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Heteroatom Analogues of Hydrocodone: Synthesis and Biological Activity

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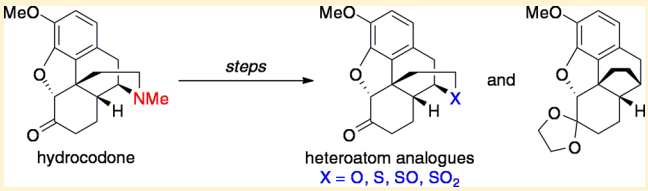
Supporting Information

ABSTRACT: Heteroatom analogues of hydrocodone, in which the *N*-methyl functionality was replaced with oxygen, sulfur, sulfoxide, and sulfone, were prepared by a short sequence from the ethylene glycol ketal of hydrocodone; a carbocyclic analogue of bisnorhydrocodone was also prepared. The compounds were tested for receptor binding and revealed moderate levels of activity for the sulfone analogue of hydrocodone.



INTRODUCTION

Morphine (**1**), codeine (**2**), thebaine (**3**), oripavine (**4**), and other opiate alkaloids (Figure 1) have been the subject of numerous structural and functional modifications in search for increased agonist activity, antagonist properties, and to develop suitable models for receptor binding.[1] The outcomes of these studies led to the development of various medicinally useful derivatives, such as oxycodone (**5**), hydrocodone (**6**), buprenorphine (**7**), and the antagonist group represented by naloxone (**8**), naltrexone (**9**), and their *N*-methylcyclobutyl analogue nalbuphine. Recently, renewed optimism for designing potent analgesics that lack the traditional side effects associated with classical opioids, including respiratory depression, reinforcing behavior, and physical dependence, was supported by the disclosure of IBNtxA (**10**).[2]

The first attempt to describe the activity of morphine alkaloids using a receptor model was put forth by Beckett and Casy in 1954,[3] but it was later rejected in favor of a multiple receptor theory proposed by Martin and Portoghese that addressed biological activity as well as the agonist and antagonist properties of derivatives.[4] The greatly diminished activities observed for epimers of morphine, as well as for its enantiomer, provided evidence in support of the latter theory.[5] Recent work has expanded on the multiple receptor theory, with three main types of opioid receptors classified to date on the basis of their radioligand binding properties: μ (MOR), δ (DOR), and κ (KOR).[6] Additional subdivisions have also been established for each receptor, following observations of pharmacologically different properties within the same subtypes, which has made it difficult, in practice, to develop opioids that elicit only the desired physiological effects.[7]

In an initial effort to address the ability of opioids to act as agonists and antagonists, Snyder proposed that these properties might depend on the orientation of the nitrogen substituent—axial versus equatorial.[8] Considerations of the orientation of nitrogen substituents in truncated versions of morphinans, such as the mixed agonist–antagonists levorphanol (**11**) and levallorphan (**12**), Figure 2, led Lemaire to synthesize and evaluate sulfur analogues of these compounds in which the orientation of the methyl or allyl group was fixed.

They prepared and tested both axial and equatorial derivatives of sulforphanol (**13**) and sulfallorphan (**14**), finding that the sulfonium analogues retained potency. Furthermore, the agonist versus antagonist activity associated with these compounds was found to depend on the conformation of the *S*-substituent in agreement with Snyder's proposal (equatorial allyl group confers antagonist activity, axial methyl confers agonist activity).[9]

To the best of our knowledge the derivatives prepared by Lemaire constitute the only examples in which the nitrogen atom present in the morphinan scaffold was replaced with another atom. In search of a more complete understanding of these systems, we chose to synthesize several heteroatom analogues of hydrocodone, which have the complete hydrocodone skeleton, whose analgesic activity is well established and understood. In this paper we report the synthesis of several oxygen, sulfur, and phosphorus analogues of hydrocodone (**15** and **16**, Figure 2), and provide direct comparisons of their potency.

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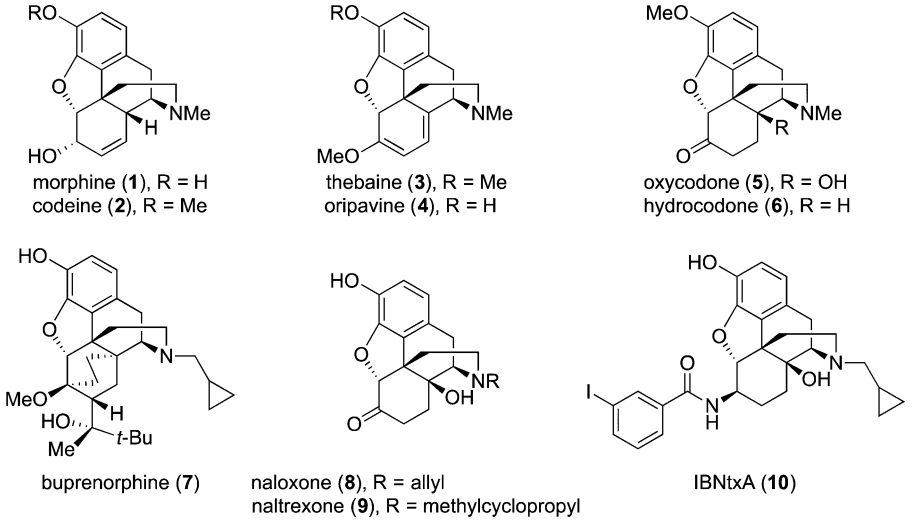

Figure 1. Morphine alkaloids and medicinally useful semisynthetic derivatives.

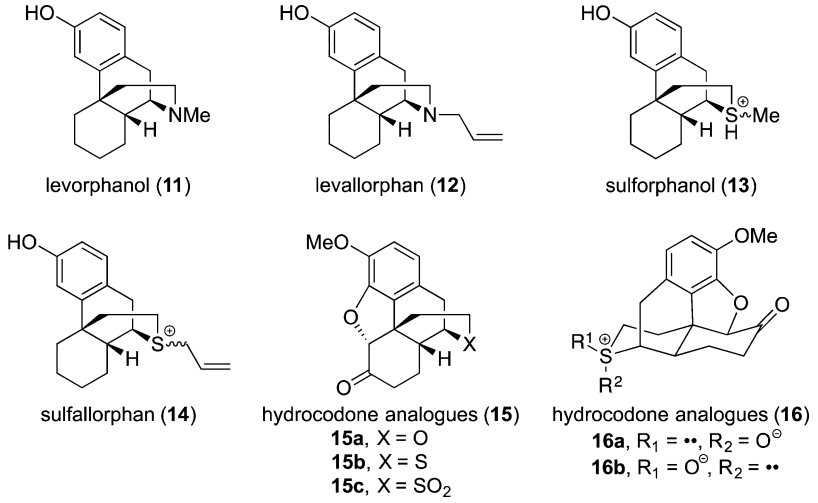

Figure 2. Morphinans, their sulfur analogues, and proposed analogues of hydrocodone.

RESULTS AND DISCUSSION

The synthesis of compounds of type **15** and **16** was envisaged to originate from a common intermediate made available by methods employed in the well-known degradation studies that led to the final structure elucidation of morphine after nearly 120 years of effort.[10] Of particular interest was the application of Hofmann's elimination procedure to codeine by von Gerichten[11] and Knorr,[12] with subsequent refinements by Hesse[13] in the 1880s. We envisioned transforming hydrocodone to a key aldehyde intermediate (**21** or **26**) by Hofmann elimination, with a subsequent Polonovksi reaction[14] of the *N*-oxide derived from the resulting *N*,*N*-dimethyl amine **19**, or its protected form **24**, Scheme 1. The Potier modification[15] of the Polonovski reaction employs trifluoroacetic anhydride and allows for the formation of the more stable iminium species, thereby controlling the regiochemistry of the incipient aldehyde. Given its potential versatility to access all of the heteroatom analogues shown in Figure 2, aldehyde **21** was targeted as the key intermediate. Selective reduction of this aldehyde would provide alcohol **22**, which could be elaborated to oxygen, sulfur, and related derivatives of hydrocodone.

The synthesis of the key aldehyde intermediate **21** is outlined in Scheme 1. Hydrocodone was converted to methiodide **18**, which afforded amine **19** following Hofmann elimination. Oxidation of this amine to the corresponding *N*-oxide **20** and subsequent exposure to trifluoroacetic acid anhydride furnished keto-aldehyde **21**. Unfortunately, reduction of aldehyde **21** to the desired alcohol **22** proved to be nonselective, affording mixtures of diols, diastereomeric at C-6. Consequently, we decided to protect the C-6 carbonyl with ethylene glycol and repeated the protocol with ketal **17**. In this way, alcohol **27** was prepared in 49% overall yield from hydrocodone on 9 g scale with a single purification by chromatography during the last step.

The oxygen analogue of hydrocodone was prepared according to the route depicted in Scheme 2. Intramolecular oxymercuration of alcohol **27** and subsequent reduction led to ether **28**, whose hydrolysis furnished the desired oxygen analogue of hydrocodone **15a**. The synthesis of sulfur analogue **15b** was accomplished by sulfonylation of alcohol **27** and successive displacement of the tosylate with potassium thioacetate to deliver **30**, as shown in Scheme 3.

