L-Selectride as a General Reagent for the O-Demethylation and N-Decarbomethoxylation of Opium Alkaloids and Derivatives[1]

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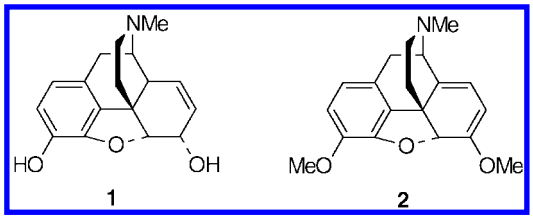
L-Selectride was shown to be an efficient and general O-demethylating agent for the opium alkaloids and their derivatives and also an efficient reagent for the cleavage of methyl carbamates, thus offering a convenient method for the N-demethylation of opioids. Further, it was shown that by choice of reaction conditions it is possible to achieve both N-decarbomethoxylation and O-demethylation in one pot, or only render N-decarbomethoxylation in high yield without accompanying O-demethylation.

The ever increasing demand for medicinal opiates, coupled with the finite supply of the raw materials from opium, necessitates the development of simple high-yielding procedures for opiate transformations. Of particular importance is aromatic O-demethylation, as the vast majority of these important opioids are 3-phenols such as morphine (**1**). A major starting material is the 3-methyl ether thebaine (**2**),[2] so an O-demethylation step is required at some stage in their synthesis. Although O-demethylations can be problematic due to the sensitive functionality present in the opioid molecules, various procedures have been developed that allow successful reaction in most cases. Boron tribromide is often the reagent of choice,[3] yet this procedure suffers from the toxicity of the reagent and its incompatibility with acid sensitive substrates, a problem with all acidic O-demethylating reagents.[4] A number of basic reagents have thus been developed for the demethylation of such compounds, the most widely used being potassium hydroxide at 200 °C.[5] In addition to problems encountered with the use of such harsh conditions, it has been observed that the reaction is somewhat unreliable on smaller (ca. 1 g) scales[6] and this has led to the increased use of thiolate anions for laboratory scale demethylations.[7] Although thiolate reactions are reliable, they are limited by the toxicity of the thiols and the preferred solvent (HMPA).[8] From the above, it is clear that the development of a less toxic alternative that can be applied universally to the opioids under mild conditions is required and, indeed, has been a major goal in the chemistry of the opium alkaloids for many years.



In addition to O-demethylation, N-demethylation is also an important transformation as the natural opiates used as raw materials in opioid synthesis are *N*-methyl-substituted, whereas opioid antagonists possess differing N-substitution.[2] The opioid antagonists, such as naltrexone, are important medications for the treatment of opiate abuse, opiate overdose, and alcohol addiction.[9−11] Traditional syntheses of these antagonists involve the conversion of *N*-methyl-substituted opioids to the carbamates or cyanamides, which are subsequently cleaved to give the *N*-noropioids. Simple N-alkylation gives the desired substitution.[2] Cleavage of the carbamates can be accomplished in good yields but generally require harsh basic[12] or acidic[13] conditions. The development of a hydrazine-mediated cleavage reaction was a procedural improvement but is limited by the toxic and potentially explosive nature of the reagent,[14] and the use of ACE-Cl (1-chloroethyl chloroformate) gives a labile carbamate[15] that cannot be exploited as a protecting group for the nitrogen.[16] Obviously, a less toxic alternative that employs mild conditions to cleave simple carbamates is highly desirable. We now present L-Selectride as a general and mild reagent for 3-O-demethylation of morphine alkaloids and their derivatives, and also as a

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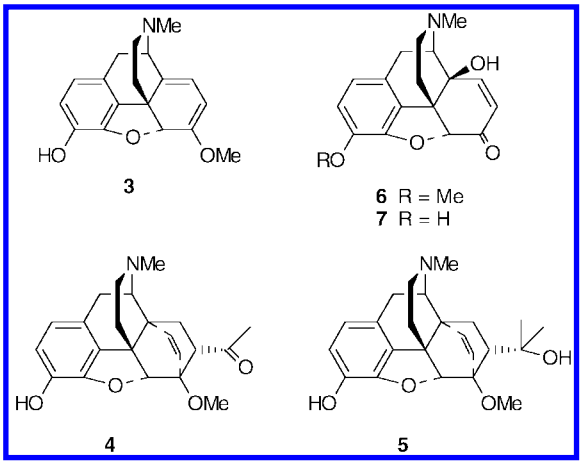
convenient reagent for the N-demethylation of these alkaloids, via cleavage of an intermediate methyl carbamate.

