Enzymatic Desymmetrization of a Meso Polyol Corresponding to the C(19)−C(27) Segment of Rifamycin S

Robert Chênevert* and Yannick Stéphane Rose

Département de chimie, Faculté des sciences et de génie, Université Laval, Québec (Québec), Canada G1K 7P4

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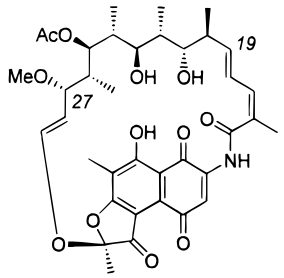
The stereoselective acylation of meso polyol **2** by vinyl acetate (solvent and acyl donor) in the presence of porcine pancreas lipase gave the corresponding monoester **5** in good yield (76%) and high enantiomeric purity (ee > 98%). The enzymatic reaction was also highly regioselective for a primary alcohol end group, and the two unprotected secondary alcohols were not involved. Compound **5** corresponds to the C(19)−C(27) fragment of rifamycin S.

Introduction

Rifamycins are antibiotics belonging to the group of naphthalenic ansamycins characterized by an aliphatic bridge linking two nonadjacent positions of an aromatic nucleus. They are active against a large variety of microorganisms, and they exert this activity by specific inhibition of bacterial DNA-dependent RNA polymerase.[1,2]

The first total synthesis of rifamycin S (**1**) was reported by Kishi et al.[3] in 1980. Following this pioneering work, several strategies have been proposed for controlling the sequence of the eight contiguous stereogenic centers on the polypropionate ansa bridge.[4,5] Harada et al.[6] reported



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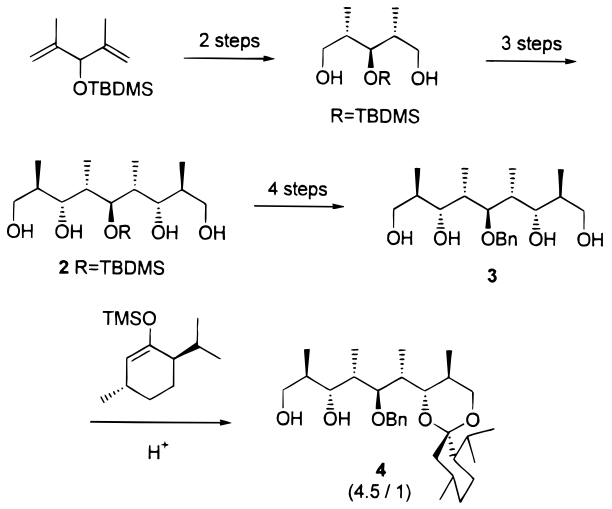
an efficient synthesis of meso tetraol **2** corresponding to the C(19)−C(27) segment of rifamycin S (Scheme 1). The problem of meso chain terminus differentiation (desymmetrization) was solved by kinetic acetalization of tetraol **3** with a *d*-menthone derivative.[6] The replacement of the OTBDMS protecting group by a benzyl (four steps) was necessary to avoid its participation in the enantiodifferentiating transformation. Treatment of **3** with *d*-menthone enol TMS ether and catalytic TsOH produced a 4.5:1 mixture (de = 64%) of separable diastereomeric

Scheme 1



menthonides **4** (yield 61%) along with the bis-menthonide (12%) and the unreacted tetraol (10%). We report here an enzymatic desymmetrization of meso tetraol **2**.

Results and Discussion

Of the enzymes and conditions studied, the esterification of **2** with vinyl acetate in the presence of porcine pancreas lipase (PPL) at room temperature (Scheme 2) gave the best result and provided the chiral nonracemic monoester **5** in good yield (76%) and high enantiomeric excess (ee > 98%). The use of *Pseudomonas fluorescens*

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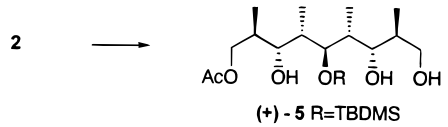
Table 1. Enzymatic Desymmetrization of Meso Tetraol 2

entry	enzyme[a]	time (h)	yield (%)	ee (%)	absolute confign
1	PPL	24	76	>98	2*R*
2	PFL	27	70	95	2*R*
3	PCL	8	70	93	2*R*

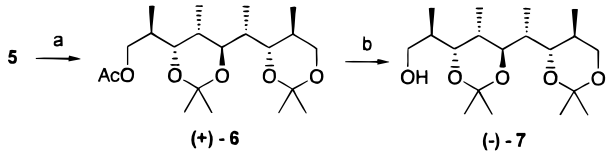
[a] PPL: porcine pancreas lipase. PFL: *Pseudomonas fluorescens* lipase. PCL: *Pseudomonas cepacia* lipase.

