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BIFUNCTIONAL CHIRAL SYNTHONS VIA BIOCHEMICAL METHODS, 4. CHIRAL PRECURSORS TO (+)-BIOTIN AND (-)-A-FACTOR.[1]

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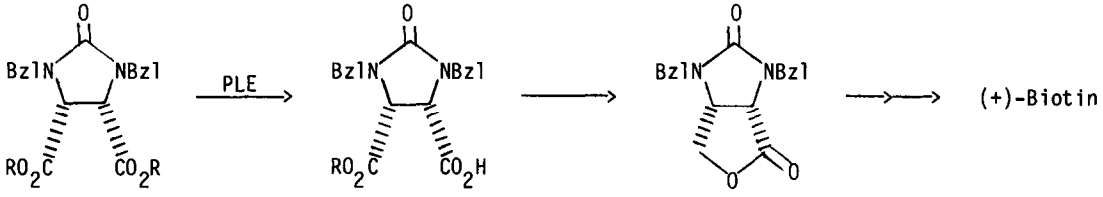
The chirons 3 and 4, derived from enzymic enantioselective hydrolysis of 1 and 2, are converted into the chiral lactones 5 and 6, key precursors to (+)-biotin and (-)-A-factor, respectively.

Enzymic hydrolyses of dicarboxylic esters generally terminate at the monoester stage.[2] In contrast, hydrolyses of diacetoxy esters by esterases do not. That is, the resulting monoacetoxy esters are further cleaved concomitantly to form diols. Since most esterases have the same stereochemical preference for diacetoxy and monoacetoxy esters, the combination of enantioselective hydrolysis and subsequent kinetic resolution provides a useful means of enhancing the optical purity of the monoacetoxy ester fraction.[1] Herein, we describe the successful application of this approach to the enantioselective hydrolyses of the diacetates 1 and 2. The resulting chiral monoacetates, 3 and 4, are transformed into the lactones, 5 and 6, important intermediates to (+)-biotin[3] and (-)-A-factor[4], respectively.

The commercial synthesis of (+)-biotin proceeds via the chiral lactone (5), which had been prepared via the reduction of 8[3] (R = cyclohexyl or cholesteryl). Recently, Iriuchijima et al.[5] attempted to prepare 8 via asymmetric hydrolysis of 7 using pig-liver esterase (PLE). As expected, the reaction terminated at the monoester stage and satisfactory chemical yields of 8 were obtained. However, the enantiomeric excess (ee) of 8 was found to be only moderate (i.e., R = CH_3, ee = 0.38, 71%; R = n-C_3H_7, ee = 0.75, 85%). The need to improve the enantioselectivity of the enzymic hydrolytic reaction prompted us to deploy our strategy of using the meso-diacetoxy ester, 1 as the substrate.



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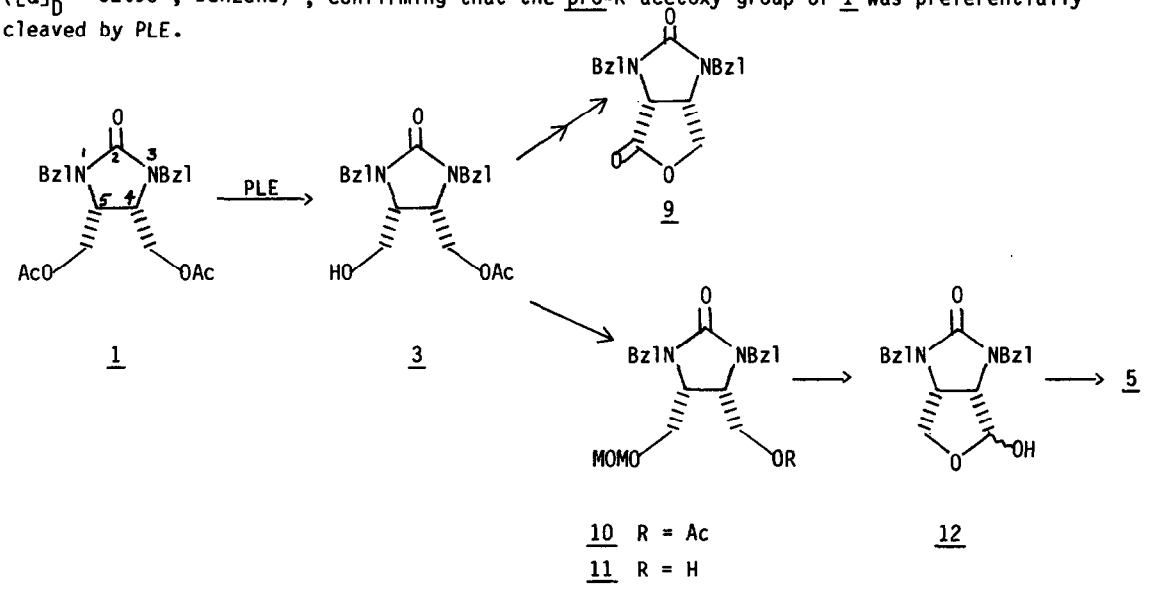
The diacetate, 1 (206 mg), was incubated with PLE (218 units, Sigma) in 50 ml of 0.1 M phosphate buffer (containing 10% methanol and 75 mg of Triton X-100), pH 7.0 at 25°C on a rotary shaker. At various intervals, the extent of conversion and ee of 3 were determined.[6] These values were used for the calculation of the kinetic constants: α = 14.5, E_1 = 0.14 and E_2 = 0.55[7], revealing that the optimal amount of 3 obtainable was 70% with an ee of 0.92.[1]

