Reactions of Nepenthone with Chromium(II) Reagents in Neutral Aqueous Medium

Károly Micskei,*[a] Julianna Gyarmati,[a] Gábor Kovács,[a] Sándor Makleit,[b] Csaba Simon,[c] Zoltán Szabó,[c] János Marton,[c] Sándor Hosztafi,[c] Helmut Reinke,[d] and Hans-Joachim Drexler[d]

Keywords: Morphine alkaloids / 6,14-Ethenomorphinans / Chromium(II) complex reagents / Organochromium(III) complex intermediates

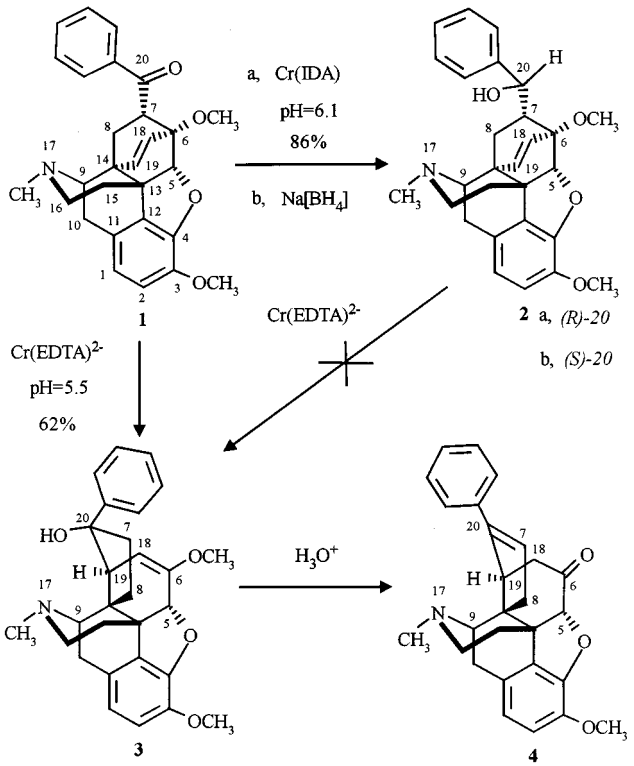
A synthetic method for the selective transformations of a selected morphine alkaloid in neutral aqueous medium is introduced. Full diastereoselectivity was achieved by the transformation of nepenthone (**1**) with $[Cr(ida)(H_2O)_3]$ into **2a** (20*R*) showing a complementary method as compared to the reactions with classical reagents to result in **2b** (20*S*). A new unexpected morphine derivative **3** was prepared by a ligand-induced modification of the reaction which involves an unprecedented rearrangement.

Introduction

There has recently been an increase in interest in the poppy alkaloids, because of the wide range of possibilities they offer for the production of biologically important semi-synthetic derivatives.[1] Thebaine is extensively used as a starting material for the preparation of a number of potent opiate agonists, agonists/antagonists or antagonists.[2] Diels−Alder cycloaddition reactions of thebaine result in numerous natural product derivatives, especially the classical "nepenthone" (**1**) (Scheme 1). The reduction of the double bond of the etheno bridge of **1** was studied without success and this finding has been explained theoretically.[3] We performed the reduction of the double bond of **1** by means of catalytic hydrogenation with a chemoselectivity of 69%.[4]

Since 1957, when Anet and LeBlanc[5a] prepared the benzylchromium(III) ion, "organochromium(III) reagents"[5b] have become one of the most powerful and selective groups of agents in modern organic synthesis. Numerous organic functional groups can be transformed selectively, thus demonstrating the effectiveness of the synthetic methodology based on Cr^{II}.[5c−e] Kochi et al. characterized some organochromium(III) complex intermediates in aqueous medium, and pointed out the key role of the coordination sphere in the regulation of reactivity.[5f] Recently, we published the application of this chemistry in neutral aqueous medium (so called "biomimetic syntheses") in the fields of carbohydrates and epoxides.[6]

