

Pure Appl. Chem., Vol. 77, No. 1, pp. 131–137, 2005.

DOI: 10.1351/pac200577010131

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

Pierre Vogel[‡], Sandrine Gerber-Lemaire, Ana T. Carmona, Kai Torsten Meilert, and Marc-Etienne Schwenter

Laboratory of Glycochemistry and Asymmetric Synthesis, Ecole Polytechnique Fédérale de Lausanne (EPFL), BCH, CH-1015 Lausanne-Dorigny, Switzerland

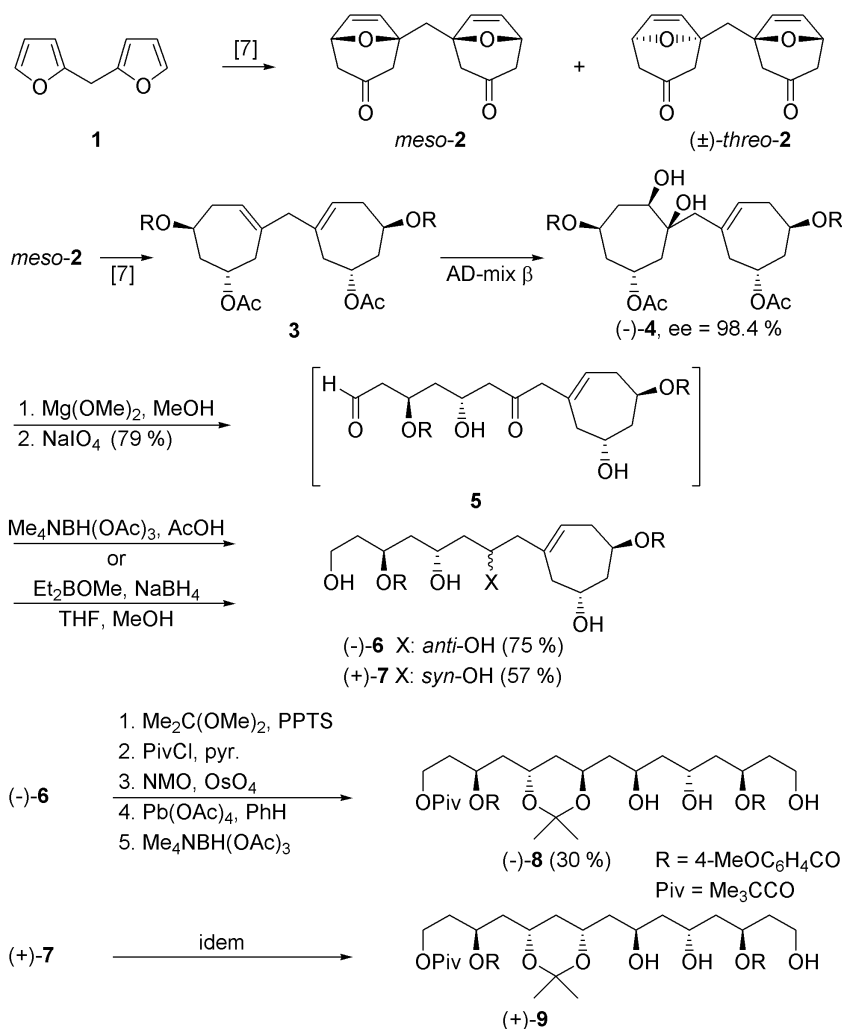
Abstract: Starting from inexpensive furan and furfuryl alcohol, a noniterative approach to the synthesis of pentadeca-1,3,5,7,9,11,13,15-octols and their derivatives has been developed. The method relies upon the double [4+3]-cycloaddition of 1,1,3-trichloro-2-oxylallyl cation with 2,2'-methylene-difuran and conversion of the adducts into *meso* and (\pm)-*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, non-iterative 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-oxylallyl cation and **1** (Scheme 1). After reductive work-up, a 45:55 mixture of *meso*-**2** and (\pm)-*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].

*Paper based on a presentation at the 24th International Symposium on the Chemistry of Natural Products and the 4th International Congress on Biodiversity, held jointly in Delhi, India, 26–31 January 2004. Other presentations are published in this issue, pp. 1–344.

