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Noniterative approach to the total asymmetric synthesis of 15-carbon polyketides and analogs with high stereodiversity*

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Abstract: Starting from inexpensive furan and furfuryl alcohol, a noniterative approach to the synthesis of pentadeca-1,3,5,7,9,11,13,15-octols and their derivatives has been developed. The method relies upon the double [4+3]-cycloaddition of 1,1,3-trichloro-2-oxylallyl cation with 2,2'-methylenedifuran and conversion of the adducts into *meso* and (±)-*threo*-1,1'-methylenebis (*cis*- and *trans*-4,6-dihydroxycyclohept-1-ene) derivatives. The latter undergo oxidative cleavage of their alkene moieties, generating 5-hydroxy-7-oxoaldehydes that are reduced diastereoselectively into either *syn* or *anti*-5,7-diols. Asymmetry is realized using either chiral desymmetrization with Sharpless asymmetric dihydroxylation or by kinetic resolution of polyols using lipase-catalyzed acetylations. All of the possible stereomeric pentadeca-1,3,5,7,9,11,13,15-octols and derivatives can be obtained with high stereoselectivity applying simple operations, thus demonstrating the high stereodiversity of this new, noniterative approach to the asymmetric synthesis of long-chain polyketides.

INTRODUCTION

A great variety of natural products of biological interest includes polyketide (1,3-polyoxo, 1,3-polyols, aldols) components [1], and several approaches to their synthesis have been proposed [2]. Inspired by the work of Lautens [3] and Hoffmann and coworkers [4], who have converted 8-oxabicyclo[3.2.1]oct-6-en-3-one into seven-carbon chain 1,3-polyols and analogs [5], and by that of Kaku et al. [6], who have transformed cyclohept-3-ene-1,6-diol into 1,3-polyols, we have proposed a new, noniterative asymmetric synthesis of long-chain 1,3-polyols starting from the now readily available 2,2'-methylenebis(furan) (**1**) [7]. This method involved a double [3+4]-cycloaddition between the 1,1,3-trichloro-2-oxyallyl cation and **1** (Scheme 1). After reductive work-up, a 45:55 mixture of *meso*-**2** and (±)-*threo*-**2** was obtained in 55 % yield and separated by fractional crystallization. The *meso* compound was converted into *meso*-**3**, which was desymmetrized into diol (–)-**4** by Sharpless asymmetric dihydroxylation [8]. Further transformations allow one to prepare, in principle, all possible stereoisomers of pentadeca-1,3,5,7,9,11,13,15-octols [9].

