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# Mechanistic Diversity of the van Leusen Reaction Applied to 6-Ketomorphinans and Synthetic Potential of the Resulting Acrylonitrile Substructures

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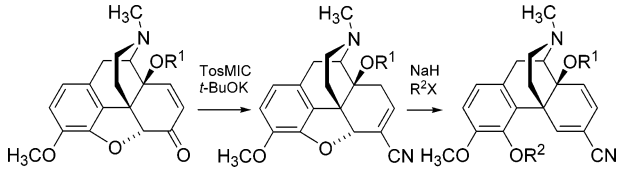
*Received February 26, 2005*

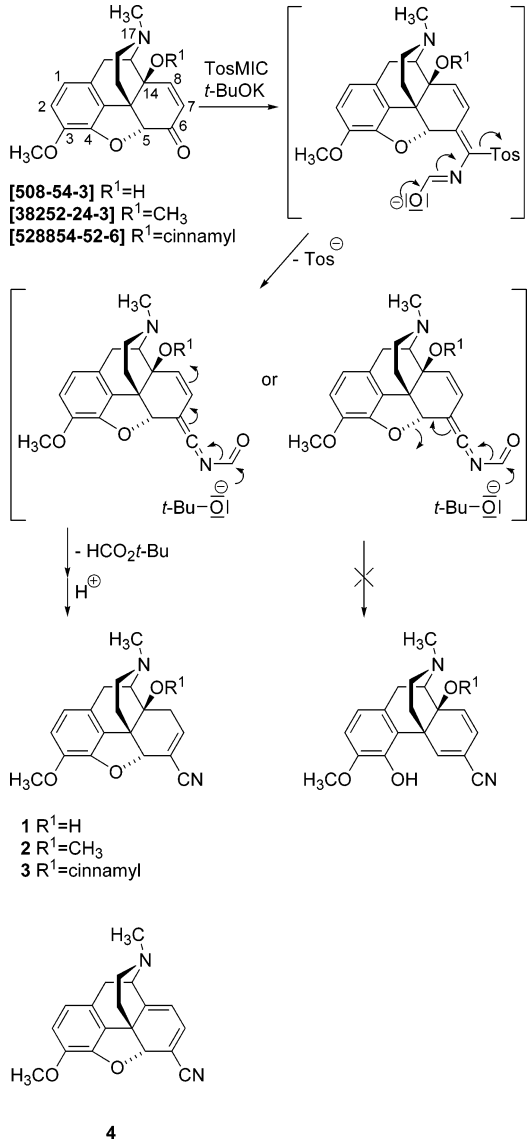



Tosylmethyl isocyanide was used to convert 7,8-didehydro-6-ketomorphinans to 6,7-didehydromorphinan-6-carbonitriles with retainment of the 4,5-epoxy ring. However, ring opening occurred in the presence of NaH giving 5,6,7,8-tetradehydromorphinan-6-carbonitriles. Addition of nucleophiles such as Li diisopropylamide or Grignard reagents to the acrylonitrile substructure yielded ring-opened 5,6-didehydro products. Seven products were characterized by X-ray crystal structure analysis and revealed insight into the mechanistic diversity of the van Leusen reaction.

Functionalization and modification of opioid alkaloids of the natural series continue to be topics of high interest in medicinal chemistry. Recently, it was found that 14-phenylpropyloxy derivatives of 6-ketomorphinans possess unanticipated opioid agonist properties[1] and analgesic potencies.[2] Therefore, 14-*O*-substituents of the compounds in this study include not only H and $CH_3$ but also cinnamyl as precursor of the phenylpropyl group.

The reductive cyanation of ketones with tosylmethyl isocyanide (TosMIC)[3] is a valuable tool for the introduction of new functionalities to 6-ketomorphinans. The mechanism of this (van Leusen) reaction[4] allows for a considerable range of diverse products depending on the conditions and substrates. As previously reported, TosMIC converted saturated 6-ketomorphinans such as oxycodone [76-42-6] into 4,5-epoxy ring-opened 5,6-didehydromorphinan-6-carbonitriles.[5]

