(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.

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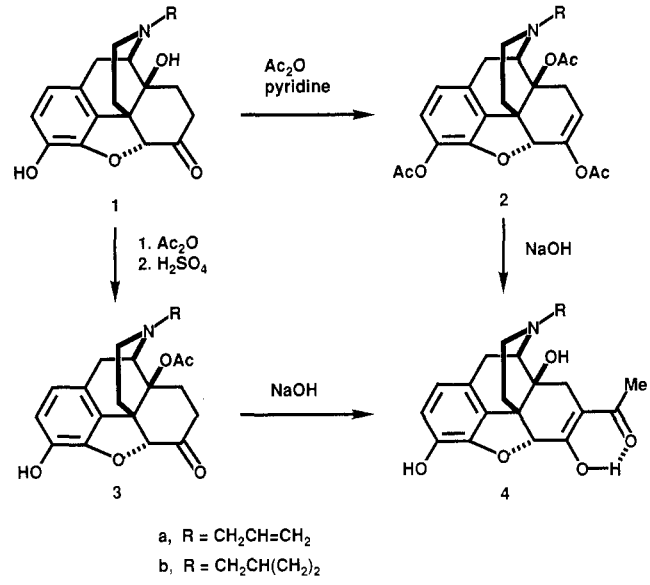
We have recently reported the facile conversion of naloxone **1a** and naltrexone **1b** to the corresponding triacetates **2**.[1] In an effort to convert **2** to the 14-acetate ester **3**, we attempted to selectively hydrolyze **2** in dilute NaOH



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

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Scheme I. Proposed Pathway for O–H → C-7 Acetyl Transfer

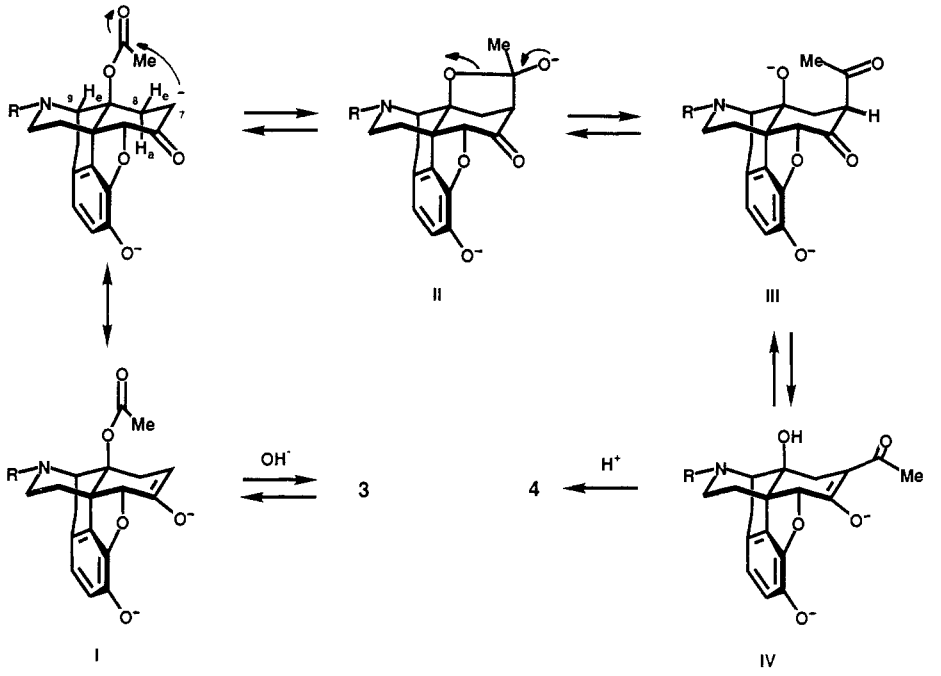

Table I. Comparison of Chemical Shifts for Relevant Protons in 1b and 3b

	chem shifts, ppm				
compd	H_{7a}	H_{7e}	H_{8e}	H_{8a}	H_{9e}
1b	3.05	2.33	1.90	1.65	3.20
3b	2.54	2.28	2.85	1.65	4.45

results in a greater separation between the furan oxygen and O-6 enolate or enol dipoles.

