Cyclooctyne and 4-Cyclooctyn-1-ol – Versatile Building Blocks in Organic Synthesis

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The readily available and highly reactive title compounds represent versatile building blocks in organic synthesis. Recent examples of 1,3-dipolar cycloadditions and Diels–Alder reactions and their applications are described. This microreview is especially devoted to cycloadducts formed between **1** and **2** and furans, and their transformations to give a variety of different classes of compounds, including derivatives of natural products. Here the conversion of oxanorbornadienes into bridged oxepines plays an important role in many cases. Different routes to enantiomerically pure compounds are also presented.

1. Introduction

Cyclooctyne (**1**) was first synthesized by oxidation of 1,2-bishydrazonocyclooctane by Blomquist and Liu in 1953. This procedure, the Curtius synthesis of alkynes, opened the door for the generation and trapping of the lower cycloalkynes by Wittig and co-workers in 1960/61.[1]

A short 1978 communication by Brandsma and Verkruijsse was a breakthrough in cyclooctyne chemistry from the perspective of synthetic chemists. The authors published a highly improved synthesis of **1** from the readily available 1-bromocyclooctene.[2] The procedure given in ref.[2] avoids the formation of the isomeric 1,2-cyclooctadiene.[3] Cyclooctyne (**1**) can be prepared in large amounts by this

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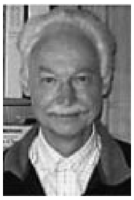

Dieter Heber, born in Dresden (Germany) in 1942, studied Pharmacy at the University of Tübingen and completed his doctoral dissertation under the direction of Jörg Schnekenburger in Kiel in 1971. After military service he started his own research on the synthesis of heterocyclic compounds with potential pharmacological activities in 1974. His scientific interest was focused on the chemistry of chromones and coumarins. In 1980 he was appointed Privatdozent at the University of Kiel. Since 1989 he has been Professor of Pharmaceutical Chemistry at the University of Kiel. His research in Kiel is concerned with the positive inotropic effect of anellated pyridines as well as pyrido[1,2-a]pyrimidines as NO synthase inhibitors and pyrido[2,3-d]pyrimidines as adenosine receptor antagonists, and also with the synthesis and reactions of enone Mannich salts.

Peter Rösner, born in Köthen (Germany) in 1944, studied Chemistry at the University of Kiel, where he received a Ph.D. in Organic Chemistry in 1981. In the same year he joined the Department of Toxicology at the Landeskriminalamt Kiel, where he serves as forensic expert for toxicological analysis. Since 1992 he has been a lecturer in mass spectroscopy at the University of Kiel. His research activities have focused on the structural elucidation of organic compounds in biologic fluids by daughter ion mass spectroscopy and software development for the evaluation and graphical representation of spectroscopic data. He wrote the computer program Chemograph and is the editor of the mass spectroscopic database Designer Drugs. In 2005 he was awarded the Jean-Servais-Stas Medal of the Society of Toxicological and Forensic Chemistry.

Werner Tochtermann, born in Pforzheim (Germany) in 1934, studied Chemistry at the Universities of Münster and Heidelberg, and completed his doctoral dissertation under the direction of Georg Wittig in 1960. After postdoctoral work as an assistant to his academic teacher, he started his own research on seven-membered ring systems. His interest was focused on the stereochemistry and intramolecular mobility of these compounds. In 1965 he was appointed Privatdozent at the University of Heidelberg and joined the faculty at the Technische Hochschule Darmstadt in 1972 as Professor. Since 1976 he has been Professor of Chemistry at the University of Kiel. His research in Kiel was mainly devoted to the construction and reactions of medium- and large-ring compounds. In this context he also synthesized macrolides with the aim of finding new musk odorants. For many years he has been a member of the advisory and consulting boards of several international journals (for the Eur. J. Org. Chem. until 2004).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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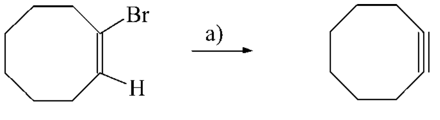
method, so this approach was also taken up in laboratory manuals for students (Scheme 1).[4]



1

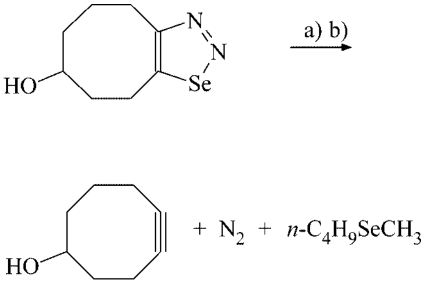
Scheme 1. Synthesis of cyclooctyne (**1**). Reagents and conditions: a) $LiN(i\text{-}C_3H_7)_2$, THF/hexane, –35 °C to +15 °C.[2]

Henceforth a great number of publications using **1** as starting material for various purposes appeared in the literature.

The enhanced reactivity of **1** is mainly due to its geometrical ring strain E. Values of E_g between 49.6 and 68.3 kJ·mol^{-1} have been published.[1f] The total sum of strain energy E_{st} was calculated to be 77.5 kJ·mol^{-1}.[5] Measured and calculated bond angles of 158.5° (exp.)[6] and 161.5–162.7° (calcd.)[7] at the distorted carbon-carbon triple bond have been reported. The consequences of this distortion on the molecular structure and the spectroscopic properties were reviewed by Krebs[1e] and Meier.[1f,5] A comparison of the electron affinities and ionization potentials of **1** with those of acyclic dialkyl acetylenes shows that the cyclic structure of cyclooctyne (**1**) enhances its electrophilic nature.

This strain is released in the transition states and products of the reactions of **1**. For the use of eight-membered cycloalkynes as reactive building blocks, functionalization of the hexamethylene unit of **1** was highly desirable. This target can be achieved by the selenadiazole pathway to eight-membered cyclic acetylenes.[1c,1f,1h] These heterocycles are readily available from ketones and can be cleaved by various methods to yield cycloalkynes. This approach has a broad scope and was used by Meier and co-workers to synthesize a large number of functionalized cyclooctynes, cyclooctenynes and heterocyclooctynes.[1c,lf,lh]

An especially useful example for our own projects was 4-cyclooctyn-l-ol (**2**). The original procedure[8] could be easily extended to a 40 g scale,[9] thus providing sufficient starting material for multistep syntheses (Scheme 2).



2

Scheme 2. Synthesis of 4-cyclooctyn-l-ol (**2**). Reagents and conditions: a) nBuLi, THF/hexane, –70 °C. b) MeI, –70 °C.[8,9]

The tendency mentioned above to release strain on going from sp to sp^2 hybridized carbon atoms is responsible for the enhanced reactivity of cyclooctyne (**1**) relative to open-chained alkynes. Electrophiles, nucleophiles, free radicals, and even lithium metal are therefore added to the triple bond. Compound **1** also serves as an electron-rich 2π component in cycloadditions, whilst metal complexations and their synthetic application also play an important role in the chemistry of cyclooctyne and related cycloalkynes. A comprehensive report of the entirety of cyclooctyne chemistry would be beyond the scope of a microreview, but these types of reactions have also been discussed in previous articles (see refs.[1a–1i] and additional references therein).[10]

This article is especially devoted to the transformations of primary cycloaddition products of **1** and **2** into different classes of target compounds. In addition to the results of our group, some selected recent related examples from others are included.

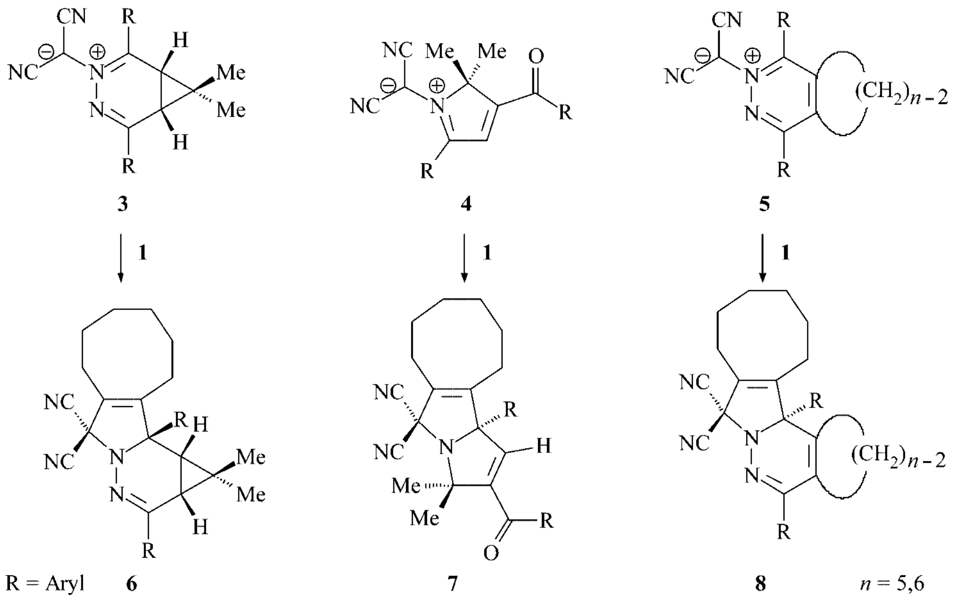
2. Reactions of Cyclooctyne – Selected Results and Applications

2.1. 1,3-Dipolar Cycloadditions

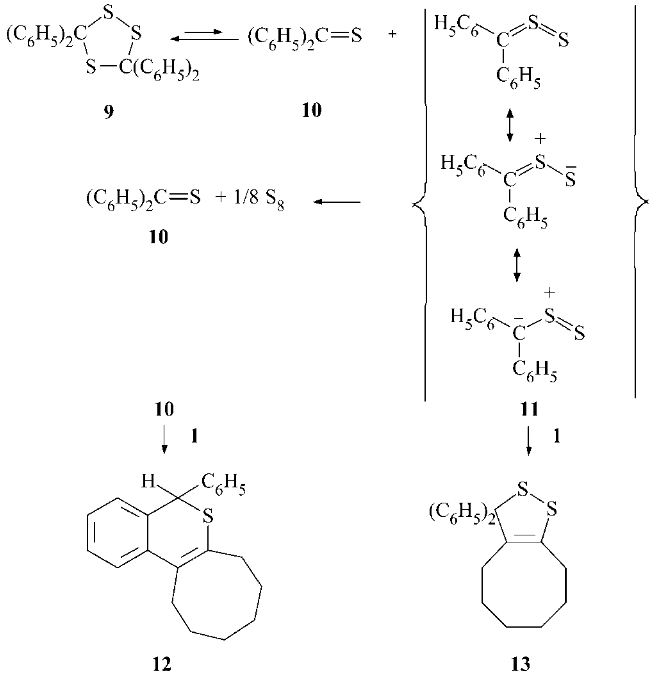
The concept of 1,3-dipolar cycloadditions was introduced by Huisgen and co-workers, who developed this reaction into a powerful method for the synthesis of five-membered heterocycles. Nonactivated alkynes often react only sluggishly, so the strained cyclooctyne (**1**) and other activated alkynes were frequently used as dipolarophiles.

Azomethine ylides are a most valuable class of 1,3-dipoles, because their cycloadditions proceed stereoselectively to give pyrrolines and pyrrolidines. In many cases these ylides exist only as reactive intermediates, which are trapped after their in situ preparation. Sauer and co-workers recently described an approach to the stable azomethine ylides **3**–**5**,[11a,11b] which proved to be useful substrates for detailed kinetic studies of their reactions with cyclooctyne (**1**) and other activated 2π components (Scheme 3). Most reactions of **3**–**5** – including those with **1** – are $LUMO_{dipole}$–$HOMO_{dipolarophile}$ controlled with concerted bond formation in the transition state. Compound **1** reacts more rapidly with electron-poor substituted ylides than with electron-rich analogues.[11c] In the case of **3**, which contains a diazadiene and a 1,3-dipole system as well, **1** and other 2π systems add regioselectively to the 1,3-dipole moiety. Compounds **1** and **3** form the pyrroline **6**, for example, whilst **1** and **4** give **7**, and **1** and **5** react to yield **8**. The obtained kinetic data were also used to test the predictive power of the global electrophilicity model for 1,3-dipolar cycloadditions.[11d]

Cyclooctyne (**1**) has also been used for the trapping and characterization of some reactive sulfur-containing intermediates. As an example, the 1,3-dipolar cycloreversion of 3,3,5,5-tetraphenyl-1,2,4-trithiolane (**9**), giving rise to an equilibrium between thiobenzophenone (**10**) and thiobenzophenone S-sulfide (**11**), was unequivocally established with the aid of the reactions between **1** and **10** and **11** (Scheme 4), a mixture of the Diels–Alder adducts **12** and the dithiole 1,3-cycloadducts **13** being isolated.[12]



Scheme 3. 1,3-Dipolar cycloadditions between **1** and stable 1,3-dipoles **3**–**5**. Reagents and conditions: dioxane, 20 °C.



