A New, Efficient Route to Titanium–Silsesquioxane Epoxidation Catalysts Developed by Using High-Speed Experimentation Techniques[**]

Paolo P. Pescarmona, Jan C. van der Waal,
Ian E. Maxwell, and Thomas Maschmeyer*

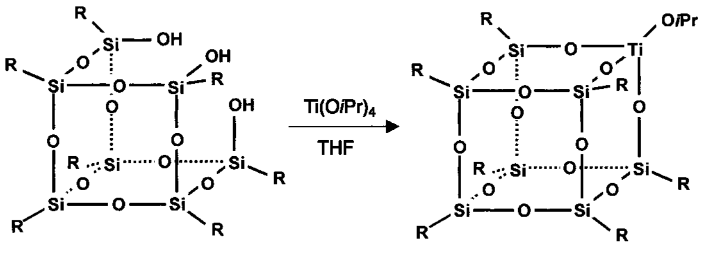
Titanium centers dispersed on, and supported by, various forms of silica are catalysts with remarkable properties for partial oxidations.[1] The character of the active site varies with the silica support used. Although it has been established that in the best (on the basis of activity per gram of titanium) heterogeneous catalysts the Ti centers are all four-coordinate,[2–4] it is still unclear whether, for optimum performance, the active catalytic species requires the specific configuration of four siloxy groups, or if being partially hydrolyzed to, say, one hydroxy and three siloxy ligands is equally good. Chemical modeling studies by various groups[5–7] have shown that Ti catalysts with fewer than four siloxy groups should also be active as catalysts. These considerations indicate that there is still some residual uncertainty regarding the active site, despite the many experimental and computational studies carried out to resolve it.[8, 9] Indeed, several mechanisms, or variations of one underlying mechanism, might operate depending on the precise configuration of the Ti site. Hence, different types of Ti centers might exhibit the desired characteristics.

For these catalysts, which are difficult to characterize, organic–inorganic hybrid compounds have proved to be useful models. Especially silsesquioxanes[10–12] $(RSiO_{1.5})_a(H_2O)_{0.5b}$ (R is an organic group; $a \geq 1$, $b \geq 0$) have been a focus of attention as model compounds for silica. Of interest for catalysis are those silsesquioxanes that contain Si–OH groups, that is partially condensed structures to which a catalytically active compound can be complexed.[13, 14] The incompletely condensed silsesquioxane trisilanol **1** ($a = 7$, $b = 3$) has recently been reported as a precursor for the soluble, titanium model compound **2** (Scheme 1), which results in an active catalyst for the epoxidation of alkenes.[5–7] Silsesquioxane **1** can be obtained by the slow hydrolytic condensation of the corresponding monosilane $RSiX_3$ [Eq. (1) and (2); R = organic group; X = Cl, OMe, OEt; $a + b = 2n$; $n = 1,2,3\ldots$;

$$RSiX_3 + 3H_2O \rightarrow RSi(OH)_3 + 3HX \qquad (1)$$

$$a RSi(OH)_3 \rightleftharpoons (RSiO_{1.5})_a(H_2O)_{0.5b} + (1.5a - 0.5b)H_2O \qquad (2)$$

$b \leq 3a$].[15] Besides compound **1**, the reaction may produce other silsesquioxane structures, some of which may also contain silanol groups that could react with titanium species to produce catalytic materials.



1 **2**

Scheme 1. Complexation of titanium to the incompletely condensed silsesquioxane $R_7Si_7O_{12}H_3$ (R = cyclohexyl, cyclopentyl), modeling the grafting of titanium on silica.

The preparation of compound **1** is time-consuming and requires a number of purification steps.[15] Here we describe the application of high-speed experimentation techniques[16] to optimize the preparation of silsesquioxanes as precursors for Ti catalysts active in the epoxidation of alkenes with peroxides. The aim is to identify a faster and cheaper way to synthesize silsesquioxane precursors for Ti catalysts. Since silsesquioxanes other than **1** may also show relevant catalytic activity after reaction with titanium, the synthesis of the silsesquioxane precursors was optimized not as a function of the yield in compound **1**, but rather as a function of the product yield due to the catalytic activity of the Ti silsesquioxanes in the epoxidation of 1-octene. The observed activity is thus the combined activity of all these compounds (vide infra).

