2-(*N*,*N*-Di-*n*-propylamino)-7-acetamido-1,2,3,4-tetrahydronaphthalene Methanesulfonate (7a). A solution of 0.2 g (0.81 mmol) of **25**, 0.11 g (1.08 mmol) of acetic anhydride, and 0.051 g (0.56 mmol) of triethylamine in 1 mL of benzene was stirred for 8 h at room temperature. The solvent was removed under reduced pressure, and the residue was taken up into 1 N HCl and extracted with ether. The aqueous layer was basified with $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was washed with water, dried ($MgSO_4$), and concentrated to yield 0.134 g (57.2%) of oil. The base was converted to the salt with methanesulfonic acid and crystallized from EtOH–Et_2O: mp 181–183 °C; TLC (10% MeOH–$CHCl_3$) R_f 0.31; ^1H NMR (free base in $CDCl_3$) δ 7.0–7.15 (m, 3, ArH), 6.75–7.15 (br s, 1, NH), 2.75–3.10 (m, 5, C(1)H, C(2)H, C(4)H), 2.39–2.58 (t, 4, J = 7.2 Hz, NCH_2), 2.14 (s, 3, $COCH_3$), 1.75–2.30 (m, 2, C(3)H), 1.30–1.70 (m, 4, $NCCH_2$), 0.79–0.97 (t, 6, J = 7.3 Hz, CH_3); CIMS 289 (MH^+); MS calcd for $C_{18}H_{28}N_2O$ 288.2202, found 288.2209.

2-(*N*,*N*-Di-*n*-propylamino)-7-methanesulfonamido-1,2,3,4-tetrahydronaphthalene (7b). To a solution of 0.2 g (0.81 mmol) of **25** in 2 mL of benzene was added, dropwise, a solution of 0.093 g (0.81 mmol) of methanesulfonyl chloride in 2 mL of benzene. The mixture was stirred for 1 h and the benzene was removed by rotary evaporation. To the residue was added 25 mL of 1 N HCl and the acidic solution was extracted with ether. The aqueous layer was basified with $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract was washed with water, dried ($MgSO_4$), and concentrated to yield 0.18 g (68.3%) of an oil. The base was converted to its oxalate salt and crystallized from EtOH–Et_2O: mp 244–247 °C dec; ^1H NMR (free base in $CDCl_3$) δ 6.85–7.10 (m, 3, ArH), 4.75–5.65 (br s, 1, NH), 2.98 (s, 3, SO_2CH_3), 2.60–4.35 (m, 5, C(1)H, C(2)H, C(4)H), 2.37–2.56 (t, 4, J = 7.7 Hz, NCH_2), 1.80–2.20 (m, 2, C(3)H), 1.25–1.70 (m, 4, $NCCH_2$), 0.79–0.96 (t, 6, J = 6.89 Hz, CH_3); CIMS 325 (MH^+); MS calcd for $C_{17}H_{28}N_2O_2S$ 324.1871, found 324.1955.

Pharmacology. Prolactin Inhibition Assay.[22] Male, Sprague–Dawley rats were housed and fed in a controlled environment. Each rat received an intraperitonal injection of reserpine (15 mg/kg), as an aqueous suspension, 18 h before the administration of test compound. Compounds for assay were dissolved in 10% ethanol and injected intraperitoneally at a standard dose vs the control group, which received a standard volume of saline solution. One hour after treatment, all rats were killed, their blood was collected and allowed to clot, and 150-μL aliquots of serum were assayed for prolactin by radioimmunoassay using a NIAMD kit. Results were measured as nanograms of NIAMD-prolactin-PR-1 per milliliter of serum and then reported as a percent decrease or increase versus the control result. Significance was evaluated between treatment and control by use of Student's t test.

Acknowledgment. We are grateful for support provided for this work by Eli Lilly and Co., Indianapolis, IN.