Scheme 4. The cycloreversion of the 1,2,4-trithiolane **9**. Reagents and conditions: 4 h, reflux in $CHCl_3$.

Thermolysis or irradiation of fluorenethione *S*-oxide (**14**) in the presence of **1** (Scheme 5), studied by Adam and co-workers,[13] generates the nonisolable 1,2-oxathiole **15**. Sulfur transfer to **1** gives the dithiin **16** and the enone **17**, the formation of **17** being indicative of a 1,3-dipolar cycloaddition between **14** and **1**. The sulfur transfer chemistry of strained alkynes was studied in detail by these workers.[14]

Doepp and co-workers[15] described the [3+2] cycloadditions between α-acceptor-substituted vinyl sulfides **18** and **1** (Scheme 6). The octahydro[*b*]thiophenes **19** are formed in good yields, accompanied by loss of isobutene.[16]

Quite another application of cyclooctyne (**1**) was reported by Banert and co-workers, who used **1** to convert labile vinyl azides into stable cyclooctatriazoles through 1,3-dipolar cycloadditions. Thus, the vinyl azide part of 2,3-diazido-1,3-butadiene (**20**) rapidly adds **1** (Scheme 7) to give **21** and **22**. The subsequent Diels–Alder reaction with the diene moiety to afford **23** is slower. Cycloadduct **23** is oxidized by air to form **24**.[17]

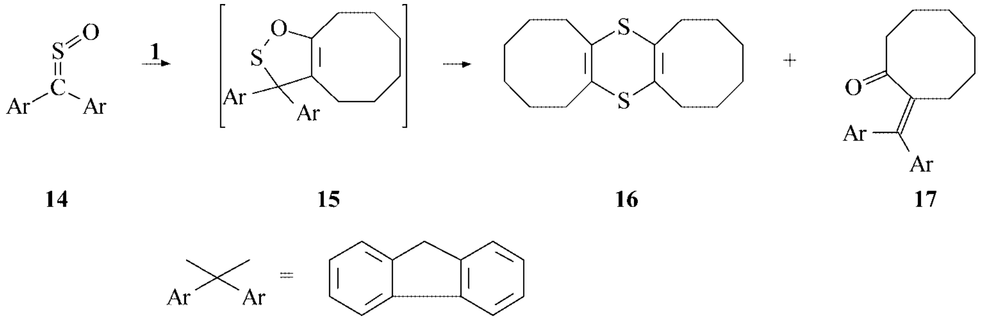
The 1,3-cycloadducts of other vinyl azides often form strong complexes with $Eu(fod)_3$ and are therefore used for the structural elucidation of the primary azides.[18] Cyclooctyne (**1**) also allows the determination of the number of azide groups in a polyazide. It could thus be shown that the purported hexaazidocyclopentadiene[19] is in fact 1,1-diazido-2,3,4,5-tetrachloro-cyclopentadiene.[20]

2.2. Diels–Alder Reactions

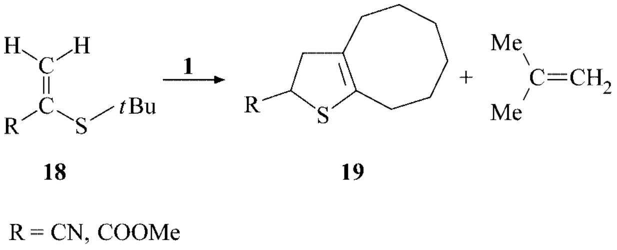
2.2.1. General Remarks

Numerous applications of cyclooctyne (**1**) and its hydroxy derivative **2** start with a Diels–Alder reaction, in which the cycloalkynes behave as reactive electron-rich dienophiles. However, because of the release of strain these cycloadditions also take place with electron-rich dienes.[1,21] The use of thiobenzophenone (see Scheme 4),[12] colchicine derivatives,[22] 1,3,5-triphosphabenzenes,[23] phthalazines,[24] tetrazines[25] and pyridones[26] as diene partners for **1** demonstrates the utility of this cycloalkyne for synthetic purposes.

This microreview is especially devoted to the reactions between **1** and **2** and furans, because the primary cycloadducts with these dienes can be transformed into a great variety of different target products.



Scheme 5. The 1,3-dipolar cycloaddition between fluorenethione *S*-oxide (**14**) and cyclooctyne (**1**). Reagents and conditions: Δ*T* (40 °C, 20–88 h) or *hv* (5 °C, 350 nm, 3 h), $CDCl_3$.



Scheme 6. [3+2] Cycloadditions between vinyl sulfides **18** and cyclooctyne (**1**). Reagents and conditions: warm dioxane, 2 days.

2.2.2. Diels–Alder Reactions between 1 and 2 and Furans

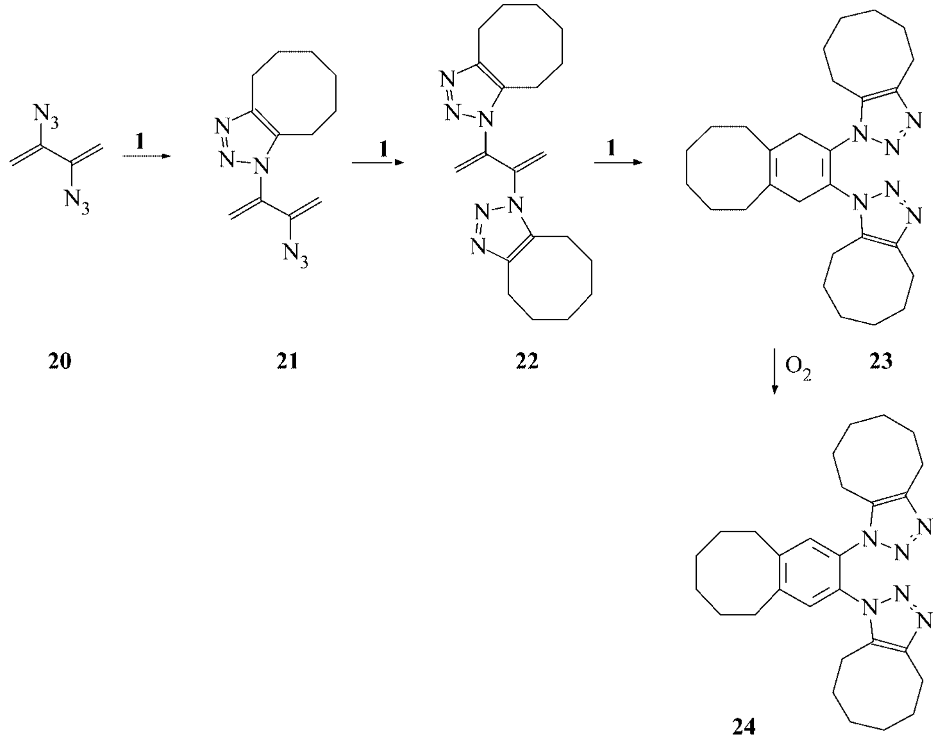
In pursuing our longstanding interest in furan chemistry,[27] we started[28] our contributions to this field soon after the publication of the Brandsma route to **1**.[2] Cycloadditions between **1** and various furans **25** proceeded at elevated temperatures in good yields (50–90% yield), providing sufficient starting material for multistep syntheses. Substituents play no important role (Scheme 8; **26g**: 78% yield; **26i**: 67% yield).[28–31]

The analogous cycloaddition between **2** and **25g** gave the corresponding oxanorbornadiene with an additional hydroxy group in position 7.[9]

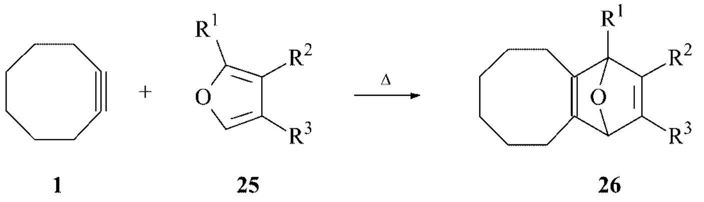
3. Transformations of the Oxanorbornadienes 26

3.1. Synthesis of γ-Lactones and Related Compounds

The oxanorbornadienes **26a** and **26c** can be converted, after regioselective hydrogenation to **27a** and **27b**, into the



Scheme 7. The cycloaddition sequence of 2,3-diazido-1,3-butadiene (**20**) with cyclooctyne (**1**). Reagents and conditions: $CDCl_3$, room temp., 6 days.



25, 26	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	CH_2OAc	H	H
d	H	CH_2OAc	H
e	H	$-(CH_2)_6-$	

25, 26	R^1	R^2	R^3
f	H	$-(CH_2)_6-$	
g	H	CO_2Et	CO_2Et
h	H	CH_2OAc	CH_2OAc
i	H	OMe	OMe

Scheme 8. Synthesis of the oxanorbornadienes **26**. Reagents and conditions: no solvent or toluene, xylene, 110–140 °C.

twelve-membered diketones **28**, which undergo an unexpected, valuable oxidative ring cleavage. On prolonged standing of **28b** in the laboratory, or by bubbling air through a cyclohexane solution of **28a**, the lactones **29a** and **29b** are obtained in yields between 50 and 70%.[31,32] We assume that a hydroperoxide is formed at first, and that this subsequently rearranges to give **29** (Scheme 9).

Compound **29a** was the starting material for our synthesis of cytotoxic acetogenin (–)-(4*R*,5*R*)-muricatacin (**30a**),[33] which was synthesized only a few months after its isolation from the seeds of *Annona muricata L.* by McLaughlin and co-workers.[34,35] The necessary separation of enantiomers was achieved through diastereomeric camphanoates of a hydroxy intermediate. The second camphanoate was converted into (+)-(4*S*,5*S*)-muricatacin (see Figure 1).[36]

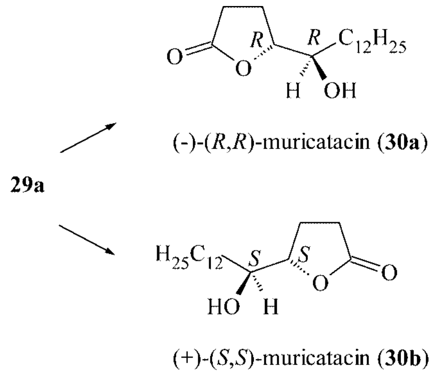
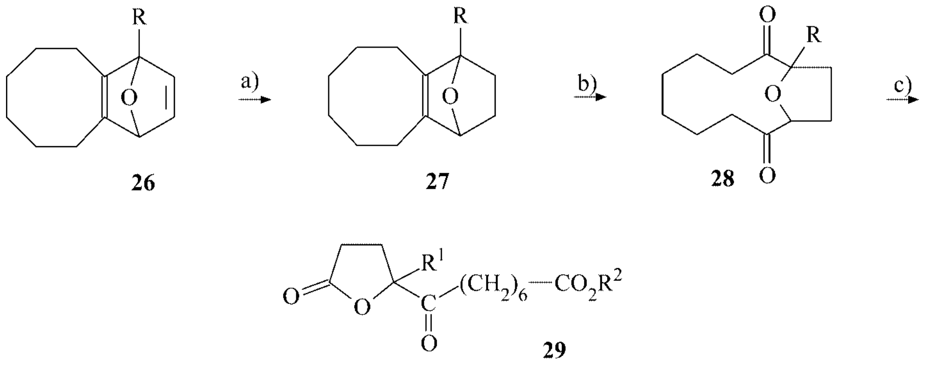


Figure 1. The enantiomers of muricatacin **30a** and **30b**.



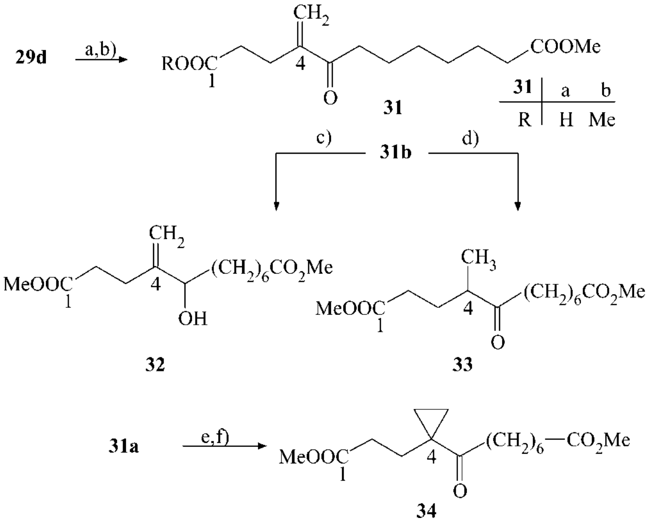
26	R
a	H
c	CH_2OAc

27, 28	R
a	H
b	CH_2OAc

29	R^1	R^2
a	H	H
b	CH_2OAc	H
c	CH_2OH	Me
d	CH_2OMs	Me

Scheme 9. Synthesis of γ-lactones **29** from oxanorbornadienes **26**. Reagents and conditions: a) H_2/Pt. b) O_3, –70 °C, $MeOH/CH_2Cl_2$. c) O_2, room temp.