Different factors may influence the reaction equilibria that determine which silsesquioxane structures and in what amounts are produced by the hydrolytic condensation of the organosilane $RSiX_3$.[10, 12] Among those factors, the solvent and the nature of the organic group R are known to play a predominant role. Both the solvent and the R group influence the kinetic rate constant and the solubility of intermediates and products. The R group also affects the thermodynamic stability of the different silsesquioxane structures.

A number of solvents and trichlorosilanes were varied systematically to investigate a wide range of parameters. The chosen solvents are water-miscible, polar solvents: acetone, acetonitrile, methanol, and tetrahydrofuran (THF). The selected trichlorosilanes $RSiCl_3$ were either those usually employed (R = cyclohexyl and cyclopentyl) or those for which the corresponding open silsesquioxane **1** has not yet been reported in the literature (R = phenyl, methyl, *n*-octyl, allyl) but which were readily available.

In the preparation of the silsesquioxane-based catalysts, two general types of behavior regarding the solvents and the organotrichlorosilanes can be identified:

a) Catalysts derived from silsesquioxane structures that were synthesized in acetonitrile show the highest catalytic activity, followed, in decreasing order of activity, by those from acetone, methanol, and tetrahydrofuran (Figure 1A). Interestingly, acetonitrile is more effective than acetone, the

---

[*] Prof. Dr. T. Maschmeyer, P. P. Pescarmona, Dr. J. C. van der Waal
Laboratory of Applied Organic Chemistry and Catalysis
DelftChemTech, TU Delft
Julianalaan 136, 2628 BL Delft (The Netherlands)
Fax: (+31) 15-278-4289
E-mail: th.maschmeyer@tnw.tudelft.nl

Dr. J. C. van der Waal, Dr. I. E. Maxwell
Avantium Technologies B.V.
Zekeringstraat 29, 1014 BV, P.O. Box 2915, 1000 CX Amsterdam
(The Netherlands)

[**] P.P.P. is grateful for a studentship from TUD.

