The fraction eluting from 150 to 250 mL was subjected to chromatography on a Sep-Pak ODS cartridge (Waters) with MeOH/H_2O (3:7, 20 mL) and then MeOH (20 mL) to give alteramide (1, 50 mg, 0.1% wet weight) in the latter fraction.

Alteramide A (1): yellow powder; mp ~200 °C dec; $[\alpha]_D^{22}$ +36.2° (*c* 0.1, MeOH); UV (MeOH) λ_{max} 268 (ϵ 30 300) and 347 nm (11 000); IR (KBr) ν_{max} 3400, 1660 (sh), 1610, and 1470 cm^{-1}; ^1H and ^{13}C NMR (Table I); FABMS (positive ion, glycerol matrix) *m/z* 533 (M^+ + Na); HRFABMS *m/z* 533.2629 (M^+ + Na; calcd for $C_{29}H_{38}N_2O_6Na$, 533.2628).

Photochemical Cycloaddition of 1. The irradiation was carried out using a mercury lamp housed in a water-cooled Pyrex jacket. A solution of 1 (3.0 mg) in 1.0 mL of degassed methanol was irradiated under argon atmosphere at 0 °C for 30 min. Removal of the methanol by evaporation under reduced pressure afforded 3.0 mg of **2**: white amorphous solid; mp ~160 °C dec; $[\alpha]^{22}_D$ + 16.7° (*c* 1.0, MeOH); UV (MeOH) λ_{max} 245 (ϵ 15 000) and 286 nm (15 500); IR (KBr) ν_{max} 3330, 1640, 1520, and 1480 cm^{-1}; ^1H NMR (CD_3OD) δ 0.90 (3 H, t, *J* = 7.3 Hz, Me-30), 0.92 (1 H, m, H-7b), 0.94 (1 H, m, H-9b), 1.04 (3 H, d, *J* = 6.4 Hz, Me-31), 1.10 (1 H, m, H-29b), 1.26 (1 H, m, H-11), 1.28 (1 H, m, H-26b), 1.34 (m, H-26a), 1.37 (1 H, m, H-10), 1.64 (1 H, m, H-29a), 1.66 (1 H, m, H-12), 1.80 (2 H, m, H-6, H-13), 1.92 (1 H, m, H-7a), 2.08 (1 H, m, H-9a), 2.76 (1 H, m, H-8), 2.86 (1 H, m, H-5), 3.00 (1 H, m, H-27b), 3.20 (1 H, m, H-27a), 3.26 (1 H, m, H-15), 3.60 (1 H, m, H-14), 4.00 (1 H, m, H-2), 4.03 (1 H, m, br s, H-23), 4.10 (1 H, m, H-25), 5.12 (1 H, m, H-18), 5.41 (1 H, dd, *J* = 5.3, 8.8 Hz, H-4), 5.57 (1 H, dd, *J* = 8.1, 8.8 Hz, H-3), 5.69 (1 H, dd, *J* = 8.3, 9.3, H-16), and 6.16 (1 H, m, H-17); ^{13}C NMR (CD_3OD) δ 13.0 (q, C-30), 18.5 (q, C-31), 27.2 (t, C-29), 30.7, (t, C-26), 36.6 (t, C-27), 36.7 (t, C-7), 41.6 (t, C-9), 45.8 (d, C-5), 47.8 (d, C-11, C-18), 50.4 (d, C-8), 51.1 (d, C-2), 54.2 (d, C-12), 54.9 (d, C-10), 58.8 (d, C-6), 59.6 (d, C-15), 65.2 (d, C-13, C-23), 78.2 (d, C-25), 81.9 (d, C-14), 108.1 (s, C-20), 128.6 (d, C-17), 129.6 (d, C-3), 135.9 (d, C-16), 136.9 (d, C-4), 175.7 (s, C-1), 176.8 (s, C-21), and 191.1 (s, C-19, C-24). FABMS (positive ion, glycerol matrix) *m/z* 533 (M + Na)$^+$; HRFABMS *m/z* 533.2624 (M^+ + Na; calcd for $C_{29}H_{38}N_2O_6Na$, 533.2628).

