104-92-7; **3** ($R^{2,3}$ = OMe, $R^{1,4}$ = H), 2859-78-1; **3** ($R^{2,4}$ = OMe, $R^{1,3}$ = H), 17715-69-4; **3** ($R^{1,4}$ = OMe, $R^{2,3}$ = H), 25245-34-5; **3** ($R^{2,3}$ = OCH_2O, $R^{1,4}$ = H), 2635-13-4; **3** (R^1 = F, $R^{\neq 1}$ = H), 1072-85-1; **5a**, 66947-60-2; **5b**, 55171-77-2; **5b'**, 22246-27-1; **5c**, 81447-58-7; **5d**, 118112-18-8; **5e**, 75833-45-3; **5f**, 118112-19-9; **5g**, 118112-20-2; **6**, 118112-25-7; *p*-dibromobenzene, 106-37-6.

Syntheses of Symmetric α,α,α-Tris(imidazolylmethyl)acetonitriles: A New Class of Tripod M^{2+}-Chelating Ligands

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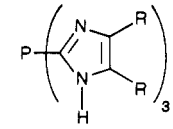
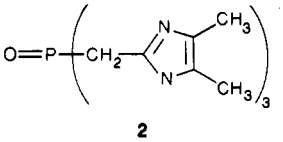
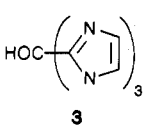
We have been interested in investigating the properties of tris(imidazolyl)·M^{2+} complexes (**1**, **2**) as potential models for the active site of carbonic anhydrase (CA).[1] Of these, **1c,d**·Zn^{2+} show good activity in facilitating attainment of the $HCO_3^- \rightleftarrows CO_2$ equilibrium in alcohol/H_2O media[1c,e] and **2**·Co^{2+} is a good spectroscopic model for Co^{2+}·CA.[1d]

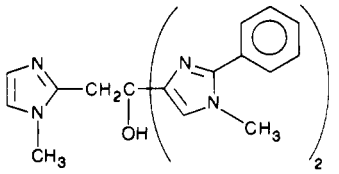






1a: R = H
b: R = CH_3
c: R = $CH(CH_3)_2$
d: R = $CH_2CH_2CH_3$

2 **3**



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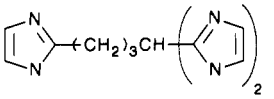

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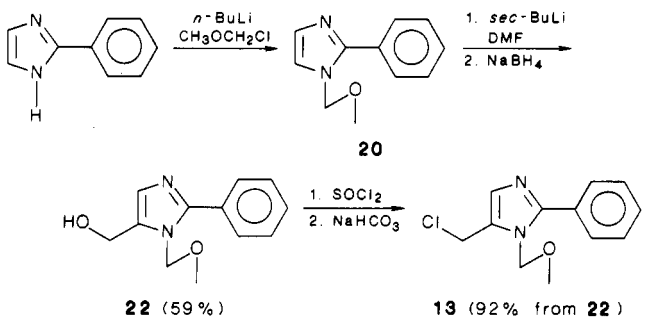
Synthetic studies have been reported by Breslow's group on related ligands including **3**–**5**,[2] but the metal complexes of these are deficient as active CA models. In the case of **3** and related tris(imidazolyl) carbinols[1a,2] the ligands are too small to encapsulate the metal in a four coordinate geometry since (2L·M^{2+}) octahedral coordination is observed. Attempts to suppress the 2:1 complexation by inserting sterically demanding groups distal to the imidazole C_2 or C_4 point of attachment to the carbinol lead to dehydration and the production of highly colored quinoid-type species.[1a,2b] Both the binding and dehydration problem were circumvented by replacing the HOC anchor with a phosphorus as in **1** or **2**. However, these compounds too were deficient since they exhibited a limited solubility in H_2O and required EtOH/H_2O solvent systems for physical study. Even so, they were unstable as their Zn^{2+} complexes for prolonged periods in these media and suffered P–C cleavage to produce bis(imidazolyl)phosphinic acid·Zn^{2+} products.[3]

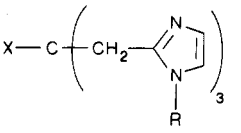
Scheme I



20

22 (59%) **13** (92% from **22**)

In order to address the above problems, we initiated a synthetic project to create symmetric ligands with a CH_2 unit inserted between the imidazole unit and a central carbon atom as in **6** or **7**. Despite the obvious interest in



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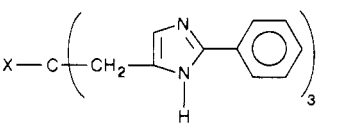

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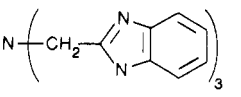


8

so-called "tripod" ligands as models for metallo enzymes,[4] we are unaware of general approaches to carbon-based examples of this class[5] although the synthesis of the tetracoordinating **8**[6] and related tris(pyrazolylmethyl)amines[7] has been reported. In this paper we describe the general method for the syntheses of **6** and **7** (X = CN): We will describe elsewhere the properties of the M^{2+} complexes.

