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SYNTHESIS OF A VERSATILE CHIRAL SYNTHON CORRESPONDING TO THE C(1) to C(7) SEGMENT OF 14-MEMBERED MACROLIDE ANTIBIOTICS

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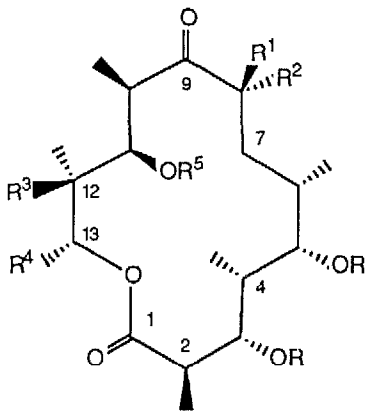
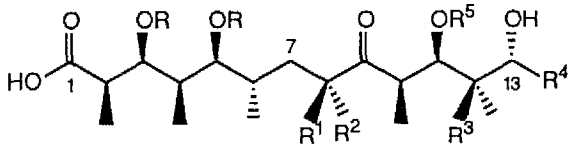
Abstract: *The synthesis of the C(1) to C(7) segment of a number of 14-membered macrolide* antibiotics is described, starting from dimethyl 3-hydroxy-2,4-dimethylglutarate.

The use of enzymes as catalysts in organic synthesis is still growing and can be considered as one of the most promising and expanding fields of organic chemistry[1]. In this regard esterases such as pig liver esterase (PLE, EC 3.1.1.1.) have shown to be very attractive. Stabilitiy, low cost and lack of the need of coenzymes are important advantages of this enzyme. Our own studies on the enantioselective hydrolysis of meso-diesters and racemic monoesters by systematic variation of the substrates[2] are directed both, to the development of a refined model for the structure-activity relationship, and the preparation of new versatile synthons for the construction of optically active compounds such as complex natural products[3].

A few years ago we reported the high enantioselectivity of the hydrolysis of the achiral dimethylester **4** by PLE. The chiral monoester **5** obtained, which we previously used for the synthesis of a moiety of rifamycin and which was used by another group[4] for the synthesis of a triene intermediate in monensin biosynthesis, served as starting material for the preparation of the hydroxyester **3**. This ester corresponds to the C(1) to C(7) segment of a number of structurally related 14-membered macrolide antibiotics[5] of type **1**, and possesses the correct stereochemistry of the five centres of chirality (Table).



1



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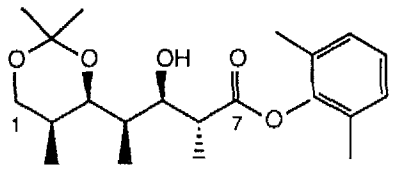


3

R = various sugar units

Table: Antibiotics of Type 1

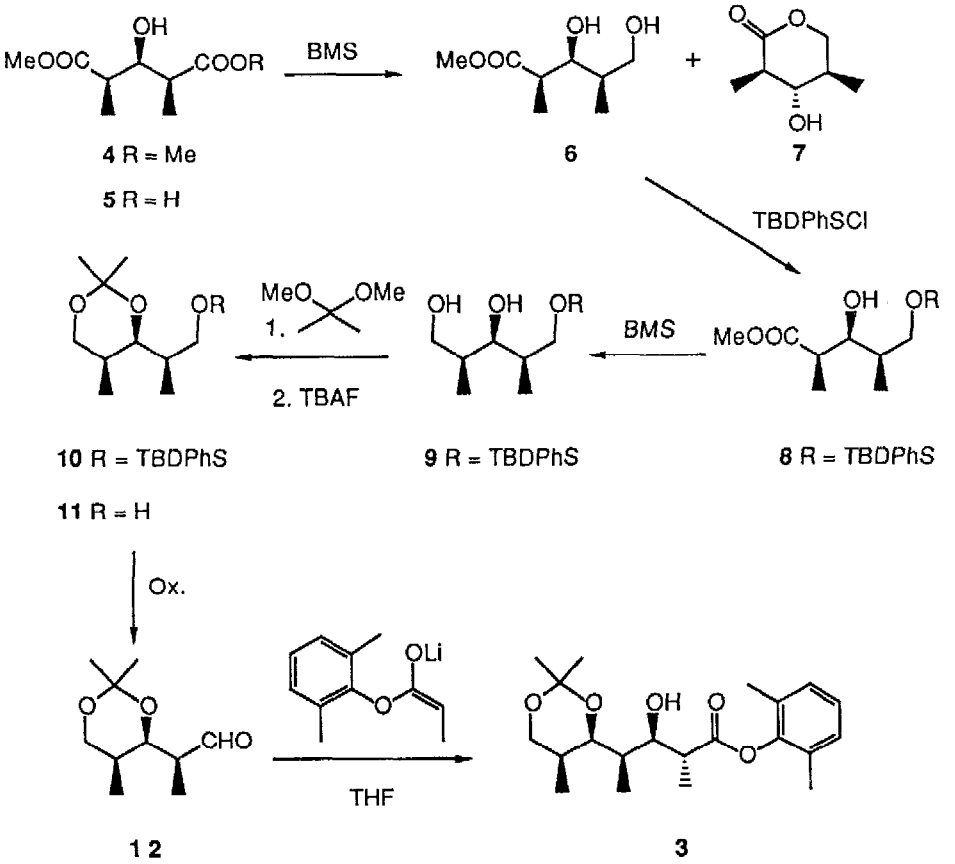
Compound	R^1	R^2	R^3	R^4	R^5
6-Deoxy-erythromycin A and C	H	CH_3	OH	Et	H
6-Deoxy-megalomycin A	H	CH_3	OH	Et	D-Rhodos-amin
6-Deoxy-erythromycin B	H	CH_3	H	Et	H
Oleandomycin	O—CH_2		H	CH_3	H
Lankamycin	OH	CH_3	H	2-Hydroxy-sec-butyl	Ac