Reductive Ozonolysis of 1. Through a solution of 1 (9.0 mg) in MeOH (1.0 mL) at −40 °C was passed ozonized oxygen for 5 min. After the excess of ozone was expelled by a nitrogen stream, the mixture was allowed to warm to 0 °C and $NaBH_4$ (9.0 mg) was added. The mixture was stirred for 45 min, and excess hydride was decomposed with 1 mL of 1 M potassium phosphate buffer (pH 7). The mixture was extracted with EtOAc (1 mL × 5), and the organic solvent was evaporated. The residue was treated with acetic anhydride/pyridine (1:1) overnight at room temperature. After evaporation under reduced pressure the residue was purified by chromatography on a silica gel column (0.7 × 7 cm) eluted with hexane/acetone (10:1) to yield compound **3** (3.0 mg) as a colorless oil: $[\alpha]_D^{22}$ −25.3° (*c* 0.6, $CHCl_3$); IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, *J* = 7.6 Hz, Me-30), 0.96 (3 H, d, *J* = 6.8 Hz, Me-31), 0.98 (1 H, m, H-9b), 1.06 (1 H, m, H-29b), 1.10 (1 H, m, H-7b), 1.20 (1 H, m, H-11), 1.34 (1 H, m, H-10), 1.60 (1 H, m, H-29a), 1.79 (1 H, m, H-13), 1.86 (1 H, m, H-12), 2.01 (1 H, dt, *J* = 7.3, 11.7 Hz, H-7a), 2.04 (3 H, s, CH_3CO), 2.05 (3 H, S, CH_3CO), 2.06 (3 H, s, CH_3CO), 2.09 (1 H, m, H-9a), 2.11 (1 H, m, H-6), 2.34 (1 H, m, H-8), 4.03 (1 H, dd, *J* = 5.9, 10.7 Hz, H-5′), 4.05 (1 H, dd, *J* = 7.8, 11.7 Hz, H-15′), 4.09 (1 H, dd, *J* = 5.9, 10.7 Hz, H-5), 4.28 (1 H, dd, *J* = 3.9, 11.7 Hz, H-15), and 5.16 (1 H, dd, *J* = 3.9, 7.8 Hz, H-14); ^{13}C NMR ($CDCl_3$) δ 12.4 (q, C-30), 17.1 (q, C-31), 20.8 (q, CH_3CO), 20.9 (q, CH_3CO), 21.1 (q, CH_3CO), 26.8 (t, C-29), 37.5 (t, C-9), 38.9 (t, C-7), 41.9 (d, C-8), 43.7 (d, C-6), 46.2 (d, C-11), 48.2 (d, H-13), 51.5 (d, H-10), 55.5 (d, C-12), 64.4 (t, C-15), 67.4 (t, C-5), 73.2 (d, C-14), 170.6 (s, CH_3CO), 170.7 (s, CH_3CO), and 171.1 (s, CH_3CO); EIMS *m/z* 309 ($M^+ - CH_3COO$), and 248 ($M^+ - 2 \times CH_3COOH$); HREIMS *m/z* 309.2094 [($M^+ - CH_3COO$); calcd for $C_{18}H_{29}O_4$, 309.2065].

Determination of L-*erythro*-β-Hydroxyornithine. Through a solution of 1 (2.0 mg) in MeOH (0.7 mL) at −40 °C was passed ozonized oxygen for 2 min. After the excess of ozone was expelled by a nitrogen stream, the solution was evaporated under reduced pressure, and to the residue 98% formic acid (0.5 mL) and 35% hydrogen peroxide (50 μL) were added. The mixture was stirred for 1 h at 0 °C and then for 18 h at room temperature. The solvent was evaporated, and the residue was chromatographed on a Sep-Pak ODS cartridge with MeOH/H_2O (3:7) to give a mixture of amino acids (0.4 mg), which was analyzed by a Hitachi amino acid autoanalyzer (Model 835; No. 2617, 4.0 × 250 mm) at a flow rate of 0.275 mL/min with 0.2 N sodium citrate buffer and detected at 570 nm. The relative stereochemistry of βHOrn was determined by comparing the retention time with those for the authentic *erythro*- and *threo*-βHOrn (91.0 and 90.4 min, respectively). The retention time of the βHOrn in the degradation products of 1 was found to be 91.0 min. The absolute stereochemistry of βHOrn was elucidated by the chiral HPLC analysis (Chiralpak WH, Daicel Chemical, 4.6 × 250 mm) at a flow rate of 1.0 mL/min with 1.0 mmol/L of $CuSO_4$ aqueous solution and detected at 254 nm. The retention times of authentic L- and D-*erythro*-βHOrn were 22 and 10 min, respectively. The retention time of the βHOrn in degradation products of 1 was found to be 22 min.

