An Approach to Substituted 4-Hydroxypyran-2-ones: The Total Synthesis of Phenoxan

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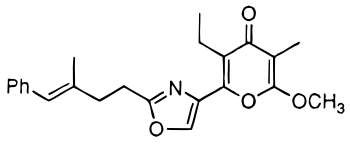
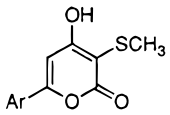
Introduction

Phenoxan, a naturally occurring heterocyclic compound, was recently isolated from a soil microorganism and discovered to have anti-HIV activity.[1] The structure of phenoxan, determined by a combination of proton/carbon-NMR and high-resolution mass spectrometry, revealed the presence of a substituted pyran-4-one attached to an oxazole. Phenoxan is closely related to other microbial metabolites that contain a pyran-4-one group.[2] The mechanism of action of phenoxan is currently unknown; however, a recent report by Parke-Davis researchers has shown that 6-substituted pyran-2-ones are inhibitors of HIV-protease by simple hydrogen bonding to the active site.[3] Similar hydrogen-bonding interactions may help explain the mechanism of action for phenoxan. In this paper, we wish to report the first total synthesis of phenoxan.



phenoxan



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Results and Discussion

There are a large number of methods for preparing substituted oxazoles.[4] A popular route to 2,4-disubstituted oxazoles is cyclodehydration of hydroxyamides, such as **3**, to an oxazoline followed by dehydrogenation.[5] Hydroxy amide **3** was prepared by coupling **2**[6] with L-serine methyl ester hydrochloride via a mixed anhydride[7] (Scheme 1). We examined several methods to construct the oxazole portion, but in our hands no discernible product could be identified. Treatment of **3** with Dess−Martin reagent and subsequent reaction with Ph_3P/I_2 did not give **4**.[8] This method has proven useful for the preparation of trisubstituted oxazoles. A recent publication has shown the utility of DDQ for the preparation of oxazoles from oxazolines;[9] however, only a conjugated oxazoline was obtained in high yield. The desired oxazole was finally obtained by treatment of the oxazoline of **3** with LDA followed by I_2. The reaction mixture afforded **4** in 40% yield, and the rest of the product (about 40%) consisted of unreacted oxazoline, which was easily recovered and recycled. The spectral data (^{1}H- and ^{13}C-NMR) of **4** closely matched the corresponding segment of phenoxan. This route demonstrated to us the difficulty in preparing the oxazole fragment at an advanced stage as the overall yields were low and that a convergent route from a suitable oxazole starting material would be more advantageous. We examined several oxazole intermediates that would allow for the construction of the pyrone fragment. Of all the myraid methods of preparing oxazoles,[4] none were suitable for yielding a 2,4-disubstituted oxazole that would allow further elaboration to phenoxan. We became intrigued with metalation studies by Lipshutz and Hungate,[10] who showed that 2,4,5-trimethyloxazole could be selectively alkylated at the 2-methyl group in high yield. We discovered that alcohol **6**, prepared by lithium aluminum hydride reduction of **5**,[11] can be selectively alkylated at the 2-methyl group. The 4-hydroxymethyl group can serve as a handle for eventual construction of the pyran-4-one (Scheme 2). Treatment of **6** with 2 equiv of LDA followed by bromide **7**[6] gave alcohol **8**.

We then turned our attention to the construction of the required pyran-4-one. There are several methods for constructing the desired γ-pyrone ring system.[12] We initially employed a literature procedure to prepare the γ-pyrone ring based on the metalation of an acylketene acetal followed by addition−condensation with an acyl halide (or imidazole).[13] Preparation of the required acylketene acetal was difficult due to the hydrolytic

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(1) Jansen, R.; Kunze, B.; Wray, V.; Reichenbach, H.; Juriewicz, E.; Hunsmann, G.; Holfe, G. *Liebigs Ann. Chem.* **1991**, 707−708. Kunze, B.; Jansen, R.; Pridzun, L.; Juriewicz, E.; Hunsmann, G.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1992**, *45*, 1549−1552.

(2) Kakinuma, K.; Janson, C. A.; Rinehart, K. L., Jr. *Tetrahedron* **1976**, *32*, 217−222. Vardaro, R. R.; Dimarzo, V.; Crispino, A.; Cimino, G. *Tetrahedron* **1991**, *47*, 5569−5576.

