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Synthesis of Naltrexone and (*R*)-Methylnaltrexone from Oripavine via Direct Oxidation of Its Quaternary Salts

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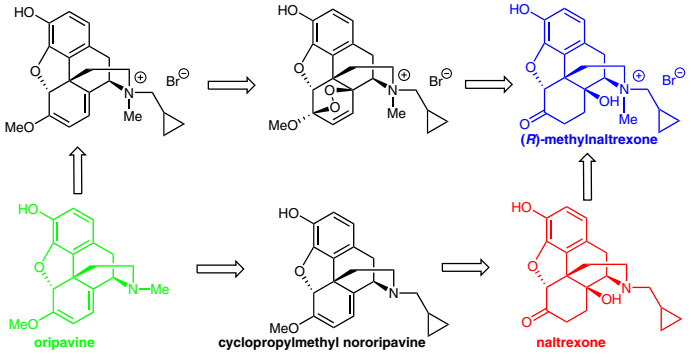

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Abstract (*R*)-Methylnaltrexone and naltrexone were each prepared in four steps from oripavine in practical yields. The procedure involved quaternization of oripavine with cyclopropylmethyl halides, singlet oxygen oxidation of the quaternary salts, and the reduction of *endo* peroxides to 14-hydroxyketone functionalities. (*R*)-Methylnaltrexone was prepared from the corresponding *R*-diastereomer of the oripavine salt. All diastereomeric mixtures of the quaternary salts were subjected to N-demethylation with sodium thiolate to yield cyclopropyl methylnororipavine, which was converted into naltrexone by peracid oxidation and hydrogenation according to established procedures.

Key words photochemical oxidation, singlet oxygen, naltrexone synthesis, (*R*)-methylnaltrexone synthesis, N-demethylation of oripavine quaternary salts

The major constituents of the opium poppy, such as morphine, codeine, thebaine, and oripavine, serve as starting materials for the synthesis of important medicinal agents. Naltrexone (**1**, Figure 1) is an opioid antagonist (μ- and κ-receptors) used for long-term treatment of opioid or alcohol dependence. Naloxone (**2**) is used primarily in treating overdose of other opiates or opiate-derived products in an emergency. Nalbuphine (**3**) is used as an analgesic, as is buprenorphine (**4**), which at higher dosage can be used to treat addiction. Suboxone®, a combination of buprenorphine and naloxone is used for the latter purpose. (*R*)-Methylnaltrexone (**5**), or (Relistor®) is a peripherally acting μ-receptor antagonist that is effective in reducing side effects, such as constipation, associated with the use of opioid analgesic agents. As it does not cross the blood–brain barrier it does not diminish analgesic effects.

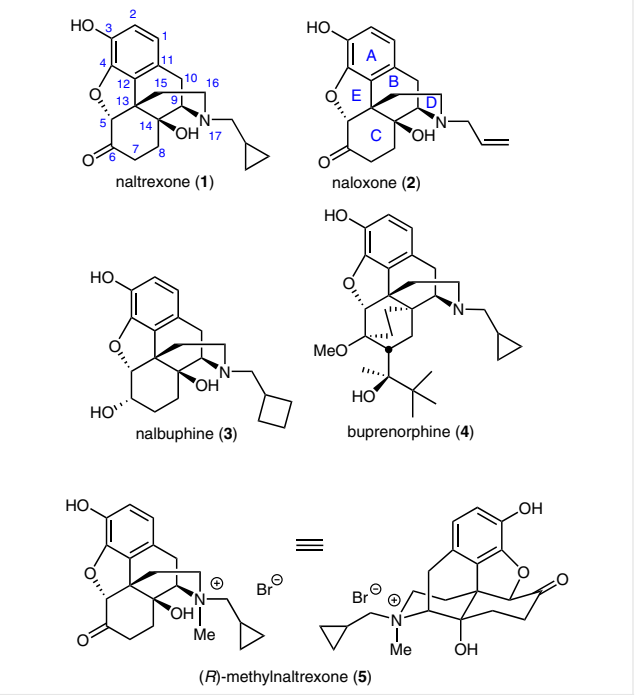
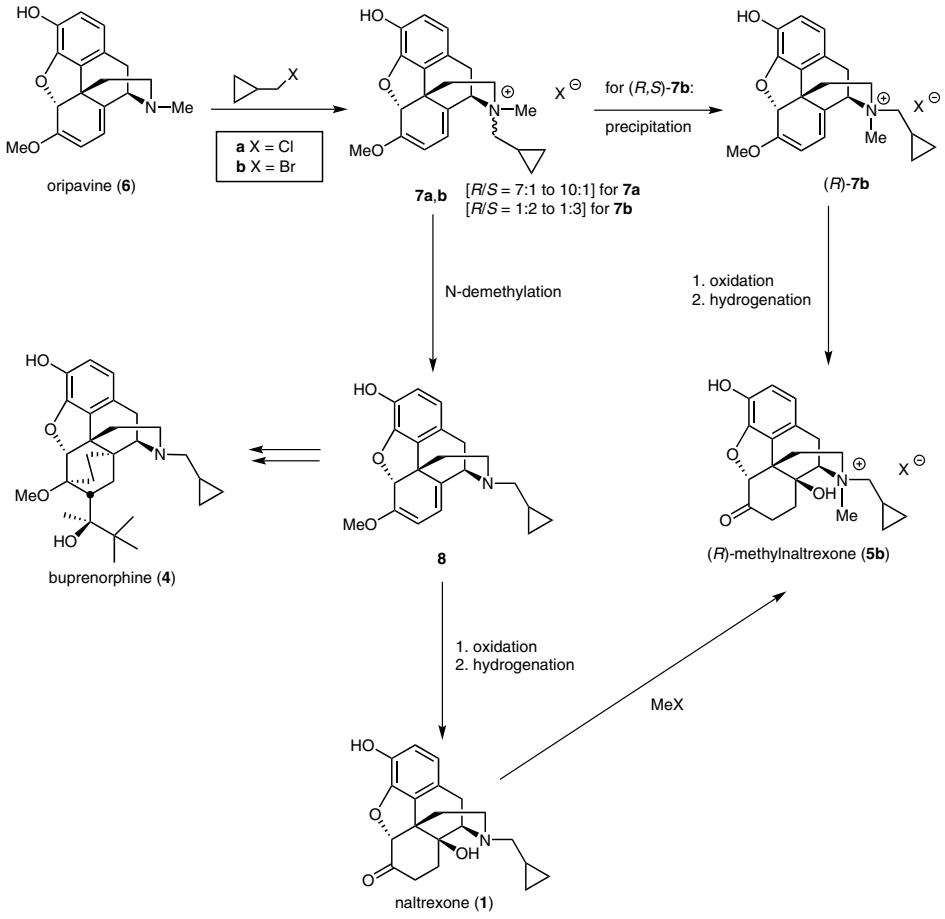