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Supplementary Material Available: ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, HMQC, HMBC, ROESY, UV, IR, FABMS, and HRFABMS spectra of 1 and 2 and ^1H NMR, ^{13}C NMR, ROESY, EIMS, and HREIMS spectra of 3 (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Practical, Highly Enantioselective Synthesis of the Taxol Side Chain via Asymmetric Catalysis

Li Deng and Eric N. Jacobsen*

Department of Chemistry, Roger Adams Laboratory, University of Illinois, Urbana, Illinois 61801

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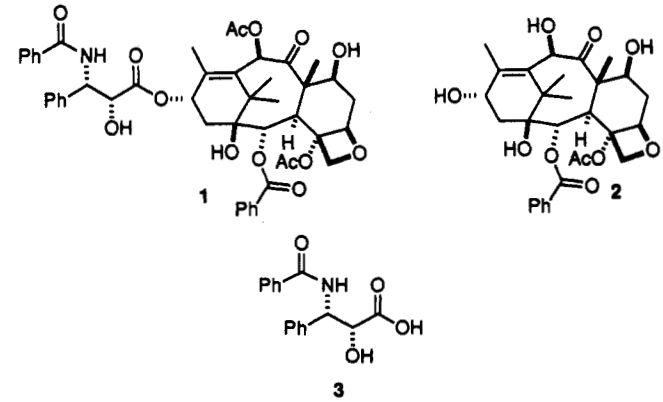
The importance of taxol's C-13 side chain to the drug's powerful antileukemic and tumor-inhibiting activity was noted in the very earliest biological studies on this remarkable molecule.[1] Side chain structure–activity relationship studies have subsequently led to other promising drug candidates[2] and to the suggestion that the 3′-amide substituent plays an important role in the preorganization of taxol for binding to microtubules.[3] Interest in synthetic routes to the *N*-benzoyl-3-phenylisoserine side chain **3** has



(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. For recent reviews, see: (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (b) Borman, S. *Chem. Eng. News* **1991**, *69*(35), 11.

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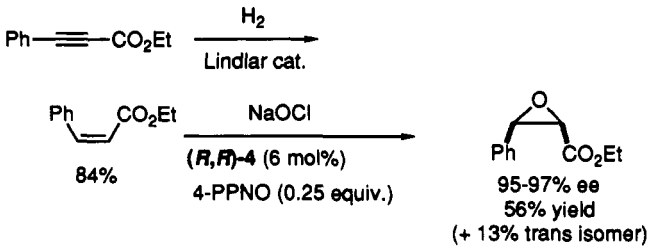
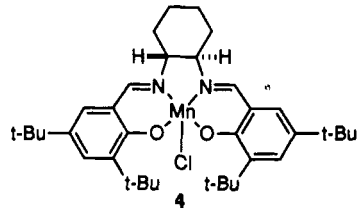
0022-3263/92/1957-4320$03.00/0

Scheme I



been further heightened by the isolation of 10-deacetylbaccatin III (**2**) from a renewable natural source in reasonably high yield (up to 1 g/kg),[4,5a] leading to optimism that routes involving coupling of synthetic side chain **3** to naturally-derived **2** may provide taxol in sufficient amounts to meet anticipated demand. Indeed, the successful application of such semisynthetic strategies to the synthesis of **1** has been achieved,[5] and this has prompted research into the development of taxol side-chain synthesis that are practical and adaptable to relatively large-scale production.

Promising approaches toward enantiomerically enriched **3** include semisynthesis drawing from the chiral pool,[6] enzymatic kinetic resolution of racemic esters of **3**,[7] diastereoselective reactions with covalently-bound chiral auxiliaries,[5b,c,8] and asymmetric catalysis.[9,10] Herein we describe a new, efficient synthesis of the taxol side chain via a highly enantioselective epoxidation reaction catalyzed by the readily available (salen)Mn(III) complex **4**.[11,12] The success of the catalytic process, the simplicity and low cost of all reagents, and the fact that preparative chromatographic separations are completely avoided may render this the most practical route to enantiomerically pure 3-phenylisoserine derivatives developed to date.