(3) Prasad, J. V. N. V.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B., Jr.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. M. A.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. *J. Am. Chem. Soc.* **1994**, *116*, 6989−6990.

(4) Bredereck, H.; Gompper, R.; Reich, F. *Chem. Ber.* **1960**, *93*, 1389−1397. Scholkopf, U.; Schroder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333. van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369−2372. Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497−501. Nagayoshi, K.; Sato, T. *Chem. Lett.* **1983**, 1355−1356. Alvarez-Ibarra, C.; Mendoza, M.; Orellana, G.; Quiroga, M. L. *Synthesis* **1989**, 560−562. Kashima, C.; Arao, H. *Synthesis* **1989**, 873−874. Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070−4072. Doyle, K. J.; Moody, C. J. *Tetrahedron Lett.* **1992**, *33*, 7769−7770. Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159−2162. Aguilar, E.; Meyers,A. I. *Tetrahedron Lett.* **1994**, *35*, 2477−2480.

(5) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961−1963.

(6) Frenking, G.; Hulskamper, L.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 2826−2835.

(7) Inanaga, J.; Hirata, K.; Saeki, H.; Katsaki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(8) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

(9) McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett.* **1992**, *33*, 2641−2644.

(10) Lipshutz, B. H.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410−1413. Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111−5123.

(11) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96−102.

(12) For example: Koreeda, M.; Akagi, H. *Tetrahedron Lett.* **1980**, *21*, 1197−1200. Morgan, T. A.; Ganem, B. *Tetrahedron Lett.* **1980**, *21*, 2773−2774. Shono, T.; Matsumura, Y.; Hamaguchi, H.; Naitoh, S. *J. Org. Chem.* **1983**, *48*, 5126−5128. Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10*, 71−98.

(13) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852−1856. Boeckman, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P.-E. *J. Am. Chem. Soc.* **1986**, *108*, 5549−5557.

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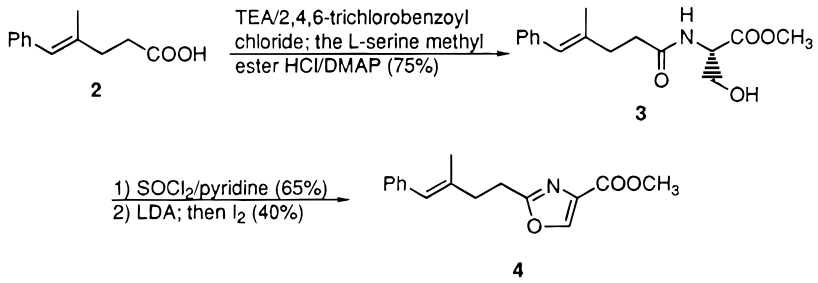
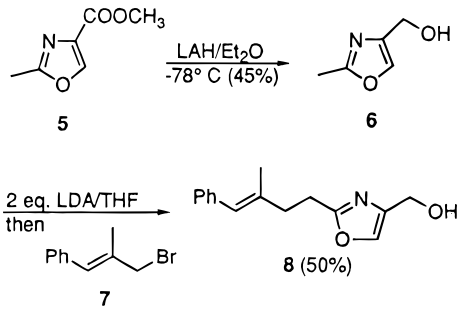
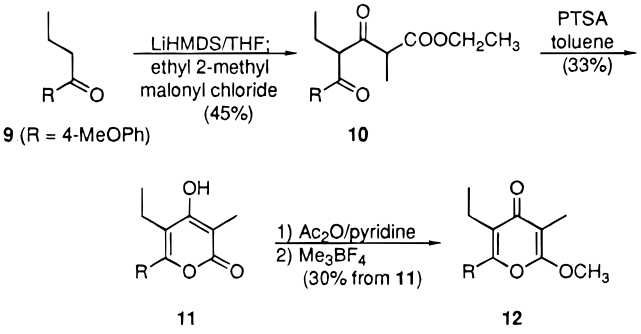
Scheme 1