0044-8249/01/11304-0762 $ 17.50+.50/0

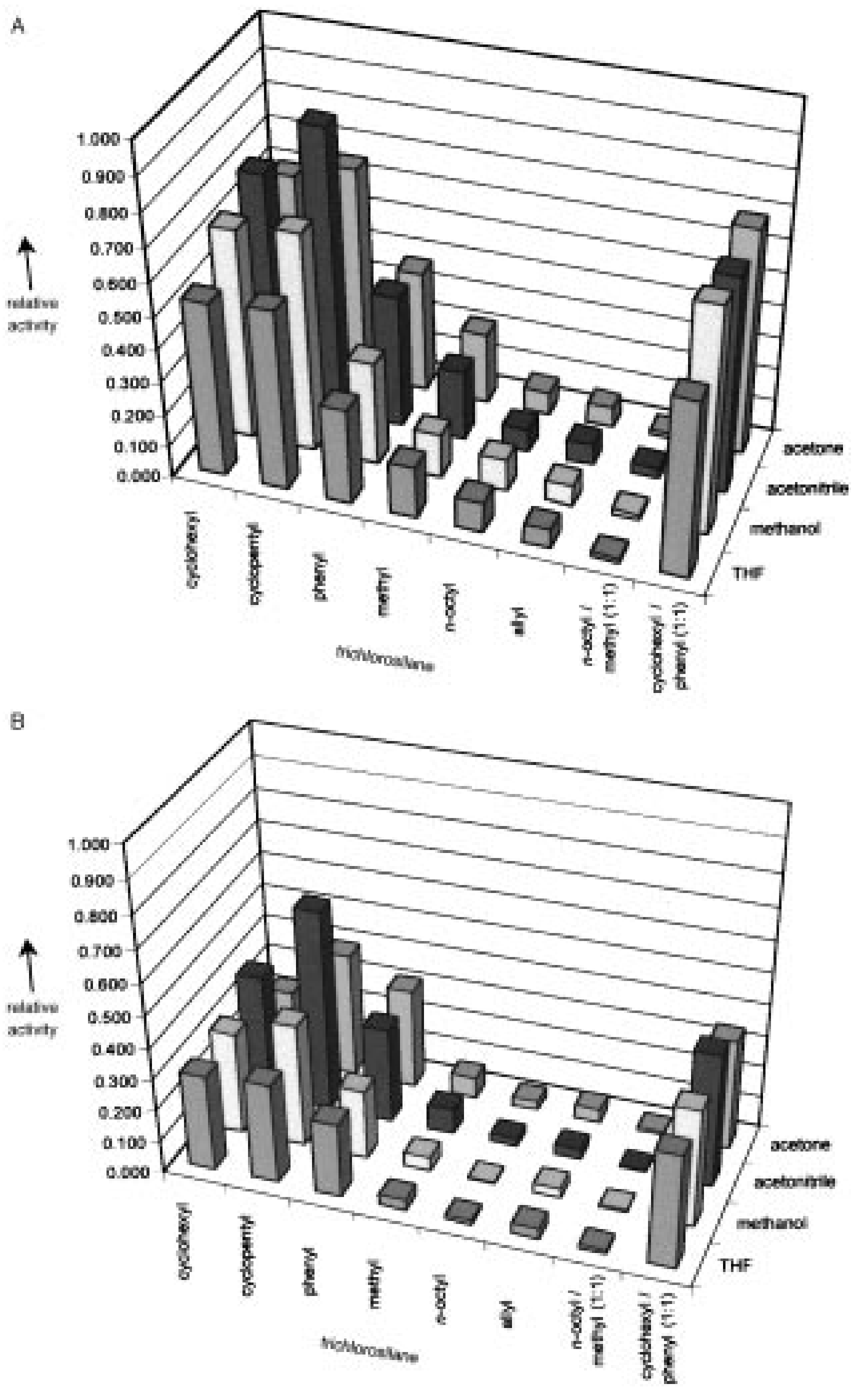


Figure 1. Activities of Ti–silsesquioxane catalysts (obtained by combining different trichlorosilanes and solvents, using water (A) or a 0.3 M HCl solution (B) as hydrolyzing agent) relative to Ti–cyclopentylsilsesquioxane catalyst **2** (activity set at 1) in the epoxidation of 1-octene.

solvent commonly reported for the synthesis of incompletely condensed silsesquioxane **1**.[15] This result can be explained in terms of electric properties: amongst the solvents used, acetonitrile has the highest dipole moment and dielectric constant. Therefore, it can stabilize silsesquioxane species containing Si–OH groups, favoring their synthesis over that of the less polar, completely condensed silsesquioxanes.

b) With respect to the silanes employed, the highest epoxidation activities were observed in the order cyclopentyl > cyclohexyl > phenyl > methyl > allyl ~ *n*-octyl ~ 0, regardless of the solvent used during the synthesis (Figure 1 A). This trend is in good agreement with the literature, where cyclopentyl- and cyclohexyltrichlorosilanes are reported to form incompletely condensed silsesquioxanes in high yields.[15] In principle, the nature of the organic group might influence which silsesquioxane structures are produced and in which ratios,[10] as well as the electronic and spatial properties of the actual catalyst. Considering that the organic groups are linked to the titanium center through a Si–O unit, electronic effects should have a negligible influence on the catalytic properties and, since the organic groups point away from the titanium center, steric effects are probably also not relevant. The principal effect of the organic group is, therefore, considered to be its role in determining which silsesquioxane structures are formed during the hydrolytic condensation and in which amounts.

The trend in the catalytic activity, as a function of the solvent used in the hydrolytic condensation, is not influenced by the nature of the organic group R. The activity trend as a function of the organic group is likewise not affected by the solvent. Therefore, regarding these trends, the solvent and organic group can be considered as independent variables.

