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Stereodivergent synthesis of both (2*S*)- and (2*R*)-1-monoricinolein derivatives by lipase-catalyzed hydrolysis or transesterification directed to new ferroelectric liquid crystals

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Dedicated to the memory of Professor Yoshihiko Ito. Deceased on December 23, 2006

Abstract—The preparation of both (2*S*)- and (2*R*)-1-monoricinolein derivatives has been developed to synthesize ferroelectric liquid crystals. Lipase-catalyzed hydrolysis of 2-protected-1,3-diricinoleins provided (2*S*)-1-monoricinolein derivatives with high diastereoselectivities, while transesterification of 2-protected glycerols with vinyl recinoleate gave (2*R*)-1-monoricinolein counterparts in good yields with high diastereoselectivities.

1. Introduction

Ferroelectric liquid crystals, which have an asymmetric structure and show a smectic phase, are possible to be utilized as an indicator device possessing a high-speed switching character and a memory function. In general, the characteristic structure contains an alkyl chain, a flexible acyclic structure at both ends of a rigid skeletal structure (core part). It is also necessary to have an asymmetric structure for ferroelectricity, namely spontaneous polarization (Fig. 1).[1]

In order to prepare ferroelectric liquid crystals, we first planned to prepare 1-monoricinolein as a chiral part including asymmetric carbons using lipase-catalyzed hydrolysis[2] of triricinolein obtained by purification of castor oil, which is commercially available and consists of approximately 90% ricinoleate (12-hydroxy-*cis*-octadecenoic) acid esters with a hydroxy group and a double bond as the dominant constitutive fatty acid. Castor oil is saponified in industry for the preparation of ricinoleic acid. The core part with a rigid skeletal structure can be introduced at the hydroxy group. However, the lipase-catalyzed hydrolysis of triricinolein to monoricinolein gave an undesired regioisomer 2-monoricinolein. We next examined the lipase-catalyzed hydrolysis of 1,3-diricinolein prepared from glycerol with ricinoleic acid. Herein, we report a diastereoselective preparation of 1-monoricinolein derivatives by lipase-catalyzed hydrolysis of 1,3-diricinolein derivatives and lipase-catalyzed transesterification of 2-protected glycerols with vinyl ricinoleate as an acyl donor.

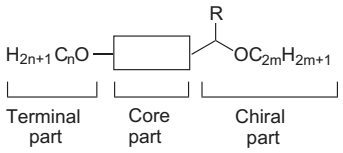

Figure 1. Ferroelectric liquid crystal compounds.

2. Results and discussion

We examined the lipase-catalyzed hydrolysis of 1,3-diricinolein **1a**, which was prepared from glycerol with ricinoleic acid, in THF–phosphate buffer at room temperature. Table 1 summarizes the results. When the lipase PS-catalyzed hydrolysis was carried out for 20 min, the desired 1-monoricinolein **2a** was obtained in 26% yield with 28% de (entry

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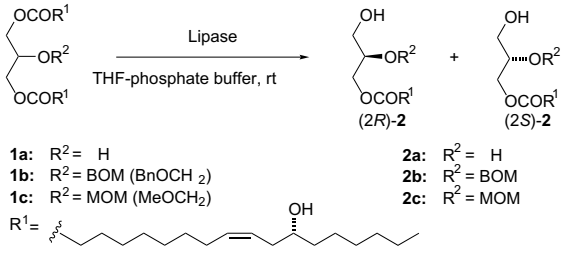
Table 1. Lipase-catalyzed hydrolysis of **1**



