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]

Acknowledgment. We express our gratitude to the following agencies for their generous financial support: the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (AI-00564, AI-19749), and the Jeffress Trust Fund.

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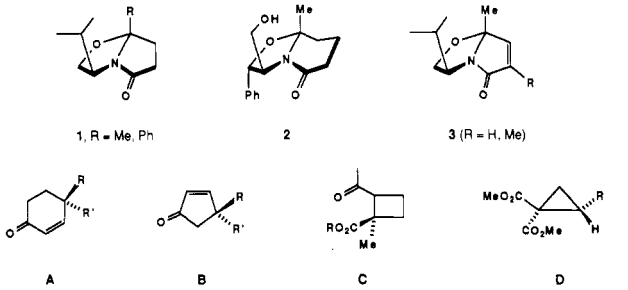
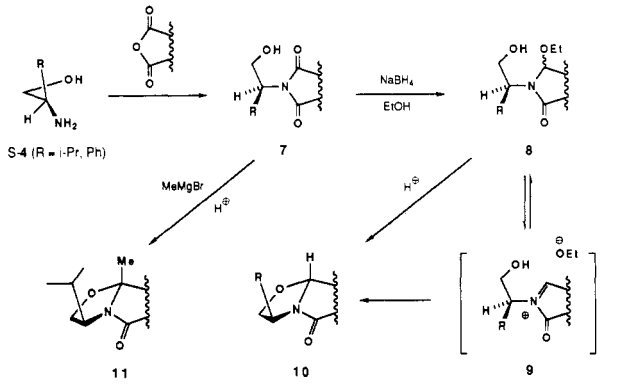
During the past several years we have described a number of novel and efficient routes to chiral quaternary carbon compounds (A-D) emanating from bicyclic lactams **1-3**.[2] Furthermore, a number of natural products have been prepared in high enantiomeric purity (95%) using this methodology.[3] During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



(1) (a) Pfizer Graduate Fellow, 1987. (b) Merck Sharp and Dohme Postdoctoral Fellow, 1988.

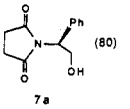
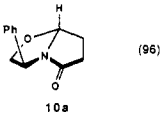
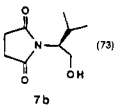
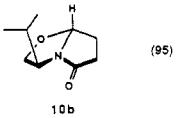
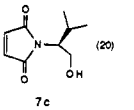
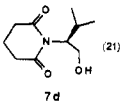
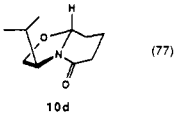
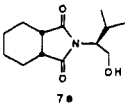
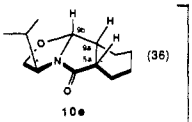
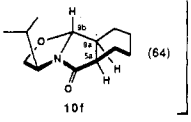
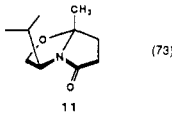
(2) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936 and earlier references cited therein.

(3) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663 and earlier references cited therein.

(4) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146.

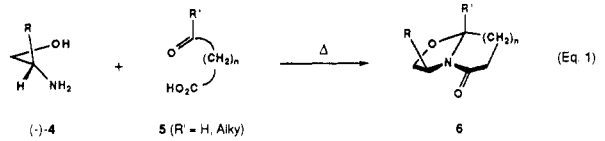
0022-3263/89/1954-4243$01.50/0

Table I. Chiral, Nonracemic Succinimides 7 and Bicyclic Lactams 10 and 11

anhydride/amino alcohol[a]	imide (yield, %)	method[b]	bicyclic lactam (yield, %)	method[b]
succinic/phenylglycinol	 7a (80)	A	 10a (96)	C
succinic/valinol	 7b (73)	B	 10b (95)	C
maleic/valinol	 7c (20)	A	**10b** (90)	C
glutaric/valinol	 7d (21)	B	 10d (77)	C
cis-1,2-cyclohexanedicarboxylic/valinol	 7e (95)	B	 10e (36)  10f (64)	C
succinic/valinol	**7b**		 11 (73)	D

[a] Equimolar quantities. [b] Method A: heated to reflux in toluene with 1 mL of Et_3N. Method B: mixture heated neat at 220 °C for time indicated in Experimental Section. Method C: imide 7 treated with $NaBH_4$. Method D: imide 7 treated with methyl magnesium bromide. [c] Crude products were >98% pure.

