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Formation of Bicyclic Ethers from Lewis Acid Promoted Cyclizations of Cyclic Oxonium Ions

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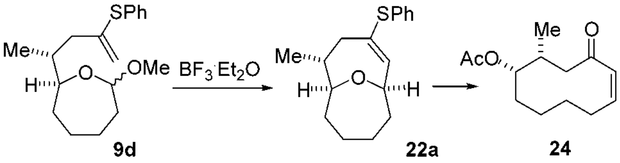
ABSTRACT



Oxacycles carrying a vinyl group and an acetal were extended with a cyclization terminator (vinyl silane or vinyl sulfide) by Suzuki coupling. Treatment with Lewis acid induced cyclization to provide bicyclic ethers in reasonable yields. In the case of the vinyl silane, an ene-like mechanism is preferred, whereas the thioenol ether enters into a Prins-type reaction channel. In one instance, the bicyclic compound was opened to give the ten-membered functionalized enone 24.

Oxonium ions are common electrophiles in organic synthesis. This has to do with the fact that they are highly reactive and that they react with a range of nucleophiles.[1] Since oxonium ions can be generated from various precursors, they can be included into a synthetic scheme very easily. Thus, oxonium ions can be formed from acetals[2] or enol ethers[3]. The most important method, however, is the generation of oxonium ions from carbonyl compounds and Lewis acids. The addition of nucleophiles to oxonium ions can be used for carbon−carbon bond formation with the simultaneous creation of stereocenters. Connecting the nucleophile and the oxonium ion allows for ring-forming reactions, making cyclic ethers and carbocycles easily accessible. Cyclic oxonium ions are special in that they are key intermediates in the formation of glycosidic bonds and spiroacetals.[4] An interesting extension of the chemistry of cyclic oxonium ions would be further intramolecular reaction with a nucleophilic group, leading to bicyclic ethers.[5,6] Such a setting could be of interest for mechanistic reasons, that is, to probe the stereoelectronics of the addition step. Moreover, bicyclic ethers might provide an interesting scaffold for combinatorial application. Finally, cleavage at the ether bridge could lead to functionalized carbocycles.

In this paper, we present our initial results in this area. The general idea is illustrated in Scheme 1. Thus, a hydroxyacetal, containing a nucleophilic group, for example, a vinylsilane moiety, might undergo cyclization to an oxonium ion that then would be trapped by the nucleophile.

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(1) For reviews, see: (a) Blumenkopf, T.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857−873. (b) Schinzer, D. *Nachr. Chem. Technol. Lab.* **1989**, *37*, 498−505.

(2) For some illustrative examples, see: (a) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556−6558. (b) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514−1515. (c) Castañeda, A.; Kucery, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695−5707. (d) Burke, S. D.; Strickland, S. M. S.; Organ, H. M.; Silks, L. A., III. *Tetrahedron Lett.* **1989**, *30*, 6303−6306. (e) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966. (f) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446−2452. (g) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811−3820. (h) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702−6703.

(3) (a) Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394−6395. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421.

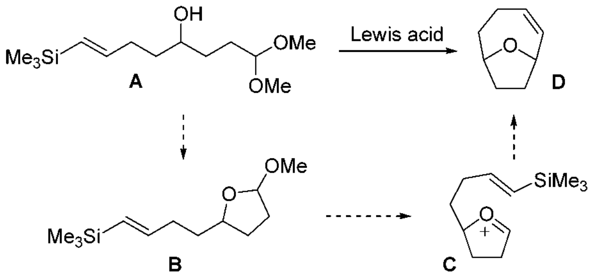
(4) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661.

(5) For some isolated examples, see: (a) Sonawane, H. R.; Maji, D. K.; Jana, G. H.; Pandey, G. *J. Chem. Soc., Chem. Commun.* **1998**, 1773−1774. (b) Ohmura, H.; Smyth, G. D.; Mikami, K. *J. Org. Chem.* **1999**, *64*, 6056−6059.

(6) For the [3 + 5] annulation route to bicyclic ethers, see: Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559−4565.