**SCHEME 1. van Leusen Reaction Applied to Codeinones**




In contrast, 7,8-didehydro-6-ketomorphinans such as 14-hydroxycodeinone [508-54-3], 14-methoxycodeinone [38252-24-3] and 14-cinnamyloxycodeinone [528854-52-6] now were found to yield 6,7-didehydromorphinan-6-carbonitriles **1**−**3** with retainment of the 4,5-epoxy ring under these conditions. Obviously, an alternative pathway is operative when a double bond is available for accepting the transfer of charge (Scheme 1). The molecular structure of **1** was confirmed by X-ray diffraction (see the Supporting Information). Compounds **2** and **3**

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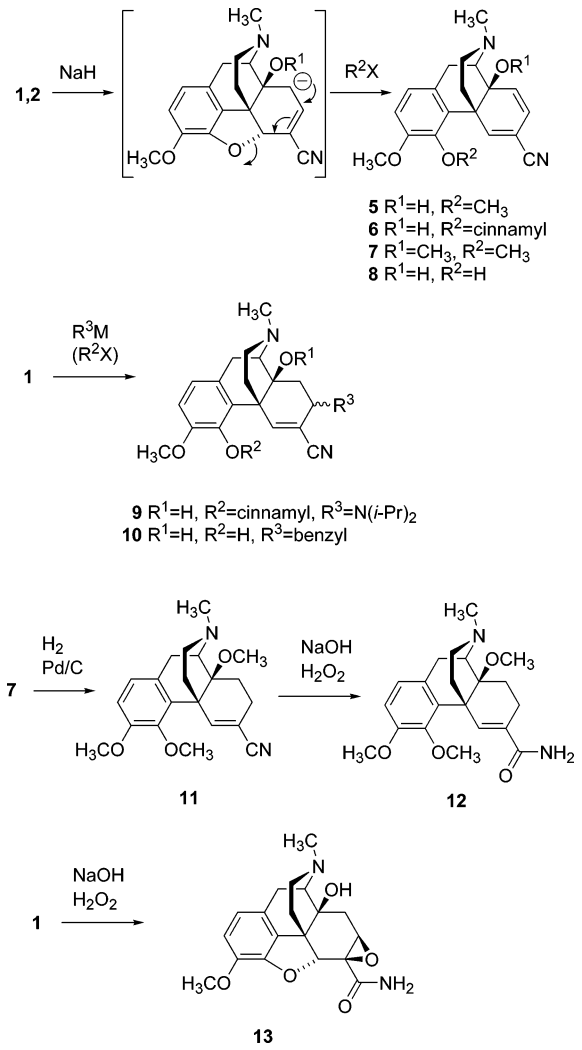
(1) Greiner, E.; Spetea, M.; Krassnig, R.; Schüllner, F.; Aceto, M.; Harris, L. S.; Traynor, J. R.; Woods, J. H.; Coop, A.; Schmidhammer, H. *J. Med. Chem*. **2003**, *46*, 1758−1763.
(2) Schütz, J.; Spetea, M.; Koch, M.; Aceto, M. D.; Harris, L. S.; Coop, A.; Schmidhammer, H. *J. Med. Chem.* **2003**, *46*, 4182−4187.
(3) Leusen, D. v.; Leusen, A. M. v. *Org. React*. **2001**, *57*, 417−666.
(4) Oldenziel, O. H.; Leusen, D. v.; Leusen, A. M. v. *J. Org. Chem*. **1977**, *42*, 3114−3118.
(5) Greiner, E.; Schottenberger, H.; Wurst, K.; Schmidhammer, H. *J. Am. Chem. Soc*. **2001**, *123*, 3840−3841.

10.1021/jo050362v CCC: $30.25 
Published on Web 06/01/2005

**SCHEME 2. Reactions of Morphinan-6-carbonitriles**




were obtained in rather low yields. A yet unidentified, unstable, tosyl group-bearing byproduct was observed in the synthesis of **2**. Another byproduct was isolated in the synthesis of **3**, the 6,8-diene **4**, which obviously originated from elimination of cinnamyl alcohol.

Known methods for 4,5-epoxy ring scission include reductive systems such as Zn/KOH, Zn/AcOH, and $LiAlH_4$.[6] Therefore, it was surprising that attempts to alkylate the 14-OH group in **1** using NaH/RX yielded ring-opened 5,7-dienes **5** and **6** with concomitant alkylation of the newly created phenolate group in position 4 (Scheme 2). The 14-$OCH_3$ analogue **2** behaved similarly and gave **7**, indicating that creation of an anion at C-8 might be the probable first step in this reaction. It was consequently shown that opening of the 4,5-epoxy ring occurred by sole action of NaH upon **1**, affording compound **8**. In this case, an equilibrium between O-14 and C-8 anions in the initial step is suggested.

