Synthesis of 2'-Amino-17-cyclopropylmethyl-6,7-dehydro-3,14-dihydroxy-4,5α-epoxy-6,7:4',5'-thiazolomorphinan from Naltrexone [1]

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Fusion of an azole moiety at C-6 and C-7 of naltrexone (**1**) is illustrated by the synthesis of the title compound **8**. Bromination of 3-*O*-methylnaltrexone led to the 1,7α-dibromo derivative which reacted with thiourea to attach the 2-aminothiazole ring to C-6 and C-7 of naltrexone. After converting the amino and alcohol groups to trimethylsilyl derivatives, the aromatic bromo group was removed by halo-lithium interchange with butyllithium, followed by hydrolysis with water. In the final step of the synthesis, the methyl ether was cleaved by boron tribromide to generate **8**. An alternate synthesis of **8** commenced with 3-*O*-acetylnaltrexone (**9**). Bromination of **9** in acetic acid in the presence of hydrobromic acid produced a mixture of 3-*O*-acetyl-7α-bromonaltrexone (**10**) and 7α-bromonaltrexone (**11**), both, as hydrobromides. Reaction of this mixture with thiourea furnished **8** (62% from **1**). While ^{1}H and ^{13}C chemical shifts of all compounds are reported, those of **11** hydrobromide and **8** dihydrochloride were established unequivocally.

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Introduction.

Naltrexone (17-cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one, **1**), is a nonspecific antagonist of the opiate receptor system which consists of at least 3 types, μ, κ and δ [2]. A current challenge in the design of potential opiate receptor active compounds is to develop an antagonist specific for the δ-subtype of the receptor. Such a compound could be used as a probe to explore pharmacological roles of the receptor and its subtypes and could have potential therapeutic uses. Recent work by Portoghese, *et al.*, [3], Bertha, *et al.*, [4] and Nelson *et al.*, [5] has shown that receptor specificity is controlled, to some extent, by substitution at C-6 and/or C-7 of **1**. In a recent report from this laboratory [6] it was shown that rotationally flexible, aromatic and heteroaromatic groups placed at the 7-position of naltrexone produced potent, but not highly specific, antagonists of the δ-subtype of the receptor. Therefore, attention has been directed at exploring the effect on antagonist specificity of fusing heteroaromatic systems to the 6,7-positions of **1**. Previous work from the laboratory of Portoghese led to the synthesis of naltrindole, the most selective antagonist reported for the δ-receptor [7]. Naltrindole and derivatives represent modifications of C-6 and C-7 of **1** in being fused to the 2,3-positions of indole [7].

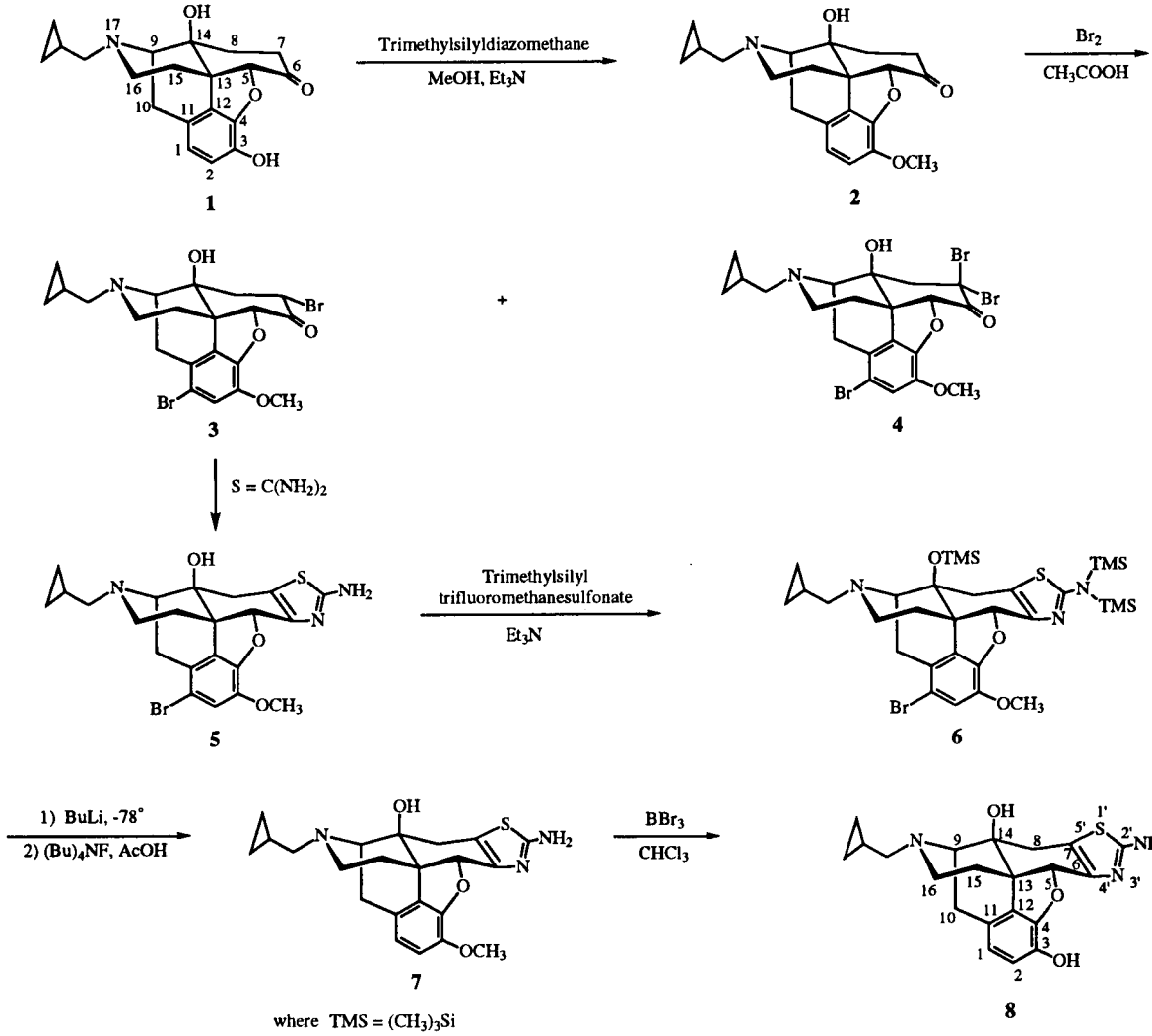
We explored the chemistry to fuse an azole at the 6,7-position of **1** by means of the well-established Hanztsch synthesis, which involves the reaction of α-halo ketones with amidines to form imidazoles and with thioamidic types of compounds to create thiazoles. Some recent examples have utilized acyclic [8] as well as cyclic [9] α-halo ketones, and also α-keto iodonium salts [10], to synthesize thiazoles. This paper describes first the preparation of the requisite 7-bromo 6-ketone derivative **3**, and second, the subsequent conversion to the condensed thiazole. While the thiazole synthesis was successful, reactions of the bromo ketone with amidines to make imidazoles yielded intractable mixtures.

