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Lipase catalysed resolution of (*R*)- and (*S*)-1-trimethylsilyl-1-alkyn-3-ols: useful intermediates for the synthesis of optically active γ-lactones

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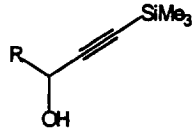
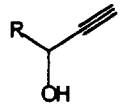
Abstract: Various (*R*)- and (*S*)-1-trimethylsilyl-1-alkyn-3-ols, chiral building units useful for the synthesis of biologically active compounds, have been efficiently resolved by enantioselective acetylation mediated by immobilized lipase PS. The resolution is applied to the synthesis of (*R*)- and (*S*)-5-octyl-2-(5H)-furanones. © 1997, Elsevier Science Ltd. All rights reserved.

Optically active 1-trimethylsilyl-1-alkyn-3-ols **1** or 1-alkyn-3-ols **2** are of synthetic value as precursors of many biologically active natural products.[1] In fact, by carboxylation of alkynols **2** (*Z*)-4-hydroxy-2-alkenyl acids are obtained, which are key intermediates in the total synthesis of such naturally occurring compounds as unsaturated or saturated lactones and bislactones,[2] leucotrienes, prostaglandins, vitamin E and steroids.[3]



1



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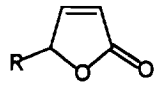

3

For preparing enantiomerically enriched alkynols **1** and **2**, various approaches have been reported including enantioface-differentiating addition of lithium acetylide to aliphatic aldehydes in the presence of a chiral ligand,[4] chemical reduction with chiral reducing agents,[5a–d] enzymatic reduction of the corresponding ketone[6] and resolution of the acetates by fermenting *Bacillus subtilis*[7] or by lyophilized cells of baker's yeast.[8] However, many of these approaches are not completely satisfactory because of low or moderate chemical yields and/or enantiomeric excess, unavailability of both enantiomers, high substrate specificity or other restrictions that limit their application. On the other hand attempted enantioselective hydrolysis of the carboxylic esters of alcohols **2**, mediated by lipase (from *Candida cylindracea*, *Pseudomonas sp.* and *Mucor sp.*) failed to discriminate[8a] between enantiomers or showed unsatisfactory enantioselection.[9] Lipases are more effective in the asymmetric hydrolysis of some acyl derivatives of 1-trimethylsilyl-1-alkyn-3-ols **1**, even if the utility of the reaction is strictly dependent on the nature of the acyl group. In fact good results were obtained in the hydrolysis of 3-propionyloxy-1-trimethylsilyl-1-octyne, mediated by Porcine Pancreatic Lipase (E^{10}=13) or by Lipase Amano PS (E=63),[9a] while the corresponding acetate was resolved only with moderate enantioselectivity (E=5.3). Finally the possibility of efficiently obtaining alkynols **1** by lipase catalysed transesterification appeared limited to only 4-trimethylsilyl-3-butyn-2-ol, having a small (methyl) and a relatively large substituent at the hydroxymethine carbon.[11]

For these reasons, when we needed to prepare and test some enantiomerically pure unsaturated lactones **3** as possible new Michael acceptors able to induce the synthesis of heat shock proteins in

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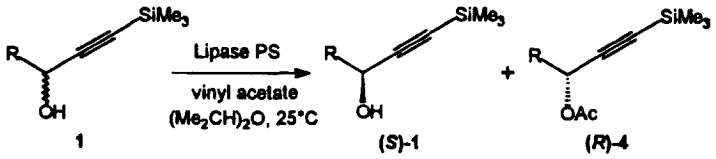
Table 1. Enzymatic resolution of racemates **1a–h**



