An Improved Synthesis of 6,8-Dimethoxy-3-methylisocoumarin, a Fungal Metabolite Precursor

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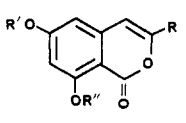
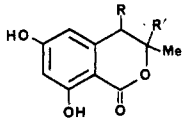
The southern pine beetle[1] and the mountain pine beetle[2] are the two most destructive insects to the pine forests of the southern United States and western North America, respectively. Fungi of the genus *Ceratocystis*, often called blue-stain fungi, are symbiotically associated with each of these pine beetles, and *Ceratocystis minor* is the principal fungus species present in each case.[3-5] Blue-stain fungal infections are known to disrupt the pine water transpiration process, which leads to wilting.[3,4,6] Although the mechanism of this pathogenic process is unknown, several isocoumarin metabolites of *C. minor* have been implicated.[4]

Isocoumarins **1a** and **1b** were isolated and identified as major metabolites of *C. minor* by Hemingway[7] and McGraw.[8] Recently, Ayer[5] reported a more lengthy list of metabolites isolated from *C. minor* cultures that included **1a-c**, **2a-c**, and ceratenolone, an iron-chelating natural product. 6,8-Dihydroxy-3-methylisocoumarin (**1a**) has also been found in other *Ceratocystis* species,[2] including *C. ulmi*,[9] the causative agent of Dutch elm disease.



1a. R = Me; R′ = R″ = H
b. R = CH_2OH; R′ = R″ = H
c. R = R′ = Me; R″ = H
d. R = R′ = R″ = Me



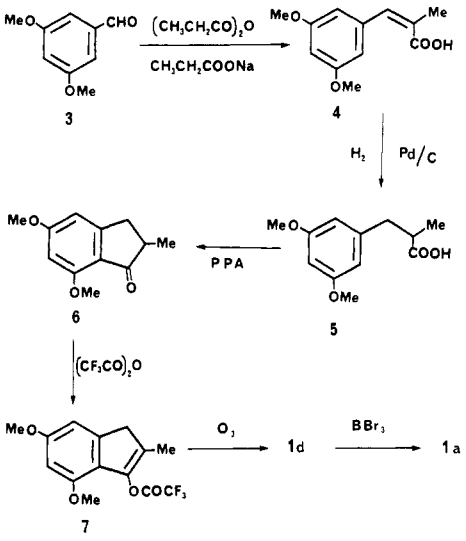
2a. R = R′ = H
b. R = H; R′ = OH
c. R = R′ = OH

The objective of this work was to develop an efficient synthesis of isocoumarin **1d** that could then be used as a precursor for syntheses of isocoumarins **1a-c** and **2a-c**. The long-range goal of this research is to determine the role that these isocoumarin fungal metabolites play in the death of the host tree.

Results and Discussion

Once the biological significance of isocoumarins 1 and 2 was recognized, several pathways leading to their synthesis were proposed.[10-16] Most of these synthetic schemes ultimately start with either orsellinic acid or 3,5-dimethoxybenzaldehyde and usually involve derivatives of one or more of the intermediate compounds: homophthalic acid, phenylpropanoic acid, *C*-acetyl-*o*-orsellinic acid, or indanone.

Scheme I



Our synthesis is a modification of the indanone approach of Carter et al.[16] (see Scheme I). A Perkin condensation of commercially available 3,5-dimethoxybenzaldehyde (**3**) with propionic anhydride and sodium propionate gave cinnamic acid **4** (stereochemistry not determined) in 74% yield. Hydrogenation of **4** at 30 psi using a 10% palladium-charcoal catalyst gave phenylpropanoic acid **5** in quantitative yield.

Next, phenylpropanoic acid **5** was cyclized to indanone **6** in 88% yield by using polyphosphoric acid,[17] because it was easier to use and gave higher yields than the mixture of trifluoroacetic anhydride and trifluoroacetic acid used earlier.[16] Conversion of indanone **6** into enol trifluoroacetate **7** was achieved in 88% yield by using the procedure of Carter.[16] Scale-up of the ozonolysis of **7** to **1d** was more difficult. The uptake of O_3 had to be closely monitored because much decomposition of the product **1d** occurred when excess ozone was used. This reaction was run about a dozen times (3.0 g/run) and the yields averaged 61%.