[a] Department of Inorganic and Analytical Chemistry, Lajos Kossuth University,
Egyetem tér 1, H-4010 Debrecen, Hungary
Fax: (internat.) + 36-52/489667
E-mail: kmicskei@tigris.klte.hu
[b] Department of Organic Chemistry, Lajos Kossuth University, Egyetem tér 1, H-4010 Debrecen, Hungary
[c] ICN-Alkaloida Hungary Company Ltd., H-4440 Tiszavasvári, Hungary
[d] Fachbereich Chemie, University of Rostock, Buchbinderstraße 9, D-18051 Rostock, Germany



Scheme 1

In this work we demonstrate a methodology based on organochromium(III) chemistry for selective transformation of the "natural product" derivative **1** in a strictly "biomimetic setup" using only additives to control the reactivity and selectivity.

Results and Discussion

Nepenthone (**1**) has two functional groups which can formally be reduced by Cr^{II}: the C-20 carbonyl and the C-

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18−C-19 double bond. We wanted to reduce this C-18−C-19 double bond by using different Cr^{II} complex species at controlled pH in aqueous medium. Using the aqua complex $[Cr(H_2O)_6]^{2+}$ the starting material was recovered quantitatively without any reaction, as shown by monitoring with TLC. The coordinated ligand in the $[Cr(ida)(H_2O)_3]$ complex enhanced the reactivity of the metal ion only towards the carbonyl group and the fully chemoselective reduction resulted in **2a**. Detailed NMR-spectroscopic studies determined the (20*R*) configuration of **2a**, demonstrating that not only has the reactivity of the complex been changed dramatically upon addition of the achiral ida ligand, but that the chirality in the substrate **1** induces a quantitative enantiomer excess on C-20 in a diastereoselective manner. The reduction of **1** was reported to give a secondary alcohol with $Na[BH_4]$ in methanol [or with $Al(iPrO)_3$ in 2-propanol] but its configuration has not been determined.[3a] We also prepared this compound in the same way and its (20*S*) configuration of **2b** was determined by NMR. The diastereoselectivity in these reactions could be explained by steric factors.[3b] Changing the coordinated ligand for edta the reactivity of the $[Cr(edta)]^{2-}$ complex increased dramatically. An unexpected reaction pathway could be observed resulting in a new morphine derivative **3** (Scheme 1). ^1H- and ^{13}C-NMR studies together with X-ray crystallography (Figure 1) support the structure and absolute configuration of **3**. The acid-catalyzed transformation of **3** resulted in **4**. It should be pointed out that transformation **1** → **3** also proceeds with quantitative diastereoselectivity.

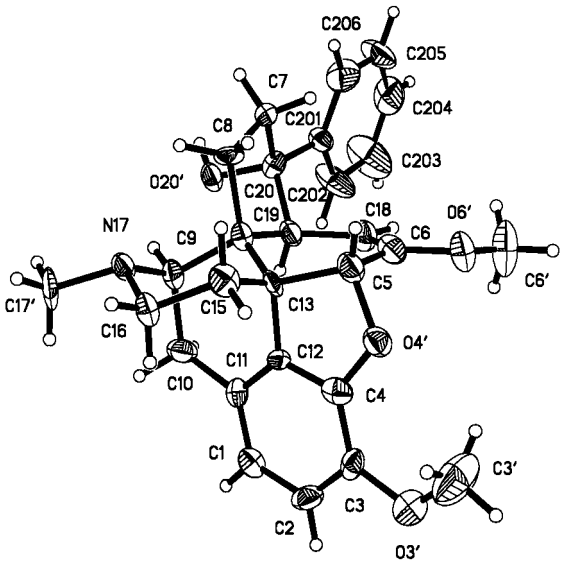


Figure 1. X-ray structure of **3**

For interpretation of the synthetic results UV/Vis spectroscopy can be used to monitor the organometallic assistance in the process of these reactions (see Figure 2). The reaction between the C-20 carbonyl group and the $Cr^{II}L$ has not been previously studied but some findings for the reaction between the Cr^{II} and benzaldehyde[7a] support the assignment of an organometallic bond. The absorption vs. time measurements in the UV region indicate the formation

