Keywords: clusters · iron · N ligands · O ligands · surface chemistry

[1] N. Guerot, GB 2009626, **1979**.
[2] B. J. McCudden, P. O'Brien, J. R. Thornback, *J. Chem. Soc. Dalton Trans.* **1983**, 2043 – 2046; A. W. Ashbrook, *Coord. Chem. Rev.* **1975**, *16*, 285 – 307.
[3] M. E. Keeney, K. Osseo-Asare, K. A. Woode, *Coord. Chem. Rev.* **1984**, *59*, 141 – 201.
[4] K. R. Manolov, *J. Russ. Inorg. Chem. (Engl. Transl.)* **1967**, *12*, 1431 – 1434.
[5] P. Lumme, *Suomen. Kem.* **1957**, *B30*, 194 – 200.
[6] a) K. Burger, K. Korecz, I. B. A. Manuala, P. Mag, *J. Inorg. Nucl. Chem.* **1966**, *28*, 1673—1678; b) K. Korecz, K. Burger, *J. Inorg. Nucl. Chem.* **1968**, *30*, 781 – 786.
[7] J. L. K. F. DeVries, J. M. Trooster, E. DeBoer, *Chem. Eng. Commun.* **1970**, 604.
[8] For salicylaldoximates(1 –) (=HSalR) and for salicylaldoximates-(2 –) (= SalR) we have crystallographically characterized several compounds, including [{VO(SalEt)(HSalEt)}$_2$], in which i) HSalEt acts as a terminal chelator; ii) SalEt forms μ-NO bridges between the two metal atoms and chelates to one of them through the phenolate group; and iii) two hydrogen bonds are formed, each of which involves a protonated oxime O atom of an HSalEt ligand and the phenolate O atom of the adjacent SalEt group; R. L. Beddoes, D. Collison, C. D. Garner, J. Grigg, M. Helliwell, P. A. Tasker, D. Thorp, J. M. Thorpe, unpublished results.
[9] An aqueous solution of iron(III) chloride was treated with salicylaldoxime in EtOH and neutralized with one equivalent of base to give a red-brown precipitate. Washing this product with hexane removed excess ligand, and subsequent extraction with CH_2Cl_2 followed by solvent evaporation in vacuo yielded a dark brown solid. Slow evaporation at room temperature of a solution of this solid in xylene gave black platelike crystals suitable for X-ray diffraction.[10]
[10] The crystal and molecular structure of a crystal of dimensions $0.03 \times 0.2 \times 0.45$ mm was determined on a Rigaku AFC5R diffractometer with graphite-monochromated $Cu_{K\alpha}$ radiation ($\lambda = 1.54178$ Å, $\mu = 67.04\ cm^{-1}$) and a 12-kW rotating anode generator at room temperature. $C_{79}H_{71}N_9O_{18}Fe_4$, triclinic, space group $P\bar{1}$ (no. 2), $a = 14.136(2)$, $b = 21.815(6)$, $c = 12.828(2)$ Å, $\alpha = 97.64(2)$, $\beta = 105.65(1)$, $\gamma = 84.95(2)^\circ$, $V = 3770(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.460\ g\,cm^{-3}$, $F(000) = 1712$. The scan was of the $\omega/2\theta$ type with a scan rate of $8.0^\circ\,min^{-1}$. Of the total of 11210 unique reflections collected with $2\theta_{max} = 120.3^\circ$, 4851 with $I > 3\sigma(I)$ were used for structure determination by direct methods.[11] An absorption correction using the program DIFABs was applied to the data (N. P. C. Walker, D. I. Stuart, *Acta Crystallogr. Sect. A* **1983**, *39*, 158 – 166). Full-matrix least-squares refinement with anomalous dispersion for all non-hydrogen atoms gave residuals of $R = 0.068$ and $R_w = 0.069$, where $R = \Sigma\,|\,\Delta\,|\,/\Sigma\,|\,F_o\,|$ and $R_w = (\Sigma\Delta^2/\Sigma wF_o^2)^{1/2}$, $\omega = 1/[\sigma^2(F_o) + 0.00022\,|\,F_o\,|^2]$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-103013. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[11] C. J. Gilmore, MITHRIL, Program for Crystal Structure Determinations, University of Glasgow, **1984**; P. T. Beurskens, DIRDIF, Program for Crystal Structure Determinations, Toernooiveld, The Netherlands, **1984**.
[12] a) M. S. Lah, M. L. Kirk, W. Hatfield, V. L. Pecoraro, *J. Chem. Soc. Chem. Commun.* **1989**, 1606 – 1608; b) P. Chaudhuri, M. Winter, P. Fleischhauer, W. Haase, U. Flörke, H.-J. Haupt, *Inorg. Chim. Acta* **1993**, *212*, 241 – 249.
[13] The IR spectrum of **1**, as an evaporated thin film or KBr disk, shows a rich, well-resolved fingerprint between 2000 and 250 cm^{-1}, typical of a salicylaldoxime complex. The UV/Vis absorption spectrum ($\lambda_{max}(\varepsilon) =$ 310 (34000), 514 nm (8000 $M^{-1}\,cm^{-1}$), EPR powder spectrum ($g \approx 2$, $\Delta B_{p-p} = 1500$ G for Q band), magnetic susceptibility in $CHCl_3$ by the Evans NMR method (5.2 μ_B per iron atom at 235 K) and mass spectrum (positive-ion FAB, *m/z*: 1308.5, 1172, 1035, 900 for $[Fe_4(C_7H_6O_2N)_n(C_7H_5O_2N)_4]^+$ with $n = 4$, 3, 2, and 1, respectively) are consistent with and diagnostic of the structure of the tetranuclear cluster.
[14] D. M. Kurtz, *Chem. Rev.* **1990**, *90*, 585 – 606.
[15] G. J. Long, W. T. Robinson, W. P. Tappmeyer, D. L. Bridges, *J. Chem. Soc. Dalton Trans.* **1973**, 573 – 579.
[16] C. T. Dziobkowski, J. T. Wrobleski, D. B. Brown, *Inorg. Chem.* **1981**, *20*, 671 – 678.
[17] R. Harrison, *Bull. Geol. Surv. G.B.* **1975**, *52*, 51 – 54.
[18] O. Baudisch, W. H. Harting, *Inorg. Synth.* **1939**, *I*, 185 – 186.
[19] H. B. Weiser, W. O. Milligan, E. L. Cook, *Inorg. Synth.* **1939**, *II*, 215 – 216.
[20] A Q panel is a small, rectangular piece of mild steel of reproducible composition and surface texture used to test the corrosion inhibition properties of organic molecules.
[21] The Fe K-edge position of the surface product and the isolated tetranuclear cluster were measured as 7127 eV with a pre-edge feature at 7113 eV, and essentially identical values were obtained for hematite (α-Fe_2O_3). These values were referenced to the Fe K-edge energy of an iron foil at 7112 eV.
[22] Although all of our experimental evidence points to the formation of a tetranuclear iron cluster, we note that other nuclearities are possible, for example, a trinuclear assembly formed with a functionalized derivative of salicylaldoxime, as described by E. Bill, C. Krebs, M. Winter, M. Gerdan, A. X. Trautwein, U. Flörke, H.-J. Haupt, and P. Chaudhuri, *Chem. Eur. J.* **1997**, *3*, 193 – 201.
[23] J. Handley, D. Collison, C. D. Garner, M. Helliwell, R. Docherty, J. R. Lawson, P. A. Tasker, *Angew. Chem.* **1993**, *105*, 1085 – 1087, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1036 – 1038.