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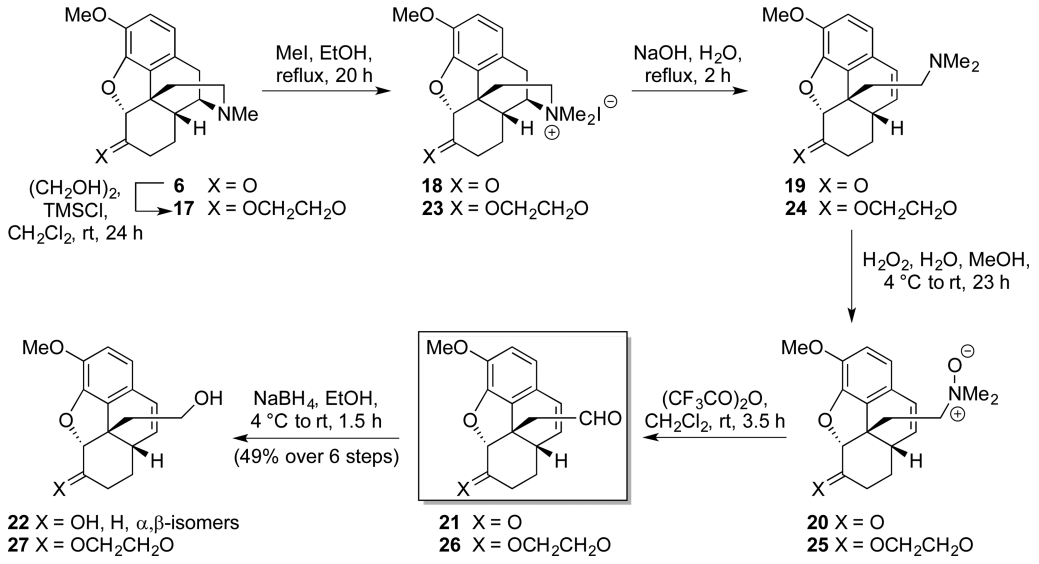
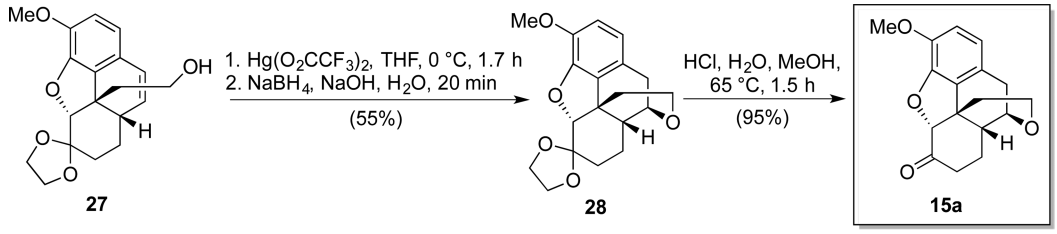
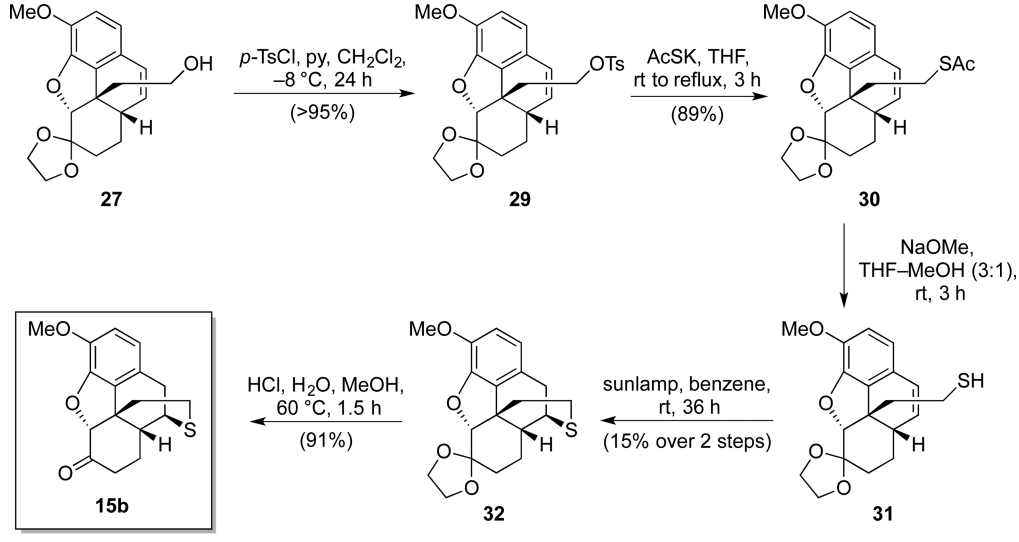
Scheme 1



Scheme 2



Scheme 3



Free thiol **31** was prepared from thioacetate **30** by treatment with freshly prepared sodium methoxide in tetrahydrofuran–methanol (3:1). The resulting thiol was dissolved in benzene and cyclized to thioether **32** by irradiation under a sunlamp, Scheme 3. Subsequent hydrolysis of the ketal delivered the sulfur analogue of hydrocodone **15b**.

Treatment of the sulfur analogue **15b** with one equivalent of sodium periodate at room temperature provided a 5:1 mixture of diastereomeric sulfoxides **16a** and **16b**, Scheme 4. Alternatively, heating sulfur analogue **15b** at 50 °C in the presence of excess periodate furnished the corresponding sulfone **15c**.

Finally, an attempt was made to prepare phosphonate analogue **37**, as shown in Scheme 5. The key intermediate, *H*-phosphinate **36**, Scheme 5, was prepared from phosphinate **34**, which was itself generated by displacing the triflyl moiety in **33** with the lithium salt of ethyl (1,1-diethoxyethyl)-phosphinate.[16] This coupling (**27** → **33** → **34**) proved to be

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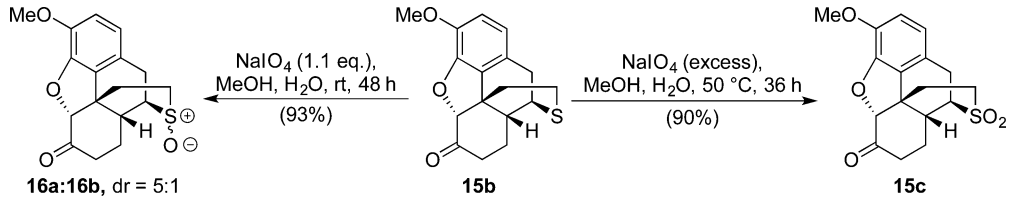
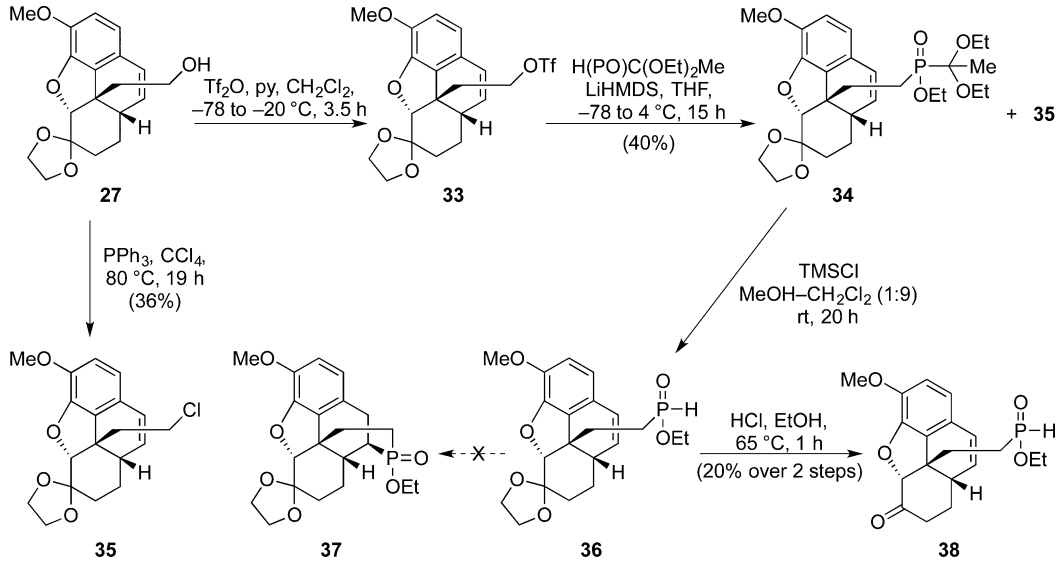
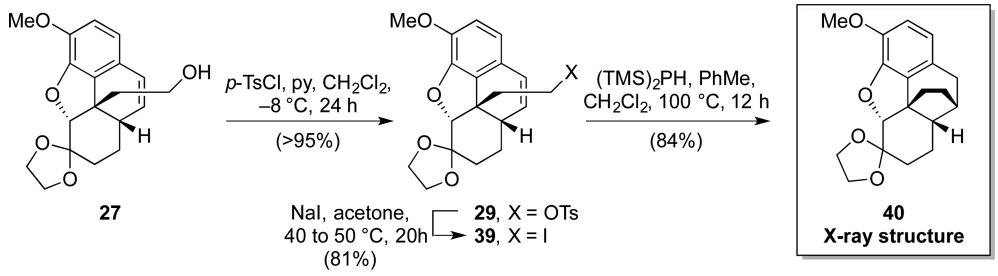
Scheme 4



Scheme 5



Scheme 6



very challenging; the best yields obtained were around 40% on a 150 mg scale, and the product was obtained as a 1:1 mixture of two diastereomers. On a 600 mg scale the yield of **34** dropped to 24% and chloride **35** (1%) was isolated as the side-product.

The structure of **35** was unambiguously confirmed by transforming alcohol **27** to chloride **35** by the Appel reaction. The chloride atom may have originated from a side reaction between dichloromethane (solvent used for the preparation of the triflate) and lithium ethyl (1,1-diethoxyethyl)phosphinate.

Notably, it was necessary to use triflate **33** as a solution, given that all attempts to isolate it led to uncharacterized decomposition products, as inferred from a color change of the crude triflate from colorless to dark blue and the corresponding TLC analysis. Given the low yield of chloride **35**, other solvents were not tested to prepare the desired triflate. Deprotection of the 1,1-diethoxyethyl group in **34** with TMSCl gave *H*-phosphinate **36**, which was used directly in the next step without further purification. Attempts to cyclize **36** to **37** under radical or basic conditions were not successful. We tested photochemically initiated cyclizations[17] and reactions initiated by $(t\text{-BuO})_2$,[18] air,[19] *t*-butyl peroxypivalate, AIBN, *n*-BuLi/HMDS, and *t*-BuOK/mercury trifluoroacetate. Following our unfruitful effort to uncover efficient cyclization conditions we decided to deprotect ketal **36** with HCl in ethanol and obtained *H*-phosphinate **38** as a 1:1 mixture of diastereomers in 20% yield over two steps from **34**. This open-chain analogue **38** was also evaluated for biological activity.

In one of our earlier approaches to form a carbon–phosphorus bond at C-9 we treated tosylate **29** under Finkelstein conditions and exposed the resulting iodide **39** to bis(trimethylsilyl)phosphine (BTSP), as shown in Scheme 6.[20] To our surprise, we isolated a carbocyclic product **40** in 84% yield, which likely formed through a radical pathway. A related reduction of iodomethyl nucleosides to methyl nucleosides by BTSP was reported by An and co-workers.[21] The structure of **40** was unambiguously confirmed by X-ray crystallography.[22]

BIOLOGICAL ACTIVITY PROFILES

Heteroatom analogues of hydrocodone and open-chain *H*-phosphinate **38** were subjected to *in vitro* radioligand

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displacement assays using human opioid receptors (subtypes δ, κ and μ) at a concentration of 10 μM. In this preliminary screen a "hit", or active compound, is defined as having displaced ≥50% of radioligand at a given opioid receptor. Sulfone **15c** selectively inhibited 69.1% of the specific binding of [^{3}H]-DAMGO to CHO-K1 cell membranes expressing human μ−opioid receptors at the concentration of 10 μM. None of the other compounds tested demonstrated any appreciable affinity for human opioid receptors. As a control, naloxone was used and showed 97.6% displacement at δ−opioid receptors, 99.1% displacement at κ−opioid receptors, and 101.9% displacement at μ−opioid receptors. Sulfone **15c** was not investigated further to determine a K_i value. Another control, hydrocodone (**6**), was also screened and exhibited affinities at the three opioid receptors that are in agreement with previous literature reports (Table 1).

