Pergamon

Tetrahedron Letters, Vol. 35, No. 29, pp. 5205-5208, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01049-8

An Efficient Synthesis of Enantiomerically Enriched Aryllactic Esters

Bruce A. Lefker,* William A. Hada, Patrick J. McGarry

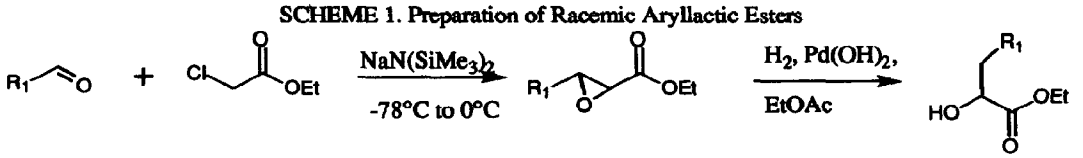
Pfizer Central Research
Eastern Point Road, Groton, CT 06340

Abstract: An efficient synthesis of enantiomerically enriched aryllactic esters or acids has been established. Darzen's condensation of arylaldehydes with ethyl chloroacetate followed by catalytic hydrogenation gave racemic aryllactic esters. Enzyme catalyzed (lipase PS-30, Amano) hydrolysis or acetylation provided enantiomerically enriched products. EE's of 65-99% were obtained without optimization of resolution conditions. This route is compatible with a variety of heterocycles and multigram quantities of enantiomerically enriched materials have been prepared. These chiral synthons are useful for the preparation of renin inhibitors as well as other therapeutic agents.

L-Phenyllactic acid has been widely used as a chiral synthon for incorporation into enzyme inhibitors as well as other molecules of biological interest.[1] In our efforts to enhance the potency and pharmacokinetic profile of a series of inhibitors of human renin, we replaced the P3 phenylalanine residue with various aryllactic acids. Incorporation of L-phenyllactic acid provided inhibitors with improved metabolic stability and promising *in vivo* properties.[2] We therefore began to examine aryllactic derivatives with aromatic groups other than phenyl. Initial targets were the L-2-thienyl- and L-1-naphthyllactic acids which could be prepared by treatment of the commercially available L-amino acids with aqueous nitrous acid.[3] This process was not very efficient (yields of 15-35%) and required large quantities of expensive ($120-$160/g) unnatural amino acids. To gain access to larger quantities and a wider range of aryllactic acids in optically active form we examined alternative strategies. A survey of the literature suggested a number of potential racemic and asymmetric routes.[1c,4] However, none seemed attractive from the standpoint that either expensive chiral reagents would be required, or the synthesis of the starting materials would require multiple steps.

We soon recognized that Darzens condensation of an arylaldehyde with ethyl chloroacetate[5] would give the glycidic ester which could be hydrogenated to give the racemic aryllactic ester. Enzymatic resolution could then provide the aryllactic acid or ester in enantiomerically enriched form.[6] This route was particularly attractive since the starting materials are cheap and readily available.

SCHEME 1. Preparation of Racemic Aryllactic Esters



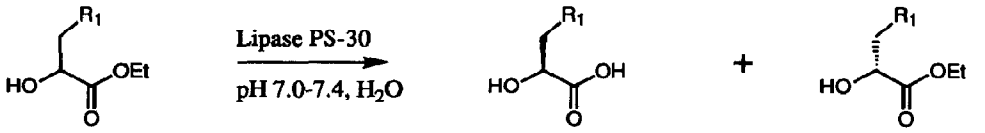
1a-i

According to Scheme 1, a variety of arylaldehydes were condensed with ethyl chloroacetate to give the glycidic ester (0.95 eq. $NaN(SiMe_3)_2$, THF, -78° to 0°C). The crude epoxide was submitted without

purification to catalytic hydrogenation[7] (H_2, 45 psi, $Pd(OH)_2$, EtOAc), and purified by column chromatography to give racemic aryllactic esters **1a-1i** (Table 1) in modest to excellent yields (28-99%).[8]

