A Stereocontrolled Alkylation of Chiral Pyridinium Salts with Grignard Reagents: Synthesis of (+)-Normetazocine and (+)-Nordextrorphan

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Received September 22, 1992

The synthesis of chiral pyridinium salts **3**, bearing lipophilic counteranions, is described. These salts, soluble in THF or toluene, undergo nucleophilic alkylation with benzylic Grignard reagents to give, after reduction of the unstable dihydropyridine intermediates, adducts **4** with regio- and stereoselective attack at position 2, the observed stereoselectivity ranging from 8:1 to 12.5:1. These results allowed an asymmetric synthesis, following Grewe's route, of (+)-normetazocine and (+)-nordextrorphan, key precursors of various benzomorphan or morphinan drugs.

Addition of carbon nucleophiles to pyridinium salts offers a general entry to substituted six-membered nitrogen heterocycles via dihydropyridine intermediates.[1] Whereas the regioselective attack at position 2/6 or 4 of the pyridine ring during these reactions has been well documented,[2] much less attention has been paid to develop general methods for the stereo- and enantioselective alkylation of these salts. Very recently, two approaches leading to chiral *N*-acyldihydropyridines were reported, one involving stereoselective addition of organocopper reagents at position 4 of the pyridinium ring,[3] while the other involved Grignard reagents at position 2.[4]

Our interest in this field stems from our effort to develop, via Zincke's reaction, a practical entry to chiral pyridinium salts in which an asymmetric carbon center is linked to the ring nitrogen.[5] Herein we report our preliminary results concerning the enantioselective alkylation of these salts with Grignard reagents. As a first practical application we also describe a new synthesis, according to Scheme I, of (+)-normetazocine and (+)-nordextrorphan,[6] which are important precursors of benzomorphan and morphinan analgesics or antitussive drugs.[7]

This synthetic pathway could be considered as an asymmetric version of the Grewe's route to benzomorphans[8] which generally involved as the first step a nonstereoselective Grignard alkylation of pyridinium salts followed by reduction of the resulting 1,2-dihydropyridines.[9]

Treatment of 3,4-dimethylpyridine and 5,6,7,8-tetrahydroisoquinoline with 1 equiv of 1-chloro-2,4-dinitrobenzene (Cl-DNP) led to Zincke's salts **1a** and **1b**, respectively. As recently reported by us,[5] treatment of salt **1a** with (*R*)-(+)-1-phenylethylamine (1.2 equiv) in refluxing dichloromethane gave the pyridinium salt **2a** in 92% isolated yield. Under the same conditions, salt **2b** was obtained in 58% yield from **1b**, albeit in this case an excess (3 equiv) of the chiral primary amine was required. The use of dichloromethane as solvent was essential for these reactions to proceed, since it helped the initial ring opening which proved to be difficult with 3,4-dialkyl-substituted Zincke's salts such as **1a** and **1b**.

With salts **2a** and **2b** in hand, we next studied their reactions with benzylic Grignard reagents. Reaction in solvents such as THF or Et_2O gave disappointing results due to the insolubility of these salts in these solvents. However, these salts could be rendered more soluble by using lipophilic sulfates or sulfonates as counteranions. The exchange of the chloride anion could be easily accomplished by using either the corresponding sulfonic acid or sulfate salt of the lipophilic moiety. For example, salts **3a** and **3b** were recovered in high yields by simply stirring **2a** and **2b** with 1 equiv of sodium dodecyl sulfate in dichloromethane followed by filtration over silica gel. Although insoluble in ether, salts **3a** and **3b** were soluble in THF and even in toluene. Thus, the alkylation of soluble salts **3** could be conveniently carried out with *p*-methoxybenzylmagnesium chloride or benzylmagnesium bromide. This also allowed us to explore optimal conditions for regio- and stereoselectivity of this process. Since dihydropyridine intermediates obtained from Grignard reaction were very unstable, the crude alkylation product was reduced with an excess of $NaBH_4$. From this two-step procedure we expected formation of diastereoisomeric adducts **4** and **5** (Scheme II), resulting from the attack at position 2 of the pyridine ring, and also formation of regioisomeric derivatives **6** and **7** (mixture of isomers) resulting from the attack at positions 6 or 4.

Thus, dropwise addition of a solution of salt **3a** in THF to an excess of *p*-methoxybenzylmagnesium chloride in THF at −78 °C led, after reduction of the corresponding 1,2-dihydropyridine intermediate with $NaBH_4$ in refluxing MeOH–10% H_2O during 1 h, to a mixture from which the main product **4a** was easily isolated in 40% yield by flash chromatography on silica gel. Its full structure and absolute configuration were established by further transformation into (+)-normetazocine (vide infra). We also isolated small amounts of two other minor compounds

