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Enantioselective preparation of asymmetrically protected 2-propanoyl-1,3-propanediol derivatives: toward the total synthesis of Kazusamycin A

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Abstract—The preparation of enantiomerically pure 2-propanoyl-1,3-propanediol derivatives, key intermediates in our studies on total synthesis of the potent antitumor compound Kazusamycin A are described. After various enzymatic protocols for desymmetrization of the prochiral diol were studied, it was found that these compounds could be prepared in 97–98% ee by means of an enzymatic kinetic resolution.

1. Introduction

Enantioselective transesterification of prochiral 2-substituted-1,3-propanediols catalyzed by an enzyme is well known as an effective tool to obtain enantiomerically pure synthetic building blocks, and much attention has been focused on this field in past decades.[1] In the course of our study on the total synthesis of Kazusamycin A **1**, a potent antitumor compound isolated from a culture broth of actinomycete sp. 81-484,[2] we planned to construct the four contiguous stereogenic centers employing a stereoselective aldol reaction between a homochiral aldehyde **2** and asymmetrically protected 1-hydroxy-2-hydroxymethyl-3-butanone **3**, according to the protocol reported by Paterson et al. (Scheme 1).[3] For the preparation of **3**, we intended to employ the above mentioned enzymatic transesterification, since this method would allow the reaction to be performed on a large scale and thus supply sufficient amounts of the enantiomerically pure **3** at an early stage in our total synthesis. In addition, it seemed to require significant work to derive enantiomerically pure **3** from readily available enantiomerically pure synthetic intermediates. However, there was no enzymatic preparative method available for enantiomerically pure 2-acyl(or acyl equivalent)-1,3-propanediol derivatives, in contrast to the widely developed protocols of enantioselective enzymatic transesterification of prochiral simple 2-alkyl- or 2-aryl-1,3-propanediols.[4] To the best of our knowledge, enzymatic transesterification of 2-dialkoxymethyl-1,3-propanediol reported by Poppe et al. is the only example of enantioselective preparation of 2-acylequivalent-3-acyloxypropanol, though the best enantiomeric excess of the product was 71% ee.[5] Herein, we describe the details of our investigation into the preparation of enantiomerically pure **3** and the first example, which gives 2-acyl-1,3-propanediol in up to 98% ee.

2. Results and discussion

2.1. Preparation of the prochiral diol 8

The prochiral diol, 1-hydroxy-2-hydroxymethyl-3-butanone **8**, was prepared in five steps starting from diol **4** as reported by Poppe et al.[5] Benzylation of the diol **4** afforded **5**, which was converted to alcohol **6** through hydrolysis of the diethylacetal moiety followed by the addition of ethylmagnesium bromide. The desired

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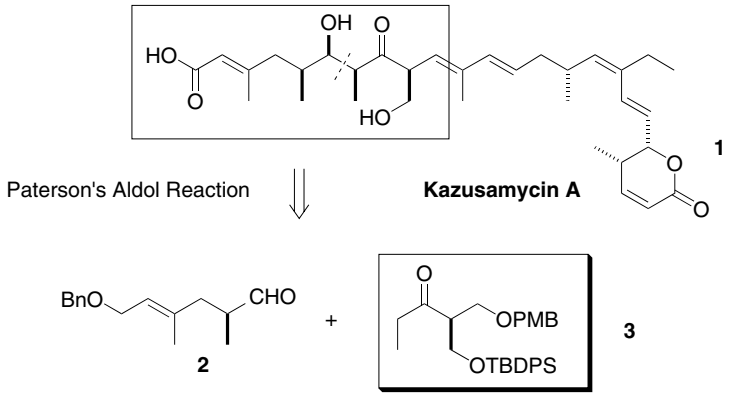


Scheme 1. Synthetic plan for Kazusamycin A (stereochemistry is speculative).

compound **8** was obtained by the oxidation of the alcohol **6** and subsequent deprotection (Scheme 2).

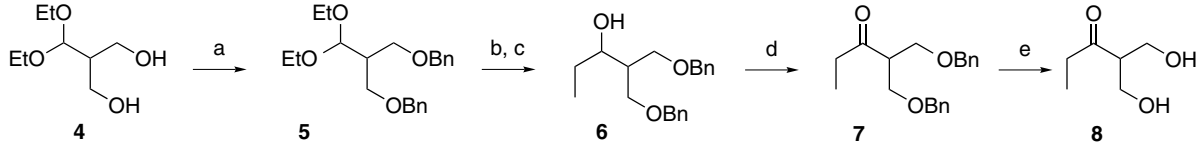
2.2. Enantioselective desymmetrization of the prochiral diol 8 by enzymatic transesterification

To obtain compound **3** in enantiomerically pure form, we first adopted desymmetrization of the prochiral diol **8** by enzymatic acetylation. When the diol **8** was treated with excess amounts (ca. 10-fold) of vinyl acetate in the presence of Lipase AK in isopropyl ether at room temperature, monoacetate **9** was obtained in 32% yield accompanied by diacetate **10** (62%) (Scheme 3, Table 1, Run 1). The enantiomeric excess of the monoacetate **9** was determined as 35% by HPLC analysis of its *tert*-butyldiphenylsilylated derivative. Determination of the absolute configuration of **9** is discussed in the next section. In the same manner, diol **8** was subjected to transesterification with Lipase PSC, PSA, OF (Runs 2–4). Though the reactions were to be stopped at approximately 50% conversion of the available hydroxyls, the yield of **9** and **10** showed some variation depending on the difference of the catalytic activity of these enzymes. Unfortunately, none of these enzymes gave an acceptable ee of **9** (11–32%). Polymer supported CAL-B afforded **9** in much modified ee (Run 5). In contrast to these examples, PPL gave mainly the opposite enantiomer (Run 6).

