(9.281 g). The carboxylic acids (9.281 g) were electrochemically oxidized in methanol (100 mL) containing sodium medthoxide (1.69 g, 30 mmol) as described in the synthesis of **8**. After 2.27 f/mol of electricity was passed, methanol was evaporated in vacuo. Extraction of the residue with ethyl acetate followed by distillation gave a mixture of **13a** and **13b** (5.422 g, 25.2 mmol). The overall yield was 52% from **12a** and **12b**.

A mixture of **13a** and **13b**: bp 103–105 °C (1 mmHg); IR (neat) 2950, 1695, 1445, 1370, 1320, 1195, 1160, 1115, 1080, 1000 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.10 (m, 4 H), 2.17 (s, 3 H), 2.20–2.73 (m, 2 H), 3.33 (s, 3 H), 3.72 (s, 3 H), 4.00–4.33 (m, 1 H), 5.14–5.33 (m, 1 H). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.53; H, 8.07; N, 6.59.

Hygroline (14a + 14b) and Pseudohygroline (14a′ + 14b′). To a stirred suspension of LAH (1 g, 26.3 mmol) in dry ether (25 mL) was added dropwise a solution of a mixture of **13a** and **13b** (1.136 g, 5.28 mmol) in ether. The mixture was refluxed for 10 h under an atmosphere of nitrogen. Usual workup gave a residue, and it was distilled (bulb-to-bulb) to afford a mixture of hygroline (**14a + 14b**) and pseudohygroline (**14a′ + 14b′**)[2a] in a ratio of 2 to 3 (611 mg, 4.27 mmol, 81% yield). Hygroline and pseudohygroline were isolated by preparative GLC and separable by column chromatography (alumina, AcOEt–hexane).

Hygroline: $[\alpha]^{21}_D$ +21.32° (ethanol, *c* 3).[11]

Pseudohygroline: $[\alpha]^{21}_D$ +45.62° (ethanol, *c* 3).

1,2-Bis(methoxycarbonyl)-5-allylpyrrolidines were prepared in 74% yield with the ratio of 72 to 28 by utilizing a similar method to the synthesis of **12a** and **12b**: IR (neat) 3090, 2960, 1760, 1705, 1645, 1450, 1385, 1280, 1200, 1180, 1130, 1118, 1005, 925, 780 cm^{-1}; NMR (CCl_4) δ 1.50–2.93 (m, 6 H), 3.65, 3.68, and 3.70 (3 s, 6 H), 3.77–4.10 (m, 1 H), 4.16–4.37 (m, 1 H), 4.88–5.22 (m, 2 H), 5.50–6.07 (m, 1 H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.98; H, 7.78; N, 6.16.

Acknowledgment. This work was partly supported by a grant from the Asahi Glass Foundation for Industrial Technology.

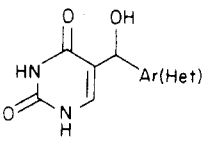
An Acid-Catalyzed Hydroxyalkylation of Uracil: A Facile Synthesis of 5-(Arylhydroxymethyl)uracils

Bing L. Lam[1] and Lendon N. Pridgen*

Smith Kline and French Laboratories, Inc., Philadelphia, Pennsylvania 19101

Received December 3, 1985

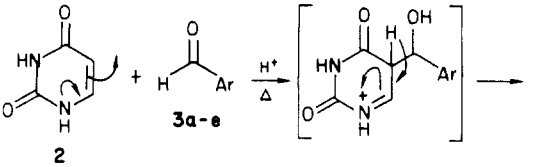
Previously reported syntheses of 5-substituted pyrimidinones **1** have usually found it expedient to incorporate formation of the pyrimidinone ring as a central part of the synthesis. Such approaches involve the use of multifunctionalized precursors such as α-formylhydrocinnamates,[2] α-(arylmethyl)cyanoacetates,[3] α-(arylmethyl)malonitriles,[3] α-(alkoxymethyl)cinnamonitriles,[4] or α-arylmethyl enamino nitriles.[5] In connection with ongoing work in this laboratory, we had the need to develop a more efficient synthesis of 2,4-pyrimidinones such as **1**. We chose to begin our synthesis with inexpensive



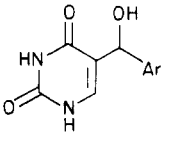
1

uracil **2** and explore functionalization of the relatively electronegative C-5 carbon with an appropriately substituted electrophilic carbon. Even though 5-hydroxymethylation[6] and 5-chloromethylation[7] of uracil have been extensively studied, we found only one other example of a successful carbon monoalkylation on *unsubstituted* uracil. Roth[2,8] reported that uracil reacts with phenolic Mannich bases to yield 5-benzyluracils in ethylene glycol at 140–160 °C.

