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Synthesis of 2,3-Disubstituted Indoles via Claisen Ortho Ester Rearrangement: An Approach for the Synthesis of Vindorosine[1]

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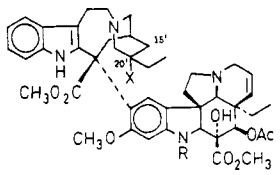
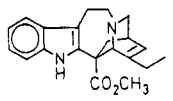
The preparation of **10**, a potentially useful synthon for the construction of the E ring of vindoline (**3**) and vindorosine (**4**), is detailed. The 2,3-disubstituted indoles **5** were prepared via Claisen ortho ester rearrangement of **15** with trimethyl orthoacetate, followed by selective amide reduction. Attempts to effect Dieckmann cyclization of **5** were not successful. Acylation of **20** with **19** provided **21**; however, thermolysis of **30** gave **31**. Acylation of **34** with **19** provided **35**, but attempts to transform **36** to **37** have not been successful.

The Cantharanthus alkaloids vinblastine (**1a**) and vincristine (**1b**) are used routinely for the treatment of various forms of human cancer.[3] It is now possible to prepare these compounds by the coupling of the Iboga alkaloid catharanthine (**2**) and the Aspidosperma alkaloid vindoline (**3**) to give anhydrovinblastine (**1c**) and subsequent functional group manipulation.[4]



1a R = Me, X = OH
1b R = CHO, X = OH
1c R = Me, $\Delta^{15'(20')}$



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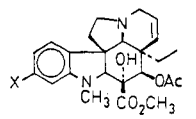
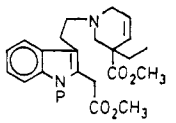


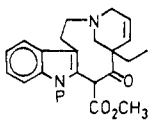
3 X = MeO
4 X = H

We have recently completed a short total synthesis of (±)-catharanthine.[5] Thus, the efficient total synthesis of vindoline (**3**)[6] could provide a fully synthetic route to **1**. We selected the closely related Aspidosperma alkaloid vindorosine (**4**)[7] as the target for our initial synthetic studies.

Our initial synthetic strategy called for the preparation of the 2,3-disubstituted indole **5**, Dieckmann cyclization to give the tetracyclic compound **6**, oxidative transannular cyclization to give the pentacyclic system **7**, and subsequent functional group manipulation. Several aspects of



5a P = CO_2Me
5b P = Ts
5c P = H



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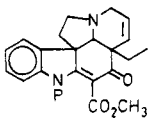

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(1) Synthesis Via Sigmatropic Rearrangements. 10. For previous paper in this series see: Raucher, S.; Chi, K.-W.; Jones, D. S. *Tetrahedron Lett.*, in press.

(2) (a) Recipient of NIH Research Career Development Award (1983–1988) and Fellow of the Alfred P. Sloan Foundation (1980–1984). (b) Chevron Graduate Fellow, 1983.

(3) (a) Neuss, N.; Johnson, I. S.; Armstrong, J. G.; Jansen C. J. *Adv. Chemother.* **1964**, *1*, 133. (b) Taylor, W. I.; Farnsworth, N. R. "The Catharanthus Alkaloids"; Marcell Dekker: New York, 1975. (c) Gerzon, K. In "Medicinal Chemistry"; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1981; Vol. 16. (d) Jewers, K. *Prog. Drug Res.* **1981**, *25*, 275. (e) Remers, W. A., Ed. "Antineoplastic Agents"; Wiley: New York, 1984.

(4) Reviews: (a) Kutney, J. P. *Lect. Heterocycl. Chem.* **1978**, *4*, 59. (b) Potier, P. *J. Nat. Prod.* **1980**, *43*, 72. (c) Lounasmaa, M.; Nemes, A. *Tetrahedron* **1982**, *38*, 223. Also see: (d) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. (e) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.

(5) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236.

(6) Total synthesis of (±)-vindoline: (a) Ando, M.; Buchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. (b) Kutney, J. P.; Bunzli-Trepp, U.; Chan, K. K.; de Souza, J. P.; Fujise, Y.; Honda, T.; Katsube, J; Klein, F. K.; Leutwiler, A.; Morehead, S.; Rohr, M; Worth, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 4220. (c) Andriamialisoa, R. A.; Langlois, N.; Langlois, Y. *J. Org. Chem.* **1985**, *50*, 961. Formal total synthesis involving the preparation of Buchi intermediates. (d) Ban, Y.; Sekine, Y.; Oishi, T. *Tetrahedron Lett.* **1978**, 151. (e) Takano, S.; Shishido, K.; Sato, M.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1699. (f) Takano, S.; Shishido, K.; Sato, M.; Yuta, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1978**, 943. (g) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909.

(7) Total synthesis of (±)-vindorosine: (a) Buchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299. (b) Buchi, G.; Matsumoto, K. E.; Nishimura, H. *Lect. Heterocycl. Chem.* **1972**, *1*, S-113. Formal total synthesis involving the preparation of Buchi intermediates: (c) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (d) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 1118. References 6b,d–g.

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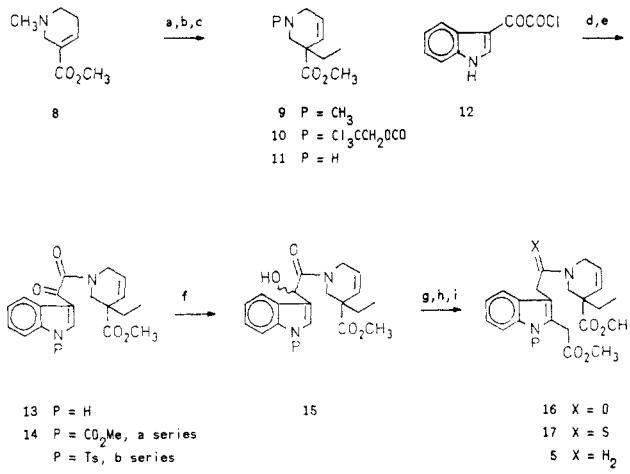
Scheme I[a]



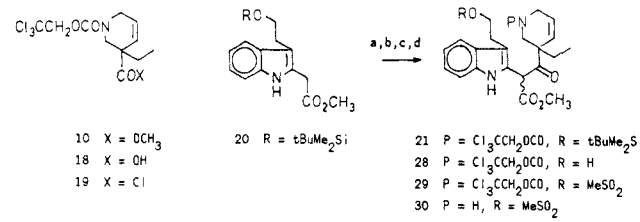
[a] (a) LDA, HMPA, THF, EtI; (b) Cl_3CCH_2OCOCl, C_6H_6, Δ; (c) Zn, AcOH; (d) propylene oxide; (e) $ClCO_2Me$ or TsCl, Et_3N; (f) $NaBH_4$; (g) $CH_3C(OCH_3)$, $ArCO_2H$, Δ; (h) P_4S_{10}, ultrasound; (i) Et_3OBF_4, CH_2Cl_2; $NaBH_4$, MeOH.

this strategy deserve comment. First, we have utilized the Claisen ortho ester rearrangement of indole-3-glycolamides in order to prepare several 2,3-disubstituted indoles, including the alkaloid secodine.[8] Second, although there are only a limited number of examples involving the formation of nine-membered rings by Dieckmann cyclization,[9] the constraints imposed by the tetrahydropyridine ring, as well as the disposition of the substituents at the 2- and 3-positions of the indole ring, should diminish unfavorable entropic factors. The Dieckmann cyclization still requires nucleophilic attack at an ester adjacent to a quaternary center,[10] and the strain imposed by the formation of the nine-membered ring may be significant. Finally, there is good precedent[11] for oxidative transannular cyclizations of tetracyclic systems related to **6**.

The Dieckmann precursors were prepared by conversion of arecoline (**8**) to the β,γ-unsaturated ester **9** using the conditions developed by Schlessinger[12] for the α-alkylation of simple α,β-unsaturated esters (Scheme I). Reaction of **9** with trichloroethyl chloroformate[13] provided **10**, which was converted to **11** by treatment with zinc in acetic acid.

Although a number of standard methods were examined for the preparation of the amide **13**, the best yields were obtained when a solution of freshly prepared indole-3-glyoxyl chloride (**12**)[14] in THF was added dropwise to a THF solution of freshly distilled **11** which contained 1.2 equiv of propylene oxide as an acid scavenger. The addition was stopped when the yellow color of **12** just persisted, and then the reaction mixture was quenched with

Scheme II[a]



[a] (a) 2 LDA, **19**; (b) HOAc; (c) $MeSO_2Cl$; (d) Zn, HOAc.

water with rapid stirring and refrigerated overnight to give **13** as colorless leaflets in 78% yield. The ^1H NMR of **13** indicated the presence of amide rotamers.

