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).

Acknowledgment. This research was supported in part by Grant-in-Aid for Scientific Research No. 63560135 from the Ministry of Education, Science, and Culture, Japan.

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Enantioselective Synthesis of (-)-Zeylena from Styrene

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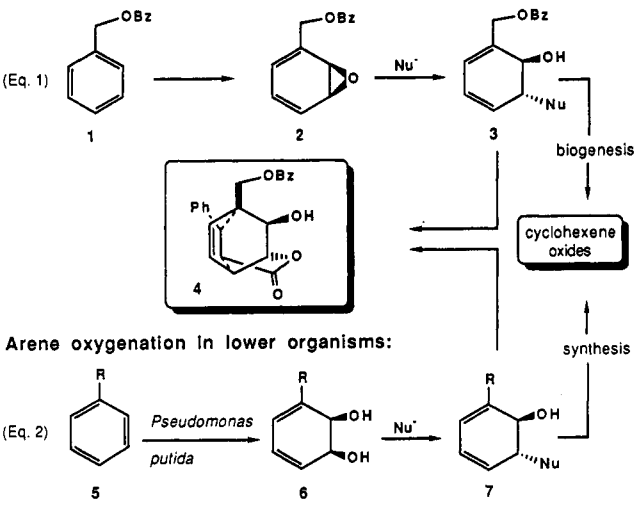
The unique hydrocarbon zeylena, **4**, was isolated from the roots of *Uvaria zeylanica* L. (annonaceae)[3] during the investigations of antitumor activities of the related cyclohexene oxides.[4,5] Although zeylena itself was found

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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(2) Undergraduate research participant, Longwood College, VA, Summer 1988.
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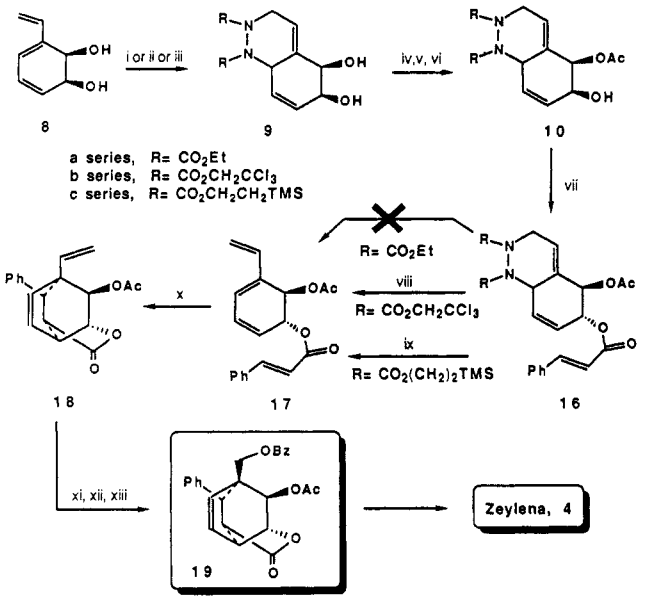
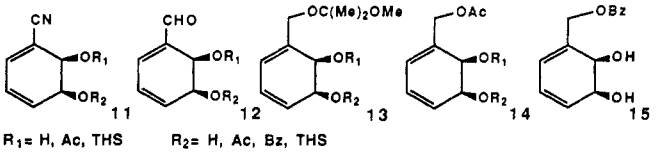
Scheme II[a]



[a] Reagents: (i) DEAD, THF, 0 °C, 95%; (ii) bis(2,2,2-trichloroethyl)azodicarboxylate, THF, 0 °C, 95%; (iii) bis((trimethylsilyl)ethyl)azodicarboxylate, THF, 67%; (iv) THSCl, imidazole, DMF, 4 °C, 89%; (v) Ac_2O, py, DMAP, 4 °C, 95%; (vi) *n*-Bu_4NF, THF, room temperature, 0.5 h, 65–75%; (vii) Ph_3P, DEAD, cinnamic acid, THF, room temperature, 18 h, 55%; (viii) Zn(Cu), 90% AcOH, room temperature, 10–60%; (ix) *n*-Bu_4NF, THF; (x) PhH, 110 °C, 15 h, 94%; (xi) O_3, CH_2Cl_2, −78 °C; then DMS, quantitative; (xii) $NaBH_4$, MeOH, 0 °C, 85%; (xiii) PhCOOH, Me_2CHCH_2OCOCl, Et_3N, THF, Δ.

During the investigations of the microbial oxidation of arenes by mutants of *Pseudomonas putida*[10,11] we were intrigued by the possibility of entering the structurally diverse cyclohexene oxide manifold by manipulations of the arene *cis*-diols of type **6**, eq 2, Scheme I. A general strategy for cyclohexene oxide synthesis would require only a C-3 inversion of an appropiately functionalized arene diol to generate intermediates of type **7** from which all known cyclohexene oxides, including zeylena, should be available.[12] The idea of combining the oxygenation of arenes, as it occurs in bacterial systems, with synthesis to bridge the relationship between *cis*- and *trans*-arenediols seemed fascinating. In this manuscript we report on the successful realization of a short enantioselective synthesis of zeylena from styrene by the strategy shown in eq 2, Scheme I, and on the use of a unique protecting and activating group for dienes.