The activities of the catalysts synthesized using high-speed experimentation techniques were compared with those of Ti(O*i*Pr)$_4$ and of the Ti–cyclopentylsilsesquioxane catalyst **2** produced by the reaction of pure cyclopentylsilsesquioxane **1** with Ti(O*i*Pr)$_4$. The high-speed experimentation catalysts with R = cyclohexyl, cyclopentyl, phenyl, and methyl show an activity higher than Ti(O*i*Pr)$_4$, confirming the formation of Ti–silsesquioxanes as the active species. Among these catalysts, the one derived from the combination of cyclopentyltrichlorosilane and acetonitrile displays the highest catalytic activity for the epoxidation of 1-octene (Figure 1 A). This activity is 87 % of that of the Ti–cyclopentylsilsesquioxane catalyst **2**. The relevance of this result lies in the fact that the synthesis of our silsesquioxane precursors does not require any purification process and is much less time-consuming than the synthesis of compound **1**. Scaling up of the experiment to 100-mL scale yielded a catalyst with an identical activity, thus demonstrating that the small-scale high-speed experiment is comparable to conventional experimentation.

Two 1:1 molar mixtures of *n*-octyl- and methyltrichlorosilane and of cyclohexyl- and phenyltrichlorosilane were used to investigate possible synergetic effects between two different organotrichlorosilanes in the formation of incompletely condensed structures (Figure 1 A). The *n*-octyl/methyl mixture gave a very low epoxidation activity. As in the case of the pure *n*-octyl compound, the hydrolytic condensation produced a gel, generated by micelle formation due, probably, to the slower hydrolysis rate of long-chain alkylsilanes.[12] Water retained in this gel would be inimical to the Ti insertion. The cyclohexyl-/phenyltrichlorosilane mixture showed considerable activity, suggesting the possibility of synergy between trichlorosilanes with different organic R groups.

Trying to further optimize the reaction, we investigated a variation of the ternary composition of the three most active silanes (cyclopentyl, cylcohexyl, and phenyl) in the best solvent (acetonitrile) (Figure 2). Although the highest epoxidation activity was found for the pure cyclopentyltrichlorosilane (i.e. the experiment did not lead to the identification of a more active catalyst), the surface of the activity diagram shows some interesting features, underpinning the utility of the experiment: various mixtures yield catalysts with higher activities than those from pure cyclohexyl- and phenyltrichlorosilanes. Such behavior would have been difficult to identify without a combinatorial approach.

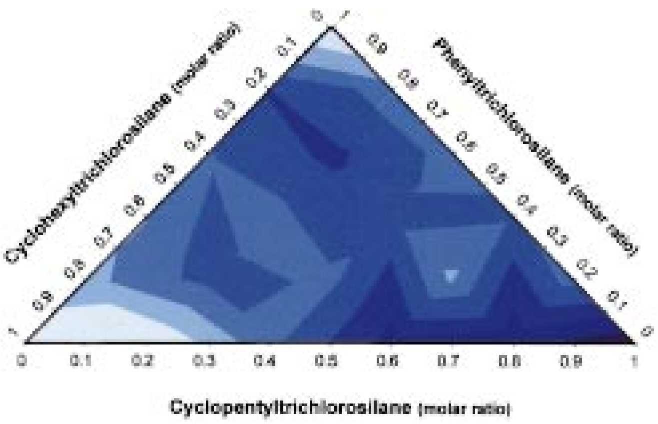


Figure 2. Activity in the epoxidation of 1-octene as a function of the ratio of cyclopentyl-, cylcohexyl- and phenyltrichlorosilanes in the initial silsesquioxane synthesis mixture (darkness of color ∝ activity).

During the hydrolysis of the trichlorosilanes, hydrochloric acid is produced [Eq. (1)], which could influence the amounts of silsesquioxanes generated.[10]. To check this potential pH effect, the experiment was performed by using either H_2O or a 0.3 M HCl/water solution to hydrolyze the silanes. The trends observed with both are very similar (Figure 1) and a higher activity is found when using a neutral water solution (70% greater on average); thus extra hydrochloric acid is not beneficial.