As previously discussed,[8] it is necessary to protect the indole nitrogen of glyoxamides such as **13** with an electron-withdrawing group both to facilitate reduction to the glycolamide and to allow these glycolamides to undergo the Claisen ortho ester rearrangement. Reaction of **13** with methyl chloroformate gave **14a**. Reduction of **14a** with 1.0 equiv of $NaBH_4$ in methanolic THF at 0 °C followed by quenching at 0 °C with saturated aqueous NH_4Cl gave the glycolamide **15a**. Care must be taken at this stage since the use of excess $NaBH_4$ can cleave the methyl carbamate group from the indole nitrogen.

The crucial Claisen ortho ester rearrangement was conducted by heating **15a** with 50 equiv of trimethyl orthoacetate and 0.15 equiv of 2,4,6-trimethylbenzoic acid, first at 130–150 °C while allowing methanol to distill off as produced and then at 210 °C for 4 h under an atmosphere of argon. Purification of the residue by flash chromatography gave **16a** in 65% yield. Again, the ^1H NMR indicated the presence of rotamers.

Since **16a** contains two methylene groups of comparable acidity, one adjacent to the ester carbonyl and the other adjacent to the amide carbonyl, which could be deprotonated under the basic conditions of the Dieckmann cyclization, we decided to convert the amide **16a** to a tertiary amine before attempting the Dieckmann cyclization. The amine **5a** contains only one acidic methylene group. In addition, possible constraints imposed by the presence of amide rotamers are absent for the amine **5a**. Conversion of **16a** to **5a** requires a selective reduction method that would not affect the ester groups, the isolated double bond, or the indole ring. This transformation was effected by utilizing our amide reduction procedure.[15] The amide **16a** was transformed to the corresponding thioamide **17a** by using P_4S_{10} in the presence of ultrasonic irradiation,[16] and **17a** was alkylated with $Et_3O^+BF_4^-$ and then treated with $NaBH_4$ in methanol to give the corresponding tertiary amine **5a** in 46% overall yield from **16a**. Treatment of **5a** with NaOMe in methanol gave the indole **5c**.

The *N*-tosylindole **5b** was prepared in an analogous fashion. Reaction of **13** with *p*-toluenesulfonyl chloride gave **14b**. Reduction of **14b** with $NaBH_4$ gave **15b**. Claisen ortho ester rearrangement of **15b** with trimethyl orthoacetate gave crude **16b**, which was reduced[15] to provide **5b**. Reaction of **5b** with Mg in buffered methanol gave **5c**, identical with that previously obtained from **5a**.

Since the carbamate group in **5a** proved to be rather labile toward basic conditions, the Dieckmann cyclization was examined extensively only with **5b** and **5c**. Attempts to effect Dieckmann cyclization of **5b** or **5c** under a variety of conditions proved unsuccessful. Starting material was

(8) (a) Raucher S.; Lui, A. S.-T. *J. Am. Chem. Soc.* **1978**, *100*, 4902. (b) Raucher, S.; Macdonald, J. E.; Lawrence, R. F. *J. Am. Chem. Soc.* **1981**, *103*, 2419. (c) Raucher S.; Lawrence, R. F. *Tetrahedron* **1983**, *39*, 3731.

(9) Schaefer, J. P.; Bloomfield, J. J. *Org. React. (N.Y.)* **1967**, *15*, 1.

(10) For an examination of the steric demand associated with similar acylation reactions, see: (a) Lion, C.; Dubois, J.-E. *J. Chem. Res. Synop.* **1980**, 44. (b) Lion C.; Dubois, J.-E. *J. Chem. Res. Miniprint* **1980**, 565. (c) Lion, C. *C. R. Seances Acad. Sci. Ser. C.* **1978**, *286*, 401.

(11) For related transannular cyclizations, see: (a) Kutney, J. P.; Piers, E.; Brown, R. T. *J. Am. Chem. Soc.* **1970**, *92*, 1700. (b) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708. (c) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1971**, *93*, 5930.

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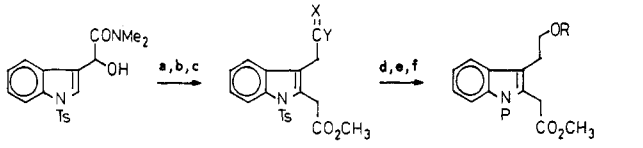
(15) (a) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, 4061. For a related procedure, see: (b) Sundberg, R. J.; Walters, C. P.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 3730.

(16) Raucher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558.

Scheme III[a]



22 23 X = O, Y = NMe_2 24 X = S, Y = NMe_2 25 X = O, Y = SEt 26 P = Ts, R = H 27 P = Ts, R = $tBuMe_2Si$ 20 P = H, R = $tBuMe_2Si$

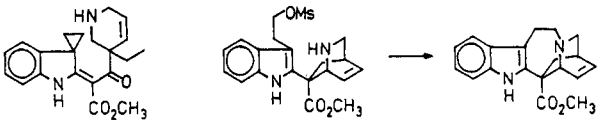
[a] (a) $CH_3C(OCH_3)_3$, Δ; (b) P_2S_5; (c) $Et_3O^+BF_4^-$, H_3O^+; (d) $NaBH_4$; (e) *t*-$BuMe_2SiCl$; (f) Mg.

recovered under mild reaction conditions, whereas extensive decomposition occurred under more vigorous reaction conditions. The results of these studies are summarized in the Experimental Section.

We then examined an alternate strategy for the synthesis of vindorosine. This strategy involved the acylation of the 3-substituted indole-2-acetic acid ester **20** with the acid chloride **19** to give the β-keto ester **21**, cyclization to the tetracylclic system **6**, and appropriate functional group manipulations (Scheme II). The formation of β-keto esters by the acylation of enolates with acid chloride has been reported.[17] This strategy has several advantages over the previous approach involving Dieckmann cyclization. The acylation would be performed at an earlier stage in the sequence and with a reactive acid chloride. In addition, the constraints imposed by the formation of a nine-membered ring would be absent during the acylation step. Finally, the cyclization of **30** to **6** would involve the formation of a carbon–nitrogen bond rather than a carbon–carbon bond.

Hydrolysis of **10** to the carboxylic acid **18** and treatment with thionyl chloride provided **19**. The acid chloride **19** was unstable to storage, and it was freshly prepared for use in the acylation reactions. The indole **20** was prepared from **23**, which was obtained by Claisen ortho ester rearrangement of **22** with trimethyl orthoacetate[8a] (Scheme III). Transformation of **23** to **20** required a method which would not reduce the ester. The amide **23** was converted to the thioamide **24** by using P_2S_5 and ultrasonic irradiation[16] and then treated with $Et_3O^+BF_4^-$ and aqueous acid[18] to afford **25**. The thio ester **25** was reduced with methanolic $NaBH_4$ to provide **26**. A related reduction procedure for thio esters has been published.[19] The alcohol **26** was then protected as the *tert*-butyldimethylsilyl ether **27**. Brief treatment of **27** with magnesium metal in buffered methanol gave **20**.[20]

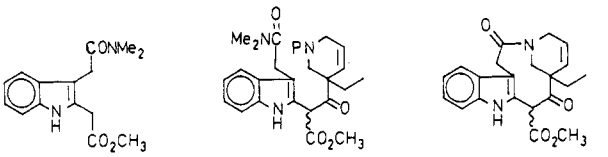
Reaction of **20** with 2 equiv of LDA at −78 °C followed by addition of **19** provided the β-keto ester **21** as mixtures of diastereomers in 74% yield. Treatment of **21** with aqueous acetic acid gave **28**, reaction of **28** with $MeSO_2Cl$[21] gave **29**, and removal of the carbamate group with zinc in acetic acid provided **30** as a mixture of diastereomers. We hoped to convert **30** to **6** in a manner analogous to that reported by Das[22] for the cyclization of **32** to **33**. However,



31 32 33

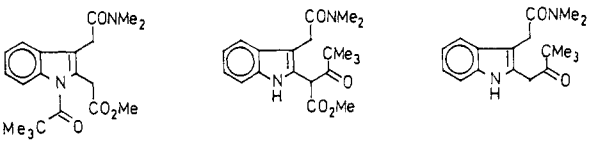
when a dilute solution of **30** in toluene was heated at 105 °C, **31** was obtained. The formation of spiro[cyclopropane-1,3′-indolenine] from tryptophyl bromide has been reported.[23] The acidity of the β-keto ester proton in **30** should serve to promote the spirocyclization to **31**.

In order to circumvent the above difficulty, we decided to examine an alternate strategy which involved the acylation of **34** with **19** to give **35**, followed by cyclization to **37**. Treatment of **23** with magnesium metal in buffered methanol afforded **34**.



