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DIPOLAR CYCLIZATION REACTIONS IN HETEROCYCLIC SYNTHESIS: A NOVEL ROUTE TO FURANOPHANES[1]

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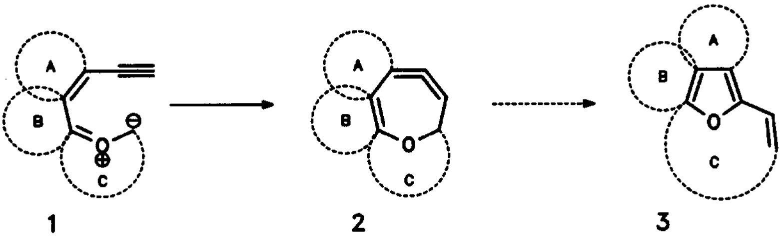
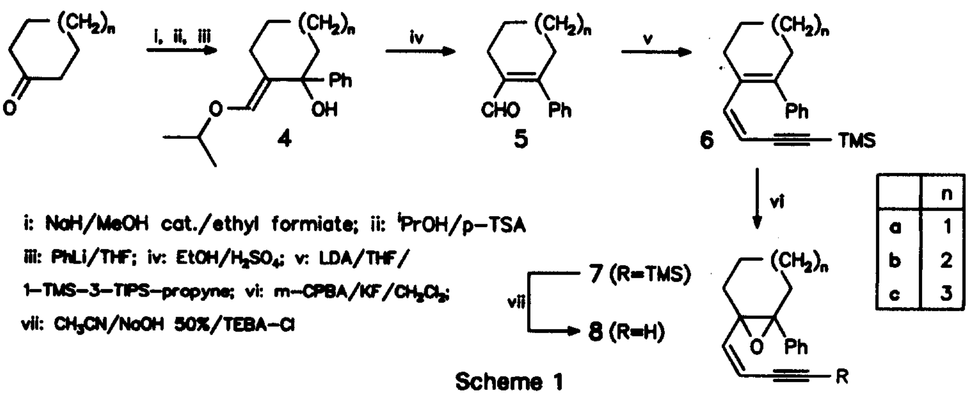
Summary: The multistep transformation of 2,3-bridged butenynyl oxiranes **8** into furanophanes **12** involving bridgehead olefins **11** as key intermediates is described. The two lower members of **12** undergo rapid air oxidation resulting in the formation of the dienediones **14a,b**. **14b** is converted by base into the bicyclo[6.3.0]undecadienone **15**.

Recently we have described a new and simple synthetic access to the furan nucleus:[2] (Z)-butenynyl carbonyl ylides **1**, obtained by thermally induced C/C-bond cleavage of the corresponding oxirane derivatives, undergo 1,7-dipolar cyclization affording the cycloallenes **2** which subsequently rearrange via radical and/or carbene intermediates into 2-vinylfurans of type **3**. During the studies on the reaction mechanism and the preparative scope of this unusual transformation we have found that bulky substituents are tolerated at basically every position,[2,3] and even systems like 1-(A) and 1-(B) can be used leading to 3,4-[2b,d] and 4,5-annulated 2-vinylfurans,[4] respectively.



We now communicate results of investigations directed to the synthesis of type (C)-annulated vinylfurans, i. e. furanophanes,[5] which deserve interest not only with respect to their occurrence as basic structure in natural products[6] but also for their application as synthetic intermediates.[7]

The preparation of the epoxy hexenynes **8** as precursors of the extended dipoles is outlined in Scheme 1. Starting with the cycloalkanones the annulated cinnamaldehydes **5** are obtained in four steps (**5a**: 17%; **5b**: 21%; **5c**: 45% overall yield). The olefination to the enyne derivatives **6** containing the mandatory Z-configuration of the exocyclic double bond is performed by using 1-trimethylsilyl-3-triisopropylsilyl-propyne as Peterson reagent[8] in good preparative (**6a**: 74%; **6b**: 75%; **6c**: 60%) and excellent stereochemical yields (Z/E > 20/1). Regioselective epoxidation of the endocyclic double bond is successfully accomplished with the m-CPBA/KF complex[10] leading to the annulated oxiranes **7** which are finally converted to the terminal alkynes **8** by phase transfer catalyzed protodesilylation.[11]

