Tetrahedron: *Asymmetry* 22 (2011) 658–661

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of enantiomerically pure (*R*)-and (*S*)-1-benzoyloxypropane-2,3-diol and revision of the stereochemical outcome of the *Candida antarctica* lipase-catalyzed benzoylation of glycerol

Silvana Casati [a], Pierangela Ciuffreda [a], Enzo Santaniello [b,*]

[a] *Università degli Studi di Milano, Dipartimento di Scienze Cliniche 'L. Sacco', via G.B. Grassi 74, 20157 Milano, Italy*
[b] *Università degli Studi di Milano, Dipartimento di Medicina, Chirurgia e Odontoiatria, via di Rudinì 8, 20142 Milano, Italy*

ARTICLE INFO

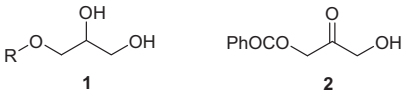
Article history:
Received 7 February 2011
Accepted 6 April 2011
Available online 4 May 2011

ABSTRACT

Enantiomerically pure (*R*)- and (*S*)-1-benzoyloxypropane-2,3-diol have been prepared from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol and used as reference compounds to correct the reported stereochemical outcome of the *Candida antarctica* lipase (CAL)-catalyzed benzoylation of glycerol.

1. Introduction

Mono-derivatives of glycerol **1a**, such as 3-benzyloxypropane-1,2-diol **1b** or 1-benzoyloxypropane-2,3-diol **1c** (Fig. 1), are valuable chiral synthons that have already been used in asymmetric synthesis.[1]



a. R = H
b. R = CH_2Ph
c. R = COPh

Figure 1. Structure of compounds **1a–c** and **2**.

A biocatalytic preparation of enantiomerically pure (*S*)-(+)-**1c**, specifically the Baker's yeast fermentation of 1-benzoyloxy-3-hydroxypropan-2-one **2**, was reported a few years ago.[2] This result has been later confirmed and extended to the bioreduction of other dihydroxyacetone derivatives.[3] Compound (*S*)-(+)-**1c** can been prepared from 1-benzoyloxy-3-hydroxypropan-2-one **2** by also utilizing other microrganisms.[4] Recently, a reported enzyme-assisted asymmetrization of prochiral glycerol **1a** has completed the availability of both enantiomeric 1-benzoyloxypropane-2,3-diols **1c**.[5–7] Specifically, it has been reported that the lipase from *Candida antarctica* (CAL) catalyzes the benzoylation of glycerol **1a** in organic solvents and the optically active (*R*)-(+)-1-benzoyloxypropane-2,3-diol **1c** (max 60% ee) can be prepared.[5] Re-crystallization in the presence of enantiomerically pure **1c** allows the preparation of enantiomerically pure **1c** in gram quantities (Scheme 1).[5,6]

Although it could appear contradictory that opposite enantiomers exhibit the same positive specific rotation, this might tentatively be explained by the fact that measurements were recorded in different solvents. In fact, the value of $[\alpha]_D^{20}$ recorded in pyridine for (*S*)-(+)-**1c** was +15.2 (*c* 2),[2] whereas the sample of (*R*)-(+)-**1c** showed an $[\alpha]_D^{20} = +18.8$ (*c* 1.00, ethanol).[5]

However, (−)-**1c** has been prepared from D-1,2-isopropylidene-*sn*-glycerol **3**[8] and has been named 1-benzoyl-D-glycerol {$[\alpha]_D = -17.5$ (*c* 10, pyridine)}[9] or 1-benzoyl-L-glycerol {$[\alpha]_D = -15$ (*c* 10, pyridine)}[1a] or (2*R*)-3-benzoyloxypropane-1,2-diol.[1b]

Finally, in a recent paper[10] (*R*)-monobenzoate glycerol with a high enantiomeric excess was used in isotopic ^{13}C NMR spectroscopy to measure the site-specific $^{13}C/^{12}C$ ratios at natural abundance. The authors specifically refer to a sample of (*R*)-monobenzoate prepared using the CAL-catalyzed benzoylation of prochiral glycerol **1a**.[5]

It seemed necessary to establish unequivocally the configuration and the specific rotation value of (*R*)-and (*S*)-1-benzoyloxypropane-2,3-diol **1c** and for this purpose we have prepared samples of (*R*)- and (*S*)-**1c** starting from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol **3**, which can be prepared from D-mannitol[11] and is commercially available.