We now report a very convenient and rather general route to these versatile chiral substances that will significantly extend the scope of this methodology. Taking a cue from the beautiful and extensive work of Speckamp,[5] we felt we should be able to generate the requisite bicyclic lactams via the intermediate acylimminium ions **9**. These are readily derived from 2-ethoxy amines **8**, which in turn are obtained by sodium borohydride reduction of imides **7**. In this fashion we were indeed able to carry out the synthesis of **10** in generally high yields (Table I). Additionally, the use of Grignard reagents in place of borohydride gave the alkyl-substituted bicyclic lactam **11**. Both routes, to **10** and **11**, respectively, occurred in nearly quantitative yields.



(-)-4 5 (R' = H, Alky) 6 (Eq 1)

The synthetic route involves heating the appropriate anhydride with a chiral 2-amino alcohol in toluene with azeotropic removal of water to afford **7** (R = Ph, i-Pr) in generally good yield. In the case of (*S*)-valinol the condensation with succinic anhydride was carried out neat using a 1:1 ratio of the two components and heating to ca. 220 °C for 2.5 h. Under these conditions the succinimide **7** was obtained in 73% yield. Several other anhydrides were also transformed into their N-substituted derivatives and these are tabulated in Table I.

The use of maleic and glutaric anhydride under either set of conditions gave only a moderate yield of maleimide or glutarimide, respectively, and the reactions were accompanied by extensive polymerization. The bicyclic imide **7e**, derived from *cis*-1,2-cyclohexanedicarboxylic acid was formed in excellent yield when heated neat with (*S*)-valinol.

Transformation of these imides to the bicyclic lactams **10** and **11** was accomplished by reduction with sodium borohydride and 1.0 equiv of hydrochloric acid in absolute ethanol as described by Speckamp.[6] In this fashion, the 2-ethoxy derivative **8** was furnished along with a small amount (20%) of the bicyclic lactam **10**. Addition of the crude material **8** to a solution of 10 equiv of trifluoroacetic acid in methylene chloride at 0 °C gave the bicyclic lactams **10** in generally excellent yields. Table I contains other examples prepared by this technique. In the case of the maleimide **7c**, reduction also occurred at the olefinic linkage and gave the saturated derivative **10b**. The reductive cyclization of the imide **7e** gave rise to a mixture of two diastereoisomers in a 1.8:1.0 ratio with the exo isomer predominating. These isomers were readily separated by flash chromatography and tentative assignments were derived from the *J* values of the angular hydrogen C9b with the adjacent hydrogen C9a in the fused six-membered ring. The all-cis compound **10e** gave a *J* value of 5.1 Hz while the trans product **10f** showed a *J* value of 3.8 Hz, making a firm assignment somewhat risky.

(5) For a review on *N*-acylimminium ion cyclization in synthesis, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(6) Wijnberg, J. A.; Shoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179.

Therefore, NOE experiments were performed on **10e** and **10f** (Table I). Irradiation of **10e** at the angular oxazolidine methine C9b gave an 8.3% enhancement of the C9a methine and a 2.5% enhancement of the C5a methine, indicating that all three protons are on the same face (syn-cis). Irradiation of **10f** at the angular C9b methine gave a 2.3% enhancement of the C9a methine and no enhancement of the C5a proton, indicating an anti-cis arrangement for C9b, C9a, and C5a.