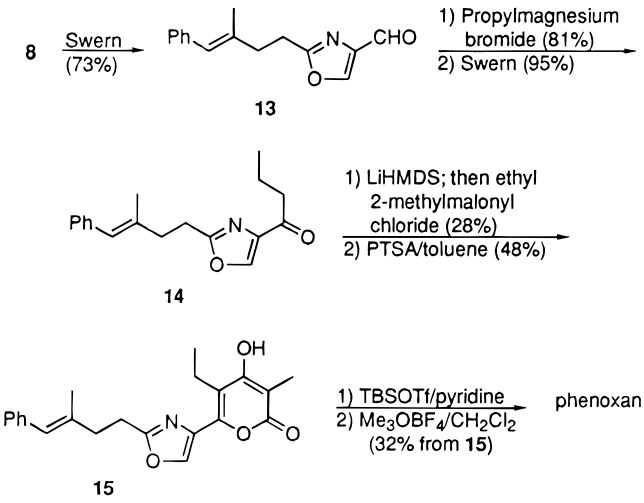
Scheme 2



Scheme 3



Scheme 4



instability and tedious separation of product from starting material. This difficulty of preparing sufficient quantities of the acylketene acetal led to an alternative route that finally provided the pyrone as shown in Scheme 3. We examined the feasibility of the route on a model system.[14] Alkylation of 4-methoxybenzaldehyde with propylmagnesium bromide followed by PCC-oxidation[15] gave ketone **9**, which was readily C-acylated[16] with ethyl 2-methylmalonyl chloride[17] to give diketo ester **10**. Best results were obtained using freshly distilled acid chloride. Acid-catalyzed lactonization[18] yielded pyran-2-one **11**. Unreacted diketo ester **10** (about 40%) was recovered and recycled to yield more product. Pyranone **11** was transformed to **12** according to a literature procedure.[19] Comparision of the ^{13}C-NMR spectra of **12** with phenoxan showed a close match of the pyran-4-one portion, indicating the validity of the route.

The two methodologies were now in place for the final push to phenoxan. Swern oxidation[20] of alcohol **8** gave **13** (Scheme 4). Addition of propylmagnesium bromide followed by Swern oxidation furnished ketone **14**. Acylation of the enolate of **14** with ethyl 2-methylmalonyl chloride, followed by acid-catalyzed cyclization of the diketo ester intermediate, yielded **15**. Conversion to the target molecule employing acetylation followed by methylation with Meerwein's reagent (Me_3OBF_4) as in **12** resulted in destruction of the pyran-2-one. Phenoxan was finally obtained by treatment of the hindered enol **15** with *tert*-butyldimethylsilyl trifluoromethanesulfonate, in the presence of pyridine, followed by methylation of the silyl enol ether with Me_3OBF_4 in CH_2Cl_2 at room temperature. Synthetic phenoxan was found to be identical to authentic material as judged by TLC, ^{1}H- and ^{13}C-NMR, HPLC analysis, and HRMS.

Conclusions

In this paper, we have described the first total synthesis of phenoxan that confirms the initial structural assignment. The two key steps developed in the total synthesis of phenoxan were (1) metalation of 2-methyl-4-hydroxymethyloxazole and (2) a method for preparing 6-aryl-substituted pyranones from an aryl ketone and ethyl 2-methylmalonyl chloride. We are currently pursuing other analogs of phenoxan through molecular modeling techniques. This work will be reported in due course.

(14) Ramirez, M.-l.; Garey, D.; Peña, M. R. *J. Heterocycl. Chem.* **1995**, *32*, 1657−1660.

(15) Piancatelli, G.; Scettri, A.; D'auria, M. *Synthesis* **1982**, 245−258.

(16) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280−1285.

(17) Prepared according to a modification of the original procedure (Marguery, F. *Bull. Chem. Soc. France* **1905,** *33*, 541−548). The ethyl hydrogen malonate (Strube, R. E. *Organic Syntheses;* Wiley: New York, 1963; Collect. Vol. IV, pp 417−419) was treated with oxalyl chloride in dichloromethane in the presence of catalytic dimethylformamide (DMF) to give the acid chloride.

(18) Ohta, S.; Tsujimura, A.; Okamoto, M. *Chem. Pharm. Bull.* **1981**, *29*, 2762−2768. Tanyeli, C.; Tarhan, O. *Synth. Commun.* **1989**, *19*, 2453−2460. Cervello, J.; Marquet, J.; Moreno-Manans, M. *Synth. Commun.* **1990**, *20*, 1931−1941. Harris, T. M.; Harris, C. M. *J. Org. Chem.* **1966**, *31*, 1032−1035.

(19) Cyr, T. D.; Poulton, G. A. *Can. J. Chem.* **1978**, *56*, 1796−1799.

