Russian Chemical Reviews **74** (7) 639 – 669 (2005) © 2005 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2005v074n07ABEH001180

Thermal and catalytic intramolecular [4 + 2]-cycloaddition in 2-alkenylfurans

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Abstract. The published data on the intramolecular Diels – Alder reaction in compounds of the 2-alkenylfuran series are generalised. The methods and conditions for the preparation of tricyclic systems are considered. The effects of the substituents in the furan and the unsaturated fragments on the cycloaddition are discussed. The application of this reaction to the synthesis of alkaloids and terpenoids is exemplified. The bibliography includes 168 references.

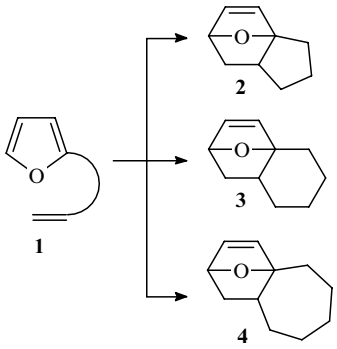
I. Introduction

In 1928, O Diels and K Alder [1] discovered the [4 + 2]-cycloaddition reaction, one of the most interesting and important, from a practical standpoint, transformations in classical organic chemistry. A quarter of a century later, Alder reported [2] on accomplishing, for the first time, an intramolecular version of this reaction. The same year, Dunlop published an 800-page treatise on the chemistry of furan.[3] This monograph provided numerous examples of intermolecular condensations where the furan ring acted as a diene. However, it was not until 1961 that the first reports on the successful involvement of furan derivatives in the intramolecular Diels – Alder reaction appeared.[4]

Subsequent years were marked by an increasing number of publications devoted to the intramolecular [4 + 2]-cycloaddition of furan derivatives containing unsaturated fragments. Here we shall list only the most important of them. The comprehensive reviews by Dean [5, 6] generalise the data on the synthesis and reactivities of furan systems published between 1968 and 1979. A special chapter in the review by Kappe *et al.*[7] summarises the data on intramolecular cycloaddition of various unsaturated fragments (alkene, alkyne, allene) to the furan ring. The reviews [8, 9] are devoted to the use of five-membered rings (including furan) in organic synthesis and in the synthesis of natural compounds. Some features of the [4 + 2]-cycloaddition are considered by Dell.[10, 11] The published data on the intramolecular Diels – Alder reaction are generalised in the reviews,[12 – 15] much attention is paid to the cyclisation of alkenylfurans.The review published in 1986 (in Japanese) [16] is an overview of the published data on intramolecular cyclisation of furan derivatives only. The stereochemical aspects of intramolecular [4 + 2]-cycloaddition are highlighted in the review by Craig.[17] And, finally, we mention the recently published papers,[18, 19] one of which is devoted to the synthesis and reactivities of 7-oxabicyclo[2.2.1]hept-2-enes (including annelated heptenes), while the other deals with the transannular Diels – Alder reaction, and a brief survey [20] of studies by Padwa *et al.* on the cyclisation of *N*-alkenyl-2-aminofurans.

The aim of this review is to generalise the experimental results of the intramolecular cycloaddition in compounds of the alkenylfuran series. The thermal and catalytic cycloaddition reactions in 2-alkenylfurans **1** will be considered where the furan ring plays the role of a diene (Scheme 1).

Scheme 1



This conversion results in the tricyclic compounds **2** – **4** containing a five-, a six- or a seven-membered ring, respectively, annelated to the 7-oxabicyclo[2.2.1]hept-2-ene fragment. The annelated ring may contain heteroatoms (as a rule, oxygen, sulfur or nitrogen).

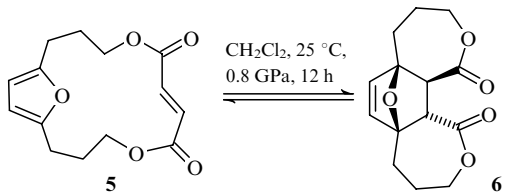
It is noteworthy that all the attempts to use this method for the preparation of this type of derivative with a four-membered third ring were unsuccessful, while the synthesis of furan derivatives with a more than seven-membered annelated ring has not been documented so far. This review encompasses the data, most of which were published mainly between 1988 and 2003.

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Received 22 November 2004
Uspekhi Khimii **74** (7) 707 – 738 (2005); translated by R L Birnova

II. The transannular Diels – Alder reactions in alkenylfurans

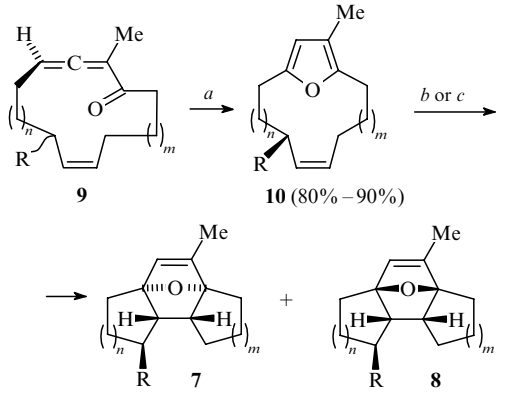
It was not until 1996 that a new report on the transannular cycloaddition in the furan series came out following the pioneering works dating back to the 1960's.[21] Using ^{1}H NMR spectroscopy, it was demonstrated that the macrocyclic ester **5** containing a furan fragment and the transannular cycloadduct **6** are in equilibrium at elevated pressure. Presumably, the formation of compound **6**, which is unstable at atmospheric pressure and contains two seven-membered lactone rings fused to the oxabicycloheptene ring, is unfavourable.



5 **6**

The tetracycles **7** contained two five- and/or six-membered annelated rings (in one case together with a diastereomer **8**).[22] The macrocyclic allenic ketones **9** were used as the starting compounds, they underwent cyclocondensation into the corresponding furans **10** catalysed by silver salts in the presence of $CaCO_3$ in aqueous acetone (Scheme 2).

Scheme 2



9 **10** (80% – 90%) **7** **8**

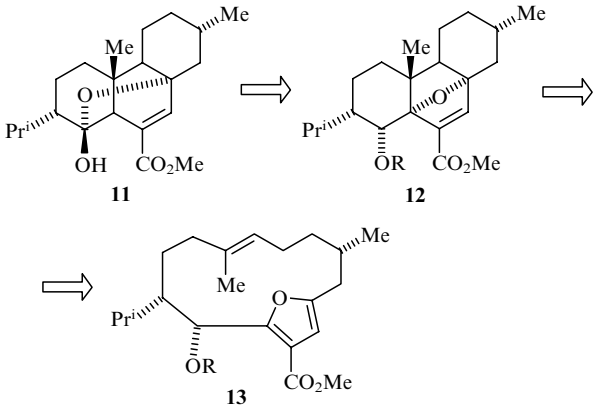
(*a*) $AgNO_3$, $CaCO_3$, Me_2CO, H_2O; (*b*) $CHCl_3$, 25 °C, 52 h; (*c*) PhMe, 80 °C, 3 h; MOM is methoxymethyl.

R	*n*	*m*	Conditions of cycloaddition	Yield (%)	
				10	**7**
H	1	1	*b*	80 – 90	100
MOMO	1	1	*b*	80 – 90	100
MOMO	2	1	*c*	95	93 [a]
MOMO	2	2	*c*	95	96

[a] Compound **8** was also obtained in 5% yield.

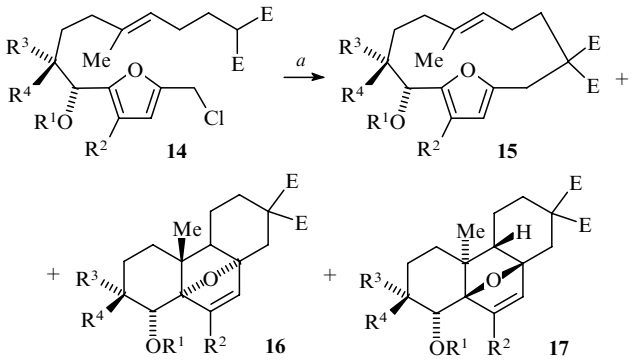
Like the original allenes **9**, the furans **10** contained a *cis*-CH = CH bond. At room temperature or upon brief heating, these compounds cyclise into the tetracyclic derivatives **7**. It is of note that the mixture of the diastereomers **7** and **8** (95 : 5) is formed only from the furan with $n = 1$, $m = 2$; in all other cases, this reaction occurs stereoselectively and yields only one diastereomer. The isomers of the macrocycles **10** having a *trans*-configuration of the endocyclic double bond do not undergo the Diels – Alder condensation.[22]

Toró *et al*. suggested [23, 24] that the transannular Diels – Alder reaction was used in the synthesis of the diterpene (+)-chatancin **11** isolated from the corals *Sarcophyton sp*. The reaction sequence relied on the retrosynthetic analysis of the natural diterpene and included the intramolecular transetherification of compound **12**, which is the intermediate cyclisation product of the alkenylfuran **13**.



11 **12** **13**

A large series of model furans **14** containing alkenyl substituents have been synthesised.



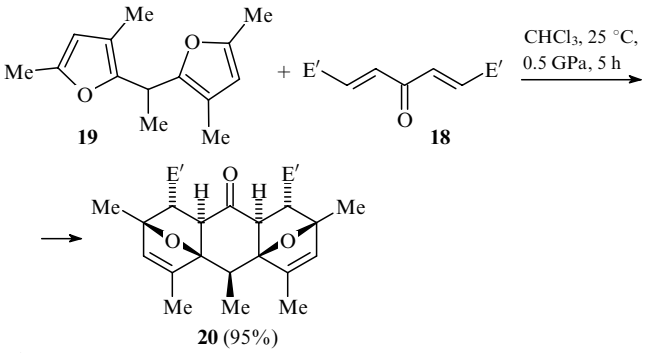
14 **15** **16** **17**

(*a*) Cs_2CO_3 (10 equiv.), MeCN, Δ;
R^1 = H, Bn, Bz; R^2 = H, E; R^3 = Pr^i, R^4 = H;
$R^3 – R^4$ = $S(CH_2)_3S$; E = CO_2Me.

The intramolecular nucleophilic substitution of chlorine in the substituted furans **14** gives the macrocycles **15** (yields 15% – 46%). Depending on the nature of the substituents in the alkenyl fragment [*e.g*., for R^1 = Bn, R^2 = H, $R^3 – R^4$ = $S(CH_2)_2S$] and the reaction conditions (*e.g*., under high dilution, 2 mmol litre^{-1}), the latter can be isolated from the reaction mixture. However, compounds **15** are prone to further spontaneous intramolecular cyclisation. This affords mixtures in which the geometrical isomers **16** and **17** (total yield 80% – 93%) predominate. It has been found that the conversions **15** ⇆ **16** ⇆ **17** were reversible, and that the isomer ratio depended on the polarity of the solvent used. However, the attempts to apply the retrosynthetic scheme to the synthesis of the target diterpene have been unsuccessful so far.[24]

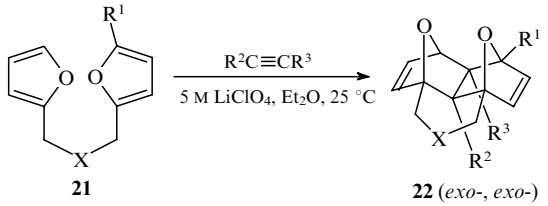
III. Tandem intramolecular cycloaddition in bisfurans

A series of transformations given below represents a two-step one-pot synthesis of bisfuran systems. Formally, the definition 'intramolecular cycloaddition of unsaturated compounds to bisfurans' can only be applied to the second step of this reaction, since the first step represents an intermolecular process. Examples of these elegant domino syntheses are scarce due to the low availability of difuryl derivatives. For the first time, the tandem intramolecular cycloaddition in bisfurans was described [25] for the reaction of (*E*,*E*)-4-oxohepta-2,5-diene (**18**) with 1,1-difurylethane **19** at elevated pressure. Diepoxyanthracene **20** is formed in a nearly quantitative yield.



E′ = CO_2Et.

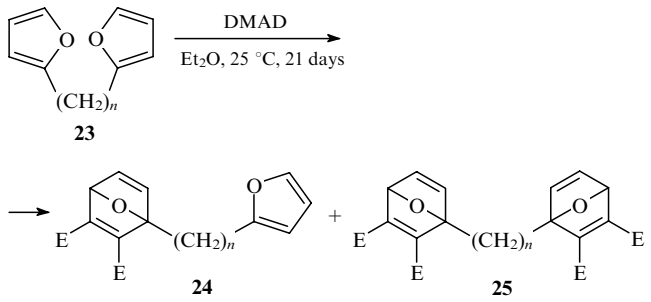
A detailed study of this type of intramolecular cycloaddition was carried out by the Canadian chemists Lautens and Fillion,[26, 27] who developed efficient procedures for the synthesis of difuryls **21** including those containing heteroatoms in the bridging alkanediyl chains.



X = CH_2, O, S, NBn, NC_6H_4OMe-4; R^1 = H, $(CH_2)_3Cl$;
R^2 = H, Me, Ac, CO_2H, CO_2Me, SO_2Ph;
R^3 = Ac, CO_2H, CO_2Me, SO_2Ph, Ts.

Alkynes containing electron-withdrawing substituents add to difuryls **21** in a regio- and stereospecific manner to give the *exo*,*exo*-adducts **22** (yields 63%–83%). The adduct of methyl 4-oxopent-2-ynoate (R^2 = CO_2Me, R^3 = Ac) with 1,3-bis(2-furyl)propane (X = CH_2), which represents a mixture of two stereoisomers (4 : 1), is an exception. The introduction of even one electron-donor substituent into the alkyne component results in complete inhibition of the cycloaddition reaction.

No sequential pincer-type [4 + 2]-cycloaddition occurs with 1,2-bis(2-furyl)ethane and 1,4-bis(2-furyl)butane (**23**).[26, 27] The reaction with an equimolar amount of dimethyl acetylenedicarboxylate (DMAD) yields linear adducts to one or two alkyne molecules (compounds **24** and **25**, respectively).



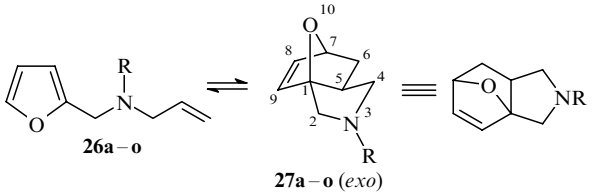
n	Yield (%)	
	24	**25**
2	38	16
4	38	22

IV. Oxabicycloheptenes fused to various rings

1. Five-membered rings

a. Synthesis of 3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes

The intramolecular cyclisation of substituted *N*-allylfurfurylamines **26**, which yields 5,7*a*-epoxyisoindoles (3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes) **27**, is the most studied intramolecular [4 + 2]-cycloaddition reaction in the 2-alkenylfuran series by virtue of high availability of the starting compounds (unsaturated fufurylamines) and smooth reaction (Table 1).



It has been found that the thermal intramolecular Diels–Alder cycloaddition of the non-substituted allylfurfurylamine and its n-alkyl derivatives cannot be realised even under drastic conditions.[28, 29] A prerequisite for the cyclisation is the presence

Table 1. Cyclisation of substituted allylfuran-2-ylmethylamines **26**.

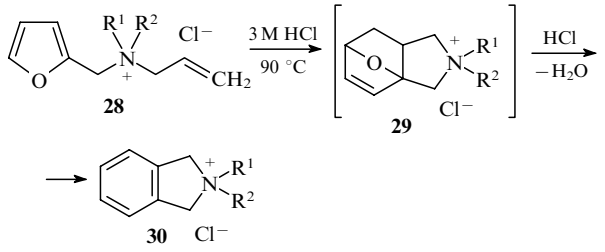
Compound **26** (see [a])	R	Reaction conditions			**26** : **27** ratio	Yield of **27** (%)	Ref.
		solvent	*T* /°C	*t* /h			
a	H	PhMe	110	> 50	–	0	28, 29
b	Bn	xylene	135	60	49 : 1	< 2	28, 29
c	Bn	xylene	135	34	1 : 1	35	28, 29
d	Ph_2CH	PhMe	110	40	1 : 32	85	28, 29
e	2,4,6-$Me_3C_6H_2CH_2$	xylene	135	60	9 : 1	< 10	28, 29
f	PhCO	PhMe	110	21	1 : 4	60	28
g	$MeCl_2CCO$	MeCN	60	20	see [b]	83	30
h	Ts	PhMe	110	21	1 : 4	60	28
i	SO_2Me	C_6D_6	80	–	–	77	31
j	SO_2Et	C_6D_6	80	–	–	78	31
k	SO_2Pr^n	C_6D_6	80	–	–	82	31
l	SO_2Pr^i	C_6D_6	80	–	–	80	31
m	SO_2Ph	C_6D_6	80	–	–	90	31
n	2,4,6-$Me_3C_6H_2SO_2$	C_6D_6	80	–	–	86	31
o	2,4,6-$Pr^i_3C_6H_2SO_2$	C_6D_6	80	–	–	92	31

[a] In the case of compounds **26i**–**o**, the reaction was carried out in an NMR tube until equilibrium was reached. The reaction time is not indicated; the calculated yields are given; [b] the formation of the reaction product takes place even at 20 °C.

of a bulky group R (compounds **26b–e**) or a substituent able to induce the transition of the nitrogen atom into the planar state (compounds **26f–o**)[28–31] (see Table 1).

In contrast to *N*-aralkyl derivatives, the cyclisation of amides and sulfonamides **26f–o** occurs more smoothly: the reaction is usually complete within several hours at 70–110 °C.[28,31] This cycloaddition is reversible, but, as can be evidenced from the data listed in Table 1, the reaction equilibrium is always shifted towards the cycloadduct (the yields of the isoindoles **27f–o** are no less than 60%).

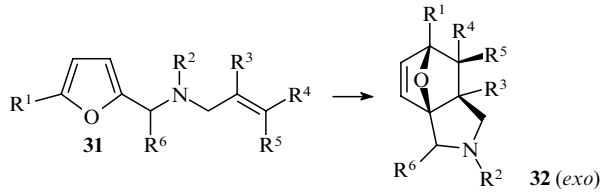
Thermal cyclisation of *N*-allyl-*N*-furfurylamine hydrochlorides **28** in 3 M HCl is accompanied by aromatisation of the tricycles **29** resulting in the isoindolium salts **30** in good yields.[32,33]



R^1, R^2 = H, Me, Et, Allyl, Pr^i, Bu^n, Bu^t, Ph;
$R^1–R^2$ = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$.

UV spectroscopic studies have shown[34,35] that the rate of formation of epoxides **29** (H_2O, 83 °C) depends on the nature of the substituents (R^1, R^2) at the nitrogen atom and decreases in the order: $(CH_2)_5$ > $O[(CH_2)_2]_2$ > Et, Et > Me, All > Me, Me > Me, Ph.

The regularities of the cyclisation of the substituted *N*-allylfurfurylamines **31** into 3-aza-10-oxabicyclo[5.2.1.0^{1,5}]dec-8-enes **32** have been studied in detail.[36–40]

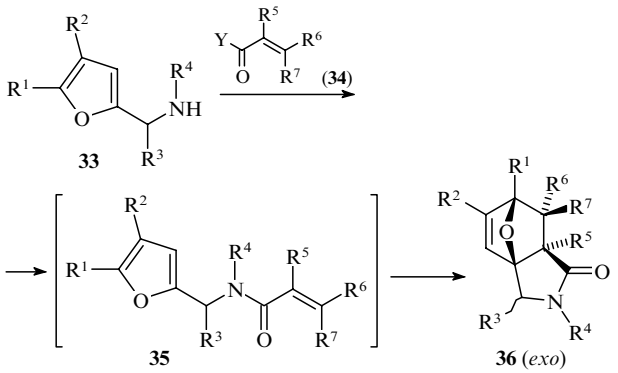


R^1 = H, Me, OMe, I, NO_2; R^2 = Ac, Cl_3CCO, 4-MeC_6H_4;
R^3 = H, $PhSO_2$; R^4, R^5 = H, Me; R^6 = H, CH=CH_2.

It has been established[36] that electron-withdrawing groups at position 5 of the furan ring (R^1) increase, while electron-donor groups, contrariwise, decrease the activity of the diene fragment in the [4+2]-cycloaddition reaction. Thus the reaction rates and the yields of the cycloaddition products of 5-nitro- and 5-iodofurfurylamines **31** are higher than those of the 5-methyl- or 5-methoxy derivatives. Studies of the substituent effect in the dienophilic fragment of furans **31** on the cyclisation have shown[36,39] that the yields of the adducts **32** decrease drastically (from 75% to 0%) for a compound with R^1 = R^3 = R^6 = H, R^2 = 4-MeC_6H_4 with an increase in the number of the methyl groups at the double bond, *i.e.,* on going from the *N*-allyl- to the but-2-enyl- and then to the isopentenyl substituent. This fact is attributed[36] to greater steric hindrance created by the alkyl substituents in the transition state. In the case of the *N*-acyl derivatives **31**, the yields of the products **32** are rather high (62%–83%) irrespective of the sizes and electronic effects of the substituents R^3 and R^6. Interestingly, epoxyisoindoline **32** (R^1 = OMe, R^2 = 4-MeC_6H_4, R^3 = R^5 = R^6 = H, R^4 = Me) is unstable and undergoes quantitative dehydration into the corresponding isoindole in the course of chromatographic isolation.[36,38] The aromatisation of some other 3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **32** demands acidic conditions (*e.g.*, HBr–AcOH).[37,38]

A one-pot procedure for the synthesis of epoxyisoindolines **32**, which involves alkylation of *N*-aryl-*N*-furfurylamines with allyl bromide in boiling benzene, has been developed.[41] The intermediate *N*-allyl derivatives **31** (R^3 = R^4 = R^5 = H) are converted into the corresponding oxabicycloheptenes **32** as a result of intramolecular [4+2]-cycloaddition.

Acylation of furfurylamines **33** by α,β-unsaturated carboxylic acid anhydrides or chlorides **34** (usually, by maleic, fumaric, acrylic and cinnamic acid derivatives) affords the unsaturated amides **35**. As the double bonds of the latter are activated by the electron-withdrawing carbonyl group, the unsaturated fragment becomes an active dienophile. As a rule, the amides of the type **35** cannot be isolated, since they are immediately cyclised into azaoxatricyclo[5.2.1.0^{1,5}]decenones **36** (Table 2).



The effect of the substituents in the dienophilic fragment of *N*-furfurylamides **35** on the yield of epoxyisoindolinones **36** has been studied in detail.[42–51] The data presented in Table 2 prompt the following conclusions.

1. The presence of a substituent R^4 at the nitrogen atom is a prerequisite for the formation of epoxyisoindolinones **36**. If R^4 = H, the reaction is stopped in the step of formation of the amide **35**.

2. Electron-withdrawing substituents in the dienophilic fragment favour the cycloaddition. If two such substituents are present at the double bond of the acylating reagent **34**, no heating is required for the cycloaddition, which occurs spontaneously at room temperature.[42,45,48–50] Thus the presence of an electron-withdrawing CF_3-group in the alkenyl fragment increases significantly the yield of the Diels–Alder adduct in comparison with its analogue possessing a donor Me-group (see Table 2).[43] Even weak donor substituents in the alkenyl fragment, *e.g.,* methyl groups, decelerate the cycloaddition reaction (long-term heating at 80–110 °C is required), however, without any appreciable effect on the product yield. No examples of successful cycloaddition in alkenylfurans containing two donor substituents in the dienophilic fragment are documented in the literature.

3. The data on the effects of substituents in the furan ring on the [4+2]-cycloaddition in compounds **35** are ambiguous. The published data[44,47,52] suggest that the donor substituents at positions 4 (see Ref. 47) and 5 (see Refs 44 and 52) of furan favour intramolecular cycloaddition. With the exception of 2-alkenyl-5-nitrofurans,[53] only one example of a successful synthesis of 3*a*,6-epoxyisoindolinones **36** starting from *N*-alkenylfurfurylamines containing an electron-withdrawing substituent in the furan ring has been described in the literature.[52]

4. The sizes of substituents at the double bond are less critical for the reaction than their electronic effects.

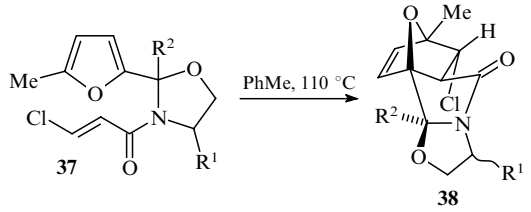
Special mention should be made of the efficient one-step synthesis of substituted 4-oxo-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]-dec-8-enes **36**, by the reaction of *N*-benzyl-*N*-furfurylamines with α,β-unsaturated acids in the presence of a catalytic system DIC–DIEA–DMAP (see Table 2).[44] This reaction proceeds under mild conditions in good yields.