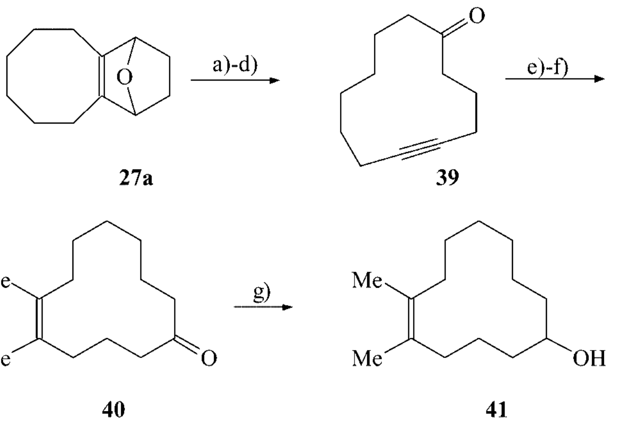
Functionalized dodecane diacid derivatives **31**–**34** are available from **29d** through the ring-opening reactions outlined in Scheme 10. Treatment of **29d** with sodium iodide and zinc was in reality carried out with the aim of reducing it to the corresponding methyl derivative. To our surprise, the α-methylene carbonyl derivative **31a** was obtained in good yield; a possible reaction path is discussed in ref.[31] Useful conversions of **31** into **32**–**34** are presented in Scheme 10.



Scheme 10. Transformations of the γ-lactone **29d** into functionalized dodecane diacid derivatives **31**–**34**. Reagents and conditions: a) NaI, Zn, dimethoxyethane. b) MeOH, Amberlist 15®. c) $Zn(BH_4)_2$, Et_2O. d) L-Selectride, THF, –78 °C. e) excess CH_2N_2, Et_2O. f) *hv*, $CDCl_3$.

The enantiomerically pure (*R*,*R*)- and (*S*,*S*)-configured *syn*-hydroxy-γ-lactones **35** and **36**, which are intermediates in our muricatacin synthesis, could also be converted into the *N*-Boc-δ-amino-γ-lactones **37b** and **38b**, which can be regarded as "hydroxyethylene dipeptide" isosteres (Scheme 11).[37]

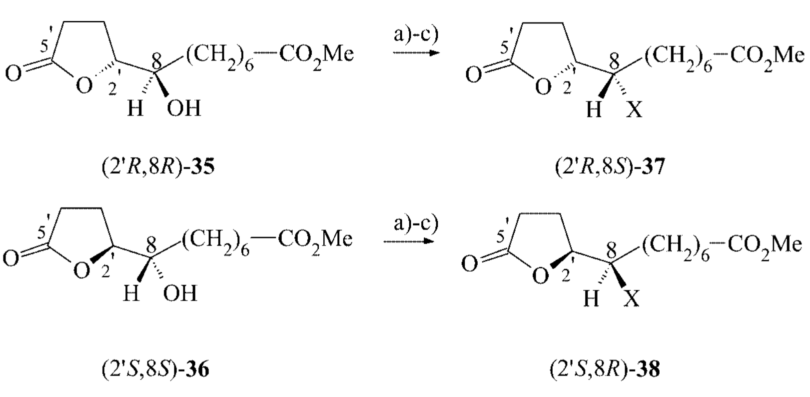
The hydrogenated Diels–Alder adduct **27a** was also the starting material for the synthesis of (*Z*)-dimethylated twelve-membered ring systems **40** and **41**. These compounds were chosen as targets because we expected them to possess interesting olfactory properties according to a molecular modelling comparison with some known fragrant substances.[38,39] Key steps of our approach to **40** and **41** were a ring enlargement through an Eschenmoser–Ohloff fragmentation[40] and a (*Z*)-dimethylation of the carbon-carbon triple bond of **39** developed by Miyaura, Suzuki and co-workers (Scheme 12).[41] Both compounds indeed possess a typical cedarwood note accompanied by some other facets.[38,39]



Scheme 12. Synthesis of the macrocyclic odorants **40** and **41**. Reagents and conditions: a)LiTBAH, Et_3B, THP. b) MnO_2, *n*-pentane. c) H_2O_2, NaOH, MeOH. d) H_2NNHTs, AcOH, CH_2Cl_2. e) Dipinacolyl hypodiborate, $Pt(PPh_3)_4$, DMF. f) MeI, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane. g) $LiAlH_4$, Et_2O.

3.2. Synthesis of 3,6-Hexanooxepines

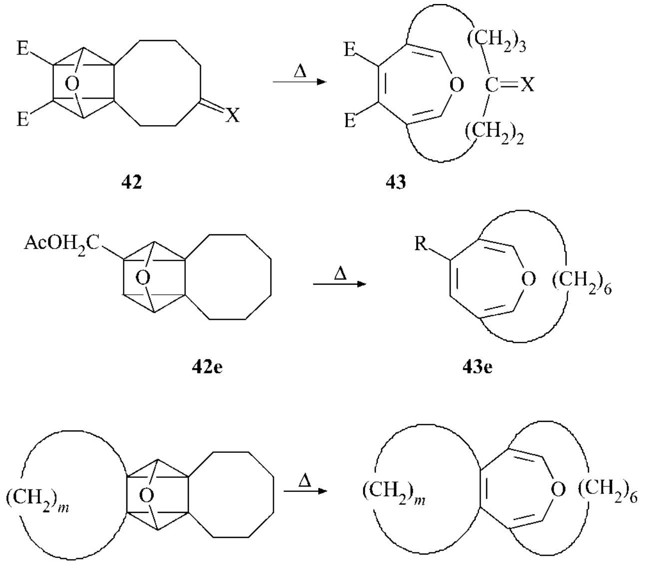
The synthesis of oxepines from oxanorbornadienes via oxaquadricyclanes – the Prinzbach sequence[42] – was first



37, 38	X
a	N_3
b	NH-Boc

Scheme 11. Synthesis of the *N*-Boc-δ-amino-γ-lactones **37b** and **38b**. Reagents and conditions: a) *p*TsCl, pyridine, DMAP. b) NaN_3, DMF. c) Pd/C, H_2, ethyl acetate, $(Boc)_2O$.

described in 1966.[43] The versatility of this conversion has been outlined in numerous publications.[27b,27c,43] The approach starts with oxanorbornadienes (see Section 2.2.2.), which are transformed into oxaquadricyclanes by direct photoexcitation with filtered UV light at low temperatures. The highly strained tetracyclic photoproducts isomerize thermally on heating (100–140 °C) to give the seven-membered ring systems. The 3σ → 3π-isomerization starts with a 1,3-dipolar cycloreversion to give a carbonyl ylide (see Scheme 13 and Scheme 14) that could be trapped by Prinzbach and co-workers with dimethyl acetylenedicarboxylate as dipolarophile.[27b] In 1998, Matsumoto and co-workers also used cyclooctyne (**1**) as trapping reagent.[45] By this procedure we prepared various oxaquadricyclanes **42** and 3,6-hexanooxepines **43** from cyclooctyne (**1**) and its hydroxy derivative **2**.[9,27b,27c,28–30,44,46]



42, 43	X	E
a	H,H	COOEt
b	H,H	COOMe
c	H,OH	COOEt
d	O	COOEt

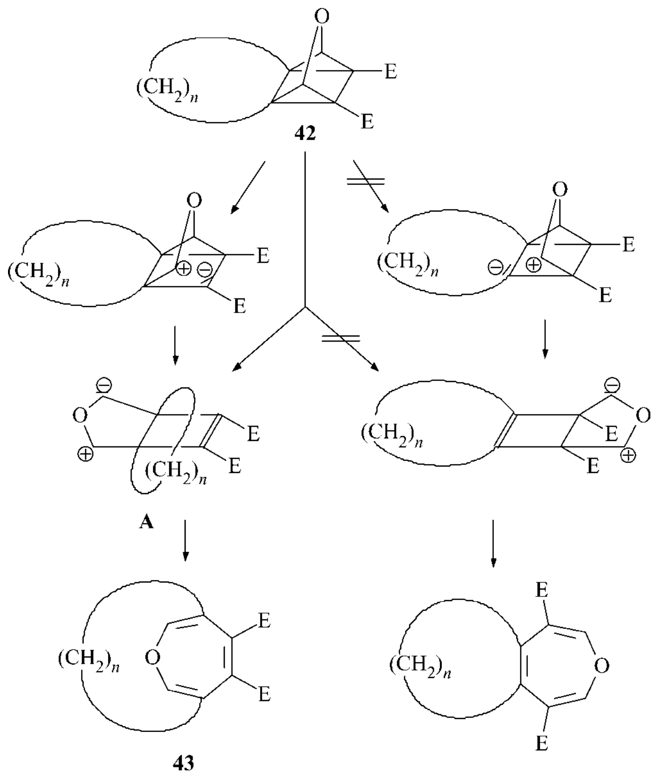
43	R
e	CH_2OAc
f	CH_2OH
g	COOH

42, 43	*m*
h	6
i	10

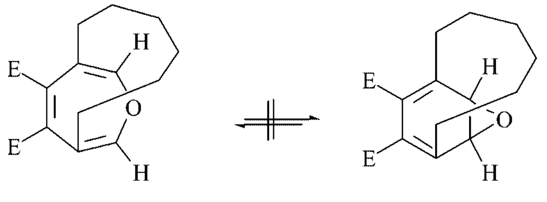
Scheme 13. Synthesis of 3,6-hexanooxepines **43** from anellated oxaquadricyclanes **42**. Reagents and conditions: toluene or xylene, reflux.

It is of preparative importance, and of mechanistic interest as well, that the isomerization proceeds with high regioselectivity in the presence of ester groups, giving predominantly one of two possible products. The preferential formation of hexanooxepines can be understood in terms of the concept of donor-acceptor-substituted cyclopropanes.[27b,47,48]

In particular, the oxepinophanes **43a** and **43d** were prepared on multigram scales, so that their synthetic potential could be studied in detail. It is noteworthy that compound **43a** was found to be stable against sulfuric acid in ethanol under reflux.[49] The rapid acid-catalysed isomerization of most oxepines and many other reactions proceed via the corresponding arene oxides. No valence tautomerism could be detected here, because the isomer would be a highly strained [6]paracyclophane oxide.[27b,27c,49] This inertness was helpful for the intended transformations; treatment of **43a** with trifluoroacetic acid, for instance, provides the useful anhydride (Figure 2)[44] (see Section 4.3).



Scheme 14. Regioselective formation of alkoxycarbonyl alkanooxepines **43** from **42** via a carbonyl ylide **A**.



43a E = COOEt

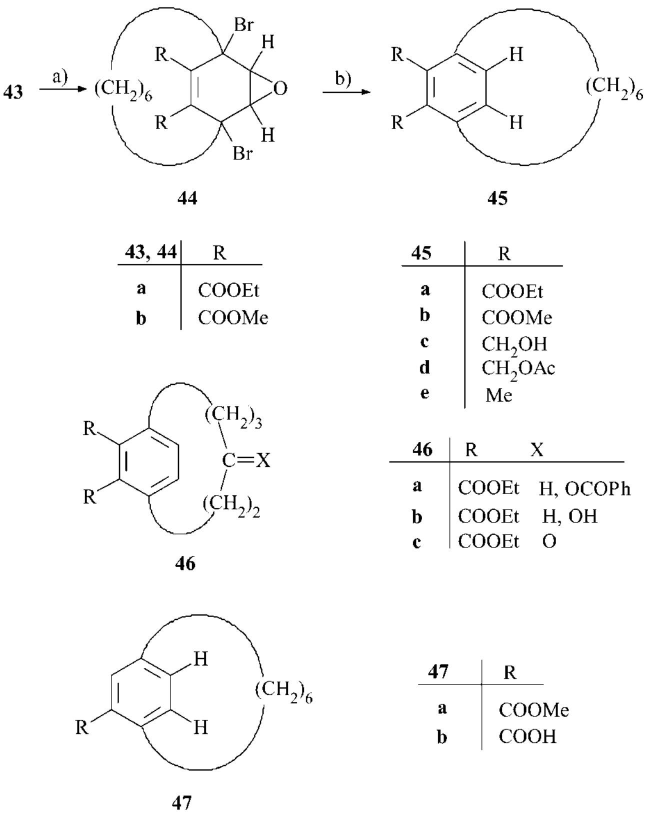
Figure 2. The (not detected) valence tautomerism of the oxepinophane **43a**.

