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Rearrangement of 5-Trimethylsilylthebaine on Treatment with L-Selectride: An Efficient Synthesis of (+)-Bractazonine

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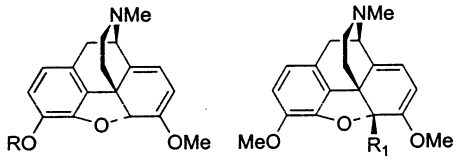
Treatment of 5-trimethylsilylthebaine with L-Selectride gave rise to a rearrangement to 10-trimethylsilylbractazonine through migration of the phenyl group, whereas treatment of thebaine with strong Lewis acids is known to lead to a similar rearrangement through migration of the alkyl bridge to give, after reduction, (+)-neodihydrothebaine. It is suggested that the rearrangement of the alkyl group of thebaine is favored due to the formation of a tertiary benzylic cation. However, for 5-trimethylsilylthebaine, the lithium ion of L-Selectride acts as the Lewis acid and the β-silyl effect dominates in the stabilization of any positive charge. This rearrangement provides a clear example of the greater relative migratory aptitude of phenyl groups over alkyl groups, and provides an efficient synthesis of (+)-bractazonine from thebaine.

Introduction

The orvinols are an important class of opioids which initially garnered interest due to their high potency as analgesics,[1] and it has become obvious that their mixed opioid actions impart unique pharmacological profiles which may prove useful in a number of conditions. For example, buprenorphine has recently been approved as a pharmacotherapy for opioid abuse,[2] and there is also interest in dihydroetorphine as a potential treatment agent.[3] These studies have led to a renewed interest in preparing novel analogues of the orvinols, and have increased the demands on the minor opium alkaloid thebaine (**1**) (Figure 1) from which they are all synthesized.[1] As thebaine contains a 3-methyl ether group, and the orvinols are 3-phenols, there is a requirement for a 3-*O*-demethylation step at some stage in their synthesis. Such demethylations have proved troublesome,[4] and we recently reported that the corresponding 3-*O*-demethylated analogue of thebaine, oripavine (**2**) (Figure 1), could be directly prepared from thebaine through L-Selectride mediated *O*-demethylation, but the yield of **2** from **1** was low (35%).[5] The numerous side products from the reaction were not isolated, but examination of crude NMR spectra indicated a lack of 6-*O*-methyl protons, suggesting that 6-*O*-demethylation was a major side reaction. We considered that if the 6-position could be sterically protected through the introduction of a large neighboring group, the bulky L-Selectride would not be able to make a close enough approach to cause 6-*O*-demethylation, thus increasing the selectivity for the 3-position, thereby increasing the yield of oripavine.



1 R = Me
2 R = H
3 R_1 = Li
4 R_1 = Me

FIGURE 1. Thebaine, oripavine, and 5-substituted thebaines.

The 5-position of thebaine is known to be somewhat amenable to functionalization through formation of the anion (**3**) with BuLi, followed by methylation with CH_3OSO_2F (methyl fluorosulfonate) to give 5-methylthebaine (**4**) (Figure 1).[6] Other small substituents have been incorporated,[7,8] but an apparent lack of reactivity has limited the number of substituents at this position. In addition, all substituents are permanent—in no cases could the substituent be subsequently removed to yield the often desired 5-unsubstituted compounds.

Herein we report our findings that the introduction of a large trimethylsilyl group can be accomplished ef-

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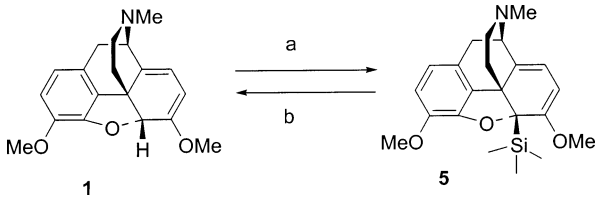
SCHEME 1[a]



[a] Reagents and conditions: (a) (i) BuLi; (ii) TMS-Cl (11%); (i) BuLi; (ii) TMS-OTf (8%); (i) BuLi, TMEDA; (ii) TMS-Cl (97%). (b) TBAF (90%).