(20) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

Experimental Section

General Methods. All solvents were distilled from calcium hydride prior to use except for THF, which was distilled from molten potassium, and ethyl ether, which was distilled from sodium benzophenone. Anhydrous methanol was distilled from Mg. All reagents were used as obtained from commercial suppliers unless otherwise noted. Thin layer chromatography was performed with glass-backed precoated plates (Si-254F). Column chromatography utilized silica gel 230−400 mesh, 60 Å. The proton and carbon NMR spectra were recorded on a 300 MHz spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C). The following deuterated solvents and their following internal reference points were used: $CDCl_3$ referenced to TMS (0.00 ppm ^{1}H) or chloroform (77.00 ppm ^{13}C); methanol-d_4 referenced to methanol (3.48 ppm ^{1}H and 39.00 ppm ^{13}C). Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab (Norcross, GA). High-resolution mass spectroscopic data were obtained by the Nebraska Center for Mass Spectrometry.

2-Methyl-4-(hydroxymethyl)oxazole (6). A solution of 2.12 g (15.0 mmol) of ester **5**[12] and 570 mg (15.0 mmol) of LAH in 40 mL of ether was stirred at 0 °C under N_2 for 3 h. The reaction mixture was cautiously quenched by the addition of a small amount of water followed by dilute aqueous NaOH. The mixture was filtered and dried over $MgSO_4$. Filtration and evaporation of solvent *in vacuo* left a yellow oil that was further purified by column chromatography (75% EtOAc/hexane) to give 760 mg (45% yield) of **6** as a viscous oil that slowly crystallized upon standing: mp 40−41 °C; R_f = 0.15 (75% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 4.35 (br s, 1H), 4.48 (s, 2H), 7.42 (s, 1H), ^{13}C NMR ($CDCl_3$) δ 162.2, 140.2, 134.8, 55.8, 13.7; MS (EI) 113 (15), 84 (35), 68 (64), 42 (100). Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.23; N, 12.38. Found: C, 52.93; H, 6.30; N, 12.29.

Alcohol 8. A solution of 0.60 mL (4.3 mmol) of diisopropylamine, 2.50 mL (4.10 mmol) of *n*-butyllithium (1.6 M), and 10 mL of THF was stirred at 0 °C under N_2 for 15 min and then chilled to −78 °C. To this solution was added *via* cannula 220 mg (1.95 mmol) of **6** dissoved in 5 mL of THF. The solution was stirred for 20 min, and then 411 mg (1.95 mmol) of **7**,[5] dissolved in 5 mL of THF, was added *via* cannula. The reaction mixture was stirred for 1 h and then allowed to warm to rt. The reaction mixture was poured into aqueous NH_4Cl and EtOAc and extracted several times with EtOAc. The combined organic layers were washed several times with water and brine and dried over $MgSO_4$. Filtration and evaporation of solvent *in vacuo* left a pale yellow viscous oil that was further purified by column chromatography (50% EtOAc/hexane) to give 240 mg (50% yield) of **8** as a viscous oil: R_f = 0.20 (50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.82 (d, 3H, J = 1.1 Hz), 2.55 (t, 2H, J = 7.8 Hz), 2.93 (t, 2H, J = 7.9 Hz), 4.51 (s, 2H), 6.22 (br s, 1H), 7.3 (m, 5H), 7.45 (s, 1H), ^{13}C NMR ($CDCl_3$) δ 164.8, 140.2, 137.9, 136.5, 134.7, 128.6, 128.0, 127.8, 125.9, 55.7, 37.4, 26.9, 17.3; MS (EI) 243 (80), 225 (26), 196 (44), 132 (100). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.75. Found: C, 73.78; H, 7.10; N, 5.52.

Aldehyde 13. To a solution of 0.47 mL (5.4 mmol) of oxalyl chloride in 10 mL of CH_2Cl_2 at −78 °C was added over 5 min 0.62 mL (8.7 mmol) of DMSO in 5 mL of CH_2Cl_2 under N_2. A solution of **8** (970 mg, 4.0 mmol) dissolved in 5 mL of CH_2Cl_2 was added *via* cannula over 3 min. The reaction mixture was stirred at −78 °C for 45 min and then quenched by the addition of 2.8 mL (38 mmol) of TEA. The reaction mixture was allowed to warm to rt and poured into a separatory funnel containing water. The organic layer was washed several times with water and brine and then dried over $MgSO_4$. Filtration and evaporation of solvent *in vacuo* left a yellow oil that was further purified by column chromatography (50% EtOAc/hexane) to give 700 mg (73% yield) of **13** as a viscous oil: R_f = 0.62 (50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3H), 2.66 (t, 2H, J = 7.5 Hz), 3.06 (t, 2H, J = 7.6 Hz), 6.26 (br s, 1H), 7.23 (m, 5H), 8.19 (s, 1H), 9.91 (s, 2H), ^{13}C NMR ($CDCl_3$) δ 183.4, 165.6, 144.7, 140.6, 137.6, 135.9, 128.5, 127.8, 126.1, 126.0, 37.1, 26.6, 17.2; MS ((EI) 241 (40), 212 (86), 132 (72). The unstable aldehyde was not fully characterized but quickly carried over to the ketone **14**.