1 (*S*)-**1** (*R*)-**4**

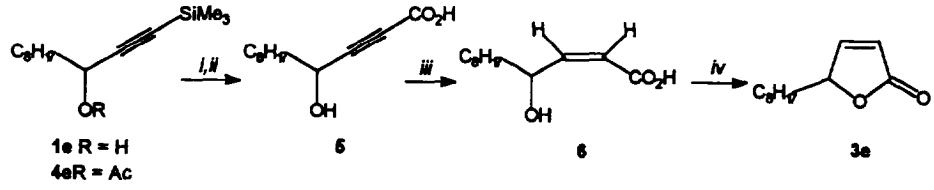
a: R = C_2H_5 **e**: R = C_8H_{17}
b: R = Me_2CHCH_2 **f**: R = $C_{11}H_{23}$
c: R = C_5H_{11} **g**: R = $C_{13}H_{27}$
d: R = $C_3H_7CH{=}CH$ **h**: R = C_6H_5

R	conv (%)[a] (time, h)	(*S*)-**1** ee %[b] (yield, %)[c]	(*R*)-**4** ee %[d] (yield, %)[c]	E
a	28 (15)	36 (71)	92 (24)	40
	51 (20)	89 (45)	85 (46)	
b	30 (20)	40 (68)	94 (25)	50
	49 (300)	87 (46)	90 (42)	
c	30 (16)	42 (67)	97 (26)	>100
	52 (300)	>98 (44)	92 (47)	
d	39 (48)	59 (58)	90 (35)	50
	54 (300)	98 (41)	81 (50)	
e	37 (16)	57 (59)	96 (34)	>100
	51 (260)	>98 (46)	94 (48)	
f	30 (14)	42 (66)	97 (25)	>100
	52 (240)	>98 (47)	91 (49)	
g	36 (16)	55 (60)	96 (31)	>100
	51 (250)	>98 (45)	93 (48)	
h	41 (90)	55 (56)	80 (36) S	16
	51 (320)	78 (45)	73 (46)	

[a] Determined by GLC after silylation of the reaction mixture. [b] Enantiomeric excess were determined by ^{1}H-NMR analysis of the Mosher esters. [c] After flash chromatography. [d] Enantiomeric excess were determined by ^{1}H-NMR using 0.2-0.4 equiv of Eu(hcf)$_3$ and by GLC an a chiral column for the compound (*S*)-**1d**, (*R*)-**4a** and (*R*)-**4b**.

cells,[12] we searched for a new and efficient enzymatic resolution of 1-trimethylsilyl-1-alkyn-3-ols **1** which, in enantiomerically pure form, were useful starting material for obtaining the desired lactones.

As a result, in the present paper we describe an excellent[13] biocatalytic resolution, mediated by immobilized lipase PS,[14] of seven 1-trimethylsilyl-1-alkyn-3-ols (**1a–g**, Table 1) with alkyl chains of various lengths. Many of the alkynols are obtained in an enantiomerically enriched form suitable for the preparation of (*R*)- and (*S*)-5-alkyl-2-(5H)-furanones **3** of high enantiomeric purity here exemplified by the preparation of both (*R*)- and (*S*)- enantiomers of **3e** (Scheme 1).



(i): K_2CO_3, MeOH/H_2O, rt, 2h. *(ii)*: nBuLi, THF, -40°C, then CO_2. *(iii)*: H_2, Lindlar, quinoline, MeOH. *(iv)*: CF_3CO_2H.

Scheme 1.

Results and discussion

Eight racemic 1-trimethylsilyl-1-alkyn-3-ols **1a–h** with alkyl or aryl chains of different lengths, prepared by reaction of trimethylsilyl acetylide with the appropriate aldehyde, were selected in order to explore their possible lipase catalysed resolution, the scope and the limitations of the process. Preliminary experiments were performed in order to screen enzymes, solvents, acylating agents and to optimise other reaction conditions. With this aim, the enantioselective transesterification of 1-trimethylsilyl-1-undecyn-3-ol **1e** was carried out in the presence of six commercial lipases,[14] using vinyl acetate or trifluoroethyl butyrate as acyl donors and diisopropyl ether or *tert*-butylmethyl ether as solvents. In these experiments, it was observed that lipase from porcine pancreas (PPL), lipase from *Candida cylindracea* and lipase from *Candida antarctica* were completely inactive, lipase from *Pseudomonas fluorescens* showed high selectivity (E >30) but poor activity, while free and immobilized[15] Lipase PS were able to catalyse the transesterification with higher and comparable enantioselectivity (E >30). Since supported lipase PS was much more active than the free enzyme, it was selected and tested for the catalysis of the enantioselective transesterification of the other substrates, using vinyl acetate and diisopropyl ether in combination with the enzyme. The results obtained show that the enantioselectivity of the reactions is always excellent for all substrates having an aliphatic chain bonded to the hydroxymethyne centre, independent of its length (Table 1). In fact, the lipase catalysed resolutions of the racemic 1-trimethylsilyl-1-alkyn-3-ols **1a–g** yield the acetylated (*R*)-compounds in enantiomeric excesses often suitable for their use in the enantioselective synthesis of natural products.