Styrene was subjected to microbial oxidation by *Pseudomonas putida* 39-D according to the protocol established by Gibson[10] and used previously in generating many *cis*-diols of simple aromatic hydrocarbons.[11] Diol **8** was isolated in excellent yield (900 mg/L, 0.50 g/batch) by extraction of the centrifuged broth with acid-free ethyl acetate, Scheme II. Reaction of **8** with diethyl azodicarboxylate (DEAD) either in the presence or in the absence of cinnamic acid led exclusively to the formation of Diels–Alder adduct **9** (95%), which was selectively alkylated at C-3 hydroxyl, acylated at C-2 hydroxyl, and deprotected to furnish acetate **10** on which Mitsunobu conditions were to be tested,[13] Scheme II. This protection turned out to be necessary because previous attempts at Mitsunobu inversion of diols **11**, **12**, **13**, and **14** and their



various derivatives proved unsuccessful, and problems of aromatization were frequently encountered. Also unsuccessful were attempts at microbial oxidation of benzyl benzoate to produce **15**.[14]

The Mitsunobu inversion[15] of **10** proceeded smoothly and provided cinnamate **16** in 55–70% yield. The attempts at thermally induced retro-Diels–Alder reaction of **16** and the subsequent intramolecular trapping of **17** by the cinnamate proved futile because of the almost insignificant tendency of diazenes such as **16** to undergo such a cycloreversion.[16,17] We therefore switched to the use of bis(2,2,2-trichloroethyl) derivative of DEAD, or TEAD, previously known from Little's generations of cyclic azo compounds as diyl precursors.[18a] Deprotection of **16b** prepared in an analogous manner under a variety of conditions gave the expected triene **17** in varying yields (10–60%) because of unoptimized reaction parameters inherent in heterogeneous systems such as Zn/Cu catalyst. More reliable results were obtained using bis[(2-trimethylsilyl)ethyl] esters **9c**.[18b] In this series the yields of triene **17** were reproducible in the 20–40% range. The expected isolation of cyclic hydrazo compound and its oxidation to the cyclic azo compound was not necessary because the cycloreversion of **16b** or **16c** took place during the deprotection operations.[19] This observation is of potential interest

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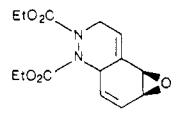
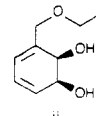
(12) Stereo- and regioselective epoxidations are known for *trans*-diols of type **3**.[7] Thus the general strategy relies on the Mitsunobu inversion of "protected" *cis*-diols **6** and functionalization of substituents to the stage of benzyl benzoate.

(13) Early attempts to invert the C-3 hydroxyl of **9** in presence of the free C-2 hydroxyl led exclusively to the isolation of epoxide **i**. This result proved that the inversion was successful, but was followed by an intramolecular nucleophilic displacement by the remaining free hydroxy group. To circumvent this problem the C-2 hydroxy group was protected as an acetate, compound **10**.



(14) Microbial oxidation of benzylic substrates was successful in the case of benzyl ethyl ether. In this instance a diol of structure **ii** was the only product of the reaction. Conversely, other benzylic substrates such as benzylic alcohol or benzyl benzoate did not afford any isolable amount of oxygenated products.



ii

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(18) (a) Cook, A. F. *J. Org. Chem.* **1968**, *33*, 3589. Little, R. D.; Carroll, G. L. *J. Org. Chem.* **1979**, *44*, 4720. Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744. (b) Bis[(2-trimethylsilyl)ethyl]azodicarboxylate was prepared in 61% overall yield from commercially available 2-(trimethylsilyl)ethanol.

regarding the mechanism of such cycloreversion and its utility in the development of protecting or activating groups for conjugated dienes.[19] Triene **17** cyclized smoothly in a sealed tube (benzene, 110 °C, 15 h, 94%) or at room temperature (2 weeks, 94%) to provide the tricyclic system **18** ($[\alpha]_D$ −4.53° (*c* 0.75, MeOH)), which was rapidly converted to zeylena acetate **19** by a three-step sequence involving the selective oxidative cleavage of the less hindered olefin ($OsO_4/NaIO_4$, 30% or O_3, saturated CH_2Cl_2 solution, 1.4 equiv, quantitative yield), reduction of the aldehyde ($NaBH_4$, 90%), and benzoylation (40%, not optimized). Acetate **19** has been previously hydrolyzed to zeylena.[3,9] The synthesis of zeylena in a chiral form and in 11 steps from styrene constitutes the shortest preparation of this compound to date. The ease of Mitsunobu inversion portends well to a facile preparation of cyclohexene oxides of biological relevance by performing the Mitsunobu inversion with benzoate at C-3 and by subsequent further oxidative manipulations that are known in the literature.[7]

Our current endeavor focuses on a detailed study of the use and possible activating parameters of the new diene-protecting groups such as bis(2,2,2-trichloroethyl) and bis[2-(trimethylsilyl)ethyl] azodicarboxylates in the context of the intramolecular Diels–Alder reaction as well as further studies on the preparation of cyclohexene oxides by this strategy.

Experimental Section

All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried under vaccum. Diethyl ether, THF, and benzene were distilled from benzophenone ketyl, dichloromethane and toluene from calcium hydride.