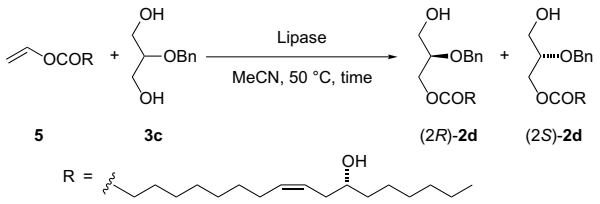
Entry	Lipase	R^2	Time (min)	Yield[a] (%)	(2*R*)-**2**:(2*S*)-**2**[b,c]	de
1	PS	H	20	26	36:64	28
2	PS	H	30	36	22:78	56
3	PS	H	40	55	47:53	6
4	PS	BOM	10	24	12:88	76
5	PS	BOM	20	40	5:95	90
6	PS	BOM	30	35	5:95	90
7	AK	BOM	30	14	15:85	70
8	PS	MOM	25	32 (51)[d]	3:97	94
9	PS	MOM	35	8	6:94	88

[a] Isolated yield.
[b] Diastereomeric excesses were determined by HPLC analysis using the chiral stationary phase column, Chiralcel-OD after transformation of **2** into its di or tribenzoate ester.
[c] Configurations of product **2a** and **2c** were assigned by analogy.
[d] Yield in the parenthesis is based on the recovered 1,3-direcinolein derivative **1c**.

1).[3] When the hydrolysis was conducted for 30 min, a moderate 56% de was obtained (entry 2). As the reaction times increased, the de of **2a** decreased presumably due to competing acyl migration (entries 1–3). To prevent the acyl migration of 1-monoricinolein **2a**, 2-protected-1,3-diricinolein derivatives **1b** and **1c**, which were prepared from 2-protected glycerols[4] with ricinoleic acid, were used as starting materials. When the lipase PS-catalyzed hydrolysis of **1b** was carried out, the des of **2b** increased (entries 4–6). The use of lipase AK, which has been found to be the most effective lipase in the hydrolysis of triricinolein to (2*R*)-2,3-diricinolein,[5] gave **2b** in low yield with moderate de (entry 7). The highest 94% de was obtained, when the hydrolysis of **1c** was conducted for 25 min (entry 8).[6]

We next examined the lipase-catalyzed transesterification of 2-protected glycerol **3** with triricinolein **4** as an acyl donor. Table 2 summarizes the results. Among the lipases

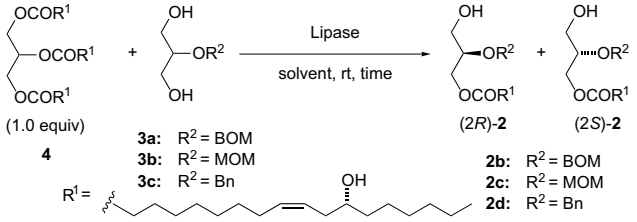
Table 3. Lipase-catalyzed transesterification of **3c** with vinyl ricinoleate **5**[a]



Entry	Lipase	Time (h)	Yield[b] (%)	(2*R*)-**2d**:(2*S*)-**2d**[c]	de
1	PPL	3.5	15	80:20	60
2	PS	3.5	29	88:12	76
3	AK	3.5	49	88:12	76
4	AK	6.0	58	96:4	92
5	AK	12.0	64	98:2	96
6	AK	18.0	65	96:4	92
7	AK	24.0	38	81:19	62

