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-oxylallyl 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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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 catalytic 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_N+2 displacement by cesium acetate to give acetate (+)-14. Selective desilylation by
Bu$_3$NF 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].
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′-methylene[(1R,1′S,3R,3′S,5S,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 SmI2 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].
Total asymmetric synthesis of 15-carbon polyketides and analogs

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