4. The Synthetic Potential of 3,6-Hexanooxepines

4.1. Synthesis and Properties of [6]Paracyclophanes

[*n*]Paracyclophanes with a short bridging methylene chain ($n < 10$) are interesting model compounds with which to explore the extent to which benzene rings can be bent and distorted. In the last five decades, various different approaches to these target molecules have been published.[50]

When the length of the bridge is reduced, preparative difficulties in synthesizing these compounds increase. For [6]paracyclophane derivatives the problem was solved by our approach using cyclooctyne (**1**) and the furan diester **25g** (see Scheme 8) as starting materials and proceeded via **26g** → **42a** to the oxepine **43a**. The addition of bromine to the oxepine diesters **43a** and **43b** occurred in transannular fashion to give the dibromo epoxides **44a** and **44b**. A modified McMurry reaction provided the [6]paracyclophanes **45a** and **45b** (Scheme 15) in yields between 58 and 70%,[51] and **45b**, for example, could be prepared on a 10 g scale.[51c] Further derivatives **45c**–**45e** are available by classical procedures.



43, 44	R
a	COOEt
b	COOMe

45	R
a	COOEt
b	COOMe
c	CH_2OH
d	CH_2OAc
e	Me

46	R	X
a	COOEt	H, OCOPh
b	COOEt	H, OH
c	COOEt	O

47	R
a	COOMe
b	COOH

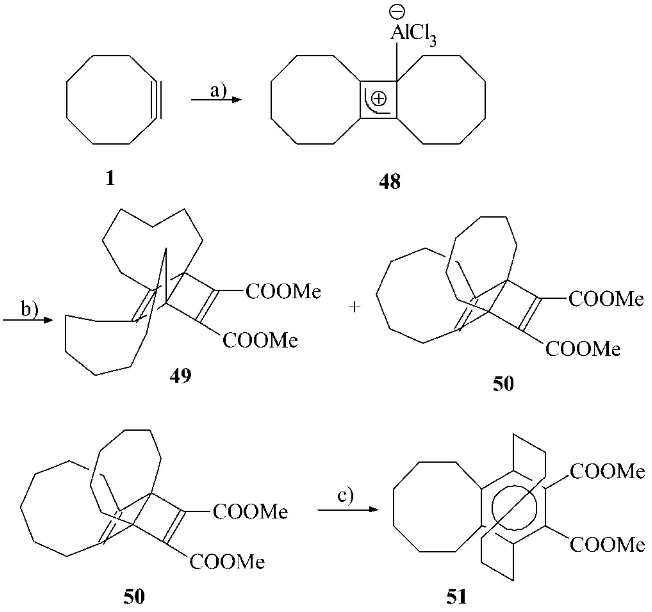
Scheme 15. Synthesis of [6]paracyclophanes from 3,6-hexanooxepines. Reagents and conditions: a) Br_2, CH_2Cl_2, room temp. b) $TiCl_3$, O_2, $LiAlH_4$, THF, ultrasound.

The cyclophanes **46a**–**46c** with oxygen functionality in the bridge were obtained in a similar way from cyclooct-4-yn-l-ol (**2**).[9] The chiral compound **26d** was converted into the chiral oxepines **43e/f** and further into the cyclophanes **47a** and **47b**.[52] Their absolute configurations could be established after resolution via diastereomeric derivatives.[46,53] The accessible amounts of [6]paracyclophanes allowed, in cooperation with other groups, detailed studies of the structures[51b,54] and the spectroscopic[9,54–56] and chemical properties[51b,57,58] of these highly strained compounds.

In summary, our studies showed that [6]paracyclophanes are an interesting borderline case. On the one hand they possess the spectroscopic properties of aromatic compounds, on the other the high strain in **45** gives rise to a reactivity typical of alkenes and dienes. Compounds **45a** and **45b** add bromine, osmium tetroxide, and dihalogen carbenes, for example, and also react as dienes in Diels–Alder reactions.[51–58] The angles of deformation of [6]paracyclophanes – α = 19.5° and β = 19.9° for **45b**[54] – have a significant influence on the UV, CD and phosphorescence spectra of these boat-shaped compounds.[46,56,59]

Unfortunately, the cyclooctyne → oxepine route could not be extended to [5]paracyclophanes.[42,60] Other methods for the generation of small [*n*]paracyclophanes ($n < 6$) have to be used.[50] However, cyclooctyne (**1**) was also used by Gleiter and Treptow[61] for a different synthesis of a [6]paracyclophane and its valence isomers.

Treatment of **1** with $AlCl_3$ produces the cyclobutadiene σ-complex **48**. Successive addition of dimethyl acetylenedicarboxylate (DMAD) and dimethyl sulfoxide yields a mixture of the Dewar benzenes **49** and **50**. On irradiation, **50** isomerizes into **51**. A photochemical equilibrium between **50** and **51** was established (Scheme 16).

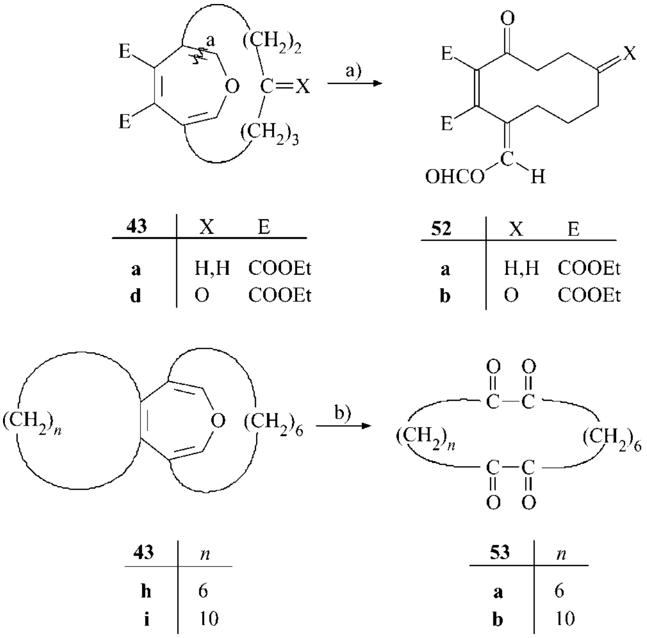


Scheme 16. A three-step synthesis of the [6]paracyclophane **51** from **1**. Reagents and conditions: a) $AlCl_3$, CH_2Cl_2, –40 °C → room temp. b) DMAD, DMSO, CH_2Cl_2, 5–20 °C. c) *hν*, 250 nm, Et_2O, 10 °C.

4.2. The Oxidation of 3,6-Alkanooxepines – Expected and Unexpected Results

The oxidation of the oxepine diesters **43a** and **43d** (Scheme 17) under mild conditions with $NaIO_4/KMnO_4$ produces the enol formates **52a** and **52b** in 91 and 52% yields, respectively, by cleavage of one double bond.[44,62]

Both esters can be converted into other functionalized ten-membered ring systems. The regioselectivity of the cleavage of the bond nearest to the keto group in **43d** was explained in terms of different transannular strain of intermediate products in these medium-sized ring systems.[62]



43	X	E
a	H,H	COOEt
d	O	COOEt

52	X	E
a	H,H	COOEt
b	O	COOEt

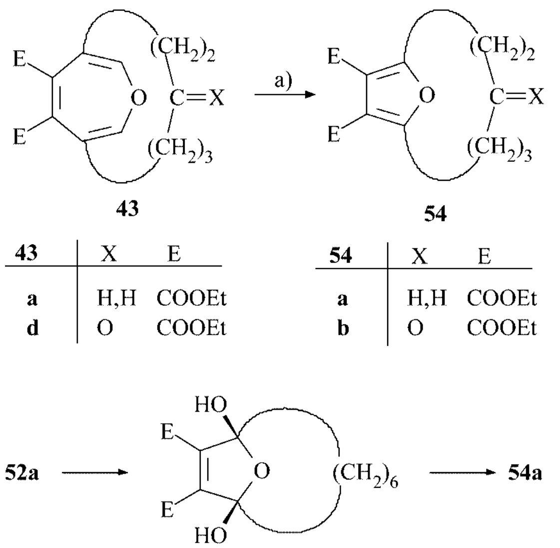
43	*n*
h	6
i	10

53	*n*
a	6
b	10

Scheme 17. Monocyclic ring systems by oxidation of oxepines **43**. Reagents and conditions: a) K_2CO_3, $NaIO_4$, $KMnO_4$, dioxane, C_6H_6, H_2O, room temp. b) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, room temp.

Macrocyclic tetraketones **53a** and **53b** were obtained by oxidation of **43h** and **43i** with ruthenium tetroxide generated by the procedure of Sharpless and co-workers.[30,63,64]

Treatment of the oxepine diesters **43a** and **43d** with the same reagent[63] took a surprising course, giving the [6](2,5)-furanophanes **54a** and **54b** (Scheme 18) through formal loss of two carbons.[65] This unusual ring-contraction can be explained as follows: ruthenium tetroxide oxidizes both enol ether double bonds of **43**. The resulting enedione diester forms the transannular double hemiacetal **55**, which eliminates hydrogen peroxide to give **54**. The structure of the isolated intermediate **55** was established by X-ray analysis.[65]



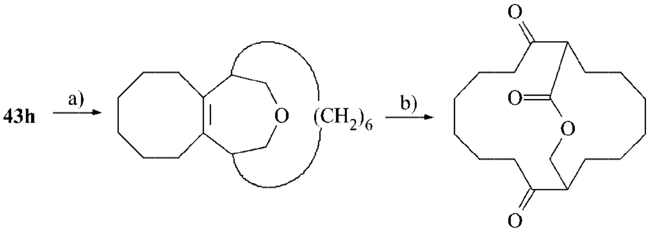
43	X	E
a	H,H	COOEt
d	O	COOEt

54	X	E
a	H,H	COOEt
b	O	COOEt

55

Scheme 18. The [6]oxepinophane → [6]furanophane ring contraction. Reagents and conditions: $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, room temp.

Oxidation of the tetrahydrooxepine **56** obtained from **43h** directly gave the bicyclic diketo macrolide **57** (Scheme 19).[66]



56 **57**

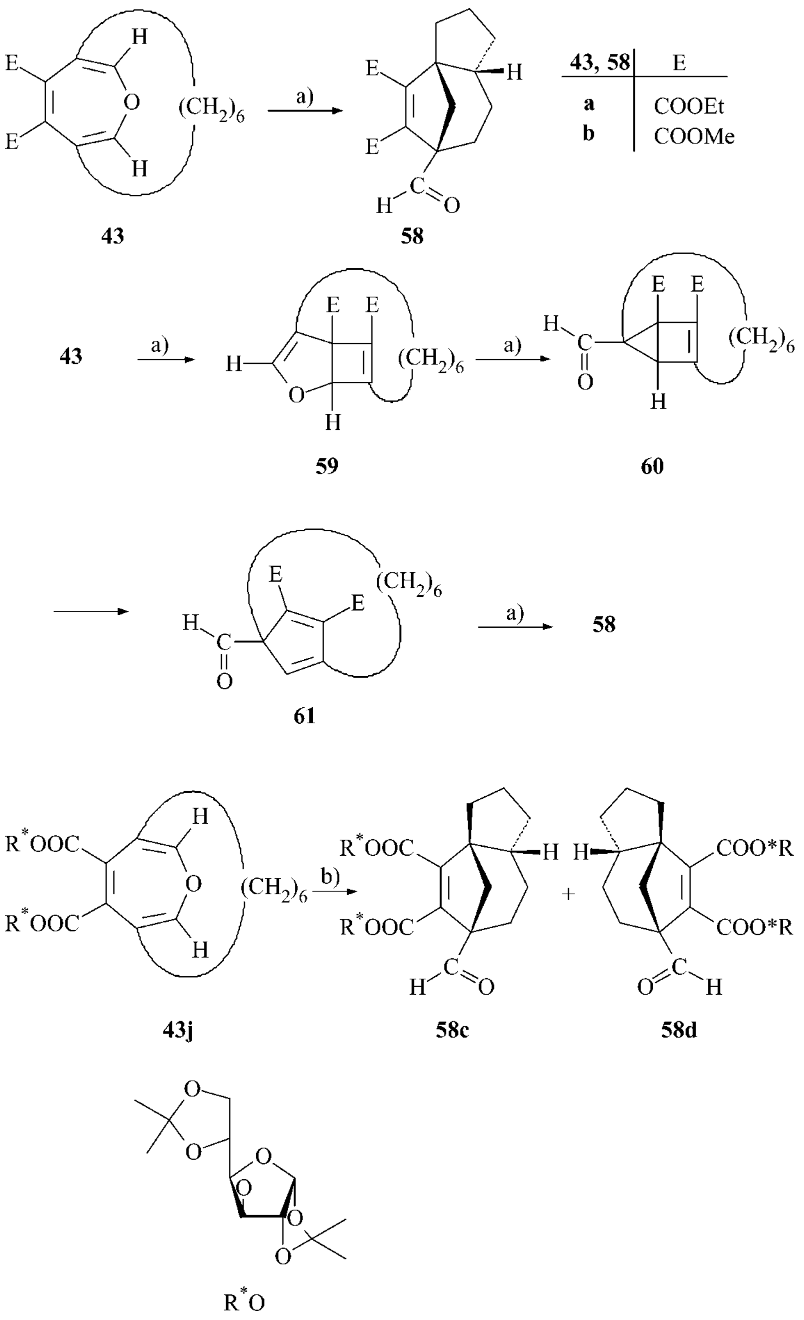
Scheme 19. Oxidation of the tetrahydrooxepine **56**. Reagents and conditions: a) Pt/C, H_2, HOAc, room temp. b) $RuCl_3{\cdot}3H_2O$, excess $NaIO_4$, CCl_4, MeCN, H_2O, 3 d room temp.