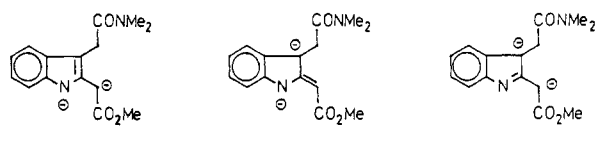
34 35 P = Cl_3CCH_2OCO 36 P = H 37

The amide **34** has two acidic methylene groups, as well as the indole NH. For this reason, model acylation studies using trimethylacetyl chloride and anions generated from **34** were conducted. When **34** was treated with 1 equiv of LDA at −78 °C and then reacted with trimethylacetyl chloride, the N-acylated product **38** was obtained. In

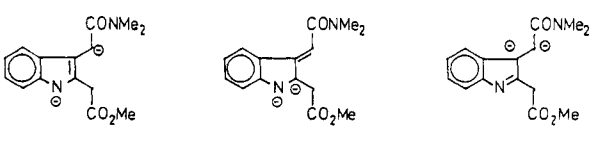


38 39 40

contrast, when **34** was treated with 2 equiv of LDA at −78 °C and then reacted with trimethylacetyl chloride, the β-keto ester **39** was obtained. Hydrolysis and decarboxylation of **39** provided **40**. These results suggest that the indole NH is the most acidic proton and that the dianion I was being generated when 2 equiv of LDA are used. It is noteworthy that no products resulting from acylation of the dianion II were observed. Examination of resonance



Ia Ib Ic



IIa IIb IIc

(17) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953.
(18) Chaturvedi, R. K.; Schmir, G. L. *J. Am. Chem. Soc.* **1969**, *91*, 737.
(19) Liu, H.-J.; Bukownik, R. R.; Pednekar, P. R. *Synth. Commun.* **1981**, *11*, 599.
(20) For other approaches to 3-substituted indole-2-acetic esters, see: (a) Kutney, J. P. *Heterocycles* **1977**, *7*, 593. (b) Kutney, J. P.; Badger, R. A.; Beck, J. F.; Bosshardt, H.; Matough, F. S.; Ridaura-Sanz, V. E.; So, Y. H.; Sood, R. S.; Worth, B. R. *Can. J. Chem.* **1979**, *57*, 289. (c) Kutney, J. P.; Karton, Y.; Kawamura, N.; Worth, B. R. *Can. J. Chem.* **1982**, *60*, 1269. (d) Wenkert, E.; Dave, K. G.; Gnewuch, C. T.; Sprague, P. W. *J. Am. Chem. Soc.* **1968**, *90*, 5251.
(21) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
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(23) (a) Closson, W. D.; Roman, S. A.; Kwiathowski, G. T.; Corwin, D. A. *Tetrahedron Lett.* **1966**, 2271. (b) Julia, M.; Sliwa, H.; Caubere, P. *Bull. Soc. Chim. Fr.* **1966**, 3359. (c) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

structures for I and II provides a possible explanation for this result. The resonance structures Ib and Ic contain a stabilized benzylic anion, whereas resonance structures IIb and IIc have negative charges on adjacent atoms.

Reaction of **34** with 2 equiv of LDA at −78 °C and addition of **19** provided the β-keto ester **35** as a mixture of two diastereomers in 53% yield. The carbamate protecting group was then cleaved with activated zinc in acetic acid to give the amine **36**. To date, a limited number of attempts to cyclize **36** to **37** have not been successful.

The above studies describe the synthesis of several 2,3-disubstituted indoles by the Claisen ortho ester rearrangement of indole-3-glycolamides.[8] The tetrahydropyridine **10**, a potentially useful synthon for the construction of the E ring of vindorosine (**4**) and vindoline (**3**), was prepared. Dieckmann cycylization of **5** to **6** could not be effected. Acylation of **20** with the acid chloride **19** provided **21**; however, thermolysis of **30** gave **31** rather than **6**. Selective acylation of **34** with **19** gave **35**. We plan to further examine the cyclization of **36**, or related derivatives, to tetracyclic systems such as **37**.

Experimental Section

General Data. ^{1}H NMR spectra were recorded on a Varian EM-360L (60 MHz) instruments with Me_4Si as an internal standard. Chemical shifts are reported in ppm downfield from Me_4Si and coupling constants are reported in Hz. IR spectra were recorded on a Beckman Acculab 4 instrument. Mass spectra were recorded on a VG 7070 instrument or an HP 5985 GC/MS instrument by direct insertion. HPLC was carried out on a Varian Model 5000 liquid chromatograph with a Supelco (5 μm, 25 cm) reversed-phase column. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. THF and ether were distilled from sodium–benzophenone ketyl immediately prior to use. Chloroform and methylene chloride were distilled from P_2O_5 and stored in brown bottles. Diisopropylamine, HMPA, benzene, toluene, and xylenes were distilled from CaH_2. Methanol was distilled from $Mg(OMe)_2$. All glassware was either dried in a 120 °C oven for several hours or flame-dried and then allowed to cool under a slight positive pressure of argon, just prior to use. Reactions were followed by TLC on Merck glass silica gel 60 plates. Flash chromatography[24] was performed with Merck silica gel 60 (230–400 mesh).

1-Methyl-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (9). Arecoline hydrobromide[25] was dissolved in an excess of aqueous $NaHCO_3$ solution then extracted six times with ether. The combined extracts were dried ($MgSO_4$), and the solvents were evaporated under vacuum to give arecoline (**8**) as the free amine. A solution of diisopropylamine (6.09 mL, 0.043 mol) in THF (80 mL) was cooled in an ice bath, and a 2.5 M solution of *n*-BuLi (17.2 mL, 0.043 mol) in hexane was added slowly. This solution was cooled to −78 °C, HMPA (7.52 mL, 0.043 mol) was added, the resulting solution was mixed vigorously for 5 min, and then a solution of freshly prepared **8** (6.56 g, 0.042 mol) in THF (40 mL) was added quickly. The reaction mixture was stirred for an additional 5 min and ethyl iodide (3.55 mL, 0.044 mol) was added neat, in one portion. The solution was stirred at −78 °C for another 90 min, then warmed slowly to 20 °C, and stirred for an additional 5 h. The solvents were evaporated under vacuum, and the resulting mixture was diluted with ether. Water was added, the layers were separated, and the aqueous layer was extracted with another two portions of ether. The combined extracts were washed four times with water and then once with brine and dried ($MgSO_4$), then the solvents were evaporated under vacuum, and the residue was vacuum distilled [80 °C (0.75 mm)] to give **9** (6.3 g, 81%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7, 3 H), 1.64 (q, J = 7, 2 H), 2.14 (d, J = 11, 1 H), 2.30 (s, 3 H), 2.7–3.2 (m, 3 H), 3.78 (s, 3 H), 5.8 (m, 2 H); IR (neat) 2970, 2770, 1740, 1470, 1250, 1210, 1170, 1150, 1120 cm^{-1}; HREIMS, calcd for $C_{13}H_{17}NO_2$ 183.1259, found 183.1255.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(25) Available from Sigma Chemical Co.

1-[(β,β,β-Trichloroethoxy)carbonyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (10). A mixture of **9** (1.83 g, 0.01 mol), K_2CO_3 (1.38 g, 0.01 mol), and benzene (20 mL) was heated at 90 °C for 5 min. The heating bath was removed, and 2,2,2-trichloroethyl chloroformate (2.75 mL, 0.02 mol) was added slowly. The mixture was then heated at 90 °C for 6 h with an oil bubbler attached, and then the cooled mixture was filtered through sintered glass under suction. The solids were washed with several small portions of CH_2Cl_2, the filtrates were combined, and the solvents were evaporated under vacuum. Unreacted trichloroethyl chloroformate was removed by Kugelrohr distillation [160 °C (0.2 mm)], and the residue was purified by flash chromatography (CH_2Cl_2) to give **10** (2.77 g, 81%) as a clear viscous liquid, which crystallized in the freezer (mp 34–38 °C): ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7, 3 H), 1.67 (q, J = 7, 2 H), 3.70 (s, 3 H), 3.8 (m, 2 H), 4.0 (m, 2 H), 4.7–4.9 (m, 2 H), 5.6–6.1 (m, 2 H); IR (neat) 1730, 1440, 1240, 1210, 1130, 720 cm^{-1}.

3-Ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (11). To a solution of **10** (971 g, 2.82 mmol) in absolute MeOH (6 mL) was added activated Zn (3.7 g). The mixture was stirred vigorously, and glacial acetic acid (1.5 mL) was added in portions. After initial bubbling had subsided, the mixture was heated at 60 °C for 10 min, cooled, and filtered, and then the solids were washed with a few small portions of ether. The combined filtrates were made basic by slow addition of 30% aqueous NH_4OH and then extracted three times with ether. The combined extracts were dried ($MgSO_4$), the solvents were evaporated under vacuum, and the residue was purified by Kugelrohr distillation [120–122 °C (0.25 mm)] to give **11** (344 mg, 72%) as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7, 3 H), 1.60 (q, J = 7, 2 H), 2.0 (m, 1 H), 2.55 (d, J = 13, 1 H), 3.2 (m, 2 H), 3.42 (d, J = 13, 1 H), 3.68 (s, 3 H), 5.8 (m, 2 H); IR (neat) 3700–2800, 1740, 1470, 1250, 1210, 1140 cm^{-1}; HRCIMS, calcd for (M^+ + 1) $C_9H_{16}NO_2$ 170.1181, found 170.1182.