In addition to reduction of the imides **7**, various substitutions are possible by simply introducing an alkyl group. Thus, addition of methylmagnesium bromide (3.0 equiv) to **7** gave the angularly substituted derivative **11** in 73% yield and it was shown to be identical with that prepared via the earlier route (eq 1).

In conclusion, a variety of highly useful chiral starting materials have been efficiently prepared by virtue of *N*-acylimminium cyclizations, which would be difficult to reach otherwise.

Experimental Section

^{1}H NMR spectra were recorded on an IBM/Bruker WP-270 (270 MHz) spectrometer and are reported in δ values. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Desert Analytics of Tucson, Az, and are within 0.4% of calculated values. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer using NaCl plates. All solvents were ACS reagent grade and were redistilled and dried according to standard procedures prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. (*S*)-(+)-Phenylglycinol and (*S*)-(+)-valinol were prepared from (*S*)-phenylglycine and (*S*)-valine (Aldrich) according to a previous procedure.[7]

General Procedure for the Synthesis of Cyclic Imides. Method A. (*S*)-(+)-*N*-(1-Phenyl-2-hydroxyethyl)succinimide (7a). Succinic anhydride (0.364 g, 3.64 mmol) and (*S*)-phenylglycinol (0.5 g, 3.64 mmol) were dissolved into 45 mL of toluene under an argon atmosphere. The mixture was heated to reflux for 1 h to afford a clear oil as a separate layer. This oil is presumably the intermediate amide acid. In order to accelerate the cyclization step, triethylamine (1 mL) was added to the stirring mixture and the solution was heated at reflux for 17 h, affording a homogeneous solution. The solvent was removed by rotary evaporation and the resulting oil was purified by flash chromatography on 20 g of Grace grade 951 silica gel contained in a 2.2 × 40 cm column using 25% hexanes in ethyl acetate as mobile phase. There was obtained 586 mg (76%) of **7a** as a colorless oil: $[\alpha]^{22}_D$ +16.5° (*c* 1.87, EtOH); FTIR (neat) 3620–3128, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 4 H), 2.80 (br s, 1 H, OH), 4.06 (dd, 1 H, *J* = 11.7, 4.9 Hz), 4.56 (dd, 1 H, *J* = 11.7, 9.3 Hz), 5.27 (dd, 1 H, *J* = 9.3, 4.9 Hz), 7.28–7.40 (m, 5 H).

(*S*)-(+)-*N*-[1-(1-Methylethyl)-2-hydroxyethyl]maleimide (7c). The product was obtained in 20% yield via method A using maleic anhydride (2.55 g, 26.04 mmol) and (*S*)-(+)-valinol (2.56 g, 24.8 mmol). The product **7e** was purified on 40 g of Grace grade 951 silica gel contained in a 4.4 × 30 cm column using 60% ethyl acetate/hexane as a mobile phase, affording 893 mg of **2c** as a colorless oil: $[\alpha]^{22}_D$ +14.8° (*c* 1.62, EtOH); FTIR (neat) 3655–3166, 1702, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, 3 H, *J* = 6.7 Hz), 0.97 (d, 3 H, *J* = 6.7 Hz), 2.230 (m, 1 H), 2.67 (br s, 1 H, OH), 3.79 (m, 2 H), 4.00 (dd, 1 H, *J* = 12.1, 7.8 Hz), 6.68 (s, 2 H). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.67; H, 7.19; N, 7.46.