Table 2. Preparation of substituted azaoxatricyclo[5.2.1.$0^{1,5}$]decenones **36**.

Y	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Reaction conditions	Yield of **36** (%)	Ref.
See[a]	H	H	H	Ph	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	86	42
See[a]	H	H	H	Bn	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	90	42
See[a]	H	H	H	C*HMePh	H	H	CO_2H	Et_2O, 0 °C, 18 h	100[c]	43
								PhH, 25 °C, 96 h	81[c]	
								CH_2Cl_2, 25 °C, 96 h	76[c]	
See[a]	H	H	H	3-ClC_6H_4	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	89	42
See[a]	H	H	H	3-$NO_2C_6H_4$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	80	42
See[a]	H	H	H	4-$NO_2C_6H_4$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	74	42
See[a]	H	H	H	tetrahydrofurfuryl	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	37	42
See[a]	H	H	H	cyclo-C_3H_7	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	35	42
See[a]	H	H	H	Cy	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	90	42
See[a]	H	H	H	$MeO(CH_2)_2$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	92	42
See[a]	H	H	H	furfuryl	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	95	42
OH	H	H	H	Bn	H	Ac	H	CH_2Cl_2, 25 °C, 1 h[d]	83	44
Cl	H	H	H	4-ClC_6H_4	H	CO_2(−)-Menth	H	$CHCl_3$, 65 °C, 20 min	65[c]	45
Cl	H	H	H	4-$MeOC_6H_4$	H	CO_2(−)-Menth	H	$CHCl_3$, 65 °C, 20 min	68[c]	45
Cl	H	H	H	4-$EtOC_6H_4$	H	CO_2(−)-Menth	H	$CHCl_3$, 65 °C, 20 min	62[c]	45
OH	H	H	H	Bn	H	CO_2Et	H	CH_2Cl_2, 25 °C, 1 h[d]	89	44
OH	H	H	H	Bn	H	4-ClC_6H_4CO	H	CH_2Cl_2, 25 °C, 1 h[d]	80	44
OH	H	H	H	Bn	H	4-CyC_6H_4CO	H	CH_2Cl_2, 25 °C, 1 h[d]	78	44
OH	H	H	H	Bn	H	H	CO_2Et	CH_2Cl_2, 25 °C, 1 h[d]	75	44
OH	H	H	H	Bn	H	H	Pr^nNHCO	CH_2Cl_2, 25 °C, 1 h[d]	70	44
OH	H	H	H	Bn	H	H	3-ClC_6H_4NHCO	CH_2Cl_2, 25 °C, 1 h[d]	74	44
Cl	H	H	H	Me	Me	H	H	PhMe, 90 °C, 3 h	27[c]	46
Cl	H	H	H	Bn	Me	H	H	PhMe, 90 °C, 3 h	36[c]	46
Cl	H	H	H	(*S*)-CHMePh	Me	H	H	PhMe, 90 °C, 3 h	97[c]	46
Cl	H	2-Th	H	cyclo-C_5H_9	H	Ph	H	PhMe, 100 °C, 1 h	23[c]	47
Cl	H	Br	H	cyclo-C_5H_9	Bn	H	H	PhMe, 100 °C, 1 h	77[c]	47
Cl	H	*m*-Tol	H	3-$EtO_2CC_6H_4$	Bn	H	H	PhMe, 100 °C, 1 h	16[c]	47
Cl	H	Ph	H	Ph	Me	H	H	PhMe, 100 °C, 1 h	97[c]	47
Cl	H	H	CN	Me	H	H	CO_2H	PhH, 80 °C, 1 h	65[c]	45
Cl	H	H	CN	Ph	H	H	CO_2H	PhH, 80 °C, 1 h	71[c]	45
Cl	H	H	CN	4-MeC_6H_4	H	H	CO_2H	PhH, 80 °C, 1 h	70[c]	45
Cl	H	H	CN	4-$MeOC_6H_4$	H	H	CO_2H	PhH, 80 °C, 1 h	75[c]	45
Cl	H	H	CN	4-$EtOC_6H_4$	H	H	CO_2H	PhH, 80 °C, 1 h	68[c]	45
Cl	H	H	CN	4-BrC_6H_4	H	H	CO_2H	PhH, 80 °C, 1 h	72[c]	45
Cl	H	H	CN	4-ClC_6H_4	H	H	CO_2H	PhH, 80 °C, 1 h	96	48
See[a]	H	H	MeAll	2-MeC_6H_4	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	89	48
See[a]	H	H	MeAll	2-$MeOC_6H_4$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	83	48
See[a]	H	H	MeAll	4-$MeOC_6H_4$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	91	48
See[a]	H	H	MeAll	4-FC_6H_4	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	95	48
See[a]	H	H	MeAll	2-BnC_6H_4	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	83	48
See[a]	H	H	MeAll	Bn	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	95	49
See[a]	H	H	MeAll	CHMePh	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	73	49
See[a]	H	H	MeAll	4-$MeC_6H_4CH_2$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	92	49
See[a]	H	H	MeAll	4-$MeOC_6H_4CH_2$	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	74	49
Cl	H	H	CN	4-ClC_6H_4	H	CO_2(−)-Menth	H	$CHCl_3$, 65 °C, 20 min	65[c]	45
Cl	H	H	Me	Bn	CF_3	H	H	CH_2Cl_2, 0 °C, 1 h	94	50
Cl	H	H	Pr^i	Bn	Me	H	H	PhMe, 140 °C, 3 h	97[c]	50
Cl	H	H	Pr^i	Bn	CF_3	H	H	CH_2Cl_2, 0 °C, 1 h	77	50
Cl	H	H	Ph	Bn	Me	H	H	PhMe, 120 °C, 12 h	29[c]	50
Cl	H	H	Ph	Bn	CF_3	H	H	CH_2Cl_2, 0 °C, 1 h	98	50
Cl	H	H	CF_3	Ph	Me	H	H	PhMe, 150 °C, 12 h	75[c]	50
Cl	H	H	CF_3	Ph	CF_3	H	H	CH_2Cl_2, 0 °C, 1 h	100	50
OH	Me	H	H	Bn	H	H	BnNHCO	CH_2Cl_2, 25 °C, 1 h[d]	65	44
OH	Me	H	H	Bn	H	Ac	H	CH_2Cl_2, 25 °C, 1 h[d]	80	44
OH	Me	H	H	Bn	H	CO_2Et	H	CH_2Cl_2, 25 °C, 1 h[d]	79	44
OH	Me	Me	H	Bn	H	CO_2Et	H	CH_2Cl_2, 25 °C, 1 h[d]	74	44
OH	Me	H	H	Bn	H	H	CO_2Et	CH_2Cl_2, 25 °C, 1 h[d]	63	44
OH	Me	Me	H	Bn	H	H	CO_2Et	CH_2Cl_2, 25 °C, 1 h[d]	60	44
OH	Me	Me	H	Bn	H	H	BnNHCO	CH_2Cl_2, 25 °C, 1 h[d]	64	44
See[a]	Me	H	MeAll	Bn	H	H	CO_2H	PhH,[b] 25 °C, 2 – 7 days	89	49

[a] The acylation was carried out using a corresponding anhydride; [b] toluene can also be used as a solvent; [c] the intermediate amide **35** was isolated; [d] a 1,3-diisopropylcarbodiimide (DIC) – diisopropylethylamine (DIEA) – 4-dimethylaminopyridine (DMAP) system was used as a catalyst.
Abbreviations: Cy is cyclo-C_6H_{11}, Menth is menthyl, 2-Th is 2-thienyl, *m*-Tol is 3-MeC_6H_4, MeAll is $CH_2=CMeCH_2$.

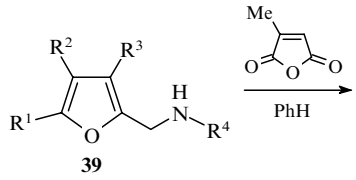
A similar intramolecular cycloaddition in *N*-furfuryl-β-chloroacrylamides **37** is the key step in the synthesis of the antibiotic ivermectin of the penicillin series possessing a broad spectrum of antiparasitic activities.[54] The chloro-substituted tetracyclic compounds **38** are formed as mixtures of diastereomers.



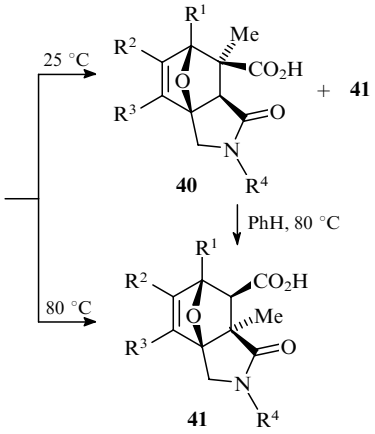
37 **38**

R^1 = H, Pr^i; R^2 = Me, CH_2OBn.

The regioselectivity of the cycloaddition of citraconic (methylmaleic) anhydride to furfurylamines **39** in benzene has been studied.[52, 55] Depending on the temperature and the nature of the substituents in the furan ring, this reaction follows one of two pathways to yield isomeric methyl-substituted epoxyisoindolinones **40** and **41** (Table 3).



39



40 **41**

The yields of the cycloaddition products **40** and **41** depend on the electronic effects of the substituents in the furan ring: donor groups (*e.g.*, SMe) favour the cycloaddition, while electron-withdrawing groups (CO_2Alk) hinder this process. Their position (3 or 4) has no appreciable effect on the reaction (see Table 3).

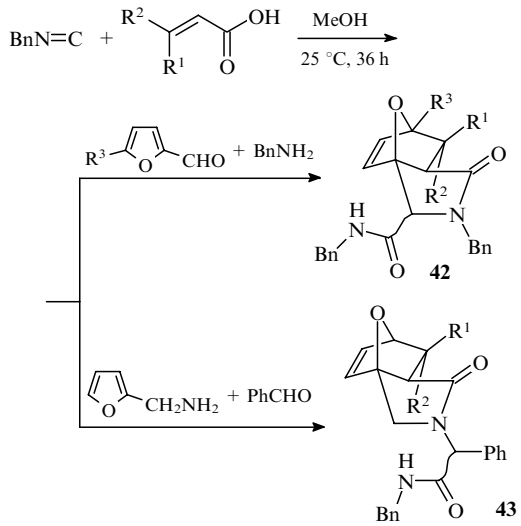
This reaction occurs in two steps. The first step includes the acylation of furfurylamine. NMR spectroscopic studies (the reaction in an NMR tube) have shown that the cycloaddition of citraconic anhydride to *N*-benzylfurfurylamine **39** (R^1 = R^2 = R^3 = H, R^4 = Bn) is reversible.[55] In the majority of cases, the amine attacks both carbonyl groups of the anhydride at room temperature (25 °C), *i.e.*, the acylation is non-regioselective and yields two regioisomers, *i.e.*, **40** and **41**. With an increase in the temperature, the thermodynamically less stable isomer **40** undergoes degradation to the starting furfurylamine **39** which undergoes acylation and cyclisation to yield eventually the isomer **41**. This process is discussed in detail by Murali *et al.*[52].

3*a*,6-Epoxyisoindolinones **42** and **43** have recently been synthesised using the four-component Ugi reaction.[56]

Table 3. Cycloaddition of citraconic anhydride to furfurylamines **39**.

R^1	R^2	R^3	R^4	T /°C	t /h	**40** : **41** ratio	Yield (%)	Ref.
H	H	H	Cy	80	< 24	0 : 100	76	52, 55
H	H	H	Bn	80	< 24	0 : 100	84	52, 55
				25	24	65 : 35	–	52, 55
				65	24	5 : 95	90 [a]	52, 55
				25	see [b]	0 : 100	30	52, 55
H	H	H	2-$MeC_6H_4CH_2$	80	< 24	0 : 100	70	52, 55
H	H	H	2-$HOC_6H_4CH_2$	80	< 24	0 : 100	83	52, 55
H	H	H	2-$MeOC_6H_4CH_2$	80	< 24	0 : 100	66	52, 55
H	H	H	4-$MeOC_6H_4CH_2$	80	< 24	0 : 100	87	52, 55
H	H	H	4-$NO_2C_6H_4CH_2$	80	< 24	0 : 100	57	52, 55
H	H	H	2-$NaphCH_2$	80	< 24	0 : 100	77	52, 55
H	H	Me	Bn	25	24	15 : 85	see [c]	52
				65	24	85 : 15	82 [a]	52
H	H	SMe	Bn	25	24	100 : 0	–	52
				65	24	100 : 0	80 [a]	52
H	H	CO_2Me	Bn	25	24	–	–	52
				65	24	10 : 90	72 [a]	52
H	SMe	H	Bn	25	24	25 : 75	–	52
				65	24	0 : 100	92 [a]	52
H	CO_2Et	H	Bn	25	24	–	see [d]	52
				65	24	–	–	52
Me	H	H	Bn	25	24	0 : 100	–	52
				65	24	0 : 100	92 [a]	52

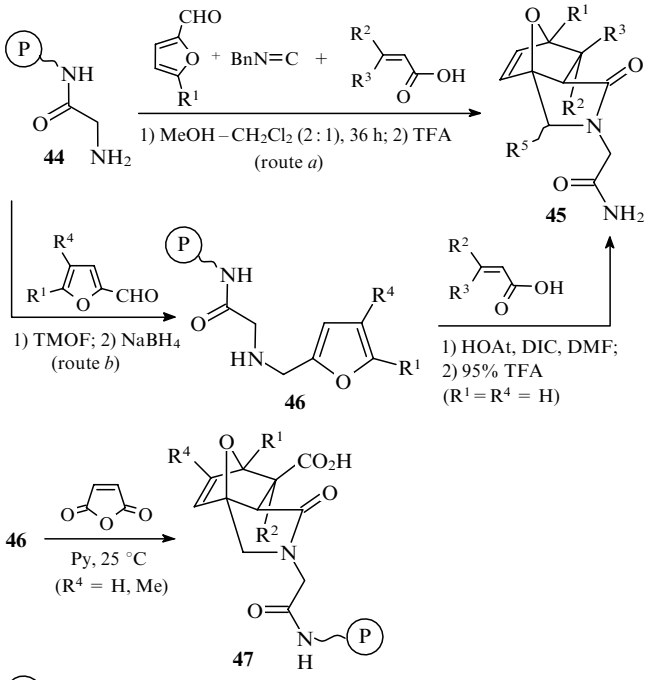
[a] The yield of the isomer **41** is indicated; [b] the reaction is complete within several hours; [c] the conversion of the substrate is 20%; [d] no product was detected. Naph is naphthyl.



R^1	R^2	Yield (%)		
		42 (R^3 = H)	**42** (R^3 = Me)	**43**
H	CO_2Et	70	72	75
H	CONHBn	85	81	88
CO_2Et	H	89	78	89

This multicomponent synthesis is carried out under mild conditions and, depending on the nature of the starting compounds (it is the aldehyde and the amine components that are usually varied), affords high yields of epoxyisoindolinones **42** or **43.** The introduction of substituted substrates enables variation of substituents at positions 2, 3, 6 and 7 of the oxaazatricyclo[5.2.1.0^{1,5}]decene system.

This conversion was also accomplished in a solid-phase version where the AgroGel-Rink resin was used.[56, 57] In this case, the role of the amine component is played by glycinamide **44** bound to the polymeric support.



(P) is a polymeric support; TMOF is trimethyl orthoformate; HOAt is 1-hydroxy-7-azabenzotriazole.

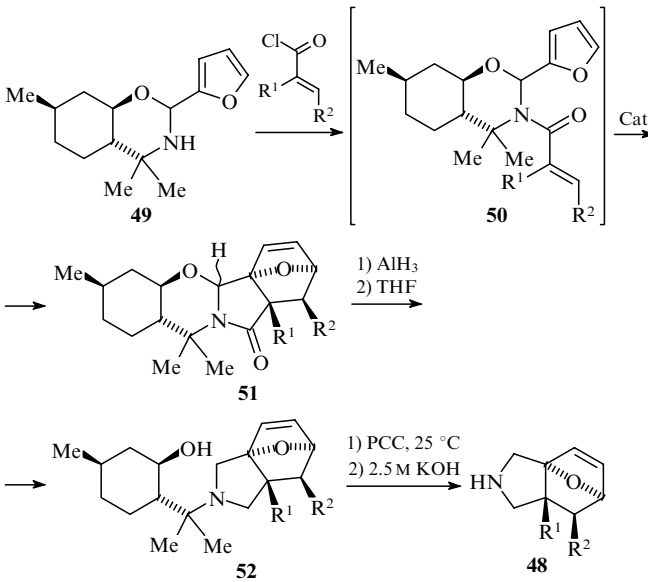
R^2	R^3	R^5 (route)	Yield of **45** (%)		Ref.
			R^1 = H	R^1 = Me	
H	CO_2Et	CONHBn (*a*)	92	88	56
		H (*b*)	95	–	57
H	CONHBn	CONHBn (*a*)	88	92	56
		H (*b*)	90	–	57
CO_2Et	H	CONHBn (*a*)	95	95	56
		H (*b*)	89	–	57

Two modifications of this reaction exist. One of them represents a solid-phase version of the Ugi reaction (route *a*) with the direct formation of the products **45**; the second variant is a consecutive two-step process (route *b*). In the latter case, the reactions of the intermediate furfurylamine **46** with acrylic acid derivatives also yield epoxyisoindolinones **45**. Acylation of the amine with maleic anhydride gives the polymer-bound compounds **47** containing an additional functionalisation site, *i.e.*, a carboxy group. In the final step, the reaction product is liberated from the polymeric substrate by treatment with trifluoroacetic acid. The acids **47** were used as starting compounds for the synthesis of a large library of amides and esters.[57]

A series of original investigations [58 – 60] have been carried out by Spanish chemists who were the first to perform the synthesis of non-substituted 3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene **48** ($R^1 = R^2$ = H) and to isolate its optical isomers in the individual state.[58] An (–)-8-aminomenthol derivative was used as a chiral inducer in the asymmetric synthesis (Scheme 3).

Acylation of optically active 2-furyltetrahydro-1,3-oxazines **49** with unsaturated acid chlorides gives intermediate alkenylfurans **50** which are spontaneously converted into isomeric oxazinoisoindoles **51**. The latter are formed in high yields as mixtures of two diastereomers; their ratios depending on the temperature of the reaction, the nature of the solvent and the Lewis acid used as a catalyst. Toluene, CH_2Cl_2 or hexane are used as solvents; the noncatalysed cycloaddition proceeds smoothly at 0 °C and that in the

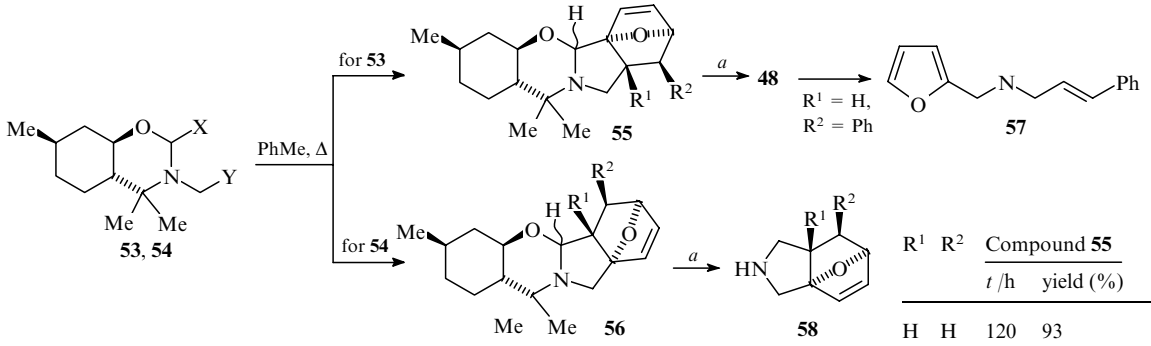
Scheme 3



R^1, R^2 = H, Me; Cat = $ZnCl_2$, $Ti(OPr^i)_4$, $BF_3 \cdot Et_2O$, Et_2AlCl, Me_3Al, $AlCl_3$; PCC is pyridinium chlorochromate.

R^1	R^2	Yield of **48** (%)	Ref.
H	H	31 – 93	58, 59
Me	H	80 – 89	59
H	Me	80 – 89	59

Scheme 4



X = 2-Fu, Y = (*E*)-CR^1=CHR^2 (**53**); X = (*E*)-CR^1=CHR^2, Y = 2-Fu (**54**), where Fu is furyl; (*a*): 1) AlH_3, 2) PCC, 3) KOH.

R^1	R^2	Compound **55**		Compound **56**	
		t /h	yield (%)	*t* /h	yield (%)
H	H	120	93	80	96
H	Me	160	80	100	80
H	Ph	300	50	200	73
Me	H	240	60	240	85

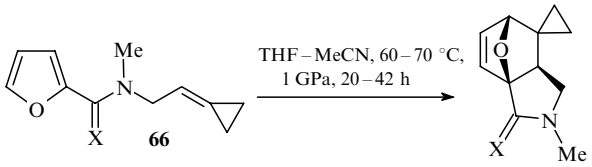
presence of catalysts at −23 °C.[59] Reduction of the 1,3-oxazine fragment in the polycycles **51** with aluminium hydride yields individual optically active stereoisomeric amino alcohols **52** (yields 80% – 94%). Subsequent oxidation of the hydroxy group with pyridinium chlorochromate and base-catalysed retro-Michael reaction yield the target compounds **48** (see Scheme 3).[58, 59]

The [4 + 2]-cycloaddition of the structurally similar isomeric alkenylfurans **53** and **54**, which are devoid of the carbonyl group, takes place only upon long-term boiling in toluene, resulting in fused hexahydroisoindoles **55** and **56**, respectively. It is interesting to note that hexahydroepoxyisoindole **48** formed upon oxidation and alkaline degradation of the polycycle **55** (R^1 = H, R^2 = Ph) is unstable and undergoes spontaneous retro-Diels – Alder reaction to alkenylfuran **57**. Oxaazatricyclodecenes **58** were obtained from oxasinoisoindoles **56** (Scheme 4). Cycloaddition of *N*-furfurylidenetryptamines served as a basis for the development of an elegant procedure for the preparation of fused tetrahydro-β-carbolines and the shortest route to the construction of the carbon skeleton of the natural alkaloid noryochimbine.[61, 62]

Acylation of furyl-substituted tetrahydro-β-carbolines **59** (synthesised by the Pictet – Spengler method) with maleic anhydride or α,β-unsaturated acid chlorides gives the amides **60** and **61**.[62] Intramolecular cycloaddition in these amides yields the corresponding adducts **62** and **63** containing both tetrahydrocarboline and isoindole rings (Table 4, route *a*). Such an approach enables the construction of a noryochimbine skeleton with a broad array of substituents in both the indole and isoindole fragments (Scheme 5).

In some cases, furyl-substituted tetrahydro-β-carbolines are prepared *in situ* (route *b*). Although this approach has been applied to compounds that are not characterised by a broad array of substituents, it enabled one-step synthesis of the derivatives **62** (see Table 4).[61] Azomethines derived from tryptophan **64** were acylated with maleic anhydride under mild conditions. The intermediate *N*-acyl derivatives **65** underwent the Pictet – Spengler cyclisation and the intramolecular Diels – Alder cycloaddition to give the heterocyclic adducts **62** in high yields.

An interesting example of an intramolecular attack of an *N*-cyclopropylidene dienophile on the furan ring of the alkenes **66** has been described.[63] This reaction yields epoxyisoindolines **67** only at elevated pressure, not at atmospheric pressure.



X = 2 H (50%), O (55%).