Similarly unreacted (*S*)-alcohols were obtained with high enantiomeric excess when the extent of conversion was allowed to proceed a little over 50%.[10] However, the presence of an aryl substituent on the hydroxymethine centre as in **1h** resulted in a significant decrease in the enantioselectivity of the reaction (E=16). The favourable results obtained in the enantioselective transesterification of the alcohols **1a–g**, prompted us to test the possibility of using the same enzyme for the reverse reaction, the enantioselective hydrolysis of the acetates. Thus we found that the enzymatic hydrolysis of the racemic acetates **4c** and **4e** in a phosphate buffer afforded the (*R*)-alcohols with excellent enantioselection (E >30).

The enantiomeric excesses and the absolute configuration of the (*S*)-1-trimethylsilyl-1-alkyn-3-ols **1a–g** were determined by ^{1}H-NMR analysis of their (*R*)- and (*S*)-Mosher esters,[16] while the enantiomeric excess of the acetates (*R*)-**4a–h** were evaluated by ^{1}H-NMR using Eu(hcf)$_3$.[17] For the compounds (*S*)-**1d**, (*R*)-**4a** and (*R*)-**4b** (see Experimental section) the enantiomeric excesses were also evaluated by GLC analysis on a chiral column. In the case of the aromatic compound **1h** the absolute configuration was also confirmed by ^{1}H-NMR analysis of the (*R*)- and (*S*)-Mosher esters of the corresponding alcohols **2h**, prepared in order to have a diagnostic proton near to the stereogenic center.[18]

The utility of the above results was then demonstrated in the synthesis of (*R*)- and (*S*)-5-octyl-2-(5H)-furanones **3e** of high enantiomeric purity (Scheme 1) starting with the acetate (*R*)-**4e** and the

alcohol (*S*)-**1e**. Each of them was separately treated with methanolic potassium carbonate which caused the elimination of the silyl group and, in the case of **4e**, the simultaneous saponification of the acetoxy group. The obtained alkynols were then transformed, according to a known reaction sequence,[4,19] into the lactones **3e** without loss of stereochemical integrity; in fact the final lactones were obtained with the same enantiomeric excess as the starting materials. The route includes the carboxylation of the terminal acetylenic carbon, the hydrogenation on Lindlar catalyst of the formed acetylenic acid **5** and a brief exposure to acid to accelerate the lactonization.

Thus we may conclude that 1-trimethylsilyl-1-alkyn-3-ols can be obtained, by biochemical kinetic resolution, with an enantiomeric enrichment suitable for the synthesis of enantiomerically pure natural products.