The research plan is summarized in Scheme 1 and, up to a point, very much follows the one published recently by Görlitzer and Schumann in the oxycodone series [11], except that at the end we removed protective groups. The critical intermediate in this synthesis is an α-bromo ketone necessary for the azole preparation. The bromination of **1**, and derivatives thereof, is fraught with many problems. One of the major obstacles is that **1** (or derivatives) can undergo both active methylene group and aromatic electrophilic substitution. The nature of the brominated products depends on the functionality of the phenol. However, if the phenolic ring is brominated, then at the end of the reaction sequence, the aromatic bromine atom needs to be removed.

Bromination of Morphinan-6-ones and Derivatives.

The bromination of morphinan-6-ones and related structures was found to be extremely complex [11-16]. The active methylene site (C-7) as well as the phenolic ring stand to be brominated and relatively little regioselectivity has been reported. It is easy to spot the site at

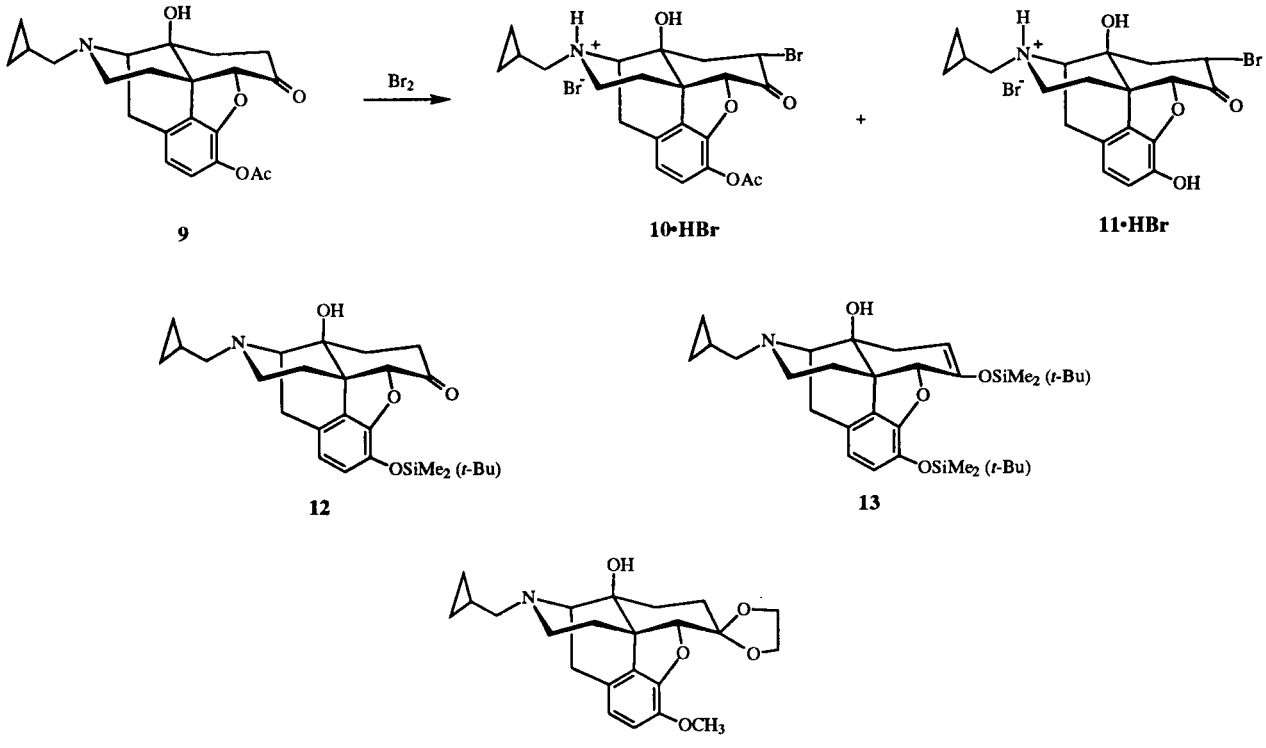
Scheme 1



which bromination takes place by examining ^1H and ^{13}C nuclear magnetic resonance (nmr) spectra of the products. If bromination takes place in the aromatic ring, the AB quartet for H-1 and H-2 (roughly between δ 6.4-6.8) changes to a singlet for the remaining aromatic proton (in our system, around δ 6.8-6.9). Carbon-13 chemical shifts reflect such changes also, with signals for C-1 in a typical morphinan around δ 118-119 (*e.g.*, for **2** in Table 1) moving to around δ 113 for 1-bromo derivatives, **3-5**. This is in keeping with the general observation that substitution of C-H by C-Br in benzene causes an upfield shift of the ^{13}C resonance of such a carbon by some 6 ppm and is attributed to the high electron density surrounding the bromo group [17]. The disappearance of signals associated with the active methylene group (C-7) would indicate successful bromination. The search for C-7 monobrominated products would be substantiated when a multiplet appears in the ^1H nmr spectrum around δ 5.0-5.5 (C*H*Br), corroborated by a ^{13}C signal around δ 50.

