to 0 °C. Diethyl azodicarboxylate (0.39 g, 2.2 mmol) was added dropwise followed by diphenylphosphoryl azide (0.61 g, 2.2 mmol) in THF (4 mL). The resulting mixture was stirred at room temperature for 48 h in the dark. The mixture was concentrated in vacuo and purified by flash column chromatography (5% ethyl acetate/hexane) without further workup to yield 0.69 g of **6** (79%) as a clear oil: R_f 0.5 (10% ethyl acetate/hexane); $[\alpha]^{25}_D$ -6.77° (*c*, 1.31, EtOH); IR (neat) 2955, 2926, 2113, 1794, 1272, 1257, 1138 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4–7.1 (m, 10 H), 3.8 (ddd, 1 H, *J* = 8.4, 7.1, 2.9 Hz), 3.7 (d, 1 H, *J* = 2.9 Hz), 3.04 (dd, 1 H, *J* = 13.5, 7.1 Hz), 2.97 (dd, 1 H, *J* = 13.5, 8.4 Hz), 2.16 (dd, 1 H, *J* = 7.1, 6.4 Hz), 2.03 (b d, 1 H, *J* = 7.8 Hz), 1.9–1.7 (m, 4 H), 1.5 (t, 1 H, *J* = 12.8 Hz), 1.3 (s, 3 H), 1.28 (s, 3 H), 0.92 (d, 3 H, *J* = 6.6 Hz), 0.9 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 149.5, 135.8, 129.4, 128.9, 128.0, 127.3, 125.9, 125.7, 115.4, 74.9, 62.7, 53.8, 49.1, 36.6, 34.7, 34.6, 29.9, 28.7, 27.6, 25.5, 21.5; MS (70 eV) *m/e* (%) 451 ($(M + NH_4)^+$, 0.3), 434 (MH^+, 1.5), 406 (1.7), 391 (0.47), 378 (0.1), 363 (0.2), 344 (0.3), 330 (2.3), 288 (19.2), 161 (5.5), 119 (100), 91 (7.6); HRMS calcd for $C_{26}H_{32}N_3O_3$ (MH^+) 434.2444, found 434.2431. Anal. Calcd for $C_{26}H_{31}N_3O_3$: C, 71.86; H, 7.19; N, 9.67. Found: C, 70.55; H, 7.22; N, 9.51.

Ethyl (2*S*,3*R*)-3-Azido-2-hydroxy-4-phenylbutanoate (7). Azidodioxolanone **6** (0.519 g, 1.19 mmol) was dissolved in HCl saturated ethanol (45 mL). The resulting solution was heated to reflux for 10 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo, diluted with methylene chloride (20 mL), and concentrated in vacuo again to yield 0.504 g of a pale yellow oil. Purification by flash column chromatography (7% ethyl acetate/hexane) yielded 0.175 g (59%) of **7** and 88.3 mg (17%) of recovered **6**: R_f 0.12 (10% ethyl acetate/hexane); $[\alpha]^{25}_D$ -7.66° (*c*, 1.11, EtOH); IR (neat) 3489, 2982, 2111, 1736, 1495, 1454, 1257, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4–7.25 (m, 5 H), 4.38–4.22 (m, 2 H), 4.11 (dd, 1 H, *J* = 5.5, 2.2 Hz), 3.78 (td, 1 H, *J* = 7.5, 2.2 Hz), 3.16 (d, 2 H, *J* = 7.5 Hz), 3.12 (d, 1 H, *J* = 5.5 Hz, OH), 1.28 (t, 3 H, *J* = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 172.5, 136.6, 129.3, 128.7, 126.9, 71.4, 64.2, 62.2, 36.1, 13.9; MS (70 eV) *m/e* (%) 250 (MH^+, 5.4), 222 (33.3), 207 (13.1), 189 (9.3), 176 (5.8), 160 (6.1), 148 (20.1), 130 (28.1), 120 (100.0), 103 (16.4), 91 (83.4); HRMS calcd for $C_{12}H_{16}N_3O_3$ (MH^+) 250.1192, found 250.1184. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.96; H, 6.07; N, 16.86. Found: C, 57.96; H, 6.29; N, 17.07.

