freshly distilled under argon from sodium/potassium alloy. Anhydrous copper(I) iodide and nickel(II) iodide were purchased from Cerac, Inc. Lithium and naphthalene were weighed out and charged into reaction flasks under argon in a Vacuum Atmospheres Co. drybox. Other commercially available reagents were used as received.

Typical Preparation of Activated Copper. A 50-mL two-necked round-bottomed flask was equipped with a rubber septum, a condenser topped with an argon inlet, and a stir bar. The flask was charged with naphthalene (8.7 mmol) and freshly cut lithium (7.2 mmol) in the drybox and was then connected to the manifold system. The freshly distilled THF (5 mL) was added via syringe, and the mixture was stirred at room temperature for 2 h. A solution of $CuIP(n\text{-}Bu)_3$ (6.7 mmol) prepared in situ from CuI (6.7 mmol) and $P(n\text{-}Bu)_3$ (7.2 mmol) in THF (10 mL) was transferred into the preformed lithium naphthalide via cannula at 0 °C and stirred at 0 °C for 0.5 h.

Reductive Coupling of Benzoyl Chloride Using Activated Copper. Benzoyl chloride (460 mg, 3.27 mmol) was added to the freshly prepared activated copper (6.7 mmol) via syringe with stirring at −78 °C in a dry ice–acetone bath. The reaction mixture was stirred at −78 °C for 10 min and then quenched with 3% aqueous HCl solution.[26] The reaction solution was extracted twice with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel to give stilbenediol dibenzoate (280 mg, 81.5%) as a white solid. Pure *cis*-α,α'-stilbenediol dibenzoate can be obtained by continuous recrystallization from a pentane–EtOAc solution: mp 157.5–158.5 °C (lit.[4] mp 159 °C); IR (KBr) 1735, 1595, 1450, 1270, 1240, 1090, 1070, 1050, 1020, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 6 H), 7.36 (t, 4 H), 7.43 (d, 4 H), 7.51 (t, 2 H), 8.09 (d, 4 H); ^{13}C NMR ($CDCl_3$) δ 128.33, 128.42, 128.90, 129.09, 129.21, 130.07, 133.34, 133.40, 139.07, 164.20.

Reductive Coupling of Benzoyl Chloride Using Activated Copper in the Presence of Trimethylchlorosilane (TMSCl). To freshly prepared activated copper (15.86 mmol) was added TMSCl (6.3 mL, 49.64 mmol) via syringe at −78 °C. Benzoyl chloride (1.12 g, 7.97 mmol) in THF (10 mL) was added dropwise via syringe over a 20-min period. The reaction mixture was stirred at −78 °C for 0.5 h. The dry ice–acetone bath was then replaced with an ice–H_2O bath. After stirring at 0 °C for 3 h, the reaction mixture was allowed to warm to room temperature. The reaction was quenched with H_2O (30 mL), and the resulting mixture was extracted with ether. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting mixture was flash chromatographed on silica gel to give benzoin (561 mg, 66.3%) as a white powder: mp 134–135 °C (lit.[28] mp 134–135.5 °C); IR (KBr) 3200–3500 (br), 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.57 (d, J = 6.0 Hz, 1 H), 5.96 (d, J = 6.0 Hz, 1 H), 7.27–7.34 (m, 5 H), 7.40 (t, 2 H), 7.53 (t, 1 H), 7.92 (d, 2 H).

Reductive Alkylation of Benzil Using Activated Copper. To freshly prepared activated copper (15.71 mmol), benzil (1.642 g, 7.81 mmol) in THF (10 mL) was added at 0 °C and stirred at 0 °C for 3 h. Excess iodomethane (3.66 g, 25.79 mmol) was added via disposable syringe at 0 °C and stirred at 0 °C for 3 h. The ice–H_2O bath was then removed and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight (ca. 10 h), the reaction mixture was quenched with H_2O (5 mL) at 0 °C. The mixture was stirred at room temperature for another 1 h and was then dried over anhydrous $MgSO_4$. The resulting mixture was concentrated under reduced pressure, and the concentrated mixture was chromatographed on silica gel to give α-methylbenzoin as a white solid (1.55 g, 87.7%): mp 65.5–66.5 °C (lit.[29] mp 66–67 °C); IR (KBr) 3300–3600 (br), 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 4.79 (s, 1 H, D_2O exchangeable), 7.27–7.69 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 26.39, 79.38, 125.94, 128.14, 128.26, 128.94, 130.20, 132.86, 133.88, 142.71, 202.05.