In various studies of the chlorination and bromination of the phenolic rings of morphinans, it was found that substitution took place *meta*, instead of the expected position *ortho* to the phenol, that is at C-1, rather that the expected site, C-2. Some theories were advanced to try and explain this apparent anomaly [14]. Although *meta* substitution took place at C-1, one cannot ignore that C-1 is *para* to the activating ether group of the dihydrofuran [14]. It is generally agreed that bromination of the phenolic methyl ethers are cleaner and we proceeded to start our synthesis from the methyl ether **2**.

Conventional room temperature methylation of **1** with methyl iodide and sodium hydride in *N,N*-dimethylformamide yielded a mixture of products (tlc, nmr) and only after chromatography was pure **2** isolated (50-75%). Using the recently introduced reagent, trimethylsilyldiazomethane [18], methylation of **1** provided a much cleaner product (**2**, 95%). In deuteriochloroform, the ^1H and ^{13}C nmr spectra of **1** and **2** were quite similar except



9 10•HBr 11•HBr

12 13

14

for the distinct singlet for the methyl ether in the ^1H nmr spectrum at δ 3.89 and the extra ^{13}C signal at δ 56.8.

It was expected that bromination of **2** would give rise to a number of bromo derivatives, monobromination at C-1 *or* C-7, dibromination at C-1 *and* C-7, *or* just at C-7, as well as tribromination at C-1 and C-7. Gates and Shepard [12] reported that the reaction of dihydrocodeinone hydrobromide with bromine in acetic acid furnished the 1,7-dibromo derivative (as the hydrobromide) in 92% yield. In a later paper, Bös *et al.*, [15] reported that the bromination of dihydrocodeinone with bromine in acetic acid yielded 1,7,7-tribromodihydrocodeinone (96%). In a more recent study, Görlitzer and Schumann [11] reacted 14-hydroxydihydrocodeinone (the *N*-methyl analog of **2**) with bromine under various conditions and isolated (from different reactions) the 1-bromo (50%), 7α-bromo (10%), 1,7α-dibromo (58%) and 1,7,7-tribromo (55%) derivatives.

Using the bromination method developed by Görlitzer and Schumann [11], the reaction of **2** with two equivalents of bromine in acetic acid afforded a mixture of the di- and tri-bromo derivatives, **3** and **4**, in the ratio 1.2:1. After neutralization, the two bromo derivatives were separated by column chromatography on silica gel. Characteristic chemical shift differences distinguished these bromo morphinans. The C-7 methylene carbon shift in **2** at δ 36.2 was replaced by one at δ 50.3 for the monobromo derivative **3** and at δ 58.9 for the dibromo compound **4**. Of course, C-8 experiences the electronic effects of one or two neighboring bromo groups at C-7 and the signal moves from δ 31.5 in **2** to δ 43.8 in **3** and to δ 51.9 in **4**. *Het*eronuclear Chemical Shift *Cor*relation (HETCOR) ^1H-^{13}C 2D nmr experiments on **3** linked the ^1H chemical shift of H-7 (15.31) with the ^{13}C chemical shift of C-7 (δ 50.3). The ^1H nmr signal of H-7 (of CHBr) in **3** at δ 5.3 consisted of a set of doublet of doublets, with coupling constants, $J_{7a,8e}$ = 5.0, $J_{7a,8a}$ = 13.5 Hz. These coupling constants are consistent with the ones reported for the *N*-methyl analog (δ 5.26), $J_{7a,8e}$ = 5.5, $J_{7a,8a}$ = 13.7 Hz [11]. From the Karplus relationship, these spin-spin coupling constants correlate with dihedral angles expected from an equatorial bromo group and axial proton at C-7. In subsequent experiments, it was found that in the hydrobromide of **11**, the ^{13}C chemical shift of C-7 (δ 51.2) correlated with the ^1H chemical shift of H-7 (δ 5.5, $J_{7a,8e}$ = 4.9, $J_{7a,8a}$ = 14.0 Hz) in deuteriodimethyl sulfoxide.

We report the successful brominations of the known 3-*O*-acetylnaltrexone (**9**) [19]. Apparently, the ester group deactivates the phenolic ring sufficiently that active methylene bromination predominates. After an acidic workup, the product consisted of a mixture of the hydrobromides of bromo acetate **10** admixed with bromo phenol **11** (presumably due to facile hydrolysis of the labile phenolic ester). Attempts to separate **10** and **11** as free bases on silica gel were quite unsuccessful, resulting in just minute recoveries of bromo ester **11**. From the crude salt mixture containing the hydrobromides of **10** and **11**, some 20% of pure **11** hydrobromide was isolated. From the practical point of view, it was possi-

Table 1

^{13}C Chemical Shifts of Selected Compounds [a,b]