Analytical TLC was performed on silica gel 60F-254 plates. Flash chromatography was performed on Kieselgel 60 (EM Reagents, 230–400 mesh). Mass spectra were recorded on a Du Pont 20-491 instrument (low resolution) or on a double focusing Du Pont 21-110C or VGT instruments (exact mass). Infrared spectra were recorded either on neat samples (NaCl plates) or in solution on a Perkin-Elmer 283B or 710B spectrometer. Proton NMR spectra were obtained on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal reference (0.00 ppm). Carbon NMR spectra were recorded on Bruker WP-270 or NR-80 instruments. Carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm), and the multiplicity is indicated by CH_3, CH_2, CH, C (INEPT experiments).

(1*S*,2*R*)-1,2-Dihydroxy-3-vinylcyclohexa-3,5-diene (8). Compound **8** was prepared as previously reported:[11] mp 57–8 °C; R_f = 0.30 (hexane/EtOAc, 1:1); IR ($CHCl_3$) 3400–3200, 3020, 2925, 1602, 1479, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (d br, OH, 1 H), 2.80 (d br, OH, 1 H), 4.35 (m, 1 H), 4.45 (m, 1 H), 5.19 (d, *J* = 11 Hz, 1 H), 5.48 (d, *J* = 18 Hz, 1 H), 5.82 (m, 1 H), 5.95 (m, 1 H), 5.98 (m, 1 H), 6.38 (dd, J_1 = 18, J_2 = 11 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 65.8 (CH), 70.8 (CH), 114.1 (CH_2), 123.7 (CH), 124.6 (CH), 132.4 (CH), 136.0 (CH), 137.1 (C).

General Procedure for Diene Protection. To a stirred solution of styrene dihydrodiol **8** (20 mmol) in THF (50 mL) at 0 °C was added the desired azodicarboxylate (20.4 mmol) in portions. After 9 h (19 h for **9c**) the solvent was evaporated to give a foamy residue, which was chromatographed (10% silica gel, hexane/EtOAc, 1:1) to obtain the corresponding adduct **9**.

2,3-Dihydroxy-7,8-bis(ethoxycarbonyl)-7,8-diazabicyclo[4.4.0]deca-4,10-diene (9a): oil, 95%; R_f = 0.09 (hexane/EtOAc, 1:1); IR (neat) 3600–3400, 2960, 1720, 1700, 1420, 1310, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (m, 6 H), 1.70 (s br, OH, 1 H), 2.86 (m, OH, 1 H), 3.70 (d br, *J* = 17 Hz, 1 H), 4.05–4.35 (m, 6 H), 4.42 (dd, J_1 = 17, J_2 = 6 Hz, 1 H), 5.10 (m, 1 H), 5.91 (m, 2 H), 6.05 (d br, *J* = 11 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 14.6 (CH_3), 43.4 (CH_2), 54.3 (CH), 62.4 (CH_2), 62.7 (CH_2), 68.4 (CH), 70.6 (CH), 116.0 (CH), 128.7 (CH), 134.4 (CH and C), 155.3 (2 C).

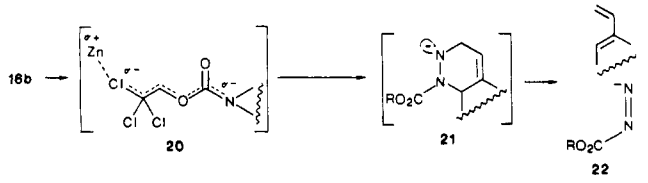
2,3-Dihydroxy-7,8-bis[(2,2,2-trichloroethoxy)carbonyl]-7,8-diazabicyclo[4.4.0]deca-4,10-diene (9b): oil, 95%; R_f = 0.29 (hexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 2.30 (OH, 1 H), 2.64 (OH, 1 H), 3.84 (d br, *J* = 17 Hz, 1 H), 4.28 (s br, 1 H), 4.48 (d br, J_1 = 7 Hz, 1 H), 4.50 (m, 1 H), 4.50–4.95 (m, 4 H), 5.55 (m, 2 H), 5.92 (m, 2 H).

2,3-Dihydroxy-7,8-bis[(2-trimethylsilyl)ethoxycarbonyl]-7,8-diazabicyclo[4.4.0]deca-4,10-diene (9c): oil, 67%; R_f = 0.28 (hexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 0.02 (s br, 18 H), 0.97 (m, 4 H), 1.53 (OH, 1 H), 2.89 (OH, 1 H), 3.71 (m, 1 H), 4.05–4.35 (m, 5 H), 4.41 (s br, 1 H), 4.43 (m, 1 H), 5.09 (m, 1 H), 5.91 (m, 2 H), 6.08 (d br, *J* = 10 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −1.5 (6 CH_3), 17.8 (CH_2), 17.9 (CH_2), 43.4 (CH_2), 54.6 (CH), 64.9 (CH_2), 65.0 (CH_2), 68.5 (CH), 70.6 (CH), 116.0 (CH), 128.7 (CH), 130.2 (C), 134.6 (CH), 155.7 (2 C).