Conversions of 2-alkenylfuran metallocomplexes are documented.[49, 50, 64] Heating of the coordination molybdenum, tungstene and manganese carbonyl compounds **68** in inert solvents yields hydrogenated epoxyisoindoles **69** (Table 5). These complexes are crystalline compounds that are relatively stable in air. No cyclisation of *N*-unsubstituted analogue **68** (R^1, R^2 = H, X = O) occurs even upon long-term heating; the same was observed with certain metallocomplexes (see Table 5). The nitrogen atom in the complexes **68** does not undergo inversion, therefore, the derivatives **69** are formed as pairs of geometrical isomers that can be separated by chromatography.

Table 4. Preparation of isoindolotetrahydrocarbolines **62** and **63**.

R^1	R^2	R^3	R^4	R^5	Route	Reaction conditions			Product [yield (%)]	Ref.
						solvent	*T* /°C	*t* /h		
H	CO_2Me	H	H	H	*a*	DCE	70	24	**62** [100]	62
H	CO_2Me	Ph	H	H	*a*	THF	60	4 – 5	**63** [90]	62
6-Cl	CO_2Me	Ph	H	H	*a*	THF	60	4 – 5	**63** [94]	62
7-F	CO_2Me	3-$CF_3C_6H_4$	H	H	*a*	THF	60	4 – 5	**63** [79]	62
6-OH	CO_2Me	Me	H	H	*a*	THF	60	4 – 5	**63** [70]	61
6-OBn	CO_2Me	2-ClC_6H_4	H	H	*a*	THF	60	4 – 5	**63** [86]	61
H	H	H	H	H	*b*	CH_2Cl_2	25	24	**62** [80]	61
H	H	H	Me	H	*b*	CH_2Cl_2	25	24	**62** [80]	61
H	H	H	CH_2OAc	H	*b*	CH_2Cl_2	25	24	**62** [76]	61
H	H	H	Me	Me	*b*	CH_2Cl_2	25	24	**62** [60]	61

DCE is 1,2-dichloroethane.

Scheme 5

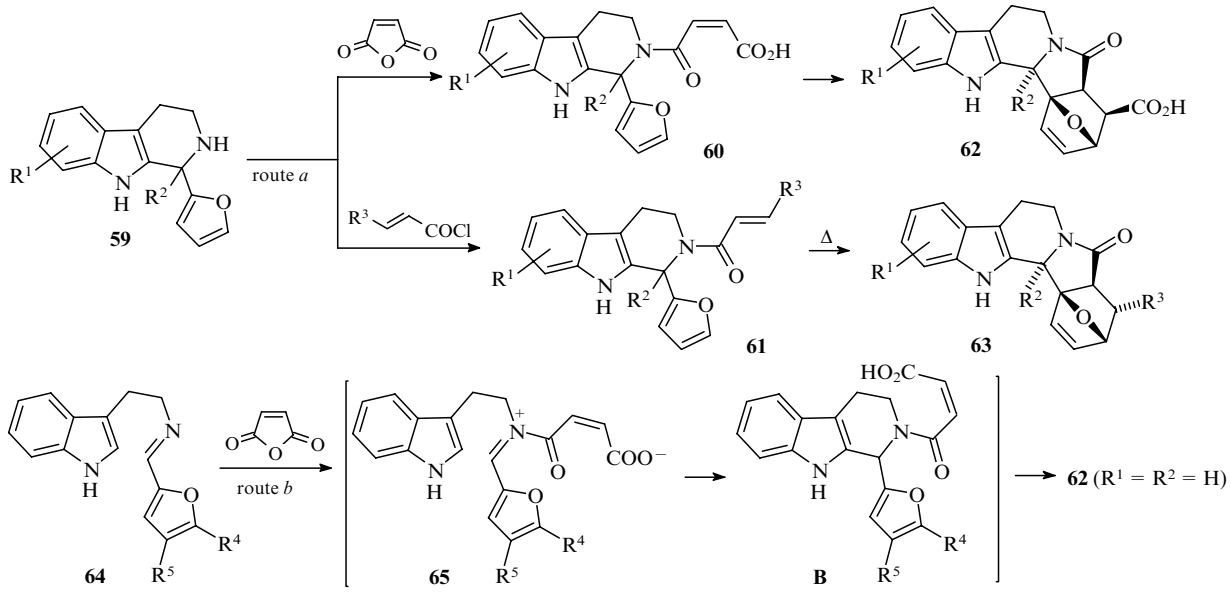
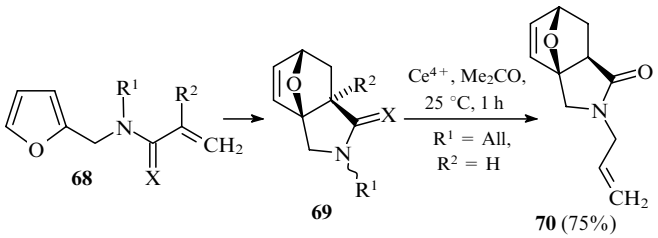


Table 5. Preparation of metallocomplexes **69**.

R^1	R^2	X	Reaction conditions			Yield (%)	Ref.
			solvent	T /°C	t /h		
H	H	$W(CO)_5$	PhMe	110	3	0	51
H	Me	$W(CO)_5$	PhMe	110	3	60	51
			PhMe	90	3	79	64
H	Me	$MeCp(CO)_2Mn$	Bu^n_2O	80	24	48	64
H	Me	Cp(CO)(NO)Mo	Bu^n_2O	90	3	0	64
			Bu^n_2O	90	120	0	64
All	H	$W(CO)_5$	CH_2Cl_2	−30 to 25	1	38	51
Me	Me	$W(CO)_5$	PhMe	90	3	100	64
Me	Me	Cp(CO)(NO)Mo	Bu^n_2O	90	3	22	64
			Bu^n_2O	70	4	19	64
			Bu^n_2O	50	24	7	64
Me	Me	$MeCp(CO)_2Mn$	Bu^n_2O	80	6	72	64
Bn	Me	$W(CO)_5$	PhMe	90	3	100	64
Bn	Me	Cp(CO)(NO)Mo	Bu^n_2O	90	3	50	64
Bn	Me	$MeCp(CO)_2Mn$	Bu^n_2O	80	4	75	64
(*S*)-CHMePh	Me	$W(CO)_5$	PhMe	90	3	100	64



The cyclisation of tungsten pentacarbonyl complexes occurs most easily. The cyclopentadienyl–molybdenum complex possessing stronger electron-donor properties and manganese carbonyl complexes are characterised by moderate reactivities. The organometallic complex **69** (R^1 = All, R^2 = H) can easily be oxidised to the amide **70** by treatment with $(NH_4)_2Ce(NO_3)_6$.

Cyclisation of *N*-furfuryl-*N*-phenylfumaramide acid and the corresponding ethyl ester at high pressures has been studied.[65] The kinetic parameters of this reaction were established at different temperatures and pressures.

b. Synthesis of 3,10-dioxatricyclo[5.2.1.0^{1,5}]dec-8-enes

The intramolecular cycloaddition of furfuryl esters of α,β-unsaturated acids is more complex than that of their nitrogen analogues and is studied in lesser detail. Like the cyclisation of nitrogen-containing alkenylfurans, this reaction yields only *exo*-isomers of 3,10-dioxatricyclo[5.2.1.0^{1,5}]dec-8-enes.

Acylation of furfuryl alcohols with acryloyl chloride and fumaric acid monomethyl ester chloride afforded the unsaturated esters **71** (X = O); their intramolecular cyclisation yielded the diastereomers **72** and **73** (Table 6).[66,67] A similar reaction of the allylic derivative **71** (R^1–R^3 = H, X = 2 H) (170–200 °C, 18 h) also resulted in a mixture of compounds **72** and **73** (X = 2 H) in a total yield of 35%.[67]

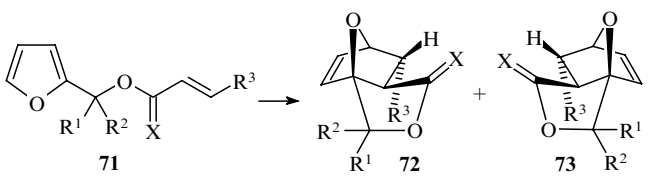


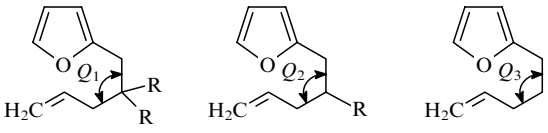
Table 6. Intramolecular cyclisation of furfuryl esters **71**.

R^1	R^2	R^3	X	Reaction conditions				**72** : **73** ratio	Yield (%)	Ref.
				solvent	T /°C	t	p /GPa			
H	H	H	O	see [a]	80	60 h	–	–	50	67
H	H	CO_2Me	O	CD_3CN	25	60 days	–	–	see [b]	66
Me	H	CO_2Me	O	CD_3CN	25	11 days	–	–	see [b]	66
Me	Me	CO_2Me	O	CD_3CN	25	< 1 h	–	–	see [b]	66
$(CH_2)_4$		CO_2Me	O	CD_3CN	25	< 1 h	–	–	see [b]	66
$(CH_2)_3$		CO_2Me	O	CD_3CN	25	11 h	–	–	see [b]	66
$(CH_2)_2$		CO_2Me	O	CD_3CN	25	12 days	–	–	see [b]	66
H	Me	CO_2Me	O	Me_2CO	40	18 g	0.7	55 : 45	96	68
H	Me	CO_2Me	O	Me_2CO	40	5–7 days	–	55 : 45	41	68
H	Et	CO_2Me	O	Me_2CO	40	18 h	0.7	68 : 32	36	68
H	Pr^i	CO_2Me	O	Me_2CO	40	18 h	0.7	90 : 10	90	68
H	Pr^i	CO_2Me	O	Me_2CO	40	5–7 days	–	78 : 22	31	68
H	Bu^t	CO_2Me	O	Me_2CO	40	18 h	0.7	93 : 7	92	68
H	Bu^t	CO_2Me	O	Me_2CO	40	5–7 days	–	92 : 8	44	68
H	neo-C_5H_{11}	CO_2Me	O	Me_2CO	40	18 h	0.7	69 : 31	93	68
H	Ph	CO_2Me	O	Me_2CO	40	18 h	0.7	23 : 77	49	68

[a] The reaction was carried out on diatomite in the absence of solvent; [b] the products **72** and **73** were not isolated and their ratio was not determined.

This reaction was studied in an NMR tube (CD_3CN, 25 °C) by determining the half-conversion times ($t_{1/2}$) of the starting compounds **71**. It was found that the cyclisation rates of the non-substituted ($R^1 = R^2 = H$) and monomethyl-substituted ($R^1 = Me$, $R^2 = H$) esters **71** were very low: $t_{1/2} = 665$ and 133 h, respectively. In contrast, in the case of dimethyl, cyclobutane and cyclopentane derivatives [$R^1 - R^2 = Me_2$, $(CH_2)_3$, $(CH_2)_4$] the intramolecular Diels–Alder reaction occurred fast: the conversion of the starting compounds was complete within less than 11 h. However, the reaction rate dropped drastically ($t_{1/2} = 145$ h) on going to the cyclopropane homologue **71** [$R^1 - R^2 = (CH_2)_2$]. These findings led Jung *et al.*[66–68] to suggest that the *gem*-dialkyl substituents R^1 and R^2 strongly influence the formation of the cycloadducts **72** and **73**.

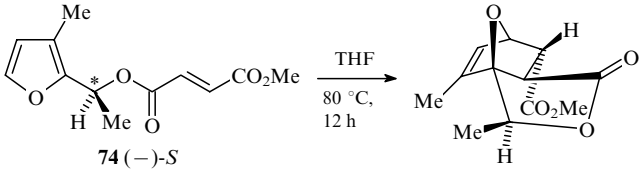
This phenomenon is often referred to as the Thorpe–Ingold effect (or the internal angle compression effect). Its essence is that the so-called internal angle Q ($Q_1 < Q_2 < Q_3$) decreases with an increase in the number and sizes of substituents at the sp^3-hybridised carbon atom in the side chain.



R = Alk.

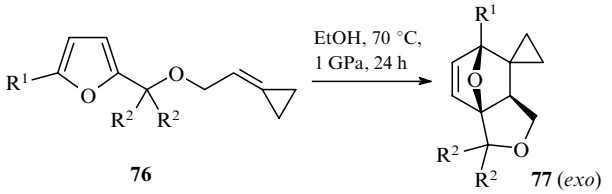
For the cases under consideration, the magnitude of the internal angle Q depends on the nature of the substituents R and decreases in the following order: H, H > H, Alk > Alk, Alk. The ordering of the transition state, *i.e.,* the entropy factor, increases with the decrease in the internal angle Q, as a result of which the rate of the intramolecular [4 + 2]-cycloaddition in this series of compounds also increases.

The cyclisation of optically active furfuryl esters has been studied.[68] At high temperatures and at elevated pressure, the racemic mixtures of the enantiomeric esters **71** are converted into the diastereomeric adducts **72** and **73** (see Table 6), while the cycloaddition of chiral starting compounds occurs stereoselectively. By illustration, the cycloaddition of the *S*-enantiomer **74** gives only one *exo*-isomer **75**.[68]



74 (−)-*S* **75** (*exo*, 38%)

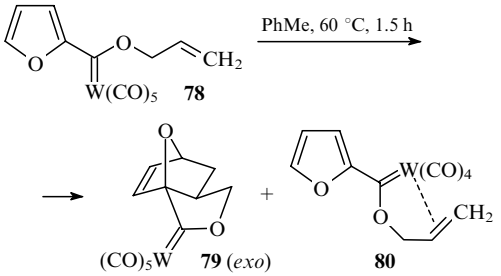
Cyclopropenylideneethyl furfuryl ethers **76** enter into the Diels–Alder reaction in the same manner as their nitrogen analogues **66**, *i.e.*, at elevated pressure. The *exo*-adducts **77** are formed in virtually quantitative yields.[63]



76 **77** (*exo*)

R^1 = H, Me, OMe; R^2 = H, Me.

The intramolecular cyclisation in the series of 2-allyloxymethylfuran metallocomplexes has also been described. However, thermolysis of the tungsten-containing complex **78** yields, in addition to the expected *exo*-adduct **79** (10%), the complex **80** (5%) as a result of extrusion of one CO ligand.[49]

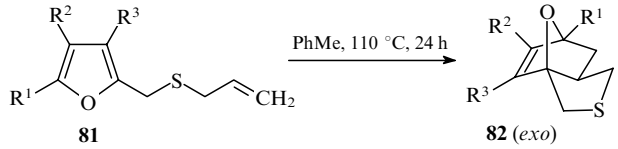


78 **79** (*exo*) **80**

c. Synthesis of 3-thia-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes

Before 2003, there were only three publications devoted to the synthesis of oxabicycloheptene systems annelated with the tetrahydrothiophene ring.[69–71] The reason for the low interest in reactions of alkenyl furfuryl sulfides **81** is not clear, since alkyla-

tion of furfurylmethanethiols with alkenyl halides normally proceeds in good yields. Subsequent intramolecular [4 + 2]-cycloaddition affords the Diels – Alder adducts **82**, which are also *exo*-isomers.

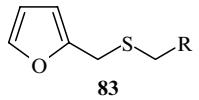


81 **82** (*exo*)

R^1	R^2	R^3	Yield (%)	Ref.
H	H	H	23	69
H	H	Me	77	69
H	H	Br	83	69
H	Me	H	40	69
Me	H	H	18	69
$BnOCH_2$	H	H	30	69
$CH_2OCH_2C_6H_4Br$-2	H	H	33	71
H	$BnOCH_2$	$BnOCH_2$	84	69
Me	H	Me	60	69, 70
Me	Me	H	60	69
Me	$BnOCH_2$	H	48	69
Me	Me	Me	92	69

It is noteworthy that in the case of 3-substituted furans **81** (R^3 = Alk, Br) the yields of the sulfides **82** are significantly higher. This fact is attributed to the interaction between the bulky sulfur atom and the α-methylene fragment, on the one hand, and the substituent R^3, on the other hand, which leads to the approximation of the alkenyl and diene fragments in the starting alkenylfuran. In addition, the structure of the adduct **82** is such that the steric interaction between these substituents decreases.

Attempts to perform the cyclisation of sulfides of the type **83** were unsuccessful: the products **82** were either not formed at all, or were formed in trace amounts (< 5%).

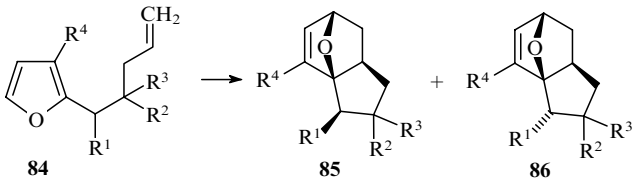


83

R = (*E*)-CH=CHMe, CMe =CH_2, CH=CMe_2, $(CH_2)_nCH$=CH_2 (*n* = 1, 2).

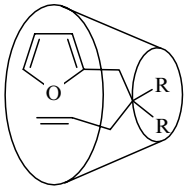
d. Synthesis of 10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes

In one of the earliest studies [72] devoted to the synthesis of oxatricyclodecene systems the effects of substituents in the substrate molecule on the intramolecular cyclisation were investigated. It was found that the unsubstituted alkenylfuran **84** could not be converted to the tricyclic compound **85** (and/or **86**). The presence of at least two substituents in the side alkenyl chain is a prerequisite for the cyclisation of compound **84**.



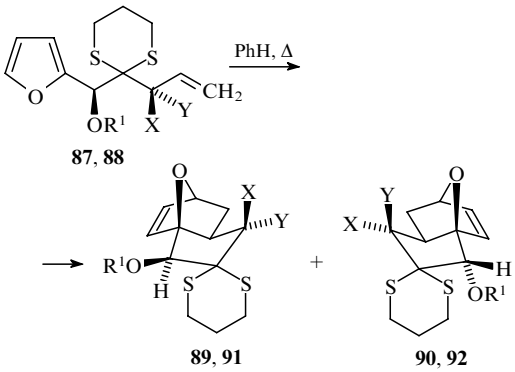
84 **85** **86**

The addition, to the reaction medium, of α- or β-cyclodextrin (α-CD or β-CD), a cyclic oligomer built up of six or seven 1,4-linked α-D-glucopyranose residues, significantly (by 10% – 20%) increases the yield of the isomeric cycloadducts **85** and **86**.[72] In the authors' opinion, the effect of cyclodextrins can be attributed to the incorporation of the starting alkene molecule into the cavity of the carbohydrate macromolecule as a result of which the alkene and the furan fragments are brought closer to each other. The size of the β-cyclodextrin cavity is probably best suited to the binding of 2-alkenylfuran and its use should be preferred.



The effects of solvents on the cyclisation of furan **84** [$R^2 - R^3$ = $S(CH_2)_3S$] have been studied.[73] The best yields of the epimers **85** and **86** were attained with protic solvents (water – ethanol, ethylene glycol); their ratios do not depend on the nature of the solvent. The cycloaddition rate of alkenylfurans **84** increases with an increase in the size of the substituents R^2 and R^3, with a concomitant shift of the reaction equilibrium towards the cyclisation products,[74] apparently due to the manifestation of the *gem*-dialkyl effect (see above).

The effect of substituents in the alkyl chain and their relative position on the composition of the intramolecular [4 + 2]-cycloaddition products of the isomeric dithianes **87** (the *syn*-isomer) and **88** (the *anti*-isomer) has been studied.[75] These reactions afford the diastereomeric pairs **89** – **90** and **91** – **92,** respectively**.**



87, **88** **89**, **91** **90**, **92**

X = OR^2, Y = H (**87**, **89**, **90**); X = H, Y = OR^2 (**88**, **91**, **92**).

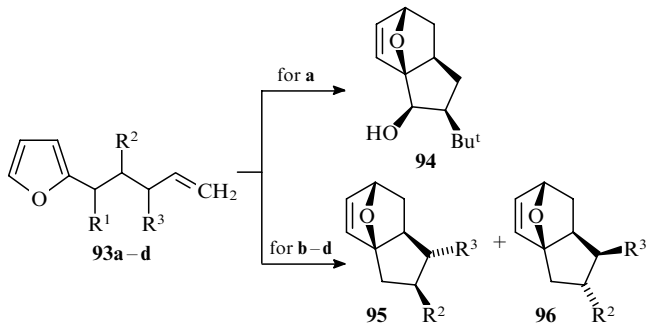
R^1	R^2	*t* /days	Ratio		Yield (%)
			89 : **90**	**91** : **92**	
H	H	2	1 : 1	–	95
		4	–	1 : 1	95
Bn	Bn	3	1 : 99	–	82
		2	–	1.1 : 1	84
Ac	Ac	4	1 : 3.4	–	80
		2	–	2 : 1	90
THP	Bn	2	1 : 99	–	91
		3	–	9 : 1	89

THP is tetrahydropyranyl.

It has been found [75] that an increase in the size of the substituents R^1 and R^2 in *syn*-alkenylfurans **87** favours the formation of the diastereomers **90** with a *trans*, *trans*-configuration of the substituents OR^1 and OR^2 relative to the epoxide bridge. In the case of benzyl substituents, the reaction proceeds in a stereoselective manner and yields only compounds **90**. The stereodirection of the intramolecular cycloaddition of the *anti*-isomers **88** also depends on the size of the substituents R^1 and R^2, but this effect is not as pronounced as in the previous case and the yield of the adduct **91** is increased. It was found also that the change in the solvent polarity (methylcyclohexanone and aqueous ethanol were used) had no appreciable effect on the stereospecificity of the cycloaddition reaction.

Cyclisation of 4-[(2-furyl)hydroxymethyl]-5,5-dimethylhex-1-ene **93a** in benzene and in toluene at 80 and 111 °C afforded only one geometrical isomer (**94**) in 70% and 60% yields, respectively. The lower yield of the adduct **94** at higher temperatures was

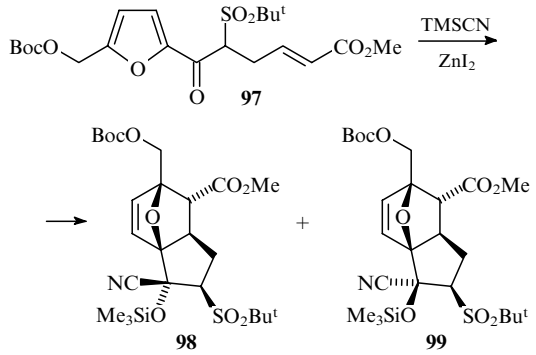
thought to be due to the retro-Diels – Alder reaction.[76] Cyclisation of 5-(2-furyl)pent-1-enes **93b – d** containing a 4-sulfonyl group (benzene, 80 °C) yielded mixtures of isomers **95** and **96**.[77]



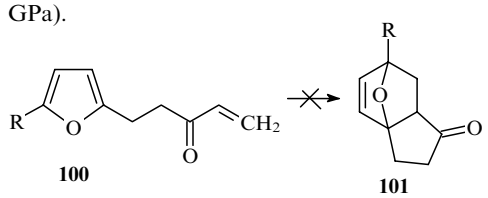
Compound **93**	R^1	R^2	R^3	Product	Yield (%)	Ref.
a	OH	Bu^t	H	**94**	70	76
b	H	SO_2Me	OH	**95** + **96**	78	77
c	H	SO_2Ph	OH	**95** + **96**	93	77
d	H	SO_2Bu^t	OH	**95** + **96**	97	77

It is of note that δ-alkenylfuran **93** (R^1 = OH, R^2 = R^3 = H) gives no intramolecular cycloaddition products.[76]

The addition of trimethylsilyl cyanide (TMSCN) to furyl ketone **97** in the presence of zinc iodide is accompanied by intramolecular cycloaddition.[77] A mixture of the adducts **98** and **99** (1.9 : 1), which differ in the orientation of the cyano- and TMSO-groups relative to the epoxide bridge, is formed in 61% yield.