We have shown that high-speed experimentation can be a valuable technique in the optimization of catalysts. A very active silsesquioxane-based catalyst for the epoxidation of 1-octene (cyclopentyltrichlorosilane hydrolyzed in acetonitrile) has been prepared by a much faster and cheaper method than conventionally possible. In addition to identifying the optimal synthesis conditions within the screened parameters, the large number of experiments performed by using high-speed experimentation techniques enabled us to gain additional insight in the system under study. Some general trends with respect to the roles of both the solvent and the organotrichlorosilane have been identified, and it has been shown that the synthesis of silsesquioxane catalysts is favored using a neutral rather than an acidified (HCl) solution. In future experiments, we plan to identify the most active Ti-silsesquioxane by a deconvolution of the complex silsesquioxane mixture. Moreover, we aim to use high-speed experimentation for further optimization of the synthesis of the silsesquioxane precursors, for the optimization of the Ti-insertion step, and for the introduction of aqueous hydrogen peroxide as oxidant.

Experimental Section

Experiments were performed on a parallel synthesis workstation[17] by using four different solvents (acetone, acetonitrile, methanol, and tetrahydrofuran) and different silanes $RSiCl_3$ (R = cyclohexyl, cyclopentyl, phenyl, methyl, *n*-octyl, allyl, and mixtures of these). In a typical experiment, 6 × 2 mL aliquots of each of the four solvents were dispensed in a rack containing 4 mL glass tubes, followed by the addition of 340 µmol of each of the six silanes to the solvent-containing reaction vessels in such a way that 24 individually different silane solutions were prepared. Hydrolysis of the silane was initiated by the addition of 0.5 mL of either water or a 0.3 M HCl solution to the reaction vessel and placing the vessel array on an orbital shaker at 50 °C for 18 h. After removal of the solvent and of the excess water and hydrochloric acid in a vacuum centrifuge, the samples were stored under argon. Titanium insertion was performed by dissolving the crude silsesquioxane mixture in THF (2 mL) under argon, followed by the addition of titanium isopropoxide. After 5 h at 50 °C, the tetrahydrofuran was removed by means of the vacuum centrifuge and the samples were stored under argon.

The catalytic activity of the materials obtained was determined by the epoxidation of 1-octene with *tert*-butyl hydroperoxide (TBHP). The reaction was performed by adding to each dried sample a solution of TBHP (~0.36 mmol) in cyclohexane (TBHP:catalyst ratio = 7.5) and 1-octene (0.0144 mol), which acted both as reactant and solvent (1-octene:catalyst ratio = 300). Prior to dispensing, 2 mL of decane was added for each 98 mL of 1-octene to serve as an internal standard in the following GC analysis. Samples were taken after the reaction had been allow to proceed for 5 h at 60 °C and were analyzed on a UNICAM Pro GC using a CP-Sil-5B column. The epoxidation reaction proceeded very slowly at room temperature for several days; thus, the yield increased until a plateau was reached. The reported activities[18] were obtained by normalizing the GC peak area for 1,2-epoxyoctane by means of the internal standard. Since the experiments were performed in 1-octene also as a solvent, it has not been possible to realize a mass balance. The reaction was completely selective in the synthesis of 1,2-epoxyoctane: no other products were detected. The conversion selectivity of TBHP towards 1,2-epoxyoctane lies between 80 and 94%.

The other catalysts ($Ti(OiPr)_4$ and Ti–silsesquioxane **2**) were tested by using the same amount of titanium and the same experimental conditions as described above.

