A Chemoenzymatic Synthesis of Enantiomerically Pure (*R*)- and (*S*)-2-Methyldecan-1-ol

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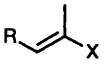
(*R*)- and (*S*)-2-methyldecan-1-ol **3a** has been prepared in >98% enantiomeric excess (ee) by transesterification with vinyl acetate in chloroform in the presence of *Pseudomonas fluorescens* lipase. Oxidation of the alcohol **3a** affords nearly optically pure 2-methyldecanoic acid **3b**.

Enantiomerically pure 2-methylalkan-1-ols **1a** can be useful building blocks for the synthesis of chiral methyl branched compounds, and a few derivatives containing various chemical functions in the structure are available by biocatalytic methods. For example, the hydrogenation of α-methyl α,β-unsaturated aldehydes **2a** or alcohols **2b** mediated by fermenting baker's yeast[1] affords only one stereoisomer of the corresponding saturated alcohol **1a** with good yields of transformation and generally high enantiomeric excess (ee). The enzyme-catalysed esterification of racemic alcohols of type **1a** can afford both enantiomers of the compounds **1a** (40–50% yields).[2]

1

a X = CH_2OH
b X = CO_2H



2

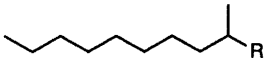
a X = CHO
b X = CH_2OH
c X = $CH(OCH_3)_2$

We have attempted both biocatalytic methods[3,4] and have collected several results, especially using the irreversible lipase-catalysed transesterification of alcohols such as **1a**.[5,6] These results are consistent with a common stereochemical outcome for the reaction for the few functionalized 2-methylalkan-1-ols that we have examined.[7] It should be mentioned that, the synthesis of the corresponding acids **1b**, which are closely related to the alcohols **1a**, seems very attractive, since both compounds can be aroma components of fruits and other foodstuffs, and exhibit different flavours in the pure enantiomeric form.[8] They can also be precious intermediates for the synthesis of insect pheromones and liquid crystals.[9]

We have addressed our investigation towards a chemoenzymatic synthesis of both enantiomers of 2-methyldecan-1-ol **3a**, a useful intermediate for the synthesis of 3,7-dimethylpentadecyl esters, components of the pheromone of pine sawflies.[9c,d]

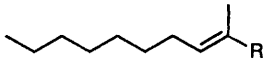
Results and Discussion

Several attempts towards the preparation of enantiomerically pure **3a** have been reported and most of these rely on the synthesis of the corresponding acid **3b** either by relatively unsatisfactory chemical methods of asymmetric introduction of the methyl group[10] or by enzyme-catalysed resolution of racemic **3b**.[11] The direct preparation of both enantiomerically pure (*R*)- and (*S*)-**3a** has not been reported previously and we report here the accomplishment of this enantioselective synthesis. At first, we wanted to prepare only the enantiomer which could be made available by fermenting baker's yeast-mediated hydrogenation of an unsaturated compound, such as **2**. From our experience in the baker's yeast hydrogenation of unsaturated compounds,[3] we learnt that incubation of an acetal **2c** was the best way of carrying out the above biotransformation, since under these conditions the hydrolysis of the acetal group made available slowly the real substrate, namely the unsaturated aldehyde **2a**.



3

a R = CH_2OH
b R = CO_2H
c R = CH_2OCOCH_3
d R = CO_2Et



4

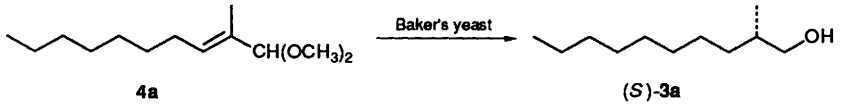
a R = $CH(OCH_3)_2$
b R = CH_2OH
c R = CO_2Et