Figure 1 Medicinally useful opiate-derived products

Manufacturing of these opiate-derived medicinal agents requires effective and large-scale solutions to two fundamental problems: the introduction of C-14 hydroxyl group and the replacement of *N*-methyl group with other alkyl functionalities, such as allyl, cyclopropylmethyl-, or cyclobutylmethyl groups. The first of these problems has been solved effectively in the industrial preparation of oxycodone and oxymorphone by oxidation of thebaine or oripavine, respectively.[1] The second problem usually involves N-demethylation by harsh methods such as the von Braun

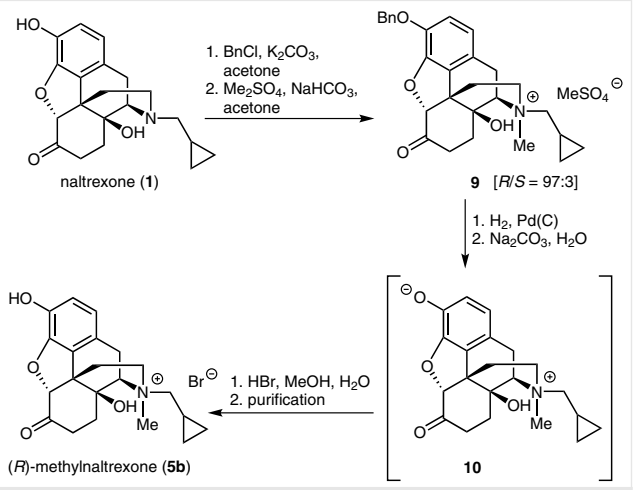


Scheme 1 General design for naltrexone, methylnaltrexone, and buprenorphine from a common intermediate

reaction or chloroformate-mediated dealkylation.[2] Recently, new methods of N-demethylation have emerged and include palladium-catalyzed demethylation/acylation,[3] iron-catalyzed demethylation of *N*-oxides,[4] demethylation catalyzed by fungal cytochromes,[5] and other methods.[6] In 2011 we reported an improved synthesis of buprenorphine from oripavine via N-demethylation of the quaternary salts with thiolates[7] to yield *N*-cyclopropylmethyl nororipavine **8**[8] (Scheme 1). This intermediate was converted into buprenorphine by known procedures. The most significant improvement was the avoidance of the use of cyanogen bromide in the demethylation protocol. The entire sequence from oripavine to buprenorphine was shortened by three steps and performed in four operations (seven chemical steps) in 32% overall yield.[8]

Nalbuphine (**3**) was synthesized in an analogous fashion. The quaternary salt derived from oripavine by alkylation with cyclobutylmethyl bromide was N-demethylated. Oxidation of the *N*-cyclobutylmethyl nororipavine to *N*-cyclobutylmethyl noroxymorphinone,[9] reduction to nalbuphone, and further stereoselective reduction of the C-6 ketone functionality led to nalbuphine.

