25.16, 29.25, 129.83; MS, *m/e* (rel intensity) 220 (M^+), 176 (1), 149 (12), 96 (18), 95 (24), 94 (21), 83 (10), 82 (25), 68 (27), 67 (53), 66 (8), 55 (42), 54 (32), 44 (17), 43 (13).

1,11-Cycloeicosadiene[2a] had the following properties: oil; IR (neat) 3005, 2925, 2895, 1590, 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (m, 20 H), 2.02 (m, 8 H), 5.38 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 26.81, 28.92, 29.07, 29.43, 129.77; MS, *m/e* (rel intensity) 276 (M^+), 135 (12), 122 (7), 121 (14), 110 (9), 109 (16), 108 (12), 107 (14), 96 (38), 95 (43), 94 (49) 93 (21), 83 (24), 82 (45), 81 (68), 80 (96), 79 (22), 69 (38), 68 (35), 67 (74), 55 (93), 54 (43), 53 (15).

Synthesis of 1-Phenyl-1,2-propanedione (7). In a 25-mL two-necked round-bottom flask equipped with a magnetic stirring bar, argon inlet, and rubber septa was placed 0.74 g (2.0 mmol) of ethyltriphenylphosphonium bromide in 20 mL of THF followed by addition of 2.2 mL (2.2 mmol) of sodium bis(trimethylsilyl)-amide via syringe. After the red solution stirred for 3 h, 1.2 mL (1.0 mmol) of benzoyl chloride was added, immediately discharging the color of the solution and producing a white precipitate. Stirring was continues for an additional 4 h, at which time 0.5 g (2.2 mmol) of oxaziridine **4** was added all at once. The reaction mixture was quenched after 0.5 h by addition of 10 mL of saturated NH_4Cl solution and 10 mL of water. The solution was transferred to a 125-mL separatory funnel, extracted with methylene chloride (3 × 10 m), and dried over anhydrous $MgSO_4$. After removal of solvent, the product was isolated by preparative TLC eluting with 20% ether–*n*-pentane to afford 0.8 g (54%) as a yellow oil identical in all respects with an authentic sample of 1-phenyl-1,2-propanedione (**7**).[19]

Acknowledgment. This work was supported by the National Institutes of Health (Institute of General Medical Science) through Grant GM 34014.

Registry No. 1 (R^1 = MeO_2C, R^2 = H), 2605-67-6; 1 (R^1 = PhCO, R^2 = H), 859-65-4; 1 (R^1 = MeCO, R^2 = H), 1439-36-7; 1 (R^1 = Ph, R^2 = H), 16721-45-2; 1 (R^1 = $CH_3(CH_2)_{10}$, R^2 = H), 54208-04-7; 1 (R^1 = PhCO, R^2 = Me), 1450-07-3; 1 (R^1 = EtO_2C, R^2 = Me), 5717-37-3; **3**, 63160-13-4; **4**, 104322-63-6; **7**, 579-07-7; $Ph_3P{=}CH(CH_2)_6CH{=}PPh_3$, 38451-22-8; $Ph_3P{=}CH(CH_2)_8CH{=}PPh_3$, 38451-25-1; (*E*)-$MeO_2CCH{=}CHCO_2Me$, 624-49-7; (*Z*)-$MeO_2CCH{=}CHCO_2Me$, 624-48-6; (*E*)-PhCOCH=CHCOPh, 959-28-4; (*E*)-$CH_3COCH{=}CHCOCH_3$, 820-69-9; (*Z*)-$CH_3COCH{=}CHCOCH_3$, 17559-81-8; (*E*)-PhCH=CHPh, 103-30-0; (*Z*)-PhCH=CHPh, 645-49-8; (*E*)-$CH_3(CH_2)_{10}CH{=}CH(CH_2)_{10}CH_3$, 76665-54-8; $PhCOCOPh$, 134-81-6; EtO_2CCOCH_3, 617-35-6; (*E*)-$EtO_2CC(CH_3){=}C(CH_3)CO_2Et$, 1587-30-0; $Ph_3PEt^+Br^-$, 1530-32-1; PhCOCl, 98-88-4; $PhCH_2(Ph)_3P^+Cl^-$, 1100-88-5; $CH_3(CH_2)_{11}P(Ph)_3^+Cl^-$, 15510-55-1; (*E,E*)-1,9-cyclohexadecadiene, 7433-62-7; (*Z,Z*)-1,9-cyclohexadecadiene, 7431-74-5; (*E,E*)-1,11-cyclocosadiene, 6568-71-4; octamethylene-1,8-bis(triphenylphosphonium bromide), 23739-64-2; decamethylene-1,10-bis(triphenylphosphonium bromide), 917-20-4.