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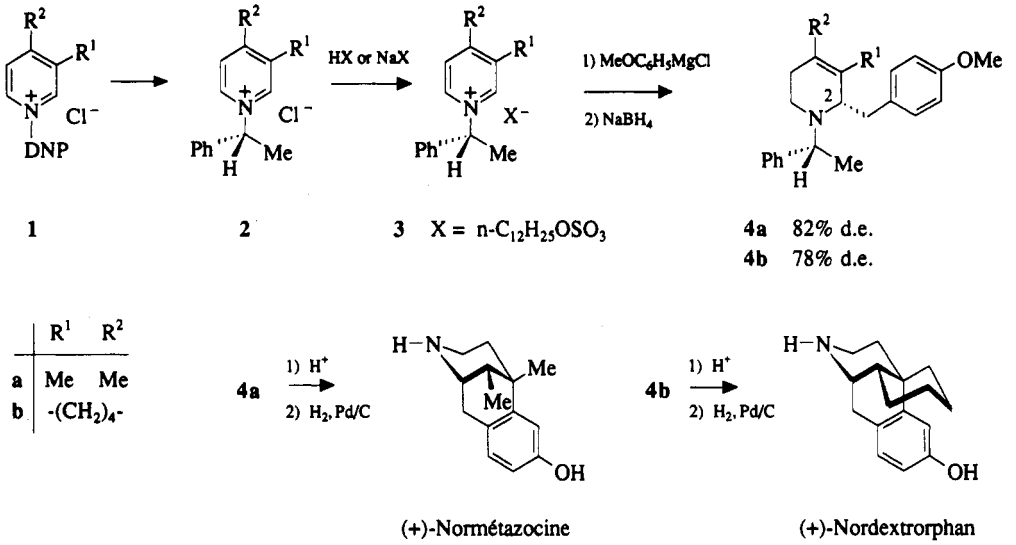
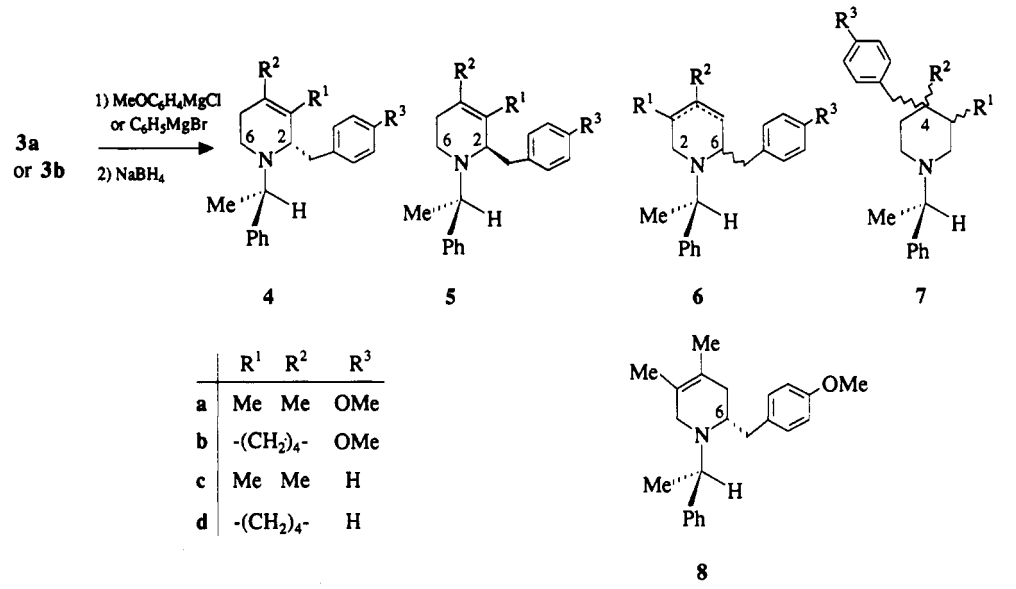
Scheme I



	R^1	R^2
a	Me	Me
b	-$(CH_2)_4$-	

Scheme II



	R^1	R^2	R^3
a	Me	Me	OMe
b	-$(CH_2)_4$-		OMe
c	Me	Me	H
d	-$(CH_2)_4$-		H

whose structures were established by mass spectrometry and NMR spectroscopy as **5a** and **8**. Thus, the electron-impact mass spectra of both these compounds displayed an intense peak at *m/z* 214 corresponding to the loss of *p*-methoxybenzyl radical thereby indicating substitution on carbon 2 or 6 of the ring. Attribution of each proton and carbon of the ^1H and ^{13}C NMR spectra was based on heteronuclear ^1H–^{13}C chemical shift correlations. No olefinic hydrogen was detected in the ^1H-NMR spectra of these two compounds, suggesting a migration of the double bond in the case of the product resulting from an initial Grignard attack at position 6 of the ring (adduct **8** was the major component of the mixture of isomeric adducts **6a**). COSY experiments did not provide definitive evidence to distinguish between structures **5a** and **8**, but this was made possible by comparing other NMR data obtained with these compounds. The main NMR features of **5a** are close to those of **4a**, in particular the chemical shift of benzyl-substituted carbon 2 and methylene carbon 6 in the ^{13}C-NMR spectra (C2 at 61.5 and C6 at 40 ppm for **5a**; C2 at 63.2 and C6 at 39.4 ppm for **4a**), in contrast to the chemical shifts of the methylene carbon 2 and benzyl-substituted carbon 6 in **8** (C6 at 55.1 and C2 at 50.8 ppm). This assignment for **8** was also supported by a comparison with analogous compounds obtained in our laboratory,[10] which additionally allowed us to propose a 6*R* configuration for compound **8**. The number and proportion of isomers formed could be determined by GC experiments on the crude reaction mixture of isomers (entry 1, Table I). GC–MS analysis allowed us, in addition, to detect some other minor components corresponding presumably to isomeric **6a** (IC: MH^+ at *m/z* 336; EI: base peak at *m/z* 214, corresponding to a loss of *p*-methoxybenzyl radical) and a mixture of isomeric products **7**, differing by two mass units (IC: MH^+ at *m/z* 338; EI: no peak at *m/z* 214) and very probably resulting from an initial attack of the Grignard reagent at position 4 of the ring, followed by reduction of the 1,4-dihydropyridine intermediates to the corresponding piperidines. The diastereoselection for the alkylation at position 2 was determined by GC as 9:1 in favor of adduct **4a**. A slightly better diastereoselectivity (10:1) and regioselectivity (less addition at position 4) was observed when the Grignard reagent was added slowly to the pyridinium salt (entry 2), but the yield did not improve,