(2*S*,3*R*)-3-Azido-2-hydroxy-4-phenylbutanoic Acid (8). Ester **7** (120 mg, 0.48 mmol) was dissolved in THF/H_2O (9.6 mL/3:1) and cooled to 0 °C. Lithium hydroxide (40 mg, 0.96 mmol) was added, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then acidified with 2 N HCl and extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 97.2 mg of **8** (91%): $[\alpha]^{25}_D$ + 8.63° (*c*, 1.13, EtOH); IR (neat) 3403, 3029, 2923, 2115, 1729, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 (b s, 2 H, COOH, OH), 7.4–7.3 (m, 5 H), 4.2 (d, 1 H, *J* = 2 Hz), 3.9 (td, 1 H, *J* = 8.2, 2 Hz), 3.2 (d, 2 H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.8, 136.6, 129.4, 128.9, 127.3, 71.1, 64.0, 36.2; MS (70 eV) *m/e* (%) 239 ($(M + NH_4)^+$, 100), 232 (0.7), 222 (0.5), 208 (0.5), 196 (24.8), 176 (0.5), 168 (0.3), 150 (8.1), 136 (25.0), 120 (67.8), 108 (7.1), 91 (4.1); HRMS calcd for $C_{10}H_{11}N_3O_3NH_4$ ($(M + NH_4)^+$) 239.1144, found 239.1149.

Benzyl *N*-[(2*S*,3*R*)-3-Azido-2-hydroxy-4-phenylbutanoyl]-L-leucinate (9). Benzyl L-leucinate p-toluenesulfonic acid salt (0.147 g, 0.37 mmol), 3-hydroxybenzotriazole (55.7 mg, 0.41 mmol), and acid **8** (74.9 mg, 0.34 mmol) were all combined in THF (1.4 mL) and cooled to 0 °C. Dicyclohexylcarbodiimide (85.8 mg, 0.42 mmol) and triethylamine (38 mg, 0.37 mmol) were then added, and the mixture was stirred at room temperature for 12 h. The resulting mixture was diluted with THF (1 mL) and filtered. The filtrate was diluted with Et_2O (20 mL) and extracted with 0.5 N HCl (1 × 10 mL), 5% aqueous $NaHCO_3$ (1 × 10 mL), and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 202 mg of an oil. Purification by flash column chromatography (40% ethyl acetate/hexane) yielded 97.2 mg (68%) of **9** (R_f 0.47) as an oil, which crystallized: mp 97–98 °C; $[\alpha]^{25}_D$ -30.6° (*c*, 2.22, $CHCl_3$); IR ($CHCl_3$) 3411, 3020, 3011, 2962, 2115, 1735, 1676, 1522, 1455, 1222, 1154 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4–7.2 (m, 10 H), 7.15 (d, 1 H, *J* = 9 Hz), 5.18 (d, 1 H, *J* = 12 Hz), 5.14 (d, 1 H, *J* = 12 Hz), 4.7 (m, 1 H), 4.1–4.0 (m, 2 H), 3.6 (d, 1 H, *J* = 7 Hz), 3.0 (d, 2 H, *J* = 7.5 Hz), 1.8–1.6 (m, 3 H), 0.9 (d, 6 H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 171.3, 136.7, 135.2, 129.3, 128.8, 128.6, 128.4, 128.2, 127.1, 72.6, 67.3, 64.7, 50.8, 41.3, 36.8, 24.9, 22.9, 21.7; MS (70 eV) *m/e* (%) 425 (MH^+, 18.8), 399 (9.1), 382 (3.2), 366 (3.0), 295 (9.0), 278 (15.6), 222 (3.4), 210 (4.7), 188 (3.8), 120 (100), 91 (41.5); HRMS calcd for $C_{23}H_{29}N_4O_4$ (MH^+) 425.2189, found 425.2179. Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 65.07; H, 6.88 N, 13.19. Found: C, 65.29; H, 6.75; N, 13.14.

