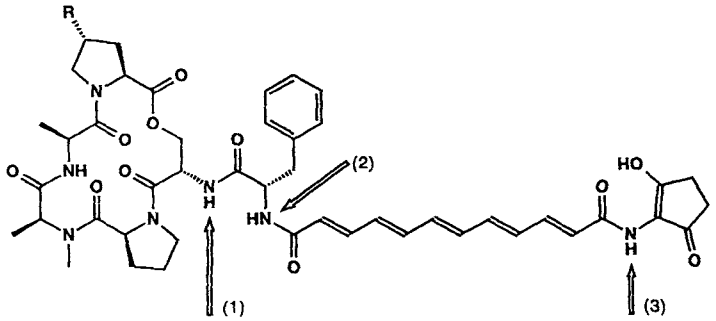
Synthesis of Enopeptin B from *Streptomyces* sp RK-1051**

Ulrich Schmidt,* Karin Neumann,
Andreas Schumacher, and Stefan Weinbrenner

The closely related enopeptins A (**1**) and B (**2**, Scheme 1) were first isolated in 1991 from the culture fluid of *Streptomyces* sp RK-1051, and their structures determined.[1] They contain a



1 R = CH_3
2 R = H

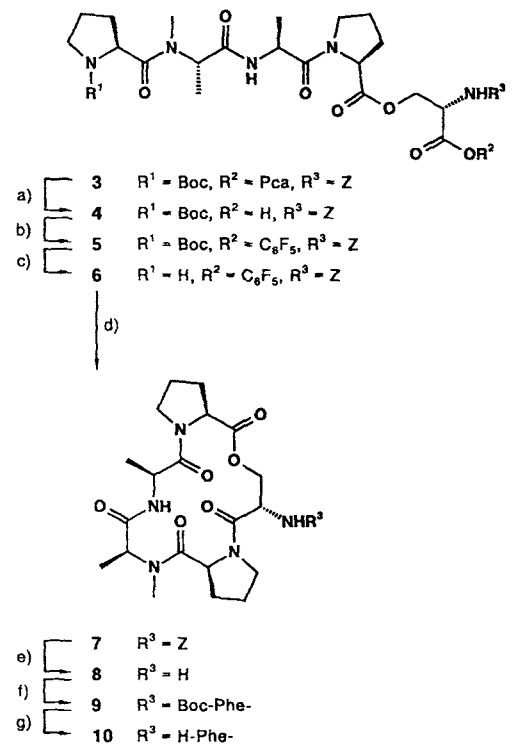
Scheme 1. Enopeptin A (**1**) and B (**2**). The amide bonds indicated by arrows were coupled in the order 1, 2, 3 (strategy 1) and 2, 3, 1 (strategy 2).

phenylalanyl cyclopeptolide connected to an aminocyclopentanedione through a dodecapentaenedioic acid residue. In contrast to the proline unit in **2**, *trans*-4-methylproline is found in **1**. Both exhibit antibiotic effects against gram-positive bacteria, especially certain strains of *Staphylococcus aureus*. The combination of a peptolide, a polyene, and a reductone in a natural product is unique. The main difficulty in the synthesis of **1** and **2** lies in coupling the three components.

