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# Novel Synthesis of the Ortho Ester Derivative of 4,5-Epoxymorphinan

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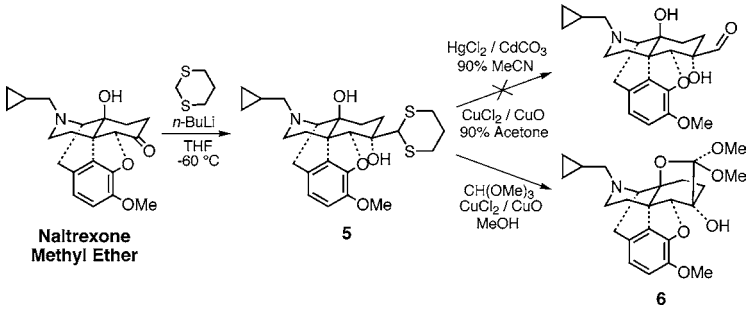
## ABSTRACT




**A method was found for the novel synthesis of ortho ester derivatives that are potentially useful as selective ϵ opioid receptor ligands. An unexpected 17-(cyclopropylmethyl)-4,5α-epoxy-6α-hydroxy-3,7,7-trimethoxy-8-oxa-6,14-endoethanomorphinan was produced when 17-(cyclopropylmethyl)-4,5α-epoxy-3-methoxy-6α,14-dihydroxy-6β-(1,3-dithia-2-yl)-morphinan was treated in methanol with trimethyl orthoformate and CuO/$CuCl_2$. This ortho ester derivative was then converted to an ester with acid. The structure of the ortho ester was determined by 2D NMR (HMBC) and mass spectra.**

Buprenorphine[1] and etorphine[2] are potent μ and ϵ opioid analgesics, and like opiate analgesics in general, they are capable of causing serious respiratory depression. However, these two particular analgesics produce respiratory depression that is especially dangerous because it cannot be reversed by the μ opioid antagonist naloxone.[1] This resistance to antagonism by naloxone is generally attributed to these opiates' high affinity for the μ receptor and their high lipophilicity.[1,3]

TAN-821 is a potent and selective ϵ opioid receptor agonist that produces strong analgesia in vivo.[4] However, it is not selective enough for the ϵ receptor and in fact has been found to bind in vitro (mouse vas deferens assay) to the μ opioid receptor type.

These three compounds all have in common a 6,14-endoethanotetrahydrothebaine skeleton with a 7,8-methylene bridge (**1**). We hypothesized that their strong affinity for μ opioid receptor may derive in part from the high lipophilicity that is conferred upon them by this bridge. If so, then we should be able to reduce their affinity for μ opioid receptor by introducing a hydrophilic group. We therefore designed a novel compound with hydrophilicity at its bridge position, namely, 17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-8-oxa-6,14-endoethanomorphinan (**2**), to improve the ϵ selectivity of TAN-821 in vitro.

Initially, we planned its synthesis by intramolecular cyclization between the 14-hydroxyl and 6β-enone in **3**. We intended to obtain **3** by a Horner−Emmons reaction[5] of

(1) Reisine, T.; Pasternak, G.*Opioid Analgesics and Antagonists. Pharmaceutical Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. E., Ruddon, R. W., Gilman, A. G., Eds.; Mcgraw-Hill: New York, 1995; pp 521−556.

(2) Xu, J. Y.; Fujimoto, J. M.; Tseng, L. F. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 246−252.

(3) Burkey, T. H.; Ehlert, F. J.; Hosohata, Y.; Quack, R. M.; Cowell, S.; Hosohata, K.; Varga, E.; Stropova, D.; Li, X.; Slate, C.; Nagase, H.; Porreca, F.; Hruby, V. J.; Roeske, W. R.; Yamamura, H. I. *Life Sci.* **1998**, *62*, 1531−1536.