Our five-step synthesis of 6,8-dimethoxy-3-methylisocoumarin (**1d**) is two steps shorter than the earlier indanone synthesis[16] and gave an overall yield of 35%.

Isocoumarin **1d** was also converted into **1a** and **2a**, two of the fungal metabolites of *C. minor*, using literature procedures.[18] Efforts to synthesize **1b,c** and **2b,c** from **1d** are in progress.

The 300-MHz ^1H NMR spectrum of **5** is interesting. The two benzylic (β) H's are diastereotopic because of the adjacent chiral center and their chemical shifts are sepa-

(1) Blanche, C. A.; Hodges, J. D.; Nebeker, T. E.; Moehring, D. M. *Southern Pine Beetle: The Host Dimension*; MAFES Bulletin 917, Mississippi State University, 1983.
(2) Ayer, W. A.; Browne, L. M.; Feng, M. C.; Orszanska, H.; Saeedi-Ghomi, H. *Can. J. Chem.* **1986**, *64*, 904.
(3) Basham, H. G. *Phytopathology* **1970**, *60*, 750.
(4) DeAngelis, J. D.; Hodges, J. D.; Nebeker, T. E. *Can. J. Bot.* **1986**, *64*, 151.
(5) Ayer, W. A.; Attah-Poku, S. K.; Browne, L. M.; Orszanska, H. *Can. J. Chem.* **1987**, *65*, 765.
(6) Paine, T. D. *Can. J. Bot.* **1984**, *62*, 556.
(7) Hemingway, R. W.; McGraw, G. W.; Barras, S. J. *J. Agric. Food Chem.* **1977**, *25*, 717.
(8) McGraw, G. W.; Hemingway, R. W. *Phytochemistry* **1977**, *16*, 1315.
(9) Claydon, N.; Grove, J. F.; Hosken, M. *Phytochemistry* **1974**, *13*, 2567.
(10) Curtis, R. F.; Harries, P. C.; Hassall, C. H. *J. Chem. Soc.* **1964**, 5382.
(11) Slates, H. L.; Weber, S.; Wendler, N. L. *Chemia* **1967**, *21*, 468.
(12) (a) Hauser, F. M.; Rhee, R. *Synthesis* **1977**, 245. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1977**, *42*, 4155.
(13) Grove, J. F.; Pople, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 337.
(14) Henderson, G. B.; Hill, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1111.
(15) Lewis, C. N.; Spargo, P. L.; Staunton, J. *Synthesis* **1986**, 944.
(16) Carter, R. H.; Colyer, R. M.; Hill, R. A.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1438.
(17) Huisgen, R.; Seidl, G.; Wimmer, I. *Liebigs Ann. Chem.* **1964**, *677*, 21.
(18) Hill, R. A.; Carter, R. H.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2570.

0022-3263/89/1954-4218$01.50/0

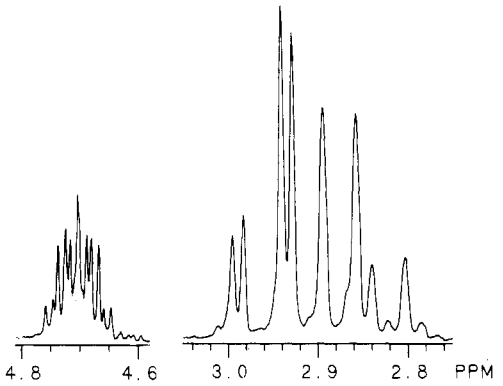


Figure 1. ABX 300-MHz spectrum of the C-3 and C-4 hydrogens of **2a**.

rated by 0.43 ppm. The single α-H appears as a clearly resolved sextet located between the two diastereotopic benzyl H's. The H,H-COSY spectrum of **5** showed a strong correlation between the benzylic H's at 2.59 and 3.02 ppm; the methyl H's were strongly correlated with the center peak at 2.76 ppm, which was also weakly correlated with each of the benzylic H's. Each diastereotopic hydrogen was split by the other (J_{gem} = 13.4 Hz) and unequally by the neighboring α-H (J_{vic} = 6.4 and 8.0 Hz). The H,C-COSY spectrum of **5** confirmed this assignment by showing that both benzylic H's are on the same carbon (β), located at 39.45 ppm; the H at 2.76 ppm correlated with the C (α) at 41.01 ppm.

