altered substitution on ring D of **3** in the P_r form, whereas in the P_{fr} form the chromophore–protein interactions discriminate between the substitution patterns of **1** and **3**. There remains the question of whether this selectivity of the chromophore–protein interactions reflects either steric and/or electronic effects (see Figure 2).

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Tweezers with Different Bite: Increasing the Affinity of Synthetic Receptors by Varying the Hinge Part**

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Despite the tremendous progress in the design and synthesis of receptor molecules with predicted binding properties, it remains a difficult task to design a molecule capable of binding to a particular ligand. Therefore, recent efforts have turned to the more "biomimetic approach" of combinatorial chemistry for the generation of libraries of synthetic receptors capable of binding certain desired ligands. The approach is inspired by nature's very own combinatorial approach so clearly demonstrated by the immune system.

Based on the successful concept of "tweezerlike" two armed synthetic receptors,[1] we have developed synthetic receptors consisting of peptidosulfonamide peptidomimetics.[2] We would like to prepare libraries of tweezerlike receptors that can be screened for their binding affinity to a variety of ligands, peptides, other biomolecules (for example, those that are present on pathogenic organisms), drugs, and signaling molecules. Although our present synthetic receptor showed a remarkable binding selectivity,[2] to have further possible applications its binding affinity with ligands had to be increased. We now describe the results of incorporating less flexible "hinges" in tweezerlike synthetic receptors.

Our present "tweezerlike" synthetic receptors consist of three different parts (Scheme 1): A hinge to which the tweezer arms are attached; a dye or a solid-phase bead attached to this hinge; and two binding arms, which at present consist of peptidosulfonamide peptidomimetics. Based on the original hinge in tweezer **1**, hinges in tweezers **2**–**6** were selected to gradually vary the flexibility and interchain distance, or both, between the amino nitrogen atoms.

The route for the preparation of the tweezerlike synthetic receptors is exemplified by the preparation of tweezers **2** and **5** in Schemes 2 and 3. The bis(aminomethyl)benzoic acid hinge present in receptor **2** was synthesized from 3,5-dimethylbenzoic acid (**7**).[3] We took advantage from the fact

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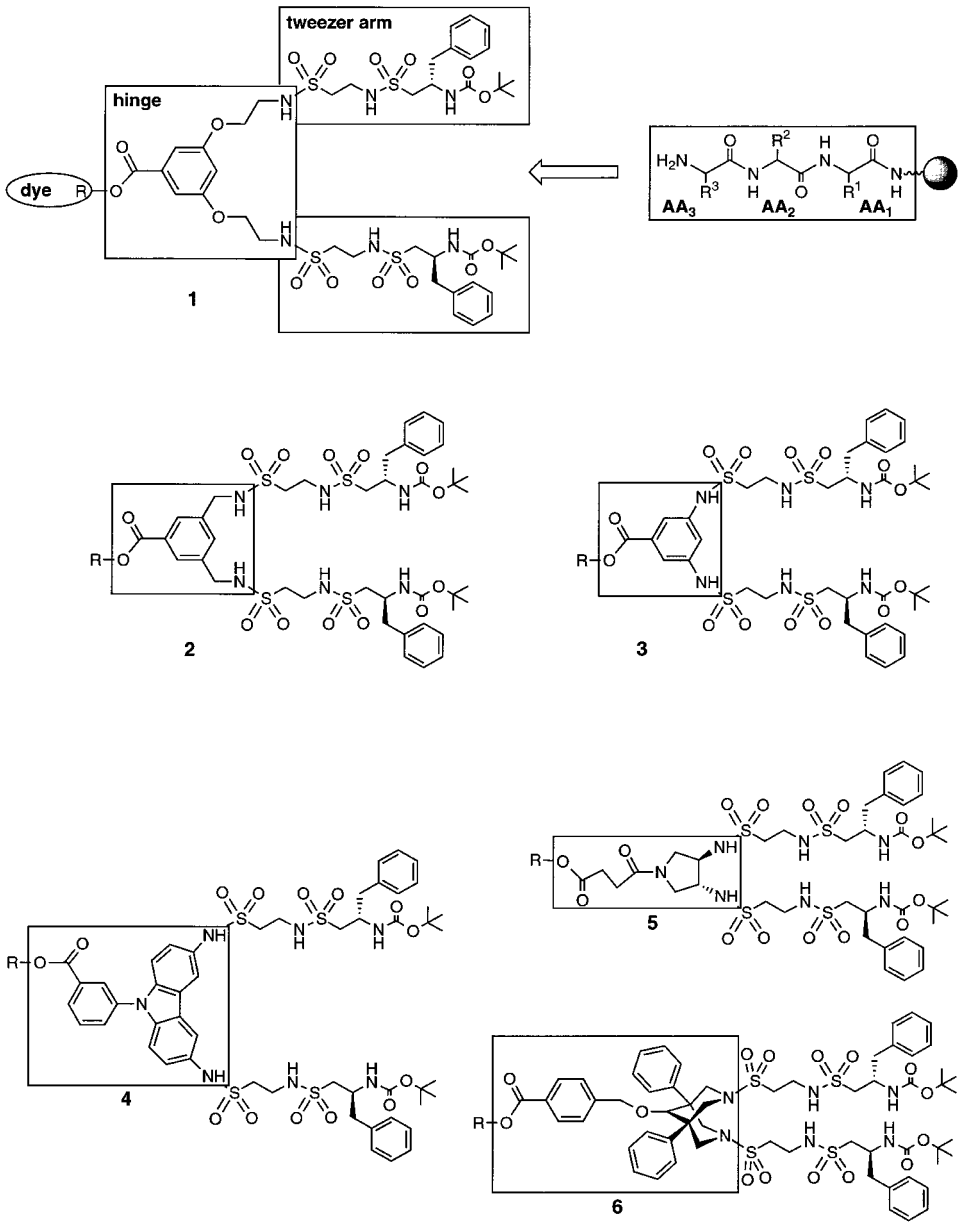

