Notes

Stereospecific Synthesis of Pseudocodeine: [2,3]-Sigmatropic Rearrangement Using Selenium Intermediates

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Received March 11, 1997

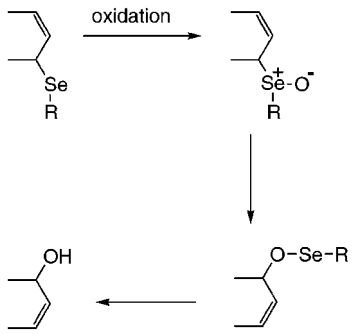
Pseudocodeine[1] (**1**), an important intermediate for the synthesis of opiate ligands, has been previously synthesized by converting codeine **2** to its 6β-chloro derivative **3**, which then was subjected to S_N2' displacement in aqueous acetic acid. Since this reaction gives rise to a mixture of isomers from which separation of **1** is tedious, we sought a stereospecific route to **1** using selenium group transfer chemistry.

Selenium and sulfur have been extensively used for indirect functionalization by the transfer of a group from the above to a carbon electrophile.[2,3] Among the most common reactions used for this purpose are the [2,3]-sigmatropic rearrangements of the selenium or sulfur oxides to an allylic carbon.[4,5] Such rearrangements using selenium involve the formation of a Se−C bond at an allylic position to a double bond to yield a seleno ether (Scheme 1). Subsequent oxidation of the ether can be accomplished by convenient methods without the possibility of over oxidation. The allylic selenoxide then often undergoes a spontaneous [2,3]-sigmatropic rearrangement to yield the selenic ester, which can be cleaved under mild acidic conditions to afford the desired alcohol. Here we describe an application of this chemistry for the stereospecific synthesis of pseudocodeine **1**.

The stereospecific route to **1** from codeine **2** is illustrated in Scheme 2. Codeine **2** was reacted with *N*-(phenylseleno)phthalimide[6] and tri-*n*-butylphosphine in dry THF to yield the 6β-(phenylseleno) intermediate **4**. This conversion involved the inversion of the C-6 chiral center via an S_N2' displacement involving a cyclic transition state that is characteristic of this type of reaction. Intermediate **4** was isolated as the HCl salt and was then oxidized to the phenylselenoxide **5** using hydrogen peroxide. This allylic selenoxide underwent a spontaneous [2,3]-sigmatropic rearrangement to yield the selenic ester **6**, which was hydrolyzed by the addition of aqueous potassium hydroxide to provide pseudocodeine (**1**). The coupling constants ($J_{5,6}$ = 3.6 Hz, $J_{6,7}$ = 10.2 Hz, $J_{7,8}$ = 1.5 Hz) are in agreement with the 8β-hydroxy stereochemistry of the product and were identical to those obtained by the reported route.[7] The overall yield of **1** from codeine by the above stereoselective procedure was 38%.

To compare the yield of **1** in our stereospecific synthesis with that of the reported procedure, we have repeated the literature synthesis involving the 6β-chloro intermediate **3**.[1b,7e,f] A mixture of isomers was obtained along with the desired product **1**, which was purified by chromatography, conversion to the hydrochloride salt, and crystallization. The overall yield of the free base was 24%.

Scheme 1



Thus, the stereospecific synthesis of **1** involving selenium intermediates has the advantage of higher yield and greatly improved efficiency because it alleviated the time-consuming purification that is necessary in the reported procedure.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF glass plates. Column chromatography was performed with silica gel (200−400 mesh, Aldrich Chemicals). Chromatographic solvent system is reported as volume/volume. Nuclear magnetic resonance spectra were recorded on a 300 MHz NMR spectrometer at room temperature (18−20 °C). The δ (ppm) scale was in reference to the deuterated solvent. The coupling constants are reported in Hz. The mass spectra were obtained from the Mass Spectrometry Laboratory of the Department of Chemistry, University of Minnesota. Microanalysis were performed by MHW laboratories, Phoenix, AZ.