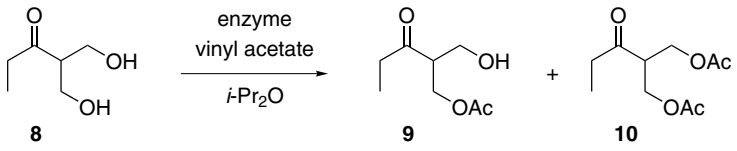
Table 1. Enantioselective desymmetrization of the prochiral diol **8** by enzymatic transesterification

Run	Enzyme	Yield/%		Ee of **9**/%	Major configuration
		9	**10**		
1	Lipase AK	32	62	35	*S*
2	Lipase PSC	11	85	32	*S*
3	Lipase PSA	75	0	24	*S*
4	Lipase OF	39	0	11	*S*
5	CAL-B	14	86	59	*S*
6	PPL	20	0	9	*R*

The results of desymmetrization of **8** with several enzymes at 0 °C are shown in Table 2. Whereas Lipase AK gave superior ee's compared to the reaction at room temperature, Lipase PSC and CAL-B afforded somewhat inferior results. Though it is expected that the enantioselectivity should increase at lower temperatures,[6] this was no the case here. The reason was not clear at this stage, however, the effect of the reaction temperature was marginal in our case. The possibility of racemization during the operation was completely excluded as described in the next section. These results led us to carry out the following preliminary studies at



Scheme 2. Preparation of prochiral diol **8**. Reagents and conditions: (a) NaH, BnBr, THF, rt, 73%; (b) TFA, $CHCl_3$–H_2O, 0 °C; (c) EtMgBr, THF, 0 °C, 72% in two steps; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 85%; (e) H_2, Pd/C, EtOH, rt, 95%.



Scheme 3.

Table 2. Enantioselective desymmetrization of the prochiral diol **8** at 0 °C

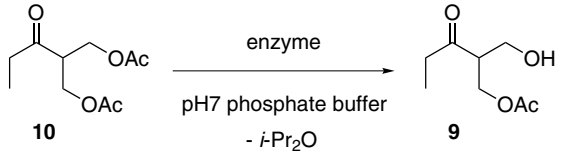
Run	Enzyme	Yield/%		Ee of **9**/%	Major configuration
		9	**10**		
1	Lipase AK	67	22	49	*S*
2	Lipase PSC	53	27	25	*S*
3	CAL-B	64	8	39	*S*

room temperature. Though vinyl benzoate and vinyl pivalate were also tested as acyl donors in place of vinyl acetate, neither of them gave modified results (with Lipase AK, vinyl benzoate: 76% yield, 28% ee, very retarded reaction, vinyl pivalate: no reaction).

From these results of the initial study, it seemed to be difficult to realize high yield and high ee simultaneously in the desymmetrization of **8**, and these results prompted us to investigate other enzymatic methods to obtain enantiomerically pure **9** or an equivalent, before the transesterification with CAL-B was fully optimized, which gave the best result in Table 1.

2.3. Enantioselective desymmetrization of the prochiral diacetate 10 by enzymatic hydrolysis

Hydrolytic desymmetrization of prochiral diacetate **10** was next investigated. The results were shown in Scheme 4 and Table 3. Hydrolysis of **10** with Lipase AK, PSA, PSC, OF afforded monoacetate **9** in moderate yield,



Scheme 4.

Table 3. Enantioselective desymmetrization of the prochiral diacetate **10** by enzymatic hydrolysis

Run	Enzyme	Yield of **9**/%	Ee of **9**/%	Major configuration
1	Lipase AK	31	11	*R*
2	Lipase PSC	38	11	*R*
3	Lipase PSA	51	12	*R*
4	Lipase OF	63	6	*R*
5	CAL-B	17	49	*R*
6	PPL	66	57	*S*

however, the ee in each case was far from acceptable (Runs 1–4). CAL-B gave a better result than the previously mentioned enzymes (Run 5). Unexpectedly, PPL, which had given a poor result in the transesterification, hydrolyzed **10**–**9** in the best yield and ee (Run 6).

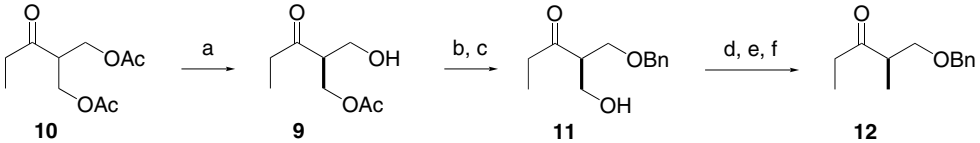
The absolute configuration of monoacetate **9** was determined as follows: Monoacetate **9** prepared by hydrolysis of **10** with PPL was transformed to the known benzyl ether **12** as shown in Scheme 5. The ether **12** thus prepared showed a negative optical rotation, $[\alpha]_D^{26} = -11.0$ (*c* 0.55, $CHCl_3$). On the other hand, the specific rotation of (*R*)-**12** was reported by Paterson et al. as $[\alpha]_D^{20} = -25.8$ (*c* 9.0, $CHCl_3$).[7] These facts indicated that monoacetate **9** prepared here had the same configuration as (*R*)-**12**, that is, its absolute configuration was *S*. Absolute configurations in other examples shown in tables were deduced from this result.

The possibility of racemization of **9** during reaction, work-up, and purification was checked as shown in Scheme 6. The PMB ether **14**, the ee of which was known (14% ee), was transformed to **15** by usual synthetic methods. The ee of **15** was determined as 14% by HPLC analysis. This result shows no racemization occurred during the operations.