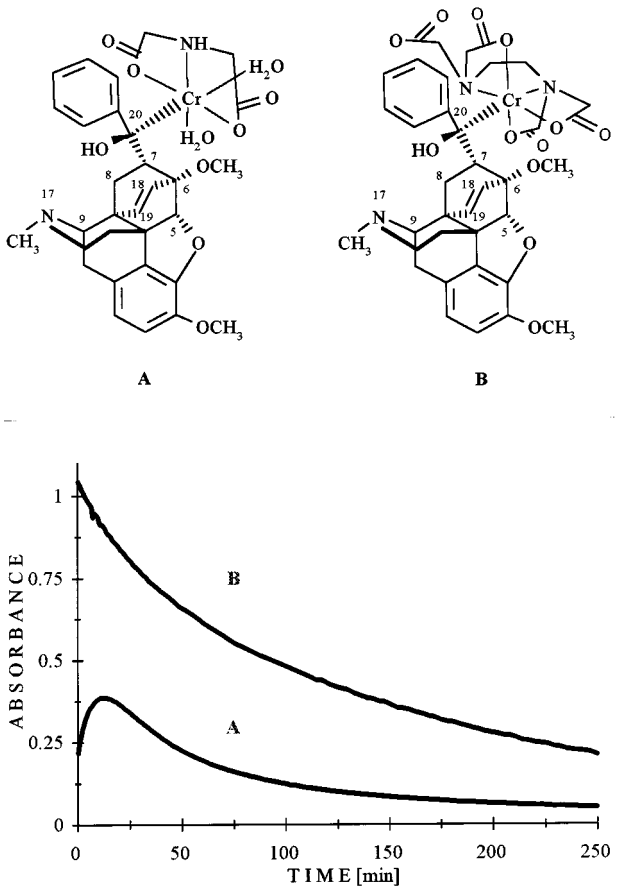
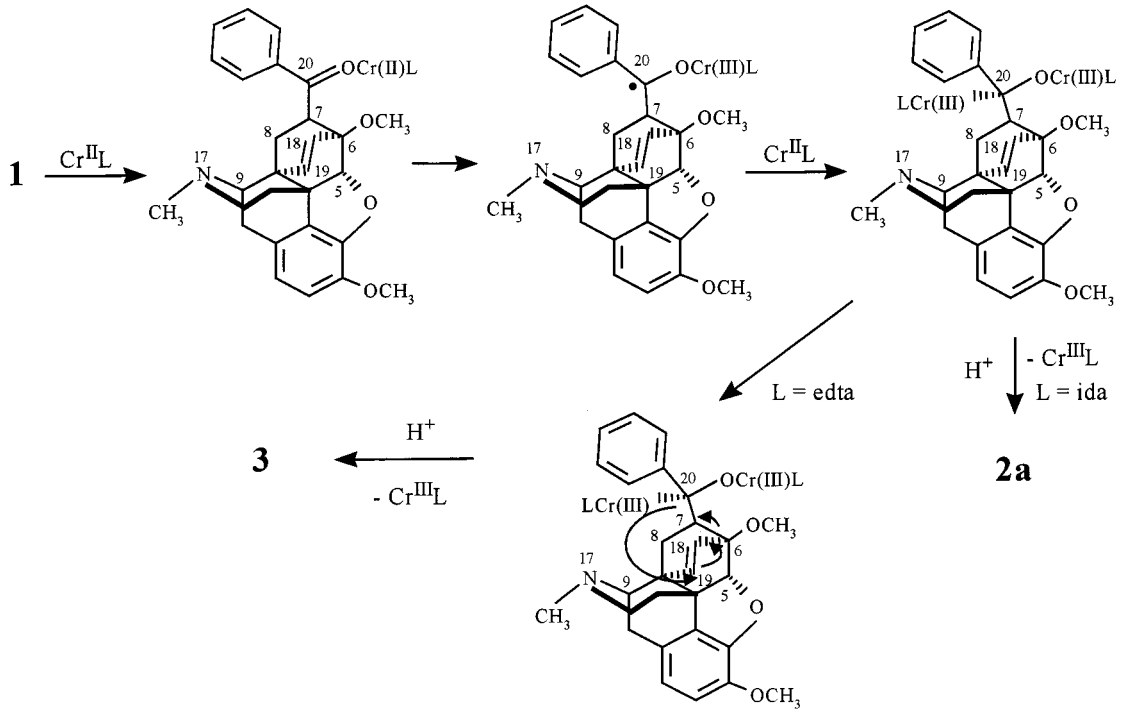