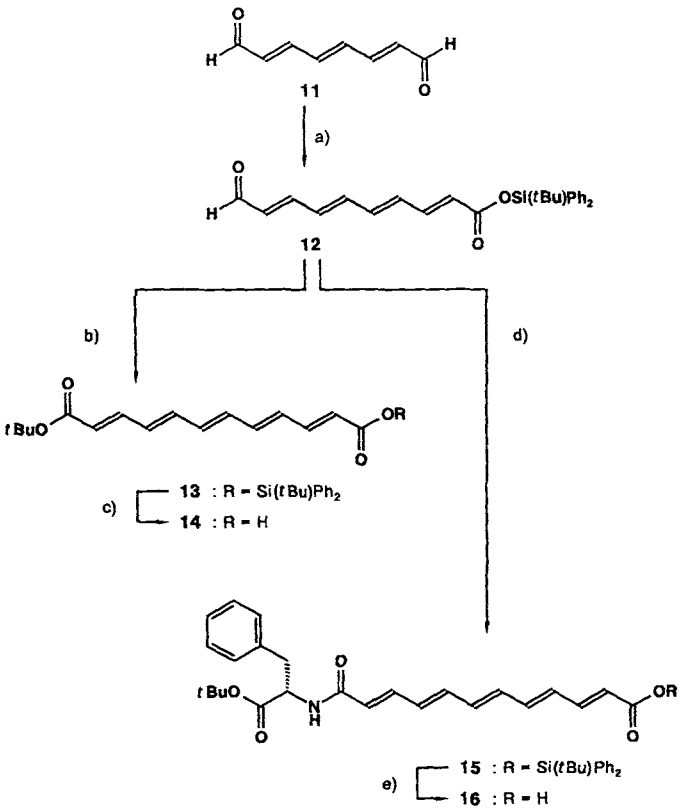
Components **8** and **10** were prepared in a few steps from pentapeptolide **3**[2] (Scheme 2); the key step is the ring closure to give **7** by the pentafluorophenyl ester method that we developed.[3] Cyclopeptide **7** was obtained in 68% yield in four steps in a two-phase system of aqueous $NaHCO_3$ and CH_3Cl. Hydrogenolytic cleavage of the benzyloxycarbonyl (Z) protecting group to form **8**, acylation with Boc-phenylalanine (Boc = *tert*-butoxycarbony) to **9**, and subsequent removal of the Boc group gave **10**, which was used just as **8** for preparing **2**.

Monoesters,[4] diesters, and amides of dodecapentaenedioic acid were prepared by Horner condensation with octatrienedial (Scheme 3).[5] Derivatives **14** and **16** were used for preparing **2**; compounds **13** and **15** contain compatible protective groups that can be selectively removed.

Numerous *N*-acyl-2-aminocyclopentane-1,3-diones have been isolated as metabolic products from microorganisms,[6-16] and some simple ones have been synthesized.[17-19] However, for the synthesis of **2** only the acylation of 2-aminocyclopentanedione, whose preparation by hydrogenation of 2-nitrocyclopentanedione was improved by using PtO_2 instead of PdO,



Scheme 2. a) Zn, 90proz. HOAc, room temperature (RT), 4 h; b) CH_2Cl_2, 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride (EDC), pentafluorophenol, −20 °C → RT, 20 h; c) HCl, dioxane, RT, 2 h; d) $CHCl_3$, $NaHCO_3$, H_2O, RT, 6 h; a)–d) 68%; e) MeOH, HCl, Pd/C/H_2, RT, 6 h: f) DMF, Boc-(*S*)-Phe-OH, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), Hünig base, 0 °C, 12 h; g) HBr, HOAc, RT, 30 min; e)–g) 84%.



Scheme 3. a) THF, $(EtO)_2P(O)CH_2COOSi(tBu)Ph_2$, NaH, RT, 3 h, 75%; b) THF, $(EtO)_2P(O)CH_2COOtBu$, NaH, RT, 2 h, 91%; c) THF, HF, H_2O, CH_3CN, 1 h, 95%; d) THF, $(EtO)_2P(O)CH_2CO$-Phe-O*t*Bu, NaH, RT, 2 h, 45%; e) THF, HF, H_2O, CH_3CN, 1 h, 85%.

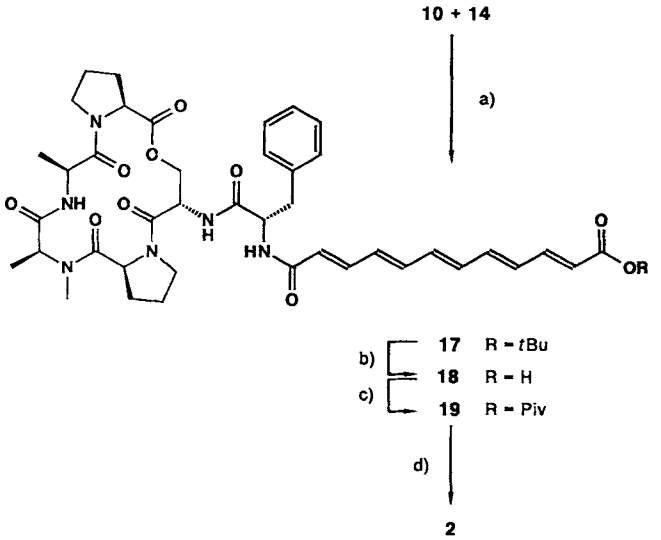
[*] Prof. Dr. U. Schmidt, Dr. K. Neumann, Dr A. Schumacher, Dr. S. Weinbrenner
Institut für Organische Chemie und Isotopenforschung der Universität
Pfafffenwaldring 55, D-70569 Stuttgart (Germany)
Fax: Int. code +(711)685-4321

[**] Concerning Aminoacids and Peptides, part 103. Concerning Cyclopeptides, part 32. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. – Parts 102 and 31: ref. [3b].