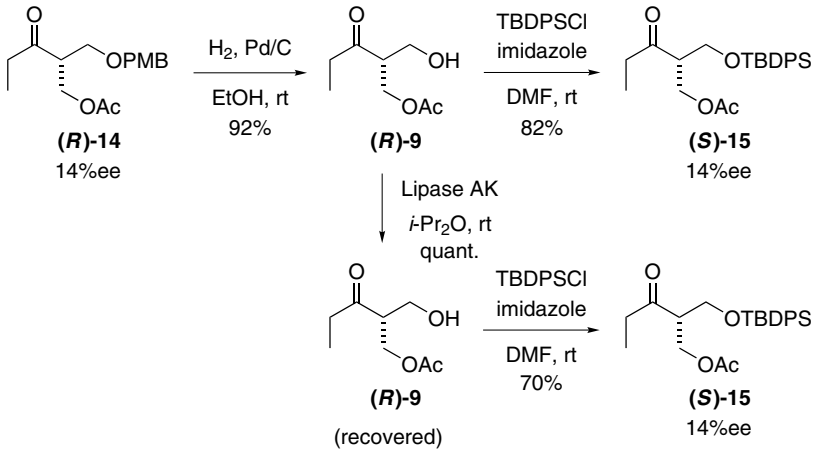
Monoester **9**, which was prepared as described above (14% ee), was subjected to the approximate conditions of the transesterification (with Lipase AK, without vinyl acetate, in diisopropylether at rt), and recovered in the usual manner. The ee of the recovered material was determined as 14% by the same method described above. This shows no racemization had occurred in the solution in the presence of lipase.

2.4. Kinetic resolution of monoprotected diol 13

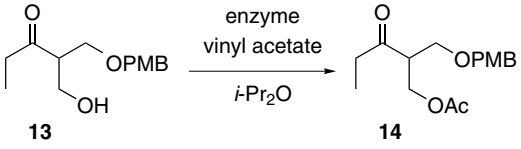
As mentioned in the previous two sections, enzymatic desymmetrization of prochiral diol **8** or diacetate **10** did not seem to be the method of choice to obtain the asymmetric building unit **3** in highly enantiomerically enriched form. So next we turned our attention to the kinetic resolution of the monoprotected diol. On the initial stage of the study, we chose compound **13** (one hydroxyl group in diol **8** was protected with PMB) as a substrate due to the preparative simplicity of **3**. The results are summarized in Scheme 7 and Table 4. Among the enzymes tried here, Lipase AK gave the best results (Run 1). Though the ee of esterified **14** was not so high, the ee of recovered alcohol **13** was found to be 97%. The



Scheme 5. Transformation of diacetate **10**. Reagents and conditions: (a) PPL, pH 7 phosphate buffer–*i*-Pr_2O, rt, 66%; (b) $CCl_3C(=NH)OBn$, cat. CF_3SO_3H, CH_2Cl_2–cyclohexane, rt, 86%; (c) PPL, pH 7 phosphate buffer–*i*-Pr_2O, rt, 76%; (d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (e) $LiAlH_4$, THF, 0 °C; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 33% in three steps.



Scheme 6.



Scheme 7.

E value[8] of this reaction was calculated as 5.5. Some investigations on solvent effects were also carried out. Other than isopropyl ether, ethyl acetate, chloroform, THF, and *tert*-butylmethyl ether were tested, however, none of them improved the results. Expecting that the more bulky protecting group would give the higher enantioselectivity, kinetic resolution of mono TBDPS ether of **8** was investigated. The investigation revealed that the TBDPS ether afforded a comparable result to **13** (24% recovery, 92% ee, when using Lipase AK). Hydrolytic kinetic resolution was also tried, however, it turned out to show much less selectivity.

The absolute configuration of recovered **13** was determined by comparing the specific rotation of ketone **18**[9] derived from **13** to the same ketone prepared from commercially available optically active ester **19** (Scheme 8).

Thus, it was revealed that the kinetic resolution of **13** by lipase AK catalyzed transesterification afforded optically active **13** in high ee, the absolute configuration of which was correct for the preparation of the synthetic unit **3**. This is the first example that giving nearly enantiomerically pure 2-acyl-1,3-propanediol derivatives. Accordingly, this key intermediate **3** was successfully prepared in 98% ee as shown in Scheme 9.

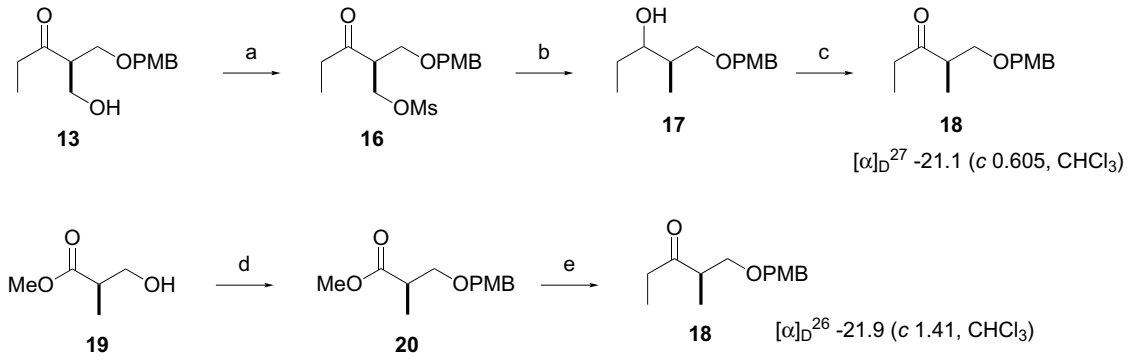
3. Conclusion

In summary, we have studied the enantioselective preparation of asymmetrically protected 2-propanoyl-1,3-propanediol derivatives by means of enzymatic methods for the total synthesis of Kazusamycin A. After screening various protocols and enzymes, it was eventually found that the kinetic resolution of monoprotected diol **13** with Lipase AK afforded nearly enantiomerically pure **13** (up to 98% ee) as recovered material at approximately 80% conversion. The derivatives of enantiomerically pure **13** seem to be very useful chiral synthetic units for combination with Paterson's stereoselective aldol reactions, and applicable to natural