The 14-membered macrolide antibiotics are a medicinally important group of secondary metabolites because of their activity against gram-positive bacteria. Therefore many synthetic efforts[6] have been made directed to the construction of the structure containing ten asymmetric centres.

Our synthesis of **3** started with the reduction of the monoester **5** with $BH_3 \cdot (CH_3)_2S$ at 0° and subsequent protection of the primary hydroxyl group of the resulting diol **6** as the silylether **8** (tert.-butyl-diphenylsilyl chloride (TBDPhSCl), imidazole, DMF). The protected hydroxyester **8** was isolated in 78% yield ($[\alpha]_D^{22}$ = -5.6°;

c = 1.5, CCl_4). The well known lactone **7** was formed as a by-product (yield 15%). Lactone **7**, which was obtained by Gerzon et al.[7] in the course of the structural determination of dihydroerythronolide A and synthesized by Wakamatsu et al.[8] had a mp. of 88-89° (toluene) and $[\alpha]_D^{22}$ = -4.4°; (c = 2, MeOH) (Lit.[7]: mp. 88-88.5°, $[\alpha]_D^{27}$ = -5.0°; c=2, MeOH; Lit.[8]: mp 88°, $[\alpha]_D$ = -4.6°; MeOH).

Reduction of the protected hydroxyester **8** with $BH_3 \cdot (CH_3)_2S$ at 40° afforded the monoprotected triol **9** in 78% yield ($[\alpha]_D^{21}$ = -3.8°; c= 2, $CHCl_3$). Lactone **7** was also converted to **9** by a four-step sequence involving subsequent treatment with KOH/MeOH; 2 mol-equiv. TBDPhSCl, imidazole, DMF; KOH/MeOH and $BH_3 \cdot (CH_3)_2S$. Thus an additional amount of 9% of **9** was made available. The hydroxyl groups of **9** were protected as acetonide (2,2-dimethoxypropane, CSA, 94%, $[\alpha]_D^{23}$ = -13.0°; c = 1.39, $CHCl_3$). After desilylation of **10** (TBAF, quant.) the resulting alcohol **11** ($[\alpha]_D^{22}$ = -7.1°; c = 1.39, $CHCl_3$) was oxidized to the aldehyde **12** by the method of Swern[9] (yield 97%). Aldehyde **12**, which was obtained by Yonemitsu[10] during his synthetic work on erythromycin A, had $[\alpha]_D^{21}$ = +5.3°; (c = 1.2, $CHCl_3$) (Lit.[10]: $[\alpha]_D^{17}$ = +5.0°, c = 1.2, $CHCl_3$).



Introduction of the remaining two chiral centres was achieved using the arylester aldol condensation of Heathcock[11]. Addition of the aldehyde **12** to a solution of the Li-enolate of 2.6-dimethylphenylpropionate in THF at -78° gave the desired hydroxyester **3** as the only product (yield 50%). The hydroxyester **3**[12] obtained from **4** in an overall yield of 30% had a mp. of 97-99° (hexane), $[\alpha]_D^{22}$ = +1.6°; (c = 1, CCl_4) and represents a most useful chiral synthon for the construction of macrolide antibiotics.

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12) The ester **3** gave correct microanalyses and spectroscopic data which corresponded to its enantiomeric form, which we had previously synthesized (see. ref. [3]).

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