Results and Discussion

Several initial attempts at simple nucleophilic approaches to a tris(imidazolylmethyl) ligand were unsuccessful. For example, attempted 3-fold displacement of I^- from tris(iodomethyl)methane[8] with 3 equiv of the lithio anions **9**, **10**, or **11** in THF (–60 °C → room temperature) afforded only the starting materials, presumably from elimination of HI. The same occurred when the coupling reactions were conducted with the cuprates prepared[9] from **9** or **10**. Although the reaction of 3 equiv of **12** with diethyl carbonate is unlikely to produce a trisalkylated product due to proton abstraction from an intermediate imidazole acetic ester,[2a] we tried the reactions with the Ce(III) anions since these are reported to be useful in nucleophilic additions to easily enolized C=O units.[9] This too was unsuccessful.

Since the nucleophilic routes were unsuccessful, sequential halide displacement from three chloromethyl im-

(1) (a) Brown, R. S.; Huguet, J. *Can. J. Chem.* **1980**, *58*, 889. (b) Brown, R. S.; Huguet, J. *J. Am. Chem. Soc.* **1980**, *102*, 7571. (c) Brown, R. S.; Curtis, N. J.; Huguet, J. *Ibid.* **1981**, *103*, 6933. (d) Brown, R. S.; Salmon, D.; Curtis, N. J.; Kusuma, S. *Ibid.* **1982**, *104*, 3188. (e) Ślebocka-Tilk, H.; Cocho, J. L.; Frakman, Z.; Brown, R. S. *Ibid.* **1984**, *106*, 2421.

(2) (a) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918. (b) Breslow, R.; Hunt, J. T.; Smiley, R.; Tarnowski, T. *Ibid.* **1983**, *105*, 5337.

(3) Ball, R. G.; Brown, R. S.; Cocho, J. L. *Inorg. Chem.* **1984**, *23*, 2315.

(4) Brown, R. S.; Huguet, J.; Curtis, N. J. In *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker, Inc.: New York, 1983; Vol. 15, pp 55–99.

(5) As far as we are aware, the only representative of this general ligand class is tris(2-pyridylmethyl)-2-picoline formed in 18% as a side product from the reaction of 2-(chloromethyl)pyridine with sodium acetylide (Zune, A. E.; Hollstein, U.; Litchman, W. M. *J. Org. Chem.* **1974**, *39*, 2461).

(6) Thompson, L. K.; Ramaswamy, B. S.; Seymour, E. A. *Can. J. Chem.* **1977**, *55*, 878.

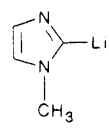
(7) (a) Mani, F. *Inorg. Nucl. Chem. Lett.* **1981**, *17*, 45. (b) Mani, F.; Scapacci, G. *Inorg. Chim. Acta* **1980**, *38*, 151. (c) Bertini, I.; Canti, G.; Luchinate, C.; Mani, F. *Ibid.* **1980**, *46*(B1), L91.

(8) Latour, S.; Wuest, J. D. *Synthesis* **1987**, 742.

(9) Normant, J. F. *Synthesis* **1972**, 63.

(10) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, 4233.

0022-3263/89/1954-1439$01.50/0



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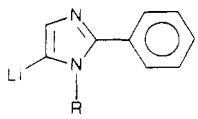
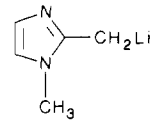


10: R = CH_2OCH_3
11: R = $SO_2N(CH_3)_2$



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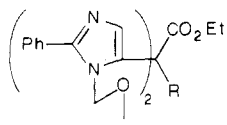


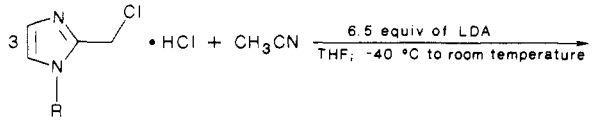
14: R = CO_2Et
15: R = H

idazoles by a suitable nucleophilic carbanion was attempted. Via the route shown in Scheme I, the HCl salt of 5-(chloromethyl)-2-phenyl-1-(methoxymethyl)imidazole (**13**·HCl) could be synthesized in 59% overall yield from 1-(methoxymethyl)-2-phenylimdazole. The neutral species (**13**) is produced from its more stable HCl salt in 92% isolated yield.