Experimental section

The ^{1}H-NMR spectra (500.13 MHz) were recorded in $CDCl_3$ at 303 K and were referenced to $CHCl_3$ at 7.24 ppm. HPLC analyses were carried out on a Merck superspher 100 RP-18 column, 4 mm×25 cm, with a flow rate of 1 mL/min and a detection performed at 241 nm. Optical rotations were measured for 1% $CHCl_3$ solutions if not otherwise reported. TLC was carried out on silica gel 60 F_{254} microplates. Column chromatography refers to flash chromatography.[20] (*S*)- and (*R*)-α-Methoxy-α-trifluoromethylphenyl acetates [(*S*)- and (*R*)-MTPA] were prepared from the appropriate (*R*)- and (*S*)-MTPA chlorides.[16] All organic solvents were dried before use. Usual workup refers to washing the organic layer with water, drying it over Na_2SO_4, and evaporating the solvent under reduced pressure. The progress of all reactions, the column chromatography and compound purity were monitored by GLC, TLC and/or HPLC. Chiral GLC analyses were performed on dimethylpentylcyclodextrin-β column (50 m, 0.25 mm ID, film thickness 0.25 μm, Mega). The 1-trimethylsilyl-1-alkyn-3-ols **1a–h** were prepared (with the reported yields) on a 2 mmol scale according to G. Traverso *et al.*[21] and, after rapid chromatography (eluting with hexane–ethyl acetate, 95:5, v:v), showed the following properties.

1-Trimethylsilyl-1-pentyn-3-ol **1a**; (76% yield): an oil. ^{1}H-NMR δ 4.28 (1H, dt, J 4.9, 6.3 Hz, H-3). Anal. Calcd for $C_8H_{16}OSi$: C, 61.49; H, 10.32. Found: C, 61.41; H, 10.27.

1-Trimethylsilyl-5-methyl-1-hexyn-3-ol **1b**; (87% yield): an oil. ^{1}H-NMR δ 4.35 (1H, dt, J 5.6, 7.0 Hz, H-3). Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94. Found: C, 65.27; H, 10.79.

1-Trimethylsilyl-1-octyn-3-ol **1c**; (86% yield): an oil. ^{1}H-NMR δ 4.33 (1H, dt, J 5.6, 6.3 Hz, H-3). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.53; H, 11.26.

(*E*)-1-Trimethylsilyl-4-octen-1-yn-3-ol **1d**; (87% yield): an oil. ^{1}H-NMR δ 5.86 (1H, dt, J 7.0, 14.7 Hz, H-5), 5.57 (1H, dd, J 5.6, 14.7, H-4), 4.80 (1H, dd, J 4.9, 5.6 Hz, H-3). Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28; H, 10.27. Found: C, 67.39; H, 10.34.

1-Trimethylsilyl-1-undecyn-3-ol **1e**; (85% yield): an oil. ^{1}H-NMR δ 4.33 (1H, dt, J 5.6, 6.3 Hz, H-3). Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 69.84; H, 11.81.

1-Trimethylsilyl-1-tetradecyn-3-ol **1f**; (87% yield): an oil. ^{1}H-NMR δ 4.33 (1H, dt, J 6.3, 7.0 Hz, H-3). Anal. Calcd for $C_{17}H_{34}OSi$: C, 72.27; H, 12.13. Found: C, 72.18; H, 12.25.

1-Trimethylsilyl-1-esadecyn-3-ol **1g**; (78% yield): an oil. ^{1}H-NMR δ 4.32 (1H, dt, J 5.6, 6.3 Hz, H-3). Anal. Calcd for $C_{19}H_{38}OSi$: C, 73.47; H, 12.33. Found: C, 73.39; H, 12.37.

3-Trimethylsilyl-1-phenylpropyn-1-ol **1h**; (75% yield; eluted with hexane–ethyl acetate 20:80, v:v): an oil. ^{1}H-NMR δ 5.44 (1H, d, J 6.3 Hz, H-1). Anal. Calcd for $C_{12}H_{16}OSi$: C, 70.53; H, 7.89. Found: C, 70.85; H, 7.62.