The acetal **4a**, prepared by a classical Wittig reaction between the ylide of octyltriphenylphosphonium bromide and dimethoxyacetone as an *E*/*Z* mixture (6:4, by ^1H NMR spectroscopy), was incubated with fermenting yeast and reacted completely in 4 days (Scheme 1). By this route, the (*S*)-(−)-2-methyldecan-1-ol **3a** was obtained (70% yield), $[\alpha]_D$ −4 (*c* 2.5, chloroform), corresponding to 48% ee as judged from the 500 MHz ^1H NMR spectrum of its ester with (*S*)-MTPA chloride.[12] The (*S*)-configuration was established for compound **3a** by comparison of the optical rotation with a literature value.[13] After incubation for 2 days, a mixture of unsaturated alcohol **4b** and (*S*)-(−)-**3a** was obtained, but the ee of the desired product was not improved. Working on different substrates and in carefully controlled conditions, better results were obtained by other authors,[14] and we did not investigate any further this microbiological approach which, in any event, could lead only to the (*S*)-isomer. Preliminary attempts to resolve enzymatically the racemic ester **3d** with pig liver esterase, porcine pancreas lipase and chymotripsin afforded the products with only moderate enantioselectivity.† We then studied the resolution of the racemic alcohol **3a** and anticipated that, due to the presence of the saturated long chain, either the racemic alcohol **3a** or its acetate **3c** could be an excellent substrate for a lipase.‡ According to our expectations, in analogy with other α-methyl primary alcohols,[17] the irreversible transesterification with vinyl acetate as acyl donor in the presence of *Pseudomonas fluorescens*§ lipase in organic solvents should lead to the (*R*)-alcohol **3a** and to the (*S*)-acetate **3c**. The racemic alcohol **3a** was conveniently prepared by an unexceptional chemical route,

† A recent study on the resolution of shorter chain α-methyl acids has appeared.[15]

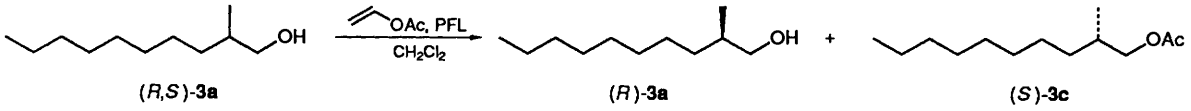
‡ It is well known that most lipases preferentially hydrolyse esters of long chain acids, since triglycerides are their natural substrates.[16]

§ According to recent indications, the previous name of *Pseudomonas fluorescens* should be changed to *Pseudomonas cepacia*.



4a (*S*)-**3a**

Scheme 1



(*R,S*)-**3a** (*R*)-**3a** (*S*)-**3c**

Scheme 2

specifically a Horner–Wittig reaction[18] between octanal and triethyl phosphonopropionate to yield the unsaturated ester **4c** (74% yield), which was quantitatively hydrogenated to the ester **3d**. $LiAlH_4$ reduction of **3d** to the racemic alcohol **3a** (85% yield) afforded the substrate for the enzymatic reaction. According to a well established experimental protocol, the acetylation was performed in dichloromethane and, if carried out towards the formation of 60% of the acetate **3b** the highest ee of the unchanged alcohol (*R*)-(+)-**3a** was obtained (38%, >98% ee, as established by the 500 MHz ^1H NMR spectroscopic analysis of its MTPA ester). If the reaction was stopped at 40% of acetate **3c**, a 98% ee (*S*)-acetate **3c** was obtained (Scheme 2). The optical purity was, in this case, evaluated by comparison of the optical rotation of the above compound with the same derivative obtained by acetylation of nearly optically pure (*R*)-**3a** previously obtained by the enzymatic reaction. Enantiomerically pure (*R*)- or (*S*)-alcohols **3a** could be oxidized in 95% yield to nearly enantiomerically pure (*R*)- and (*S*)-acids **3b** by the Jones reagent,[19] which oxidizes similar compounds with no loss of configurational integrity.[2] In conclusion, we have shown that title compounds **3a** can be obtained enantiomerically pure as both isomers using the PFL-catalysed transesterification procedure. The stereochemical outcome of this reaction is in agreement with those obtained for similar substrates **1a** already studied[7,17] and recently extended also to a special class of epoxy alcohols, *i.e.* oxiranylmethanols.[20] Further studies are in progress, in order to establish the enzyme requirements for other structurally related substrates.

Experimental

PFL was purchased from Fluka (Switzerland) and used without further purification. The IR spectra were recorded on a 1420 Perkin-Elmer spectrometer for solutions in chloroform. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. ^1H NMR spectra, were recorded at 60 MHz on a Varian EM 360 L spectrometer for solutions in $CDCl_3$, using $SiMe_4$ as internal standard. The 500 MHz spectra of the MTPA esters were recorded in $CDCl_3$ on a Brucker AM-500 spectrometer. *J* Values are given in Hz. For the workup of the reactions, at the end of the extractions, the solvent was dried (Na_2SO_4) and removed at reduced pressure. Distillations for analytical purposes were carried out on a glass tube oven Buchi GKR-50. TLC analyses were carried out on silica gel Merck 60 F254 plates and column chromatography was performed on silica gel Merck 60 (230–400 mesh).