Figure 2. Absorbance vs. time plots of the (nepenthone)chromium(III) complex intermediates detected at 320 nm; $[Cr^{2+}]$ = 4.7 mM, [nepenthone] = 0.5 mM, [edta] = 15 mM, [tda] = 100 mM; pH = 5.7 and 6.4, respectively, solvent H_2O; T = 25°C; I = 0.1 M KCl in 1.00-cm cell

of the organochromium(III) complex intermediates[7b] to be different depending on the ligand used. In the case of ida the formation of the organometallic species requires some minutes (**A**: max. abs. after 13 min) while in the case of edta it is almost two orders of magnitude faster (**B**: max. abs. before 10 s), due to the higher reactivity of the $[Cr(edta)]^{2-}$ complex. The supposed formation mechanism of these intermediates (see Scheme 2) can be divided[7c] into three ligand-independent steps: coordination of the $Cr^{II}L$ to the carbonyl oxygen atom, followed by electron transfer resulting in a radical at C-20, and its reaction with another $Cr^{II}L$ species forming the organochromium bond. The subsequent fate of these intermediates ($\tau_A \approx 49$ min; $\tau_B \approx 130$ min) is completely different because of the different coordination spheres. **A** contains two water molecules in the first coordination sphere which can react with the organochromium bond as an internal electrophile resulting in **2a**. The coordinated edta ligand in **B** together with the hydrophobic skeleton pushes out the water molecules from the organometallic complex intermediate, therefore, protonation of the C−Cr bond as in **A** is no longer probable. In **B** the benzylic C-20 carbanion attacks the C-19 carbon atom of the etheno bridge which is followed by a concerted electron shift as depicted in Scheme 2. Finally, the carbanion on C-



Scheme 2

7 is protonated. The coordinated alcoholato group should also be protonated during the reaction, probably after the radical formation. The observation that neither thevinone (CH_3−C-20) nor the secondary alcohols (**2a**, **2b**) react under these conditions supports our suggested mechanism. The methyl group of thevinone cannot stabilize the carbanion at C-20 and the formation of a carbanion can also be excluded in the cases of secondary alcohols (Scheme 1).

