Synthesis and κ-Opioid Antagonist Selectivity of a Norbinaltorphimine Congener. Identification of the Address Moiety Required for κ-Antagonist Activity

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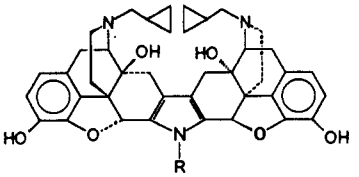
Compound **2**, which represents a structurally simplified congener of norbinaltorphimine **1a**, was synthesized in order to evaluate the role of its second basic nitrogen in conferring κ-opioid receptor antagonist selectivity. Congener **2** was found to be at least twice as selective as **1a** as a κ antagonist, while its *N*-carbobenzoxy derivative (**3**) was inactive at κ-receptors. This study establishes the importance of the second basic nitrogen of **1a** for κ-receptor recognition. It is proposed that this basic group mimics the guanidinium moiety of Arg^7, which may be the key κ-address component of dynorphin.

The bivalent ligands norbinaltorphimine (**1a**) and its methyl derivative (**1b**) are prototypical κ-selective opioid



1a, R = H
1b, R = CH_3

receptor antagonists.[1] They exhibit high pharmacologic selectivity in vitro and in vivo as well as high binding selectivity and are employed widely as pharmacologic tools in opioid research.[2]

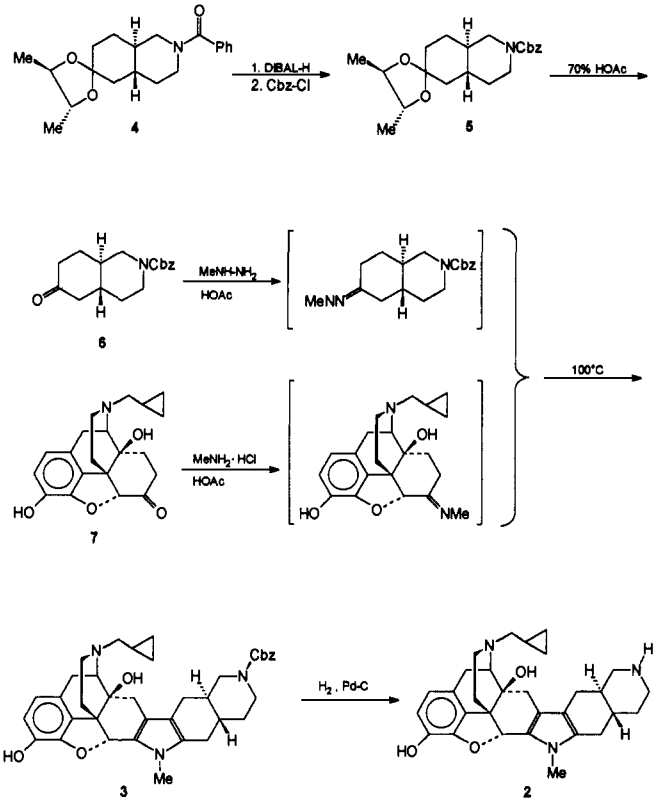
The design of **1a** was based originally on the concept of bridging two opioid recognition sites as a means of conferring selectivity.[3-5] However, subsequent studies revealed that a second antagonist pharmacophore is not required for κ-antagonist selectivity.[6,7] In this connection, we had postulated that the second basic nitrogen is the selectivity-conferring group, and that its orientation relative to the antagonist pharmacophore is important for κ-selectivity. Furthermore, we have suggested that this basic nitrogen serves as an Arg^7 mimic of the endogenous κ-selective opioid peptide dynorphin, which is believed[8] to be an important component of its "κ-address".

In the present study we have evaluated further the role of the second basic nitrogen by synthesizing a ligand (**2**) whose second basic nitrogen occupies the same position as that in **1a**, without the presence of other peripheral groups. The opioid antagonist activity of **2** was compared to that of its N-protected derivative (**3**), and the biological results have been found to be consistent with the idea that a basic nitrogen is essential for κ-selectivity.

