Pergamon

Tetrahedron Letters 43 (2002) 6267–6270

TETRAHEDRON LETTERS

Convenient enantioselective synthesis of new 1,4-sulfanylalcohols from γ-lactones

Jean-Jacques Filippi, Xavier Fernandez, Louisette Lizzani-Cuvelier* and André-Michel Loiseau

Laboratoire Arômes Synthèses Interactions, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice Cedex 2, France

Received 6 June 2002; accepted 25 June 2002

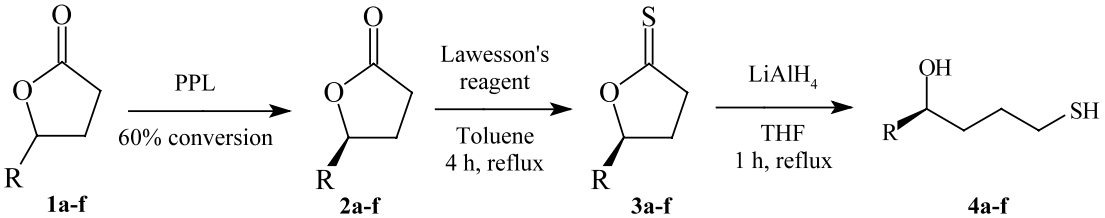
Abstract—A synthetic strategy based upon three basic reactions—enzymatic resolution, oxygen–sulfur exchange, reduction—allowed us to carry out an easy and useful synthesis of a series of new 1,4-sulfanylalcohols from aliphatic γ-lactones. Final products have been obtained in good yields with enantiomeric excesses in a 66–91% range.

In the last few years, sulfanylalcohols have forged ahead in flavour chemistry. Since their identification in fruits and vegetables, they have been the subject of intense research for many flavourists.[1] This class of organosulfur compounds, generally found within a unique stereomeric form in natural products, presents both various odours and low thresholds.[2] Moreover, they are thought to be the precursors of many natural compounds known for their contribution to food aromas and their application in flavour chemistry. For example, 3(*S*)-sulfanylhexanol[3] identified in yellow passion-fruit and guava, gives rise to 3(*S*)-methylthiohexanol,[3] 2(*R*)-methyl-4(*S*)-propyl-1,3-oxathiane[4] and 3(*S*)-propyl-γ-sultine.[5]

Even though 1,3-sulfanylalcohols have already been extensively investigated,[2,6] 1,4-sulfanylalcohols, and particularly their stereoselective synthesis have, to our knowledge, been reported in few cases. The preparation of 1,4-sulfanylalcohols is usually carried out using nucleophilic sulfur reagents and leads to racemic mixtures.[7] Recently, Schellenberg et al.[8] have reported the synthesis of enantiomerically pure 1,4-sulfanylalcohols: the racemic compounds resulting from reduction of γ-thiolactones were derivatised with a chiral auxiliary in order to separate the stereomers by means of semi-preparative HPLC.

Herein, we describe the first enantioselective synthesis of new 1,4-sulfanylalcohols from aliphatic γ-lactones.

The first step consisted in the enzymatic resolution of γ-lactones **1a–f** using porcine pancreatic lipase (PPL). The enantiomerically enriched γ-lactones **2a–f** were



	R		R
a	Me	**d**	*n*-Bu
b	Et	**e**	*n*-Pent
c	*n*-Pr	**f**	*n*-Hex

Scheme 1. Synthesis of 1,4-sulfanylalcohols.

Keywords: 1,4-sulfanylalcohols; γ-lactones; enzymatic resolution; thionation reaction; reduction.

* Corresponding author. Fax: +33(0)492076517; e-mail: cuvelier@unice.fr

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01268-6

submitted to a thionation reaction to give the corresponding γ-thionolactones **3a**–**f**. A subsequent $LiAlH_4$ reduction of **3a**–**f** afforded the expected 1,4-sulfanylalcohols **4a**–**f** (Scheme 1). All results are reported in Table 1.

PPL offers many possibilities to afford enantiomerically enriched γ-lactones by enantioselective lactonisation of the corresponding γ-hydroxyesters[9] and enantioselective hydrolysis of racemic lactones.[10a] Since the crude enzyme is a very useful and inexpensive material, we have selected that method to obtain optically active γ-lactones.

