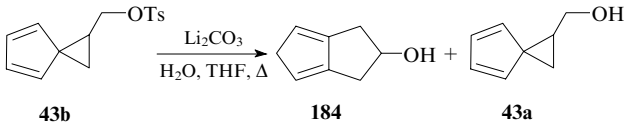
Scheme 98



1 **183**

Another example of reactions with SHD is the solvolysis of tosylate **43b** giving alcohol **184** in 44% yield *via* isomerization of the spiro[2.4]hepta-4,6-diene skeleton.[84] Besides, this reaction affords hydrolysis product of the starting compound (**43a**, 34% yield) (Scheme 99).

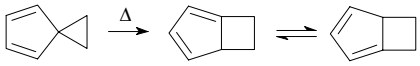
Scheme 99



43b **184** **43a**

Some thermal transformations of spiro-[2.4]hepta-4,6-dienes were studied. At 300–400 °C, SHD and its monosubstituted analogues undergo irreversible isomerization *via* 1,2-shift of the methylene unit of the three-membered carbon ring accompanied by 1,2-hydride transfer. The isomerization affords bicyclo[3.2.0]hepta-1,3-dienes **185**, which are unstable under the reaction conditions and can be trapped in the Diels–Alder reaction by reactive dienophiles (Scheme 100).[2]

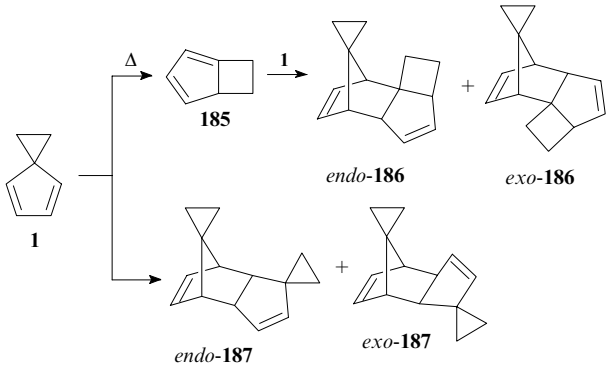
Scheme 100



1 **185**

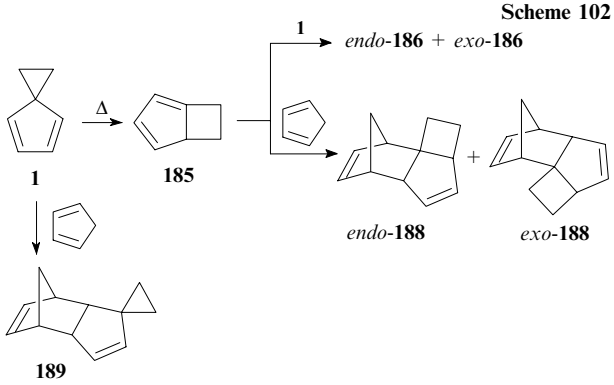
The heating of SHD to 230–250 °C is accompanied by its isomerization. Intermediate **185** undergoes the Diels–Alder reaction with the starting compound **1** giving a mixture of isomers **186** in 45%–55% yield. Isomeric dimers **187** were detected as side products (3%–6% yield) (Scheme 101).[193, 194]

Scheme 101



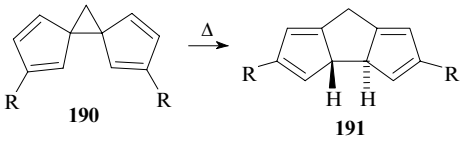
Upon heating of a mixture of SHD and cyclopentadiene, isomerization product **185** undergoes the Diels–Alder reaction with both SHD and CPD giving isomers **186** (in a total yield of ~25%) and **188** (18%–20% yield), respectively. In this reaction compound **189** — an adduct of SHD with cyclopentadiene — was detected as a side product (14%–15% yield) (Scheme 102).[193, 194]

Scheme 102



Thermal rearrangements of homopentafulvalenes **190** take place at ambient temperature (20–36 °C) and are accompanied by the stereoselective cyclopropane ring opening, resulting in the formation of 3a,3b-dihydro-7*H*-cyclopenta[*a*]pentalenes **191** (Scheme 103).[103]

Scheme 103

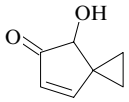


190 **191**

R = H, Bu^t

The biodegradation of SHD with the bacteria *Pseudomonas* sp. strain NCIB 9816-4 living in wastewaters was investigated.[195] Due to the presence of naphthalene dioxygenase in these bacteria, they efficiently and virtually completely oxidize SHD (95% conversion). Only two conversion products of SHD — spiro[2.4]hept-6-ene-4,5-diol (**183**) and spiro[2.4]hept-6-en-4-ol-5-one (**192**) — were identified in insignificant amounts (each in a yield of < 1%).

Structure 192



192

This fact attests to the environmental safety of SHD.

* * *

The analysis of the published data summarized in this review shows that spiro[2.4]hepta-4,6-dienes are promising compounds both for the direct use and as intermediates in organic synthesis, in particular, for the preparation of physiologically active compounds and cage structures.[113, 118, 141, 142] Besides, these compounds are attracting interest in the context of problems of spiroconjugation[97, 98, 196–202] and complexation.[203–207]

The development of chemistry of spiro[2.4]hepta-4,6-dienes greatly depends on efficient methods for their synthesis. The available procedures for the preparation of SHD and its derivatives, primarily through phase-transfer-catalyzed cycloalkylation of cyclopentadiene, provide access to mono- and 1,2-disubstituted spiroheptadienes. The continuous process for the synthesis of SHD in a flow microreactor[68] is suitable for the industrial production of unsubstituted, mono- and 1,2-disubstituted spiro[2.4]hepta-4,6-dienes.

The cyclomethylenation of the exocyclic double bond in fulvenes remains a promising synthetic route to *gem*-disubstituted, as well as to tri- and tetrasubstituted SHDs. It can be expected that new preparative methods for the synthesis of such compounds will be developed along this trend.

As can be seen from the above data, the chemical transformations of SHD and its derivatives were examined mainly for compounds that are most easy to prepare. Evidently, as other derivatives of this class of compounds become available, a comprehensive investigation of their properties, including chemical ones, will be conducted.

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