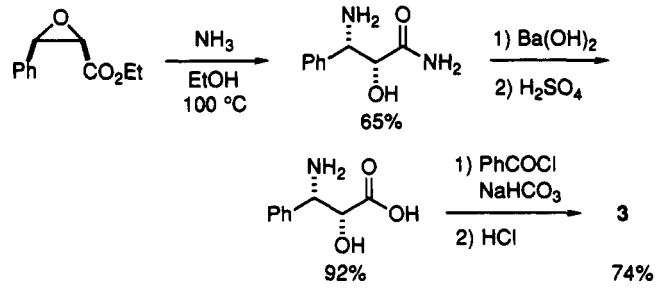


4

Results and Discussion

Partial hydrogenation of commercial ethyl phenylpropiolate to *cis*-ethyl cinnamate was effected in good yield with Lindlar's catalyst and a solvent system composed of hexane and 1-hexene (7:2 v/v) (Scheme I).[13] The product mixture contained 9% overreduced material and trans alkene, but these byproducts did not interfere with subsequent steps and were easily removed later in the synthetic sequence. Epoxidation of *cis*-ethyl cinnamate thus obtained was effected with commercial bleach in the presence of 6 mol % (*R*,*R*)-**4** to afford the corresponding cis epoxide in 95–97% ee favoring the (*R*,*R*)-(+)-enantiomer. The enantioselectivity of the reaction proved to be quite sensitive to the identity of the ester group, with *cis*-methylcinnamate being epoxidized under similar conditions but in only 87–89% ee.[11] Addition of 4-phenylpyridine *N*-oxide (4-PPNO) or other similar hydrophobic pyridine *N*-oxide derivatives was also crucial to the success of the reaction, since in the absence of such additives epoxidation took place with 10–15% lower selectivity and proceeded to only partial conversion of olefin, even with 15–20 mol % added catalyst. We have ascertained through control experiments and spectroscopic studies that the *N*-oxide does not act as an oxygen-atom source, but rather as an axial ligand to manganese.[14] Coordination of *N*-oxide to the mildly Lewis acidic Mn(III) and/or Mn(V) oxo intermediate appears to effectively inhibit catalyst decomposition by pathways involving complexation of epoxide to the manganese center. It also appears that enantioselectivity enhancement induced by *N*-oxide is due to suppression of a nonselective minor pathway involving Lewis acid-catalyzed conjugate addition of bleach to the unsaturated ester.

Scheme II



Trans epoxide was generated as a significant byproduct of the epoxidation reaction (cis:trans ≈ 3.5:1 in the crude reaction mixture), presumably as a result of a stepwise oxygen-atom transfer mechanism involving a discrete benzylic radical or cation intermediate.[15] Although separation of the diastereomeric epoxides could be effected by flash chromatography, the mixture could be carried forward in the synthetic sequence. Thus, the distilled mixture of cis and trans epoxides was treated directly with ammonia in ethanol to generate 3-phenylisoserinamide in a highly regioselective ring-opening process (Scheme II).[16] No regioisomeric products could be detected by ^{1}H NMR analysis of the crude product mixture, and the diastereomeric impurity resulting from ring opening of the trans epoxide was successfully removed by recrystallization of the crude product mixture from methanol. Hydrolysis of the amide was effected without epimerization using Ba(OH)$_2$ in water.[15] After acidification of the reaction mixture with H_2SO_4, precipitated barium sulfate was removed by centrifugation, and (+)-3-(2*R*,3*S*)-3-phenylisoserine was obtained directly by crystallization from the supernatant aqueous solution. This material was converted to the taxol side chain **3** by treatment with benzoyl chloride/NaHCO$_3$

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in a two-phase reaction in good yield.[8a] Isolation of analytically pure 3 from the benzoic acid byproduct was accomplished without chromatography by crystallization from acetone/hexane. The enantiomeric purity of 3 was determined to be >97% by HPLC analysis of its methyl ester (Pirkle column) and by ^{19}F NMR and ^{1}H NMR analysis of its corresponding Mosher ester. The rotation of 3 prepared from (*R,R*)-4 matched that of the side chain from natural taxol ($[\alpha]^{25}_D$ = −35.9° (*c* 0.56, EtOH) (lit.[8a] $[\alpha]^{25}_D$ = −37.78°)).