The proton NMR spectrum of **6** contains a doublet of doublets at 3.26 ppm with half the intensity of the complex multiplet at 2.5–2.7 ppm. The peak at 3.26 ppm is not the single α-H[16] but is instead the diastereotopic proton at C-3 trans to the C-2 methyl group (J_{gem} = 17 Hz, J_{vic} = 7.5 Hz). The H,H-COSY spectrum showed that the methyl doublet at 1.26 ppm is strongly correlated with one of the overlapping H's at 2.5–2.7 ppm. Also the H,C-COSY spectrum showed that both the 3.26 ppm peak and one of the 2.5–2.7 ppm peaks correlated with the C-3 carbon located at 34.76 ppm; the other 2.5–2.7 ppm proton correlated with C-2 located at 42.02 ppm; the aromatic protons at 6.29 and 6.46 ppm correlated with the carbons at 101.32 and 97.15 ppm, respectively.

Both the 60-MHz and 200-MHz ^{1}H NMR spectra of the fungal metabolite **2a** have been reported.[5,18] Our assignments of the 3,4-hydrogens of **2a**, based on one- and two-dimensional 300-MHz NMR spectra of **2a**, differ from literature assignments.[5,18] The three 3,4-hydrogens form an ABX system (see Figure 1), where the X hydrogen at C-3 is a complex multiplet with vicinal coupling constants to the methyl of 6.3 Hz, to the cis H-4 of 11 Hz, and to the trans H-4 of 3.6 Hz. The AB hydrogens at 2.8–3.0 ppm show that the hydrogen cis to the methyl group is located at 2.96 ppm (J_{gem} = 16 Hz, J_{trans} = 3.6 Hz) and the hydrogen trans to the methyl group is located at 2.85 ppm (J_{gem} = 16 Hz, J_{cis} = 11 Hz). The outer doublet pair of each quartet is only 32% as intense as the inner pair because J/δ is about 0.6 for this AB system. No geminal couplings between the diastereotopic C-4 hydrogens were reported by either of the earlier studies.[5,18]

Very little ^{13}C NMR spectral data have been reported for these isocoumarin compounds. Ayer[5] reported the ^{13}C NMR spectrum of **2c** and its 4,6,8-triacetoxy derivative. Our H,C-COSY spectrum of **1d** showed that the higher field aromatic proton (H-5) correlated with the lower field carbon (C-5) peak at 99.3 ppm. The C-4a carbons of **1a**, **1d**, **2a**, and **2c**[5] all are low-intensity peaks at 142 ± 2 ppm, while the adjacent C-8a carbons in the same compounds come between 99 and 105 ppm. The other ^{13}C assignments are given in the Experimental Section.

Experimental Section

All ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer. Melting points are uncorrected. 3,5-Dimethoxybenzaldehyde (**3**) was obtained from Aldrich.

3-(3,5-Dimethoxyphenyl)-2-methylpropenoic Acid (4). A mixture of 40.2 g (0.242 mol) of 3,5-dimethoxybenzaldehyde, 24.0 g (0.25 mol) of sodium propionate, and 32 mL (0.25 mol) of propionic anhydride was heated at 155–160 °C for 15 h. Water was added and the mixture was filtered. The solid obtained was dissolved in 125 mL of 2 N NaOH, and the solution was washed 4 times with ether. The ether was extracted (4×) with 10% sodium bicarbonate. The combined basic layers were acidified to pH 2 from which a tan solid was filtered and dried: yield, 39.9 g (74%); mp 152–153 °C (lit.[19] mp 153–154 °C); ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 3.81 (s, 6 H), 6.46 (t, 1 H, J = 2.2 Hz), 6.56 (d, 2 H, J = 2.2 Hz), 7.75 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.86 (Me), 55.39 (OMe), 100.81 (C-4), 107.76 (C-2), 128.06 (C-α), 137.36 (C-β), 141.03 (C-1), 160.62 (C-3), 174.01 (CO_2H) ppm; MS m/e 222 (M^+, 100), 177 (65), 176 (40), 161 (17), 91 (18); IR (KBr pellet) cm^{-1} 2850–3050, 1686, 1600, 1424, 1281, 1211, 1159; UV λ_{max} (ϵ) 264 (3800), 218 (6700) nm.

