Unsymmetrical Ozonolysis of a Diels−Alder Adduct: Practical Preparation of a Key Intermediate for Heme Total Synthesis

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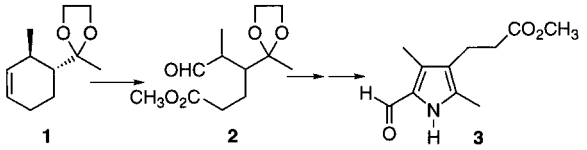
Introduction

In the course of other work, we needed to prepare gram quantities of the pyrrole **3**, an important precursor for the preparation of hemes and porphyrins.[1] Although the pyrrole **3** has been known for many years, the preparation is somewhat tedious.[1] It occurred to us that if the simple Diels−Alder-derived ketal **1** could be selectively ozonolyzed to the aldehyde **2**, ketal removal followed by condensation and formylation could give **3**.

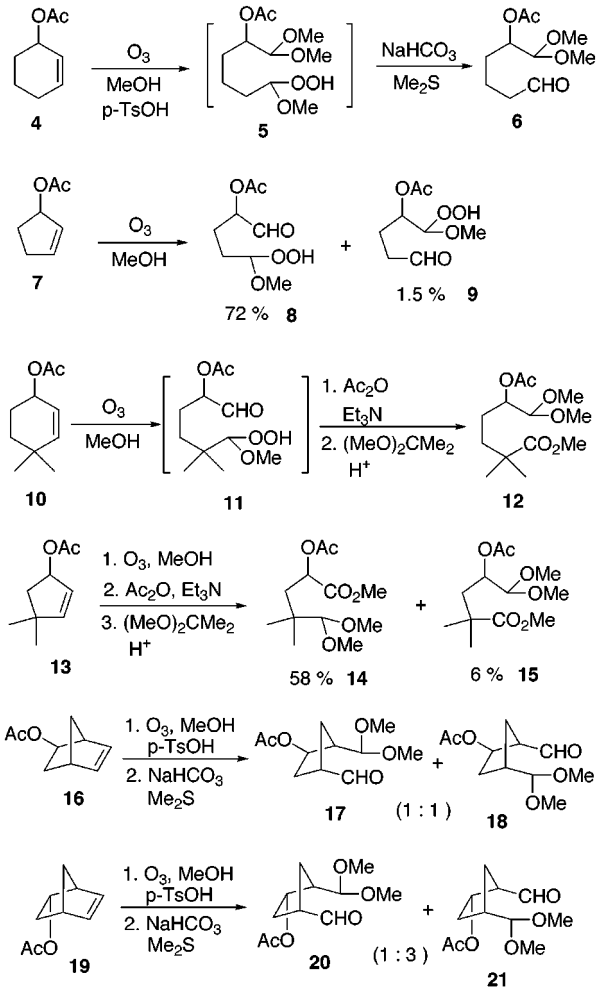


1 **2** **3**

Results

Unsymmetrical Ozonolysis. The key question was whether the ozonolysis of **1** would be regioselective. Unsymmetrical ozonolysis, first reported by Schreiber et al. in 1982[2] and subsequently employed by others,[3] provides terminally differentiated products from cycloalkenes. When an *unsymmetrical* cycloalkene is ozonolyzed, two products can be formed. There were only six prior examples of selective cleavage of an unsymmetrical disubstituted cycloalkene such as **1** (Scheme 1). An electron-withdrawing acetoxy group at the allylic position in both cyclohexene **4** and cyclopentene **7** directed the alkene cleavage, to give the intermediate methoxy hydroperoxide predominantly on the distal carbon. This effect was still observed with **10**, despite the alkyl branching at the other allylic position. However, in cyclopentene **13**, the effect of the allylic dimethyl substitution became dominant, reversing the regioselectivity of the cleavage. The only other examples were those first reported by Schreiber et al., **16** and **19**. It seemed likely in this pair of examples that the influence of the acetoxy group was steric, rather than electronic.

