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Stereodivergent synthesis of (2*R*)-2,3-diricinolein by lipase-catalyzed hydrolysis of triricinolein

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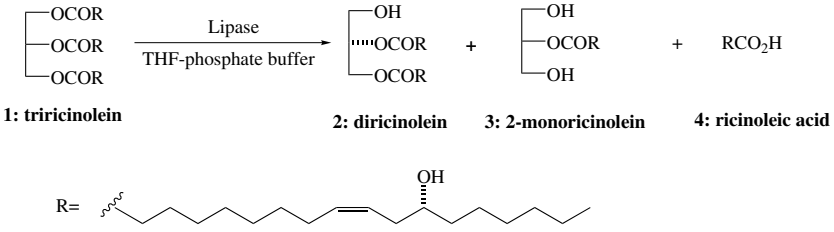
Abstract—The preparation of 2,3-diricinolein by lipase-catalyzed hydrolysis of triricinolein has been developed. Lipase-catalyzed hydrolysis of triricinolein provided (2*R*)-2,3-diricinolein in high diastereoselectivity.

1. Introduction

The development of synthetic methods for diacylglycerols (DAG) is important because of their usefulness as emulsifiers in food, pharmaceuticals, and cosmetics. DAG oil is a useful substitute for triacylglycerol oil in food.[1] Castor oil consists of approximately 90% ricinoleic (12-hydroxy-*cis*-octadecenoic) acid with a hydroxy group and a double bond as the dominant constitutive fatty acid, and is made mixed use of as lacquers, leatherettes, printing inks, lubricants, cosmetics, insulators, and drugs. Although castor oil is saponified in industry for the preparation of ricinoleic acid, which is useful in the pharmaceutical and cosmetics industries, this method has some disadvantages such as the large amount of by-products and coloring of the products. To solve the above problems, lipase catalyzed hydrolysis of castor oil has been studied.[2] McKeon et al. reported lipase-catalyzed methanolysis of triricinolein in organic solvent to produce 1,2(2,3)-diricinolein.[3] However, little attention has been paid to the stereodivergent synthesis of diricinoleins. In connection with the growing importance of the structure-acting relationship of chiral materials, the stereocontrolled hydrolysis of triricinolein is of increasing importance. Herein, we report a diastereoselective preparation of 2,3-diricinolein by lipase-catalyzed hydrolysis of triricinolein (Scheme 1).

2. Results and discussion

We first examined lipase PS-catalyzed hydrolysis of triricinolein[4] in THF-phosphate buffer at room temperature for several reaction times[5] with the results shown in Table 1. When the hydrolysis was carried out for 10 min, the desired diricinolein **2** was obtained in 12% yield with 82.0%



Scheme 1.

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Table 1. Lipase PS-catalyzed hydrolysis of triricinolein at rt

Entry	Temp. (°C)	Time (min)	Yield (%)				2*R*:2*S*[a]
			1	**2**	**3**	**4**	
1	rt	10	57	12	13	9	91.0:9.0
2	rt	20	52	20	15	18	95.2:4.8
3	rt	30	51	26	12	20	96.1:3.9
4	rt	40	47	25	14	16	89.1:10.9
5	rt	50	18	25	32	28	88.3:11.7
6	rt	60	9	21	51	42	72.9:27.1
7	rt	120	Trace	25	65	54	66.0:34.0
8	rt	360	Trace	25	53	54	50.5:49.5
9	rt	720	Trace	11	35	57	51.7:48.3
10	0	10	80	12	5	6	93.7:6.3
11	0	20	72	11	3	12	94.6:5.4
12	0	30	49	23	12	25	92.4:7.6
13	0	40	61	19	12	11	90.9:9.1
14	0	50	49	20	16	21	92.9:7.1
15	0	60	44	23	28	23	86.1:13.9
16	0	90	45	28	35	19	86.6:13.4
17	0	120	32	18	24	17	88.1:11.9

[a] Diastereomeric excesses were determined by the HPLC analysis using the chiral column, Chiralcel-OD after transformation of **2** into its tribenzoate ester.