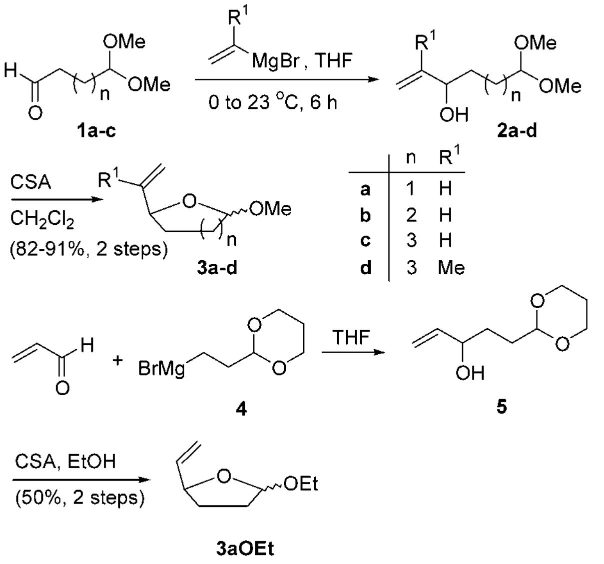
10.1021/ol025570d CCC: $22.00

Scheme 1. Tandem Cyclization of Hydroxyacetals Containing a Nucleophilic Group



The synthesis of the appropriate substrates is shown in Scheme 2. Beginning with the acetal aldehydes[7] **1a−c** in Grignard reaction with vinyl- or 2-propenylmagnesium bromide provided the allylic alcohols **2a−d**. These compounds could be cyclized very easily to the cyclic hemiacetals **3a−d** as anomeric mixtures.[8] As opposed to a report in the literature,[9] compound **2b** did not cyclize spontaneously. Since the procedure for obtaining the aldehyde **1a** by ozonolysis of 1,5-cyclooctadiene[10] turned out to be quite unreliable in our hands, another route to a compound of type **2a** was usually employed. Thus, Grignard addition of the C3 reagent **4** to acrolein gave the allylic alcohol **5**,[11] which was subjected to transacetalization with ethanol giving **3aOEt**.

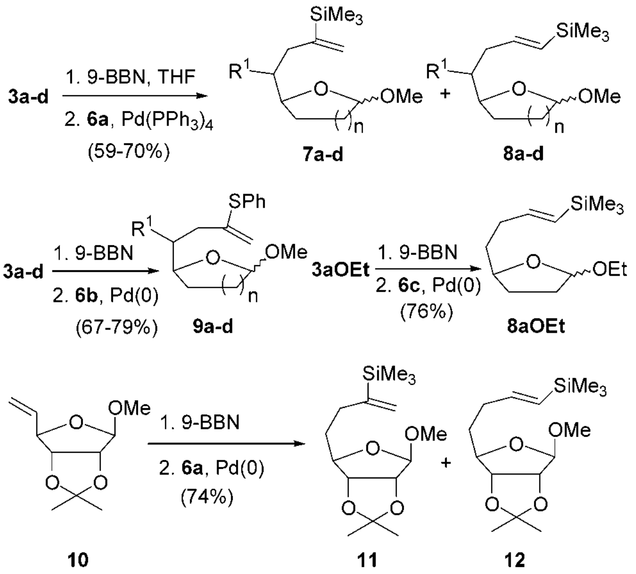
Scheme 2. Synthesis of 2-Alkoxy-vinyloxacycles



	n	R1
a	1	H
b	2	H
c	3	H
d	3	Me

To install the nucleophilic group, a Suzuki cross-coupling reaction was employed.[2e,12] Thus, hydroboration of the alkenes **3a−d** with 9-BBN followed by the addition of the alkenyl bromide **6a** [1-bromo-1-trimethylsilylethene] or **6b** [1-bromo-1-(phenylthio)ethene], tetrakistriphenylphosphinepalladium, aqueous NaOH, and benzene and refluxing of the mixture provided the cyclization substrates **7−9** (Scheme 3).[13] In a similar fashion, compound **3aOEt** was subjected to Suzuki coupling with **6c** [1-bromo-2-trimethylsilylethene] to afford compound **8aOEt**.

Scheme 3. Synthesis of the Cyclization Substrates by Suzuki Cross-coupling Reaction



In the case of **6a**, the desired coupling product **7** was always accompanied with the rearranged product **8** (ratio of **7**:**8** ≈ 2:1). Most likely, this rearrangement, which has been observed by other groups,[14] takes place via *β*-hydride elimination from the alkenylpalladium species **E** (Figure 1).

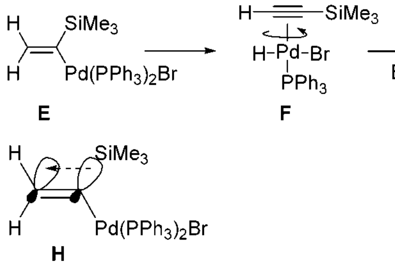


Figure 1. Possible stereoelectronic effect during the rearrangement of **E** to **G**.