Addition of nucleophiles to the acrylonitrile moiety, however, gave ring-opened 5,6-didehydromorphinan-6-carbonitriles (Scheme 2). The 7$\beta$-diisopropylamino derivative **9** was obtained when alkylation of **1** was attempted in the presence of Li diisopropylamide (LDA), as evidenced by the X-ray structure. The asymmetric addition of lithium amides[7] opens a plethora of possibilities such as synthesis of 7-aminomorphinans, thus facilitating the subsequent construction of heterocycles involving the nitrile or derived functional groups. Similarly, addition of Grignard reagents as observed in a related system[8] resulted in ring-open 5,6-didehydro compounds, exemplified by the 7-benzyl derivatives **10a**,**b**. The ratio of isolated 7$\alpha$/$\beta$ epimers was approximately 1:9. The stereochemistry of the major product **10b** was shown to be 7$\beta$-benzyl by X-ray diffraction.

It is envisioned that the new acrylonitrile system created by the scission of the ether bridge would allow another nucleophilic addition, thus further functionalizing the morphinan backbone. Furthermore, hydrolysis of the nitrile group is expected to give pharmacologically very interesting compounds due to the increased polarity of the functional groups created. These products are likely to exhibit enhanced peripheral activity.[10] Hydrolysis with $NaOH/H_2O_2$ necessitated the presence of a sacrificial tertiary amine ($Et_3N$) in order to avoid oxidation of the morphinan nitrogen by the intermediate peroxyimidate.[11] Thus, 5,6-didehydro-3,4,14-trimethoxy-17-methylmorphinan-6-carbonitrile **11**, obtained by selective catalytic hydrogenation of the 5,7-diene **7**, was converted to the corresponding amide **12** in good yield. However, hydrolysis of **1** yielded the unusual 6$\beta$,7$\beta$-epoxyamide **13** as the only isolable product (Scheme 2).

In the first paper on TosMIC cyanation of 6-ketomorphinans,[5] it was reasonably argued that the 4-phenolate leaving group ability and structural strain imposed by the 4,5-ether bridge are the major driving forces of the preferred course of the reaction to 4,5-ring-opened products.

There is now evidence that a different mechanism is possible, at least in addition to the previously proposed one. Upon reaction of 14-*O*-(3-phenylpropyl)oxycodone [528854-53-7] with excess TosMIC, along with the expected ring-opened product, a byproduct was isolated and identified by X-ray diffraction as the imidazole **14**. The fact that this compound retained the 4,5-epoxy ring reveals that in saturated ring systems the formation of a 5,6-double bond is not the only viable path but the 6,7-double bond is also feasible. The loss of toluenesulfinate must have occurred in an earlier step than previously suggested, and the ketenimine intermediate apparently was not skipped in this case, enabling the addition of a second TosMIC molecule. TosMIC is known to react with aldimines to give imidazoles,[9] and obviously this pathway is also viable for a ketenimine as outlined in Scheme 3 to give an alkenylimidazole. Another intermediate was isolated after cyanation of 14-*O*-methyloxycodone[5] [38252-

(6) Linders, J. T. M.; Adriaansens, R. J. O.; Lie, T. S.; Maat, L. *Recl. Trav. Chim. Pay-Bas* **1986**, *105*, 27−29.

(7) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc*. **2003**, *125*, 2886−2887 and references therein.