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(5) (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1734−1738. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

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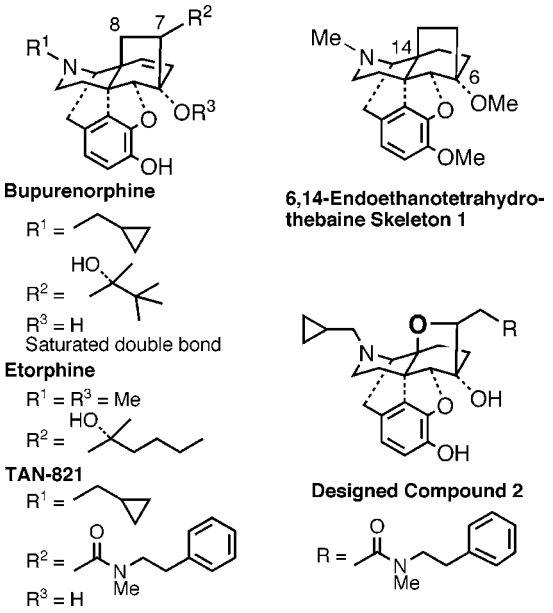


**Figure 1.**

aldehyde **4** with a phosphonate reagent, after first obtaining **4** from the 1,3-dithiane precursor **5**[6] by reaction of naltrexone methy ether[7] with a carbanion of 1,3-dithiane.

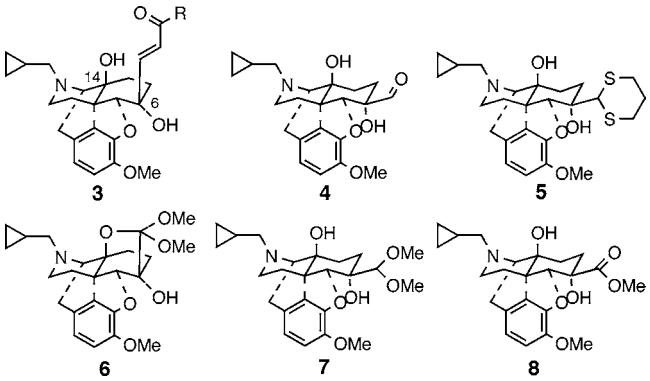


**Figure 2.**

We began by attempting to obtain **4** by hydrolysis of **5** using $CuCl_2$/CuO or $HgCl_2/CdCO_3$ in aqueous MeCN or $CH_3COCH_3$.[8] However, this was not successful. We next tried the approach of subjecting **5** to an acetal exchange reaction with $CuCl_2$/CuO (2 and 4 equiv) and trimethyl orthoformate in MeOH at 50 °C, the goal being to obtain the dimethyl acetal **7**. Surprisingly, this resulted instead in yield (55%) of the ortho ester (**6**). The structure of **6** was confirmed by NMR and mass spectra, and its stereochemistry was elucidated by $^1$H NMR and NOE experiments. NOE was observed between the C5- and C15-protons, the C5- and C6-hydoroxyl protons, and the C5- and C7′-protons. Long-range coupling was also observed between the C5- and C7′-protons ($J$ = 1.5 Hz). In the HMBC spectrum of **6**, the proton signals at 5.35 ppm (C6−OH) and 4.47 ppm (C5−H) showed a correlation with the carbon signals at 74.77 ppm (C6) and 113.71 ppm (C7), respectively (Figure 3).

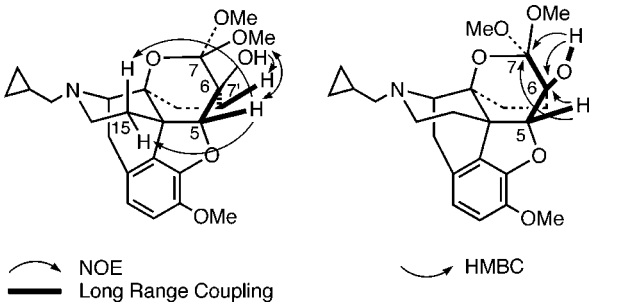


**Figure 3.** Structure of **6**.

This was the first time that use of an oxidation method had succeeded in introducing a 6$\beta$-carboxylic acid functional group onto naltrexone without oxidation of any other functional groups (such as N, OH). Moreover, this approach also produced the first 8-oxa bicyclo[2.2.2] derivative (**6**) in opioid chemistry. We therefore sought to find conditions that optimized this reaction.