1-(2-Indol-3-ylglyoxyloyl)-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (13). To a solution of freshly distilled **11** (344 mg, 2.03 mmol) and propylene oxide (0.175 mL, 2.5 mmol) in THF (4 mL) was added a solution of freshly prepared indole-3-glyoxyl chloride (**12**),[14] dissolved in a minimum amount of THF, dropwise with stirring until the yellow color of **12** just persisted. The mixture was stirred for 15 min, water (20 mL) was added, and the mixture was stirred vigorously for 5 min and then refrigerated overnight. The mixture was filtered, and the solids were washed with water and dried under vacuum to give **13** (538 mg, 78%) as colorless leaflets (mp 189–190 °C). The proton NMR of **13** indicates the presence of amide rotamers: ^{1}H NMR (Me_2SO-d_6) δ 0.60 (t, J = 7) and 0.88 (t, J = 7) (total 3 H), 1.5 (m, 2 H), 3.2–4.2 (m, 7 H), 5.7–6.0 (m, 2 H), 7.1–7.7 (m, 3 H), 7.9–8.3 (m, 2 H), 12.3 (br s, 1 H); IR (KBr) 3150, 3100, 1730, 1645, 1620, 1530, 1450 cm^{-1}; HREIMS, calcd for $C_{19}H_{20}N_2O_4$ 340.1423, found 340.1417.

1-[2-(1-Carbomethoxyindol-3-yl)glyoxyloyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (14a). A suspension of **13** (340 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was treated with methyl chloroformate (93 μL, 1.2 mmol) and cooled in an ice bath, and then Et_3N (0.21 mL, 1.5 mmol) was added dropwise. The mixture was stirred for 3 min, the ice bath was removed, the mixture was stirred an additional 50 min, and 3 N aqueous HCl (5 mL) was added. The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4), and the solvents were evaporated under vacuum to give a white foam, which was recrystallized from ether to provide **14a** (355 mg, 89%) as a white powder (mp 120.5–122 °C). The proton NMR indicates the presence of amide rotamers: ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7) and 0.96 (t, J = 7) (total 3 H), 1.6 (m, 2 H), 3.42 (s) and 3.76 (s) (total 3 H), 3.8–4.3 (m, 4 H), 4.06 (s, 3 H), 5.9 (m, 2 H), 7.1–7.6 (m, 2 H), 7.9–8.6 (m, 3 H); IR (KBr) 1775, 1740, 1665, 1650, 1550, 1460, 1450 cm^{-1}; HREIMS, calcd for $C_{21}H_{22}N_2O_6$ 398.1478, found 398.1500.

1-[2-(1-Carbomethoxyindol-3-yl)glycolyloyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (15a). To a solution of **14a** (310 mg, 0.78 mmol) in THF (2 mL) and MeOH (2 mL) cooled in an ice bath was added $NaBH_4$ (15 mg, 0.39 mmol), and the resulting mixture was stirred with an oil bubbler attached for 10 min. The reaction was quenched at

0 °C with aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were evaporated under vacuum to give **15a** (312 mg, 100%) as a white foam: ^1H ($CDCl_3$) δ 0.5–1.1 (m, 3 H), 1.3–2.0 (m, 2 H), 3.4–5.0 (m, 5 H), 3.73 (s, 3 H), 4.00 (s, 3 H), 5.3–6.1 (m, 3 H), 7.3–8.6 (m, 5 H); IR (neat) 3600–3000, 1750, 1650, 1470 cm^{-1}; HREIMS, calcd for $C_{21}H_{24}N_2O_6$ 400.1634, found 400.1625.

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)-2-oxoethyl]-1-carbomethoxyindole-2-acetic Acid, Methyl Ester (16a). A solution of **15a** (312 mg, 0.78 mmol), trimethyl orthoacetate (7 mL), and 2,4,6-trimethylbenzoic acid (10 mg, 0.06 mmol) were combined and heated at 110–130 °C for 10 min in a 100-mL flask equipped with a short-path distillation head, and MeOH was allowed to distill off as formed. Another portion of 2,4,6-trimethylbenzoic acid (10 mg, 0.06 mmol) was added, and heating was resumed at 130–140 °C for 6 min, again allowing MeOH to distill off as formed. The distillation head was replaced by a reflux condenser and then the solution was heated at 210 °C for 4 h. Most of the remaining trimethyl orthoacetate was distilled off under aspirator vacuum. The cooled residue was dissolved in CH_2Cl_2, washed with 5% aqueous HCl, and dried (Na_2SO_4), and the solvents were evaporated under vacuum to give the crude product, which was purified by flash chromatography (eluting with 10% EtOAc–CH_2Cl_2 then with 20% EtOAc–CH_2Cl_2) to give **16a** (227 mg, 65%) as a pale foam: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7, 3 H), 1.59 (q, J = 7, 2 H), 2.80 (d, J = 14, 1 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 3.97 (s, 3 H), 3.5–4.7 (m, 7 H), 5.8 (m, 2 H), 7.2–8.3 (m, 4 H); IR (KBr) 1750, 1650, 1475 cm^{-1}; HREIMS, calcd for $C_{24}H_{28}N_2O_7$ 456.1896, found 456.1930.

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)-2-thiooxoethyl]-1-carbomethoxyindole-2-acetic Acid, Methyl Ester (17a). To a solution of **16a** (227 mg, 0.5 mmol) in THF (5 mL) was added P_4S_{10} (222 mg, 0.5 mmol) and the mixture treated with ultrasonic irradiation while stirring[16] for 1 h. Another portion of P_4S_{10} (222 mg, 0.5 mmol) was added, and ultrasonic irradiation and stirring were continued for an additional 3 h. The resulting mixture was filtered through Celite under suction, and the solids were washed with several small portions of CH_2Cl_2. The filtrates were combined, the solvents were evaporated under vacuum, and the residue was immediately purified by flash chromatography (eluting with CH_2Cl_2 and then with 3% EtOAc–CH_2Cl_2) to give **17a** (161 mg, 68%) as a pale yellow foam: ^1H NMR ($CDCl_3$) δ 0.65 (t, J = 7, 3 H), 1.3–1.9 (m, 2 H), 2.90 (d, J = 13, 1 H), 3.7 (m, 6 H), 3.97 (s, 3 H), 4.0–4.8 (m, 6 H), 5.1–5.6 (m, 1 H), 5.8 (m, 2 H), 7.2–8.2 (m, 4 H); IR (KBr) 1745, 1730, 1470, 1450 cm^{-1}; HREIMS, calcd for $C_{24}H_{28}N_2O_6S$ 472.1668, found 472.1669.

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)ethyl]-1-carbomethoxyindole-2-acetic Acid, Methyl Ester (5a). To a solution of **17a** (135 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) was slowly added a 1 M solution of $Et_3O^+BF_4^-$ in CH_2Cl_2 (0.6 mL). The solution was stirred for 1 h, the solvents were evaporated under vacuum, the residue was dissolved in MeOH (4 mL) and cooled in an ice bath, and then $NaBH_4$ (150 mg, 4 mmol) was added in small portions over 5 min. The reaction mixture was stirred for 25 min, quenched by addition of aqueous NH_4Cl, and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated under vacuum, and the residue was purified by flash chromatography (eluting with 15% EtOAc–CH_2Cl_2 and then with 30% EtOAc–CH_2Cl_2) to give **5a** (86 mg, 67%) as a viscous liquid: ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7, 3 H), 1.69 (q, J = 7, 2 H), 2.27 (d, J = 11, 1 H), 2.4–3.1 (m, 6 H), 3.26 (d, J = 11, 1 H), 3.72 (s, 6 H), 3.96 (s, 3 H), 4.0 (s, 2 H), 5.8 (m, 2 H), 7.2–7.7 (m, 3 H), 8.0–8.3 (m, 1 H); IR (neat) 1750, 1470, 1450 cm^{-1}; HREIMS, calcd for $C_{24}H_{30}N_2O_6$ 442.2104, found 442.2111.