4.3. Two Approaches to Hydroazulenes via the Oxepines 42a/b and 42d

About 20 years ago we accidentally found that irradiation of **43a** or **43b** gives the methanohydroazulenes **58a** or **58b** in 50–65% yields (Scheme 20).[67] NMR spectroscopic studies revealed that the photochemical rearrangement **43** → **58** takes place via dihydrofurans **59**, cyclopropane carbaldehydes **60** and cyclopentadiene carbaldehydes **61**. Finally a transannular hydrogen shift from the hexamethylene chain to the cyclopentadiene moiety gives **58**.[68] Fortunately, irradiation of an aqueous suspension of the crystalline di-*O*-isopropylidene-α-D-glucofuranosyl ester **43j** affords the hydroazulenes **58c** and **58d** in 54% yields with 92% de in favour of **58c** on a preparative scale. Different local conformations of the two ester functions may be responsible for the high degree of this diastereoselectivity. Isomers **58c** and **58d** could be easily separated, and the absolute (3*aS*,6*R*,8*aR*) configuration of (+)-**58a** was established. The enantiomeric series with (*R*,*S*,*S*) configuration was prepared through the use of di-*O*-isopropylidene-α-L-glucofuranose as chiral auxiliary (Scheme 20).[69]

The photoproducts **58** are useful starting materials for the synthesis of other hydroazulenes,[70] *trans*-hydrindanes[71] and functionalized piperidines.[72] Some examples [*rac*-**62**, (+) –**63**, (–) –**64**] are shown in Scheme 21. The equatorial positions of the two ester groups in the piperidine ring were established by X-ray analysis of the corresponding aldehyde (**64**, R = CHO instead of $CH(OMe)_2$).[72]

Our second approach to hydroazulenes derives a benefit from the presence of the keto group in **43d**. Treatment of **43d** (COOMe instead of COOEt) with excess sodium methoxide yields the hydroazulenone **65** by transannular intramolecular cyclization.[73] To our surprise the methylenated hydroazulene **66** was formed directly in 81% yield from **43d** and triphenylphosphonium methylide (Scheme 22).[74,75] Normally the Wittig reaction is famous for the olefination



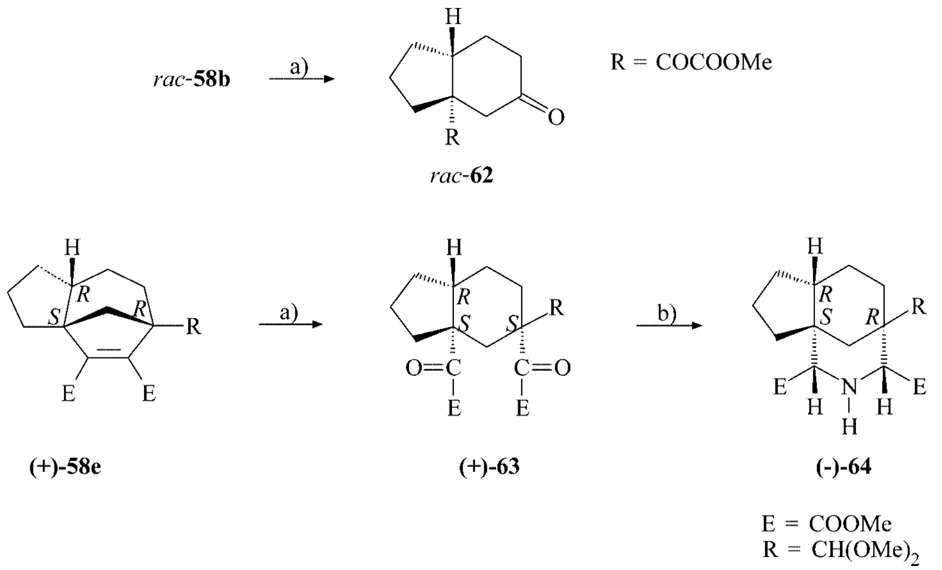
43, 58	E
a	COOEt
b	COOMe

Scheme 20. Synthesis of methanohydroazulenes **58** from **43**. Reagents and conditions: a) 1 L duran photoreactor Hanau TQ 150 or 718. 15–22 °C, 50 h, Et_2O. b) 1 L Duran photoreactor, Hanau TQ 718, room temp., aqueous suspension, 3–4 mmol in 1 L H_2O, 10 h.

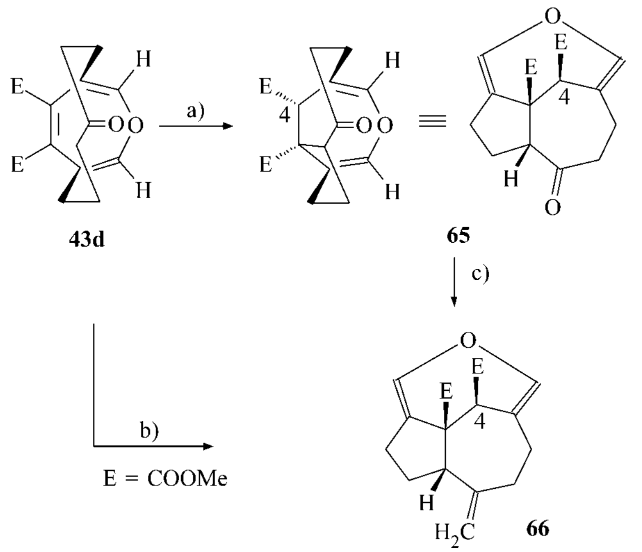
of carbonyl groups in their original position. The unexpected formation of **66** from **65** can be explained as follows: carbonyl groups in medium sized rings undergo addition reactions slowly because of the strain in the resulting intermediates or products. The ylide therefore reacts with **43d** as base to provide **65** in the first step. The carbonyl group in the seven-membered ring of **65** is now more reactive and undergoes clean methylenation in excellent yield.

Compounds **65** and **66** were converted into a large number of functionalized hydroazulenes.[76] One example, the synthesis of (±)-8a-*epi*-tremulenolide **70**, a compound with the skeleton of the tremulane sesquiterpenes,[77,78] is described in Scheme 23.[74,79] Our approach to **70** proceeds via the hydroazulenes **67**–**69**.

A preparative route to enantiomerically pure compounds is possible via the (–)-quinine salt of the monocarboxylic



Scheme 21. Synthesis of *trans*-hydrindanes and piperidines (+)-**62**, (+)-**63** and (–)-**64**. Reagents and conditions: a) $NaIO_4$, $RuCl_3{\cdot}3H_2O$, CCl_4, MeCN, H_2O, room temp. b) NH_4Br, $NaBH_3CN$, MeOH, THF, room temp., 2 days.



Scheme 22. Transannular cyclization of **43d** to bridged hydroazulenes. Reagents and conditions: a) Excess NaOMe, Et_2O. b) $(C_6H_5)_3PCH_3Br$, KO*t*Bu, Et_2O, room temp. c) $(C_6H_5)_3PCH_3Br$, KHDMS, toluene, 50 °C.

acid (**65**, COOH instead of COOMe on C-4), which is available by regioselective saponification of **65** with dilute NaOH.[74]

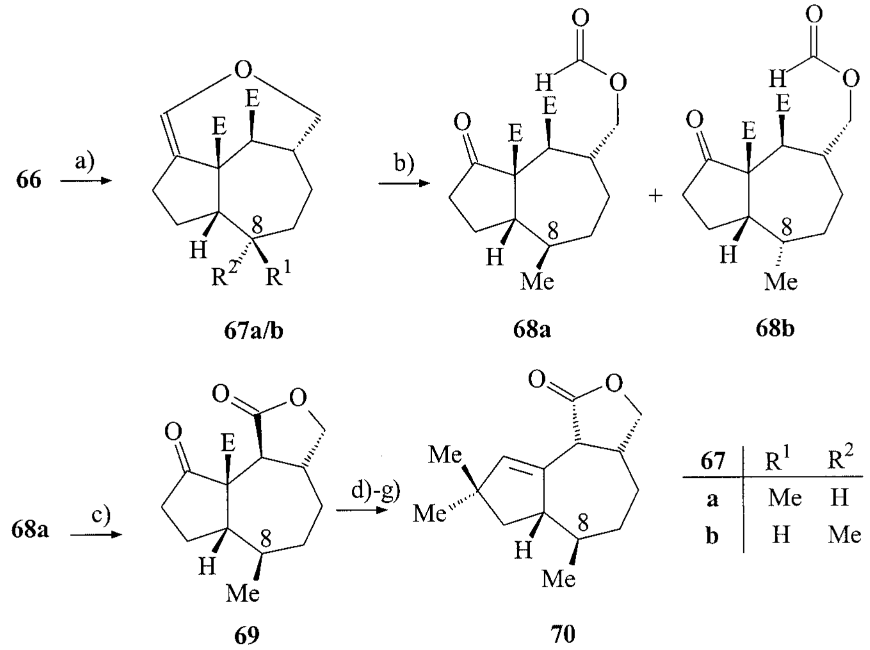
4.4. Synthesis of Bridged Deoxyfuranoside and Deoxypyranoside Derivatives

Unnatural or modified carbohydrate derivatives have attracted much attention in the past decade.[80] Our observation that the oxepine **43b** readily undergoes a photochemical electrocyclic ring-closure to give the cyclobutene intermediate **59** resulted in an approach to bridged deoxyfuranosides and pyranosides (Scheme 24). Irradiation of **71** furnished the cyclobutene **72** in excellent yield. Oxidative cleavage of the C=C double bond, basic degradation of the α-keto ester function of **73** to give **74**, esterification and stereoselective sodium borohydride reduction provided the racemic furanoside **75a**, and treatment with lithium aluminium hydride afforded **75b**. Hydrolysis with dilute acid gave the free lactols **76a** and **76b**. Compound *rac*-**75b** was resolved via diastereomeric dicamphanoates, X-ray analyses establishing the stereochemistry and absolute configurations.[81] A molecule of **76a** is depicted in Figure 3.[81d]

The ring-enlargement of our furanoside system to a pyranoside was performed by addition of dichlorocarbene to the enol ether **77**. The intermediate **78** undergoes a cyclopropyl–allyl rearrangement to form the chloropyrane **79**. Oxidation of **79** to **80** and a stereoselective reduction of the keto group furnished the target **81a**. X-ray analysis and NMR spectra of the monoacetate **81b** revealed a $_4C^1$ conformation with an axial methoxy group in the six-membered ring (see Figure 4, with an enantiomer of the molecule **81b** depicted in Scheme 25).[82] We have already prepared the enantiomerically pure enol ethers **77**.