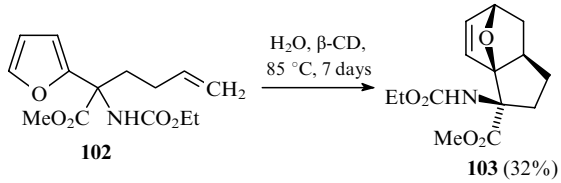


It has been shown [78] that [2-(2-furyl)ethyl] vinyl ketones **100**, the carbonyl group of which is conjugated with the double bond, are not converted into the derivatives **101** either upon long-term heating in toluene or at elevated pressures (CH_2Cl_2, 20 °C, 24 h, 1.9 GPa).

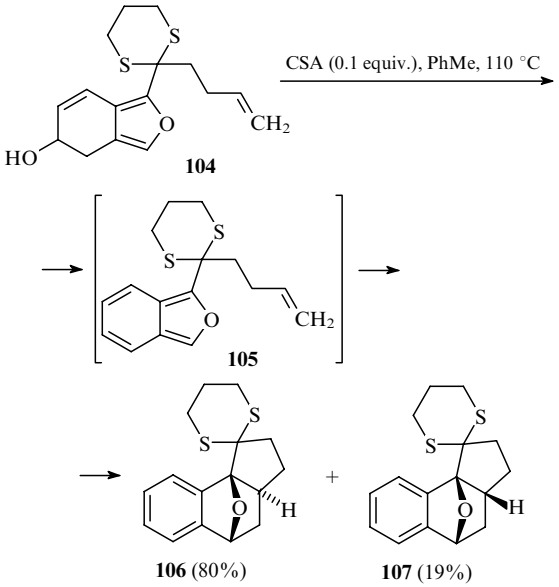


R = H, Me.

Intramolecular cyclisation of alkenylfuran **102** in the presence of β-cyclodextrin occurs in a stereoselective manner and yields the tricyclic *exo*-adduct **103**.[79]

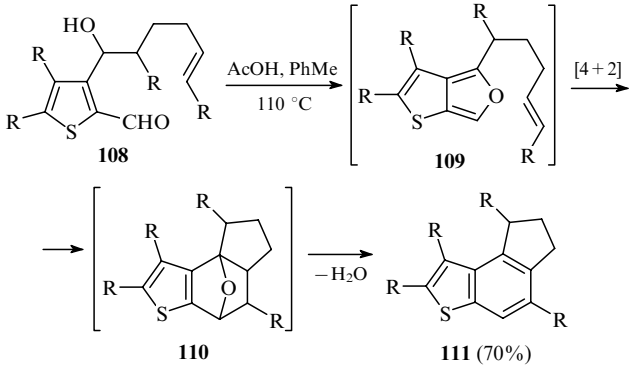


Cyclisation of 2-alkenylfurans [*c*]-fused to other carbo- and heterocycles has been investigated.[80 – 87] The cycloaddition of dihydroisobenzofuran **104** is preceded by dehydration by camphorsulfonic acid. The isobenzofuran **105** formed is unstable and is converted into a mixture of *exo*- (**106**) and *endo*-epoxy derivatives (**107**).[80]



CSA is camphorsulfonic acid.

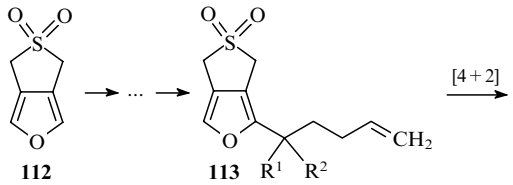
The German chemists Friedrichsen *et al.*[81 – 83] have carried out the synthesis of 2-alkenylfurans fused to the thiophene ring. These compounds underwent the intramolecular Diels – Alder reaction.

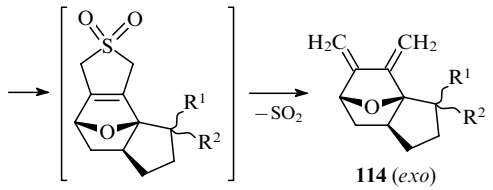


R = H, Me.

Acid-catalysed conversion of unsaturated thiophenecarbaldehydes **108** to intermediate 4-alkenylthieno[2,3-*c*]furans **109** is the key step in this reaction sequence. Further cycloaddition yields the tetracycle **110**, which is immediately dehydrated to yield fused benzothiophenes **111**.

A preparative procedure for the synthesis of 4,6-dihydrothieno[3,4-*c*]furan 1,1-dioxide **112** (see Ref. 84) developed in 1990 has made it possible to study the intramolecular cycloaddition of its derivatives **113**.[85 – 87]



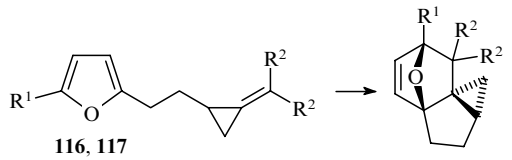


115 **114** (*exo*)

R^1-R^2	Reaction conditions	Yield (%)
O	*o*-xylene, 140 °C, 48 h	0
$S(CH_2)_2S$	*o*-xylene, 140 °C, 2 h	74
	PhMe, 110 °C, 8 h	70
	PhH, 80 °C, 144 h	70
CN, Me_3SiO	PhH, 80 °C, 24 h	63

It was found that the thermal Diels–Alder reaction is inapplicable to the ketone **113** (R^1-R^2 = O). The presence of an sp^3-hybridised carbon atom at the α-position of the substituent at position 2 of the furan ring is a prerequisite for the successful realisation of this reaction. The dienes **114** are formed as a result of sulfur(IV) oxide extrusion from the intermediate Diels–Alder adduct **115**. As the extrusion of SO_2 is carried out at high temperatures, *o*-xylene appears to be the solvent of choice for this reaction (b.p. = 140 °C).

An interesting example of an intramolecular cycloaddition in furans **116** and **117** containing a cyclopropylidene fragment has been described.[88] At elevated pressure, this reaction occurs in a stereoselective manner. X-Ray diffraction analysis revealed that compounds **118** and **119** are *exo*-adducts, the 4,5-methylene groups of which have a *trans*-configuration with respect to the epoxide bridge. The attempts at the intramolecular cyclisation of furans **116** and **117** at normal pressure were unsuccessful.



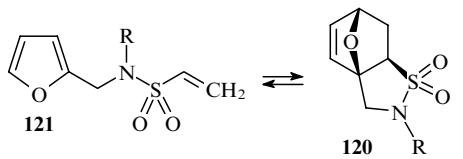
116, **117** **118**, **119**

R^1 = H, OMe; R^2 = H (**116**, **118**); R^1 = H, R^2-R^2 = $(CH_2)_2$ (**117**, **119**).

R^1	R^2-R^2	Reaction conditions	Yield (%)
H	2 H	PhMe, 110 °C	0
		n-C_5H_{12}, 90 °C, 43 h, 1 GPa	32
OMe	2 H	n-C_5H_{12}, 85 °C, 20 h, 1 GPa	95
H	$(CH_2)_2$	n-C_5H_{12}, 110 °C, 17 h, 1 GPa	82

e. Synthesis of 3-aza- and 3-oxa-4-thia-10-oxatricyclo-[5.2.1.0^{1,5}]dec-8-enes

Only two examples of the synthesis of systems containing two additional heteroatoms, *viz*., N, S or O, S, in the 10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene structure are known. 3-Aza-4-thia-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene 4,4-dioxides (**120**) were synthesised by Wibbeling *et al*.[89,90]

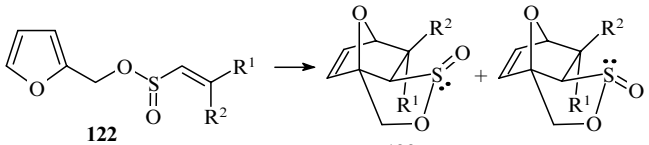


121 **120**

R	Reaction conditions	Yield (%)	Ref.
H	PhMe, 110 °C, 12 h	0	89
Me	PhMe, 110 °C, 7 h	29	89
Bn	PhMe, 110 °C, 30 h	91	89
S-(−)CH*MePh	PhMe, 110 °C, 16 h	73	91
	CH_2Cl_2, 20 °C, 14 h, 1.3 GPa	94	91

Cyclisation of vinylsulfonamides **121** into tricyclic compounds **120** is reversible; the reaction equilibrium depends on the size of the substituent R at the nitrogen atom: the larger the size the higher the concentration of the *exo*-adduct, sultam **120**.[89] The configuration of a chiral substituent at the nitrogen atom in the sulfonamide **121** is retained in the course of cyclisation; the optically active substrate yields a mixture of diastereomeric adducts.[90]

Furfuryl vinylsulfinates **122** are unstable[91] and cyclise *in situ* into isomeric thiocholanes **123** and **124**, which differ in the position of the oxygen atom at the sulfur atom relative to the epoxide bridge, under very mild conditions. Conditions have been found that favoured stereoselective formation of the epimer **123**. Where the double bond of the alkenyl fragment had the *E*-configuration, the reaction was carried out in the presence of 2,6-di-*tert*-butyl-4-methylphenol, a radical reaction inhibitor and an antioxidant. It is of note that the sulfur atom in the tricycles **123** and **124** is not inverted at room temperature as can be judged from the X-ray diffraction data.[91]



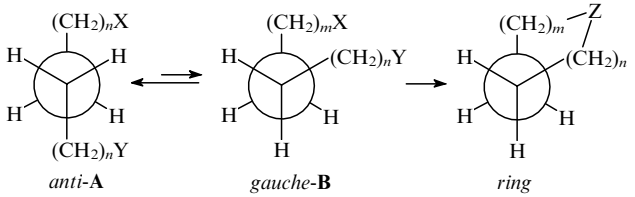
122 **123** **124**

R^1	R^2	Reaction conditions	Yield (%)	
			123	**124**
CO_2Me	H	CH_2Cl_2, 0.1 equiv. BHT, −30 °C, 19 h	71	12
		CH_2Cl_2, 0.1 equiv. BHT, −77 °C, 9 h	77	0
H	CO_2Me	CH_2Cl_2 , −50 °C, 19 h	47	0

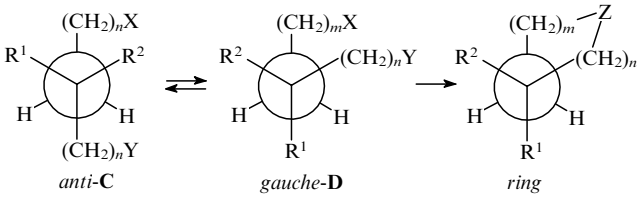
BHT is 2,6-di-*tert*-butyl-4-methylphenol.

In conclusion, mention should be made of the studies devoted to the theoretical aspects of the intramolecular Diels–Alder reaction of 2-alkenylfurans which yields oxabicycloheptenes fused to five-membered rings.

The dependence of this process on the Thorpe–Ingold effect (changes in the internal angle *Q* as the function of substituents in the alkenyl fragment, see Section IV.1.b) and the 'reactive rotamer effect', *i.e*., the stabilities of the reactive *gauche*-conformers leading to the transition state, was studied by Jung *et al*.[92–95] The latter was demonstrated in the studies of kinetics of the intramolecular cyclisation of ethyl 6-(2-furyl)-6,6-*R*,*R*′-4-oxohex-2-enoates and furfuryl fumarates. The observed effect can be interpreted in the following way. Alkenylfurans exist predominantly in the *anti*-conformation (X and Y are the diene and the dienophile, respectively).



anti-**A** *gauche*-**B** *ring*



The cycloaddition occurs when the molecule **A** adopts a much less favourable *gauche*-conformation **B**. The introduction of alkyl substituents at the carbon atoms in the alkenyl chain levels off the energies of the *anti*-(**C**) and *gauche*-(**D**) conformations due to steric interactions, this effect being directly correlated with the size of the substituents. This favours the attainment of the transition state and, correspondingly, the cyclisation.

Dolata [96] has developed an axiomatic model of this reaction which takes into account the energy characteristics of the transition state (a combination of WIZARD and MM2 programmes). This model can be used for predicting the stereochemistry of the adducts formed with a high degree of probability.

It has been demonstrated [97,98] that the rate of intramolecular cyclisation of *N*-alkyl-*N*-furfurylacrylamides increases when the reaction is carried out in water or aqueous alcohols. In the authors' opinion, the abnormally high rate of the cycloaddition in water is due to stabilisation of the transition state as a result of the formation of hydrogen bonds and reduction of the hydrophobic surface of the substrate in the course of activation (since this reaction is accompanied by the reduction of the molecular volume).

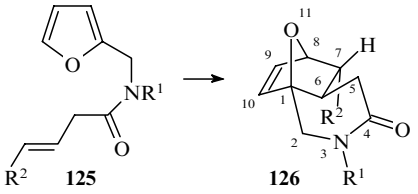
Interesting results illustrating the effect of complexation on the intramolecular cyclisation of (*E*)-3-(*N*-furfurylcarbamoyl)-acrylic acid have been reported.[99] It was found that the cyclisation rate decreased in the presence of *N*,*N*′-bis(2-methylpyridin-6-yl)terephthalamide and increased in the presence of *N*,*N*′-bis(2-methylpyridin-6-yl)isophthalamide due to the ability of the latter to stabilise the transition state owing to complexation. Similarly, terephthalamide stabilises the starting *N*-furfurylfumaramide and thus hinders the cyclisation.

2. Six-membered rings

a. Synthesis of 3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes

The formation of six-membered nitrogen-containing rings by intramolecular cycloaddition of furan derivatives requires more drastic conditions (*e.g.*, high temperature, high pressure) than the annelation of five-membered rings. The reaction products also contain predominantly *exo*-isomers.

Studies of the intramolecular cycloaddition of *N*-furfurylamides **125** containing a β,γ-double bond in the acyl fragment revealed [100] that *N*-unsubstituted derivatives ($R^1 = H$) do not react even under drastic conditions, whereas *N*-substituted furfurylamides **125** yield hydrogenated epoxyisoquinolinones **126**.

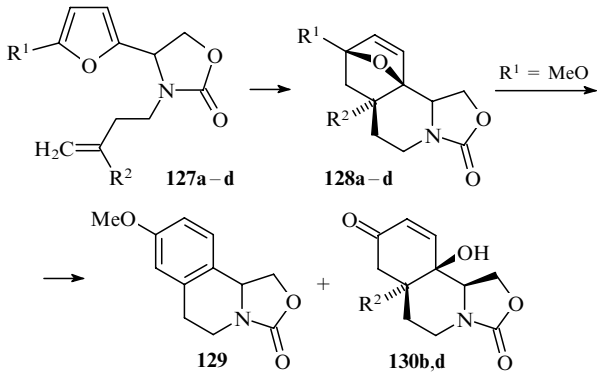


125 **126**

R^1	R^2	Reaction conditions	Yield (%)
H	H	180 °C	0
H	$(CH_2)_2CO_2Me$	130 °C	0
Bn	H	PhMe, 120 °C, 72 h	85
Bn	$(CH_2)_2CO_2Me$	PhMe, > 250 °C, 90 h	14
DBAn	$(CH_2)_2CO_2Me$	PhMe, 130 °C, 90 h	72

DBAn is 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yl.

The intramolecular cyclisation of furyloxazolidones **127a**–**d** containing a non-activated alkenyl fragment at the nitrogen atom has been described.[79] The structure of the cycloadduct depends on the substituents in the furan and alkenyl fragments of the original molecule. In the case of furyloxazolidone **127a** ($R^1 = H$), the reaction stops at the *exo*-tetracycle **128**. In the presence of a methoxy group (compounds **127b**,**d**) at position 5 of furan, the primary adduct **128** eliminates a molecule of water or methanol to give a mixture of hydrogenated isoquinolinooxazolidones **129** and/or **130**. A phenyl substituent at the double bond of the oxazolidones inhibits this reaction; no cycloadducts are formed from compound **127a,** while oxazolidone **127d** gives a hydroxy derivative **130d** in low yield. All these reactions were carried out in sealed tubes.

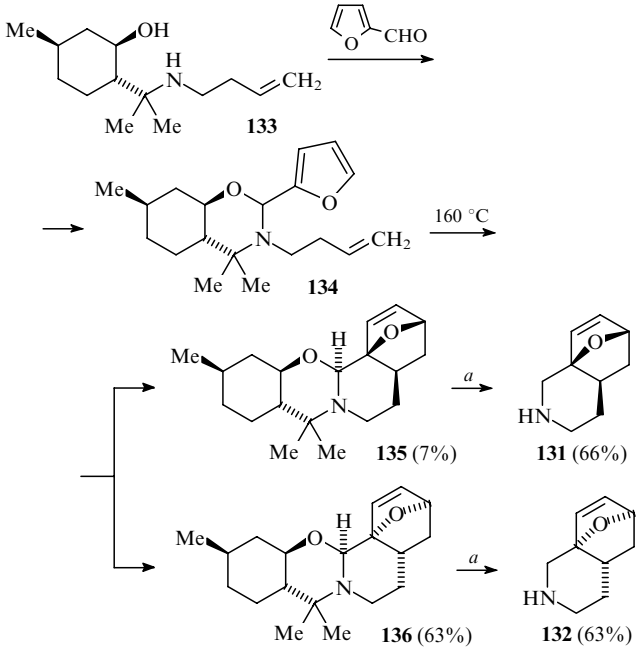


127a–**d** **128a**–**d** **129** **130b**,**d**

Compound **127**	R^1	R^2	Reaction conditions	Product [yield (%)]
a	H	H	PhMe, 200 °C, 130 h	**128** (56)
			H_2O, β-CD (1 equiv.) [a]	**128** (84)
b	OMe	H	PhH, 165 °C, 120 h	**129** (40), **130** (55)
c	H	Ph	PhMe, > 250 °C	–
d	OMe	Ph	PhMe, > 250 °C, 90 h	**130** (13)

[a] The following temperature conditions were used: 55 °C, 30 h; 75 °C, 60 h; 90 °C, 3 days.

Enantiomers of 3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene (**131** and **132**) were synthesised and isolated in the individual state.[101] The starting amino alcohol **133** was synthesised from the optically active (−)-8-aminomenthol. Its reaction with furfural



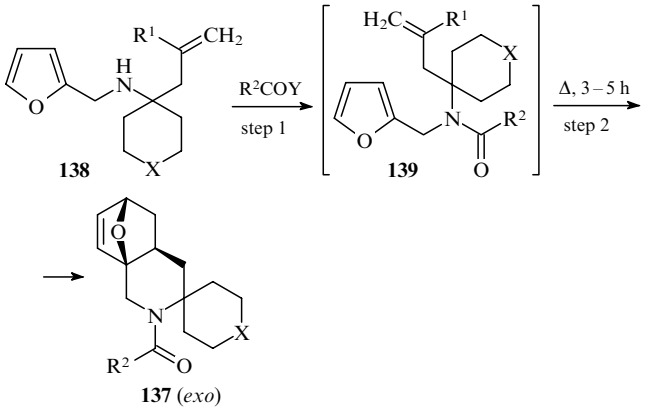
133 **134** **135** (7%) **131** (66%) **136** (63%) **132** (63%)

(*a*): 1) AlH_3, 2) PCC, 3) KOH.

yields alkenylfuran **134**, which yields a mixture of intramolecular cycloaddition products **135** and **136** upon heating to 160 °C.

The diastereomers **135** and **136** were separated chromatographically and converted into the target tricycles **131** and **132** using the aforementioned reaction sequence (see Section IV.1.a).

The recently published papers [102, 103] are devoted to the synthesis and analysis of chemical properties [104, 105] of 4-spiroannelated epoxyoctahydroisoquinolines **137** (Table 7).

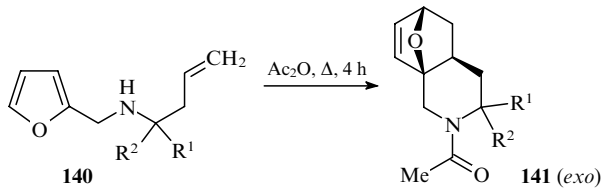


137 (*exo*)

Y = R^2CO_2, Cl.

The formation of compounds **137** from homoallylamines **138** (R^1 = H) occurs under the action of carboxylic anhydrides (or chlorides) *via* the intermediate *N*-acyl derivatives **139**, which could be isolated in none of the cases studied. The best yields (50% – 70%) of the Diels – Alder adducts were obtained when the reaction was carried out in boiling acetic anhydride. It was found [102] that the size of the spiro-fused ring and the nature of the acyl radical R^2 have little effect on the reaction (see Table 7). The failure to perform the cyclisation of the methallyl-substituted analogues **138** (R^1 = Me) under identical conditions can be explained by steric reasons. In this case, the reaction stops in the step of formation of the *N*-acetyl derivatives **139**.

In a similar way, mono- and disubstituted furfurylamines **140** were transformed to hydrogenated epoxyisoquinolines **141** (yields 34% – 42%).[102]

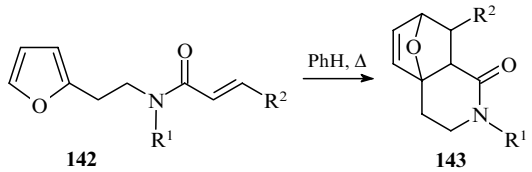


140 **141** (*exo*)

R^1 = Ph, 4-PhC_6H_4; R^2 = H, Me, Ph.

b. Synthesis of 4-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-ones

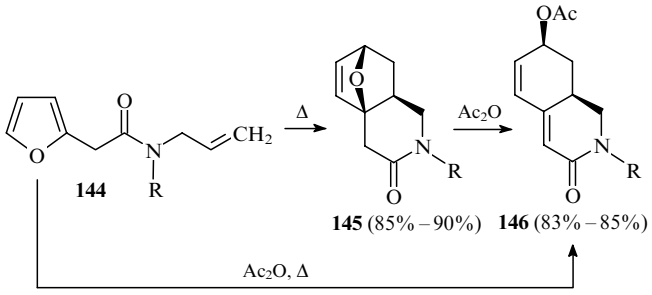
There are only a few examples of the synthesis of these tricyclic systems.[106, 107] One of the first reports describes unsuccessful attempts of monocyclisation of *N*-unsubstituted acrylamide **142** (R^1 = R^2 = H). However, the *N*-methyl derivative gives the tricyclic adduct **143** in quantitative yield. The methyl group at the double bond of the alkenyl substituent considerably hinders this reaction: the expected epoxyoctahydroisoquinolone **143** (R^1 = R^2 = Me) could only be isolated in low yield.



142 **143**

R^1 = Me: R^2 = H (100%), Me (12%).

Synthesis of analogues of berberine alkaloids involved the intramolecular cyclisation of unsaturated furylacetic amides **144**.[106] They cyclise on heating in toluene to give epoxyoctahy-



R = H, Me, 3,4-$(MeO)_2C_6H_3(CH_2)_2$.

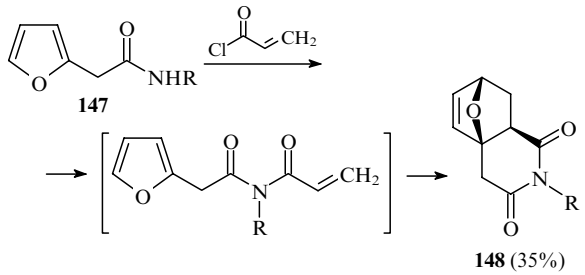
Table 7. Preparation of 4-spiroannelated 3-aza-11-oxatricycloundecenes **137**.