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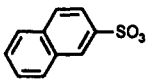
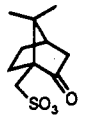
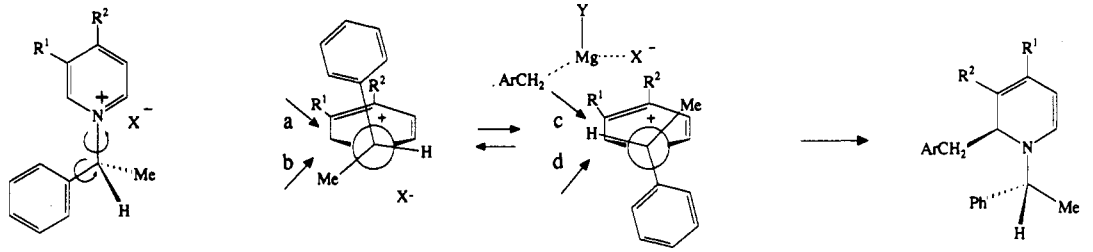
Table I. Reaction of Pyridinium Salts 3 with Benzylic Grignard Reagents

entry	salt	X	R^3	condns[a]	adducts (% ratio)[b]	4:5 ratio	major adduct; % isolated yield[c]
1	3a	$C_{12}H_{25}OSO_3$	OMe	−78 °C, THF (A)	4a (63) 5a (7) 6a (13) 7a (16)	9:1	4a, 40
2	3a	$C_{12}H_{25}OSO_3$	OMe	−78 °C, THF (B)	4a (70) 5a (7) 6a (13) +7a (6)	10:1	4a, 40
3	3a	$C_{12}H_{25}OSO_3$	H	−10 to 0 °C, THF–Et_2O (A)	4c (54) 5c (13) 6c (16) 7c (17)	4:1	4c, 33
4	3a	$C_{12}H_{25}OSO_3$	H	−78 °C, THF–Et_2O (A)	4c (66) 5c (10) 6c (12) 7c (12)	6.5:1	4c, 45
5	3a		H	−78 °C, THF–Et_2O (A)	4c (61) 5c (10) 6c (12) 7c (17)	6:1	4c, 39
6	3a		H	−78 °C, THF–Et_2O (A)	4c (57) 5c (15) 6c (9) 7c (20)	4:1	4c, 25
7	3a	$C_{12}H_{25}OSO_3$	H	−78 °C, THF, $CeCl_3$ (3 equiv) (A)	4c (66) 5c (8) 6c (9) 7c (17)	8:1	4c, 29
8	3a	$C_{12}H_{25}OSO_3$	H	−78 °C, THF–Et_2O (B)	4c (75) 5c (6) 6c (8) 7c (11)	12.5:1	4c, 47
9	3b	$C_{12}H_{25}OSO_3$	OMe	−78 °C, THF (B)	4b (87) 5b (11) 6b (1) 7b (2)	8:1	4b, 53
10	3b	$C_{12}H_{25}OCO_3$	H	−78 °C, THF–Et_2O (B)	4d (85) 5d (11) 6d (1) 7d (3)	8:1	4d, 64

[a] Method A: the pyridinium salt was added dropwise to an excess of the Grignard reagent in solution. Method B: an excess of the Grignard reagent was added dropwise to the pyridinium salt in solution. [b] Chromatographically purified individual products, such as 4 and 5, were used in order to attribute GC peaks and to determine the de ratios. [c] Combined yield of the Grignard alkylation/$NaBH_4$ reduction procedure.

Scheme III



presumably due to some more decomposition of the intermediate 1,2-dihydropyridine under these conditions.

Other alkylation experiments (entries 3–8) performed on salt **3a** with benzylmagnesium bromide showed that the temperature of the reaction influenced the stereo- and regioselectivity (compare entries 3 and 4). The nature of the counteranion (entries 5, 6) was practically of no consequence to the product distribution. Use of cerium trichloride (entry 7) gave lower yields with no significant improvement of selectivity. As for adduct **4a**, the best conditions corresponded to a slow addition of the Grignard reagent (entry 8) resulting in a 12.5:1 diastereoselection in favor of **4c**. Finally, these last conditions were chosen for the alkylation of salt **3b** with *p*-methoxybenzylmagnesium chloride and benzylmagnesium bromide, affording adducts **4b** and **4d**, respectively, with a good diastereoselection (8:1, entries 9 and 10). Interestingly, the regioselectivity was significantly higher than for salt **3a**, allowing **4b** and **4d** to be obtained in better yields.

Thus, in addition to good regioselectivity, a significant and preparatively useful level of diastereoselection, ranging from 8:1 up to 12.5:1, could be achieved during the alkylation with benzylic Grignard reagents at carbon 2 of pyridinium salts **3**. This relatively high selectivity was rather unexpected in view of the mobility of the chiral inducing group which could be considered as rotating relatively freely around the N–C and the C-phenyl bonds (**3a–b**, Scheme III). Generally, high stereoselectivities during nucleophilic addition to related imminium salts were found when some factors such as chelation with polar groups or 1,3-strain might favor or freeze one conformation.[11] Although such factors could not be invoked here, a tentative explanation of our results could be suggested as follows (Scheme III). According to literature data,[12] it can be assumed that the favored conformations for compounds such as **3** are those in which the C–H bond of the chiral auxiliary is lying in the same plane or near the plane of both the pyridinium and the phenyl rings. On the other hand, the largest group, i.e., the phenyl ring, is expected to be roughly perpendicular to the plane of the pyridinium ring. We can then draw two sets of favored and interconverting conformations which are close to conformations **A** and **B**. Nucleophilic attack can then occur following trajectories a or b on **A** or alternatively according to trajectories c or d on **B**. Trajectory c, leading effectively to compounds **4a–d**, is the only one allowing an approach of the Grignard reagent between the small (H) and medium size (Me) groups of the auxiliary, a

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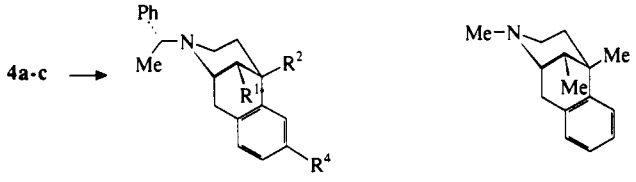
Scheme IV



9 a $R^1 = R^2 = Me$, $R^3 = OH$
b $R^1 - R^2 = -(CH_2)_4-$, $R^3 = OH$
c $R^1 = R^2 = Me$, $R^3 = H$
d $R^1 - R^2 = -(CH_2)_4-$, $R^3 = H$

10

situation which is in agreement with the analogous Felkin–Anh[13] model for nucleophilic addition to carbonyl compounds.[14] The same considerations could also be applied to explain the stereoselectivity in the formation of the regioisomeric minor adduct **8**.