Stereoselective Solid-Phase Synthesis of β-Lactams—A Novel Cyclization/Cleavage Step towards 1-Oxacephams**

Bartłomiej Furman, René Thürmer, Zbigniew Kałuża, Robert Łysek, Wolfgang Voelter, and Marek Chmielewski*

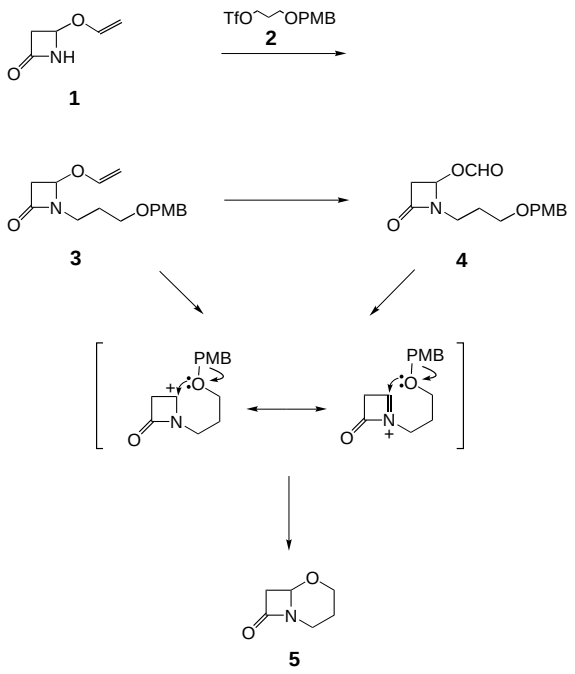
The solid-phase method is an extremely efficient approach for the synthesis of small molecules.[1] A current trend is to extend the principles of organic reactions that take place in homogenous phase to analogous reactions that take place on solid supports. To date, the syntheses of a variety of classes of heterocycles by solid-phase synthesis methodology have been reported.[1] However the solid-phase synthesis of β-lactams, though attractive structures because of their antibiotic activity, have been barely reported.[2] Herein we describe new resin-based chemistry for the straightforward construction of 1-oxacephams, which represent a class of compounds with potential biological activity.[3] The development of new

[*] Prof. Dr. M. Chmielewski, Dr. B. Furman, Dr. Z. Kałuża, R. Łysek
Institute of Organic Chemistry of the Polish Academy of Sciences
Kasprzaka 44/52, 01-224 Warszawa (Poland)
Fax: (+48) 22-632-6681
E-mail: chmiel@ichf.edu.pl
R. Thürmer, Prof. Dr. W. Voelter
Abteilung für Physikalische Biochemie des Physiologisch-chemischen Instituts der Universität
Hoppe-Seyler-Strasse 4, D-72076 Tübingen (Germany)

[**] This work was partially supported by the Deutsche Forschungsgemeinschaft and the Polish Academy of Sciences exchange program (DFG 436POL113/88). B. F. thanks the Foundation for Polish Science for the FNP98 stipend.

antibiotics is of the highest interest because of the increasing bacterial resistance against commonly used drugs.

Recently Kałuża et al.[4] reported a new approach to 1-oxacephams from 4-vinyloxyazetidin-2-one **1**. The strategy consists of N-alkylation of **1** by the 1,3-propanediol derivative **2** that bears sulfonyl and 4-methoxybenzyl substituents, oxidation of the vinyloxy group in **3** to the formyloxy (or acetoxy group), and finally cyclization of compound **4** by the nucleophilic displacement at C-4 of the azetidin-2-one ring (Scheme 1). The 4-methoxybenzyl protection of the hydroxyl