General Procedure for the Synthesis of Cyclic Imides. Method B. (*S*)-(+)-*N*-[1-(1-Methylethyl)-2-hydroxyethyl]-succinimide (7b). (*S*)-(+)-Valinol (2.61 g, 25.3 mmol) and succinic anhydride (2.53 g, 25.3 mmol) were added to a 25-mL flask equipped with a magnetic stir bar. The mixture was heated with a heat gun for 30 s to allow the formation of a homogeneous oil and then put in a sand bath and heated at 220 °C for 3 h. A black tarry mixture resulted, which was purified by flash chromatography on 40 g of Grace grade 951 silica gel contained in a 4.4 × 30 cm column using ethyl acetate as eluent, giving 3.79 g (73% – based on 90% purity by ^{1}H NMR) of **7b** as a brownish oil: $[\alpha]^{22}_D$ +10.1° (*c* 1.84, EtOH). The material was bulb-to-bulb distilled (bp, 200 °C at 0.01 Torr) and recrystallized from ethyl acetate/hexane: mp 59–61 °C; FTIR (CH_2Cl_2 film) 3600–3700, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75 (d, 3 H, *J* = 6.7 Hz), 0.99 (d, 3 H, *J* = 6.7 Hz), 2.36 (m, 1 H), 2.70 (s, 4 H), 3.76 (m, 3 H), 4.00 (dd, 1 H, *J* = 11.7, 7.2 Hz).

(*S*)-(+)-*N*-[1-(1-Methylethyl)-2-hydroxyethyl]glutarimide (7d). The product was obtained in 21% yield via method B using glutaric anhydride (1.60 g, 14.0 mmol) and (*S*)-(+)-valinol (1.45 g, 14.0 mmol) heated at 210 °C for 4 h. The resulting black tarry mixture was purified by flash chromatography on 40 g of Davidson Chemical silica alumina grade 135X using 25% hexanes in ethyl acetate as the mobile phase, affording 0.592 g of **7d** as a faintly amber oil: $[\alpha]^{22}_D$ +19.1° (*c* 2.10, EtOH); FTIR (neat) 1733, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.72 (d, 3 H, *J* = 6.7 Hz), 0.99 (d, 3 H, *J* = 6.7 Hz), 1.79 (dt, 1 H, *J* = 14.7, 7.4 Hz), 1.90 (dt, 1 H, *J* = 13.1, 6.4 Hz), 2.23 (dd, 2 H, *J* = 14.7, 7.4 Hz), 2.39 (m, 1 H, $CH(CH_3)_2$), 2.63 (dd, 2 H, *J* = 13.1, 6.4 Hz), 2.70 (br s, 1 H, OH), 4.37–4.55 (m, 3 H).

***cis*-(2′*S*)-(+)-*N*-[1-(1-Methylethyl)-2-hydroxyethyl]-3a,4,5,6,7,7a-hexahydro-1*H*-isoindolimide (7e).** The product was obtained in 95% yield via method B using *cis*-1,2-cyclohexanedicarboxylic anhydride (3.72 g, 24.1 mmol) and (*S*)-(+)-valinol (2.49 g, 24.1 mmol) heated at 220 °C for 2.5 h. This light brown oil was purified by flash chromatography on 40 g of Grace grade 951 silica gel using ethyl acetate as mobile phase, affording 5.49 g of **7e** as a light orange solid. Recrystallization from ethyl acetate/hexane gave a white solid: mp 80–82 °C; $[\alpha]^{22}_D$ +11.2° (*c* 2.00, EtOH); FTIR (neat) 3633–3144, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.77 (d, 3 H, *J* = 6.7 Hz), 0.98 (d, 3 H, *J* = 6.7 Hz), 1.40 (m, 4 H), 1.61–1.90 (m, 4 H), 2.334 (m, 1 H, $CH(CH_3)_2$), 2.83 (m, 2 H), 3.19 (br s, 1 H, OH), 3.73 (m, 2 H), 3.97 (m, 1 H). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84. Found: C, 65.41; H, 8.82.