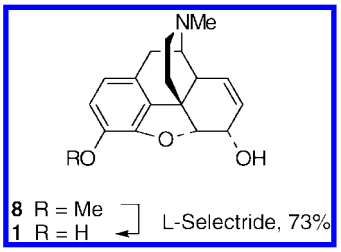
Results and Discussion

Oripavine. L-Selectride was recently reported to be an efficient O-demethylating agent for simple systems.[17] On the basis of this work,[18] we showed[1] that L-Selectride effects the O-demethylation of thebaine (**2**) to the corresponding 3-phenol oripavine (**3**) in 35% yield, a transformation which, despite many attempts for over 60 years, had not previously been accomplished due to the sensitivity of the allylic and dienol ether functions. The ease of this transformation allowed ready access to significant quantities of oripavine and raised the possibility that the extensive range of opioids currently prepared from thebaine could now alternatively be prepared from oripavine, with the advantage that a later O-demethylation step would be avoided. To this end, we demonstrated that the chemistry of oripavine is very similar to that of thebaine. Diels−Alder reaction with 1-buten-3-one gave the orvinone (**4**) (82%), and subsequent Grignard addition of MeMgI gave orvinol (**5**) (81%), a member of a potent and important class of opioids.[2] Oxidation of thebaine to give 14-hydroxycodeinone (**6**) is a very important transformation leading to the opioid antagonists.[19] Similar oxidation of oripavine proved somewhat problematic with performic acid, the major product being water soluble and only minor yields of the desired 14-hydroxymorphinone (**7**) could be isolated. Although the major product was not identified, it was obvious that oripavine was much more sensitive to the reaction conditions than thebaine. Oxidation of thebaine has been reported with *m*-CPBA in hot acidic media,[20] but this was considered too vigorous for oripavine. However, we discovered that this *m*-CPBA-mediated oxidation proceeded well in water at room temperature to give a 62% yield of **7**. Similar treatment of thebaine gave **6** in 87% yield demonstrating the utility of this simple and mild oxidation procedure.

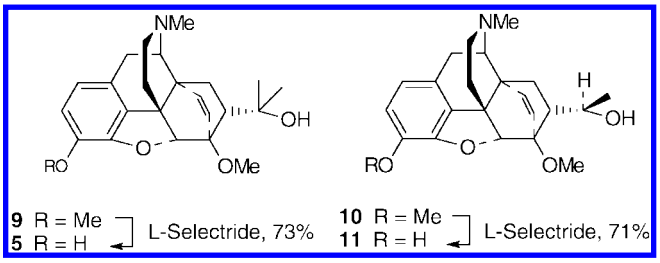
O-Demethylation Studies. This work demonstrated that oripavine is a useful starting material in opioid synthesis; unfortunately the modest yield (35%) of oripavine from thebaine probably limits its use to certain specialized cases, where particularly sensitive functionality is required in the desired product. Hence thebaine remains as the key raw material for opioid synthesis and a 3-O-demethylation step will still be required to produce the desired 3-phenols. The success of L-Selectride with such a sensitive opiate as thebaine, prompted us to investigate the action of this reagent on other important opioids.

