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Enzyme-catalyzed Asymmetric Hydrolysis of meso-Substrate. The Facile Synthesis of Both Enantiomers of cis-2,5-Disubstituted Tetrahydrofuran Derivatives

Koichiro NAEMURA,* Nobuo TAKAHASHI, and Hiroaki CHIKAMATSU
Department of Chemistry, Faculty of Engineering Science,
Osaka University, Toyonaka, Osaka 560

The enzyme-catalyzed asymmetric hydrolysis of the meso-diesters derived from cis-2,5-bis(hydroxymethyl)tetrahydrofuran in presence of PLE, PPL, and CCL afforded the optically active half-esters. The both enantiomers of cis-5-(hydroxymethyl)tetrahydrofuran-2-carboxylic acid with high optical purity were prepared from the half-esters.

The use of hydrolytic enzymes as practical chiral catalysts have well been documented[1] and of particular value in this regard are the abilities of hydrolytic enzymes to induce stereospecific transformations of meso-substrates to chiral products. Many naturally occuring antibiotics have cis-2,5-disubstituted tetrahydrofuran unit as a common structural feature.[2] In this context we recently described the preparation of optically active trans-2,5-disubstituted tetrahydrofuran derivative and of chiral ionophores having this derivative as a chiral unit.[3] We report here the synthesis of the optically active cis-2,5-disubstituted tetrahydrofuran derivatives by enzyme-catalyzed asymmetric hydrolysis of meso-diesters.

cis-2,5-Bis(hydroxymethyl)tetrahydrofuran (1), bp 148-151 °C (10 mmHg), was prepared from cis-2,5-bis(hydroxymethyl)furan, prepared according to the known procedure,[4] by catalytic hydrogenation with Raney-Ni. Treatment 1 with acetyl, propionyl, isobutyl, and vareryl chloride in ether-pyridine gave the diesters 2a (bp 105.5-106.5 °C (0.5 mmHg)), 2b (bp 115-116.5 °C (0.4 mmHg)), 2c (bp 122-124 °C (0.5 mmHg)), and 2d (bp 120.5-121.5 °C (0.4 mmHg)), respectivery.

Asymmetric hydrolysis of 2a-2d catalyzed by pig liver esterase (PLE)[5] were performed at pH 8.0 in 0.1 M (1 M=1 mol dm^{-3}) phosphate buffer solution (2.4 L) at 0 °C on 19 mmol scale. In every cases, the product was extracted with chloroform and purified by alumina column chromatography followed by distillation to give the corresponding half-esters, and the resulting meso-diol 1 was not isolated, because it is readily soluble in water. Asymmetric hydrolysis catalyzed by lipase from porcine pancreas (PPL)[5] and lipase from Candida cylindracea (CCL)[5] were performed at pH 8.0 and 7.0 in 0.1 M phosphate buffer solution at room temperature, respectively. The results are summarized in Table 1.

Oxidation of 3a, $[\alpha]_D$ -4.45°, with CrO_3 in acetone followed by esterification with diazomethane gave 4a, bp 125-127 °C (0.5 mmHg); $[\alpha]_D$ -15.3° ($CHCl_3$). The ester 4a was hydrolyzed with aqueous solution of sodium carbonate at room temperature to provide (-)-cis-5-(hydroxymethyl)tetrahydrofuran-2-carboxylic acid (5), $[\alpha]_D$ -2.82° ($CHCl_3$). Treatment of 5 with diazomethane in ether provided (+)-

(2S,5R)-6, $[\alpha]_D$ +21.4° ($CHCl_3$) (96% enantiomeric excess (e.e.)), whose absolute configuration and e.e. value have been reported by Jones.[6] The information on the absolute configuration and e.e. value of (+)-6 permitted us to assign the 2R,5R configuration to (-)-3a and estimate 96% e.e. for (-)-3a obtained by PLE-catalyzed hydrolysis. Analogously, the absolute configuration and the e.e. value of the half esters 3b,3c, and 3d were determined by conversion into 6 via (-)-4b, $[\alpha]_D$ -6.81° ($CHCl_3$), (-)-4c, $[\alpha]_D$ -8.81° ($CHCl_3$), and (-)-4d, $[\alpha]_D$ -9.05° ($CHCl_3$), respectively. By the same procedure described above, (+)-5 with 80% e.e. was also prepared from (+)-3b obtained by CCL-catalyzed hydrolysis of 2a.