2-*Methyldec*-2-*enal Dimethyl Acetal* **4a**.—To a solution in anhydrous tetrahydrofuran (THF) (100 cm^3) of octyltriphenylphosphonium iodide (prepared in 94% yield by refluxing equimolar amounts of triphenylphosphine and 1-iodooctane in anhydrous toluene for 52 h) crystallized from toluene (10.5 g, 21.2 mmol) a solution of butyllithium in THF (1.6 mol dm^{-3}; 16 cm^3) was added under nitrogen at room temp. After 30 min, dimethoxyacetone (2.5 g, 21.2 mmol) in THF (20 cm^3) was added to the red solution, and the solution was kept at the same temperature (18 h). The reaction was quenched by the addition of 1 mol dm^{-3} HCl to neutrality and the solution was concentrated at reduced pressure. Water was added and the products were extracted with dichloromethane (3 × 50 cm^3), which was then dried and evaporated. From the residue (4.2 g), the acetal **4a** (3.3 g, 73%) was obtained by distillation at 110 mmHg; b.p. 180 °C (Found: C, 73.0; H, 12.2. Calc. for $C_{13}H_{26}O_2$: C, 72.9; H, 12.15%); δ_H 0.7–1.1 (3 H, m, CH_3), 1.1–1.6 (10 H, m, CH_2), 1.65 (3 H, *Z* CH_3C=), 1.75 (3 H, s, *E* CH_3C=), 1.90–2.30 (2 H, m, CH_2C=), 3.4 (6 H, s, CH_3O), 4.60 (1 H, s, *Z* CHO), 5.10 (1 H, s, *E* CHO) and 5.4–5.9 (1 H, m, CH=).

Ethyl (R,S)-2-*Methyldec*-2-*enoate* **4c**.—Triethyl phosphonopropionate was prepared by refluxing, at 170 °C (2 h), ethyl 2-bromopropionate (10 g, 55 mmol) and triethylphosphite (9.1 g, 55 mmol). After continued heating at the same temperature for another 2 h without the condenser, the phosphonate (12.7 g) was obtained and used without further purification.

At −60 °C, a solution of the above phosphonate (10.7 g, 45 mmol) in dichloromethane (10 cm^3) was added to a suspension of potassium *tert*-butoxide (5 g, 45 mmol) in dichloromethane (40 cm^3). At the same temperature, a solution of octanal (5.76 g, 45 mmol) in the same solvent (10 cm^3) was added and the reaction was kept, with stirring, at room temp. for 3 h. The solvent was removed and ethyl acetate (30 cm^3) was added to the residue. The organic phase was washed with saturated aqueous ammonium chloride and water, then dried and evaporated. The crude mixture was purified by column chromatography and the fractions eluted with hexane contained pure **4c** (7.1 g, 74%); δ_H 0.7–1.55 (6 H, m, CH_3), 1.15–1.70 (12 H, m, CH_2), 1.95 (3 H, s, CH_3), 2.1–2.65 (2 H, m, CH_2CH=C), 4.40 (2 H, q, CH_2) and 7.05 (1 H, t, CH=). The compound was used directly for the hydrogenation to the saturated ester **3d**.

Ethyl (R,S)-2-*Methyldecanoate* **3d**.—The above unsaturated ester **4c** (4.2 g, 20 mmol) was dissolved in ethyl acetate (45 cm^3), Pd black (0.42 g) was added, and the hydrogenation was carried out at ambient pressure, until the reaction was complete, as judged by ^1H NMR spectroscopy (12 h). The product was recovered by filtration on Celite and evaporation of the solvent (4.1 g, 96%). A sample was distilled at 0.1 mmHg, b.p. 57 °C (Found: C, 73.05; H, 12.25. Calc. for $C_{13}H_{26}O_2$: C, 72.9; H, 12.15%); ν_{max}/cm^{-1} 1740; δ_H 0.7–2.1 (23 H, m, CH_3 and CH_2), 2.20–2.70 (1 H, m, CH) and 4.25 (2 H, q, CH_2O).

(R,S)-2-*Methyldecan*-1-*ol* **3a**.—To a suspension of lithium aluminium hydride (1.4 g, 36.9 mmol) in anhydrous THF (30 cm^3), a solution of the ester **3d** (2.6 g, 12 mmol) in THF (10 cm^3) was added dropwise. After being stirred for 4 h at room temp., water (1.4 cm^3), 15% sodium hydroxide (1.4 cm^3) and water (4.2 cm^3) were sequentially added. The precipitate which formed was removed by filtration on Celite and the crude product was purified by column chromatography. Fractions eluted with hexane–ethyl acetate (9:1) contained pure title

