The [4 + 2] Addition of Singlet Oxygen to Thebaine: New Access to Highly Functionalized Morphine Derivatives via Opioid Endoperoxides

Dolores López, Emilio Quiñoá, and Ricardo Riguera*

Departamento de Química Orgánica, Facultad de Química, and Instituto de Acuicultura, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

ricardo@usc.es

Received March 2, 2000

The photooxidation of thebaine (**3**) with a sun lamp affords two main products: hydrodibenzofuran **10** (major) and benzofuran **11** (minor). The latter compound becomes predominant if a Hg lamp is used instead of a sun lamp. The formation of **10** proceeds via an endoperoxide intermediate that undergoes oxidation at the nitrogen atom. Protection of the nitrogen either by protonation or quaternization prevents its oxidation and thus the photooxidation of **3** in acid media constitutes a one-pot procedure for the preparation of 14-hydroxycodeinone **35**. Photooxidation of the thebaine ammonium salt **31** allows the isolation in good yields of the corresponding to thebaine endoperoxide **32**. The selective protection and reduction of the keto, aldehyde, and olefinic groups of hydrodibenzofuran **10** allowed the preparation of several diol and keto alcohol derivatives. This is the first report on the use of photooxidation to functionalize thebaine at C(6) and C(14) and also the first on the isolation of opioid endoperoxides.

Introduction

The search for new opioid derivatives that act on the CNS and have pain-relieving properties and are devoid of undesired side effects, such as addiction, has been the goal of a large number of scientists for many years. Consequently, a wide variety of modifications of the well-known alkaloids morphine (**1**), codeine (**2**) and thebaine (**3**) have been described. As a result, a large number of compounds with pharmacological properties (antitusive, analgesic, sedative, etc.) have been obtained, and many of them are commercially available and employed in a large number of diverse therapies.[1]

In previous investigations, thebaine (**3**) has played a very important role as a starting material for a number of reasons: it is readily available, its cost is lower than other opiates and, in addition, it contains a conjugated diene system at ring C, which has allowed the preparation of many pharmaceutical products by Diels−Alder cycloadditions with a large number of dienophiles. Classical examples of drugs prepared using this approach are etorphine[1e] (Immobilon, **4**), buprenorphine[2] (temgesic, buprenex, Buprex, Prefin, **5**) and many other adducts (Chart 1), reported mainly by Bentley.[3]

Surprisingly, no references are found in the literature on the cycloaddition to thebaine (**3**) of the well-known dienophile singlet oxygen ($^1O_2$). This is despite the fact that the expected cycloaddition, if it were to take place, would open a direct way for the introduction of oxygen atoms at C(6) and C(14) via the corresponding endoperoxide. These positions are especially relevant to analgesic activity,[4] as indicated by the clinical use of oxycodone (Eucodal, 14-hydroxydihydrocodeinone, **6**), oxymorphone (Numorphan, 14-hydroxydihydromorphone, **7**), and (−)-naloxone (**8**), as analgetics.[1] This gap in the chemistry of thebaine may well be attributed either to the difficulties usually associated with photooxygenation processes (i.e. complex mixtures and difficult work up due to the presence of the colored sensitizer) or to the high reactivity of the electron-rich methoxydiene moiety.

Nevertheless, a few reports have been published that describe the photooxidation of other morphine derivatives and these reactions have different outcomes. One example is the *N*-demethylation of codeine (**2**) to norcodeine (**9**).[5] The photooxidations of *N*-acyl morphine derivatives bearing a diene moiety in ring C (*N*-methoxycarbonyl-9,17-secothebaine, *N*-(ethoxycarbonyl)norcodeinone pyrrolidine dienamine and *N*-(ethoxycarbonyl)norcodeinone dienol acetate) have also been described.[6,7] In these cases, the photooxidation products were not isolated. Instead, the reaction mixtures were immediately submitted to reduction yielding 14-hydroxy derivatives.

* To whom correspondence should be addressed. FAX/Phone: 34-81-591091.

(1) (a) Lenz, G. R.; Evans, S. M.; Walters, D. E.; Hopfinger, A. J.; Hammond, D. L. *Opiate*s; Academic Press: Orlando, 1986. (b) Casy, A. F.; Parfitt, R. T. *Opioid Analgesics: Chemistry and Receptors*; Plenum Press: New York, 1986. (c) *Central Analgetics*; Lednicer, D., Ed.; John Wiley & Sons: New York, 1982. (d) Zimmerman, D. M.; Leander J. D. *J. Med. Chem.* **1990**, *33*, 895. (e) Bentley, K. W. *The Alkaloids, Chemistry and Pharmacology*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1971; Vol. XIII, p 75, and references therein. (f) *The Merck Index*; 12th ed. on CD-ROM, ver. 12: 2; Chapman & Hall/CRCnetBASE.

(2) Lewis, J. W. Discovery of Buprenorphine, a Potent Antagonist Analgesic. In *Medicinal Chemistry. The Role of Organic Chemistry in Drug Research*; Roberts, S. M., Price, B. J., Eds.; Academic Press: London, 1985; p 119, and references therein.

(3) (a) Bentley, K. W.; Hardy, D. G.; Meek, B. *J. Am. Chem. Soc.* **1967**, *89*, 3273. (b) id. *J. Am. Chem. Soc* **1967**, *89*, 3293. (c) id. *J. Am. Chem. Soc.* **1967**, *89*, 3312.

(4) Schmidhammer, H.; Schratz, A.; Schmidt, C.; Patel, D.; Traynor, J. R. *Helv. Chim. Acta* **1993**, *76*, 476.

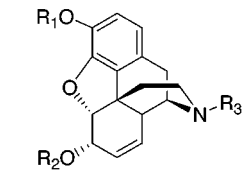
(5) Lindner, J. H. E.; Kuhn, H. J.; Gollnick, K. *Tetrahedron Lett.* **1972**, 1705.

(6) Schwartz, M. A.; Wallace, R. A. *J. Med. Chem.* **1981**, *24*, 1525.

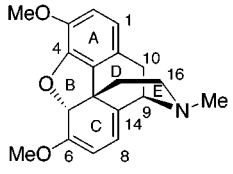
(7) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, 3257.