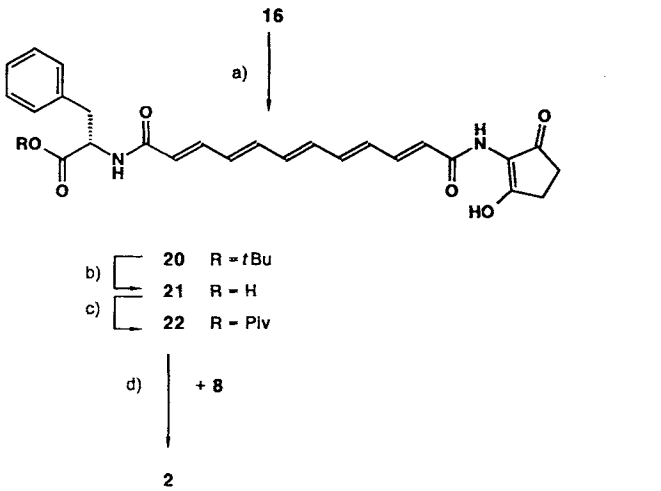
  0570-0833/97/3610-1110 $ 17.50+.50/0

is suitable. Difficulties in the acylation of aminoreductones are due to the very low nucleophilicity of the amino group and the lability of the free amino compound, which undergoes rapid autocondensation. These problems can only be overcome with highly reactive acylation components, such as anhydrides or acid chlorides, and inverse addition.

We have prepared **2** by successive coupling of the amide bonds 1, 2, and 3 (strategy 1) and 2, 3, and 1 (strategy 2, see Scheme 1). Removing the Boc group of **9** to form phenylalanyl-cyclopeptide **10** took place only under drastic conditions. The steric hindrance of the amino group of the phenylalanine was evident from the low yield (17%) of the subsequent acylation with half ester **14** to form polyenepeptolide **17.** Coupling of **18** with the aminocyclopentanedione to **2** was only achieved by inverse reaction of the mixed anhydride **19** in 6% yield (simultaneous, dropwise addition of four equivalents each of 2-aminocyclopentane-1,3-dione hydrochloride and *N*-methylmorpholine (NMM) to a solution of **19**, Scheme 4.



Scheme 4. a) DMF, HATU, Hünig base, 0 °C, 12 h, 17%; b) CH_2Cl_2, trifluoroacetic acid (TFA), RT, 2 h; c) THF, pivaloyl(Piv)-OCl, NMM, RT, 2 h; d) DMF, 2-aminocyclopentane-1,3-dione hydrochloride, NMM, RT, 3 h; b)–d) 6%.



Scheme 5. a) THF, *i*BuOCOCl, NMM, 0 °C , 2 h; DMF, 2-aminocyclopentane-1,3-dione hydrochloride, NMM, 0 °C, 3 h, 49%; b) CH_2Cl_2, TFA, RT, 2 h; c) THF, PivOCl, NMM, 0 °C , 2 h; d) DMF, NMM, RT, 12 h; b)–d) 8%.

The mixed anhydride from phenylalanine monoamide of the polyenedioic acid **16**, and *i*BuOCOCl were converted by the inverse method with aminocyclopentanedione to **20** in 49% yield (Scheme 5). After cleavage of the *tert*-butyl ester to form **21**, the mixed anhydride **22** was prepared and coupled with peptolide **8** to form **2** in 8% yield.

The final products of the two syntheses were isolated and purified (preparative thin layer chromatography)[20] only with difficulty. The R_f value and high-resolution mass spectra were identical to that of the natural product. Due to unexplained solvent effects, the signals of the amide protons in the ^1H NMR spectrum (500 MHz, $CDCl_3$) deviate from those reported by Isono et al.[1] In [D_6]DMSO the chemical shifts were almost identical to those obtained for **1** in [D_6]DMSO[20] (Table 1).