General Procedure for Reduction–Cyclization to Bicyclic Lactams 10. Method C. (3*S*,7a*R*)-3-Isopropyl-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (10b). (*S*)-Valinol-derived succinimide **7b** (1.10 g, 5.9 mmol) was dissolved in 55 mL of absolute ethanol contained in an oven-dried, 100-mL flask equipped with a magnetic stir bar, argon atmosphere, and rubber septum. The solution was cooled to 0 °C and $NaBH_4$ (2.24 g, 59.4 mmol) was added with stirring. Hydrochloric acid (2 M) in absolute ethanol (15–20 drops every 15 min) was added via syringe over a 3-h period unitl 1 equiv of acid was added (5.9 mmol, 3 mL). The solution was acidified to pH 1–3 by addition of 2 M HCl in absolute ethanol over a 15-min period, affording a white suspension, which was stirred an additional 3 h at room temperature. The mixture was quenched by addition to 50 mL of saturated $NaHCO_3$ and this mixture was extracted with 3 × 50 mL of $CHCl_3$. The combined organic extracts were dried (K_2CO_3) and solvent was removed to afford 1.25 g (98%) of a colorless oil as a mixture of 5-ethoxypyrrolidinone diastereomer (**8b**) and approximately 15% of cyclized bicyclic lactam **10b**. This material was not purified but carried directly on to the next step.

Trifluoroacetic acid (6.61 g, 4.64 mL, 58.0 mmol) was added via syringe to 100 mL of CH_2Cl_2 containing the an oven-dried, 250-mL flask equipped with magnetic stir bar, argon atmosphere, and rubber septum. This solution was cooled to 0 °C and 5-ethoxy-2-pyrrolidinone **8b** (1.25 g, 5.8 mmol) dissolved in 7 mL of CH_2Cl_2 was added via syringe over a 1-min period. The solution was allowed to warm to room temperature and stirred an additional hour. The reaction was quenched by addition to 100 mL of saturated $NaHCO_3$ solution. (*CAUTION*: Vigorous CO_2 evolution!) This mixture was extracted with 2 × 50 mL portions of CH_2Cl_2, the combined organic extracts were dried (K_2CO_3), and the solvent was removed to afford 930 mg (95%) of **10b** as a colorless oil. This material thus obtained did not require further purification: $[\alpha]^{22}_D$ +70.0° (*c* 1.44, $CHCl_3$); FTIR (neat) 2961, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3 H, *J* = 6.7 Hz), 0.97 (d, 3 H, *J* = 6.7 Hz), 1.62 (m, 1 H, $CH(CH_3)_2$), 2.03 (m, 1 H), 2.26–2.68 (m, 3 H), 3.62 (m, 2 H), 4.13 (dd, 1 H, *J* = 8.1, 6.8 Hz), 5.03 (dd, 1 H, *J* = 6.2, 2.3 Hz, angular H). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.67; H, 9.11; N, 8.08.

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(3*S*,7a*R*)-5-Oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (10a). Compound **10a** was obtained in 80% yield via method C using the (*S*)-phenylglycinol-derived succinimide **7a** (0.120 g, 0.55 mmol) and $NaBH_4$ (0.207 g, 5.5 mmol) in 10 mL of absolute ethanol. Workup afforded 107 mg of a colorless oil as a mixture of 5-ethoxy-2-pyrrolidinone diastereomers **8a** and approximately 10% of cyclized bicyclic lactam **10a**. This material was carried directly on to the next step. The bicyclic lactam was obtained in 96% yield from crude 5-ethoxy-2-pyrrolidinone **8a** (0.107 g, 0.43 mmol) and trifluoroacetic acid (0.49 g, 0.33 mL, 4.3 mmol) in 45 mL of CH_2Cl_2. This gave 84 mg (96%) of **10a** isolated as a slightly yellowish solid: mp 64–67 °C; $[\alpha]^{22}_D$ +154.1° (*c* 1.29, EtOH); FTIR ($CHCl_3$ film) 3018, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (m, 1 H), 2.340–2.81 (m, 3 H), 3.810 (dd, 1 H, *J* = 8.7, 7.5 Hz), 4.56 (dd, 1 H, *J* = 8.7, 7.5 Hz), 510 (dd, 1 H, *J* = 7.5, 7.5 Hz), 5.28 (dd, 1 H, *J* = 6.2, 2.5 Hz, angular H), 7.21–7.37 (m, 5 H). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.67; H, 6.34; N, 6.77.

