Synthesis of enantiomerically pure (*R*)- and (*S*)-2-sulfanylpropanoic acids ('thiolactic acid') from ethyl (*S*)-lactate using pig liver esterase

Robert P. Hof and Richard M. Kellogg *
Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

The methanesulfonates of optically pure ethyl (*S*)-lactate or ethyl (*R*)-2-chloropropanoate **5**, obtained with inversion of configuration from ethyl (*S*)-lactate on treatment with $SOCl_2$, can be substituted by caesium thiolates with inversion of configuration to yield (*R*) and (*S*) ethyl 2-(acetylsulfanyl)propanoate, **2a** and **2b**, respectively. Hydrolysis of the carboxy ester of **2a**, **2b** to the acid under common acidic or basic conditions always leads to substantial racemisation. However, the use of the mild biocatalyst pig liver esterase (PLE) at neutral pH yields the carboxylic acids **4a** and **4b** without racemisation. The acetylsulfanyl group remains unaffected during this process. Subsequent treatment of the acetylsulfanyl group of **4a** or **4b** with 2 mol dm^{-3} aqueous ammonia leads to the useful optically pure building block (*R*)- or (*S*)-2-sulfanylpropanoic acid ('thiolactic acid') **3a**, **3b** in an overall yield of 65% based on cheap ethyl (*S*)-lactate.

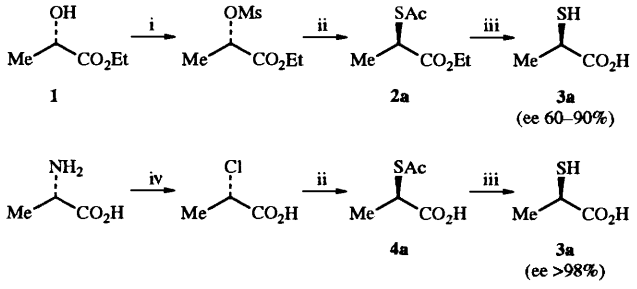
Several years ago we described preparative methods for obtaining enantiomerically pure (or enriched) 2-sulfanyl acids from either α-amino acids or from alkyl esters of α-hydroxy acids.[1] These methods entail either substitution of the methanesulfonates of enantiomerically pure α-hydroxy esters by caesium thiolates with inversion of configuration or diazotation of α-amino acids to form α-halogeno acids with retention of configuration followed by substitution with a caesium thiolate with inversion of configuration.

We note that the interest in one of the α-sulfanyl acids obtained, 2-sulfanylpropanoic acid ('thiolactic acid') **3**, has increased substantially. Both enantiomers of this compound have recently been used in the synthesis of new platelet activating factor (PAF) receptor antagonists[2,3] and it was found that the activity was dependent on the absolute configuration.[4] Active antiulcer agents derived from optically pure (*R*)-**3a** also have been reported,[5] and **3a** has been used as an analogue of Ala-82 in the backbone of T4 lysozyme.[6] It should also be noted that thiols can be absorbed on gold surfaces to form highly ordered monolayers. The macroscopic properties of these layers, such as the wettability, can be correlated to the structure at the atomic level.[7] The use of chiral non racemic thiols such as **3a** or **3b** offers access to monolayers, in which relationships between chirality and properties can be studied.

The synthesis of (*R*)-**3a** can be achieved *via* cheap ethyl (*S*)-lactate whereas the more expensive ethyl (*R*)-lactate is required for the preparation of (*S*)-**3b**.[1a] There is a complication, however, starting from either enantiomer of ethyl lactate. During the hydrolysis of the carboxy ester of enantiomerically pure ethyl (*R*)- or (*S*)-2-(acetylsulfanyl)propanoate **2a, b** there is always substantial racemisation (Scheme 1).[1] This problem can be circumvented by use of the expensive (L)-alanine for preparation of (*R*)-**3a** and even more expensive (D)-alanine for (*S*)-**3b**. In this case direct substitution of the unprotected (*S*)- or (*R*)-2-chloropropionic acid, obtained with retention of configuration from the amino acid, affords optically pure (*R*)- or (*S*)-thiolactic acid *via* the thioactate in 45% overall yield. However, neither the overall yields nor the somewhat involved work-up procedures are entirely satisfactory.