Improved Synthesis of Symmetrical and Unsymmetrical 5,11-Methanodibenzo[*b,f*][1,5]diazocines. Readily Available Nanoscale Structural Units[1]

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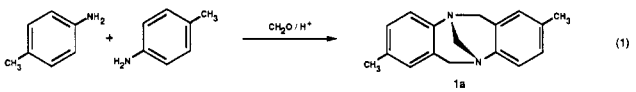
Enzymes and biogenic receptors are impressive examples of nanoscale devices. The development of nanoscale (10–500 Å) functional devices and the growth of a nanotechnological capability will require methods to prepare and characterize larger molecules or molecular aggregates than have heretofore been prepared.[3] A goal in our lab has been to develop general synthetic methods for preparing large and relatively rigid molecules of unambiguous shape.[4] These molecules are of interest as components of synthetic receptors and orderly functional group arrays.

Symmetrical 5,11-methanodibenzo[*b,f*][1,5]diazocines have been shown to be conveniently available chiral structural units for preparing such devices.[4b,f] We report here a process which makes available for the first time unsymmetrical 5,11-methanodibenzo[*b,f*][1,5]diazocines and illustrate the use of this new process by preparing some simple examples of such molecules.

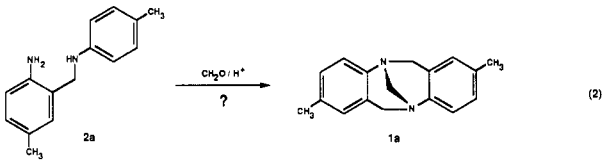
The preparation of 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (**1a**, eq 1) was described by Tröger in 1887.[5] Since that time several additional



(1)

1a

examples of the reaction of aniline derivatives with formaldehyde have been reported.[4a-d,f,h-j,6] These reactions afford symmetrical, chiral dibenzodiazocines. Consideration of the possible mechanisms for formation of **1a** led to the hypothesis (eq 2) that (2-aminobenzyl)amine **2a** might, in the presence of formaldehyde and acid, afford a diazocine product.



(2)

2a 1a

To explore this idea, benzylamine **2a** was prepared (Scheme I) by two-step reduction (83%) of the 2-nitrobenzamide **3a** obtained through dicyclohexylcarbodiimide-mediated condensation (94%) of toluidine and 5-methyl-2-nitrobenzoic acid.[7,8] In the crucial test, treatment of diamine **2a** with formaldehyde and HCl afforded a 97% yield of Tröger's base, the symmetrical dibenzodiazocine **1a**.

The success of this simple experiment provides for the first time a way of preparing unsymmetrical 5,11-methanodibenzo[*b,f*][1,5]diazocines that bear *electron-withdrawing* substituents. Prior experiments had indicated that such molecules (not previously reported) are not available by the classical method described by Tröger.[4f,6] It was reasoned that the present method circumvents the need for electrophilic aromatic substitution at one of the

(1) Number 11 in a series on the Chemistry of Synthetic Receptors and Functional Group Arrays. Number 9: Wilcox, C. S.; Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Lynch, V. in *Proceedings of the 5th International Symposium on Inclusion Phenomena*; Atwood, J., Ed.; Plenum Press: New York, 1989.

(2) Fellow of the Alfred P. Sloan Foundation, 1989–1990.