Scheme 1



With these scanty results in hand, it was desirable to investigate the directing effects of other substituents. We have found, as described below, that the unsymmetrical ozonolysis of **1** indeed proceeds with significant regioselectivity, opening a simple route to the target pyrrole **3**.

Preparation of Ketal 1. Following the literature precedent,[4a] cycloaddition of piperylene and methyl vinyl ketone in the presence of $BF_3{\cdot}OEt_2$ provided a mixture of *endo* and *exo* adduct **22** in a ratio of 96:4 (^{1}H NMR integration). Ketalization (Scheme 2) with concomitant epimerization then produced **1** as a 3:1 diastereomeric mixture, based on ^{1}H NMR integration of the methyl doublets at δ 1.11 and δ 0.99, respectively (the trans diastereomer, δ 1.11, was dominant). Since the two stereogenic centers at C-3 and C-4 become sp^2 centers in the target pyrrole **3**, the separation of the diastereomeric ketals was not required.

Ozonolysis of Ketal 1. Ozonolysis of **1** in CH_2Cl_2-alcohol in the presence of $NaHCO_3$ followed by treatment with acetic anhydride and triethylamine afforded an inseparable mixture of **2a** and **25a** (Scheme 2). This mixture contained four diastereomeric and constitutional

(1) For leading references, see: (a) Davies, J. L. *J. Chem. Soc. (C)* **1968**, 1392. (b) Al-Hazimi, H. M. G.; Jackson, A. H.; Knight, D. W.; Lash, T. D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 265. (c) Padney, R. K.; Leung, S. H.; Smith, K. M. *Tetrahedron Lett.* **1994**, *35*, 8093. (d) Lash, T. D.; Mani, U. N.; Lyons, E. A.; Thientanavanich, P.; Jones, M. A. *J. Org. Chem.* **1999**, *64*, 478.

(2) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Organic Synthesis*; Wiley: New York, 1990; Collect. Vol. VII, p 168.

(3) (a) Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* **1992**, *57*, 729. (b) Kawamura, S.; Yamakoshi, H.; Nojima, M. *J. Org. Chem.* **1996**, *61*, 5953.

(4) (a) Güner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1988**, *53*, 5348. For ^{1}H NMR data of **22**, see: (b) Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Hersh, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6070.

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Scheme 2

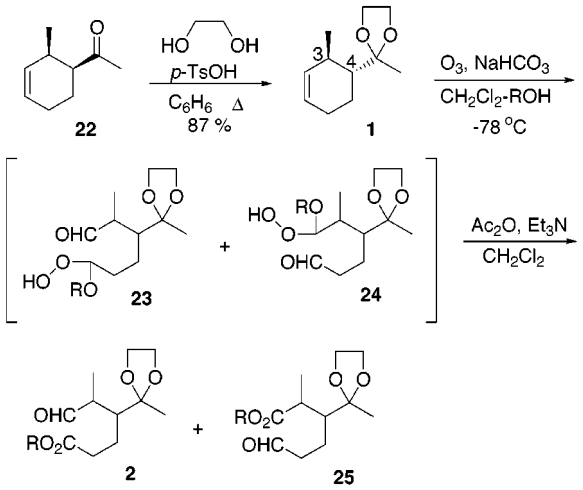


Table 1. Yield of 2 and 25 from Ozonolysis of 1

entry	R	yield (%)	ratio of **2** and **25**
1	Me (**a**)	68	3.6:1
2	Et (**b**)	71	3.6:1
3	*i*-Pr (**c**)	73	3.6:1
4	Bn (**d**)	75	4.8:1
5	*t*-Bu (**e**)	48	6.0:1

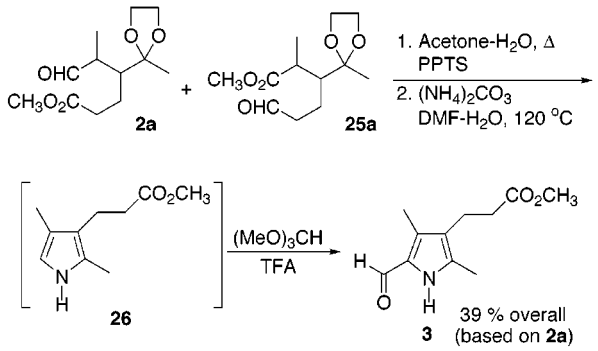
isomers. The ratio of **2a** and **25a** (3.6:1) was determined by ^{1}H NMR integration of the aldehyde signals, doublets from **2a** (δ 9.64), and triplets from **25a** (δ 9.77, δ 9.76). This regioselectivity was favorable for the subsequent conversion to pyrrole **3**, which can be obtained only from **2**.[5]