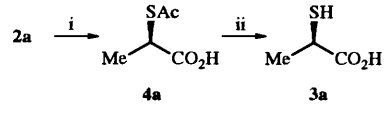
Results and discussion

We have developed an alternative procedure to obtain both enantiomerically pure (*R*)- and (*S*)-thiolactic acids from the cheap and readily available ethyl (*S*)-lactate as the single starting material. On the basis of experience gained with the use of enzymes for chiral resolutions[8] we examined the use of these mild and selective biocatalysts for the hydrolysis of the enantiomerically pure carboxy ester (*R*)-**2a**. Although lipases and esterases are most often used for the resolution of racemates, there have also been reports of their use as chemoselective catalysts in, for example, peptide[9] and carbohydrate synthesis.[10] We now report that at neutral pH pig liver esterase (PLE) hydrolyses selectively the ethyl ester of **2a** without racemisation. In enzymic hydrolysis experiments using PPL[11] or lipases from *Pseudomonas sp.*[12] as catalysts, acetylsulfanyl groups rather than ester groups are usually hydrolysed preferentially. With PLE this group in compound (*R*)-**2a** only begins to react after the ethyl ester has completely been hydrolysed, but at a much lower rate. To obtain the free α-sulfanyl acid **3a** the resulting thioacetate (*R*)-**4a** was deacylated with 2 mol dm^{-3} aqueous ammonia.[1] No racemisation could be detected in this step. These two steps can even be combined to a one pot procedure! (*R*)-Thiolactic acid can be obtained enantiomerically pure in an overall yield of > 65% from ethyl (*S*)-lactate (Scheme 2).



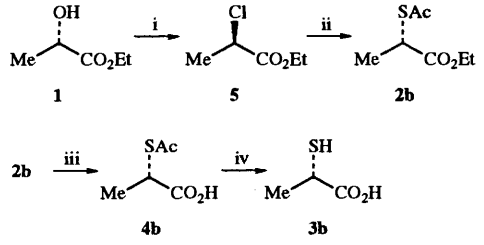
Scheme 1 *Reagents and conditions*: i, MsCl, NEt_3, ether; ii, CsSAc, DMF; iii, chemical hydrolysis; iv, $NaNO_2$, 6 mol dm^{-3} HCl (Ms = $MeSO_2$)

By appropriate modification of experimental procedure this



Scheme 2 *Reagents and conditions*: i, PLE, pH 7.00; ii, 2 mol dm^{-3} NH_3

approach was extended to the preparation of (*S*)-thiolactic acid **3b** as well. In an improved synthesis neat ethyl (*S*)-lactate was treated with $SOCl_2$ to yield ethyl (*R*)-2-chloropropanoate **5** with inversion of configuration [13a] in 75% yield and 95% ee. This material could subsequently be inverted with CsSCOMe to yield ethyl (*S*)-2-(acetylsulfanyl)propanoate **2b** without racemisation (Scheme 3).[1] It is notable that PLE is also capable of hydrolysing



Scheme 3 *Reagents and conditions*: i, $SOCl_2$, heat; ii, CsSAc, DMF; iii, PLE, pH 7.00; iv, 2 mol dm^{-3} NH_3

the ester group of (*S*)-**2b** selectively although the reaction time is nearly doubled compared with the (*R*) enantiomer.

Because the traces of the (*R*) enantiomer present in (*S*)-**2b** completely hydrolyse to the volatile (*R*)-**3a**, which is easily removed by distillation, during reaction, it is possible to prepare optically pure (*S*)-**4b** from (*S*)-**2b** having an optical purity of only 95%. Subsequent hydrolysis of (*S*)-**4b** with 2 mol dm^{-3} aqueous ammonia yields the free α-sulfanyl acid (*S*)-**3b** without racemisation.

In summary this methodology allows preparation of both enantiomers of thiolactic acid, **3a** and **3b**, readily from the cheap starting material, ethyl (*S*)-lactate. We hope that this improved procedure may stimulate further applications of both (*R*)- and (*S*)-thiolactic acids as enantiomerically pure intermediates in organic synthesis and pharmacology.