Preparation of 10b and 10a. 2-Acetoxy-3-hydroxy-7,8-bis[(2,2,2-trichloroethoxy)carbonyl]-7,8-diazabicyclo[4.4.0]deca-4,10-diene (10b). To a stirred solution of diol **9** (1.45 g, 2.79 mmol) in DMF (6 mL) was added thexyldimethylsilyl chloride (554 mg, 31 mmol) in portions followed by imidazole (422 mg, 6.2 mmol), and the resulting solution was stirred at 4 °C for 24 h. The mixture was then diluted with Et_2O (50 mL) and poured into brine (20 mL), and the organic layer was successively washed with H_2O, saturated aqueous $CuSO_4$, H_2O, and brine (2×). After drying, the solvent was evaporated to give an oil, which was chromatographed (10% deactivated silica gel, hexane/EtOAc, 90:10) to afford the monoprotected alcohol as a clear oil: 1.64 g, 89%; R_f = 0.37 (hexane/EtOAc, 80:20); IR (neat) 3520 (br), 2962, 1727, 1407, 1214, 1137, 1071 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.85 (m, 12 H), 1.61 (m, 1 H), 3.0 (s br, OH, 1 H), 3.83 (d br, *J* = 17 Hz, 1 H), 4.26 (m, 2 H), 4.48 (dd br, J_1 = 17, J_2 = 6 Hz, 1 H), 4.6–4.9 (m, 4 H), 5.44 (d br, *J* = 10 Hz, 1 H), 5.55 (m, 1 H), 5.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −2.8 (CH_3), −2.5 (CH_3), 18.6 (2 CH_3), 20.1 (CH_3), 20.3 (CH_3), 25.1 (C), 34.2 (CH), 43.3 (CH_2), 52.5 (CH), 71.8 (CH), 73.6 (CH), 75.6 (2 CH_2), 94.9 (2 C), 118.6 (CH), 128.6 (CH), 130.9 (CH), 132.1 (C), 153.5 (2 C).

To a stirred solution of monoprotected alcohol (1.47 g, 2.22 mmol) in acetic anhydride (3.4 g, 33 mmol) was added pyridine (265 mg, 3.34 mmol) followed by DMAP (54 mg, 0.45 mmol), and the resulting solution was stirred at 4 °C. After 6 h, the mixture was diluted with Et_2O (50 mL) and poured into cold saturated aqueous Na_2CO_3 (15 mL) (vigorous gas evolution was observed). The aqueous layer was extracted with Et_2O, and the combined

(19) We believe that a potential acceleration of the cycloreversion in **16b** and **16c** occurs by the presence or the incipient development of nonparticipating π-electron density close to the reacting centers. As soon as the generation of dichloroethylene and CO_2 begins to take place in **16b**, for example, the amine receives an increased electron density whose presence in a fully charged intermediate such as **21** would accelerate the cycloreversion to a degree inherent in such processes as oxy anion Cope,[20] enolate anion Claisen,[21] enolate anion divinylcyclobutane,[22] immonium ion Diels–Alder,[23] and others.[24] A variety of possible transition states with substantially lower activation energies for the cycloreversion can be envisioned and these can range from a polarized structure **20** to a fully charged species **21**. In cases where a regenerated diene may participate in a subsequent new intramolecular Diels–Alder reaction, a transition state may begin to develop before the complete departure of the carboalkoxy diazene takes place. Such suppositions are being currently tested in our laboratory.



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organic layer was washed with H_2O, saturated aqueous $CuSO_4$, and brine. After drying with $MgSO_4$, the solvent was evaporated and the residue was chromatographed (10% silica gel, hexane/EtOAc, 90:10) to give pure acetate: oil, 1.48 g, 95%; R_f = 0.52 (hexane/EtOAc, 80:20); ^1H NMR ($CDCl_3$) δ 0.09 (s, 3 H), 0.11 (s, 3 H), 0.83 (m, 12 H), 1.60 (m, 1 H), 2.07 (s, 3 H), 3.83 (d br, J = 17 Hz, 1 H), 4.35 (m, 1 H), 4.52 (m, 1 H), 4.55–4.9 (m, 4 H), 5.38 (m, 1 H), 5.57 (d br, J = 10 Hz, 1 H), 5.61 (m, 1 H), 5.86 (m, 1 H), 5.98 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ -2.9 (2 CH_3), 18.6 (2 CH_3), 20.2 (2 CH_3), 21.2 (CH_3), 25.1 (C), 34.1 (CH), 43.5 (CH_2), 52.6 (CH), 70.4 (CH), 74.6 (CH), 75.5 (2 CH_2), 94.7 (2 C), 120.2 (CH), 127.4 (CH), 130.6 (C), 132.9 (CH), 153.3 (2 C), 170.7 (C).

To a solution of the diprotected alcohol (2-acetoxy, 3-thexyldimethylsilyl) (1.65 g, 2.34 mmol) in dry THF (10 mL) was added tetrabutylammonium fluoride (3.51 mL of a 1.0 M solution in THF) at ambient temperature, and the reaction was monitored by TLC. After 30 min the resulting dark brown mixture was diluted with Et_2O (70 mL) and poured into brine (5 mL). The organic layer was washed with brine (2 × 5 mL) and dried, and the solvent was evaporated to afford a yellow oil, which was chromatographed (10% silica gel, hexane/EtOAc, 1:1) to give the monoalcohol **10b**: oil, 0.85 g, 65%; R_f = 0.35 (hexane/EtOAc, 1:1); IR (neat) 3600–3200, 2960, 1730 (br), 1420, 1215, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H), 2.3 (s br, OH, 1 H), 3.84 (d br, J = 17 Hz, 1 H), 4.5 (dd, J_1 = 17, J_2 = 6 Hz, 1 H), 4.64 (m, 1 H), 4.6–4.95 (m, 4 H), 5.35 (m, 1 H), 5.58 (m, 2 H), 5.97 (m, 1 H), 6.04 (m, 1 H).