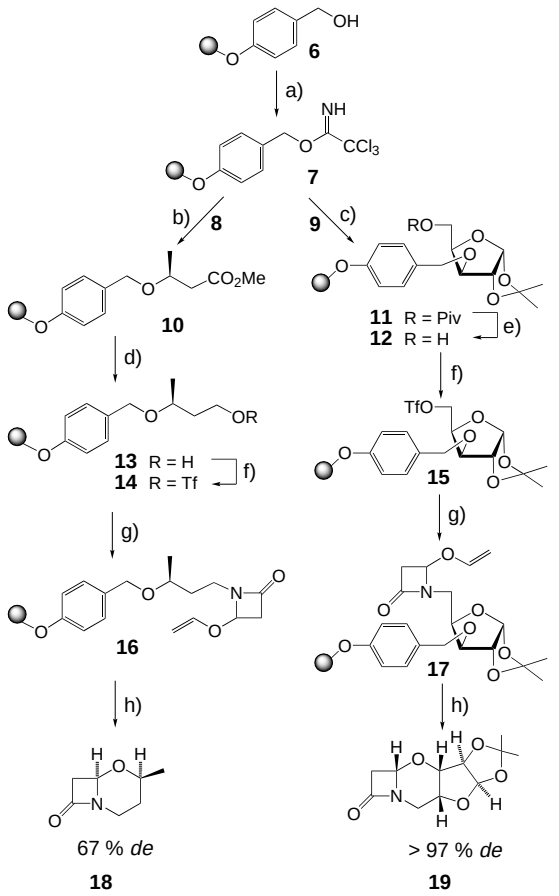


Scheme 1. Synthesis of 1-oxacepham **5**.[4, 5] TfO = trifluoromethylsulfonyl, PMB = 4-methoxybenzyl.

group increases the nucleophilicity of the oxygen atom and allows efficient cyclization with the liberation of the 4-methoxybenzyl cation. Further studies on the cyclization step have shown that conversion of the vinyloxy into the acyloxy group is not essential to perform the cyclization.[5] The 4-vinyloxy-*N*-substituted-β-lactam **3** gave the 1-oxacepham **5**, in 51% yield in the presence of Lewis acids. It should be pointed out that the strategy based on N-alkylation prior to the cyclization step when applied to chiral compounds **2** and **1** as a starting material has offered better asymmetric induction at C-4 of the azetidin-2-one ring than that found for the commonly used condensation of 4-acetoxyazetidin-2-one with chiral alcohols.[6]

A new concept in solid-phase synthesis is the so-called cyclization/cleavage approach.[7–10] The last step of the reaction sequence on the solid support involves formation of the oxazine ring and proceeds with simultaneous cleavage of the molecule from the resin. The first solid-phase synthesis in which cyclization was performed on a solid support was reported by Hobbs DeWitt et al.[7] in the synthesis of hydantoin libraries. Most of the reports that take advantage of cyclization/cleavage strategy result in the formation of an amide function.[8] The metathesis for the synthesis of cycloolefins[9] and formation of macrocyclic lactones by a intramolecular ketophosphonate – aldehyde condensation reaction have been reported recently.[10] The high purity of the detached final products is an important advantage of the well designed cyclization/cleavage strategy because only the required precursor of the target molecule undergoes cyclization.

Our synthetic strategy is outlined in Scheme 2. Commercially available Wang resin **6** (Rapp polymer, 1.13 mmol of OH per gram of resin) was treated with trichloroacetonitrile



Scheme 2. Solid-phase synthesis of 1-oxacephams **18** and **19**. a) CCl_3CN, DBU, CH_2Cl_2, 20 °C, 3 h; b) methyl (*S*)-3-hydroxybutyrate (**8**), $BF_3 \cdot Et_2O$, CH_2Cl_2/cyclohexane 1/1, 20 °C, 5 min; c) 1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-xylofuranose (**9**), $BF_3 \cdot Et_2O$, CH_2Cl_2/cyclohexane 1/1, 20 °C, 5 min; d) DIBAL-H, THF, 20 °C, 4 h; e) MeONa, MeOH, 20 °C, 2 h; f) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 6 h; g) **1**, *n*BuLi, Bu_4NHSO_4, THF, −70 → 20 °C, 12 h; h) $BF_3 \cdot Et_2O$, CH_2Cl_2, 20 °C, 3 h. Piv = pivaloyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride.

and DBU and transformed into the Wang trichloroacetimidate resin **7**, which was recently shown to be a polymer-bound benzylating reagent and capable of immobilizing alcohols under mild conditions.[11] The resin **7** was coupled with the chiral methyl (*S*)-3-hydroxybutyrate (**8**) or with the 1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-xylofuranose (**9**) in the presence of catalytic amounts of $BF_3 \cdot Et_2O$ in CH_2Cl_2/cyclohexane (1/1) for 5 min at room temperature according to the procedure of Hanessian and Xie[11] to afford **10** and **11**, respectively. The IR spectra of **10** and **11** showed the absence of the strong C=N stretching band at 1664 cm^{-1}, present in the

  1433-7851/99/3808-1122 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 8

starting polymer **7**, whereas the carbonyl stretching band at 1740 cm^{-1} and 1734 cm^{-1}, respectively, appeared. Reduction of the ester group in the resin-bound methyl (*S*)-3-hydroxybutyrate (**10**) with DIBAL-H (3 equiv) at 20 °C in THF yielded the expected alcohol **13**. On the other hand the pivaloyl group of the resin-bound sugar derivative **11** was removed with sodium methoxide (10 equiv) in methanol to afford the alcohol **12**, after 2 h the infrared spectrum showed no carbonyl stretching band of the pivaloyl group.

