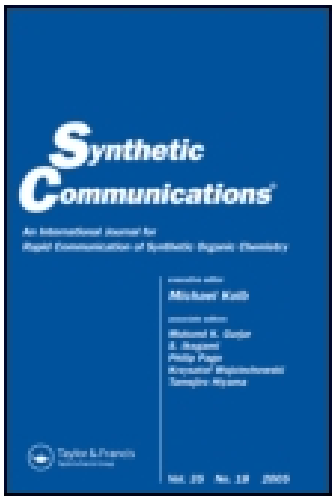

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Porcine Liver Esterase Catalyzed Kinetic Resolution of Baylis-Hillman (B-H) Adducts†

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ABSTRACT

Esterase from porcine liver smoothly resolves varieties of racemic 2-methylene-3-substituted-3-hydroxypropanoates (B-H adducts) to obtain the corresponding unreacted esters in very good to excellent ee (94 to >99%, seven examples) and hydrolyzed acids in good ee (58–75%). Substitution in B-H adducts, chosen for resolution, are funtionalized phenyl, thiophen-3-yl, cinnamyl, and alkyl groups.

†DRL Pub. No. 232. Dedicated to Dr. A. Venkateswarlu on the occasion of his 63rd birth anniversary.

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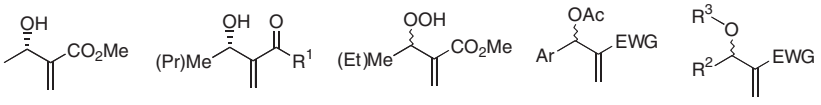
Key Words: Baylis-Hillman adducts; Kinetic resolution; Porcine liver esterase.

INTRODUCTION

Synthesis of 2-(methylene)-3-hydroxypropanoate(s), the Baylis-Hillman (B-H) adducts,[1] in homochiral form is a challenging task.[2] Initial attempts from various research groups to obtain enantiopure B-H adducts yielded only few successful reports mainly based on the strategies of kinetic resolution. Noyori and co-workers while doing asymmetric hydrogenation of various racemic allylic alcohols, reported kinetic resolution of (±)-**1** by carrying out (*S*)-BINAP-Ru diacetate catalyzed hydrogenation which led to isolation of (*S*)-**1** in >99% ee.[3,4] However both the Refs. [3] and [4] lack generality of the approach on kinetic resolution of B-H adducts as substrates. Lipase catalyzed resolution of racemic B-H adducts was studied independently by different groups[5] where originally Burgess and Jennings[5a] reported 72 to >95% ee for (*S*)-**2** (10 examples, R^1: lower alkyl and alkoxy). Horseradish peroxide (HRP) catalyzed kinetic resolution of hydroperoxide derivatives of B-H adducts, (±)-**3** (two examples), were studied by Adam et al. where >99% ee have been achieved.[6] *Interestingly*, *the B-H adducts*, *chosen in the above citations*, *except two examples in Ref*. [4], *are based on aliphatic aldehydes i.e.*, *3-alkyl substituted cases*. To the best of our knowledge, only Basavaiah and Dharma Rao reported kinetic resolution of a series of B-H adducts derived from aromatic aldehydes using pig liver acetone powder (PLAP).[7] They reported a highest ee of 86% for deacetylated product obtained from (±)-**4** when Ar is 1-napthyl and EWG is cyano, and for the rest of examples ee ranges from 46 to 70%.[7] Figure 1 represents the compounds **1–4**. Owing to the difficulty in achieving successful asymmetric synthesis of B-H products, partly due to the slow progress of the reaction,[8] an efficient, convenient, and general way to resolve racemic B-H products is still a quest for many research groups. As it reflects from a recent work from Trost et al., who studied C_2-symmetric ligand-Pd(0) complex assisted



(*S*) - **1** (*S*) - **2** (±) - **3** (±) - **4** (±) - **5**

Figure 1.

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dynamic kinetic asymmetric transformation (DYKAT) of several racemic B-H adducts (±)-**5** (Fig. 1: R^3 is methoxycarbonyl group) and obtained the corresponding *O*-aryl derivatives (*S*)-**5** (R^3 is aryl) in 39 to >99% ee. Here also R^2 in **5** is limited to only aliphatic groups.[9]

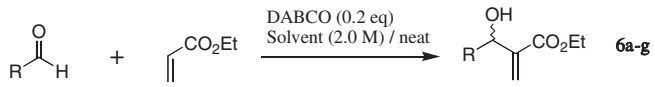
In this communication, we disclose porcine liver esterase catalyzed kinetic resolution of B-H adducts **6** obtained from aromatic, hetero-aromatic, cinnamyl as well as aliphatic aldehydes reacting with ethyl acrylate.