Scheme 1. Structures of tweezerlike synthetic receptor: R = Disperse Red 1; the hinge parts are shown in the frames; AA_{1-3}.[12]

that some monobrominated product **10** always occurred on bromination of **8** by using **10** for the preparation of the so-called amputated tweezer containing only one arm (**2a,** see above). After removal of the Boc protective groups in **11**, the peptidosulfonamide arms were introduced through the sulfonyl chloride approach.[4] Saponification of the methyl ester followed by coupling to Disperse Red 1 (DispR) completed the synthesis of the intensely blood-red synthetic receptor **2**. The amputated receptor **2a** was prepared analogously (Scheme 2).

The pyrrolidine hinge[5] in tweezer **5** was prepared form L-tartaric acid (Scheme 3). The pyrrolidine diol **14** was prepared according to Nagel et al.[6] This diol was converted into the diazide,[7] then reduced, and the resulting amino groups protected to afford **15**. The dye was attached to a spacer group by hydrogenolysis of the benzyl group.[8] Subsequently, the Boc protecting groups in **16** were removed and introduction of the peptidosulfonamide arms by the sulfonyl chloride approach completed the synthesis of **5**.

In synthetic receptor **3** the commercially available diaminobenzoic acid hinge was used. The carbazole hinge present in tweezer **4** was prepared according to Rebek et al.[9] The choice for the preorganized tweezer hinge present in receptor **6** was inspired by the work of Diederich et al.[10] and this hinge was obtained after reduction and attachment of the dye part.[11]

The thus obtained receptors **1**–**6** were screened for binding against a 24389 ($=29^3$) member encoded sidechain-deprotected tripeptide library on TentaGel (AA_3–AA_2–AA_1–N(H)–TentaGel).[12] The bead-supported tripeptide library was equilibrated in a chloroform solution of the receptor (Figure 1).[13] Immediately it can be seen that receptors **2**, **3**, and **4** showed an increased binding affinity, since the concentration for binding of these receptors to the beads was lower than the concentration for binding of the original receptor (Table 1). The binding by the pyrrolidine receptor **5** is comparable to that of the original receptor **1**, and clearly two tweezer arms are needed for a significant binding, since the "amputated" receptor having one arm (**2a**) does not give rise to an appreciable binding even at a concentration of 425 μM. At first glance the absence of any binding whatsoever by receptor **6** was surprising. However, we reasoned that repulsion between the lone pairs on the oxygen atoms of the sulfonamide groups attached to the diazobicyclonane system might disfavor the chair–chair shape and as a consequence favor the formation of a boat–chair conformation and lead to the opening of the tweezerlike structure.[14]