Reductive Coupling of Benzoyl Chloride Using Activated Nickel. Activated nickel powder (7.46 mmol) was generated by stirring Li^0 (16.93 mmol), nickel(II) iodide (7.46 mmol), and naphthalene (0.75 mmol) in glyme (25 mL) at room temperature for 30 h. Benzoyl chloride (1.043 g, 7.42 mmol) was added dropwise via syringe at 0 °C, and the reaction mixture was stirred at room temperature for 36 h. The reaction was quenched with H_2O (5 mL), and CH_2Cl_2 (50 mL) was added. The mixture was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel to give benzil (180 mg, 23%) and *trans*-α,α'-stilbenediol dibenzoate (170 mg, 22%). Benzil: mp 94.0–94.5 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (t, 4 H), 7.68 (t, 2 H), 7.99 (d, 4 H). *trans*-α,α'-Stilbenediol dibenzoate: mp 188.5–189.0 °C (lit.[4] mp 189 °C); IR (KBr) 1740, 1595, 1490, 1445, 1255, 1235, 1115, 1080, 1030, 1010, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (m, 6 H), 7.48 (t, 4 H), 7.62 (t, 2 H), 7.67 (d, 4 H), 8.10 (d, 4 H); MS (EI) m/e (relative intensity) 421 (2.5), 420 (M^+, 9.1), 210 (0.1), 106 (7.5), 105 (100.0), 77 (27.6). Calcd for $C_{28}H_{20}O_4$ (M^+) m/e 420.1362, found m/e 420.1365.

Acknowledgment. The financial support provided by the National Institutes of Health (Grant No. GM 35153) is gratefully acknowledged.

(27) The reaction has also been conducted at 0 °C and at room temperature. Yields are comparable under these conditions.
(28) Koenigkramer, R. E.; Zimmer, H. *J. Org. Chem.* **1980**, *45*, 3994.
(29) Hunig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062.
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Epimerization and Oxidation of the Bridgehead Hydrogen of Some Indoloquinolizideines

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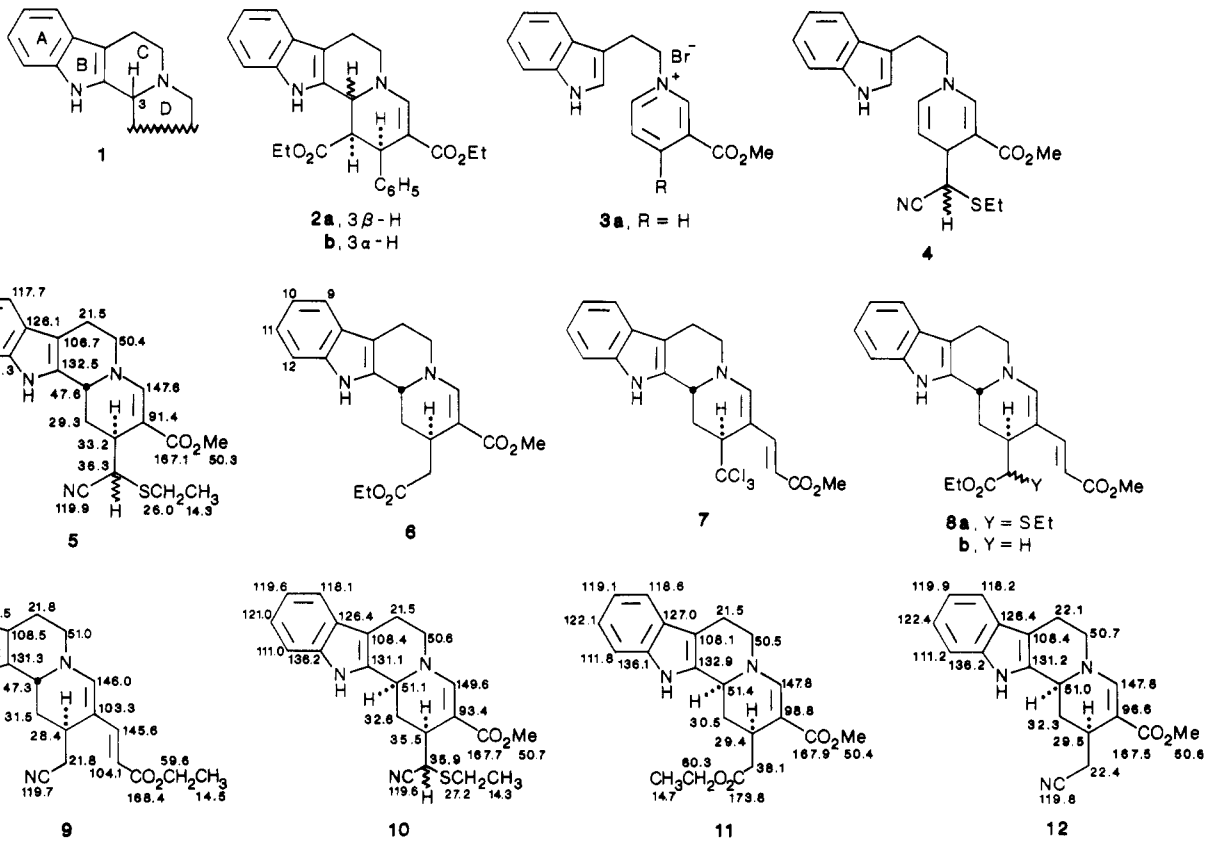
It has been known for a long time that the bridgehead, aminomethine hydrogen of indole alkaloids of the yohimboid, heteroyohimboid, and corynanthoid types (H-3 in formula 1, Chart I) can be epimerized in acid media.[1] In view of the general inefficiency of this process most isomerizations have been performed over the years by oxidation–reduction operations.[2] In light of this accumulated experience the recently reported,[3] facile, acid-induced **2a** → **2b** conversion was surprising and required further scrutiny. Since vinylogous urethanes of type **2a** have been the pivotal intermediates in syntheses of the aforementioned indole bases[4] and can be prepared easily by a two-step reaction sequence of carbon nucleophile addition to 1-tryptophyl-3-acylpyridinium salts and subsequent acid-induced ring closure (e.g., the **3a**[5] → **4** → **5** transformations described in detail in the Experimental Section), five vinylogous urethanes—**5**, **6**,[6] **7**,[6] **8b** (prepared from **8a**[6] on reduction with Raney nickel), and **9**[7]—were on hand for a study of their response to exposure to trifluoroacetic acid.

