Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7381–7384

TETRAHEDRON LETTERS

Isolation and synthesis of 2-chloro-10-α-hydroxynaltrexone, a new naltrexone degradant

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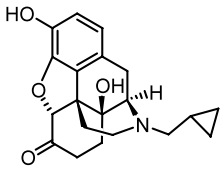
Received 2 April 2003; revised 14 July 2003; accepted 23 July 2003

Abstract—The putative structure of a new degradant from REVIA® tablets was assigned 2-chloro-10-α-hydroxynaltrexone **2**. A route for the independent synthesis was developed wherein a *N*,*N*-diethylcarbamate derivative directed an *ortho*-metallation of the naltrexone nucleus, leading to the desired 2-chloro functionality. Oxidation of the 10-position, followed by deprotection provided **2**, which was identical in all respects to the original isolate.

Naltrexone HCl (**1**, REVIA®) is a δ-opiod receptor antagonist that has found new use in the treatment of alcoholism.[1] A new degradant was isolated in commercially formulated samples through extraction and preparative reverse phase HPLC.[2] Based on mass spectroscopy, proton and carbon NMR, the putative structure 2-chloro-10-α-hydroxynaltrexone (**2**) was assigned.[3] Because the prep HPLC method provided only milligram quantities of impure **2**, a synthetic route was needed to authenticate the structure of **2** and to provide high purity material for follow-up studies.[4]



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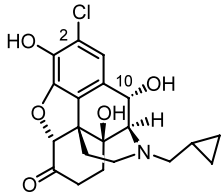

2

Although the mechanism for the formation of **2** was speculative,[5] our initial synthetic approach was based on an electrophilic chlorination strategy. There was some literature precedent within the thebaine literature to suggest that the phenol functionality of **1** could promote the halogentation of the aromatic ring.[6] Our attempts to monochlorinate naltrexone **1** using either NCS in CH_3CN or aq. hypochlorite were unsuccessful. In order to simplify the reactive functionalities of naltrexone, the carbonyl was protected as the dioxolane **3** using *p*-TSA (110 mol%), ethylene glycol, toluene (Scheme 1) followed by methylation of the phenol using Me_2SO_4, powd. K_2CO_3, acetone provided ether **4** in 86% yield. Although attempts to chlorinate **3** under electrophilic conditions were unsuccessful, chlorination of **4** under NCS/CH_3CN provided a product **5** that lacked one aromatic proton in the ^1H NMR. When product **5** was oxidized using CrO_3 in aqueous H_2SO_4,[7] the 10-hydroxylation product **6** was obtained in 30% yield. Although the yield for the sequence was low, analysis of **6** by 2D NMR suggested that the chlorination occurred at the undesired 1-position of naltrexone aromatic ring. From this finding, the methyl ether could not be used to affect *ortho*-chlorination in the presence of the strong *para*-directing effects of the ring-fusion ether; therefore, this chlorination strategy was abandoned.[8]

An alternative strategy for the regiospecific installation of the 2-chloro functionality had to be developed. Snieckus has shown the diethylcarbamoyl group to be good directing group for *ortho*-metallation of phenols.[9] As shown in Scheme 2, the diethylcarbamate **8** required for this chemistry was prepared from **3** in 90% yield. Metallation was affected with *s*-BuLi, TMEDA, −78°C, and provided a colored lithiate, which was quenched