Table 1. Binding Affinity Assay of the Compounds for Human Opioid Receptors (subtypes δ, κ, and μ)

	opioid receptors (%)		
compound	δ	κ	μ
15a	7.1	−21.6	−1.2
15b	0.8	−16.3	6.1
16a, 16b	−5.1	−21.2	−0.3
38	1.7	−19.3	6.6
15c	−3.2	−15.5	69.1
Naloxone	97.6	99.1	101.9
Hydrocodone (K_i, nM)	7760	15.2 ± 0.2	5500

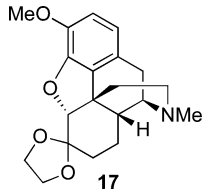
CONCLUSIONS

Several heteroatom analogues of hydrocodone were synthesized and evaluated in preliminary opioid screening assays to establish their binding potential for human opioid receptors. We expected that sulfoxides **16a** and **16b** would display activities similar to those reported by Lemaire for diastereomers of **13** and **14**, but to our surprise, the only derivative that demonstrated modest activity, compared to hydrocodone and naloxone, was sulfone **15c**. Furthermore, sulfone **15c** only exhibited displacement at the μ−opioid receptor. It is difficult to interpret this result, as there is no axial or equatorial distinction in the orientation of substituents, but it is not surprising that heteroatom substitution at the *N*-17 position diminishes activity relative to that of compounds containing nitrogen. Given that all attempts to cyclize *H*-phosphinate **36** were unsuccessful, we were unable to evaluate phosphorus analogue **37**. However, future work in this area should address the isoelectronic series of phosphorus analogues at position 17, such as *P*-Me, *P*-allyl, and *P*-cyclopropylmethyl. Such compounds could be compared with the known *N*-substituted analgesics for biological activity profiles. We will report on this, and other endeavors in this area, in the near future.

EXPERIMENTAL SECTION

General. All nonaqueous reactions were performed in oven or flame-dried glassware under inert atmosphere, with exclusion of moisture from reagents and glassware, unless otherwise stated. Anhydrous solvents were obtained by distillation: dichloromethane, *N*,*N*-dimethylformamide, *N*,*N*-diisopropylethylamine, and pyridine from calcium hydride; methanol from magnesium methoxide; tetrahydrofuran from sodium−benzophenone; and toluene from sodium. Reactions were monitored by thin-layer chromatography (TLC) carried out on precoated 60 Å 250 μm silica gel TLC plates with F-254, indicator visualized under UV light, and developed using ceric ammonium molybdate, 2,4-dinitrophenylhydrazine, or potassium permanganate stains followed by heating. Column chromatography was performed using 40−66 μm silica gel. Gravity column chromatography was performed without external pressure, while flash column chromatography was performed under slightly elevated pressure (0.1−0.4 bar). Specific rotation measurements are reported in units of deg·cm^3·g^{-1}·dm^{-1}, with the concentration, *c*, given in units of grams per 100 mL of solution. IR spectra were obtained on an FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded at 300 MHz or at 600 MHz and are reported as follows: chemical shift (multiplicity, coupling constant (Hz), and integration). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets. ^{13}C NMR spectra were recorded at 75 MHz or at 151 MHz and are reported in terms of chemical shift. All chemical shifts were calibrated using residual nondeuterated solvent as an internal reference and are reported in parts per million relative to trimethylsilane. High-resolution mass spectra (HRMS) were recorded on a high resolution E/B mass spectrometer using a double-focusing magnetic-sector mass analyzer.

*(4R,4aR,7aR,12bS)-9-Methoxy-3-methyl-1,2,3,4,4a,5,6,7a-octahydrospiro[4,12-methanobenzofuro[3,2-e]isoquinoline-7,2′-[1,3]dioxolane] (**17**).*



17

A solution of hydrocodone (9.22 g, 30.8 mmol) in dichloromethane (100 mL) and ethylene glycol (110 mL, 1.95 mmol) was treated with trimethylsilyl chloride (23 mL, 181 mmol), and the resulting yellow mixture was stirred at room temperature for 24 h. The reaction mixture was then poured into a cooled (4 °C), saturated aqueous solution of sodium bicarbonate (500 mL) and stirred until effervescence ceased (≈1 h). The mixture was diluted with dichloromethane (300 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (4 × 400 mL) and the combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide crude ketal **17** (10.6 g) as a colorless solid, which was used in the next step without further purification. R_f 0.30 (2:1 CH_2Cl_2−MeOH); IR (KBr disc): ν 3450 (w), 3026 (m), 3003 (w), 2986 (w), 2948 (s), 2923 (s), 2899 (s), 2880 (m), 2862 (m), 2834 (m), 2790 (m), 2767 (w), 1638 (m), 1614 (s), 1503 (s), 1445 (s), 1414 (w), 1384 (m), 1371 (m), 1350 (m), 1332 (m), 1278 (s), 1246 (s), 1195 (s), 1182 (s), 1138 (m), 1104 (s), 1057 (s), 1012 (m), 997 (m), 973 (m), 958 (s), 922 (s), 902 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.74 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.49 (s, 1H), 4.19 (td, J = 6.8, 5.4 Hz, 1H), 4.03 (dd, J = 12.8, 6.5 Hz, 1H), 3.92−3.84 (m, 4H), 3.79 (td, J = 6.4, 5.5 Hz, 1H), 3.11 (dd, J = 4.7, 2.6 Hz, 1H), 3.00 (d, J = 18.4 Hz, 1H), 2.53 (dd, J = 12.1, 3.8 Hz, 1H), 2.43−2.31 (m, 4H), 2.27−2.16 (m, 2H), 1.88 (td, J = 12.2, 4.9 Hz, 1H), 1.73−1.62 (m, 2H), 1.59−1.47 (m, 2H), 1.15 (qd, J = 12.6, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.6, 142.3, 129.2, 126.4, 118.8, 113.6, 108.7, 94.5, 66.6, 65.0, 59.7, 56.7, 47.3, 43.7, 43.0, 42.6, 36.6, 33.5, 22.5, 20.3; LRMS-EI (*m*/*z*): 344 (23), M$^+$ 343 (100), 244 (17), 99 (71), 59 (21), 42 (19); HRMS-EI (*m*/*z*): M$^+$ calcd for $C_{20}H_{25}NO_4$, 343.1784; found, 343.1782.

Physical and spectral data were found to be in accordance with those reported by Mulzer.[23]

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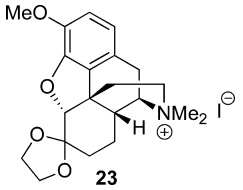
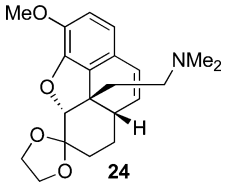
*(4R,4aR,7aR,12bS)-9-Methoxy-3,3-dimethyl-1,2,3,4,4a,5,6,7a-octahydrospiro[4,12-methanobenzofuro[3,2-e]isoquinoline-7,2′-[1,3]dioxolan]-3-ium iodide (**23**).*



23

A suspension of crude **17** (10.6 g, theor. 30.8 mmol) in ethanol (65 mL) was treated with iodomethane (22 mL, 353 mmol) and the mixture was refluxed for 8 h. It was treated with additional iodomethane (2 mL, 32 mmol) and stirred at 60 °C for 12 h before it was cooled to 4 °C. The precipitate was filtered off, washed with cold Et_2O (100 mL), and dried to obtain crude methiodide **23** (15.1 g) as a colorless solid, which was used in the next step without further purification.

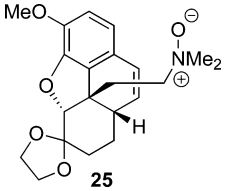
*2-((3a′R,3a$^{1′}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)-N,N-dimethylethanamine (**24**).*



24

A suspension of crude salt **23** (15.1 g, theor. 30.8 mmol) in water (75 mL) was stirred at 90 °C until the solid dissolved, then treated with an aqueous 6.7 M solution of sodium hydroxide (6 mL), and stirred at reflux for 2 h before it was cooled to 25 °C. The mixture was diluted with water (100 mL) and extracted with dichloromethane (6 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford crude amine **24** (10.62 g) as a thick colorless syrup, which was used in the next step without further purification. On a smaller, 3 g scale, the syrup gradually crystallized on standing. R_f 0.32 (2:1 CH_2Cl_2–MeOH); mp 68–70 °C; $[\alpha]_D^{22}$ +29.0 (*c* 1.0, chloroform); IR (KBr disc): ν 3426 (w), 3029 (w), 2942 (s), 2916 (m), 2892 (m), 2858 (m), 2815 (m), 2763(m), 1638 (m), 1623 (m), 1576 (w), 1501 (s), 1467 (m), 1447 (s), 1385 (s), 1339 (m), 1326 (w), 1274 (s), 1256 (s), 1211 (m), 1200 (m), 1179 (m), 1164 (m), 1098 (s), 1058 (s), 1042 (s), 1002 (m), 976 (m), 919 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.70 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.36 (d, *J* = 9.8 Hz, 1H), 5.78 (dd, *J* = 9.5, 5.7 Hz, 1H), 4.73 (s, 1H), 4.22 (td, *J* = 6.9, 4.9 Hz, 1H), 4.03 (q, *J* = 6.8 Hz, 1H), 3.90–3.85 (m, 4H), 3.81 (td, *J* = 6.6, 5.1 Hz, 1H), 2.45–2.38 (m, 2H), 2.16–2.10 (m, 7H), 1.79 (ddd, *J* = 13.3, 11.2, 4.9 Hz, 1H), 1.74–1.70 (m, 1H), 1.66 (ddd, *J* = 13.4, 11.0, 4.9 Hz, 1H), 1.58 (ddd, *J* = 13.1, 4.0, 2.3 Hz, 1H), 1.41 (td, *J* = 13.6, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 146.2, 143.8, 129.7, 128.2, 123.2, 123.0, 117.4, 112.6, 108.3, 94.3, 66.6, 64.9, 56.3, 54.9, 45.7, 45.5, 38.9, 36.1, 31.6, 25.3; LRMS-EI (*m*/*z*): M^+ 357 (25), 286 (53), 284 (22), 199 (22), 198 (78), 185 (15), 99 (100), 73 (48), 58 (50), 45 (83); HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1940.

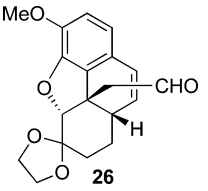
*2-((3a′R,3a$^{1′}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)-N,N-dimethylethanamine Oxide (**25**).*



25

A solution of crude amine **24** (10.62 g, theor. 29.71 mmol) in methanol (80 mL) was cooled to 4 °C and treated with aqueous 30% (w/w) hydrogen peroxide over 30 min. The mixture was stirred at 4 °C for 1.5 h, then at 25 °C for 21 h, before small portions of manganese(IV) oxide (several spatula tips) were added over 2 h (until effervescence ceased and potassium iodide/starch test for peroxides was negative). The mixture was filtered through Celite (washed with methanol), concentrated under reduced pressure, and dried under high vacuum to afford crude *N*-oxide **25** (10.94 g) as a colorless solid, which was used directly in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.74 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.39 (d, *J* = 9.4 Hz, 1H), 5.83 (dd, *J* = 9.4, 5.7 Hz, 1H), 4.72 (s, 1H), 4.25–4.17 (m, 1H), 4.04–3.96 (m, 1H), 3.92–3.78 (m, 2H), 3.89 (s, 3H), 3.42–3.30 (m, 1H), 3.09 (s, 3H), 3.05–2.94 (m, 1H), 2.99 (s, 3H), 2.47–2.37 (m, 1H), 2.30 (td, *J* = 12.8, 4.9 Hz, 1H), 2.16 (td, *J* = 12.4, 4.9 Hz, 1H), 1.64–1.54 (m, 1H), 1.42 (td, *J* = 13.6, 2.3 Hz, 1H), 1.33–1.15 (m, 2H).