Although similar base-catalyzed O → C acyl transfer reactions have been reported,[2-6] they have been carried out in the presence of strong bases ($NaNH_2$ or *t*-BuOK), and the products are formed in moderate yields. The present example is unique in that it is promoted by hydroxide ion under mild conditions. Moreover, this procedure provides access to 7-acyl-14-hydroxymorphinans in high yield. Prior to this study, the preparation of such compounds was accomplished in low overall yields by means of a multistep synthesis.[7]

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by M-W-H Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer. NMR spectra were recorded at ambient temperature on IBM-Bruker AC-300 using $CDCl_3$ as solvent and Me_4Si as internal standard. 2D NMR spectra were determined in $CDCl_3$ by using JEOL JNM-GX400 at Toray Research Center, 1111, Tebiro Kamakura, 248, Japan. Mass spectra were obtained on AEI MS 30, Finnigan 4000 CI, and VG 70,70 EHF instruments. All TLC data were determined with Analtech, Inc. Silica gel GHF 21521 and EM Science Inc. DC-Fertigplatten Kieselgel 60 F_{254} silanisiert Art. 5747-7 (reversed phase RP-2). Unless otherwise stated, all reagents and solvents were reagent grade and used without subsequent purification.

14-Acetoxy-4,5α-epoxy-3-hydroxy-6-oxo-17-(3′-propenyl)-morphinan (3a). A solution of naloxone **1a** (200 mg, 0.61 mmol) in Ac_2O (10 mL) was stirred under reflux for 1 h and worked up as reported previously;[8] yield 135 mg (60%), mp 194–196 °C (reported[8] mp 193–194 °C); IR (KBr, cm^{-1}) 1732 (OAc carbonyl); ^1H NMR ($CDCl_3$) δ 1.63 (ddd, 1 H, J = 14.4, 13.3, 3.7 Hz, 8-H_a), 2.20 (s, 3 H, OAc), 2.30 (m, 1 H, 7-H_e), 2.82 (ddd, 1 H, J = 13.3, 5.0, 2.7 Hz, 8-H_e), 4.28 (d, 1 H, J = 5.4 Hz, 9-H), 4.69 (s, 1 H, 5-H); high-resolution MS (EI), m/e 369.1577 (calcd for $C_{21}H_{23}O_5N$ 369.1574).

14-Acetoxy-17-(cyclopropylmethyl)-3-hydroxy-6-oxo-4,5α-epoxymorphinan (3b). A solution of naltrexone hydrochloride (**1b**·HCl, 500 mg, 1.47 mmol) in Ac_2O (20 mL) was treated as described for the preparation of **3a** to give a crude product (550 mg) which was recrystallized (MeOH) to yield **3b** (350 mg, 62%), mp 205–207 °C, with spectral properties similar to those of **3a**; MS (EI), m/e 383 (M^+). Anal. Calcd for $C_{22}H_{25}O_5N$: C, 68.93; H, 6.53; N, 3.66. Found: C, 68.81; H, 6.65; N, 3.57.

7-Acetyl-3,14-dihydroxy-4,5α-epoxy-6-oxo-17-(3′-propenyl)morphinan (4a). A solution of **3a** (100 mg, 0.27 mmol) in a mixture of 1 N NaOH (0.5 mL) and MeOH (2 mL) was allowed to stand at room temperature for 2 h. After neutralization of the mixture with 1 N HCl, the resulting mixture was extracted with $CHCl_3$ (3×). The combined organic phases were washed with brine, dried, and concentrated to give a crude product, which was crystallized from MeOH to afford pure **4a** (80 mg; 80%), mp 191–193 °C; IR (KBr, cm^{-1}) 1633 (β-diketone); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H, Ac), 2.18 (d, 1 H, J = 15.5 Hz, 8-H_a), 2.35 (d, 1 H, J = 15.5 Hz, 8-H_e), 3.06 (d, J = 6.4 Hz, 9-H), 4.92 (s, 1 H, 5-H), 15.1 (s, 1 H enolic, OH); MS (EI), m/e 369 (M^+). Anal. Calcd for $C_{21}H_{23}O_5N$: C, 68.29, H, 6.23; N, 3.79. Found: C, 68.16; H, 6.22; N, 3.82.

7-Acetyl-17-(cyclopropylmethyl)-3,14-dihydroxy-4,5α-epoxy-6-oxomorphinan (4b). Method A. A solution of **3b** (100 mg, 0.26 mmol) was treated as described for the synthesis of **4a** to afford a crude product, which was crystallized from MeOH to afford **4b** (88 mg, 88%), mp 169–171 °C; IR (KBr, cm^{-1}) 1631 (β-diketone); ^1H NMR ($CDCl_3$) δ 2.14 (s, 3 H, Ac), 2.20 (d, 1 H, J = 15.1 Hz, 8-H_a), 2.38 (d, 1 H, J = 15.1 Hz, 8-H_e), 3.28 (d, 1 H, J = 6.4 Hz, 9-H), 4.92 (s, 1 H, 5-H); high-resolution MS (EI), m/e 383.1726 (calcd for $C_{22}H_{25}O_5H$ 383.1731).

Method B. Compound **2b** (200 mg, 0.43 mmol) when subjected to the same procedure as described above afforded 150 mg (88%) of **4b**.