10.1021/jo000288a CCC: $19.00
Published on Web 07/01/2000

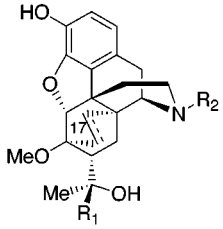
Chart 1



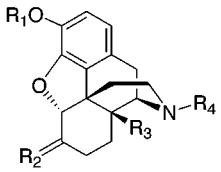
1 R_1 = H, R_2 = H , R_3= Me
2 R_1 = Me, R_2 = H , R_3= Me
9 R_1 = Me, R_2 = H , R_3 = H



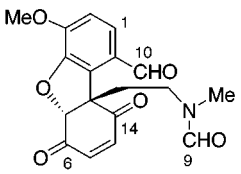
3



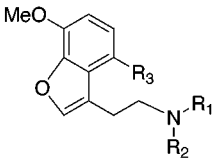
4 R_1 = $[CH_2]_2CH_3$, R_2 = Me, Δ^{17}
5 R_1 = $CH_2C(CH_3)_3$, R_2 =



6 R_1 = Me, R_2 = O, R_3 = OH, R_4 = Me
7 R_1 = H, R_2 = O, R_3 =OH, R_4 = Me
8 R_1 = H, R_2 = O, R_3 = OH, R_4 =



10



11 R_1 = Me, R_2 = CHO, R_3 = CHO
18 R_1 = Me, R_2 = CHO , R_3= CH_2OH
19 R_1 = Me, R_2 =Me , R_3 = CH_2OH

Table 1. ^{1}H and ^{13}C Chemical Shifts for the Two Rotamers in Equilibrium of Compound 10 in $CDCl_3$ at Room Temperature

	^{1}H NMR		^{13}C NMR		^{1}H NMR		^{13}C NMR
atom no.	major	minor	major/minor	atom no.	major	minor	major/minor
1	7.59 (d, J = 8.5 Hz)	7.57 (d, J = 8.5 Hz)	112.8/112.8	**10**	10.21 (s)	10.06 (s)	189.5/189.4
2	6.94 (d, J = 8.5 Hz)	6.94 (d, J = 8.5 Hz)	128.1/126.0	**11**			127.0/127.3
3			150.0/150.3	**12**			128.1/128.5
4			147.9/148.0	**13**			61.6/61.4
5	5.29 (s)	4.98 (s)	85.7/86.8	**14**			191.0/191.0
6			194.3/193.8	**15**	2.30−2.38 (m)	2.39−2.50 (m)	35.4/34.6
					2.64−2.72 (m)	2.52−2.60 (m)	
7	6.96 (d, J = 10.4 Hz)	6.92 (d, J = 11.1 Hz)	140.5/140.0	**16**	3.02−3.18 (m)	3.18−3.32 (m)	40.5/45.3
					3.45−3.75 (m)	3.45−3.75 (m)	
8	6.87 (d, J = 10.4 Hz)	6.88 (d, J = 11.1 Hz)	142.6/142.9	3-OMe	3.97 (s)	3.91 (s)	56.3/56.2
9	7.87 (s)	7.89 (s)	162.8/162.6	NMe	2.93 (s)	2.80 (s)	34.4/29.5

In a previous communication[8] we gave a short account of the photooxidative transformation of thebaine (**3**) to hydrodibenzofuran **10**. We wish to report here full details of this photooxidation under different conditions as well as the modifications performed on the photooxidation products.

Results and Discussion

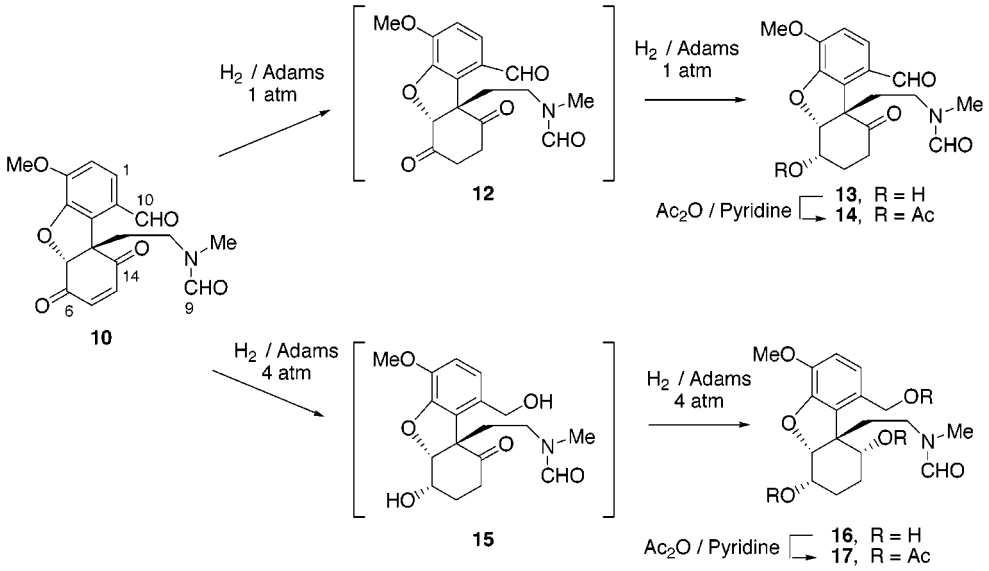
Our initial attempts to find a practical use for the photooxidation of thebaine consisted of a number of experiments in which oxygen was bubbled through solutions of thebaine (**3**) in different solvents (dioxane, ethyl acetate, butan-1-ol). The solutions were then submitted to irradiation with a 300 W sun lamp in the presence of methylene blue or rose bengal as photosensitizers and monitored by TLC. Complex mixtures of compounds resulted in all cases, the isolated yields of **10** and **11** were very low and the photosensitizers were found particularly difficult to separate from the reaction mixture.

Nevertheless, when the reaction was performed with *meso*-tetraphenylporphyrin (5, 10, 15, 20-tetraphenyl-21 *H*, 23 *H*-porphine; TPP) as sensitizer and dichloromethane as solvent, the reaction was much cleaner by TLC, TPP could be easily recovered from the reaction mixture and compounds **10** and **11** could be isolated in reasonable yields (62% and 5%, respectively) by column chromatography. The structures of the two products were established on the basis of spectroscopic data and chemical transformations.

Structure of the Photooxygenation Products. Compound **10**, a pale yellow solid, showed a molecular ion (HRMS) at *m/z* 343.1055, indicating the molecular formula $C_{18}H_{17}NO_6$. The ^{1}H and ^{13}C NMR spectra of this compound (Table 1) were complicated by the fact that a pair of signals was observed for each hydrogen and each carbon present in the molecule. The ratio between the two sets of signals varied with the solvent (2:1 in $CDCl_3$ and C_6D_6; 1:1 in DMSO-d_6 at 298 K) and also with the temperature. A complete coalescence to a single set of signals in ^{1}H NMR was observed at 393 K. These results could be attributed to the presence of two rotamers in equilibrium, generated by the presence of a formamide group.

Analysis of the 1D- and 2D-NMR spectra of **10** allowed the assignment of all the signals in the spectra and the identification of all the spin systems. These data, along with a comparison of the chemical shifts with those of thebaine and other opiates, helped to establish that rings A and B of **10** remained unchanged, that rings D and E were opened, and that ring C included a but-2-ene-1,4-dione moiety. The two remaining carbonyl groups were assigned to a benzaldehyde on ring A and to a formamide group that completed the structure. The IR and UV spectra showed bands that are in agreement with the

Scheme 1



functional groups and chromophores assigned to the molecule. The carbon framework and functional groups proposed for **10** were further confirmed by a series of hydrogenation reactions, which are summarized in Scheme 1.

Smooth catalytic hydrogenation of **10** (Adams, 1 atm, rt) allowed the selective reduction of the carbonyl at C(6) to yield keto alcohol **13**, as a single isomer, in quantitative yield. Compound **13** was further transformed into its acetate **14**. Diketone **12**, an intermediate in this reaction, can be isolated if the reaction is stopped before completion, confirming that the double bond is hydrogenated first.