Finally, the approach described here allowed a new access to chiral benzomorphans and morphinans of therapeutic interest by using Grewe's route. Treatment of adduct **4a** with 38% HBr at 140 °C led to the tricyclic intermediate **9a** (Scheme IV) in 64% yield. Catalytic hydrogenation finally gave (+)-normetazocine in 69% yield (14% overall yield from Zincke's salt **1a**, 18% from salt **3a**). This benzomorphan is a key precursor of analgesic drugs, such as metazocine or pentazocine,[15] which differ by their substituents on nitrogen. Under similar conditions the morphinan analgesic or antitussive drugs precursor (+)-nordextrorphan was obtained in 35% yield from the adduct **4b** (9% overall from **1b**, 18% from **3b**). The benzomorphan **10** was also obtained from **4c** (13% overall yield from **1a**, 17% from **3a**).

In conclusion, these results demonstrate the usefulness of the stereoselective alkylation of chiral pyridinium salts, now easily available by the Zincke's reaction, with organometallic reagents. Further developments of this approach are under investigation in our laboratory.

Experimental Section

3,4-Dimethyl-1-(2,4-dinitrophenyl)pyridinium Chloride (1a). 1-Chloro-2,4-dinitrobenzene (20 g, 99 mmol) was added to a solution of 3,5-dimethylpyridine (11 g, 99 mmol) in MeOH (50 mL), and the mixture was refluxed 48 h. After removal of the solvent under reduced pressure, salt **1a** (24.8 g, 80.16 mmol, 81%) was obtained by precipitation from acetone and filtration: mp 200–205 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 9.24 (1 H, d, J = 2 Hz), 9.07 (1 H, s), 8.98 (1 H, d, J = 6 Hz), 8.87 (1 H, dd, J = 8, 2 Hz), 8.26 (1 H, d, J = 8 Hz), 8.13 (1 H, d, J = 6 Hz), 2.78 (3 H, s), 2.60 (3 H, s); ^{13}C NMR (50.2 MHz, CD_3OD), δ 164.0, 150.7, 144.9, 144.5, 143.6, 140.1, 139.9, 133.0, 131.2, 129.5, 123.2, 21.2, 17.2; MS (FAB) m/z (relative intensity) 274 (M^+, 100), 108 (39). Anal. Calcd for $C_{12}H_{12}ClN_3O_4$: C, 50.37; H, 3.90; Cl, 11.50; N, 13.56; O, 20.66. Found: C, 50.11; H, 3.92; Cl, 11.25; N, 13.49; O, 20.52.

2-(2,4-Dinitrophenyl)-5,6,7,8-tetrahydroisoquinolinium Chloride (1b). To a solution of 5,6,7,8-tetrahydroisoquinoline (6 g, 46.4 mmol) in MeOH (30 mL) was added 1-chloro-2,4-dinitrobenzene (9.35 g, 46.2 mmol). After the solution was refluxed for 48 h, the solvent was removed under reduced pressure and the crude product was filtered over silica gel with CH_2Cl_2–MeOH as eluent. Pure Zincke's salt **1b** (9.8 g, 29.2 mmol, 63%) was recovered as a brown foam which was used without further purification: ^{1}H NMR (200 MHz, CD_3OD) δ 9.25 (1 H, d, J = 2 Hz), 9.01 (1 H, s), 8.87 (1 H, dd, J = 8, 2 Hz), 8.87 (1 H, d, J = 7 Hz), 8.26 (1 H, d, J = 8 Hz), 8.00 (1 H, d, J = 7 Hz), 3.23 (2 H, m), 3.05 (2 H, m), 2.00 (4 H, m); ^{13}C NMR (50.2 MHz, CD_3OD) δ 163.7, 150.5, 145.4, 144.3, 142.2, 140.2, 132.7, 130.9, 128.9, 123.0, 30.9, 27.2, 21.8; MS (FAB) m/z (relative intensity) 300 (M^+, 100), 134 (29).

(+)-3,4-Dimethyl-1-[(1*R*)-1-phenylethyl]pyridinium Chloride (2a). (+)-(1*R*)-1-Phenylethylamine (2 mL, 15.5 mmol) was added dropwise to a stirred suspension of **1a** (4 g, 12.9 mmol) in anhydrous CH_2Cl_2 (150 mL). The mixture, which turned slowly to a deep red color, was stirred 1 h at 20 °C and then refluxed during 36 h. Evaporation of the solvent gave the crude product which was dissolved in a mixture of water and EtOAc. The aqueous phase was collected by decantation, and the EtOAc phase was extracted twice with water. The water extracts were combined, washed with CH_2Cl_2, and evaporated under reduced pressure to give salt **2a** (3.26 g) as a pale brown gum contaminated with 10% (+)-(1*R*)-1-phenylethylamine hydrochloride (ratio estimated by ^{1}H NMR). Purification was achieved by filtration on neutral alumina using CH_2Cl_2 as eluent, affording pure **2a** (2.94 g, 92%) as a very hygroscopic gum which crystallized on standing in a dry atmosphere. Colorless crystals were obtained from dry acetone: mp 183–185 °C; $[\alpha]_D$ +33° (c 2.7, EtOH); ^{1}H NMR (200 MHz, CD_3OD) δ 8.92 (1 H, s), 8.82 (1 H, d, J = 6 Hz), 7.88 (1 H, d, J = 5 Hz), 7.40–7.58 (5 H, m), 6.13 (1 H, q, J = 8 Hz), 2.57 (3 H, s), 2.5 (3 H, s), 2.1 (3 H, d, J = 8 Hz); ^{13}C NMR (50.2 MHz, CD_3OD) δ 160.4, 142.9, 141.1, 140.2, 139.0, 130.6, 129.8, 130.5, 126.4, 70.9, 20.7, 20.3, 17.0; MS (FAB) m/z (relative intensity) 212 (M^+, 100), 108 (66), 105 (44). Anal. Calcd for $C_{15}H_{18}ClN$-0.2 H_2O: C, 71.60; H, 7.38; Cl, 14.18; N, 5.57. Found: C, 71.55; H, 7.11; Cl, 14.57; N, 5.48.