In summary, the four-step synthesis of (*R,R*)-3-phenylisoserine outlined in Schemes I and II begins with commercially available ethyl phenylpropiolate and employs H_2, household bleach, NH_3, and $Ba(OH)_2$ as stoichiometric reagents. The yields and conditions described above correspond to a complete sequence carried out on 5 g of *cis*-ethyl cinnamate that afforded 1.65 g of 3 (25% overall yield). Adaptation of this methodology to the preparation of substituted and isotopically labeled analogs of 3 is currently under investigation in our laboratories.

Experimental Section

General. Melting points were obtained in open capillary tubes and are uncorrected. All boiling points are also uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the University of Illinois.

Analytical thin-layer chromatography (TLC) was conducted on Merck glass plates coated with 0.25 mm of silica gel 60 F_{254}. TLC plates were visualized with UV light and/or in an iodine chamber unless noted otherwise. Gas–liquid chromatographic (GC) analyses were performed on a J & W Scientific 0.32-mm × 30-m DB-5 capillary column.

The buffered bleach solutions employed in the epoxidation reactions were prepared from Clorox according to the published method.[17] Unless otherwise noted, all starting materials were purchased from Aldrich and were used as received.

Preparation of Catalyst 4.[18] **3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (Di-*tert*-butylsalicylaldehyde).** The procedure described by Casiraghi et al.[19] was followed with several modifications. Prior to use, 2,6-lutidine was distilled from KOH, toluene was distilled from Na/benzophenone ketyl, and paraformaldehyde was dried over P_2O_5 at 100 °C under vacuum. All glassware for this step was oven-dried overnight.

A 200-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser with a nitrogen inlet was charged with 2.80 mL of 2,6-lutidine (24.1 mmol, 0.4 equiv) and 12.40 g of 2,4-di-*tert*-butylphenol (59.9 mmol, 1.0 equiv) in 12 mL of dry toluene. $SnCl_4$ (5.99 mmol, 0.1 equiv) was added dropwise to the solution, and the addition funnel was rinsed with 3 mL of dry toluene to wash in the last traces of $SnCl_4$. The heterogeneous yellow mixture was stirred at room temperature under nitrogen for 1 h, after which the nitrogen purge was shut off and 5.95 g of paraformaldehyde (198 mmol, 3.3 equiv) was added quickly as a solid. The nitrogen purge was reestablished, the addition funnel was replaced with a glass stopper, and the mixture was heated in a 100 °C oil bath. After 3 h, GC analysis indicated >99% disappearance of starting di-*tert*-butylphenol, and the reaction mixture appeared as a slightly yellow solution over a thick, medium brown, oily layer. The mixture was allowed to cool to room temperature, and stirring was continued while 100 mL of water was added to the flask. The thick mixture was transferred to a separatory funnel, and the flask was rinsed with an additional 100-mL portion of water. The aqueous layer was acidified to approximately pH 2 with a few milliliters of 2 N HCl and shaken with 150 mL of ether. An intractable emulsion resulted, and the entire mixture was filtered through Celite to facilitate subsequent phase separation. The aqueous layer was extracted with two additional 150-mL portions of ether. The combined ether extracts were washed with 200 mL of water and 200 mL of brine and dried over sodium sulfate.

Removal of the ether by rotary evaporation afforded a thick yellow oil (12.088 g). The mixture was recrystallized once at −10 °C from 18 mL of absolute ethanol to yield 9.70 g (69%) 3,5-di-*tert*-butylsalicylaldehyde as fine, pale yellow needles (purity 99.5% by GC), mp 54–56 °C (lit.[20] mp 58–60 °C; lit.[21] mp 62–63 °C): ^{1}H-NMR ($CDCl_3$) δ 11.66 (s, 1 H), 9.86 (s, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 7.35 (d, *J* = 2.4 Hz, 1 H), 1.43 (s, 9 H), 1.33 (s, 9 H); ^{13}C-NMR ($CDCl_3$) δ 197.3, 159.0, 141.6, 137.5, 131.8, 127.8, 119.9, 35.0, 34.2, 31.3, 29.2.