RESULTS AND DISCUSSION

Examples **6a–d** were conveniently synthesized in gram scale (50–60% yield) using equimolar quantities of ethyl acrylate and the corresponding aldehydes in MeCN, DMF, or dioxane solvent (2.0 M) using 20 mol% of DABCO at RT.[10a] For **6e–g**, reactions were done by heating (70°C) overnight at neat condition in sealed tube (40–60% yield).[10b,c] Table 1 outlines these synthesis.

Esterase from porcine liver (Sigma, EC 3.1.1.1, Lot No. 40K7060, 41 units per mg solid) was chosen for hydrolysis of the B-H adducts **6a–g**. We designed the incubation protocol in such way that the hydrolysis cum resolution proceeds reasonably faster and the procedure becomes useful for laboratory synthesis of homochiral B-H adducts. Initially the hydrolysis reaction was standardized using the substrates **6a** and **6b** in aqueous phosphate buffer (pH 7.2) along with organic co-solvents (1–10% with respect to buffer) like acetone, DMSO, DMF, DMA, and

Table 1. Synthesis of Baylis-Hillman adducts **6a–g**.



R	Solvent	Condition	Isolated yield	B-H adducts
p-NO_2-phenyl	MeCN	RT, 24 h	60%	**6a**
m-NO_2-phenyl	MeCN	RT, 24 h	55%	**6b**
p-F-Phenyl	DMF	RT, 24 h	55%	**6c**
m-Hydroxy-phenyl	Dioxane	RT, 24 h	50%	**6d**
Thiophen-3-yl	Neat	70°C, 16 h	60%	**6e**
Cinnamyl	Neat	70°C, 16 h	40%	**6f**
Isobutyl	Neat	70°C, 16 h	40%	**6g**

1,4-dioxane. Reaction temperature was preferred at 35–36°C. We observed that all the studied co-solvents gave more or less similar results both in terms of yield and ee of the products. However, hydrolysis practically did not proceed in the absence of co-solvent. Hence for illustration purpose we are presenting the results based on reactions carried out using DMSO as co-solvent (Table 2).

As it was expected the ee of hydrolyzed acid and recovered ester were found to be very much dependent on progress of hydrolysis, which also supports kinetic resolution. Thus when the reactions, in general, were stopped in the late stage (approx. 70% conversion) the recovered esters showed excellent ee (i.e., 94 to >99%) for **6**. On the other hand when the hydrolysis was interrupted at the early stage (approx. 25–30% conversion), the corresponding acids **7** were obtained in the range of 58–75% ee. A compromised ee (in the range of 76–92%) of the recovered esters could also be obtained with improved isolated yield of 40–46%, as indicated by the Entries 1a, 2a, 3a (Table 2). Based on the literature evidences[11] (see also Table 2), stereochemistry of all the resolved esters **6** were assigned as (*S*), and opposite stereochemistry were assigned for the acids **7**. It is to be noted here that the resolved **6e** and **7e**, though possess general trend of absolute stereochemistry, are assigned to have respectively (*R*) and (*S*) stereochemistry due to change in priority. This indicates that the enzyme recognizes the D-stereochemistry of ester for hydrolysis.

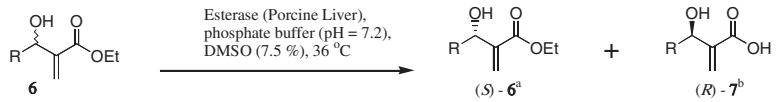
From the structural diversity of the examples disclosed in Table 2, it also indicates that this approach could be made general for kinetic resolution of B-H adducts derived from ethyl acrylate and aromatic, aliphatic, hereoaromatic, α,β-unsaturated aldehydes.

Enantiomeric ratio (*E*) is another important parameter for any kinetic resolution study specially of present interest. For each enzymatic hydrolysis studied here, the calculated *E* value[12] has been shown in Table 2. *E* is a constant and specific to a substrate and enzyme used for kinetic resolution. We also substantiate this principle. As for example *E* for kinetic resolution of **6a** remains same (9.6, 9.5, 9.0) in three different extent of hydrolysis.