After 72 h equilibration the colored beads were separated and decoded by photolytic release of the molecular tags, as monitored by electron-capture gas chromatography (EC-GC).[15] The number of beads which were decoded for each synthetic receptor are shown in Table 1. This table also shows the consensus sequences bound by each receptor, the frequencies with which they were found among the decoded

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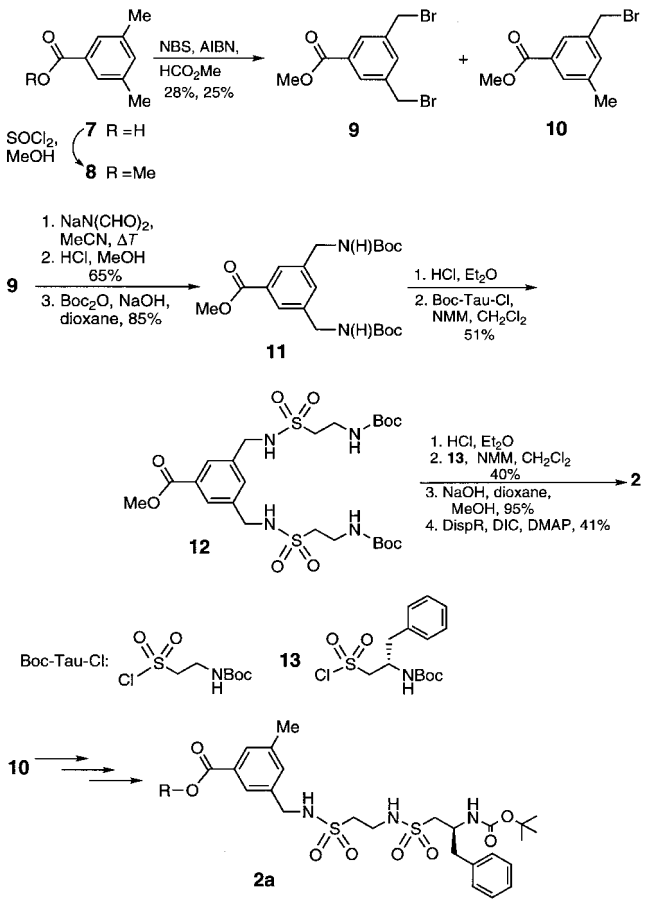
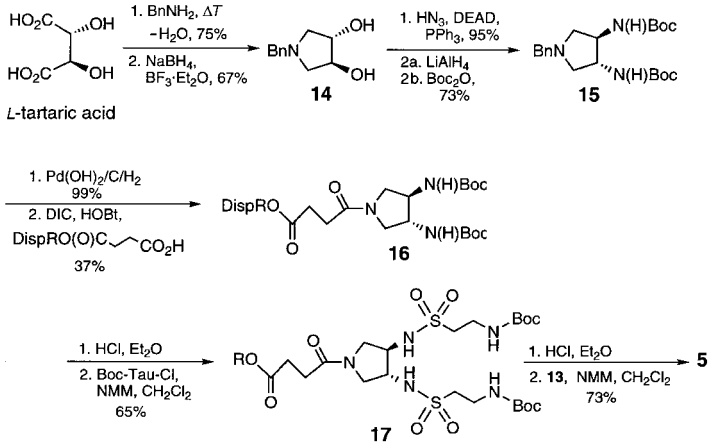


Scheme 2. Synthesis of the receptors **2** (with the bis(aminomethyl)benzoic acid hinge) and the amputated tweezer **2a**; NBS = *N*-bromosuccinimide, AIBN = azobisisobutyronitrile, Boc = *tert*-butoxycarbonyl, NMM = *N*-methylmorpholine, DIC = diisopropylcarbodimide, DMAP = *N,N*-dimethylaminopyridine, R = Disperse Red.



Scheme 3. Synthesis of the receptors **5** with the pyrrolidine hinge; Bn = benzyl, HOBt = 1-hydroxybenzotriazole, DEAD = diethylazodicarboxylate, R = Disperse Red.

beads, and the frequency of their occurrence in the bead-supported tripeptide library.