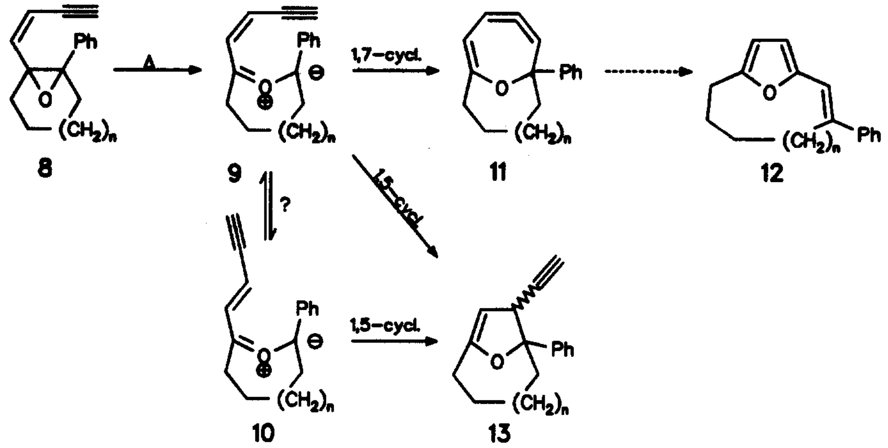


i: NaH/MeOH cat./ethyl formiate; ii: ⁱPrOH/p-TSA
iii: PhLi/THF; iv: EtOH/H_2SO_4; v: LDA/THF/
1-TMS-3-TIPS-propyne; vi: m-CPBA/KF/CH_2Cl_2;
vii: CH_3CN/NaOH 50%/TEBA-Cl

	n
a	1
b	2
c	3

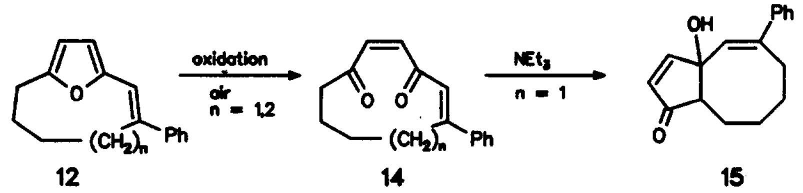
Scheme 1

The transformations of the oxirane derivatives **8a-c** were executed under short time thermolysis conditions as described previously[2b] (temperature 350°C; contact time ca. 10 sec). The reaction of **8c** afforded three monomeric products in the ratio 12:1:1. The main compound turned out to be the expected furanophane **12c**, isolated in 70% yield as stable, colorless crystals (mp. 48°C) after flash chromatography, whereas the minor components were identified as the cis- and trans-dihydrofuranophanes **13c** resulting from competitive 1,5-electrocyclization of either **9c** or **10c**. Some characteristic NMR data of the main compounds are given in Table 1.



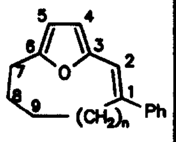
Scheme 2

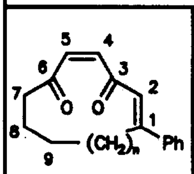
Similar results were obtained with the next lower homologue **8b**. According to the ^{1}H-NMR analysis of the crude reaction mixture 65% of the furanophane **12b** and ca. 10% of each diastereomer of the dihydrofurans **13b** were formed; however, in this case a substantial decrease of products occurred during the chromatographic separation. The main loss is obviously due to an oxidation process converting **12b** into the cyclotrienedione **14b**. In fact it could be shown by a control experiment with pure **12b** that in the presence of air the furan nucleus is cleaved very easily affording **14b** in almost quantitative yield. Furthermore, **14b** turned out to be an appropiate precursor for an intramolecular aldol reaction which on base catalysis (e.g. triethylamine) results in the efficient formation of the bicyclo[6.3.0]-undecadienone **15b**.[12]