Treatment of the resin-bound alcohols **12** and **13** with Tf_2O (5 equiv) and 2,6-lutidine (7 equiv) in CH_2Cl_2 at 0 °C for 6 h, yielded the corresponding triflates **14** and **15**. The N-alkylation of 4-vinyloxyazetidin-2-one (**1**) with triflates **14** and **15** was achieved with a mixture of tetrabutylammonium hydrogen sulphate (5.25 mmol), *n*BuLi (10.5 mmol) and **1** (5 mmol) in dry THF.[4b] The mixture was stirred at − 70 °C for 20 min to generate the deprotonated azetidin-2-one. Subsequently, the resin-bound triflates **14** or **15** (2 mmol) were added and the respective solutions were allowed to warm up to room temperature and stirred overnight. The characteristic absorption bands of the carbonyl functions in the β-lactam rings at 1765 cm^{-1} and 1774 cm^{-1} of the resins **16** and **17**, respectively, proved the successful N-alkylation reaction had occurred in both cases. This N-alkylation method when applied in solution to compounds related to **14** and **15** with the 4-methoxybenzyl protection in place of the resin afforded respective *N*-substituted azetidinones in 55 % and 65 %, respectively.[4b, 5] It should be stressed that cleavage of intermediates **16** and **17** from the resin to analyze any resin-bound by-products can not be performed because of the sensitivity of both intermediates to acid conditions.

The 1-oxacephams **18** and **19** were obtained in good overall yield (26 – 30 %, over six steps) and high diastereomeric purity (67 and 97 % *de*, respectively) by the cyclization/cleavage step from the corresponding resins **16** or **17** with $BF_3 \cdot Et_2O$ (1 equiv) in CH_2Cl_2. The release of the products from the resins was completed after 3 h, and no carbonyl bands in the IR spectra of either remaining resins were observed. Also after additional treatment of the remaining resins with $BF_3 \cdot Et_2O$ no release of the oxacephams was detectable.

In summary we have demonstrated that our synthetic strategy for the formation of 1-oxacephams can be performed on a solid phase with excellent results. The good yield and purity of the products, and simple procedure for both reaction sequences make this a very attractive method for the synthesis of 1-oxacephams.

Experimental Section

Typical procedure for a cyclization/cleavage reaction: The resin **16** or **17** (0.3 mmol) was swelled in CH_2Cl_2 (4 mL), and $BF_3 \cdot Et_2O$ (0.3 mmol) added. The reaction was stirred at room temperature for 3 h, then Et_3N (0.1 mL) added and stirring, continued for 10 min. The resin was separated and the solution collected. The resin was washed with CH_2Cl_2 several times, and all solutions were combined, and evaporated. The oily residue was dried in vacuo and purified by chromatography on silica gel to afford products **18** (67 % *de*) or **19** (> 97 % *de*), respectively. The spectral and analytical data of **18** and **19** were identical to those published earlier.[12]

Received: September 23, 1998 [Z 12448 IE]
German version: *Angew. Chem.* **1999**, *111*, 1193 – 1195

Keywords: antibiotics · cyclizations · lactams · solid-phase synthesis

[1] Reviews: a) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zachel, *Angew. Chem.* **1996**, *108*, 2436 – 2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288 – 2337; b) L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555 – 600; c) R. C. D. Brown, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3293 – 3320.

[2] a) B. Ruhland, A. Bhandari, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1996**, *118*, 253 – 254; b) B. Ruhland, A. Bombrun, M. A. Gallop, *J. Org. Chem.* **1997**, *62*, 7820 – 7826; c) Y. Pei, R. A. Houghten, J. S. Kiely, *Tetrahedron Lett.* **1997**, *38*, 3349 – 3352; d) E. G. Matta, *Tetrahedron Lett.* **1997**, *38*, 6335 – 6338; g) V. Molteni, R. Annunziata, H. Cinquini, F. Cozzi, M. Benaglia, *Tetrahedron Lett.* **1998**, *39*, 1257 – 1260.