Chemistry

The optically pure *trans*-octahydroisoquinoline **4** was prepared following a reported literature procedure.[9] The benzoyl group was removed with diisobutylaluminum hydride and the crude product was treated with benzyl chloroformate to give the carbobenzoxy derivative **5** in 58% yield (Scheme I). The ketal was hydrolyzed in

Scheme I



aqueous acetic acid to afford the ketone **6** in 94% yield. The ketone **6** was converted to the methylhydrazone in situ and was then reacted with the methylimine derivative of naltrexone (**7**) in acetic acid at 100 °C to give compound **3** in low yield (2%). No other octahydroisoquinoline product was detected. The major product, binaltorphimine (**1b**) (15%), was formed presumably by transfer of the methylhydrazone group to naltrexone during the reaction. The remainder of the reaction mixture contained unreacted naltrexone. The carbobenzoxy group of **3** was removed by hydrogenation in the presence of palladium catalyst to give compound **2** in 96% yield. The purity of **2** and **3** was evaluated and confirmed in two HPLC systems.

The NMR data was inconclusive in distinguishing between structure **3** and its possible regioisomer **8**. However, molecular models show that the octahydroisoquinoline ring in the nonlinear isomer **8** is sterically

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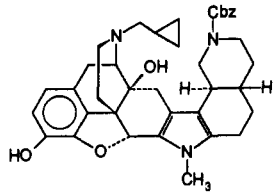


8

crowded due to the proximity of ring C of the morphinan, making it likely that 8 would be the preferred regioisomer formed in the reaction. Moreover, there is precedent for the formation of only the linear isomer from *N*-benzoyl-*trans*-octahydrohydroisoquinoline and (4-methoxyphenyl)hydrazine under Fischer indole reaction conditions.[10]

Pharmacological Testing

Testing was carried out on electrically stimulated guinea pig ileal longitudinal muscle[11] and mouse vas deferens[12] preparations as described previously.[13] The compounds **2** and **3** were converted to their HCl salts, dissolved in modified Krebs solution, and incubated with the preparations 15 min prior to testing with either morphine (M), ethylketazocine (EK), or [D-Ala^2,D-Leu^5]enkephalin[14] (DADLE). These agonists are selective for μ-, κ-, and δ-opioid receptors, respectively. Concentration–response curves were obtained in the absence (control) and presence of the antagonist in the same preparation and were expressed as IC_{50} values. The IC_{50} ratios listed in Table I represent the IC_{50} in the presence of antagonist divided by the control IC_{50} value. None of the antagonists possessed agonist activity at a concentration of 100 nM.

Compound **2** was about one-quarter the potency of the reference standard **1a** in the antagonism of EK. However, because **2** was also less effective in antagonizing the agonist effect of morphine and DADLE, its κ-selectivity ratios are 2 times greater than those of **1a**. The *N*-carbobenzoxy derivative **3**, by contrast, was not a κ-antagonist and was not κ-selective.

Discussion

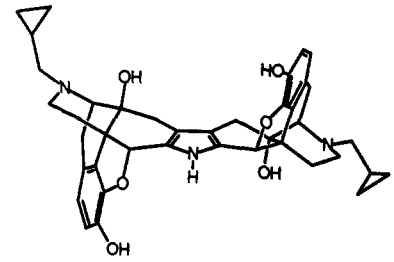
As illustrated in Figure 1, the orientation of the basic nitrogens in the bivalent ligand norbinaltorphimine (**1a**) is similar relative to that of its simplified congener **2**. Moreover, the octahydroisoquinoline trans ring juncture of **2** confines its basic nitrogen to a single conformation. The fact that **2** is a selective κ-opioid receptor antagonist strongly suggests that the peripheral groups of **1a** do not play a key role in determining κ-selectivity. In this regard, the importance of the basic nitrogen was demonstrated further by the inactivity of **3** at κ-receptors, as the carbobenzoxy group renders this nitrogen neutral at physiologic pH.

The results of the present study are consistent with a model that envisages the κ-opioid receptor to contain two key recognition subsites,[2] a "message" subsite and an "address" subsite.[15] The message subsite, which is involved in signal transduction, presumably is located within the cavity formed by the seven transmembrane helices of the G-protein-coupled opioid receptor, as is the case for receptors in this class.[16] This subsite normally would interact with the message component of the opioid peptide and this would trigger a conformational change in the receptor which in turn would result in the activation of the coupled G-protein.