We first tried running the reaction with some metals that are commonly used to catalyze the hydrolysis of thioacetal, namely, $HgCl_2/CdCO_3$, $AgNO_3$/AgO, and $FeCl_3$/CuO. We found that the hydrolysis (oxidation) proceeded with $FeCl_3$/CuO and, alternatively, with $CuCl_2$/CuO, but it did not with $HgCl_2/CdCO_3$ or $AgNO_3$/AgO. Between $FeCl_3$/CuO and $CuCl_2$/CuO, the latter produced the shortest reaction time, so it was made the focus of our optimization effort thereafter. Good yields of **6** were obtained under a variety of conditions that included trimethyl orthoformate (Table 1, entries 1−6), with the best yields being obtained when running the reaction at 50 °C (59% and 55%, respectively; entries 3 and 4). Without trimethyl orthoformate, however, very little of **6** was obtained (entries 7−9).

Subsequently, we examined the effects of varying the amount of catalyst (Table 2). We found that no **6** was produced when the level of $CuCl_2$ was less than 0.25 equiv (entries 3 and 8). However, good yields were obtained when we included 1 equiv of $CuCl_2$ (entries 1 and 4). As for CuO, use of less than 0.5 equiv gave remarkably low yields (entries 2, 5, and 6), and varying the ratio of $CuCl_2$ to CuO led to the synthesis of other novel compounds (**9**, **10**, and **11**) along

(6) (a) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434−436. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231−237.

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(8) (a) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553−3560. (b) Mori, K.; Hashimoto, H.; Takenaka, Y.; Takigawa, T. *Synthesis* **1975**, 720−721.

**Table 1.** Products for the Acetal Exchange Reaction (1)

| entry | substrate (**5**) (mmol) | MeOH (mL) | $CH(OMe)_3$ (mL) | $CuCl_2$ (equiv) | CuO (equiv) | temp (°C) | time (h) | **6** (%) | **7** (%) | **8** (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2.21 | 20 | 10 | 2 | 4 | reflux | 24 | 27 | | 10 |
| 2 | 0.1 | 10 | 5 | 2 | 4 | reflux | 29 | 38 | | 34 |
| 3 | 0.123 | 2.4 | 1.2 | 2 | 4 | 50 | 23 | 59 | | |
| 4 | 0.159 | 3 | 1.5 | 2 | 4 | 50 | 23 | 55 | | |
| 5 | 0.1 | 0.5 | 2 | 2 | 4 | rt | 60 | 18 | | 13 |
| 6 | 0.112 | 3 | 1.5 | 2 | 4 | rt | 228 | 39 | | 30 |
| 7 | 0.164 | 5 | | 2 | 4 | reflux | 22 | | 14 | 40 |
| 8 | 0.1 | 5 | | 2 | 4 | 50 | 22 | 6 | | 57 |
| 9 | 0.1 | 2.5 | | 2 | 4 | rt | 216 | | | 23 |

**Table 2.** Products of Acetal Exchange Reaction (2)[a]

| entry | substrate (**5**) (mmol) | $CuCl_2$ (equiv) | CuO (equiv) | time (h) | **6** (%) | **7** (%) | **8** (%) | **9** (%) | **10** (%) | **11** (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.1 | 1 | 1 | 24 | 78 | | | 9 | | |
| 2 | 0.1 | 0.5 | 0.5 | 24 | 25 | | | | | 6 |
| 3 | 0.1 | 0.25 | 0.25 | 96 | | | | | | |
| 4 | 0.1 | 1 | 0.5 | 36 | 70 | | | 7 | 11 | |
| 5 | 0.1 | 1 | 0.25 | 24 | 22 | | *b* | *b* | 18 | |
| 6 | 0.1 | 1 | | 31 | 22 | | | | 7 | |
| 7 | 0.1 | 0.5 | 1 | 42 | *b* | | | | | *b* |
| 8 | 0.1 | 0.1 | 1 | 42 | | | | | | |
| 9 | 0.1 | 10 | | 7.5 | | *b* | *b* | | | |
| 10 | 0.1 | 10 | 20 | 6.5 | 19 | *b* | *b* | | | |
| 11 | 0.1 | 2 | 4 | 9 | 53 | *b* | *b* | | | |

[a] Reaction was performed with MeOH (1 mL) and $CH(OMe)_3$ (4 mL) at 50 °C. Precipitated metal copper was observed followed by progress of reaction. [b] Mixture (not isolated).

with **6** (entries 1−8). Combining a large amount of $CuCl_2$ (10 equiv) and a short reaction time (6−8 h) produced only little or no **6** but resulted instead in a mixture of the dimethyl acetal **7** and methyl ester **8** (entries 9 and 10). In contrast, good yields of **6** were obtained when $CuCl_2$ and CuO were included in equal amounts (either 2 or 4 equiv; see also Table 1), and this remained true even when the reaction time was reduced to only 9 h (53%, Table 2, entry 11). Under these conditions, the dimethyl acetal **7** and methyl ester **8** were produced also.