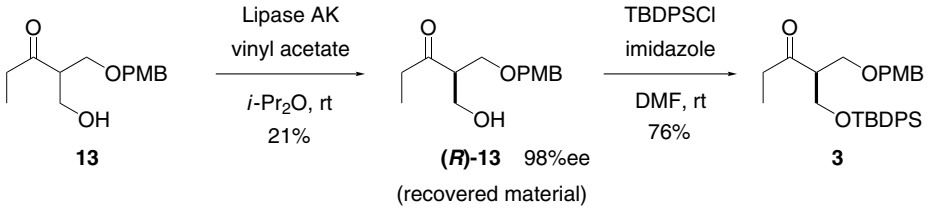
Table 4. Kinetic resolution of half-protected diol **13** by enzymatic transesterification

Run	Enzyme	**13**		**14**		*E* value[a]	Major configuration of **13**
		Recovered/%	Ee/%[b]	Yield/%	Ee/%[c]		
1	Lipase AK	20	97	76	24	5.5	*R*
2	Lipase PSC	13	70	83	4	1.7	*R*
3	Lipase PSA	76	9	20	40	2.6	*R*
4	Lipase OF	92	3	6	5	1.2	*R*
5	Lipase MY	30	12	65	3	1.2	*R*
6	CCL	79	3	15	8	1.2	*R*
7	CRL	78	3	16	5	1.1	*R*
8	PSL	10	17	86	8	1.3	*S*
9	CAL	26	37	72	10	1.6	*R*
10	CAL-B	67	8	33	20	1.6	*R*
11	PPL	57	8	38	26	1.8	*S*

[a] $E = \ln[1 - c(1 + \mathrm{ee}(\mathbf{14}))]/\ln[1 - c(1 - \mathrm{ee}(\mathbf{14}))]$, $c = \mathrm{ee}(\mathbf{13})/(\mathrm{ee}(\mathbf{13}) + \mathrm{ee}(\mathbf{14}))$. See Ref. 7.
[b] The ee of **13** was determined by HPLC analysis of its TBDPS ether.
[c] The ee of **14** was determined by HPLC analysis.



Scheme 8. Transformation of **13**. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (b) $LiAlH_4$, THF, 0 °C; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 94% in three steps; (d) $CCl_3C(=NH)OPMB$, cat. CSA, CH_2Cl_2, rt, 83%; (e) MeONHMe·HCl, EtMgBr, THF, −20 °C to rt, 55%.



Scheme 9. Preparation of the key intermediate **3**.

product syntheses especially of highly functionalized polyketides.

4. Experimental

4.1. General

NMR spectra were obtained on a JEOL ECP500 spectrometer. IR spectra were recorded on JASCO FT/IR-420 spectrophotometer. Mass spectra were taken on JEOL JMS-700 instrument. Optical rotations were taken on JASCO P-1010 polarimeter. Silica gel column chromatography was performed with Kanto Chemical Co., Inc. Silica Gel 60N (63–210 μm). Preparative thin layer chromatography was carried out with Wako Gel B-5F (Wako Pure Chemical Industries, Ltd.). GPC was performed on Japan Analytical Industry Co., Ltd. LC-918 with JAIGEL 1H and 2H columns. Enzymes used in this study were obtained from the following suppliers: Lipase AK, Lipase PSC, Lipase PSA: Amano Pharmaceutical Co., Ltd.; Lipase OF, Lipase MY: Meito Sangyo Co., Ltd.; CAL-B (carrier-fixed): Boehringer Mannheim; CCL, CRL, PSL, CAL, PPL: Sigma-Aldrich.

4.2. 3-Benzyloxy-2-(benzyloxymethyl)-propanal diethylacetal 5

Diol **4** (18.4 g, 0.104 mol) was treated with NaH (60% oil dispersion, 12.4 g, 0.31 mol) in THF (150 mL) at room temperature for 1 h, followed by the addition of benzyl bromide (43 mL, 0.36 mol). The reaction mixture was stirred for 4 h at room temperature, before quenching with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 20:1 to 10:1) to afford dibenzylated compound **5** (26.9 g, 73%). IR (KBr, neat, cm^{-1}) 3031, 2975, 1779, 1454, 1364, 1094, 737, 697; ^1H NMR (500 MHz, $CDCl_3$) δ 1,17 (distorted t, 6H), 2.23–2.29 (m, 1H), 3.46–3.52 (m, 2H), 3.60–3.71 (m, 6H), 4.49 (d, $J = 11.9$ Hz, 2H), 4.52 (d, $J = 11.9$ Hz, 2H), 4.63 (d, $J = 6.4$ Hz, 1H), 7.27–7.37 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.28, 43.72, 62.88, 67.29, 73.09, 101.90, 127.34, 127.49, 128.21, 138.66. HRMS(FAB), m/z ($M+Na^+$) calcd 381.2042, obsd 381.2060.

4.3. 1-Benzyloxy-2-(benzyloxymethyl)-3-pentanol 6

To a solution of diethylacetal **5** (23.5 g, 65.9 mmol) in chloroform (88 mL) was added a 50% aqueous solution of TFA (44 mL) at 0 °C. The reaction mixture was stirred for 15 h at 0 °C, then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with chloroform (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure, giving the aldehyde. IR (KBr, neat, cm^{-1}) 3031, 2862, 1726, 1496, 1454, 1363, 1099, 738, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 2.83–2.88 (m, 1H), 3.80 (dd, $J = 9.6$, 5.5 Hz, 2H), 3.86 (dd, $J = 9.6$, 6.0 Hz, 2H), 4.53 (s, 4H), 7.29–7.37 (m, 10H), 9.80 (d, $J = 1.4$ Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 52.75, 66.22, 73.35, 127.59, 127.70, 128.37, 137.82, 202.28. HRMS(FAB), m/z (M+H$^+$) calcd 285.1491, obsd 285.1489. This material was used in the next reaction without further purification.