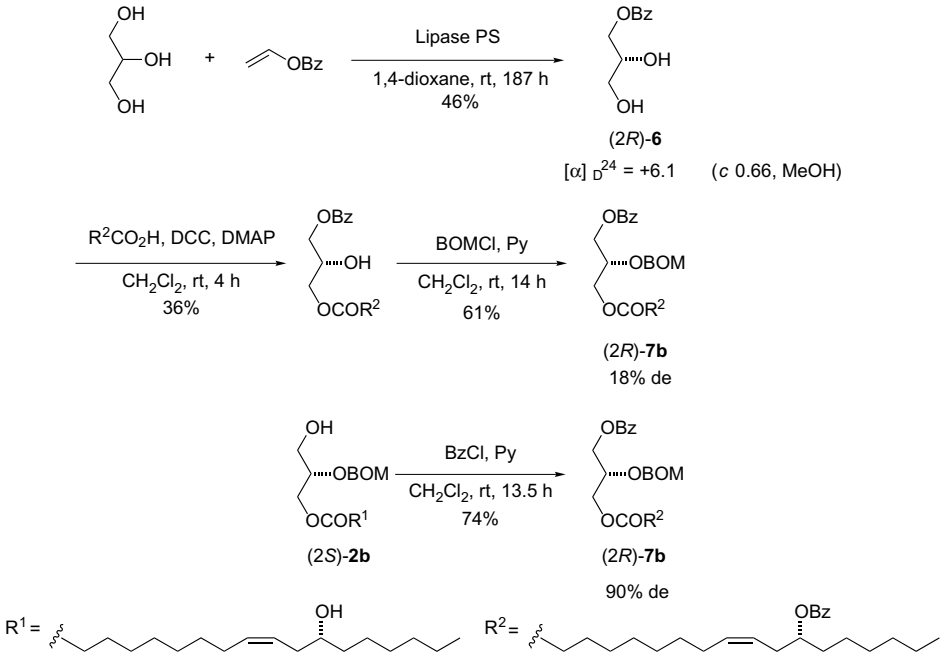
[a] **5** (1.0 equiv) in entries 1–3. **5** (2.0 equiv) in entries 4–7.
[b] Isolated yield.
[c] Diastereomeric excesses were determined by the HPLC analysis using the chiral stationary phase column, Chiralcel-OD after transformation of **2d** into its dibenzoate ester.

Table 2. Lipase-catalyzed transesterification of 2-protected glycerol derivatives **3** with triricinolein **4**

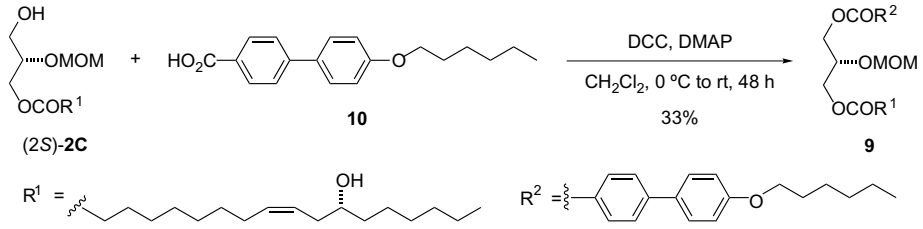


Entry	Lipase	R^2	Solvent	Time (h)	Yield (%)[a]	(2*R*)-**2**:(2*S*)-**2**[b]	de
1	PPL	BOM	MeCN	3.5	22	85:15	70
2	AYS	BOM	MeCN	3.5	Trace	ND	
3	CCL	BOM	MeCN	19.0	Trace	ND	
4	Novozym 435	BOM	MeCN	3.5	43	50:50	0
5	AK	BOM	EtCN	6.5	3	80:20	60
6	PPL	BOM	EtCN	3.5	13	67:33	34
7	PPL	BOM	PrCN	3.5	3	86:14	72
8	PPL	BOM	MeCN:THF (2:1)	3.5	3	87:13	74
9	PPL	BOM	MeCN:*t*BuOMe (2:1)	3.5	31	80:20	60
10	PPL	BOM	MeCN:DME (2:1)	3.5	4	82:18	64
11	PPL	MOM	MeCN	3.5	32	85:15	70
12	PPL	Bn	MeCN	3.5	10	85:15[c]	70

[a] Isolated yield.
[b] Diastereomeric excesses were determined by the HPLC analysis using the chiral stationary phase column, Chiralcel-OD after transformation of **2** into its dibenzoate ester.
[c] Product **2d** configuration was assigned by analogy.



Scheme 1. Determination of product **2b** configuration.