Ketone 14. A solution of 5.8 mL (5.8 mmol) of propylmagnesium bromide was slowly added to 700 mg (2.9 mmol) of **13** in 20 mL of ether at 0 °C under N_2. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was poured into a separatory funnel containing aqueous NH_4Cl followed by extraction with several portions of EtOAc. The combined organic layers were washed with several portions of water and brine and then dried over $MgSO_4$. Filtration and evaporation of solvent *in vacuo* left an oil that was further purified by column chromatography (75% EtOAc/hexane) to give 670 mg (81% yield) of the alcohol, which was not fully characterized but carried over to the next step: R_f = 0.40 (50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.2 Hz),1.41 (m, 2H), 1.76 (m, 2H), 1.86 (s, 3H), 2.58 (t, 2H, J = 7.6 Hz), 2.95 (t, 2H, J = 7.9 Hz), 4.62 (t, 1H, J = 6.4 Hz), 6.25 (br s, 1H), 7.2 (m, 5H), 7.41 (s, 1H), ^{13}C NMR ($CDCl_3$) δ 164.5, 143.6, 137.9, 136.6, 133.6, 128.7, 128.3, 127.9, 126.0, 66.5, 38.1, 37.6, 27.0, 18.6, 17.4, 13.7; MS ((EI) 285 (60); HRMS calcd for $C_{18}H_{23}NO_2$ 285.172 99, found 285.172 87 (−0.05 ppm deviation). To a solution of 0.30 mL (3.3 mmol) of oxalyl chloride in 10 mL of CH_2Cl_2 at −78 °C was added over 5 min 0.47 mL (6.6 mmol) of DMSO in 5 mL of CH_2Cl_2 under N_2. A solution of the alcohol (230 mg, 0.81 mmol) dissolved in 10 mL of CH_2Cl_2, was added *via* cannula and then stirred at −78 °C for 1 h. The reaction was quenched by the addition of 2.5 mL (18 mmol) of TEA and 4 mL of water. The reaction mixture was poured into a separatory funnel containing aqueous $NaHCO_3$. The organic layer was washed several times with water and brine and then dried over $MgSO_4$. Filtration and evaporation of solvent *in vacuo* left a yellow oil that was further purified by column chromatography (12% EtOAc/hexane) to give 220 mg (95% yield) of **14** as a viscous oil: R_f = 0.59 (25% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 2H, J = 7.4 Hz), 1.72 (m, 2H), 1.88 (d, 3H, J = 1.65 Hz), 2.63 (t, 2H, J = 7.7 Hz), 2.84 (t, 2H, J = 7.7 Hz), 6.27 (br s, 1H), 7.20 (m, 5H), 8.09 (s, 1H), ^{13}C NMR ($CDCl_3$) δ 195.2, 164.8, 141.8, 137.9, 136.3, 128.7, 128.2, 128.0, 126.3, 126.2, 41.7, 37.6, 27.0, 17.5, 17.3, 13.7; MS ((EI) 283 (100), 227 (28), 131 (86); HRMS calcd for $C_{18}H_{21}NO_2$ 283.157 33, found 283.156 98 (−0.87 ppm deviation).