(3) Nanotechology deals with devices that have dimensions and tolerances in the 0.5–100-nm range: Taniguchi, N. *Proc. Int. Conf. Prod. Eng. Tokyo, Part 2*, **1974**, 18–23. For a review, see: Francks, A. *J. Phys. E: Sci. Instrum.* **1987**, 1442–1451. A provocative picture of the future of nanotechnology is provided by: Drexler, K. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5275–5278.

(4) (a) Wilcox, C. S. *Tetrahedron Lett.* **1985**, *26*, 5749–5742. (b) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865–1867. (c) Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6204–6210. (d) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563–5566. (e) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463–471. (f) Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 98–104. (g) Wilcox, C. S.; Cowart, M. D. *Carbohydr. Res.* **1987**, *171*, 141–160. (h) Larson, S.; Wilcox, C. S. *Acta Crystallogr.* **1986**, *C42*, 224–227. (i) Larson, S.; Wilcox, C. S. *Acta Crystallogr.* **1986**, *C42*, 376–378.

(5) Tröger, J. *J. Prakt. Chim.* **1887**, *36*, 225–245.

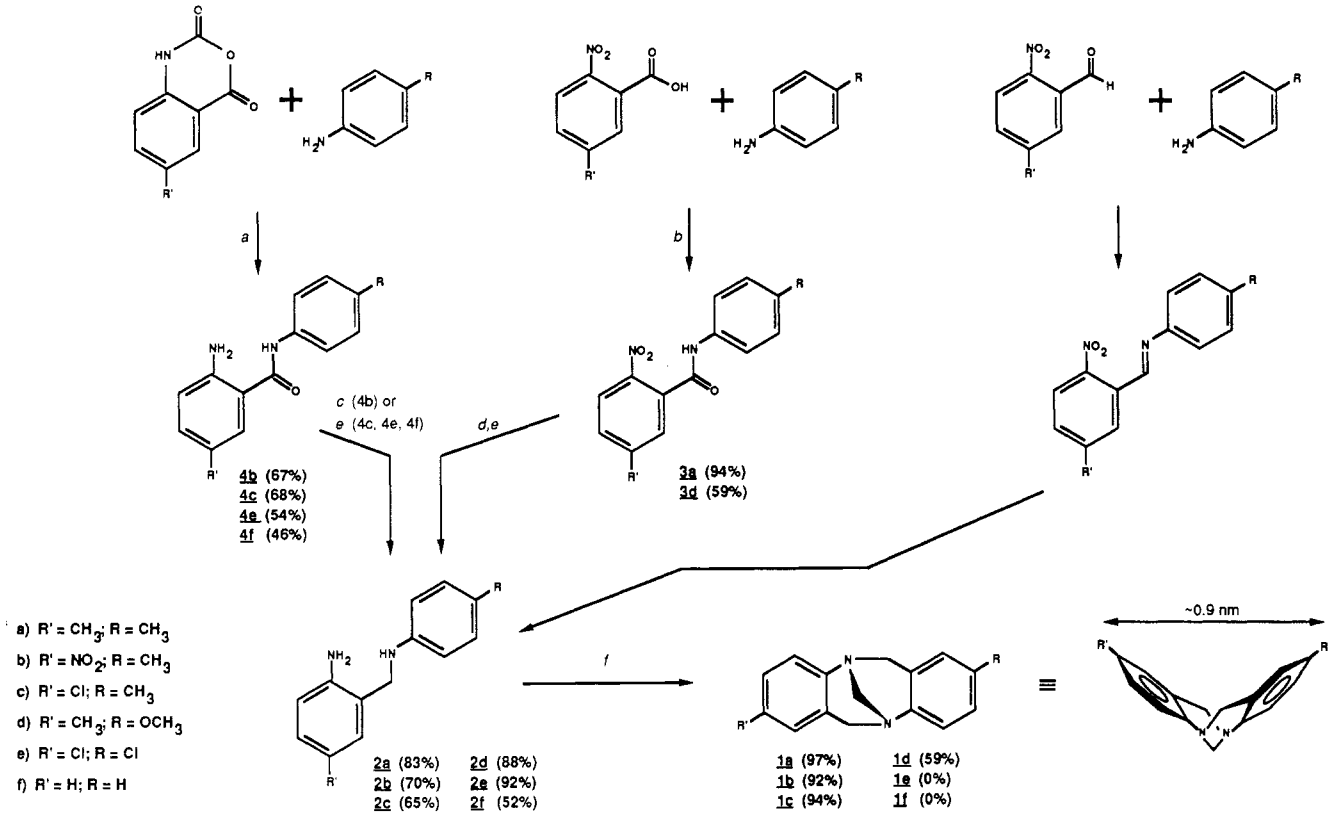
(6) Farrar, W. V. *J. Appl. Chem.* **1964**, *14*, 389–399.