Scheme 2. Preparation of 1,3-acyl glycerol derivative **9**.

tested in transesterification of **3a**[4] with **4**, lipase PPL was found to be the most effective (entries 1–5). Regarding the solvent, acetonitrile (MeCN) gave **2b** in better yields with good diastereomeric excesses (entries 1, 6–10). The effect of a substituent on the 2-protected glycerols was investigated.[7] The desired products **2b**, **2c**, and **2d** were obtained with similar des (entries 1, 11 and 12). In an effort to improve both the yield and de, vinyl ricinoleate **5**[8] was used as an acyl donor. Table 3 summarizes the results. Among the lipases tested, lipase AK gave **2d** in good yields with good des (entries 1–3). The lipase AK-catalyzed transesterifications were carried out for several reaction times. The desired product **2d** was obtained in high yields with des 6.0, 12.0 and 18.0 h, respectively (entries 4–6).[9]

The absolute configuration of **2b** was determined by comparing the retention time of (2*R*)-**7b**, which was transformed from 1-monobenzoyl glycerol (2*R*)-**6**,[10] prepared according to the literature method as shown in Scheme 1, in the HPLC analysis. The result indicated that the major diastereomer of 1-monoricinolein derivative **2b** prepared by lipase PS-catalyzed hydrolysis of **1b** had an (*S*)-configuration.[11] On the other hand, the examination into the retention time in HPLC indicated that the major diastereomer of **2b** prepared by lipase PPL-catalyzed transesterification of **3a** with **4** had an (*R*)-configuration.

The 1,3-diacyl glycerol derivative **9** was synthesized using the general condensation of the 1-monoricinolein derivative (2*S*)-**2c** (94% de) with 4-(4-hexyloxyphenyl)benzoic acid **10** as a rigid skeletal structure as shown in Scheme 2.[12] A preliminary result from differential scanning calorimetry (DSC) of 1,3-diacyl glycerol derivative **9** showed a liquid crystal phase from −20 to 75 °C.

3. Conclusion

In conclusion, we have demonstrated the preparation of both (2*S*)- and (2*R*)-1-monoricinolein derivatives by lipase-catalyzed hydrolysis of 2-protected-1,3-diricinolein derivatives or transesterification of 2-protected glycerols with vinyl ricinoleate as an acyl donor, respectively. 1,3-Diacyl glycerol derivative **9** was prepared from 1-monoricinolein (2*S*)-**2c** and showed a liquid crystal phase.

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2. For reviews, see (a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140; (b)

Nakamura, K.; Hirose, Y. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 668–677.