Although PPL presents a better affinity towards the (*S*)-enantiomers of the γ-lactones,[9,10a] the resolution needs to be carried out with more than 50% conversion as described in previous reports.[10] A 60% conversion was set for all the performed enzymatic resolutions. However, the solubility of the γ-lactones in an aqueous medium depends on the length of their alkyl chain. Small and hydrophilic γ-lactones (**1a**–**c**) were submitted to the PPL hydrolysis in a phosphate buffer[10a] (pH 7.2, $T=20°C$) with a mixture of organic solvents (hexane/Et_2O; 2/1) to complete the resolution. On the other hand, γ-lactones substituted by an aliphatic side chain longer than *n*-propyl (R ≥ Bu, **1d**–**f**, entries 9–14) presented a strong insolubility in water and tended to form hydrophobic aggregates, involving a dramatic decrease of yields. Carrying out the resolution at pH 7.6 and using calcium chloride[10a] induced a better precipitation of the formed enzyme inhibiting γ-hydroxyacid as a calcium salt. Moreover, an emulsifier such as gum arabic was added (2% water solution) and allowed the reaction to reach the expected conversion.

Under these applied conditions, the PPL enantioselectivity (*E*)[11,12] which is maximum in the case of γ-heptalactone **1c** ($E=12.4$, ee 91%, entry 5), tended to decrease when the length of the side chain increased. Enantiomeric excesses, in a 26–91% range, were determined by enantioselective gas chromatography.[13]

In order to achieve an oxygen–sulfur exchange, Lawesson's reagent (L.R.)[14] was used to afford selectively the

Table 1.

Entry	1	2						3			4	
	Starting	Resolution conditions	Yield[a] (%)	Conversion (%)	ee[b] (%)	*E*[c]	Abs. config.[d]	Yield[e] (%)	ee[b] (%)	Abs. config.[d]	Yield[e] (%)	ee[f] (%)
1	**a**	A: PPL 10 g, 9 days	75	61	78	6.7	*R*	65	79	*R*	85	79
2	**a**	B: PPL 10 g, 7 days	67	62	44	2.6	*R*	–	–	–	–	–
3	**b**	A: PPL 10 g, 6 days	82	60	85	9.3	*R*	85	85	*R*	88	85
4	**b**	B: PPL 10 g, 8 days	85	60	84	9.0	*R*	–	–	–	–	–
5	**c**	A: PPL 10 g, 5 days	85	60	91	12.4	*R*	89	91	*R*	93	91
6	**c**	B: PPL 10 g, 2 days	94	60	78	7.2	*R*	91	78	*R*	–	–
7	**c**	B: PPL 15 g, 2 days	90	60	89	11.2	*R*	87	89	*R*	–	–
8	**d**	A: PPL 10 g, 5 days	45	63	26	1.7	*R*	–	–	–	–	–
9	**d**	B: PPL 10 g, 6 days	62	64	74	5.1	*R*	–	–	–	–	–
10	**d**	C: PPL 10 g, 2 days	83	60	82	8.3	*R*	93	82	*R*	84	82
11	**e**	B: PPL 10 g, 9 days	65	60	71	5.7	*R*	82	71	*R*	92	71
12	**e**	C: PPL 10 g, 9 days	83	52	54	5.0	*R*	–	–	–	–	–
13	**f**	B: PPL 10 g, 10 days	75	53	34	2.5	*R*	–	–	–	–	–
14	**f**	C: PPL 10 g, 8 days	79	61	66	4.7	*R*	80	66	*R*	80	66

A: Na_2HPO_4/hexane/Et_2O; B: $CaCl_2$ aq. 10%; C: $CaCl_2$ aq. 3.5%/gum arabic 2%.

[a] Calculated from the isolated and purified compound according to the reached conversion.

[b] Determined by enantioselective GC.[13]

[c] Enantioselectivity[11,12] of the enzyme calculated from conversion and ee values.

[d] In agreement with literature reports.[10a,15a]

[e] Calculated from the isolated and purified compound.

[f] Determined by enantioselective GC after derivatisation into 2,2-dimethyloxathiepanes.[13]

expected γ-thionolactones[15] **3a–f** in good yields (65–91%). Thionation of optically active γ-lactones **2a–f**, in toluene, requires exclusively the use of half an equivalent of L.R. to avoid the formation of γ-dithiolactones as side-products. Enantioselective GC enabled us to note that both enantiomeric excesses (66–91%) and initial absolute configuration (*R*) of the optically active γ-lactones **2a–f** were not affected by thionation, according to the elution order previously established by Beck et al.[15a] on the same chiral stationary phase.