O-Demethylation of codeine (**8**) to morphine (**1**) was first investigated, which was problematic until the use of BBr_3 (91%).[3] The strongly basic reagent was expected to deprotonate the 6-hydroxyl group, and vigorous evolution of hydrogen was indeed observed. The presence of this 6-alkoxide group in the molecule did not inhibit the subsequent 3-O-demethylation with a second equivalent of L-Selectride, which occurred smoothly at reflux to give a 73% yield of **1**.[21] It was noted that the O-demethylation of **8** was far more rapid (3.5 h) than was reported for simple compounds (ca. 18 h),[17] and this was attributed to the presence of an ortho ether group at C-4, allowing for stronger coordination to the lithium ion.[22]





The orvinols are a class of potent opioids that includes the important analgesic buprenorphine.[23] O-Demethylation of the 3-ethers (thevinols) to the corresponding phenols (orvinols) is often difficult due to their sensitivity to acidic conditions.[4] It was found that treatment of both **9** and **10** with 3 equiv of L-Selectride at reflux gave a clean conversion to the orvinols **5** (73%) and **11** (71%) and offers a convenient alternative with comparable yields to the traditional and often troublesome KOH or toxic thiolate methods.



The indoles **13a**,**b** are currently receiving a great deal of attention due to their δ opioid receptor selectivity.[24] This receptor has attracted considerable interest since

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(18) It should also be noted that the related Super-Hydride has been reported to cause O-demethylation of certain opioid compounds as a minor side reaction (ca. 5% yield). See: Fleischhacker, W.; Richter B. *Chem. Ber.* **1979**, *112*, 2539.

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(20) Hauser, F. H.; Chen, T.-K.; Carroll, F. I. *J. Med. Chem.* **1974**, *17*, 1117.

(21) Isolation of the phenolic products from these reactions was accomplished by simple extraction into aqueous NaOH, followed by acidification with HCl and rebasification to pH 9 with NH_4OH. Nonphenolic starting material and the organoborane species remained in the original organic layer.

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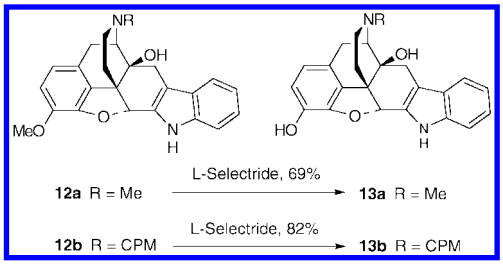
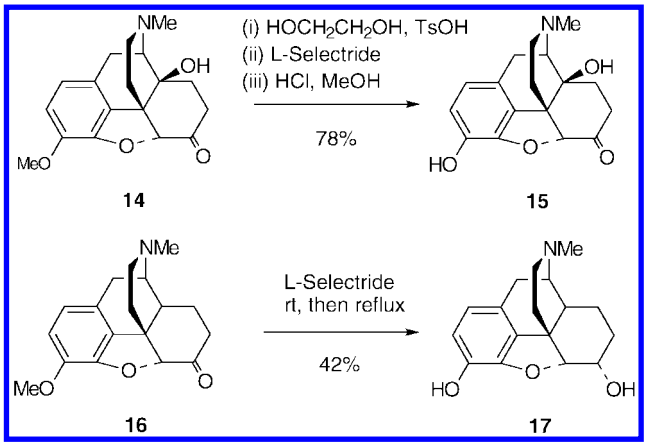
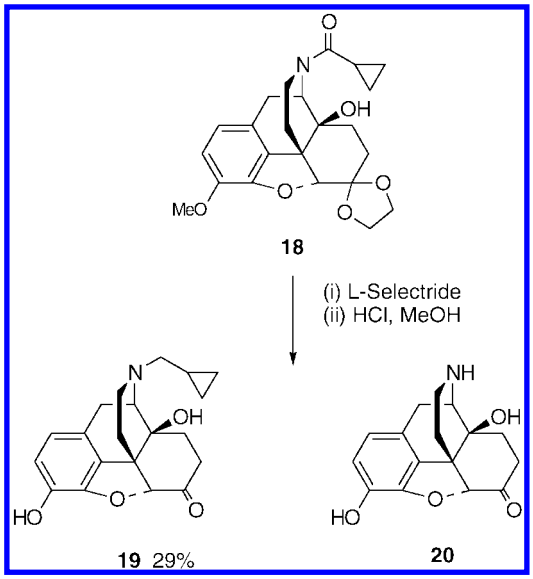
it is associated with many biological processes.[25] Again it was found that L-Selectride cleanly gave O-demethylation of **12a**,**b** to the corresponding phenols in good isolated yields (69% and 82%, respectively). The isolation of naltrindole differed from that described above for morphine due to its poor solubility in aqueous NaOH. It was found however that crystallization as the hydrochloride salt from the crude reaction product led to pure material.