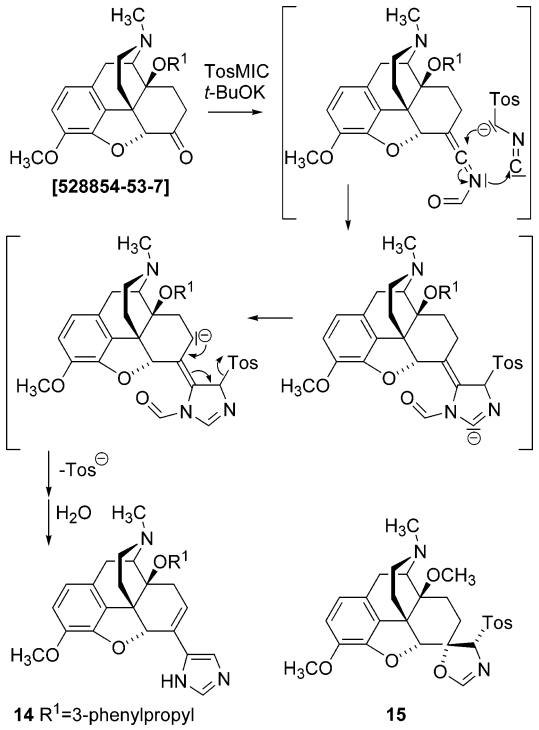
(8) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem*. **1977**, *62*, 4883−4885 and references therein.

(9) (a) Leusen, A. M. v.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem*. **1977**, *42*, 1153−1159. (b) Grimmett, M. R. In *Science of Synthesis*; Neier, R., Ed.; Thieme: Stuttgart, New York, 2002; Vol. 12, pp 325−528.

(10) Schütz, J.; Schmidhammer, H. *PCT Int. Appl*. 2003. Patent No. WO 03/051888 A1.

(11) Laus, G. *J. Chem. Soc., Perkin Trans. 2* **2001**, 864−868.

**SCHEME 3. Byproducts of the van Leusen Reaction Applied to Saturated 6-Ketomorphinans**




28-7] under protic conditions, which was demonstrated for the first time by X-ray diffraction to be the postulated primary van Leusen adduct,[4] the spiro oxazoline **15**.

In summary, the van Leusen reaction applied to 6-ketomorphinans shows a high degree of mechanistic diversity, and the resulting acrylonitriles provide extremely versatile access to a structural pool of functional combinations. Biological and pharmacological studies on the described compounds are in progress and will be published in due course.

## Experimental Section

**6,7-Didehydro-4,5α-epoxy-14*β*-hydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile (1).** *t*-BuOK (5.61 g, 50.0 mmol) was added to a stirred and cooled (−40 °C) solution of TosMIC (4.30 g, 22.0 mmol) in 50 mL of anhydrous DME. After the solution was stirred for 10 min under $N_2$, a solution of 14-hydroxycodeinone [508-54-3] (6.27 g, 20.0 mmol) in DME (15 mL) was added, and the mixture was stirred at 0 °C for 90 min. Then 2-propanol (1.68 mL, 22.5 mmol) was added, and stirring was continued at room temperature for another 90 min. The solution was diluted with water (200 mL) and brine (30 mL) and extracted with $CH_2Cl_2$ (2 × 50 mL, 2 × 20 mL). The combined extracts were washed with water (3 × 200 mL) and brine (100 mL), dried over $Na_2SO_4$, and evaporated to afford a foam which was crystallized from MeOH to yield compound **1** (4.07 g, 63%): mp 262−266 °C dec; $[\alpha]^{20}_D$ −359 ($CHCl_3$, *c* 0.9); $^1$H NMR ($CDCl_3$, ppm) $\delta$ 6.73 (d, 1H ar, $J$ = 8.6 Hz), 6.70 (dd, 1H olef, $J$ = 5.8 Hz, $J$ = 2.6 Hz), 6.64 (d, 1H ar, $J$ = 8.6 Hz), 4.97 (s, 1H), 3.89 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR ($CDCl_3$, ppm) $\delta$ 147.2, 144.7, 144.4, 130.8, 126.0, 120.2, 118.3, 116.0, 112.8, 85.6, 70.6, 64.4, 57.7, 45.8, 43.7, 33.7, 31.4, 22.7; IR (KBr, cm$^{-1}$) 3361, 2963, 2942, 2911, 2829, 2216, 1638, 1509, 1453, 1286, 1167, 1055, 929, 786; HRMS (FAB) calcd for $C_{19}H_{21}N_2O_3$ $(M + H)^+$ 325.1547, found 325.1534. Crystal structure: see the Supporting Information (CCDC 236727).