compound **3a** (1.75 g, 85%). The chemico-physical properties were in full agreement with those reported.[9c] For the determination of the ee of the samples of optically active **3a**, prepared by baker's yeast and enzymatic biotransformation, a sample of MTPA ester of (*R,S*)-**3a** was prepared as follows. A solution of (*R,S*)-**3a** (0.03 g, 0.174 mmol) in carbon tetrachloride (0.6 cm^3) was treated with (*S*)-(+)-MTPA chloride (JPS, Switzerland) (0.06 g, 0.24 mmol) in the presence of pyridine (0.6 cm^3). After 18 h, 3-dimethylaminopropan-1-amine (0.041 cm^3) and dichloromethane (1 cm^3) were added and the organic phase was washed with 1 mol dm^{-3} HCl and saturated aqueous sodium carbonate, dried and evaporated. The 500 MHz ^1H NMR spectrum of this sample showed a complex system for the hydrogens corresponded to CH_2O. Specifically, two double doublets centred at δ_H 4.05 and 4.22 (0.5 H, respectively) and a doublet at δ_H 4.13 (1 H) were present.

Baker's Yeast Hydrogenation of Acetal **4a**.—To a solution of sucrose (3.9 g) in water (66 cm^3), commercial baker's yeast (Eridania, Italy, 7.44 g) was added and the mixture was set aside at 30 °C for 1 h, in order to start the fermentation. The acetal **4a** (1 g, 4.67 mmol) was added and the mixture was set aside at 30 °C for 96 h, with vigorous stirring. The reaction was filtered through Celite and the aqueous phase, saturated with NaCl, was extracted with diethyl ether (3 × 100 cm^3). The organic solution was dried and evaporated, leaving a residue which was purified by column chromatography (hexane–ethyl acetate, 8:2). Pure (*S*)-(−)-**3a** was obtained (0.6 g, 75%); $[\alpha]_D$ −4 (*c* 2.5, chloroform) (lit.,[9c] +9.8, for the *R* isomer, neat). The chemico-physical properties were in full agreement with those recorded for the racemic **3a**, reported below. For the ee determination, a sample of the MTPA ester of (*S*)-(−)-**3a** (0.03 g, 0.174 mmol) was prepared as described for (*R,S*)-**3a**. The 500 ^1H NMR spectrum showed the hydrogens corresponding to CH_2O presented as a doublet at δ_H 4.13 (0.26 H) and the two double doublets centred at δ_H 4.05 and 4.22 (0.37 H, respectively). From these integrations, a 48% ee was calculated for (S)-(−)-**3a**.

Enzymatic Transesterification of (R,S)-**3a**.—To a solution of (R,S)-**3a** (0.3 g, 1.74 mmol) in chloroform (3.2 cm^3), vinyl acetate (0.6 cm^3, 0.56 g, 6.5 mmol) and PFL (0.024 g, 31.5 U/mg) were added. The mixture was kept at 30 °C, monitoring the reaction by NMR spectroscopy. When the desired conversion was reached, the enzyme was removed by filtration and the solvent evaporated. The mixture of alcohol (*R*)-**3a** and acetate (*S*)-**3c** was purified by column chromatography (hexane–ethyl acetate, 9:1 for the alcohol and 8:2 for the acetate).

(R)-(+)-2-*Methyldecan*-1-*ol* **3a**. At 60% acetylation (reaction time 4 h), pure (*R*)-(+)-**3a** was obtained (0.114 g, 38%); $[\alpha]_D$ +8.7 (*c* 2.5, chloroform) (lit.,[9c] +9.8, neat). The chemico-physical properties were in full agreement with those recorded for the racemic **3a**. For the ee determination, a sample of (*R*)-(+)-**3a** (0.03 g, 0.174 mmol) was converted into its MTPA ester, as described for (*R,S*)-**3a**. The 500 ^1H NMR spectrum showed only a broad doublet at δ_H 4.13 for the two hydrogens of CH_2O and the ee of the enzymatically prepared sample was therefore >98%.

(S)-(−)-*Acetate* **3c**. At 40% acetylation (reaction time, 1 h), pure (*S*)-(−)-**3c** was obtained (0.145 g, 39%); $[\alpha]_D$ −1.1 (*c* 2.5, chloroform); ν_{max}/cm^{-1} 1730; δ_H 0.85–1.15 (6 H, m, CH_3), 1.15–2.0 (15 H, m, CH_2 and CH), 2.1 (3 H, s, $COCH_3$) and 4.0 (2 H, d, CH_2O). The value of the optical rotation for the (*R*)-(+)-**3c** obtained by acetylation of the previously prepared (*R*)-(+)-**3a** was +1.1 under the same conditions as above.