Scheme 2[a]



[a] Key: porcine pancreas lipase, vinyl acetate, rt, 76%, ee > 98%.

Scheme 3[a]



a Key: (a) acetone, 2,2-dimethoxypropane, p-TsOH, rt, 95%; (b) $LiAlH_4$, ether, 0 °C to rt, 100%.

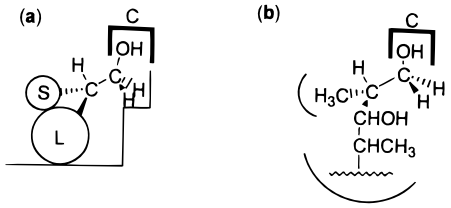


Figure 1. Side perspective view of the Naemura active site model. (a) Good fit of a primary alcohol. S: small hydrophobic binding site. L: large hydrophobic binding site. C: catalytic site. (b) Favorable fit of polyol **2**.

lipase or *Pseudomonas cepacia* lipase gave similar results with slightly lower yields and enantiomeric excesses (Table 1). The enantiomeric composition of **5** was measured by ^{19}F NMR (282 MHz, in benzene-d_6) analysis of the corresponding (+)-α-methoxy-α-trifluoromethyl-α-phenyl acetate (Mosher's ester). Only the ester of the primary alcohol was formed because of the steric crowding in both reagents. The absolute configuration of monoacetate **5** was determined by chemical correlation with bis-acetonide **7**, an intermediate in Kishi's synthesis[3] of rifamycin S (Scheme 3). Monoacetate **5** was treated with dimethoxypropane in acetone under acidic catalysis, thus provoking the removal of the TBDMS protecting group as well as the bis-acetalization to afford **6** in high yield. Reduction of **6** with $LiAlH_4$ gave bis-acetonide **7**, which has spectroscopic data and specific rotation in agreement with those previously reported.[3] This correlation proved that compound **5** had the 2*R*,3*R*,4*S*,5*R*,6*R*,-7*S*,8*S* absolute configuration corresponding to the configuration of rifamycin S.

The enantioselectivity (2*R*) observed for PFL can be rationalized by the active site model of Naemura et al.[7] for the acylation of primary alcohols (Figure 1). The empirical model proposed by Kazlauskas et al.[8] for the enantiopreference of PCL toward primary alcohols without oxygen at the stereocenter suggests a 2*R*-selectivity toward **2**. The Jones active site model for PPL[9] also predicts the same enantioselectivity. These last two models were developed for the hydrolysis reactions, but with meso compounds, the hydrolysis and the acylation reactions are usually complementary and occur at the same stereocenter.

The enzymatic desymmetrization of meso polyol **2** is highly regio- and stereoselective for a primary alcohol end group, and the two unprotected secondary alcohols remained untouched. Monoacetate **5** corresponds to the C(19)−C(27) fragment of rifamycin S.

Experimental Section

General Methods. NMR spectra were recorded at 300 MHz (^1H), 282 MHz (^{19}F) and 75 MHz (^{13}C). Melting points are uncorrected. Flash column chromatography was carried out using 230−400 mesh silica gel. Lipases were purchased from Amano Enzyme Co. (PCL), from Fluka (PFL) and from Sigma (PPL). Tetraol **2** was prepared according to the procedure of Harada and Oku.[6]

(2*R*,3*R*,4*S*,5*R*,6*R*,7*S*,8*S*)-5-(*tert*-Butyldimethylsilyloxy)-3,7,9-trihydroxy-2,4,6,8-(tetramethyl)nonalyl Acetate (5). A solution of tetraol **2** (150 mg, 0.40 mmol) in vinyl acetate (15 mL, solvent and acyl donor) containing crude porcine pancreas lipase (100 mg) was stirred for 12 h at room temperature. Another portion of crude PPL (100 mg) was added, and the mixture was stirred for 12 h at room temperature. The reaction was monitored by thin-layer chromatography and quenched when the starting material was completely converted into monoacetate **5** and the corresponding diacetate. The mixture was filtered, and the solvent was evaporated. The residue was purified by flash chromatography (EtOAc/hexanes 9:11) to yield the monoacetate **5** (128 mg, 76%) as a colorless oil: $[\alpha]^{25}_D = +2.13$ (*c* 1.27, $CHCl_3$); IR (neat) 3470, 1740, 1254, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.03 and 0.00 (2s, 6H), 0.74 (s, 9H), 0.83, 0.73, 0.68, 0.57 (4d, J = 7 Hz, 12H), 1.78−1.71 (m, 4H), 1.90 (s, 3H), 3.55−3.48 (m, 3H), 3.74−3.71 (m, 2H), 3.97 (dd, J_1 = 3.8 Hz, J_2 = 11.1 Hz, 1H), 4.15 (dd, J_1 = 4.9 Hz, J_2 = 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.33, −3.62, 9.60, 11.37, 13.00, 13.64, 18.30, 20.88, 26.18, 35.55, 36.48, 37.11, 37.36, 67.25, 69.12, 70.76, 76.46, 80.81, 171.49; HRMS (CI, NH_3) calcd for $C_{21}H_{44}O_6Si$ $(M + H)^+$ 421.2985, found 421.2980 ± 0.0013.