Catalyst Synthesis. A 1-L, three-necked, round-bottomed flask equipped with a reflux condenser, an addition funnel, and a mechanical stirrer was charged with 4.70 g (20.0 mmol) of 3,5-di-*tert*-butylsalicylaldehyde in 200 mL of 95% EtOH. A solution of 1.14 g of *trans*-1,2-diaminocyclohexane (10.0 mmol) in 100 mL of 95% EtOH was added. The flask was heated at reflux for 15 min with appearance of the Schiff base as a bright yellow slurry. A solution of 0.5 M KOH (40.0 mL, 20.0 mmol) in 95% EtOH was then added dropwise. The mixture was vigorously stirred at reflux until all of the salen had dissolved to give a deep yellow solution.[22] A solution of $Mn(OAc)_2 \cdot (H_2O)_4$ (25.0 mmol) in 20 mL of water was then added slowly. The reaction mixture immediately became opaque, the solution turned brown, and a flocculent, off-white precipitate quickly formed. Stirring was continued at reflux for 30 min and then continued for 30 min as the reaction was allowed to cool to room temperature. A solution containing 1.27 g of LiCl (30 mmol) in 10 mL of water was added, and the mixture was stirred at room temperature for 0.5 h. TLC analysis at this stage showed a single spot (R_f: 0.42, 5% EtOH/CH_2Cl_2), with no evidence of free ligand. The resulting dark brown solution was then filtered through a 1-cm pad of Celite, and the filtrate was reduced to a volume of approximately 100 mL by rotary evaporation and then poured into a 2-L Erlenmeyer flask containing 500 mL of water, resulting in the precipitation of a fine brown powder which was collected by filtration. The damp powder was redissolved in CH_2Cl_2 (100 mL) and extracted twice with 100 mL of water. The organic phase was dried over sodium sulfate and filtered, and the solvent was removed under vacuum. The resulting dark brown powder was dried overnight in a vacuum desiccator over $CaSO_4$. Yield of 4: 5.84 g (92%). Anal. Calcd for $C_{36}H_{52}ClMnN_2O_2$: C, 67.19; H, 8.31; Cl, 5.22; Mn, 8.09; N, 4.12. Found: C, 67.05; H, 8.34; Cl, 5.48; Mn, 8.31; N, 4.28.

***cis*-Ethyl Cinnamate.** The literature procedure was followed with modifications.[23] Under an atmosphere of dry nitrogen, ethyl phenylpropiolate (10.8 g, 0.062 mol) was dissolved in a mixture of hexane and 1-hexene (7:2 v/v, 540 mL), followed by addition of quinoline (11.2 g) and palladium on calcium carbonate (lindlar catalyst, 3.6 g). The resulting reaction mixture was connected to a hydrogen-filled balloon (1 atm) and stirred at room temperature, and the progress of the reaction was monitored by GC analysis. The reaction was stopped by displacement of the hydrogen atmosphere with nitrogen after the starting alkyne was completely consumed. The resulting mixture was filtered through a Celite pad, and the filtrate was washed with 10% acetic acid (4 × 500 mL), water (3 × 500 mL), and saturated $NaHCO_3$ (4 × 500 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure, and the residue (10.1 g) was determined to be a mixture containing 91.8% *cis*-ethyl cinnamate (84% yield), 5.7% over-reduced alkane, and 3.5% *trans*-ethyl cinnamate by integration of its gas chromatogram and comparison with authentic samples. This material was used without further purification.

(2*R*,3*R*)-Ethyl 3-Phenylglycidate. *cis*-Ethyl cinnamate obtained as described above (5.0 g, 25.5 mmol) and 4-phenylpyridine *N*-oxide (1.16 g, 25 mol %) were dissolved in CH_2Cl_2 (60 mL). Catalyst (*R,R*)-4 (1.08 g, 6.5 mol %) was added. The

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(22) If yellow solid remains after 15 min of refluxing, ethanol should be added in 50-mL portions until all solids just dissolve.
(23) Akbulut, N.; Hartsough, D.; Kim, J.-I.; Schuster, G. B. *J. Org. Chem.* **1989**, *54*, 2549.