The aldehyde was dissolved in THF (95 mL), and this solution was treated with ethylmagnesium bromide (0.89 M in THF, 89 mL, 79 mmol) at 0 °C. After stirring for 1.5 h at the temperature, the reaction was quenched with saturated aqueous ammonium chloride, and extracted with ether (200 mL × 3). The extracts were dried over anhydrous magnesium sulfate, filtered, evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 2:1) to afford the alcohol **6** (14.9 g, 72%). IR (KBr, neat, cm^{-1}) 3501 (br), 3031, 2871, 1496, 1454, 1364, 1093, 737, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (distorted t, 3H), 1.47–1.61 (m, 2H), 1.96–2.01 (m, 1H), 3.12 (d, J = 5.5 Hz, 1H), 3.66–3.77 (m, 5H), 4.48–4.54 (m, 4H), 7.28–7.38 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.46, 27.90, 43.34, 68.43, 70.49, 73.41, 73.47, 74.60, 127.63, 128.39, 137.98, 138.15. HRMS(FAB), m/z (M+Na$^+$) calcd 337.1780, obsd 337.1771.

4.4. 1-Benzyloxy-2-(benzyloxymethyl)-3-pentanone 7

To a solution of alcohol **6** (6.56 g, 20.9 mmol) in dichloromethane (100 mL) was added Dess–Martin periodinane[10] (9.75 g, 23.0 mmol) at room temperature, and the mixture was stirred for 1 h. The suspension was diluted with ether (100 mL), then quenched with aqueous $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with ether (100 mL × 3), and extracts were dried over anhydrous magnesium sulfate, filtered, evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 2:1) to afford the ketone **7** (5.51 g, 85%). IR (KBr, neat, cm^{-1}) 3031, 2863, 1714, 1496, 1454, 1364, 1095, 738, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3H), 2.56 (q, J = 7.3 Hz, 2H), 3.11–3.17 (m, 1H), 3.62 (dd, J = 9.2, 5.5 Hz, 2H), 3.70 (dd, J = 9.2, 6.9 Hz, 2H), 4.46 (d, J = 11.9 Hz, 2H), 4.49 (d, J = 11.9 Hz, 2H), 7.27–7.36 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.32, 36.53, 52.41, 68.41, 73.25, 127.52, 127.61, 128.33, 137.96, 211.66. HRMS(FAB), m/z (M+H$^+$) calcd 313.1804, obsd 313.1788.

4.5. 1-Hydroxy-2-(hydroxymethyl)-3-pentanone 8

To a solution of ketone **7** (5.51 g, 17.7 mmol) in ethanol (55 mL) was added Pd on activated carbon (10%, ca. 0.3 g), and the mixture was stirred under an atmospheric pressure of hydrogen at room temperature until the starting material disappeared on TLC. The suspension was filtered through a Celite pad, and the filtrate was evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 2:1) to afford the ketone **8** (2.23 g, 95%). IR (KBr, neat, cm^{-1}) 3374 (br), 2942, 2888, 1704, 1461, 1408, 1378, 1038; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3H), 2.59 (q, J = 7.3 Hz, 2H), 2.78–2.82 (m, 1H), 3.09 (br s, 2H), 3.89–3.91 (br m, 2H), 3.95–3.98 (br m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.29, 35.58, 54.76, 61.85, 213.78. HRMS(FAB), m/z (M+Na$^+$) calcd 155.0684, obsd 155.0697.

4.6. 2-(1-Oxopropyl)propan-1,3-diyl diacetate 10

To a solution of **8** (52.0 mg, 0.393 mmol) in dichloromethane (2 mL) were added acetic anhydride (120 mL, 1.27 mmol), pyridine (105 mL, 1.30 mmol), and DMAP (1.7 mg, 0.014 mmol), successively. After stirring for 1 h, the reaction was quenched with water, and the mixture was extracted with ether (10 mL × 3). Combined organic layer was washed with water then brine, and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 2:1) to afford the diacetate **10** (81.3 mg, 96%). IR (KBr, neat, cm^{-1}) 2979, 1743, 1718, 1461, 1368, 1042; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, J = 7.3 Hz, 3H), 2.00 (s, 3H), 2.52 (q, J = 7.3 Hz, 2H), 3.07–3.12 (m, 1H), 4.22 (dd, J = 11.5, 6.0 Hz, 2H), 4.27 (dd, J = 11.5, 6.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.27, 20.63, 35.85, 49.64, 61.49, 170.51, 208.63. HRMS(FAB), m/z (M+H$^+$) calcd 217.1076, obsd 217.1095.

4.7. Enzymatic transesterification of 8 (typical procedure)

To a solution of diol **8** (34.2 mg, 0.260 mmol) and vinyl acetate (119 μL, 1.30 mmol) in diisopropyl ether (2.6 mL) was added Lipase AK (52 mg) in one portion at room temperature. After stirring vigorously for 30 min, the mixture was filtered through a Celite pad, and the filtrate was evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 3:1) to afford the monoacetate **9** (14.2 mg, 32%) and diacetate **10** (34.6 mg, 62%). *2-Hydroxymethyl-3-oxopentyl acetate* **9**: $[\alpha]_D^{27}$ = +7.8 (*c* 0.660, $CHCl_3$), 35% ee (*S* major); IR (KBr, neat, cm^{-1}) 3438 (br), 2941, 1740, 1714, 1462, 1370, 1246, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 2.02 (s, 3H), 2.55 (q, J = 7.3 Hz, 2H, involving br s, 1H), 2.95–2.99 (m, 1H), 3.76–3.78 (br m, 1H), 3.82–3.84 (br m, 1H), 4.30 (d, J = 6.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.26, 20.72, 36.01, 52.64, 60.37, 61.80, 179.96, 211.45. HRMS(FAB), m/z (M+H$^+$) calcd 175.0970, obsd 175.0971.