(-)-Bestatin (4). Catalytic hydrogenation of **9** (153 mg, 0.36 mmol) over 5% Pd on carbon (220 mg) was carried out at atmospheric pressure in methanol (7.2 ml) for 48 h. The mixture was filtered through Celite and concentrated in vacuo to yield 95 mg of **4** (86%) as the free zwitterion, which was recrystallized from methanol/ethyl acetate, mp 231–236 °C dec [lit.[3] mp 233–236 °C dec]. Crystallization of this solid from 1 N HCl formed the HCl salt of **4**, which matched the authentic HCl salt obtained from Sigma (lot no. 76 F-58201): $[\alpha]^{25}D$ -14.3° (*c* 0.5, 1 N HCl); authentic sample $[\alpha]^{25}_D$ -13.0° (*c* 0.5, 1 N HCl); IR (KBr) 3397, 2961, 1713, 1662, 1539, 1256, 1184, 1158 cm^{-1}; ^{1}H NMR (300 MHz, acetic acid-d_4) δ 10.89 (s, 3 H, OH, COOH, HCl), 7.4–7.2 (m, 5 H), 4.7–4.5 (m, 2 H), 4.05 (s, 1 H), 3.25 (dd, 1 H, *J* = 15.6 Hz), 3.08 (dd, 1 H, *J* = 15, 8 Hz), 1.9–1.7 (m, 3 H), 0.94 (m, 6 H); ^{13}C NMR (90 MHz, acetic acid-d_4) δ 177.5, 173.9, 136.6, 130.9, 130.2, 128.7, 70.6, 57.3, 52.6, 41.1, 35.8, 26.1, 23.4, 22.2.

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Registry No. **1**, 104196-76-1; **4**, 58970-76-6; **4**·HCl, 65391-42-6; **5a**, 121445-49-6; **5b**, 121521-81-1; **6**, 121445-50-9; **7**, 121445-51-0; **8**, 121445-52-1; **9**, 121445-53-2; H-Leu-OBn·TsOH, 1738-77-8; $PhCH_2CHO$, 122-78-1.

Biotransformation of Some Keto Esters through the Consecutive Reuse of Immobilized *Nicotiana tabacum* Cells

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A number of biotransformations have recently been reported employing freely suspended or immobilized plant cell cultures. Most of these reports, however, were confined to the biotransformation of secondary metabolites produced by plant cell cultures;[1] there have been few examples on the biotransformation of synthetically important foreign substrates.[2,3]

For some years now we have been investigating the possibility of using immobilized biocatalysts such as bakers' yeast entrapped with calcium alginate or carrageenan in organic synthesis.[4,5] Very recently we reported the first

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Table I. Consecutive Reuse of Immobilized *N. tabacum* Cells in the Biotransformation of Keto Esters 1–5 to Hydroxy Esters 1a–5a

	% yield					% ee[a]				
reuse number	1a	2a	3a	4a	5a	1a	2a	3a	4a	5a
1	11	30	26	20	12	99	67	80	97	94
2	18	33	26	20	12	97	69	81	97	99
3		38	30	21	15		71	82	99	99
4		46	31	23			71	82	99	
5			34	23				85	99	
6			34	28				87	98	
7				20					98	

[a] Specific rotations of the compounds **1a–5a**. $[\alpha]^{20}_D$ (*c*, $CHCl_3$): **1a**, ranging from +41.90 (0.0105) to +43.28 (0.0097); **2a**, +32.25 (0.0231) to +33.72 (0.0215); **3a**, +31.33 (0.0142) to +33.55 (0.0152); **4a**, +16.35 (0.0489) to +19.09 (0.0432); **5a**, −32.31 (0.008) to −33.34 (0.006).