6β-(Phenylseleno)desoxycodeine (4). To a solution of **2** (300 mg, 1.0 mmol) and *N*-(phenylseleno)phthalimide (600 mg,

(1) (a)Portoghese, P. S.; Moe, S. T.; Takemori, A. E. *J. Med. Chem.* **1994**, *37*, 1886. (b) Lutz, R. E.; Small, L. *J. Am. Chem. Soc.* **1932**, *54*, 4715. (c) Small, L.; Lutz, R. E. *J. Am. Chem. Soc.* **1934**, *56*, 1741. (d) Small, L.; Lutz, R. E. *J. Am. Chem. Soc.* **1934**, *56*, 1928. (e) Hosztafi, S.; Makleit, S.; Miskolczi, Z. *Acta Chim. Hung.* **1983**, *114*, 63−68. (f) Chatterjie, N.; Umans, J. G.; Inturrisi, C. E.; Chen, W.-T. C.; Clarke, D. D.; Bhatnagar, S. P.; Weiss, U. *J. Org. Chem.* **1978**, *43*, 1003−1005. (g) Fleischhacker, W.; Richter, B. *Chem. Ber.* **1980**, *113*, 3866−3880.

(2) Reich, H. J. [2,3]-Sigmatropic Rearrangements of Organoselenium Compounds. In *Organoselenium Chemistry*; Liotta, D., Ed.; John Wiley and Sons: New York, 1987; pp 365−394.

(3) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(4) Clive, D. L.; Chittattu, G.; Neville, J. C.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 770.

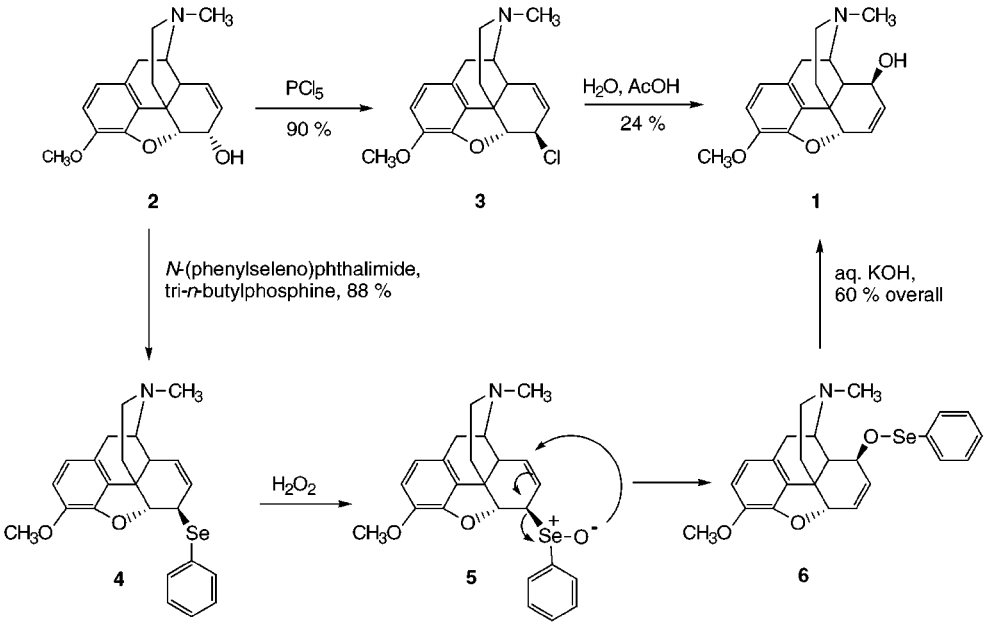
(5) Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570.

(6) Grieco, P. A.; Jaw, J. Y. *J. Org. Chem.* **1981**, *46*, 1215.

(7) (a) Small, L.; Lutz, R. E. In *Chemistry Of Opium Alkaloids*; Government Printing Office: Washington, DC, U.S. Health Services Suppl. 103, Public Health Reports, pp 215−229. (b) Yeh, H. J. C.; Wilson, R. S.; Klee, W. A.; Jacobson, A. E. *J. Pharm. Sci.* **1976**, *65*, 902. (c) Bentley, K. W. *The Chemistry of Morphine Alkaloids*; Clarendon Press: 1954; pp 126−148. (d) Batterham, T. J.; Bell, K. H.; Weiss, U. *Aust. J. Chem.* **1965**, *18*, 1799. (e) Knorr, L. *Ber.* **1908**, *41*, 972. (f) Speyer, E. *Ann.* **1923**, *432*, 246.