Synthesis and Biological Evaluation of 4,6-Diethyl-1,3,4,5-tetrahydropyrano[4,3-*b*]indole-4-acetic Acid, an Isomer of Etodolac

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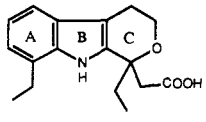
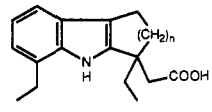
The synthesis of 4,6-diethyl-1,3,4,5-tetrahydropyrano[4,3-*b*]indole-4-acetic acid, an isomer of the antiinflammatory agent etodolac, is described. The compound was found to have an ED_{50} of 3 mg/kg po in the rat curative adjuvant arthritis assay, and an IC_{50} of 50 nM for inhibiting prostaglandin production in cultured chondrocytes.

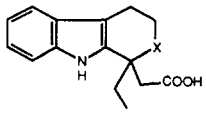
Etodolac,[1] 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic acid (1), is a clinically effective antiinflammatory agent with the potential to retard the progression of skeletal changes in rheumatoid arthritis, and it has been found to possess an exceptional safety profile with respect to the gastrointestinal tract and renal function.[2]



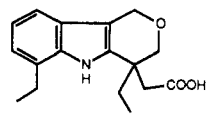
1



2: n = 1
3: n = 2
4: n = 3



5: X = S
6: X = O



7

Among the analogues of etodolac which have been studied are **2–5**, in which the pyrano[3,4-*b*] ring C was replaced by the cyclopentano, cyclohexano, cycloheptano, and thiopyrano[3,4-*b*] systems, respectively.[3,4] Compounds **1–5** were evaluated in the curative adjuvant edema assay[5] and in vitro for their effects on prostaglandin E_2 production in cultured chondrocytes,[6] and the results are shown in Table I. It is apparent that replacing etodolac's pyrano oxygen by a methylene group gives a compound, **3**, that is of the same order of potency as etodolac. Replacement of the oxygen by a sulfur atom however gave

Table I. Biological Evaluation of Etodolac Analogues

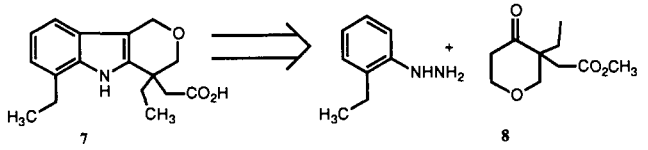
compd	adjuvant edema assay: ED_{50}, mg/kg	chondrocyte assay: $IC_{50} \times 10^{-8}$ M
1 (etodolac)	0.7	2.3
2	6.2	
3	1.9	2.0
4	>50	
5	>25	30
6	6.8	10
7	3.0	5.0

† Present address: Excel Inc., 3508 Market Street, Philadelphia, PA 19104.

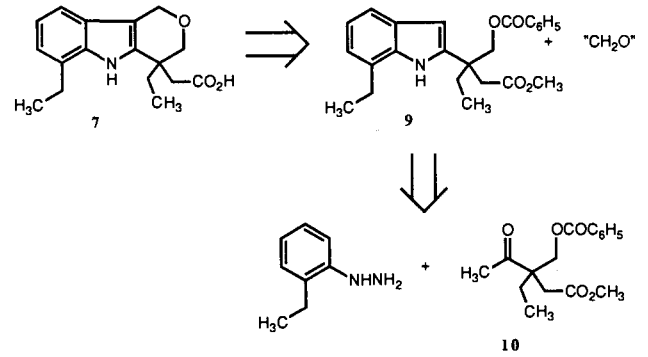
(1) ULTRADOL and LODINE are registered trademarks of Wyeth-Ayerst Laboratories, Radnor, PA.
(2) For a review on etodolac, see: Humber, L. G. *Med. Res. Rev.* **1987**, *7*, 1.
(3) Asselin, A. A.; Humber, L. G.; Dobson, T. A.; Komlossy, J.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 787.
(4) Jirkovsky, I.; Humber, L. G.; Noureldin, R. *J. Heterocyl. Chem.* **1975**, *12*, 937.
(5) Martel, R. R.; Klicius, J. *Can. J. Physiol. Pharmacol.* **1976**, *54*, 245.
(6) Neuman, G. R.; Wilson, B. D.; Barkley, M.; Kimball, E. S.; Weichman, B. M.; Wood, D. D. *Agents Actions* **1987**, *21*, 160.