2-Acetoxy-3-hydroxy-7,8-bis(ethoxycarbonyl)-7,8-diazabicyclo[4.4.0]deca-4,10-diene (10a). A similar procedure for the ethoxycarbonyl derivatives afforded for the first intermediate **2-hydroxy-3-[(dimethylthexylsilyl)oxy]-7,8-bis(ethoxycarbonyl)-7,8-diazabicyclo[4.4.0]deca-4,10-diene**: oil, 89%; R_f = 0.30 (hexane/EtOAc, 70:30); ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.85 (m, 12 H), 1.22 (m, 6 H), 1.62 (m, 1 H), 2.33 (s br, OH, 1 H), 3.65 (m, 1 H), 4.00–4.25 (m, 5 H), 4.30 (s br, 1 H), 4.43 (m, 1 H), 5.05 (s br, 1 H), 5.82 (m, 2 H), 5.96 (m, 1 H).

For the second intermediate **2-acetoxy-3-[(dimethylthexylsilyl)oxy]-7,8-bis(ethoxycarbonyl)-7,8-diazabicyclo[4.4.0]deca-4,10-diene**: oil, 92%; R_f = 0.75 (hexane/EtOAc, 80:20); ^1H NMR ($CDCl_3$) δ 0.10 (s br, 6 H), 0.85 (m, 12 H), 1.22 (m, 6 H), 1.60 (m, 1 H), 1.97 (s, 3 H), 3.65 (d br, J = 17 Hz, 1 H), 4.05–4.30 (m, 4 H), 4.32 (s br, 1 H), 4.50 (m, 1 H), 5.07 (s br, 1 H), 5.35 (m, 1 H), 5.72 (m, 1 H), 5.92 (m, 1 H), 6.02 (d br, J = 10 Hz, 1 H).

For **10a**: oil, 50%; R_f = 0.20 (hexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 1.22 (m, 6 H), 2.04 (s, 3 H), 2.43 (OH, 1 H), 3.68 (m, 1 H), 4.05–4.30 (m, 4 H), 4.50 (m, 2 H), 5.09 (s br, 1 H), 5.34 (s br, 1 H), 5.80 (m, 1 H), 5.93 (m, 1 H), 6.10 (d br, J = 10 Hz, 1 H).

Preparation of 10c. 2-Acetoxy-3-hydroxy-7,8-bis[((trimethylsilyl)ethoxy)carbonyl]-7,8-diazabicyclo[4.4.0]deca-4,10-diene (10c). To a stirred solution of diol **9c** (1.25 g, 2.74 mmol) in CH_2Cl_2 (9 mL) was added acetic anhydride (0.285 g, 2.8 mmol) followed by DMAP (0.34 g, 2.8 mmol), and the resulting solution was stirred at -10 °C. After 8 h, the mixture was diluted with Et_2O (50 mL) and poured into 10% aqueous KOH (15 mL). The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with H_2O, saturated aqueous $CuSO_4$, and brine. After drying with $MgSO_4$, the solvent was evaporated and the residue (1.29 g) was chromatographed (10% silica gel, hexane/EtOAc, 70:30 to 50:50) to give four fractions: the diacetate (21%, R_f = 0.79 in hexane/EtOAc, 1:1), the undesired monoacetae (42%, R_f = 0.47 in hexane/EtOAc, 1:1), **10c** (7%), and unreacted **9c** (14%, R_f = 0.22 in hexane/EtOAc, 1:1). Both the diacetate and the undesired monoacetate were recycled by hydrolysis to **9c** (MeOH, K_2CO_3).

10c: oil, 95 mg; R_f = 0.34 (hexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 0.02 (s br, 18 H), 0.97 (m, 4 H), 1.43 (d br, OH, J = 11 Hz, 1 H), 2.17 (s, 3 H), 3.68 (m, 1 H), 4.10–4.25 (m, 4 H), 4.32 (m, 1 H), 4.46 (dd br, J_1 = 17, J_2 = 6 Hz, 1 H), 5.18 (m, 1 H), 5.39 (s br, 1 H), 5.84 (m, 1 H), 5.90 (m, 1 H), 6.05 (d br, J = 10 Hz, 1 H).

General Procedure for the Mitsunobu Inversion of a Secondary Alcohol. A typical inversion procedure was performed as follows: to a stirred solution of alcohol **10** (1 mmol), triphenylphosphine (1.7 mmol), and cinnamic acid (3.0 mmol) in THF (10 mL) at ambient temperature was added the desired azodicarboxylate (1.7 mmol in 1 mL of THF) dropwise, and the resulting yellow solution was stirred overnight. The reaction mixture was then concentrated at reduced pressure, and the resulting semisolid residue was dissolved in CH_2Cl_2. The organic solution was washed with saturated aqueous Na_2CO_3, H_2O, and brine and dried over $MgSO_4$ to afford a semisolid crude, which was purified by column chromatography (10% deactivated silica gel, hexane/EtOAc, 65:35) to give pure **16** in 55–70% yield.