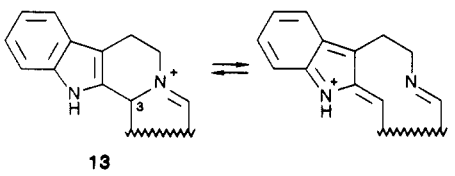
(1) Cf.: Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053.
(2) Cf.: Weisenborn, F. L.; Diassi, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 2022. Wenkert, E.; Roychaudhuri, D. K. *J. Org. Chem.* **1956**, *21*, 1315.
(3) Rosentreter, U.; Born, L.; Kurz, J. *J. Org. Chem.* **1986**, *51*, 1165.
(4) (a) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645; **1982**, *104*, 6166. (b) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *Ibid.* **1979**, *101*, 5370; **1982**, *104*, 6166. (c) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *Ibid.* **1980**, *102*, 7971. (d) Wenkert, E.; Pyrek, J. St.; Uesato, S.; Vankar, Y. D. *Ibid.* **1982**, *104*, 2244. (e) Spitzner, D.; Wenkert, E. *Angew. Chem.* **1984**, *96*, 972.
(5) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461.
(6) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. St.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995.
(7) This compound has been prepared by (a) treatment of the *N*-tryptophyl salt of ethyl β-(β-pyridyl)acrylate with sodium hydride, (b) exposure of the product first to ethylthioacetonitrile in dimethylsulfoxide solution and then to trifluoroacetic acid in methylene chloride solution, and (c) Raney nickel desulfurization of the resultant tetracyclic product (Wenkert, E.; Shi, Y.-J., unpublished observations).

0022-3263/88/1953-2383$01.50/0

Chart I



Scheme I



Treatment of vinylogous urethanes **5** and **6** with freshly distilled and/or degassed trifluoroacetic acid yielded bridgehead hydrogen epimers **10** (99%) and **11** (80%), respectively, the former of which was converted into nitrile **12** on Raney nickel desulfurization. On the other hand, similar treatment of the doubly vinylogous urethanes **7**, **8b**, and **9** left the tetracycles structurally unchanged.