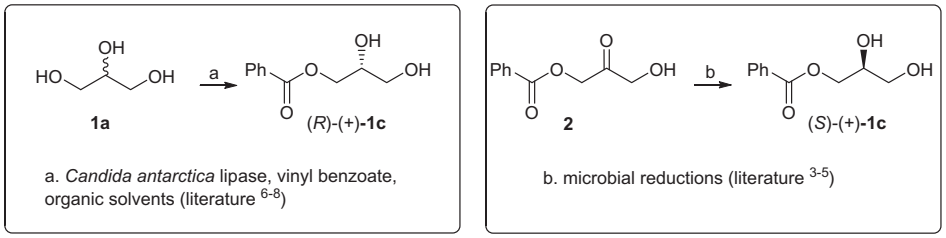
2. Results and discussion

The chemical synthesis of (*S*)-1-benzoyloxypropane-2,3-diol **1c** from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol **3** is described in Scheme 2. Thus, acetonide **3** was converted into (*S*)-**4** in a conventional manner[12] and the acetonide protection of compound (*S*)-**4** satisfactorily removed by hydrolysis in the presence of a resin with a sulfonic acid functionality (Amberlyst 15).[13]

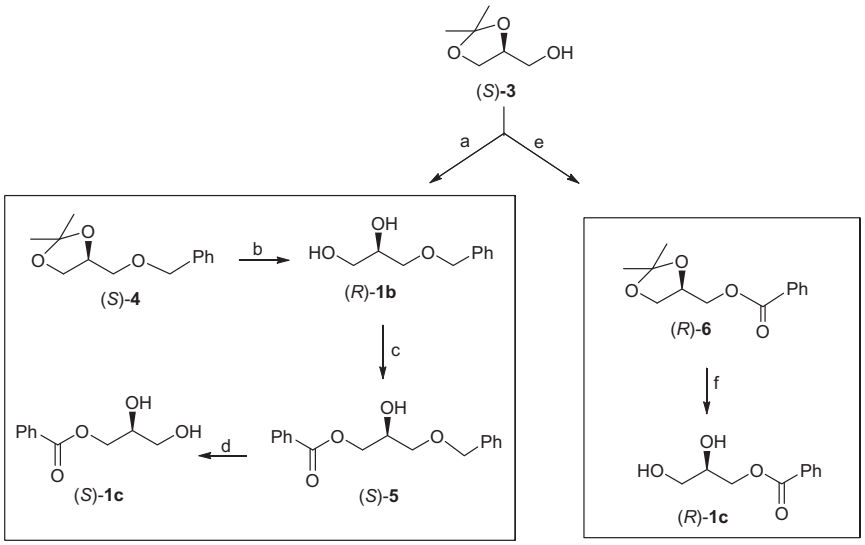
(*R*)-3-Benzyloxypropane-1,2-diol **1b** was then selectively monobenzoylated to (*S*)-**5** utilizing the recently described enzy-

* Corresponding author. Tel.: +39 025 031 9691; fax: +39 025 031 9631.
E-mail address: enzo.santaniello@unimi.it (E. Santaniello).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.04.003



Scheme 1. Biocatalytic approach to (*R*)- and (*S*)-1-benzyloxypropane-2,3-diol **1c**, according to the literature.[3–8]



Scheme 2. Reagents and conditions: (a) BnBr, NaH, THF, rt, 3 h, 76%; (b) Amberlyst 15, MeOH, rt, 3 h, 85%; (c) BzCl, TEA, CH_2Cl_2, rt, 1 h, 67%; (d) Pd/C, MeOH, rt, 6 h, 81%; (e) BzCl, TEA, CH_2Cl_2, rt, 1 h, 72%; (f) Amberlyst 15, MeOH, rt, 3 h, 87%.

matic regioselective benzoylation procedure.[14] Removal of the benzyl protection by hydrogenolysis afforded quantitatively a sample of pure (*S*)-(+)-**1c** (Scheme 2). The enantiomeric excess of the sample obtained by our chemical synthesis was established as >98% by analysis of the ^{1}H NMR of the related Mosher ester.[15] The specific rotations of (*S*)-1-benzoyloxypropane-2,3-diol **1c** were recorded in ethanol {$[\alpha]_D$ = +15.8 (*c* 1)} and pyridine {$[\alpha]_D$ = +13.9 (*c* 1)}, and showed a positive value in both solvents for (*S*)-**1c**. Therefore, the configuration of (+)-1-benzoyloxypropane-2,3-diol **1c** prepared by the CAL-catalyzed benzoylation of glycerol **1a**[5–7] should be reversed from (*R*) to (*S*).