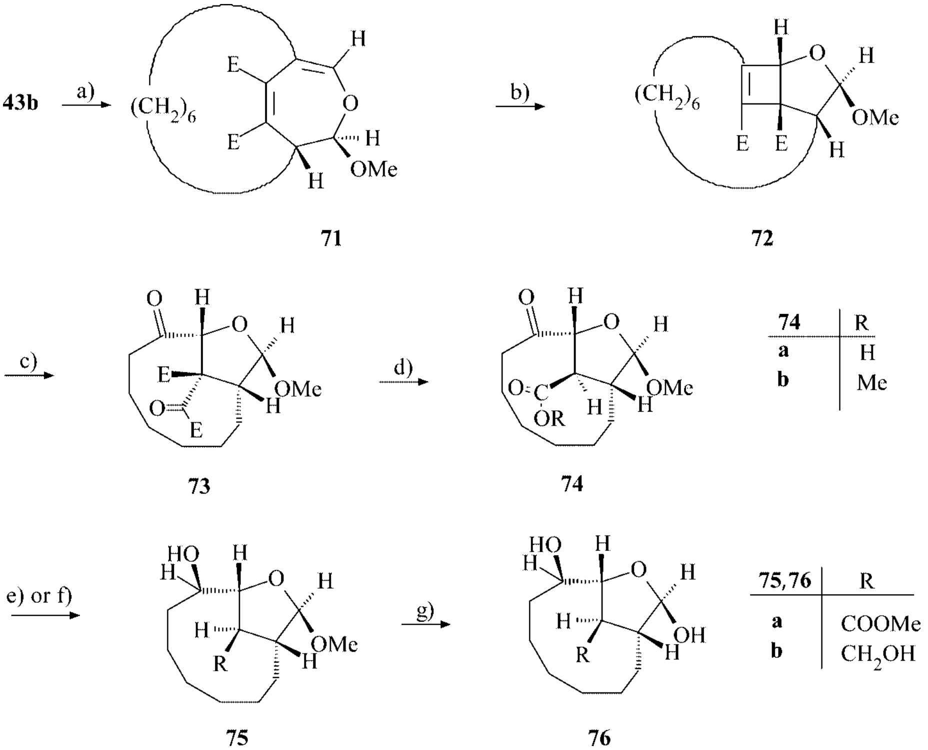
4.5. Unexpected Formation of Bridged Bicyclobutane and Cyclopropane Derivatives

With the aim of testing our approach to furanosides, we chose the carboxylic acid **43g**, for which we had reported the synthesis of the *M*-(+)- and *P*-(–)-**43g** enantiomers,[46,53] as chiral precursor. The addition of methanol to the ester



67	R^1	R^2
a	Me	H
b	H	Me

Scheme 23. Synthesis of (±)-8a-epi-tremulenolide **70**. Reagents and conditions: a) Wilkinson catalyst, H_2, C_6H_6. b) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O. c) $MeSO_3H$, CH_2Cl_2. d) Addition of **69** and MeI in THF to KHDMS in THF at –78 °C. e) NaCl, H_2O, DMSO, 150 °C. f) $NaBH_4$, EtOH. g) $POCl_3$, C_5H_5N.



74	R
a	H
b	Me

75,76	R
a	COOMe
b	CH_2OH

Scheme 24. Synthesis of bridged deoxyfuranose derivatives. Reagents and conditions: a) NaOMe, MeOH, Et_2O. b) *hv*, Hanau TQ 718, Et_2O. c) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O. d) 2 M NaOH, MeOH. CH_2N_2, Et_2O. e) $NaBH_4$, THF. f) $LiAlH_4$, THF, g) 0.1–1 M H_2SO_4, THF.

M-(+)-**43g** (COOMe instead of COOH) gave the acetal (+)-**82**, and irradiation furnished the bicyclobutane (+)-**83** (Scheme 26) in 77% yield, its structure following from its ^1H and ^{33}C NMR spectra.[83] Recent computations[84] have provided a possible explanation for the photochemical behaviour of (+)-**82**.

We next examined the photochemistry of the epoxyoxepine *rac*-**84**, formed from **43b** and *m*-chloroperoxy benzoic

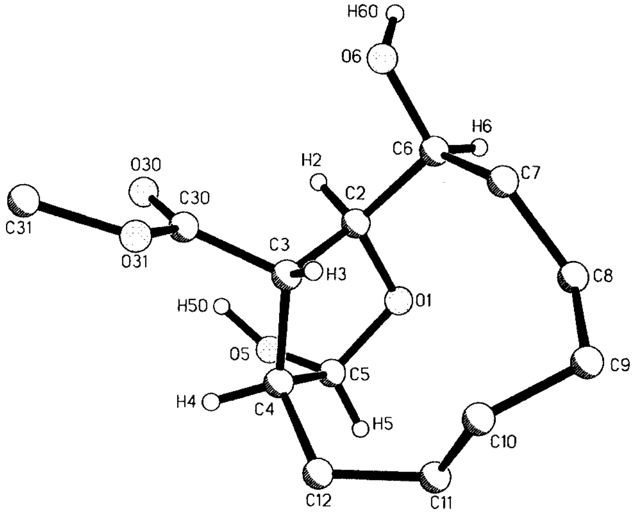


Figure 3. A molecule of *rac*-**76a** in the crystal.[81d]

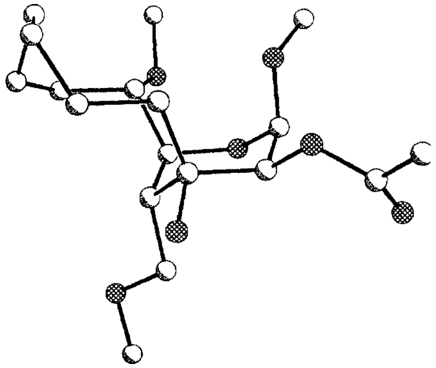
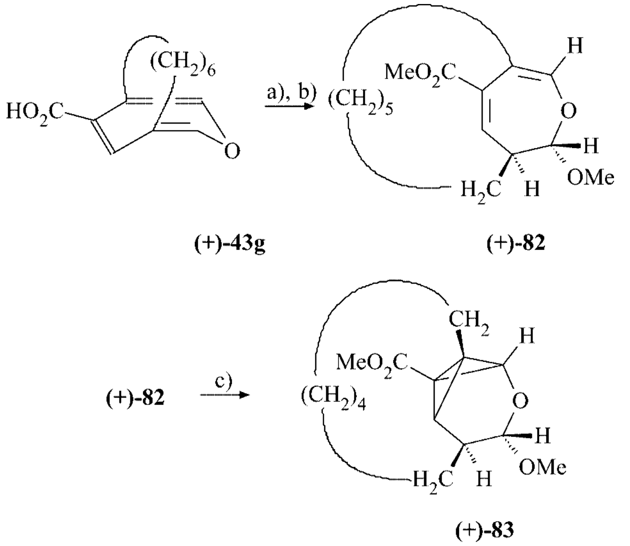
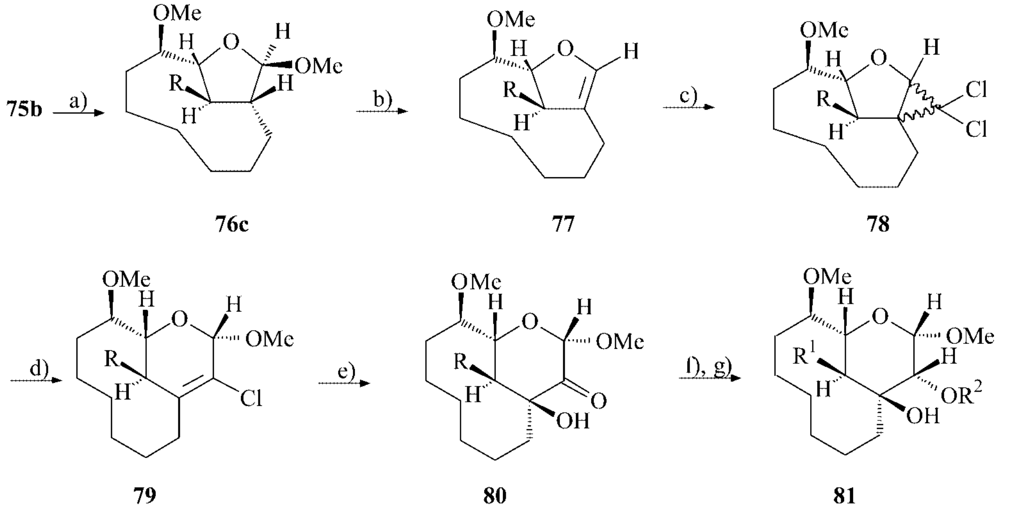


Figure 4. A molecule of *rac*-**81b** in the crystal.[82]



Scheme 26. Formation of the bicyclobutane (+)-**83**. Reagents and conditions: a) CH_2N_2, Et_2O. b) NaOMe, MeOH, MeOAc, room temp. c) *hν*, Hanau TQ 150, Et_2O.

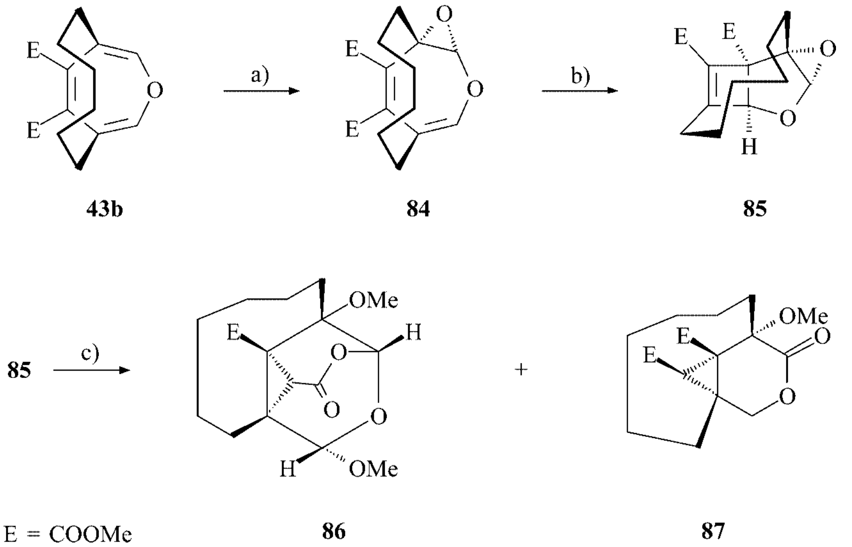
acid (MCPBA). Irradiation of **84** followed the expected course, giving the cyclobutene **85**. However, our attempts to open the oxirane ring of **85** had a surprising result. X-ray analyses of the isolated products revealed that two isomeric cyclopropanes **86** (31%) and **87** (35%) had been formed (Scheme 27).[85] In a tentative proposal for their formation we assume an attack by methoxide on the donor-accepted substituted[47] cyclobutene, accompanied by a concerted



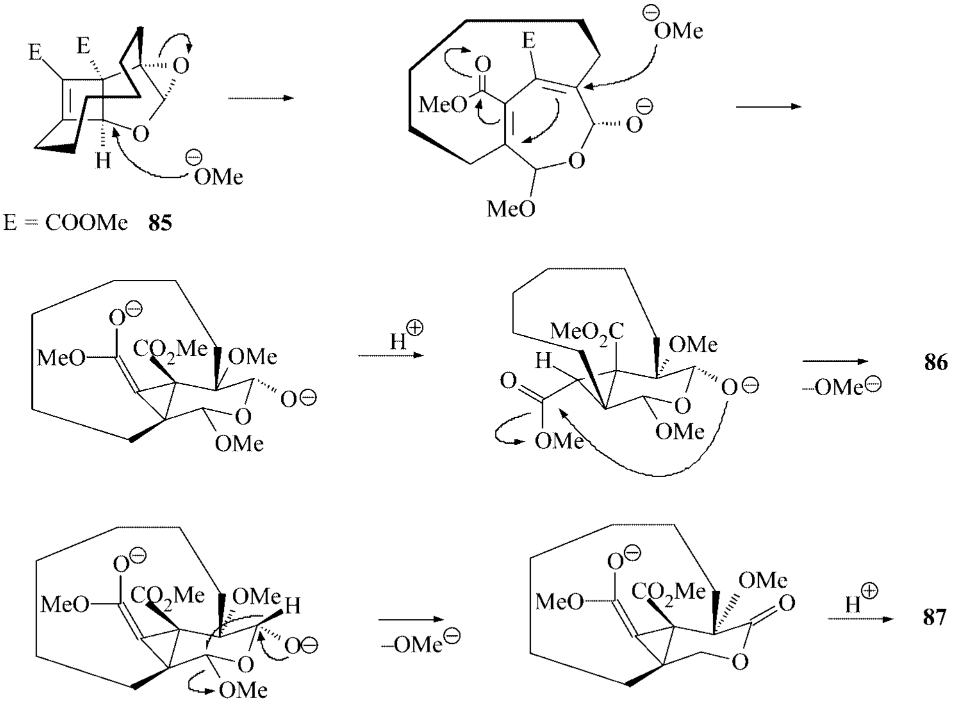
76c-80 R = CH_2OMe

81	R^1	R^2
a	CH_2OMe	H
b	CH_2OMe	Ac

Scheme 25. Synthesis of bridged pyranoside derivatives. Reagents and conditions: a) NaH, MeI, THF, room temp. b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temp. c) $CHCl_3$, TBABr, 50% aq. KOH, 0 °C. d) K_2CO_3, MeOH reflux. e) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, room temp. f) LTBAH, THF, 0 °C to room temp. g) Ac_2O, C_5H_5N, room temp.