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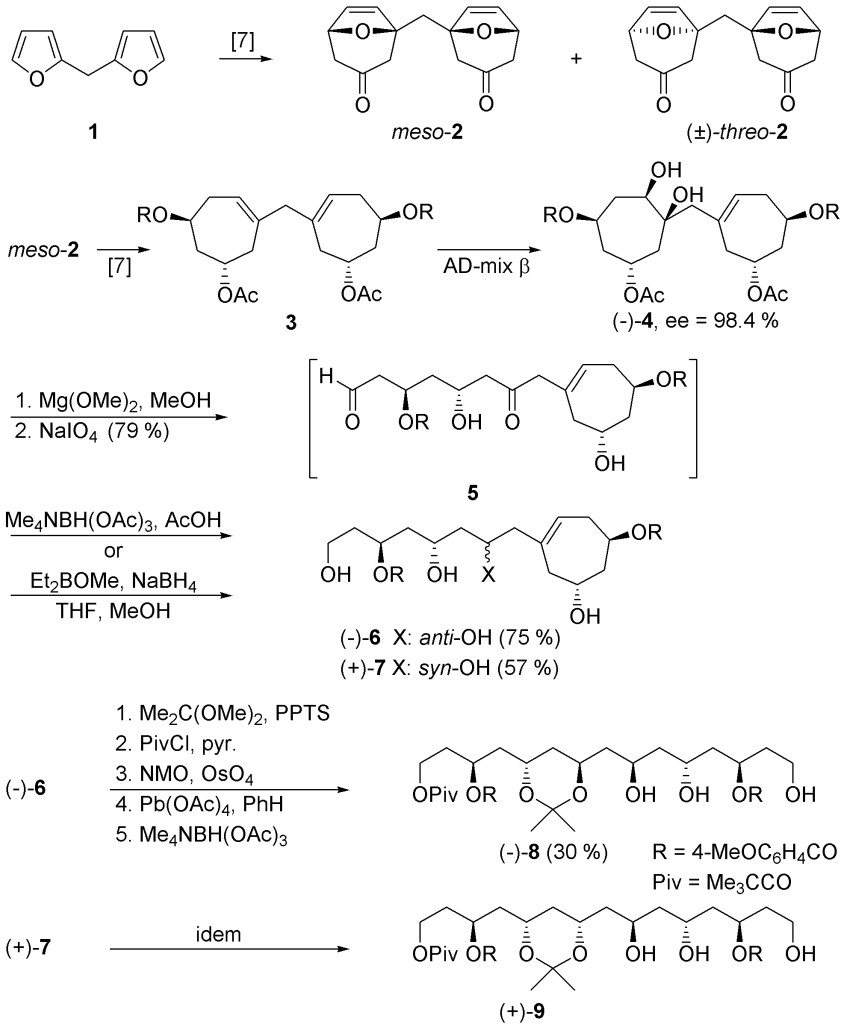
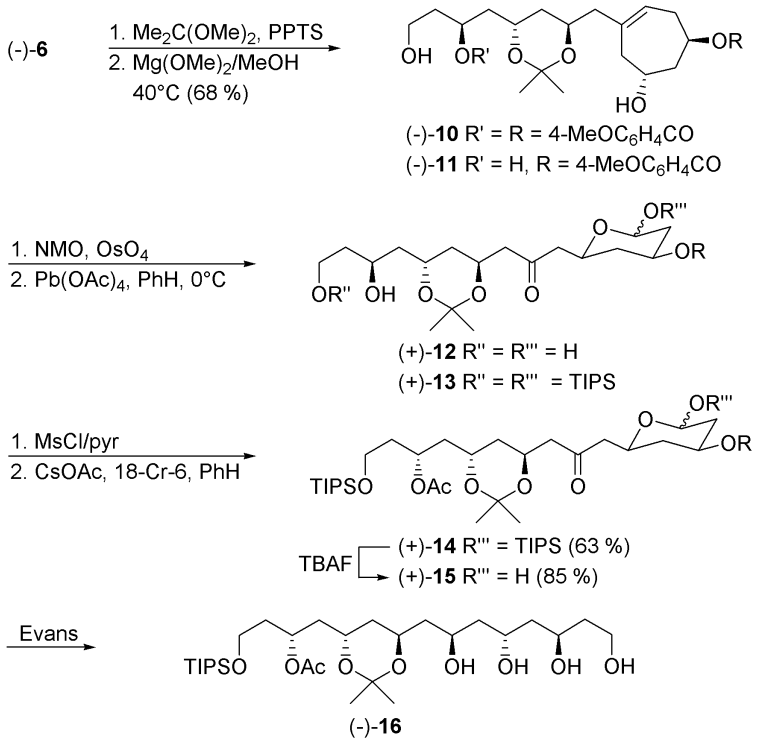


Scheme 1 Examples of long-chain polyketide synthesis by Sharpless desymmetrization.

DESYMMETRIZATION BY SHARPLESS ASYMMETRIC DIHYDROXYLATION

The oxoaldehyde intermediate **5** resulting from the oxidative cleavage of diol (–)-**4** was reduced stereoselectively into triol (–)-**6** and (+)-**7**, applying the conditions of Evans [10] and Narasaka [11], respectively. These compounds have been then converted into semi-protected pentadeca-1,3,5,7,9,11,13,15-octols (–)-**8** and (+)-**9** [7]. These procedures combined with the fact that AD-mix α can be used instead of AD-mix β for the desymmetrization of **3** allows the preparation of 8 possible stereomeric polyols. Further stereodivergence has been realized in the following way. In the presence of $Mg(OMe)_2$ in MeOH, the bis(4-methoxybenzoate) (–)-**10** derived from triol (–)-**6** was converted selectively into the monoester (–)-**11** in 68 % yield. The acyclic ester is methanolyzed more rapidly than the cyclic ester. After oxidative cleavage of the cycloheptene moiety (*N*-morpholine oxide and a catalytical amount of OsO_4, then $Pb(OAc)_4$) pyranose (+)-**12** was obtained in 92 % yield. Silylation of (+)-**12** with $(i\text{-Pr})_3SiCl$/imidazole in DMF provided (+)-**13** selectively in 73 % yield leaving the secondary alcohol free for an esterification with methanesulfonyl chloride and pyridine. This produced a mesylate that underwent smooth S_N2 displacement by cesium acetate to give acetate (+)-**14**. Selective desilylation by