Experimental Section

Melting points (uncorrected): Büchi-535 instrument. − TLC: DC-Fertigplatten, Kieselgel 60 F254 (Merck-5719). Eluent systems (each v/v): benzene/methanol (8:2) [A], chloroform/methanol (9:1) [B], chloroform/acetone/diethylamine (5:4:1) [C]. The spots were visualised with UV light or with the Dragendorff reagents. − Elemental analyses: Carlo Erba automatic analyser. − ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz): Varian Gemini-200 instrument using a 5-mm dual probe head at 25°C, TMS at $\delta = 0$ or $CDCl_3$ at $\delta = 77.0$ or C_6D_6 at $\delta = 128.7$ as internal standards. Carbon multiplicities could be determined with the aid of standard Varian APT (Attached Proton Test) sequence using a 7 ms delay period which gives quaternary or secondary carbon atom signals up and primary or tertiary carbon atom signals down. Proton and carbon assignments are based on COSY-45 and HETCOR experiments. Non-protonated carbon atoms were assigned by one-dimensional selective INEPT spectra using DANTE-type excitation of suitable protons. For the standard Varian NOEDIF experiments a presaturation time of 6 s was applied. Since the proton spectra of compounds **3** and **4** were quite crowded in $CDCl_3$, we used C_6D_6 as solvent. In this solvent less overlap of the multiplets could be observed and there was a possibility of their selective excitation for the homonuclear NOE difference and long-range INEPT experiments. The configuration of compound **3** is based on the following observation: The 2D COSY-45 spectrum showed the existence of two ethano bridges (C-15−C-16 and C-7−C-8). By selective saturation of 9-H, besides the 10-H and N−CH_3 signals, an NOE could be observed on a signal at $\delta = 2.65$, which is coupled by 5-H (J = 1.5 Hz). It can be explained by a five-bond homoallylic coupling through C-5, C-6, C-18, and C-19, so the signal mentioned can be assigned to 19-H. (Similar coupling can be observed in morphine and codeine derivatives between 6-H and 14-H). Selective saturation of the signal at $\delta = 3.8$ gives NOE on the 6-OCH_3 signal as well as on 19-H. Considering this observation and the coupling with 19-H (J = 2.2 Hz), the mentioned proton must be 18-H. Saturating the signal of 19-H, significant NOE was observed on 18-H and on the phenyl protons, reflecting their proximity. The selective INEPT experiments are in accordance with the NOE results and also confirm the structure. Namely, the 5-H proton is long-range-coupled with C-6, C-4, and C-12. 9-H is coupled to C-11, C-14, C-16, and C-13. 18-H showed long-range couplings with C-6, C-20, C-5, and C-14, while 8-H coupled with C-6, C-18, and C-20, confirming the supposed structure. In the case of compounds **2a** and **2b** the configuration of C-20 was confirmed by recently reported NOE-difference-spectroscopic studies.[4] The difference between the couplings of 20-H and 7-H are in accordance with the the observed NOEs by saturation of 20-H, and confirm the configurations of C-20.

Preparation of 2a: Iminodiacetate (ida) (0.53 g, 4 mmol H_2ida) with 5.57 mmol of OH^- (2.00 mL, 2.783 M KOH) was dissolved in 35 mL of water at room temp. and the solution magnetically stirred while bubbling argon through it for 15 min. $[Cr(OAc)_2 \cdot H_2O]_2$ (0.38 g, 1 mmol, 2 mmol Cr^{II}) was added in one portion under argon. The colour of the solution turned slowly blue indicating the formation of the reactive complex [Cr^{II}(ida)] in a high concentration. (For the preparation of the reactive $[Cr^{II}(L)_i(H_2O)_x]^{n+}$ complexes (L = ida, edta) equilibrium calculations[8a] were necessary, using the known formation constants,[8b] to give the sample compositions in the 5 < pH < 7 range. Thus, if necessary the pro-

tonation of the OAc^- as well as of the tertiary nitrogen atom in the morphine skeleton was also considered. Nepenthone bitartrate (0.59 g, 1 mmol) was added in one portion to the solution of the complex and the colour of the mixture began to turn deep violet. The reaction vessel was than stoppered under a slight overpressure of argon, and the stirring continued for 18 h. Then the pH of the mixture was carefully adjusted to 10 with satd. NH_3 solution and extracted with chloroform (3 ×). The organic phase was washed with water (3 ×), than dried with Na_2SO_4. The solvent was evaporated under reduced pressure. A small amount of the unreacted starting material **1** was separated from the product by column chromatography. Yield: 0.38 g (86%), m.p. 185−186°C. − $C_{28}H_{31}NO_4$ (445.6): calcd. C 75.48, H 7.01, N 3.14; found C 75.32, H 7.10, N 3.18.