S0022-3263(97)00447-7 CCC: $15.00
Published on Web 02/14/1998

Scheme 2



1.98 mmol) in THF (50 mL) at 0 °C was added dropwise over a period of 5 min *n*-Bu_3P (500 μL, 1.98 mmol) in an inert atmosphere. After 2 h at 0 °C, the solvent was evaporated under vacuum. The residue was chromatographed on a 1 × 5 in. vacuum-flash column (gradient elution with hexane/EtOAc 8:1 to hexane/EtOAc 1:8) to provide an oil **4** (approximately 400 mg, 88%). This material was further purified by precipitating the HCl salt from an ether solution with ethereal HCl. The precipitate was filtered and washed with ether (3 × 20 mL) to provide **4**·HCl (300 mg, 63%): mp 219−220 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.30 (m, 3H), 6.56 (doublets, 2H, J = 8.2 Hz), 5.95 (m, 1H), 5.48 (dd, 1H, J = 2.0 Hz, 2.6 Hz), 4.99 (d, 1H), 3.79 (s, 3H), 3.29 (m, 1H), 3.06 (d, 1H), 2.54 (dd, 1H), 2.43 (s, 3H), 1.73 (dd, 1H); CIMS m/z 439 (M + 1). Anal. Calcd for $C_{24}H_{25}NO_2Se$·HCl: C, 60.70; H, 5.52; N, 2.95. Found C, 60.70; H, 5.67; N, 2.93.

Pseudocodeine (1). Method A. From 6β-Chlorocodeine (3). To a mixture of **3** (5 g, 15.7 mmol) suspended in H_2O (50 mL) at 100 °C was added glacial AcOH dropwise (2.1 mL) until the opiate had completely dissolved. The reaction was stirred at 100 °C for 3 h under nitrogen and was then cooled to room temperature and made basic with solid $NaHCO_3$. The mixture was extracted with $CHCl_3$ (4 × 30 mL), and the combined extracts were dried (anhydrous Na_2SO_4) and evaporated to give an oil (5.4 g) that was chromatographed on a 2 × 5 in. vacuum-flash column ($CHCl_3$/MeOH/NH_3 81:12:1). Fractions containing the product were pooled, and the solvent was removed under vacuum to give an oil (3.6 g) that was dissolved in absolute EtOH (20 mL). Concentrated HCl (~30 drops) was added until the solution was acidic, and the ethanolic solution was evaporated to dryness under vacuum. This solid was dissolved in hot 95% EtOH (32 mL), filtered, and refrigerated at −5 °C for 12−18 h. The crystalline material was collected on a filter and washed with ice-cold 95% EtOH (2 mL) to give **1**·HCl, (1.29 g, 24.5%), mp 217−218 °C (lit. 217−218 °C).[7f] A part of the product was converted to the free base by treatment of the aqueous solution with solid $NaHCO_3$ and subsequent extraction with $CHCl_3$: ^{1}H NMR (300 MHz, $CDCl_3$, free base) δ 6.67 (doublets, 2H, J = 7.1 Hz), 5.87 (dd, 1H, J = 10.2 Hz, 1.5 Hz), 5.74 (dd, 1H, J = 10.2 Hz, 3.6 Hz), 4.98 (d, 1H, J = 3.6 Hz), 3.85 (s, 3H), 3.10 (d, 1H), 2.46 (s, 3H), 2.31 (dt, 1H), 2.25 (dd, 1H), 1.94 (dt, 1H); CIMS m/z 300 (M + 1). Anal. Calcd for $C_{18}H_{21}NO_3$·HCl: C, 64.37; H, 6.60, N, 4.17. Found C, 64.21; H, 6.61, N, 3.96.

Method B. From 6β-(Phenylseleno)desoxycodeine (4). The HCl salt of **4** (1.6 g, 3.37 mmol) was suspended in H_2O (20 mL), and hydrogen peroxide (687 μL, 30 wt % in H_2O) was added dropwise at 25 °C. After 10 min, concd aqueous KOH was added to precipitate **1**. The solid was collected and dried to give **1** (607 mg, 60%). Physical and spectral properties of this material were identical in all respects with that of **1** prepared by method A.

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