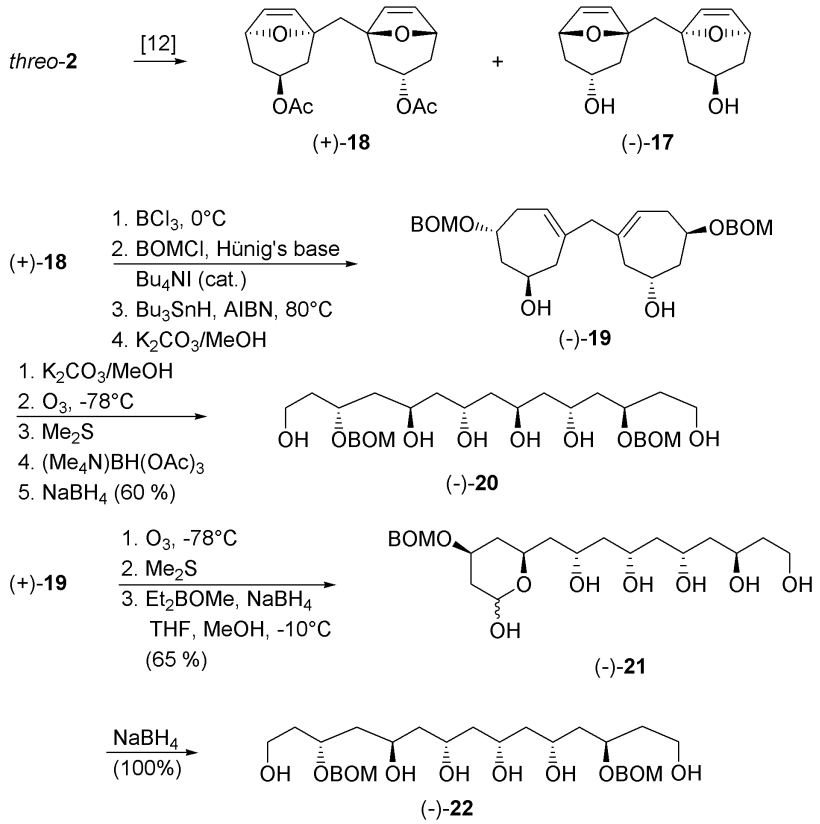
Bu_4NF liberated the pyranose (+)-**15** which could be reduced under Evans' conditions [10] into the semi-protected long-chain polyol (–)-**16** (Scheme 2) [9].



Scheme 2 Selective inversion of acyclic secondary alcohol and polyketide synthesis.

DOUBLE OXIDATIVE CLEAVAGE

The racemic diketone (±)-*threo*-**2**, which can be separated readily from *meso*-**2**, has been reduced into diol (±)-**17** with K-Selectride in THF. Kinetic resolution with *Candida cylindracea* lipase-catalyzed transesterification with vinyl acetate allows one to obtain enantiomerically enriched diacetate (+)-**18** (98 % ee) and diol (–)-**17** (98 % ee) [12]. Diacetate (+)-**18** has been converted into (–)-**19** (Scheme 3) [13] by the same procedure [9] as that converting *meso*-**2** into **3** (Scheme 1). Double ozonolysis of (–)-**19**, followed by the diastereoselective reduction of the resulting double β-hydroxyketone intermediate applying Evans' [10] and Narasaka's [11] conditions allows the preparation of enantiomerically pure (98 % ee) polyols (–)-**20** (65 %) and (–)-**22** (60 %), respectively. Differentiation of the terminal centers of these 15-carbon polyketides is thus possible by control of temperature and excess of the reducing agent. For instance, pyranose (–)-**21** can be isolated in 65 % yield from (–)-**19** (Scheme 3) [13].