Experimental

General

Ethyl (*S*)-lactate **1** and $SOCl_2$ were obtained from Merck. PLE was obtained from Amano Enzyme Europe Ltd, and was used as such. Ether refers to reagent grade diethyl ether, which was distilled from P_2O_5 prior to use. Ethyl (*R*)-2-(acetylsulfanyl)propanoate **2b** was prepared as described.[1] Ethyl (*S*)-2-(acetylsulfanyl)propanoate **2b** was prepared following the same procedure starting from ethyl (*R*)-2-chloropropanoate **5**. As **2a** and **2b** slowly racemise on prolonged standing at room temperature they should be stored in the dark and cold. (*R*)-**3a** can be prepared from the corresponding **4a** as described.[1] Enzymic reactions were performed with a Radiometer PHM 82 pH stat, equipped with a TTT 80 titrator and an ABU 80 autoburette. Optical rotations were determined at room temperature using a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Chiral GLC was performed on a Hewlett-Packard 5890A gas chromatograph equipped with a 50 m WCOT fused silica capillary GLC column coated with CP cyclodextrin-B-2,3,6-M-19 (Chrompack No. 7501) and a Hewlett-Packard HP 3396 Series II integrator.

Preparation of ethyl (*R*)-2-chloropropanoate 5

To neat ethyl (*S*)-lactate (50 g, 424 mmol) containing dimethylformamide (DMF) (0.3 cm^3) was carefully added neat $SOCl_2$ (33 cm^3). The mixture was refluxed until the evolution of SO_2 ceased (3 h). The crude mixture was poured onto ice and was extracted three times with ether. The combined ether extracts were washed with brine and dried ($MgSO_4$) and the ether was evaporated under reduced pressure at room temperature. The resulting yellow oil was distilled to provide the title compound **5** (43.6 g, 319 mmol, 75%), colourless oil; bp 143–145 °C; ee 95% (chiral GLC); $[\alpha]_D$ +19.1 (neat) (lit., [11b] +19.8); op 96%.

Preparation of (*R*)-2-(acetylsulfanyl)propanoic acid 4a

Ethyl (*R*)-2-(acetylsulfanyl)propanoate **2a** (2.06 g, 11.7 mmol) was suspended in phosphate buffer (pH 7.00; 50 cm^3) with PLE (50 mg) under vigorous stirring; the pH of the solution was kept at 7.00 by continuous addition of aqueous NaOH (2 mol dm^{-3}) by means of an autoburette. After addition of the theoretical amount of base (22 h) the reaction mixture was acidified by the addition of aqueous HCl (2 mol dm^{-3}). Ether (150 cm^3) was added and the mixture was filtered over Celite to remove the remaining enzyme. The organic layer was separated, and the aqueous layer was extracted three times with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4) and then evaporated to give the title compound **4a** (1.54 g, 10.4 mmol, 89%) as an oil, which was purified by bulb-to-bulb distillation (bp 115°/0.3 mmHg), $[\alpha]_D$ +136 (*c* 1.06 in $CHCl_3$) {lit., [14] $[\alpha]_D$ +137 (*c* 3.9 in $CHCl_3$)}; op >98%.

Preparation of (*S*)-2-(acetylsulfanyl)propanoic acid 4b

In a procedure analogous to that described above **2b** (2.06 g, 11.7 mmol) was converted at pH 7.00 with PLE (50 mg) in 39 h into crude **4b** containing traces of (*R*)-**3a**. Pure title compound **4b** (1.31 g, 8.85 mmol, 76%) was isolated by bulb-to-bulb distillation (bp 95°/0.08 mmHg), $[\alpha]_D$ −135.5 (*c* 4.35 in $CHCl_3$); op >98%. All other physical properties were in accordance with the known enantiomer **4a**.

One-pot procedure for the preparation of (*R*)-2-sulfanylpropanoic acid 3a

Compound **2a** (5.00 g, 28.4 mmol) was suspended in phosphate buffer pH 7.00 (60 cm^3) and PLE (100 mg) was added under vigorous stirring; the pH of the suspension was kept at 7.00 by continuous addition of aqueous NaOH (2 mol dm^{-3}). After 46 h the theoretical amount of base had been consumed and aqueous NH_3 (2 mol dm^{-3}; 60 cm^3) was added to the mixture. After stirring for another 5 h, ether (150 cm^3) was added and the mixture was filtered over Celite. The Celite was thoroughly washed with ether and the organic layer was separated. The water layer was extracted three times with ether and the combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation the title compound (*R*)-**3a** was obtained (2.97 g, 28.0 mmol, 99%) as a slightly yellow oil. After bulb-to-bulb distillation (120 °C/15 mmHg) a pure sample was obtained with identical properties to a sample prepared according to ref. 1*a*, $[\alpha]_D$ +56.5 (*c* 4.17 in EtOAc); op >98%.