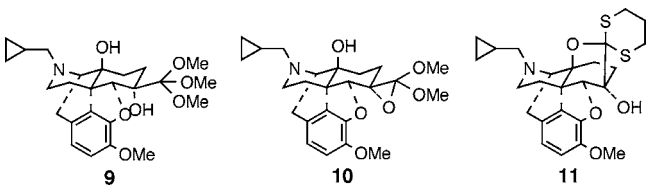



**Figure 4.**

We then examined the effects of substituting 20 equiv of $K_2CO_3$ or 5 equiv of 10-camphorsulfonic acid for CuO, keeping other conditions the same as in entries 9 and 10 in Table 2.

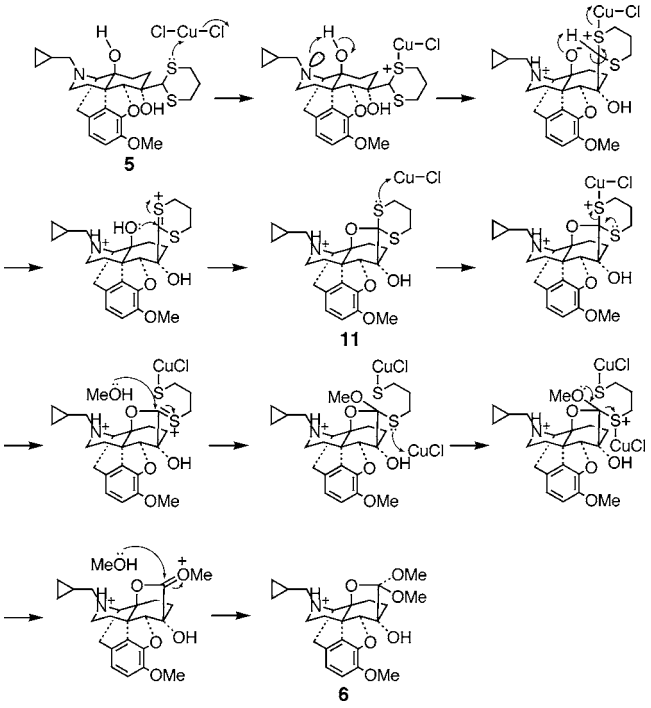
Substitution of $K_2CO_3$ for CuO resulted in the generation of **6** in high yield (80%) as the only product. In contrast, when 10-camphorsulfonic acid was used, the result was little or no **6** but a good yield of **7** (65%) along with a small amount of the cyclic acetal **13** (18%). In summary then, substitution of $K_2CO_3$ for CuO was useful in obtaining **6** without the related compounds **7**−**11** and **14**, and substitution of 10-camphorsulfonic acid for CuO was useful in obtaining the dimethyl acetal **7**.

We propose that this synthesis of **6** proceeds via the sequence of mechanisms depicted in Scheme 1. A key step in this sequence is abstraction of the proton in the 2′-position by the alcoxide ion derived from the 14-hydroxide of dithiane derivative **5**. Participation of this 14-hydroxyl group in the formation of naltrexone derivatives has been previously reported.[9] According to our scheme, the 14-hydroxyl group of naltrexone is activated intramolecularly by the lone pair electron on the 17-nitrogen that extracts the axial hydrogen from the 7-position of naltrexone, resulting in an easy enolization that gives enol acetate by $Ac_2O$/Py at room temperature (Scheme 2).

Consistent with this proposal, we found that the key intermediate **11** was isolated and easily hydrolyzed to **6** under

(9) Nagase, H.; Abe, A.; Portoghese, P. S. *J. Org. Chem.* **1989**, *54*, 4120−4125.