The conversion of oxycodone (**14**) to oxymorphone (**15**) is a very important commercial transformation, at present being performed with the toxic BBr_3 in 75% yield.[19] This transformation can be performed with L-Selectride, via protection as the ethylene ketal, in 78% yield. Protection of the 6-ketone was necessary as L-Selectride will reduce ketones,[26] as was demonstrated by the conversion of hydrocodone (**16**) to dihydromorphine (**17**) (42%).



N-Dealkylation Studies. To further exploit the reducing power of L-Selectride, its reactivity with other reducible groups in opioid systems was investigated. Although the related Super-Hydride is known to cleave amides,[27] little work has been performed on the reaction of L-Selectride with such groups. This was of interest as many opioid antagonists contain a *N*-cyclopropylmethyl (*N*-CPM) group, which can be introduced from the norcompound by acylation followed by $LiAlH_4$ reduction.[5] We envisaged that L-Selectride may perform both reduction of the amide and O-demethylation, thus removing one step from their synthesis. Unfortunately, treatment of ketal protected (**18**) with L-Selectride followed by hydrolysis gave only a 29% yield of the desired naltrexone (**19**). The major product was noroxymorphone (**20**), formed by cleavage of the amide group.



This finding suggested that L-Selectride may be capable of cleaving carbamates to yield the corresponding *N*-nor compounds. The potential use of L-Selectride as a reagent for the cleavage of carbamates has not been fully investigated.[28] It was found that treatment of *N*-carbomethoxynorcodeine (**21**) with 3 equiv of L-Selectride at room temperature cleanly gave N-decarbomethoxylation to give norcodeine (**22**) in 92% yield, an obvious improvement over the 80−90% obtained from the cleavage of the carbophenoxy derivative with hydrazine.[14] This rapid cleavage of the carbamate at room temperature allowed selective N-decarbomethoxylation without accompanying O-demethylation as the latter is a slower reaction. Indeed, further treatment of norcodeine with L-Selectride at reflux gave the expected O-demethylation to normorphine (**23**) in 58% yield. The excellent yield of secondary amine and the very mild conditions make this a very convenient method for the cleavage of methyl carbamates in the opioids and for the alkaloids in general. The treatment of other carbamates, such as *N*-carbethoxy, with L-Selectride gave rise to a very slow reaction, suggesting the possibility of selective carbamate cleavage. Studies into this possible application and of determining the mechanism of the reaction are currently underway.

The finding that L-Selectride is capable of both O-demethylating and cleaving methyl carbamates prompted us to investigate the possibility that both transformations could be rendered in one pot to give the *N*-norphenols, important intermediates in opioid synthesis.[2] Both conversions have previously been performed in one pot, but only by the use of KOH at 200 °C.[5] As stated above, these conditions have proved unreliable on laboratory scales and the use of L-Selectride would be a major improvement. Treatment of **21** with L-Selectride at reflux gave **23** in 56% yield. In addition, **24** was smoothly converted into *N*-norphenol (**26**) in 59% yield through formation of the methyl carbamate and treatment with L-Selectride. However, a similar procedure utilizing the