To resolve the aryllactic esters, we initially examined the enzyme catalyzed hydrolysis of **1a-f** with Amano Lipase PS-30 (Method A). Lipase PS-30 is relatively inexpensive and has been shown to efficiently resolve a wide variety of substrates.[9] An aqueous solution of the racemic ester was stirred at room temperature with 1.5 wt.% of Lipase PS-30 while maintaining the pH between 7.0-7.4 by the controlled addition of 0.25 or 0.5 N NaOH with a Chemcadet^R pHstat controller. Reactions were carried to ~35% conversion by stopping the reaction after ~0.35 equivalents of base had been consumed.[10] While this procedure was efficient for the resolution of **1a** and **1b**, compounds **1c** and **1d** were hydrolyzed with variable selectivity. Since the enantiomerically enriched acids were easily separated from the unreacted ester by acid-base extraction, and could then be crystallized to higher enantiomeric purity, this was the preferred resolution method for preparation of compounds **1a** and **1b**.

SCHEME 2. Enzyme Catalyzed Hydrolysis of Aryllactic Esters by Method A



1 **2**

TABLE 1.

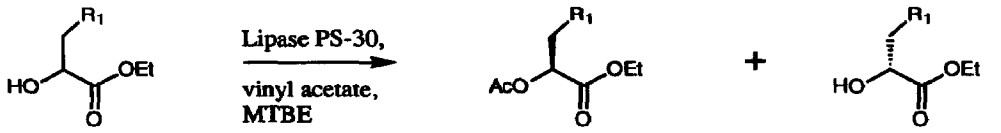
Entry	R_1	Yield of **1**[a]	Resolution by Method A			Resolution by Method B		
			Yield of **2**[b]	rxn time	ee(%)[c]	Yield of **3**[d]	rxn time	ee(%)[e]
1a	1-naphthyl	34%	51%	18 h	81%[f]			
1b	3-fluorophenyl	77%	64%	5 h	89%[g]			
1c	2-thienyl	64%	66%	18 h	68%[g]	72%	2 h	95%[g]
1d	2,3-methylene-dioxyphenyl	53%	65%	5.5 h	14%[g]	46%	21 h	66%[g]
1e	2-furyl	49%				41%	2.5 h	66%[g]
1f	2-(4-Cl-thienyl)[11]	40%				71%	3 h	>98%[g]
1g	3,4-methylene-dioxyphenyl	99%				60%	6 h	>96%[g]
1h	2-pyridyl	28%				56%	24 h	72%[g]
1i	3-pyridyl	66%				45%	28 h	92%[g]

a) yields are unoptimized, isolated yields. b) unoptimized yield, after crystallization, reported as a percentage of theoretical max. yield (50%). c) ee determined after conversion of acids (2) to methyl esters, 4. d) unoptimized yield, after chromatography, reported as a percentage of theoretical max. yield (50%). e) ee determined after conversion of acetates (3) to methyl esters, 4. f) ee determined by comparison of optical rotation to material derived from L-amino acid and by ^{1}H-NMR integration of the Mosher ester of 4a. g) ee determined by HPLC using Chiracel OJ column.

Upon realization that this resolution would not be general for disparate aryl groups, we began to examine the lipase catalyzed acetylation of the racemic aryllactic esters. Typical reactions were carried out in methyl-t-butylether (MTBE), with 0.4-1.0 weight equivalents of enzyme (Lipase PS-30, Amano) and 1-2 equivalents of

vinyl acetate.[12] Reaction times varied considerably, with the fused aromatic systems typically taking >18h for 30% conversion to the acetate. The progress of the resolution was easily followed by ^{1}H-NMR integration of the α–proton resonance. At approximately 30% conversion, the heterogeneous reaction mixture was

SCHEME 3: Enzyme Catalyzed Acetylation of Aryllactic Esters, Method B

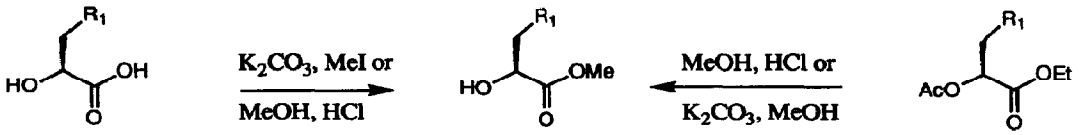


1 **3**

filtered through a plug of Celite^R and concentrated. The desired acetates (**3c-i**) were then separated from the unconverted ester by column chromatography. With the exception of entries **3d** and **3e** (Table 1), all of the substrates we examined gave good ee's without optimization of reaction conditions or solvents. This kinetic acetylation of **1** provided more reliable access to enantiomerically enriched esters **3** (Scheme 3, Method B).