$LiAlH_4$ reduction (1 equiv. in dry THF) of these γ-thionolactones led to the corresponding 1,4-sulfanylalcohols[16] **4a–f** with high yields (80–93%) (Table 1). These compounds were not efficiently resolved by enantioselective GC. Therefore, an easy derivatisation into their corresponding 2,2-dimethyloxathiepanes[13] was achieved to determine the final enantiomeric excesses (66–91%), by enantioselective GC.[13] Since the absolute configuration of the stereocentre was not affected by reduction,[17] we assume that the 1,4-sulfanylalcohols were enantiomerically enriched into the (*R*)-form.

Conclusion

A new and convenient enantioselective synthesis of a series of new 1,4-sulfanylalcohols has been achieved in good yields with enantiomeric excesses in a 66–91% range. The works are currently in progress to improve the enantiomeric excesses, to obtain the reverse configuration (*S*) and to further extend this new synthesis to other substrates.

These 1,4-sulfanylalcohols constitute a new class of potent flavouring compounds and very interesting key-intermediates for the synthesis of heterocyclic derivatives.

Acknowledgements

We wish to thank Maxens S.A. (Grasse) for acquiring HRMS data.

References

1. (a) Widder, S.; Dittner, T.; Sabater-Luntzel, C.; Pickenhagen, W.; Voolhardt, J. Dragoco, Gerberding & Co AG, European Patent, 1999, 0,924,198; (b) Widder, S.; Sabater-Luntzel, C.; Dittner, T.; Pickenhagen, W. *J. Agric. Food Chem.* **2000**, *48*, 418–423; (c) Acuna, G.; Gautschi, M.; Kumli, F.; Schmid, J.; Zsindely, J., Givaudan SA, European Patent, 2001, 1,055,667.
2. Sabater-Luntzel, C.; Widder, S.; Vossing, T.; Pickenhagen, W. *J. Agric. Food Chem.* **2000**, *48*, 424–427.
3. (a) Nishimura, O.; Yamaguchi, K. *J. Agric. Food Chem.* **1989**, *37*, 139–142; (b) Engel, K. H.; Tressl, R. *J. Agric. Food Chem.* **1991**, *39*, 2249–2252.
4. (a) Winter, M.; Furrer, A.; Willhalm, B.; Thommen, W. *Helv. Chim. Acta* **1976**, *59*, 1613–1620; (b) Pickenhagen, W.; Brönner-Schindler, H. *Helv. Chim. Acta* **1984**, *67*, 947–952; (c) Singer, G.; Heusinger, G.; Frölich, O.; Schreier, P.; Mosandl, A. *J. Agric. Food Chem.* **1986**, *34*, 1029–1033.
5. Yolka, S.; Duñach, E.; Lizzani-Cuvelier, L.; Fellous, R.; Rochard, S.; Schippa, C.; George, G. *Flavour Frag. J.* **2002**, *17*, 425–431.
6. Shiraki, H.; Nishide, K.; Node, M. *Tetrahedron Lett.* **2000**, *41*, 3437–3441.
7. (a) Iglesias, L. E.; Baldessari, A.; Gros, E. G. *Org. Prep. Proced. Int.* **1996**, *28*, 319–324; (b) Hu, J.; Fox, M. A. *J. Org. Chem.* **1999**, *64*, 4959–4961.
8. (a) Schellenberg, A.; Schmarr, H. G.; Eisenreich, W.; Engel, K. H. *Frontiers of Flavour Science*; Deutsche Forschungsanstalt für Lebensmittelchemie: München, 1999; (b) Engel, K. H.; Schellenberg, A.; Schmarr, H. G. *Abstr. Pap.-Am. Chem. Soc.* **2000**, 220th AGFD-051.
9. (a) Gutman, A. L.; Zuobi, K.; Boltansky, A. *Tetrahedron Lett.* **1987**, *28*, 3861–3864; (b) Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546–3552.
10. (a) Blanco, L.; Guibé-Jampel, E.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 1915–1918; (b) Enzelberger, M. M.; Bornscheuer, U. T.; Gatfield, I.; Schmid, R. D. *J. Biotechnol.* **1997**, *56*, 129–133.
11. Chen, C. S.; Fujimoto, Y.; Giradaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
12. The enantiomeric ratios (*E*),[11] a measure of the enantioselectivity of the lipase, can be related to the extent of conversion and the enantiomeric excess and were calculated using the following equation,