Scheme 27. Formation of the bridged cyclopropanes **86** and **87**. Reagents and conditions: a) MCPBA, CH_2Cl_2. b) *hν*, Hanau TQ 150, Et_2O. c) NaOMe, MeOH, reflux, 1 h.

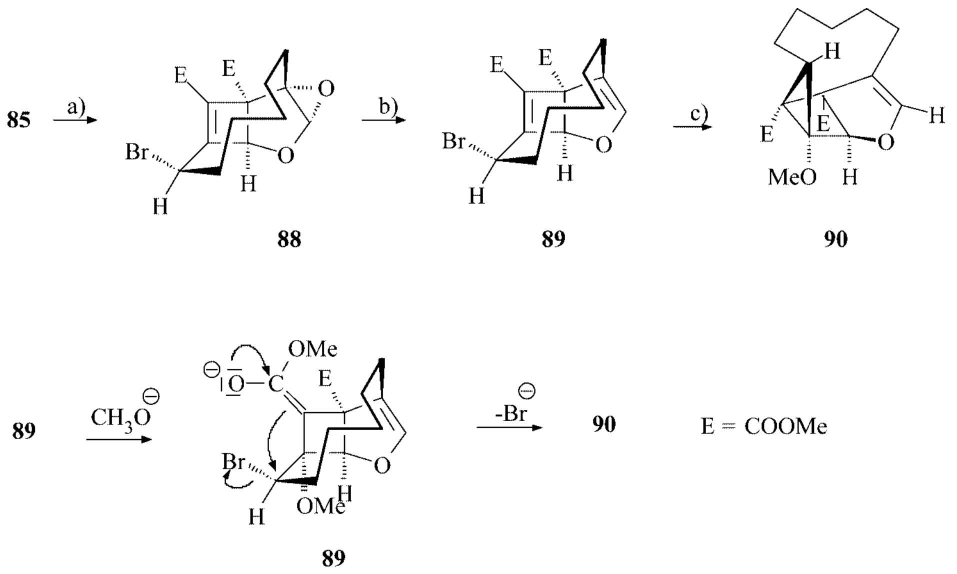


Scheme 28. Tentative mechanism for the formation of **86** and **87**.

ring-opening of the oxirane ring (see Scheme 28) as first step.

The functionality of **86** and **87** allows the synthesis of various new bridged cyclopropanes.[85] Moreover, all products could be prepared in enantiomerically pure form through the highly diastereoselective epoxidation of the diisopropylidene-D-glucose ester **43j**,[86] which furnished the (*S*,*S*)-oxirane **84** after transesterification with sodium methoxide.[85]

The formation of three-membered rings seems to be favoured in our bridged systems. Thus, experiments to convert the bromo derivative **89** (obtained by deoxygenation of **88**) into a methyl ether by nucleophilic substitution with methoxide resulted in the formation of the bicyclo[2.1.0]pen-



Scheme 29. Synthesis of the bicyclo[2.1.0]pentane **90**. Reagents and conditions: a) NBS, dibenzoyl peroxide, CCl_4, reflux. b) WCl_6, THF, *n*BuLi, –78 °C. c) NaOMe, MeOH, KI, room temp.

tane **90** with an *in* configuration of the cyclopropyl hydrogen (Scheme 29).[87]

5. Conclusion

This microreview has the aim of outlining how the primary cycloadducts of the title compounds, obtained via 1,3-dipolar cycloaddition or Diels–Alder reaction, can be converted into a variety of different classes of compounds (Figure 5). Functional groups can easily be introduced into the precursors. Many preparative transformations proceed via bridged oxepines **43**. The use of the readily available and highly reactive cycloalkynes **1** and **2** as starting materials for organic syntheses is a valuable opportunity that will also be pursued in the future. This is confirmed by a very recent experimental and theoretical study by Herges et al.[88] on the *cis*-bromination of alkynes, in which cyclooctyne (**1**) was used as one of the substrates.

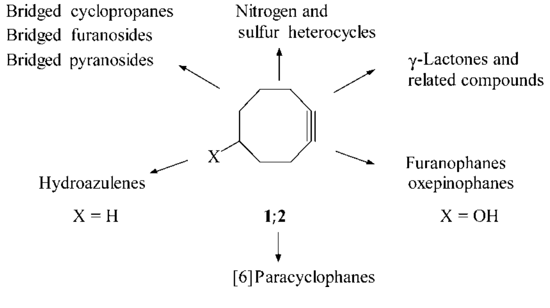


Figure 5. Survey of classes of compounds synthesized from **1** and **2**.

Acknowledgments

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[1] Previous reviews: a) R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Verlag Chemie, Weinheim, **1967**; b) A. Krebs, “Cyclic Acetylenes”, in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Marcel Dekker, New York, **1969**, pp. 987–1062; c) H. Meier, *Synthesis* **1972**, 235–253; d) M. Nakagawa, “Cyclic Acetylenes”, in *The Chemistry of the Carbon–Carbon Triple Bond* (Ed.: S. Patai), Wiley, New York, **1978**, 635–712; e) A. Krebs, J. Wilke, *Top. Curr. Chem.* **1984**, *109*, 189–233; f) H. Meier, “Cyclic Alkynes, Enynes and Dienynes”, in *Advances in Strain in Organic Chemistry*, JAI Press, **1991**, *1*, 215–272; g) R. Gleiter, *Angew. Chem.* **1992**, *104*, 29–46; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 27–44; h) R. Gleiter, R. Merger, “Cyclic Alkynes: Preparation and Properties”, in *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1995**, pp. 284–319; i) W. M. Jones, J. Klosin, *Adv. Organomet. Chem.* **1998**, *42*, 147–221.
[2] L. Brandsma, H. D. Verkruijsse, *Synthesis* **1978**, 290.
[3] G. Wittig, G. H.-L. Dorsch, J. Meske-Schüller, *Justus Liebigs Ann. Chem.* **1968**, *711*, 55–64.
[4] a) L. Brandsma, H. D. Verkruijsse, *Synthesis of Acetylenes, Allenes and Cumulenes*, Elsevier, Amsterdam, **1981**, pp. 119–120; b) L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd ed., p. 39 ff., Thieme, Stuttgart, New York, **1991**.
[5] H. Detert, H. Meier, *Liebigs Ann. Recueil* **1997**, 1565–1570.
[6] a) J. Haase, A. Krebs, *Z. Naturforsch. A.* **1971**, *26*, 1190–1193; b) M. Traetteberg, W. Lüttke, R. Machinek, A. Krebs, H. J. Hohlt, *J. Mol. Struct.* **1985**, *128*, 217–232.
[7] H. Meier, H. Petersen, H. Kolshorn, *Chem. Ber.* **1980**, *113*, 2398–2409 and earlier references therein.
[8] a) H. Meier, H. Petersen, *Synthesis* **1978**, 596–598; b) H. Petersen, H. Meier, *Chem. Ber.* **1978**, *111*, 3423–3428; c) M. Hanack, W. Spang, *Chem. Ber.* **1980**, *113*, 2015–2024.

[9] J. L. Jessen, C. Wolff, W. Tochtermann, *Chem. Ber.* **1986**, *119*, 297–312.

[10] Our search for papers describing work with the title compounds produced about 200 references.

[11] a) P. Riebel, A. Weber, T. Troll, J. Sauer, J. Breu, *Tetrahedron Lett.* **1996**, *37*, 1583–1586; b) K. Elender, H. Nöth, P. Riebel, A. Weber, J. Sauer, *Tetrahedron* **2000**, *56*, 5443–5463; c) K. Elender, P. Riebel, A. Weber, J. Sauer, *Tetrahedron* **2000**, *56*, 4261–4265; d) P. Pérez, L. R. Domingo, M. José Aurell, R. Contreras, *Tetrahedron* **2003**, *59*, 3117–3125. Many reviews on the 1,3-dipolar cycloaddition are quoted in these articles.

[12] a) R. Huisgen, J. Rapp, *J. Am. Chem. Soc.* **1987**, *109*, 902–903; b) R. Huisgen, J. Rapp, *Tetrahedron* **1997**, *53*, 939–960; J. Rapp, R. Huisgen, *Tetrahedron* **1997**, *53*, 961–970.

[13] W. Adam, B. Fröhling, S. Weinkötz, *J. Org. Chem.* **1998**, *63*, 9154–9155.

[14] W. Adam, S. G. Bosio, B. Fröhling, D. Leusser, D. Stalke, *J. Am. Chem. Soc.* **2002**, *124*, 8316–8320.

[15] D. Doepp, M. Hof, *ARKIVOC* **2001**, *2*, 1124–1127.

[16] For reactions of **1** with thiocarbonyl ylides, see T. Gendek, G. Moston, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 451–463 and earlier references therein.

[17] K. Banert, *Chem. Ber.* **1989**, *122*, 123–128.

[18] a) K. Banert, M. Hagedorn, C. Liedtke, A. Melzer, C. Schöffler, *Eur. J. Org. Chem.* **2000**, 257–267; b) K. Banert, F. Köhler, *Angew. Chem. Int. Ed.* **2001**, *40*, 174–177.

[19] W. L. Stepp, US. Pat. 3.217.017, **1965**, *Chem. Abstr.* **1966**, *64*, 1896f.

[20] B. Müller, Dissertation, TU Chemnitz **2002**; K. Banert, private communication.

[21] T. Molz, P. König, R. Goes, G. Gauglitz, H. Meier, *Chem. Ber.* **1984**, *117*, 833–839.

[22] R. Brecht, F. Haenel, G. Seitz, G. Frenzen, A. Pilz, D. Guenard, *Eur. J. Org. Chem.* **1998**, 2451–2560.

[23] C. Peters, S. Stutzmann, H. Disteldorf, S. Werner, U. Bergsträßer, C. Krüger, P. Binger, M. Regitz, *Synthesis* **2000**, 529–536.

[24] J. Laue, G. Seitz, *Liebigs Ann.* **1996**, 773–775.

[25] a) N. Biedermann, J. Sauer, *Tetrahedron Lett.* **1994**, *35*, 7935–7938; b) J. Sauer, D. K. Heldmann, J. Hetzenegger, J. Krauthan, H. Sichert, J. Schuster, *Eur. J. Org. Chem.* **1998**, 2885–2896.

[26] K. Matsumoto, M. Ciobanu, M. Yoshida, T. Uchida, *Heterocycles* **1997**, *45*, 15–18.

[27] Previous Reviews: a) W. Tochtermann, *Chimia* **1972**, *26*, 565–572; b) W. Tochtermann, G. Olsson, *Chem. Rev.* **1989**, *89*, 1203–1214; c) S. von Angerer, W. Tochtermann, in: *Methoden Org. Chem.* (Ed.: E. Schaumann), Houben-Weyl, vol. E 9d, pp. 1–64.

[28] W. Tochtermann, P. Rösner, *Tetrahedron Lett.* **1980**, *21*, 4905–4908.

[29] U. Vagt, M. Haase, J. Konusch, W. Tochtermann, *Chem. Ber.* **1987**, *120*, 769–774.

[30] W. Tochtermann, R. Dibbern, M. Haase, T. Bruhn, C. Wolff, *Chem. Ber.* **1991**, *124*, 923–931.

[31] W. Tochtermann, F. Weidner, *Liebigs Ann. Chem.* **1994**, 593–600.

[32] G. Scholz, J. Konusch, W. Tochtermann, *Liebigs Ann. Chem.* **1990**, 593–597.

[33] G. Scholz, W. Tochtermann, *Tetrahedron Lett.* **1991**, *32*, 5535–5538.

[34] M. J. Rieser, J. F. Kozlowski, K. V. Wood, J. L. McLaughlin, *Tetrahedron Lett.* **1991**, *32*, 1137–1140.