At higher hydrogen pressures (4 atm, rt) the carbonyl groups at C(10) and C(14) also undergo hydrogenation to give 6,10,14-triol **16** as single product, which can be transformed into its triacetate **17** by standard treatment. 6,10-Diol **15** can be isolated during the course of the reaction, indicating that the benzaldehyde group is reduced before the carbonyl group at C(14), which is less prone to hydrogenation.

These experiments show that in this polyfunctionalized structure the Δ^7 double bond is the most sensitive to hydrogenation followed, in order, by the carbonyl groups at C(6), C(10), and C(14). In addition, it is interesting to note that both keto groups at ring C are hydrogenated in a highly stereoselective way to give exclusively one of the four possible stereoisomers (the *cis*-1,4-diol **16**), indicating that the acyclic ethylamine chain does not impede the approach of the molecule to the catalyst surface. The regio- and stereochemistry of the reductions were determined by extensive use of 1D and 2D NMR studies of the products and their corresponding acetates, including selective decouplings and analysis of the *J* values.

The second product formed in the photooxygenation of thebaine was obtained in low yield and identified as the benzofuran **11**. This is an optically inactive compound; its NMR spectra suggest a much simpler structure than the major reaction product **10**, although it still showed two sets of signals for hydrogen and carbon atoms in a similar way to those due to rings A and B of the starting material. Spectroscopic data and hydride reductions to **18** and **19** confirmed the structure proposed.

The Formation of 10 from Thebaine. The mechanism of the formation of **10** from **3** was investigated next. Inspection of the structure of **10** indicated that any mechanism proposed should justify the incorporation of two molecules of O_2 into the thebaine framework and also the breaking of rings D and E along with the concomitant functionalization, suggesting that a multistep transformation is involved.

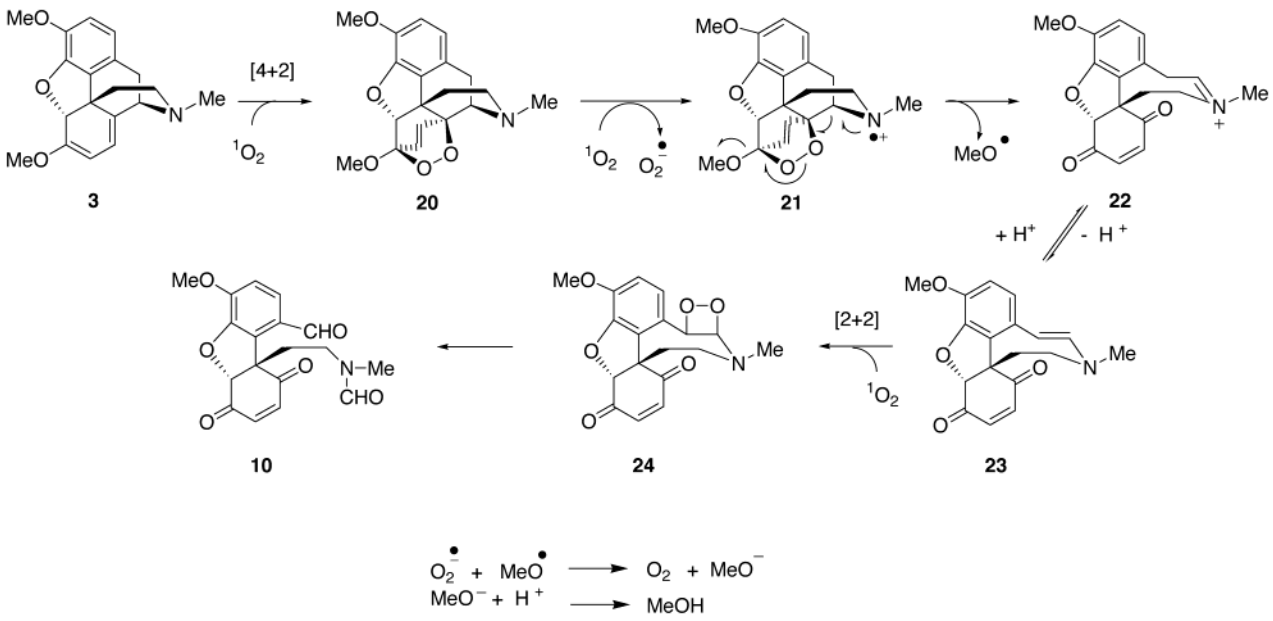
The well-known dienophile character of singlet oxygen together with the presence of the electron-rich 1,3-diene on ring C of thebaine strongly suggested a [4+2] cycloaddition to be the most likely starting point for the process. The fact that the resulting endoperoxide (**20**) is also part of a ketal moiety (at C-6) must make it more labile than usual endoperoxides: the methoxy group can act as a leaving group and, if the peroxide bridge were broken, a ketone would be formed at C-6. The oxidation of the tertiary nitrogen to an amino radical cation (**21**) by a second molecule of oxygen could be the trigger for such a transformation through the cleavage of the C-9/C-14 bond. The immonium intermediate **22** already has the correct functionalization for ring C. The isomerization of the immonium double bond to give the styrene/enamine **23** leads to an extremely electron rich double bond due to the presence of both the nitrogen and the *p*-methoxyphenyl group. This double bond can subsequently undergo a [2+2] cycloaddition with a third molecule of $^1O_2$ to form a 1,2-dioxetane intermediate (**24**). Finally, the opening of the four-membered ring causes the cleavage of the C-9/C-10 bond and the formation of the two formyl groups that are present in **10**. The overall transformation is depicted in Scheme 2.[9]

To demonstrate the plausibility of the above mechanistic pathway, a number of experiments were performed. First, in an attempt to detect the intermediates involved, for example endoperoxide **20**, the reaction was carried

(8) López, D.; Quiñoá, E.; Riguera, R. *Tetrahedron Lett.* **1994**, *35*, 5727. Three patents have been issued: Riguera, R.; Quiñoá, E.; López, D., Patents P9602716, P9602717 and P9602718, 1996.

(9) For a general reference on peroxides see: Clennan, E. L.; Foot, C. S. Endoperoxides. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992. See also: Akaeshi, T.; Ando, W. Peroxides from Photosentitized Oxidation of Hetero Atom Compounds. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992.

Scheme 2



out at low temperature (243 K). However, no intermediates were isolated or detected by NMR.

As already indicated above, the two most likely reasons for the instability of endoperoxide **20**, if it is indeed generated, are the presence of the ketal function at C-6 and the nitrogen lone pair. We therefore decided to block alternately the two possible sites of reaction (the diene and the amine) and then to assess the course of the transformation in each case.

Thus, reaction of thebaine with methyl vinyl ketone yielded the Diels–Alder adduct thevinone **25**,[10] which was submitted to the standard photooxidation conditions and afforded the *N*-demethylated derivative (northevinone, **26**) in 73% yield. This result confirms that the nitrogen does undergo oxidation to the amine radical cation. When ring C is blocked, the reaction leads to the loss of the *N*-methyl group by hydrolysis of the resulting immonium ion. An alternative mechanism for the transformation of thebaine into **10**, based on the involvement of the lone pair of the amine group to open the endoperoxide in a retro-Mannich-like reaction with methoxy as the leaving group, does not now seem reasonable.