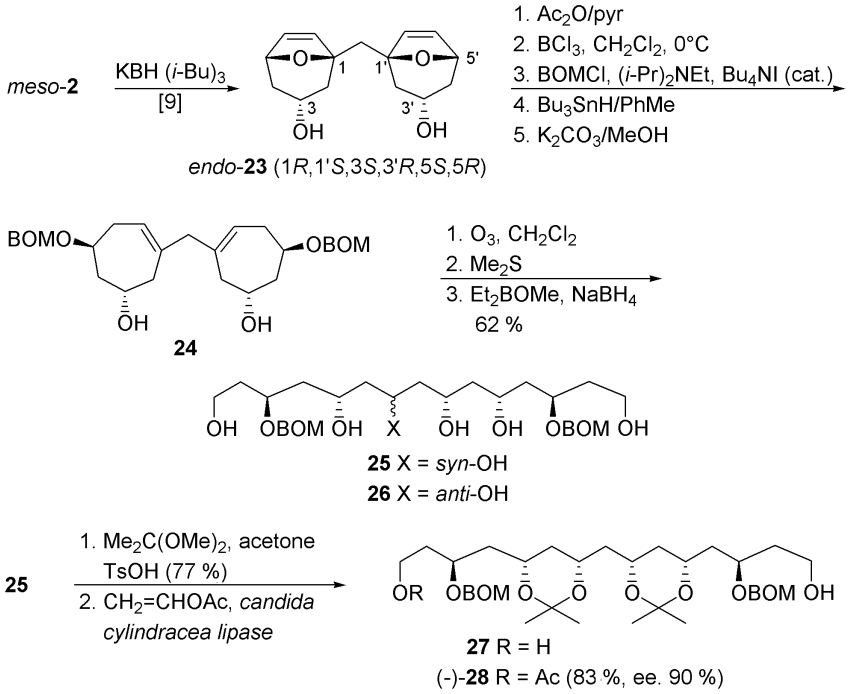


Scheme 3 Long-chain polyols via double oxidative cleavage.

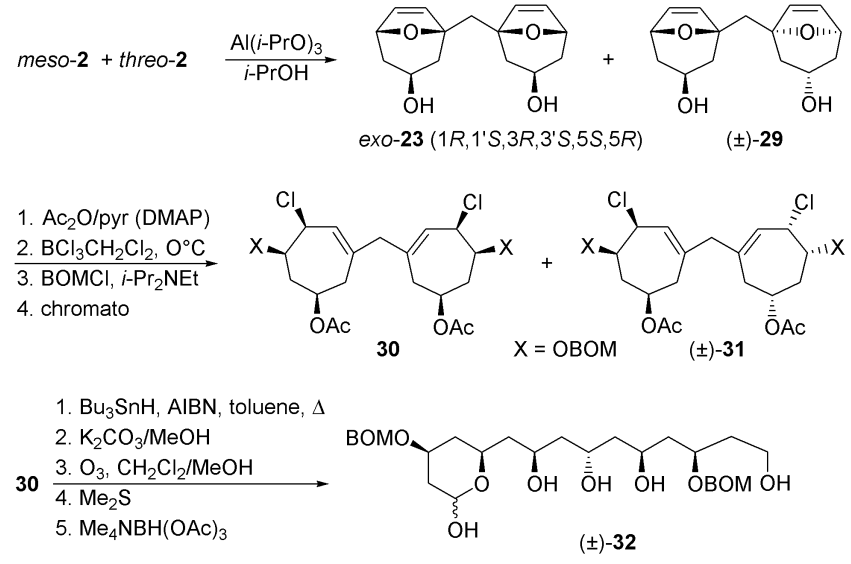
FURTHER STEREODIVERSITY

We disclose here that the double oxidative cleavage of **3** (with R = BOM) leads to *meso* polyol intermediates that can be resolved by lipase-catalyzed acetylation (Scheme 4). Methanolysis of **3** (R = BOM) (derived from *endo*-**23** [9]) gave diol **24** (52 % based on *endo*-**23**) that was submitted to ozonolysis and subsequent Narasaka's reduction furnishing a 6:1 mixture of hexols **25** and **26** in 62 % yield. Pure **25** was obtained by flash chromatography and was converted into the bis-acetonide **27** (77 %). In pure vinyl acetate and in the presence of *C. cyclindracea* lipase, the monoacetate (–)-**28** (90 % ee, Mosher's ester) was obtained in 83 % yield