Preparation of (*S*)-2-sulfanylpropanoic acid 3b

Compound **4b** (870 mg, 5.88 mmol, op 95%) was stirred for 5 h in aqueous NH_3 (2 mol dm^{-3}; 20 cm^3). After acidification with aqueous HCl (2 mol dm^{-3}) the mixture was extracted three times with ether. The combined organic layers were washed with brine and dried (Na_2SO_4). After evaporation the remaining yellow oil was purified by bulb-to-bulb distillation to yield the title compound (*S*)-**3b** (510 mg, 4.81 mmol, 82%), bp 130 °C/15 mmHg; $[\alpha]_D$ −54.3 (*c* 5.76 in EtOAc); op 95%. All other physical properties were in accordance with the known enantiomer (*R*)-**3a**.

Acknowledgements

This work was supported in part in the form of a grant to R. P. H. from the Dutch National Science Foundation (N. W. O.) administered through the Office for Chemical Research (S.O.N.). A generous gift of PLE by Amano Enzyme Europe Ltd. is gratefully acknowledged.

References

1 (*a*) B. Strijtveen and R. M. Kellogg, *J. Org. Chem.*, 1986, **51**, 3664; (*b*) B. Strijtveen and R. M. Kellogg, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 539.
2 Y. Tanabe, Y. Kubota, Y. Sanemitsu, N. Itaya and G. Suzukamo, *Tetrahedron Lett.*, 1991, **32**, 383.
3 A. Tanabe (Sumitomo Kagaku Kogyo K. K.), *Jpn. Kokai Tokkyo Koho*, JP 0495 092/1992 (*Chem. Abstr.*, 1993, **118**, 234049e).
4 Y. Tanabe, G. Suzukamo, Y. Komuro, S. Imaishi, S. Morooka, M. Enomoto, A. Kojima, Y. Sanemitsu and M. Mizutani, *Tetrahedron Lett.*, 1991, **32**, 379.
5 N. Masai, M. Enomoto, A. Kojima, H. Masumori, N. Hara, Y. Hara and S. Morooka (Sumitomo Pharmaceuticals Co., Ltd.), EP Appl. 325496/1989 (*Chem. Abstr.*, 1990, **113**, 115295u).
6 J. A. Ellman, D. Mendel and P. G. Schultz, *Science*, 1992, **255**, 197.
7 C. D. Bain and G. M. Whitesides, *J. Am. Chem. Soc.*, 1988, **110**, 3665.
8 (*a*) R. P. Hof and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1994, **4**, 565; (*b*) H. van der Deen, R. P. Hof, A. van Oeveren, B. L. Feringa and R. M. Kellogg, *Tetrahedron Lett.*, 1994, **35**, 8441; (*c*) H. Moorlag and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1991, **2**, 705.
9 D. Waldmann, *Liebigs Ann. Chem.*, 1988, 1175.
10 H. M. Sweers and C.-H. Wong, *J. Am. Chem. Soc.*, 1986, **108**, 6421.
11 D. Bianchi and P. Cesti, *J. Org. Chem.*, 1990, **55**, 5657.
12 N. Baba, M. Mimura, J. Oda and J. Iwasa, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1990, **68**, 208 (*Chem. Abstr.*, 1991, **114**, 184892u).
13 (*a*) W. Gerrard, J. Kenyon and H. Phillips, *J. Chem. Soc.*, 1937, 153; (*b*) J. Biedermann, A. León-Lomelí, H. O. Borbe and G. Prop, *J. Med. Chem.*, 1986, **29**, 1183.
14 L. N. Owen and M. B. Rahman, *J. Chem. Soc. C*, 1971, 2432.

Paper 4/07564A
Received 12*th December* 1994
Accepted 27*th January* 1995