2a: ^{1}H NMR (in $CDCl_3$): δ = 1.35 (dd, 1 H, (8α-H, J_1 = 12.5 Hz, J = 6.6 Hz), 1.70−1.95 [m, 2 H, 15(2)-H], 2.05 (s, 1 H, 20-OH), 2.10−2.50 [m, 5 H, 7-H, 8β-H, 10α-H, 16(2)-H], 2.29 (s, 3 H, NCH_3), 3.12 (d, 1 H, 9-H, J = 6.2 Hz), 3.18 (d, 1 H, 10β-H, J = 18.2 Hz), 3.71 (s, 3 H, 6-OCH_3), 3.81 (s, 3 H, 3-OCH_3), 4.61 (d, 1 H, 5-H, J = 1.5 Hz), 5.20 (d, 1 H, 20-H, J = 2.0 Hz), 5.49 (d, 1 H, 19-H, J = 8.7 Hz), 5.88 (dd, 1 H, 18-H, J_1 = 8.7 Hz, J_2 = 1.5 Hz), 6.51 (d, 1 H, 1-H, J = 8.0 Hz), 6.62 (d, 1 H, 2-H, J = 8.0 Hz), 7.20−7.40 (m, 5 H, phenyl protons). − ^{13}C NMR (in $CDCl_3$): δ = 22.07(C-10), 25.01(C-8), 33.26(C-15), 42.87(C-13), 43.24(C-7), 43.66(N−CH_3), 45.31(C-16), 47.26(C-14), 52.53(6-OCH3), 56.46(3-OCH_3), 58.89(C-9), 69.93(C-20), 80.56(C-6), 94.68(C-5), 113.48(C-2), 119.33(C-1), 126.77(C-18), 128.38(C-11), 134.25(C-12), 136.43(C-19), 141.93(C-3), 148.35(C-4), 125.76, 126.91, 128.20, and 143.43 (phenyl carbon atoms).

Preparation of 2b: See ref.[3a]

2b: ^{1}H NMR (in $CDCl_3$): δ = 0.51 (dd, 1 H, 8α-H, J_1 = 12.7 Hz, J_2 = 5.5 Hz), 1.79 (ddd, 1 H, 15(eq)-H, J_1 = 13.2 Hz, J_2 = 4.0 Hz, J_3 = 1.8 Hz), 1.93 (ddd, 1 H, 15(ax)-H, J_1 = 13.2 Hz, J_2 = 6.0 Hz, J_3 = 6.0 Hz), 2.20−2.43 [m, 5 H, 7-H, 8β-H, 10α-H, 16(2)-H], 2.23 (s, 3 H, NCH_3), 2.98 (d, 1 H, 9-H, J = 6.5 Hz), 3.15 (d, 1 H, 10β-H, J = 18.7 Hz), 3.83 (s, 6 H, 6-OCH_3, 3-OCH_3), 4.32 (d, 1 H, 20-H, J = 9.0 Hz), 4.63 (d, 1 H, 5-H, J = 1.5 Hz), 5.39 (s, 1 H, 20-OH), 5.57 (d, 1 H, 19-H, J = 9.0 Hz), 6.05 (dd, 1 H, 18-H, J_1 = 8.8 Hz, J_2 = 1.2 Hz), 6.51 (d, 1 H, 1-H, J = 8.2 Hz), 6.62 (d, 1 H, 2-H, J = 8.2 Hz), 7.20−7.40 (m, 5 H, phenyl protons). − ^{13}C NMR (in $CDCl_3$): δ = 22.14 (C-10), 30.37 (C-8), 32.95 (C-15), 42.55 (C-13), 43.35 (C-7), 44.05 (N−CH_3), 45.35 (C-16), 46.69 (C-14), 54.96 (6-OCH_3), 56.71 (3-OCH_3), 59.76 (C-9), 77.65 (C-20), 84.43 (C-6), 97.41 (C-5), 112.66 (C-2), 119.33 (C-1), 124.70 (C-18), 128.32 (C-11), 134.31 (C-12), 137.41 (C-19), 141.87 (C-3), 147.69 (C-4), 127.58, 128.06, 128.22, and 141.83 (phenyl carbon atoms).