The ease of preparation of *N*-cyclopropylmethyl nororipavine **8** prompted us to consider a general approach to naltrexone by oxidation of **8** and to methylnaltrexone by direct oxidation of the quaternary salts **7**. Naltrexone, prepared from oxymorphone in several steps, is converted into (*R*)-methylnaltrexone[10] by alkylation with iodomethane, bromomethane, or dimethyl sulfate, followed by multiple crystallizations to pure (*R*)-methylnaltrexone (MNTX). Although direct methylations of naltrexone have been reported[10,11] it is more customary to protect the C-3 phenol with benzyl,[12] acyl,[13] ethyloxycarbonyl,[14] or silyl[15] protecting groups (Scheme 2). After deprotection the NMTX salt is carefully deprotonated to obtain zwitterion **10**, which, because of its limited solubility, is easily filtered off and later dissolved in aqueous HBr. This protocol improves product purity and more importantly allows for feasible anion exchange on an industrial scale.



Scheme 2 Example of a synthetic route towards MNTX[12]

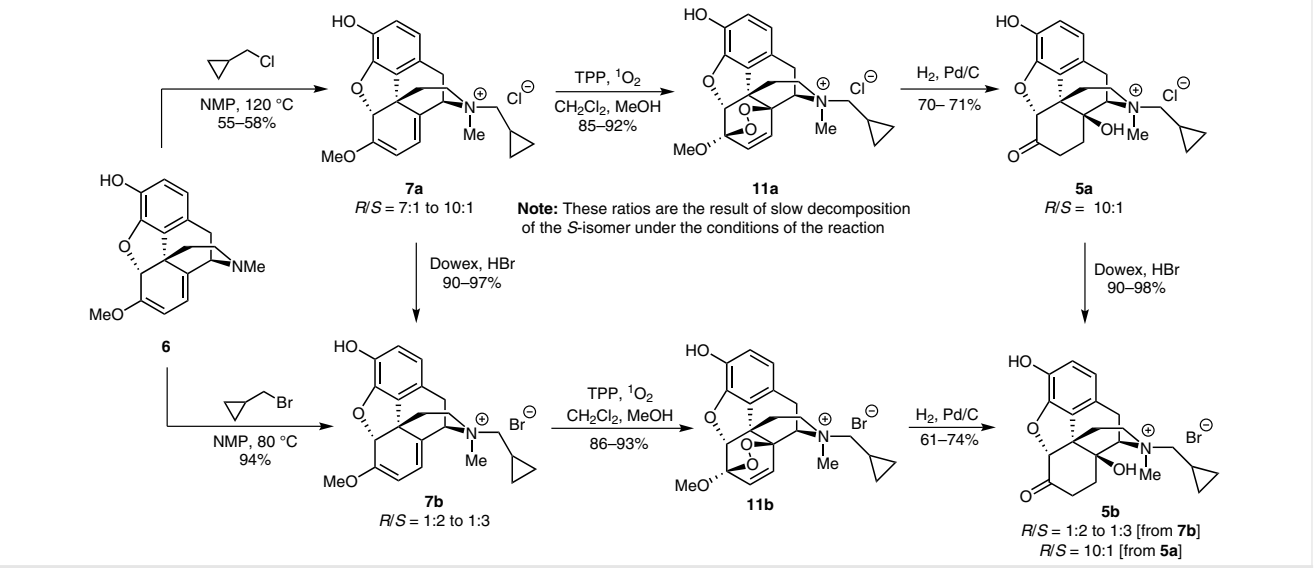
Because the quaternization of naltrexone is not stereospecific and the undesired *S*-isomer is usually present in less than 5% yield, the final product must be recrystallized several times to meet FDA requirements. Alkylation of oxymorphone with cyclopropylmethyl bromide furnished (*S*)-methyl naltrexone. The reaction is very slow hence this method is not viable for preparation of a potential active pharmaceutical ingredient (API).[16] Here we report the details of the singlet-oxygen oxidation of the quaternary salts and compare the efficiency of preparing (*R*)-methylnaltrexone either directly from **7** or from **8** via oxidation to naltrexone (**1**) and subsequent methylation.

Quaternary salts **7a** and **7b** were prepared by heating oripavine with cyclopropylmethyl chloride or bromide in 55% and 94% yield, respectively (Scheme 3). The salts were obtained as mixtures of *R*- and *S*-diastereomers (configuration at N-17, morphine numbering) in varying ratios depending on the conditions used. The isomers were separable by chromatography to provide standard samples that were then used to determine the ratios of these diastereomers in the reaction mixtures by HPLC analysis. The quaternary chloride salt was transformed into the corresponding bromide by passing its solution through an ion-exchange resin.

Chloride salt **7a** was obtained by heating oripavine with cyclopropylmethyl chloride in *N*-methylpyrrolidone at 120 °C for more than 24 hours. Under these conditions **7a** was produced in ca. 55% as a mixture of *R*/*S* diastereomers (7:1). The mixtures could be further enriched in the *R*-isomer by heating at elevated temperatures for 48 hours as it was found that the *S*-isomer was slowly degraded. This procedure led to improved ratios of *R*/*S* isomers (ca. 10:1 to ca. 20:1) at the expense of isolated yield. Whereas this method could ultimately produce the pure *R*-isomer, it was not effective because of the dramatic depletion of useful mass.