3. The diastereomeric excess of 1-momoricinolein **2a** was determined by the HPLC analysis of its tribenzoate ester.
4. 2-Benzyloxymethoxypropane-1,3-diol (**3a**) and 2-methoxymethoxypropane-1,3-diol (**3b**) were prepared according to the literature method and its modification, respectively. Chong, J. M.; Sokoll, K. K. *Tetrahedron Lett.* **1992**, *33*, 879–882.
5. Hachiya, I.; Makino, A.; Shimizu, M.; Akita, M.; Hamaguchi, T. *Tetrahedron: Asymmetry* **2004**, *15*, 2451–2454.
6. *General procedure for the synthesis of 1-monoicinolein derivatives* **2**. To a solution of 1,3-diricinolein derivative **1c** (1186.2 mg, 1.70 mol) in THF (8.0 mL) and phosphate buffer (24.0 mL) was added lipase PS (101.6 mg) at room temperature under an air. The mixture was stirred at room temperature for 25 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 was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give 1-monoricinolein derivative **2c** (224.4 mg, 32%, 51% based on the recovered **1c**) as a colorless oil and a mixture of the recovered **1c** and ricinoleic acid (942.2 mg, 48%, 39%, respectively, by ^{1}H NMR analysis). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.24–1.40 (m, 16H), 1.40–1.53 (m, 2H), 1.55–1.72 (m, 3H), 2.00–2.09 (m, 2H), 2.18–2.24 (m, 2H), 2.30–2.37 (m, 2H), 2.70 (s, 1H), 3.43 (s, 3H), 3.56–3.73 (m, 3H), 3.78–3.88 (m, 1H), 4.17 (dd, $J = 5.2$, 11.6 Hz, 1H), 4.21 (dd, $J = 5.6$, 11.6 Hz, 1H), 4.74 (s, 2H), 5.35–5.46 (m, 1H), 5.52–5.60 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 13.9, 14.0, 22.5, 24.7, 25.6, 27.2, 28.9, 29.0, 29.2, 29.4, 31.7, 34.0, 35.2, 36.7, 55.5, 62.3, 63.2, 71.4, 76.5, 96.4, 125.2, 132.9, 173.6. IR (neat): 3418, 2927, 2855, 1737, 1459, 1156, 1113, 1034, 919, 725 cm^{-1}. $[\alpha]_D^{21} = +8.2$ (*c* 0.093, $CHCl_3$).
The diastereomeric excesses of 1-momoricinolein derivatives **2b** and **2c** were determined by HPLC analysis of their dibenzoates **7b** and **7c**. To a solution of 1-monoricinolein derivative **2c** (2.7 mg, 0.0065 mmol) in CH_2Cl_2 (1.5 mL) was added pyridine (0.020 mL, 0.25 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at 0 °C for 5 min. Benzoyl chloride (0.040 mL, 0.34 mmol) was added to the resulting mixture at 0 °C. The mixture was warmed to room temperature and then stirred for 14.0 h. HCl (2 M) 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 was purified on preparative TLC (hexane/EtOAc = 9/1) to give **7c** along with a small amount of impurities. Further purification on preparative TLC (hexane/EtOAc = 1/1) gave pure **7c** (10.9 mg, 99%) as a colorless oil. The de of **7c** was determined as 94% by HPLC analysis (DAICEL CHIRALCEL OD, hexane/2-propanol = 50/1 (v/v)), at a flow rate of 0.3 mL min^{-1}. The minor (2*R*)-**7c** was eluted first ($t_{2R} = 32.5$ min), followed by major (2*S*)-**7c** ($t_{2S} = 37.0$ min).^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.6$ Hz, 3H), 1.26–1.38 (m, 16H), 1.59–1.70 (m, 4H), 2.01–2.05 (m, 2H), 2.33 (t, $J = 7.6$ Hz, 2H), 2.43 (dd, $J = 5.9$, 11.6 Hz, 2H), 3.39 (s, 3H), 4.15–4.51 (m, 5H), 4.76 (s, 2H), 5.11–5.16 (m, 1H), 5.38–5.47 (m, 2H), 7.40–7.47 (m, 4H), 7.52–7.57 (m, 2H), 8.00–8.06 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 24.8, 25.4, 27.3, 29.0, 29.1, 29.2, 29.5, 31.7, 32.0, 33.7, 34.1, 55.6, 63.4, 64.0, 72.7, 74.6, 77.2, 96.0, 124.1, 128.2, 128.4, 129.5, 129.6, 129.7, 130.7, 132.7, 133.2, 166.2, 173.5. IR (neat): 2928, 2856, 1721, 1602, 1453, 1273, 1172, 1111, 1070, 1031, 921, 712, 447, 418 cm^{-1}. $[\alpha]_D^{20} = +14.6$ (*c* 0.091, $CHCl_3$).