0022-2623/89/1832-2134$01.50/0

Scheme I



Scheme II



analogue **5**, which was devoid of antiinflammatory activity in vivo, while retaining, in vitro, one third of the potency of the corresponding pyrano analogue **6**. The in vivo inactivity of **5**, coupled with substantial in vitro activity, suggests that the thiopyrano analogue **5** may be metabolized in vivo to an inactive derivative. The cycloheptano analogue **4** was devoid of activity in vivo while the cyclopentano analogue **2** retained about $^1/_{10}$ of the activity of etodolac in vivo.

Thus, high antiinflammatory activity is associated with the pyrano[3,4-*b*] system of etodolac, and with the tetrahydrocarbazole ring of **3**. As part of a continuing investigation of ring C analogues of etodolac, we herein describe the synthesis and biological evaluation of **7**, in which ring C is a pyrano[4,3-*b*] system.

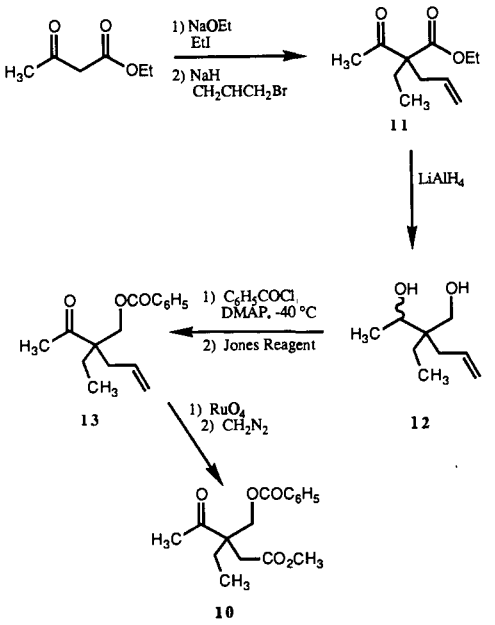
Chemistry

Two approaches to the pyrano[4,3-*b*]indole system of **7** can be envisioned. In the first approach (Scheme I), the nucleus would be derived from a Fisher indole synthesis using a phenylhydrazine and the disubstituted 4-pyrone **8**, analogous to the method currently used in the construction of tetrahydrocarbazoles.[3] A second approach (Scheme II) would utilize a ring closure of isotryptophol **9** with a formaldehyde equivalent. Isotryptophol **9** would be derived from a Fisher indole synthesis using a phenylhydrazine and the appropriately functionalized methyl ketone **10**.

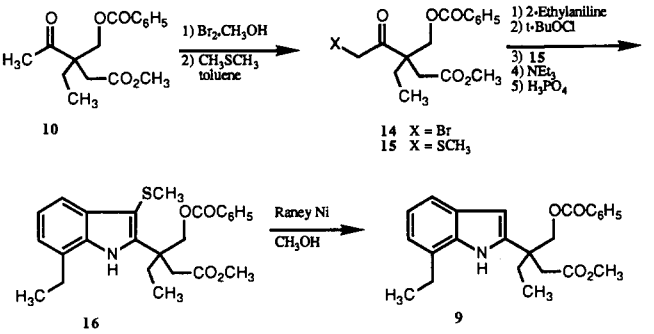
Initial attempts to synthesize the pyrano[4,3-*b*]indole etodolac isomer **7** followed the first approach and centered on synthesis of the disubstituted 4-pyrone **8**. However, attempts to synthesize the desired 4-pyrone by alkylation of 4-pyrone itself or by forming the pyrano ring via ether formation were unsuccessful.

Attention was then turned to the second approach. Synthesis of the required methyl ketone **10** (Scheme III) was straightforward. Ethyl acetoacetate was alkylated first with iodoethane and then with allyl bromide to give ethyl 2-allyl-2-ethylacetoacetate (**11**) (73%). Reduction with lithium aluminum hydride gave diol **12** (83%). The primary alcohol of diol **12** was selectively acylated with benzoyl chloride at −40 °C and then oxidized with Jones reagent to give methyl ketone **13** (76%). Oxidative cleavage of the olefin with ruthenium tetroxide,[7] followed

Scheme III



Scheme IV



by esterification with diazomethane, gave the desired methyl ketone **10** (87%).