We now report that under aqueous acidic conditins unsubstituted uracil **2** reacts with aromatic aldehydes containing an electron-deficient ring **3a-e** (especially heterocyclic aldehydes) to yield 5-(arylhydroxymethyl)-2,4(1*H*,3*H*)-pyrimidinones **4a–e** in good to excellent yields (Table I). Equimolar quantities of **2** and **3** were heated under reflux in aqueous mineral acids (e.g., concentrated HCl, HBr, HI, or H_2SO_4; preferably HCl) for 1–8 h to yield upon neutralization the product **4** (eq 1). These represent,



2 **3a-e**



(1)

4a-e

to the best of our knowledge, the first successful examples utilizing the enamino ketone character of unsubstituted uracil to alkylate C-5 with an aldehyde other than formaldehyde.[6b,9–11] We have been unable to effect this reaction

(1) Present address: Smith Kline Chemicals, Conshohocken, PA 19428.

(2) Roth, B.; Falco, E. A.; Hitchings, G.; Bushby, S. R. *J. Med. Pharm. Chem.* **1962**, *5*, 1103.

(3) (a) Swaringen, R. A.; Yeowell, D. A.; Wistowaty, J. C.; El-Sayad, H. A.; Steward, E.; Darnofall, M. *J. Org. Chem.* **1979**, *44*, 4825. (b) Baker, B. R.; Santi, D. V. *J. Pharm. Sci.* **1965**, *54*, 1252.

(4) (a) Hoffer, M.; Grunsberg, E.; Mitrovic, M.; Bross, A. *J. Med. Chem.* **1971**, *14*, 462. (b) Stogryn, E. *J. Heterocycl. Chem.* **1974**, *11*, 251.

(5) Kompis, I.; Mueller, W.; Boehni, E.; Then, R.; Montavan, M. *Eur. J. Med. Chem*—Chim. *Ther.* **1977**, *12*, 536.

(6) (a) Cline, R. E.; Fink, R.; Fink, K. *J. Am. Chem. Soc.* **1959**, *81*, 2521. (b) Brown, D. J. *The Pyrimidines*; Weisburger A., Ed.; Wiley: New York, 1962; Chapter 1.

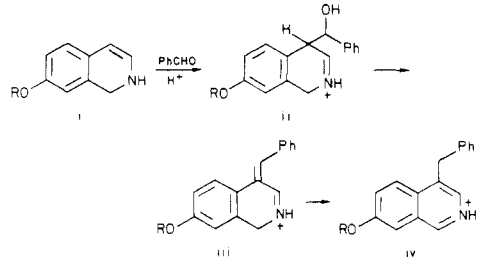
(7) Skinner, W. A.; Schelstraete, M. G. M.; Baker, B. R. *J. Org. Chem.* **1960**, *25*, 149.

(8) (a) Roth, B.; Strelitz, J. Z. British Patent 1 128 234, 1968. (b) Roth, B.; Strelitz, J. Z.; Rauckman, B. S. *J. Med. Chem.* **1980**, *23*, 379. (c) Rauckman, B. S.; Roth, B. *J. Med. Chem.* **1980**, *23*, 384. (d) Roth, B.; Aig, E.; Lane, K.; Rauckman, B. S. *J. Med. Chem.* **1980**, *23*, 535.

(9) Chevrier, M.; Bensaude, O.; Guillerez, J.; Dubois, J. E. *Tetrahedron Lett.* **1980**, 3359 and references therein.

(10) (a) Iida, H.; Aoyagi, S.; Kawano, K.; Kibayashi, C. *Chem. Pharm. Bull.* **1978**, *26*, 3229. (b) For a review on enamino ketones, see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

(11) Dyke,[12a] has reviewed the reaction of 1,2-dihydroisoquinolines, a heterocyclic enamine, with aromatic aldehydes to form β-substituted derivatives. Included is an appropriate example initially reported by Bobbitt[13] but refined by Dyke[12b] where 1,2-dihydroisoquinoline i reacted with benzaldehyde in refluxing concentrated HCl to yield the 4-benzylisoquinoline iv via the proposed intermediates ii and iii.