This elimination might be facilitated by hyperconjugation of the C−SiMe$_3$ bond to the σ*-orbital of the C−H bond. If the cross-coupling reaction between **3c** and **6a** was carried out at lower temperatures, the rearranged product even becomes the major product (ratio ≈ 1:2, 61% yield). It should be noted that in this instance, modified conditions were used (5% (dppf)$_2$PdCl$_2$, 5% Ph$_3$As, Cs$_2$CO$_3$, DMF/THF/H$_2$O, 23

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[7] Claus, R. E.; Schreiber, S. L.; Jeong, N.; Semmelbeck, M. F. *Org. Synth.* **1986**, *64*, 150−156.

[8] Diastereomeric ratios: **3a**, 1.4:1; **3b**, 2.2:1; **3c**, 2.3:1; **3d**, 4.7:1; **3aOEt**, 1.4:1.

[9] Felkin, H.; Gault, Y.; Roussi, G. *Tetrahedron* **1970**, *26*, 3761−3778.

[10] Li, P.; Wang, J.; Zhao, K. *J. Org. Chem.* **1998**, *63*, 3151−3152.

[11] Kawashima, M.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1, 3377−3379.

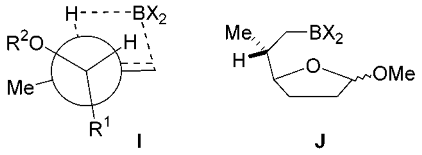

Figure 2. Diastereoselective hydroboration of the propenyl derivative **3d**.

Table 1. Lewis Acid Induced Cyclization to Bicyclic Ethers

entry	substrates[a]	promotor[b]	products
1	**8aOEt**	$SnCl_4$	**13b** (53%)
2	**7a**, **8a** (2:1)	$SnCl_4$	**13a**, **13b** (2:1, 48 %)[19]
3	**7b**[c]	$SnCl_4$	**14a** (12%), **14b** (43%)
4	**7b**[c]	TMSOTf	**14b** (56%)
5	**7c**[c]	$SnCl_4$	**15** (50%)
6	**7d**[c]	$SnCl_4$	**16** (8:1, 60%)
7	**11**, **12** (2:1)	$SnCl_4$	**17a** (5%), **17b** (33%), **17c** (19%)
8	**11**, **12** (2:1)	TMSOTf	**17b**, **17c** (2:1, 59%)
9	**9a**	BF_3·Et_2O	**19a**, **19b** (2:1, 69%)
10	**9b**	BF_3·Et_2O	**20** (72%)
11	**9c**	BF_3·Et_2O	**21** (71%)
12	**9d**	BF_3·Et_2O	**22a**, **22b** (8:1, 73%)

[a] Concentration of the starting material, 0.02 M; reaction scale, 30−60 mg. [b] TMSOTf (1.5 equiv), $SnCl_4$ (1.5 equiv), and BF_3·Et_2O (2.0 equiv) were used; reactions with TMSOTf and $SnCl_4$ were carried out in CH_2Cl_2 and reactions with BF_3·Et_2O in *t*BuOMe. [c] Particular pure fractions (containing less than 10% of the rearranged isomer **8**) were used. In these small-scale cyclizations, the $^{\Delta}$3,4-bicyclic ether could not be detected.

°C).[15] This result is in contrast to the findings described by Gilchrist et al.

In the case of the propenyl derivative **3d**, the hydroboration was highly diastereoselective (8:1). The relative stereochemistry was assigned on the basis of the model of Houk et al.[16] According to this model, anti-diols are produced via a staggered transition state **I** where the substituents R^1 and OR^2 occupy the anti and outside positions, respectively (Figure 2). This assignment could be confirmed at a later stage (vide infra).

To probe the influence of an alkoxy substituent, located next to the acetal function, on the cyclization reaction, the substrate **10** was prepared from D-ribose via a sequence of acetalization, acetonide formation, Swern oxidation, and Wittig olefination.[17] A subsequent hydroboration and Suzuki coupling with **6a** provided the compound **11** together with **12** in good yield (**11**:**12** = 2:1).

Cyclization Reactions. As has been described by Overman et al.,[18] alkenylsilane cyclizations onto acetals are best performed with tin(IV) chloride or trimethylsilyl triflate as promoters in dichloromethane as the solvent. On the other hand, cyclization with vinyl sulfide terminators seems to be more efficient with borontrifluoride etherate (BF_3·Et_2O) in *tert*-butylmethyl ether. Accordingly, we applied similar conditions with our substrates. These results are summarized in Table 1 (for the structures, see Figure 3).