CONCLUSIONS

We have discovered a convenient way of achieving optically pure Baylis-Hillman (B-H) products based on esterase-catalyzed hydrolysis cum kinetic resolution. The approach is shown to be quite general as varieties of B-H adducts, based on ethyl acrylate and aromatic, aliphatic, α,β-unsaturated, as well as heteroaromatic aldehydes, could be resolved

Table 2. Kinetic resolution of B-H adducts **6a–g** through esterase-catalyzed hydrolysis.



Entry	*R*-	B-H adduct	Reaction time (h)	(*S*)-**6** Yield[c]	(*S*)-**6** % ee[d]	(*R*)-**7** Yield[c]	(*R*)-**7** % ee[d]	*E*[f]
1a		**6a**	16	40	92	55	50[e]	9.6
1b			24	30	>99	65	35	9.5
1c			2	65	42[e]	30	70	9.0
2a		**6b**	7	46	91[e]	50	40[e]	6.8
2b			16	35	>99	60	15[e]	5.2
2c			0.5	60	48[e]	30	75	11.4
3a		**6c**	4	45	76	52	38	4.9
3b			16	30	>99	65	17[e]	5.4
3c			0.5	70	20[e]	25	64	5.4
4a		**6d**	24	30	99	65	10	4.3
4b			2	65	18[e]	28	60	4.8
5a		**6e**	24	32	97	65	25	5.7
5b			2	65	16[e]	30	66	6.2
6a		**6f**	28	25	99	56	26	7.1
6b			2	55	20[e]	25	72	7.1
7a		**6g**	28	35	94	60	15	3.7
7b			1	65	14[e]	28	58	6.1

[a]Specific rotation of resolved **6a–e** are positive, and the same is negative for **7a–e**. Whereas specific rotation of resolved **6f–g** are negative, and the same is positive for **7f–g**. Comparison of specific rotation of **6a**, **6f**, and **6g** with the literature value[11] justified the (*S*)-configuration. For others, in general, it is tentative assignment based on analogy. See text for stereochemistry assignment of **6e**. [b]Absolute configuration of **7a–d**, and **7f–g** was assigned as (*R*), and for **7e** as (S), after esterifying the acids into their ethyl esters and comparing the specific rotation with **6**. [c]Isolated yield of recovered ester **6** and the corresponding acid **7** which were characterized by routine spectra. [d]% ee were determined by chiral HPLC method, unless mentioned. [e]% ee was calculated based on comparison of specific rotation with authentic sample for which the % ee was determined by chiral HPLC. [f]Calculated following the equation: $E = \ln[(1-c)(1-\mathrm{ee}_S)]/\ln[(1-c)(1+\mathrm{ee}_S)]$. The extent of conversion $c = \mathrm{ee}_S/(\mathrm{ee}_S + \mathrm{ee}_P)$, where ee_S and ee_P are for resolved esters and hydrolyzed acids respectively.[12]

in very high to excellent ee (94 to >99%). Though kinetic resolution of B-H adducts either via enzyme assisted[5–7] or using chemical discrimination approach[3,4,9] have been reported in the past, each of them has their own limitation as described in the introduction part. The present study shows that using procine liver esterase the structural limitations of B-H adducts may be overcome.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Mercury Plus (Varian 400 MHz), and Gemini (Varian 200 MHz) spectrometer in $CDCl_3$ with TMS as internal standard: chemical shifts are quoted in ppm and *J* values are given in Hz. IR spectra were recorded on FT-IR spectrophotometer from Perkin-Elmer 1600 series. Mass spectra were recorded on Hewlett-Packard 5989A LC-Mass spectrometer using isobutene as chemical ionizer gas (source temp. 250°C and quadruple temp. 100°C), or on triple quadrupole mass spectrometer, PE Sliex model API 3000 (at +5000 V). Elemental analysis were done on Perkin-Elmer II series.

In a typical procedure for esterase-catalyzed hydrolysis, **6e** (600 mg, 2.83 mmol) was added to a mixture of phosphate buffer (pH 7.2, 240 mL) and DMSO (18 mL). Finally enzyme (20 mg) was added and the mixture was stirred at 35–36°C for 24 h, at which time TLC indicated approximately 70% conversion. The reaction mixture was acidified to adjust the pH at 2–3. Ethyl acetate extraction gave the crude mass containing unreacted (*R*)-**6e** and the corresponding acid (*S*)-**7e**, which were isolated by column chromatography. Yield: (*R*)-**6e** (192 mg, 32%), and (*S*)-**7e** (338 mg, 65%).