0022-3263/86/1951-2592$01.50/0

Table I. 5-(Arylhydroxymethyl)-2,4(1*H*,3*H*)-pyrimidinones 4a–e

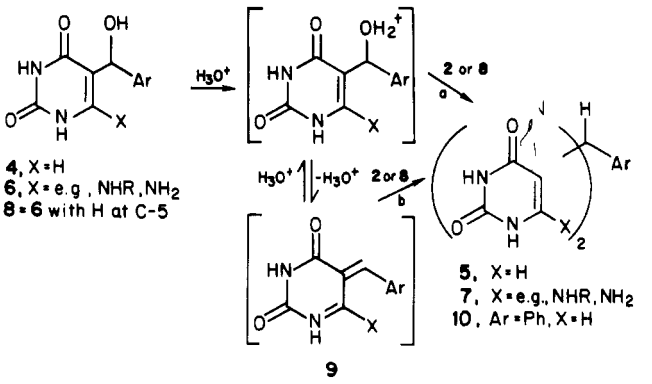
product 4,[a] Ar	yield,[b] %	mp, °C	high-resolution MS, *m/e*	^{1}H NMR (Me_2SO-d_6), δ
a, 6-methyl-3-pyridinyl	70	312–316	calcd for $C_{11}H_{11}N_3O_3$, 233.080 found, 233.080	2.43 (s, 3 H), 5.45 (q, J = 5 Hz, 2 H),[c,e] 7.35 (q, J = 9.0 Hz, 2 H), 7.32 (d, J = 6.0 Hz, 1 H),[c,d] 8.45 (d, 1 H), 10.6 (NH, d, J = 6 Hz, 1 H),[c] 10.9 (NH, 1 H)
b, 3-quinolyl	64	300 dec	calcd for $C_{14}H_{11}N_3O_3$, 269.0800 found, 269.079	5.75 (q, J = 5 Hz, 2 H),[c,e] 7.32 (d, J = 6 Hz, 1 H),[c,d] 7.5–8.0 (m, 5 H), 8.90 (d, J = 2.5 Hz, 1 H), 10.75 (NH, d, J = 6 Hz, 1 H),[c] 10.94 (NH, 1 H)
c, 4-nitrophenyl	74	256–258	calcd for $C_{11}H_9N_3O_5$, 263.054 found, 263.055	5.25 (5, 1 H), 7.2 (d, J = 6 Hz, 1 H),[c,d] 7.8 (q, J = 9 Hz, 4 H), 10.8 (NH, d, J = 6 Hz, 1 H),[c] 11.1 (NH, 1 H)
d, 4-pyridinyl	66	263 dec	calcd for $C_{10}H_9N_3O_3$, 219.064 found, 219.065	5.55 (q, J = 5 Hz, 2 H),[c,e] 7.35 (m, 3 H), 8.5 (br d, 2 H), 10.75 (NH, d, J = 6 Hz, 1 H),[c] 11.1 (NH, 1 H)
e, 4-quinolyl	82	277–278	calcd for $C_{14}H_{11}N_3O_3$; 269.0800 found, 269.0798	6.40 (s, 1 H), 7.25 (d, J = 6 Hz, 1 H),[c,d] 7.7–8.4 (m, 5 H), 9.28 (d, J = 6 Hz, 1 H), 11.1 (NH, d, J = 6 Hz, 1 H),[c] 11.45 (NH, 1 H)

[a] Satisfactory combustion analyses and infrared data weree obtained for all new compounds listed in the table. [b] Isolated yield. [c] Collapses to a one-proton singlet on addition of D_2O. [d] This signal is assigned to the uracil C-6 proton thereby indicating coupling to the N-1 proton.[17] [e] The methine proton in this case exhibits distinct 5 Hz coupling to the hydroxyl proton in Me_2SO-d_6.

in nonaqueous media or under Friedel-Crafts conditions using uracil or 2,4-dimethoxypyrimidine. This is presumably due to the insolubility of uracil in organic solvents and the lower reactivity of its dimethoxy derivative.