R^1	R^2	X	Reaction conditions			Yield (%)	Ref.
			reagent (solvent)	T /°C	t /h		
H	Me	–	Ac_2O	140	4	48	102, 103
H	Me	CH_2	Ac_2O	140	3	68 – 71	102, 103, 105
H	Me	$(CH_2)_2$	Ac_2O	140	3	66	102, 103
H	Me	$CHBu^t$	Ac_2O	140	5	69	102, 103
H	Me	NMe	Ac_2O	140	3	50	102
H	Me	NEt	Ac_2O	140	3	48	102, 103
H	H	CH_2	HCO_2H, Ac_2O (3 : 1)	101	5	22	102
H	Et	CH_2	$(EtCO)_2O$	160	4	52	102
H	CH_2Cl	CH_2	$ClCH_2COCl$, Et_3N (MeCN)	25	4	40	102
H	Ph	CH_2	PhCOCl, Et_3N (PhMe)	110	3	61	102
H	CF_3	CH_2	$(F_3CCO)_2O$ (*o*-xylene)	140	5	40	102
H	H	$(CH_2)_2$	HCO_2H, Ac_2O (3 : 1)	101	5	23	102
H	Et	$(CH_2)_2$	$(EtCO)_2O$	160	4	56	102
H	CH_2Cl	$(CH_2)_2$	$ClCH_2COCl$, Et_3N (MeCN)	25	4	38	102
H	Ph	$(CH_2)_2$	PhCOCl, Et_3N (PhMe)	110	3	56	102
H	CF_3	$(CH_2)_2$	$(F_3CCO)_2O$ (*o*-xylene)	140	5	40	102
Me	Me	CH_2	Ac_2O	140	4	69 [a]	102
Me	Me	$(CH_2)_2$	Ac_2O	140	4	67 [a]	102

[a] The yields of compounds **139** are indicated.

droisoquinolones **145**; opening of the oxygen bridge upon treatment with acetic anhydride results in diene **146**. These compounds can also be prepared in one step by heating alkenylfurans **144** with an excess of acetic anhydride.

Acylation of the amide **147** with acryloyl chloride yields the tricyclic compound **148** in one step. In both cases considered, the [4 + 2]-cycloaddition is stereoselective: compounds **145** and **148** represent *exo*-adducts.



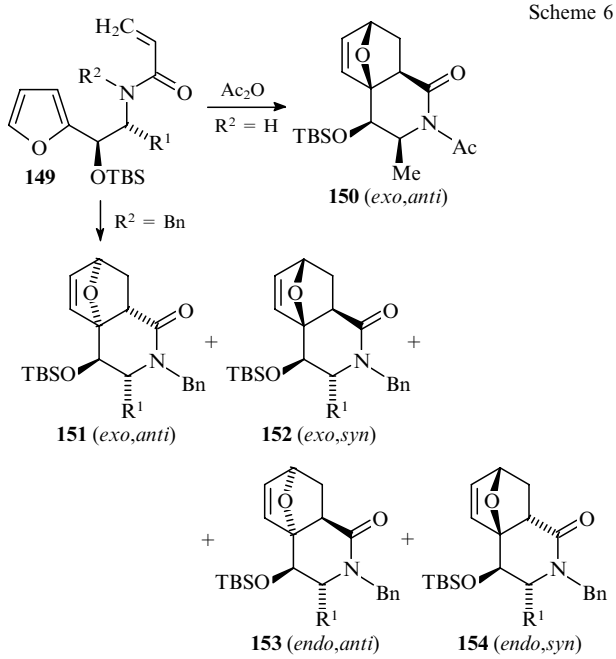
147 **148** (35%)

R = 3,4-$(MeO)_2C_6H_3(CH_2)_2$.

The thermal intramolecular [4 + 2]-cycloaddition in the amides **149** occurs smoothly; the reaction products are formed in high yields.[107, 108] The hydrogenated *N*-acetylepoxyisoquinolone **150** was prepared by treatment of alkenylfuran **149** (R^2 = H) with acetic anhydride (yield 47%) (Scheme 6).

The stereoselectivity of the intramolecular cycloaddition of *N*-acryloylfurylethylamine **149** (R^2 = Bn) depends on the steric effect of the substituent R^1. Of the four possible geometric isomers, in the case of small groups (R^1 = H, Me, CN), the *exo*,*anti*-adduct **151** is predominant. The selectivity of the cycloaddition decreases with an increase in the size of the substituent. For R^1 = Et, *exo*,*syn*- (**152**) and *endo*,*anti*-adducts (**153**) appear; for R^1 = Ph, the latter becomes predominant. It is interesting to note that the *endo*,*syn*-isomer **154** was found in none of the cases studied. The yields of compounds were determined after separation of the isomers by column chromatography.

Scheme 6



149 **150** (*exo*,*anti*) **151** (*exo*,*anti*) **152** (*exo*,*syn*) **153** (*endo*,*anti*) **154** (*endo*,*syn*)

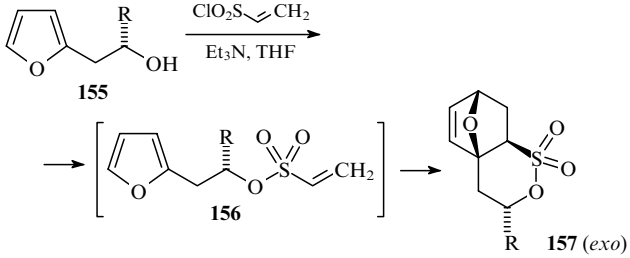
R^1 = H, Bn; TBS is *tert*-butyldimethylsilyl.

R^1	Product [yield (%)]
H	**151** [90]
Me	**151** [74]
Et	**151** [42], **152** [22], **153** [20]
Ph	**151** [8], **153** [42]
CN	**151** [87]

c. Synthesis of 11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes containing heteroatoms

This section considers annelation of an additional six-membered ring containing different heteroatoms (except for nitrogen considered above) to 7-oxabicyclo[2.2.1]hept-2-enes.

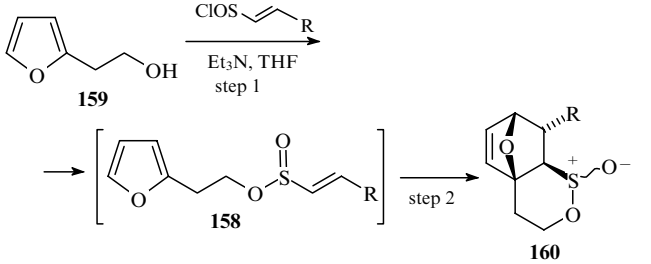
Esterification of alcohols **155** with ethylenesulfonyl chloride yields the corresponding esters **156**.[109] However, these undergo intramolecular cycloaddition in the course of isolation; the Diels – Alder *exo*-adducts (sultones **157**) are formed in high yields.



155 **156** **157** (*exo*)

R	*T* /°C	*t* /h	Yield (%)
Me	25	3	90
Et	25	3	92
Pr^i	0	1	87

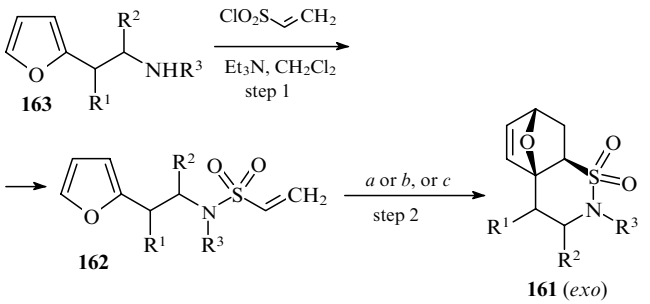
A similar conversion of sulfinates **158** prepared from 2-(2-furyl)ethanol **159** and unsaturated sulfinyl chlorides has been described.[91] The presence of tetravalent sulfur hinders the intramolecular cycloaddition in comparison with sulfonates **156**; this reaction occurs either on heating or in the presence of Lewis acids as catalysts. The *exo*-adducts **160** are usually formed as mixtures of two isomers, like compounds **123** and **124** (see above), which differ in the relative positions of the S = O (or $S^+ - O^-$) bond and the epoxide bridge. The isomer ratio depends on the reaction conditions and the catalyst used.[91]



159 **158** **160**

R	Conditions of step 2	Yield (%)
H	PhMe, 68 °C, 24 days	54
	PhMe, Et_2AlCl (1.2 equiv.), 62 °C, 7 h	53
	CH_2Cl_2, Et_2AlCl (1.2 equiv.), 25 °C, 2 days	37
	PhMe, $ZnBr_2$ (1.2 equiv.), 25 °C, 5 days	30
CO_2Me	CH_2Cl_2, −30 °C, 19 h	42
	CH_2Cl_2, $ZnBr_2$ (1.2 equiv.), 25 °C, 3.5 h	63

A two-step synthesis of sultams **161**, which includes the [4 + 2]-cycloaddition of vinylsulfonylamides **162** (see also Section IV.1.d, synthesis of compound **120**), has been described.[89, 90] *N*-Benzylvinylsulfonamide derivatives **162** prepared from substituted 2-(2-furyl)-ethylamines **163** undergo cyclisation to *exo*-δ-sultams **161** even at room temperature.

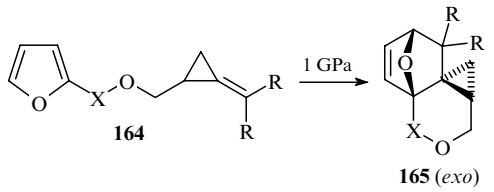


(*a*) Et_3N, CH_2Cl_2, 0 to 25 °C, 3 h; (*b*) PhMe, 110 °C, 16 h;
(*c*) CH_2Cl_2, 25 °C, 1.3 GPa, 14 h.

R^1	R^2	R^3	Conditions of step 2	Yield (%)	Ref.
H	Me	Bn	*a*	78	89
H	Me	(*S*)-C*HMePh	*b*	85–87	90
			c	98	90
Me	H	Bn	*a*	92	89

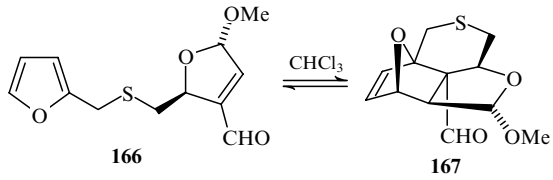
The stereochemistry of the intramolecular Diels–Alder reaction of diastereomeric amides **162** (R^2 = Me) prepared from the optically active (*S*)-(−)-α-methylbenzylamine has been studied. A detailed analysis of the diastereomeric composition of the tricyclic sultams **161** formed is carried out.[90] It is noteworthy that the cyclisation of *N*-phenethyl-substituted alkenylfurans **162** requires more drastic conditions than that of their *N*-benzyl analogues;[89] however, the yields of the adducts **161** are high in all cases.

A series of novel oxabicycloheptanes containing an oxygen atom or oxygen and silicon atoms in the annelated six-membered rings were prepared by intramolecular cycloaddition of methylenecyclopropylmethyl furyl ethers **164** at elevated pressure.[88] As in the previous cases, *exo*-3,11-dioxatricyclo[6.2.1.$0^{1,6}$]undec-9-enes **165**, the fused cyclopropane ring of which occupies the *trans*-position relative to the epoxide bridge, are formed selectively.

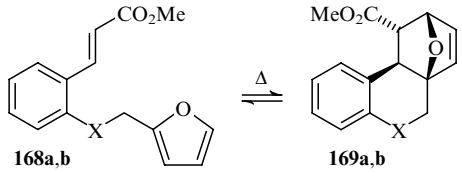


R–R	X	Solvent	*T* /°C	*t* /h	Yield (%)
2 H	CH_2	MeCN–THF (1 : 1)	85	45	47
		MeCN–THF (1 : 1)	100	20	50
2 H	$SiMe_2$	Et_2O	125	30	25
$(CH_2)_2$	CH_2	MeCN–THF (1 : 1)	70	48	46
		MeCN–THF (1 : 1)	75	70	42
$(CH_2)_2$	$SiMe_2$	Et_2O	130	20	83

The equilibrium between the sulfide **166** and the intramolecular cycloaddition product **167** in chloroform has been studied at different temperatures.[110] It was found that the equilibrium is established slowly and the concentration of the Diels–Alder adduct **167** increases with a decrease in the temperature. After 70 h at 25 °C, the ratio **166** : **167** was 72 : 28, whereas after 53 h at 60 °C it had changed to 56 : 44. The adduct **167** formed with diastereoselectivity > 99% was isolated by column chromatography on silica gel (eluent, heptane–Et_3N) (yield 71%).

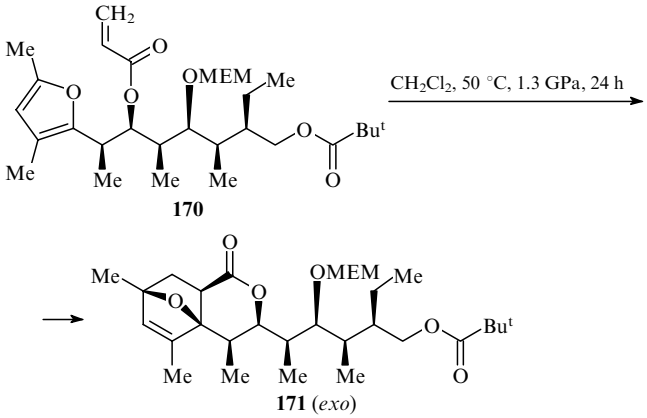


A similar reversible intramolecular [4 + 2]-cycloaddition was described for the *ortho*-substituted cinnamates **168a**,**b**.[111] Upon boiling in toluene (**168b**, 7 h) or xylene (**168a**, 47 h), these compounds are converted to fused heterocycles **169** in low yields.



X = O (**a**, 8%), NEt (**b**, 34%).

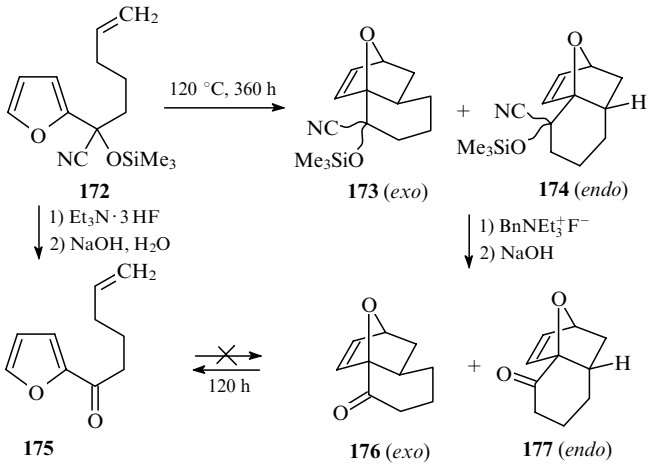
The cyclisation of unsaturated furan derivative **170** can be achieved only at elevated pressure.[112] The *exo*-adduct **171**, which represents an individual stereoisomer, is formed in 28% yield.



MEM = $CH_2O(CH_2)_2OMe$.

d. Synthesis of 11-oxatricyclo[6.2.1.$0^{1,6}$]undec-9-enes

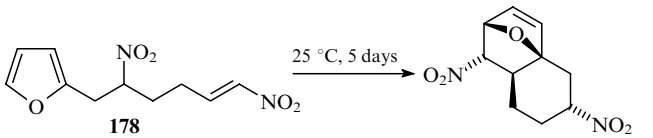
The intramolecular Diels–Alder reaction of unsaturated furan derivatives that results in 11-oxatricyclo[6.2.1.$0^{1,6}$]undec-9-enes is explored much better (in a large measure, owing to the studies by Keay *et al.* and by De Clercq *et al.*) than the cyclisation of their aforementioned heterocyclic analogues. This can be attributed to the fact that the hydrogenated epoxynaphthalenes thus formed are easily converted into polysubstituted decalins which represent structural fragments of steroids and terpenes. This reaction is attractive from the synthetic standpoint, since the formation of *exo*-adducts occurs with high stereoselectivity with only few exceptions. Successful intramolecular cycloaddition usually requires the presence of electron-withdrawing groups at the double bond of the alkenyl substituent. There are only a few examples concerning successful cyclisation of alkenylfurans containing non-activated unsaturated fragments.[113,114] Thus cyanotrimethylsilyloxyhexenyl derivative **172** undergoes slow cyclisation on heating at 120 °C to yield a mixture of isomers **173** and **174**. The stereoselectivity of this reaction is rather low: the *exo:endo* ratio is 88 : 12 and the total yield is 77%.[114]



172 **173** (*exo*) **174** (*endo*) **175** **176** (*exo*) **177** (*endo*)

Attempts to perform the intramolecular cycloaddition of acylfuran **175**, which is a furan **172** analogue, failed. Epoxynaphthalenones **176** and **177**, which represent the desilylation products of the isomers **173** and **174,** are quantitatively converted into acylfuran **175** upon retro-Diels–Alder reaction at high temperatures.

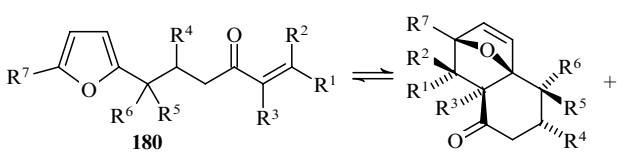
Stereoselective cyclisation of 2-alkenylfuran **178**, which contains a dienophile fragment activated by a nitro group, occurs smoothly even at 25 °C and yields tricyclic *exo*-adduct **179**.[115] In all probability, the transition state that would yield the *endo*-isomer is destabilised by the 1,3-diaxial interaction of the oxygen atom of the epoxide bridge with the nitro group.



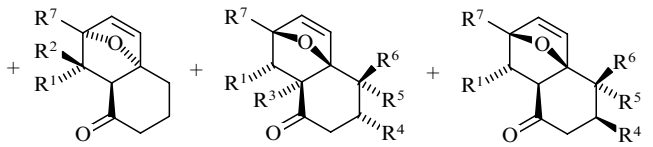
178 **179** (*exo*, 91%)

In one of the pioneering works [116] devoted to the synthesis of unsubstituted 11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene, the thermal intramolecular cyclisation of 3-furylpropylvinyl ketone **180** (R^1-R^7 = H) under variable conditions was studied. This reaction was found to be reversible; the best yield of the adduct **181** (> 70%) was attained in boiling CH_2Cl_2 or at room temperature in the presence of Florisil® (a weak Lewis acid which represents a mixture of magnesium silicates). The equilibrium could be shifted towards the adduct **181** (R^1-R^7 = H) only at elevated pressure.[78, 117] Using NMR spectroscopy, it was shown that 10 min exposure of the ketone **180** (R^1-R^7) at room temperature and 1 GPa resulted in its quantitative cyclisation to yield a mixture of *exo*- and *endo*-epoxyoctahydronaphthalenes **181** and **182** (95 : 5).[78, 117]

The intramolecular Diels–Alder reaction of substituted 3-furylalkylvinyl ketones **180** yields four stereoisomeric cycloadducts, *viz*., compounds **181**–**184** (in the absence of substituents, the *exo*-structures are degenerate). This process was studied in great detail (see Table 8; the cited data were predominantly taken from the works by Keay *et al*.).



180 **181** (*exo*)



182 (*endo*) **183** (*exo*) **184** (*exo*)

In addition to the experimental work,[118–125] the same group of investigators have performed a series of theoretical calculations [127, 128] of the effects of substituents R^1-R^7 and reaction conditions (*e.g*., the use of Lewis acids as catalysts, variation of temperature) on the intramolecular Diels–Alder reactions of methyl-substituted 3-furylpropylvinyl ketones **180**, which yield 11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes.

Based on the data obtained (Table 8), the following conclusions can be made. Lewis acids shift the equilibrium of the intramolecular cycloaddition of alkenylfurans **180** towards the adducts **181** and **182**. These included ZnI_2 (see Refs 121 and 125), $SnCl_4$, $BF_3\cdot OEt_2$, $TiCl_4$,[121] Et_2AlCl, $MeAlCl_2$,[120–123] 2 M $CaCl_2$,[118, 119, 121] Florisil,[120, 121, 123, 124] molecular sieves 3 Å [125] and some other catalysts in various solvents in the temperature interval from −78 to 80 °C (see Table 8). Hexane and toluene are undesirable as solvents for this reaction. Dichloromethane proved to be the solvent of choice, while ethyl- and methylaluminium dichlorides ($RAlCl_2$, R = Me, Et) and Florisil were the most efficient catalysts. A high degree of conversion of the substrates was also observed in the presence of titanium chloride or boron trifluoride etherate, but this was accompanied by resinification even at low temperatures.[121] $MeAlCl_2$ manifested the highest catalytic activity from −78 to 65 °C,[120] while Florisil ensures good yields of the Diels–Alder adducts **183** and **184** at room or elevated temperatures (25–40 °C).

Interestingly, the cyclisation rate depended on the amount of the catalyst used. For example, the yield of the Diels–Alder adducts with 10 mol.% of $MeAlCl_2$ was higher than in the presence of its 110% molar excess.[121] In this case, the equilibrium **183** ⇆ **180** was established after 5 min and the product : substrate ratio was ~1 : 2. A second stereoisomer (compound **184**, 14%) was detected in the reaction medium after 5 min in the presence of 0.1 equiv. of $MeAlCl_2$; its concentration dropped to zero with time.[121–123] The NMR [127] and quantum chemical calculations [128] suggest that the position of equilibrium of the cycloaddition is controlled by the Lewis acid. The amount of catalyst required for this reaction is determined by the relative basicities of the functional groups in the starting compounds and cyclisation products, since the latter form complexes with the Lewis acid. If the basicities of the functional groups in the final product are lower than in the original alkenylfuran **180**, the epoxyoctahydronaphthalene–Lewis acid complex formed easily dissociates with the regeneration of the catalyst. In this case, the latter should be used in catalytic amounts in order to promote the reaction. If the basicities of the functional groups in the product exceed those in the original alkenylfuran **180**, the complex formed is stable and 1 equiv. of the Lewis acid should be added.

No unambiguous conclusions concerning the effect of substituents on the cyclisation of alkenylfurans **180** can be made. It is evident, however, that the introduction of methyl groups ($R^5 = R^6$ = Me) into the alkenyl fragment of furan **180** favours the reaction due to manifestation of the *gem*-dialkyl effect.

It was demonstrated[124] that in the presence of a 10-fold excess (by weight) of Florisil an equilibrium was established between alkenylfuran **180** and the *exo*-adducts **181** and **183**; the yields of the latter increase with temperature and reaction time.

The cyclisation of methyl-substituted alkenylfurans **180** [$R^1(R^3, R^7)$ = Me] was studied under varied conditions including aqueous media and elevated pressure.[118, 119] These studies showed that the presence of methyl groups in both the furan ring and at the double bond of the starting compounds prevents the formation of

Table 8. Cyclisation of 3-furylpropyl vinyl ketones **180**.