4.8. Enzymatic hydrolysis of 10 (typical procedure)

To a solution of diacetate **10** (333.4 mg, 1.54 mmol) in a mixed solvent of diisopropyl ether (2.4 mL), pH 7 phosphate buffer (1.2 mL), and water (12 mL) was added PPL (0.3 g) in one portion at room temperature. After stirring vigorously for 20 min, the mixture was filtered through a Celite pad, and the filtrate was evaporated at reduced pressure. The crude product was purified by

silica gel column chromatography (eluent, hexane–ethyl acetate = 3:1) to afford the monoacetate **9** (176.3 mg, 66%).

4.9. Determination of the absolute configuration of 9

Monoacetate **9** (3.46 g, 19.9 mmol) prepared as described in the former section was dissolved in dichloromethane–cyclohexane (1:2 (v/v), 200 mL). To this solution was added benzyl trichloroimidate[11] (2.3 mol dm^{-3} in hexane, 17 mL, 40 mmol) and trifluoromethanesulfonic acid (0.17 mL, 2 mmol) successively, and the mixture was stirred for 4 h at room temperature. The reaction mixture was filtered through a cotton plug, and the filtrate was washed with saturated sodium hydrogen carbonate, dried over anhydrous sodium sulfate, filtered again, and then evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 5:1) to afford the corresponding benzyl ether (4.53 g, 86%). Acetoxy moiety of this compound (4.34 g, 16.5 mmol) was hydrolyzed under neutral condition according to the procedure described in Section 4.8 to avoid epimerization or elimination, affording β-hydroxyketone **11** (2.76 g, 76%).

To a solution of **11** (55.7 mg, 0.251 mmol) in dichloromethane (2.5 mL) was added triethylamine (84 μL, 0.60 mmol) and methanesulfonyl chloride (23 μL, 0.30 mmol) at 0 °C. After stirring at the temperature for 1.5 h, the reaction was quenched with pH 7 phosphate buffer. The mixture was extracted with dichloromethane (20 mL × 2), and the extracts were dried over anhydrous sodium sulfate, filtered, and then evaporated at reduced pressure, to afford a crude mesylate (70.8 mg). This mesylate was dissolved in THF (2.3 mL), and the solution was added to a suspension of $LiAlH_4$ (21.9 mg, 0.578 mmol) in THF (0.6 mL) at room temperature with stirring. After 20 min, water was added to the reaction mixture at 0 °C, and the mixture was extracted with ether (20 mL × 2), dried over anhydrous magnesium sulfate. Concentration of the extracts gave a crude reduced compound (49.4 mg). This compound was dissolved in dichloromethane (2.4 mL) and treated with Dess–Martin periodinane (150.8 mg, 0.356 mmol) at room temperature for 15 min. After conventional work-up, the resulting mixture was purified by GPC to afford the ketone **12** (16.9 mg, 33% based on **11**). $[\alpha]_D^{27} = -11.0$ (*c* 0.550, $CHCl_3$), lit.[7] $[\alpha]_D^{20} = -25.8$ (*c* 9.0, $CHCl_3$).

4.10. Stereochemical stability of 9

A solution of (*R*)-**14** (530.4 mg, 1.81 mmol, obtained by kinetic resolution of **13**) in ethanol was stirred for 2 h at room temperature under atmospheric pressure of hydrogen in the presence of Pd/C. After removal of the catalyst by filtration, the solution was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 1:1) to afford (*R*)-**9** (290.9 mg, quant.). To a solution of this (*R*)-**9** (51.1 mg, 0.294 mmol) and imidazole (40 mg, 0.59 mmol) in DMF (0.5 mL) was added TBDPSCl (115 μL, 0.441 mmol). After stirring for 25 min, cold water was added, and the resulting mixture was extracted with hexane–ethyl acetate (1:1) (20 mL × 1). The extract was washed with water, brine, then dried over anhydrous sodium sulfate. After filtration, the solution was evaporated at reduced pressure. The crude product was purified by silica gel thin layer chromatography (hexane–ethyl acetate = 6:1, developed three times) to afford (*S*)-**15** (98.9 mg, 82%). $[\alpha]_D^{26} = +2.8$ (*c* 1.09, $CHCl_3$). IR (KBr, neat, cm^{-1}) 2934, 1745, 1716, 1472, 1428, 1364, 1239, 1113, 1040, 704; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.06 (t, $J = 7.3$ Hz, 3H), 1.97 (s, 3H), 2.46–2.61 (m, 2H), 3.02–3.07 (m, 1H), 3.82 (dd, $J = 11.1$, 5.5 Hz, 1H), 3.86 (dd, $J = 11.1$, 6.0 Hz, 1H), 4.25 (dd, $J = 11.0$, 6.0 Hz, 1H), 4.32 (dd, $J = 11.0$, 6.9 Hz, 1H), 7.37–7.46 (m, 6H), 7.62–7.64 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.29, 19.11, 20.73, 26.68, 36.42, 52.86, 61.83, 61.93, 127.74, 129.82, 132.88, 135.48, 170.61, 210.34. HRMS(FAB), *m*/*z* ($M+H^+$) calcd 413.2148, obsd 413.2160.

The ee of this sample was determined as 14% (*S* major) by HPLC analysis (DAICEL CHIRALCEL OD-H, hexane–2-propanol = 99.7:0.3 (v/v), at a flow rate of 0.5 mL min^{-1}). The *R* isomer was eluted first ($t_R = 35.2$ min), followed by *S* isomer ($t_R = 42.2$ min).