The results in Table I demonstrate that aryl aldehydes with electron-deficient rings react to yield the (hydroxymethyl)uracil **4** as the major product. Other more electron-rich aromatic aldehydes (including benzaldehyde), that are also stable to these rigorous acidic conditions, yield mainly the 5-(arylmethylene)di-2,4(1*H*,3*H*)-pyrimidinones **5**[14] as determined by spectral data. Specifically, 5-(phenylmethylene)*di*-2,4(1*H*,3*H*)-pyrimidinone (**10**) was isolated as the major product from the reaction of uracil and benzaldehyde. The trisubstituted methane **5a** is also formed on prolonged heating of **4a**, presumably through disproportionation. The literature[15,16] contains many examples of the condensation of 6-substituted uracils **8** with aromatic aldehydes to form **7**, the 6-substituted uracil analogue of **5**. In fact the reaction of **8** with many electrophiles has been explored extensively in 5-deazaflavin synthesis. Isolation of the 6-substituted (hydroxymethyl)uracil **6**, however, has not been reported. Most probably this is because of the facile displacement of the protonated hydroxyl (pathway a, Scheme I) by the C-5 of uracil (either unreacted or from disproportionation of **6**[14]), yielding **7** in both cases. Alternatively, **5** or **7** could be formed from the benzylidene **9** (pathway b) which is similar to the materials prepared and proposed as intermediates by F. Yoneda.[15] Aliphatic aldehydes studied, e.g., acetaldehyde, propionaldehyde, and cinnamaldehyde, yielded only tarry substances.

Scheme I



Our synthesis of 5-substituted uracils thus provides a facile entry to the pyrimidine nucleus of 5-substituted 2′-deoxyuridines and other biologically active pyrimidinones.[18] Work on the reduction of 5-(arylhydroxymethyl)uracils **4** to corresponding 5-(arymethylene) uracil derivatives will be reported at a later date.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian CFT-20 (80 MHz) with Me_4Si as internal standard. Infrared spectra were obtained on a Perkin-Elmer 580 spectrometer. High-resolution mass spectra were obtained on a Varian MAT-CH5 double-focusing spectrometer.

A Representative Example for Preparation of 4a–e: 5-[(6-Methyl-3-pyridinyl)hydroxymethyl]-2,4(1*H*,3*H*)-pyrimidinedione (4a). Uracil (224 g, 2 mol) was added to 1.4 L of concentrated HCl, and the slurry was warmed to 60 °C. To this warmed suspension was added 2-methyl-5-formylpyridine (**3a**) (270 g, 2.2 mol).[19] The suspension was then heated under reflux for 8 h and allowed to cool to ambient temperature. The solution was then filtered to remove trace quantities of **5a** and the filtrate was basified to pH 8–8.5 with 10 N sodium hydroxide, at which point the solid product precipitated. The precipitate was collected by vacuum filtration, washed with 300 mL of acetone, and dried at 60 °C to yield 325 g (70%).

(12) (a) Dyke, S. In *Advances in Heterocyclic Chemistry*; Katritsky, A. R.; Boulton, A. J., Eds.; Academic: New York, 1972; Vol. 14, pp 279–329. (b) Brown, D. W.; Dyke, S. F.; Sainsbury, M. *Tetrahedron* **1969**, *25*, 101.

(13) Bobbitt, J. M.; Winter, D. P.; Kiely, J. M. *J. Org. Chem.* **1965**, *30*, 2459.

(14) Pfleiderer, W.; Sagi, F.; Grözinger, I. *Chem. Ber.* **1966**, *99*, 3530.

(15) (a) Yoneda, F.; Mori, K.; Sakuma, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 978. (b) Yoneda, F.; Asano, T.; Tsukuda, K. *Heterocycles* **1979**, *12*, 691. (c) Yoneda, F.; Takayama, F.; Koshiro, A. *Chem. Pharm. Bull.* **1979**, *27*, 2507. (d) Nishigaki, S.; Sato, J.; Shimizu, K., Furukawa, K.; Senga, K.; Yoneda, F. *Chem. Pharm. Bull.* **1980**, *28*, 142. (e) Mori, K.; Shinozuka, K.; Sakuma, Y.; Yoneda, F. *J. Chem. Soc., Chem. Commun.* **1978**, 764. (f) Yoneda, F.; Tsukuda, K.; Shinozuka, K.; Hiruyama, F.; Uekama, K.; Koshira, A. *Chem. Pharm. Bull.* **1980**, *28*, 3049.

(16) For a synthesis of 5-substituted uracils from 5-bromouracils, see: Mulvey, D. M.; Babson, R. D.; Zawoiski, S.; Ryder, A. M. *J. Heteroycl. Chem.* **1973**, *10*, 79.