[‡]Corresponding author: Fax: +41 21 693 93 72; E-mail: pierre.vogel@epfl.ch

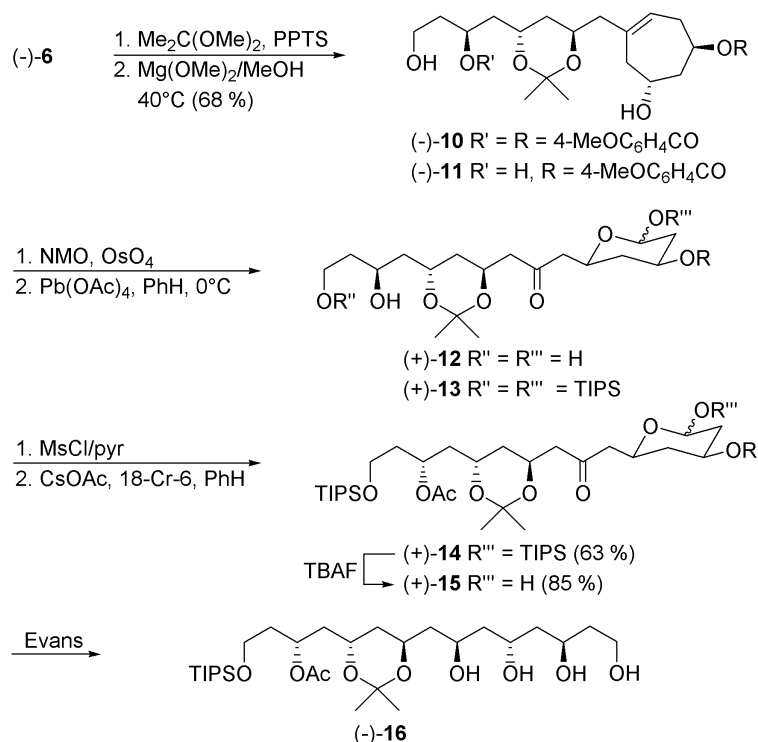


Scheme 1 Examples of long-chain polyketide synthesis by Sharpless desymmetrization.

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-occols (-)-**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 methanolized more rapidly than the cyclic ester. After oxidative cleavage of the cycloheptene moiety (*N*-morpholine oxide and a catalytical amount of OsO₄, then Pb(OAc)₄) pyranose (+)-**12** was obtained in 92 % yield. Silylation of (+)-**12** with (*i*-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

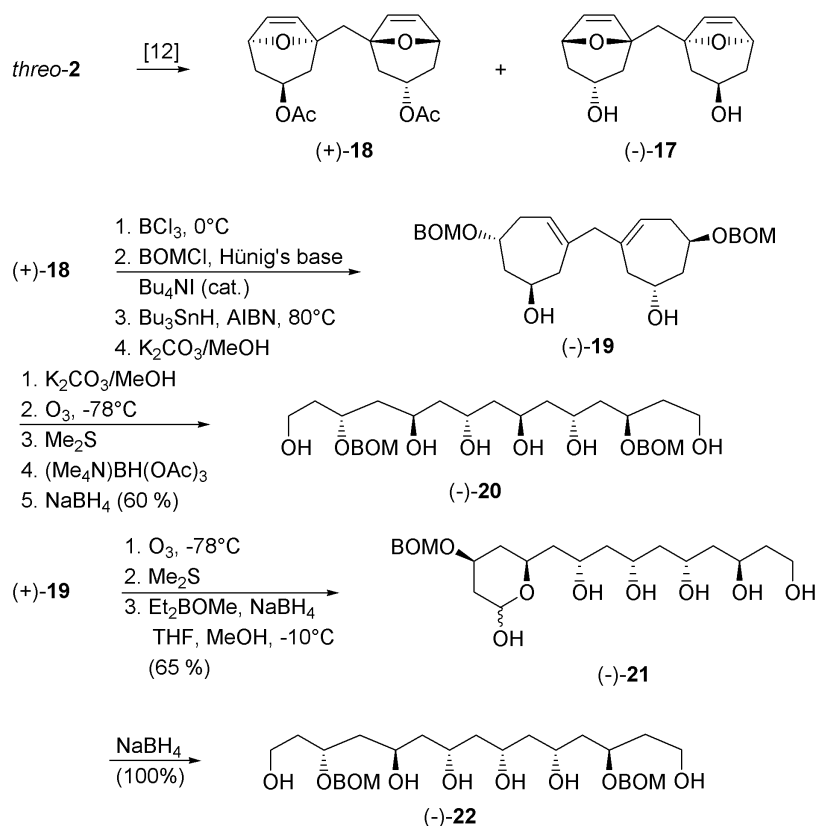
Bu_4NF liberated the pyranose (+)-**15** which could be reduced under Evans' conditions [10] into the semi-protected long-chain polyol (–)-**16** (Scheme 2) [9].