*Lipase-mediated acylation of racemic 1-trimethylsilyl-1-alkyn-3-ols (**1a–h**) in organic solvents. General procedure*

Vinyl acetate (2 mmol) and immobilized Lipase PS (250 mg; 30% on Hyflo Super Cell) were added to a solution of each racemic 1-trimethylsilyl-1-alkyn-3-ol (**1a–h**; 1 mmol) in diisopropyl ether (10 mL). The resulting suspension was then shaken at 25°C and monitored by GLC, after silylation (pyridine–trimethylchlorosilane–hexamethyldisilazane, 10:4:2, v:v:v, rt, 1 h) of the hydroxy group of

the unreacted alcohol. The final conversion extent was however established by ^{1}H-NMR analysis of the isolated crude mixture. When the desired conversion was reached, the enzyme was recovered by filtration and the solvent was evaporated under reduced pressure. The unreacted alcohols (*S*)-**1a–h** and the acetate (*R*)-**4a–h** were then separated by flash chromatography, eluting with hexane–ethyl acetate (100:5; v:v), and were obtained with the yields and the enantiomeric excess shown in Table 1. When the reactions were stopped at a conversion higher than 50% (see Table 1), the unreacted (*S*)-alcohols **1a–h** (purity >98% by GLC after silylation) showed correct physicochemical properties, identical to those observed for their racemates, and the following optical rotations: $[\alpha]_D^{25}$ −4.1 for (*S*)-**1a**, −10.2 for (*S*)-**1b**, −1.8 for (*S*)-**1c**, +38.5 for (*S*)-**1d**, +1.1 for (*S*)-**1e**, +1.2 for (*S*)-**1f**, +2.4 for (*S*)-**1g**, −13.3 for (*S*)-**1h**.

Similarly when the reactions were terminated at the conversions lower than 50% (see Table 1), the acetates (*R*)-**4a–h** showed ^{1}H-NMR spectra with appropriate proton signals and the following optical rotations: $[\alpha]_D^{25}$ +123.3 for (*R*)-**4a**, +77.6 for (*R*)-**4b**, +86.8 for (*R*)-**4c**, −13.9 for (*R*)-**4d**, +71.4 for (*R*)-**4e**, +67.7 for (*R*)-**4f**, +63.8 for (*R*)-**4g**, +28.6 for (*R*)-**4h**.

*Lipase-mediated hydrolysis of racemic 1-trimethylsilyl-1-alkyn-3-ol acetates (**4c** and **4e**). General procedure*

Lipase PS (75 mg) and each racemic 1-trimethylsilyl-1-alkyn-3-ol acetate (**4c** and **4e**; 0.5 mmol) dissolved in acetone (0.5 ml) were shaken at 25°C in phosphate buffer (5 mL; 0.1 M; pH 7) and the reaction was monitored by GLC, after the derivatization described above for the transesterification procedure. After about 150 h a satisfactory hydrolysis was reached in both cases and the mixture was extracted and worked up to afford respectively the alcohol (*R*)-**1c** (conv. 50%; ee 90%; 45% yield; $[\alpha]_D^{25}$ −1.3) and (*R*)-**1e** (conv. 51%; ee 94%; 45% yield; $[\alpha]_D^{25}$ −1.0).

*Synthesis of (*R*)- and (*S*)-5-octyl-2-(5H)-furanones [(*R*)- and (*S*)-**3e**]*

i) Desilylation. (*S*)-1-Trimethylsilyl-1-undecyn-3-ol [(*S*)-**1e**; 315 mg; 1.3 mmol] was dissolved in a saturated solution of K_2CO_3 in moist methanol (15 mL containing 1 mL of H_2O) and stirred at room temperature for 2 h. The solvent then was evaporated under reduced pressure, the residue was recovered with diethyl ether and worked-up to afford crude (*S*)-1-undecyn-3-ol (96% yield). A sample was purified by rapid chromatography and showed $[\alpha]_D^{25}$ −10.1 (dioxane, *c* 2).[8a] The crude compound was then used for the successive carboxylation without purification. The enantiomeric (*R*)-alkynol was obtained (95% yield) by reacting in similar conditions the 3-acetoxy-1-trimethylsilyl-1-undecyne [(*R*)-**4e**] and the purified sample showed $[\alpha]_D^{25}$ +9.9 (dioxane, *c* 2).[19]