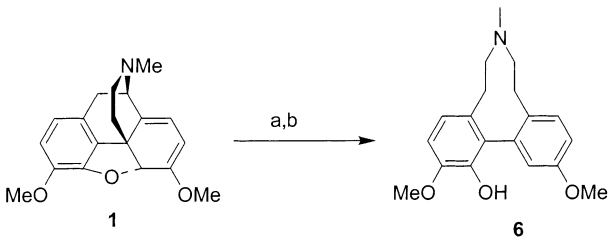
ficiently and be removed to regenerate thebaine, but does not give the desired selective 3-*O*-demethylation upon treatment with L-Selectride. Indeed, treatment with L-Selectride gives rise to a rearrangement that, after desilylation, gave (+)-bractazonine,[9] a little studied isomer of (+)-neodihydrothebaine.[10] The rearrangement occurs through migration of the phenyl group, whereas with thebaine migration of a methylene occurs upon treatment with a strong Lewis acid to give, after reduction, the isomeric (+)-neodihydrothebaine.[11,12]

Results and Discussion

Introduction of the 5-Substituent. Initial studies concentrated on introducing the 5-trimethylsilyl group into **1** through similar conditions as those for 5-methylthebaine (**4**).[6] Treatment of the thebaine anion (**3**) with trimethylsilyl chloride (TMS-Cl) gave rise to only a minor yield (11%) of the desired product (**5**) (Scheme 1), with the majority of the balance of material being starting material. Increasing reaction times did not lead to increased yields, consistent with previous findings that the anion is relatively inert toward organic electrophiles. Treatment with trimethylsilyl trifluoromethanesulfonate (TMS-OTf) actually led to a reduced yield of **5** (8%). As the apparent lack of reactivity of anion **3** may be due to coordination of the lithium ion to both the oxygens at the 5 and 6 positions, we considered that the addition of tetramethylethylenediamine (TMEDA) may compete for coordination to the lithium, thereby increasing the reactivity of the anion. Indeed, simple addition of TMEDA led to an excellent yield of **5** (97%) with TMS-Cl as the electrophile (Scheme 1). Minor side products complicated purification through column chromatography; however, it was shown that purification through the oxalate salt was possible in 73% yield, removing any need for chromatography.

Removal of the 5-Substituent. To show the potential utility of the 5-trimethylsilyl group as a protecting group for thebaine, it was necessary to show that the substituent could be removed from **5** to regenerate **1**. Scheme 1 shows that simple treatment with TBAF (tetrabutylammonium fluoride) efficiently removed the 5-substituent to give high yields of **1**. Thus, the use of a silyl protecting group at the 5 position of thebaine represents a potential method to protect the sensitive diene system of thebaine during synthetic manipulation of other parts of the molecule.

SCHEME 2[a]



[a] Reagents and conditions: (a) MeI_2. (b) $LiAlH_4$.

Treatment with L-Selectride. As the large 5-substituent should prevent close approach of the bulky L-Selectride to the 6-methoxyl group, treatment of **5** with L-Selectride was expected to give increased yields of the 3-*O*-demethylated product. Indeed, TLC analysis indicated the formation of one major product, but ^{1}H NMR analysis indicated the presence of two methoxyl groups indicating that the product was not the expected 5-trimethylsilyloripavine. MS analysis showed a mass of two units above **5** suggesting a reduction, and the lack of aliphatic protons in the ^{1}H NMR suggested a rearrangement of the carbon−nitrogen skeleton. ^{13}C NMR indicated 12 carbons in the aromatic region suggesting two aromatic rings, again supporting the theory of a rearrangement. Desilylation of the product was unsuccessful with TBAF, but gave rise to one major product with an optical rotation of +35.5° when desilylated with TFA. Previous studies have shown that thebaine is unstable under acidic conditions yielding a variety of products, but the rearrangement to (+)-neodihydrothebaine (**6**) (Scheme 2) when treated with MgI_2 followed by reduction was of prime interest. **6** contains only aromatic and benzylic protons, together with protons α to a basic nitrogen. ^{1}H NMR analysis was performed on (+)-neodihydrothebaine when it was initially reported, but only at 60 MHz.[10] Thus, although our desilylated product appeared to give rise to a similar spectrum, we decided that the only way of confirming the product was through the preparation of an authentic sample as shown in Scheme 2. Treatment of **1** with MgI_2 followed by reduction with $LiAlH_4$ gave rise to **6** with a very similar NMR spectrum to our product, but very subtle differences were noted.