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

DOUBLE OXIDATIVE CLEAVAGE

The racemic diketone (\pm)-*threo*-**2**, which can be separated readily from *meso*-**2**, has been reduced into diol (\pm)-**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].

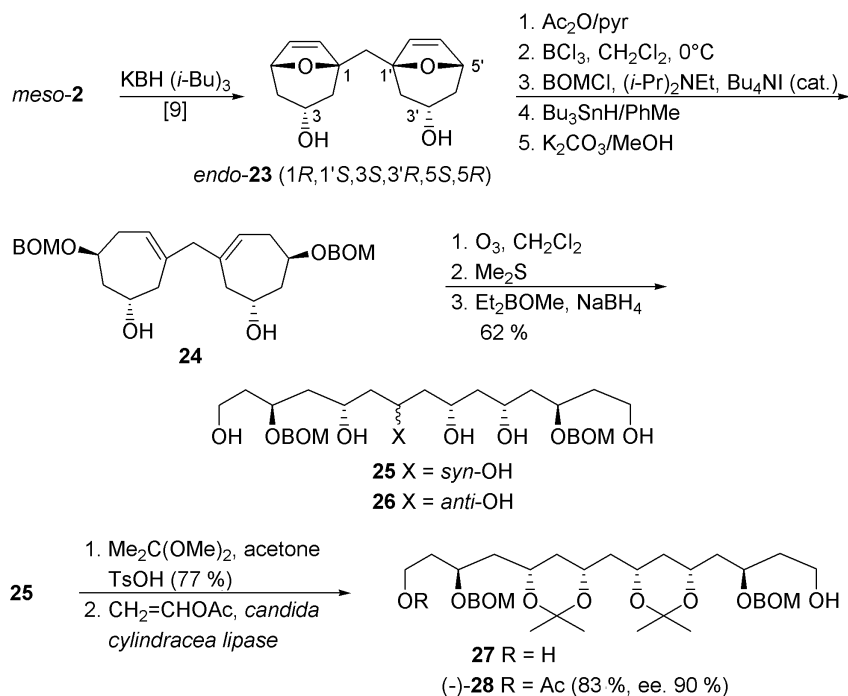
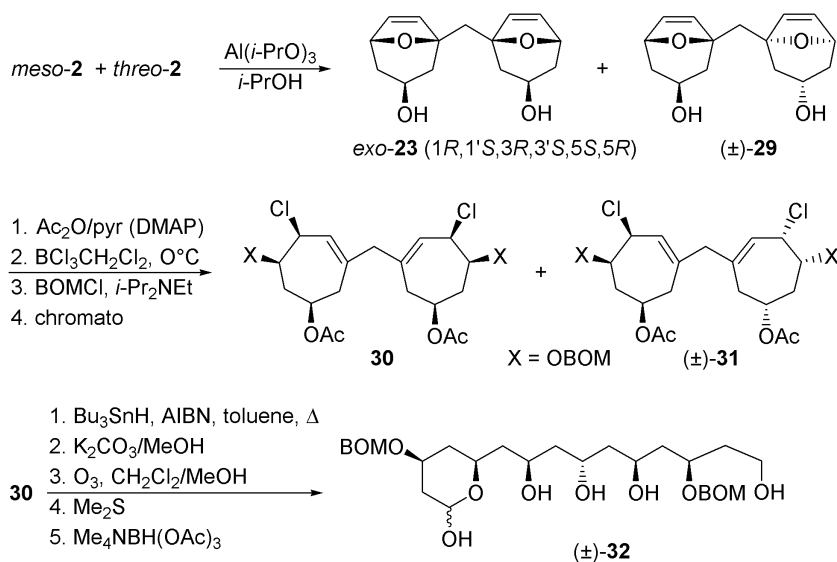


Scheme 3 Long-chain polyols via double oxidative cleavage.

FURTHER STERIODIVERSITY

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. cylindracea* lipase, the monoacetate (–)-**28** (90 % ee, Mosher's ester) was obtained in 83 % yield.

We disclose also that 1,1'-methylenebis[(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 *exolendo* 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 (Ac₂O, pyr, DMAP) an inseparable mixture of diacetates was obtained. It was submitted to the usual ethereal bridge-opening conditions (BCl₃, CH₂Cl₂, 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 methanolized 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.

ACKNOWLEDGMENTS

This work was supported by the Swiss National Science Foundation and the Office Fédéral de l'Éducation et de la Science (OFES, COST D13/010/01), which are gratefully acknowledged. We thank also the University of Seville for a grant to one of us (A.T.C.A.).

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