(7) (a) Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, *11*, 1208–1213. (b) Ishikawa, F.; Watanabe, Y.; Saegusa, J. *Chem. Pharm. Bull.* **1980**, *28*, 1357–1364.

(8) All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis.

0022-3263/90/1955-0363$02.50/0

Scheme I[a]



[a] (a) EtOH, reflux; (b) DCC, DMF; (c) BH_3–THF, THF, reflux; (d) PtO_2–H_2/MeOH; (e) $LiAlH_4$/THF, reflux; (f) H_2CO/HCl.

aromatic components and that therefore the presence of an electron-withdrawing group on that ring should not preclude dibenzodiazocine formation.

In accord with this expectation, both nitro- and chloro derivatives of 5,11-methanodibenzo[*b*,*f*][1,5]diazocine can be prepared by this new process. The necessary diamines were prepared by reaction of the appropriate isatoic anhydride derivatives with toluidine in ethanol followed by reduction of the 2-aminobenzamides (**4b** and **4c**) so obtained. Both of these diamines (**2b** and **2c**) provided new analogues of Tröger's base when treated with formaldehyde and hydrochloric acid (Experimental Section). In each case, formation of the dibenzodiazocine proceeds in over 90% yield (Scheme I).

To test the effect of substituents in the aniline ring (the moiety undergoing electrophilic substitution), (2-aminobenzyl)amine **2d** was prepared. This amine, too, affords a dibenzodiazocine, but the yield is reduced to 59%. The reaction is subject to (unexamined) multiple byproduct formation. In one attempt, a chlorine substituent in the aniline moiety (**2e**, R = Cl) completely suppressed dibenzodiazocine formation under these conditions, while the analogous substrate which bore a methyl group instead of a chlorine atom provided dibenzodiazocine in 94% yield. Prior attempts to prepare the symmetrical 2,8-dichloro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1e**) directly from *p*-chloroaniline also met with failure.[6,9] When the positions para to the amines are not substituted (cf. **2f**, Scheme I), polymer formation is the predominant result.

These experiments demonstrate a new and generally useful method for preparation of molecules related to Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, **1a**). The process allows the preparation of unsymmetrical dibenzodiazocines from (2-aminobenzyl)(*N*-aryl)amines. The reaction accommodates electron-withdrawing or electron-donating substituents on the benzyl moiety of the key (2-aminobenzyl)amine (**2a–f**) but deactivating substituents on the *N*-aryl moiety may preclude dibenzodiazocine formation under the general reaction conditions.

The requisite(2-aminobenzyl)amines are easily prepared by known procedures.[7] Examples here were synthesized either by reaction of isatoic anhydride derivatives with aniline derivatives or by *N*-aryl amide formation from 2-nitrobenzoic acid derivatives. A third very convenient strategy for preparing (2-aminobenzyl)amines (shown in Scheme I) is founded upon the reduction of *N*-arylimines that are available in very high yield through the reaction of 2-nitrobenzaldehyde derivatives with anilines.[7b] A number of more complex (2-aminobenzyl)amines have been prepared in this laboratory by the latter process and will be described in future reports.

These and other related methanodibenzo[*b*,*f*][1,5]diazocines are useful as structural units for preparing synthetic receptors and functional group arrays. Such molecules will find use whenever two molecular fragments are to be held 8–10 Å apart and a crescentic rather than linear connecting bridge is desired. The incorporation of this new method into the preparation of novel and rigid water-soluble cyclophanes and orderly functional group arrays will be reported in due course.