(+)-2-[(1*R*)-1-Phenylethyl]-5,6,7,8-tetrahydroisoquinolinium Chloride (2b). The procedure utilized for the preparation of salt **2a** was applied to Zincke's salt **1b** (5 g, 14.9 mmol), except that an excess of (+)-(1*R*)-1-phenylethylamine (5.8 mL, 45 mmol) was used. Under these conditions a mixture of salt **2b**, (+)-(1*R*)-phenylethylamine (which could be partially recovered by bulb to bulb distillation), and (+)-(1*R*)-1-phenylethylamine hydrochloride was obtained. Pure **2b** (2.35 g, 58% yield) was isolated by chromatography over neutral alumina with CH_2Cl_2 as eluant. Colorless hygroscopic crystals were obtained from dry MeOH–acetone: mp 205–207 °C; $[\alpha]_D$ +42° (c 1.1, EtOH); ^{1}H-NMR (200 MHz, CD_3OD) δ 8.92 (1 H, s), 8.72 (1 H, d, J = 6.5 Hz), 7.77 (1 H, d, J = 6.5 Hz), 7.39–7.59 (5 H, m), 6.12 (1 H, q, J = 7 Hz), 2.88–3.10 (4 H, m), 2.09 (3 H, d, J = 7 Hz), 1.82–1.92 (4 H, m); ^{13}C NMR (50.2 MHz, CD_3OD) δ 160.1, 143.4, 140.3, 139.8, 138.5, 130.56, 129.3, 130.3 (2C), 128.3 (2C), 70.8, 30.3, 27.2, 21.9, 20.7; MS (FAB) m/z (relative intensity) 212 (M^+, 100). Anal. Calcd for $C_{17}H_{20}ClN$: C, 74.51; H, 7.36; Cl, 13.01; N, 5.11. Found: C, 74.32; H, 7.20; Cl, 12.75; N, 5.04.

(+)-3,4-Dimethyl-1-[(1*R*)-1-phenylethyl]pyridinium Dodecylsulfate (3a). A solution of Zincke's salt **2a** (2.93 g, 11 mmol) and sodium dodecylsulfate (3.17 g, 11 mmol) in CH_2Cl_2 (200 mL) was refluxed overnight. Filtration over silica gel (30 g) with CH_2Cl_2–MeOH (95:5) as eluent gave salt **3a** (4.8 g, 85% yield) as a colorless gum.

(+)-2-[(1*R*)-1-Phenylethyl]-5,6,7,8-tetrahydroisoquinolinium Dodecylsulfate (3b). Salt **2b** (2.35 g, 9.5 mmol) was treated with sodium dodecylsulfate (2.88 g, 10 mmol) as above to give salt **3b** (3.94 g, 87% yield) as a colorless gum.

(2*S*)-(−)-3,4-Dimethyl-2-[(*p*-methoxyphenyl)methyl]-1-[(1*R*)-1-phenylethyl]-1,2,5,6-tetrahydropyridine (4a) and Minor Isomers 5a and 8. A solution of *p*-methoxybenzylmagnesium chloride[16] in THF (22.4 mmol, 56 mL) was added dropwise to a solution of pyridinium salt **3a** (4.9 g, 10.3 mmol) in THF (200 mL) during 30 min at −78 °C. After 0.5 h at this temperature, the solution was warmed to 0 °C and stirred for 2 h. The resulting mixture was poured into a vigorously stirred ice-cooled solution of 32% aqueous ammonia saturated with NH_4Cl. This solution was then extracted with Et_2O, and the extract was dried with Na_2SO_4, filtered, and concentrated to ca. 20 mL. After addition of MeOH (180 mL) and water (20 mL), an excess of $NaBH_4$ (2 g, 53 mmol) was added portionwise. The reaction mixture was refluxed for 1 h, and after evaporation of solvents under reduced pressure, Et_2O was added to it. The organic phase was washed