2-Acetoxy-3-(cinnamoyloxy)-7,8-bis(carbethoxy)-7,8-diazabicyclo[4.4.0]deca-4,10-diene (16a): glassy solid; R_f = 0.55 (hexane/EtOAc, 1:1); IR (neat) 2982, 1737, 1712, 1636, 1417, 1380, 1337, 1331, 1227, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (m, 6 H), 2.04 (s, 3 H), 3.72 (d br, J = 17 Hz, 1 H), 4.19 (m, 4 H), 4.52 (dd br, J_1 = 17, J_2 = 6 Hz, 1 H), 5.25 (s br, 1 H), 5.34 (m, 1 H), 5.42 (s br, 1 H), 5.80 (m, 1 H), 6.08 (m, 1 H), 6.18 (d br, J = 10.5 Hz, 1 H), 6.41 (d, J = 16 Hz, 1 H), 7.38 (m, 3 H), 7.51 (m, 2 H), 7.68 (d, J = 16 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 14.8 (CH_3), 20.9 (CH_3), 43.0 (CH_2), 51.2 (CH), 62.4 (CH_2), 62.5 (CH_2), 69.1 (CH), 74.1 (CH), 117.1 (CH), 122.9 (CH). 124.8 (CH and C), 128.1 (2 CH), 128.9 (2 CH), 130.1 (CH), 133.8 (CH), 134.3 (C), 145.8 (CH), 155.2 (2 C), 165.2 (C), 169.5 (C).

2-Acetoxy-3-(cinnamoyloxy)-7,8-bis[(2,2,2-trichloroethoxy)carbonyl]-7,8-diazabicyclo[4.4.0]deca-4,10-diene (16b): glassy solid; R_f = 0.22 (hexane/EtOAc, 80:20); IR (neat) 2960, 1732, 1632, 1407, 1217, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H), 3.89 (d br, J = 17 Hz, 1 H), 4.55–4.95 (m, 5 H), 5.31 (m, 1 H), 5.36 (m, 1 H), 5.41 (m, 1 H), 5.86 (m, 1 H), 6.12 (m, 1 H), 6.24 (m, 1 H), 6.36 (d, J = 16 Hz, 1 H), 7.36 (m, 3 H), 7.50 (m, 2 H), 7.64 (d, J = 16 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 43.6 (CH_2), 52.0 (CH), 69.2 (CH), 73.8 (CH), 75.6 (2 CH_2), 94.9 (2 C), 117.2 (CH), 122.3 (CH). 124.2 (C), 126.1 (CH), 128.2 (2 CH), 128.9 (2 CH), 130.6 (CH), 133.5 (CH), 134.2 (C), 146.1 (CH), 153.2 (2 C), 165.4 (C), 169.3 (C).

2-Acetoxy-3-(cinnamoyloxy)-7,8-bis[((trimethylsilyl)ethoxy)carbonyl]-7,8-diazabicyclo[4.4.0]deca-4,10-diene (16c): oil; R_f = 0.25 (hexane/EtOAc, 80:20); ^1H NMR ($CDCl_3$) δ 0.02 (s br, 18 H), 1.01 (m, 4 H), 2.12 (s, 3 H), 3.65 (m, 1 H), 4.05–4.30 (m, 4 H), 4.50 (m, 1 H), 5.36 (m, 1 H), 5.61 (m, 3 H), 5.80 (s br, 1 H), 6.01 (m, 1 H), 6.40 (d, J = 16 Hz, 1 H), 7.38 (m, 3 H), 7.50 (m, 2 H), 7.66 (d, J = 16 Hz, 1 H).

(2*R*,3*R*)-2-Acetoxy-1-(cinnamoyloxy)-3-vinylcyclohexa-3,5-diene (17). From 16b. To a stirred solution of $Cu(OAc)_2$ in AcOH (3 mL) was added Zn (70 mg, dried for 2 h at 120 °C), and the liquid became colorless within 2 min. The mixture was then diluted with 90% AcOH (1 mL), and a solution of the bicyclic system **16b** (18 mg, 0.03 mmol) in 90% AcOH (0.5 mL) was added at ambient temperature. After 20 h the mixture was diluted with EtOAc (15 mL) and filtered through Celite. The filter was rinsed with EtOAc, the combined filtrate was washed with saturated aqueous Na_2CO_3 (until alkaline reaction to litmus paper), water, and brine and dried. The solvent was evaporated, and the residue was chromatographed (preparative TLC, hexane/EtOAc, 75:25) to give pure **17**: oil, 5.5 mg, 60%; R_f = 0.50 (hexane/EtOAc, 75:25); IR (neat) 3060, 2930, 1740, 1712, 1635, 1227, 1158, 1003 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 5.17 (d, J = 13 Hz, 1 H), 5.33 (dd, J_1 = 6.2, J_2 = 2.3 Hz, 1 H), 5.39 (d, J = 21 Hz, 1 H), 5.91 (d, J = 2.3 Hz, 1 H), 6.08 (dd, J_1 = 11.4, J_2 = 6.2 Hz, 1 H), 6.21 (d, J = 7 Hz, 1 H), 6.30 (dd, J_1 = 11.4, J_2 = 7 Hz, 1 H), 6.39 (dd, J_1 = 21, J_2 = 13 Hz, 1 H), 6.41 (d, J = 18 Hz, 1 H), 7.39 (m, 3 H), 7.49 (m, 2 H), 7.67 (d, J = 18 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 66.4 (CH), 68.5 (CH), 115.0 (CH_2), 117.6 (CH), 123.5 (CH), 125.7 (CH), 127.7 (CH), 128.2 (CH), 128.9 (2 CH), 130.3 (CH), 130.4 (CH), 133.3 (C), 134.4 (C), 135.6 (CH), 145.8 (CH), 165.4 (C), 170.7 (C).