Finally, starting from [(*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol] **3**, the complementary synthesis of enantiomerically pure (*R*)-**1c** was achieved efficiently in two steps, that is, benzoylation and hydrolysis of the acetonide protection (63% overall yield, Scheme 2). In order to avoid racemization in the hydrolytic step, we performed the cleavage of the protecting group under a few conditions described for the specific purpose[16] and the use of a resin with a sulfonic acid functionality (Amberlyst 15)-ethanol (95%) system[13] gave the most satisfactory results.

The sample of (*R*)-**1c** showed a negative specific rotation {$[\alpha]_D^{20} = -15.9$ (*c* 1, ethanol) and −13.8 (*c* 1, pyridine} and a >98% ee was established by the ^{1}H NMR analysis of the corresponding Mosher ester.

3. Conclusion

Starting from D-1,2-isopropylidene-*sn*-glycerol [(*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol] **3**, we have prepared enantiomerically pure (*R*)-(−) and (*S*)-(+)-**1c**. Therefore, the (+)-monobenzoate **1c** that has been prepared by the CAL-catalyzed asymmetrization of glycerol **1a**,[5–7] is not (*R*)-(+)-**1c** and the configuration originally proposed, should be reversed to (*S*).[17]

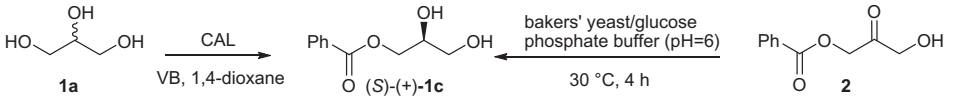
Therefore, the two main biocatalytical approaches, that is, the enzymatic benzoylation of glycerol **1a** and the Baker's yeast bioreduction of the hydroxyacetone monobenzoate **2**[3,6] lead to the same enantiomer, namely (*S*)-(+)-**1c** (Scheme 3).

Enantiomerically pure (*R*)-**1c** is, at present, only available via a chemical approach which starts from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol **3**.[18]

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at 298 K in the indicated deuterated solvents on a Bruker AVANCE 500 spectrometer equipped with a 5 mm broadband reverse probe with field *z*-gradi-



Scheme 3. Biocatalytic approaches to (*S*)-(+)-1-benzoyloxypropane-2,3-diol **1c**.

ent operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C. Chemical shifts (δ) are given as parts per million relative to the residual solvent peak and coupling constants (J) are in Hertz. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br, broad peak. Column chromatography was performed on Silica Gel 60 (70–230 mesh) using the specified eluants. Optical rotations were measured on a Perkin–Elmer 241 polarimeter (sodium D line at 25 °C). Melting points were determined with a Stuart Scientific SMP3 melting point apparatus and are uncorrected. The progress of the reaction was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates (Silica Gel 60 F254-plate-Merck, Darmstadt, Germany) and the products were visualized by UV light. The purity of all compounds (⩾99%) was verified by thin layer chromatography and NMR measurements. The optical purity of alcohols (*R*)-**1c** and (*S*)-**1c** (>98% ee) was determined by ^{1}H NMR analysis of its Mosher's ester. Elemental analyses were obtained for all intermediates and are within ±0.4% of theoretical values. The chemicals and solvents were obtained from Sigma–Aldrich and used without further purification.