Methyl ketones have been notoriously difficult to convert to indoles by the Fisher indole synthesis, though some exceptions are known.[8] Methyl ketone **10** proved not to be an exception, failing to form a hydrazone with phenylhydrazine even in refluxing xylene. At higher temperatures, only decomposition of starting materials was seen.

The Gassman indole synthesis,[9] which involves reacting an α-methylthiocarbonyl compound with an aniline, was then investigated (Scheme IV) as a viable alternative to the Fisher indole synthesis. To obtain the required starting material, methyl ketone **10** was brominated with bromine in methanol to give bromomethyl ketone **14** (96%). Reaction of bromomethyl ketone **14** with dimethyl sulfide in refluxing toluene gave the methylthiomethyl ketone **15** (64%) required for the Gassman indole synthesis. Addition of ketone **15** to a −40 °C acetonitrile/methylene chloride solution of *N*-chloro-2-ethylaniline (prepared in situ by addition of *tert*-butyl hypochlorite to the aniline), followed by triethylamine and later methanolic phosphoric acid, gave the 3-(methylthio)indole **16** (53%). Removal of the methylthio function with Raney nickel in methanol gave the desired protected isotryptophol **9** (96%).

(7) Carlsen, P. H. K.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(8) Robinson, B. *The Fisher Indole Synthesis*; Wiley: New York, 1982.

(9) Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590.

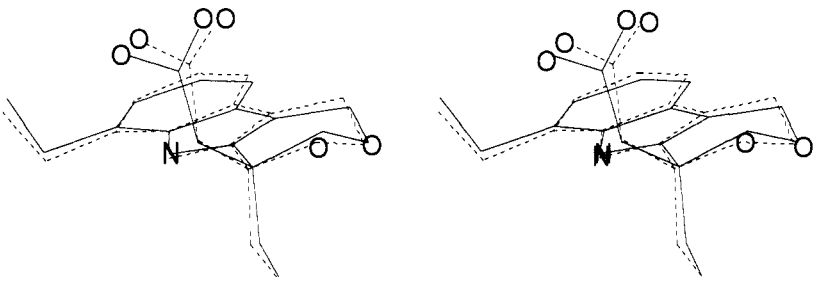
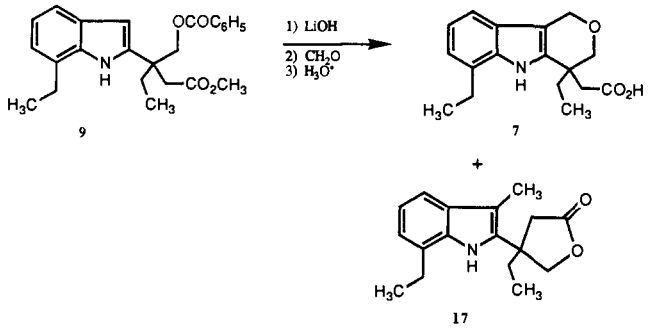


Figure 1. Stereoview of the overlap of etodolac (1) (- -) and its pyrano[4,3-*b*]indole isomer 7 (—).

Scheme V



Cyclization of isotryptophol 9 to the pyrano[4,3-*b*]indole 7 (Scheme V) was effected by first hydrolyzing the benzoyl and methyl esters with lithium hydroxide in aqueous dioxane. The reaction mixture was then treated with formalin solution (37% aqueous formaldehyde) and heated to 145 °C in a Parr reactor for 24 h at around 90 psi. Workup with 1 N HCl and ether, followed by chromatography, gave a 3/2 mixture of 7 and butyrolactone 17 (from ^{1}H NMR integration). Although the free acid of 7 could be purified at this stage, attempts to obtain a crystalline sample were unsuccessful due to the instability of the free acid. On standing, the free acid decomposed to a number of products (by TLC analysis). This instability probably arises from an acid-catalyzed opening of the pyrano ring. However, treatment of the mixture in ether with 1 equiv of benzylamine gave pure 7 (16% from 9) as a stable benzylamine salt.