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Reaction conditions	Composition of the reaction mixture [product, yield (%)] [a]	Ref.
H	H	H	H	H	H	H	H_2O, 25 °C, 4 days	**181** : **180** = 1 : 1 (69) [b]	119
							$CaCl_2$ (2 M), 25 °C, 4–6 days	**181** : **180** = 1 : 1 (66) [b]	118, 119
							Florisil, CH_2Cl_2, 25 °C, 6 days	**181** : **180** = 9 : 1 (**181**, 62–72)	116, 118–121
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 1 h	**181** (99)	120, 121
							CH_2Cl_2, 0.5 GPa, 20 °C, 12 h	**181** (65)	118
							CH_2Cl_2, 1 GPa, 20 °C, 10 min	**181** : **182** = 95 : 5	78
							CH_2Cl_2, 1.2 GPa, 25 °C, 25 h	**181** (51)	118, 120
H	H	H	H	H	H	Me	H_2O, 25 °C, 4 days	**181** : **180** = 1 : 3 (**181**, 72)	119
							$CaCl_2$ (2 M), 25 °C, 4–6 days	**181** : **180** = 1 : 2 (68–78) [b]	118, 119
							fluorosil,[c] CH_2Cl_2, 25 °C, 14 days	**181** : **180** = 7 : 1 (**181**, 65)	119
							Florisil, CH_2Cl_2, −78 °C, 14 days	**181** : **180** = 88 : 12 (**181**, 65)	121
							Florisil, CH_2Cl_2, 25 °C, 14 days	**181** : **180** = 88 : 12 (**181**, 52)	120
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 1 h	**181** (99)	120, 121
							CH_2Cl_2, 1 GPa, 20 °C, 10 min	**181** (100)	78
							CH_2Cl_2, 1.25 GPa, 25 °C, 24 h	**181** (56)	118, 120
H	H	Me	H	H	H	H	H_2O, 25 °C, 4 days	**181** : **180** = 2 : 1 (70) [b]	119
							fluorosil,[c] CH_2Cl_2, 25 °C, 14 days	see [d]	119
							Florisil, CH_2Cl_2, 25 °C, 14 days	**181** : **180** = 7 : 1 (65)	118
							$CaCl_2$ (2 M), 25 °C, 4–6 days	**181** : **180** = 1 : 2 (68) [b]	118
							$CaCl_2$ (2 M), 25 °C, 4 days	**181** : **180** = 4 : 1 (73) [b]	119
							$CaCl_2$ (2 M), 25 °C, 4 days	**181** : **180** = 1 : 1	121
							ZnI_2, CH_2Cl_2, −78 °C, 1 h	see [d]	121
							ZnI_2, CH_2Cl_2, 25 °C, 3 h	**181** : **180** = 31 : 69	121
							ZnI_2, CH_2Cl_2, 25 °C, 39 h	**181** : **180** = 35 : 65	121
							$SnCl_4$, CH_2Cl_2, −78 °C, 1 h	**181** : **180** = 76 : 24	121
							$BF_3 \cdot OEt_2$, CH_2Cl_2, −78 or −50 °C, 2.5–3.5 h	**181** : **180** = 72 : 28	121
							$TiCl_4 \cdot Ti(OPr^i)_4$, CH_2Cl_2, −78 or 50 °C, 2.5–4.5 h	**181** : **180** = 68 : 32	121
							$MeAlCl_2$, CH_2Cl_2, −78 °C, 2.5 h	**181** : **180** = 78 : 22 (**181**, 76)	120
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 or −50 °C, 2.5 h	**181** : **180** = 65 : 35 (**181**, 63)	121
							$EtAlCl_2$, CH_2Cl_2, −78 or −50 °C, 2.5 h	**181** : **180** = 65 : 35	121
							Me_2AlCl, CH_2Cl_2, −50 °C, 2.5 h	**181** : **180** = 68 : 32	121
							Et_2AlCl, CH_2Cl_2, −50 °C, 2.5 h	**181** : **180** = 65 : 35	121
							CH_2Cl_2, 0.5 GPa, 20 °C, 12 h	see [d]	118
							CH_2Cl_2, 1.25 GPa, 20 °C, 24 h	**181** (55)	118
H	Ac	H	H	H	H	H	CH_2Cl_2, 1.9 GPa, 20 °C, 24 h	**181** : **182** = 15 : 85	78
Me	H	H	H	H	H	H	H_2O, 25 °C, 4 days	**181** : **180** = 2 : 1 (70) [b]	119
							Florisil or fluorosil,[c] CH_2Cl_2, −78 or 25 °C, 14 days	see [d]	118–121
							$CaCl_2$ (2 M), 25 °C, 4–6 days	**181** : **180** = 4 : 1 (73)	118
							$CaCl_2$ (2 M), 25 °C, 4 days	**181** : **180** = 2 : 1 (69) [b]	119
							$MeAlCl_2$, CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 22 : 78 (**181**, 11)	120
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 22 : 78 (**181**, 11)	121, 122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 or −78 °C, 2 h	**181** : **180** = 69 : 31 (**181**, 66–69)	121, 122
							CH_2Cl_2, 1.25 GPa, 20 °C, 24 h	**181** (52)	118
Ac	H	H	H	H	H	H	CH_2Cl_2, 1.9 GPa, 20 °C, 24 h	**181** : **182** : **180** = 70 : 15 : 15	78
H	H	H	H	H	Me	Me	Florisil, CH_2Cl_2, 25 °C, 13 days	**183** : **181** = 87 : 13 (**183**, 70)	123
							Florisil, CH_2Cl_2, 40 °C, 24 h	**183** : **181** : **180** = 84 : 16 : 1 (**183**, 67)	123
							Florisil, CH_2Cl_2, 40 °C, 2 days	**183** : **181** : **180** = 75 : 18 : 7 (**183**, 60)	123
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 15 min	**183** : **181** = 9 : 1 (**183**, 88)	123
H	H	H	H	Me	H	Me	Florisil, CH_2Cl_2, 20 °C, 1 h	**181** : **183** : **180** = 21 : 73 : 6	124
							Florisil, CH_2Cl_2, 20 °C, 12 h	**181** : **183** : **180** = 43 : 43 : 14	124
							Florisil, CH_2Cl_2, 40 °C, 24 h	**181** : **183** : **180** = 78 : 15 : 7	124
							Florisil, CH_2Cl_2, 40 °C, 2 days	**181** : **183** : **180** = 75 : 18 : 7	124
							Florisil, CH_2Cl_2, 20 °C, 14 days	**181** : **183** : **180** = 85 : 13 : 2	124
H	H	H	H	Me	Me	H	Florisil, CH_2Cl_2, 25 °C, 6 days or −78 °C, 12 h	**181** (88)	120, 121
H	H	H	Me	H	H	Me	Florisil, CH_2Cl_2, 20 °C, 12 h	**181** (100)	124
							Florisil, CH_2Cl_2, 25 °C, 6 days	**183** (85)	123

Table 8 (continued).

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Reaction conditions	Composition of the reaction mixture [product, yield (%)] [a]	Ref.
H	H	Me	H	H	H	Me	H_2O, 25 °C, 4 days	**181** : **180** = 1 : 1 (71) [b]	119
							$CaCl_2$ (2 M), 25 °C, 4–6 days	**181** : **180** = 2 : 1 (69–78) [b]	118, 119
							CH_2Cl_2, 1.25 GPa, 20 °C, 24 h	**181** (50)	118
H	H	Me	H	H	Me	Me	Florisil, CH_2Cl_2, 25 °C, 24 h	**183** : **181** : **180** = 27 : 1 : 73 (**183**, 22)	123
							Florisil, CH_2Cl_2, 25 °C, 4 days	**183** : **181** : **180** = 35 : 1 : 65 (**183**, 28)	123
							Florisil, CH_2Cl_2, 25 °C, 13 days	**183** : **181** : **180** = 47 : 4 : 48 (**183**, 38)	123
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 5 min	**183** : **181** : **180** = 88 : 3 : 9 (**183**, 81)	123
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 81 : 19 (**181**, 80)	120–122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**181** (98)	122
H	H	Me	H	H	H	Me	$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −78 °C, 2 h	**181** (99)	121
H	Ac	H	H	H	H	Me	CH_2Cl_2, 1.9 GPa, 20 °C, 24 h	**181** : **182** = 34 : 30	78, 117
Me	H	H	H	H	H	Me	$CaCl_2$ (2 M), 25 °C, 4–6 days	**181** : **180** = 1 : 2 (61) [b]	118, 119
							Florisil, CH_2Cl_2, 25 or −78 °C, 6 days	see [d]	118, 120, 121
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 18 : 82 (**181**, 18)	120–122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**181** : **180** = 76 : 24 (**181**, 73)	122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −78 °C, 2 h	**181** : **180** = 76 : 24 (**181**, 74)	121
							CH_2Cl_2, 1.25 GPa, 20 °C, 24 h	**181** (43)	118
Ac	H	H	H	H	H	Me	CH_2Cl_2, 1.9 GPa, 20 °C, 24 h	**181** : **182** = 95 : 5	78, 117
Ac	H	H	H	H	OMe	H	CH_2Cl_2, 20 °C, 24 h	see [d]	125
							Et_2O, SiO_2, 20 °C, 0.5 h	**181** (15)	125
							3 Å sieves, PhMe, 110 °C, 24 h	see [d]	125
							3 Å sieves, CH_2Cl_2, 0 °C, 6 h	**181** (27)	125
							3 Å sieves, CH_2Cl_2, 20 °C, 24 h	**181** (40)	125
							Florisil, CH_2Cl_2, 20 °C, 2 days	**181** (44)	125
							ZnI_2, CH_2Cl_2, 20 °C, 2 days	**181** (67)	125
Me	H	H	Me	H	H	H	$MeAlCl_2$, CH_2Cl_2, −78 °C, 5 h	**181** : **184** = 8.6 : 1 (92)	126
Me	H	Me	H	H	H	H	$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 2 h	see [d]	121
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −78 °C, 2 h	**181** : **180** = 5 : 95 (**181**, 4)	121
H	H	H	H	Me	Me	Me	Florisil, CH_2Cl_2, 25 °C, 12 h	**181** (96)	120
							Florisil, CH_2Cl_2, −78 °C, 12 h	**181** (96)	121
H	H	Me	Me	H	H	Me	Florisil, CH_2Cl_2, 20 °C, 5 days	**183** : **180** = 38 : 62	123, 124
							Florisil, CH_2Cl_2, 20 °C, 9 days	**183** : **180** = 48 : 52	123, 124
							Florisil, CH_2Cl_2, 20 °C, 19 days	**183** : **180** = 50 : 50	123, 124
							Florisil, CH_2Cl_2, 40 °C, 24 h	**183** : **180** = 45 : 55	123, 124
							Florisil, CH_2Cl_2, 40 °C, 2 days	**183** : **180** = 44 : 56 (**183**, 37)	123, 124
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 5 min	**183** : **180** = 89 : 11 (**183**, 88)	124
H	H	Me	H	Me	Me	H	Florisil, CH_2Cl_2, 25 °C, 24 h	**181** : **180** = 17 : 83 (**181**, 6)	120
							Florisil, CH_2Cl_2, −78 °C, 24 h	**181** : **180** = 17 : 83 (**181**, 16)	121
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 32 : 68 (**181**, 31)	120–122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**181** : **180** = 6 : 4 (**181**, 58)	122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −78 °C, 2 h	**181** : **180** = 60 : 40 (**181**, 60)	121
Me	H	H	H	Me	Me	H	Florisil, CH_2Cl_2, 25 °C, 192 h or −78 °C, 8 days	**181** : **180** = 13 : 87 (**181**, 12)	120, 121
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 27 : 73 (**181**, 22)	120–122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 or −78 °C, 2 h	**181** : **180** = 73 : 27 (**181**, 70)	121, 122
Me	H	H	H	Me	H	Me	Florisil, CH_2Cl_2, 25 °C, 24 h	**183** : **180** = 69 : 3	123
							Florisil, CH_2Cl_2, 25 °C, 4 days	**183** : **181** : **180** = 11 : 1 : 89 (**183**, 9)	123
							Florisil, CH_2Cl_2, 25 °C, 13 days	**183** : **181** : **180** = 19 : 8 : 73 (**183**, 15)	123
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 5 min	**183** : **181** : **180** = 16 : 5 : 79 (**183**, 15)	123
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**183** : **181** : **180** = 75 : 4 : 17 (**183**, 74)	123
Me	H	H	Me	H	H	Me	Florisil, CH_2Cl_2, 40 °C, 24 h	**183** : **180** = 15 : 85 (**183**, 13)	123, 124
							Florisil, CH_2Cl_2, 20 °C, 5 days	**183** : **180** = 17 : 83	123, 124
							Florisil, CH_2Cl_2, 25 °C, 8 days	**183** : **180** = 1 : 4 (**183**, 16)	123, 124
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −65 °C, 5 min	**183** : **184** : **180** = 31 : 8 : 61 (**183**, 30)	122, 123
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −65 °C, 15 min	**183** : **180** = 19 : 81	122
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −65 °C, 30 min	**183** : **180** = 22 : 78	122
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −65 °C, 1 h	**183** : **180** = 33 : 67	122
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**183** : **180** = 28 : 72	122
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −65 °C, 4 h	**183** : **180** = 30 : 70	122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 5 min	**183** : **184** : **180** = 14 : 14 : 72	122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 15 min	**183** : **184** : **180** = 27 : 18 : 55	122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 30 min	**183** : **184** : **180** = 41 : 27 : 32	122

Table 8 (continued).

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Reaction conditions	Composition of the reaction mixture [product, yield (%)] [a]	Ref.
Me	H	H	Me	H	H	Me	$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 1 h	**183** : **184** : **180** = 58 : 13 : 29	122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**183** : **184** : **180** = 87 : 2 : 11 (**183**, 83)	122, 123
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 4 h	**183** : **184** : **180** = 77 : 6 : 17	122
H	H	Me	H	Me	Me	Me	Florisil, CH_2Cl_2, 25 °C, 10 days or −78 °C, 10 days	**181** : **180** = 23 : 77 (**181**, 19)	120, 121
H	H	Me	H	Me	Me	Me	$MeAlCl_2$, CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 23 : 78 (**181**, 22)	120
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**181** : **180** = 22 : 78 (**181**, 18 – 22)	121, 122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 to −78 °C, 2 h	**181** : **180** = 77 : 23 (**181**, 75)	121, 122
Me	H	H	H	Me	Me	Me	Florisil, CH_2Cl_2, 25 °C, 14 days or −78 °C, 14 days	**181** : **180** = 15 : 85 (**181**, 13)	121, 122
							$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 8 h	**183** : **184** : **180** = 18 : 6 : 78 (**181**, 15 – 18)	120, 122
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −78 °C, 2 h	**181** : **180** = 31 : 69 (**181**,30)	121
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −65 °C, 2 h	**183** : **184** : **180** = 79 : 4 : 17 (**181**, 81)	122
Me	H	Me	H	Me	Me	H	$MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C, 2 h	see [d]	121
							$MeAlCl_2$ (0.1 equiv.), CH_2Cl_2, −78 °C, 2 h	see [d]	121

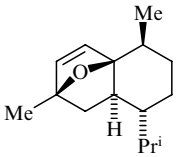
[a] The yields of isolated products are indicated; the compositions of the reaction mixtures were determined by ^1H NMR spectroscopy; [b] the yield of the adduct **181** calculated with respect to the amount of alkenylfuran **180** introduced into the reaction is indicated; [c] fluorosil is fluoroalkylsilicon; [d] the reaction does not occur.

the Diels – Alder adducts (see Table 8). The reaction equilibrium can be shifted towards the tricycles **181** either by increasing the pressure (1.25 GPa) or by conducting the reaction at room temperature in water with the addition of 2 M calcium chloride. It is interesting to note that no epoxynaphthalene **181** is formed in the presence of β-cyclodextrin or upon boiling in 2 M $CaCl_2$.[119]

The cyclisation of alkenylfurans **180** containing an acetyl group at the double bond [R^1(R^2) = Ac] occurs at 1.9 GPa and yields a mixture of the *exo*- and *endo*-adducts **181** and **182**. The latter revert to the starting compounds at atmospheric pressure.[78, 117]

The cyclisation of 1,4-diketone **180** (R^1 = Ac, R^6 = OMe) was studied in detail.[125] It was established that the cycloaddition is successful only in the presence of Lewis acids, ZnI_2 being the most active (the yield of the adduct **181** was 67%).

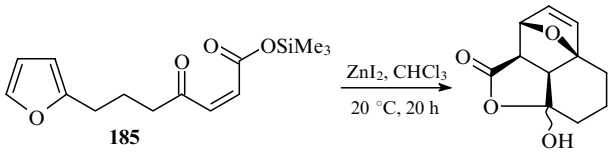
These results were successfully applied to the total synthesis of 1,4-epoxycadinane, a terpene isolated from the brown alga *Dilophus fasciola*.[123, 124]



1,4-Epoxycadinane

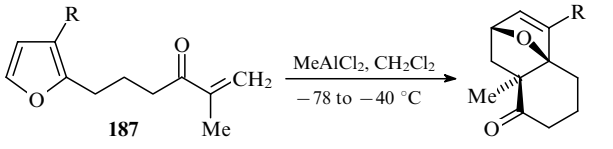
Some chemical properties of 11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes have been studied. Thus the reactions of epoxyoctahydronaphthalenes **181** and **183** (see Refs 118, 121, 124 and 125) with nucleophiles (primarily, with organolithium and organomagnesium derivatives),[129] and the Wagner – Meerwein rearrangement of compounds **181** were reported.[130]

The intramolecular cycloaddition in the keto ester **185**, a structural analogue of the above-described ketones **180**, in the presence of ZnI_2 is accompanied by desilylation. This reaction yields the tetracyclic lactone **186**.[125]



185 **186** (58%)

Only one paper[131] describes the effects of the substituents at position 3 of the furan ring on the course of the intramolecular Diels – Alder reaction of furylpropyl isopropenyl ketones **187**. In the presence of methylaluminium dichloride, the cyclisation proceeds stereoselectively and yields the *exo*-adducts **188**. For R = CH_2OAlk, the yield of the product **188** was nearly quantitative. However, the reaction did not go to completion if an ester group (CO_2Pr^i) was introduced into the furan ring. In this case, the tricyclic ketone **188** was isolated from the reaction mixture in a moderate yield.



187 **188** (*exo*, 63% – 95%)

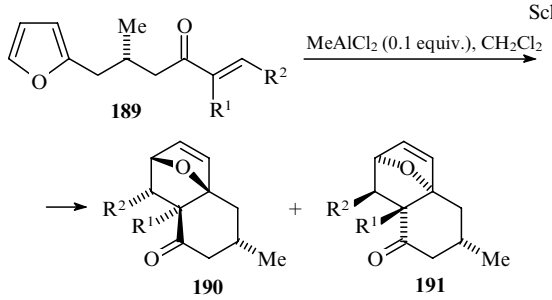
R = CH_2OMe, CH_2OBn, CO_2Pr^i.

The catalytic cyclisation of the optically active alkenylfuran **189** yields a mixture of diastereomeric methyl-substituted 11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes **190** and **191** (Scheme 7).[132]

Several publications are devoted to the intramolecular cyclisation of furans [*c*]-annelated to partially hydrogenated benzene or thiophene rings.[80, 85, 133]

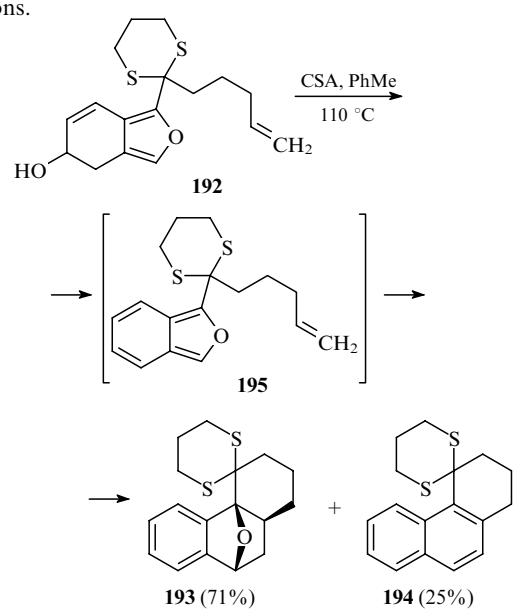
Upon boiling in toluene in the presence of catalytic amounts of camphorsulfonic acid, dihydroisobenzofuran **192** is converted into a mixture of spirans **193** and **194**.[80] Initially, dehydration results in unstable isobenzofuran **195**, which undergoes further rapid intramolecular cyclisation to the spiro-annelated octahydroepoxyphenanthrene **193**. The latter is partly aromatised

Scheme 7

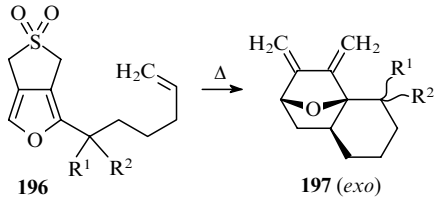


R^1	R^2	T /°C	t /h	Ratio of **189** : **190** : **191**	Product [yield (%)]
H	H	−78	–	10 : 61 : 15	**189** [10], **190** + **191** [76]
Me	H	−78	2	0 : 74 : 26	–
		−78	5.5	0 : 100 : 0	**190** [96]
H	Me	−78	2	10 : 55 : 35	–
		−78	5.5	9 : 81 : 10	**190** + **191** [92]
		−60	0.1	34 : 47 : 19	–
		−60	0.5	6 : 83 : 11	–
		−60	2	4 : 92 : 4	–

into the tetrahydrophenanthrene **194** under the reaction conditions.

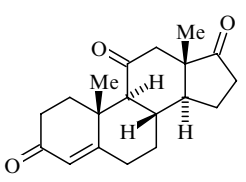


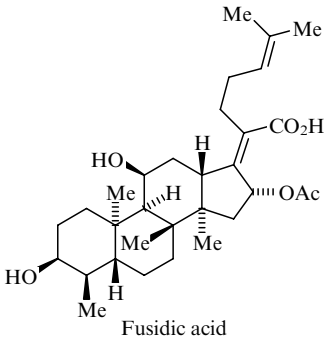
Thienofurans **196** are converted into the *exo*-adducts **197** upon boiling in xylene or benzene.[85]

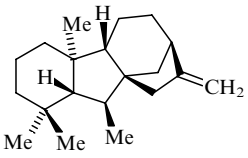


R^1–R^2	Reaction conditions	Yield (%)
O	xylene, 140 °C, 48 h	0
$S(CH_2)_2S$	xylene, 140 °C, 2 h	70
$O(CH_2)_3O$	xylene, 140 °C, 2 h	74
CN, $OSiMe_3$	PhH, 80 °C, 24 h	59

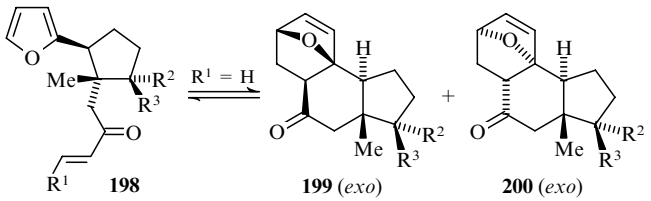
The stereodirection of the cycloaddition of furyl-substituted cyclopentanes has been studied by De Clercq *et al.*[134–139] This reaction is the key step in the total synthesis of a series of tetracyclic natural compounds, *e.g.*, 11-ketosteroids (including adrenosterone) and diterpenoids. The natural antibiotic fusidic acid (ent-fusidic acid) and substituted gibberelines (ent-gibberelline) that possess phytohormonal properties and are used as plant growth factors provide illustrative examples of such compounds.


Adrenosterone


Fusidic acid


Gibbereline

The intramolecular cyclisation of the water-soluble hydroxy ketones **198** into diastereomeric *exo*-adducts **199** and **200** was studied.[134, 135] For compound **198** ($R^1 = R^2 = H$, $R^3 = OH$), this reaction is stereoselective and yields only the *exo*-adduct **200**. Water appeared to be the best solvent for this reaction. NMR studies have shown that compound **200** ($R^2 = H$, $R^3 = OH$) is formed in water within 10 min, whereas in chloroform or dichloromethane the equilibrium is shifted towards the starting furyl-containing cyclopentane **198**.[134]

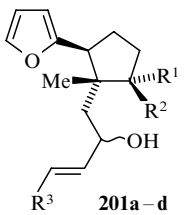


R^1 = H, Me.

R^2	R^3	Reaction conditions	Ratio **198** : **199** : **200**	Product [yield (%)]	Ref.
H	OH	$CDCl_3$, 25 °C, 3 days	0 : 0 : 100	**200** [< 10]	134
		$(CD_3)_2SO$, 25 °C, 3 days	0 : 0 : 100	**200** [50]	134
		D_2O, 25 °C, 10 min	0 : 0 : 100	**200** [> 95]	134
$O(CH_2)_2O$		CH_2Cl_2, 25 °C, 7 days	25 : 20 : 55	–	135
		PhH, 80 °C, 24 h	13 : 80 : 5	–	135

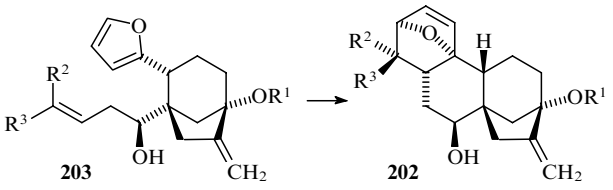
In the case of the dioxolane derivative **198** [$R^1 = H$, R^2–$R^3 = O(CH_2)_2O$], the ratio of the substrate and the cyclisation products **199** and **200** in the reaction mixture depends on the reaction conditions.[135] The methyl group at the double bond of the vinyl fragment (R^1 = Me) fully inhibits the [4 + 2]-cycloaddition.[134]

It is of note that attempts to perform cycloaddition in compounds **201a**–**d**, the precursors of unsaturated ketones **198**, failed.



R^3 = H: R^1 = H, R^2 = OH (**a**), OTBS (**b**);
R^1–R^2 = O (**c**); R^1 = H, R^2 = OTBS, R^3 = Ac (**d**).