Table 1. Characteristic ^1H NMR signals (300 and 500 MHz, [D_6]DMSO) of enopeptin A (**1**) and synthesized enopeptin B (**2**).

	δ(**1**)	δ(**2**)
Ala-NH	8.39 (d, J = 9.3 Hz)	8.39 (d, J = 9.8 Hz)
Ser-NH	8.94 (d, J = 9.6 Hz)	8.95 (d, J = 9.8 Hz)
Phe-NH	7.51 (d, J = 6.6 Hz)	7.46 (br.)
Reductone-NH	10.05 (br. s)	9.95 (br.)
MePro-, Pro-αH	4.39 (d, J = 8.4 Hz)	4.36 (m)
Ala-αH	4.86 (m)	4.85 (m)
MeAla-αH	4.72 (q, J = 6.6 Hz)	4.70 (q, J = 6.6 Hz)
Pro-αH	5.11 (d, J = 6.9 Hz)	5.09 (d, J = 9.9 Hz)
Ser-αH	4.46 (t, J = 9.6 Hz)	4.43 (t, J = 9.5 Hz)
Phe-αH	4.59 (dd, J = 6.3, 6.6 Hz)	4.56 (m)
MeAla-NCH_3	2.70 (s)	2.68 (s)

Received: November 28, 1996 [Z 9831 IE]
German Version: *Angew. Chem.* **1997**, *109*, 1152–1154

Keywords: amides · antibiotics · macrocycles · peptides · polyenes

[1] Isolation: H. Osada, T. Yano, H. Koshino, K. Isono, *J. Antibiotics* **1991**, *44*, 1463; structure: H. Koshino, H. Osada, T. Yano, J. Uzawa. K. Isono, *Tetrahedron Lett.* **1991**, *32*, 7707.

[2] The linear pentapeptolide was prepared conventionally: K. Neumann, Ph.D. dissertation, Universität Stuttgart, **1995**.

[3] a) U. Schmidt, A. Lieberknecht, H. Griesser, J. Talbiersky, *J. Org. Chem.* **1982**, *47*, 3261; review: b) U. Schmidt, J. Langner, *J. Peptide Res.* **1997**, *49*, 67.

[4] Preparation of monoesters by partial saponification of diesters: S. Masamune, Y. Nishitani, T. Takemasa, D. Boschelli, *Tetrahedron Lett.* **1985**, *26*, 5239. However, this route is not suitable here.

[5] Synthesis of dodecapentaenedioic acid derivatives by the Wittig reaction: B. G. Kovalev, A. A. Shamshurin, *J. Org. Chem. (USSR)* **1966**, *2*, 1584.

[6] AM-6201: M. Onda, Y. Konda, K. Hinotozowa, S. Omura, *Chem. Pharm. Bull.* **1982**, *30*, 1210.

[7] Asukamycin: S. Omura, C. Kitao, R. Oiwa, Y. Takashashi, A. Nakagawa, M. Shimada, Y. Iwai, *J. Antibiotics* **1991**, *44*, 1463; K. Kakinuma, N. Ikekawa, A. Nakagawa, S. Omura, *J. Am. Chem. Soc.* **1979**, *101*, 3402; A. Nakagawa, T.-S. Wu, P. J. Keller, J. P. Lee, S. Omura, H. G. Floss, *J. Chem. Soc. Chem. Comm.* **1985**, 519.

[8] Bafilomycin B_1: G. Werner, H. Hagenmaier, H. Drautz, A. Baumgartner, H. Zähner, *J. Antibiotics* **1984**, *37*, 110.

[9] Colambomycin A: R. Grote, A. Zeeck, H. Drautz, H. Zähner, *J. Antibiotics* **1988**, *41*, 1274; R. Grote, A. Zeeck, J. M. Beale, Jr., *ibid.* **1988**, *41*, 1186.

[10] L-155,175: M. A. Goetz, P. A. McCormick, R. L. Monaghan, D. A. Ostlind, O. D. Hensens, J. M. Liesch, G. Albers-Schönberg, *J. Antibiotics* **1985**, *38*, 161.

[11] Limocrocin: H. Brockmann, H.-U. May, W. Lenk, H. Brockmann, Jr., *Chem. Ber.* **1969**, *102*, 3217.