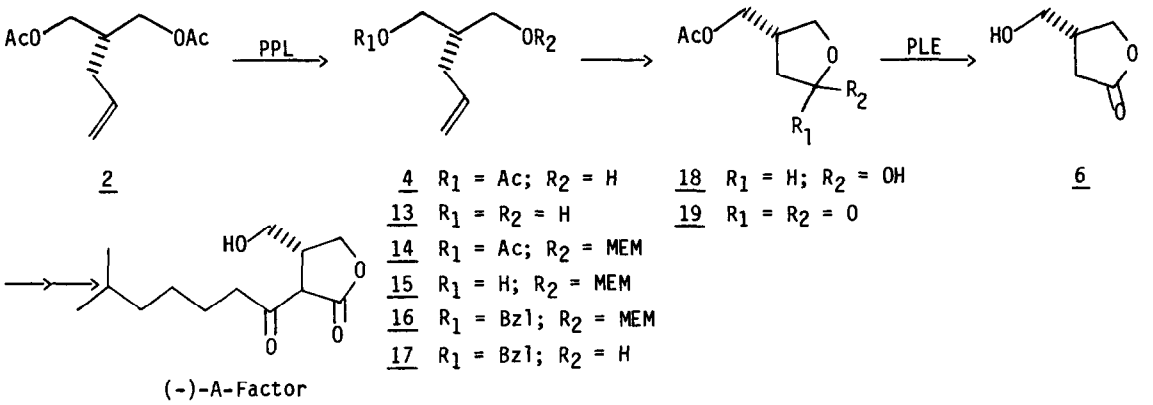
The absolute stereochemistry of 3 ($[\alpha]_D^{23}$ +5.01°, $CHCl_3$, ee = 0.90) was established by its

transformation (Jones oxidation; basic hydrolysis and lactonization) into the known lactone, 9 ($[\alpha]_D^{23}$ -52.96°, benzene)[8], confirming that the pro-R acetoxy group of 1 was preferentially cleaved by PLE.



Reaction of 3 ($[\alpha]_D^{23}$ +5.12°, $CHCl_3$) with methoxymethyl chloride (MOM chloride) and N,N-diisopropylethylamine in dichloromethane gave 10 ($[\alpha]_D^{23}$ +10.95°, $CHCl_3$, 93%). After reductive cleavage of the acetoxy group (LAH/ether-THF), the resulting alcohol, 11 ($[\alpha]_D^{23}$ +0.98°, $CHCl_3$), was oxidized (Collins oxidation) and the MOM protecting group removed [HCl/THF:H_2O (95:5)] to yield the lactol, 12 (70% from 10). Collins oxidation of 12 afforded the desired (4S,5R)-lactone, 5 ($[\alpha]_D^{23}$ +53.9°, benzene, ee = 0.93) in 85% yield. Crystallization from benzene-Skelly B (3:5) gave optically-pure 5, m.p. 119-119.5°C, $[\alpha]_D^{23}$ +58.3° (c, 1 benzene).

The lactone, 6, is a valuable chiron for the synthesis of microbial growth factors[9] such as the (-)-A-factor. We envisaged that 6 may be conveniently prepared from 4, which in turn may be prepared via enantioselective hydrolysis of the prochiral diacetate, 2. Pig pancreatic lipase (PPL) was found to be the most suitable enzyme for this purpose.