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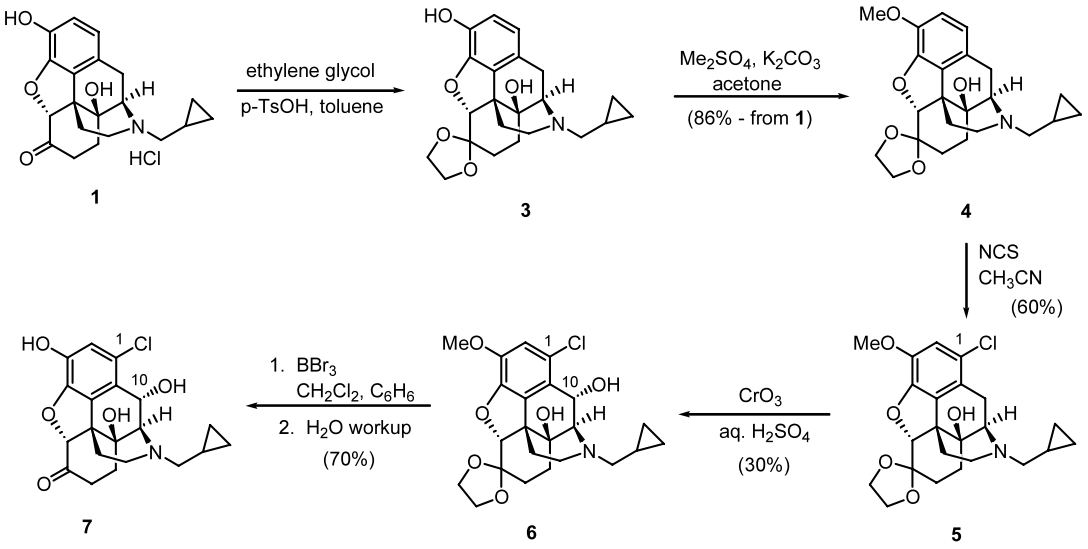
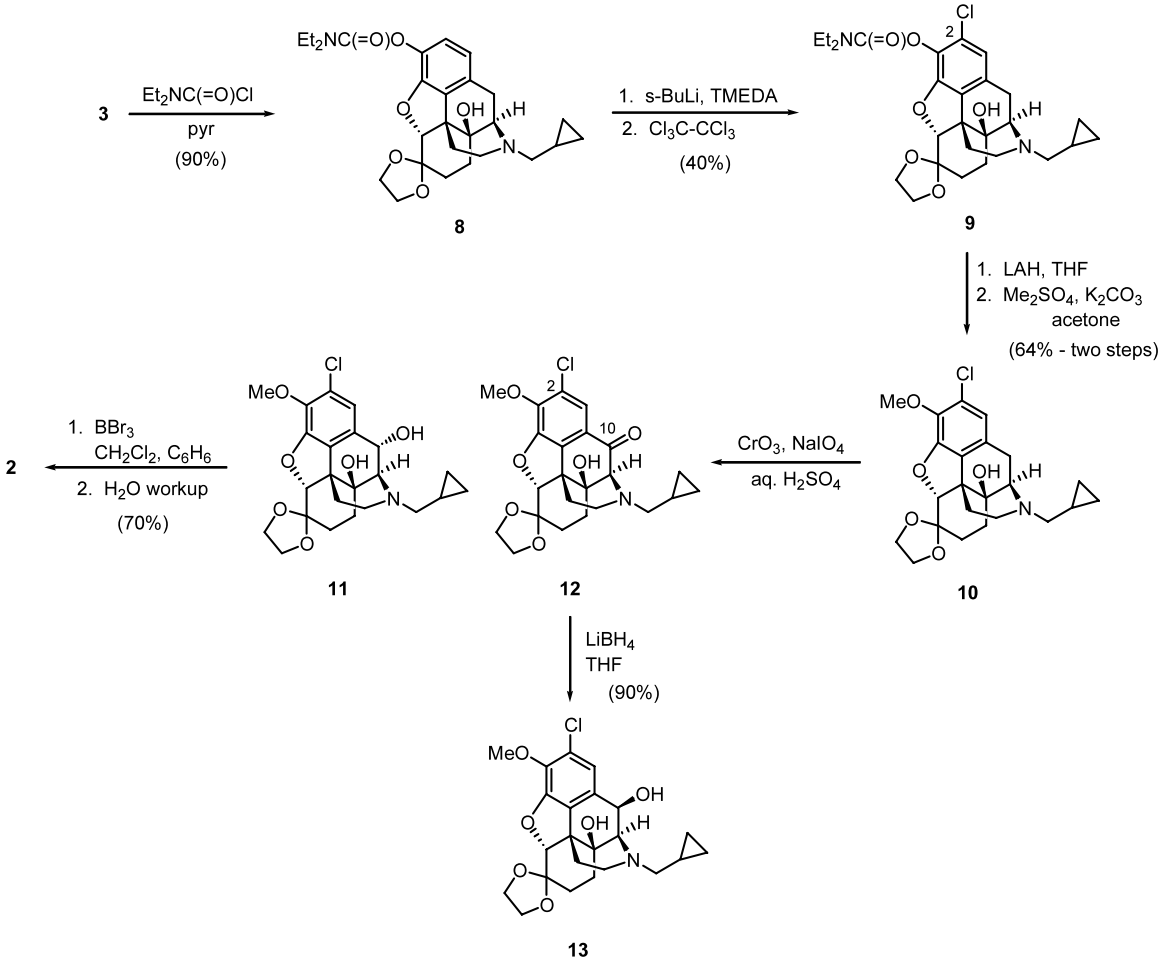
doi:10.1016/S0040-4039(03)01797-0