Compounds **6a–d**, **6f–g** were also resolved to obtain the corresponding optically pure (*S*)-**6a–d**, and (*S*)-**6f–g** respectively following the typical procedure described for **6e**. Characterization of all resolved B-H adducts are as below.

Characterization of (*S*)-6a. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:EtOH::95:05 (1.0 mL/min); uv-273 nm; t_R of (*R*)-**6a**: 29.91 min (0.25% area), t_R of (*S*)-**6a**: 32.35 min (99.60% area). $[\alpha]_D$ +93.8° (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, $J = 7.0$ Hz, 3H), 3.38 (bs, 1H, -OH), 4.18 (q, $J = 7.0$ Hz, 2H); 5.61 (s, 1H), 5.83 (t, $J = 1.0$ Hz, 1H), 6.37 (d, $J = 0.8$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 2H), 8.17 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.91, 61.20, 72.32, 123.45 (2C), 126.76, 127.37 (2C), 141.27, 147.24, 148.88, 165.84. MS (ES) *m/z*: 525.3 [$M_2 + Na^+$], 520.3 [$M_2 + NH_4^+$], 274.0 [$M + Na^+$], 269.0 [$M + NH_4^+$],

252.1 [M + 1], 233.9 [M−17(OH)]. IR (neat) cm^{-1}: 3489, 2984, 1711, 1522, 1349. Anal. calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.25; H, 5.28; N, 5.51.

Characterization of (*S*)-6b. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:EtOH::95:05 (1.0 mL/min); uv-273 nm; t_R of (*S*)-**6b**: 22.50 min (99.86% area), t_R of (*R*)-**6b**: 28.40 min (0.14% area). $[\alpha]_D$ +86.1° (*c* 2.25, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, $J = 7.0$ Hz, 3H), 3.30 (d, $J = 6.2$ Hz, 1H, -OH), 4.18 (q, $J = 7.0$ Hz, 2H), 5.61 (d, $J = 6.2$ Hz, 1H), 5.85 (t, $J = 1.0$ Hz, 1H), 6.38 (t, $J = 0.8$ Hz, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.71–7.73 (aromatics, 1H), 8.11–8.13 (aromatics, 1H); 8.23–8.24 (aromatics, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.91, 61.19, 72.29, 121.53, 122.60, 126.74, 129.24, 132.72, 141.26, 143.78, 148.16, 165.84. MS (ES) *m*/*z*: 525.2 [$M_2 + Na^+$], 520.3 [$M_2 + NH_4^+$], 274.3 [$M + Na^+$], 269.1 [$M + NH_4^+$], 252.3 [M + 1], 234.1 [M−17(OH)]. IR (neat) cm^{-1}: 3484, 2985, 1711, 1531, 1351. Anal. calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.19; H, 5.25; N, 5.61.

Characterization of (*S*)-6c. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:*i*-PrOH::95:05 (1.0 mL/min); uv-220 nm; t_R of (*S*)-**6c**: 10.30 min (99.63% area), t_R of (*R*)-**6c**: 10.97 min (0.37% area). $[\alpha]_D$ +98.3° (*c* 3.25, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, $J = 7.2$ Hz, 3H), 3.20 (bs, 1H, -OH), 4.16 (q, $J = 7.2$ Hz, 2H), 5.52 (s, 1H), 5.78 (t, $J = 1.0$ Hz, 1H), 6.31 (s, 1H), 7.00 (t, $J = 8.8$ Hz, 2H), 7.32 (dd, $J = 8.2$, 5.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.95, 60.93, 72.52, 115.00 (d, $J = 21.5$ Hz, 2C), 125.68, 128.30 (d, $J = 8$ Hz, 2C), 137.15 (d, $J = 3$ Hz, 1C), 142.15, 162.11 (d, $J = 244.5$ Hz, 1C), 166.19. MS (CI) *m*/*z*: 224 [M], 207 [M−17 (OH)]. IR (neat) cm^{-1}: 3456, 2985, 1713. Anal. calcd. for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84. Found: C, 64.25; H, 5.87.