resulting solution and the buffered bleach (160 mL, pH = 11.25) were cooled separately in an ice bath and then combined at 4 °C. The two-phase mixture was stirred for 12 h. *tert*-Butyl methyl ether (500 mL) was then added to the solution, and the organic phase was separated and filtered through a Celite pad, washed with water (2 × 400 mL) and brine (2 × 400 mL), and then dried over Na_2SO_4. The solvent was removed under vacuum, and GC analysis of the residue indicated the presence of cis and trans epoxides in a 3.5:1 ratio. The ee of the cis epoxide was determined to be 95–97% by ^1H NMR analysis with $Eu(hfc)_3$ as chiral shift reagent, and the ee of the trans isomer was determined to be 78% by the same method. The residue was purified by short-path distillation (104–105 °C (0.5 mm)) to afford 4.0 g of a mixture containing 70% cis epoxide (56% yield), 13% trans epoxide (10% yield), and remaining trace impurities arising from starting material (all yields determined by GC analysis). This material was suitable for subsequent reactions and was used without further purification. Alternatively, for smaller scale procedures the residue was purified by flash chromatography (petroleum ether/ether (87:13), v/v) to afford the epoxides in a 10:1 cis/trans ratio. *cis*-Ethyl-3-phenylglycidate: ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 3 H), 3.83 (d, J = 4.8 Hz, 1 H), 3.9–4.1 (m, 2 H), 4.27 (d, J = 4.8 Hz, 1 H), 7.2–7.5 (aromatic, 5 H); *trans*-ethyl 3-phenylglycidate: ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3 H), 3.51 (d, J = 2.1 Hz, 1 H), 4.09 (d, J = 1.8 Hz, 1 H), 4.2–4.4 (m, 2 H), 7.2–7.5 (aromatic, 5 H).

(2*R*,3*S*)-3-Phenylisoserinamide. The (2*R*,3*R*)-ethyl 3-phenylglycidate obtained as described above (3.9 g of a mixture containing 14.2 mmol of *cis*-ethyl 3-phenylglycidate) was dissolved in a solution of 60 mL of ethanol saturated with ammonia (prepared by passing NH_3 through ethanol at −15 °C). This solution was placed in a stainless steel Parr reactor and heated to 100 °C for 3 H with mechanical stirring. After the solution was cooled to room temperature, solvent was removed under vacuum and the residue was dissolved in 70 mL of boiling methanol. The solution was cooled to −20 °C and a first crop of beige crystals (1.6 g) was collected after 8 h. The mother liquor was concentrated to approximately 20 mL and then cooled to −20 °C, and a second crop of crystals was collected (0.5 g). The two crops were combined and found to contain 5–7% of the anti diastereomer by integration of the ^1H NMR spectrum. Recrystallization from methanol (50–60 mL) following the same protocol described above led to isolation of diastereomerically pure product (1.66 g, 65%): mp 172–173 °C; ^1H NMR (DMSO-d_6/D_2O) δ 3.87 (d, J = 3.3 Hz, 1 H), 4.08 (d, J = 3.3 Hz, 1 H), 7.0–7.5 (aromatic, 5 H); ^{13}C NMR (DMSO-d_6) δ 57.3, 75.6, 126.3, 127.0, 127.7, 144.4, 174.9. Anal. Calcd for $C_9H_{12}O_2N_2$: C, 60.00; H, 6.67; N, 15.55. Found: C, 59.90; H, 6.71; N, 15.25.

The corresponding racemate was synthesized by an analogous sequence with epoxide prepared with (±)-4: mp 192–193 °C (lit.[16] mp 187–188 °C).

(2*R*,3*S*)-3-Phenylisoserine. The literature procedure was followed with minor modifications.[16] (2*R*,3*S*)-3-Phenylisoserinamide (1.63 g, 9.05 mmol) was combined with 2.88 g (9.1 mmol) of $Ba(OH)_2 \cdot 8H_2O$ and water (16 mL). The resulting suspension was heated to reflux under nitrogen for 8 h. The release of ammonia from the reaction mixture was monitored periodically by holding a strip of moistened pH paper above the solution, and the reaction was judged to be complete once the vapor above the solution was neutral. The reaction mixture was then cooled to 80 °C, and water (120 mL) was added. The temperature of the solution was maintained at 80 °C for 20 min before a solution of 910 mg of H_2SO_4 in 8 mL of water was added. The acidified solution was determined to have a pH between 5 and 7. Heating at 80 °C was maintained for another 10 min, and the mixture was then cooled to room temperature. The resulting precipitate ($BaSO_4$) was removed by centrifugation, the supernatant liquid was separated, and the solvent was removed under vacuum to provide the desired product as a white solid (1.51 g, 92% yield), mp 238 °C dec: ^1H NMR (D_2O/NaOD) δ 3.94 (d, J = 3.9 Hz, 1 H), 4.01 (d, J = 3.9 Hz, 1 H), 7.0–7.5 (aromatic, 5 H). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.07; N, 7.73. Found: C, 59.33; H, 6.13; N, 7.67.