Compound	2	9 [c]	12	13	14	3	4	10	11•HBr	5	7	8	8•2HCl [d]
Solvent	C	C	C	C	C	C	C	D	D	C	C	D	D
Position													
1	119.4	119.4	122.3	121.4	118.1	119.4	113.4	119.6	120.9	113.3	118.3	118.0	120.4
2	114.8	122.9	119.1	118.1	113.6	118.3	118.6	123.0	118.7	116.4	114.2	116.9	118.5
2'	-	-	-	-	-	-	-	-	-	167.2	166.1	165.7	168.9
3	142.9	132.5	138.0	138.4	142.2	144.2	144.0	131.8	140.5	144.2	141.6	139.5	140.9
4	145.0	147.7	146.8	147.0	146.2	144.4	144.4	146.9	143.5	144.4	144.8	143.0	142.7
5	90.4	90.6	89.9	89.0	93.9	90.7	87.4	90.5	89.4	87.2	86.7	85.8	81.3
6	208.6	207.8	208.2	146.8	109.0	198.7	192.0	198.8	199.5	140.9	143.2	141.1	130.8
7	36.2	36.1	36.2	105.7	31.3	50.3	58.9	50.9	51.2	120.9	121.4	118.9	118.1
8	31.5	31.2	31.3	31.4	29.2	43.8	51.9	43.2	46.3	30.7	29.7	30.5	30.9
9	62.1	61.8	62.1	61.6	62.4	61.4	61.6	60.4	60.8	61.5	61.8	61.1	60.3
10	22.6	22.9	22.7	23.1	22.6	24.0	23.6	22.3	23.1	24.6	24.0	22.4	23.6
11	124.9	130.1	125.3	126.0	125.0	124.4	124.1	129.3	121.0	125.1	125.5	123.8	121.7
12	129.5	130.3	129.5	131.8	131.0	130.0	129.6	131.0	127.4	132.2	130.9	130.6	128.3
13	50.9	50.7	50.7	46.9	48.1	51.7	51.5	51.8	49.7	47.3	47.1	46.5	52.2
14	70.2	70.0	70.2	70.6	69.8	71.0	69.8	71.8	71.1	71.9	72.3	71.9	71.8
15	30.7	30.7	30.9	29.7	28.9	30.5	30.0	29.6	27.3	31.3	30.8	30.9	27.9
16	43.6	43.4	43.6	43.4	43.9	43.2	43.2	42.9	42.7	43.3	43.6	43.1	45.9
N-CH_2	59.2	59.2	59.2	59.5	59.2	59.1	60.9	58.1	57.1	59.4	59.4	58.5	57.2
CH(cp)	-	9.4	9.5	9.5	9.5	9.3	9.3	8.9	6.0	9.4	9.3	9.0	6.0
CH_2(cp)	9.4	4.0	4.0	4.0	4.0	4.0	4.1	3.7	5.6	4.2	4.1	3.7	5.6
CH_2(cp)	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.5	3.0	3.8	3.7	3.4	2.9
OCH_3	56.8	-	-	-	56.5	57.1	57.1	57.1	-	56.5	56.6	-	-
$COCH_3$	-	168.5	-	-	-	-	-	168.2	-	-	-	-	-
$COCH_3$	-	20.8	-	-	-	-	-	20.3	-	-	-	-	-

[a] Downfield in ppm (δ) from internal tetramethylsilane; C, stands for deuteriochloroform; D for deuteriodimethyl sulfoxide. The spectrum of **6** was not recorded. [b] cp stands for cyclopropyl. [c] The following ^{13}C chemical shifts have been recorded for **9**: δ 119.4 (C-1), 122.9 (C-2), 132.5 (C-3), 147.7 (C-4), 70.0 (C-14), 20.8 ($COCH_3$), 168.5 ($COCH_3$), Ref 19. [d] Values determined by HMBC and HMQC.

ble to react the crude mixture of **10** and **11** hydrobromides directly with thiourea to obtain **8** (62% from **1**).

Attempts were made to react other functional derivatives of **1** with various other brominating reagents in order to obtain better yields of suitable 7-bromo 6-ketonic precursors. The reaction of **1** with *tert*-butyldimethylsilyl chloride produced both the mono silyl phenolic ether **12** and the enol silyl ether **13** [20]. Attempts to brominate position 7 of **12** with cupric bromide lead to a hopeless mixture, as did an attempted bromination with lithium di(trimethylsilyl)amide, followed by bromine at -78°. The reaction of **12** or **13** with either *N*-bromosuccinimide at 0° or with phenyltrimethylammonium tribromide [21] yielded none of the desired bromo derivatives. Nor would the disilyl enol ether **13** react with *N*-bromosuccinimide to provide any recognizable bromo derivative. In yet another futile approach, ketal **14** was made and characterized. Although **14** reacted very fast with bromine in benzene or phenyltrimethylammonium tribromide in tetrahydrofuran at room temperature, no recognizable product could be identified.

Thiazole Synthesis.

Two approaches for the synthesis of **8** are described. In following Görlitzer and Schumann's [11] procedure for their *N*-methyl series, **3** was reacted with thiourea in ethanol to provide **5**, which was characterized also as the dihydrochloride. However, to arrive at the target compound, the protective groups (namely, the bromo and the methyl ether groups) need to be removed. We chose to remove the aromatic halo group first. While numerous methods exist, many of the attractive published methods to reduce the bromo group in **5** failed. Catalytic reduction (hydrogen over a 10% palladium on charcoal) in acetic acid containing sodium acetate [22] led to quantitative recovery of **5**. Attempts to reduce **5** with cuprous hydride (0.5 equivalent) and sodium borohydride (10 equivalents) in methanol at 0° (2 hours), according to the method of Narisada *et al.* [23], gave back starting material (100%).

Removal of the aromatic bromo group of **5** by hydrolysis of the corresponding Grignard or organolithium reagent was investigated. Exposure of **5** to butyllithium at -78° for one minute, followed by hydrolysis led to countless products (tlc). A modification of this experiment proved successful. It appeared necessary to mask the 2'-amino and 14-hydroxyl groups of **5** as silyl derivatives. The silylation of **5** with trimethylsilyl trifluoromethanesulfonate formed **6**, whose structure was confirmed by its ^1H nmr spectrum. The amino proton resonance signals around δ 5.7 had disappeared and there were two new sin-

glets at δ 0.17 and 0.08 (in the ratio of 2:1 in deuteriochloroform), indicative of two *N*-trimethylsilyl and one *O*-trimethylsilyl groups of **6**. Addition of butyllithium at -78° for one minute, followed by aqueous acetic acid, removed the aromatic bromo group. Since the *O*-silyl protecting group was not completely removed, the reaction mixture was treated with aqueous acetic acid, or more efficiently with tetrabutylammonium fluoride, to provide **7** (0.5 hour). The ^{1}H nmr spectrum of **7** in deuteriochloroform clearly exhibited the AB pattern expected of H-1 and H-2, centered at δ 6.59 and 6.68 ppm, respectively (J = 6.0 Hz). Also, ^{13}C chemical shifts of C-1 and C-2 were at δ 118.3 and 114.2, closely resembling the corresponding ones of **2**, δ 119.4 and 114.8 (Table 1).