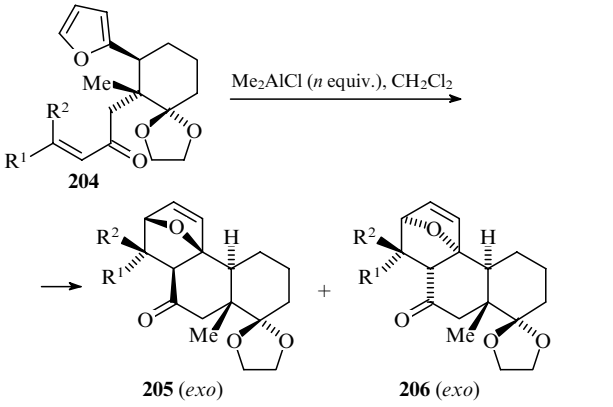
Epoxy derivatives of diterpenes of the gibbereline series **202** were prepared in high yields from furyl-substituted bicyclo[3.2.1]octanes **203**.[136–138] This reaction occurred stereospecifically as *exo*-cycloaddition in boiling benzene or upon heating in aqueous solutions in the presence of β-cyclodextrin.



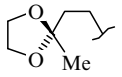
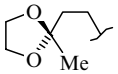
203 **202**

R^1	R^2	R^3	Reaction conditions	Yield (%)	Ref.
H	H	CO_2Me	PhH, 80 °C, 96 h	75	136
H	CO_2Me	H	PhH, 80 °C, 40 h	95	136
H	CO_2Me	H	H_2O, β-CD, 50 °C, 12 h	92	136
H	CO_2Me	H	H_2O, β-CD, 90 °C, 90 h	72	137
TBS	CO_2Me	H	H_2O, β-CD, 55 °C, 90 h	80	137, 138

In conclusion of this section, let us consider the synthesis of homoketosteroid precursors, *viz*., hydrogenated epoxyphenanthrenes, by catalytic cycloaddition of ketones **204**.[139] Dimethylaluminium chloride proved to be the best catalyst for this reaction. The ratio and the yield of the *exo*-addition products **205** and **206** depended on the amount of the catalyst and the reaction temperature.



204 **205** (*exo*) **206** (*exo*)

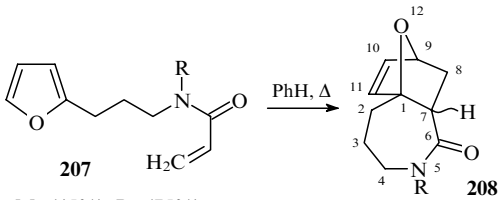
R^1	R^2	*n*	*T* /°C	*t* /h	Product [(yield (%)]
H		1.1	−35	24	**205** [23]
		2	−78	2	**206** [53]
	H	0.1	−25	2	**206** [86]
		0.1	25	24	**206** [29] + **205** [54]

3. Seven-membered rings

There are very a few examples of the annelation of seven-membered rings **4** upon the intramolecular Diels–Alder reaction in the series of 2-alkenylfurans. This may be due to enhanced (in comparison with five- and six-membered analogues) effects of entropic factors upon closure of seven-membered rings. Very often, such conversions require elevated pressure; the polycycles **4** formed are not always stable under ordinary conditions (see also Section II, synthesis of compound **6**). Moreover, in this case the intramolecular cycloaddition occurs with a rather low stereoselectivity and yields *exo*- and *endo*-adducts. Before 2003, there were no reports of successful annelation of eight-membered rings to 7-oxabicyclo[2.2.1]hept-2-ene by intramolecular [4 + 2]-cycloaddition.

a. Synthesis of 5-aza-12-oxatricyclo[7.2.1.0^{1,7}]dodec-10-en-6-ones

A description of this heterocyclic system, which has been prepared by the cyclisation of *N*-(3-furylpropyl)acrylamides **207** in boiling benzene, can be found in only one early publication.[140] This reaction did not occur if the double bond in the alkenyl fragment of the molecule **207** (*e.g.,* crotylamide derivatives) was not terminal. No spectral confirmation of the structure and stereochemistry of the tricyclic lactams **208** synthesised was provided.



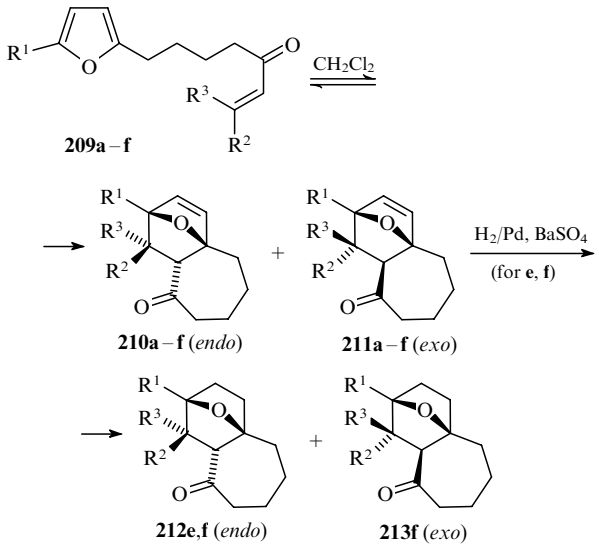
207 **208**

R = Me (45%), Bn (75%).

b. Synthesis of 12-oxatricyclo[7.2.1.0^{1,7}]dodec-10-en-6-ones

The first synthesis of tricyclic 12-oxatricyclo[7.2.1.0^{1,7}]dodec-10-en-6-ones by intramolecular cyclisation of 4-furfurylbutyl vinyl ketones **209a–f** was carried out in 1985.[141] The isomeric cycloaddition products *endo*- (**210**) and *exo*-adducts (**211**) (see compounds **209a–f**, Table 9) appeared to be unstable and rapidly reverted to the starting ketones **209** at atmospheric pressure. The half-life of the more stable *endo*-adduct **210a** ($R^1–R^3$ = H) was 1100 min, that of the *exo*-isomer **211a** was 90 min.

The double bonds in the adducts **210e,f** and **211e,f** were reduced under conditions of catalytic hydrogenation without isolation of the adducts from the reaction mixture. Interestingly, these compounds were not detected later[78] (see Table 9). The hydrogenated derivatives **212** and **213** are fairly stable and were used for the preparation of terpenoids of the daphnane series.[78, 117]



209a–f **210a–f** (*endo*) **211a–f** (*exo*) **212e,f** (*endo*) **213f** (*exo*)

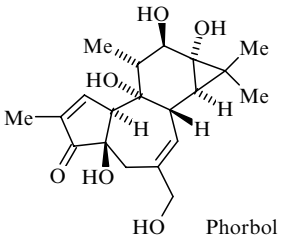
In addition to high pressure, the efficiency of the cycloaddition of alkenylfurans **209** can be increased if methylaluminium dichloride is used as a catalyst.[121, 122] The degree of conversion of the non-substituted compound **209a** at low temperature in the presence of 0.1 equiv. of $MeAlCl_2$ reaches >90%. The ratio of the *endo*- and *exo*-adducts is variable in this case, but the *endo*-isomers usually predominate.

A series of interesting experiments aimed at the annelation of seven-membered rings upon [4 + 2]-cycloaddition have been carried out by Harwood *et al.*[142–144] In elaborating a new approach to the synthesis of phorbol-type diterpenes (irrigants isolated from different species of the African spurge, *Euphorbia coeruleuscens*, *E. coperi*, *E. franckian*, *E. resinifera*), these authors investigated the intramolecular Diels–Alder reaction of ketals **214** (see Table 9).

Table 9. Cyclisation of substituted 7-(2-furyl)hept-1-en-3-ones.

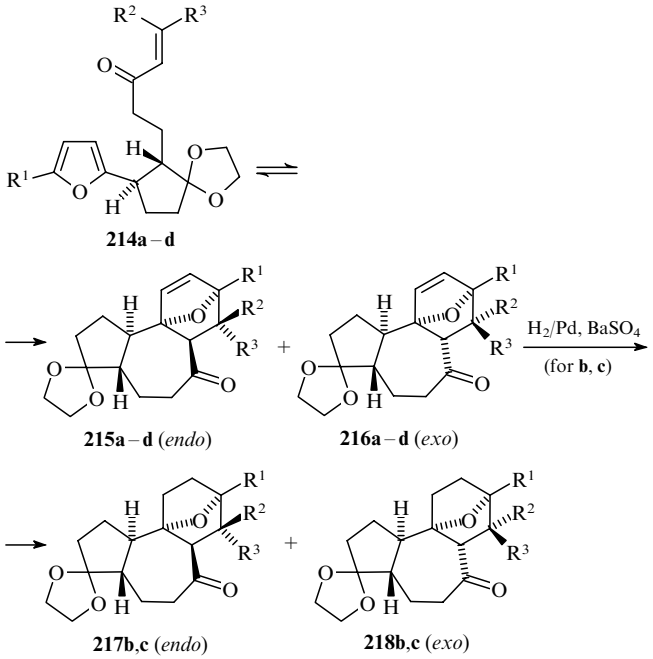
Substrate	R^1	R^2	R^3	Reaction conditions [a]	Composition of the reaction mixture [b] [product, yield (%)]	Ref.
209a	H	H	H	1.2 GPa, 20 °C, 24 h	**210a** : **211a** = 1 : 1	78
				$MeAlCl_2$ (0.1 equiv.), −65 °C, 2 h	**210a** : **211a** : **209a** = 81 : 11 : 8 (**210** + **211**, 91)	121, 122
				$MeAlCl_2$ (0.1 equiv.), −78 °C, 2 h	**210a** : **211a** : **209a** = 84 : 8 : 8	121
209b	H	H	Ac	1.9 GPa, 20 °C, 24 h	see [c]	78
209c	H	Ac	H	1.9 GPa, 20 °C, 24 h	**210c** : **211c** : **209c** = 2 : 3 : 5	78
209d	Me	H	H	1.2 GPa, 20 °C, 24 h	**210d** : **211d** : **209d** = 5 : 4 : 1	78
				1.4 GPa, 20 °C	(**210d** + **211d**)	141
209e	Me	H	Ac	1.9 GPa, 20 °C, 24 h	see [c]	78
				1.9 GPa, 20 °C, 24 h (see [d])	(**212e**, 35)	117
209f	Me	Ac	H	1.9 GPa, 20 °C, 24 h	see [c]	78
				1.9 GPa, 20 °C, 24 h (see [d])	(**212f**, 25) + (**213f**, 5)	117
214a	H	H	H	SiO_2, 25 °C, 16 h (see [e])	**216a** : **215a** : **214a** = 1 : 2 : 1	142
				SiO_2, −12 °C, 7 days (see [e])	**215a** : **216a** = 1 : 2	142
214b	H	H	CO_2Et	1.9 GPa, 20 °C, 5 min (see [d])	(**217b**, 11) + (**218b**, 48)	143
214c	H	CO_2Et	H	1.9 GPa, 20 °C, 5 min (see [d])	(**217c**, 38) + (**218c**, 18)	143
214d	SCH_2Me	CO_2Et	H	1.9 GPa, 20 °C, 13 h	(**215d**, 68)	144

[a] CH_2Cl_2 was used as solvent; [b] the compositions of the reaction mixtures were determined using ^1H NMR spectroscopy; [c] the reaction does not occur; [d] hydrogenation *in situ*; [e] $CHCl_3$ was used as solvent.



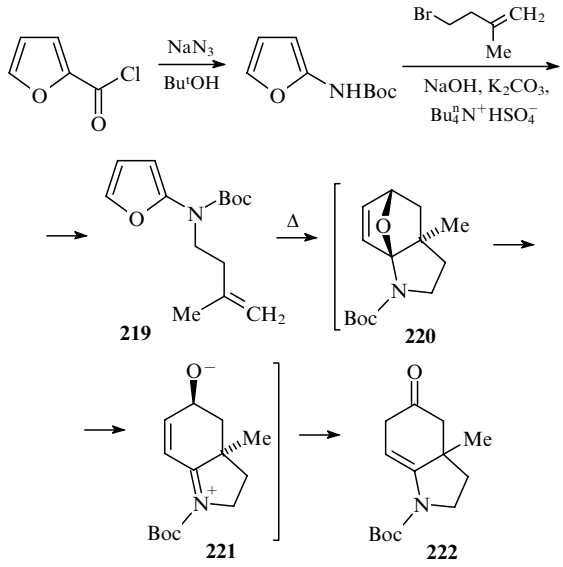
Phorbol

As for the above-described conversions of alkenylfurans **209**, in certain cases (*e.g.*, for derivatives **214b**,**c**), the cycloadducts **215** and **216** formed were not isolated in the individual state, but their equilibrium mixture with the starting compound was subjected to catalytic hydrogenation into derivatives **217** and **218**.



V. Intramolecular cyclisation of *N*-alkenyl-2-aminofurans

Several novel types of intramolecular cycloaddition of substituted furans were disclosed in the past 8 years. It is well-known that, *N*-unsubstituted 2-furylamines are unstable under ordinary conditions, therefore, their reactions are virtually unexplored. In 1997, Padwa and coworkers developed a simple preparative procedure for the synthesis of unsaturated 2-furylcarbamates **219**,[145, 146] which proved to be exceptionally reactive dienes.

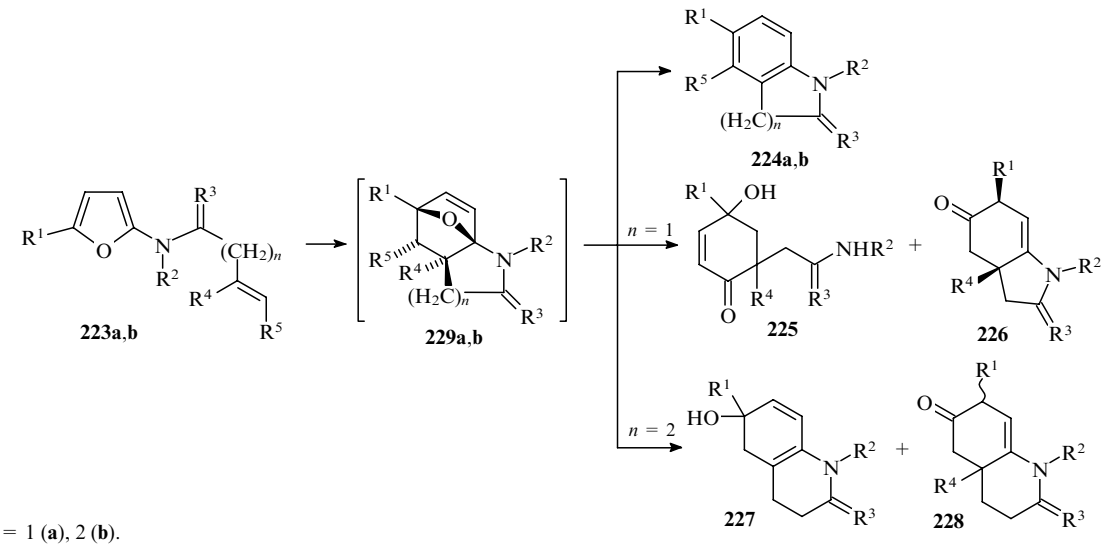


Boc is *tert*-butoxycarbonyl.

In contrast to the above-considered cyclisation reactions, the intramolecular cycloaddition of *N*-substituted 2-furylcarbamates **219** seldom yields the annelated oxabicycloheptene **220**. The latter undergoes spontaneous opening of the epoxide bridge; the ambident ion **221** formed is stabilised in various ways, *e.g.*, by conversion into hexahydroindolone **222**.

In the majority of cases, the intramolecular cycloaddition in *N*-alkenyl-2-furylamides and -carbamates **223a**,**b** differing in the lengths of the alkenyl chains occurs in boiling benzene or toluene; sometimes, this is carried out in a sealed tube. In the presence of 4–5 M ethereal lithium perchlorate, the temperature can be

Scheme 8

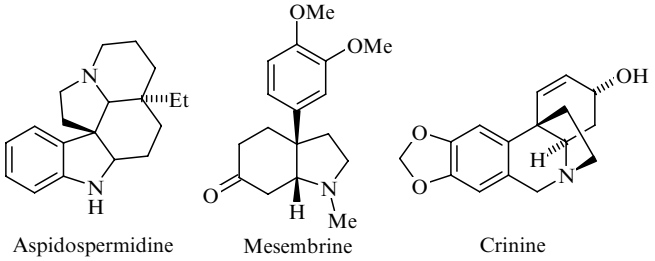


n = 1 (**a**), 2 (**b**).

reduced; sterically hindered alkenylfurans react under these conditions.[147] The mechanism of the catalytic effects of ethereal $LiClO_4$ and other examples are considered in a review.[148]

Depending on the nature of substituents $R^1 - R^5$ in the starting furans **223a**,**b**, eight products **224** – **229** can be obtained,[147, 149–158] six of which are formed upon cleavage of the epoxide bridge in the primary adducts **229a**,**b**, (Scheme 8). It is of note that the intermediate epoxyindole **229a** could be isolated in only one case.[151] The intramolecular cycloaddition always proceeds *via* the intermediate *exo*-transition state. The reaction conditions and the product yields are presented in Table 10.

Based on these data, the following general conclusions have been made. The annelation of five-membered rings to oxabicycloheptene proceeds more smoothly than that of six-membered rings, which often results in mixtures of reaction products. The reaction occurs with furans containing both electron-withdrawing (CO_2Alk) and electron-donor (SMe) groups. Thus, the nature of the substituent at position 5 of the furan ring affects neither the reaction conditions nor the yield of the cycloadducts. Bulky substituents at the amide nitrogen atom (R^2) and radicals at the double bond (R^4 and R^5) of the dienophile do not inhibit this reaction either.

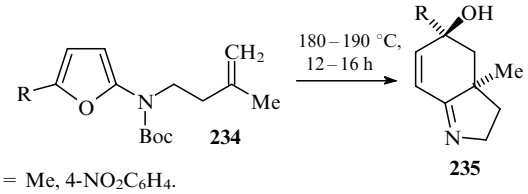


Aspidospermidine Mesembrine Crinine

In the case of R^4 = 3,4-$(MeO)_2C_6H_3$ [or 3,4-$(OCH_2O)C_6H_3$], compounds **226**, which represent close precursors of the alkaloids mesembrine and crinine, respectively, are formed. The former were isolated from South African plants of the Mesembryanthemaceae family (genus *Sceletium*); the latter were found in the bulbs and seeds of the African lily *Crinum bulbispermum* (Amaryllidaceae). Total synthesis of these and other structurally similar alkaloids by intramolecular cycloaddition of *N*-alkenylaminofurans **223** has been described.[19, 153, 154]

The Diels – Alder reaction of 5-substituted *N*-alkenyl-*N*-furylsulfonamides is also accompanied by conversions of the primary adducts.[147, 150] In the case of 5-nitro derivatives, **230a**,**b**, the elimination or migration of the nitro group in the intermediate tricycles **231a**,**b** and subsequent oxygen-induced aromatisation result in a mixture of mono- (**232a**,**b**) and disubstituted (**233a**,**b**) indolines ($n = 1$) or tetrohydroquinolines ($n = 2$) (Scheme 9).[147]

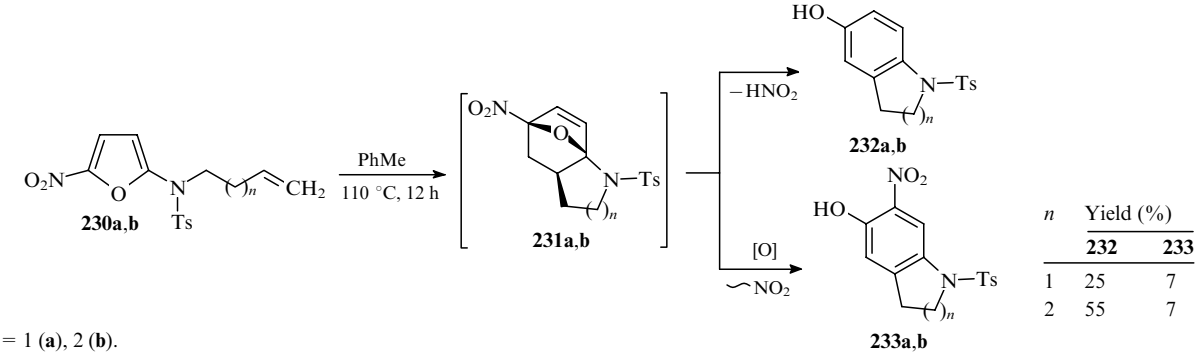
An unexpected elimination of the *N*-*tert*-butoxycarbonyl group was observed in the cyclisation of 5-methyl- and 5-nitrophenyl-substituted furylcarbamates **234** leading to 3,3*a*,4,5-tetrahydro-2*H*-indoles (**235**) in good yields.[150]



R = Me, 4-$NO_2C_6H_4$.

It is interesting to note that the thermal cyclisation of the *N*-butenyl analogue yields an unstable adduct of the type **229a** (see above); the latter is further aromatised into the corresponding indoline.[152]

Scheme 9



n	Yield (%)	
	232	**233**
1	25	7
2	55	7

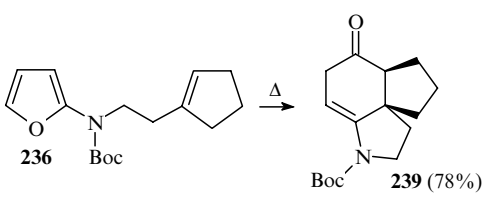
n = 1 (**a**), 2 (**b**).

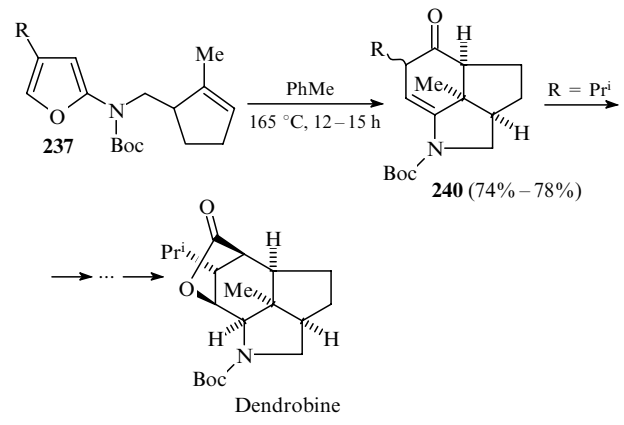
Table 10. Cyclisation of acylated (*N*-alkenyl)aminofurans **223a**,**b**.