Practically all consensus sequences of all tweezers show the presence of an acidic amino acid residue mostly occurring at position AA_3. AA_2 is almost invariably a polar amino acid residue (Asn and very often His). Like the earlier described synthetic receptor **1**, both the diamino receptor **3** and the pyrrolidine receptor **5** show some degree of diastereoselectivity since L-Glu–D-His or D-Glu–L-His are found, but not the corresponding diastereomeric sequences L-Glu–L-His or

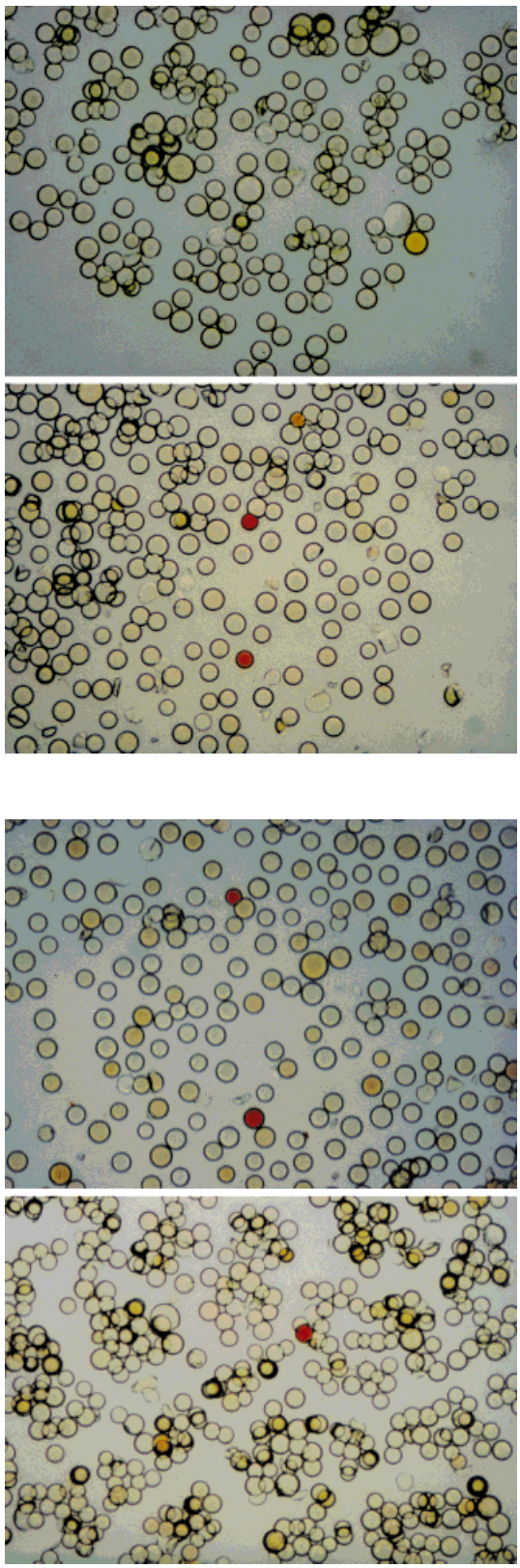


Figure 1. Photographs of the screening assays of tweezer receptors **1**, **2**, **3**, and **5** for binding to the bead-supported tripeptide library.

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Table 1. Binding selectivity of receptors **1**–**6** for tripeptides in a 24389 ($=29^3$) member encoded sidechain-deprotected tripeptide library on TentaGel (AA_3-$-AA_2-AA_1-N(H)-$TentaGel).

Receptor	Equilibrium concentration [μM]	Decoded beads number	Consensus sequence $AA_3-AA_2-AA_1$	Found frequency [%][a]	Library member frequency [%][b]
1[e]	70	34	L/D-Ala-D/L-Asp-L/D-Xxx[d]	50	0.1
			L-Glu–D-His/Asn–Xxx	20	0.3
2	40	28	Glu–Xxx–Xxx[c]	61	6.9
			L/D-Glu–D/L-His–Xxx[d]	32	0.2
			L/D-Glu–Xxx–L/D-Val	21	0.2
			Gly–Asn/His–Asp/Glu	21	0.07
2a	425	3	Glu/Asp–Xxx–Xxx	100	14
3	20	33	Glu–Xxx–Xxx	64	6.9
			Xxx–His–Xxx	70	6.9
			Xxx–Xxx–Asp	27	6.9
			L/D-Glu–D/L-His–Xxx[d]	61	0.2
4	40	16	Glu–Xxx–Xxx	63	6.9
			Xxx–His–Xxx	56	6.9
			L/D-Glu–D/L-His–Xxx[d]	38	0.2
5	80	19	L/D-Glu–D/L-His–Xxx	95	0.2
			L/D-Glu–D/L-His–Phe[d]	26	0.02
6	500	none	none		