Received: August 28, 2000 [Z15709]

---

[1] B. Notari, *Adv. Catal.* **1996**, *41*, 253.
[2] G. Bellussi, M. S. Rigutto, *Stud. Surf. Sci. Catal.* **1994**, *85*, 177.
[3] T. Maschmeyer, F. Rey, G. Sankar, J. M. Thomas, *Nature* **1995**, *378*, 159.
[4] M. C. Klunduk, T. Maschmeyer, J. M. Thomas, B. F. G. Johnson, *Chem. Eur. J.* **1999**, *5*, 1481.
[5] T. Maschmeyer, M. C. Klunduk, C. M. Martin, D. S. Shephard, J. M. Thomas, B. F. G. Johnson, *Chem. Commun.* **1997**, 1847.
[6] M. Crocker, R. H. M. Herold, A. G. Orpen, *Chem. Commun.* **1997**, 2411.
[7] a) H. C. L. Abbenhuis, S. Krijnen, R. A. van Santen, *Chem. Commun.* **1997**, 331; b) S. Krijnen, H. C. L. Abbenhuis, R. W. J. M. Hanssen,

J. H. C. van Hooff, R. A. van Santen, *Angew. Chem.* **1998**, *110*, 374; *Angew. Chem. Int. Ed.* **1998**, *37*, 356.

[8] L. Marchese, T. Maschmeyer, E. Gianotti, S. Coluccia, J. M. Thomas, *J. Phys. Chem. B* **1997**, *101*, 8836.

[9] a) P. E. Sinclair, G. Sankar, C. R. A. Catlow, J. M. Thomas, T. Maschmeyer, *J. Phys. Chem. B* **1997**, *101*, 4232; b) D. Tantanak, M. A. Vincent, I. H. Hiller, *Chem. Commun.* **1998**, 1031.

[10] M. G. Voronkov, V. I. Lavrent'yev, *Top. Curr. Chem.* **1982**, *102*, 199.

[11] F. J. Feher, T. A. Budzichowski, *Polyhedron* **1995**, *14*, 3239.

[12] P. G. Harrison, *J. Organomet. Chem.* **1997**, *542*, 141.

[13] T. Maschmeyer, J. M. Thomas, A. F. Masters, *NATO ASI Ser. Ser. C* **1997**, *498*, 461.

[14] H. C. L. Abbenhuis, *Chem. Eur. J.* **2000**, *6*, 25.

[15] a) F. J. Feher, D. A. Newman, J. F. Walzer, *J. Am. Chem. Soc.* **1989**, *111*, 1741; b) F. J. Feher, T. A. Budzichowski, R. L. Blanski, K. J. Weller, J. W. Ziller, *Organometallics* **1991**, *10*, 2526.

[16] Formerly, high-speed experimentation was commonly referred to as parallel combinatorial chemistry and high-speed screening. For a review over these techniques, see P. P. Pescarmona, J. C. van der Waal, I. E. Maxwell, T. Maschmeyer, *Catal. Lett.* **1999**, *63*, 1.

[17] Experiments were performed by using a liquid handling system, developed in-house by Shell SRCTA, and a 24-tube based rack with the dimensions of the 96-well plate. The equipment and the experimental time were kindly donated by Shell and later by Avantium Technologies.

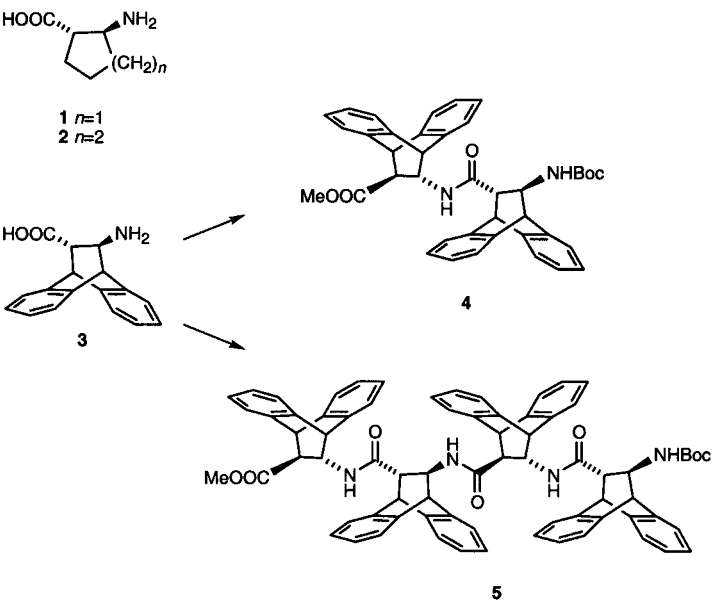
[18] The values for the activities are the averages of the results from different experiments. The deviation of each set of results from the average lies in a range between 0 and 10% of the average value. To test the robustness of our equipment, our results were also compared to the results from similar experiments performed at Shell Research Laboratories Amsterdam; the results were in good agreement.