4.2. Preparation of (*S*)-1-benzyloxy-2,3-isopropylidene glycerol (*S*)-4

At first, 1 g of 60% NaH in mineral oil was added to a solution of (*S*)-**3** (1.00 g, 7.6 mmol) in anhydrous THF (10 mL). After 10 min, 1 mL of benzyl bromide (1 mL, 8.4 mmol) was added portion wise. The mixture was stirred for 3 h at room temperature and monitored by TLC (petroleum ether/ethylacetate 9:1). The mixture was cautiously poured in a 10% solution of ammonium chloride into water and extracted with dichloromethane (3 × 10 mL). Evaporation of the solvents under vacuum and purification by chromatography column on silica gel (petroleum ether/ethylacetate 9:1) afforded 1.3 g (5.8 mmol, 76%) of (*S*)-**4** as a colorless oil. $[\alpha]_D^{20} = +21.9$ (*c* 1, $CHCl_3$), {lit.[12] $[\alpha]_D^{25} = +18.0$ (neat)}. R_f (20% ethyl acetate/hexane) 0.6; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.50 (1H, dd, *J* = 5.6, 9.8 Hz, 1-C*H*HO), 3.59 (1H, dd, *J* = 5.9, 9.8 Hz, 1-CH*H*O), 3.77 (1H, dd, *J* = 6.6, 8.4 Hz, 3-C*H*HO), 4.09 (1H, dd, *J* = 6.6, 8.4 Hz, 3-CH*H*O), 4.33 (1H, dddd, *J* = 5.6, 5.9, 6.6, 6.6, 2-C*H*O), 4.59 (1H, d, *J* = 11.9 Hz, OC*H*HPh), 4.62 (1H, d, *J* = 11.9 Hz, OCH*H*Ph), 7.34–7.38 (5H, m, OCH_2Ph); ^{13}C NMR δ 25.4 (CH_3), 26.8 (CH_3), 66.9 (3-C), 71.1 (1-C), 73.5 (OCH_2Ph), 74.8 (2-C), 109.4 ($C(CH_3)_2$), 127.7 (*o*-PhCH, *p*-PhCH), 128.4 (*m*-PhCH), 137.9 (PhC).

4.3. Preparation of (*R*)-1-benzyloxy-2,3-propanediol (*R*)-1b

To 1.3 g (5.8 mmol) of (*S*)-**4** (10 mL), 1.0 g of Amberlyst 15 was added. After 3 h at room temperature under stirring, the reaction was filtered and the solvent removed under vacuum. Purification by chromatography column on silica gel (petroleum ether/ethylacetate 7:3) afforded 920 mg (4.9 mmol; 85%) of (*R*)-**1b** as a viscous liquid. $[\alpha]_D^{20} = +5.9$ (*c* 1, $CHCl_3$), {lit.[19] $[\alpha]_D^{25} = +5.6$ (*c* 20, $CHCl_3$)}. R_f (40% ethyl acetate/hexane) 0.13; ^{1}H NMR ($CDCl_3$) δ 3.55 (1H, dd, *J* = 6.3, 10.0 Hz, 3-C*H*HOH), 3.59 (1H, dd, *J* = 4.2, 10.0 Hz, 3-CH*H*OH), 3.63 (1H, dd, *J* = 5.9, 11.5 Hz, 1-CH*H*OPh), 3.71 (1H, dd, *J* = 3.8, 11.5 Hz, 1-C*H*HOPh), 3.91 (1H, dddd, *J* = 3.8, 4.2, 5.9, 6.3 Hz, 2-C*H*OH), 4.57 (2H, s, OCH_2Ph), 7.31–7.39 (5H, m, OCH_2Ph); ^{13}C NMR δ 64.1 (3-C), 70.7 (2-C), 71.8 (1-C), 73.6 (OCH_2Ph) 127.8 (*o*-PhCH), 127.9 (*p*-PhCH), 128.5 (*m*-PhCH), 137.7 (PhC).