We proceeded to investigate the effect of the deactivation of the lone pair of the thebaine nitrogen atom through quaternization with a methylating agent (such as methyl iodide) or by its transformation into an *N*-oxide with MCPBA.[11] The products (thebaine methylammonium iodide **27** and thebaine *N*-oxides **28** and **29**) were submitted to photooxygenation. However, the corresponding endoperoxides were not detected and complex mixtures of products were obtained instead. Only the salt **30** was identified in the reaction of **27**, suggesting that the endoperoxide was actually formed but then rapidly transformed into **30**.

Thebaine Peroxides. Finally, treatment of thebaine with methyl triflate gave **31** as a crystalline salt that, when submitted to photooxygenation, gave endoperoxide **32** in almost quantitative yield.[12] In contrast to the elusive endoperoxide **20**, compound **32** is perfectly stable for several weeks. When dissolved in dilute TFA at 25 °C, **32** does not decompose for several hours, but if this solution is gently heated, **32** is transformed into keto alcohol **33** in 7 h. If this transformation is carried out in an NMR tube and monitored by ^1H or ^{13}C NMR spectroscopy, the presence of hydroperoxide **34** as an intermediate is observed. Indeed, if the reaction is stopped after 90 min, **34** can be isolated from the reaction mixture as the sole product. Hydroperoxide **34** shows NMR data that are almost identical to those of keto alcohol **33**. The main difference is found in the chemical shift of C(14): 81.1 ppm in **34** versus 70.0 ppm in **33**. Addition of Ph_3P to **34** in the NMR tube led, as one would expect, to the disappearance of the signals corresponding to the hydroperoxide and its rapid transformation into keto alcohol **33**. (+)-FAB and EIMS further confirmed the difference of one oxygen between the two compounds.

One-Pot Procedure to 14-Hydroxycodeinone. In a practical extension of these studies, we tried to transform thebaine directly into the keto alcohol by carrying out the photooxidation in acid media. Thus, when thebaine was photooxygenated in a 1% TFA/CH_2Cl_2 solution, 14-hydroxycodeinone (oxycodone)[1a,b] salt **35** was isolated as the sole reaction product in 61% yield. This constitutes an excellent one-pot method for the simultaneous functionalization at C(6) and C(14) of thebaine and its analogues (Chart 2).

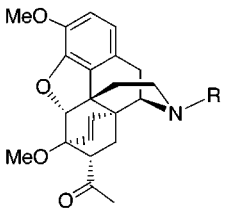
On the Origin of 11. Once a reasonable mechanistic pathway had been established to explain the generation of **10** from thebaine, our next goal was to determine the mechanistic relationship between thebaine, **10** and **11**. To this end, a series of experiments with thebaine (**3**) and hydrodibenzofuran **10** as starting materials was carried out. These experiments indicated **10** to be the precursor of **11** and ruled out a direct transformation of

(10) Bentley, K. W.; Hardy, D. G.; Meek, B. *J. Am. Chem. Soc.* **1967**, *89*, 3267.

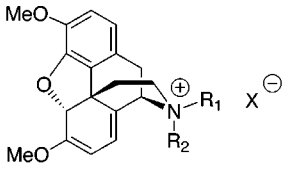
(11) (a) Phillipson, J. D.; Handa, S. S.; El-Dabbas, S. W. *Phytochemistry* **1976**, *15*, 1297. (b) Theus, H. G.; Jansen, R. H. A. M.; Biessels, H. N. A.; Salemink, C. A. *J. Chem. Soc., Perkin Trans.* **1984**, 1701. (c) Caldwell, G. W.; Gautier, A. D.; Mills, J. E. *Magn. Reson. Chem.* **1996**, *34*, 505.

(12) The stereoselectivity of Diels–Alder reactions of thebaine is known to produce exclusively the adducts formed at the less hindered face of the diene (see ref 1e). The transformation of **32** into **35** (a known compound), confirmed the assigned stereochemistry of **32**.

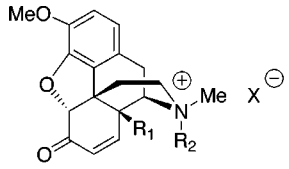
Chart 2



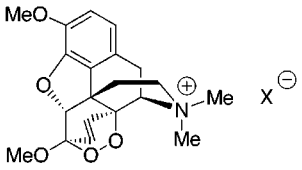
25 R = Me
26 R = H



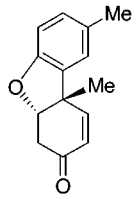
27 R_1 = Me, R_2 = Me, X^- = I^-
28 R_1 = Me, R_2 = O^-
29 R_1 = O^-, R_2 = Me
31 R_1 = Me, R_2 = Me, X^- = $CF_3SO_3^-$



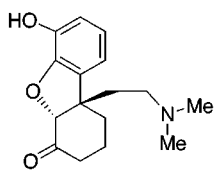
30 R_1 = OH, R_2 = Me, X^- = I^-
33 R_1 = OH, R_2 = Me, X^- = $CF_3SO_3^-$
34 R_1 = OOH, R_2 = Me, X^- = $CF_3SO_3^-$
35 R_1 = OH, R_2 = H, X^- = $CF_3CO_2^-$



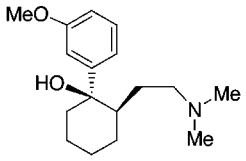
32 X^- = $CF_3SO_3^-$



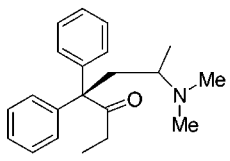
36



37



38



39

Table 2. Photooxidative, Photochemical, and Thermal Experiments Carried out To Determine the Origin of Compound 11

		conditions[a]					
			light source				
entry	substrate	atmosphere[b]	sun lamp	Hg lamp	sensitizer (TPP)	*T* (°C)	products (yields, %)
1	**3**	O_2	yes		yes	40	**10** (62) + **11** (<5)
2	**3**	Ar		yes		40	complex mixture[c]
3	**3**	O_2		yes	yes	20	**11** (57)[d]
4	**10**	O_2	yes		yes	40	**11** (85)
5	**10**	O_2	yes			40	**11** (87)
6	**10**	Ar	yes			40	**11** (88)
7	**10**	Ar		yes		40	**11** (95)
8	**10**	O_2				20	no reaction
9	**10**	O_2				40	no reaction
10	**10**	Ar				20	no reaction
11	**10**	Ar				40	no reaction
12	**10**	Ar				66[e]	no reaction
13	**10**	Ar				120[f]	decomposition[c]
14	**10**					110[g]	no reaction