(3*S*,8a*R*)-3-Isopropyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (10d). Compound **10d** was obtained in 77% yield via sodium borohydride reduction (0.96 g, 25.4 mmol) of (*S*)-valinol-derived glutarimide (0.51 g, 2.5 mmol) in 25 mL of absolute ethanol. Workup, as above, gave 450 mg of a colorless oil that proved to be mainly the cyclized material **10d**. However, it was still subjected to the cyclization step using trifluoroacetic acid (2.18 g, 1.47 mL, 19.1 mmol). Workup gave 281 mg of pure **10d**: $[\alpha]^{22}_D$ +19.4° (*c* 2.3, EtOH); FTIR (neat) 2960, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz), 1.39 (m, 1 H), 1.64 (m, 1 H), 1.87 (m, 1 H) 2.07–2.32 (m, 3 H), 2.49 (m, 1 H), 3.63 (dd, 1 H, *J* = 8.7, 6.9 Hz), 4.00 (dd, 1 H, 8.7, 7.2 Hz), 4.156 (m, 1 H), 4.70 (dd, 1 H, *J* = 8.7, 4.7 Hz). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.22; H, 9.52; N, 7.77.

(3*S*,5a*S*,9a*R*,9b*R*)-3-Isopropyl-5-oxo-2,3,6,7,8,9,9a,9b-octahydrooxazolo[2,3-*a*]isoindole (10e) and (3*S*,5a*R*,9a*S*,9b*R*)-3-Isopropyl-5-oxo-2,3,6,7,8,9,9a,9b-octahydrooxazolo[2,3-*a*]isoindole (10f). Compounds **10e** and **10f** were obtained in 91% yield via method C using cyclohexane 1,2-dicarboximide **7e** (0.86 g, 3.6 mmol) and sodium borohydride (1.36 g, 36.0 mmol) in 30 mL of absolute ethanol. Workup gave 880 mg of a colorless oil composed of a mixture of ethoxy diastereomers **8e** and **8f** and 20% of cyclized material **10e** and **10f**. This mixture without any further handling, was subjected to the cyclization step. The material above (880 mg) and trifluoroacetic acid (3.7 g, 2.5 mL, 32.7 mmol) were dissolved in 50 mL of dichloromethane and gave 775 mg (99%) of cyclized products as a colorless oil.

The diastereomers **10e** and **10f** were separated by flash chromatography on 22 g of Amicon 50-μm silica gel using 15% ethyl acetate in hexane as eluent. The first eluting diasteromer **10e** was isolated (36%) as a white solid: mp 45–46 °C; $[\alpha]^{22}_D$ +54.8° (*c* 2.47, EtOH); FTIR (neat) ($CHCl_3$ film) 2932, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H, *J* = 6.7 Hz), 0.92 (d, 3 H, *J* = 6.7 Hz), 0.97–1.77 (m, 8 H), 2.07 (m, 1 H), 2.56 (m, 1 H, C*H*$(CH_3)_2$), 2.84 (m, 1 H), 3.71–8.86 (m, 2 H)8 4.08 (dd, 1 H, *J* = 8.5, 7.0 Hz), 5.24 (d, 1 H, *J* = 5.1 Hz, angular H). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.22; H, 9.57; N, 6.20. The second eluting diastereomer **10f** was isolated (64%) as a colorless oil: $[\alpha]^2_2D$ +32.5° (*c* 2.55, EtOH); FTIR (neat) 2933, 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, *J* = 6.7 Hz), 0.96 (d, 3 H, *J* = 6.7 Hz), 1.27–1.73 (m, 8 H), 1.88 (m, 1 H), 2.29 (m, 1 H), 2.54 (m, 1 H), 3.67 (m, 2 H), 4.09 (m, 1 H), 4.86 (d, 1 H, *J* = 3.8 Hz, angular H).