(17) For a detailed study of N–H to C(6)–H proton coupling in uracils, see: Nollet, A. J. H.; Koomen, G. J.; Grose, W. F. A.; Pandit, U. K. *Tetrahedron Lett.* **1969**, 4607.

(18) (a) Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106. (b) Biala, E.; Jones, A. S.; Walker, R. T. *Tetrahedron* **1980**, *36*, 155.

(19) Callihan, R. H.; Wilt, M. H. *J. Org. Chem.* **1961**, *26*, 4912.

5,5′-[(6-Methyl-3-pyridinyl)methylene]bis(2,4(1*H*,3*H*)-pyrimidinedione) (5a) was isolated by filtration from the reaction above: mp 300 °C; IR (KBr) 3450 (N–H), 1710 (C=O) cm^{-1}; ^1H NMR (80 MHZ, Me_2SO-d_6) δ 8.55 (d, $J_{6,4}$ = 2.5 Hz, 1 H), 8.3 (dd, $J_{4,3}$ = 8.0 Hz, $J_{4,6}$ = 2.5 Hz, 1 H) 7.75 (d, $J_{3,4}$ = 8.0 Hz, 1 H), 7.15 (d, $J_{6,NH}$ = 6 Hz, 2 H, pyrimidinyl, collapses to singlet on deuterium exchange), 5.15 (s, 1 H), 2.75 (s, 3 H); high-resolution mass spectrum, *m/e* calcd for $C_{15}H_{13}N_5O_4$ 327.097, found 327.097.

5,5′-(Phenylmethylene)bis(2,4(1*H*,3*H*)-pyrimidinedione) (10). Uracil (1.0 g, 8.9 mmol) and benzaldehyde (0.946 g, 8.6 mmol) were heated under refluxing concentrated hydrochloric acid (20 mL). After 2 h the solution was cooled to ambient temperature, and the white precipitate that formed was removed by filtration and dried under vacuum, 1.3 g (4.4 mmol, 93% based on uracil): mp >300 °C; IR (KBr) 3450 (N–H), 1750 and 1650 (C=O) cm^{-1}; ^1H NMR (80 MHz, Me_2SO-d_6) δ 7.25 (m, 5 H), 6.75(d, $J_{6,NH}$ = 6 Hz, 2 H), 5.05 (s, 1 H); high-resolution mass spectrum, *m/e* calcd for $C_{15}H_{12}N_4O_4$ 312.086, found 312.087.

Acknowledgment. We are indebted to the Analytical and Physical Chemistry Department for the analytical data: E. Reich for combustion analyses, David B. Staiger and Gary E. Zuber for NMR/IR spectra, and Walter P. Johnson and Gerald D. Roberts for mass spectra.

Registry No. **2**, 66-22-8; **3a**, 53014-84-9; **3b**, 13669-42-6; **3c**, 555-16-8; **3d**, 872-85-8; **3e**, 4363-93-3; **4a**, 83902-97-0; **4b**, 102396-61-2; **4c**, 102396-62-3; **4d**, 102396-63-4; **4e**, 102396-64-5; **5a**, 102396-65-6; **10**, 102396-66-7; benzaldehyde, 100-52-7.

Formation of the Neopinone/Codeinone Ring System via Intramolecular 1,6-Addition of an Amino Moiety to a Dienyl Ketone[1]

J. E. Toth and P. L. Fuchs*

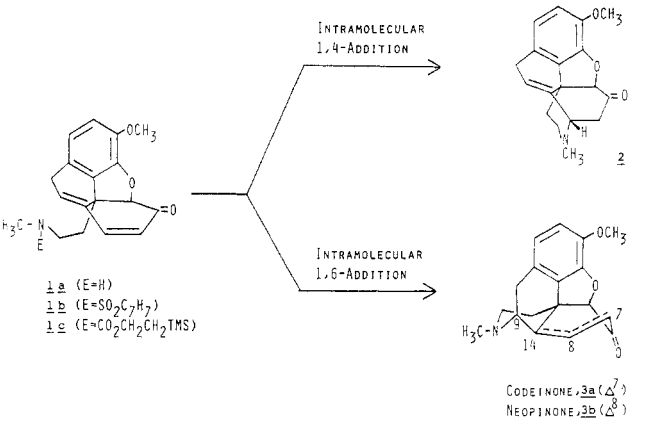
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received December 23, 1985