Deprotection of the methyl ether of **7** was accomplished with boron tribromide in ice-cold chloroform using the method of Rice [24]. The reaction of **7** with boron tribromide in ice-cold chloroform for 15 minutes yielded **8** in 81% yield. The ^{1}H and ^{13}C nmr spectra of **8** were almost identical to that of **7**, differing only for the *O*-methyl signals of **7**. The free base **8** was also characterized as the dihydrochloride. The simplest method to prepare **8** was already described above, when the mixture of the hydrobromides of **10** and **11** reacted directly with thiourea to provide **8**. The last route seems to be more attractive, overall.

NMR Analyses.

Considerable ^{1}H and ^{13}C nmr data for the morphinan system have been published [25-28]. Since some of the morphinans in the current study were handled as salts, with limited solubility in chloroform, nmr spectra had to be recorded frequently in deuteriodimethyl sulfoxide (Tables 1 and 2). There were relatively few, and then little, chemical shift differences between spectra in these two solvent systems. Spectra for the majority of these new compounds were determined in deuteriochloroform. Reported ^{13}C chemical shifts of naltrexone (**1**) in deuteriochloroform [25] differ from those in deuteriodimethyl sulfoxide by no more than 0.2 ppm. Also, in deuteriochloroform and deuteriodimethyl sulfoxide, ^{13}C chemical shift differences for **8** are less than 1 ppm for all carbons, except for C-7, whose chemical shifts differ by 2.5 ppm.

The ^{1}H and ^{13}C chemical shifts for **8** dihydrochloride and **11** hydrobromide were established unequivocally using a number of different nmr experiments. Chemical shifts listed for the other compounds were assigned by analogy, with the reservation that chemical shift differences up to 2 ppm in these carbon-13 spectra may be considered to be interchangeable. One ^{1}H signal in these morphinans was prone to shift more than all of the others. This is the singlet associated with H-5 in all of these compounds. With a ^{1}H chemical shift around δ 4.75 for H-5 in naltrexone and its phenolic derivatives, this proton became more deshielded when electronegative or electron-attracting substituents exerted an anisotropic effect as these were introduced at neighboring C-6 and/or C-7. The 7-bromo derivatives saw that signal move to about δ 5.0 and with the aromatic thiazole substituent, to about δ 5.5.

Most of the ^{13}C chemical shifts of the morphinan skeleton remained fairly constant. The introduction of bromo substituents and the thiazole ring at C-6 and C-7 causes changes in a few of the ^{13}C chemical shifts. For example, the ^{13}C chemical shifts of C-6 and C-7 in **3** moved from δ 192.0 and 58.9 to δ 140.9 and 120.9 in **5**, respectively. The additional ^{13}C signal in **5**, at δ 166.1 arose from C-2'. The ^{13}C chemical shifts of the three thiazole carbons, equivalent to C-2, C-4 and C-5 in thiazole (now C-2', C-6 and C-7, were generally around δ 165, 140 and 120, in our series of compounds. These shifts are in agreement with those reported for thiazole (deuteriochloroform), C-2, C-4 and C-5 at δ 153.6, 143.3 and 119.6, respectively [17]. Certainly, the downfield shift of C-2 in **5**, compared to C-5 in thiazole, can be attributed to the introduction of an 2'-amino group.

Table 2

^{1}H Chemical Shifts of Selected Compounds [a,b]

Compound Position	**11**•HBr	**8**•2HCl
1	6.65	6.69
2	6.71	6.78
5	5.25	5.48
7	5.48	–
8a	2.00	2.44
8b	2.64	2.88
9	4.03	4.15
10a	3.08	3.22
10b	3.38	3.43
15a	1.54	1.75
15b	2.54	2.55
16a	2.45	2.69
16b	2.62	3.14
N-CH_2a	2.92	2.98
N-CH_2b	3.40	3.34
CH (cp)	1.06	1.10
CH_2 (cp)	0.66	0.68
CH_2'(cp)	0.47	0.47

[a] Shifts are reported downfield from tetramethylsilane. [b] cp stands for cyclopropyl.

EXPERIMENTAL

Research chemicals and solvents were purchased from either Aldrich Chemical Co. or Fisher Scientific and were used without further purification. Naltrexone hydrochloride was obtained

through the kindness of Dr. P. Hillery, National Institute of Drug Abuse, NIH. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Thin layer chromatography (tlc) was performed on aluminum-backed silica gel plates (Aldrich 60 F254) and compounds were detected either by uv light (254 nm) and/or iodine vapor. Flash chromatography was carried out on silica gel (Merck Kieselgel 60, 230 mesh).

The ^1H and ^{13}C nmr spectra were recorded on either a Varian XL-300 or a Varian Unity 500 spectrometer. Chemical shifts are recorded in ppm (δ), downfield from internal tetramethylsilane. Attached proton tests were utilized when necessary. Reverse detected heteronuclear shift correlation (HMQC) and reverse detected long range heteronuclear chemical shift correlation (HMBC) spectra were recorded on a GE-Omega 500 MHz nmr spectrometer operating at 500.11 Hz for ^1H and at 125.75 MHz for ^{13}C resonances. We thank the Research Resources Center (University of Illinois at Chicago) for the use of their facilities. Regular or high resolution (hr) electron impact (ei) or chemical ionization (ci, methane) mass spectra were obtained at 70 eV on a Finnigan Mat 90 mass spectrometer. Ions with relative intensities less than 10% of the base peak are usually not reported.

All reactions were followed either by tlc, or if tlc was not conclusive, by ^1H nmr spectra. If an extraction was necessary during the general workup, the solvent was dichloromethane, unless stated otherwise. The organic extracts were washed with brine, dried (sodium sulfate) and evaporated, *in vacuo*, using a flash evaporator (20-40 Torr). Petroleum ether refers to that fraction bp 30-60°.

17-Cyclopropylmethyl-4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-one (**2**).

Method A.