We have briefly explored the use of other alcohols (entries 2−5 in Table 1) in this unsymmetrical ozonolysis. Although *tert*-butyl alcohol appears to show enhanced regioselectivity, the lower yield leaves open the possibility that the improved ratio is due to selective loss of the minor regioisomer. In contrast to the results from the ozonolysis of **1** in the *presence* of methanol (Scheme 2), a control experiment in which methanol was added *after* the formation of the ozonide from **1** in CH_2Cl_2 did not lead to the formation of **2a** *or* **25a**. This suggested that the alcohol trapping likely is occurring *prior* to the formation of the secondary ozonide.

The conversion of the intermediate alkoxyhydroperoxides **23** and **24** (Scheme 2) to the esters was found to proceed smoothly in only 1 h at room temperature. This was in contrast to the literature procedure,[3b] which with the same solvents and concentrations specified a room-temperature reaction for 20 h.

Pyrrole Synthesis. The inseparable mixture of **2a** and **25a** (3.6:1 ratio) was subjected to ketal hydrolysis (Scheme 3) in acetone−water with catalytic pyridinium *p*-toluenesulfonate (PPTS). The resulting keto aldehyde mixture was immediately heated with ammonium carbonate to effect the Paal−Knorr pyrrole synthesis.[6] The resulting crude methyl 2,4-dimethyl-1*H*-pyrrole-3-propanoate **26**[1b] was then formylated at C-2 with trimethyl orthoformate in TFA to afford **3**[7] in 39% overall yield from

Scheme 3



2a. The ^{1}H NMR, ^{13}C NMR and mp of **3** were in excellent agreement with the literature data.[1d] No attempt was made to locate the product or products from **25a**.

Conclusion

We have observed *regioselective* ozonolytic cleavage of **1** in the presence of an alcohol, to give **2** as the major product. We have found the overall procedure described here to be very satisfactory for the preparation of **3**, a key intermediate for porphyrin and heme syntheses.[8]

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were obtained as solutions in deuteriochloroform ($CDCl_3$) at 400 MHz (^{1}H NMR), with tetramethylsilane = 0.00 as in internal standard. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d", from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. Mass spectra (MS) were obtained at an ionizing potential of 15 eV. Substances for which C, H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF, unless otherwise noted, and developed in the solvent system indicated. Column chromatography was carried out with Merck 35−60 μm silica gel, following the procedure described by Taber.[9] The solvent mixtures used are volume/volume mixtures. All glassware was flame dried under a dry nitrogen stream immediately before use. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from sodium metal/benzophenone ketyl under dry nitrogen. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride under dry nitrogen. MTBE is methyl *tert*-butyl ether. All reaction mixtures stirred magnetically, unless otherwise noted.

Ketone 22. A mixture of piperylene (60% cis−trans isomers, 90 mL, 0.54 mol) and methyl vinyl ketone (95% grade, 15 mL, 0.18 mol) was cooled to 0 °C, and BF_3·OEt_2 (3.0 mL, 24 mmol) was slowly added. An exothermic reaction was observed, and polymeric materials precipitated to the bottom of the flask. The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residual oil was subjected to a bulb-to-bulb distillation (bp 35 °C (pot)/0.1 mm) to afford 18.3 g (76%) of **22** as a colorless oil: ^{1}H NMR δ 5.71−5.62 (m, 2 H), 2.75−

(5) Previously, a similar keto aldehyde had been prepared by ozonolysis of a silyl enol ether, prepared by Diels−Alder cycloaddition to a silyloxy diene: Jacobi, P. A.; Cai, G. *Heterocycles* **1993**, *35*, 1103.