Table I. Antagonist Potencies in Smooth Muscle Preparations

	IC_{50} ratio[a] ± SEM			selectivity ratio	
compd	EK (κ)[b]	M (μ)[b]	DADLE (δ)[c]	κ/μ	κ/δ
1a[d]	181 ± 7	8.3 ± 1.8	10.4 ± 2.9	22	17
2	40 ± 10	1.0 ± 0.09	1.1 ± 0.1	40	36
3	1.6 ± 0.5	1.7 ± 0.6	9.2 ± 2.4	0.9	0.2

[a] The IC_{50} of the agonist in the presence of the antagonist (100 nM) divided by the IC_{50} of the agonist alone in the same preparation. The number of replicate assays ≥3. [b] Determined in the guinea pig ileum preparation using ethylketazocine (EK) or morphine (M). [c] Determined in the mouse vas deferens preparation using [D-Ala^2,D-Leu^5]enkephalin (DADLE). [d] Data taken from ref 19.



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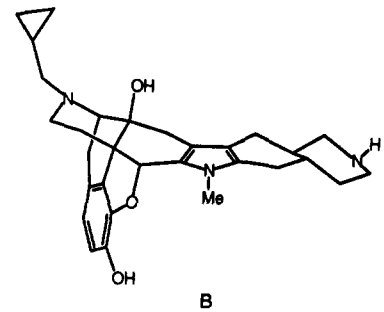
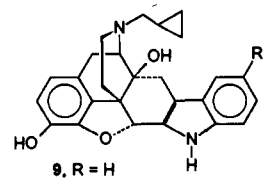


B

Figure 1. Comparison of a 3-dimensional representation of norbinaltorphimine (**1a**) (A) with that of its congener, **2** (B). Note the very similar orientation of the basic groups in **1a** and **2**.

Although the message–address concept was proposed[15] originally for agonists, it may serve as a model for antagonists if they interact with the message subsite to stabilize the receptor in an antagonist state. In the case of **1** and **2**, such stabilization would be promoted by the *N*-(cyclopropylmethyl)tyramine moiety.

The address subsite serves merely as a recognition locus for enhancing affinity and it is not involved in signal transduction. Accordingly, the key recognition element in the address domain of dynorphin is believed to be Arg^7 and possibly Arg^{6,8,17} It is conceivable that the second basic nitrogen in **1** and **2** may confer κ-selectivity to these ligands by mimicking the key selectivity determinants in the dynorphin address domain. Indeed, we have very recently demonstrated the importance of a κ-address mimic by transforming the δ opioid antagonist naltrindole (**9**) into a κ-antagonist (**10**) merely by the attachment of an amidine group.[18]



9, R = H
10, R = $CH_2NH(CNH)$alkyl

As the basic groups of **1a** and **2** are ~11 Å apart, it seems reasonable that anionic groups in the extracellular domains

of the κ-receptor could serve as components of the address subsite.[16] The report that ligands whose basic groups are held at shorter distances are less κ-selective suggests that the cationic address element in 1 and 2 must extend a critical distance in order to associate with a counterion on the address domain of the receptor.[19] This assumes that the message subsite is located approximately in the upper third of the cavity formed by the transmembrane domains, as suggested from the position of Asp 138 of the κ-receptor.[16] This residue, which has been implicated in all G-protein-coupled receptors that bind cationic ligands,[20] might associate with the tyramine cationic nitrogen in 1 and 2.

Experimental Section

Nuclear magnetic resonance spectra were performed on IBM-Bruker AC-300, IBM-Bruker AC-200, and Varian Unigy-500 spectrometers, and chemical shifts are reported as δ values (ppm) relative to Me_4Si or $CDCl_3$. IR spectra were recorded on a Nicollet 5DXC FT-IR spectrometer and peak position are expressed in cm^{-1}. Mass spectra were obtained on AEI MS 30, Finnigan 4000 CI, VG70, 70EHF, and Sciex API III instruments. TLC data were determined with Merck Art. 5554 DC-Alufolien Kieselgel 60 F_{254}. Column chromatography was carried out on E. Merck silica gel 60 (230–400 mesh) or alumina oxide from M. Woelm Eschwege. HPLC columns are REGIS 10D-60 ODS-FEC, 50 cm × 21.1 mm i.d. and 7.1 cm × 21.1 mm i.d., and Dynamax macro HPLC Si column, 250 × 21.1 mm, purchased from Rainin. Melting points were determined in open capillary tubes on Thomas-Hoover apparatus and were uncorrected.