This methylation is adapted from the procedure published by Toyohiko *et al.* [18]. Naltrexone (**1**, 400 mg, 1.16 mmoles) was dissolved in methanol-acetonitrile (1:9, 8 ml) in a round bottom flask equipped with a rubber septum with a needle outlet. To this stirred mixture was added, at room temperature, triethylamine (0.24 ml, 1.7 mmoles) and then (trimethylsilyl)diazomethane (0.58 ml, 2.0 *M*, 1.16 mmoles). Evolution of a gas was observed after 1 minute. The resulting solution was stirred at room temperature for 12 hours. Solvents were removed, *in vacuo*. The residue was dissolved in dichloromethane (2 ml) and the solution was applied at the top of a silica gel column (silica gel 10 g, 1.9 x 45 cm column). Elution with dichloromethane (10 ml), followed by dichloromethane-ether (6:1, 70 ml) produced **2** (377 mg, 95%) as a gum, which seemed pure from its ^1H nmr spectrum. After 2 days, some crystals were formed, embedded in the gum. The crystals were isolated by washing quickly with benzene (1 ml), followed by petroleum ether (1 ml), mp 85-86°; R_f = 0.27 (dichloromethane-methanol, 25:1); ms: (ci) m/z 356 (M+1).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.63; H, 7.15; N, 4.07.

Method B.

To 60% sodium hydride in mineral oil (35 mg, 0.67 mmole, 1.1 equivalents) was added anhydrous hexane (1 ml), under nitrogen. The mixture was stirred vigorously for 1 minute. The supernatant liquid was removed by syringe and residual sodium hydride was covered with DMF (1 ml). Naltrexone (**1**, 200 mg, 0.58 mmole) in DMF (3 ml) was now added (25°). After stirring for 15 minutes gas evolution ceased. The solution was cooled to 4° in an ice bath and methyl iodide (0.04 ml, 0.65 mmole, 1.1 equivalents) was added. After stirring the mixture for another 15 minutes, solvents were removed (<1 torr). The residue was dissolved in a solution of hexane-ethyl acetate (6:1, 2 ml) and chromatographed on silica gel (5 g, 70-230 mesh, 1.2 x 20 cm column). Elution with hexane-ethyl acetate (6:1, 70 ml; 3:1, 100 ml) afforded **2** (163 mg, 78%), identical to the sample prepared by Method A.

17-Cyclopropylmethyl-1,7α-dibromo-4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-one (**3**) and 17-Cyclopropylmethyl-1,7,7-tribromo-4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-one (**4**).

The procedure is a modification of the one published by Görlitzer and Schumann [11]. To a stirred solution of **2** (397 mg, 1.12 mmoles) in acetic acid (40 ml) was added, dropwise, bromine (0.11 ml, 2.1 mmoles) in acetic acid (5 ml). After 1 hour at room temperature, solvents were removed, *in vacuo*. The residue was diluted with ether (10 ml) and the resultant precipitate was filtered. Due to the inherent instability of the bromo derivatives, this impure solid is usually used without further purification in the next step.

Separation and characterization of the two major components were achieved as follows. The impure solid was suspended in water (10 ml) and cooled to 4° (ice bath). The *p*H of the mixture was adjusted to 8 by the dropwise addition of concentrated aqueous ammonia (30%). Organic material was extracted into dichloromethane (3 x 10 ml). The extract was washed with brine (3 x 10 ml), dried (sodium sulfate) and the solvent removed, *in vacuo*. The residue was purified by flash column chromatography on silica gel (10 g, 1.9 x 45 cm column). Elution with dichloromethane (80 ml) provided **4** (177 mg, 27%), mp 75°; tlc, R_f = 0.78 (dichloromethane-methanol, 25:1); ms: (ci) m/z 592 (M+1, ^{79}Br, 100%).

Anal. Calcd. for $C_{21}H_{22}Br_3NO_4$: C, 42.60; H, 3.74; N, 2.37. Found: C, 42.59; H, 3.78; N, 2.29.

Continued elution with dichloromethane-ether (10:1, 30 ml) furnished **3** (188 mg, 33%) initially as a gum. After 2 days, crystalline **3** formed, which was washed with a small amount of benzene (*ca.* 1 ml), mp 147-149°; tlc, R_f = 0.74 (dichloromethane-methanol, 25:1); ms: (ci) m/z 514 [^{81}Br, (M+1), 100%].

Anal. Calcd. for $C_{21}H_{23}Br_2NO_4$: C, 49.15; H, 4.52; N, 2.73. Found: C, 49.37; H, 4.64; N, 2.84.

2'-Amino-1-bromo-17-cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-14-hydroxy-3-methoxy-6,7:4',5'-thiazolomorphinan (**5**).

The crude mixture of **3** and **4**, (from the previous reaction, generated from 900 mg of **2**, 2.53 mmoles) and thiourea (240 mg, 3.16 mmoles) was suspended, and then refluxed in 95% ethanol (80 ml) for 12 hours. Solvents were removed, *in vacuo*, and the residue was diluted with water (20 ml). The mixture was cooled (4°) and the *p*H of the mixture was adjusted to 8 by the dropwise addition of concentrated aqueous ammonium hydroxide. The mixture was extracted with dichloromethane (3 x 15 ml) and the crude product was purified by flash column chromatography (silica gel, 10 g, 1.9 x 45 cm column). Using dichloromethane-ether (3:1, 40 ml), two unidentified byproducts (total 506 mg, R_f = 0.78, 0.41 respectively, dichloromethane-methanol, 25:1) were eluted. Continuous elution with dichloromethane-ether (1:1, 70 ml), dichloromethane-methanol (25:1, 150 ml) provided **5** (457 mg, 37%), mp 135-140°; tlc, R_f = 0.23 (dichloromethane-methanol, 25:1); ms: (ci) m/z 490 [^{79}Br, (M+1), 100%].

The *dihydrochloride* was prepared by treating a solution of **5** (100 mg, 0.20 mmole) in dichloromethane (5 ml) with dry hydrogen chloride. The colorless precipitate was filtered and dried, *in vacuo*, to provide the *salt* (19 mg, 81%), mp 228° dec, which was recrystallized from concentrated hydrochloric acid, mp >250° dec.