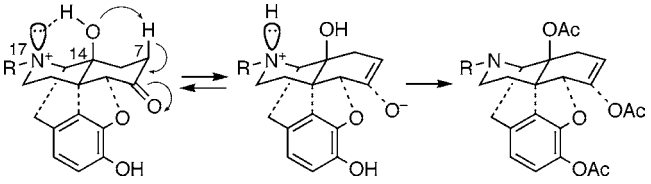
**Scheme 1.** Possible Mechanism for the Synthesis of **6**



the same conditions as those that enabled the acetal exchange reaction in **5**.

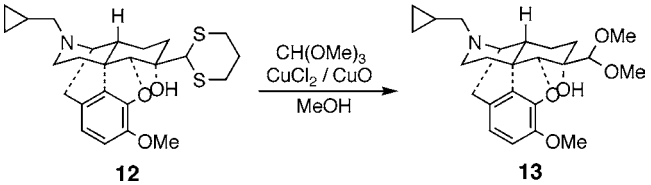
As a further test, we then tried to convert the 14-hydroxyl group to hydrogen in **5**, our goal being to confirm that

**Scheme 2.** Anchimeric Assistance in Enolization of Naltrexone Derivatives



hydroxyl group participates in abstraction of 2′-hydrogen of the 1,3-dithiane in **5**. Compound **12** was synthesized from

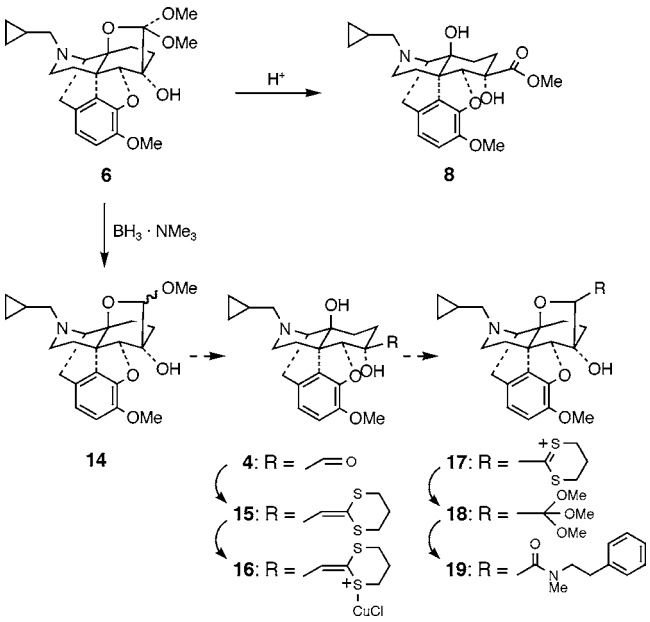
**Scheme 3.** Acetal Exchange Reaction of the 14-H Compound



naltrexone methyl ether and then subjected to the same acetal exchange reaction as above. Under these conditions, acetal **13** was obtained instead of the objective ortho ester, consistent with our hypothesis that the 14-hydroxyl group participates in the ortho ester formation (Scheme 3).

Subsequently, the obtained ortho ester **6** was easily hydrolyzed by acid to give an ester **8**. Reduction of **6** by borane-trimethylamine and aluminum chloride then gave an acetal **14** that will serve as a key intermediate in the synthesis of our final goal, 8-oxa-TAN-821 **19**, as shown in Scheme 4.

**Scheme 4.** Application of Ortho Ester



In conclusion, we have found a novel method for the synthesis of ortho ester **6** from the dithiane derivative **5**. This synthesis is based on use of the acetal exchange reaction**,** and we have determined optimum conditions for running this reaction. We have also proposed a mechanism for this reaction.

**Acknowledgment.** We acknowledge the Institute of Instrumental Analysis of Kitasato University, School of Pharmaceutical Sciences for its facilities. We also acknowledge the Shorai Foundation for Science and Technology for financial support.

**Supporting Information Available:** Experimental procedures, full characterization of compounds **5**−**11** and **14**, $^{1}$H NMR and $^{13}$C NMR spectra of compound **6**, and $^{1}$H NMR spectra of compounds **5**, **7**−**11**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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