Results and Discussion

Compound 7 was tested by oral administration in the rat curative adjuvant arthritis assay[5] and in vitro for its effect on prostaglandin production in cultured chondrocytes.[6] The latter assay is carried out at neutral pH over a short time period and provides a more valid assessment of the intrinsic activity of a labile drug. The results obtained are shown in Table I and indicate that the activity in vitro is about one-half that of etodolac, while in vivo it has about one-quarter of the activity of etodolac. The diminished activity of 7 on oral administration may be due to the instability of the compound in acid media (vide supra); however, the high intrinsic activity shown in vitro suggests that prostaglandin synthetase, the presumed "receptor" for 7 and etodolac, does not significantly distinguish between the two isomeric ring systems. Figure 1 shows the superpositioning of minimized structures[10] of etodolac and 7. It is apparent that the pyrano[3,4-*b*] and the pyrano[4,3-*b*] systems of etodolac and 7 respectively adopt similar conformations and that their carboxyl groups are quite close. We have suggested previously[11,12] that the unique orientation of the carboxyl group with respect to the indole ring was an important determinant of etodolac's activity, and the results reported here suggest that this may also be a requisite to obtain potent analogues of etodolac.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. E. Merck Kieselgel 60 (230–400 mesh) was used for all flash chromatography. ^{1}H NMR spectra were made on a Varian CFT-20 (80 MHz) or a Bruker AM-400 (400 MHz) instrument. Microanalyses were obtained on crystalline intermediates and were done on a Control Equipment Corp. modified Perkin-Elmer 240 analyzer. Infrared spectra were recorded on a Perkin-Elmer 781 IR spectrophotometer.

Ethyl 2-Allyl-2-ethylacetoacetate (11). In a 2-L three-neck round-bottom flask, equipped with an overhead stirrer and a reflux condenser, sodium hydride (15.2 g, 633 mmol) in THF (1 L) was treated with ethyl 2-ethylacetoacetate (100 g, 633 mmol) under nitrogen. After stirring for 1 h, allyl bromide (230 g, 164.3 mL, 1.9 mol) was added and the reaction mixture was heated at reflux overnight. On cooling, the reaction mixture was treated with water (600 mL), and the layers were separated. The aqueous layer was washed with ether (200 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and distilled through a Vigreux column (10 cm, 70 °C at 0.3 mmHg) to give 110 g (88%) of the product as a clear oil: IR ($CHCl_3$) 1650, 1710, 1740, 2850–3100 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.79 (3 H, t, J = 7.3 Hz), 1.26 (3 H, t, J = 7.1 Hz), 1.92 (2 H, q, J = 7.3 Hz), 2.12 (3 H, s), 2.60 (2 H, d, J = 6.9 Hz), 4.20 (2 H, q, J = 7.1 Hz), 4.9–5.9 (3 H, m).

2-Ethyl-2-(2-propenyl)-1,3-butanediol (12). Ethyl 2-allyl-2-ethylacetoacetate (11, 130 g, 657 mmol) was dissolved in ether (2 L) under nitrogen and, with cooling in an ice bath, treated with lithium aluminum hydride (1 L of a 1 M ether solution, 38 g, 1 mol) dropwise. After stirring for 3 days, the reaction was quenched by cautious sequential addition of water (38 mL), 15% NaOH (38 mL), and water (114 mL). The mixture was then filtered through Celite, concentrated, and distilled through a Vigreux column (10 cm, 103 °C at 0.3 mmHg) to give 86 g (83%) of the product as a clear oil containing a mixture of diastereomers: IR ($CHCl_3$) 2800–3100, 3200–3700, 3610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–0.9 (3 H each, 2 t), 1.14 and 1.33 (1 H, 2 m), 1.22 and 1.24 (3 H each, 2 d), 1.55 (2 H, dd), 1.88, 2.14, 2.28, and 2.36 (2 H, 4 dd), 2.8 (1 H, br s), 3.54 and 3.72 (2 H, 2 dd), 3.88 (1 H, m), 5.1 (2 H, m), 5.84 (1 H, m).