We disclose also that 1,1'-methylenedi[(1*R*,1'*S*,3*R*,3'*S*,5*S*,5'*R*)-8-oxabicyclo[3.2.1]oct-6-en-3-ol] (*exo*-**23**) can be obtained in 60 % yield, with 99:1 *exo*/*endo* diastereoselectivity, by direct reduction of diketone *meso*-**2** with SmI_2 in THF (–78–20 °C). Similar yield and diastereoselectivity were observed using *i*-PrOH/Ti(-O-*i*-Pr)$_4$ as reducing agent. The latter could be applied to the 45:55 mixture of diketone *meso*-**2** and (±)-*threo*-**2**. After acetylation (Ac_2O, pyr, DMAP) an inseparable mixture of diacetates was obtained. It was submitted to the usual ethereal bridge-opening conditions (BCl_3, CH_2Cl_2, quenching with BOMCl) that gave products **30** and (±)-**31** that were readily separated by flash chromatography (Scheme 5). The *meso* compound **30** was dechlorinated, then methanolyzed and submitted to ozonolysis and reductive work-up under Evans' conditions. This gave a major pyranose (±)-**32**, the optical resolution of which is under study at this moment. One enantiomer of (±)-**32** is a potential precursor for the synthesis of oxo-polyene macrolide RK-397 [14,15].



Scheme 4 Desymmetrization of *meso*-derivatives by lipase-catalyzed acetylation.



Scheme 5 Synthesis of 1,1'-methylenebis(*cis*-4,6-dihydroxycyclohept-1-ene) derivatives and their conversion to long-chain polyketides.

CONCLUSION

Starting with inexpensive furan and furfuryl alcohol, a noniterative approach to the synthesis of long-chain polyketides has been developed. High enantioselectivities and stereodiversity are realized applying simple procedures. They rely upon the Sharpless asymmetric dihydroxylation of 3,5-dihydroxycyclohept-1-ene systems, on diastereoselective reductions of aldols using the Narasaka's or Evans' conditions, and/or on kinetic resolution using lipase-catalyzed acylations.