Table 2. Lipase AK or PPL-catalyzed hydrolysis of triricinolein at rt

Entry	Lipase	Time (min)	Yield (%)				2*R*:2*S*[a]
			1	**2**	**3**	**4**	
1	AK	15	75	19	Trace	9	96.4:3.6
2		30	41	35	18	21	96.0:4.0
3		45	45	30	11	23	95.7:4.3
4		60	30	40	11	24	96.5:3.5
5		120	Trace	46	28	49	89.3:10.7
6	PPL	20	62	16	19	13	65.6:34.4
7		40	21	26	46	40	58.4:41.6
8		60	38	27	34	19	60.6:39.4
9		90	Trace	22	59	45	50.6:49.4

[a] Diastereomeric excesses were determined by the HPLC analysis using the chiral column, Chiralcel-OD after the transformation of **2** into its tribenzoate ester.

de along with the recovered triricinolein **1** (57%), 2-monoricinolein **3** (13%), and ricinoleic acid (9%). The diastereomeic excess of diricinolein **2** was determined as being 82.0% by HPLC analysis of its tribenzoate ester.[6] The highest (92.2% de) was obtained, when the hydrolysis was conducted for 30 min (entry 3). As the reaction times increased, the des of **2** decreased presumably due to the competing acyl migration. The hydrolysis proved sensitive to the reaction temperature. The lipase PS-catalyzed hydrolysis at 0 °C generally gave lower discriminations.

We next examined lipase AK and PPL-catalyzed hydrolysis of triricinolein **1** in THF-phosphate buffer at room temperature with the results shown in Table 2. Lipase AK gave superior yields and des when compared to those in lipase PS-catalyzed hydrolysis of triricinolein **1**. In particular, when the hydrolysis was carried out for 60 min, the desired 2,3-diricinolein **2** was obtained in 40% yield with 93.0% de (entry 4). On the other hand, lipase PPL-catalyzed hydrolysis of triricinolein **1** gave lower des of diricinolein **2**.

The effects of organic solvents on the lipase AK-catalyzed hydrolysis are shown in Table 3. In all the organic solvents, the observed des of **2** were lower than those in THF (entries 1–7). Although hydrolysis proceeded in the phosphate buffer itself, a low de of **2** was obtained (entry 8).

The absolute configuration of diricinolein **2** was determined by measuring the specific rotation of **6** transformed according to the method reported by Meguro et al. as shown in Scheme 2.[7] The result indicated that the major diastereomer of diricinolein **2** prepared by lipases PS, AK, and PPL-catalyzed hydrolysis of tricinolein **1** was 2,3-di-*O*-ricinoleoyl-*sn*-glycerol.

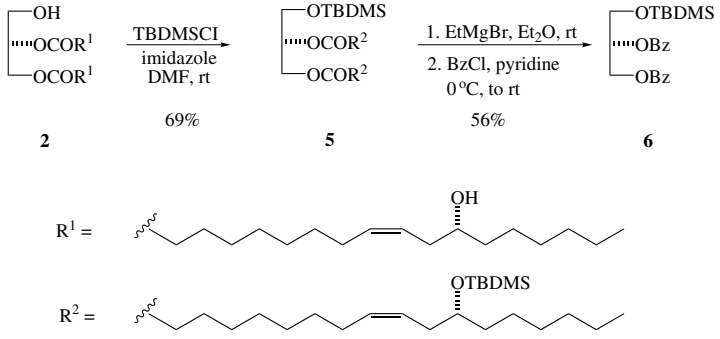
3. Conclusion

In summary, we have found a diastereoselective preparation of (2*R*)-2,3-diricinolein by lipase-catalyzed hydrolysis of triricinolein. Although lipase-catalyzed hydrolysis or methanolysis of triricinolein have been studied, to the best of our knowledge, the diastereoselective preparation of 2,3-diricinolein by lipase-catalyzed hydrolysis of triricinolein has not been reported. In the present reaction, 2,3-diricinolein can be easily obtained

Table 3. Effects of the organic solvents in the lipase AK-catalyzed hydrolysis of triricinolein

Entry	Organic solvent	Time (min)	Yield (%)				2*R*:2*S*[a]
			1	**2**	**3**	**4**	
1	Et_2O	30	31	40	19	28	73.5:26.5
2	Et_2O	60	9	44	39	38	73.2:26.8
3	Et_2O	120	11	48	25	48	69.5:30.5
4	1,4-Dioxane	60	7	42	29	50	87.1:12.9
5	1,4-Dioxane	120	Trace	37	46	60	83.7:16.3
6	Toluene	60	83	11	Trace	3	95.7:4.3
7	Toluene	120	93	4	Trace	Trace	92.3:7.7
8	None	60	24	36	21	25	69.4:30.6

[a] Diastereomeric excesses were determined by HPLC analysis using the chiral column, Chiralcel-OD after the transformation of **2** into its tribenzoate ester.



Scheme 2.

with high diastereoselectivity (up to 93.0% de) because lipase-AK is commercially available and hydrolysis can be carried out under mild reaction conditions.