3-[(Benzoyloxy)methyl]-3-ethyl-5-hexen-2-one (13). A solution of 2-ethyl-2-(2-propenyl)-1,3-butanediol (12, 100 g, 633 mmol) in methylene chloride (1 L) containing 4-(dimethylamino)pyridine (4 g, 33.3 mmol) and triethylamine (176.4 mL, 128.1 g, 1.3 mol) was cooled to −40 °C and treated with benzoyl chloride (73.5 mL, 89 g, 633 mmol) dissolved in methylene chloride

(10) Molecular modeling was done using Allinger's MM2 force field as found in the MODEL program (version K.S.-2.92) written by Prof. Clark Still. The low-energy conformations were found by exhaustive rotation of torsion angles by a rigid-rotor approximation and subsequent minimization of local minima. The overlap was performed after hydrogen removal with equal weighting of all non-hydrogen atoms. The overlap showed an average deviation of 0.162 Å and an RMS deviation of 0.193 Å.

(11) Demerson, C. A.; Humber, L. G.; Dobson, T. A.; Martel, R. R. *J. Med. Chem.* **1975**, *18*, 189.

(12) Humber, L. G.; Demerson, C. A.; Swaminathan, P.; Bird, P. H. *J. Med. Chem.* **1986**, *29*, 8719.

(50 mL) dropwise over 5 h. The reaction mixture was warmed to room temperature and treated with 5 N HCl (500 mL). The layers were separated, and the aqueous layer was reextracted with methylene chloride (400 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an orange oil containing a diastereomeric mixture of starting material and mono- and diacylated products. The orange oil was dissolved in acetone (1 L), cooled to 0 °C, and treated with Jones reagent [CrO_3 (53.4 g, 534 mmol) and sulfuric acid (46 mL) dissolved in water (to 200 mL), 8 M in e^-, 200 mL]. After 2 h, the reaction mixture was treated with 2-propanol, filtered through Celite, and concentrated. The residue was partitioned between ether (600 mL) and water (200 mL). The layers were separated, and the ether layer was washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to a brown oil. The product was purified by Kugelrohr distillation (110–115 °C at 0.3 mmHg) to give 126 g (76% from the diol) of the product as a clear oil: IR ($CHCl_3$) 1275, 1710, 2850–3120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3 H, t, J = 7.5 Hz), 1.73 (2 H, m), 2.19 (3 H, s), 2.47 (2 H, m), 4.44 (2 H, s), 5.1 (2 H, m), 5.7 (1 H, m), 7.43 (2 H, t), 7.56 (1 H, t), 7.98 (2 H, d).

Methyl 3-[(Benzoyloxy)methyl]-3-ethyl-4-oxopentanoate (10). In a 5-L three-neck flask under nitrogen and equipped with an overhead stirrer, a solution of 3-[(benzoyloxy)methyl]-3-ethyl-5-hexen-2-one (**13**, 125 g, 481 mmol) in acetonitrile and carbon tetrachloride (900 mL each) was cooled in an ice bath and treated with sodium periodate (463 g, 2.16 mol) in water (1.35 L) and ruthenium trichloride hydrate (1.0 g, 4.9 mmol). After 3 h, more ruthenium trichloride hydrate (1.0 g, 4.9 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then filtered through Celite. The layers were separated and the aqueous layer was extracted with methylene chloride (400 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to an oil. The oil was redissolved in ether (1 L) and treated with diazomethane. The excess diazomethane was quenched with acetic acid and the solution was filtered through Celite and concentrated to give 121.5 g (87%) of the product as a clear oil: IR ($CHCl_3$) 1110, 1280, 1720, 1785, 2820–3120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3 H, t, J = 7.5 Hz), 1.81 (2 H, q, J = 7.5 Hz), 2.3 (3 H, s), 2.8 (2 H, s), 3.6 (3 H, s), 4.59 (2 H, dd, J = 11.6 Hz), 7.44 (2 H, t), 7.55 (1 H, t), 7.99 (2 H, d).