(6) (a) Bean, G. P. In *The Chemistry of Heterocyclic Compounds*; Jones, R. A., Ed.; Wiley: New York, 1990; Vol. 48, Part 1, p 206. (b) Wasserman, H. H.; Gosselink, E.; Keith, D. D.; Nadelson, J.; Sykes, R. J. *Tetrahedron* **1976**, *32*, 1863.

(7) We also prepared **3** from **22** by sequential ozonolysis in CH_2Cl_2−MeOH, esterification with Ac_2O and Et_3N, Paal−Knorr pyrrole synthesis with ammonium carbonate and formylation. This was a shorter path to **3**, but resulted in a poorer yield (15% overall), due to a lower yield and poorer regioselectivity for the ozonolysis step.

(8) For leading references to alternative approaches to pyrroles and porphyrins, see (a) Liu, D.; Williamson, D. A.; Kennedy, M. L.; Williams, T. D.; Morton, M. M.; Benson, D. R. *J. Am. Chem. Soc.* **1999**, *121*, 11798. (b) Cho, D. H.; Lee, J. H.; Kim, B. H. *J. Org. Chem.* **1999**, *64*, 8048.

(9) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

2.62 (m, 2 H), 2.16 (s, 3 H), 2.15−1.93 (m, 2 H), 1.79−1.60 (m, 2 H), 0.94 (d, J = 7.1 Hz, 3 H for *exo* **22**), 0.84 (d, J = 7.0 Hz, 3 H, for *endo* **22**). This was in excellent agreement with literature data.[4b]

Ketal 1. A mixture of ketone **22** (13.8 g, 0.100 mol), *p*-toluenesulfonic acid monohydrate (1.89 g, 9.95 mmol), and ethylene glycol (56 mL, 1.0 mol) in benzene (150 mL) was heated to reflux for 24 h in a flask equipped with a Dean−Stark water separator. After cooling to room temperature, the mixture was partitioned between MTBE and saturated aqueous K_2CO_3. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Bulb-to-bulb distillation (bp 55 °C (pot)/0.1 mm) afforded 15.9 g (87%) of **1** as a colorless oil, TLC R_f (5% MTBE−petroleum ether) = 0.50 and 0.69. The ratio of the isomers was determined by ^{1}H NMR: common signals assigned to both isomers δ 5.70−5.45 (m, 2 H), 4.00−3.85 (m, 4 H), 2.25−1.83 (m, 4 H), 1.50−1.30 (m, 2 H); the major isomer δ 1.29 (s, 3 H), 1.11 (d, J = 6.9 Hz, 3 H); the minor isomer δ 32 (s, 3 H), 0.99 (d, J = 7.0 Hz, 3 H); ^{13}C NMR: the major isomer δ 134.0, 125.5, 48.0, 31.9, 21.9, 20.3, u 112.4, 64.3, 63.6, 24.8, 24.1; the minor isomer δ d 133.6, 125.3, 45.9, 30.2, 22.4, 16.2, u 111.4, 65.1, 63.8, 26.3, 17.4; IR 1455, 1216 cm^{-1}; MS (CI) *m*/*z* 183 (M + H$^+$, 100), 167 (50); HRMS calcd for $C_{11}H_{18}O_2$ (M$^+$) 182.1307, obsd 182.1300.