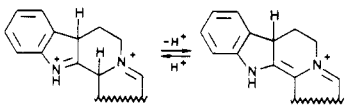
The ease of the acid-induced isomerizations of tetrahydronicotinates **2a**, **5**, and **6** is in line with the known, facile epimerizations of indoloquinolizideinium salts **13**, formulated to occur by way of carbon–nitrogen bond rupture without H(3) expulsion (Scheme I[8]), in view of the nicotinic esters being in equilibrium with iminium cations of type **13** in acid medium (e.g., the conjugate acid of urethane vinylogue **6** being cation **14**[9]). Whereas the **2a** → **2b** isomerization has been considered later to be generated by the tautomeric equilibria of Scheme II[10] on the basis of the observation of H(3) exchange accompanying a reaction in deuteriotrifluoroacetic acid,[3] the absence of comparison rate data of isomerization and hydrogen exchange precludes at this time adoption of this alternate mechanism as the preferred explanation of the isomerization of the tetrahydronicotinates.[11]

The easy isomerization of tetracycles **2a**, **5**, and **6** permits now a false impression in the literature[13] to be corrected. Dithionite reduction of pyridinium salts **3** (R = Me or *n*-Pr) and acid-catalyzed cyclization of the dihydro products have been reported to yield tetracycles **16a**, whereas acid-induced cyclization of the isolated reduction products **15** have yielded tetracycles **16b**.[13] The dissimilarity of cyclization behavior has been attributed to the intermediacy of sulfinates of dihydronicotinates **15** in the first reaction sequence and has been claimed to have the following consequence: "Compared with some other methods ..., the sodium dithionite reduction has the advantage of permitting the C(3)–C(15) stereochemical relationship to be chosen with a high degree of stereoselectivity by slight modification of the last step of the synthesis."[13] The implication of the cyclization of *N*-tryptophyl, γ-alkylated

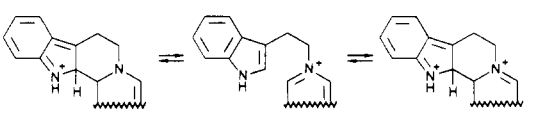
(8) Brown, R. T.; Chapple, C. L.; Platt, R.; Spencer, H. *J. Chem. Soc., Chem. Commun.* **1974**, 929. Brown, R. T.; Leonard, J.; Sleigh, S. K. *Ibid.* **1977**, 636.

(9) Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G.; Oishi, T.; Stevens, R. V.; Terashima, M. *J. Org. Chem.* **1968**, *33*, 747.

(10) In principle, in strong acid Scheme II should be portrayed as follows.

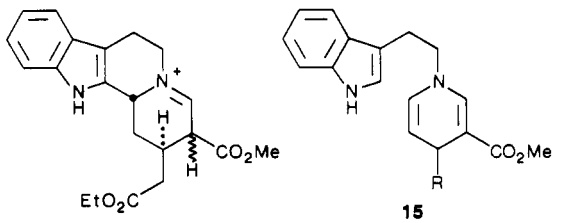


(11) The acid-catalyzed C(3) epimerizations are possible via three pathways:[12] (a) carbon–nitrogen bond cleavage (Scheme I), (b) carbon–hydrogen bond cleavage (Scheme II) and (c) carbon–carbon bond cleavage (shown below). However, the last alternative is least likely in the tetrahydronicotinate cases in view of the nitrogen being a poor electron donor when part of a vinylogous urethane unit or part of an iminium cation species.

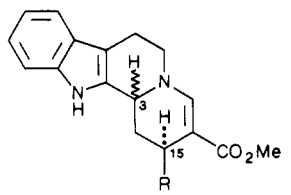


(12) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kirstead, R. W. *Tetrahedron* **1958**, *2*, 1.

(13) Lounasmaa, M.; Johansson, C.-J. *Tetrahedron* **1977**, *33*, 113.



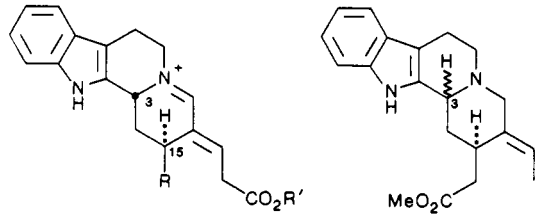
14 15



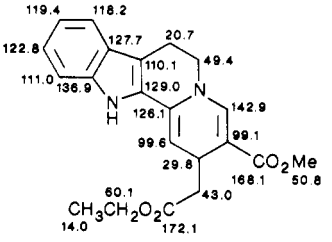
16a, 3β-H
b, 3α-H

dihydro- or tetrahydropyridines yielding more than one stereoisomeric product flies in the face of the well-known fact of ubiquitous H(3)–H(15) trans product formation.[14] Thus the proper interpretation of the unusual, experimental results is founded on the intermediacy of dihydropyridine **15** and the formation of the kinetic product **16a** in both reaction sequences, but transformation of the latter into the more stable isomer **16b** in the second reaction sequence as a consequence of overexposure to acid.