Methyl 3-[(Benzoyloxy)methyl]-5-bromo-3-ethyl-4-oxopentanoate (14). A solution of methyl 3-[(benzoyloxy)-methyl]-3-ethyl-4-oxopentanoate (**10**, 120 g, 411 mmol) in methanol (250 mL) was cooled to 0 °C and treated dropwise with bromine (21.1 mL, 65.7 g, 411 mmol) in methanol (350 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. A solution of sodium thiosulfate [10 g in water (200 mL)] was then added and the mixture was concentrated to remove methanol. The residue was partitioned between ether (700 mL) and water (200 mL), and the layers were separated. The aqueous layer was washed with ether (300 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give 146 g (96%) of the product as a slightly yellow oil containing traces of starting material and dibrominated product: IR ($CHCl_3$) 705, 1110, 1270, 1720, 1785, 2820–3110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3 H, t, J = 7.5 Hz), 1.40 (2 H, m), 2.84 (2 H, s), 3.6 (3 H, s), 4.3 (2H, s), 4.60 (2 H, 2 d, J = 11.62 Hz), 7.45 (2 H, t), 7.58 (1 H, t), 7.99 (2 H, d).

Methyl 3-[(Benzoyloxy)methyl]-3-ethyl-5-(methylthio)-4-oxopentanoate (15). Methyl 3-[(benzoyloxy)methyl]-5-bromo-3-ethyl-4-oxopentanoate (**14**, 145.5 g, 392.3 mmol) was dissolved in a mixture of toluene (900 mL) and dimethyl sulfide (300 mL) and heated at reflux at 67 °C. After 1 day, the mixture was cooled and concentrated to increase the toluene/sulfide ratio and reheated to reflux at 70 °C. After another day, the reaction mixture was concentrated and heated at reflux at 77 °C. After another day, the reaction mixture was cooled, concentrated to remove dimethyl sulfide, filtered to remove sulfonium salts, and concentrated to an oil. The oil was chromatographed in two portions (silica gel, 15 i.d. × 15 cm ht, 30/30/1 methylene chloride/hexane/ethyl acetate) to give 84.8 g (64%) of the product as a clear oil: IR ($CHCl_3$) 1110, 1270, 1720, 1790, 2810–3120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3 H, t, J = 7.5 Hz), 1.89 (2 H, m), 2.12 (3 H, s), 2.84 (2 H, dd), 3.53 (2 H, s), 3.63 (3 H, s), 4.62 (2 H, dd,), 7.43 (2 H, t), 7.57 (1 H, t), 7.99 (2 H, d).

Methyl β-[(Benzoyloxy)methyl]-β,7-diethyl-3-(methylthio)-1*H*-indole-2-propanoate (16). A solution of 2-ethylaniline (4.0 mL, 3.94 g, 32.5 mmol) in acetonitrile/methylene chloride (9/1, 600 mL) was cooled to −40 °C under nitrogen with rapid stirring and treated dropwise with *tert*-butyl hypochlorite (3.77 mL, 3.43 g, 32.5 mmol). After stirring for 30 min, methyl 3-[(benzoyloxy)methyl]-3-ethyl-5-(methylthio)-4-oxopentanoate (**15**, 10.0 g, 29.6 mmol) in acetonitrile (100 mL) was added dropwise over 45 min. After 1 h, triethylamine (4.13 mL, 3.0 g, 29.6 mmol) in acetonitrile (10 mL) was added and the solution was warmed to room temperature and stirred for 30 min. The reaction mixture was then acidified with 2% phosphoric acid in methanol until the reaction mixture tested acidic with moist pH paper. After stirring an additional 30 min, the reaction mixture was concentrated and partitioned between ether (600 mL) and water (300 mL). The aqueous layer was extracted with ether (300 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 9.5 cm i.d. × 15 cm ht, 7.5% ethyl acetate in hexane) to give 6.9 g (53%) of the product as a clear oil. Trituration of the oil with hexanes gave white crystals: IR ($CHCl_3$) 710, 1270, 1280, 1710, 1720, 2800–3100, 3200–3400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3 H, t, J = 7.5 Hz), 1.38 (3 H, t, J = 7.6 Hz), 2.16 (1 H, m), 2.26 (3 H, s), 2.56 (1 H, m), 2.92 (2 H, q), 3.08 (1 H, d), 3.30 (1 H, d), 3.56 (3 H, s), 4.92 (1 H, d), 5.05 (1 H, d), 7.04 (1 H, d), 7.12 (1 H, t), 7.38 (2 H, t), 7.52 (1 H, t), 7.58 (1 H, d), 7.92 (2 H, d), 9.8 (1 H, s). Anal. Calcd for $C_{25}H_{29}NO_4S$: C, H, N.