Spiro[(benzyloxycarbonyl)-1,3,4,5,7,8,9(*R*),10(*R*)-octahydroisoquinoline]-6,2′-(4′(*R*),5′(*R*)-dimethyl-1′,3′-dioxolane)], 5. Compound 4[9] [1.0019 g, 3.0412 mmol; $[\alpha]_D$ −9.4° (lit.[9] $[\alpha]_D$ −8.75°)] in toluene (40 mL) cooled in a dry ice/acetone bath was added dropwise to 1 M diisobutylaluminum hydride (DIBAL-H) solution in hexane (3.1 mL, 3.1 mmol). Additional DIBAL-H solution (10.5 mL) was added in divided portions until TLC monitoring of the reaction showed no further decrease in starting material 4. After allowing the reaction mixture to warm to room temperature, 1 M NaOH (20 mL) was added and it was shaken with sodium tartrate. To the separated toluene layer was added 1 M NaOH (10 mL), sodium bicarbonate (saturated, 10 mL), and benzyl chloroformate (0.55 mL, 0.60 g, 3.9 mmol), and the mixture was stirred vigorously at 25 °C for 4 h. The toluene layer was separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (20 mL × 3), dried ($MgSO_4$), filtered, and concentrated to give a residue which was dried under vacuum at 55–60 °C overnight to give an oil (1.08 g). The oil was purified by flash-chromatography (silica, EtOAc/hexane 1:3) to afford 5 as an oil (633 mg, 1.76 mmol, 58%): ^1H NMR ($CDCl_3$) δ 1.02–1.35 (m, 10 H, two methyls can be distinguished: 1.21 (d, J = 5.7 Hz), 1.23 (d, J = 5.8 Hz)), 1.35–1.47 (t, 1 H), 1.47–1.62 (m, 3 H), 1.73 (m, 2 H), 2.39 (m, 1 H), 2.73 (m, 1 H), 3.60 (m, 2 H, H4 and H5), 4.15 (m, 2 H), 5.10 (s, 2 H, benzyl), 7.31 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 16.834 and 17.016 (2 Me), 27.211 (C_8), 32.415 (C_4), 35.501, 43.446, 44.246 and 49.401 (C_1, C_3, C_5 and C_7), 38.223 and 40.599 (C_9 and C_{10}), 66.692 (benzyl), 77.932 and 78.123 (C_4' and C_5'), 107.855 (C_6), 127.838, 127.894, 128.446 and 136.983 (Ph), 155.242 (carbamate); IR (KBr) 2970, 2930, 2865, 1700, 1435, 1374, 1363, 1219, 1145, 1100 cm^{-1}; mass spectrum m/e 359 (M^+, EI); R_f = 0.43 (silica gel, 75% hexane/25% EtOAc); $[\alpha]_D$ −7.7° (c = 1.09, $CHCl_3$).

2-(Benzyloxycarbonyl)-1,3,4,5,7,8,9(*R*),10(*R*)-octahydro-6-isoquinolone, (6). The ketal 5 (2.98 g, 8.29 mmol) in acetic acid/water (7:3, 200 mL) was heated on a steam bath for 100 min. Solvent was removed on a rotary evaporator and the residue was dissolved in EtOAc (150 mL) and washed successively with brine (30 mL), 1 M sodium carbonate (30 mL × 2), and brine (30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to afford an oil which was purified by flash chromatography (silica gel, EtOAc/hexane 1:1) to afford 6 (2.3074 g, 8.03 mmol, 94%) as a solid: ^1H NMR ($CDCl_3$) δ 1.05–1.65 (m, 5H), 1.89 (m, 1 H), 2.03 (m, 1 H), 2.2–2.43 (m, 4 H), 2.85 (m, 1 H), 4.20 (m, 2 H), 5.10 (s, 2 H, benzyl), 7.3 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 29.472 (C_8), 32.770 (C_4), 40.000 and 41.548 (C_9 and C_{10}), 40.707, 43.739, 47.430, and 48.981 (C_1, C_3, C_5, and C_7), 67.076 (benzyl), 127.840, 127.974, 128.461, and 136.762 (Ph), 155.092 (carbamate), 209.660 (C_6), IR (KBr) 2925, 2862, 1716, 1690, 1435, 1235, 1137, 1080 cm^{-1}; mass spectrum m/e 287 (M^+, EI); R_f = 0.41 (silica, 50% hexane/50% EtOAc); $[\alpha]_D$ −41.8° (c = 0.93, $CHCl_3$).