Single-crystal X-ray analysis clearly showed the structure proposed for **6** to be correct (see Supporting Information), and our desilylated product to be the isomeric bractazonine (**7**)[9] (see Supporting Information). Thus, we propose that treatment of **5** with L-Selectride is causing rearrangement as shown in Scheme 3. (+)-Bractazonine (**7**) has been prepared previously from **1**,[9,13] but only in very low yield by treatment with UV irradiation. We considered that this product could only be formed via a migration of the phenyl group of **5** to the 14-position (Figure 2) with the lithium ion of L-Selectride acting as the Lewis acid, followed by reduction of the iminium ion to give **8**. Simple desilylation leads to **7**. In contrast, in the treatment of **1** with MgI_2, the alkyl bridge migrates to leave the stable tertiary cation. Reduction of the

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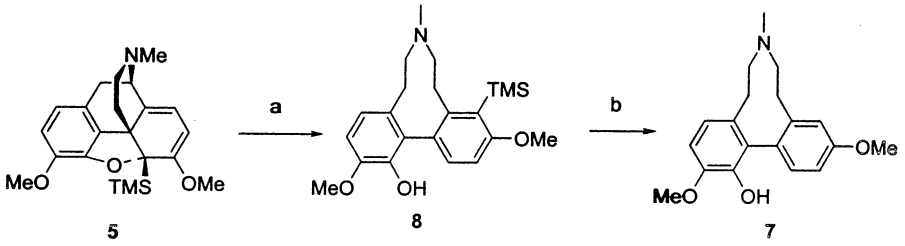
SCHEME 3[a]



[a] Reagents and Conditions: (a) L-Selectride, reflux. (b) TFA, rt.

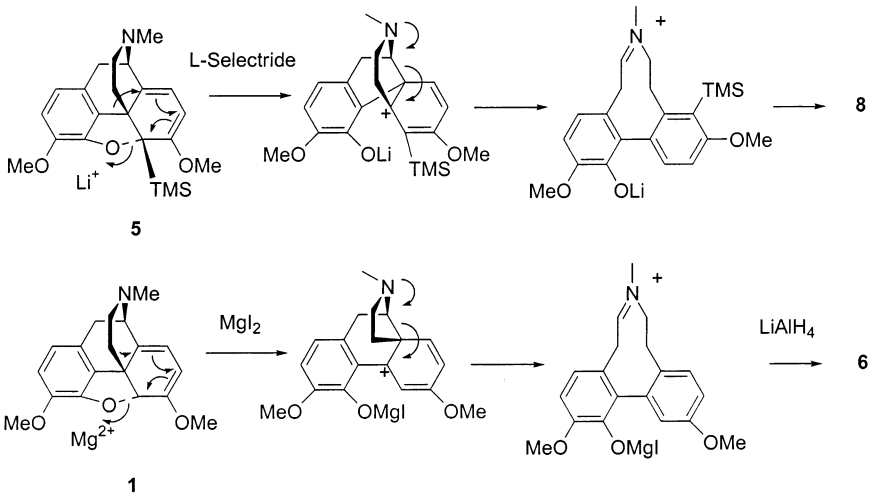


FIGURE 2. Proposed mechanism of rearrangement.

resulting iminium ion with $LiAlH_4$ gives **6**. The action of the lithium ion of L-Selectride acting as a Lewis acid was confirmed by the result of the action of K-Selectride on **5**. When subjected to similar conditions as for L-Selectride, desilylation to **1** was the only reaction.