Bromide salt **7b** was obtained by heating oripavine with cyclopropylmethyl bromide in anhydrous DMF at 80 °C for more than 12 hours. In order to attain full conversion the crude mixture was subjected to a second cycle with 0.5 equivalents of cyclopropylmethyl bromide to provide **7b** in 94% yield as a mixture of *R*/*S* diastereomers (1:3). From this reaction mixture we were able to precipitate pure (*R*)-**7b** in the approximate yield of ca. 20%. Separation of pure (*R*)-**7b** was accomplished by simple filtration of cold reaction mixture of **7b** and was possible only in the case of the bromide salt.

The pure *R*-isomer was to be used eventually in direct oxidation while the filtrates from the filtrations/precipitations would be subjected to N-demethylation with thiolate



Scheme 3

to produce cyclopropylmethyl nororipavine (**8**), which can serve as a convenient precursor to buprenorphine and naltrexone. In this fashion, the total mass of the quaternary salts can be used to access three useful products.

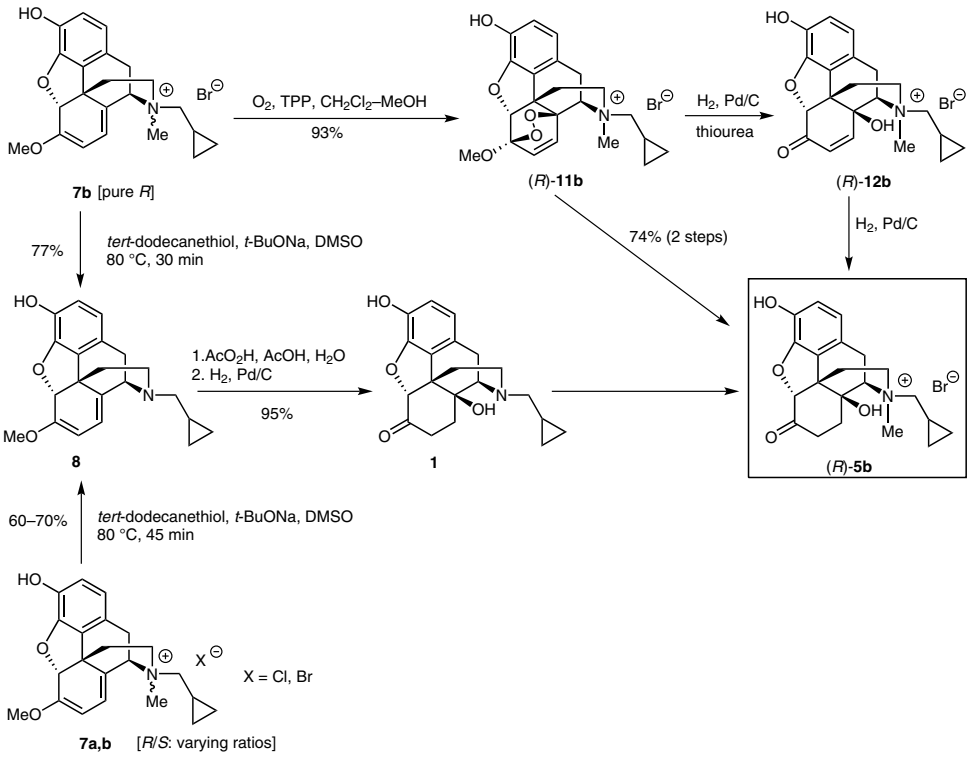
The oxidation of salt **7b** with peracids, performed with pure isomers as well as *R*/*S* mixtures, was not successful primarily because of low yields of the desired product and the formation of a large number of side products, in contrast to the results obtained with conversion of oripavine to oxymorphone by such established procedures.[17]

We therefore turned to singlet-oxygen oxidation of **7a**,**b** as means of introduction of the C-14 hydroxyl group, as shown in Scheme 3. We were inspired by an earlier report that described the oxidation of thebaine salts with singlet oxygen.[18] Irradiation of a solution of **7a**,**b** (of varying isomeric composition) in dichloromethane and methanol in the presence of oxygen and tetraphenylporphyrin (TPP) produced high yields of the corresponding *endo*-peroxides **11a**,**b**, whose hydrogenation led directly to methylnaltrexone chloride or bromide **5a** or **5b**, respectively.

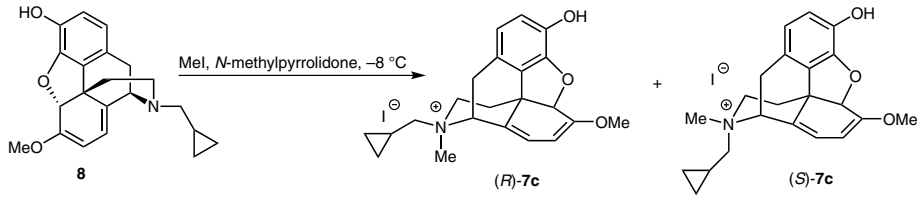
The experiments shown in Scheme 3 were initially conducted with isomeric mixtures, some of which were enriched with the desired *R*-diastereomer (*R*/*S* ratio = ca. 7:1 to 10:1). As we were able to obtain pure (*R*)-**7b** from the crude mixtures we turned to investigations of more effective mass management in the synthesis of (*R*)-methylnaltrexone bromide (**5b**) from pure (*R*)-**7b** by oxidation and subsequent hydrogenation. (*R*)-Methylnaltrexone bromide (**5b**) can also be prepared from **8** by known oxidation and quaternization protocols. The two routes were then compared for the best overall mass yield. The summary and details of these transformations are shown in Scheme 4.