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(25) Fundytus, M. E.; Schiller, P. W.; Shapiro, M.; Weltrowska, G.; Coderre, T. J. *Regul. Pept.* **1994**, *54*, 97.
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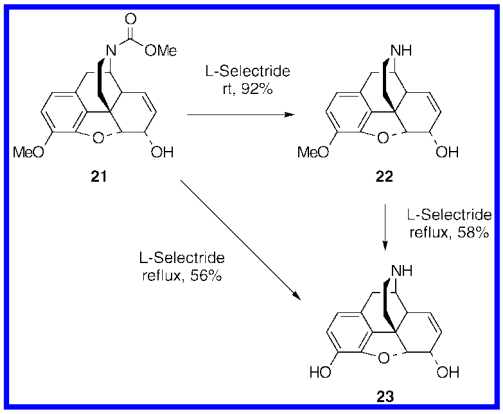
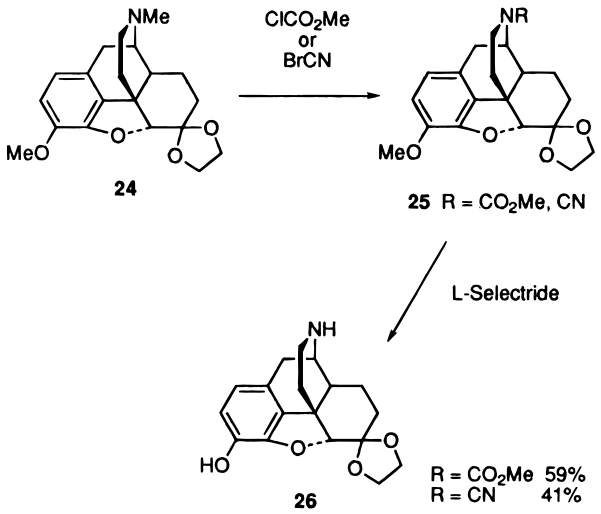
(28) (a) Link, J. T., Danishefsky, S., J. *Tetrahedron Lett.* **1994**, *35*, 9135. (b) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825.



corresponding cyanamide gave a mixture of products from which 41% of **26** was isolated. The N-deprotection reactions were again observed to be rapid at room temperature in both cases (TLC) while the O-demethylation step required heating, confirming the high degree of selectivity that is possible by controlling the conditions.[29]



Summary. L-Selectride has been shown to be an efficient and general O-demethylating agent for the opium alkaloids and their derivatives and an efficient reagent for the cleavage of methyl carbamates, thus offering a convenient method for the N-demethylation of opioids. Further, when conditions are controlled, it is possible to achieve both N-decarbomethoxylation and O-demethylation in one pot, or only render N-decarbomethoxylation in high yield without accompanying O-demethylation.

Experimental Section

The spectral and other physical data for all known compounds agreed with literature values, and these compounds were shown to be identical to authentic samples, which were obtained from Mallinckrodt and Co. if possible and synthesized when necessary. Melting points are uncorrected. Column chromatography was performed with Fluka silica gel 60 (mesh 220−240). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. All reactions were performed under an atmosphere of argon, and all solutions were evaporated to dryness on a rotary evaporator under reduced pressure. L-Selectride (1 M in THF) was purchased from Aldrich and used undiluted unless otherwise noted. Phenolic products were separated from the nonphenolic components in the aqueous workup by extraction into a 15% NaOH solution, followed by acidification (pH 1) with HCl (10%) and then rebasification (pH 9) with an ammonia solution. Simple extraction into an organic solvent gave the crude products. With the exception of the preparation of oripavine, all reactions are unoptimized.

Oripavine (3). Method A. A mixture of thebaine (**2**) (3.64 g, 11.7 mmol) and L-Selectride (1 M in THF, 60 mL) was stirred at room temperature for 14 days. The reaction was quenched with water (50 mL) followed by aqueous NaOH solution (15%, 30 mL) and removal of the THF. The resulting mixture was washed with CH_2Cl_2 (2 × 50 mL), cooled to 0−5 °C, and acidified (pH 1) with HCl (10%). After basification with an ammonia solution (pH 9), the mixture was extracted into $CHCl_3$ (3 × 60 mL) and the organic phase was washed with brine (100 mL) and dried (Na_2SO_4). Removal of the solvent gave crude **3**. Crystallization as the oxalic acid salt from MeOH gave oripavine oxalate·$1.5H_2O$ (1.69 g, 35%). The original CH_2Cl_2 extracts were washed with water (2 × 100 mL), followed by brief treatment with basic hydrogen peroxide (50 mL, 0.5%). The organic layer was separated, washed with brine (100 mL), and dried (Na_2SO_4). Removal of the solvent gave a brown foam. Crystallization as the (+)-tartaric acid salt from MeOH gave thebaine tartrate (270 mg, 5%). **Method B.** The same as method A but treatment with 2 equiv of L-Selectride at reflux for 0.5 h to give oripavine oxalate hydrate (23%) and thebaine tartrate (31%): mp (oxalate) 198−200 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H, NCH_3), 3.31 (d, 1H, J = 18.5, 10β-H), 3.59 (s, 3H, 6-OCH_3), 5.04 (d, 1H, J = 6.2, 8-H), 5.28 (s, 1H, 5-H), 5.55 (d, 1H, J = 6.2, 7-H), 6.54 (d, 1H, J = 8.2, 1-H), 6.62 (d, 1H, J = 8.2, 2-H); MS m/z (CI) 298 (M + 1, 100%). Anal. Calcd for $C_{20}H_{21}NO_7$·$1.5H_2O$: C, 57.96; H, 5.84; N, 3.38. Found: C, 58.22; H, 5.82; N, 3.41.