Experimental Section

General Preparation of Substituted 2-Nitrobenzamides (3) from 2-Nitrobenzoic Acid Derivatives. A solution of a 2-nitrobenzoic acid derivative (1.0 mol equiv) and a para-substituted aniline (1.0 mol equiv) in DMF (reactant concentration 0.5 M) was chilled in an ice bath, and dicyclohexylcarbodiimide

(9) Unpublished work carried out by I. Sucholeiki in this laboratory. For additional discussion, see ref 4f.

(1.2 mol equiv) was slowly added. After 10 min, the solution was warmed to room temperature and stirred until thin-layer chromatography indicated that the reaction had gone to completion (2–4 h). The precipitated dicyclohexylurea was filtered off, and the filtrate was diluted with methylene chloride and extracted with saturated aqueous NaCl. The organic layer was dried over anhydrous magnesium sulfate and filtered, and volatile filtrate components were removed under reduced pressure. The crude product so obtained was recrystallized from 95% ethanol to give **3a** or **3d** in the yields indicated in Scheme I.

General Preparation of Substituted 2-Aminobenzamides (4) from Isatoic Anhydride Derivatives. The appropriate para-substituted aniline (1.0 mol equiv) was slowly added to a stirred suspension of the substituted isatoic anhydride (4.0 mol equiv) in dry ethanol (0.5 M in anhydride). The mixture was heated at reflux under nitrogen until the reaction had gone to completion (30–60 min, judged by thin-layer chromatography). A heavy precipitate forms in some cases. The mixture was poured into water and the precipitated product was separated by filtration and recrystallized from 95% ethanol to afford **4b,c,e,f** in the yields tabulated in Scheme I.

General Preparation of Substituted 5,11-Methanodibenzo[*b,f*][1,5]diazocines (1) from Substituted (2-Aminobenzyl)amines (2). To a stirred solution of **2** (1.0 mol equiv) in 95% ethanol (0.5–1.0 M) was added 37% formalin solution (6.0 mol equiv of formaldehyde) and 12 N HCl (6.0 mol equiv of HCl). The solution was stirred at either room temperature or 50 °C for 24 h, concentrated under reduced pressure to one-half the original volume, and poured into excess 1.6 N ammonium hydroxide solution. The resulting strongly basic mixture was extracted with methylene chloride, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layers were then dried over anhydrous $MgSO_4$. Filtration and removal of volatile filtrate components under vacuum gave, after chromatography on silica gel, diazocines **1a–d** in the yields tabulated in Scheme I.

Acknowledgment. This work was made possible through funds provided by the National Institute of General Medical Sciences (GM-34846) and by the Alfred P. Sloan Foundation.

Registry No. **1a**, 529-81-7; **1b**, 123333-41-5; **1c**, 123333-42-6; **1d**, 123333-43-7; **2a**, 73086-50-7; **2b**, 123333-37-9; **2c**, 123333-38-0; **2d**, 123333-39-1; **2e**, 123333-40-4; **2f**, 20887-06-3; **3a**, 123333-34-6; **3d**, 123333-35-7; **4b**, 123333-36-8; **4c**, 30686-42-1; **4e**, 24680-04-4; **4f**, 4424-17-3; *p*-$MeC_6H_4NH_2$, 106-49-0; *p*-$ClC_6H_4NH_2$, 106-47-8; $PhNH_2$, 62-53-3; *p*-$MeOC_6H_4NH_2$, 104-94-9; 1,2-dihydro-6-nitro-4*H*-3,1-benzoxazine-2,4-dione, 4693-02-1; 1,2-dihydro-6-chloro-4*H*-3,1-benzoxazine-2,4-dione, 4743-17-3; isatoic anhydride, 118-48-9; 2-nitro-5-methylbenzoic acid, 3113-72-2.

Supplementary Material Available: Complete physical data, including ^1H NMR, ^{13}C NMR, IR, MS, and elemental analyses for 17 substances: **1a–d**, **2a–f**, **3a,d**, and **4a–c,f** (10 pages). Ordering information is given on any current masthead page.