Scheme 1.



Scheme 2.

using an organic soluble chlorine source hexachloroethane.[10] The chlorinated carbamate **9** was isolated in 40% yield after chromatography. For purposes of the oxidation, it was necessary to switch the phenol protecting group to the methyl ether because of its favorable solubility in the aqueous H_2SO_4 used for the oxidation. This was achieved by unmasking the phenol using LAH, THF, 0°C to reduce the diethylcarbamate,

followed by methylation using Me_2SO_4, powdered K_2CO_3 in acetone, providing ether **10** in 64% yield (two steps). It is important to note that the reaction conditions for the hydride reaction were optimized conditions. When the reaction temperature was raised in an attempt to reduce the reaction time, a considerable amount of dechlorinated **3** was observed. Treatment of **10** with CrO_3 in aq. H_2SO_4 provided oxidation products 10-α-hydroxylated **11** (30%) and over-oxidation by-product **12** (60%). Retrospective product analysis of the oxidation of **5** showed similar 10-keto by-product (60% yield), suggesting that the positional changes of the halogen had little electronic influence on the oxidation potential of the 10-position on the naltrexone nucleus.

In order to corroborate the α-configuration of isomers **6** and **11**, the coupling pattern of the 10-H protons were examined in detail. Rapaport and co-workers had reported earlier that chromium-based oxidations on the 10-hydroxycodeines provided the 10-α-OH configuration, while hydride reduction of the 10-keto group provided 10-β-OH groups.[11] Although their analysis was based on IR and cLogP evidence, their findings were later confirmed by NMR analysis in similar ring systems.[6c,12] In our case, the ^1H NMR analysis of **6** and **11** had similar ^1H splitting patterns ($J_{9-10}=0$ Hz) of the 10-H and the H-9 methine. Although this finding was certainly suggestive of the 10-α-OH configuration, we sought to confirm this finding in the naltrexone series. Reaction of the ketone **12** with a large excess of $LiBH_4$, THF provided **13** in 90% yield. The larger coupling constant ($J_{9-10}=5.3$ Hz) seen for **13** confirmed the assignment of the epimers as shown.

With the correct configuration established, synthetic **2** was realized after deprotection of the methyl ether using BBr_3 in chlorobenzene. It is important to note that under these conditions, the ketal protecting group was smoothly cleaved to the ketone as a consequence of the hot aqueous hydrolysis used in the work-up. The yield for the deprotection (70%) could be improved upon further investigation of the pH ranges that would enhance optimal partitioning into an organic solvent.[13] The product 2-chloro-10-α-hydroxynaltrexone **2** obtained from this procedure was identical in every respect to the initial HPLC isolates.