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REFERENCES

1. (a) S. Omura and H. Tanaka. *Macrolide Antibiotics: Chemistry, Biology and Practice*, Academic Press, New York (1984); (b) S. D. Rychnovsky, G. Griesgraber, R. Schlegel. *J. Am. Chem. Soc*. **117**, 197 (1995); (c) T. I. Richardson and S. D. Rychnovsky. *J. Org. Chem*. **61**, 4219 (1996); (d) B. H. Lipschutz, B. Ullman, C. Lindsley, S. Recchi, D. J. Buzard, D. Dickson. *J. Org. Chem.* **63**, 6092 (1998); (e) J. Pawlak, P. P. Sowinski, E. Borowski, P. Gariboldi. *J. Antibiot*. **48**, 1034 (1995); (f) G. J. McGarvey, J. A. Mathys, K. J. Wilson, K. O. Overly, P. T. Buonova, P. G. Spours. *J. Org. Chem*. **60**, 7778 (1995); (g) T. Mukhopadhyay, E. K. S. Vijayakumar, S. R. Nadkarni, H. W. Fehlhaber, H. Kogler, S. Petry. *J. Antibiot*. **57**, 582 (1998).
2. For recent proposal, see e.g.: (a) S. Allerheiligen and R. Brückner. *Liebigs Ann./Receuil* 1667 (1997); (b) C. Schneider. *Angew. Chem., Int. Ed*. **37**, 1375 (1998); (c) D. Muñoz-Torero and R. Brückner. *Eur. J. Org. Chem*. 1031 (1998); (d) S. D. Rychnovsky, O. Fryzman, U. R. Khine. *Tetrahedron Lett*. **40**, 41 (1999); (e) C. Schneider and M. Rehfeuter. *Chem. Eur. J.* **5**, 2850 (1999); (f) K. B. Jørgensen, T. Suenaga, T. Nakata. *Tetrahedron Lett*. **40**, 8855 (1999); (g) D. Enders and T. Hundertmark. *Tetrahedron Lett*. **40**, 4169 (1999); (h) A. B. Smith III and S. M. Pitram. *Org. Lett*. **1**, 2001 (1999); (i) G. J. McGarvey, J. A. Mathys, K. J. Wilson. *Tetrahedron Lett.* **41**, 6011 (2000); (j) P. B. Greer and W. A. Donaldson. *Tetrahedron Lett*. **41**, 3801 (2000); (k) P. A. Wender and B. Lippa. *Tetrahedron Lett*. **41**, 1007 (2000); (l) J. Kiegiel, J. Józwik, K. Wozniak, J. Jurczak. *Tetrahedron Lett.* **41**, 4959 (2000); (m) A. G. M. Barrett, D. C. Braddock, P. D. de-Koning, A. J. P. White, D. J. Williams. *J. Org. Chem*. **65**, 375 (2000); (n) S. T. Sarraf and J. L. Leighton. *Org. Lett.* **2**, 403 (2000); (o) M. J. Zacuto and J. L. Leighton. *J. Am. Chem. Soc*. **122**, 8587 (2000); (p) S. I. Kiyoota, M. A. Hena, T. Yabukami, K. Murai, F. Goto. *Tetrahedron Lett*. **41**, 7511 (2000); (q) S. Bouzbouz and J. Cossy. *Org. Lett.* **2**, 3975 (2000); *Org. Lett.* **2**, 501 (2000); (r) T. Trieselmann and R. W. Hoffmann. *Org. Lett.* **2**, 1209 (2000); (s) I. Paterson and L. A. Collett. *Tetrahedron Lett*. **42**, 1187 (2001); (t) T. J. Hunter and G. A. O'Doherty. *Org. Lett*. **3**, 1049 (2001); (u) C. J. Sinz and S. D. Rychnovsky. *Angew. Chem., Int. Ed*. **40**, 3224 (2001); (v) D. J. Kopecky and S. D. Rychnovsky. *J. Am. Chem. Soc*. **123**, 8420 (2001); (w) S. A. Burova and F. E. McDonald. *J. Am. Chem. Soc*. **124**, 8188 (2002).
3. M. Lautens, S. Ma, A. Yee. *Tetrahedron Lett*. **36**, 4185 (1995).
4. (a) T. F. J. Lampe and H. M. R. Hoffmann. *Chem. Commun*. 1931 (1996); (b) R. Dunkel and H. M. R. Hoffmann. *Tetrahedron Lett*. **55**, 8385 (1999); (c) R. Dunkel, M. Mentzel, H. M. R. Hoffmann. *Tetrahedron* **53**, 14929 (1997); (d) A. Vakalopoulos and H. M. R. Hoffmann. *Org. Lett*. **3**, 177 (2001); (e) A. Vakalopoulos, T. F. J. Lampe, H. M. R. Hoffmann. *Org. Lett*. **3**, 929 (2001).
5. A. M. Montaña, F. Garcia, P. M. Grima. *Tetrahedron* **55**, 5483 (1999).

6. H. Kaku, M. Tanaka, Y. Norimine, Y. Miyashita, H. Suemune, K. Sakai. *Tetrahedron: Asymmetry* **8**, 195 (1997).
7. (a) M.-E. Schwenter and P. Vogel. *Chem. Eur. J.* **6**, 4019 (2000); (b) K. T. Meilert, M.-E. Schwenter, Y. Schatz, S. R. Dubbaka, P. Vogel. *J. Org. Chem*. **68**, 2964 (2003).
8. K. B. Sharpless, H. C. Kolb, M. S. Van Nieuwenhze. *Chem. Rev*. **94**, 2483 (1994).
9. M.-E. Schwenter and P. Vogel. *J. Org. Chem*. **66**, 7869 (2001).
10. D. A. Evans, K. T. Chapman, E. M. Carreira. *J. Am. Chem. Soc*. **110**, 3560 (1988).
11. (a) K. Narasaka and F. G. Pai. *Tetrahedron* **40**, 2233 (1984); (b) K. N. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro. *Tetrahedron Lett*. **28**, 155 (1987).
12. A. G. Csákÿ and P. Vogel. *Tetrahedron: Asymmetry* **11**, 4935 (2000).
13. S. Gerber-Lemaire and P. Vogel. *Eur. J. Org. Chem*. 2959 (2003).
14. K. Kobinata, H. Koshino, T. Kudo, K. Isono, H. Osada. *J. Antibiot*. **46**, 1616 (1993).
15. C. Schneider, F. Tolksdorf, M. Rehfeuter. *Synlett* 2098 (2002).