Facile Intramolecular O-14 → C-7 Acetyl Transfer in Opiate 14-Acetate Esters

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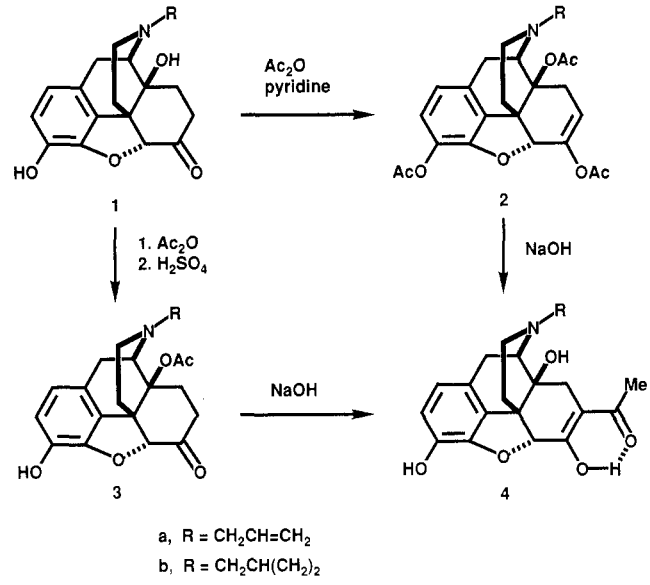
We have recently reported the facile conversion of naloxone **1a** and naltrexone **1b** to the corresponding triacetates **2**.[1] In an effort to convert **2** to the 14-acetate ester **3**, we attempted to selectively hydrolyze **2** in dilute NaOH



solution at 23 °C. However, the product that was produced in high yield was not the expected ester **3**, as it exhibited an IR carbonyl absorption (1631 cm^{-1}) corresponding to a β-diketone. Also, its NMR spectrum contained a methyl peak, consistent with a methyl ketone moiety, and a proton singlet at unusually low field (15.1 ppm).

These spectral data together with the fact that the product had a molecular weight identical with that of a monoacetyl compound suggested that base hydrolysis had occurred at the less hindered positions (C-3 and C-6) to yield **3**, followed by O-14 → C-7 migration of the remaining acetyl group to afford β-diketone **4**. The low-field resonance at 15.1 ppm therefore is consistent with the presence of an enolic proton that is internally hydrogen bonded as illustrated in **4**.

That the 7-acetyl group in **4** was transferred from the O-14 rather than the O-6 position was demonstrated by converting the 14-acetate **3** under identical conditions to the same product **4** in high yield.

The mild conditions under which the acyl transfer occurred probably are related to the ease of base-catalyzed enolate formation and the relatively hindered access of the 14-acetoxy carbonyl carbon to attack by hydroxide ion. This would render this carbonyl group relatively more susceptible to intramolecular attack by the neighboring carbanion C-7 (I) derived from the enolate (Scheme I). The resulting pentacyclic transition state II could then open to afford the 7-acetyl intermediate III, which can undergo rapid H-7 exchange to give the β-diketone enolate IV. The driving force for the formation of IV is very likely related to its greater resonance stabilization relative to that of III and to the elimination of the O-14–Ac-7 diaxial interaction.

Significantly, the equatorial protons at positions C-8 and C-9 that flank the 14-acetoxy group of **3** exhibit large downfield shifts (0.9–1.25 ppm) relative to those of **1**, while the axial C-7 proton is shifted upfield by 0.5 ppm (Table I). These data suggest that the acetyl carbonyl group of **3** may be in a conformation that is amenable to attack by a carbanion I as illustrated in Scheme I.

The major reason for depicting **4** as the endocyclic enol rather than the exocyclic enol is based upon studies[1] that suggest greater stability of an endocyclic C-6 double bond in the opiate system. Two factors have been implicated in conferring this stability. The first is relief of torsional strain in ring C by introduction of a Δ^6 bond, and the second is that the ring flattening that occurs in such a case

(1) Nagase, H.; Abe, A.; Portoghese, P. S. *J. Org. Chem.*, **1989**, *54*, 4120.

0022-3263/90/1955-0365$02.50/0