[a] Only consensus sequences found in $\geq 20\%$ of the beads are listed here. [b] Frequency with which these are actually present in the tripeptide library. [c] No prefix L- or D- indicates no preference for either enantiomer by the synthetic receptor. [d] The prefixes L- and D- placed in this manner indicate that, for example, L-Glu-D-His-Xxx and D-Glu-L-His-Xxx are found but not L-Glu-L-His-Xxx or D-Glu-D-His-Xxx. [e] See reference [2].

was observed on using the more rigid tweezer **3**, a receptor that has less space between the peptidosulfonamide arms. This tweezer, like the previous tweezer **2**, also improved the binding affinity of similar tripeptides, for example L-Glu–D-His–L-Val, which bound to the original tweezer **1**. Although a coloring of the tripeptide containing beads comparable to that with the benzyl tweezer **2** took place upon incubation with a concentration of the carbazole tweezer **4**, none of the beads were dark orange or red. Therefore, the binding affinity was considered not be significantly enhanced relative to the original receptor **1**. Apparently, despite the rigid character of the carbazole hinge the distance between the arms is too large for a clear increase in the binding affinity. The pyrrolidine hinge seemed a very attractive one with respect to rigidity and chirality, and the selectivity of binding of the tweezer containing this hinge was very high. In 95% of the decoded beads the sequence L/D-Glu–D/L-His–Xxx was found. Moreover L-Glu–D-His–Xxx and D-Glu–L-His–Xxx were found, but not the corresponding diastereomeric sequences L-Glu–L-His–Xxx or D-Glu–D-His–Xxx (Table 1). However, the binding affinity was a little disappointing. Apparently, the tweezer arms point too far away from each other for a significant increase of binding to occur.

D-Glu–D-His. This diastereoselectivity is also shown, albeit less clearly, by the other two receptors **2** and **4** that were capable of recognizing the Glu-His sequence. As was the case with the original receptor **1**, most variability is found in the amino acid residue that is nearest to the polymer support (AA_1). However, in the original receptor **1** this is predominantly a polar amino acid residue while in the receptors **2** and **3** (which contain less flexible hinges than the hinge of **1**) and in the carbazole receptor **4** the distribution of polar to nonpolar amino acids in AA_1 is about equal whereas in the pyrrolidine-based receptor **5** there is a shift to an apolar amino acid for AA_1.

Although the trends are clear and we seem to be on our way towards realizing our main aim with an increase in the binding affinity, binding of the peptide sequences determined by decoding the beads had to be verified by binding experiments with these peptides obtained by independent synthesis and determination of some representative binding constants.

Based on the sequences found from the decoding experiments we selected the indicated sequences for resynthesis (Table 2). Several binding constants were determined. Indeed, the binding affinity of the sequence D-Ala–L-Asp–D-Ser that bound with high selectivity to the original receptor **1** was increased more than tenfold (from 330 to 4100 M^{-1}) with synthetic receptor **2**. An increasing affinity was also observed with the sequence L-Glu–D-Asn–L-Val that bound with a lower affinity to the original receptor (95 M^{-1}) but that bound to tweezer **2** with a respectable affinity of $K_a = 1680\,M^{-1}$. A twofold increase in binding affinity of D-Ala–L-Asp–D-Ser

Table 2. Binding affinity of receptors **1**–**6** for peptides, which were synthesized according to the sequences found by decoding.