4.11. 2-Hydroxymethyl-1-(4-methoxybenzyloxy)-3-pentanone 13

To a solution of **8** (294.8 mg, 2.23 mmol) in dichloromethane (9 mL) was added 4-methoxybenzyl trichloroimidate[12] (0.51 mL, 2.5 mmol), followed by addition of a catalytic amount of (1*S*)-(+)-10-camphorsulfonic acid (25.9 mg, 0.224 mmol). Stirring was continued for 1 day, then the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane (20 mL × 3), and extracts were dried over anhydrous sodium sulfate, filtered, evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 10:1 gradually to 3:1) to afford the monoprotected compound **13** (371.8 mg, 66%). IR (KBr, neat, cm^{-1}) 3450 (br), 2938, 1708, 1612, 1514, 1461, 1363, 1302, 1248, 1175, 1091, 1034, 821; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, $J = 7.3$ Hz, 3H), 2.48–2.61 (m, 2H), 2.92–2.97 (m, 1H), 3.66 (dd, $J = 9.6$, 6.0 Hz, 1H), 3.69 (dd, $J = 9.6$, 6.0 Hz, 1H), 3.77–3.79 (br dd, 1H), 3.79 (s, 3H), 3.87–3.90 (br dd, 1H), 4.42 (s, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.21 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.30, 36.04, 53.66, 55.20, 61.73, 68.51, 73.06, 113.79, 129.24, 129.69, 159.25, 212.72. HRMS(FAB), *m*/*z* ($M+Na^+$) calcd 275.1259, obsd 275.1263.

4.12. Kinetic resolution of 13 by enzymatic transesterification (typical procedure)

To a solution of **13** (761.7 mg, 3.02 mmol) and vinyl acetate (2.8 mL, 30.2 mmol) in diisopropyl ether (50 mL)

was added Lipase AK (0.6 g) at room temperature. After stirring vigorously for 35 min, the mixture was filtered through a Celite pad, washed thoroughly with ether, and the filtrate was concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 3:1) to afford the acetate **14** (670.8 mg, 76%). Unreacted **13** (155.4 mg, 20%) was recovered. $[\alpha]_D^{26} = +18.4$ (*c* 0.710, $CHCl_3$).

2-(4-Methoxybenzyloxymethyl)-3-oxopentyl acetate **14**: $[\alpha]_D^{27} = +2.6$ (*c* 1.56, $CHCl_3$). IR (KBr, neat, cm^{-1}) 2939, 1742, 1715, 1613, 1514, 1462, 1366, 1247, 1174, 1098, 1036, 821; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.3$ Hz, 3H), 1.99 (s, 3H), 2.45–2.58 (m, 2H), 3.05–3.11 (m, 1H), 3.57 (dd, $J = 9.6$, 6.0 Hz, 1H), 3.61 (dd, $J = 9.6$, 6.9 Hz, 1H), 3.79 (s, 3H), 4.23 (dd, $J = 11.0$, 5.5 Hz, 1H), 4.29 (dd, $J = 11.0$, 7.3 Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.41 (d, $J = 11.5$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.19 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.29, 20.72, 36.17, 51.02, 55.18, 62.16, 67.52, 72.94, 113.76, 129.19, 129.72, 159.23, 170.61, 210.23. HRMS(FAB), *m/z* ($M+Na^+$) calcd 317.1365, obsd 317.1383.

The ee of **14** was determined as 24% (*R* major) by HPLC analysis (DAICEL CHIRALPAK AD-H, hexane–2-propanol = 96:4 (v/v), at a flow rate of 0.5 mL min^{-1}). The *R* isomer [corresponding to acetylated (*S*)-**13**] was eluted first ($t_R = 30.8$ min), followed by *S* isomer ($t_R = 33.3$ min). On the other hand, the ee of recovered **13** was determined after transformation to silylated form **3**. HPLC analysis (DAICEL CHIRALCEL OD-H, hexane–2-propanol = 99:1 (v/v), at a flow rate of 0.5 mL min^{-1}) of **3** disclosed that the ee was 97% (*S*). The *R* isomer (corresponding to silylated (*S*)-**13**) was eluted first ($t_R = 17.0$ min), followed by *S* isomer ($t_R = 19.2$ min).

4.13. Absolute configuration of 13

To a cooled solution (0 °C) of **13** (174.4 mg, 0.691 mmol) in dichloromethane (3 mL) was added triethylamine (120 μL, 0.86 mmol), followed by the addition of methanesulfonyl chloride (64 μL, 0.83 mmol). After stirring for 30 min, the reaction was quenched with pH 7 phosphate buffer. The mixture was separated and the aqueous phase was extracted with ether (10 mL × 2). The combined organic phase was washed with water, then brine, and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated under reduced pressure to give almost pure mesylate **15** (227.2 mg, 0.688 mmol), which was used in the next reaction without further purification. IR (KBr, neat, cm^{-1}) 2938, 1715, 1612, 1514, 1461, 1357, 1248, 1175, 1099, 1033, 959, 834; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, $J = 7.3$ Hz, 3H), 2.44–2.60 (m, 2H), 2.98 (s, 3H), 3.12–3.17 (m, 1H), 3.63 (d, $J = 5.5$ Hz, 2H), 3.81 (s, 3H), 4.36 (dd, $J = 9.6$, 5.5 Hz, 1H), 4.39 (d, $J = 11.5$ Hz, 1H), 4.44 (d, $J = 11.5$ Hz, 1H), 4.51 (dd, $J = 9.6$, 7.3 Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.31, 35.73,36.98, 51.29, 55.26, 66.63, 67.52, 73.09, 113.86, 129.37 (overlapped), 159.43, 208.92. To a cooled solution (0 °C) of the mesylate **16** in THF (4 mL) was added $LiAlH_4$ (assay: >80%, 85.7 mg, 1.8 mmol) in one portion. After stirring for 1 h at room temperature, the reaction was quenched with 3 M NaOH at 0 °C. The mixture was extracted with ether (10 mL × 3), and extracts were dried over anhydrous magnesium sulfate, filtered, evaporated at reduced pressure, to give the reduced material **17** (170.7 mg) as a mixture of diastereomers (approx. 1:1).