17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5β-epoxy-6,7:2′,3′-[[*N*-(benzyloxycarbonyl)piperidino][3,4-*f*](*N*-methyl-4′,5′(*R*),6′(*R*),7′-tetrahydroindolo)]morphinan, 3. Naltrexone free base (1.9679 g, 5.7641 mmol) was dissolved in hot acetic acid (4.1 mL) and methylamine (40% aqueous solution, 497 μL, 179 mg, 5.77 mmol) was added. In another flask the ketone 6 (1.4898 g, 5.1843 mmol) was dissolved in hot acetic acid (2.9 mL), and methylhydrazine (276 μL, 239 mg, 5.19 mmol) was added. Both flasks were heated on a steam bath with occasional stirring for 6 min. The two solutions were mixed, and the combined solution was heated on a steam bath with occasional stirring for 2.5 h. Acetic acid was evaporated in vacuo and the residue was shaken with ethyl acetate/water/ammonium hydroxide. The aqueous phase was extracted twice with ethyl acetate. The combined organic solution was dried ($MgSO_4$), filtered, and concentrated to give an oil which was subjected to gradient elution column chromatography (silica gel, 168 g; column diameter, 6.7 cm). The solvent (4 L) was 3–20% methanol/48.5–40% EtOAc/48.5–40% hexanes/0.5% ammonium hydroxide, followed by 950 mL of 99.5 methanol/0.5% ammonium hydroxide. Fractions which showed a singlet at 5.5 ppm for H_5 proton on NMR were collected and purified further by gradient elution column chromatography (alumina, 91 g; column diameter, 4.0 cm). The solvent (3.9 L) was 3–20% methanol/48.5–40% ethyl acetate/48.5–40% hexanes/0.4% ammonium hydroxide, followed by methanol (850 mL). The product was purified further by HPLC (Dynamax macro HPLC Si column, 250 × 21.1 mm; flow rate, 9 mL/min, solvent, 8% methanol/1% ammonium hydroxide/45.5% EtOAc/45.5% hexane; t_R = 9.52 min) to give compound 3 (50 mg, 1.6%): ^1H NMR ($CDCl_3$) δ 0.12–0.14 (m, 2 H, H_{20} and H_{21}), 0.53–0.55 (m, 2 H, H_{20} and H_{21}), 0.86 (m, 1 H, H_{19}), 1.2–1.6 (m, 3 H), 1.6–1.85 (m, 2 H), 1.85–2.1 (m, 2 H), 2.1–2.6 (m, 10 H), 2.6–2.85 (m, 3 H), 3.06 (d, J = 18.3 Hz, 1 H, H_{10}), 3.23 (d, J = 6 Hz, 1 H, H_9), 3.45 (s, 3 H, methyl), 4.1–4.3 (m, 1 H), 4.95 (broad, 1 H), 5.11 (s, 2 H, benzyl), 5.59 (s, 1 H, H_5), 6.48 (d, J = 8.1 Hz, 1 H, H_1), 6.59 (d, J = 8.1 Hz, 1 H, H_2), 7.33 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 3.553 and 3.794 (C_{20} and C_{21}), 9.180 (C_{19}), 22.865 (C_{10}), 24.962, 28.453, 28.922, 31.580, and 32.656 (C_8, C_{15}, C_{25}, C_{26}, and C_{27}), 28.777 (methyl), 37.262 (C_{28} and C_{29}), 43.456 (C_{16}), 44.142 and 49.807 (C_{22} and C_{24}), 47.743 (C_{13}), 59.241 (C_{18}), 62.095 (C_9), 66.797 (benzyl), 73.045 (C_{14}), 85.582 (C_5), 112.580 and 115.555 (C_7 and C_{31}), 116.365 (C_2), 118.060 (C_1), 121.555 (C_{11}), 125.138 (C_{12}), 127.584, 127.685, 128.233, and 128.8 (Ph), 130.796 and 136.675 (C_6 and C_{30}), 138.629 (C_4), 142.994 (C_3), 155.014 (carbamate); IR (KBr) 3325, 2924, 2854, 1701, 1504, 1455, 1321, 1230, 1117, 752 cm^{-1}; mass spectrum m/e 622 ($M + 1^+$, FAB), 622.3237 ($M + H^+$, FAB, calcd for $C_{38}H_{44}N_3O_5$ 622.3281), 622 ($M + 1^+$, ion spray); R_f = 0.50 (silica gel, 8% MeOH/1% NH_4OH/45.5% EtOAc/45.5% hexane); mp >180 °C; $[\alpha]_D$ −307° (c = 1.14%, EtOH). The product 3 was chromatographically pure in two HPLC systems, reverse-phase HPLC (preparative column; flow rate, 10 mL/min; solvent, 30% water/30% methanol/40% acetonitrile with 0.1% trifluoroacetic acid; t_R = 12.80 min) and normal phase HPLC (preparative column; flow rate, 10 mL/min; solvent, 8% methanol/46% ethyl acetate/46% hexane; ethyl acetate and hexane were shaken with ammonium hydroxide before mixing with methanol; t_R = 12.03 min).