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with water, dried, and concentrated. The gummy residue was dissolved in MeOH saturated with HCl, and the resulting salts were precipitated with pentane and collected after centrifugation. To this precipitate was added a saturated aqueous solution of $NaHCO_3$, and the organic bases were extracted with Et_2O. The crude product, obtained after removal of Et_2O under reduced pressure, was purified by flash chromatography on silica gel (100 g, heptane–EtOAc (95:5) to afford adduct **4a** as an oil which eluted first (1.37 g, 4.1 mmol, 40% yield) showing a single peak by GC: $[\alpha]_D = -46°$ (c 1.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.12–7.30 (7 H, m), 6.85 (2 H, d, J = 8 Hz), 3.81 (3 H, s), 3.70 (1 H, q, J = 6 Hz), 3.16–3.28 (1 H, m), 2.94 (1 H, ddd, J = 5, 12, 14 Hz), 2.66–2.85 (2 H, m), 2.51 (1 H, dd, J = 6, 14 Hz), 1.99–2.22 (1 H, m), 1.64 (6 H, s), 1.34–1.50 (1 H, m), 0.95 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$), δ 157.8, 146.9, 134.1, 130.5, 128.2, 127.5, 126.6, 125.8 (2 C), 113.3 (2 C), 61.6, 58.1, 55.4, 40.0, 37.6, 26.7, 22.5, 19.0, 17.5; HRMS (IC) calcd for $C_{23}H_{30}NO$ m/z 336.2327, obsd m/z 336.2314. Further elution allowed the isolation of small amounts of two minor diastereomers **5a** and **8** (single peaks by GC, for respective proportions see Table I). **Minor isomer 5a**: ^1H NMR (200 MHz, $CDCl_3$) δ 6.80–7.16 (7 H, m), 6.73 (2 H, d, J = 8 Hz), 3.79 (3 H, s), 3.66 (1 H, q, J = 6 Hz), 3.00–3.30 (2 H, m), 2.73–2.88 (1 H, m), 2.58–2.72 (2 H, m), 2.09–2.32 (1 H, m), 1.65 (3 H, s), 1.54–1.60 (1 H, m), 1.47 (3 H, s), 1.27 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$), δ 157.6, 146.7, 133.3, (130.5, 127.9, 127.5, 126.2), 125.59 (2 C), 113.3 (2 C), 58.9, 51.4, 39.4, 37.7, 26.9, 22.1, 18.9, 17.5; HRMS (IC) calcd for $C_{23}H_{30}NO$ m/z 336.2327, obsd m/z 336.2332. **Minor isomer 8** (tentative structure): ^1H NMR (200 MHz, $CDCl_3$) δ 7.23–7.50 (5 H, m), 6.69 (4 H, s), 3.69–3.83 (4 H, m), 3.29–3.94 (1 H, m), 2.86–3.02 (1 H, m), 2.73–2.85 (2 H, m), 2.30 (1 H, dd, J = 13, 11 Hz), 1.90–2.11 (1 H, m), 1.68 (3 H, s), 1.62 (3 H, s), 1.58 (1 H, m), 1.41 (3 H, d, J = 7 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$), δ 157.7, 145.9, 133.2, 130.1, 128.6, 127.5, 127.1, 123.4, 123.0, 113.8, 61.4, 55.3, 55.1, 50.8, 33.6, 28.6, 22.8, 18.8, 16.7; HRMS calcd for $C_{23}H_{30}NO$ m/z 336.2327, obsd m/z 336.2323.

(1*S*)-(−)-1-[(*p*-Methoxyphenyl)methyl]-2-[(1*R*)-1-phenylethyl]-1,2,3,4,5,6,7,8-octahydroisoquinoline (4b). Salt **3b** (1.86 g, 3.67 mmol) was treated with *p*-methoxybenzylmagnesium chloride (8 mmol), and the resulting adduct was reduced with $NaBH_4$ in MeOH–H_2O (9:1) following the procedure described for the preparation and purification of **4a** to give adduct **4b** as a colorless oil (0.698 g, 1.93 mmol, 53% yield): $[\alpha]_D = -50°$ (c 1.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.12–7.28 (7 H, m), 6.83 (2 H, d, J = 8 Hz), 3.79 (3 H, s), 3.54 (1 H, q, J = 6 Hz), 3.16 (1 H, m), 2.98 (1 H, ddd, J = 5, 11, 14 Hz), 2.75 (2 H, m), 2.54 (1 H, dd, J = 6, 14 Hz), 1.56–2.16 (9 H, m), 1.39 (1 H, m), 1.00 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 157.8, 146.7, 134.0, 130.5 (2 C), 129.9, 128.1 (2 C), 127.8, 127.5 (2 C), 126.6, 113.2 (2 C), 60.6, 58.2, 55.3, 40.0, 37.5, 30.3, 28.6, 25.9, 23.5, 23.3, 22.5; HRMS calcd for $C_{25}H_{32}NO$ m/z 362.2483, obsd m/z 362.2511.

(2*S*)-(−)-3,4-Dimethyl-2-(phenylmethyl)-1-[(1*R*)-1-phenylethyl]-1,2,5,6-tetrahydropyridine (4c). Salt **3a** (4.86 g, 10.2 mmol) in THF (200 mL) was treated with benzylmagnesium bromide in Et_2O (8 mmol) and then reduced with $NaBH_4$ in MeOH–H_2O (9:1), following the same procedure as for the preparation and purification of adduct **4a**. Adduct **4c** was obtained as a colorless oil (1.46 g, 4.78 mmol, 47% yield): $[\alpha]_D = -37°$ (c 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.13–7.33 (10 H, m), 3.70 (1 H, q, J = 6 Hz), 3.22–3.33 (1 H, m), 2.66–3.08 (3 H, m), 2.52 (1 H, dd, J = 6, 14 Hz), 2.12 (1 H, m), 1.66 (6 H, s), 1.43 (1 H, m), 0.94 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 147.0, 141.9, 129.7, 128.2, 127.8, 127.5, 125.9, 126.6, 125.6, 61.5, 58.0, 40.0, 38.6, 26.7, 22.6, 19.1, 17.5; HRMS calcd for $C_{22}H_{28}N$ m/z 306.2222, obsd m/z 306.2243.