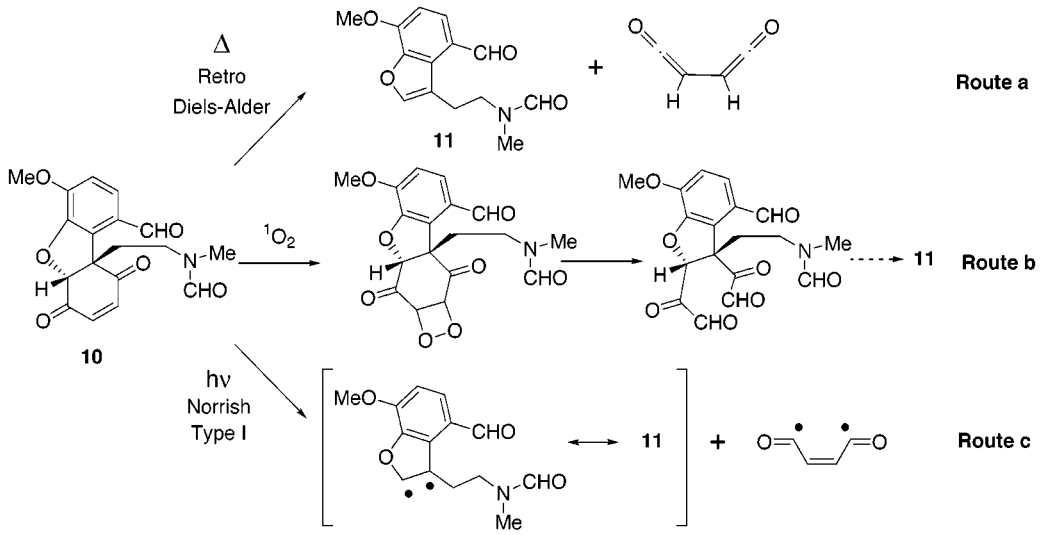
[a] All the reactions were carried out in CH_2Cl_2 as solvent except entries 12, 13, and 14. [b] The reaction was carried out under continuous gas bubbling. [c] Neither **10** nor **11** was detected. [d] The formation of compound **10** as intermediate and its convertion into **11** can be observed while monitoring this reaction. [e] In THF. [f] In DMSO. [g] In a sealed tube with toluene as solvent.

thebaine into **11** (Table 2). In these experiments, the roles played by different reaction variables (the photoirradiation source, oxygen, the nature of the photosintetizer and the temperature) were investigated in order to decide which of the three plausible possibilities was most likely to account for the formation of **11**. The three main possibilities are (a) a thermal retro Diels−Alder reaction (retro [4+2]), (b) a direct photooxygenation of the double bond (photochemical [2+2]) followed by the breaking of ring C, and (c) a double Norrish type I photochemical reaction (routes a, b and c in Scheme 3, respectively).

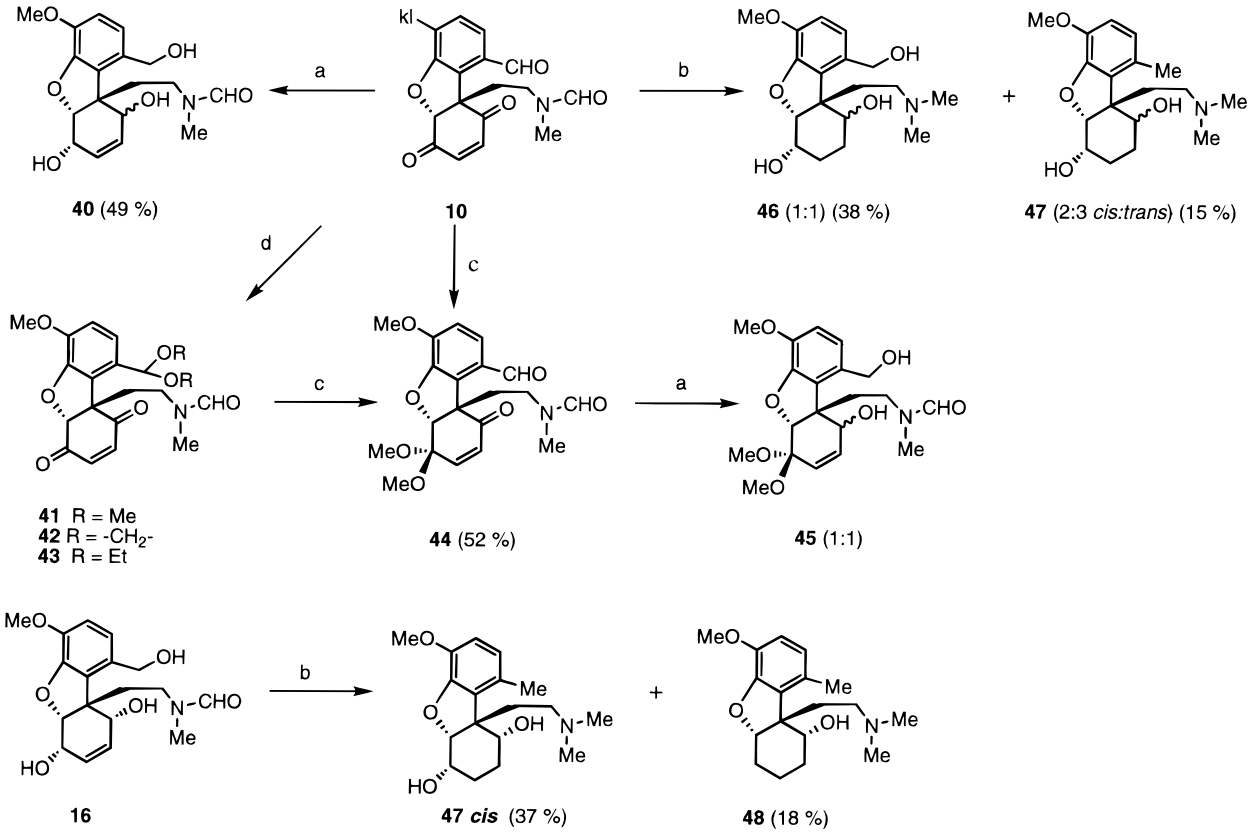
Pathways a and b can be discounted on the basis of experiments that showed that neither heating (thermal process, entries 8−14, Table 2), oxygen (entries 6 and 7) or the presence of a sensitizer ($^1O_2$ addition, entries 5−7) are necessary for this reaction to take place. Entries 6 and 7 show that only light is necessary, clearly indicating that the photochemical α-cleavage of the carbonyl groups (Norrish type I reaction, route c) is a satisfactory explanation for the conversion of **10** into **11**. In fact, the sun lamp photooxidation of thebaine to **10** and the photochemical cleavage of **10** to give **11** can be conveniently represented as a single chemical operation: photooxidation of thebaine with a mercury lamp and TPP as a sensitizer in CH_2Cl_2 under argon afforded **11** in 57% yield (entry 3, Table 2).

Structural Modifications on 10. Once the structure of the products and the mechanistic pathways were

Scheme 3



Scheme 4[a]



[a] Key: (a) $NaBH_4$/MeOH; (b) $NaBH_4/BF_3$; (c) HCl/MeOH/Δ; (d) **41**: MeOH, 30 h (quantitative) or glycol/MeOH/CITMS (88%); **42**: glycol/C_6H_6/*p*TsOH (84%) or glycol/toluene/oxalic acid (84%); **43**: glycol/*p*TsOH/$CH(OEt)_3$ (70%).

known, the transformation of the carbonyl and the formamide groups of **10** into the pharmacologically more important hydroxy and amino groups[13] was investigated.