3-(3,5-Dimethoxyphenyl)-2-methylpropanoic Acid (5). A solution of 11.0 g (0.05 mol) of acid **4** in ethyl acetate was hydrogenated by using 0.5 g of a 10% Pd/C catalyst at 30 psi for 20 h. After filtration and evaporation, acid **5** was obtained as an oil[16] in quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6.9 Hz), 2.59 (dd, 1 H, J = 13.3 and 8.0 Hz), 2.76 (sextet, 1 H, J = 6.9 Hz), 3.02 (dd, 1 H, J = 13.3 and 6.4 Hz), 3.75 (s, 6 H), 6.34 (s, 3 H), 11.13 (br s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.44 (Me), 39.45 (C-β), 41.01 (C-α), 55.13 (OMe), 98.32 (C-4), 106.94 (C-2), 141.28 (C-1), 160.66 (C-3)), 182.55 (CO_2H) ppm; UV λ_{max} (ϵ) 277 (1100), 271 (1140), 222 (5800) nm; MS m/e 224 (M^+, 89), 179 (95), 152 (100), 151 (77).

5,7-Dimethoxy-2-methylindan-1-one (6). To 40.3 g (0.18 mol) of propanoic acid **5** was added 200 g of polyphosphoric acid that had been heated to 90 °C, and the thick mixture was hand stirred for 7 min. An additional 120 g of hot PPA was added and stirred for 5 more min at which time 500 mL of water was added and the resulting orange heterogeneous solution was stirred overnight. The aqueous solution was extracted with chloroform several times and the chlorform solution was washed with 10% sodium bicarbonate and water, dried (Na_2SO_4), and evaporated. Distillation at 144–146 °C/0.15 Torr yielded 32.4 g (88%) of a peach-white solid with a coconut odor: mp 76–77 °C (lit.[16] mp 76–79 °C); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 7.2 Hz), 2.5–2.7 (m, 2 H, H-2 and H-3), 3.26 (dd, 1 H, J = 17 and 7.5 Hz), 3.87 (s, 3 H), 3.90 (s, 3 H), 6.29 (d, 1 H, J = 1.5 Hz), 6.46 (d, 1 H, J = 1.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 16.76 (Me), 34.76 (C-3), 42.02 (C-2), 55.45 (OMe), 97.15 (C-6), 101.32 (C-4), 118.15 (C-7a), 158.32 (C-3a), 159.17 (C-7), 166.72 (C-5), 205.19 (C-1) ppm; UV λ_{max} (ϵ) 297 sh (3040), 271 (9200), 229 sh (9400), 224 (10 100) nm; MS m/e 206 (M^+, 100), 205 (48), 191 (51), 177 (81), 175 (33), 163 (27), 161 (36).

4,6-Dimethoxy-2-methylinden-3-yl Trifluoracetate (7). To 5.1 g (0.025 mol) of indanone **6** was added 50 mL of trifluoroacetic anhydride, and the reaction was stirred for 1.5 h at room temperature. The excess anhydride was removed under vacuum and distillation at 125–128 °C/0.1 Torr gave 6.6 g (88%) of product: mp 96–98 °C (lit.[16] mp 90–99 °C); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 3.26 (s, 2 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 6.33 (d, 1 H, J = 1.7 Hz), 6.57 (d, 1 H, J = 1.7 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 11.22 (Me), 39.23 (C-1), 55.17 (OMe), 55.52 (OMe), 97.24 (C-5), 102.18 (C-7), 114.69 (q, $^1J_{CF}$ = 285 Hz), 118.90 (C-3a), 124.73 (C-2), 141.47 (C-7a), 143.10 (C-3), 152.14 (C-4), 155.55 (CO, q, $^2J_{CF}$ = 42 Hz), 159.75 (C-6) ppm; UV λ_{max} (ϵ) 298 sh (2400), 271 (7300), 230 sh (7500), 224 (8100) nm; MS m/e 302 (M^+, 100), 205 (63), 189 (84), 69 (23).