Pure *R*-diastereomer **7b**, obtained as described above, was subjected to oxidation with singlet oxygen, which led to *endo*-peroxide **11b** in 93% yield. Direct hydrogenation of **11b** provided (*R*)-methylnaltrexone bromide (**5b**); however, the product contained 10–15% of the C-6 alcohol resulting from overreduction. This problem was solved by partial reduction of **11b** to **12b** accomplished by the use of the Pd/C catalyst poisoned with thiourea (1% by weight). The hydroxyenone **12b** was then cleanly hydrogenated to (*R*)-methylnaltrexone bromide (**5b**).

To approach the synthesis of naltrexone we utilized all isomeric mixtures of **7a** or **7b** that were produced by quaternization or resulting from purification of **7b**. These mixtures, containing varying ratios of *R*- and *S*-diastereomers, were subjected to N-demethylation conditions with sodium thiolate, as previously reported,[7] to produce *N*-cyclopropylmethyl nororipavine (**8**) in 60–70% yields. In this manner all oripavine mass committed to the initial quaternization was used either to produce (*R*)-methylnaltrexone bromide (**5b**) or **8**, from which naltrexone is made by reliable oxidation



Scheme 4



Scheme 5

protocols. Naltrexone (**1**) can also be converted into (*R*)-methylnaltrexone bromide (**5b**) by alkylation with methyl iodide according to established protocols.[10–12]

Finally, we examined the quaternization of *N*-cyclopropylmethyl nororipavine (**8**) in order to determine if a more favorable ratio of *R*- and *S*-diastereomers of salts **7** may become available. This compound was prepared from oripavine for the first time in 2009 during our studies on the synthesis of buprenorphine.[8a]

Oripavine, thebaine, and *N*-cyclopropylmethyl nororipavine (**8**) have been shown to be good substrates for quaternization, in contrast to other morphinans and analogues such as oxymorphone or intermediates used in the synthesis of buprenorphine. Madyastha made this observation in 1983,[7] reporting that thebaine is converted into its quaternary salts in 12 hours (95% yield) in contrast to codeine (48 hours, 90%) and morphine (72 hours, 60%). He also reasoned that the unique conformation of these substrates, imparted by the methoxydiene moiety and lacking 1,3-interactions between the C-14 sp^3 substituent and the incoming electrophile is responsible for the enhanced reactivity in oripavine or thebaine derivatives. Alkylation of **8** with methyl iodide in *N*-methylpyrrolidone at –8 °C led to diastereomeric mixtures of **7c** in which the *R*-isomer was preferred (*R*/*S* = 3.6:1.0), as shown in Scheme 5. This observation implies that the incoming electrophile will preferentially occupy the axial position in the quaternary salt and that alkylation of **8** provides essentially the opposite ratio of diastereoisomers than that obtained by alkylation of oripavine with cyclopropylmethyl halides at higher temperatures (*R*/*S* = 1:3, at 80 °C for cyclopropylmethyl bromide).

The use of the quaternary salts **7a** or **7b** in N-demethylation has proven to be superior to analogous experiments with N-demethylation of salts derived from thebaine. While such salts were formed in good yields their treatment with sodium thiolate led to complex mixtures and decomposition, presumably as a result of competing O-demethylation, which can also be problematic when applied to thebaine as a free base.[7,19]

We have provided an efficient four-step conversion of oripavine to naltrexone and/or (*R*)-methylnaltrexone via quaternary salts derived from oripavine by alkylation with cyclopropylmethyl halides.[20] The ratio of *R*- and *S*-diastereomers in each case was found to be highly dependent on the conditions of the reaction as well as on the nature of the halide. The pure *R*-diastereomer of the quaternary salt yielded (*R*)-methylnaltrexone by singlet-oxygen oxidation followed by hydrogenation. All residual material containing varying ratios of *R*- and *S*-diastereomers was subjected to N-demethylation with sodium thiolate to provide *N*-cyclopropylmethyl nororipavine, which was converted into naltrexone by known procedures. Naltrexone can be converted into (*R*)-methylnaltrexone by alkylation. Thus the reported process provides for a very efficient conversion of oripavine to either naltrexone or (*R*)-methylnaltrexone, with all of the mass of the starting material committed to either product. At four steps, the procedure reported here is much shorter than some of the commercially used processes, which are ten steps or more.

It should be noted that large-scale industrial processes that employ photochemistry are not common because of safety and efficiency issues on scale-up. An exception was recently reported by the Sanofi group: Photochemically generated singlet oxygen was used in a large-scale synthesis of artemisinin (370 kg obtained from 600 kg of artemisinic acid).[21] In addition, the efficiency (as well as safety) issues may be solved further by employing continuous-flow reactors, as was recently demonstrated by the conversion of α-pinene to pinocarvone.[22]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378808. Experimentals for compounds **5a**, **7a**, **7c**, **11a**, **11b**, **12b** and NMR spectra (^{1}H and ^{13}C) of **1**, (*R*)-**5b**, (*R*)-**7b**, (*S*)-**7b**, **8**, **11a** (^{1}H NMR only), (*R*)-**12b** are included.