The alcohol **17** was dissolved in dichloromethane (3 mL) and treated with Dess–Martin periodinane (382.7 mg, 0.902 mmol) at room temperature for 1 h. Saturated aqueous $NaHCO_3$ was then added and the mixture was extracted with ether (10 mL × 3). The extracts were washed with saturated aqueous $NaHCO_3$, then brine, and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated under reduced pressure to give the crude ketone. The crude material was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 4:1) to afford the ketone **18** (153.6 mg, 94% based on **13**). $[\alpha]_D^{27} = -21.1$ (*c* 0.605, $CHCl_3$). IR (KBr, neat, cm^{-1}) 2974, 1714, 1613, 1513, 1460, 1362, 1248, 1173, 1092, 1035, 821; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.3$ Hz, 3H), 1.06 (d, $J = 7.3$ Hz, 3H), 2.50 (q, $J = 7.3$ Hz, 2H), 2.82–2.89 (m, 1H), 3.42 (dd, $J = 9.2$, 5.5 Hz, 1H), 3.59 (dd, $J = 9.2$, 7.8 Hz, 1H), 3.80 (s, 3H), 4.39 (d, $J = 11.5$ Hz, 1H), 4.42 (d, $J = 11.5$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.21 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.49, 13.58, 35.21, 46.18, 55.19, 72.04, 72.85, 113.69, 129.11, 130.19, 159.14, 213.70. HRMS(FAB), *m/z* ($M+Na^+$) calcd 259.1310, obsd 259.1314.

4.14. Preparation of authentic 2-methyl-1-(4-methoxybenzyloxy)-3-pentanone 18

To a solution of (*R*)-(−)-methyl 3-hydroxy-2-methylpropanoate **19** (359.2 mg, 3.04 mmol) and 4-methoxybenzyl trichlroimidate[12] (2 M in hexane, 2.5 mL, 5 mmol) in dichloromethane (6 mL) was added (1*S*)-(+)-10-camphorsulfonic acid (66.7 mg, 0.287 mmol) in one portion at room temperature. After stirring for 29 h, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with ether (20 mL × 2). The extracts were washed with water, then brine, dried over anhydrous sodium sulfate. Concentration of the solution after filtration gave the crude product. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 15:1 to 9:1) to afford the PMB ether **19** (601.0 mg, 83%).

To a cooled suspension (−23 °C) of the PMB ether **20** (459.4 mg, 1.93 mmol) and *N*-methylhydroxylamine hydrochloride (280.5 mg, 2.88 mmol) in THF (4 mL) was added EtMgBr (0.9 M in THF, 16.8 mmol) dropwise over 30 min.[13] After stirring at the temperature for 10 min, the reaction was allowed to warm to room temperature and stirring was continued for 4 h. The reaction was quenched with 1 M HCl at 0 °C and pH of the mixture was adjusted around 2. The mixture was

extracted with ethyl acetate (20 mL × 3) and the extracts were washed successively with saturated aqueous $NaHCO_3$, and brine, then dried over anhydrous sodium sulfate. Concentration of the solution after filtration gave the crude product, which was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 9:1 to 7:1) to afford **18** (250.5 mg, 55%). $[\alpha]_D^{26} = -21.9$ (*c* 1.41, $CHCl_3$). ^1H NMR spectrum was identical to that of **18** derived from **13**.

4.15. Preparation of (*S*)-1-(*tert*-butyldiphenylsiloxy)-2-(4-methoxybenzyloxymethyl)-3-pentanone 3

To a solution of kinetically resolved **13** (98.4 mg, 0.390 mmol) prepared as described in Section 4.11 and imidazole (53.2 mg, 0.781 mmol) in DMF (4 mL) was added TBDPSCl (152 μL, 0.586 mmol). After stirring for 3 h, saturated aqueous ammonium chloride was added, and the resulting mixture was extracted with hexane–ethyl acetate (1:1) (20 mL × 2). The extracts were washed with brine, then dried over anhydrous sodium sulfate, filtered, evaporated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent, hexane–ethyl acetate = 10:1) to afford **3** (145.2 mg, 76%). $[\alpha]_D^{27} = +6.8$ (*c* 1.06, $CHCl_3$) (98% ee, *S*). IR (KBr, neat, cm^{-1}) 2933, 1715, 1613, 1513, 1248, 1112, 703; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.04 (t, $J = 7.3$ Hz, 3H), 2.50–2.58 (m, 2H), 3.03–3.08 (m, 1H), 3.55 (dd, $J = 9.2$, 6.0 Hz, 1H), 3.64 (dd, $J = 9.2$, 7.8 Hz, 1H), 3.78 (dd, $J = 10.1$, 6.0 Hz, 1H), 3.79 (s, 3H), 3.86 (dd, $J = 10.1$, 6.9 Hz, 1H), 4.34 (d, $J = 11.5$ Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 2H), 7.16 (d, $J = 8.3$ Hz, 2H), 7.36–7.38 (m, 4H), 7.41–7.44 (m, 2H), 7.60–7.62 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.30, 19.14, 26.71, 36.89, 54.38, 55.21, 62.39, 67.80, 72.89, 113.71, 127.69, 129.14, 129.71, 130.10, 133.09, 133.20, 135.50, 135.53, 159.14, 211.98. HRMS(FAB), m/z ($M+Na^+$) calcd 513.2437, obsd 513.2418.

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