[35] Muricatacin was also an attractive target for other groups, who have synthesized **30** by different approaches. Some examples: a) B. Figadère, J.-C. Harmange, A. Laurens, A. Cavé, *Tetrahedron Lett.* **1991**, *32*, 7539–7542; b) A. Marshall, G. S. Welmaker, *Synlett* **1992**, 537–538; c) Z. M. Wang, X.-L. Zhang, K. B. Sharpless, S. C. Sinha, A. Sinha-Baghi, E. Keinan, *Tetrahedron Lett.* **1992**, *33*, 6107–6110; d) M. Saiah, M. Bessodes, K. Antonakis, *Tetrahedron Lett.* **1993**, *34*, 1597–1598; e) C. Bonini, C. Frederici, L. Rossi, G. Righi, *J. Org. Chem.* **1995**, *60*, 4803–4812; f) M. P. M. van Aar, L. Thijs, B. Zwanenburg, *Tetrahedron* **1995**, *51*, 11223–11234 and further references therein; g) S. Raghavan, S. C. Joseph, *Tetrahedron: Asymmetry* **2003**, *14*, 101–105 and further references therein. Review on acetogenins: h) A. Cavé, B. Figadère, A. Laurens, D. Cortes, in *Progress in the Chemistry of Organic Natural Products* (Eds.: W. Herz), Springer, New York, **1997**, *70*, 81–288.

[36] W. Tochtermann, G. Scholz, G. Bunte, C. Wolff, E.-M. Peters, K. Peters, H. G. von Schnering, *Liebigs Ann. Chem.* **1992**, 1069–1080.

[37] M. Meints, C. Wolff, W. Tochtermann, *Liebigs Ann. Chem.* **1993**, 527–530.

[38] P. Kraft, W. Tochtermann, *Liebigs Ann. Chem.* **1994**, 827–830.

[39] W. Tochtermann, P. Kraft, *Synlett* **1996**, 1029–1035.

[40] D. Felix, J. Schreiber, G. Ohloff, A. Eschenmoser, *Helv. Chim. Acta* **1971**, *54*, 2896–2912.

[41] T. Ishiyama, N. Matsuda, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc.* **1993**, *115*, 11018–11019.

[42] L. W. Jenneskens, G. B. M. Kostermans, H. J. ten Brink, W. H. de Wolf, F. Bickelhaupt, *J. Chem. Soc., Perkin Trans. 1* **1985**, 2119–2122.

[43] a) H. Prinzbach, M. Arguelles, E. Druckrey, *Angew. Chem.* **1966**, *78*, 1057; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 1039; b) H. Prinzbach, *Pure Appl. Chem.* **1968**, *16*, 17–46; c) H. Prinzbach, H. Bingmann, J. Markert, G. Fischer, L. Knothe, W. Eberbach, J. Brokatzky-Geiger, *Chem. Ber.* **1986**, *119*, 589–615.

[44] W. Tochtermann, P. Rösner, *Chem. Ber.* **1981**, *114*, 3725–3736.

[45] K. Matsumoto, H. Taketsuna, Y. Ikemi, A. Kakehi, T. Uchida, S. Otani, *Heterocycles* **1998**, *49*, 79–83.

[46] W. Tochtermann, U. Vagt, G. Snatzke, *Chem. Ber.* **1985**, *118*, 1996–2010.

[47] H.-U. Reissig, *Top. Curr. Chem.* **1988**, *144*, 73–135.

[48] W. Tochtermann, C. Vogt, E.-M. Peters, K. Peters, H. G. von Schnering, E.-U. Würthwein, *Chem. Ber.* **1991**, *124*, 2577–2582.

[49] P. Rösner, C. Wolff, W. Tochtermann, *Chem. Ber.* **1982**, *115*, 1162–1169.

[50] Selected recent reviews: a) F. Vögtle, Cyclophane Chemistry, *Synthesis Structures and Reactions*, Wiley, New York **1993**, pp. 32–48; b) V. V. Kane, W. H. De Wolf, F. Bickelhaupt, *Tetrahedron* **1994**, *50*, 4575–4622; c) Y. Tobe, *Top. Curr. Chem.* **1994**, 1–40; d) H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim **2000**, pp. 321–378, and references therein.

[51] a) J. Liebe, C. Wolff, W. Tochtermann, *Tetrahedron Lett.* **1982**, *23*, 171–172; b) J. Liebe, C. Wolff, C. Krieger, J. Weiss, W. Tochtermann, *Chem. Ber.* **1985**, *118*, 4144–4178; c) W. Tochtermann, L. Rodefeld, H. Dreeskamp, S. M. Sarge, *Liebigs Ann.* **1996**, 1959–1962.

[52] The racemic ester **47a** was also prepared in a different way by Y. Tobe, K. Kakiuchi, Y. Odaira, T. Hosaki, Y. Kai, N. Kasai, *J. Am. Chem. Soc.* **1983**, *105*, 1376–1377.

[53] a) G. Beitz, U. Vagt, W. Tochtermann, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1985**, *26*, 721–724; b) W. Tochtermann, G. Olsson, C. Vogt, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1987**, *120*, 1523–1532.

[54] X-ray structural analysis: see ref. 51b and C. Krieger, J. Liebe, W. Tochtermann, *Tetrahedron Lett.* **1983**, *24*, 707–710. Compound **45b** has a boat conformation with angles $\alpha = 19.5°$ and $\beta = 19.9°$ of deformation.

[55] NMR spectra: a) C. Wolff, J. Liebe, W. Tochtermann, *Tetrahedron Lett.* **1982**, *23*, 1143–1146; b) H. Günther, P. Schmitt, H. Fischer, W. Tochtermann, J. Liebe, C. Wolff, *Helv. Chim. Acta* **1985**, *68*, 801–812.

[56] CD spectra: see ref. 46 and W. Tochtermann, G. Olsson, A. Mannschreck, G. Stühler, G. Snatzke, *Chem. Ber.* **1990**, *123*, 1437–1439.

[57] Additions and Cycloadditions; see ref. 51b and a) J. Liebe, C. Wolff, W. Tochtermann, *Tetrahedron Lett.* **1982**, *23*, 2439–2442; b) J. Liebe, W. Tochtermann, J. Weiss, *Tetrahedron Lett.* **1983**, *24*, 2549–2552; c) V. Königstein, W. Tochtermann, *Tetrahedron Lett.* **1986**, *27*, 2961–2964; d) V. Königstein, W. Tochtermann, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1987**, *28*, 3483–3486.

[58] Valence isomerization and calorimetry: see ref. 51c and a) H. Dreeskamp, P. Kapahnke, W. Tochtermann, *Radiat. Phys. Chem.* **1988**, *32*, 537–539; b) F. Bokisch, H. Dreeskamp, T. von Haugwitz, W. Tochtermann, *Chem. Ber.* **1991**, *124*, 1831–1835; c) H. Dreeskamp, S. M. Sarge, W. Tochtermann, *Tetrahedron* **1995**, *51*, 3137–3140.

[59] H. Hopf, M. Haase, J. Hunger, W. Tochtermann, M. Zander, *Chem. Phys. Lett.* **1986**, *127*, 145–148.

[60] J. L. Jessen, G. Schröder, W. Tochtermann, *Chem. Ber.* **1985**, *118*, 3287–3298.

[61] R. Gleiter, B. Treptow, *Angew. Chem.* **1990**, *102*, 1452–1454; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1427–1429; R. Gleiter, B. Treptow, *J. Org. Chem.* **1993**, *58*, 7740–7750.

[62] W. Tochtermann, K. Luttmann, C. Wolff, K. Peters, E.-M. Peters, H. G. von Schnering**,** *Chem. Ber.* **1989**, *122*, 1653–1660.

[63] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.

[64] W. Tochtermann, M. Haase, R. Dibbern, *Tetrahedron Lett.* **1988**, *29*, 189–190.

[65] a) W. Tochtermann, K. Luttmann, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1987**, *28*, 2521–2524; b) W. Tochtermann, K. Luttmann, N. Sdunnus, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1992**, *125*, 1485–1494.

[66] B. Seyberlich, diploma thesis, University of Bonn, **1995**; E.-M. Peters, K. Peters, B. Seyberlich, W. Tochtermann, *Z. Kristallogr. NCS* **2001**, *216*, 218–220.

[67] A. Sczostak, F. Sönnichsen, W. Tochtermann, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1985**, *26*, 5677–5680.

[68] W. Tochtermann, G. Olsson, A. Sczostak, F. Sönnichsen, H. Frauenrath, J. Runsink, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1989**, *122*, 199–207.

[69] a) W. Tochtermann, U. Schlösser, B. Popp, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1989**, *30*, 6855–6858; b) W. Tochtermann, U. Schlösser, F. Ott, B. Popp, N. Sdunnus, G. Snatzke, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1993**, *126*, 1733–1742.

[70] B. Popp, F. Sönnichsen, W. Tochtermann, *Tetrahedron: Asymmetry* **1993**, *4*, 281–284.

[71] W. Tochtermann, F. Sönnichsen, C. Wolff, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1989**, *122*, 1969–1975.

[72] W. Tochtermann, U. Peters, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1991**, *32*, 483–486.

[73] W. Tochtermann, T. Habeck, C. Wolff, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1993**, *126*, 2691–2696.

[74] W. Tochtermann, T. Panitzsch, M. Petroll, T. Habeck, A. Schlenger, C. Wolff, E.-M. Peters, K. Peters, H. G. von Schnering, *Eur. J. Org. Chem.* **1998**, 2651–2657.

[75] K. Peters, E.-M. Peters, A. Schlenger, W. Tochtermann, *Z. Kristallogr. NCS* **1998**, *213*, 89–90.

[76] T. Panitzsch, *Synthese von Tremulanen und Merulanen*, Ph. D. thesis, Univ. Kiel, Germany **1997**.

[77] For the isolation and structural elucidation of tremulanes see: W. A. Ayer, E. R. Cruz, *J. Org. Chem.* **1993**, *58*, 7529–7534.

[78] For other approaches to tremulane derivatives and related hydroazulenes see a) H. M. L. Davies, B. D. Doan, *Tetrahedron Lett.* **1996**, *37*, 3967–3970; b) H. M. L. Davies, B. D. Doan, *J. Org. Chem.* **1998**, *63*, 657–660; c) H. M. L. Davies, D. D. Stafford, J. H. Doan Houser, *J. Am. Chem. Soc.* **1998**, *120*, 3326–3331.

[79] a) T. Habeck, C. Wolff, W. Tochtermann, *Tetrahedron Lett.* **1995**, *36*, 2041–2044; b) W. Tochtermann, T. Panitzsch, T. Habeck, C. Wolff, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron* **1999**, *55*, 1027–1042.

[80] *Carbohydrate Mimics* (Ed.: Y. Chapleur), Wiley-VCH, Weinheim, **1998**.

[81] a) B. Popp, N. Sdunnus, F. Sönnichsen, W. Tochtermann, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron Lett.* **1992**, *33*, 8023–8026; b) W. Tochtermann, B. Popp, A.-K. Mattauch, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1993**, *126*, 2547–2551; c) W. Tochtermann, A.-K. Mattauch, M. Kasch, E.-M. Peters, K. Peters, H. G. von Schnering, *Liebigs Ann.* **1996**, 317–322; d) W. Tochtermann, A.-K. Mattauch, E.-M. Peters, K. Peters, H. G. von Schnering, *Eur. J. Org. Chem.* **1998**, 683–688.

[82] V. Kirsch, C. Wolff, C. Näther, W. Tochtermann, *Eur. J. Org. Chem.* **2000**, 1741–1744.

[83] W. Tochtermann, T. Panitzsch, M. Peschanel, C. Wolff, E.-M. Peters, K. Peters, H. G. von Schnering, *Liebigs Ann. Recueil* **1997**, 1125–1129.

[84] M. Olivucci, F. Bernardi, S. Ottani, M. A. Robb, *J. Am. Chem. Soc.* **1994**, *116*, 2034–2048.

[85] R. Glaser, M. Neumann, F. Ott, E.-M. Peters, K. Peters, H. G. von Schnering, W. Tochtermann, *Tetrahedron* **2001**, *57*, 3927–3937.

[86] W. Tochtermann, B. Popp, F. Ott, E.-M. Peters, K. Peters, H. G. von Schnering, *Tetrahedron* **1993**, *49*, 4581–4588.

[87] W. Tochtermann, N. Sdunnus, C. Wolff, M. Reggelin, *Chem. Ber.* **1994**, *127*, 1263–1267.

[88] R. Herges, A. Papafilippopoulos, K. Hess, C. Chiappe, D. Lenoir, H. Detert, *Angew. Chem.* **2005**, *117*, 1437–1441; *Angew. Chem. Int. Ed.* **2005**, *44*, 1412–1416.

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