(-)-(1*R*,2*R*,5*R*,6*R*,7*R*,10*S*)-6-Acetoxy-9-oxo-10-phenyl-5-vinyl-8-oxatricyclo[4.3.1.0^{2,7}]dec-3-ene (18). Olefin **17** (15 mg, 0.05 mmol) was dissolved in benzene (1 mL) and heated in a sealed tube at 110 °C. After 15 h the solvent was evaporated, and the residue was chromatographed (10% deactivated silica gel, hexane/EtOAc, 80:20) to give pure **18**: white solid, 14 mg, 94%; mp 164–166 °C; $[\alpha]_D$ = -4.53° (c 0.75, MeOH); R_f = 0.22 (hexane/EtOAc, 80:20); IR (KBr plate) 2930, 2860, 1788, 1732, 1275, 1242, 1143, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.79 (m, 1 H), 3.07 (d br, J = 2 Hz, 1 H), 3.70 (m, 1 H), 4.30 (d br, J = 4.5 Hz, 1 H), 4.96 (d, J = 17.5 Hz, 1 H), 5.07 (s, 1 H), 5.12 (d, J = 11 Hz, 1 H), 5.69 (dd, J_1 = 17.5, J_2 = 11 Hz, 1 H), 6.28 (d, J = 8 Hz, 1

H), 6.44 (t br, J = 8 Hz, 1 H), 6.96 (m, 2 H), 7.17 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 40.3 (CH), 47.4 (CH), 50.5 (CH), 50.7 (C), 77.5 (CH), 81.7 (CH), 117.3 (CH_2), 125.8 (CH), 127.3 (CH), 127.7 (CH), 129.7 (3 CH), 134.4 (CH), 137.0 (CH), 139.4 (C), 169.5 (C), 177.5 (C); mass spectrum (70 eV), m/e (rel intensity) 310 (3), 268 (22), 181 (10), 149 (23), 131 (100), 120 (75), 103 (18); exact mass calcd for $C_{19}H_{18}O_4$ 310.1205, found 310.1190. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.84. Found: C, 72.87; H, 5.83 (the analysis was performed on only 0.678 mg).

Preparation of Zeylena Acetate: (-)-(1*R*,2*R*,5*R*,6*R*,7*R*,10*S*)-6-Acetoxy-5-[(benzoyloxy)methyl]-9-oxo-10-phenyl-8-oxatricyclo[4.3.1.0^{2,7}]dec-3-ene (19). To a solution of diene 18 (6.3 mg, 0.02 mmol) in CH_2Cl_2 (0.20 mL) cooled to -78 °C was added a saturated solution of O_3 in CH_2Cl_2 (0.7 mL, 0.04 M in O_3 at -78 °C), and the resulting clear solution was monitored by TLC while stirring. After 3 min at -78 °C, dimethyl sulfide (15 μL) was added, the cooling bath was removed, and the mixture was stirred for 2 h while reaching ambient temperature. The solvent was then evaporated, and the residual oil was taken in Et_2O (20 mL) and H_2O (0.5 mL). The organic layer was washed with brine (2 × 2 mL), dried, and filtered through a small plug of silica gel, and the solvent was evaporated to give the aldehyde as a thick clear oil, which was more than 95% pure by NMR: glassy solid, 6 mg, quantitative; R_f = 0.18 (hexane/EtOAc, 80:20); IR (neat) 3030, 2925, 2854, 1785, 1750, 1730, 1228, 1040, 1011 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.78 (m, 1 H), 3.60 (d br, J = 2 Hz, 1 H), 3.78 (m, 1 H), 4.36 (d br, J = 4.5 Hz, 1 H), 5.33 (s, 1 H), 6.52 (t br, J = 8 Hz, 1 H), 6.63 (d, J = 8 Hz, 1 H), 6.96 (m, 2 H), 7.21 (m, 3 H), 9.62 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 29.7 (CH), 41.1 (CH), 46.4 (CH), 58.9 (C), 74.4 (CH), 80.9 (CH), 126.5 (CH), 128.0 (CH) 128.6 (2 CH), 128.8 (2 CH), 129.6 (CH), 137.8 (C), 169.4 (C), 176.6 (C), 197.6 (CH); mass spectrum (70 eV), m/e (rel intensity) 312 (1), 207 (30), 178 (55), 165 (40), 147 (100), 131 (25), 103 (25); calcd for $C_{18}H_{17}O_5$ (MH)$^+$ (CI mode) 313.1076, found 313.1070.