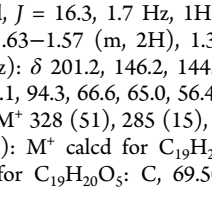
*2-((3a′R,3a$^{1′}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)-acetaldehyde (**26**).*



26

An orange solution of *N*-oxide **25** (10.94 g, theor. 29.30 mmol) in dichloromethane (200 mL) was treated with trifluoroacetic anhydride (21 mL, 149 mmol) at room temperature over 30 min; the solution darkened during this time. After 3.5 h the reaction mixture was slowly poured into a cooled (4 °C) saturated aqueous solution of sodium bicarbonate (400 mL), and extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to furnish crude aldehyde **26** (8.72 g) as a colorless foam, which was used directly in the next step without further purification. An analytical sample was obtained by flash column chromatography (2:1 hexanes–ethyl acetate). R_f 0.45 (1:1 hexanes–EtOAc); mp 110–112 °C (Et_2O); $[\alpha]_D^{20}$ +37.6 (*c* 0.5, $CHCl_3$); IR (KBr disc): ν 3415 (w), 3044 (w), 3028 (w), 2952 (m), 2927 (m), 2890 (m), 2853 (w), 2833 (w), 2754 (w), 2739 (w), 1718 (s), 1638 (w), 1627(w), 1576 (w), 1500 (m), 1554 (m), 1437 (m), 1385 (s), 1331 (w), 1283 (m), 1251 (m), 1200 (w), 1162 (m), 1105 (m), 1061 (m), 1045 (m), 1026 (m), 960 (w), 906 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.57 (s, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 9.6 Hz, 1H), 5.78 (dd, *J* = 9.5, 5.7 Hz, 1H), 4.83 (s, 1H), 4.26–4.19 (m, 1H), 4.02 (dd, *J* = 12.6, 6.3 Hz, 1H), 3.92–3.78 (m, 5H), 2.73 (dd, *J* = 16.3, 1.7 Hz, 1H), 2.59–2.50 (m, 2H), 1.81–1.72 (m, 1 H), 1.63–1.57 (m, 2H), 1.35–1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.2, 146.2, 144.2, 129.5, 126.9, 123.7, 123.0, 117.8, 113.3, 108.1, 94.3, 66.6, 65.0, 56.4, 50.9, 44.9, 38.6, 31.3, 25.3; LRMS-EI (*m*/*z*): M^+ 328 (51), 285 (15), 199 (53), 198 (16), 99 (100); HRMS-EI (*m*/*z*): M^+ calcd for $C_{19}H_{20}O_5$, 328.1311; found, 328.1308; Anal. calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; found: C, 69.47; H, 6.23.

*2-((3a′R,3a$^{1′}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)-ethanol (**27**).*



27

A brown solution of crude aldehyde **26** (8.72 g, theor. 26.5 mmol) in ethanol (200 mL) at 4 °C was treated with sodium borohydride (3.22 g, 85.0 mmol) in three portions over 30 min. The resulting suspension was stirred at 4 °C for 30 min, and at 25 °C for 1 h before it was cooled to 4 °C, and diluted slowly with water (200 mL). The mixture was further diluted with ethyl acetate (200 mL) and treated with solid

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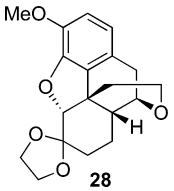
potassium carbonate (200 g). The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide crude alcohol **27** as a colorless oil (8.79 g). Flash column chromatography (3:2 hexanes−ethyl acetate) afforded **27** (5.0 g, 49% overall from hydrocodone **6**) as a pale yellow solid. Recrystallization from diethyl ether afforded an analytically pure sample of alcohol **27** as a colorless solid. R_f 0.26 (1:1 hexanes−EtOAc); mp 100−101 °C (Et_2O); $[\alpha]_D^{18}$ +44.2 (*c* 0.5, $CHCl_3$); IR (KBr disc): ν 3492 (s), 3450 (s), 2997 (w), 2954 (m), 2929 (m), 2894 (m), 2861 (m), 2838 (w), 2362 (w), 2343 (w), 1635 (m), 1578 (w), 1504 (s), 1451 (m), 1435 (m), 1385 (s), 1340 (w), 1276 (m), 1241 (w), 1186 (m), 1162 (m), 1095 (m), 1058 (m), 1038 (m), 1004 (m), 951 (w), 915 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.72 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.81 (dd, *J* = 9.5, 5.6 Hz, 1H), 4.81 (s, 1H), 4.22 (td, *J* = 6.9, 4.8 Hz, 1H), 4.01 (q, *J* = 6.8 Hz, 1H), 3.89−3.85 (m, 4H), 3.81 (td, *J* = 6.6, 4.7 Hz, 1H), 3.58−3.51 (m, 2H), 2.44−2.39 (m, 1H), 1.94 (dt, *J* = 13.9, 6.1 Hz, 1H), 1.78 (dt, *J* = 13.8, 6.8 Hz, 1H), 1.76−1.71 (m, 1H), 1.60−1.56 (m, 2H), 1.43 (td, *J* = 13.6, 2.6 Hz, 1H), 1.26 (qd, *J* = 13.8, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 146.3, 143.9, 129.9, 127.6, 123.2, 123.1, 117.7, 112.8, 108.1, 95.2, 66.6, 64.9, 59.5, 56.3, 45.6, 42.0, 39.7, 31.5, 25.3; LRMS-EI (*m*/*z*): M^+ 330 (18), 285 (11), 199 (20), 99 (100); HRMS-EI (*m*/*z*): M^+ calcd for $C_{19}H_{22}O_5$, 330.1467; found, 330.1465; Anal. calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71; found: C, 69.19; H, 6.77.

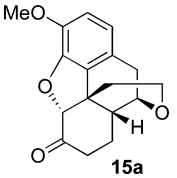
*(4R,4aR,7aR,12bS)-9-Methoxy-2,4,4a,5,6,7a-hexahydro-1H-spiro-[4,12-methanobenzofuro[3,2-e]isochromene-7,2′-[1,3]dioxolane] (**28**).*



28

A solution of alcohol **27** (400 mg, 1.21 mmol) in tetrahydrofuran (22 mL) was treated with mercury(II) trifluoroacetate (784 mg, 1.70 mmol) at 0 °C and the mixture was stirred at 0 °C for 1.7 h. An aqueous solution of sodium hydroxide (20 mL, 20 mmol) was added, followed immediately by sodium borohydride (183 mg, 4.84 mmol). The mixture was stirred at 0 °C for 20 min, diluted with water (40 mL) and ethyl acetate (75 mL), then saturated with potassium carbonate. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 75 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography (2:1 hexanes−ethyl acetate) afforded ether **28** (220 mg, 55%) as a colorless solid. R_f 0.37 (1:1 hexanes−EtOAc); mp 176−177 °C (Et_2O); $[\alpha]_D^{18}$ −131.7 (*c* 1.0, $CHCl_3$); IR (KBr disc): ν 3449 (w), 2951 (m), 2918 (s), 2864 (m), 2837 (m), 1638 (m), 1614 (m), 1503 (s), 1440 (s), 1384 (s), 1326 (m), 1277 (s), 1244 (m), 1194 (s), 1175 (m), 1129 (w), 1107 (w), 1065 (s), 1016 (m), 960 (m), 920 (m), 904 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.66 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 4.46 (s, 1H), 4.21 − 4.17 (m, 2H), 4.05 (q, *J* = 6.7 Hz, 1H), 3.92−3.87 (m, 4H), 3.80 (td, *J* = 6.6, 5.4 Hz, 1H), 3.68 (dd, *J* = 12.1, 5.1 Hz, 1H), 3.57 (td, *J* = 12.3, 3.1 Hz, 1H), 2.92 (d, *J* = 18.4 Hz, 1H), 2.86 (dd, *J* = 18.6, 5.0 Hz, 1H), 2.26 (dt, *J* = 12.6, 3.8 Hz, 1H), 1.90 (td, *J* = 12.4, 5.4 Hz, 1H), 1.68 −1.60 (m, 2H), 1.56−1.50 (m, 2H), 1.01 (qd, *J* = 12.9, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 146.5, 142.3, 128.6, 125.7, 118.7, 113.7, 108.3, 94.0, 72.9, 66.4, 64.9, 60.0, 56.5, 43.5, 41.9, 37.1, 32.9, 29.3, 21.2; LRMS-EI (*m*/*z*): 331 (22), M^+ 330 (100), 125 (11), 112 (10), 99 (72), 55 (13); HRMS-EI (*m*/*z*): M^+ calcd for $C_{19}H_{22}O_5$, 330.1467; found, 330.1467; Anal. calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71; found: C, 68.91; H 6.72.

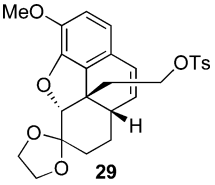
*(4R,4aR,7aR,12bS)-9-Methoxy-1,2,4,4a,5,6-hexahydro-4,12-methanobenzofuro[3,2-e]isochromen-7(7aH)-one (**15a**).*



15a

A solution of ketal **28** (220 mg, 0.66 mmol) in methanol (22 mL) was treated with an aqueous solution of hydrochloric acid (3 mL, 36 mmol) and vigorously stirred at 65 °C for 1.5 h. The reaction mixture was cooled to 25 °C, diluted with water (20 mL), basified slowly with a saturated aqueous solution of sodium bicarbonate (9 mL), and diluted with dichloromethane (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 25 mL). The combined organic layers were washed with brine (40 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography (2:3 hexanes−ethyl acetate) afforded hydrocodone oxygen analogue **15a** (182 mg, 95%) as a colorless solid. R_f 0.16 (1:1 hexanes−EtOAc); mp 177−178 °C (Et_2O); $[\alpha]_D^{18}$ −154.3 (*c* 0.77, $CHCl_3$); IR (KBr disc): ν 3435 (w), 2935 (m), 2922 (m), 2859 (m), 1727 (s), 1633 (w). 1611 (m), 1503 (s), 1444 (s), 1384 (m), 1346 (w), 1323 (m), 1275 (s), 1240 (w), 1199 (m), 1181 (m), 1162 (w), 1124 (m), 1078 (s), 1066 (s), 1038 (m), 1006 (w), 993 (w), 962 (m), 949 (m), 901 (m) cm^{-1}; 1H NMR ($CDCl_3$, 600 MHz): δ 6.74 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.65 (s, 1H), 4.28 (t, *J* = 3.9 Hz, 1H), 3.91 (s, 3H), 3.74 (dd, *J* = 12.2, 5.3 Hz, 1H), 3.55 (td, *J* = 12.3, 3.0 Hz, 1H), 2.94 (d, *J* = 18.7 Hz, 1H), 2.83 (dd, *J* = 18.7, 5.3 Hz, 1H), 2.64 (dt, *J* = 12.9, 3.7 Hz, 1H), 2.45 (dt, *J* = 13.9, 3.2 Hz, 1H), 2.38 (td, 13.9, 4.6 Hz, 1H), 2.11 (td, *J* = 12.4, 5.4 Hz, 1H), 1.86−1.82 (m, 1H), 1.74 (dd, *J* = 12.5, 2.5 Hz, 1H), 1.12 (qd, *J* = 13.5, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 207.2, 145.4, 143.0, 126.7, 125.5, 119.9, 114.9, 91.1, 72.5, 59.9, 56.7, 46.7, 42.1, 40.1, 36.0, 29.2, 24.5; LRMS-EI (*m*/*z*): 287 (19), M^+ 286 (100), 185 (12); HRMS-EI (*m*/*z*): M^+ calcd for $C_{17}H_{18}O_4$, 286.1205; found, 286.1202; Anal. calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34; found: C, 70.76; H, 6.37 (discrepancy due to presence of residual H_2O/Et_2O).