4.4. Preparation of (*S*)-1-benzoyloxy -3-benzyloxy-2-propanol (*S*)-5

A solution of benzoyl chloride (0.7 mL, 5.6 mmol) in dichloromethane was added slowly to an ice-cooled solution of (*R*)-**1b** (920 mg, 4.7 mmol) and triethylamine (1.3 mL, 9.4 mmol) in dichloromethane (10 mL) with stirring. After 1 h, the reaction mixture was poured into water, the organic layer was separated and the aqueous phase extracted with dichloromethane (2 × 5 mL). After evaporation of the solvent, purification by chromatography column on silica gel (petroleum ether/ethylacetate 8:2 and 7:3) afforded 900 mg (3.1 mmol, 67%) of (*S*)-**5** as a viscous liquid. $[\alpha]_D^{20} = +6.1$ (*c* 1, $CHCl_3$), {lit.[20] $[\alpha]_D^{25} = +6.25$ (*c* 6.28, Et_2O)}. R_f (20% ethyl acetate/hexane) 0.2; ^{1}H NMR ($CDCl_3$) δ 3.62 (1H, dd, *J* = 5.9, 9.5 Hz, 3-C*H*HO), 3.67 (1H, dd, *J* = 4.2, 9.5 Hz, 3-CH*H*O), 4.21 (1H, dddd, *J* = 4.2, 4.9, 5.6, 5.9 Hz, 2-C*H*OH), 4.42–4.48 (2H, m, part AB of ABX system, 1-CH_2O), 4.61 (2H, s, OCH_2Ph), 7.35–7.39 (5H, m, OCH_2Ph); 7.46 (2H, dd, *J* = 7.0, 7.0 Hz, *m*-Ph H), 7.60 (1H, t, *J* = 7.0, *p*-Ph H), 8.05 (2H, d, *J* = 7.0, *o*-Ph H); ^{13}C NMR δ 66.0 (1-C), 69.0 (2-C), 70.9 (3-C), 73.6 (OCH_2Ph), 127.8 (*o*-PhCH), 127.9 (*p*-PhCH), 128.4 (*m*-PhCH), 128.5 (*m*-PhCH), 129.7 (*o*-PhCH), 129.9 (PhC), 133.1 (*p*-PhCH), 137.7 (PhC), 166.7 (CO).

4.5. Preparation of (*S*)-1-benzoyloxy-2,3-propanediol (*S*)-1c

To a solution of (*S*)-**5** (900 mg, 3.1 mmol) in methanol, 10% Pd/C (90 mg) was added. The reaction was put under hydrogen atmosphere at room temperature for 6 h. After filtration on a Celite pad, the residue was evaporated and purified by column chromatography on silica gel (dichloromethane/methanol 95:5), affording (*S*)-**1c** (500 mg, 81%) as a viscous liquid. $[\alpha]_D^{20} = +15.8$ (*c* 1, EtOH), $[\alpha]_D^{20} = +13.9$ (*c* 1, pyridine), {lit.[3] $[\alpha]_D^{25} = +13.7$ (*c* 2, pyridine)}. R_f (40% ethyl acetate/hexane) 0.13; ^{1}H NMR ($CDCl_3$) δ 3.69 (1H, dd, *J* = 6.0, 11.5 Hz, 3-C*H*HOH), 3.79 (1H, dd, *J* = 3.5, 11.5 Hz, 3-CH*H*OH), 4.05–4.11 (1H, m, C*H*OH), 4.41–4.46 (2H, m, part AB of ABX system, 1-CH_2O), 7.43 (2H, dd, *J* = 7.0, 7.0 Hz, *m*-Ph H), 7.56 (1H, t, *J* = 7.0, *p*-Ph H), 8.04 (2H, d, *J* = 7.0, *o*-Ph H); ^{13}C NMR δ 63.5 (3-C), 65.7 (1-C), 70.4 (2-C), 128.4 (*m*-PhCH), 129.5 (*o*-PhCH), 129.7 (PhC), 133.3 (*p*-PhCH), 166.9 (CO).

4.6. Preparation of (*R*)-1-benzoyloxy-2,3-isopropylidene glycerol (*R*)-6

A solution of benzoyl chloride (1.0 mL, 9.0 mmol) in dichloromethane was added slowly to an ice-cooled solution of (*S*)-**3** (1.00 g, 7.6 mmol) and triethylamine (2.0 mL, 15.2 mmol) in dichloromethane (10 mL) with stirring. After 1 h, the reaction mixture was poured into water, the organic layer was separated and the aqueous phase extracted with dichloromethane (2 × 5 mL). After evaporation of the solvent, purification by chromatography column on silica gel (petroleum ether/ethylacetate 8:2) afforded 1.3 g (5.3 mmol, 72%) of (*R*)-**6** as a viscous liquid. $[\alpha]_D^{20} = +14.8$ (*c* 1, $CHCl_3$), {lit.[1a] $[\alpha]_D^{25} = +14.4$ (*c* 1, $CHCl_3$)}. R_f (40% ethyl acetate/hexane) 0.73; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, s, CH_3), 1.48 (3H, s, CH_3), 3.90 (1H, dd, *J* = 6.6, 8.4 Hz, 3-C*H*HO), 4.16 (1H, dd, *J* = 6.6, 8.4 Hz, 3-CH*H*O), 4.36–4.44 (2H, m, part AB of ABX system, 1-CH_2O), 4.46–4.50 (1H, m, 2-C*H*O), 7.46 (2H, dd, *J* = 7.0, 7.0 Hz, *m*-PhH), 7.54 (1H, t, *J* = 7.0, *p*-PhH), 8.08 (2H, d, *J* = 7.0, *o*-PhH); ^{13}C NMR δ 25.4 (CH_3), 26.8 (CH_3), 65.1 (1-C), 66.4 (3-C), 73.7 (2-C), 109.9 ($C(CH_3)_2$), 128.4 (*m*-PhCH), 129.7 (*o*-PhCH), 130.6 (PhC), 133.2 (*p*-PhCH), 166.4 (CO).