1-[2-(1-((4-Methylphenyl)sulfonyl)indol-3-yl)glyoxyloyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (14b). To a suspension of **13** (6.72 g, 19.8 mmol) in CH_2Cl_2 (60 mL) was added toluenesulfonyl chloride (3.81 g, 20 mmol) followed by Et_3N (3.5 mL, 25 mmol) dropwise. The mixture was stirred for 60 h, washed with 5% aqueous HCl and brine, and dried (Na_2SO_4). The solvents were evaporated under vacuum to give **14b** (10.46 g, 100%) as a white foam (mp 69–74 °C). The NMR indicates the presence of amide rotamers: ^1H NMR ($CDCl_3$) δ 0.72 (t, J = 7, 3 H), 1.3–1.9 (m, 2 H), 2.30 (s, 3 H), 3.41 (s) and 3.83 (s) (total 3 H), 3.2–5.7 (m, 4 H), 5.9 (m, 2 H), 7.1–7.6 (m, 4 H), 7.7–8.2 (m, 3 H), 8.2–8.6 (m, 2 H).

1-[2-(1-((4-Methylphenyl)sulfonyl)indol-3-yl)glycolyloyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid, Methyl Ester (15b). To a solution of **14b** (10.46 g, 20 mmol) in THF (50 mL) and MeOH (50 mL) was added $NaBH_4$ (1.2 g, 32 mmol) in portions over 5 min. The mixture was stirred for 20 min, aqueous NH_4Cl was added, and the resulting mixture was extracted three times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated under vacuum to provide **15b** (10.72 g, 100%) as a white foam, which was recrystallized from toluene–hexanes to give a white powder (mp 64 °C): ^1H NMR ($CDCl_3$) δ 0.5–1.1 (m, 3 H), 1.2–1.9 (m, 2 H), 2.30 (s, 3 H), 3.7 (m, 3 H), 3.2–4.0 (m, 4 H), 4.4–4.7 (m, 1 H), 5.4–6.1 (m, 3 H), 7.0–7.5 (m, 4 H), 7.5–8.2 (m, 5 H).

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)-2-oxoethyl]-1-[(4-methylphenyl)sulfonyl]indole-2-acetic Acid, Methyl Ester (16b). A solution of **15b** (10.72 g, 20 mmol), trimethyl orthoacetate (50 mL), and 2,4,6-trimethylbenzoic acid (177 mg, 1.08 mmol) was heated at 140 °C for 30 min in a 250-mL flask equipped with a short-path distillation head allowing MeOH to distill off as formed. The distillation head was replaced by a reflux condenser and then the solution was heated at 200 °C for 4 h. Most of the trimethyl orthoacetate was distilled off under aspirator vacuum while still hot. The cooled residue was dissolved in CH_2Cl_2, washed with 5% aqueous HCl, and dried ($MgSO_4$), the solvents were evaporated under vacuum, and then the residue was purified by flash chromatography (eluting with 40% ether–hexanes, 50% ether–hexanes, 60% ether–hexanes, and then with 80% ether–hexanes) to give impure **16b** (8.58 g): ^1H NMR ($CDCl_3$) δ 0.5–1.0 (m, 3 H), 1.2–1.8 (m, 2 H), 2.3 (m, 3 H), 2.8 (m, 1 H), 3.7 (m, 6 H), 3.5–4.4 (m, 5 H), 5.8 (m, 2 H), 7.0–7.5 (m, 4 H), 7. (m, 3 H), 7.9–8.2 (m, 1 H); IR (neat) 1730, 1665, 1645, 1455 cm^{-1}.

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)-2-thiooxoethyl]-1-[(4-methylphenyl)sulfonyl]indole-2-acetic Acid, Methyl Ester (17b). Impure **16b** (1.5 g) dissolved in THF (50 mL) and P_4S_{10} (623 mg, 1.4 mmol) was treated with ultrasonic irradiation while stirring[16] for 15 min. Another portion of P_4S_{10} (623 mg, 1.4 mmol) was added, and ultrasonic irradiation with stirring was resumed for 90 min. A final portion of P_4S_{10} (623 mg, 1.4 mmol) was added, and ultrasonic irradiation with stirring was resumed for 3 h more. The reaction mixture was cooled, ether (30 mL) was added, and the mixture was filtered through celite under suction. The solids were washed with several small portions of CH_2Cl_2, the filtrates were combined, the solvents were evaporated under vacuum, and then the residue was purified by flash chromatography (ether) to give impure **17b** (860 mg): ^1H NMR ($CDCl_3$) δ 0.56 (t, J = 6, 3 H), 1.2–1.8 (m, 2 H), 2.30 (s, 3 H), 2.9 (m, 1 H), 3.67 (s, 6 H), 3.6–4.7 (m, 5 H), 5.8 (m, 2 H), 7.1–7.5 (m, 4 H), 7.5–7.9 (m, 3 H), 8.0–8.3 (m, 1 H).

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)ethyl]-1-[(4-methylphenyl)sulfonyl]indole-2-acetic Acid, Methyl Ester (5b). To a solution of impure **17b** (860 mg, 1.51 mmol) in CH_2Cl_2 (5 mL) was slowly added a 1 M solution of $Et_3O^+BF_4^-$ in CH_2Cl_2 (2.26 mL). The solution was stirred for 30 min, the solvents were evaporated under vacuum, the residue was dissolved in MeOH (20 mL) and cooled with an ice bath, and then $NaBH_4$ (454 mg, 12 mmol) was added in portions over 1 min. The reaction mixture was stirred for 2 min, the cooling bath was removed, and the reaction was stirred for 30 min. The reaction was quenched by addition of aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), evaporated under vacuum, and then purified by flash chromatography (eluting with 20% EtOAc–hexanes, 30% EtOAc–hexanes, and then 100% EtOAc) to give **5b** (421 mg, 52%). Reversed-phase HPLC (30% H_2O–CH_3CN) showed this material to be greater than 98% pure: ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7, 3 H), 1.65 (q, J = 7, 2 H), 2.30 (s, 3 H), 2.1–3.7 (m, 8 H), 3.70 (s, 6 H), 4.09 (s, 2 H), 5.80 (s, 2 H), 7.1–7.9 (m, 7 H), 8.0–8.3 (m, 1 H); IR (neat) 1745, 1460, 1375, 1180, 1135, 745, 670 cm^{-1}; CIMS, m/e 539 ($M^+ + 1$), 182.

3-[2-(3-Ethyl-1,2,3,6-tetrahydro-3-carbomethoxypyridinyl)ethyl]indole-2-acetic Acid, Methyl Ester (5c). Method A. A solution of **5a** (91 mg, 0.2 mmol) in MeOH (2 mL) was cooled in an ice bath, and NaOMe (54 mg, 1.0 mmol) was

added. The reaction was stirred for 1 min, the cooling bath was removed, the reaction was stirred for 7 min, and then aqueous NH_4Cl was added. The resulting mixture was extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were evaporated under vacuum to give the indole **5c** (77 mg, 100%) as a viscous liquid.

Method B. Mg metal (130 mg) was soaked for 1 min in 5% methanolic $HgCl_2$ (10 mL) and then transferred to a mixture of the **5b** (720 mg, 1.34 mmol) and KH_2PO_4 (801 mg, 5.9 mmol) in MeOH (10 mL). The mixture was stirred vigorously for 1 h and filtered through Celite under suction, and the solids were washed with MeOH. The filtrates were combined, the solvents were evaporated under vacuum, the residue was dissolved in CH_2Cl_2, washed with water and dried (Na_2SO_4), and the solvents were evaporated under vacuum to give the indole **5c** (475 mg, 92%), identical with **5c** prepared by method A: ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7, 3 H), 1.76 (q, J = 7, 2 H), 2.33 (d, J = 11, 1 H), 2.5–3.2 (m, 6 H), 3.33 (d, J = 11, 1 H), 3.78 (s, 6 H), 3.85 (s, 2 H), 5.9 (m, 2 H), 7.0–7.8 (m, 4 H), 8.7 (br s, 1 H); IR (neat) 3400, 1745, 1470 cm^{-1}; HREIMS, calcd for $C_{22}H_{28}N_2O_4$ 384.2049, found 384.2073.

Attempted Dieckmann Cyclization of 5b. The following reaction conditions led to the recovery of **5b**: LDA (2 equiv) in THF (5×10^{-3} M), –78 to +20 °C; LDA (2 equiv) in THF–HMPA (9×10^{-3} M), –78 to +20 °C; $NaN(SiMe_3)_2$ (2 equiv) in ether (2×10^{-3} M), –78 to 0 °C; NaOMe (2 equiv) in ether (5×10^{-3} M), –78 to +20 °C; NaOMe (20 equiv) in MeOH (4×10^{-3}), 20–70 °C; NaH (10 equiv) in THF (1×10^{-3} M), 20 °C; *t*-AmONa (2 equiv) in ether (5×10^{-3} M), –78 °C; *t*-AmONa (2 equiv) in THF (2×10^{-3} M), –78 °C, dual syringe pump addition of substrate and base; *t*-AmONa (2 equiv) in THF (2×10^{-3} M), 20 °C, dual syringe pump addition of substrate and base. The following reaction conditions led to extensive decomposition of **5b** and a complex mixture of products: $NaN(SiMe_3)_2$ (4 equiv) in THF (1×10^{-3} M), –78 to +20 °C; KH (10 euiv) in THF (5×10^{-3} M), 20 °C; NaOMe (2 equiv) in THF (5×10^{-3} M), –78 to +20 °C; *t*-BuOK (1 equiv) in *t*-BuOH (2×10^{-3} M), 20 °C; *t*-BuONa (4 equiv) in *t*-BuOH (9×10^{-3} M), 20 °C; *t*-AmONa (2 equiv) in toluene (6×10^{-3} M), –78 to +20 °C; *t*-AmONa (2 equiv) in ether (5×10^{-3} M), –78 to +20 °C; *t*-AmONa (2 equiv) in THF (7×10^{-3} M), –78 °C.