*2-((3a′R,3a$^{1′}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)ethyl 4-Methylbenzenesulfonate (**29**).*



29

To a solution of alcohol **27** (515 mg, 1.56 mmol) in dichloromethane (8 mL) and pyridine (8 mL) at −8 °C was added *p*-toluenesulfonyl chloride (577 mg, 3.03 mmol) and the mixture was allowed to stand at −8 °C for 24 h. The mixture was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL), water (10 mL), and dichloromethane (25 mL) and the mixture was vigorously stirred at 25 °C for 10 min. The layers were separated and the aqueous layer extracted with dichloromethane (4 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The remaining oil, which contained residual pyridine, was triturated with toluene (3 × 6 mL) and then purified by flash column chromatography (2:1 hexanes−ethyl acetate) to afford tosylate **29** (717 mg, 95%) as a colorless solid. R_f 0.25 (2:1 hexanes−EtOAc 2:1); mp 119−120 °C (Et_2O); $[\alpha]_D^{18}$ +20.0 (*c* 0.6, $CHCl_3$); IR (KBr disc): ν 3450 (w), 3066 (w), 3031 (w), 3006 (w), 2963 (m), 2938 (s), 2916 (m), 2895 (m), 2881 (m), 2852 (m), 1929 (w), 1821 (w), 1735 (w), 1697 (w), 1637 (m), 1622 (m), 1598 (m), 1575 (m), 1504 (s), 1450 (s), 1385 (m), 1356 (s), 1339 (m), 1308 (w), 1278 (s), 1249 (m), 1214 (m), 1179 (s), 1119 (w), 1096 (m), 1064 (s), 1043 (s), 1021 (m), 997 (m), 964 (s), 918 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.30

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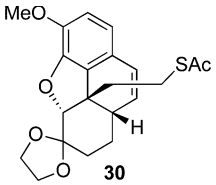
(d, J = 8.1 Hz, 2H), 6.70 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 5.75 (dd, J = 9.5, 5.6 Hz, 1H), 4.59 (s, 1H), 4.19 (td, J = 6.9, 4.9 Hz, 1H), 4.05 (ddd, J = 10.1, 8.9, 5.8 Hz, 1H), 3.98 (q, J = 13.5, 6.8 Hz, 1H), 3.93 (ddd, J = 10.2, 8.7, 6.3 Hz, 1H), 3.87−3.83 (m, 4H), 3.79 (td, J = 6.6, 4.8 Hz, 1H), 2.44 (s, 3H), 2.35−2.30 (m, 1H), 2.00 (ddd, J = 14.8, 8.8, 6.3 Hz, 1H), 1.85 (ddd, J = 14.1, 8.6, 5.8 Hz, 1H), 1.73−1.68 (m, 1H), 1.55 (ddd, J = 13.2, 3.8, 2.4 Hz, 1H), 1.36 (td, J = 13.6, 2.5 Hz, 1H), 1.24−1.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 146.2, 144.6, 144.0, 133.0, 129.8, 129.5, 127.8, 126.5, 123.2, 123.1, 117.7, 113.2, 108.0, 94.5, 67.3, 66.5, 64.9, 56.4, 45.0, 39.1, 38.1, 31.4, 25.3, 21.6; LRMS-EI (m/z): M$^+$ 484 (1), 199 (14), 99 (100), 57 (10), 45 (12), 43 (43); HRMS-EI (m/z): M$^+$ calcd for $C_{26}H_{28}O_7S$, 484.1556; found, 484.1558; Anal. calcd for $C_{26}H_{28}O_7S$: C, 64.45; H, 5.82; found: C, 64.60; H, 5.91.

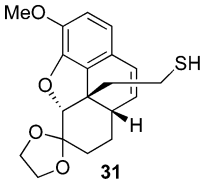
*S-(2-((3a′R,3a$^{1'}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1'}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1'}$-yl)-ethyl) Ethanethioate (**30**).*



30

A solution of tosylate **29** (490 mg, 1.01 mmol) in tetrahydrofuran (15 mL) was treated with potassium thioacetate (381 mg, 3.33 mmol) and the mixture was refluxed for 3 h. The mixture was concentrated and subsequently partitioned between dichloromethane (15 mL) and water (15 mL). The phases were separated and the organic phase extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (14 mL), dried through a phase separator cartridge, and concentrated under reduced pressure. Flash column chromatography (5:2 hexanes−ethyl acetate) provided thioester **11** (350 mg, 89%) as a solid. R_f 0.38 (2:1 hexanes−EtOAc); mp 109−110 °C (Et_2O−pentane); $[\alpha]_D^{18}$ +17.9 (c 1.0, $CHCl_3$); IR (KBr disc): ν 3448 (w), 3039 (w), 2991 (m), 2957 (m), 2939 (m), 2890 (m), 2833 (w), 1692 (s), 1637 (m), 1623 (m), 1577 (w), 1506 (s), 1453 (s), 1437 (s), 1385 (m), 1347 (m), 1305 (w), 1281 (s), 1252 (m), 1221 (m), 1161 (s), 1137 (m), 1117 (m), 1098 (s), 1063 (s), 1049 (m), 1026 (m), 993 (m), 949 (m), 925 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.71 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 9.5 Hz, 1H), 5.80 (dd, J = 9.5, 5.6 Hz, 1H), 4.77 (s, 1H), 4.23 (td, J = 6.9, 5.0 Hz, 1H), 4.02 (q, J = 6.8 Hz, 1H), 3.90−3.85 (m, 4H), 3.81 (td, J = 6.6, 5.4 Hz, 1H), 2.91 (ddd, J = 13.2, 11.9, 5.0 Hz, 1H), 2.61 (ddd, J = 13.3, 11.8, 5.0 Hz, 1H), 2.43−2.37 (m, 1H), 2.26 (s, 3H), 1.86 (ddd, J = 13.3, 12.0, 5.0 Hz, 1H), 1.79−1.72 (m, 2H), 1.58 (ddd, J = 13.1, 3.8, 2.4 Hz, 1H), 1.42 (td, J = 13.6, 2.5 Hz, 1H), 1.26 (qd, J = 13.8, 2.2 Hz,1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.7, 146.3, 143.9, 129.7, 127.1, 123.3, 123.0, 117.6, 113.0, 108.1, 94.3, 66.5, 65.0, 56.3, 46.6, 39.4, 39.0, 31.5, 30.5, 25.4, 24.4; LRMS-EI (m/z): M$^+$ 388 (19), 285 (19), 199 (24), 99 (100); HRMS-EI (m/z): M$^+$ calcd for $C_{21}H_{24}O_5S$, 388.1344; found, 388.1341.

*2-((3a′R,3a$^{1'}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1'}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1'}$-yl)-ethanethiol (**31**) and (4R,4aR,7aR,12bS)-9-Methoxy-2,4,4a,5,6,7a-hexahydro-1H-spiro[4,12-methanoisothiochromeno[5,4a-b]-benzofuran-7,2′-[1,3]dioxolane] (**32**).*



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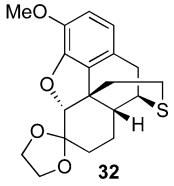


32

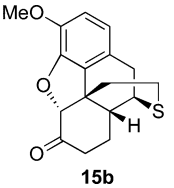
A solution of thioacetate **30** (137 mg, 0.35 mmol) in deoxygenated tetrahydrofuran (3 mL) and methanol (1 mL) was treated with freshly prepared sodium methoxide (57 mg, 1.1 mmol) and the mixture was stirred at 25 °C for 3 h. Argon was bubbled through all liquids used during the workup for 25 min prior to use. The reaction mixture was acidified with aqueous citric acid (15 mL, 5% w/v) and diluted with dichloromethane. The layers were separated and the aqueous layer extracted with dichloromethane (4 × 25 mL). The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide crude thiol **31** (88 mg) as an oil that was used directly in the next step without further purification.

A solution of thiol **31** (44 mg) in deoxygenated benzene (2 mL) was stirred under a sunlamp for 36 h at 25 °C. Evaporation and flash column chromatography (3:1 hexanes−EtOAc) afforded **32** (9 mg, 15% yield) as a solid.

Data for **31**: R_f 0.40 (2:1 hexanes−EtOAc); LRMS-EI (m/z): M$^+$ 346 (44), 285 (15), 199 (29), 99 (100), 84 (25).

Data for **32**: R_f 0.38 (2:1 hexanes−EtOAc); mp 197−198 °C (Et_2O); $[\alpha]_D^{21}$ −279.3 (c 0.5, $CHCl_3$); IR (KBr disc): ν 3448 (w), 2997 (w), 2949 (m), 2931 (m), 2906 (s), 2883 (m), 2832 (m), 1633 (m), 1606 (m), 1502 (s), 1438 (s), 1384 (s), 1352 (w), 1327 (m), 1277 (s), 1242 (m), 1194 (s), 1140 (m), 1113 (m), 1097 (m), 1061 (s), 1034 (w), 1022 (m), 1011 (m), 968 (m), 957 (m), 931 (w), 918 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.76 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 4.42 (s, 1H), 4.19 (q, J = 6.2 Hz, 1H), 4.00 (q, J = 6.6 Hz, 1H), 3.89−3.84 (m, 4H), 3.77 (q, J = 6.0 Hz, 1H), 3.20 (s, 2H), 2.98 (s, 1H), 2.74 (s, J = 11.5 Hz, 1H), 2.52 (d, J = 12.7 Hz, 1H), 2.32 (d, J = 13.7 Hz, 1H), 2.17 (d, J = 12.7 Hz, 1H), 1.94 (td, J = 12.7, 3.6 Hz, 1H), 1.66 (d, J = 12.8 Hz, 1H), 1.55 (t, J = 12.4 Hz, 2H), 1.18 (dd, J = 26.5, 13.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 146.7, 142.3, 128.1, 126.2, 119.3, 113.6, 108.1, 95.4, 66.5, 64.9, 56.5, 44.4, 44.0, 38.3, 37.9, 33.0, 32.8, 24.9, 23.2 ppm; LRMS-EI (m/z): 347 (15), M$^+$ 346 (67), 285 (12), 260 (10), 200 (15), 199 (38), 99 (100); HRMS-EI (m/z): M$^+$ calcd for $C_{19}H_{22}O_4S$, 346.1239; found, 346.1245.