4.7. Preparation of (*R*)-1-benzoyloxy-2,3-propanediol (*R*)-1c

To 1.3 g (5.3 mmol) of (*R*)-**6** in methanol (10 mL) was added 1.0 g of Amberlyst 15. After 3 h at room temperature under stirring, the reaction was filtered and the solvent removed under vacuum. Purification by chromatography column on silica gel (petroleum ether/ethylacetate 6:4) afforded 900 mg (4.6 mmol; 87%) of (*R*)-**1c** as a viscous liquid. $[\alpha]_D^{20} = -15.9$ (*c* 1, EtOH), $[\alpha]_D^{20} = -13.8$ (*c* 1, pyridine), {lit.[18] $[\alpha]_D^{25} = -13.3$ (*c* 1.3, pyridine)}. R_f (40% ethyl acetate/hexane) 0.13; ^{1}H NMR ($CDCl_3$) δ 3.69 (1H, dd, *J* = 6.0, 11.5 Hz,

3-C*H*HOH), 3.79 (1H, dd, *J* = 3.5, 11.5 Hz, 3-CH*H*OH), 4.05–4.11 (1H, m, 2-C*H*OH), 4.41–4.46 (2H, m, part AB of ABX system, 1-CH_2O), 7.43 (2H, dd, *J* = 7.0, 7.0 Hz, *m*-Ph H), 7.56 (1H, t, *J* = 7.0, *p*-Ph H), 8.04 (2H, d, *J* = 7.0, *o*-Ph H); ^{13}C NMR δ 63.5 (3-C), 65.7 (1-C), 70.4 (2-C), 128.4 (*m*-PhCH), 129.5 (*o*-PhCH), 129.7 (PhC), 133.3 (*p*-PhCH), 166.9 (CO).

4.8. General procedure for Mosher's ester preparation

To a stirred solution of alcohol (*R*)-**1c** or (*S*)-**1c** (20 mg, 0.1 mmol), (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (24 mg, 0.106 mmol), and 4-dimethylaminopyridine (2 mg) in dry CH_2Cl_2 (3 mL) was added dropwise a solution of DCC (22 mg, 0.106 mmol) in CH_2Cl_2 (2 mL) at 0 °C under a nitrogen atmosphere and stirred at the same temperature for 30 min. Then the reaction mixture was brought to room temperature and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with saturated aqueous $NaHCO_3$ solution followed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate/hexane (4:96) to give the Mosher's ester in 87% yield.

4.8.1. Mosher's ester of alcohol (*R*)-1c

Colorless oil; ^{1}H NMR ($CDCl_3$) representative signals δ 3.47 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H), 4.47 (1H, dd, *J* = 4.2, 12.2 Hz, 3-C*H*HO), 4.49 (1H, dd, *J* = 5.9, 11.0 Hz, 1-CH*H*O), 4.59 (1H, dd, *J* = 3.5, 11.0 Hz, 1-CH*H*O), 4.76 (1H, dd, *J* = 3.5, 12.2 Hz, 3-CH*H*O), 5.75 (1H, dddd, *J* = 3.5, 3.5, 4.2, 5.9, 2-C*H*O).

4.8.2. Mosher's ester of alcohol (*S*)-1c

Colorless oil; ^{1}H NMR ($CDCl_3$) representative signals δ 3.41 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H), 4.39 (1H, dd, *J* = 4.2, 12.2 Hz, 3-C*H*HO), 4.42 (1H, dd, *J* = 5.9, 11.0 Hz, 1-CH*H*O), 4.54 (1H, dd, *J* = 3.5, 11.0 Hz, 1-CH*H*O), 4.81 (1H, dd, *J* = 3.5, 12.2 Hz, 3-CH*H*O), 5.70 (1H, dddd, *J* = 3.5, 3.5, 4.2, 5.9, 2-C*H*O).