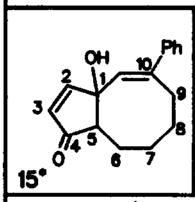


Scheme 3

Table 1: *Selected ^1H- and ^{13}C-NMR data of 12 a-c, 14a-c and 15*

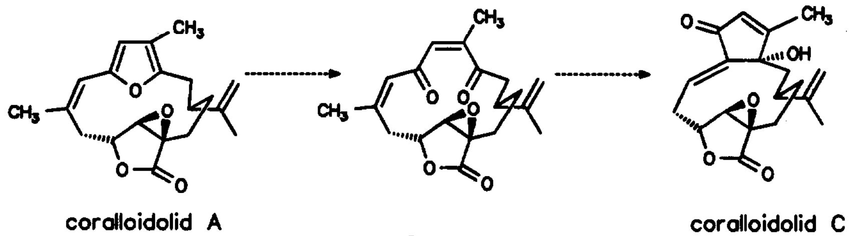
		n	2–H	4–H	5–H	7–CH$_2$	other CH$_2$					Ph–H		$^3J_{4,5}$
	12a*	1	6.27	6.20	6.12	2.88	2.35, 1.4 – 1.8					7.2 – 7.5		3.5
	12b**	2	6.47	6.25	6.06	2.72	2.90, 1.84, 1.24					7.22–7.40		3.5
	12c**	3	6.54	6.27	6.05	2.71	2.83, 1.65, 1.89, 1.48, 1.73					7.17–7.61		3.5
		n	C–1	C–2	C–3	C–4	C–5	C–6	C–7	C–8	C–9	C–10	C–11	C–12
	12b**	2	144.0	116.3	152.8	111.2	107.1	157.2	29.5	33.0	31.5	31.4	36.5	–
	12c**	3	141.0	115.6	152.1	111.1	107.0	156.6	28.4	25.6	25.1	29.3	27.7	30.4

		n	2–H	4–H	5–H	7–CH$_2$	other CH$_2$			Ph–H	$^3J_{4,5}$
	14a*	1	6.20	6.75	6.40	2.42	3.00, 1.8, 1.2			7.25	12
	14b**	2	6.35	6.59	6.43	2.46	3.01, 1.72, 1.34			7.32	12
		n	C–1	C–2	C–3	C–4	C–5	C–6	C–7	other CH$_2$–C	Ph–C
	14b**	2	155.1	129.9	203.8	136.8	135.1	195.7	27.6	24.1, 21.8, 25.1, 43.6	140.4, 129.0, 128.7, 126.9

	2–H	3–H	5–H	6–CH$_2$	9–CH$_2$	11–H	OH	other CH$_2$	$^3J_{2,3}$	$^3J_{5,6}$	$^2J_{6,6}$	$^2J_{9,9}$
	7.52	6.18	2.65	~1.5/2.22	2.60/3.25	5.76	2.44	1.37–2.10	6	10.5 2.3	9	14
	C–1	C–2	C–3	C–4	C–5	C–6,–7,–8,–9		C–10	C–11	Ph–C		
	81.1	165.2	130.8	207.2	63.4	30.9, 27.1, 26.4, 31.1		143.5	127.0	149.3, 128.0, 128.4, 128.7		

* = CDCl$_3$/ 250 MHz or 100 MHz; ** = C$_3$D$_6$O/ 400 MHz or 100 MHz; δ–values in ppm; J–values in Hz

It is of special interest that derivatives of both reaction products, 2,5-furanophanes[6] and 1-hydroxy-bicyclo[6.3.0]undecan-9-ones,[13] are components of naturally occurring products. Analogous ring cleavage/ring forming reactions have been proposed as important steps in the biogenetic transformation of *coralloidolid A* into the cembranolid *coralloidolid C* isolated from Algcygonium Coralloides.[14]



Scheme 4

Thermolysis of **8a** under standard conditions (350°C/10 sec) gave only 10% of the desired furanophane **12a** besides starting compound (ca. 45%) and polymeric material. At 380°C complete conversion of **8a** could be achieved; but due to a strongly increasing amount of decomposition products the yield of **12a** decreased to ca. 5%. The isolation of pure **12a** was additionally complicated by the instability of the compound; as in the case of **12b** rapid air oxidation afforded the diketone **14a** as the major secondary product.

In contrast to purely methylene-bridged [6](2,5)furanophanes described as stable substances by Tochtermann et al.[15] the double bond in the bridge of **12a** causes a higher ring strain resulting in a significant increase of the reactivity.[16] Within the furanophane series compound **12a** represents the member with the shortest bridge so far.

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