*(4R,4aR,7aR,12bS)-9-Methoxy-1,2,4,4a,5,6-hexahydro-4,12-methanoisothiochromeno[5,4a-b]benzofuran-7(7aH)-one (**15b**).*



15b

A solution of ketal **32** (29 mg, 0.084 mmol) in deoxygenated methanol (8 mL) was treated with aqueous hydrochloric acid (2 mL, 24 mmol) and the reaction mixture was vigorously stirred at 60 °C for 1.5 h. The mixture was then cooled to 25 °C, diluted with water (5 mL), and basified slowly with saturated aqueous solution of sodium bicarbonate (8 mL). The mixture was diluted with dichloromethane (8 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (5 × 8 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography (3:2 hexanes−ethyl acetate) afforded **15b**, the sulfur analogue of hydrocodone (23 mg, 91%) as a colorless solid. R_f 0.35 (hexanes−EtOAc); mp 200−201 °C (Et_2O); $[\alpha]_D^{23}$ −187.0 (c 0.25, $CHCl_3$); IR (KBr disc): ν 3447 (m), 2995 (w), 2956 (w), 2934 (m), 2919 (m), 2865, (w), 2834 (w), 1724 (s), 1627 (w), 1606 (w), 1499 (m), 1439 (m), 1326 (w), 1311 (w), 1268 (m), 1243 (w), 1182 (w), 1144 (w), 1099 (m), 1054 (m), 995 (w), 953 (m), 926 (w), 901 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.73 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 4.62 (s, 1H), 3.91 (s, 3H), 3.26−3.14 (m, 2H), 3.06 (d, J = 5.6 Hz, 1H), 2.91 (ddd, J = 12.7, 4.2, 2.5 Hz, 1H), 2.71 (s, 1H), 2.44−2.36 (m, 3H), 2.30 (d, J = 12.7 Hz, 1H), 2.17 (td, J = 12.7, 4.0 Hz, 1H), 1.93−1.88 (m, 1H), 1.31−1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.8, 145.8, 143.2, 126.3, 126.2, 120.5, 114.8, 92.3, 56.8, 48.2, 44.0, 39.8, 37.9, 37.3, 32.9, 28.4, 23.1; LRMS-EI (m/z): 303 (21), M$^+$ 302 (100), 242 (14), 241 (52), 213 (16), 199 (13), 185 (29), 86 (11), 84 (13), 55 (14); HRMS-EI (m/z): M$^+$ calcd for $C_{17}H_{18}O_3S$, 302.0977; found, 302.0976.

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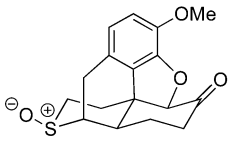
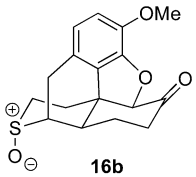
*(3S,4R,4aR,12bS)-9-Methoxy-2,4,4a,5,6,7a-hexahydro-1H-spiro[4,12-methanoisothiochromeno[5,4a-b]benzofuran-7,2′-[1,3]dioxolane] 3-Oxide (**16a**) and (3R,4R,4aR,12bS)-9-Methoxy-2,4,4a,5,6,7a-hexahydro-1H-spiro[4,12-methanoisothiochromeno[5,4a-b]-benzofuran-7,2′-[1,3]dioxolane] 3-Oxide (**16b**).*



16a



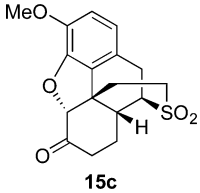
16b

A solution of **15b** (40 mg, 0.13 mmol) in methanol (2 mL) and water (4 drops) was treated with sodium periodate (30 mg, 0.14 mmol) and the resulting suspension was stirred at 25 °C for 48 h. The mixture was concentrated under reduced pressure and the residue purified by gravity column chromatography (200:1 to 100:1 dichloromethane−methanol) to afford **16a** and **16b** (39 mg, 93%) as an inseparable 5:1 mixture of two diastereomers, obtained as a colorless solid.

Data of the major isomer collected from 5:1 mixture: R_f 0.15 (95:5 CH_2Cl_2−MeOH); mp >260 °C (Et_2O); $[\alpha]_D^{21}$ −155.47 (*c* 1, $CHCl_3$); IR (KBr disc): ν 3446 (m), 3000 (w), 2972 (w), 2926 (w), 2894 (w), 2870 (w), 2840 (w), 2361 (w), 2341 (w), 1726 (s), 1635 (m), 1614 (m), 1504 (s), 1443 (s), 1323 (w), 1276 (s), 1240 (w), 1187 (w), 1161 (w), 1142 (w), 1101 (m), 1035 (s), 1003 (m), 971 (w), 952 (m), 918 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.79 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 4.71 (s, 1H), 3.94 (s, 3H), 3.50 (ddd, J = 12.6, 4.2, 2.4 Hz, 1H), 3.38 (br. d, J = 9.0 Hz, 1H), 3.10 (dd, J = 19.8, 9.0 Hz, 1H), 2.82−2.73 (m, 3H), 2.54 (dd, J = 13.2, 4.2 Hz, 1H), 2.50 (dt, J = 13.7, 3.5 Hz, 1H), 2.13 (td, J = 15.6, 4.8 Hz, 1H), 2.01(ddd, J = 13.8, 4.2, 2.4 Hz, 1H), 1.82 (dq, $J \approx$ 13.4, 4.0 Hz, 1H), 1.37 (qd, J = 13.2, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.0, 145.7, 143.7, 125.8, 121.7, 121.0, 115.6, 91.5, 56.9, 54.0, 47.1, 40.1, 29.1, 27.3, 22.4; LRMS-FAB(+) (*m*/*z*): 320 (22), $[M+H]^+$ 319 (100), M^+ 318 (46), 241 (16), 155 (15), 154 (39), 152 (17), 137 (29), 136 (90), 120 (16), 107 (35), 105 (21), 95 (20), 91 (20), 90 (27), 89 (34), 81 (21), 79 (16), 77 (38), 73 (29), 71 (20), 69 (31), 67 (18), 57 (44), 55 (56), 43 (46), 41 (35); HRMS-FAB(+) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{19}O_4S$, 319.1004; found, 319.0998.

Data of the minor isomer collected from 5:1 mixture: ^1H NMR ($CDCl_3$, 600 MHz): δ 6.79 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 4.69 (s, 1H), 3.93 (s, 3H), 3.73 (d, J = 19.2 Hz, 1H), 3.50 (m, 1H), 3.04 (dq, $J \approx$ 13.2, 1.8 Hz, 1H), 2.82−2.73 (m, 2H), 2.54 (td, J = 13.2, 4.2 Hz, 1H), 2.50 (m, 1H), 2.43 (td, J = 13.8, 4.8 Hz, 1H), 2.34 (td, J = 13.2, 4.2 Hz, 1H) 2.21(ddd, J = 13.8, 4.2, 3.6 Hz, 1H),) 2.15 (td, J = 13.8, 3.0 Hz, 1H) 1.97 (dq, $J \approx$ 13.5, 3.8 Hz, 1H), 1.51 (qd, J = 13.2, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 205.8, 145.5, 143.4, 125.2, 124.5, 121.7, 115.4, 90.9, 56.8, 54.5, 46.6, 43.4, 39.6, 37.3, 33.8, 27.9, 16.2.

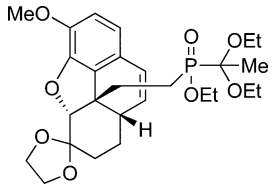
*(4R,4aR,7aR,12bS)-9-Methoxy-1,2,4,4a,5,6-hexahydro-4,12-methanoisothiochromeno[5,4a-b]benzofuran-7(7aH)-one 3,3-dioxide (**15c**).*



15c

To a solution of **15b** (17 mg, 0.056 mmol) in methanol (3 mL) and water (0.3 mL) was added sodium periodate (50 mg, 0.23 mmol) and the resulting suspension was stirred at 50 °C for 24 h, then treated with additional sodium periodate (50 mg, 0.23 mmol) and stirred at 50 °C for 12 h. The mixture was concentrated under reduced pressure and the residue purified by gravity column chromatography (200:1 to 100:1 dichloromethane−methanol) afforded **15c** (18 mg, 90%) as a colorless solid. R_f 0.75 (95:5 CH_2Cl_2−MeOH); mp >260 °C ($CHCl_3$); $[\alpha]_D^{22}$ −162.81 (*c* 1, $CHCl_3$); IR (KBr disc): ν 3446 (m), 2968 (w), 2926 (w), 2904 (w), 2866 (w), 2836 (w), 2362 (w), 2345 (w), 1729 (s), 1633 (w), 1608 (m), 1499 (m), 1443 (m), 1427 (w), 1396 (w), 1357 (w), 1338 (w), 1296 (s), 1257 (s), 1219 (m), 1153 (w), 1121 (s), 1082 (w), 1029 (m), 1001 (m), 959 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.83 (d, J = 8.18 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 4.76 (s, 1H), 3.94 (s, 3H), 3.56 (d, J = 19.5 Hz, 1H), 3.38 (ddd, J = 2.7, 4.5, 12.6 Hz, 1H), 3.27 (dt, J = 7.5, 2.7 Hz, 1H), 3.02 (dd, J = 7.5, 18.6 Hz, 1H), 2.97 (dq, $J \approx$ 11.1, 3.0 Hz, 1H), 2.65 (td, J = 13.2, 4.5 Hz, 1H) 2.55−2.45 (m, 3H), 2.30 (ddd, J = 2.7, 3.9, 12.9 Hz, 1H), 1.96 (dq, J = 13.5, 4.2 Hz, 1H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.4, 145.9, 143.9, 124.5, 121.8, 121.4, 116.0, 91.0, 60.6, 56.9, 46.9, 46.8, 39.3, 38.1, 33.3, 26.9, 23.1; MS (FAB) (*m*/*z*): $[M+H]^+$ 335 (85), M^+ 334 (97) 241 (50) 155 (42), 138 (51), 137 (73), 136 (83),107 (70), 105 (47), 95 (47), 91 (64), 90 (44), 89 (62), 83 (40), 81 (44), 77 (74), 73 (83), 69 (73), 57 (76), 55 (99), 43 (100), 41 (61) ; HRMS-FAB (*m*/*z*): M^+ calcd for $C_{17}H_{18}O_5S$, 334.0875; found, 334.0866.

*Ethyl (1,1-Diethoxyethyl)(2-((3a′R,3a$^{1′}$S,9a′S)-5′-methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)ethyl)phosphinate (**34**).*



34

*Preparation of Triflate from Alcohol **27**:* A solution of **27** (150 mg, 0.454 mmol) in dichloromethane (2.5 mL) and pyridine (0.1 mL, 1.2 mmol) was treated with trifluoromethanesulfonic anhydride (90 μL, 0.535 mmol) at −78 °C. The mixture was stirred for 3.5 h while the temperature was allowed to reach −20 °C, before it was recooled to −78 °C. The solution of triflate **33** was used in the procedure given below.