Acknowledgment

This work was financially supported by Università degli Studi di Milano (Fondi FIRST).

References

1. (a) Padmakumari Amma, J.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 468–473; (b) Leurquin, F.; Ozturk, T.; Pilkington, M.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3173–3177; (c) Nacro, K.; Sigano, D. M.; Yan, S.; Nicklaus, M. C.; Pearce, L. L.; Lewin, N. E.; Garfield, S. H.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2001**, *44*, 1892–1904.
2. Aragozzini, F.; Maconi, E.; Potenza, D.; Scolastico, C. *Synthesis* **1989**, 225–227.
3. Balint, J.; Egri, G.; Kolbert, A.; Dianoczky, C.; Fogassy, E.; Novak, L.; Poppe, L. *Tetrahedron: Asymmetry* **1999**, *10*, 4017–4028.
4. Tsujigami, T.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2543–2549.
5. Kato, Y.; Fujiwara, I.; Asano, Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3207–3210.
6. Kato, Y.; Fujiwara, I.; Asano, Y. *J. Mol. Catal. B: Enzym.* **2000**, *9*, 193–200.
7. Xu, J.-H.; Kato, Y.; Asano, Y. *Biotechnol. Bioeng.* **2001**, *73*, 493–499.
8. Baer, E.; Cushing, I. B.; Fischer, H. O. L. *Can. J. Res., B* **1943**, *21*, 119–124.
9. LeCocq, J.; Ballou, C. E. *Biochemistry* **1964**, *3*, 976–980.
10. Caytan, E.; Cherghaoui, Y.; Barril, C.; Jouitteau, C.; Rabiller, C.; Remaud, G. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1622–1624.
11. For a review see: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488.
12. Fondy, T. P.; Pero, R. W.; Karker, K. L.; Ghangas, G. S.; Batzold, F. H. *J. Med. Chem.* **1974**, *17*, 697–702. We used sodium hydride instead of Na metal and have fully characterized the compound by ^{1}H and ^{13}C NMR analysis.
13. Yu, C. C.; Lee, Y.-S.; Cheon, B. S.; Lee, S. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1229–1231.
14. Santaniello, E.; Ciuffreda, P.; Casati, S.; Alessandrini, L.; Repetto, A. *J. Mol. Catal. B: Enzym.* **2006**, *40*, 81–85.
15. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
16. (a) Poon, K. W. C.; Lovell, K. M.; Dresner, K. N.; Datta, A. *J. Org. Chem.* **2008**, *73*, 752–755; (b) Lee, J.-D.; Ueno, M.; Miyajima, Y.; Nakamura, H. *Org. Lett.* **2007**, *9*, 323–326; (c) Katoch, R.; Trivedi, G. K.; Phadke, R. S. *Bioorg. Med. Chem.* **1999**, *7*, 2753–2758.
17. Kato et al. (Refs. 5–7) assigned an (*R*)-configuration to (+)-**1c** referring to the negative specific rotation recorded for (−)-3-*O*-benzyl-*sn*-glycerol by Yodo, M.; Matsushita, Y.; Ohsugi, E.; Harada, H. *Chem. Pharm. Bull.* **1988**, *36*, 902–913. erroneously referring to this compound as to (*S*)-**1c**.
18. Compound (*R*)-**1c** has been prepared by another enzymatic approach; see: Breitgoff, D.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1523–1524. This biocatalytic protocol starts with the asymmetrization of the 1,3-diacetate of 2-benzyloxyglycerol *via* lipase-catalyzed hydrolysis. This allowed the preparation of the corresponding monoacetate (53% conversion, 75% yield of purified product) which was transformed into (*R*)-(−)-**1c** in three additional steps (yields not reported).
19. Sawant, R. T.; Waghmode, S. B. *Tetrahedron* **2010**, *66*, 2010–2014.
20. Noe, C. R.; Knollmüller, M.; Miculka, C.; Dungler, K.; Wagner, E.; Ettmayer, P. *Chem. Ber.* **1994**, *127*, 887–892.