From these experiments, the following conclusions can be made (Figure 4). (a) The 2-trimethylsilylalkenes prefer an ene-type cyclization (leading to **N** via transition state **L** and intermediate **M**) irrespective of the ring size of the cyclic oxonium ion. An intramolecular Prins reaction would generate products with an exocyclic methylene group, but no such product was observed in any of these cases. Usually, ene cyclizations are accompanied by protodesilylation, presumably by adventitious HCl generated inside the reaction flask or during workup (**N**, R = H). (b) The cyclization of the vinyl sulfide derivatives (2-thiophenylalkenes) proceeds most likely via an intramolecular Prins cyclization (intermediate **O** generating **N** and/or **P**). This pathway is supported by the electronic nature of the thiophenyl group. The subsequent elimination of a proton from the carbocation can take place in two directions. The regiochemistry of the elimination depends on the size of the cyclic oxonium ion and the stability of the cyclized products. The six-membered oxonium ion gave only the $^{\Delta}$4,5-bicyclic ether, whereas the seven-membered oxonium ions gave mainly the $^{\Delta}$3,4-bicyclic ether. In the case of five-membered oxonium ions, a mixture of the two possible double-bond isomers is formed. The product ratio is in part reflected in the calculated heat of formation (HyperChem 6.02).[20]

The ribose derivative could also be induced to cyclize. For the cyclization, a 2:1 mixture of the 2- and 1-trimeth-

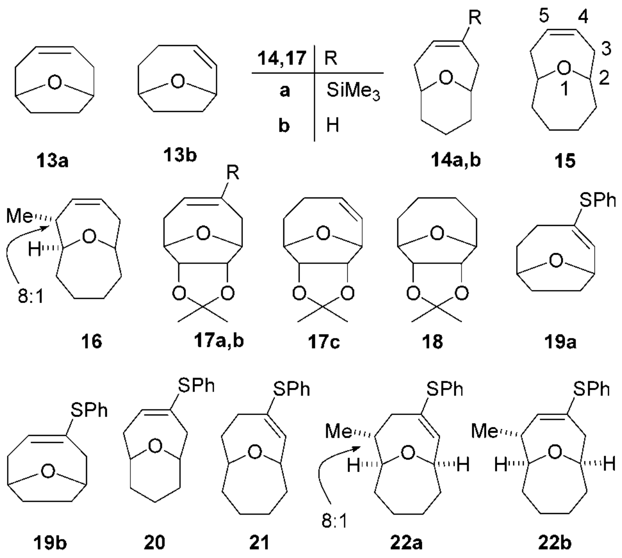

Figure 3. Structures of cyclization products (cf. Table 1).

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(12) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem.* **2001**, *113*, 4676−4701; **2001**, *40*, 4544−4568.

(13) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321.

(14) Ennis, D. S.; Gilchrist, T. L. *Tetrahedron* **1990**, *46*, 2623−2632.

(15) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818−6819.

(16) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257−2274.

(17) Ugarkar, B. G.; DaRe, J. M.; Kopcho, J. J.; Brown, C. E., III; Schanzer, J. M.; Wiesner, J. B.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 2883−2893.

(18) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386-4399.

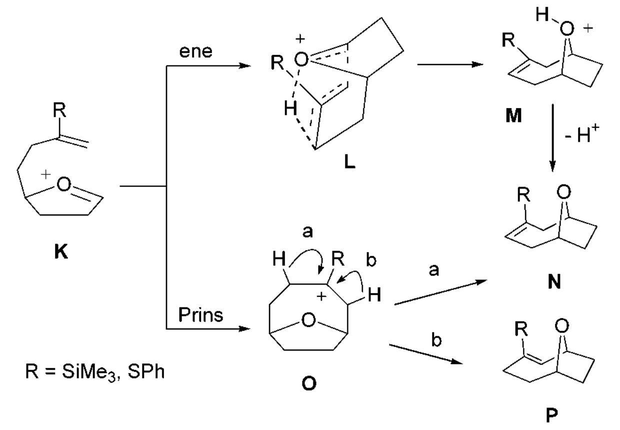


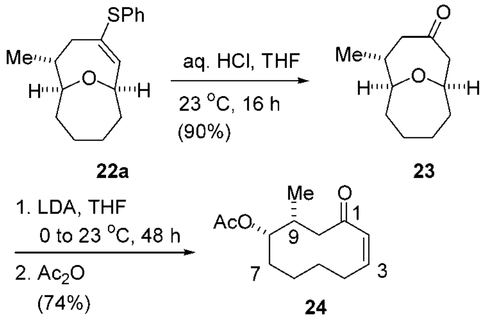
Figure 4. Mechanistic pathway for the reaction of the oxonium ion **K**.

ylsilyl alkene **11** and **12** was employed. Use of $SnCl_4$ as a Lewis acid afforded a mixture of three products with a $^{\Delta}$4,5/$^{\Delta}$3,4 ratio of 2:1 (57% total yield).