*Preparation of **34**:* A solution of hexamethyldisilazane (0.39 mL, 1.8 mmol) in tetrahydrofuran (2 mL) was treated with a 2.4 M solution of *n*-butyllithium in hexanes (0.7 mL, 1.68 mmol) at 4 °C. The mixture was stirred at 4 °C for 2 h and 25 °C for 45 min before it was recooled to 4 °C. Ethyl (1,1-diethoxyethyl)phosphinate (382 mg, 1.82 mmol) was added and the mixture stirred at 4 °C for 1.5 h, 25 °C for 15 min, and then cooled to −78 °C. A freshly prepared solution of triflate **33** (*vide supra*) was added, the mixture was allowed to reach 4 °C over 3 h, and it was stirred at 4 °C for 12 h. The mixture was poured into a cooled (4 °C), saturated aqueous solution of ammonium chloride (10 mL), water (13 mL) was added, and the mixture was stirred for 10 min before it was extracted with dichloromethane (5 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:1 chloroform−ethyl acetate) to afford phosphinate **34** (94 mg, 40%) as a 1:1 mixture of two diastereomers, obtained as a pink oil. On a 600 mg scale the yield of **34** dropped to 24% and chloride **35** (1%) was isolated as the side-product. Data for **34**: R_f 0.20 (100% EtOAc); IR ($CHCl_3$): ν 3031 (w), 2983 (s), 2898 (w), 2839 (w), 1637 (w), 1624 (w), 1578 (w), 1506 (m), 1455 (w), 1439 (m), 1390 (w), 1372 (w), 1364 (w), 1341 (w), 1278 (m), 1256 (m), 1165 (s), 1112 (m), 1087 (m), 1036 (s), 990 (w), 954 (m), 926 (w), 911 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, 1:1 mixture of two diastereomers): 6.71 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 6.35 (d, J = 9.8 Hz, 1H), 6.34 (d, J = 9.8 Hz, 1H), 5.76 (2q, J = 9.8, 5.3 Hz, 2H), 4.63 (2s, 2H), 4.23 (*m*, 2H), 4.17−4.04 (m, 4H), 4.03−3.98 (m, 2H), 3.88−3.84 (m, 2H), 3.84 (s, 6H), 3.83−3.79 (m, 2H), 3.70−3.48 (m, 8H), 2.37−2.30 (m, 2H), 2.14−2.05 (m, 1H), 1.96−1.69 (m, 7H), 1.60−1.55 (m, 2H), 1.56−1.32 (m, 4H), 1.41 (d, J = 11.3 Hz, 9H), 1.34 (d, J = 11.3 Hz, 9H), 1.30−1.20 (m, 2H), 1.26 (t, J = 6.8 Hz, 3H), 1.23 (t, J = 6.8 Hz, 3H), 1.19−1.09 (m, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz, 1:1 mixture of two diastereomers): 146.5, 146.4, 144.00, 143.96, 129.84, 129.79, 127.3, 127.0, 123.51, 123.48, 123.17, 123.16, 117.79, 117.76, 113.14, 113.08, 108.4, 101.8 (d, $^1J_{PC}$ = 138.7 Hz), 100.9 (d, $^1J_{PC}$ = 138.7 Hz), 94.3, 94.1, 66.8, 65.1, 61.6 (d, $^2J_{CP}$ = 7.0 Hz), 61.5

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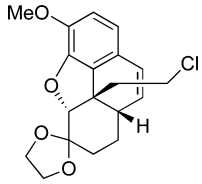
(d, $^2J_{CP}$ = 7.0 Hz), 58.3−58.2 (two doublets), 57.64 (d, $^3J_{CP}$ = 7.6 Hz), 57.63 (d, $^3J_{CP}$ = 7.0 Hz), 56.54, 56.52, 46.6 (d, $^3J_{CP}$ = 6.6 Hz), 46.5 (d, $^3J_{CP}$ = 6.5 Hz), 39.90, 39.40, 31.69, 30.47 (d, $^1J_{CP}$ = 95.0 Hz), 30.44 (d, $^1J_{CP}$ = 95.0 Hz), 25.55, 21.26−20.42 (multiple signals), 16.78 (d, $^3J_{CP}$ = 5.4 Hz) 16.72 (d, $^3J_{CP}$ = 5.3 Hz), 15.59, 15.58, 15.40, 15.38; LRMS-EI (m/z): [M-EtOH]$^+$ 476 (4), 248 (20), 199 (10), 163 (19), 117 (100), 99 (43), 89 (21), 61 (41), 60 (11), 43 (28), 42 (10); HRMS-EI (m/z): M$^+$ calcd for $C_{27}H_{39}O_8P$, 522.2383; found, 522.2401.

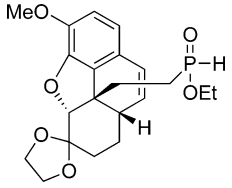
*(3a′R,3a$^{1′}$S,9a′S)-3a$^{1′}$-(2-Chloroethyl)-5′-methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]-furan] (**35**).*



35

Data for **35**: Colorless oil. R_f 0.33 (5:1 hexanes−EtOAc); IR ($CHCl_3$): ν 3031 (w), 3009 (m), 2956 (m), 2935 (m), 2900 (m), 2854 (w), 2840 (w), 1731 (w), 1637 (w), 1623 (w), 1578 (w), 1506 (s), 1453 (m), 1438 (m), 1387 (w), 1374 (w), 1358 (w), 1340 (w), 1305 (w), 1279 (s), 1264 (m), 1164 (s), 1112 (m), 1093 (s), 1064 (s), 1030 (s), 993 (w), 976 (w), 952 (w), 909 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.73 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.38 (d, J = 9.4 Hz, 1H), 5.81 (dd, J = 9.4, 5.7 Hz, 1H), 4.69 (s, 1H), 4.26−4.18 (m, 1H), 4.05−3.97 (m, 1H), 3.92−3.77 (m, 1H), 3.89 (s, 3H), 3.54 (td, $J \approx$ 11.0, 5.0 Hz, 1H), 2.29 (td, $J \approx$ 11.0, 5.0 Hz, 1H), 2.37 (dt, $J \approx$ 11.7, 5.3 Hz, 1H), 2.18 (ddd, $J \approx$ 13.6, 11.5, 5.5 Hz, 1H), 1.99 (ddd, J = 13.6, 11.3, 4.9 Hz, 1H), 1.80−1.69 (m, 1H), 1.63−1.53 (m, 1H), 1.42 (td, $J \approx$ 13.7, 2.6 Hz, 1H), 1.33−1.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 144.2, 129.8, 126.6, 123.42, 123.37, 117.9, 113.2, 108.2, 94.9, 66.8, 65.1, 56.5, 46.4, 43.2, 40.8, 39.7, 31.6, 25.5; LRMS-EI (m/z): M$^+$ 348 (25), [M-C_2H_4Cl]$^+$ 285 (20), 199 (32), 185 (14), 99 (100), 49 (13); HRMS-EI (m/z): M$^+$ calcd for $C_{19}H_{21}ClO_4$, 348.1128; found, 348.1132.

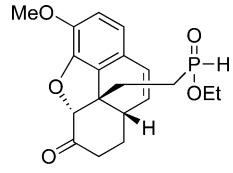
*Ethyl (2-((3a′R,3a$^{1′}$S,9a′S)-5′-Methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]furan]-3a$^{1′}$-yl)ethyl)phosphinate (**36**).*



36

A solution of **34** (85 mg, 0.163 mmol) in methanol (0.2 mL) and dichloromethane (1.8 mL) was treated with trimethylsilyl chloride (35 μL, 0.276 mmol) at 25 °C, and the mixture was stirred for 20 h. The mixture was concentrated under reduced pressure to provide crude *H*-phosphinate **36** (75 mg) as a pale yellow solid comprising a 1:1 mixture of two diastereomers, which was used in the next step without further purification. R_f 0.12 (100% EtOAc); IR ($CHCl_3$): ν 3414 (w), 3024 (w), 3005 (s), 2955 (m), 2903 (m), 2852 (w), 2841 (w), 2350 (w), 1734 (w), 1637 (w), 1625 (w), 1579 (w), 1507 (s), 1455 (m), 1438 (m), 1390 (w), 1360 (w), 1342 (w), 1279 (s), 1256 (s), 1176 (m), 1165 (s), 1086 (m), 1063 (s), 1047 (s), 1000 (m), 969 (s), 923 (m), 902 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 150 MHz, 1:1 mixture of two diastereomers): δ 6.89 (d, J = 532 Hz), 6.87 (d, J = 533 Hz), 6.71 (d, J = 7.9 Hz, 2H), 6.64 (d, J = 7.9 Hz, 2H), 6.35 (d, J = 9.4 Hz, 2H), 5.77 (d, J = 9.4 Hz, 2H), 5.76 (d, J = 9.4 Hz, 2H), 4.61, 4.60 (2s, 2H), 4.22−4.17 (m, 2H), 4.12−3.94 (m, 6H), 3.91−3.82 (m, 2H), 3.87 (s, 6H), 3.82−3.77 (m, 2H), 2.35−2.27 (m, 2H), 1.94−1.20 (several m, 18H); ^{13}C NMR ($CDCl_3$, 150 MHz, 1:1 mixture of two diastereomers): δ 146.4, 144.09, 144.06, 129.69, 129.67, 129.65, 126.51, 126.47, 126.40, 126.37, 124.0, 123.4, 123.37, 123.36, 123.32, 123.30, 123.24, 123.22, 117.95, 117.92, 117.90, 113.12, 113.07, 108.18, 108.17, 94.43, 94.42, 66.7, 65.1, 62.5−62.4 (multiple signals), 56.4, 46.3, 46.2, 39.85, 39.82, 39.80, 39.77, 31.6, 30.10, 30.09, 30.04−30.01 (multiple signals), 29.8, 25.5, 24.3, 23.79 (d, $^1J_{CP}$ = 93.2 Hz), 23.77 (d, $^1J_{CP}$ = 93.2 Hz), 16.32 (d, $^3J_{CP}$ = 6.6 Hz), 16.30 (d, $^3J_{CP}$ = 5.6 Hz); LRMS-EI (m/z): M$^+$ 406 (4), 285 (21), 99 (19), 85 (75), 83 (100), 48 (17), 47 (33); HRMS-EI (m/z): M$^+$ calcd for $C_{21}H_{27}O_6P$, 406.1545; found, 406.1538.