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(20) **Key Experimental Procedures**

***N*-Cyclopropylmethyl Nororipavine Methyl Bromide (7b)**

A. From Chloride Salt 7a

Compound **7a** (0.150 g, 0.39 mmol) was dissolved in a minimum amount of aq MeOH (H_2O–MeOH, 3:1). The solution was filtered through a column packed with Dowex®-1 resin (Sigma, strongly basic bromine loaded, 50–100 mesh) and eluted with distilled H_2O (500 mL). The majority of the solvent was removed under reduced pressure. The residue was lyophilized to give the title compound **7b** as a white solid (0.16 g, 95%). ^{1}H NMR and ^{13}C NMR spectra were identical to the spectra of compound **7a**. MS–FAB$^+$: *m/z* = 785 $[(C_{22}H_{26}NO_3)_2Br]^+$.

B. From Oripavine and Cyclopropylmethyl Bromide

A flame-dried, argon-purged round-bottomed flask with an attached reflux condenser was charged a suspension of oripavine (1.84 g, 6.18 mmol) in anhydrous DMF (10 mL). Cyclopropylmethyl bromide (1.8 mL, 18.5 mmol, 3.0 equiv) was added to the vigorously stirred suspension of oripavine in one portion and at r.t. The flask was immersed in an 80 °C oil bath, and the mixture was stirred under argon atmosphere for 12 h. After cooling, an aliquot was analyzed by HPLC (285 nm) and determined to contain approximately 3.6% (integration, area under curve) oripavine (as the HBr salt). $NaHCO_3$ (0.02 g, 0.24 mmol, 4 mol%) was added to the reaction mixture, which was stirred for 1 h prior to the addition of additional cyclopropylmethyl bromide (0.30 mL, 3.1 mmol, 0.5 equiv) at r.t. The reaction mixture was immersed in the 80 °C oil bath for an additional 8 h. Analysis by HPLC (285 nm) revealed that approximately 1% oripavine remained in the reaction mixture. The reaction mixture (fine beige slurry) was cooled to r.t. and filtered through a fine-fritted funnel. The residue was washed with MeOH (1.5 mL), and the product precipitated after slow addition of the filtrate to a vigorously stirred volume of toluene (ca. 100 mL). After the precipitate was filtered and washed with toluene (2 × 10 mL), it was dried under vacuum to provide a slightly off-white solid in greater than quantitative yield. This material was stirred in acetone (50 mL) at r.t. for 2 h prior to a second filtration. The solid was collected and dried under vacuum to yield 2.60 g (94% yield) of *N*-cyclopropylmethyl oripavine ammonium bromide salt (**7b**) as a white, free-flowing solid; mp 194–200 °C; isomeric ratio determined by HPLC (*S*/*R* = 2.6:1).

***R*-Isomer**

Mp 219–221 °C (EtOH); R_f = 0.30 (CH_2Cl_2–MeOH, 5:1); $[\alpha]_D^{20}$ –109.38 (*c* 1, MeOH). ^{1}H NMR (600 MHz, DMSO): δ = 9.37 (s, 1 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 6.55 (d, *J* = 8.1 Hz, 1 H), 6.01 (d, *J* = 6.6 Hz, 1 H), 5.42 (s, 1 H), 5.29 (d, *J* = 6.6 Hz, 1 H), 4.67 (d, *J* = 7.2 Hz, 1 H) 3.71 (m, 1 H), 3.70 (m, 1 H), 3.61 (s, 3 H), 3.45 (dd, *J* = 13.5, 4.6 Hz, 1 H), 3.39 (dd, *J* = 13.7, 7.6 Hz, 1 H), 3.29 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1 H) 3.19 (s, 3 H), 3.06 (dd, *J* = 19.4, 7.2 Hz, 1 H), 2.59 (ddd, *J* = 14.1, 14.1, 5.1 Hz, 1 H), 1.86 (dd, *J* = 14.2, 2.9 Hz, 1 H), 1.21 (m, 1 H), 0.75 (m, 2 H), 0.51 (m, 1 H), 0.44 (m, 1 H). ^{13}C NMR (150 MHz, DMSO): δ = 154.6, 143.5, 140.4, 132.6, 124.1, 122.5, 120.2, 119.8, 117.6, 96.1, 87.2, 68.1, 67.1, 55.6, 54.0, 46.1, 44.2, 31.5, 30.4, 5.1, 4.4, 4.2.