The diacetate, 2 (100 mg), suspended in 15 ml of 0.1 M phosphate buffer, pH 7.0, was incubated with 150 mg of PPL [Sigma Type II (Pfs)] on a rotary shaker at 25°C. At various intervals, the amount of 2, 4 and the diol, 13, were quantitatively assayed[10] to allow the calculation of the kinetic constants (α = 3.60; E_1 = 0.04 and E_2 = 0.15). These kinetic constants indicate that for an ee of 0.95 the optimal recoverable yield of the monoacetoxy ester, 4, was 34%. The following reaction sequence was used to transform the monoacetate, 4, into 17: reaction of 4 ($[\alpha]_D^{23}$ -7.65°) with β-methoxyethoxymethyl chloride (MEM chloride) and N,N-diisopropylethylamine gave 14 (90% yield). After hydrolysis (1 N NaOH), the resulting alcohol, 15, was benzylated ($NaH/C_6H_5CH_2Br$) to yield 16 ($[\alpha]_D^{23}$ -1.97°) in 86% yield. The MEM protecting group was removed via acidic hydrolysis (TsOH reflux) affording 2(S)-allyl-3-benzyloxypropan-1-ol (17), $[\alpha]_D^{23}$ -11.8° [lit.[11] (2R): $[\alpha]_D^{22}$ +13.6°]. This correlation confirms that PPL has a stereochemical preference for the pro-R acetoxy group of 2.

Transformation of 4 into 6 was achieved via the following reaction sequence: ozonolysis [1) O_3/EtOAc; 2) Zn/CH_3OH-HOAc, 61%] of 4 afforded the lactol, 18, which was oxidized (Collins oxidation) to the lactone ester, 19 ($[\alpha]_D^{23}$ -33.1°, $CHCl_3$). Hydrolysis of the acetoxy group was achieved using PLE to give the desired (3R)-lactone, 6 ($[\alpha]_D^{23}$ +46.1°, $CHCl_3$, 35%).[12]

The successful preparation of the chirons, 3 and 4, of high optical purities, further illustrates the general applicability of this concept to biochemical processes involving enantiotopic group differentiation. Moreover, this strategy extends the usefulness of esterases of low to moderate enantioselectivity for asymmetric synthesis.

Acknowledgment

This investigation was supported in part by Grant HL25772 of the National Institutes of Health.

References and Notes

1) For part 3 of this series, see: Y. F. Wang, C. S. Chen, G. Girdaukas and C. J. Sih, J. Am. Chem. Soc. 106, 3695 (1984).
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4) a) K. Mori and K. Yamada, Tetrahedron 38, 2919 (1982);
   b) K. Mori, ibid. 39, 3107 (1983).
5) S. Iriuchijima, K. Hasegawa and G. Tsuchihashi, Agric. Biol. Chem. 46, 1907 (1982).
6) a) Compounds 1 and 3 were quantitatively assayed via HPLC using a 50 cm microporasil (10 μ) column (ID 4.6 mm). The column was eluted with ethyl acetate-Skelly B (1:1) at a flow rate of 1.9 ml/min. The absorbance at 254 nm was monitored and the retention times were: 1, 5.7 min; 3, 10 min.
   b) The ee of 3 was determined as follows: treatment of 3 with MOMCl and diisopropylethylamine gave the MOM acetate, 10 (15 mg), which was analyzed by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ (75 mg).
7) Methods for the determination of the kinetic parameters α, E_1 and E_2 are described in reference 1.

8) M. Gerecke, J. P. Zimmermann and W. Aschwanden, Helv. Chim. Acta 53, 991 (1970).
9) U. Gräfe, W. Shade, I. Eritt, W. F. Fleck and L. Radics, J. Antibiotics 35, 1722 (1982).
10) These compounds (2, 4 and 13) were assayed by GLC analysis on a 3 ft chromosorb WHP column with 5% OV-101 as the stationary phase. The column temperature was 95°C and the flow rate was 30 ml/min. The retention times were: 2, 9.83 min; 4, 4.67 min; and 13, 2.67 min. The monoacetate, 3, was converted into its (+)MTPA ester (35 mg), which was analyzed by ^{1}H NMR spectroscopy in the presence of 53 mg of Eu(hfc)$_3$ for the determination of ee.
11) T. Fukuyama, C. L. J. Wang and Y. Kishi, J. Am. Chem. Soc. 101, 260 (1979).
12) All compounds herein described gave satisfactory elemental or MS analyses and their IR and NMR spectra were consistent with assigned structures.

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