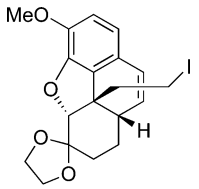
*Ethyl 2-((2aS,2a1S,5aR)-7-Methoxy-5-oxo-2a,2a1,3,4,5,5a-hexahydrophenanthro[4,5-bcd]furan-2a1-yl)ethylphosphinate (**38**).*



38

A solution of the crude ketal **36** (theor. 0.163 mmol) in ethanol (5 mL) was treated with a concentrated aqueous solution of hydrochloric acid (0.7 mL) and the mixture was stirred at 65 °C for 1 h. It was then cooled to 25 °C, poured into a cold (4 °C), saturated aqueous solution of sodium bicarbonate (15 mL), and extracted with dichloromethane (5 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Gravity column chromatography (30:1 dichloromethane−methanol) afforded ketone **38** as a 1:1 mixture of two diastereomers (12 mg, colorless oil, 20% from **34**) and a 3:1 mixture of **38** and **36** (3 mg). Data for **38**: R_f 0.27 (30:1 CH_2Cl_2−MeOH); IR ($CHCl_3$): ν 3682 (w), 3441 (w), 3003 (s), 2932 (m), 2840 (w), 2348 (w), 1735 (s), 1637 (w), 1623 (w), 1578 (w), 1509 (s), 1454 (m), 1438 (m), 1390 (w), 1365 (w), 1336 (w), 1287 (s), 1274 (s), 1249 (s), 1165 (m), 1159 (m), 1105 (m), 1080 (m), 1057 (s), 1045 (s), 996 (m), 966 (s), 927 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz, 1:1 mixture of two diastereomers): δ 6.98 (d, J = 534 Hz), 6.69 (d, J = 534 Hz), 6.70 (d, J = 8.3 Hz, 2H), 6.67 (d, J = 8.3 Hz, 2H), 6.41 (d, J = 9.1 Hz, 2H), 5.83 (dd, $J \approx$ 9.1, 6.0 Hz, 2H), 4.87, 4.86 (2s, 2H), 4.15−4.07 (m, 2H), 4.05−3.97 (m, 2H), 3.91 (s, 6H), 2.75−2.68 (m, 2H), 2.37−2.27 (m, 4H), 2.15−2.04 (m, 4H), 1.97−1.86 (m, 4H), 1.64−1.52 (m, 2H), 1.32 (2q, J = 12.8, 6.8 Hz, 6H), 1.32−1.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, 1:1 mixture of two diastereomers): δ 206.61, 206.56, 145.7, 144.8, 144.7, 128.70, 128.67, 124.5, 124.1, 123.1, 123.0, 118.98, 118.97, 113.94, 113.91, 91.6, 62.71 (d, $^2J_{CP}$ = 6.7 Hz), 62.69 (d, $^2J_{CP}$ = 6.8 Hz), 56.5, 51.1, 51.0, 40.3, 38.00, 37.98, 29.8, 28.9−28.8 (multiple signals), 28.3, 24.21 (d, $^2J_{CP}$ = 94.4 Hz), 24.19 (d, $^2J_{CP}$ = 93.9 Hz), 16.4 (d, $^3J_{CP}$ = 5.8 Hz), 16.3 (d, $^3J_{CP}$ = 6.1 Hz); LRMS-EI (m/z): M$^+$ 361 (29), [M − OEt]$^+$ 317 (3), 242 (18), 241 (86), 185 (27), 122 (100), 94 (91), 93(15), 85(29), 83(36), 78(21), 66(16); HRMS-EI (m/z): M$^+$ calcd for $C_{19}H_{23}O_5P$, 362.1283; found 362.1286.

*(3a′R,3a$^{1′}$S,9a′S)-3a$^{1′}$-(2-Iodoethyl)-5′-methoxy-2′,3a′,3a$^{1′}$,9a′-tetrahydro-1′H-spiro[[1,3]dioxolane-2,3′-phenanthro[4,5-bcd]-furan] (**39**).*



39

A solution of tosylate **29** (307 mg, 0.634 mmol) and sodium iodide (1.71 g, 11.4 mmol) in acetone (20 mL) was stirred at 40 °C for 14 h and at 50 °C for 6 h. The solvent was evaporated and the residue was diluted with ethyl acetate (15 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate (5 mL), brine (15 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Crude iodide **39** was purified by crystallization from diethyl ether−hexanes to afford analytically pure **39** (225 mg,

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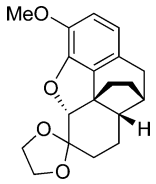
81%) as a yellow solid. R_f 0.79 (2:1 hexanes−EtOAc); mp 119−121 °C (Et_2O−hexanes); $[\alpha]_D^{20}$ −10.5 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): ν 3032 (w), 3008 (m), 2955 (m), 2899 (m), 2851 (w), 2840 (w), 1637 (w), 1623 (w), 1578 (w), 1506 (s), 1454 (m), 1438 (m), 1387 (w), 1340 (w), 1300 (w), 1278 (s), 1165 (s), 1121 (w), 1091 (m), 1064 (m), 1034 (m), 987 (w), 951 (w), 924 (m), 909 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): 6.73 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.79 (dd, *J* = 9.6, 5.7, 1H), 4.66 (s, 1H), 4.26−4.18 (m, 1H), 4.06−3.96 (m, 1H), 3.92−3.77 (m, 2H), 3.89 (s, 3H), 3.19 (ddd, *J* = 13.0, 9.4, 4.6 Hz, 1H), 2.89 (ddd, *J* = 10.0, 9.4, 4,9 Hz, 1H), 2.40−2.27 (*m*, 2H), 2.15 (td, *J* = 13.2, 4.7 Hz, 1H), 1.80−1.69 (m, 1H), 1.63−1.52 (m, 1H), 1.40 (td, *J* = 13.2, 2.4 Hz, 1H), 1.34−1.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): 146.5, 144.2, 129.8, 126.3, 123.44, 123.38, 117.9, 113.1, 108.2, 94.6, 66.8, 65.2, 56.5, 48.9, 45.3, 39.5, 31.6, 25.5, 0.4; LRMS-EI (*m*/*z*): M^+ 440 (14), 285 (18), 199 (25), 100 (11), 99 (100); HRMS-EI (*m*/*z*): M^+ calcd for $C_{19}H_{21}IO_4$, 440.048; found, 440.0492; Anal. calcd for $C_{19}H_{21}IO_4$: C, 51.83; H, 4.81; found: C, 51.76; H, 4.83.

(3R,3aS,6aR,11bS)-8-Methoxy-2,3,3a,4,5,6a-hexahydro-1H-spiro-[3,11-methanoindeno[4,3a-b]benzofuran-6,2′-[1,3]dioxolane] (**40**).



40

A 50 mL flask equipped with a Dimroth condenser was charged with ammonium hypophosphorous acid (417 mg, 5.02 mmol), toluene (20 mL), and hexamethyldisilazane (1.08 mL, 5.09 mmol), the suspension was immersed in a preheated oil bath (100 °C) and stirred for 110 min, before a solution of iodide **39** (107 mg, 0.243 mmol) in dichloromethane (5 mL) was added, and the mixture stirred for 12 h. The solvent was evaporated and the resulting yellow, oily residue was dissolved in diethyl ether (10 mL) and washed with an aqueous 4 M solution of hydrochloric acid. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic extracts were filtered through cotton wool and evaporated. Gravity column chromatography (4:1 hexanes−ethyl acetate) afforded **40** (64 mg, 84%) as colorless solid. R_f 0.27 (4:1 hexanes−EtOAc); mp 132−135 °C (hexanes−EtOAc); IR ($CHCl_3$): 3632 (w), 3009 (m), 2956 (s), 2907 (m), 2868 (m), 2838 (m), 1638 (w), 1607 (w), 1504 (s), 1453 (s), 1440 (m), 1341 (m), 1277 (s), 1260 (m), 1177 (m), 1079 (s), 1063 (s), 1017 (m), 951 (m), 922 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.70 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 8.3, Hz 1H), 4.60 (s, 1H), 4.15−4.05 (m, 2H), 3.96−3.92 (m, 1H), 3.89−3.84 (m, 1H), 3.85 (s, 3H), 2.79 (dd, *J* = 16.6, 3.8 Hz, 1H), 2.49−2.45 (m, 1H), 2.45−2.40 (m, 1H), 2.08−2.00 (m, 2H), 1.93 (ddd, *J* = 12.0, 9.4, 3.0 Hz, 1H), 1.77 (td, *J* = 11.7, 6.4 Hz, 1H), 1.69−1.62 (m, 1H), 1.59 (dt, *J* = 13.6, 5.7 Hz, 1H), 1.52−1.40 (m, 2H), 1.23−1.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.5, 142.1, 133.3, 124.1, 120.2, 113.3, 109.3, 90.4, 66.0, 65.0, 56.5, 51.4, 41.3, 39.1, 36.0, 31.8, 31.2, 29.3, 19.3; LRMS-EI (*m*/*z*): 315 (21), M^+ 314 (100), 229 (10), 228 (59), 199 (45), 174 (10), 99 (75); HRMS-EI (*m*/*z*): M^+ calcd for $C_{19}H_{22}O_4$, 314.1518; found, 314.1516. Anal. calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05; found: C, 71.99; H, 7.05. Recrystallization from hexanes−EtOAc afforded crystals that were suitable for single crystal X-ray diffraction analysis; refer to the Supporting Information document for additional information.

Cell Culture. CHO-K1 cells stably transfected with opioid receptor subtypes μ, δ, and κ were a generous gift from Roth laboratories (University of North Carolina at Chapel Hill, Chapel Hill, N.C., U.S.A.). These cells were maintained at 37 °C and 5% CO_2 in a DMEM nutrient mixture supplemented with 2 mM L-glutamine, 10% fetal bovine serum, 0.5% penicillin−streptomycin, and either G418 (600 mg/mL) or hygromycin B (300 mg/mL). Membranes were prepared by scraping the cells in a 50 mM Tris-HCl buffer, homogenized by sonication and centrifuged for 40 min at 13650 rpm at 4 °C. These were kept at −80 °C until used for bioassays. Protein concentration was determined using Bio-Rad Protein Assay.[24]

Radio-ligand Binding for Opioid Receptor Subtypes. All compounds evaluated in the assay were run in competition binding against opioid receptor subtypes (δ, κ, μ). Opioid binding assays were performed under the following conditions: 10 μM of each compound was incubated with [^{3}H]-DAMGO (μ), [^{3}H]-U-69,593 (κ), or [^{3}H]-Enkephlin (δ) for 60 min in a 96-well plate. Tritium and membrane concentration for each cell line was determined by saturation experiments performed after each batch of membrane was scraped. The reaction was terminated via rapid vacuum filtration through GF/B filters presoaked with 0.3% BSA using a 96-well UniFilter followed by 10 washes of 50 mM Tris-HCl. Microplates were read using a liquid scintillation counter. Total binding was defined as binding in the presence of 1.0% DMSO. Nonspecific binding was the binding observed in the presence of 10 μM DAMGO (μ), nor-Binaltorphimine (κ), or DPDPE (δ). Specific binding was defined as the difference between total and nonspecific binding. Percent binding was calculated using the following formula:

$$100 - (\text{Binding of compound} - \text{Nonspecific binding}) \times 100 / \text{Specific binding}$$

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra corresponding to all reported compounds, as well as crystallographic information for carbocyclic analogue **40** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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