***S*-Isomer**

Mp 195–197 °C (MeOH–*i*-PrOH); R_f = 0.28 (CH_2Cl_2–MeOH, 5:1); $[\alpha]_D^{20}$ –43.73 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, DMSO): δ = 9.37

(s, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 5.98 (d, *J* = 6.6 Hz, 1 H), 5.39 (s, 1 H), 5.26 (d, *J* = 6.6 Hz, 1 H), 4.75 (d, *J* = 6.9 Hz, 1 H), 3.77 (d, *J* = 19.6 Hz, 1 H), 3.64 (dd, *J* = 13.4, 6.1 Hz, 1 H), 3.60 (s, 3 H), 3.49 (dd, *J* = 13.4, 3.2 Hz, 1 H), 3.35 (m, 1 H), 3.29 (s, 3 H), 3.28 (m, 1 H), 3.06 (dd, *J* = 19.5, 7.0 Hz, 1 H), 2.56 (ddd, *J* = 14.0, 14.0, 4.5 Hz, 1 H), 1.79 (d, *J* = 11.9 Hz, 1 H), 1.21 (m, 1 H), 0.72 (m, 2 H), 0.52 (m, 1 H), 0.39 (m, 1 H). ^{13}C NMR (150 MHz, DMSO): δ = 154.6, 143.4, 140.4, 132.6, 124.1, 122.6, 120.2, 119.7, 117.6, 96.0, 87.3, 68.6, 63.9, 55.6, 54.0, 48.6, 43.7, 31.3, 30.6, 4.9, 4.6, 4.3. MS–FAB$^+$: *m/z* (%) = 55 (31), 98 (24), 112 (38), 239 (12), 352 (100). HRMS: *m/z* calcd for $C_{22}H_{26}NO_3^+$: 352.1907; found: 352.1898.

N-Cyclopropylmethyl Nororipavine (8)

To a slurry of NaO*t*-Bu (0.88 g, 9.20 mmol) in freshly distilled DMSO (6 mL) was added *tert*-dodecanethiol (1.86 g, 9.20 mmol, distilled) in one portion. The vigorously stirred mixture was purged with argon for 3 min. The flask was immersed in a 90 °C oil bath for 10 min, then the oil bath (and the mixture) was allowed to cool to 80 °C. A solution of *N*-cyclopropylmethyl oripavine ammonium bromide (**7b**, 1.32 g, 3.07 mmol; *R*/*S* ratio = 66:34) in DMSO (6 mL) at r.t. was added to the preformed mixture of *tert*-dodecanethiolate in DMSO at 80 °C over 10 min. A sharp color change from a clear, slightly yellow solution to a black-colored mixture occurred after the addition of the first few drops of the *N*-cyclopropylmethyl oripavine ammonium bromide solution. The reaction mixture was stirred at 80 °C for 45 min following the addition and monitored by HPLC (285 nm). After complete consumption of starting material the reaction mixture was allowed to cool to r.t. with stirring, then it was poured into H_2O (80 mL). The pH of the aqueous mixture was adjusted to pH 2 with HCl (6 M) and washed with hexanes (1 × 20 mL, 1 × 10 mL). The pH of the aqueous mixture (milky yellow suspension) was readjusted to pH 8 with NaOH (aq, 15%). The fine, white precipitate was observed upon pH adjustment and dissolved upon extraction with EtOAc (1 × 20 mL, 1 × 15 mL). The pH of the aqueous phase was adjusted again to pH 8 (white precipitate was observed) and extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), then dried over $MgSO_4$, filtered, and concentrated to provide crude material, which was crystallized from acetone–cyclohexane mixture (1:1) to afford 0.61 g (59% yield) of *N*-cyclopropylmethyl nororipavine (**8**) as a pale-yellow crystalline solid. Column chromatography (MeOH–EtOAc, 1:5) of mother liquor afforded 0.07 g (6% yield) of title compound. R_f = 0.25 (MeOH–EtOAc, 1:5); mp 165–166 °C (CH_2Cl_2), 166–167 °C (MeOH); $[\alpha]_D^{20}$ –168.60 (*c* 1, $CHCl_3$). IR (KBr): ν = 3445, 2908, 1630, 1458, 1234, 1046, 1016, 926, 868 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.65 (d, *J* = 8.4 Hz, 1 H), 6.55 (d, *J* = 8.4 Hz, 1 H), 5.59 (d, *J* = 6.6 Hz, 1 H), 5.29 (s, 1 H), 5.07 (d, *J* = 6.6 Hz, 1 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 3.61 (s, 3 H), 3.29 (d, *J* = 18.0 Hz, 1 H), 3.00 (dd, *J* = 12.6, 4.2 Hz, 1 H), 2.90 (m, 1 H), 2.76 (dd, *J* = 18.0, 7.2 Hz, 1 H), 2.55 (m, 2 H), 2.24 (m, 1 H), 1.71 (d, *J* = 11.4 Hz, 1 H), 0.97 (m, 1 H), 0.56 (d, *J* = 8.4 Hz, 2 H), 0.19 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.2, 143.1, 138.8, 133.2, 132.6, 126.7, 119.7, 116.5, 112.1, 96.4, 89.4, 58.6, 58.6, 55.0, 46.8, 43.8, 36.2, 31.2, 9.2, 3.9 (2 × CH_2). MS (EI$^+$): *m/z* (%) = 43 (100), 58(19), 84 (56), 227 (8), 282 (12), 337 (41). HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$: 337.1678; found: 337.1681.