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Registry No. **1a**, 465-65-6; **1b**·HCl, 16676-29-2; **2b**, 123621-72-7; **3a**, 41135-96-0; **3b**, 121962-99-0; **4a**, 123621-70-5; **4b**, 123621-71-6.

Practical Synthesis of (3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsiloxy)-ethyl]-4-(methylsulfonyl)-2-azetidinone from Dibromopenicillanic Acid *S*,*S*-Dioxide: A Penem Synthon

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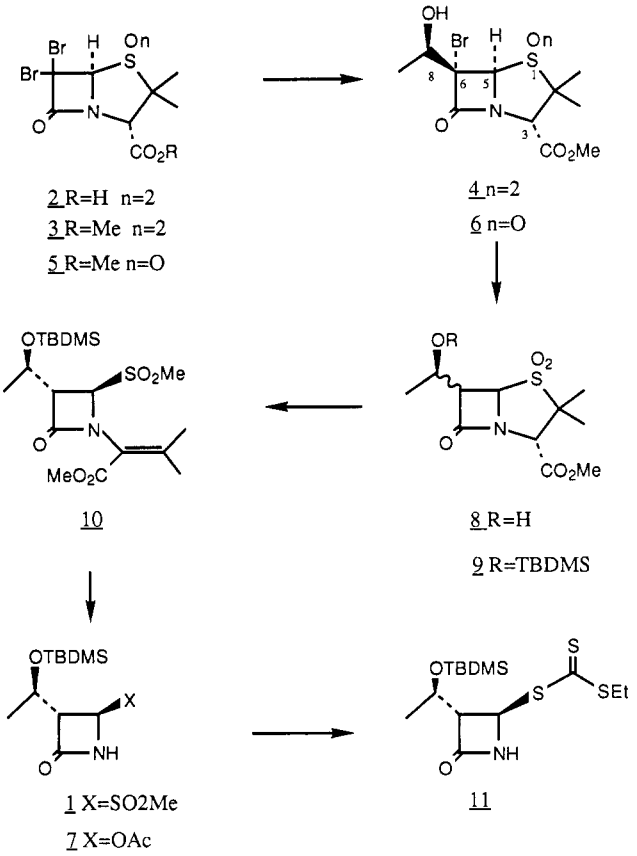
β-Lactams have intrigued chemists for decades.[1] The allurement has been the result of their labyrinthine chemical structure in tandem with their valuable biological activity. Woodward introduced a new dimension to β-lactam research by synthesizing the first penem and demonstrating the inherent antibacterial activity[2] present in this ring system. His pioneering strategy of thiazoline ring construction onto an appropriately substituted azetidinone is still the most commonly employed approach to penems.[3] Our penem research, as well as others, targeted 3,4-disubtituted azetidinones as key synthons.

6-Aminopenicillanic acid and other enantiomerically pure compounds have been converted into azetidinones of this type.[4] Two fundamental problems were persistent in the penicillin-based routes. Aldol reaction with the sulfide oxidation level of the penicillin gave a mixture of isomers that required crystallization and/or chromatography to isolate the desired 8R isomer.[5] Subsequent isomerization of the cis C_5–C_6 relationship, in the dominate 8*R* aldol isomer, to trans was not complete (91:9) and required chromatography to isolate the pure trans compound.[5b] Therefore, a penicillin-based azetidinone process was sought that did not necessitate chromatography. Recently, some researchers have found methods to overcome these two obstacles.[6] The subject of this note is an efficient route to sulfone **1** starting with 6,6-dibromopenicillanic acid *S*,*S*-dioxide.[7]

Scheme I



Results and Discussion

The synthesis commenced with Fisher esterification of 6,6-dibromopenicillanic acid *S*,*S*-dioxide (DBPAS, **2**), which afforded an 88% yield of the methyl ester **3** as a crystalline white solid,[8] Scheme I. Transmetalation of the DBPAS methyl ester **3** with methylmagnesium chloride at −85 °C and subsequent addition of acetaldehyde produced, after workup and aqueous trituration, exclusively **4** in 71% yield. The crude reaction mixture contained a mixture of three isomeric products, prior to aqueous trituration, in a ratio of 89:7:4.[9] For comparison, in the sulfide series, aldol reaction of **5** produced a mixture of all four possible diastereomers in the ratio of 72:19:5:3.[5b,9] The dominant sulfide aldol isomer **6** has been converted into acetoxyazetidinone **7** and methyl sulfone **1**.[5,10] Sulfide oxidation of this dominant aldol isomer **6**, methyl (3*S*,5*R*,6*S*)-6-bromo-6-[(*R*)-1-hydroxyethyl]penicillanate, with *m*-CPBA produced a compound identical with sulfone aldol adduct **4** by high-field proton and carbon NMR. The 6*S*,8*R* stereochemistry determined by chemical correlation in aldol **4** was confirmed by X-ray analysis, Figure 1.[11]

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