To this end, selective protection of the keto groups was performed and hydride reductions were carried out. The high degree of functionalization of the starting material rendered these processes difficult and in most cases mixtures of epimers were generated in moderate yields. Scheme 4 shows a selection of these transformations and the derivatives obtained.

Conclusion

Several modulations of the framework of morphine and its analogues have been carried out in the search for new pharmacologically useful opiates. The cleavage of ring B leads to morphinanes, whereas cleveage of rings B and C leads to benzomorphanes. The maintenance of rings A and E is the exclusive origin of a whole series of

(13) The importance of the presence of free amino and hydroxy groups in opioids and their interactions with the opiate receptors is well documented, with numerous pharmacologically active derivatives incorporating such groups within their structures. See ref 1.

phenylpiperidines whereas diphenylpropylamines only retain ring A and the ethylamine chain.[14] A different, and very rarely explored, modification is based on the cleavage of rings D and E, which leads to hydrodibenzofurans that are structurally similar to Pummerer's ketone (**36**). This class of compound is represented by **37**, which showed selectivity for μ and κ receptors in binding assays.[15]

Partially reduced dibenzofurans[16] and structurally related compounds, such as tramadol (**38**)[17] and methadone (**39**),[18] are of interest due to their analgesic activity and their use in the treatment of opiate-dependent drug addiction, respectively. Although several methods describe the preparation of this class of compound, all involve multi-stage synthesis and are nonstereoselective. The photooxidations of thebaine described here represent the simplest access to functionalized hydrodibenzofurans and to 14-hydroxycodeinone described to date. In addition, the study constitutes the first report on the isolation of an endoperoxide of a morphine alkaloid and its use in a synthetic method.

Experimental Section

General Methods. Reagents were purchased from Aldrich and used without purification. Reaction solvents were purified according to standard procedures. Chromatographic solvents were used without purification. Thin-layer chromatography was carried out on TLC aluminum-backed sheets of silica gel 60 F_{254}. Visualization was achieved with Liebermann or Hanessian reagent or iodine. Flash column chromatography was gravity fed and carried out with silica gel 60 (230−240 mesh). NMR spectra were recorded at 250 or 300 MHz. Multiplicity of carbon signals was determined by DEPT experiments. Melting points are uncorrected.

General Procedure for the Photooxygenation.

Method A. Oxygen was bubbled through a solution of the corresponding compound and *meso*-tetraphenylporphyrin (5,10,15,20-tetraphenyl-21*H*,23*H*-porphine; TPP) in CH_2Cl_2, in a round-bottomed flask fitted with a cooling water-jacket. The mixture was irradiated from a distance of 45 cm with an Osram Ultra-Vitalux sun lamp (300 W).

Method B. Oxygen was bubbled through a solution of the corresponding compound and TPP in CH_2Cl_2. The solution was irradiated using a 400 W high-pressure mercury lamp in a Pyrex immersion apparatus until TLC analysis [silica gel, CH_2Cl_2/MeOH (95:5) or ethyl acetate] showed that all the starting material had been consumed.

Preparation of Compound 10 from Thebaine (3). Thebaine (**3**) (200 mg, 0.64 mmol) and TPP (20 mg, 0.03 mmol) were dissolved in 150 mL of CH_2Cl_2, and the solution was irradiated, as described in method A, until TLC indicated that no starting material remained (90 min). Removal of the solvent under reduced pressure, followed by flash chromatography [hexane/CH_2Cl_2 (50:50) to CH_2Cl_2/MeOH (98:2)], afforded 136 mg (62%) of **10** as a yellow solid.

Compound 10. ^{1}H NMR (250.13 Mz) and ^{13}C NMR in $CDCl_3$ can be found in Table 1. ^{1}H NMR [250.13 Mz, DMSO-d_6, 25 °C, major rotamer, δ (ppm)]: 10.09 (s, 1H), 7.84 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.03 (1H), 7.02 (1H), 5.39 (s, 1H), 3.85 (s, 3H), 3.3−3.0 (m, 2H), 2.6−2.2 (m, 2H), 2.64 (s, 3H). ^{1}H NMR [250.13 Mz, DMSO-d_6, 25 °C, minor rotamer, δ (ppm)]: 10.14 (s, 1H), 7.84 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.01 (s, 1H), 7.02 (s, 1H), 5.35 (s, 1H), 3.85 (s, 3H), 3.3−3.0 (m, 2H), 2.6−2.2 (m, 2H), 2.83 (s, 3H). ^{1}H NMR [250.13 Mz, DMSO-d_6, 140 °C, two rotamers, δ (ppm)]: 10.17 (s, 1H), 7.88 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.98 (s, 2H), 5.33 (s, 1H), 3.93 (s, 3H). IR ($CHCl_3$): υ_{max} 1670, 1610, 1570, 1290, 1120, 1090 cm^{-1}. UV ($CHCl_3$): λ_{max} 318 (ϵ = 5509), 280 (ϵ = 8870), 244 (ϵ = 13664). CD ($c = 3.4 \times 10^{-3}$ M, CH_3OH) $\lambda_{max/nm}$ ($\Delta\epsilon$/cm^2 mol^{-1}): 358 (37.74), 322 (−150.19), 286 (43.60), 261 (−28.14), 234 (−87.41), 221 (11.44). Mp (amorphous solid): 103 °C. $[\alpha]_D$: −105.3° (*c* 7.2 mg/mL, $CHCl_3$). FAB$^+$(NBA): 344 (M + H, 100), 314 (13), 285 (28), 273 (18), 258 (21), 243 (14), 203 (21). MS (EI): 343 (15), 315 (8), 284 (32), 272 (29), 271 (49), 269 (11), 258 (22), 257 (38), 256 (45), 255 (10), 244 (21), 243 (27), 228 (11), 202 (43), 202 (100). HRMS (EI) $C_{18}H_{17}NO_6$ calcd 343.1051, obsd 343.1055, Δm 0.4 mu. Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.96; N, 4.08; H, 5.00. Found: C, 62.95; N, 4.10; H, 4.98.

Preparation of Compound 11 from 10. (a) Hydrodibenzofuran **10** (30 mg, 0.087 mmol) was dissolved in 50 mL of CH_2Cl_2. The solution was irradiated as described in method A, without oxygen or TPP, until TLC (AcOEt) indicated that no starting material remained (7 h). Removal of solvent under reduced pressure followed by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH [98:2]), afforded 20 mg of **11** (88% yield). **(b)** Hydrodibenzofuran **10** (35 mg, 0.100 mmol) was dissolved in 50 mL of CH_2Cl_2. The solution was irradiated as described in method B, without oxygen or TPP, until TLC (AcOEt) indicated that no starting material remained (45 min). Removal of solvent under reduced pressure followed by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH [98:2]), afforded 26.2 mg of **11** (95% yield).