[12] Manumycin A–D: K. Schröder, A. Zeeck, *Tetrahedron Lett.* **1973**, *50*, 4995; I. Sattler, C. Gröne, A. Zeeck, *J. Org. Chem.* **1993**, *58*, 6583.

[13] Moenomycin A: R. Tschesche, D. Lenoir, H. L. Weidenmüller, *Tetrahedron Lett.* **1969**, *3*, 141; P. Welzel, F.-J. Witteler, D. Müller, W. Riemer, *Angew. Chem.* **1981**, *93*, 130; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 121.

[14] Senacarcin: H. Nakano, M. Yoshia, K. Shirahata, S. Ishii, Y. Arai, M. Morimota, F. Tomita, *J. Antibiotics* **1982**, *35*, 760.

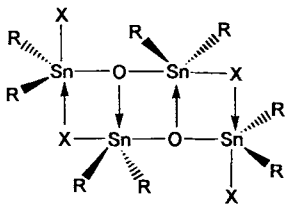
[15] U-56,407: T. F. Brodasky, D. W. Stroman, A. Dietz, S. Miszak, *J. Antibiotics* **1983**, *36*, 950.
[16] Virustomycin A: S. Omura, N. Imamura, K. Hinotozawa, K. Otoguro, G. Lukacs, R. Faghih, R. Tolmann, R. H. Arison, J. L. Smith, *J. Antibiotics* **1983**, *36*, 1783.
[17] W. J. Ebenezer, *Synth. Commun.* **1991**, *21*, 351.
[18] Structure: Y. Konda, M. Onda, K. Hinotozawa, S. Omura, *J. Antibiotics* **1981**, *34*, 1222; Y. Shizuri, M. Ojika, K. Yamada, *Tetrahedron Lett.* **1981**, *22*, 4291; synthesis: M. Ojika, H. Niwa, Y. Shizuri, K. Yamada, S. Iwadare, *J. Chem. Soc. Chem. Comm.* **1982**, 628.
[19] Structure and synthesis: M. Ojika, Y. Shizuri, H. Niwa, K. Yamada, S. Iwadare, *Tetrahedron Lett.* **1982**, *23*, 4977.
[20] J.-J. Young, L.-J. Jung, W.-T. Liu, S.-N. Ho, L.-R. Chang, Y.-C. Tsai, R. Bhaskaran, C. Yu, *J. Antibiotics* **1994**, *47*, 922.

Trimethylene-Bridged Tri- and Tetratin Compounds as Building Blocks for Unusual Double and Triple Ladders

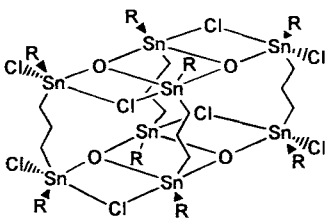
Michael Mehring, Markus Schürmann, Hans Reuter, Dainis Dakternieks, and Klaus Jurkschat*

Dedicated to Professor Adolf Zschunke on the occasion of his 60th birthday

Controlled hydrolysis of diorganotin dichlorides usually affords dimeric tetraorganodistannoxanes $[R_2XSnOSnXR_2]_2$ (X = Cl, OH) of type **A**. These compounds attract attention



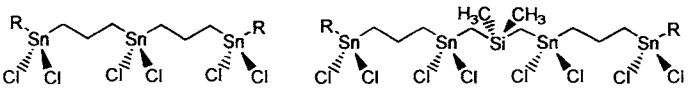
A



B

because of their interesting structural features[1-5a] and their applications as catalysts in organic chemistry.[6-11] The characteristic structural feature of this class of compounds is a planar $Sn_4Cl_4O_2$ layer with a centrosymmetric Sn_2O_2 ring, known as a ladder-type structure.[5]

We have been working for some time on the linkage of dimeric ladder units of type **A**. We have shown that the trimethylene-bridged double ladder of type **B** is formed on reaction of 1,3-bis[(trimethylsilylmethyl)dichlorostannyl]propane $[Me_3SiCH_2(Cl_2)SnCH_2]_2CH_2$ with di-*tert*-butyltin oxide $(tBu_2SnO)_3$. This result led to the question whether pillar-shaped triple and quadruple ladders can be constructed from the tri- and tetratin compounds **1** and **2**.