(1*S*)-(−)-1-(Phenylmethyl)-2-[(1*R*)-1-phenylethyl]-1,2,3,4,5,6,7,8-octahydroisoquinoline (4d). Salt **3b** (0.28 g, 0.55 mmol) in THF (200 mL) was treated with benzylmagnesium bromide (1.2 mmol) in Et_2O (2.4 mL) and then reduced with $NaBH_4$ in MeOH–H_2O (9:1), following the same procedure as for the preparation and purification of adduct **4a**. Adduct **4c** was obtained as a colorless oil (0.116 g, 0.35 mmol, 64% yield): $[\alpha]_D = -49°$ (c 2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.15–7.25 (10 H, m), 3.75 (1 H, q, J = 6 Hz), 3.14–3.32 (1 H, m), 2.99 (1 H, ddd, J = 5, 11, 14 Hz), 2.89–2.90 (2 H, m), 2.55 (1 H, dd, J = 6 Hz), 1.54–2.07 (9 H, m), 1.30–1.50 (1 H, m), 0.98 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 146.7, 141.8, 129.7 (2 C), 128.2 (2 C), 127.9 (2 C), 127.8 (2 C), 127.5 (2 C), 126.6, 125.6, 125.6, 60.5, 58.2, 40.0, 38.5, 30.24, 28.6, 25.8, 23.4, 23.2, 22.4; HRMS calcd for $C_{24}H_{30}N$ m/z 332.2429, obsd m/z 332.2401.

(1*S*,5*S*,9*S*)-(+)-5,9-Dimethyl-2′-hydroxy-2-[(1*R*)-1-phenylethyl]-6,7-benzomorphan (9a). Tetrahydropyridine **4a** (0.5 g, 1.49 mmol) in a solution of 48% HBr in water (3 mL) was stirred at 135–140 °C during 36 h. The resulting mixture was poured on ice, 32% aqueous ammonia was added, and the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried, filtered, and concentrated. The residue was flash chromatographed on silica gel with heptane–EtOAc (60:40) affording benzomorphan **9a** (0.308 g, 0.96 mmol, 64% yield) as a foam: $[\alpha]_D = +126°$ (c = 1.4, $CHCl_3$); ^1H-NMR (200 MHz, $CDCl_3$) δ 7.21–7.43 (5 H, m), 6.94 (1 H, d, J = 8 Hz), 6.70 (1 H, d, J = 3 Hz), 6.61 (1 H, dd, 1 H, J = 3, 8 Hz), 3.71 (1 H, q, J = 6 Hz), 2.84–3.05 (2 H, m), 2.66–2.80 (1 H, m), 2.43 (1 H, dd, J = 6, 18 Hz), 2.01–2.21 (1 H, m), 1.71–2.00 (2 H, m), 1.30–1.43 (4 H, m), 1.27 (3 H, s), 0.65 (3 H, d, J = 6 Hz); ^{13}C-NMR (50.2 MHz, $CDCl_3$) δ 154.4, 145.3, 143.4, 128.6 (2 C), 128.2 (2 C), 127.6 (2 C), 127.0, 113.6, 112.6, 61.3, 54.8, 42.9, 42.2, 41.4, 36.3, 25.5, 23.6, 22.1, 14.3; EIMS m/z (rel intensity) 321 (33), 306 (100), 244 (17), 105 (20); exact mass calcd for $C_{22}H_{27}NO$ 321.2093, found 321.2100.

(9*S*,13*S*,14*S*)-(+)-3-Hydroxy-17-[(1*R*)-1-phenylethyl]morphinan (9b). A solution of the tetrahydropyridine **4b** (0.35 g, 0.98 mmol) in 85% orthophosphoric acid (3 mL) was stirred for 60 h at 140–145 °C. Purification following the same procedure as for **9a** gave morphinan **9b** (0.167 g, 0.48 mmol, 49% yield): $[\alpha]_D = +127°$ (c 1.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.22–7.46 (5 H, m), 6.96 (1 H, d, J = 7 Hz), 6.72 (1 H, d, J = 2 Hz), 6.63 (1 H, dd, J = 2, 7 Hz), 3.71 (1 H, q, J = 6 Hz), 2.853.06 (2 H, m), 2.64–2.75 (1 H, m), 2.37 (1 H, dd, J = 6, 18 Hz), 2.08–2.28 (1 H, m), 1.63–1.89 (2 H, m), 0.83–1.59 (9 H, m), 1.34 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 154.7, 145.4, 142.0, 129.4, 128.6 (3 C), 127.6 (2 C), 127.0, 113.6, 112.4, 61.4, 53.5, 44.8, 42.8, 42.1, 37.6, 36.6, 26.9, 26.6, 24.5, 22.4, 22.2; EIMS m/z (rel intensity) 347 (28), 332 (100), 270 (19); exact mass calcd for $C_{24}H_{29}NO$ 347.2249, found 347.2244.

(1*S*,5*S*,9*S*)-(+)-5,9-Dimethyl-2-[(1*R*)-1-phenylethyl]-6,7-benzomorphan (9c). A solution of the tetrahydropyridine **4c** (0.502 g, 1.64 mmol) in 85% orthophosphoric acid (4 mL) was stirred for 60 h at 140–145 °C. Purification following the same procedure as for **9a** gave morphinan **9c** (0.236 g, 0.77 mmol, 47% yield): $[\alpha]_D = +156°$ (c 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.00–7.46 (9 H, m), 3.72 (1 H, q, J = 6 Hz), 3.04 (1 H, d, J = 18 Hz), 2.83–2.96 (1 H, m), 2.70–2.77 (1 H, m), 2.51 (1 H, dd, J = 6, 18 Hz), 2.00–2.16 (1 H, m), 1.73–2.00 (2 H, m), 1.26–1.46 (1 H, m), 1.35 (3 H, s), 1.29 (3 H, d, J = 6 Hz), 0.68 (3 H, d, J = 7 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 146.5, 142.4, 137.0, 128.5 (2 C), 127.3 (2 C), 127.2, 126.8, 126.1, 125.6, 125.5, 60.9, 54.6, 42.9, 42.3, 42.1, 36.3, 24.7, 25.6, 22.8, 14.3; EIMS m/z (rel intensity) 305 (20), 290 (100), 228 (17), 105 (20); exact mass calcd for $C_{22}H_{27}N$ 305.2144, found 305.2145.