6,8-Dimethoxy-3-methylisocoumarin (1d). The enol trifluoroacetate **7** was ozonolyzed by using a Welsbach Model T-408 ozone generator at 101 V, 7.5 psi oxygen, and a flow rate of 0.5 SLPM (standard liters per minute). Ozone was passed into 3.0

(19) Mauthner, F. *J. Prakt. Chem.* **1924**, *107*, 103.

g (0.01 mol) of 7 in 180 mL of ethyl acetate at −55 °C for 15 min. The reaction was stopped before the characteristic blue color of ozone was obvious, to minimize decomposition of the isocoumarin product. The system was flushed with nitrogen for 15 min and then 1 mL of dimethyl sulfide was added; the stirred solution was then allowed to warm to room temperature overnight. The solution was then washed with sodium bicarbonate (2×), 2 N HCl (2×), and saturated NaCl. After drying (Na_2SO_4), the solution was evaporated and the product was recrystallized from methanol: yield, 1.33 g (61%); mp 154–156 °C (lit.[16] mp 157–160 °C); ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.88 (s, 3 H), 3.95 (s, 3 H), 6.08 (s, 1 H), 6.29 (d, 1 H, J = 2.2 Hz), 6.40 (d, 1 H, J = 2.2 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 19.40 (Me), 55.51 (OMe), 56.17 (OMe), 98.03 (C-7), 99.31 (C-5), 102.65 (C-8a), 103.61 (C-4), 142.36 (C-4a), 155.37 (C-3), 159.51 (C-1), 163.14 (C-8), 165.28 (C-6) ppm; H,C-COSY 2D NMR correlated the H's at 2.20, 3.88, 3.95, 6.08, 6.29, and 6.40 ppm with the C's at 19.40, 55.51, 56.17, 103.61, 102.65, and 99.31 ppm, respectively; UV λ_{max} (ε) 320 br (540), 288 sh (580), 276 sh (810), 242 (6400), 235 sh (4100) nm; MS m/e 220 (M^+, 100), 219 (31), 191 (65), 177 (20), 175 (21), 149 (71).

6,8-Dihydroxy-3-methylisocoumarin (1a). The demethylation of isocoumarin **1d** was done by scaling up the procedure of Hill.[18] The solid product obtained was sublimed at 0.1 Torr with the product coming over between 150 and 180 °C; a minor impurity that sublimes at less than 150 °C was removed. The yield was 87%: 1.37 g of **1a**, mp 250–252 °C (lit.[18] mp 250–252 °C); ^{1}H NMR (acetone-d_6) δ 2.22 (s, 3 H), 6.37 (s, 3 H), 9.6 (br s, 1 H), 11.2 (s, 1 H) ppm; ^{13}C NMR (acetone-d_6) δ 19.25 (Me), 99.56 (C-8a), 102.15 (C-7), 103.11 (C-5), 105.03 (C-4), 140.98 (C-4a), 155.30 (C-3), 164.56 (C-8), 166.31 (C-6), 166.99 (C-1) ppm; UV λ_{max} (ε) 329 sh (1900), 304 (3600), 252 (12 000), 241 (9200) nm; MS (solid probe) m/e 192 (M^+, 100), 177 (52), 149 (23), 121 (49), 69 (28), 60 (27), 57 (21), 55 (24).

3,4-Dihydro-6,8-dihydroxy-3-methylisocoumarin (2a). Using the procedure of Hill[18], isocoumarin **1d** was hydrogenated with a 10% Pd/C catalyst to give 3,4-dihydro-6,8-dimethoxyisocoumarin, which was then demethylated as above with BBr_3 in methylene chloride to give **2a**: mp 209–211 °C (lit.[18] mp 214–215 °C); ^{1}H NMR (acetone-d_6) δ 1.45 (d, 3 H, J = 6.3 Hz), 2.85 (AB q, 1 H, J = 16 Hz, J' = 11 Hz), 2.96 (AB q, 1 H, J = 16 Hz, J' = 3.6 Hz), 4.70 (m, 1 H), 6.27 (s, 1 H), 6.29 (s, 1 H), 9.44 (s, 1 H), 11.30 (s, 1 H) ppm; ^{13}C NMR (acetone-d_6) δ 20.82 (Me), 35.03 (C-4), 76.33 (C-3), 101.71 (C-4a), 101.92 (C-7), 107.41 (C-5), 143.21 (C-8a), 165.09 (C-8), 165.23 (C-6), 170.69 (C-1) ppm; H,C-COSY showed that the H's at 1.45, 2.85/2.96, 4.70, 6.27, and 6.29 ppm were connected to the C's at 20.82, 35.03, 76.33, 101.92, and 107.41 ppm, respectively; UV λ_{max} (ε) 308 (10 000), 243 (3800) nm.