Aldehyde Methyl Esters 2a and 25a. An ozone stream was bubbled through a suspension of ketal **1** (3.40 g, 18.7 mmol) and $NaHCO_3$ (6.31 g, 75.1 mmol) in a 5:1 mixture of CH_2Cl_2:MeOH (36 mL) at −78 °C until complete consumption of **1** was observed by TLC analysis. The mixture was then flushed with nitrogen, and $NaHCO_3$ was removed by filtration. The filtrate was concentrated in vacuo to give the crude mixture of **23** and **24** as a colorless oil, which was taken up in CH_2Cl_2 (30 mL). The mixture was cooled to 0 °C, and acetic anhydride (8.8 mL, 93 mmol) and triethylamine (3.9 mL, 28 mmol) were added. The mixture was stirred at room temperature for 1 h and then partitioned between MTBE and, sequentially, 3 M aqueous HCl, 3 M aqueous KOH, and brine. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the crude product afforded 3.11 g (68%) of an inseparable mixture of **2a** and **25a** as a colorless oil, TLC *Rf* (30% MTBE−petroleum ether) = 0.26. The ratio of **2a** and **25a** (3.6:1) was determined by ^{1}H NMR of their aldehyde signals δ 0.77 (t, J = 1.5 Hz, 1 H), 9.76 (t, J = 1.3 Hz, 1 H), 9.64 (d, J = 0.7 Hz, 1 H), 4.00−3.79 (m, 4 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 2.66−1.70 (m, 6 H), 1.38−1.10 (a mixture of singlets and doublets, 6 H); ^{13}C NMR: (Only signals corresponding to the major isomer are described.) δ d 203.5, 51.5, 47.3, 46.1, 22.7, 9.7, u 173.5, 111.2, 63.9, 63.8, 32.8, 22.8; IR 2888, 2725, 1732, 1211 cm^{-1}; MS (CI) *m*/*z* 245 (M + H$^+$, 70), 229 (100); HRMS calcd for $C_{12}H_{21}O_5$ (M + H$^+$) 245.1389, obsd 245.1025.

Following the same procedure for **2a** and **25a**, aldehyde esters **2b**−**e** and **25b**−**e** were prepared, and their data are described below.

Aldehyde Ethyl Esters 2b and 25b. TLC R_f (30% MTBE−petroleum ether) = 0.36. An oil (3.6:1 ratio); ^{1}H NMR δ 9.77 (t, J = 1.6 Hz, 1 H), 9.76 (t, J = 1.3 Hz, 1 H), 9.64 (d, J = 0.8 Hz, 1 H), 4.20−4.05 (m, 2 H), 4.00−3.78 (m, 4 H), 2.70−1.68 (m, 6 H), 1.30−1.10 (a mixture of singlets, doublets and triplets, 9 H); ^{13}C NMR signals for a major isomer δ d 203.3, 47.1, 46.0, 22.6, 14.0, 9.5, u 172.9, 111.1, 63.74, 63.70, 60.2, 32.9, 22.7; IR 2889, 2719, 1729, 1181 cm^{-1}; MS (CI) *m*/*z* 259 (M + H$^+$, 65), 229 (100); HRMS calcd for $C_{13}H_{23}O_5$ (M + H$^+$) 259.1545, obsd 259.1170.

Aldehyde Isopropyl Esters 2c and 25c. TLC R_f (30% MTBE−petroleum ether) = 0.47. An oil (3.6:1 ratio); ^{1}H NMR δ 9.761 (t, J = 1.6 Hz, 1 H), 9.757 (t, J = 1.4 Hz, 1 H), 9.63 (d, J = 0.5 Hz, 1 H), 5.03−4.92 (m, 1 H), 4.00−3.76 (m, 4 H), 2.65−1.70 (m, 6 H), 1.35−1.08 (a mixture of singlets and doublets, 12 H); ^{13}C NMR signals for a major isomer δ δ 203.4, 67.6, 47.1, 46.0, 22.7, 21.7, 9.6, u 172.5, 111.2, 63.8 (2 C), 33.2, 22.9; IR 2886, 2715, 1727, 1182 cm^{-1}; MS (CI) *m*/*z* 273 (M+H$^+$, 15), 213 (100); HRMS calcd for $C_{14}H_{25}O_5$ (M + H$^+$) 273.1702, obsd 273.1333.