(1*S*,5*S*,9*S*)-(+)-5,9-Dimethyl-2-methyl-6,7-benzomorphan (10). Benzomorphan **9c** (0.205 g, 0.67 mmol) was dissolved in a mixture of AcOEt (10 mL), EtOH (10 mL), and 2.5 N aqueous HCl (5 mL). Palladium on carbon (0.02 g) was added to this solution which was stirred overnight under a hydrogen atmosphere. After filtration on Celite, the solvents were evaporated under reduced pressure. The resulting hydrochloride was dissolved in acetonitrile (20 mL), and to this solution were added aqueous formaldehyde (37%, 0.4 mL) and $NaCNBH_3$. After 0.25 h under stirring the pH of the solution was adjusted to 7 and maintained at this value during 0.75 h by addition of a few drops of AcOH. After basification with 2 N KOH (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined extracts were evaporated under reduced pressure. Flash chromatography on silica gel with a gradient of CH_2Cl_2 and CH_2Cl_2–MeOH (90:10) afforded pure **10** as an oil (0.108 g, 0.5 mmol, 75% yield): $[\alpha]_D = +63°$ (c 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.03–7.28 (4 H, m), 3.03 (1 H, d, J = 18 Hz), 2.84–2.91 (1 H, m), 2.69 (1 H, dd, J = 6, 18 Hz), 2.35–2.57 (1 H, m), 2.40 (3 H, s), 1.76–2.15 (3 H, m), 1.28–1.41 (1 H, m), 1.37 (3 H, s), 0.86 (3 H, d, J = 7 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 140.9, 135.2, 127.3, 126.6, 126.0, 125.7, 60.0, 47.6, 42.2, 41.4, 41.1, 35.5, 25.1, 23.7, 13.9; EIMS m/z (rel intensity) 215 (100), 200 (93), 124 (38); exact mass calcd for

$C_{15}H_{21}N$ 215.1674, found 215.1677. **10-HCl** was crystallized from acetone: mp 150–170 °C; $[\alpha]_D = +31°$ (c 1.2, EtOH). Anal. Calcd for $C_{15}H_{22}ClN$–$0.75H_2O$: C, 67.84; H, 8.93; Cl, 13.43; N, 5.28. Found: C, 68.06; H, 8.98; Cl, 13.62; N, 5.34.

(+)-Normetazocine [(1*S*,5*S*,9*S*)-2′-Hydroxy-6,7-benzomorphan]. Benzomorphan **9a** (0.28 g, 0.87 mmol) was dissolved in a mixture of AcOEt (15 mL), EtOH (15 mL), and 2.5 N aqueous HCl (7.5 mL). Palladium on carbon (0.03 g) was added, and the solution was stirred overnight under a hydrogen atmosphere. After filtration on Celite the solvents were evaporated under reduced pressure, dilute NH_4OH was added, and the product was extracted with CH_2Cl_2–MeOH (9:1, 3 × 20 mL). The combined organic phases were evaporated under reduced pressure and the crude product was crystallized from acetone to give **(+)-normetazocine** (0.13 g, 0.6 mmol, 69% yield): mp 259–263 °C (lit.[17] mp 260–262 °C); $[\alpha]_D = +69°$ (c 1.2, EtOH) [lit.[17] $[\alpha]_D = +70°$ (c 1, EtOH)]; ^1H NMR (200 MHz, $CDCl_3$) δ 6.89 (1 H, d, J = 8 Hz), 6.68 (1 H, d, J = 3 Hz), 6.57 (1 H, dd, J = 3, 8 Hz), 3.01–3.18 (2 H, m), 2.45–2.78 (3 H, m), 1.57–1.86 (2 H, m), 1.33 (3 H, s), 1.25–1.29 (1 H, m), 0.83 (3 H, d, J = 6 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 156.1, 143.6, 129.1, 128.2, 114.3, 113.3, 53.6, 43.4, 43.0, 39.8, 37.6, 32.4, 26.3, 14.2; EIMS m/z (rel intensity), 217 (20), 202 (70), 110 (60). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.11; O, 7.62. Found: C, 77.42; H, 8.81; N, 6.11; O, 7.36.

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(+)-Nordextrorphan [(9*S*,13*S*,14*S*)-3-Hydroxymorphinan]. Catalytic hydrogenation of **9b** (0, 166 g, 0.48 mmol), according to the procedure used for **9a**, gave (+)-nordextrorphan (0.08 g, 0.35 mmol, 69% yield) after crystallization from acetone: mp 258–259 °C (lit.[18] mp 260–262 °C); $[\alpha]_D = +40°$ (c 0.5, MeOH), [lit.[18] (–)-form, $[\alpha]_D = -41°$ (c 1, MeOH)]; ^1H NMR (200 MHz, $CDCl_3$) δ 6.81 (1 H, d, J = 8 Hz), 6.59 (1 H, d, J = 2 Hz), 6.46 (1 H, dd, J = 2, 8 Hz), 2.34–2.67 (3 H, m), 2.14–2.25 (1 H, m), 1.10–1.64 (9 H, m), 0.89–1.07 (1 H, m); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 157.2, 142.2, 129.7, 129.3, 114.4, 112.9, 52.3, 46.5, 43.3, 39.6, 39.0, 38.0, 33.3, 28.0, 27.9, 23.3. Anal. Calcd for $C_{16}H_{21}NO$–$0.12H_2O$: C, 78.24; H, 8.72; N, 5.70; O, 7.33. Found: C, 78.10; H, 8.68; N, 5.64; O, 7.63.

Acknowledgment. We thank G. Henry for efficient technical assistance.

Supplementary Material Available: ^{13}C and/or ^1H NMR spectra for compounds **1**, **2**, **3a–b**, **4a–d**, **9a–c**, **10**, (+)-normetazocine, and (+)-nordextrorphan and typical GC analysis corresponding to entries 2 and 10 (Table I) (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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