Compound 11. ^{1}H NMR [250.13 Mz, $CDCl_3$, (major rotamer), δ (ppm)]: 9.97 (s, 1H), 7.86 (s, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 6.95 (d, J = 8.2 Hz, 1H), 4.10 (s, 3H), 3.59−3.47 (m, 2H), 3.28−3.23 (m, 2H), 2.97 (s, 3H). ^{13}C NMR [$CDCl_3$, (major rotamer), δ (ppm)]: 191.3, 163.3, 151.8, 146.0, 145.6, 134.8, 131.5, 124.6, 118.9, 105.8, 56.3, 50.9, 29.9, 25.4. ^{1}H NMR [250.13 Mz, $CDCl_3$, (minor rotamer), δ (ppm)]: 10.03 (s, 1H), 7.85 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.56 (s), 6.93 (d, J = 8.2 Hz, 1H), 4.09 (s, 3H), 3.59−3.47 (m, 2H), 3.28−3.23 (m, 2H), 3.01 (s, 3H). ^{13}C NMR [$CDCl_3$, (minor rotamer), δ (ppm)]: 191.0, 163.0, 150.6, 146.0, 145.7, 133.7, 131.6, 124.7, 118.9, 105.7, 56.3, 45.3, 35.0, 23.5. IE: 523 (19), 262 (100), 264 (8). IR ($CHCl_3$): υ_{max} 2967, 2903, 2851, 1651, 1617, 1562, 1418, 1396 cm^{-1}. UV ($CHCl_3$) λ_{max}: 304, 298, 246. FAB$^+$(glycerol): 263 (M + H, 19), 262 (100), 234 (7), 203 (9), 175 (22), 243 (14), 203 (21). FAB$^+$(NBA): 262 (37), 207 (24), 175 (22), 149 (62). MS (EI): *m*/*z* 261 (6), 243 (8), 232 (6), 204 (4), 203 (15), 202 (100), 189 (29). HRMS (EI): $C_{14}H_{15}NO_4$ calcd 261.1001, obsd 261.1005, Δm 0.4 mu. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; N, 5.36; H, 5.78. Found: C, 64.34; N, 5.33; H, 5.77.

Preparation of Compound 26. The methyl vinyl ketone adduct of thebaine **25** (60 mg, 0.157 mmol) was combined with TPP (3 mg, 0.004 mmol) in 50 mL of CH_2Cl_2, and the solution was irradiated and oxygenated for 11h 20 min. Removal of solvent under reduced pressure followed by flash chromatography afforded 57 mg (98%) of the N-demethylated methyl vinyl adduct of thebaine **26**.

Compound 26. ^{1}H NMR [250.13 MHz, $CDCl_3$, δ (ppm)]: 6.64 (d, J = 8.2 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H), 5.92 (d, J = 8.9 Hz, 1H), 5.53 (d, J = 8.9 Hz, 1H), 4.55 (s, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 3.3−1.2 (m, 10H), 2.15 (s, 3H). ^{13}C NMR [$CDCl_3$, δ (ppm)]: 209.0, 147.9, 141.8, 135.6, 133.8, 127.8, 126.0, 119.4, 113.5, 95.0, 81.1, 60.0, 56.5, 53.4, 50.4, 47.3, 45.4, 43.1, 33.1, 30.5, 29.8, 22.5. MS (EI): *m*/*z* 368 (3), 367 (8), 352 (2), 324 (3), 296 (1), 215 (6), 214 (8), 192 (11), 189 (6), 150 (12), 148 (13), 121 (16), 115 (9). HRMS (EI): $C_{22}H_{25}NO_4$ obsd 367.1770, calcd 367.1784, Δm 1.4 mu.

Preparation of Compound 31. To a stirred solution of thebaine **(3)** (200 mg, 0.64 mmol) in dry nitromethane (4 mL)

(14) Reference 1c, pp 139−213.

(15) Labidalle, S.; Zhang, Y. M.; Moskowitz, H.; Thal, C.; Miocque, M.; Degryse, M.; Fortin, M.; Delevallée, F. *Eur. J. Med. Chem.* **1989**, *24*, 385.

(16) (a) Zhang, Y. M.; Boukaache, A.; Mayrargue, J.; Moskowitz, H.; Miocque, M.; Thal, C. *Synth. Commun.* **1992**, *22*, 1403. (b) Labidalle, S.; Min, Z. Y.; Reynet, A.; Moskowitz, H.; Vierfond, J.-M.; Miocque, M. *Tetrahedron* **1988**, *44*, 1159. (c) id. *Tetrahedron* **1988**, *44*, 1171.

(17) (a) Salazar, L. A.; Martínez, R. V.; López-Muñoz, F. *J. Drug Dev. Res.* **1995**, *36* (3), 119. (b) Raffa, R. B. *Am. J. Med.* **1996**, *101*(1A), 40S.

(18) (a) Kreek, M. J. *Pharmacol. Biochem. Behav.* **1997**, *573*, 551. (b) Brackbill, R. M.; MacGowan, R. J.; Rugg, D. *Am. J. Drug. Alcohol Abuse* **1997**, *233*, 397.

at 0 °C, methyl trifluoromethanesulfonate (0.20 mL, 1.8 mmol) was added dropwise via syringe. The mixture was stirred for 30 min at 0 °C. A 25 mL portion of ethyl ether was added, and 281 mg (92%) of the salt **31** was obtained as a white crystalline precipitate.

Compound 31. ^{1}H NMR [250.13 Mz, $CDCl_3$, δ (ppm)]: 6.60 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.86 (d, J = 6.7 Hz, 1H), 5.24 (s, 1H), 4.98 (d, J = 6.7 Hz, 1H), 4.32 (d, J = 6.7 Hz, 1H), 3.69 (s, 3H), 3.56 (m, 1H), 3.48 (s, 3H), 3.31 (m, 2H), 3.15 (s, 3H), 3.09 (s, 3H), 2.99 (d, J = 7.7 Hz, 1H), 2.28 (m, 1H), 1.80 (m, 1H). ^{13}C NMR [$CDCl_3$, δ (ppm)]: 154.5, 144.2, 143.3, 130.6, 122.5, 121.5, 120.6, 119.9, 114.2, 94.9, 87.2, 71.6, 56.0, 54.9, 55.3, 51.9, 49.2, 43.0, 31.7, 30.3. CD ($c = 1.4 \times 10^{-3}$ M, CH_3OH) $\lambda_{max./nm}$ ($\Delta\epsilon$/cm^2 mol^{-1}): 286 (−5.85), 229 (4.90). Mp: 213−215 °C. $[\alpha]_D$: 96.9° (c 0.64 mg/mL, $CHCl_3$). FAB$^+$-(NBA): 326 (M − OTf, 100). MS (EI) m/z 326 (2), 325 (7), 254 (7), 239 (6), 165 (4), 58 (100). HRMS (EI): ($C_{20}H_{24}NO_3$) calcd 326.1756, obsd 326.1756, Δm 0.0 mu.

Preparation of Compound 32. A solution of **31** (62 mg, 0.13 mmol) and 10 mg (0.015 mmol) of TPP in 40 mL of CH_2-Cl_2, was irradiated and oxygenated following method A for 2 h. The mixture was concentrated to 15 mL under reduced pressure and ethyl ether was added, affording 56 mg (85%) of the endoperoxide **32** as a white solid precipitate.