It is very likely that the $^{\Delta}$4,5 isomers are formed via the ene pathway (boatlike transition state), whereas the $^{\Delta}$3,4 isomers result from the terminal vinylsilane via a Prins mechanism. Although it was not possible to separate the two isomers **17b** and **17c**, they could easily be distinguished in the ^{1}H and ^{13}C NMR spectra due to their different symmetry.[21] Hydrogenation of the **17b/17c** mixture over palladium hydroxide in ethyl acetate gave the saturated bicyclic ether **18**.

To study the cleavage of the ether bridge, the thioenolether moiety of **22a/b** was hydrolyzed with aqueous HCl to the bicyclic ketone **23**. This ketone was treated with LDA to give the monocyclic keto alcohol, which was directly converted to the acetate **24**, a functionalized ten-membered carbocycle. The base-induced ring opening of **23** is very slow, but longer reaction times gave a better yield.[22] In principle, the vinyl sulfide cyclization products could be opened to from eight- to ten-membered carbocycles, which are important structural motifs in several natural products[23] or serve as precursors for cyclic peptide mimetics.[24]

Scheme 4. Base-Induced Ring-opening of the Bicyclic Keto Ether **22**



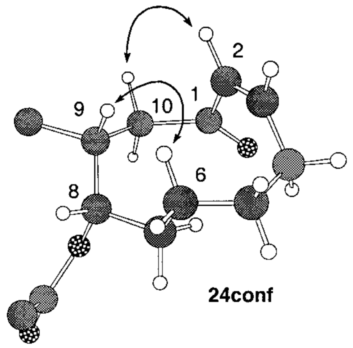


Figure 5. Calculated conformation of **24conf** and important NOESY cross-peaks.

NMR data of **24** are in accordance with the conformer **24conf**.[25] This conformation is characterized by a pseudoaxial O-acetoxy group. Prominent NOESY cross-peaks were observed between H-2/H-9, H-2/H-10, H-6/H-8, and H-6/H-9, supporting the calculated conformation.

To summarize, we were able to show that the cyclization of cyclic oxonium ions represents an efficient strategy for obtaining unsaturated bicyclic ethers. Particularly, the attachment of the nucleophilic terminators via a Suzuki cross-coupling reaction makes the whole sequence very concise. The general strategy might also be applicable for the synthesis of bicyclic amines.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. P. K. Sasmal thanks the Alexander von Humboldt foundation for a fellowship.

Supporting Information Available: Experimental procedures for the sequence of Grignard reaction, cyclic acetal formation, Suzuki coupling, and bicyclic ether formation and the conversion of **22** to **24**, NMR spectra for important compounds, and the NOESY spectrum of compound **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Two of the compounds, **13a** and **13b**, have been prepared before for 1,5-cyclooctadiene: Cope, A. C.; McKervey, M. A.; Weinshenker, N. M. *J. Org. Chem.* **1969**, *34*, 2229−2231.

[20] The following values were obtained: **19a** −41.19, **19b** −26.54, **21** −86.65, **21-$^{\Delta}$4,5-isomer** −72.22 kJ/mol. For **20**, calculations predict the 3,4-isomer to be more stable by 4.66 kJ/mol. In this case, the ene-type pathway might dominate.

[21] For example, the C_s-symmetric **17b** shows two ^{13}C signals in the region between 80 and 90 ppm (2 RCHOR carbons). The minor isomer **17c** shows the expected four peaks.

[22] For the ring-opening of bicyclic ethers, see: Lautens, M.; Ma, S.; Chiu, P. *J. Am. Chem. Soc.* **1997**, *119*, 6478−6487.

[23] For example, germacranes can be mentioned: Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1207−1211.

[24] Olson, G.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 323−333.

[25] This conformation turned out to be the global minimum in a conformational search using MacroModel 7.0 (1000 starting conformations, 50 kJ/mol cutoff, MM^{+} force field). (a) Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419−1427. (b) Kolossváry, I.; Guida, W. C. *J. Comput. Chem.* **1993**, *14*, 691−698.