(R)-(−)-2-*Methyldecanoic Acid* **3b**.—To a solution of (*R*)-(+)-**3a** (0.3 g, 17.4 mmol) in acetone (5 cm^3) at 0–5 °C, a freshly prepared Jones' solution was added at room temp. When the orange colour remained, propan-2-ol was added until the solution became green. This solution was filtered through Celite and the acetone was evaporated. The residue was distilled at 0.5 mmHg, b.p. 110 °C (Found: C, 80.05; H, 11.95. Calc. for $C_{11}H_{22}O_2$: C, 70.97, H, 11.83%). The chemico-physical properties were in agreement with those reported in Ref. 9*d*; $[\alpha]_D$ −10.5 (*c* 2.5, chloroform) [lit.,[9c] for optically pure (*S*)-(+)-**3b**, +15.5, neat].

Acknowledgements

We thank Ministero dell'Università e Ricerca Scientifica e Tecnologica (MURST) for financial support. Many thanks are due to Mr. Carlo Cavarretta and Miss Elisa Verza for technical assistance.

References

1 C. Fuganti, P. Grasselli, S. Servi and H. E. Högberg, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3061.
2 P. E. Sonnet, *J. Org. Chem.*, 1987, **52**, 3477.
3 P. Ferraboschi, R. Casati, P. Grisenti, A. Fiecchi and E. Santaniello, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1743.
4 P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello, *J. Org. Chem.*, 1990, **55**, 6214.
5 M. Degueil-Castaing, B. De Jeso, S. Drouillard and B. Maillard, *Tetrahedron Lett.*, 1987, **28**, 953.
6 Y. F. Wang, J. J. Lalonde, M. Momongan, D. E. Bergbreiter and C.-H. Wong, *J. Am. Chem. Soc.*, 1988, **110**, 7200.
7 P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello, *Bioorganic Chemistry in Healthcare and Technology*, eds., U.K. Pandit and F. C. Alderweireldt, NATO ASI Series, Vol. 207, Plenum, New York, 1991, p. 245.
8 K. Rettinger, C. Burschka, P. Scheeben, H. Fuchs and A. Mosandl, *Tetrahedron Asymmetry*, 1991, **2**, 965.
9 (*a*) T. Hirai, K. Furuhashi, A. Yoshizawa, I. Nishiyama and M. Fukumasa, *Jpn. Kokai Tokkyo Koho, JP 62,243,058, Chem. Abstr.*, 1989, **111**, 23095j; (*b*) K. Furuhashi, *Jpn. Kokai Tokkyo Koho, JP* 1,100,138, *Chem. Abstr.*, 1989, **111**, 232077u; (*c*), S. Byström, H.-E. Högberg and T. Norin, *Tetrahedron*, 1981, **37**, 2249; (*d*) H.-E. Högberg, E. Hedenström, A.-B. Wassgren, G. Bergström, J. Löfqvist and T. Norin, *Tetrahedron*, 1981, **46**, 3007; (*e*) E. Zeeck, J. D. Hardege, H. Bartels-Hardege and G. Wesselmann, *Tetrahedron Lett.*, 1991, **31**, 5613.
10 (*a*) L. Guoqiang, M. Hjalmarsson, H.-E. Högberg, K. Jernstedt and T. Norin, *Acta Chem. Scand., Ser. B*, 1984, **38**, 796; Y. Petit, C. Sanner and M. Larcheveque, *Tetrahedron Lett.*, 1990, **31**, 2149.
11 H. Holmberg, M. Holmquist, E. Hedenström, P. Berglund, T. Norin, H.-E. Högberg and K. Hult, *Appl. Microbiol. Biotechnol.*, 1991, **35**, 572.
12 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
13 D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.
14 H.-E. Högberg, E. Hedenström, J. Fägerhag and S. Servi, *J. Org. Chem.*, in the press. We thank Prof. Servi for a preview of his manuscript.
15 K.-H. Engel, Tetrahedron Asymmetry, 1991, **2**, 165.
16 *Lipases*, eds., B. Borgstroem, H. L. Brockman, Elsevier, Amsterdam, 1984.
17 (*a*) P. Ferraboschi, P. Grisenti and E. Santaniello, *Synlett*, 1990, 545; (*b*) P. Ferraboschi, D. Brembilla, P. Grisenti and E. Santaniello, *Synlett*, 1991, 310.
18 For a review on the Horner–Wittig reaction, see: J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74**, 87.
19 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*; Wiley: New York, 1967; vol. 1, p. 142.
20 P. Ferraboschi, D. Brembilla, P. Grisenti and E. Santaniello, *J. Org. Chem.*, 1991, **56**, 5478.

Paper 1/06357J
Received 19*th December* 1991
Accepted 10*th February* 1992