Design and Synthesis of Foldamers Based on an Anthracene Diels–Alder Adduct**

Jeffrey D. Winkler,* Evgueni L. Piatnitski,
John Mehlmann, Jiri Kasparec, and Paul H. Axelsen*

Dedicated to Professor Ronald Breslow
on the occasion of his 70th birthday

The design and synthesis of peptides and peptide analogues with predictable and reproducible folding patterns is an important goal.[1] β-peptides are resistant to cleavage by most proteases and are therefore of considerable interest as building blocks in drug design.[2] The groups of Seebach, Gellman, and DeGrado have demonstrated that oligomers derived from β-amino acids such as **1** and **2** can adopt predictable conformations that are a direct consequence of the nature of the monomeric building blocks **1** and **2** (Scheme 1).[3] We reasoned that incorporation of two aromatic rings into **2** would constrain the amino acid backbone of oligomeric derivatives, creating foldamers with novel and well-defined hydrogen-bonding patterns.



Scheme 1.

We describe herein the preparation of the protected β-amino acid **9** from **6** (Scheme 2), the Diels–Alder adduct of anthracene and dimenthyl fumarate, and the synthesis and study of both the dipeptide **4** and the tetrapeptide **5**. The presence of the dihydroanthracene moieties leads to a high level of structural definition in both **4** and **5**. The structure of **4** exhibits a unique level of organization. The NMR-derived solution structure of **5** reveals a twelve-membered ring helical conformation with a molecular volume of about 1200 Å.

The synthesis of the tetracyclic β-amino acid monomer is outlined in Scheme 2. Reaction of anthracene with dimenthyl fumarate under Lewis acid catalysis leads to the formation of **6** in 88% yield and 99% *ee*.[4] Conversion of **6** to the corresponding dimethyl ester **7**[5] in acidic methanol[6] followed by saponification of **7** under mild basic conditions produces a statistical mixture of the desired monoacid **8**, along with the starting diester **7** and the corresponding diacid (not shown) which can be efficiently recycled. Curtius reaction of the acyl azide derived from **8** gave the *N*-Boc amino ester **9** in 34% yield over three steps. Reaction of **9** with NaOH gave the corresponding acid **10**, whereas exposure of **9** to trifluoroacetic acid led to the formation of the deprotected amino ester **11**. Condensation of **12**, the acid chloride derived from **10**, with **11** gave dipeptide **4** in 79% overall yield from **9**.

---

[*] Prof. Dr. J. D. Winkler, E. L. Piatnitski, J. Mehlmann, J. Kasparec
Department of Chemistry, University of Pennsylvania
231 South 34th Street, Philadelphia, PA 19104-6323 (USA)
Fax: (+1) 215-573-6329
E-mail: winkler@sas.upenn.edu

Prof. Dr. P. H. Axelsen
Department of Pharmacology, University of Pennsylvania (USA)

[**] We thank Professor Samuel H. Gellman (University of Wisconsin) and Professors William F. DeGrado and Stanley J. Opella (University of Pennsylvania) for valuable discussions. We also thank Ms. Lori Krim and Mr. Daniel Macks for their experimental and computational contributions to the early stages of this work. Generous financial support from Boehringer-Ingelheim and Alfred P. Bader (J.K.: Alfred E. Bader Fellow, 1996–1998) is gratefully acknowledged.

Supporting information for this article (synthetic procedures and spectroscopic data for dipeptide **4**, tetrapeptide **5**, and all synthetic intermediates) is available on the WWW under http://www.angewandte.com or from the author.