The stability of doubly vinylogous urethanes **7**, **8b**, and **9** in trifluoroacetic acid in light of the isomerizations of tetrahydronicotinates **2a**, **5**, and **6** appears, at first glance, to be anomalous. However, on recognition of the fact of cation **17** being the equilibrating species and the H(3)–H(15) trans isomer being the more stable equilibrant of such a system in analogy with the greater stability of ester **18a** over isomer **18b**[16] the inertness of compounds **7**, **8b**, and **9** toward acid becomes understandable.



17 18a, 3β-H
b, 3α-H



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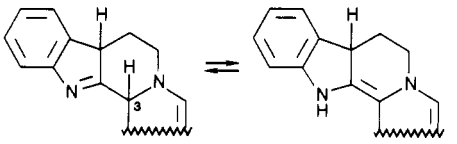
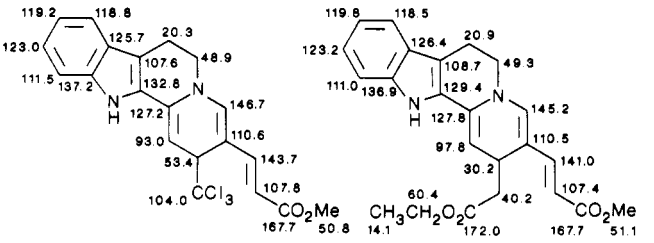
When the reactions with trifluoroacetic acid were carried out in the open air, bridgehead oxidation took place, causing tetracycles **6**, **7**, **8b**, and **9** to be transformed into didehydro products **19** (90%), **20** (99%), **21** (92%), and **22**

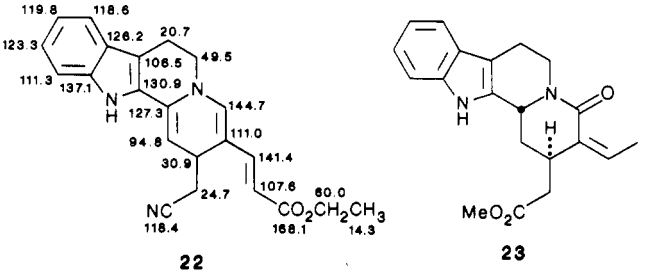
Scheme II



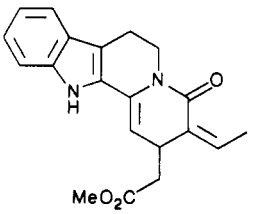
(87%), respectively. These results are reminiscent of the conversion of lactam **23** into **24** on reaction with oxygen in trifluoroacetic acid under cupric acetate catalysis.[17]



20 21



22 23



24

Experimental Section

Melting points were recorded on a Reichert micro-hot stage and are uncorrected. Infrared spectra of chloroform solutions and ultraviolet spectra of methanol solutions were measured on Perkin-Elmer 1330 and IBM 9400 spectrophotometers, respectively. ^1H NMR spectra of deuteriochloroform solutions (Me_4Si as internal standard) were obtained on Varian EM-390 and Nicolet QE-300 spectrometers and ^{13}C NMR spectra of deuteriochloroform solutions on the latter instrument, operating at 75.5 MHz in the Fourier transform mode. Complete ^1H and ^{13}C NMR signal assignments were based on COSY and ^{13}C–^1H correlated spectroscopies, respectively. The carbon shifts depicted on formulas **9**, **10**, **11**, **12**, **19**, **21**, and **22** are in parts per million downfield from Me_4Si, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm, and those on formulas **5** and **20** are based on DMSO-d_6 solutions, $\delta(Me_4Si) = \delta(\text{DMSO-}d_6) + 39.5$ ppm. All crude products were extracted with methylene chloride and the extracts washed with brine and dried over anhydrous Na_2SO_4.

Cyanide 5. A solution of 1.1 mL (7.5 mmol) of diisopropylamine in 20 mL of anhydrous tetrahydrofuran under nitrogen at −78 °C was mixed with 5.3 mL (7.5 mmol) of a 1.4 M hexane solution of *n*-butyllithium. The temperature was allowed to rise to 0 °C and the mixture stirred for 0.5 h. A solution of 758 mg (7.5 mmol) of ethylthioacetonitrile in 5 mL of dry tetrahydrofuran was added to the stirring mixture at −78 °C and the stirring continued for 1 h. Salt **3a** (0.90 g, 2.5 mmol) was added in one portion and the suspension stirred at −78 °C for 2 h. The tem-