Attempted Dieckmann Cyclization of 5c. The following reaction conditions led to the recovery of **5c**: LDA (1.2 equiv) in THF (3×10^{-3} M), –78 to 0 °C, **5c** added by syringe pump. The following reaction conditions led to extensive decomposition of **5c** and a complex mixture of products: $NaN(SiMe_3)_2$ (6 equiv) in benzene (3×10^{-3} M), 80 °C, **5c** added by syringe pump; NaH (6 equiv) in THF (3×10^{-2} M), 20 °C, **5c** added by syringe pump.

1-[(β,β,β-Trichloroethoxy)carbonyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid (18). A 1.5 M solution of NaOH in water (4 mL) was added to a solution of **10** (1.034 g, 3.0 mmol) in THF (4 mL), and the mixture was stirred vigorously for 5 days. The reaction mixture was washed twice with CH_2Cl_2, and the aqueous phase was acidified with excess 10% aqueous HCl and extracted three times with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and evaporated under vacuum to give **18** (778 mg, 79%) as a viscous liquid: ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 6, 3 H), 1.73 (q, J = 6, 2 H), 3.7–4.2 (m, 4 H), 4.82 (m, 2 H), 5.7–6.2 (m, 2 H), 11.0 (br s, 1 H); IR (neat) 3400–2800 (broad), 1730, 1450, 1255, 1145, 715 cm^{-1}.

1-[(β,β,β-Trichloroethoxy)carbonyl]-3-ethyl-1,2,3,6-tetrahydro-3-pyridinecarboxylic Acid Chloride (19). Thionyl chloride (0.60 mL, 8.2 mmol) was slowly added to a solution of **18** (674 mg, 2.04 mmol) in CH_2Cl_2 (4 mL). The solution was stirred for 15 h and evaporated under vacuum, and the residue was purified by Kugelrohr distillation [175–178 °C (0.1 mm)] to give **19** (663 mg, 93%) as a clear liquid, which was unstable to prolonged storage: ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7, 3 H), 1.85 (q, J = 7, 2 H), 3.2–4.4 (m, 4 H), 4.6–4.8 (, 2 H), 5.98 (s, 2 H); IR (neat) 1780, 1720, 1430, 1280, 1250, 1235, 1140, 1115, 800, 755, 715 cm^{-1}.

1-[(4-Methylphenyl)sulfonyl]-3-[(*N*,*N*-dimethylcarbamyl)methyl]indole-2-acetic Acid, Methyl Ester (23). A solution of **22**[8a] (4.06 g, 10.9 mmol), trimethyl orthoacetate (40 mL), and 2,4,6-trimethylbenzoic acid (180 mg, 1.1 mmol) in a 250-mL flask equipped with a short-path distillation head was heated at 110–125 °C for 10 min, and MeOH was allowed to distill off as formed. Another portion 2,4,6-trimethylbenzoic acid (180 mg, 1.1 mmol) was added, and heating was resumed at 130–140 °C for 10 min, again allowing MeOH to distill off as formed. The distillation head was replaced by a reflux condenser, and the solution was heated at 210 °C for 3 h. Most of the trimethyl orthoacetate was removed under vacuum. The residue was cooled, dissolved in CH_2Cl_2, washed with 10% aqueous HCl, and dried (Na_2SO_4). The solvents were evaporated under vacuum, and the residue was purified by flash chromatography (eluting with 35% to 40% EtOAc–CH_2Cl_2) to give a foam, which was crystallized from CH_2Cl_2–ether to provide **23**[8a] as colorless plates (2.96 g, 63%): mp 98–100 °C; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.88 (s) and 2.92 (s) (total 6 H), 3.69 (s, 3 H), 3.7 (m, 2 H), 4.2 (m, 2 H), 7.1–7.9 (m, 7 H), 8.0–8.3 (m, 1 H); IR (KBr) 1755, 1655, 1610, 1505, 1465, 1405, 1370, 1290, 1260, 1185, 1140, 825, 760, 720, 675 cm^{-1}.

1-[(4-Methylphenyl)sulfonyl]-3-[(*N*,*N*-dimethylthiocarbamyl)methyl]indole-2-acetic Acid, Methyl Ester (24). To a soltuion of **23** (1.0 g, 2.3 mmol) in THF (30 mL) was added P_4S_{10} (1.4 g, 3.2 mmol) in four equal portions at 30-min intervals, while the mixture was being irradiated with ultrasound and stirred.[16] Irradiation with ultrasound and stirring was continued for an additional 4 h. The resulting mixture was filtered through Celite, and the solids were washed with CH_2Cl_2. The filtrates were combined, the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (7% EtOAc–CH_2Cl_2) to give **24** (747 mg, 72%) as a white foam: ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.10 (s, 3 H), 3.40 (s, 3 H), 3.70 (s, 3 H), 4.20 (s, 2 H), 4.26 (s, 2 H), 7.0–7.8 (m, 7 H), 7.9–8.2 (m, 1 H); IR (KBr) 1750, 1535, 1465, 1375, 1185, 675 cm^{-1}.

1-[(4-Methylphenyl)sulfonyl]-2-[(carbomethoxy)methyl]indole-3-thioacetic *S*-Acid, Methyl Ester (25). To a solution of **24** (3.06 g, 6.9 mmol) in CH_2Cl_2 (25 mL), cooled in an ice bath, was added a 1 M solution of $Et_3O^+BF_4^-$ in CH_2Cl_2 (8.6 mL). The solution was stirred for 5 min, the cooling bath was removed, and 25 min later the solvents were evaporated under vacuum. The residue was treated with 2 N aqueous HCl (60 mL) and THF (60 mL). The mixture was stirred for 23 h and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (5% EtOAc–CH_2Cl_2) to give **25** (2.63 g, 86%) as a viscous liquid: ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 7, 3 H), 2.25 (s, 3 H), 2.76 (q, J = 7, 2 H), 3.66 (s, 3 H), 3.82 (s, 2 H), 4.16 (s, 2 H), 7.0–7.8 (m, 7 H), 7.9–8.2 (m, 1 H); IR (neat) 1755, 1695, 1690, 1465, 1375, 1275, 1225, 1185, 1165, 1140, 750, 670 cm^{-1}.

1-[(4-Methylphenyl)sulfonyl]-3-(2-hydroxyethyl)indole-2-acetic Acid, Methyl Ester (26). To a solution of **25** (2.63 g, 5.9 mmol) in MeOH (30 mL), cooled in an ice bath, was added $NaBH_4$ (2.23 g, 59 mmol) in portions over 15 min, and the reaction mixture was stirred for 10 min. The cooling bath was removed, and after another 20 min the reaction was quenched by the addition of aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were evaporated under vacuum to give **26** (2.3 g, 95%): ^1H NMR ($CDCl_3$) δ 2.28 (s, 3 H), 2.7 (br s, 1 H), 2.83 (t, J = 6, 2 H), 3.70 (s, 3 H), 3.73 (t, J = 6, 2 H), 4.07 (s, 2 H), 6.9–7.8 (m, 7 H), 7.9–8.2 (m, 1 H); IR (neat) 3600–3100, 1750, 1470, 1375, 1230, 1185, 1165, 1140, 755, 675 cm^{-1}.

1-[(4-Methylphenyl)sulfonyl]-3-[2-((*tert*-butyldimethylsilyl)oxy)ethyl]indole-2-acetic Acid, Methyl Ester (27). To a solution of **26** (2.28 g, 5.9 mmol) in DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (980 mg, 6.5 mmol) and imidazole (885 mg, 13 mmol), and the mixture was heated at 40 °C for 12 h while stirring. The solution was cooled, CH_2Cl_2 (50 mL) was added, the mixture was washed three times with water and dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (40% ether–hexanes to give **27** (2.26 g, 77%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ –0.08 (s, 6 H), 0.80 (s, 9 H), 2.27 (s, 3 H), 2.83 (t, J = 6, 2 H), 3.67 (s, 3 H), 3.72 (t, J = 6, 2 H), 4.09 (s, 2 H), 7.0–7.8 (m, 7 H), 7.9–8.2 (m, 1 H).