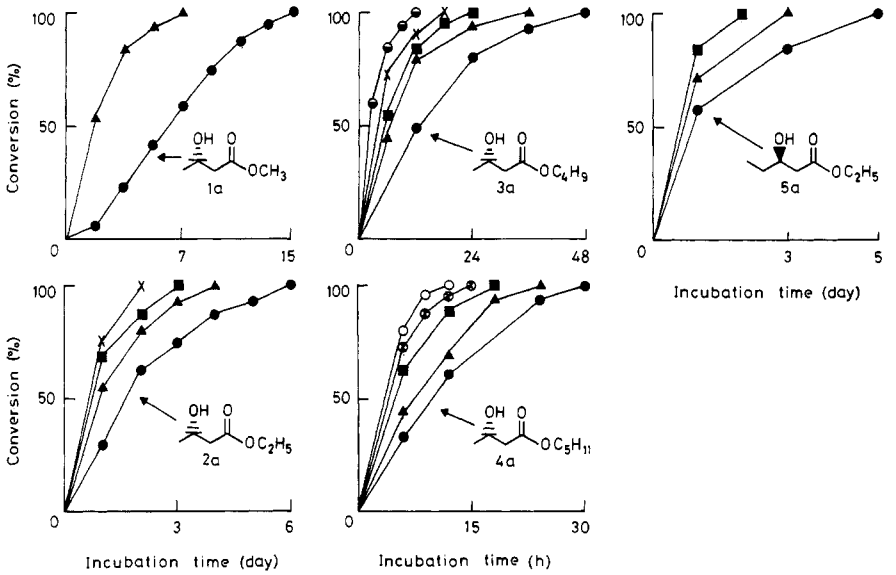

Figure 1. Conversion of keto esters (1–5) to hydroxy esters (**1a–5a**) by immobilized *N. tabacum* cells as a function of incubation time: ●, first use; ▲, second use; ■, third use; X, fourth use; ⊗, fourth and fifth use; ⊖, fifth and sixth use; ○, sixth and seventh use.

biotransformation of 3-oxobutanoates with immobilized *Nicotiana tabacum* (INT) cells.[6] The transformations were limited to the determination of the ee and absolute configuration of 3-hydroxy esters produced as the main product and suffered from poor chemical yields of the hydroxy esters. The repetitive use of the immobilized plant cell cultures was not attempted. In an effort to obtain more information concerning the biotransformation of organic foreign substrates with immobilized plant cell cultures, we have newly prepared INT cells entrapped with calcium alginate beads and further examined the biotransformations of the five keto esters 1–5 by consecutively reusing the immobilized cells.

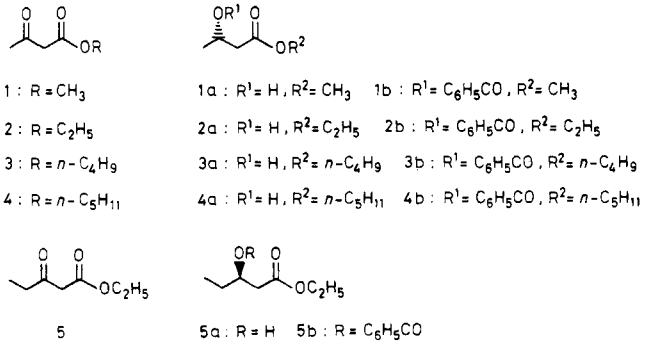

Table I exemplifies the biotransformations of 1–5 through the consecutive reuse of INT cells. Organic foreign substrates 1–4 were stereoselectively reduced to the corresponding (*S*)-(+)-3-hydroxybutanoates **1a–4a**, respectively, in chemical yields of 11–18%, 30–46%, 26–34%, and 20–28% and in optical yields of 97–99% ee, 67–71% ee, 80–87% ee, and 97–99% ee. In the biotransformations of **3** and **4**, after six to seven consecutive reuses over a period of about 3 weeks, the biocatalyst still maintained the activity providing 34% and 20% yields of **3a** and **4a**. Similarly, the biotransformations of ethyl 3-oxopentanoate (**5**) each proceeded in high optical yields of 94–99% ee, a chiral hydroxy ester (*R*)-(−)-**5a** being obtained.[7] As shown in Figure 1, the time-course experiments of the present biotransformations clearly revealed that the rates of each biotransformation of **1–5** were accelerated by consecutively reusing the immobilized biocatalyst. For example, the first use of INT cells in the bioreductions of **3** and **4** required 48 h and 30 h to reach 100% conversion, while for the fifth and sixth uses each biotransformation was complete within 12 h as determined by disappearance of **3** and **4** by GLC. The biotransformations of other keto esters showed similar rate increases. The marked increases in reaction rates may be related to the multiplication of *N. tabacum* cells in the immobilized beads. Note the appreciable differences of the reaction rates in the biotransformations of 1–4. This could be due to alkyl-chain length in their alkoxycarbonyl functions.[6]

Experimental Section

All compounds were fully characterized on the basis of their spectral data. Chemical yields refer to compounds purified by

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(7) A bioreduction of **5** by bakers' yeast afforded **5a** with only a 40% ee.[10]

a combination of column chromatography and micro vacuum distillation with a Kugelrohr distilling apparatus. Optical yields (% ee) of **1a–5a** were determined by HPLC analysis of their benzoate esters **1b–5b** in comparison with racemic ones (column, Daicel Chiralcel OB; eluent, 2-propanol–hexane; flow rate, 1.0 mL/min; detection, 220-nm light).[6] Capillary GLC was performed with a PEG-20M 25 m × 0.25 mm WCOT fused silica capillary column at 130 °C. Optical rotations were measured on a Horiba SEPA-200 high-sensitivity polarimeter. Column chromatography was carried out with 70–230-mesh silica gel (Merck Kieselgel 60 Art. No. 7734).