(14) Inter alia ref 4a. For an explanation of the sole exception to the universality of this reaction, see ref 15.
(15) Wenkert, E.; Han, A-L.; Michelotti, E. L. *Croat. Chem. Acta* **1985**, *58*, 737.
(16) (a) Winterfeldt, E. "The Stereospecificity of Indole–Alkaloid Transformations" *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic: New York, 1980; pp 219–228. (b) Wenkert, E.; Pestchanker, M. J.; Shi, Y-J., unpublished observations.
(17) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. *Liebigs Ann. Chem.* **1985**, 1752.

perature was allowed to rise to 0 °C and the mixture stirred for another 2 h. Enough dry benzene, saturated with hydrogen bromide, was added dropwise to bring the pH to 5 and stirring continued at 0 °C for 1 h. The mixture was poured into 100 mL of saturated sodium bicarbonate solution and extracted. Florisil chromatography and elution with 9:1 hexane–ethyl acetate yielded 82 mg (9%) of a mixture of cyanide **5** diastereomers and 250 mg (26%) of a colorless, crystalline **5** diastereomer: mp 238–240 °C (MeOH); UV λ_{max} 204 nm (log ϵ 4.25), 223 (4.46), 291 (4.51); IR [NH] 3460 (m), [C≡N] 2195 (w), [C=O] 1660 (s), 1610 (s), [C=C] 1585 (s) cm^{-1}; ^1H NMR δ 1.40 (t, 3 J = 7 Hz, Me), 2.84 (q, 2, J = 7 Hz, SCH_2), 3.14 (t, 1, J = 5 Hz, allyl H), 3.72 (s, 3, OMe), 4.29 (d, 1, J = 5 Hz, SCH), 5.06 (dd, 1, J = 11, 2 Hz, NCH), 7.13 (t, 1, J = 7 Hz, H-11), 7.20 (t, 1, J = 7 Hz, H-10), 7.36 (d, 1, J = 7 Hz, H-9), 7.49 (d, 1, J = 7 Hz, H-12), 7.74 (s, 1, olefinic H); exact mass, m/e 381.1510 (calcd for $C_{21}H_{23}O_2N_3S$ m/e 381.1509).

Ester 8b. A Raney nickel slurry in water (12 mL of 50%, pH 10) was washed three times with 60 mL of water each, 50 mL of methanol each, and 50 mL of acetone each and a suspension of the solid in 50 mL of acetone refluxed for 0.5 h. The solvent was decanted and a solution of 1.153 g (2.6 mmol) of ester **8a** in 35 mL of methanol and 35 mL of acetone added to the residue. The stirring suspension was refluxed for 1.5 h and filtered. The precipitate was washed exhaustively with methanol and the combined filtrate and washings evaporated to dryness. The residue was taken up with methylene chloride and washed with saturated ammonium chloride solution and brine. The organic solution was dried and evaporated, leaving 1.010 g (99%) of colorless, crystalline ester **8b**: mp 192–193 °C (MeOH); UV λ_{max} 224 nm (log ϵ 4.45), 356 (4.62); IR [NH] 3460 (m), [C=O] 1725 (s), 1680 (s), 1610 (s), [C=C] 1580 (s), 1560 (s) cm^{-1}; ^1H NMR δ 1.33 (t, 3, J = 7 Hz, Me), 1.82 (m, 1, ring D CH_2 α-H), 2.33 (dd, 1, J = 11, 4 Hz, $COCH_2$ H), 2.40 (br d, 1, J = 17 Hz, ring D CH_2 β-H), 2.81 (m, 1, $COCH_2$ H), 2.84 (m, 2, ring C CH_2), 3.13 (br d, 1, J = 6 Hz, allyl H), 3.55 (d, 2, J = 7 Hz, NCH_2), 3.72 (s, 3, OMe), 4.22 (q, 2, J = 7 Hz, OCH_2), 4.59 (br d, 1, J = 12 Hz, NCH), 5.46 (d, 1, J = 15 Hz, acrylic α-H), 6.61 (s, 1, olefinic NCH), 7.10 (t, 1, J = 7 Hz, H-11), 7.17 (t, 1, J = 7 Hz, H-10), 7.26 (d, 1, J = 15 Hz, acrylic β-H), 7.31 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12); exact mass, m/e 394.1879 (calcd for $C_{23}H_{26}O_4N_2$ m/e 394.1891).