As the apparent change in migratory aptitudes of the two groups may be related to a change in their relative orientations to the plane of the diene on the introduction of the silyl group, molecular models of thebaine and 5-trimethylsilylthebaine were obtained from quantum mechanical calculations. Analysis of the structures showed that both groups are at approximately the same angles to the plane of the diene system in thebaine and 5-trimethylsilylthebaine. For the methylene, the angles to the plane of the diene system are 47° and 42° for thebaine and 5-trimethylsilylthebaine, respectively, while the angles of the phenyl group to the plane are 70° and 72°, respectively (see Supporting Information). Thus, the addition of the silyl group does not significantly alter the migratory aptitudes of either group by changing their orientations to the plane of the diene. Which group migrates, therefore depends on the stability of the resulting cation and migratory aptitude of the group. Although phenyl is generally considered to possess a greater migratory aptitude,[14] an alkyl group will often migrate preferentially due to the stability of the resulting benzylic cation. This is apparently the case with **1**, where the alkyl group migrates. However, with **5** the β-silicon effect[15] stabilizes the cation allowing the group with the greatest inherent migratory aptitude to migrate, and still leave the silyl-stabilized cation (Figure 2). This rearrangement is a clear example of the greater migratory aptitude of phenyl groups over alkyl groups.

In conclusion, protection of the 5-position of thebaine is possible as the trimethylsilyl derivative, but the β-silicon effect allows a facile rearrangement upon treatment with L-Selectride. Importantly, this rearrangement clearly demonstrates the greater relative migratory aptitudes of phenyl groups over alkyl groups, and represents the first efficient synthesis of (+)-bractazonine from thebaine.

Experimental Section

General Procedures. All reactions were performed under an atmosphere of nitrogen, and all solvents were removed on a rotary evaporator under reduced pressure. TLC was performed on plates coated with silica gel GHLF-0.25 mm plates (60 F_{254}). BuLi was titrated by using the method of Kofron and Baclawski.[16] Melting points are uncorrected. Microanalyses were performed by Atlantic Microlabs, Norcross, GA, and are within ±0.4% of expected values.

5-Trimethylsilylthebaine (5). To a stirred solution of TMEDA (0.78 mL, 5.1 mmol) in dry THF (10 mL), cooled to −78 °C, was added a solution of BuLi (4.62 mL of a 1.11 M solution in hexane, 5.1 mmol). The mixture was allowed to stir for 30 min before the slow addition of a solution of **1** (0.93 g, 3.0 mmol) in dry THF (20 mL). The solution was allowed to

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stir at −78 °C for 1 h, followed by the addition of TMS-Cl (1.56 mL, 12.3 mmol). After being stirred for a further 30 min at −78 °C, the solution was allowed to come to room temperature over 2 h, then stirred at room temperature overnight. After removal of the solvent, the residue was taken into $CHCl_3$ (50 mL), washed with $NaHCO_3$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by the following methods: (a) flash chromatography on silica gel (gradient from 2% to 10% MeOH in CH_2Cl_2) to afford **5** (1.12 g, 97%) as a colorless foam; (b) crystallization as the oxalic acid salt from EtOH to give **5**·oxalate hydrate as a white solid, which was freebased with $NaHCO_3$ to give **5** (0.84 g, 73%) as a colorless foam. Mp (**5**·oxalate) 142.0−144.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 1.66 (dt, 1H, J = 11.8, 2.2 Hz), 2.29 (td, 1H, J = 11.8, 5.9 Hz), 2.44 (s, 3H), 2.57−2.69 (m, 3H), 3.26 (d, 1H, J = 17.6 Hz), 3.49 (s, 3H), 3.63 (d, 1H, J = 6.6 Hz), 3.87 (s, 3H), 4.95 (d, 1H, J = 6.6 Hz), 5.57 (d, 1H, J = 6.6 Hz), 6.58 (d, 1H, J = 8.1 Hz), 6.64 (d, 1H, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.61, 30.66, 34.38, 42.63, 46.45, 50.75, 54.47, 56.77, 62.11, 92.55, 95.01, 113.22, 113.96, 119.39, 127.06, 131.11, 134.18, 143.14, 145.47, 156.89. ESIMS m/z 382.9 (M^+, 100%). Anal. Calcd for $C_{24}H_{31}NO_7Si$·$2H_2O$: C, 56.56; H, 6.92; N, 2.75. Found: C, 56.75; H, 6.84; N, 2.70.

Removal of the 5-Trimethylsilyl Group from 5. To a stirred solution of **5** (0.19 g, 0.5 mmol) in THF (15 mL) and distilled water (0.5 mL) was added (n-Bu)$_4$NF (TBAF) (1.0 M in THF, 1.0 mL, 1.0 mmol) at room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated, and the residue was taken into $CHCl_3$ (50 mL), washed with $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (gradient: 2% to 10% MeOH in CH_2Cl_2) to afford **1** (0.14 g, 90%) as a white foam, which gave spectral data identical with those of an authentic sample.