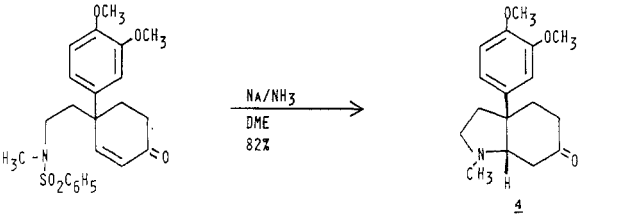
As part of a program directed toward the total synthesis of morphine and codeine[1] we wished to explore the possibility of effecting construction of the pentacyclic ring system via an intramolecular 1,6-addition of an amino residue to some suitably constituted dienyl ketone of the general type 1. Clearly the main issue is whether the desired addition mode (to afford **3a** or **3b**[2]) will be obtained in the presence of a potentially competitive 1,4-addition pathway (which would generate β-amino ketone **2**). Molecular models indicate that both pathways have excellent geometries and it seemed highly prudent to settle this question prior to the penultimate steps in a total synthesis (Scheme I).

For a number of reasons, we were initially attracted to examine a variant of the Sanchez reaction.[3] This reaction involves the direct reductive cyclization of sulfonamide enones under disolving metal conditions to afford β-amino ketones, as successfully demonstrated in the synthesis of (±)-mesembranone (**4**) (Scheme II). While the vinylogous reaction on a dienone like **1b** was unknown we felt it would be worth investigation. At the same time we also wished

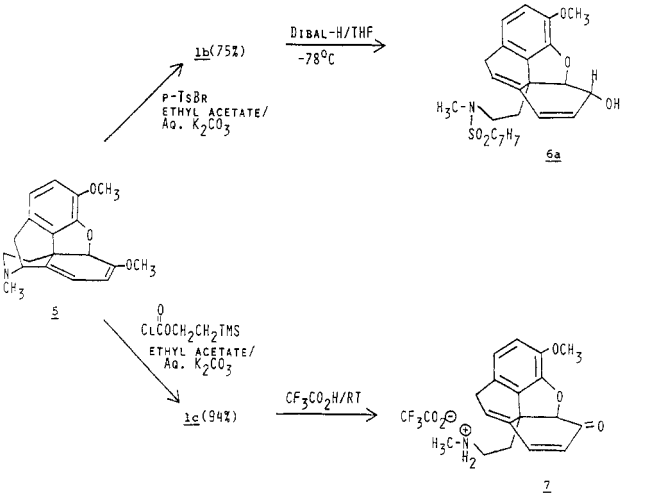
Scheme I



Scheme II



Scheme III



to prepare urethane **1c**, a progenitor of the parent amino dienone **1a**.

Treatment of thebaine (**5**)[4] with *p*-toluenesulfonyl bromide[5] (*p*-toluenesulfonyl chloride is ineffective in this reaction) under Schotten–Baumann acylation conditions, affords sulfonamide dienone **1b** in 75% yield. Unfortunately, reaction of **1b** under the dissolving metal conditions of Sanchez[3] yields an intractable mixture which did not exhibit a singlet methine resonance in the 4.3–5.3 ppm region of the 90-MHz NMR spectrum. In an effort to simplify the sulfonamide cleavage, dienone **1b** was reduced with DIBAL-H to generate dienyl alcohol **6a**[6] in 75% yield. Numerous attempts to desulfonylate this material under conditions previously shown to be effective at sulfonamide reduction[7] were either insufficient to effect cleavage or

(1) Morphine Support Studies. 2. For paper 1, see: Hamann, P. R.; Toth, J. E; Fuchs P. L. *J. Org. Chem.* **1984**, *49*, 3865.
(2) Barber, R. B.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1175.
(3) (a) Sanchez, I. H.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551. (b) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Diaz, E. *Heterocycles* **1985**, *23*, 593.
(4) Thebaine alkaloid powder, No. T-2019, Sigma Chemical Co., St. Louis, MO.
(5) Litvinenko, L. M.; Dadali, U. A.; Savelova, U. A.; Krichevtsova, T. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1964**, *34*, 3780.
(6) Assignment of C-6 stereochemistry in **6a** is based on ^1H NMR coupling constants. See Experimental Section.

0022-3263/86/1951-2594$01.50/0