Anal. Calcd. for $C_{22}H_{24}BrN_3O_3S \cdot 2HCl \cdot 1.5H_2O$: C, 44.76; H, 4.95; N, 7.12; S, 5.43. Found: C, 44.68; H, 4.98; N, 6.99; S, 5.67.

The free base was protected as its silyl derivative. A solution of **5** (100 mg, 0.20 mmole) was dried by azeotropic distillation with benzene (10 ml). After evaporation of benzene, **5** was dissolved in dichloromethane (3 ml) and dry triethylamine (0.09 ml, 0.68 mmole). To this solution was added, dropwise, trimethylsilyl trifluoromethanesulfonate (0.13 ml, 0.67 mmole) at 0-4° under nitrogen. The solution was stirred at room temperature for 0.5 hour and poured into a mixture of dichloromethane (10 ml), water (2 ml) and ice (2 g). The aqueous layer was separated and extracted with dichloromethane (2 x 10 ml). The combined dichloromethane extracts were washed rapidly with ice cold water (3 x 10 ml), brine (10 ml), and dried (sodium sulfate) for one hour. Solvents were removed, *in vacuo*. 1-Bromo-17-cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-3-methoxy-2'-[*N*,*N*-di(trimethylsilyl)amino]-14-(trimethylsilyl)oxy-6,7:4',5'-thiazolomorphinan (**6**) was obtained after column chromatography (silica gel 5 g, 1.2 x 30 column), being eluted as an oil (116 mg, 80%) by petroleum ether-ethyl acetate (3:1, 40 ml); tlc, R_f = 0.48 (dichloromethane-methanol, 25:1); ms: (ci) m/z 708 [^{81}Br, (M+1), 100%].

2'-Amino-17-cyclopropylmethyl-6,7-dehydro-14-hydroxy-4,5α-epoxy-3-methoxy-6,7:4',5'-thiazolomorphinan (**7**).

After drying **6** (273 mg, 0.39 mmole) at ~ 1 torr, it was dissolved in dry tetrahydrofuran (10 ml). To the solution was added, under nitrogen, butyllithium (0.31 ml, 2.5 *M*, 0.78 mmole) at -78° and the resulting solution was stirred for 1 minute. The reaction mixture was decomposed with water (2 ml), acetic acid (10 ml) and tetrabutylammonium fluoride (0.84 ml, 1.0 *M*). The mixture was stirred at 50° for 30 minutes. Solvents were removed, *in vacuo*. The residue was then suspended in water (20 ml) and cooled to 4° in an ice bath. The *p*H of the suspension was adjusted to 8 by adding dropwise concentrated aqueous ammonia (30%) at 4° with stirring. The mixture was extracted with dichloromethane-isopropyl alcohol (3:1, 3 x 13 ml). The combined extracts were washed with water (10 ml), brine (10 ml) and dried (sodium sulfate). Solvents were removed, *in vacuo*, and the residue was purified on silica gel by flash column chromatography (silica gel 10 g, 1.9 x 45 cm column). Elution with dichloromethane-ether (1:1, 40 ml), then dichloromethane-methanol (25:1, 150 ml) yielded **7** (134 mg, 85%), as a gum; tlc, R_f = 0.18 (dichloromethane-methanol, 25:1); ms: (ci) m/z 412 (M+1).

2'-Amino-17-cyclopropylmethyl-6,7-dehydro-3,14-dihydroxy-4,5α-epoxy-6,7:4',5'-thiazolomorphinan (**8**) Dihydrochloride.

The procedure followed was that of Rice [20]. To a stirred ice cold solution of boron tribromide (0.07 ml, 1.16 mmoles) in chloroform (3 ml) was added, dropwise at 0-4°, a solution of **7** (60 mg, 0.15 mmole) in chloroform (3 ml). The mixture was stirred at room temperature for 15 minutes and re-cooled to 0-4° in an ice bath and diluted by a 30% ammonium hydroxide (2.4 ml) and ice (2 g). After 10 minutes, the organic layer was separated and the aqueous layer was extracted with chloroform and isopropyl alcohol (3:1, 2 x 4 ml). The combined organic extract was washed with water (10 ml), brine (10 ml) and dried (sodium sulfate). After evaporation of solvents, *in vacuo*, the residue was purified on silica gel by flash column chromatography (silica gel 8 g, 1.9 x 45 cm column). Using dichloromethane-methanol (25:1, 300 ml; 25:2, 50 ml), **8** (47 mg, 81%) was eluted as a solid, mp 175-185° dec; tlc, R_f = 0.06 (dichloromethane-methanol, 25:1); hrms: (ei) Calcd. for $C_{21}H_{23}N_3O_3S$: 397.1460. Found: 397.1452.

To a solution of **8** (15 mg) in dichloromethane (1 ml) was added 1 drop of methanol. To this was introduced dry hydrogen chloride to furnish the *salt* (12 mg, 63%) as a colorless solid, mp 240° dec.

Anal. Calcd. for $C_{21}H_{23}N_3O_3S \cdot HCl \cdot 2H_2O$: C, 49.80; H, 5.77; N, 8.30. Found: C, 49.48; H, 5.32; N, 8.04.

17-Cyclopropylmethyl-4,5α-epoxy-14-hydroxy-3-acetoxymorphinan-6-one (**9**).

This experiment represents a modification of the literature method [19]. Acetic anhydride (94 µl, 1.05 mmoles) was added dropwise to an ice-cold stirred solution of naltrexone (**1**, 300 mg, 0.88 mmole) in dichloromethane (10 ml) containing triethylamine (184 µl, 1.32 mmoles). After the addition, the mixture was allowed to warm to room temperature and stirred for 4 hours (until **1** disappeared (tlc, R_f = 0.34, chloroform-methanol, 47:3). After addition of water (10 ml), the mixture was extracted by chloroform (3 x 20 ml) and the usual mode of isolation provided **9** (325 mg, 96%) as a colorless gum, which was pure (^{1}H nmr and tlc) and was used as such in the next step. After some 16 hours, the gum crystallized and the solid was recrystallized from ethyl acetate-petroleum ether (3:1). The product was filtered, washed with ethyl acetate-petroleum ether (1:5); mp 114-115°, lit [19] mp 103-104°; tlc, R_f = 0.65 (chloroform-methanol, 47:3).