In conclusion, we have developed a synthesis to authenticate the impurity in commercially formulated Naltrexone HCl (**1**, REVIA®) tablets. The seven step protocol which was developed required a regiospecific metallation of the diethylcarbamate protected phenol followed by chlorination with hexachloroacetone, switching of protecting groups to facilitate the benzylic oxidation using aq. CrO_3 and final demethylation step. The stereochemistry was judged to be the 10-α-OH based on the expected coupling pattern as was consistent with earlier reported values.

Acknowledgements

We thank Mr. Ernest Schubert for the detailed NMR analysis of intermediate **6**.

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2. Naltrexone tablets were ground and dissolved in pH 11 ammonia buffer. The solution was extracted four times with chloroform. The pH of the aqueous layer was adjusted to 8.5 and extracted four times with chloroform. The organic layer was dried, concentrated and applied to a Phenomenex Lichrosorb reverse-phase HPLC column (10 RP-8, 250×10 mm). A mobile phase consisting of H_2O, MeOH, monobasic phosphate and sodium octanesulfonate was used under gradient conditions (20–40% MeOH over 25 min.), flow rate 7 mL/min., with 280 nm UV detection. The collected fractions were allowed to dry in an evaporating dish and protected from light. The isolates were dissolved in water, pH buffered to 8.5 (ammonia buffer) and extracted with chloroform. After evaporation the sample was dissolved in $CDCl_3$ for NMR analysis.
3. ^1H NMR ($CDCl_3$) δ 7.03 (s, 1H), 4.99 (s, 1H), 4.72 (s, 1H), 3.22 (s, 1H), 3.07 (ddd, $J=14.2$, 14.2, 5.8 Hz, 1H), 2.71 (dd, $J=12.2$, 4.9 Hz, 1H), 2.59 (dd, $J=12.9$, 6.3 Hz, 1H), 2.49 (dd, $J=12.9$, 6.3 Hz, 1H), 2.43 (ddd, $J=12.7$, 12.7, 5.6 Hz, 1H), 2.42 (ddd, $J=14.2$, 3.1, 3.1 Hz, 1H), 2.06 (ddd, $J=12.2$, 12.7, 3.9 Hz, 1H), 1.99 (m, 2H), 1.58 (ddd, $J=12.7$, 3.9, 1.0 Hz, 1H), 0.92 (m, 1H), 0.59 (m, 2H), 0.18 (m, 2H); ^{13}C NMR δ 209.02, 143.96, 137.60, 128.28, 126.92, 122.92, 120.60, 91.29, 69.26, 69.09, 63.75, 59.45, 51.73, 43.82, 36.40, 32.19, 30.36, 9.45, 4.13, 3.89.; Mass spec: m/e 392 ($M+H^+$, 100%), 394 (35.08%).
4. The mechanism for the formation of **2** is presently unknown. It is speculated that in the presence of air, the hydrochloride could be oxidized to elemental chlorine, which could be trapped in the solid-state matrix of the tablet. It should be noted that our unsuccessful chlorination attempts (infra vide) do not support this hypothesis; however, our results may simply suggest a difference in the solution-phase versus solid-state reactivity of **1**.
5. The level of contamination generally increased with time. As much as 0.2–0.3% was found in samples stored for 4–6 years; whereas samples stored for shorter times had 0.1–0.2%.
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8. An explanation for the regiochemistry of halogenations/nitration of morphine, a structurally related thebaine, can be found in Singh, B. B.; Chauhan. R. S.; Madyastha, K. M.; Bhatnagar, S. P.; Kirk, K. L.; Weiss, U. *Hetereocycles*, **1982**, 19, 837. These authors also provide details for the formation of 2-chloromorphine by initial nitration and reactions subsequent therein.

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13. In other thebaines investigated in our laboratories, liquid–liquid extraction of the aqueous fractions using 20% MeOH in $CHCl_3$ has improved the recovery of the demethylation product.