Tetrahedron: Asymmetry Vol. 1, No. 9, pp. 583-586, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

LIPASE-CATALYSED KINETIC RESOLUTION OF N,O-DIACETYL-2-AMINO-1-BUTANOL IN DIISOPROPYL ETHER.

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(*Received* 10 *July* 1990)

Abstract : N,O-Diacetyl-2-amino-1-butanol (2) on lipase-catalysed transesterification with 1-butanol in diisopropyl ether gave (S)-(-) -2 and (R)-(+)-N-acetyl-2-amino-1-butanol (3); proper stereochemistry and correct optical rotations of chiral 2 and 3, incorrectly reported in literature, were determined after their conversion to chiral 2-amino-1-butanol (1).

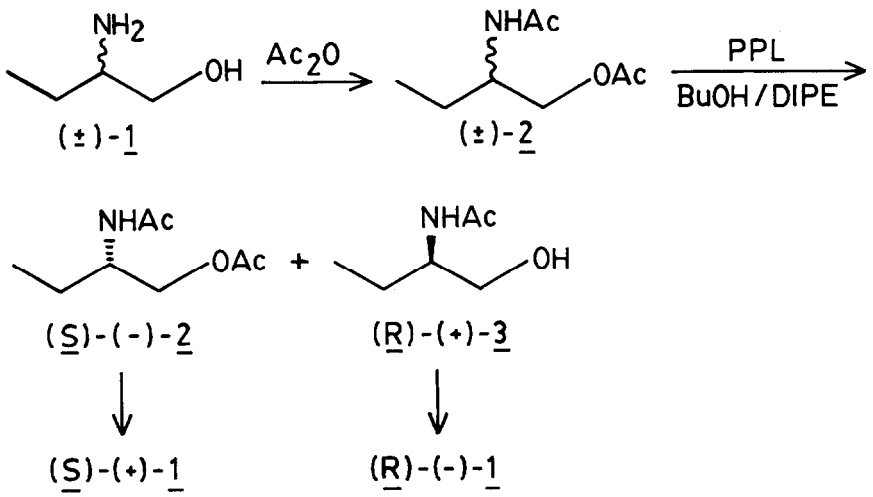
Ethambutol is an important antitubercular drug, with annual production in India alone exceeding 400 tons per annum. Successful preparation of (S)-(+)-2-amino-1-butanol (1), the chiral precursor to Ethambutol, through lipase-catalysed kinetic resolution[1] has been recently reported by two different groups.[2,3] While Gotor et al's direct acetylation method[3] looks economically more attractive, our own efforts to achieve the desired results, in line with Francalanci et al's observations[2], met with little success. As we found that protection of amino group was necessary to retain lipase activity (Gotor et al used 7.5 g lipase to resolve 0.9 g 1), we report herein an alternative, practical synthesis of (S)-1 via lipase-catalysed transesterification of N,O-diacetyl-2-amino-1-butanol (2) with 1-butanol in diisopropyl ether (DIPE)[4].

The required diacetate 2 was easily prepared from (±)-1 using an industrially suitable 'no work-up' procedure. Treating 1 with Ac_2O at 80°C for 30 min. followed by removal of AcOH and Ac_2O and distillation (112-116°C/0.5 mm) yielded 91% of 2, m.p. 67°C.

Diacetate 2 was subjected to lipase-catalysed transesterification with 1-butanol in DIPE.[5] Of five lipases tried - porcine pancreatic (PPL), Candida cylindracea (both Sigma), Mucor miehei (Lipozyme), Aspergillus oryzae (Lipolase) (both from Novo) and Pseudomonas cepacia (Lipase PS "Amano"), PPL showed best selectivity. Stopping the reaction at 40% conversion (24 h) yielded (-)-2, $[\alpha]_D^{25}$- 14.9 (7.EtOH) and (+)-N-acetyl-2-amino-1-butanol (3), $[\alpha]_D^{25}$+ 28.3 (12,EtOH). Hydrolysis of (+)-3, which according to Gotor et al[3] should have been the desired (S)-isomer with 100% optical purity, however led to the unwanted (R)-(-)-1 with only 62% ee, $[\alpha]_D^{25}$= -6.25 (neat) (Lit[6] $[\alpha]_D^{25}$10.1). This was further confirmed by preparing an authentic (R)-(+)-3 from (R)-(-)-1 (1 in H_2O, Ac_2O, column purification, 75%), $[\alpha]_D^{25}$+ 44.5 (EtOH). Authentic (S)-(+)-1, on the other hand, gave (S)-(-)-3, $[\alpha]_D^{25}$-43.9 (5, EtOH).

As these results showed that we were dealing with the wrong isomer for conversion to desired (S)-1, the correct one being the unreacted fraction of the diacetate 2, we allowed the PPL-catalysed reaction to attain 60% conversion (48h) to give optically enriched (-)-2, $[\alpha]_D^{25}$- 32.5 (7, EtOH) and (+)-3, $[\alpha]_D^{25}$+19.0 (10,EtOH). Hydrolysis of (-)-2 obtained, which again should have been the (R)-isomer with 85% ee according to previous report[3], however, gave the desired (S)-(+)-1 with only 66% ee. Preparation of an authentic sample of (S)-(-)-2, m.p.103°C, $[\alpha]_D^{25}$-48.9 (6,EtOH), from (S)-(+)-1 further confirmed our results.

Interestingly, a single recrystallisation of the partially optically pure (S)-2 obtained from any of the above reactions (ee 40 or 66%) in DIPE led to the isolation of enantiomerically enriched (S)-2 with 95% ee and 90% theoretical yields. While this behaviour can be explained on the basis of the large difference in the melting points of chiral



and racemic 2 (103 and 67°C respectively), inability of hexane, though found suitable solvent for recrystallisation, to effect enantiomeric enrichment is yet to be understood. A similar trend was recently observed by us while working with butyl N-benzoylalaninate[7].

To summarise, we have studied the lipase-catalysed kinetic-resolution of industrially important 2-amino-1-butanol (1) through a different approach. We have, in the process, established and unambigously assigned proper configurations (with correct optical rotations) to chiral 2 and 3, which were wrongly reported before.

Acknowledgements: We thank Dr B N Roy for encouragement and, Novo-Nordisk A/S, Amano Pharmaceutical Co.Ltd. (Japan) and Lupin Laboratories Ltd. (India) for providing free samples of Lipozyme, Lipase PS "Amano" and (R)-1 respectively. Financial support was provided by ICI India Limited.

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5. Stirring a mixture of 2 (5.2g, 30 mmol), 1-butanol (11 ml, 120 mmol) and lipase (6g) in DIPE (90 ml) at ambient temperature till the desired conversion (GC), followed by removal of solvent and purification by silica gel column chromatography gave (-)-2 and (+)-3 in 90% theoretical yields; spectral data for (-)-2, IR 3265, 1720, 1635 cm^{-1}; ^1H NMR ($CDCl_3$), δ 0.92 (t, 3H, J 7.2 Hz, CH_3), 1.50 (m, 3H, CH_2CH), 1.97 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 4.07 (d, 2H, J 2.1, OCH_2), 6.0 (br s, 1H,NH)

(+)-3 : IR, 3300, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J 7.2, CH_3), 1.6 (m, 2H, CH_2), 2.0 (s, 3H, CH_3), 3.7 (m, 4H, CH_2CH OH), 6.4 (br d, 1H, NH).

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