Preparation of 3: Ethylenediaminetetraacetate (edta) Na_2edta · 2 H_2O (0.82 g, 2.2 mmol) with 3.34 mmol of OH^- (1.20 mL, 2.783 M KOH) was dissolved in 35 mL of water (further procedures as for **2a**). The main product was separated with column chromatography from the minor products. Monitoring by TLC and HPLC-MS three more derivatives could be observed in addition to the main product, which are currently the subject of studies. Yield: 0.28 g (62%), m.p. 234−235°C. − $C_{28}H_{31}NO_4$ (445.6): calcd. C 75.48, H 7.01, N 3.14; found C 75.69, H 6.97, N 3.20. − MS (FAB or TSP); *m*/*z*: 446 $[M + H]^+$. − MS (EI, 70eV); *m*/*z* (%): 445 (17) $[M^+]$, 430 (16) $[M - CH_3]^+$.

3: ^{1}H NMR (in C_6D_6): δ = 1.15 (br., 1 H, 20-OH), 1.50−2.00 [m, 4 H, 15(2)-H, 8α-H, 7-H], 2.15−2.40 [m, 3 H, 16(2)-H, 7-H], 2.30 (s, 3 H, NCH_3), 2.65 (dd, 1 H, 19-H, J_1 = 2.2 Hz, J_2 = 1.5 Hz), 2.78 (s, 3 H, 6-OCH_3), 2.80−3.00 (m, 2 H, 10α-H, 8β-H), 3.15 (d, 1 H, 10β-H, J = 18 Hz), 3.61 (s, 3 H, 3-OCH_3), 3.80 (d,1 H, 18-H, J = 2.2 Hz), 4.08 (d, 1 H, 9-H, J = 5.2 Hz), 4.78 (d, 1 H, 5-H, J = 1.5 Hz), 6.68 (d, 1 H, 1-H, J = 8.0 Hz), 6.75 (d, 1 H, 2-H, J = 8.0 Hz), 7.00−7.20 (m, 5 H, phenyl protons). − ^{13}C NMR (in C_6D_6): δ = 21.80 (C-10), 29.94 (C-8), 32.71 (C-15), 35.87 (C-7), 44.52 (N−CH_3), 45.93 (C-13), 46.94 (C-16), 49.98 (C-14), 51.94 (C-19), 54.13 (6-OCH_3), 57.62 (3-OCH_3), 63.90 (C-9), 87.45 (C-5), 87.74 (C-20), 101.63 (C-18), 116.64 (C-2), 119.64 (C-1), 128.81 (C-11), 134.35 (C-12), 144.61 (C-3), 145.53 (C-4), 152.50 (C-6), 127.60, 128.07, 128.99, and 146.30 (phenyl carbon atoms).

Preparation of 4: 160 mg (0.36 mmol) of **3** was dissolved in 50 mL of 3% HCl solution and refluxed for 3 h. After cooling, the acidic solution was made alkaline with satd. NH_3 solution and extracted with chloroform. The pruduct (140 mg, 94%) remaining after removal of the solvent was sufficiently pure for structural elucidation by ^{1}H and ^{13}C NMR. − $C_{27}H_{27}NO_3$ (413.5): calcd. C 78.42, H 6.58, N 3.39; found C 78.21, H 6.50, N 3.43.