***N*-Benzoyl-(2*R*,3*S*)-3-phenylisoserine (3).** (2*R*,3*S*)-3-Phenylisoserine (1.50 g, 8.25 mmol) was dissolved in 10% aqueous $NaHCO_3$ (200 mL) with stirring. The solution was cooled to 4 °C, and benzoyl chloride (3 mL, 3.57 g, 25 mmol) was added. This mixture was stirred for 6 h at 4 °C and then acidified to pH = 1 by addition of aqueous HCl solution (18%). This resulted in formation of a white precipitate suspended in the aqueous solution. The aqueous mixture was extracted with THF/CH_2Cl_2 (4:1, 3 × 250 mL), and the organic phases were combined, dried over Na_2SO_4, and removed under reduced pressure to provide a white crystalline mixture containing both desired product and benzoic acid. The latter was removed by dissolution of the mixture in a minimum amount of acetone (40 mL) and subsequent addition of 800 mL of hexane. The resulting product **3** was isolated as a white solid by filtration (1.74 g, 74% yield) and was determined to be diastereomerically pure by ^1H NMR: mp 177–179 °C (lit.[5c] mp 167–169 °C). FABMS m/z 286 (M^+ + 1); ^1H NMR (DMSO-d_6) δ 4.37 (d, J = 4.5 Hz, 1 H), 5.46 (dd, J = 8.7, 4.5 Hz, 1 H), 5.3–5.7 (b, 1 H), 7.2–7.6 (m, 9 H), 7.84 (d, J = 7.5 Hz, 1 H), 8.58 (d, J = 9.0 Hz, 1 H), 12.5–13.0 (br, 1 H); ^{13}C NMR (acetone-d_6) δ 56.5, 74.3, 128.0, 128.1, 129.0, 129.2, 132.2, 135.5, 141.0, 167.1, 173.9; FABHRMS calcd for $C_{16}H_{16}NO_4$ 286.1079, obsvd 286.1068; $[\alpha]^{25}_D$ −35.9° (*c* 0.565, EtOH) (lit.[5c] $[\alpha]^{25}_D$ +36.5° (*c* 1.45, EtOH) (for the 2*S*,3*R* isomer); $[\alpha]^{25}_D$ −37.78° (*c* 0.9, EtOH) (for the 2*S*,3*S* isomer)). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.31; H, 5.26; N, 4.87.

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Registry No. 1, 33069-62-4; 3, 132201-33-3; 3 (de-benzoyl derivative), 136561-53-0; 3 amide (de-benzoyl derivative), 141901-21-5; (*R*,*R*)-4, 138124-32-0; PhC≡CCO_2Et, 2216-94-6; (*Z*)-PhCH=$CHCO_2$Et, 4610-69-9; (*E*)-PhCH=$CHCO_2$Et, 4192-77-2; $Ph(CH_2)_2CO_2$Et, 2021-28-5; $Mn(OAc)_2 \cdot (H_2O)_4$, 6156-78-1; ethyl (2*R*,3*R*)-3-phenylglycidate, 126060-73-9; ethyl *trans*-3-phenylglycidate, 2272-55-1; 2,4-di-*tert*-butylphenol, 96-76-4; 3,5-di-*tert*-butylsalicaldehyde, 37942-07-7; (1*R*-*trans*)-1,2-diaminocyclohexane, 20439-47-8.

Ireland–Claisen Rearrangements of Chiral (*Z*)-Vinylsilanes. Highly Diastereoselective Synthesis of *anti*-α-Alkoxy-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates

James S. Panek* and Thomas D. Clark[1]

Department of Chemistry, Metcalf Center for Science and Engineering, Boston University, Boston, Massachusetts 02215

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Introduction

Recent reports from our laboratory have described the use of functionalized (*E*)-crotylsilanes as carbon nucleophiles in diastereo- and enantioselective addition reactions to acetals and aldehydes.[3] We have reported the stereo-

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