Pyran-2-one 15. A solution of 1.5 mL (6.9 mmol) of hexamethyldisilazane (HMDS), 4.2 mL (6.7 mmol) of *n*-butyllithium (1.6 M), and 20 mL of THF was stirred at −78 °C under N_2 for 20 min before a solution of **14** (590 mg, 2.1 mmol) in 5 mL of THF was added *via* cannula. The reaction was stirred at −78 °C for 45 min before it was diluted with 30 mL of hexane. A solution of ethyl 2-methylmalonyl chloride (310 mg, 1.9 mmol) dissolved in 10 mL of hexane was added *via* cannula to the enolate and stirred at −78 °C for 2 h. The reaction was allowed to warm to rt and quenched by pouring into a separatory funnel containing EtOAc and dilute aqueous NH_4Cl. The organic layer was washed with water and brine and then dried over $MgSO_4$. Filtration and evaporation of solvent *in vacuo* left a yellow oil that was purified by column chromatography (12% EtOAc/hexane) to give 233 mg (27% yield) of a yellow oil. The diketo ester was not fully characterized but quickly carried over to the next step as it was prone to decomposition: R_f = 0.15 (12% EtOAc/hexane); MS ((EI) 411 (100). A solution of the diketo ester (37.1 mg, 0.09 mmol) in 25 mL of toluene containing a single crystal of PTSA was heated to reflux overnight under N_2. The reaction was quenched by the addition of 0.25 mL of TEA followed by solvent removal *in vacuo*. The brown residue was purified by column chromatography (50% EtOAc/hexane) to give 18 mg (48% yield) of **15** as a viscous oil that slowly crystallized upon standing: mp 103 °C; R_f = 0.34 (50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.88 (s, 3H), 2.02 (d, 3H, J =1.6 Hz), 2.64 (t, 2H, J = 7.7 Hz), 3.0 (q, 2H, J = 7.7 Hz), 3.01 (m, 2H), 6.29 (br s, 1H), 7.22 (m, 5H), 8.04 (s, 1H), ^{13}C NMR ($CDCl_3$) δ 165.1, 165.0, 164.5, 147.0, 138.9, 138.0, 136.5, 135.0, 128.7, 128.0, 126.2, 126.1, 100.3, 37.4, 26.9, 17.5, 16.0, 14.1, 8.9 (1 missing sp^2 carbon); MS ((EI) 365 (100); HRMS calcd for $C_{22}H_{23}NO_4$ 365.162 79, found 365.163 22 (1.4 ppm deviation).

Phenoxan. A solution of 13.9 mg (0.038 mmol) of **15**, 0.018 mL (0.23 mmol) of pyridine, 0.035 mL (0.15 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate, and 4 mL of CH_2Cl_2 was stirred under N_2 for 30 min. The reaction was poured into a separatory funnel containing aqueous $NaHCO_3$ and extracted with several portions of EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4 for 3 h. Filtration and evaporation of solvent *in vacuo* left a yellow oil that was not purified but quickly carried over to the last step. A solution of crude silyl enol ether, 15 mg (0.10 mmol) of Me_3OBF_4, and 4 mL of CH_2Cl_2 was stirred under N_2 for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with several portions of EtOAc. The

combined organic layers were washed with water and brine and then dried over Na_2SO_4. Filitration and evaporation of solvent *in vacuo* left an oil that was further purified by preparative TLC (50% EtOAc/hexane) to give 6.3 mg (32% yield based on **15**) of a white crystalline solid: mp 89−90 °C (lit.[1] mp 92−93 °C); R_f = 0.55 (CH_2Cl_2/MeOH, 19:1 (R_f = 0.57 for authentic phenoxan); t_R = 8.2 min (MeOH/water, 4:1; 1.5 mL/min; λ = 282 nm, 300 × 3.9 mm C-18 Alltech column); ^{1}H NMR (MeOH-d_4) δ 1.06 (t, 3H, J = 7.4 Hz), 1.83 (s, 3H), 1.88 (d, 3H, J = 1.6 Hz), 2.66 (t, 2H, J = 7.4 Hz), 2.84 (q, 2H, J = 7.4 Hz), 3.09 (t, 2H, J = 7.4 Hz), 4.04 (s, 3H), 6.27 (br s, 1H), 7.13 (m, 3H), 7.23 (m, 2H), 8.33 (s, 1H), ^{13}C NMR (MeOH-d_4) δ 182.4, 166.7, 164.2, 149.5, 140.5, 139.4, 137.6, 135.1, 129.8, 129.0, 127.6, 127.2, 126.1, 100.9, 56.6, 38.6, 27.6, 18.4, 17.6, 13.8, 7.1; HRMS calcd for $C_{23}H_{25}NO_4$ 379.178 45, found 379.178 32 (−0.10 ppm deviation).

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Supporting Information Available: Copies of the ^{13}C-NMR spectra of compounds **13**−**15** and phenoxan (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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