7. 2-Benzyloxypropane-1,3-diol **3c** was prepared according to the literature method Nali, M.; Rindone, B. *Gazz. Chim. Ital.* **1986**, *116*, 25–27.
8. Waldinger, C.; Schneider, M. *J. Am. Oil. Chem. Soc.* **1996**, *73*, 1513–1519.
9. *General procedure for the synthesis of (2R)-1-monoicinolein derivatives* **2** *using lipase-catalyzed transesterification of the 2-protected glycerol* **3** *with vinyl ricinoleate* **5**. To vinyl ricinoleate **5** (32.5 mg, 0.100 mol) was added a solution of 2-benzyloxypropane-1,3-diol (**3c**) in MeCN (1.5 mL) at room temperature under an argon atmosphere and the mixture was stirred at 50 °C for 5 min. Lipase AK (20.0 mg) was added to the resulting mixture at 50 °C. The mixture was stirred at 50 °C for 12.0 h 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 was purified by silica gel column chromatography (hexane/EtOAc = 1/2) to give **2d** (29.7 mg, 64%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.7$ Hz, 3H), 1.23–1.38 (m, 16H), 1.41–1.47 (m, 3H), 1.59–1.64 (m, 3H), 2.04 (t, $J = 7.0$ Hz, 2H), 2.20 (t, $J = 7.3$ Hz, 2H), 2.32 (t, $J = 7.3$ Hz, 2H), 3.57–3.66 (m, 2H), 3.68–3.74 (m, 2H), 4.23–4.24 (m, 2H), 4.60 (d, $J = 11.6$ Hz, 1H), 4.72 (d, $J = 11.6$ Hz, 1H), 5.37–5.42 (m, 1H), 5.52–5.58 (m, 1H), 7.30–7.36 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 173.8, 137.8, 133.3, 128.5, 128.0, 127.8, 125.2, 77.2, 72.1, 71.5, 62.6, 62.0, 36.8, 35.3, 34.2, 31.8, 29.5, 29.3, 29.1, 29.0, 29.0, 27.3, 25.7, 24.9, 22.6, 14.1. 14.1, 22.6, 24.9, 25.7, 27.3, 29.0, 29.0, 29.1, 29.3, 29.5, 31.8, 34.2, 35.3, 36.8, 62.0, 62.6, 71.5, 72.1, 77.2, 125.2, 127.8, 128.0, 128.5, 133.3, 137.8, 173.8. IR (neat): 3418, 2927, 2857, 1736, 1457, 1178, 1117, 1060, 737, 699 cm^{-1}. $[\alpha]_D^{24} = -8.5$ (*c* 0.218, $CHCl_3$).
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11. Configurations of product **2a** and **2c** were tentatively assigned by analogy.
12. *Procedure for the synthesis of 1,3-diacyl glycerol derivative* **9**. To a mixture of 1-monoricinolein (2*S*)-**2c** (94.2% de, 55.5 mg, 0.133 mmol) and 4-dimethylaminopyridine (DMAP) (37.4 mg, 0.306 mmol) was added a solution of 4-(4-hexyloxyphenyl)-benzoic acid (59.6 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) at room temperature under an argon atmosphere and the mixture was stirred at 0 °C for 5 min. A solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (68.7 mg, 0.333 mmol) in CH_2Cl_2 (2.0 mL) was added to the resulting mixture at 0 °C. The mixture was allowed to warm to room temperature and then stirred for 48 h. The mixture was filtered through a Celite pad, which was washed with EtOAc. The filtrate was washed with 0.5 M HCl and dried over Na_2SO_4. The solvents were evaporated in vacuo, and then the residue was purified on preparative TLC (hexane/EtOAc = 6/1) to give 1,3-diacyl glycerol derivative **9** (30.5 mg, 33%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80–0.90 (m, 6H), 1.20–1.40 (m, 20H), 1.40–1.53 (m, 4H), 1.52–1.72 (m, 3H), 1.76–1.86 (m, 2H), 1.98–2.12 (m, 2H), 2.18–2.23 (m, 2H), 2.35 (t, $J = 7.4$ Hz, 2H), 3.41 (s, 3H), 3.55–3.68 (m, 1H), 4.01 (t, $J = 6.6$ Hz, 2H), 4.11–4.58 (m, 5H), 4.77 (s, 2H), 5.37–5.44 (m, 1H), 5.50–5.59 (m, 1H), 6.95–7.00 (m, 2H), 7.48–7.64 (m, 4H), 8.04–8.09 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 14.0, 14.1, 22.6, 24.8, 25.7, 27.4, 29.0, 29.1, 29.2, 29.3, 29.5, 31.6, 31.8, 34.1, 35.4, 36.8, 55.6, 63.4, 63.9, 71.5, 72.7, 77.2, 96.0, 114.9, 125.2, 126.3, 126.5, 127.7, 128.0, 128.3, 130.2, 132.0, 133.3, 145.6, 159.5, 166.2, 173.5. IR (neat): 2929, 2857, 1721, 1605, 1497, 1466, 1274, 1186, 1111, 1035, 829, 757 cm^{-1}. $[\alpha]_D^{26} = +0.9$ (*c* 0.29, $CHCl_3$).