1 R = CH_2SiMe_3 **2**

The reaction of **1** with $(tBu_2SnO)_3$ leads in quantitative yield to **3** as colorless crystals [Eq. (a)]. The X-ray structure analysis

$$\mathbf{1} + 3/2\ (tBu_2SnO)_3 \xrightarrow[-2\ tBu_2SnCl_2]{CH_2Cl_2} 1/4\ \{[R(Cl)Sn(CH_2)_3Sn(Cl)(CH_2)_3Sn(Cl)R]O_{3/2}\}_4 \quad \text{(a)}$$

3 R = CH_2SiMe_3

[13] of **3** shows a triple ladder structure (Figure 1) in which three almost planar $Sn_4Cl_4O_2$ layers are linked by four trimethylene chains. The average deviation of the atoms from the central plane (0.024 Å) is smaller than that of the outer layers (0.182 Å). In analogy to **B**[12] all tin atoms are pentacoordinate and have a distorted trigonal-bypyramidal coordination environment. The solid-state structure is retained in solution. The $^{119}Sn\{^1H\}$ NMR spectrum in $CH_2Cl_2/D_2O_{cap.}$ shows four signals at $\delta = -94.0, -114.4, -134.0$, and -142.8 with an integral ratio of 2:1:2:1. The $^2J(^{119}Sn,^{117}Sn)$ coupling constants (61-65 Hz) are of the same order of magnitude as those of the dimeric

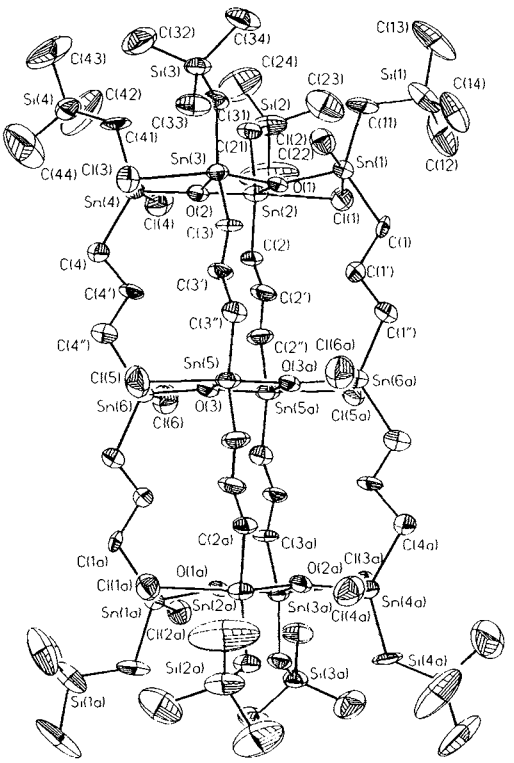


Figure 1. Molecular structure of **3** (SHELXTL-Plus, thermal ellipsoids for 50% probability). Selected bond lengths [Å] and angles [°]: Sn-$Cl_{terminal}$ 2.428(5)-2.434(6), Sn-$Cl_{bridging}$ 2.616(5)-2.783(6), Sn-O_{eq} 2.003(11)-2.032(11), Sn-O_{ax} 2.127(11)-2.155(11); O_{ax}-Sn-Cl_{ax} 150.2(3)-151.8(3), Cl_{ax}-Sn-Cl_{ax} 164.9(2)-166.1(2), Sn_2O_2 rings: O-Sn-O 73.2(4)-73.8(4), Sn-O-Sn 105.6(5)-106.3(5), Sn_2ClO rings: Sn-O-Sn 122.6(5)-130.6(6), Sn-Cl-Sn 81.53(14)-83.7(2), O-Sn-Cl 74.8(3)-78.1(3), C-Sn(1,2,3,4)-C 130.8(7)-136.4(6), C-Sn(5,6)-C 122.3(7)-123.7(7).

[*] Prof. Dr. K. Jurkschat, Dipl.-Chem. M. Mehring, Dr. M. Schürmann
Lehrstuhl für Anorganische Chemie II der Universität
Otto-Hahn-Strasse 6, D-44227 Dortmund (Germany)
Fax: Int. code +(231)755-3797
e-mail: kjur@platon.chemie.uni-dortmund.de
Prof. Dr. H. Reuter
Institut für Anorganische Chemie, Universität Osnabrück (Germany)
Prof. Dr. D. Dakternieks
Department of Chemistry, Deakin University, Geelong (Australia)

[**] We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.