Table 1. Asymmetric hydrolysis of the meso-diesters

Entry	Substrate	Enzyme	Product[7] (% isolated)[a]	e.e. (%)	Time/h	$[\alpha]_D$/°($CHCl_3$)
1	2a	PLE	(2S,5R)-3a (86)	96	18	-4.45
2	2b	PLE	(2S,5R)-3b (54)	42	2.3	-2.84
3	2c	PLE	(2S,5R)-3c (62)	94	2.8	-3.17
4	2d	PLE	(2S,5R)-3d (72)	55	7.5	-1.20
5	2a	PPL	(2S,5R)-3a (53)	41	305	-1.91
6	2b	PPL	(2S,5R)-3b (57)	33	22	-2.25
7	2c	PPL	(2S,5R)-3c (68)	32	20	-1.08
8	2d	PPL	(2S,5R)-3d (71)	16	56 (d)	-0.34
9	2a	CCL	(2R,5S)-3a (50)	70	96	+3.26
10	2a	CCL	(2R,5S)-3a (20)	80	214	+3.72
11	2b	CCL	(2R,5S)-3b (69)	26	22	+1.77
12	2c	CCL	(2R,5S)-3c (75)	28	3.5	+0.94
13	2d	CCL	(2R,5S)-3d (71)	4	41 (d)	+0.09

a) After alumina column chromatography.

As can be seen from Table 1, among the asymmetric hydrolysis of the diesters, hydrolysis of 2a with PLE provided the half-ester 3a with the highest e.e. value. In the cases of PLE-catalyzed and PPL-catalyzed hydrolysis, the CH_2OCOR-group located at the (S)-chirality center was dominantly hydrolyzed. In CCl-catalyzed hydrolysis, a clear reversal of the stereospecificity was observed and elongation of the reaction time raised the e.e. value of the product 3a from 70% to 80% (Entries 9, 10). The rate of hydrolysis of these diesters was considerably influenced by the nature of the acyl group. The diesters having relatively large acyl graoups; 2b and 2c were hydrolyzed faster than 2a with all enzymes examined here, but the 2,2-dimethylpropionyloxy group reduced remarkably the rate of hydrolysis of the diester.

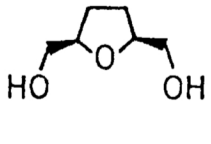
Next we turned attention to resolve the racemic cis-monoacetate 3a and trans-diacetate 8 by enantioselective hydrolysis with PLE and CCL. The hydrolysis of (±)-3a and (±)-8 was carried out under the similar conditions described for the hydrolysis of meso-substrates and terminated at, or close to, the 50%-of-hydrolysis

point. The results are summarized in Table 2.

Table 2. Enantioselective hydrolysis of racemic substrates

Entry	Substrate	Enzyme	Product[7] (% yield)	e.e. (%)	Time/h	$[\alpha]_D$/°
14	(±)-3a	PLE	(-)-(2S,5R)-3a (47)	53	17	-2.46
15	(±)-3a	CCL	(+)-(2R,5S)-3a (54)	7	115	+0.31
16	(±)-8	PLE	(-)-(2R,5R)-8 (47)	58	3.5	-24.8
			(+)-(2S,5S)-9 (48)	58		+22.8
17	(±)-8	CCL	(+)-(2S,5S)-8 (38)	<1	52.5	+0.18
			(-)-(2R,5R)-9 (49)	<1		-0.10