Anal. Calcd. for $C_{22}H_{25}NO_5 \cdot 0.3H_2O$: C, 67.96; H, 6.64; N, 3.60. Found: C, 67.95; H, 6.75; N, 3.63.

Bromination of **9**, and Subsequent Conversion to **8**.

Bromine (81 µl, 1.56 mmoles) in acetic acid (10 ml) was added to a stirred solution of **9** (400 mg, 1.04 mmoles) in acetic acid (30 ml) at 25° and the mixture heated under reflux (1 hour). The mixture was cooled and solvents were evaporated, *in vacuo*. The residue contained **10•HBr** and **11•HBr**. When a small amount of methanol-ethyl acetate (1:1) were added to this residue, **11•HBr** (103 mg) crystallized out. This *salt* was recrystallized from methanol-ethyl acetate (1:1), mp 232° dec; R_f = 0.40 [chloroform-methanol-ammonium hydroxide, 47:3:1 drop (per 50 ml)].

Anal. Calcd. for $C_{20}H_{22}BrNO_4 \cdot HBr \cdot H_2O$: C, 46.26; H, 4.85; N, 2.70. Found: C, 46.03; H, 4.52; N, 2.62.

The original reaction mixture proved to contain both 7α-bromonaltrexone (**11**) and its 3-*O*-acetyl derivative **10**, both as hydrobromides, in the ratio of 3:2, based on H-5, δ 5.37, 5.22 ppm, respectively; in deuteriodimethyl sulfoxide. Careful neutralization of the crude mixture of hydrobromides with saturated cold aqueous sodium bicarbonate solution, extraction into dichloromethane provided an unstable mixture of compounds. Attempts to purify this mixture by chromatography (silica gel, 230-400) and elution with petroleum ether-ethyl acetate (1:2) generated a very small amount of pure **10** (R_f = 0.72, ethyl acetate, which proved to be unstable as a free base.

A stirred mixture of crude **10•HBr** and **11•HBr** (from above) was reacted with thiourea (160 mg, 2.08 mmoles) in boiling ethanol (30 ml) for 26 hours. Solvent was removed *in vacuo*, and the brown residue was suspended in water (20 ml) and made basic (*p*H 10) with saturated potassium bicarbonate solution. The product was extracted with chloroform-2-propanol (3:1, 3 x 40 ml). After drying and removal of the solvents, *in vacuo*, the residue was flash chromatographed on silica gel (50 g). Elution with a gradient solvent system, chloroform-methanol (3:1 to 2:1), provided **8** as a colorless solid (278 mg, 62% from **1**), identical to the sample prepared above.

3-[(*tert*-Butyldimethylsilyl)oxy]-17-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxymorphinan-6-one (**12**).

To a stirred solution of naltrexone hydrochloride (**1•HCl**) (0.2 g, 0.53 mmole) and imidazole (0.2 g, 2.94 mmoles) in DMF (1 ml) was added *tert*-butyldimethylsilyl chloride (0.2 g, 1.32 mmoles). The solution was stirred at room temperature for 40 minutes and quenched with water. The resulting mixture was extracted with ethyl acetate (3 x 20 ml), and the combined organic phases were washed with brine (2 x 10 ml), dried over sodium sulfate, and concentrated to give the crude product. Recrystallization from ethanol afforded pure **12** (200 mg, 83%); R_f = 0.58 (chloroform/methanol, 94:6); mp 92-93°, lit [20] mp 94-95°.

17-(Cyclopropylmethyl)-3,6-bis[(*tert*-butyldimethylsilyl)oxy]-6,7-didehydro-4,5α-epoxy-14-hydroxymorphinan (**13**).

To a stirred solution of naltrexone hydrochloride (**1•HCl**, 0.40 g, 1.06 mmoles) and imidazole (0.40 g, 5.88 mmoles) in DMF (1.5 ml) was added *tert*-butyldimethylsilyl chloride (0.40 g, 2.64 mmoles). The solution was stirred at room temperature for 2 days, and then water was added. The resulting mixture was extracted with ethyl acetate (3 x 20 ml), the combined organic phases were washed with brine and dried (sodium sulfate). Solvents were removed, *in vacuo*, and the gummy residue was purified by flash column chromatography on silica gel (45 g). Elution with ethyl acetate-petroleum ether (1:2, 210 ml), produced **13** (370 mg, 61%, R_f = 0.70, chloroform-methanol, 47:3). Further elution with ethyl acetate-petroleum ether (3:2, 300 ml) gave **12** (170 mg, 28%, R_f = 0.58). Recrystallization of **13** from ethanol afforded the silyl enol ether, mp 86-87°, lit [20] mp 93-94°.

17-Cyclopropylmethyl-4,5α-epoxy-14-hydroxy-6,6-(1,2-ethylenedioxy)-3-methoxymorphinan-6-one (**14**).

A solution of **2** (312 mg, 0.88 mmole), ethylene glycol (0.25 ml, 4.39 mmoles) and 4-toluenesulfonic acid (253 mg, 1.32 mmoles) was refluxed in benzene (30 ml) with the azeotropic removal of water (26 hours). The resulting mixture was cooled to room temperature and poured slowly into an ice-cold saturated aqueous sodium bicarbonate solution. After extraction with ethyl acetate (3 x 20 ml) and the usual workup, the product was chromatographed (silica gel, 15 g). Elution with ethyl acetate-petroleum ether (1:2 to 1:1) provided colorless **14** (232 mg, 66%), mp 202-203° (recrystallized from ethyl acetate-petroleum ether, 1:2); tlc, R_f = 0.63 (chloroform-methanol, 47:3).

Anal. Calcd. for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.32; H, 7.45; N, 3.55.

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