Orvinone (4).[30] A solution of **3** (1.26 g, 4.24 mmol) and 1-buten-3-one (10 mL) in toluene (10 mL) was heated at reflux for 2.5 h. After cooling and removal of the solvents, crystallization from MeOH gave **4** (1.28 g, 82%): mp 202−3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H, 21-H), 2.37 (s, 3H, NCH_3), 3.21 (d, 1H, J = 18.5, 10β-H), 3.57 (s, 3H, 6-OCH_3), 4.60 (d, 1H, J = 1.1, 5-H), 5.56 (d, 1H, J = 8.7, 19-H), 5.88 (d, 1H, J = 8.6, 18-H), 6.49 (d, 1H, J = 8.1, 1-H), 6.62 (d, 1H, J = 8.1, 2-H); MS m/z (CI) 368 (M + 1, 100%). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.64; H, 6.92; N, 3.73.

20-Methylorivinol (5).[5] Methyl iodide (0.75 mL, 12 mmol) was added dropwise to a stirred suspension of magnesium turnings (280 mg, 11.5 mmol) in dry Et_2O (30 mL). After complete consumption of the magnesium, a solution of **4** (840 mg, 2.3 mmol) in dry THF (30 mL) was added and the solution was stirred for 1.5 h. After quenching of the reaction with saturated ammonium chloride and removal of the solvents, the product was extracted into CH_2Cl_2 (3 × 40 mL). The organic extracts were washed with brine and dried (Na_2SO_4). After removal of the solvent, crystallization from acetone gave **5** (710 mg, 81%).

14-Hydroxymorphinone (7).[31] Sulfuric acid (10%, 4.5 mL) was added to a suspension of **3** (1.20 g, 4.04 mmol) in water (50 mL) at room temperature, and the mixture stirred until complete dissolution. To this solution was added an excess of *m*-CPBA (1.55 g, technical grade), and the mixture was stirred for 1.5 h. The mixture was then cooled in an ice bath (0−5 °C), the solid was removed by filtration, and the resulting clear solution was treated with sodium metabisulfite until a negative starch iodide test result was obtained. After basification to pH 9 with an ammonia solution, the product

(29) Similar treatment of the 14-hydroxy derivatives also gave the desired *N*-norphenols, but the reaction was complicated by attack of the 14-alkoxide on the N-substituent.

(30) Hori, M.; Kataoka, T.; Shimizu, H.; Imai, E.; Iwamura, T.; Nozaki, M.; Niwa, M.; Fujimura, H. *Chem. Pharm. Bull.* **1984,** *32*, 1268.

(31) Carroll, F. I.; Moreland, C. G.; Brine, G. A. *J. Org. Chem.* **1976**, *41*, 996.

was extracted with $CHCl_3$:MeOH (3:1, 5 × 60 mL). Removal of the solvents gave **7** (751 mg, 62%).

14-Hydroxycodeinone (6).[19] **2** (500 mg, 1.6 mmol) was treated with *m*-CPBA as for **3** above. The product was extracted into $CHCl_3$ (3 × 30 mL) and, after removal of the solvent, recrystallized from EtOH containing a little $CHCl_3$ to give **6** (439 mg, 87%).