Methyl β-[(Benzoyloxy)methyl]-β,7-diethyl-1*H*-indole-2-propanoate (9). A 50% slurry of Raney nickel (Aldrich, 160 mL) was washed with water until neutral to pH paper and then washed with methanol and transferred as a methanol slurry (200 mL) to a solution of methyl β-[(benzoyloxy)methyl]-β,7-diethyl-3-(methylthio)-1*H*-indole-2-propanoate (**16**, 8.44 g, 19.23 mmol) in methanol/acetone (1/1, 350 mL). The mixture was stirred overnight at room temperature with an overhead stirrer. The mixture was then filtered through Celite and rinsed with methanol (200 mL), ethyl acetate (200 mL), and methylene chloride (200 mL). The filtrate was concentrated to give 7.24 g (96%) of the product as a clear oil: IR ($CHCl_3$) 710, 1110, 1270, 1720, 2800–3100, 3220–3500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3 H, t), 1.39 (3 H, t), 2.07 (2 H, m), 2.91 (2 H, q), 2.96 (2 H, dd), 3.68 (3 H, s), 4.68 (2 H, dd), 6.38 (1 H, d), 7.01 (1 H, t), 7.05 (1 H, t), 7.42 (2 H, d), 7.45 (1 H, t), 7.46 (1 H, d), 8.04 (2 H, d), 9.56 (1 H, br s).

4,6-Diethyl-1,3,4,5-tetrahydropyrano[4,3-*b*]indole-4-acetic Acid (7) Benzenemethanamine Salt. A solution of methyl β-[(benzoyloxy)methyl]-β,7-diethyl-1*H*-indole-2-propanoate (**9**, 5.0 g, 12.7 mmol) in dioxane (250 mL) was treated with lithium hydroxide hydrate (1.6 g, 38.2 mmol) dissolved in water (125 mL) and heated at reflux overnight. The reaction mixture was cooled, treated with formalin (37% aqueous formaldehyde soltuion, 19 mL, 7.62 g, 254 mmol), transferred to a Parr minireactor (600 mL volume), and heated to 145 °C with stirring overnight. The pressure was at 90 psi. The reaction mixture was cooled, concentrated, and partitioned between ether (400 mL) and 1 N HCl (50 mL). The layers were separated, and the aqueous layer was washed with ether (50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), concentrated, and purified by chromatography (silica gel treated with H_3PO_4, 7.5 cm i.d. × 15 cm ht, 15% ethyl acetate in hexane) to give 1.27 g of a clear oil consisting of a 3/2 mixture of the desired product and a lactone (from ^1H NMR integration). The mixture was dissolved in ether (50 mL), treated with benzylamine (284 mg, 2.65 mmol, 1 equiv), and stored at 0 °C. The white crystals which formed overnight were filtered to give 773 mg (16%) of the product as a benzylamine salt: IR ($CHCl_3$) 1070, 1403, 1533, 1560, 1620, 2000–3500, 3370 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.80 (3 H, t), 1.23 (3 H, t), 1.86 (2 H, m), 2.46 (2 H, dd), 2.82 (2 H, q), 3.64 (1 H, d), 3.84 (1 H, d), 3.86 (2 H, s), 4.73 (2 H, dd), 6.82–6.88 (2 H, m), 7.12 (1 H, dd), 7.25–7.42 (5 H, m). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, H, N.