Compound	R^1	R^2	R^3	R^4	R^5	Product	Yield (%)	Reaction conditions	Ref.
223a	H	CO_2Me	2 H	3,4-$(OCH_2O)C_6H_3$	H	**226**	85	PhMe, 180 °C, 15 h	153
	H	CO_2Et	2 H	Me	H	**226**	90	PhH, 165 °C, 14 h	150
	H	CO_2Et	2 H	CO_2Me	H	**226**	80	PhH, 80 °C, 6 h	150
	H	CO_2Et	2 H	3,4-$(MeO)_2C_6H_3$	H	**226**	78	PhMe, 155 °C, 20 h	153
	OH [a]	CO_2Et	2 H	Br	H	**224a**	80	PhH, 160 °C, 7 h	152
	H	CO_2Bu^t	2 H	H	H	**224a**	16	PhH, 165 °C, 16 h	149, 152
	H	CO_2Bu^t	2 H	Me	H	**226**	71	PhH, 165 °C, 14 h	149, 152
	OH [a]	CO_2Bu^t	2 H	Br	H	**224a**	5	thermolysis	152
	OH [a]	CO_2Bu^t	2 H	SPh	H	**224a**	87	PhH, 160 °C, 6 h	152
	H	CO_2Bu^t	2 H	CO_2Me	H	**226**	87	PhH, 80 °C, 6 h	149, 150
	H	CO_2Bu^t	2 H	OBO [b]	H	**226**	70	PhH, 165 °C, 14 h	150
	H	CO_2Bu^t	2 H	3,4-$(MeO)_2C_6H_3$	H	**226**	77	PhH, 165 °C	149
	Me	CF_3CO	2 H	H	H	**224a**	–	PhMe, 130 °C, 4 h	151
	Me	CO_2Bu^t	2 H	H	H	**224a**	77	PhH, 160 °C, 15 h	152
	Me	SO_2CF_3	2 H	H	H	**224a**	96	PhMe, 130 °C, 4 h	151
	Me	SO_2CF_3	2 H	Me	H	**229**	85	PhMe, 130 °C, 4 h	151
	CO_2Me	CO_2Et	2 H	H	H	**224a**	66	4 M $LiClO_4$,[c] 100 °C, 26 h	147
	CO_2Me	PhCO	2 H	H	H	**224a** [d]	25	PhMe, 190 °C, 19 h	147
	CO_2Me	2-Br-3,4-$(MeO)_2C_6H_2CO$	2 H	H	H	**224a**	79	4 M $LiClO_4$,[c] 100 °C, 36 h	147
	CO_2Me	2-Br-3,4-$(OCH_2O)C_6H_2CO$	2 H	H	H	**224a**	80	5 M $LiClO_4$,[c] 100 °C, 36 h	147
	4-$NO_2C_6H_4$	CO_2Bu^t	2 H	H	H	**224a**	57	PhH, 165 °C, 15 h	152
	CO_2Me	PhCO	2 H	H	Me	**224a**	73	CSA, 4 M $LiClO_4$,[c] 100 °C, 48 h	147
	CO_2Me	PhCO	2 H	H	MeO_2C	**224a**	70	4 M $LiClO_4$,[c] 100 °C, 24 h or PhMe, 160 °C, 24 h	147
	CO_2Me	PhCO	2 H	Me	H	**225**	68	4 M $LiClO_4$,[c] 95 °C, 24 h	147
	MeS	Me	O	H	H	**226**	72	PhMe, 110 °C, 2 h	158
	MeS	3,4-$(MeO)_2C_6H_3(CH_2)_2$	O	H	H	**226**	63	PhMe, 110 °C, 3 h	157
	MeS	Me	O	Me	H	**226**	42	PhMe, 110 °C, 3 h	158
	MeS	Me	O	Ph	H	**226**	61	PhH, 80 °C, 8 h	157
	MeS	Me	O	CO_2Me	H	**226**	68	MeCN, 25 °C, < 1 h	158
223b	H	CO_2Et	2 H	Me	H	**228**	68	PhH, 200 °C, 36 h	150
	H	CO_2Bu^t	2 H	H	H	**224b** + **227**	28 + 33	PhH, 165 °C, 18 h	149, 152
	CO_2Me	PhCO	2 H	H	H	**224b** + **227**	33 61	PhMe, 190 °C, 20 h	147
	H	H	O	H	Me	**224b**	89	PhH, 200 °C, 36 h	152
	H	4-$(MeO)C_6H_4CH_2$	O	H	Me	**224b**	80	PhH, 160 °C, 24 h	152
	CO_2Me	H	O	H	H	**224b**	66	PhMe, 200 °C, 24 h	147
	CO_2Me	Me	O	H	H	**224b** + **227**	13 + 77	PhMe, 160 °C, 24 h	147
	MeS	Me	O	H	H	**228**	0	PhMe, 200 °C, > 2 h	158

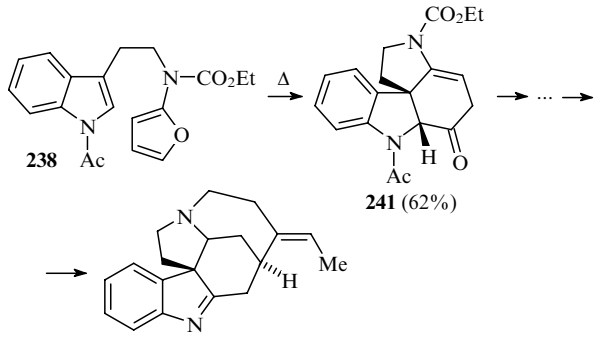
[a] The substituent R^1 for the reaction product is indicated; in the starting furan, R^1 = H; [b] OBO is 2,6,7-trioxabicyclo[2.2.2]octane; [c] the concentration of $LiClO_4$ in diethyl ether is indicated; [d] the yield of methyl 1-benzoyl-5-hydroxy-2,3,4,5-tetrahydro-1*H*-indole-5-carboxylate was also obtained, yield 52%.

Alkylfurylcarbamates **236** and **237** and a tryptamine derivative **238** underwent intramolecular cycloaddition.[140, 153] These conversions yield the adducts **239** – **241**, which represent synthons for the preparation of the polycyclic alkaloids dendrobine (found in the Chinese orchid *Dendrobium nobile*), aspidospermidine and dehydrotubifoline isolated from South American tree-frogs.



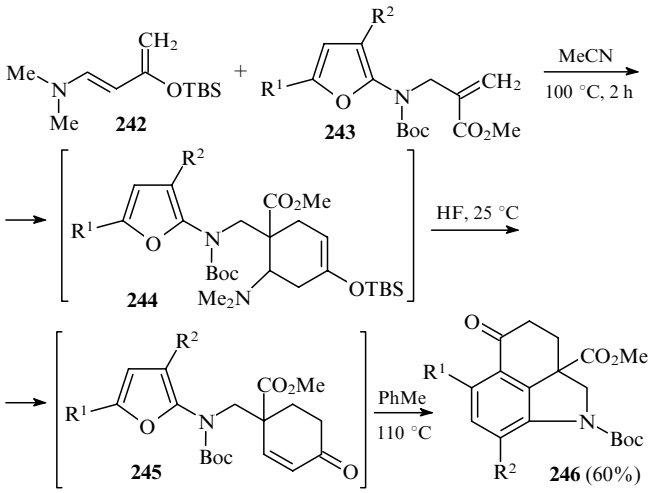


R = H, Pr^i



Dehydrotubifoline

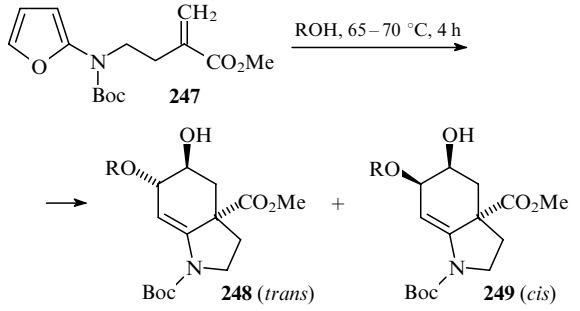
Alkenylfurylcarbamates for intramolecular Diels – Alder reactions can be prepared *in situ*. The sequence of transformations[155] begins with the intermolecular [4 + 2]-cycloaddition of protected 4-dimethylaminobuta-1,3-dien-2-ol **242** to furylcarbamate **243**.



R^1, R^2 = H, Me.

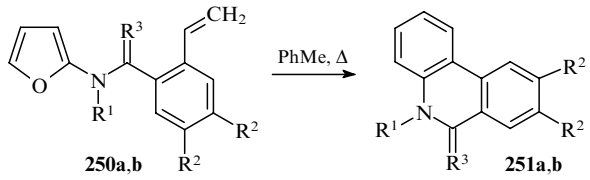
Dimethylamine and the protecting silyl group are eliminated from compound **244** under the action of hydrofluoric acid resulting in cyclohexenone **245**. The latter undergoes thermal cycloaddition to be further converted into the tricyclic indole derivatives **246**.

The cycloaddition of a carbamate **243** homologue, *viz*., methyl 4-(*tert*-butoxycarbonyl-2-furyl)amino-2-methylenebutyrate (**247**), carried out in an alcoholic medium (MeOH or BnOH) yields mixtures of monoalkylated 5,6-dihydroxy derivatives **248** and **249** (but not the ketones of the type **228**, see above).[150, 154] The total yield of these compounds is 80% – 85%; the ratio of the *trans*- and *cis*-isomers is 3 : 1 in both cases.



R = Me, Bn.

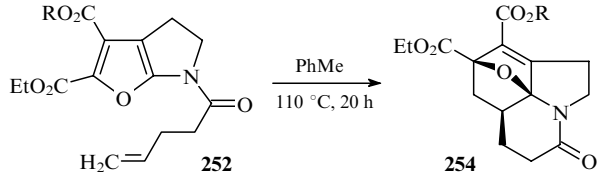
The cyclisation of 2-aminofurans can be used for the synthesis of azaphenanthrene systems.[152] Thus the cyclisation of the *N*-nonsubstituted alkenylfuran **250a** occurs under more drastic conditions (160 °C, 4 days) than that of its ethoxycarbonyl analogue **250b** (110 °C, 24 h). The yields of the substituted phenanthridines **251** are high in both cases.



R^1 = R^2 = H, R^3 = O (**a**, 97%); R^1 = CO_2Et, R^2 – R^2 = OCH_2O, R^3 = 2 H (**b**, 79%)

The intramolecular Diels – Alder reaction in the series of furan derivatives annelated to nitrogen-containing heterocycles with *N*-alkenyl substituents, *viz*., furopyrrolines **252** and furotetrahydropyridines **253**, has been described.[156 – 160] Conversions of such systems lead to polyheterocyclic compounds. Unfortunately, the starting fused heterocycles are not easily accessible, which restricts significantly prospects of their practical application in the synthesis of biologically active compounds.

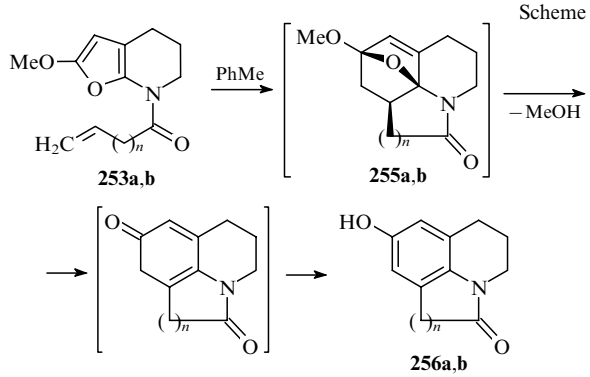
If the furan ring contains electron-withdrawing groups (CO_2Alk), the cycloaddition stops at the formation of epoxy derivatives of the tetracyclic compounds **254**.



254: R = Bu^t (70%), Me (24%).

Contrariwise, electron-donor groups (*e.g*., MeO) make the Diels – Alder adducts **255** unstable, which results in spontaneous cleavage of the epoxide bridge. These compounds are stabilised upon elimination of methanol.[156, 157] It was shown that the formation of hydrogenated pyridoquinoline from methoxy-substituted furotetrahydropyridine occurs under more drastic conditions than that of pyrrolo[3,2,1-*ij*]quinoline **256a** (Scheme 10).

Scheme 10



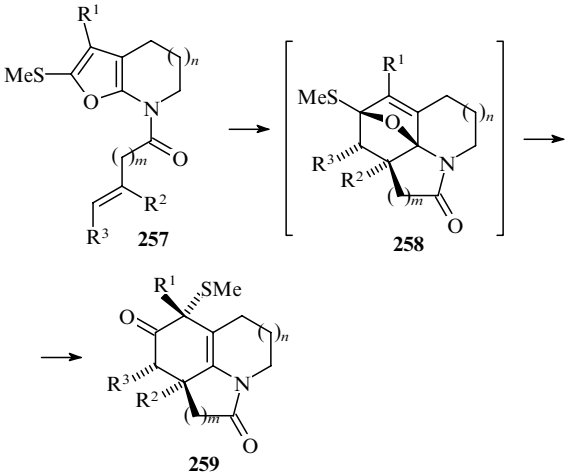
Compound **256**	*n*	Reaction conditions	Yield (%)
a	1	110 °C, 0.5 h	58
b	2	180 °C, 12 h	30

The [4 + 2]-cycloaddition of various *N*-acylazinofurans **257** [*e.g.,* hydrogenated furopyridines (n = 1) and furoazepines (n = 2)] containing an electron-donor MeS group at position 5 of the furan ring was studied.[158 – 160] These compounds afforded both the Diels – Alder adducts and their subsequent conversion products. It is interesting to note that, in contrast to the methoxy derivatives **255**, the sulfur-containing analogues **258** undergo a 1,2-shift of the thiomethyl group to yield oxo amides **259** (Table 11).

Table 11. Cyclisation of *N*-acylazinofurans **257**.

R^1	R^2	R^3	*n*	*m*	Reaction conditions	Product	Yield (%)	Ref.
H	H	H	1	1	PhMe, 110 °C, 1 h	**259**	92	158
H	H	H	1	2	PhMe, 150 °C, 15 h	**259**	76	158
H	H	CH_2CO_2Me	1	1	PhMe, 110 °C, 3 h	**259**	66	160
H	Me	H	1	1	PhMe, 110 °C, 7 h	**259**	61	158
H	CO_2Me	H	1	1	PhH, 80 °C, 1 h	**259**	77	158
H	CO_2Me	H	1	1	CH_2Cl_2, 0 °C, 3 h	**258**	77	158
Et	H	H	1	1	PhMe, 110 °C, 1 h	**259**	70	158
H	H	H	2	1	MeCN, 25 °C, < 1 h	**259** [a]	64	158
H	H	H	2	2	PhMe, 150 °C, 4 h	**258**	75	158
H	H	CH_2CO_2Me	2	1	MeCN, 25 °C, < 1 h	**259** [a]	79	160

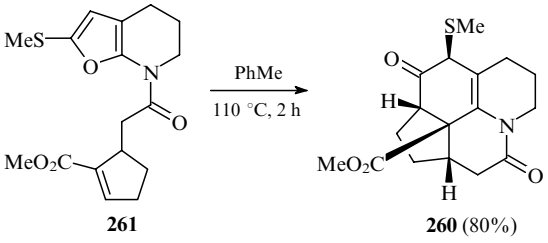
[a] The configuration of the SMe group was not determined.



257 **258** **259**

Substituents at the double bond of the unsaturated fragment in the fused furans **257** and the size of the annelated ring have no appreciable effect on the yield of the tricyclic compounds **258** and **259**.

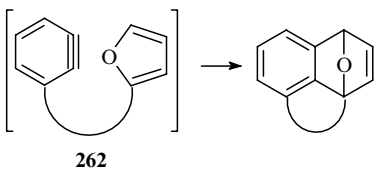
An elegant stereoselective synthesis of the tetracyclic system **260** upon heating of furotetrahydropyridine **261** can be mentioned in conclusion of this section.[158]



261 **260** (80%)

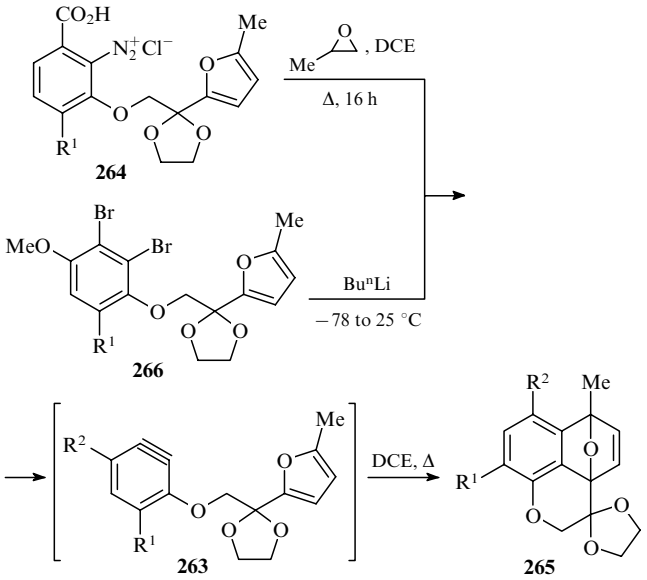
VI. Intramolecular cycloaddition in furylalkyldehydrobenzenes

This is one of the least investigated intramolecular cycloaddition reactions in the furan series; the first report appeared in 1981.[161] It is of note that no information about this type of cyclisation is given in a recent review [162] of dehydrobenzene reactions published in 2003.



262

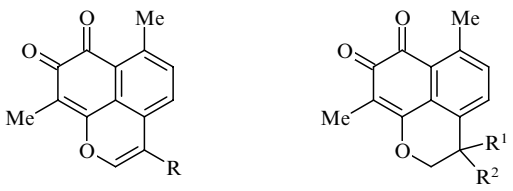
Several approaches to the generation of furylalkyldehydrobenzenes of the type **262** exist. The two major types include decomposition of the corresponding diazonium salts prepared from substituted anthranilic acids and dehalogenation of furyl-containing *ortho*-dihalobenzenes. The intermediate dehydrobenzenes **263** are formed smoothly upon heating of the diazonium salts **264** in the presence of propylene oxide which binds the evolving hydrogen chloride. Further boiling in dichloroethane gives the thermal cyclisation products, *viz*., the epoxytetracycles **265** (yields 74% – 90%). Similar compounds are formed in good yields upon treatment of dibromo-derivatives **266** with butyllithium.



264 **266** **263** **265**

R^1 = H, Me; R^2 = H, OMe.

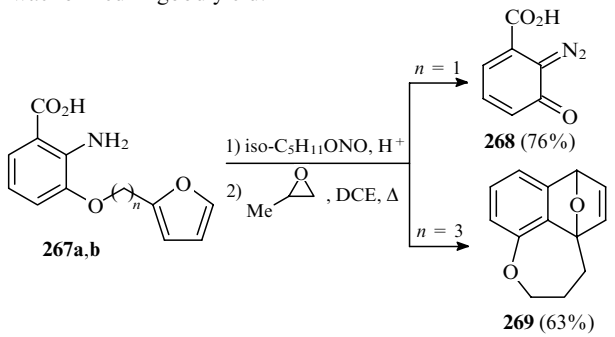
Both approaches were employed by Australian chemists in the synthesis of naphtho[1,8-*bc*]pyran,[161, 163, 164] which is a skeleton of isoprenoids biflorin and mansonones E, I and F possessing a rare *o*-quinonoid structure. Biflorin was isolated from the blossoms and leaves of *Capraria biflora* L., while mansonones E, I and F



R = $(CH_2)_2CH{=}CMe_2$ (biflorin), Me (mansonone F);
R^1 = Me: R^2 = H (mansonone E), OH (mansonone I).

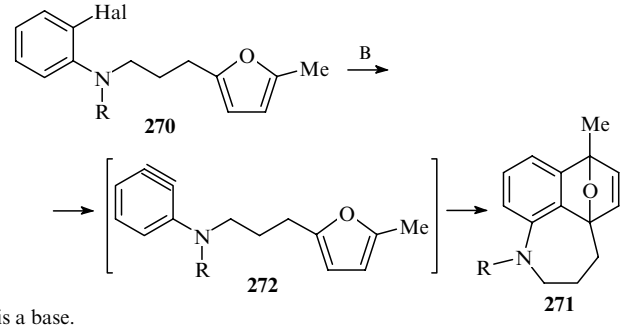
were isolated from the wood of the African tree *Mansonia altissima*.

The length of the chain linking the dehydrobenzene fragment to the furan ring is critical for the cyclisation.[161] No intramolecular Diels – Alder cyclisation occurred of furylalkoxydehydrobenzene formed upon diazotisation of anthranilic acid **267a** with isoamyl nitrite; instead, only diazoquinone **268** was obtained as the elimination product of the furfuryl substituent. However, the annelation of the seven-membered ring in a diazonium salt prepared from the derivative **267b** was more successful: the adduct **269** was formed in good yield.[161]



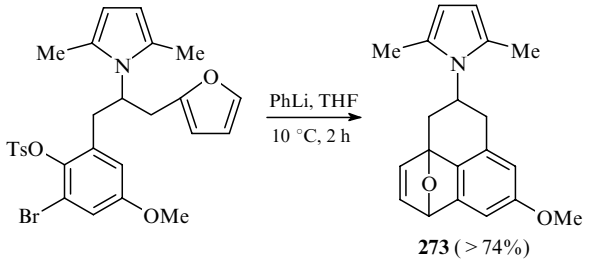
n = 1 (**a**), 3 (**b**).

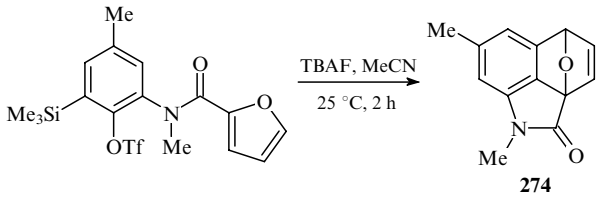
The conversion of *o*-furylpropylaminohalobenzenes **270** into fused azepines **271** (Table 12) containing an epoxynaphthalene fragment has been described.[165] Lithium diisopropylamide (LDA) and lithium-2,2,6,6-tetramethylpiperidide (LiTMP) in THF proved to be the most suitable bases for generating dehydrobenzene **272**. The yields of naphthoazepines **271**were low.



B is a base.

Short communications[166, 167] outline approaches to the synthesis of the partly hydrogenated phenalenes **273** and the fused indole systems **274**, respectively. These syntheses employed conventional techniques for the generation of the dehydrobenzene intermediates.

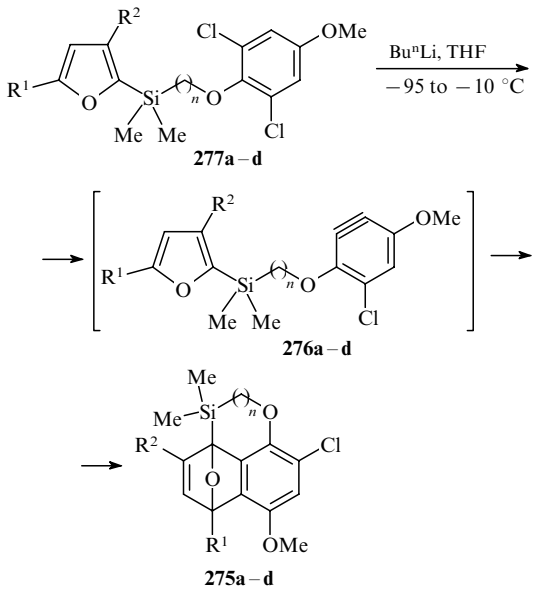


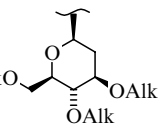


Tf is trifluoromethylsulfonyl,
TBAF is tetrabutylammonium fluoride.

The labile adduct **274** was synthesised in quantitative yield.

Intramolecular cyclisation in epoxynaphthalenes **275a – d** fused to a silaoxacyclohex(hept)ane fragment has recently been described.[168] The intermediate furyl-substituted dehydrobenzenes **276** were generated by treatment of compounds **277** with *tert*- or *sec*-butyllithium in THF from −95 to −10 °C.



X, Y =  (Alk = Me (X), Bn (Y);

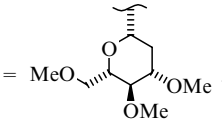
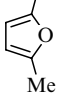
Z =  .

Table 12. Preparation of epoxynaphthazepines **271**.

Hal	R^2	Reaction conditions [a]			Yield (%)
		base (equiv.)	T /°C	t /h	
Cl	Me	Bu^nLi (4)	−78 to 25	24	10
		LDA (4)	−40 to 25	20	40
		LiTMP (4)	−78 to 25	24	49
Br	Me	$NaNH_2$ (5)	25	20	0
		$NaNH_2$ (5.5) + + $NaOBu^t$ (1.1)	−60	60	0
		$NaCH_2SOMe$ (3.5) [b]	100	16	< 5
Cl	$(CH_2)_3$ 	Bu^nLi (3.5)	−78 to 25	24	0
		LDA (3.5)	−40 to 25	20	29
		LiTMP (3.5)	−78 to 25	24	34

[a] THF was used as solvent; [b] DMSO was used as solvent.

Compound **275**	n	R^1	R^2	Yield (%)
a	1	X	H	68
b	2	X	H	81
c	1	H	Z	91
d	1	X	Y	61

* * *

The data reviewed clearly demonstrate that the intramolecular Diels – Alder reactions of alkenylfurans provide an efficient and often the only way to fused 7-oxabicycloheptane systems.

The best results are achieved with substrates containing a three-membered chain between the dienophile (alkenyl) and the diene (furan) fragments (annelation of five-membered rings). The cyclisation that yields six-membered derivatives is less smooth. In any case, a decrease in the degree of freedom of unsaturated fragments (*e.g.*, as a result of introduction of additional substituents, complex formation or the presence of sp^2-hybridised atoms) favours cyclisation. The contribution of electronic factors that is critical for intermolecular interactions from the standpoint of boundary orbital theory fades into the background in the case of intramolecular interactions. With rare exception, the stereochemistry of intramolecular [4 + 2]-cycloaddition usually follows the Diels – Alder *endo*-rule.

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[a] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
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