Morphine (1).[3] Codeine (**8**) (482 mg, 1.6 mmol) was treated with 2.5 equiv of L-Selectride at reflux for 3.5 h. After aqueous workup, crystallization from water gave **1**·H_2O (355 mg, 73%). Starting material **8** was recovered from the nonphenolic extracts and purified by crystallization from water (71 mg, 14%).

20-Methylorvinol (5).[5] 20-Methylthevinol (**9**)[5] (1.78 g, 4.48 mmol) was treated with 3 equiv of L-Selectride at reflux for 3 h. After aqueous workup, crystallization from acetone gave **5** (1.25 g, 73%).

***iso*-Orvinol (11).**[5] *iso*-Thevinol (**10**)[5] (550 mg, 1.3 mmol) was treated with 5 equiv of L-Selectride (0.25 M in THF) at reflux for 48 h. After aqueous workup, purification via column chromatography (silica, EtOAc:NH_3 99:1) gave **11** (370 mg, 71%).

Oxymorphindole (13a).[24] Oxycodone indole (**12a**)[32] (1.12 g, 2.90 mmol) was treated with 3.5 equiv of L-Selectride at reflux for 18 h. After aqueous workup, the product was isolated as the methanesulfonic acid salt from MeOH (943 mg, 69%).

Naltrindole (13b).[24] A mixture of **12b**[24] (240 mg, 0.56 mmol) and L-Selectride (1 M in THF, 2.5 mL) was heated at reflux for 4 h. After cooling, the reaction was quenched with water (10 mL) and NaOH (15%, 10 mL). After removal of the THF, the aqueous solution was extracted with CH_2Cl_2 (2 × 20 mL). (Note: naltrindole did not remain in the basic aqueous phase.) The organic extracts were then washed with brine (30 mL) and dried (Na_2SO_4) and the solvent was removed to give a foam. Formation of the HCl salt in MeOH followed by replacement of the solvent with 2-propanol gave **13b**·HCl (226 mg, 82%).

Oxymorphone (15).[19] A solution of **14**·HCl (2.5 g, 6.9 mmol), ethylene glycol (5 mL), and catalytic toluenesulfonic acid in dry toluene (200 mL) was heated at reflux for 1 h with azeotropic removal of water. After cooling, the solution was basified with ammonia solution and partitioned between water and $CHCl_3$ and the aqueous phase was further extracted with $CHCl_3$. The organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent gave the crude ketal (2.46 g). The crude ketal was treated with 3 equiv of L-Selectride (0.5 M in THF) at reflux for 23 h. After aqueous workup, the crude product was redissolved in MeOH (40 mL), water (20 mL), and HCl (20%, 20 mL) and the solution was refluxed for 1 h. After cooling, the reaction was diluted with water (50 mL), basified with ammonia (pH 9), saturated with salt, and extracted into $CHCl_3$ (3 × 70 mL). After removal of the solvent, the product (**15**) was crystallized as the oxalic acid salt from EtOH (2.11 g, 78%).

Dihydromorphine (17).[31,33] Dihydrocodeinone (**16**) (540 mg, 1.8 mmol) was treated with 3 equiv of L-Selectride at room temperature for 0.5 h, followed by reflux for 3 h. After aqueous workup, crystallization from water gave **17**·H_2O (230 mg, 42%).

Naltrexone (19).[31] Ketal **18**[34] (1.34 g, 3.24 mmol) was treated with 5 equiv of L-Selectride at reflux for 16 h. After cooling, the reaction was quenched with water (30 mL) and then acidified to pH 1 with HCl (10%). The solution was heated at reflux for 0.75 h and then allowed to cool overnight. After removal of the THF, the solution was basified to pH 14 with NaOH (15%), washed with CH_2Cl_2 (50 mL), acidified with HCl (10%), and then rebasified to pH 9 with an ammonia solution. Attempted extraction into $CHCl_3$ revealed material soluble in neither phase; this material was recovered by filtration and shown to be impure noroxymorphone (**20**)[35] (510 mg). The $CHCl_3$ extracts were washed with brine and dried (Na_2SO_4). The solvent was removed, and the resulting crude material was subjected to column chromatography (EtOAc:MeOH:NH_3, 95:5:0.5) to give **19** (321 mg, 29%).