Urethane Vinylogues 10,11, and 12. A solution of 40 mg (0.10 mmol) of cyanide **5** in 3 mL of freshly distilled trifluoroacetic acid (de-aired by argon) was stirred under nitrogen at room temperature for 2 h. It was diluted with 100 mL of methylene chloride, washed thoroughly with water, 10% sodium hydroxide solution, and brine, dried, and evaporated, yielding 39 mg (99%) of colorless, crystalline nitrile **10**: mp 106–108 °C (Et_2O); UV λ_{max} 223 nm (log ϵ 4.69), 292 (4.72); IR [NH] 3460 (m), [C=O] 1660 (s), 1610 (s) cm^{-1}; ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me), 1.90 (m, 1, ring D CH_2 α-H), 2.65 (m, 1, ring D CH_2 β-H), 2.69 (q, 2, J = 7 Hz, SCH_2), 3.10 (m, 1, allyl H), 3.62 (s, 3, OMe), 4.32 (br d, 1, J = 11 Hz, NCH), 5.01 (d, 1, J = 4 Hz, SCH), 7.12 (t, 1, J = 7 Hz, H-11), 7.19 (t, 1, J = 7 Hz, H-10), 7.34 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12), 7.68 (s, 1, olefinic H); exact mass, m/e 381.1531 (calcd for $C_{21}H_{23}O_2N_2S$ m/e 381.1509).

A solution of 110 mg (0.30 mmol) of ester **6** in 4 mL of freshly distilled trifluoroacetic acid (de-aired by argon) was stirred under nitrogen at room temperature for 2 h. Workup as above, chromatography of the crude product on silica gel and elution with 6:1 hexane–ethyl acetate gave 88 mg (80%) colorless, amorphous ester **11**: UV λ_{max} 223 nm (log ϵ 4.37), 292 (4.40); IR [NH] 3460 (m), [C=O] 1720 (s), 1690 (s), 1670 (s), 1610 (s) cm^{-1}; ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me), 1.69 (dd, 1, J = 15, 11 Hz, α-keto H), 2.20, 2.42 (m, 1 each, ring D CH_2), 2.94 (dd, 1, J = 15, 3 Hz, α-keto H), 3.08 (m, 1, allyl H), 3.67 (s, 3, OMe), 4.15 (q, 2, J = 7 Hz, OCH_2), 4.61 (br s, 1, NCH), 7.09 (t, 1, J = 7 Hz, H-11), 7.14 (t, 1, J = 7 Hz, H-10), 7.34 (d, 1, J = 7 Hz, H-9), 7.45 (d, 1, J = 7 Hz, H-12), 7.53 (s, 1, olefinic H); exact mass, m/e 368.1740 (calcd for $C_{21}H_{24}O_4N_2$ m/e 368.1733).

A mixture of 80 mg (0.21 mmol) of nitrile **10** and a Raney nickel slurry (1 mL of 50%, pH 10), pretreated as in the above preparation of ester **8b**, in 10 mL of methanol and 10 mL of acetone was stirred and refluxed for 1.5 h. The suspension was filtered through a Celite pad and the filtrate evaporated to dryness. Chromatography of the residue on Florisil and elution with 9:1 hexane–ethyl acetate yielded 43 mg (61%) of colorless, amorphous, solid cyanide **12**: IR [NH] 3460 (m), [C=O] 1675 (s), 1610 (s) cm^{-1}; ^1H NMR δ 2.00 (d, 2, J = 6 Hz, $NCCH_2$), 2.15, 2.60 (m, 1 each, ring D CH_2), 3.62 (s, 3, OMe), 4.57 (br s, 1, NCH), 7.12 (t, 1, J = 7 Hz, H-11), 7.20 (t, 1, J= 7 Hz, H-10), 7.38 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12), 7.57 (s, 1, olefinic H); exact mass, m/e 321.1475 (calcd for $C_{19}H_{19}O_2N_3$ m/e 321.1477).

Tetracycles 19, 20, 21, and 22. A stirring solution of 364 mg (0.99 mmol) of ester **6** in 8 mL of trifluoroacetic acid was exposed to a slow stream of air and the stirring continued at room temperature for 2 h. Workup as above gave 325 mg (90%) of colorless, foamy ester **19**: UV λ_{max} 209 nm (log ϵ 4.15), 262 (4.02), 310 (4.23); IR [NH] 3460 (m), [C=O] 1720 (s), 1670 (s), 1605 (s) cm^{-1}; ^1H NMR δ 1.21 (t, 3, J = 7 Hz, Me), 2.41 (dd, 1, J = 9, 5 Hz, α-keto H), 2.70 (dd, 1, J = 15, 4 Hz, α-keto H), 3.71 (s, 3, OMe), 3.96 (m, 1, allyl H), 4.11 (q, 2, J = 7 Hz, OCH_2), 5.32 (d, 1, J = 5 Hz, olefinic H), 7.04 (t, 1, J = 7 Hz, H-11), 7.13 (t, 1, J = 7 Hz, H-10), 7.26 (d, 1, J = 7 Hz, H-9), 7.31 (s, 1, olefinic NCH), 7.42 (d, 1, J = 7 Hz, H-12); exact mass (M^+ – H), m/e 365.1476 (calcd for $C_{21}H_{21}O_4N_2$ m/e 365.1451).