3-[2-((*tert*-Butyldimethylsilyl)oxy)ethyl]indole-2-acetic Acid, Methyl Ester (20). Mg metal (97 mg) was soaked for 1 min in 5% methanolic $HgCl_2$ (5 mL) then transferred to a mixture containing **27** (400 mg, 0.8 mmol), KH_2PO_4 (600 mg, 4.4 mmol), and MeOH (12 mL). The reaction mixture was stirred vigorously for 40 min, aqueous NH_4Cl was added, and the mixture was extracted three times with CH_2Cl_2. The combined extracts were

dried (Na_2SO_4), and the solvents were evaporated under vacuum to give **20** (280 mg, 95%): ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.87 (s, 9 H), 2.92 (t, J = 7, 2 H), 3.71 (s, 3 H), 3.76 (t, J = 7, 2 H), 3.80 (s, 2 H), 7.0–7.7 (m, 4 H), 8.6 (br s, 1 H).

Acylation of 20. To a solution of diisopropylamine (60 μL, 0.42 mmol) in THF (0.5 mL), cooled in an ice bath, was added a 2.6 M solution of *n*-BuLi in hexane (0.154 mL). The solution was cooled to −78 °C, and a solution of **20** (69 mg, 0.2 mmol) in THF (0.75 mL) was added. The solution was stirred at −78 °C for 3 min, and then freshly prepared **19** (70 mg, 0.2 mmol) was added. The reaction mixture was stirred for 30 min at −78 °C, and the cooling bath was removed. After 15 min the reaction was quenched by the addition of aqueous NH_4Cl, and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (15% EtOAc–hexanes) to give **21** (97 mg, 74%) as a mixture of two diastereomers as indicated by normal phase HPLC (6% EtOAc–hexanes): ^1H NMR ($CDCl_3$) δ −0.05 (s) and 0.0 (s) (total 6 H), 0.81 (s) and 0.85 (s) (total 9 H), 0.5–1.0 (m, 3 H), 1.4–1.9 (m, 2 H), 2.7–3.1 (m, 3 H), 3.5–4.2 (m, 8 H), 4.5–4.9 (m, 2 H), 5.4 (m) and 5.5 (m) (total 1 H), 5.8–6.0 (m, 2 H), 6.9–7.7 (m, 4 H), 8.7 (m) and 8.9 (m) (total 1 H); IR (neat) 3470–3350, 1735, 1470, 1450, 1260, 1165, 1100, 845, 785, 745, 725 cm^{-1}; HREIMS, calcd for $C_{30}H_{41}N_2O_6Cl_3Si$ 658.1800, found 658.1848, *m/e* 346, 284, 214, 170, 154, 108.

Alcohol 28. To a solution of **21** (117 mg, 0.18 mmol) in THF (1 mL) were added water (1 mL) and glacial acetic acid (1 mL), and the mixture was stirred vigorously for 4 h. Water (6 mL) was added, and the mixture was extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (55% EtOAc–hexanes) to give **28** (98 mg, 95%) as a white foam. Normal phase HPLC (40% EtOAc–hexanes) indicated the presence of two diastereomers: ^1H NMR ($CDCl_3$) δ 0.66 (t, J = 7) and 0.86 (t, J = 7) (total 3 H), 1.6 (m, 2 H), 2.7–3.2 (m, 3 H), 3.65 (s) and 3.70 (s) (total 3 H), 3.5–4.4 (m, 5 H), 4.4–4.9 (m, 2 H), 5.4–5.6 (m, 1 H), 5.8–6.1 (m, 2 H), 6.9–7.7 (m, 4 H), 8.8 (m) and 9.0 (m) (total 1 H); HREIMS, calcd for $C_{24}H_{27}N_2O_6Cl_3$ 544.0935, found 544.0911, *m/e* 284, 232, 215, 202, 170, 154, 108.

Methanesulfonate 29. Methanesulfonyl chloride (20 μL, 0.26 mmol) was added to a solution of **28** (98 mg, 0.18 mmol) and Et_3N (46 μL, 0.33 mmol) in CH_2Cl_2 (2 mL), and the reaction was stirred for 4 h. The solution was washed with ice-cold 10% aqeuous HCl (3 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and was evaporated under vacuum to give **29** (111 mg, 95%) as a beige foam. The proton NMR indicates the presence of two diastereomers: ^1H NMR ($CDCl_3$) δ 0.66 (t, J = 7) and 0.87 (t, J = 7) (total 3 H), 1.7 (m, J = 7, 2 H), 2.68 (s) and 2.71 (s) (total 3 H), 2.9–3.4 (m, 3 H), 3.67 (s) and 3.72 (s) (total 3 H), 3.6–4.9 (m, 7 H), 5.5 (m, 1 H), 5.9–6.1 (m, 2 H), 6.9–7.7 (m, 4 H), 9.0 (m, 1 H).

Amine 30. To a solution of **29** (37 mg, 0.06 mmol) in MeOH (3 mL) was added activated Zn (65 mg) followed by glacial acetic acid (50 μL). The mixture was stirred vigorously for 15 min, then another portion of activated Zn (65 mg) was added, and stirring was continued for an additional 10 min. The mixture was filtered through Celite, and the solids were washed with ether. The filtrates were combined, the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (10% MeOH–CH_2Cl_2) to give **30** (20 mg, 74%) as a viscous liquid. The proton NMR indicates the presence of two diastereomers: ^1H NMR ($CDCl_3$) δ 0.6–1.1 (m, 3 H), 1.4–1.9 (m, 2 H), 2.72 (s) and 2.75 (s) (total 3 H), 3.0–3.9 (m, 6 H), 3.69 (s) and 3.75 (s) (total 3 H), 4.2–4.6 (m, 2 H), 5.4–5.6 (m, 2 H), 7.0–7.7 (m, 4 H), 9.5 (br s, 1 H).

Spirocycle 31. A solution of **30** (18 mg) in toluene (5 mL) was added over 4 h by syringe pump to a flask containing toluene (5 mL) heated at 105 °C. The reaction solution was heated at 105 °C for an additional 2 h, the solution was cooled, the toluene was evaporated under vacuum, and the residue was purified by flash chromatography (3% MeOH–CH_2Cl_2) to give **31** (10 mg): ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7, 3 H), 1.3–2.1 (m, 6 H), 2.7–4.0 (m, 4 H), 3.68 (s, 3 H), 5.0 (br s, 1 H), 5.4–6.2 (m, 2 H), 6.7–7.4 (m, 4 H); IR (neat) 3500–3100, 2930, 1710, 1620, 1550, 1470, 1420, 1370, 1335, 1290, 1245, 1180, 970, 750; HREIMS, calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1785, *m/e* 320, 184, 156, 154, 129, 108.

3-[(*N*,*N*-Dimethylcarbamyl)methyl]indole-2-acetic Acid, Methyl Ester (34). To a mixture of **23** (1.72 g, 4.0 mmol) KH_2PO_4 (2.99 g, 22 mmol), and MeOH (40 mL) was added Mg metal (486 mg), which had been pretreated for 1 min with 5% methanolic $HgCl_2$ (20 mL). The mixture was stirred vigorously for 75 min, aqueous NH_4Cl (20 mL) and CH_2Cl_2 (30 mL) were added, and the two-phase mixture was filtered through Celite. The solids were rinsed with CH_2Cl_2. The filtrates were combined, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was crystallized from EtOAc–hexanes to provide **34** (850 mg, 78%) as beige needles (mp 170 °C): ^1H NMR ($CDCl_3$) δ 2.90 (s) and 2.93 (s) (total 6 H), 3.61 (s, 3 H), 3.7 (m, 4 H), 6.9–7.7 (m, 4 H), 9.2 (br s, 1 H); IR (KBr) 3340–3100, 1745, 1635, 1470, 1430, 1410, 1320, 1235, 1205, 1170, 1150, 740 cm^{-1}.

1-(Trimethylacetyl)-3-[(*N*,*N*-dimethylcarbamyl)-methyl]indole-2-acetic Acid, Methyl Ester (38). To a solution of diisopropylamine (31 μL, 0.22 mmol) in THF (0.6 mL), cooled in an ice bath, was added a 2.6 M solution of *n*-BuLi in hexane (0.08 mL). The solution was cooled to −78 °C, and a solution of **34** (55 mg, 0.2 mmol) in THF (2 mL) was added. The mixture was stirred at −78 °C for 15 min, and then a solution of trimethylacetyl chloride (37 μL, 0.3 mmol) in THF (0.4 mL) was added in one portion. The reaction mixture was stirred for 15 min at −78 °C, and then the cooling bath was removed. After 25 min the reaction was quenched with aqueous NH_4Cl and extracted twice with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (30% EtOAc–CH_2Cl_2) to give **38**: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.92 (s) and 2.97 (s) (total 6 H), 3.68 (s, 3 H), 3.76 (s, 2 H), 3.96 (s, 2 H), 7.0–7.7 (m, 4 H); IR (neat) 1745, 1700, 1645, 1465, 1405, 1315, 1185, 1070, 745 cm^{-1}.