In the case of PLE-catalyzed hydrolysis, 3a having the acetoxy group located at the (S)-chirality center was dominantly hydrolyzed to give 1, and (-)-(2S,5R)-3a with 53% e.e. was recovered after alumina chromatography. A reversal of the stereospecificity was also observed in CCL-catalyzed hydrolysis of (±)-3a, and (+)-3a with 7% e.e. was recovered. The hydrolyzed product 1 was not isolated in both cases. Both acetoxy groups of (+)-8 locate at the (S)-chilality center, however, the PLE-catalyzed hydrolysis of 8 terminated exclusively at the half-ester stage to give (+)-(2S,5S)-9 in 48% yield, and (-)-(2R,5R)-8 was recovered. The absolute configuration and e.e. value of 8 and 9 were determined by conversion to the known diol 7.[3] In CCL-catalyzed hydrolysis of (±)-8, the half-ester 9 undergo further cleavage to yield the diol 7 which was not isolated, and the enantiomer selectivity of this reaction was extremely low. Oxidation of (+)-9 with CrO_3 in acetone followed by hydrolysis with sodium carbonate in water gave (+)-trans-5-(hydroxymethyl)tetrahydrofuran-2-carboxylic acid (10), $[\alpha]_D$ +3.1° ($CHCl_3$) (58% e.e.).



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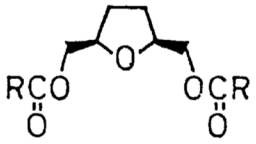
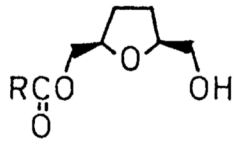
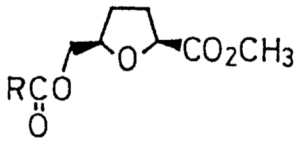


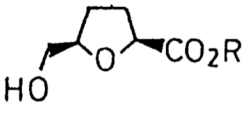
2a R=CH_3
2b R=CH_2CH_3
2c R=$CH(CH_3)_2$
2d R=$C(CH_3)_3$



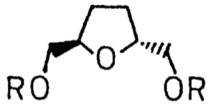
(-)-3a R=CH_3
(-)-3b R=CH_2CH_3
(-)-3c R=$CH(CH_3)_2$
(-)-3d R=$C(CH_3)_3$



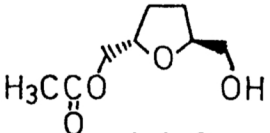
(-)-4a R=CH_3
(-)-4b R=CH_2CH_3
(-)-4c R=$CH(CH_3)_2$
(-)-4d R=$C(CH_3)_3$



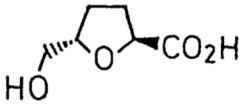
(-)-5 R=H
(+)-6 R=CH_3



(-)-7 R=H
(-)-8 R=$COCH_3$



(+)-9



(+)-10

As mentioned above, the enzyme-catalyzed asymmetric hydrolysis of the meso-diesters provided the method of the facile preparation of both enantiomers of the chiral cis-2,5-disubstituted tetrahydrofuran derivatives, and PLE-catalyzed hydrolysis of the racemic diacetate was useful for the convenient synthesis of the half-ester in an optically active form.

References

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4) P. A. Finan, J. Chem. Soc., 1963, 3917.

5) P.L.E.: BMY 104698 100 Units/mg; P.P.L.: Sigma, Type II , 16 Units/mg; C.C.L.: Sigma, Type VII , 400-900 Units/mg.

6) J. B. Jones, R. S. Hinks, and P. G. Hultin, Can. J. Chem., 63, 452 (1985).

7) All new compounds gave satisfactory spectral data and elemental analyses. Boiling points of the esters, 3a; bp 92.0-92.5 °C (0.3 mmHg), 3b; bp 99.0 °C (0.3 mmHg), 3c; bp 96.0-97.0 °C (0.2 mmHg), 3d; bp 93.0 °C (0.2 mmHg), 8; bp 87-90 °C (0.2 mmHg), 9; bp 96.5-97.5 °C (0.2 mmHg).

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