The same reaction with 140 mg (0.33 mmol) of chloride **7** in 10 mL of trifluoroacetic acid afforded 133 mg (96%) of yellow, amorphous chloride **20**: UV λ_{max} 210 nm (log ϵ 4.34), 258 (4.06), 311 (4.46), 369 (4.23); IR [NH] 3460 (m), [C=O] 1700 (s), 1660 (s), 1610 (s), [C=C] 1590 (s), 1570 (m), 1550 (s) cm^{-1}; ^1H NMR δ 3.65 (s, 3, OMe), 4.68 (d, 1, J = 6 Hz, allyl H), 5.74 (d, 1, J = 6 Hz, olefinic H), 5.97 (d, 1, J = 15 Hz, acryl α-H), 7.04 (t, 1, J = 7 Hz, H-11), 7.19 (t, 1, J = 7 Hz, H-10), 7.40 (d, 1, J = 7 Hz, H-9), 7.51 (d, 1, J = 15 Hz, acryl β-H), 7.53 (d, 1, J = 7 Hz, H-12), 7.58 (s, 1, olefinic NCH).

The same reaction with 34 mg (0.086 mmol) of ester **8b** in 4 mL of trifluoroacetic acid led to 31 mg (91%) of yellow, foamy ester **21**: UV λ_{max} 208 nm (log ϵ 4.33), 311 (4.42), 318 (4.44), 391 (4.09); IR [NH] 3460 (m), [C=O] 1720 (s), 1670 (s), 1600 (s), [C=C] 1560 (s) cm^{-1}; ^1H NMR δ 1.26 (t, 3, J = 7 Hz, Me), 2.38 (dd, 1, J = 16, 8 Hz, α-keto H), 2.74 (dd, 1, J = 16, 3 Hz, α-keto H), 3.74 (s, 3, OMe), 3.95 (m, 1, allyl H), 4.15 (q, 2, J = 7 Hz, OCH_2), 5.25 (d, 1, J = 5 Hz, olefinic H), 5.64 (d, 1, J = 15 Hz, acryl α-H), 6.52 (s, 1, olefinic NCH), 7.10 (t, 1, J = 7 Hz, H-11), 7.20 (t, 1, J = 7 Hz, H-10), 7.31 (d, 1, J = 15 Hz, acryl β-H), 7.32 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12); exact mass, m/e 392.1722 (calcd for $C_{23}H_{24}O_4N_2$ m/e 392.1736).

The same reaction with 375 mg (1.05 mmol) of cyanide **9** in 10 mL of trifluoroacetic acid yielded 317 mg (87%) of yellow, foamy cyanide **22**: UV λ_{max} 206 nm (log ϵ 4.35), 309 (4.31), 318 (4.30), 389 (3.98); IR [NH] 3460 (m), [C≡N] 2240 (w), [C=O] 1680 (s), 1660 (s), [C=C] 1580 (s), 1550 (m) cm^{-1}; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, Me), 2.4–2.6 (m, 2, $NCCH_2$), 2.92 (t, 2, J = 6 Hz, benzyl Hs), 3.5–3.7 (m, 2, NCH_2), 3.85 (m, 1, allyl H), 4.22 (q, 2, J = 7 Hz, OCH_2), 5.20 (d, 1, J = 5 Hz, olefinic H), 5.54 (d, 1, J = 15 Hz, acryl α-H), 6.56 (s, 1, olefinic NCH), 7.10 (t, 1, J = 7 Hz, H-11), 7.20 (t, 1, J = 7 Hz, H-10), 7.32 (d, 1, J = 15 Hz, acryl β-H), 7.33 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12); exact mass (M^+ + H, by FAB), m/e 360.1706 (calcd for $C_{22}H_{22}O_2N_3$ m/e 360.1712).

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Synthesis of a Novel Thiadiazacyclazine

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Cyclazines, tricyclic compounds containing a central ring nitrogen and conjugated perimeter, continue to be the

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