**5,6,7,8-Tetradehydro-3,4,14*β*-trimethoxy-17-methylmorphinan-6-carbonitrile (7).** Compound **1** (1.00 g, 3.08 mmol) was added to a cooled (0 °C) suspension of NaH (0.30 g 60%, 7.50 mmol) in 15 mL of anhydrous DMF, and the mixture was stirred for 30 min. Then $CH_3I$ (0.42 mL, 6.73 mmol) was added, and the brown solution was stirred for another 90 min. After addition of ice and water (100 mL), the mixture was extracted with $CH_2Cl_2$ (2 × 50 mL, 2 × 20 mL). The combined extracts were washed with water (5 × 200 mL) and brine (200 mL), dried over $Na_2SO_4$, and evaporated to afford a foam which was crystallized from 2-propanol to give compound **7** (338 mg, 31%): mp 160−164 °C; $[\alpha]^{20}_D$ 151 ($CHCl_3$, *c* 0.7); $^1$H NMR ($CDCl_3$, ppm) $\delta$ 7.24 (br s, 1H), 6.76 (s, 2H ar), 6.01 (dd, 1H olef, $J$ = 9.5 Hz, $J$ = 1.5 Hz), 5.85 (d, 1H olef, $J$ = 9.5 Hz), 3.82 (s, 6H), 3.24 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR ($CDCl_3$, ppm) $\delta$ 156.0, 152.3, 146.5, 131.2, 125.5, 122.6, 119.3, 112.2, 106.3, 74.1, 61.2, 56.4, 55.6, 51.1, 47.6, 43.9, 43.2, 29.3, 26.2; IR (KBr, cm$^{-1}$) 2932, 2835, 2216, 1487, 1279, 1089, 1048; HRMS (FAB) calcd for $C_{21}H_{25}N_2O_3$ $(M + H)^+$ 353.1860, found 353.1868.

Compound **7** was also obtained by the following procedure: **2** (130 mg, 0.38 mmol) was added to a cooled (0 °C) suspension of NaH (14 mg 95%, 0.55 mmol) in 2.5 mL of anhydrous DMF, and the mixture was stirred for 30 min. Then $CH_3I$ (30 $\mu$L, 0.48 mmol) was added, and the brown solution was stirred for another 50 min. After addition of ice and water (25 mL), the mixture was extracted with $CH_2Cl_2$ (1 × 25 mL, 2 × 10 mL). The combined extracts were washed with water (5 × 50 mL) and brine (50 mL), dried over $Na_2SO_4$, and evaporated to afford a foam which was crystallized from 2-propanol to give compound **7** (35 mg, 26%).

**4-Cinnamyloxy-5,6-didehydro-14*β*-hydroxy-3-methoxy-17-methyl-7*β*-(diisopropylamino)morphinan-6-carbonitrile (9).** A solution of LDA·THF (3.5 mL 1.5 M in cyclohexane, 5.25 mmol) was added dropwise to a cooled (−70 °C) suspension of **1** (1.10 g, 3.39 mmol) in 30 mL of anhydrous THF, and the mixture was stirred for 35 min at −40 °C. Cinnamyl bromide (0.85 g, 4.10 mmol) was added, and stirring was continued for 20 h at room temperature. Then water (5 mL) was added, and volatiles were removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (100 mL), the solution was washed with water (2 × 100 mL) and brine (100 mL), dried over $Na_2SO_4$, and evaporated to afford a foam which was purified by repeated column chromatography (100 g silica, mesh 230−400) eluting with $CH_2Cl_2$/MeOH/$NH_4OH$ concd (500:4:1). Crystallization from MeOH yielded compound **9** (0.23 g, 13%): mp 174−178 °C dec; $[\alpha]^{20}_D$ −9.4 ($CHCl_3$, *c* 0.8); $^1$H NMR ($CDCl_3$, ppm) $\delta$ 7.17−7.51 (m, 6H), 6.90 (d, 1H olef, $J$ = 16.0 Hz), 6.81 (s, 2H ar), 6.52 (Dt, 1H olef, $J$ = 16.0 Hz, $J$ = ∼6 Hz), 4.89 (dd, 1H, $J$ = 11.4 Hz, $J$ = 5.5 Hz), 4.44 (dd, 1H, $J$ = 11.4 Hz, $J$ = 6.8 Hz), 3.85 (s, 3H), 2.34 (s, 3H), 1.12 (d, 6H, $J$ = 6.6 Hz), 1.01 (d, 6H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$, ppm) $\delta$ 154.2, 152.1, 145.8, 137.5, 135.7, 134.0, 129.2, 129.0, 128.4, 127.5, 125.7, 123.3, 121.3, 117.8, 111.9, 73.3, 68.5, 62.8, 56.4, 48.1, 46.1, 43.3, 42.1, 38.4, 33.2, 25.0, 24.1, 23.5; IR (KBr, cm$^{-1}$) 3321, 2962, 2857, 2217, 1599, 1484, 1276, 1220, 1113, 1049, 960, 802, 729; HRMS (FAB) calcd for $C_{34}H_{44}N_3O_3$ $(M + H)^+$ 542.3378, found 542.3336. Crystal structure: see the Supporting Information (CCDC 236732).