[3] a) W. Nagata, *Pure Appl. Chem.* **1989**, *61*, 325 – 336; b) S. Shibahara, T. Okonogi, Y. Murai, T. Kudo, T. Yoshida, S. Kondo, B. G. Christensen, *J. Antibiot.* **1988**, *41*, 1154 – 1157; c) H. C. Neu in *The Chemistry of β-Lactams* (Ed.: M. I. Page), Blackie, Glasgow, **1992**, pp. 101 – 128.

[4] a) Z. Kałuża, S. H. Park, *Synlett* **1996**, 895 – 896; b) Z. Kałuża, R. Łysek, *Tetrahedron: Asymmetry* **1997**, *8*, 2553 – 2560.

[5] Z. Kałuża, *Tetrahedron Lett.* **1999**, *40*, 1025 – 1026

[6] a) D. Hoppe, T. Hilpert, *Tetrahedron* **1987**, *43*, 2467 – 2474; b) S. De Bernardo, J. P. Tengi, G. J. Sasso, M. Weigele, *J. Org. Chem.* **1985**, *50*, 3457 – 3462; c) M. Murakami, M. Matsuura, T. Aoki, W. Nagata, *Synlett* **1990**, 681 – 683; d) M. Murakami, T. Aoki, W. Nagata, *Synlett* **1990**, 684 – 686.

[7] S. Hobbs DeWitt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. Reynolds Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909 – 6913.

[8] a) B. A. Dressman, L. A. Spangle, S. W. Kaldor, *Tetrahedron Lett.* **1996**, *37*, 937 – 940; b) S. A. Kolodziej, B. C. Hamper, *Tetrahedron Lett.* **1996**, *37*, 5277 – 5280; c) L. F. Tietze, A. Steinmetz, *Synlett* **1996**, 667 – 668; d) L. F. Tietze, A. Steinmetz, F. Balkenhohl, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303 – 1306; e) J. Matthews, R. A. Rivero, *J. Org. Chem.* **1997**, *62*, 6090 – 6092; f) S. W. Kim, S. Y. Ahn, J. S. Koh, J. H. Lee, S. Ro, H. Y. Cho, *Tetrahedron Lett.* **1997**, *38*, 4603 – 4606; g) J. Stadlwieser, E. P. Ellmerer-Müller, A. Takó, N. Maslouh, W. Bannwarth, *Angew. Chem.* **1998**, *110*, 1487 – 1489; *Angew. Chem. Int. Ed.* **1998**, *37*, 1402 – 1404; h) P. P. Fantauzzi, K. M. Yager, *Tetrahedron Lett.* **1998**, *39*, 1291 – 1294; i) K. H. Park, E. Abbate, S. Najdi, M. M. Olmstead, M. J. Kurth, *Chem. Commun.* **1998**, 1679 – 1680.

[9] J. H. van Maarseveen, J. A. J. den Hartog, V. Engelen, E. Finner, G. Visser, C. G. Kruse, *Tetrahedron Lett.* **1996**, *37*, 8249 – 8252.

[10] K. C. Nicolaou, J. Pastor, N. Winssinger, F. Murphy, *J. Am. Chem. Soc.* **1998**, *120*, 5132 – 5133.

[11] a) S. Hanessian, F. Xie, *Tetrahedron Lett.* **1998**, *39*, 733 – 736; b) S. Hanessian, F. Xie, *Tetrahedron Lett.* **1998**, *39*, 737 – 740.

[12] a) Z. Kałuża, B. Furman, M. Patel, M. Chmielewski, *Tetrahedron: Asymmetry* **1994**, *5*, 2179 – 2186; b) B. Furman, Z. Kałuża, M. Chmielewski, *J. Org. Chem.* **1997**, *62*, 3135 – 3139.

  1433-7851/99/3808-1123 $ 17.50+.50/0