Immobilization of *N. tabacum* Cells. Freely suspended *N. tabacum* cells (60 g) were immobilized with a 5% aqueous solution of sodium alginate (600 mL) and a 0.6% aqueous solution of $CaCl_2$ according to the procedures described previously.[6,8]

Biotransformation of Foreign Substrates through the Consecutive Reuse of the Immobilized Cells. *N. tabacum* cells (60 g) immobilized with calcium alginate gels as described were added to freshly prepared Murashige and Skoog's (MS) medium[9] (1000 mL) containing 2,4-dichlorophenoxyacetic acid (2 ppm) and sucrose (3%), and the medium was shaken for 2 days. An organic substrate (200 mg of keto ester) was administered to the precultured MS medium containing INT cells and the mixture incubated at 25 °C on a rotary shaker (95 rpm) in the dark. The reaction mixture was filtered, and the immobilized cells were washed with MS medium. The cultured medium from the immobilized cells and washings was combined and extracted with ethyl acetate. Workup of the extracts gave a crude product (70–80 mg for **1**, 110–120 mg for **2**, 70–90 mg for **3**, 70–90 mg for **4**, 50–60 mg for **5**), which was purified by column chromatography and micro vacuum distillation to yield a chiral hydroxy ester.

After each use, INT cells were separated from the reaction mixture by filtration or decantation, washed with MS medium, and added to the next fresh MS medium (1000 mL). After the medium had been precultured anew, the next substrate (200 mg) was administered.

For the time-course experiments on the biotransformations, at a regular time, a part of the incubated mixture was pipetted off and extracted with ethyl acetate. Each extract was analyzed by capillary GLC. The conversion ratios were determined on the basis of the peak areas of substrates (keto esters) and products (hydroxy esters).

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Enantioselective Synthesis of (-)-Zeylena from Styrene

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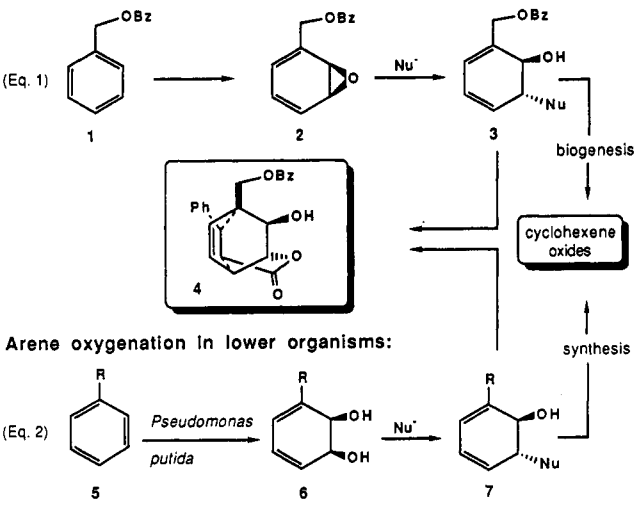
The unique hydrocarbon zeylena, **4**, was isolated from the roots of *Uvaria zeylanica* L. (annonaceae)[3] during the investigations of antitumor activities of the related cyclohexene oxides.[4,5] Although zeylena itself was found

Scheme I



inactive in the P-388 lymphocytic leukemia screen,[6] its relationship to the active cyclohexene oxides was established and several syntheses of these interesting compounds were reported.[7] The biogenesis of zeylena and other cyclohexene oxides has been suggested to take place in higher organisms through the nucleophilic opening of arene oxides **2** generated by the enzymatic oxygenation of benzyl benzoate as shown in eq 1, Scheme I.[3]

All known cyclohexene oxides can be derived by further manipulations of *trans*-diol **3** (Nu = OH).[7] If the agent of the nucleophilic opening is *trans*-cinnamic acid, then **3** will generate zeylena **4** upon intramolecular Diels–Alder reaction. Such biogenetic Diels–Alder reaction has also been postulated for the formation of various natural product skeletons[8] and has been used in the synthesis of zeylena itself.[9]

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