Compound 32. ^{1}H NMR [250.13 Mz, $CDCl_3$, δ (ppm)]: 6.67 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.23 (d, J = 9.1 Hz, 1H), 6.06 (d, J = 9.1 Hz, 1H), 4.58 (s, 1H), 4.33 (d, J = 6.9 Hz, 1H), 3.94−3.10 (m, 4H), 3.48 (s, 3H), 3.47 (s, 3H), 3.32 (s, 3H), 3.23 (s, 3H), 2.65−2.50 (m, 1H), 2.22−2.14 (m, 1H). ^{13}C NMR [$CDCl_3$, δ (ppm)]: 145.7, 144.4, 136.7, 130.8, 129.6, 121.9, 120.2, 117.1, 96.0, 90.8, 80.4, 69.3, 58.5, 55.8, 51.9, 49.4, 46.8, 28.0, 26.3. UV ($CHCl_3$) υ_{max}: 418 (ϵ = 74), 292 (ϵ = 209), 242 (ϵ = 645). CD ($c = 1.5 \times 10^{-3}$ M, CH_3OH) $\lambda_{max./nm}$ ($\Delta\epsilon$/cm^2 mol^{-1}): 292 (−1.72), 251 (0.99), 226 (−9.4), 207 (5.52). Mp (amorphous solid): 213−215 °C. $[\alpha]_D$: −13.3° (c 0.75 mg/mL, $CHCl_3$). FAB$^+$(NBA): 358 (M − OTf, 100). MS (EI): m/z 357 (2), 343 (1), 256 (1), 254 (1), 240 (2), 58 (100). MS (IE): 358 (M − OTf, 100). HRMS (EI): ($C_{20}H_{24}NO_5$) calcd 358.1654, obs 358.1654, Δm 0.0 mu. Anal. Calcd for $C_{20}H_{24}NO_5$: C, 49.69; N, 2.76; H, 4.78; S, 6.31. Found: C, 49.68; N, 2.74; H, 4.75; S, 6.28.

Preparation of Compounds 33 and 34. A solution of the endoperoxide **32** (20 mg, 0.039 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (0.2 mL) was acidified with trifluoroacetic acid to pH = 4. The mixture was refluxed for 7 h and the solvent removed at reduced pressure until dryness, affording the hydroxycodeinone salt **33** quantitatively. This reaction was monitored by ^{1}H and ^{13}C NMR spectroscopy. At shorter reaction times (90 min), hydroxyperoxide **34** was obtained as the sole product. Its isolation was carried out as follows: the solvent was evaporated at reduced pressure until dryness, an the crude dissolved in 3 mL of CH_2Cl_2. Slow addition of ethyl ether gave a precipitate of pure **34** as a white solid. The structure of **34** was corroborated by reaction with Ph_3P, in the NMR tube, giving compound **33**.

Compound 33. ^{1}H NMR [250.13 Mz, $CDCl_3$, δ (ppm)]: 6.89 (d, J = 10.1 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 5.99 (d, J = 10.1 Hz, 1H), 4.88 (s, 1H), 4.08 (m, 1H), 3.94−3.10 (m, 4H), 3.65 (s, 3H), 3.30 (s, 3H), 3.20 (s, 3H), 2.65−2.50 (m, 1H), 2.22−2.14 (m, 1H). ^{13}C NMR [$CDCl_3$, δ (ppm)]: 193.7, 146.3, 144.4, 143.3, 132.5, 128.9, 120.9, 120.6, 116.2, 85.9, 73.3, 70.0, 59.6, 59.0, 50.9, 46.2, 28.3, 24.3. UV ($CHCl_3$) λ_{max}: 330, 286, 244. $[\alpha]_D$: −42.1° (c 3.2 mg/mL, CH_2Cl_2/MeOH [85:15]). FAB$^+$(NBA): 328 (M − OTf, 100). MS (EI): m/z 328 (M − OTf, 6), 327 (8), 313 (9), 257 (5), 256 (22), 241 (13), 228 (6), 58 (100). HRMS (EI): ($C_{19}H_{22}NO_4$) calcd 328.1548, obsd 328.1556, Δm 0.8 mu.

Compound 34. ^{1}H NMR [250.13 Mz, $CDCl_3$/CD_3OD, δ (ppm)]: 6.75 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 10.1 Hz, 1H), 6.22 (d, J = 10.0 Hz, 1H), 4.88 (s, 1H), 4.33 (m, 1H), 3.92−2.99 (m, 4H), 3.77 (s, 3H), 3.38 (s, 3H), 3.27 (s, 3H), 2.82−2.72 (m, 1H), 1.97−1.91 (m, 1H). ^{13}C NMR [$CDCl_3$/CD_3OD, δ (ppm)]: 193.2, 144.3, 139.5, 135.7, 128.1, 120.6, 120.5, 116.2, 87.1, 81.1, 70.2, 58.8, 57.2, 56.5, 45.2, 28.3, 24.2. FAB$^+$(NBA): 345 (15), 344 (75), 329 (21), 328 (100). IE: m/z 344 (M − OTf, 1), 343 (2), 342 (2), 341 (6), 328 (17), 327 (19), 326 (10), 315 (5), 314 (9), 313 (39), 311 (7), 300 (8), 298 (6), 270 (10), 258 (6), 256 (44), 241 (35), 225 (59).

Preparation of Compound 35. Thebaine **(3)** (35 mg, 0.11 mmol) was combined with TPP (5 mg, 0.03 mmol) in 50 mL of CH_2Cl_2. The solution was acidified with trifluoracetic acid to pH = 4 and irradiated and oxygenated following method A for 55 min. The mixture was concentrated to 20 mL under reduced pressure, and then 50 mL of ethyl ether was added. The resulting precipitate was decanted and washed with ethyl ether, affording 25 mg of the trifluoroacetate salt **35** (61%).

Compound 35. ^{1}H NMR [250.13 Mz, $CDCl_3$, δ (ppm)]: 6.73 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 11.0 Hz, 1H), 6.14 (d, J = 10.4 Hz, 1H), 4.79 (s, 1H), 3.94 (m, 1H), 3.82 (s, 3H), 3.67−3.25 (m, 2H), 3.01 (s, 3H), 2.90−2.76 (m, 2H), 1.83−1.78 (m, 2H). ^{13}C NMR [$CDCl_3$, δ (ppm)]: 193.1, 145.7, 144.7, 143.8, 134.0, 128.8, 121.1, 120.3, 116.3, 86.0, 67.2, 64.9, 56.8, 47.6, 45.4, 41.5, 26.6, 23.5. FAB$^+$(NBA): 314 (M − X$^-$, 100), 296 (32), 254 (21), 226 (13). MS (EI): m/z 314 (M − X$^-$, 24), 313 (100), 256 (10), 230 (16), 229 (54), 214 (29), 188 (20).

Acknowledgment. This work was financially supported by grants from CICYT (PM98-0227, FEDER-CICYT 1FD97-2157) and from Xunta de Galicia (XUGA-20908B97, XUGA-PGIDT99PXI20906B XUGA-PGIDT99BIO20901).

Supporting Information Available: Experimental data relative to compounds **12**−**19**, **25**, and **40**−**48.** Preparation of compounds **12**−**19**, **25**, and **40**−**48**. Table S1 with ^{13}C and ^{1}H NMR data of compounds **33** and **34** for comparative purposes. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000288A