**7α-Benzyl-5,6-didehydro-4,14*β*-dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile (10a) and 7*β*-Benzyl-5,6-didehydro-4,14*β*-dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile (10b).** To a cooled (−40 °C) suspension of **1** (0.20 g, 0.62 mmol) in 10 mL of anhydrous THF was added a solution of benzylmagnesium chloride (1.86 mL 1M in $Et_2O$, 1.86 mmol). The mixture was stirred at room temperature for 5 h. To the resulting solution saturated $NH_4Cl$ solution (50 mL) was added, pH was adjusted to 8.5 with concentrated $NH_4OH$, THF was removed under reduced pressure, and the remaining mixture was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined extracts were washed with water (4 × 100 mL) and brine (100 mL), dried over $Na_2SO_4$, and evaporated to afford a foam which was subjected to column chromatography (60 g silica, mesh 230−400) eluting with $CH_2Cl_2$/MeOH/$NH_4OH$ conc (500:4:1). The isomeric products **10a** (10 mg, 4%) and **10b** (90 mg, 35%) were crystallized from MeOH.

Minor isomer **10a**: mp 205−211 °C; $^1$H NMR ($CDCl_3$, ppm) $\delta$ 7.28 (d, 1H olef, $J$ = 2.2 Hz), 7.04−7.20 (m, 5H ar), 6.67 (d, 1H

ar, $J = 8.4$ Hz), 6.55 (d, 1H ar, $J = 8.4$ Hz), 3.87 (s, 3H), 2.30 (s, 3H); IR (KBr, $cm^{-1}$) 3385, 2924, 2851, 2210, 1610, 1489, 1438, 1280, 1224, 1109, 1045, 797, 702; HRMS (FAB) calcd for $C_{26}H_{29}N_2O_3$ $(M + H)^+$ 417.2173, found 417.2170.

Major isomer **10b**: mp. 217−222 °C; $[\alpha]^{20}_D$ −46 ($CHCl_3$, *c* 0.9); $^1H$ NMR ($CDCl_3$, ppm) $\delta$ 7.20−7.34 (m, 6H), 6.67 (d, 1H ar, $J =$ 8.4 Hz), 6.53 (d, 1H ar, $J = 8.4$ Hz), 3.83 (s, 3H), 2.34 (s, 3H); $^{13}C$ NMR ($CDCl_3$, ppm) $\delta$ 151.5, 145.5, 143.9, 141.3, 130.4, 129.0, 128.5, 127.3, 126.7, 120.7, 118.9, 114.8, 109.8, 69.3, 63.4, 56.8, 46.7, 43.1, 42.7, 40.1, 37.1, 31.0, 29.5, 24.8; IR (KBr, $cm^{-1}$) 3385, 2939, 2848, 2221, 1605, 1486, 1441, 1283, 1224, 1048, 807; HRMS (FAB) calcd for $C_{26}H_{29}N_2O_3$ $(M + H)^+$ 417.2173, found 417.2142. Crystal structure: see the Supporting Information (CCDC 236730).

**Acknowledgment.** We thank Tasmanian Alkaloids Pty, Ltd., Australia, for the generous gift of thebaine [115-37-7] as starting material. We are indebted to Dr. M. Andre, Sandoz, Austria, for the optical rotation determinations.

**Supporting Information Available:** Experimental procedures and spectral data of compounds **2**−**5**, **6**, **8**, and **11**−**14**; crystal data and structure refinement details of **1**, **2**, **9**, **10b**, and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050362V