Receptor	Resynthesized peptide	Screening affinity[a]	Binding affinity[b]	K_a [M^{-1}][c]	ΔG [kJ mol^{-1}]
1	D-Ala–L-Asp–D-Ser	+	++	320	−14.2
	L-Glu–D-Asn–L-Val	+	+	95	−11.2
2	D-Ala–L-Asp–D-Ser	[f]	+++	4100	−20.5
	L-Glu–D-Asn–L-Val	+++	+++	1680	−18.3
3	D-Ala–L-Asp–D-Ser	[e]	++	760	−16.4
	L-Glu–D-Asn–L-Val	[e]	+	[d]	[d]
	L-Glu–D-His–L-Val	++	+++	210	−13.2
	Gly–L-His–L-Asp	++	+++	[d]	[d]
4	Gly–L-His–L-Asp	+	+	[d]	[d]
5	D-Ala–L-Asp–D-Ser	[e]	++	~40	~−9
	L-Glu–D-His–L-Val	+++	++	80	−10.8

[a] As determined from incubation with the bead-supported tripeptide library: +++ red beads; ++ dark orange to red beads; + dark orange beads. [b] By incubation in chloroform of the resynthesized peptide on the bead with the colored receptor. [c] As derived from UV measurements, the error is ±10%, with the exception of 4100 M^{-1}: ±5% and 210 and 40 M^{-1}, each ±15%. [d] Not determined. [e] Not found. [f] Not found, however the related sequence D-Ala–L-Asp–D-Thr was found.

In conclusion, we have shown that by varying the hinge part of tweezerlike synthetic receptor molecules it is possible to increase the binding affinity of tripeptides significantly while maintaining the selectivity. The availability of a variety of hinges or scaffolds and building blocks inspired by "natural diversity" will provide access to all sorts of required libraries capable of binding compounds other than peptides.

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[12] AA_{1-3}: Gly, D- and L-Ala, D- and L-Val, D- and L-Leu, D- and L-Phe, D- and L-Pro, D- and L-Ser, D- and L-Thr, D- and L-Asn, D- and L-Gln, D- and L-Asp, D- and L-Glu, D- and L-His, D- and L-Lys, D- and L-Arg.

[13] We attempted to reach a concentration of the receptor slightly lower than that required for binding approximately 1 % of the library beads. These concentrations are listed in Table 1.

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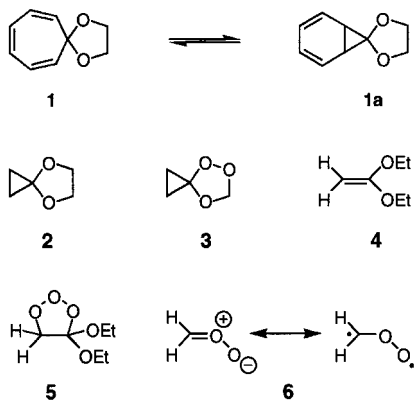
A Spontaneous Fragmentation: From the Criegee Zwitterion to Coarctate Möbius Aromaticity**

Christian Berger, Christian Bresler, Ulrich Dilger, Daniel Geuenich, Rainer Herges,* Herbert Röttele, and Gerhard Schröder*

Dedicated to Professor William von E. Doering on the occasion of his 80th birthday

Coarctate reactions[1] are defined as those in which two bonds are simultaneously formed and broken at one or more atoms. Like the pericyclic reactions, they form an independent and coherent class of concerted reactions. Rules are available for predicting the stereochemical course of coarctate reactions,[1] similar to the Woodward–Hoffmann rules for pericyclic reactions. We now describe an unusual fragmentation reaction which is in accordance with these stereochemical rules and for which such a coarctate transition state was confirmed by theoretical calculations.

Tropone ethylene acetal (**1**) is in equilibrium with the norcaradiene derivative **1a**. Above 100 °C **1** undergoes sigmatropic rearrangements ($E_a = 23.9$ kcal mol^{-1}).[2] Moreover, above 110 °C **1** decomposes via **1a** to give carbon dioxide, benzene, and ethene ($E_a = 31.6$ kcal mol^{-1}).[2] The fragmentation of **1a** was interpreted as a chelotropic cycloreversion to give benzene and 2-carbena-1,3-dioxolane. The authors speculate that the decomposition of the 2-carbena-1,3-dioxolane and the chelotropic cycloreversion might be part of a single concerted step.[2] The parent structural element in the fragmentation of **1a** is the 4,7-dioxaspiro[2.4]-heptane **2**. If a C–O bond in **2** is replaced by a O–O bond (**3**),



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