ii) Carboxylation. To a stirred solution of the (*S*)-1-undecyn-3-ol (186 mg; 1.1 mmol) in THF (5 mL), *n*-BuLi (1.65 mL of a 1.6 M solution in hexane; 2.64 mmol) was added dropwise at −40°C and, after 0.5 h, CO_2 was bubbled for 1 h. The mixture was then treated with a saturated cold aqueous solution of NaCl and extracted with hexane. The aqueous solution was then acidified to pH 3 by addition of cold diluted HCl and extracted with diethyl ether to afford, after usual work-up, the crude (*S*)-4-hydroxy-2-dodecynoic acid [(*S*)-**5**] which was used for the next reaction without purification. A sample was purified from pentanoic acid contaminant by rapid chromatography and showed: m.p. 78°C; $[\alpha]_D^{25}$ −13.0 (dioxane, *c* 2); ^{1}H-NMR δ 5.70 (2H, broad signal, -COO*H* and O*H*), 4.51 (1H, t, J 7.5 Hz, H-4), 1.75 (2H, m, H_2-5), 1.44 (2H, m, H_2-6), 1.27 (10H, m, 5×CH_2), 0.86 (3H, t, J 7.5 Hz, H_3-12).

Starting from (*R*)-3-hydroxyundec-1-yne the enantiomeric (*R*)-**5** was obtained. A purified sample showed: m.p. 78°C; $[\alpha]_D^{25}$ +12.7 (dioxane, *c* 2).[19] The crude product was then directly reached.

iii) Hydrogenation and lactonization. The above crude acid (*S*)-**5** (190 mg) was hydrogenated in methanol (30 mL) under a hydrogen atmosphere in the presence of Lindlar catalyst (50 mg) and pure quinoline (10 μL). After filtration of the catalyst, the solution was evaporated under reduced pressure to leave a crude hydroxyacid (*S*)-**6** which was treated with trifluoroacetic acid (10 μL) in dichloromethane (2 mL) at room temperature for 10 min. After usual work-up, the crude compound

was purified by distillation under reduced pressure to afford the (*S*)-5-octyl-2-(5H)-furanone [(*S*)-**3e**]: b.p. 100°C (Buchi GKR-50, 0.2 mmHg); $[\alpha]_D^{25}$: +76.2 (dioxane, *c* 2); ^{1}H-NMR δ 7.62 (1H, dd, J 6.1, 1.5 Hz, H-4), 6.24 (1H, dd, J 6.1, 2.3 Hz, H-3), 5.20 (1H, dddd, J 6.9, 6.9, 2.3, 1.5 Hz, H-5), 0.88 (5H, t, J 7.3 Hz, CH_3-).

A similar reaction sequence afforded the (*R*)-5-octyl-2-(5H)-furanone [(*R*)-**3e**]: $[\alpha]_D^{25}$ −73.3 (dioxane, *c* 2).[19]

Acknowledgements

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13. We accept the suggestion of Professor K. Faber to refer an excellent enantiomeric ratio (E) greater than 30 (see ref. 1a, p. 34).
14. Tested lipases were described as follows: lipase from *Pseudomonas sp.* (SAM-II, Amano), lipase from *Pseudomonas fluorescens* (Sam-2, Fluka), lipase from *Candida cylindracea* (CCL, type VII, SIGMA), lipase from *Candida antarctica* SP 435 L (LCA, immobilized on a macroporous acrylic resin, Novo Nordisk, Denmark), lipase from *porcine pancreas* (PPL, type II, crude SIGMA), lipase from *Pseudomonas cepacia* (Lipase PS, Amano), Lipase PS was also immobilized on Hyflo Super Cell according to reference 15.
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18. It is important to consider that due to inversion of the priority between the phenyl and the ethynyl group in the compounds **1h** and **2h** the silylated compound (*S*)-**1h** affords the unsilylated compound (*R*)-**2h** and (*R*)-**1h** affords (*S*)-**2h**. This consideration clarifies the apparent contrast between our

and the reported rotatory value for the alcohol (*S*)-**1h** (Giacomelli, G.; Lardicci, L.; Palla, F. *J. Org. Chem.*, **1984**, *49*, 310).
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