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4. Triricinolein was obtained by purification of castor oil using silica gel column chromatography.
5. General procedure for the synthesis of diricinolein **2**. To a solution of triricinolein **1** (93.3 mg, 0.100 mol) in THF (0.5 mL) and phosphate buffer (1.5 mL) was added lipase AK (5.0 mg) at room temperature. The mixture was stirred at room temperature for 60 min and then filtered through a Celite pad, which was washed with EtOAc. The filtrate was washed with brine and dried over Na_2SO_4. The solvents were evaporated in vacuo, and then the residue purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to give diricinolein **2** (26.0 mg, 40%) as a colorless oil, 2-monoricinolein **3** (4.2 mg, 11%), and a mixture of recovered **1** and ricinoleic acid (28.3 mg, 30%, 24%, respectively, by ^{1}H NMR analysis). IR (neat): 3384, 2927, 2855, 1739, 1461, 1375, 1173, 1052, 857, 756, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 5.53–5.58 (m, 2H), 5.38–5.43 (m, 2H), 5.06–5.10 (m, 1H), 4.32 (dd, J = 11.9, 4.6 Hz, 1H), 4.23 (dd, J = 11.9, 5.8 Hz, 1H), 3.73 (br s, 2H), 3.59–3.64 (m, 2H), 2.31–2.36 (m, 4H), 2.20–2.25 (m, 5H), 2.03–2.07 (m, 4H), 1.60–1.63 (m, 6H), 1.43–1.51 (m, 4H), 1.25–1.31 (m, 32H), 0.89 (t, J = 6.7 Hz, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$): 173.7, 173.4, 133.2, 125.2, 72.1, 71.5, 62.1, 61.3, 36.8, 35.3, 34.2, 34.0, 31.8, 29.5, 29.3, 29.0, 27.3, 25.7, 24.8, 24.7, 22.6. $[\alpha]_D^{24} = +4.45$ (*c* 0.245, $CHCl_3$).
6. General procedure for the synthesis of the tribenzoate ester of diricinolein **2**. To a solution of diricinolein **2** (24.5 mg, 0.038 mmol) in CH_2Cl_2 (2.5 mL) was added pyridine (19.5 mg, 0.24 mmol) at 0 °C under an argon atmosphere, and the mixture stirred at 0 °C for 5 min. Benzoyl chloride (48.4 mg, 0.34 mmol) was added to the resulting mixture at 0 °C. The mixture was warmed to room temperature and then stirred for 21 h. 1 M HCl was added to quench the reaction. The mixture was extracted with EtOAc. The combined extracts were washed with H_2O, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvents were evaporated in vacuo and then the residue purified on preparative TLC (*n*-hexane/EtOAc = 2/1) to give 1-benzoyl-2,3-di(12-benzoyloxy-*cis*-9-octadecenoyl)-*sn*-glycerol along with small amounts of impurities. Further purification on preparative TLC (*n*-hexane/EtOAc = 4/1) gave pure 1-benzoyl-2,3-di[(12*R*)-benzoyloxy-*cis*-9-octadecenoyl]-*sn*-glycerol (33.6 mg, 87%). IR (neat): 3065, 3010, 2929, 2856, 1718, 1602, 1453, 1358, 1314, 1274, 1174, 1113, 1069, 1025, 910, 733, 713, 649 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): 8.00–8.05 (m, 6H), 7.52–7.60 (m, 3H), 7.40–7.47 (m, 6H), 5.30–5.50 (m, 5H), 5.09–5.18 (m, 2H), 4.52 (dd, J = 11.9, 4.3 Hz, 1H), 4.29–4.42 (m, 2H), 4.24 (dd, J = 11.9, 5.9 Hz, 1H), 2.39–2.46 (m, 4H), 2.27–2.35 (m, 4H), 1.99–2.04 (m, 4H), 1.55–1.75 (m, 8H), 1.22–1.38 (m, 32H), 0.85 (t, J = 6.6 Hz, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$):

173.2, 172.8, 166.2, 165.9, 133.2, 132.7, 130.7, 129.7, 129.5, 128.4, 128.2, 124.1, 74.6, 68.8, 62.8, 62.1, 34.1, 34.0, 33.7, 32.0, 31.7, 29.5, 29.1, 29.1, 29.1, 29.0, 29.0, 27.3, 25.4, 24.8, 24.8, 22.5, 14.0. $[\alpha]_D^{23} = +11.3$ (*c* 0.336, $CHCl_3$). The de of 1-benzoyl-2,3-di[(12*R*)-12-benzoyloxy-*cis*-9-octadecenoyl]-*sn*-glycerol was determined to be 93.0% by HPLC analysis (DAICEL CHIRALCEL OD), hexane/2-propanol=50/1 (v/v), at a flow rate of 0.7 mL min^{-1}. The 2,3-diricinolein was eluted first ($t_{2,3}$ = 22.0 min), followed by 1,2-diricinolein ($t_{1,2}$ = 29.2 min).

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