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Manipulation of Enzymatic Regioselectivity by Structural Modification of Substrates

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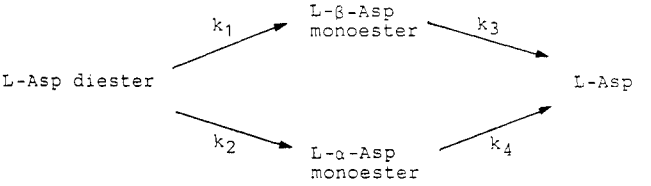
In recent years, hydrolytic enzymes such as proteases and lipases have been extensively used as catalysts for the preparation of optically active compounds.[1] This application has attracted attention of the organic chemists because of their usefulness as chiral catalysts.[2] For organic reactions, selectivity such as enantioselectivity, diastereoselectivity, and regioselectivity is one of the challenges[3] and may often be overcome by biocatalytic reactions.[4] In this article, we describe novel observations which demonstrate that either the α- or β-ester of L-aspartic acid diester may be preferentially hydrolyzed by chymotrypsin by changing the alcohol moiety of esters.

Scheme I



As shown in Scheme I, L-aspartic acid diester is enzymatically converted into two monoesters, which in turn may be further hydrolyzed to free L-aspartic acid. This two-step regioselective ester hydrolysis reaction is similar to that of the tandem asymmetric induction–kinetic resolution described by Sih and his co-workers.[5] Therefore, quantitative prediction of the amount of the diester, the monoesters, and the free amino acid at any extent of conversion can be calculated by using the kinetic parameters E_1, E_2, and α. These three kinetic parameters are defined by the ratios of the four kinetic constants (k_1, k_2, k_3, and k_4).[5] For the dimethyl, diisopropyl, and dibenzyl L-aspartate, the enzymes, subtilisin Carlsberg (Sigma, type VIII) and α-chymotrypsin (from bovine pancreas, 3× crystallized, Sigma, type II), cleave the α-ester group much faster than the β-ester group in both steps ($k_1 \gg k_2$; $k_4 \gg k_3$). Therefore, β-monoesters could accummulate in high yield, but the amount of α-monoesters is too low to be measured at any extent of conversion in the reaction

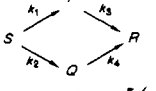
(1) (a) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. (b) Whitesides, G. M.; Wong, C. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. (c) Chen, C. S.; Wu, S. H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812. (d) Cambou, B.; Klibanov, A. M. *Ibid.* **1984**, *106*, 2687.

(2) (a) Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y. F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. (b) Wang, Y. F.; Izawa, T.; Kobayashi, S.; Ohno, M. *Ibid.* **1982**, *104*, 6465. (c) Fischli, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle/Sauerlander: Frankfurt, 1980; Vol. 2, p 269. (d) Hsu, C. T.; Wang, N. Y.; Latimer, L. H.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 593. (e) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *Ibid.* **1986**, *108*, 4603. (f) Drueckhammer, D. G.; Barbas III, C. F.; Nozaki, K.; Wong, C. H.; Wood, C. Y.; Ciufolini, M. A. *J. Org. Chem.* **1988**, *53*, 1607.

(3) (a) Mosher, H. S.; Morrison, J. D. *Science* **1982**, *221*, 1013. (b) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (c) Trost, B. M. *Science* **1983**, *219*, 245. (d) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (e) Halpern, J. *Science* **1982**, *217*, 401.

(4) (a) Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 309. (b) Sweers, H. M.; Wong, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 6421. (c) Riva, S.; Chopineau, J.; Kieboom, A. P. G.; Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 584.

(5) Wang, Y. F.; Chen, C. S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. The two-step reactions which have divergent reaction in the first step and convergent reaction in the second step can be expressed quantitatively as follows:



$$P = \frac{\alpha S_0}{(\alpha+1)(1-E_1)}\left[\left(\frac{S}{S_0}\right)^{E_1} - \left(\frac{S}{S_0}\right)\right] \quad (1)$$

$$Q = \frac{S_0}{(\alpha+1)(1-E_2)}\left[\left(\frac{S}{S_0}\right)^{E_2} - \left(\frac{S}{S_0}\right)\right] \quad (2)$$

$$R = S_0 - S - P - Q$$

k_1, k_2, k_3, and k_4 are apparent first-order rate constants. S_0 is the initial concentration of the substrate, where $\alpha = k_1/k_2$, $E_1 = k_3/(k_1 + k_2)$, and $E_2 = k_4/(k_1 + k_2)$.

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