β-Keto Ester 39. To a solution of diisopropylamine (56 μL, 0.4 mmol) in THF (0.5 mL), cooled in an ice bath, was added a 2.2 M solution of *n*-BuLi in hexane (0.15 mL). The solution was cooled to −78 °C, and a solution of **34** (55 mg, 0.2 mmol) in THF (2.5 mL) was added. The mixture was stirred at −78 °C for 15 min, and then a solution of trimethylacetyl chloride (37 μL, 0.3 mmol) in THF (0.5 mL) was added in one portion. The reaction mixture was stirred for another 15 min at −78 °C, and then the cooling bath was removed. After another 15 min the reaction was quenched with aqueous NH_4Cl. The resulting mixture was extracted twice with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were evaporated under vacuum to give **39** (68 mg, 95%): ^1H NMR ($CDCl_3$) δ 1.19 (s, 9 H), 2.88 (s, 6 H), 3.65 (s, 3 H), 3.6–3.9 (m, 2 H), 6.02 (s, 1 H), 7.0–7.7 (m, 4 H), 9.1 (br s, 1 H).

Ketone 40. To a solution of **39** (68 mg, 0.2 mmol) in THF (2 mL) was added 0.3 M aqueous NaOH (2 mL), and the mixture was stirred vigorously for 20 h. The reaction was quenched with 5% aqueous HCl (4 mL), and extracted twice with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were evaporated under vacuum to give **40** (50 mg): ^1H NMR (Me_2SO-d_6) δ 1.15 (s, 9 H), 2.87 (s, 3 H), 3.05 (s, 3 H), 3.8 (m, 4 H), 6.9–7.7 (m, 4 H), 10.6 (br s, 1 H); IR (neat) 3400–3100, 1730, 1610, 1470 cm^{-1}.

β-Keto Ester 35. To a solution of diisopropylamine (0.155 mL, 1.1 mmol) in THF (1 mL), cooled in an ice bath, was added a 2.6 M solution of *n*-BuLi in hexane (0.423 mL). The solution was cooled to −78 °C, and a solution of **34** (137 mg, 0.5 mmol) in THF (4 mL) was added slowly. The mixture was stirred for 13 min at −78 °C, and then a solution of freshly prepared **19** (220 mg, 0.63 mmol) in THF (0.5 mL) was added in one portion. The reaction mixture was stirred for 15 min at −78 °C, and the cooling bath was removed. After 15 min the reaction was quenched with aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (20% EtOAc–CH_2Cl_2) to give **35** (155 mg, 53%) as a white foam. The proton NMR indicates the presence of two diastereomers: ^1H NMR ($CDCl_3$) δ 0.62 (t, J = 7) and 0.89 (t, J = 7) (total 3 H), 1.5–2.1 (m, 2 H), 2.87 (s) and 2.90(s) (total 6 H), 3.61 (s) and 3.67 (s) (total 3 H), 2.8–4.9 (m, 8 H), 6.0 (m, 1 H), 5.8–6.1 (m, 2 H), 7.0–7.7 (m, 4 H), 8.8 (m) and 9.0 (m) (total

1 H); IR (KBr) 3600–3200, 1735, 1650, 1640, 1470, 1450, 1250, 1155, 1135 cm^{-1}.

Amine 36. A mixture of **35** (30 mg, 0.03 mmol), activated Zn (65 mg), MeOH (1.5 mL), and glacial acetic acid (0.2 mL) was stirred vigorously and heated at 60 °C for 30 min. The reaction mixture was cooled, and the solids were filtered through Celite and washed with MeOH. The combined filtrates were made basic by the addition of 30% aqueous NH_4OH (5 mL) and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (EtOAc) to give **36** (14 mg, 68%): ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7, 3 H), 1.72 (q, J = 7, 2 H), 2.90 (s) and 2.95 (s) (total 6 H), 3.71 (s, 3 H), 2.8–4.6 (m, 6 H), 5.9 (m, 2 H), 6.9–7.7 (m, 4 H), 9.2 (m, 1 H); EIMS, m/e 411 (M^+), 366, 215, 170, 144.

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Registry No. (±)-**4**, 33190-27-1; (±)-**5a**, 99619-21-3; (±)-**5b**, 99619-25-7; (±)-**5c**, 99619-26-8; **8**, 63-75-2; **8**·HBr, 300-08-3; (±)-**9**, 99619-13-3; (±)-**10**, 99619-14-4; (±)-**11**, 99619-15-5; **12**, 22980-09-2; (±)-**13**, 99619-16-6; (±)-**14a**, 99619-17-7; (±)-**14b**, 99619-22-4; **15a**, 99619-18-8; **15b**, 99619-23-5; (±)-**16a**, 99619-19-9; (±)-**16b**, 99619-24-6; (±)-**17a**, 99619-20-2; (±)-**17b**, 99631-60-4; (±)-**18**, 99619-27-9; (±)-**19**, 99619-28-0; **20**, 99619-34-8; (±)-**21** (isomer 1), 99619-35-9; (±)-**21** (isomer 2), 99619-48-4; (±)-**22**, 99619-29-1; **23**, 67593-15-1; **24**, 99619-30-4; **25**, 99619-31-5; **26**, 99619-32-6; **27**, 99619-33-7; (±)-**28** (isomer 1), 99619-36-0; (±)-**28** (isomer 2), 99619-45-1; (±)-**29** (isomer 1), 99619-37-1; (±)-**29** (isomer 2), 99619-46-2; (±)-**30** (isomer 1), 99619-38-2; (±)-**30** (isomer 2), 99619-47-3; (±)-**31**, 99619-39-3; **34**, 99619-40-6; (±)-**35** (isomer 1), 99619-44-0; (±)-**35** (isomer 2), 99619-49-5; (±)-**36** (isomer 1), 99631-61-5; (±)-**36** (isomer 2), 99619-50-8; **38**, 99619-41-7; (±)-**39**, 99619-42-8; **40**, 99619-43-9; $Me_3C(OMe)_3$, 1445-45-0; propylene oxide, 16033-71-9.

The Reactions of α-Arylsulfonoxy Ketones with Nucleophiles

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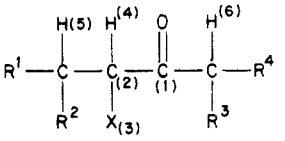
α-(*p*-Nitrophenyl)sulfonoxy ketones can be converted to α-hydroxy ketals and α-hydroxy ketones by reaction with potassium carbonate and basic or acidic workup, respectively. They also react with amines to give α-amino ketones in high yields. Nonnucleophilic amines give an intramolecular aromatic substitution in the derived enolate. Factors which dictate the reaction patterns in these compounds are discussed.

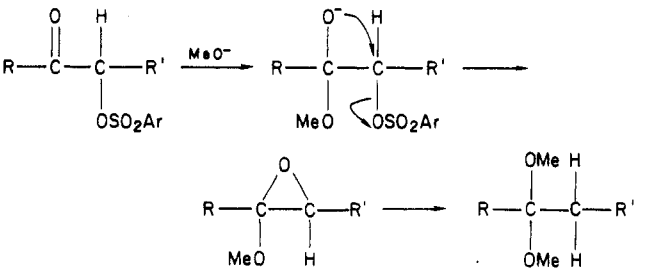
The chemistry of α-halo ketones is an area of great interest due to the wide variety of transformations they undergo. They react with both nucleophiles and bases; however, there is a variety of positions (six altogether) that may be attacked. A superb recent review details these



processes, all of which have been identified. The pathway(s) actually followed depend(s) on the structure of the substrate, the presence of α- and α′-hydrogens, the particular halogen present (chlorine or bromine), and the nucleophile/base used.[1]

α-Sulfonoxy ketones have received much less attention. Since they contain the same general features as α-halo ketones in that they have a leaving group attached next to the carbonyl group, it is not surprising that behavior similar to that of α-halo ketones has been observed for these compounds. Thus Conia has reported that they are Favorski rearrangement substrates,[2] and it is claimed that

Scheme I



α-mesyl ketones are thiol-specific electrophiles.[3]

On the other hand, sulfonoxy groups are much better leaving groups than halogens. Creary has effectively exploited this property of α-sulfonoxy ketones to generate and study α-keto carbocations.[4] Furthermore, the sulfonoxy group is a strong electron-withdrawing group[5] which can acidify the α-hydrogen significantly. Some interesting chemistry of the derived anion has also been reported.[4]

We have recently described facile routes to α-arylsulfonoxy ketones by the reaction of enol esters, silyl enol

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