Aldehyde Benzyl Esters 2d and 25d. TLC R_f (30% MTBE−petroleum ether) = 0.31. An oil (4.8:1 ratio); ^{1}H NMR δ 9.72 (t, J = 1.5 Hz, 1 H), 9.69 (t, J = 1.3 Hz, 1 H), 9.58 (d, J = 0.6 Hz, 1 H), 7.40−7.28 (m, 5 H), 5.15−5.08 (m, 2 H), 4.00−3.72 (m, 4 H), 2.70−1.68 (m, 6 H), 1.30−1.07 (a mixture of singlets and doublets, 6 H); ^{13}C NMR signals for a major isomer δ d 203.4, 128.4 (2 C), 128.2 (2 C), 128.1, 47.1, 46.1, 22.7, 9.6, u 172.8, 135.7, 111.1, 66.1, 63.78, 63.76, 32.9, 22.8; IR 2887, 2718, 1731, 1170 cm^{-1}; MS (CI) *m*/*z* 321 (M + H$^+$, 35), 229 (75), 113 (100); HRMS calcd for $C_{18}H_{25}O_5$ (M + H$^+$) 321.1702, obsd 321.1347.

Aldehyde *tert*-Butyl Esters 2e and 25e. TLC R_f (30% MTBE−petroleum ether) = 0.55. An oil (6.0:1 ratio); ^{1}H NMR δ 9.76 (t, J = 1.4 Hz, 1 H), 9.63 (s, 1 H), 3.92−3.76 (m, 4 H), 2.65−1.70 (m, 6 H), 1.46 (s, 9 H), 1.44 (s, 9 H), 1.32 (s, 3 H), 1.12 (d, J = 7.1 Hz, 3 H); ^{13}C NMR signals for a major isomer δ 203.6, 47.2, 46.1, 28.0, 22.9, 9.6, u 172.5, 111.3, 80.4, 63.9 (2 C), 34.2, 23.1; IR 2887, 2715, 1725, 1154 cm^{-1}; MS (CI) *m*/*z* 213 (M$^+$ − *t*-BuOH, 100); HRMS calcd for $C_{11}H_{17}O_4$ (M$^+$ − *t*-BuOH) 213.1127, obsd 213.1117.

Pyrrole 3. A solution of the mixture of **2a** and **25a** (3.6:1 ratio, 830 mg, 3.40 mmol) and pyridinium *p*-toluenesulfonate (256 mg, 1.02 mmol) in a 3:1 mixture of acetone:water (8 mL) was heated to reflux for 4 h. After cooling to room temperature, the mixture was diluted with acetone (8 mL), and ammonium carbonate (6.60 g, 68.8 mmol) was added. The acetone was carefully removed by rotatory evaporation. DMF (12 mL) was added to the residue, and the mixture was stirred at 120 °C for 30 min. Sublimed ammonium carbonate had to be pushed back into the flask from the reflux condenser periodically through the reaction. The cooled mixture was partitioned between MTBE and water. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo to give the crude methyl 2,4-dimethyl-1*H*-pyrrole-3-propanoate **26**[1b] as an orange oil. This was taken up in TFA (4.0 mL). Trimethyl orthoformate (2.0 mL, 18 mmol) was added dropwise, and the mixture was stirred at room temperature for 10 min. The resulting product was partitioned between $CHCl_3$ and, sequentially, water, 10% aqueous NH_4OH and water. The combined organic extract was dried ($MgSO_4$) and concentrated. Chromatography of the crude product over silica gel (deactivated with Et_3N) provided a light brown solid (242 mg, mp 118−121 °C), TLC R_f (50% MTBE−petroleum ether) = 0.30. Recrystallization from $CHCl_3$−petroleum ether afforded 218 mg (39% overall based on **2a** content) of **3** as yellow crystals: mp 123−124 °C (lit.[1d] 125−127 °C; lit.[1b] 123−125 °C; lit.[1a] 128−129 °C); ^{1}H NMR δ 9.41 (br, 1 H). 9.46 (s, 1 H), 3.67 (s, 3 H), 2.72 (t, J = 7.7 Hz, 2 H), 2.45 (t, J = 7.7 Hz, 2 H), 2.28 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR δ 175.6, 51.6, 11.4, 8.7, u 173.3, 136.7, 132.6, 127.8, 120.9, 34.5, 19.2.

When this reaction was scaled up (5.27 g of **2a** and **25a**), 1.05 g of **3** was obtained.

Acknowledgment. We thank the NIH (GM60287) for support of this work.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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