To a stirred solution of the tricyclic aldehyde (6 mg, 0.02 mmol) in MeOH (0.9 mL) was added $NaBH_4$ (1.0 mg, 0.026 mmol) at 0 °C. After 20 min of stirring at 0 °C, H_2O (1 drop) was added and the solvent was evaporated. The residue was dissolved in Et_2O (10 mL) and 2% aqueous H_2SO_4 (0.2 mL). The aqueous layer was extracted with Et_2O, the combined organic layer was washed with saturated aqueous Na_2CO_3 and with brine and dried, and the solvent was evaporated to give an oil, which was chromatographed (10% silica gel, hexane/EtOAc, 1:1) to yield the corresponding alcohol: 5.3 mg, 85%; mp 170-172 °C; R_f = 0.27 (hexane/EtOAc, 1:1); IR (neat) 3400 (br), 2940, 1780, 1740, 1240, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 2.74 (s br, OH, 1 H), 2.76 (m, 1 H) 3.16 (m, 1 H), 3.60 (d, J = 11.5 Hz, 1 H), 3.68 (m, 1 H), 3.75 (m, 1 H), 4.37 (d br, J = 4.5 Hz, 1 H), 4.67 (d, J = 11.5 Hz, 1 H), 5.80 (d, J = 8 Hz, 1 H), 6.51 (t, J = 8 Hz, 1 H), 7.03 (m, 2 H), 7.22 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 40.3 (CH), 45.7 (CH), 47.4 (CH), 50.3 (C), 62.1 (CH_2), 73.1 (CH), 83.3 (CH), 127.5 (CH), 127.6 (CH), 128.3 (2 CH), 129.4 (2 CH), 132.3 (CH), 139.0 (C), 169.0 (C), 177.0 (C).

To a stirred solution of benzoic acid (3.9 mg, 0.032 mmol) and triethylamine (4.5 μL, 0.032 mmol) in THF (0.5 mL) at 0 °C was added isobutylchloroformate (4.3 μL, 0.032 mmol), and the mixture was stirred for 10 min at 0 °C. The tricyclic alcohol (5 mg, 0.016 mmol) was dissolved in THF (1 mL) and added at 0 °C, and the mixture was then brought to reflux within a 2-h period. After heating for 48 h the reaction mixture was diluted with Et_2O (40 mL) and poured into 7% aqueous KOH. The organic layer was successively washed with H_2O, saturated aqueous $CuSO_4$, and brine (2×), dried, and concentrated to give a thick yellowish oil, which was chromatographed (10% deactivated silica gel, hexane/EtOAc, 75:25) to afford zeylena acetate **19** as an oil that crystallized upon standing: white solid, 2.5 mg, 40%; R_f = 0.30 (hexane/EtOAc, 80:20); $[\alpha]_D$ -68° (c 0.25, $CHCl_3$) [lit.[9] $[\alpha]_D$ -71° ($CHCl_3$)]. The melting point, IR, and ^1H NMR spectral data were in accordance with those described for an authentic sample.[3]

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Supplementary Material Available: Spectral data (^1H NMR and/or ^{13}C NMR) for compounds **9a**, **9c**, **10b**, **16a**, **18**, **19**, and the intermediates obtained during the conversion of **9b** to **10b** and **18** to (19 pages). Ordering information is given on any current masthead page.

A Facile Synthesis of Chiral Bicyclic Lactams Utilized in the Formation of Chiral Quaternary Carbon Compounds

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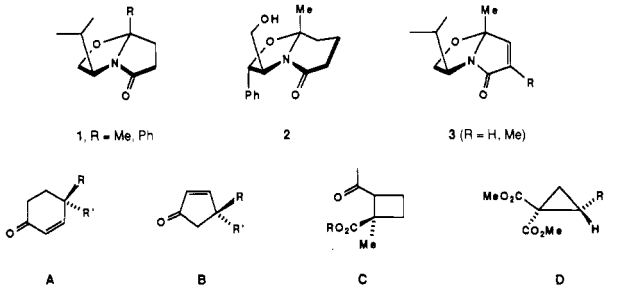
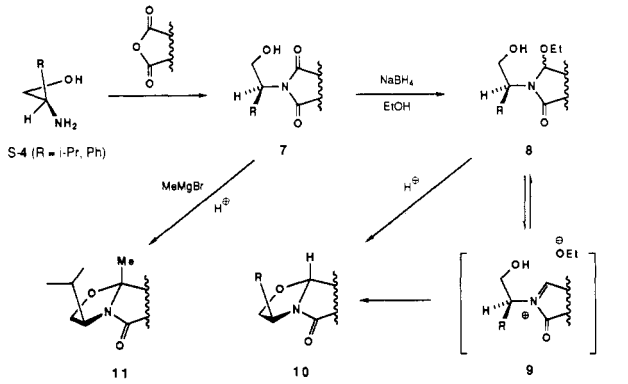
During the past several years we have described a number of novel and efficient routes to chiral quaternary carbon compounds (A-D) emanating from bicyclic lactams **1-3**.[2] Furthermore, a number of natural products have been prepared in high enantiomeric purity (95%) using this methodology.[3] During the course of these studies we have prepared these materials (**1-3**) according to a previous



procedure,[4] which involved cyclodehydration of chiral amino alcohols **4** with δ- and γ-keto acids (eq 1). However, a number of limitations were encountered when aldehydic acids **5** (R′ = H) were employed. The latter were both tedious to prepare and sensitive to the reaction conditions, making this route to starting materials **6** less than satisfactory.



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