10-Trimethylsilylbractazonine (8). A mixture of **5** (0.27 g, 0.7 mmol) and L-Selectride (1 M in THF, 2 mL, 2 mmol) was heated under reflux for 3 h. The reaction was quenched with water, the THF removed, and the resulting mixture taken into $CHCl_3$ (50 mL), washed with $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (gradient: 5% to 15% MeOH in CH_2Cl_2) to afford **8** (0.25 g, 92%) as a colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.34 (s, 9H), 2.27 (s, 3H), 2.31−2.57 (m, 5H), 2.58−2.71 (m, 1H), 2.73−2.86 (m, 1H), 2.94−3.09 (m, 1H), 3.83 (s, 3H), 3.91 (s, 3H), 5.35 (br s, 1H, OH, exchangeable with D_2O), 6.77 (d, 1H, J = 8.3 Hz), 6.80 (d, 1H, J = 8.3 Hz), 6.85 (d, 1H, J = 8.3 Hz), 7.11 (d, 1H, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.43, 146.08, 145.53, 143.30, 132.46, 130.07, 129.26, 128.19, 127.16, 120.92, 110.73, 109.17, 58.26, 56.77, 56.35, 55.31, 44.96, 30.34, 29.86, 2.75. ESIMS m/z 385.4 (M^+, 100%).

(+)-Bractazonine (7).[9,13] To a stirred solution of **8** (0.19 g, 0.5 mmol) in CH_2Cl_2 (10 mL) was added TFA (1 mL) at room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated, and the residue was taken into $CHCl_3$ (50 mL), washed with $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (gradient: 2% to 10% MeOH in CH_2Cl_2) to afford **7** (0.15 g, 96%) as a white foam. Evaporative recrystallization from MeOH provided crystals suitable for X-ray analysis. Mp 101.0−103.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.37−2.45 (m, 1H), 2.47−2.78 (m, 7H), 3.85 (s, 3H), 3.91 (s, 3H), 5.39 (br s, 1H, OH, exchangeable with D_2O), 6.75 (d, 1H, J = 8.3 Hz), 6.81−6.90 (m, 3H), 7.10 (d, 1H, J = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.64, 145.37, 143.11, 142.36, 134.15, 131.20, 128.52, 127.64, 120.40, 115.51, 112.05, 110.40, 57.71, 57.61, 56.28, 55.48, 47.03, 34.68, 33.83. ESIMS m/z 314.1 (M^+ + 1, 100%). $[\alpha]^{20}_D$ +35.5 (c 0.6, $CHCl_3$).

Reaction of 5 with K-Selectride. A mixture of **5** (0.11 g, 0.29 mmol) and K-Selectride (1 M in THF, 1 mL, 1 mmol) was heated under reflux for 3 h. The reaction was quenched with water, and the THF was removed. The resulting mixture was taken into $CHCl_3$ (50 mL), washed with $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (gradient: 5% to 15% MeOH in CH_2Cl_2) to afford **1** (0.078 g, 85%) as a colorless foam, which gave spectral data identical with those of an authentic sample.

(+)-Neodihydrothebaine (6). 6 was prepared following the method of Bentley.[10] Evaporative recrystallization from 2-butanone/H_2O provided crystals suitable for X-ray analysis. Mp 99.0−101.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.32−2.68 (m, 8H), 3.79 (s, 3H), 3.92 (s, 3H), 5.36 (br s, 1H, OH, exchangeable with D_2O), 6.73 (d, 1H, J = 2.8 Hz), 6.75 (d, 1H, J = 8.3 Hz), 6.86 (d, 1H, J = 8.3 Hz), 6.90 (dd, 1H, J = 8.3, 2.8 Hz), 7.19 (d, 1H, J = 8.3 Hz). ESIMS m/z 314.1 (M^+ + 1, 100%).

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Supporting Information Available: ^{1}H spectra of compounds **5**, **6**, **7**, and **8**, X-ray crystallographic data for compounds **6** and **7**, and modeling data concerning the rearrangement of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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