(3*S*,7a*R*)-3-Isopropyl-7a-methyl-5-oxo-2,3,5,6,7,7a-hexahydropyrolo[2,1-*b*]oxazole (11). Method D. Valinol-derived succinimide **7b** (0.54 g, 2.9 mmol) was dissolved into 25 mL dry THF contained in a dry 50-mL flask equipped with magnetic stir bar, argon atmosphere, and rubber septum. To this stirring solution at room temperature was added methylmagnesium bromide (5.8 mL, 8.8 mmol, 3.0 equiv) over a 3-min period producing a cloudy yellowish mixture.[8] The mixture was stirred for 3 h at room temperature before being quenched by addition to 25 mL of saturated NH_4Cl solution. This mixture was extracted with 3 × 25 mL portions of Et_2O, the combined organic extracts were dried (K_2CO_3), and the solvent was removed to afford 315 mg of a colorless oil. The aqueous extracts were evaporated and the resulting salts extracted with 2 × 50 mL of Et_2O, furnishing an additional 114 mg of product (73% overall yield). This material was carried on directly to the cyclization step without further purification. The crude adduct (430 mg, 2.1 mmol) was added to 50 mL of dichloromethane and trifluoroacetic acid (2.4 g, 1.6 mL, 21.3 mmol). After workup, 361 mg of **11** (93%) was obtained as a tan-colored oil: $[\alpha]^{22}_D$ +89.3° (*c* 2.60, EtOH); $[\alpha]^{22}_D$ lit.[9] +95.5° (*c* 2.8, EtOH); ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H, *J* = 6.6 Hz), 1.01 (d, 3 H, *J* = 6.6 Hz), 1.45 (s, 3 H, angular CH_3), 1.63 (m, 1 H, C*H*$(CH_3)_2$), 2.14 (m, 2 H), 2.45 (m, 1 H), 2.75 (m, 1 H), 3.56 (m, 1 H), 3.83 (dd, 1 H, *J* = 8.7, 6.2 Hz), 4.13 (dd, 1 H, *J* = 8.7, 7.5 Hz).

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4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(tributylstannyl)-(*E*)-2-buten-1-ol: A Useful Precursor for Tetrahydrofuran Synthesis

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In the course of our studies toward the synthesis of the southern zone of avermectin A_{2b},[1] we desired an efficient route to prepare cis-fused octahydrobenzofurans. In particular we required a methodology that permitted diastereoisomeric control in the construction of three contiguous asymmetric centers as well as the incorporation of an *E* exocyclic double bond. We wish to report that 4-[(*tert*-butyldiphenylsilyl)oxy]-2-(tributylstannyl)-(*E*)-2-buten-1-ol (**2**) has proven to be a valuable precursor to such functionalized octahydrobenzofurans, as well as a variety of other substituted tetrahydrofurans.

Critical to the approach was the formation of dianion **3**.[2] Diol **1**, which was prepared according to the procedure of Fleming et al.,[3] was regioselectively protected using *tert*-butyldiphenylsilyl chloride to provide the monosilyl derivative **2** (93%). Treatment of **2** with 2.1 equiv of *n*-butyllithium for 2 h at 35 °C in THF gave the dianion **3**. Maintenance of the temperature at −35 °C was crucial; higher temperatures led to severe decomposition of the dianion and lower temperatures led to its incomplete formation. A small amount of protonated dianion was recovered from each reaction. However, attempts to alter the basicity of the dianion by transmetalation with trimethylaluminum or cerium trichloride did not improve the yield. Reactions of dianion **3** with various carbonyl compounds are summarized in Scheme I.

The dianion also smoothly added to a variety of epoxy aldehydes and epoxy ketones (Scheme II). Reaction of dianion **3** with 2,3-epoxycyclohexan-1-one resulted in the

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