$$E=\frac{\ln[(1-c)(1-\mathrm{ee})]}{\ln[(1-c)(1+\mathrm{ee})]}$$

where *c* is the lactone conversion, and ee is the enantiomeric excess of the unreacted lactone. This equation is based on the assumption that resolution proceeds irreversibly, that the two enantiomers compete for the same active site, and that there is no product inhibition.
13. Experimental section: **Enzymatic resolution of the γ-lactones 1a–f:** in a typical experiment, the crude lipase (purchased from Sigma chemicals Co., L3126.) was carefully diluted, at 20°C, in 100 ml of the appropriate medium (A, B or C) adjusting pH at the desired value (7.2 or 7.6) with 0.5N NaOH. 15 ml of an hexane/Et_2O mixture was added in the case of phosphate buffer. 5×10^{-2} mole of γ-lactone was quickly added. The reaction course was monitored with a pH-stat with continuous addition of the same freshly prepared 0.5N NaOH solution. The reaction was stopped at 60% conversion (60 ml added), by filtering off the enzyme over Celite. The aqueous filtrate was, then, extracted three times with 100 ml of a Et_2O/EtOAc mixture (1/1), the combined organic layers were dried over $MgSO_4$, and evaporated to afford the optically active γ-lactone. All the enantiomeric excesses were determined by gas chromatography on a Chiraldex B-TA silica capillary column (30 m×0.25 mm) (Astec, Whippany, USA) (80°C to 220°C, 2°C/min). **Thionation of the optically active γ-lactones 2a–f:** 10 mmol of optically active γ-lactone, 0.5 equiv. of L.R. and 20 ml of toluene were refluxed, under nitrogen atmosphere, during 4 h. After cooling and filtration, toluene was evaporated in vacuo. At room temperature, the crude mixture was stirred in hexane/Et_2O (80/20) to precipitate

most of the Lawesson's residue. The solvent was evaporated and the corresponding optically active γ-thionolactone was purified on silica gel using a mixture of hexane/Et_2O (85/15). Enantiomeric excesses were determined on a LS Hydrodex β-6TBDM silica capillary column (25 m×0.25 mm) (Macherey & Nagel, Düren, Germany) (80°C to 220°C, 2°C/min). **Reduction of the optically active γ-thionolactones 3a–f:** Optically active γ-thionolactones were submitted to $LiAlH_4$ reduction (1 equiv. in dry THF under nitrogen atmosphere, reflux, 1 h) leading to the corresponding 1,4-sulfanylalcohols **4a–f**, purified by silica gel chromatography with hexane/Et_2O (60/40). Enantiomeric excesses were determined on a LS Hydrodex-β-6-TBDM silica capillary column (25 m×0.25 mm) (Macherey & Nagel, Düren, Germany) (80°C to 220°C, 2°C/min) after derivatisation into their corresponding 2,2-dimethyloxathiepanes from condensation with acetone, in $CHCl_3$ under acidic conditions.

14. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061–5087.
15. (a) Beck, T.; Mosandl, A. *J. High Resol. Chromatogr.* **1998**, *22*, 89–92; (b) Hayashi, S.; Hashimoto, S.; Kameoka, H.; Sugimoto, K. In *Flavours and Fragrances*; Swift, K. A. D., Ed.; Cambridge, 1997; (c) Scheibye, S.; Kristensen, J.; Lawesson, S. O. *Tetrahedron* **1979**, *20*, 1339–1343.
16. All new compounds were characterised by ^1H and ^{13}C NMR, MS and HRMS. Data for the **1-sulfanylheptan-4-ol 4c**: ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, m), 1.35–1.47 (2H, 2m), 1.36 (1H, t, $J=7.6$ Hz), 1.44 (1H, m), 1.51 (1H, m), 1.60 (1H, m), 1.69 (1H, m), 1.79 (1H, m), 2.57 (2H, q, $J=7.6$ Hz), 3.63 ppm (1H, m). ^{13}C NMR (200 MHz, $CDCl_3$): δ 14.11, 18.92, 24.77, 30.17, 36.05, 39.80, 71.22 ppm. MS (EI, 70 eV): m/z (%) 148 (M^+, 0.1), 101 (14.6), 87 (100), 81 (13.3), 71 (25.9), 59 (45.1), 55 (51.9), 43 (54.1), 42 (20.3), 41 (32.8), 39 (13.8). HRMS calculated for $C_7H_{16}OS$: 148.0922, found: 148.0916.
17. Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett.* **1994**, *35*, 8241–8242.