Esterification of aryllactic acids **2a-c** was accomplished by treatment with methanol/HCl or potassium carbonate/methyl iodide to give the methyl esters (**4a-c**) in >90% yield (Scheme 4). The chromatographed acetates **3c-i** were converted to the aryllactic esters by treatment with anhydrous potassium carbonate in methanol, or methanol/HCl. When converting **3** to **4** with K_2CO_3 in methanol, it was necessary to ensure that the methanol and all glassware were rigorously dried to avoid concomitant hydrolysis of **3** to **2**.

SCHEME 4. -Conversion of Resolution Products to L-Aryllactic Esters



2a-c **4a-i** **3c-i**

Esters **4a** and **4c** were independently prepared by sodium nitrite treatment of the commercially available L-amino acids. Comparison of optical rotations of material derived from the L-amino acids with products derived from either enzymatic resolution method established the absolute configuration of **4a** and **4c** as the S-enantiomers.[13] It is interesting to note that in both the hydrolysis and the acetylation reactions (Schemes 2 and 3), the S-enantiomer was preferentially recognized and converted by the enzyme. The observed enantioselectivity for each resolution method is in accordance with the Lipase P model developed by Kazlauskas,[9] where the aryl group is considered to be R_L and the ester is R_M. Although the enzyme was quite tolerant of aryl groups of varying size and polarity, we were not able to rationalize the variations in resolution efficiency for the various substrates. Enantiomeric excesses of the aryllactic esters were routinely determined by chiral HPLC using a Chiracel-OJ column in hexane/isopropanol (typically 85/15) or by ^{1}H-NMR analysis of the mosher esters of **4**.

In summary, this method provides rapid access to a wide range of enantiomerically enriched aryllactic acids and esters on multigram scale from commercially available or easily prepared arylaldehydes.

REFERENCES AND NOTES:

1. a) For a leading reference on α-hydroxy acids see: Brown, H. C.; Pai, G. G.;Padhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531. b) Plattner, J. J.; Marcotte, P. A.; Kleinert, H. D.; Stein, H. H.; Greer, J.; Bolis, G.; Fung, A. K. L.; Bopp, B. A.; Luly, J. R.; Sham, H. L.; Kempf, D. J.; Rosenberg, S. H.; Deltaria, J. F.; De, B.; Merits, I.; Perun, T. *J. Med. Chem.* **1988**, *31*, 2277. c)Stanton, J. L.; Ksander, G. M.; Jesus, R.; Sperbeck, D. M. *Biorg. Med. Chem. Lett.* **1993**, , 539.
2. Manuscript in preparation.
3. Cohen, S. G.; Weinstein, S. Y. *J. Am. Chem. Soc.* **1964**, *86*, 5326. L-1-naphthyllactic acid has been prepared previously from L-1-naphthylalanine by Hester, J. B.; Pals, D. T.; Saneii, H. H.; Sawyer, T. K.; Schostarez, H. J.; Thaisrivongs, S. *Eur. Pat. Appl. EP 173,481*, **1986**.
4. Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. Akiyami, T.; Nishimoto, H.;Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1335. Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *J. Org. Chem.* **1988**, *53*, 2589. Flynn, G. A.; Beight, D. W. *Tetrahedron Lett.* **1988**, *29*, 423. Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435. Casy, G.; Lee, T. V.; Lovell, H. *Tetrahedron Lett.* **1992**, *33*, 817. Larcheveque, M.; Petit, Y. *Bull. Chem. Soc. France*, **1989**, 130. Zwanenburg,B.; Legters, J.; Thijs, L. *Tetrahedron Lett.* **1989**, *30*, 4881.
5. Newman, M. S.; Magerlein, B. J. *Org. Reactions* **1949**, *5*, 413. Diastereoselective Darzens condensations using chiral α-chloroesters have been reported: Schwartz, A.; Madan, P. B.; Mohasi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851. For resolutions of glycidic esters see: Gou, D.; Liu, Y.; Chen, C. *J. Org. Chem.* **1993**, *58*, 1287 or: Gentile, A.; Giordano, C.; Fuganti, C.; Ghirotto, L.; Servi, S. *J. Org. Chem.* **1992**, *57*, 6635.
6. Enzymatic resolutions of phenyllactic esters have been reported. For a leading reference see: Baldaro, E.; D'Arrigo, P.; Pedrocchi-Fantoni, G.; Rosell, C.M.; Servi, S.; Tagliani, A.; Terreni, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1031.
7. Park, G. J.; Fuchs, R. *J. Org. Chem.* **1957**, *22*, 93. When reducing the glycidic esters in EtOAc, complete selectivity for reduction of the benzylic C-O bond was observed. Hydrogenations in methanol led to significant amounts of products derived from addition of solvent to the oxirane.
8. To a stirred solution of 17g (137 mmol) of 3-Fl-benzaldehyde and 16.8g (137 mmol) ethyl chloroacetate in 100 mL of dry THF under nitrogen at -78° C, 130 mL of a 1.0 M solution of sodium hexamethyldisilazane was added dropwise while maintaining an internal temperature of <-50° C. The reaction was stirred at -78° for 30 min., warmed to 0° C, quenched with water and concentrated. The mixture was partitioned between ether and water, extracted with water, brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in 200 mL EtOAc, and added under nitrogen to a Parr bottle containing 3g of $Pd(OH)_2$. The bottle was charged with 45 psi of H_2, shaken for 2 h, filtered, and the residue chromatographed (silica gel, 9:1 hexanes/EtOAc) to give 21.3g (77%) of **1b**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.20 (m, 1H), 6.90 (m, 3H), 4.42 (dd, 1H), 4.23 (q, 2H), 3.10 (dd, 1H), 2.96 (dd, 1H), 1.23 (t, 3H).
9. Kazlauskas, R. J.; Weissfloch, A. N.E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
10. Compound **1b** (10g, 47.2 mmol) was added to a magnetically stirred solution of 150 mL water containing 150mg of lipase PS-30. The pH of the solution was maintained between 7.0-7.4 by the controlled addition of 0.25N NaOH using a Chemcadet^R (Cole Palmer) pHstat controller. After 5 h, 63 mL (66% of theory) of NaOH had been added. The the mixture was made basic (pH ~11) by the addition of 2N NaOH, and extracted with ether (2 X 200 mL). The aqueous layer was acidified with 6N HCl, and extracted with EtOAc (2 X 200 mL). The combined EtOAc washes were extracted with 1N HCl, brine, dried (MgSO4), concentrated, and crystallized from refluxing benzene to give 2.80g of **2b** (64% of theory). ^{1}H-NMR (250 MHz, CD_3OD) δ 7.20 (m, 1H), 6.90 (m, 3H), 4.23 (dd, 1H), 3.01 (dd, 1H), 2.79 (dd, 1H).
11. Iriarte, J.; Martinez, E.; Muchowski, J. M. *J. Heterocyclic Chem.* **1976**, *13*, 393.
12. To a solution containing 12.6g of compound **1f** and 10 g of vinyl acetate in 100 mL of MTBE, 4.6g of lipase PS-30 was added. The heterogeneous mixture was stirred at room temperature for 3h, filtered through celite, and chromatographed (silica gel (5% ether/hexanes) to give 5.3g of **3f** (71% of theory). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.97 (d, 1H), 6.77 (d, 1H), 5.18 (dd, 1H), 4.20 (q, 2H), 3.34 (dd, 1H), 3.29 (dd, 1H), 2.16 (s, 3H), 1.26 (t, 3H).
13. Absolute configuration of the products was also confirmed by incorporation of the aryllactic esters into tripeptide renin inhibitors (manuscript in preparation). In all cases we examined, compounds derived from the S-enantiomer were significantly more active than those having the R-configuration.

(*Received in USA* 5 *May* 1994; *accepted* 27 *May* 1994)