Characterization of (*S*)-6d. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:*i*-PrOH::95:05 (1.0 mL/min); uv-220 nm; t_R of (*R*)-**6d**: 49.15 min (0.48% area), t_R of (*S*)-**6d**: 52.40 min (99.52% area). $[\alpha]_D$ +74.1° (*c* 1.9, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, $J = 7.1$ Hz, 3H); 3.50 (bs, 1H, -OH), 4.16 (q, $J = 7.1$ Hz, 2H), 5.50 (s, 1H), 5.82 (s, 1H), 6.32 (s, 1H), 6.37 (bs, 1H, phenolic-OH); 6.73 (ddd, $J = 8.2$, 1.5, 1.0 Hz, 1H); 6.84–6.86 (aromatics, 2H), 7.16 (t, $J = 8.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.77, 61.10, 72.59, 113.69, 114.99, 118.57, 126.06, 129.484, 141.61, 142.50, 155.96, 166.53. MS (CI) *m*/*z*: 222 [M], 205 [M−17(OH)]. IR (neat) cm^{-1}: 3392, 2985, 1701. Anal. calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.69; H, 6.37.

Characterization of (*R*)-6e. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:EtOH::95:05 (1.0 mL/min); uv-235 nm; t_R of (*S*)-**6e**: 15.7 min (1.29% area), t_R of (*R*)-**6e**: 16.8 min (97.91% area). $[\alpha]_D$ +120° (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, $J = 7.3$ Hz, 3H), 3.34

(s, 1H, -OH), 4.17 (q, $J = 7.3$ Hz, 2H), 5.58 (s, 1H), 5.80 (t, $J = 1.2$ Hz, 1H), 6.28 (s, 1H), 7.00 (dd, $J = 4.9$, 1.2 Hz, 1H), 7.18 (dd, $J = 2.9$, 1 Hz, 1H), 7.24 (dd, $J = 5.4$, 2.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.78, 60.66, 69.08, 121.61, 125.11, 125.58, 126.07, 141.91, 142.89, 166.05. MS (ES) m/z: 447.1 [$M_2 + Na^+$], 235.1 [$M + Na^+$], 195.1 [M−17(OH)]. IR (neat) cm^{-1}: 3442, 2982, 1712, 1268, 1149, 1039. Anal. calcd. for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70. Found: C, 56.61; H, 5.81.

Characterization of (*S*)-6f. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:*i*-PrOH::94:06 (0.5 mL/min); uv-254 nm; t_R of (*S*)-**6f**: 27.18 min (98.12% area), t_R of (*R*)-**6f**: 28.53 min (0.67% area). $[\alpha]_D$ −14.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (t, $J = 7.3$ Hz, 3H), 2.95 (d, $J = 6.4$ Hz, 1H, -OH), 4.24 (q, $J = 7.3$ Hz, 2H), 5.11 (t, $J = 6.4$ Hz, 1H), 5.88 (s, 1H), 6.27 (s, 1H), 6.28 (dd, $J = 15.6$, 5.8 Hz, 1H), 6.64 (d, $J = 15.6$ Hz, 1H), 7.22–7.38 (aromatics, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.98, 60.85, 71.73, 125.36, 126.45 (2C), 127.64, 128.41 (2C), 129.26, 131.19, 136.39, 141.48, 166.21. MS (ES) m/z: 255.1 [$M + Na^+$] , 250.4 [$M + NH_4^+$], 215.1 [M−17(OH)]. IR (neat) cm^{-1}: 3434, 2983, 1713. Anal. calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.41; H, 7.03.

Characterization of (*S*)-6g. HPLC: Chiralpak AD-H (250 × 4.6 mm); Hexane:*i*-PrOH::98:02 (1.0 mL/min); uv-220 nm; t_R of (*R*)-**6g**: 10.32 min (3.04% area), t_R of (*S*)-**6g**: 11.13 min (95.56% area). $[\alpha]_D$ −27° (*c* 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (d, $J = 2.4$ Hz, 3H), 0.91 (d, $J = 2.5$ Hz, 3H), 1.27 (t, $J = 7.3$ Hz, 3H), 1.30–1.60 (m, 2H), 1.62–1.82 (m, 1H), 2.81 (bs, 1H, -OH), 4.19 (q, $J = 7.3$ Hz, 2H), 4.43 (dd, $J = 8.7$, 4.6, 1H), 5.75 (s, 1H), 6.17 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.99, 21.65, 23.19, 24.65, 45.48, 60.65, 69.52, 124.18, 143.31, 166.53. MS (CI) m/z: 187 [M + 1] , 169 [M−17(OH)]. IR (neat) cm^{-1}: 3422, 2958, 1716. Anal. calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.35; H, 9.81.

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