Norcodeine (22).[36] Carbamate **21**[37] (5.4 g, 16 mmol) was treated with L-Selectride (130 mL, 0.5 M in THF) at room temperature for 48 h. After quenching of the reaction with water (50 mL), HCl (3 M, 50 mL) was added and the mixture was cooled in an ice bath. Simple filtration gave **22**·HCl·$3H_2O$ (5.45 g, 92%).

Normorphine (23).[36] **Method A.** Norcodeine (**22**) (450 mg, 1.6 mmol) was treated with 6 equiv of L-Selectride at reflux for 18 h. The reaction was quenched with water, and the THF was removed. The resulting mixture was acidified to pH 1 (3 M HCl) and rebasified to pH 9 with ammonia, and the solid was collected by filtration. Recystallization from water gave **23**·$1.5H_2O$ (273 mg, 58%).

Method B. Carbamate **21**[37] (565 mg, 1.65 mmol) was treated with 6 equiv of L-Selectride as in method A to give **23**·$1.5H_2O$ (275 mg, 56%).

Dihydronormorphinone 6-Ethylene Ketal (26). Method A. A mixture of dihydrocodeinone 6-ethylene ketal (**24**)[38] (461 mg, 1.34 mmol), methyl chloroformate (0.5 mL), and K_2CO_3 (1.5 g) in dry $CHCl_3$ (20 mL) was heated under reflux for 18 h. After cooling, water (50 mL) was added and the products were extracted into $CHCl_3$ (3 × 50 mL). The organic extracts were washed with brine (50 mL), dried (K_2CO_3), and concentrated to give a foam (510 mg). This crude carbamate was treated with 5 equiv of L-Selectride at reflux for 4.5 h. After the solution was cooled to room temperature, the reaction was quenched with water (10 mL) and NaOH (1 M, 5 mL). The THF was removed under reduced pressure, and the mixture was washed with CH_2Cl_2, acidified (pH 1) with HCl (10%), and rebasified (pH 9) with an ammonia solution. The aqueous solution was saturated with salt and extracted with $CHCl_3$:MeOH (3:1). After removal of the solvents, the product was isolated as the HCl salt from MeOH (280 mg, 59%): mp >300 °C (dec); ^{1}H NMR (300 MHz, D_2O) (HCl salt) δ 2.98 (1H, d J = 18.5 Hz, 10β-H), 4.70 (1H, s, 5-H), 6.76 (1H, d J = 8.2 Hz, 1-H), 6.82 (1H, d J = 8.2 Hz, 2-H); MS m/z (CS LSIMS) 316 (M + 1, 100%). Anal. Calcd for $C_{18}H_{22}NO_4Cl$: C, 61.45; H, 6.30; N, 3.98. Found: C, 61.28; H, 6.30; N, 3.93.

Dihydronormorphinone 6-Ethylene Ketal (26). Method B. A mixture of dihydrocodeinone 6-ethylene ketal (**24**)[38] (1.41 g, 4.11 mmol) and cyanogen bromide (1.4 mL, 3 M in CH_2Cl_2) in dry $CHCl_3$ (30 mL) was heated under reflux for 24 h. After cooling, $NaHCO_3$ (50 mL) and NaOH (5 mL) were added and the mixture was stirred for 1 h. The product was extracted into $CHCl_3$ (3 × 50 mL), and the organic extracts were washed with brine (50 mL), HCl (10%, 50 mL), and $NaHCO_3$ (50 mL), dried (K_2CO_3), and concentrated to give a foam (1.25 g). This crude cyanamide was treated with 5 equiv of L-Selectride as in method A and isolated as the HCl salt from MeOH (589 mg, 41%).

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Supporting Information Available: ^{1}H NMR and mass spectral data for compounds **1**, **5**, **6**, **7**, 11, 13a, 13b, **15**, **17**, **19**, 22, and **23** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information

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