Naltrexone (1)

A solution of *N*-methylcyclopropyl nororipavine (**8**, 0.52 g, 1.52 mmol) in H_2O–AcOH (1:1 v/v) was chilled to 5 °C with stirring. A solution of peracetic acid (0.40 g, 1.67 mmol; 32 wt%) in AcOH was added dropwise over 2 min. The mixture was stirred at 5 °C for 10 min prior to warming to r.t. Monitoring of the reaction by TLC (MeOH–EtOAc = 1:10) showed consumption of starting material 35 min after addition of peracetic acid. The reaction mixture at r.t. was diluted with *i*-PrOH (2.5 mL), then Pd/C (0.05 g, 10 wt%) was added, and the reaction mixture was subjected to a hydrogen atmosphere (Parr shaker, 3.45 bar) for 15 h. The mixture was filtered through a pad of Celite, which was subsequently washed with *i*-PrOH. AcOH was removed as an azeotrope with toluene prior to concentration to dryness. Naltrexone (0.51 g, 95% yield) was obtained after further drying under vacuum; R_f = 0.55 ($CHCl_3$–MeOH, 92:8); mp 167–169 °C [$CHCl_3$, lit.[23] 174–176 °C (acetone)]; $[\alpha]_D^{20}$ –84.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 7.6 Hz, 1 H), 6.59 (d, *J* = 7.6 Hz, 1 H), 5.66 (s, 2 H), 4.76 (s, 1 H), 3.22 (d, *J* = 5.6 Hz, 1 H), 3.12–3.03 (m, 2 H), 2.73 (dd, *J* = 4.1, 11.6 Hz, 1 H), 2.58 (dd, *J* = 5.8, 18.6 Hz, 1 H), 2.52–2.30 (m, 4 H), 2.16 (td, *J* = 5.9, 3.0 Hz, 1 H), 1.92 (d, *J* = 12.0 Hz, 1 H), 1.75–1.50 (m, 3 H), 0.87 (m, 2 H), 0.56 (d, *J* = 7.4 Hz, 2 H), 0.16 (d, *J* = 4.4 Hz, 2 H).

General Procedure for the Photooxygenation Reactions[18]

To a solution of the quaternized morphine alkaloid (0.25–0.30 mmol) in CH_2Cl_2–MeOH (4:1, 8 mL) in a double-glass wall mini reactor was added tetraphenylporphyrin (0.02 g). Oxygen was bubbled through the reaction mixture for 4 h, while irradiated from a distance of 30 cm with a street lamp (500 W) at a reaction temperature of 5–15 °C. The strongly colored solution was transferred to an Erlenmeyer flask, and the corresponding endoperoxide was precipitated by the addition of Et_2O. The slightly purple solid was dissolved in MeOH and precipitated with Et_2O to afford the endoperoxide as slightly colored solid. Because of the instability of the endoperoxide intermediates, only ^{1}H NMR data were obtained.

General Procedure for the Reduction of Endoperoxide Intermediates

To a solution of the endoperoxide intermediate (0.20–0.30 mmol) dissolved in a mixture of H_2O–*i*-PrOH–formic acid (1:1:1, 2.4 mL) was added Pd/C (10%, 10 wt%). The reaction mixture was flushed three times with H_2 and then stirred at 1 atm of H_2 for 24 h. The suspension was filtered through a short plug of Celite, and the plug was washed with MeOH. The filtrate was concentrated in vacuo, and the residue was lyophilized. Flash column chromatography on silica (eluent CH_2Cl_2–MeOH, 9:1) provided the corresponding product.

Methylnaltrexone Bromide (5b)

A. From Chloride Salt by Ion Exchange

Compound **5a** (0.05 g, 0.13 mmol) dissolved in a minimum amount aq MeOH (H_2O–MeOH, 3:1), and the solution was filtered through a column packed with Dowex®-1 resin (Sigma, strongly basic bromine loaded, 50–100 mesh) and eluted with distilled H_2O (400 mL). The majority of the solvent was removed under reduced pressure, then the residue was lyophilized to give the title compound **5b** as a white solid (0.054 g, 98%). ^{1}H NMR and ^{13}C NMR spectra were identical to the spectra of **5b** obtained from compound **11b**. MS–FAB$^+$: *m/z* = 793 $[(C_{21}H_{26}NO_4)_2Br]^+$.

B. By Reduction of Endoperoxide 11b

Following the general procedure for the reduction of endoperoxide intermediates, compound **11b** (0.10 g, 0.22 mmol) yielded methylnaltrexone bromide salt **5b** as a colorless solid (0.08 g, 74%). MS–FAB$^+$: *m/z* = 793 $[(C_{21}H_{26}NO_4)_2Br]^+$.

C. By Reduction of Enone 12b

To a solution of the enone **12b** (0.20 g, 0.46 mmol) dissolved in MeOH (3 mL) was added Pd/C (0.02 g; 10 wt%). The reaction mixture was hydrogenated in Parr shaker at 40 psi for 12 h. The

suspension was filtered through a short plug of Celite, and the plug was washed with MeOH. The evaporation of MeOH furnished 0.19 g of essentially pure product (checked by HPLC and by ^{1}H NMR).

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