17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5β-epoxy-6,7:2′,3′-[piperidino[3,4-*f*](*N*-methyl-4′,5′(*R*),6′-(*R*),7′-tetrahydroindolo)]morphinan, 2. Compound 3 (6.5 mg, 10.5 μmol) in EtOAc/MeOH (1:1, 2 mL) and HOAc (0.1 mL) was stirred with 10% Pd/C (5 mg) under hydrogen at room temperature for 40 min. The catalyst was removed by filtration and solvent was evaporated to give a crude compound 2 (4.9 mg, 96%). The crude product was combined with products from other batch reactions and purified by reverse-phase HPLC: ^1H NMR ($CDCl_3$) δ 0.06–0.12 (m, 2 H, H_{20} and H_{21}), 0.48–0.53 (m, 2 H, H_{20} and H_{21}), 0.85 (m, 1 H, H_{19}), 1.05–1.5 (m, 3 H), 1.5–1.9 (m, 5 H), 1.9–2.1 (m, 2 H), 2.1–2.5 (m, 7 H), 2.5–2.7 (m, 3 H),

2.95–3.15 (m, 2 H), 3.185 (d, J = 6 Hz, 1 H, H_9), 3.47 (s, 3 H, methyl), 4.8 (broad, 1 H), 5.52 (s, 1 H, H_5), 6.299 (d, J = 7.8 Hz, 1 H, H_1), 6.381 (d, J = 7.8 Hz, 1 H, H2); ^{13}C NMR ($CDCl_3$) δ 3.776 and 3.966 (C_{20} and C_{21}), 9.434 (C_{19}), 22.682, 23.003, 25.722, 28.414, 31.913, and 32.474 (C_8, C_{10}, C_{15}, C_{25}, C_{26}, and C_{27}), 30.135 (methyl), 36.528 and 36.855 (C_{28} and C_{29}), 43.776 (C_{16}), 47.846 (C_{13}), 55.911 and 62.131 (C_{22} and C_{24}), 59.517 (C_{18}), 62.461 (C_9), 73.233 (C_{14}), 85.069 (C_5), 112.670 and 115.308 (C_7 and C_{31}), 115.647 (C_2), 117.660 (C_1), 122.140 (C_{11}), 123.874 (C_{12}), 129.147 (C_6), 131.142 (C_{30}), 140.567 (C_4), 143.669 (C_3); IR (KBr) 3409, 2924, 1630, 1461, 1384, 1321, 674 cm^{-1}; mass spectrum m/e 488 (M + 1$^+$, FAB), 488.2867 (M + H$^+$, calcd for $C_{30}H_{38}N_3O_3$ 488.2913), 488 (M + 1$^+$, electrospray); $[\alpha]_D$ −267° (c = 0.16%, EtOH); R_f = 0.55 (silica, 10% MeOH/1% NH_4OH/89% $CHCl_3$). The product **2** was chromatographically pure in two HPLC systems, reverse-phase HPLC (preparative column; flow rate, 10 mL/min; solvent, 30% water/30% methanol/40% acetonitrile with 0.1% trifluoroacetic acid; t_R = 8.94 min) and normal-phase HPLC (preparative column; flow rate, 10 mL/min; solvent, 55% methanol/22% ethyl acetate/22% hexane/1% ammonium hydroxide; t_R = 8.57 min).

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