(2*R*,3*R*,4*S*,5*R*,6*R*,7*S*,8*S*)-(3,5:7,9-Di-O-isopropylidene)-2,4,6,8-tetramethylnonanyl Acetate (6). A solution of monoacetate **5** (139 mg, 0.33 mmol) in acetone (1 mL) containing 2,2-dimethoxypropane (0.1 mL) and *p*-TsOH (10 mg) was stirred at room temperature for 2.5 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (ether/hexanes 1:4) to give **6** as a white solid (121 mg, 95%): mp 73 °C; $[\alpha]^{20}_D = +18.1$ (*c* 1.07, $CHCl_3$); IR (KBr) 1733, 1380, 1176, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (d, J = 6.7 Hz, 3H), 0.91−0.86 (m, 9H), 1.37, 1.34, 1.27, 1.25 (4s, 12H), 1.93−1.62 (m, 4H), 2.05 (s, 3H), 3.26 (dd, J_1 = 6.5 Hz, J_2 = 9.5 Hz, 1H), 3.50 (t, J = 11.1 Hz, 1H), 3.60 (dd, J_1 = 3.7 Hz, J_2= 9.6 Hz, 1H), 3.68 (dd, J_1 = 5.0 Hz, J_2 = 11.5 Hz, 1H), 3.84 (dd, J_1 = 1.8 Hz, J_2 = 10.4 Hz, 1H), 4.05 (dd, J_1 = 5.9 Hz, J_2 = 10.5 Hz, 1H), 4.16 (dd, J_1 = 3.0 Hz, J_2 = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 7.62, 11.95, 12.59, 12.79, 18.89, 20.77, 23.24, 25.52, 29.68, 30.25, 32.43, 36.24, 39.12, 66.45, 66.51, 69.58, 72.66, 74.09, 97.88, 100.25, 171.08; HRMS (CI, NH_3) calcd for $C_{21}H_{38}O_6$ $(M + H)^+$ 387.2746, found 387.2751 ± 0.0011.

(2*R*,3*R*,4*S*,5*R*,6*R*,7*S*,8*S*)-(3,5:7,9-Di-O-isopropylidene)-2,4,6,8-tetramethylnonanol (7). To a solution of acetate **6**

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(89 mg, 0.23 mmol) in diethyl ether was added $LiAlH_4$ (9 mg, 0.23 mmol) at 0 °C. The mixture was stirred at room temperature for 2.5 h. The mixture was treated with saturated aqueous NH_4Cl and extracted three times with EtOAc. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (ether/hexanes 2:3) to give **7** (79 mg, quantitative) as a white solid: mp 90 °C; $[\alpha]^{20}_D = -6.25$ (*c* 1.22, $CHCl_3$) (lit.[6a] $[\alpha]^{25}_D = -5.07$ (*c* 1.10, $CHCl_3$), lit.[3a] $[\alpha]^{25}_D = -3.49$ (*c* 1.52, $CHCl_3$)); IR (KBr) 3460, 1380, 1176, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87, 0.80, 0.71, 0.63 (4d, $J = 7$ Hz, 12H), 1.31, 1.30, 1.28, 1.24 (4s, 12H), 1.81−1.67 (m, 4H), 3.23 (dd, $J_1 = 6.4$ Hz, $J_2 = 10.3$ Hz, 1H), 3.53−3.20 (m, 4H), 3.65−3.72 (m, 2H), 3.72 (dd, $J_1 = 1.9$ Hz, $J_2 = 10.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.58, 11.92, 12.43, 12.81, 18.88, 23.29, 25.93, 29.66, 30.21, 34.66, 36.51, 39.11, 66.41, 69.04, 72.58, 74.13, 75.80, 97.86, 100.30.

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Supporting Information Available: Spectrometric information (^1H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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