4: ^{1}H NMR (in C_6D_6): δ = 1.39 (ddd, 1 H, 15(eq)-H, J_1 = 16.5 Hz, J_2 = 4.1 Hz, J_3 = 3.3 Hz), 1.66 (ddd, 1 H, 15(ax)-H, J_1 = 16.5 Hz, J_2 = 13.2 Hz, J_3 = 3.3 Hz), 2.20 (s, 3 H, NCH_3), 2.00−2.28 [m, 5 H, 16(2)-H, 18(eq)-H, 10α-H, 8α-H], 2.30 (dd, 1 H, 18a-H, J_1 = 13.8 Hz, J_2 = 9.9 Hz), 2.62 (d, 1 H, 9-H, J = 5.7 Hz), 2.83 (d, 1 H, 10β-H, J = 18 Hz), 2.87 (ddd, 1 H, 19-H, J_1 = 9.9 Hz, J_2 = 1.5 Hz, J_3 = 1.5 Hz), 3.41 (dd, 1 H, 8β-H, J_1 = 18.2 Hz, J_2 = 3.3 Hz), 3.63 (s, 3 H, 3-OCH_3), 4.52 (d, 1 H, 5-H, J = 1.7 Hz), 5.97 (dd, 1 H, 7-H, J_1 = 3.3 Hz, J_2 = 2.2 Hz), 6.62 (d, 1 H, 1-H, J = 8.0 Hz), 6.78 (d, 1 H, 2-H, J = 8.0 Hz), 6.95−7.10 (m, 5 H, phenyl protons). − ^{13}C NMR (in C_6D_6): δ = 21.08 (C-10), 34.50 (C-15), 39.27 (C-18), 39.32 (C-8), 43.73 (N−CH_3), 45.91 (C-16), 47.99 (C-13), 48.50 (C-19), 48.82 (C-14), 57.67 (3-OCH_3), 62.00 (C-9), 92.35 (C-5), 117.23 (C-2), 120.91 (C-1), 128.85 (C-11), 126.42 (C-7), 133.38 (C-20), 135.41 (C-12), 144.09 (C-3), 144.74 (C-4), 204.51 (C-6), 126.72, 128.10, 129.50, and 147.07 (phenyl carbon atoms).

Details of the Crystal-Structure Determination: Crystal dimensions (mm): 0.12 × 0.2 × 0.24; crystal system: orthorhombic; space group: $P2_12_12_1$; unit cell dimensions and volume: a = 7.3240(15) Å, b = 13.342(3) Å, c = 23.298(5) Å, V = 2276.6(8) Å^3; $\rho_{calcd.}$: 1.300; $2\Theta_{max}$: 46°; radiation: Mo-K_α; wavelength: 0.71069; scan mode: laser-scanned imaging plate; temp. of measurement: 293 K; no. of measured and independent reflections: 6007/3046; no. of reflections included in the refinement: 3042; σ limits: $I > 2\sigma(I)$; no absorption corrections because of low μ [mm^{-1}]: 0.086; method of structure solution and program: direct methods (Siemens SHELXTL); method of refinement and program: full-matrix least squares (Siemens SHELXTL); no. of parameters: 310; treatment of H atoms: riding model; *R*: 0.0559 for observed; *wR2*: 0.1694 for all; refinement against $|F^2|$; residual electron density: 0.22/−0.254 e/Å^3. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100884. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (internat.) + 44-1223/336−033; E-mail: deposit@ccdc.cam.ac.uk).

UV/Vis Measurements: A deoxygenated ligand (L) and aqueous solution of **1** were placed in a quartz tandem cell. The cell was sealed by means of silicon rubber caps and flushed with Ar, using hypodermic needles as inlet and outlet. A known volume of $CrCl_2$ solution[8b] was added through a hypodermic needle from a specially designed vessel which stored a stock solution. The cell was then closed under a small overpressure, shaken and then placed in the spectrophotometer (HP 8452A, 300−800 nm region).

Acknowledgments

This work was supported by the Hungarian Scientific Research Foundation (Grants: OTKA No. T19413 and No. T25047). Dr. Zoltán Dinya is thanked for the MS measurements, Dr. László Somsák (Department of Organic Chemistry) and Dr. József Emri (Department of Inorganic and Analytical Chemistry) for discussion of the manuscript. Prof. Gyula Pályi (Department of Chemistry, University of Modena, Italy) is also thanked for his advice, particularly in the field of organometallic chemistry.

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Received July 15, 1998
[O98321]