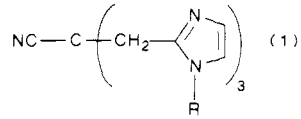
Successive bisalkylation of diethyl malonate with **13** was accomplished in 53% yield to give diethyl (imidazolylmethyl)malonate, **14**. This material was saponified with alcoholic KOH, and the resulting diacid was decarboxylated and reesterified in a single step with 32% H_2SO_4 in EtOH to give ethyl bis(imidazolyl) acetate (**15**). (For preparation of **14** and **15** see the supplementary material). Attempts to further alkylate **15** with **13** in the presence of LDA in THF alone or in combination with HMPA[11] (−60 °C → room temperature) failed to yield the α,α,α-trisubstituted ethyl acetate, and it became clear that steric encumbrance in the anion of **15** prevented the introduction of a third imidazolylmethyl group.

Nitrile-stabilized carbanions have been extensively used in nucleophilic displacements of halides,[12] but there are relatively few reports of trisalkylation,[13] particularly with bulky alkylating agents. However, it seemed reasonable that replacement of the ester unit by a linear C≡N group would alleviate the steric problems in the alkylation of **15**, so as a final approach, successive trisalkylation of CH_3CN with (chloromethyl)imidazoles **13** and **16** was attempted.

The general procedure adopted (illustrated with **16**) is given in eq 1 and involves mixing acetonitrile and 3 equiv of the imidazolylmethyl chloride hydrochloride salt in THF (−40 °C) and subsequent treatment with 6.5 equiv of LDA over a 90-min period. The mixture is then allowed to come



16a: R = CH_3
b: R = CH_2OCH_3

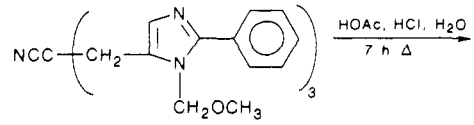


(1)

17a: R = CH_3
b: R = CH_2OCH_3

to room temperature with continued stirring overnight. In our hands, the nonoptimized yields of isolated purified trisalkylated product are low (**17a**, 16%; **17b**, 14%; **18**, 18%) but tolerable considering the simplicity of the method and otherwise scarcity of the targets.

For the synthesis of tris(imidazolylmethyl)acetonitriles, an *N*-methoxymethyl substituent, despite its difficulty in removal,[14] is the protecting group of choice since more sterically demanding protecting groups interfere with the alkylation. The deprotection is accomplished (53%) as in eq 2 by a reported method[15] wherein the tris(*N*-methoxymethyl)imidazole precursor is heated at reflux for 7 h in a 10:1:1 (v/v mixture) HOAc–concentrated HCl–H_2O mixture. Under these conditions the CN group remains intact, its reticience to hydrolyze presumably being attributable to steric crowding.



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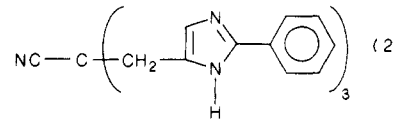

(2)

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In summary, a new class of tris(imidazolyl) ligands can be obtained by three sequential alkylations of acetonitrile in a single pot using 3 equiv of an N-protected 2- or 5-(chloromethyl)imidazole and a strong nonnucleophilic base. While we have not initiated studies to this effect, it seems likely that the methodology could simply be extended to other tris chelating agents where the heterocyclic base is pyridine, benzimidazole or (benz)thiazole.

Experimental Section

General. Melting and boiling points are uncorrected. ^1H NMR spectra were recorded with a Bruker WP-80 spectrometer.

General Procedure for the Preparation of 1-(Methoxymethyl)imidazoles. The appropriate imidazole was dissolved in dry THF (0.21 mol of 2-phenylimidazole in 1.5 L or 0.37 mol of imidazole in 700 mL of THF) and cooled to −10 °C with stirring under Ar. *n*-BuLi (1.1 equiv of 2.5 M in hexane) was added through a double-ended needle at such a rate that the temperature did not rise above 0 °C. The resulting slurry was stirred for 30 min at 0 °C. Chloromethyl methyl ether (1.1 equiv) (**CAUTION**: cancer suspect agent) was slowly added to the reaction mixture at −10 °C in the case of 2-phenylimidazole and at 0 °C in the case of imidazole. The reaction mixture was allowed to warm to room temperature and stirred overnight under Ar. THF was evaporated, water (60–100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 250 mL). After usual workup, the crude oil was distilled with a Kugelrõhr apparatus to yield 30.8 g (78%) of **20** and 24.8 g (60%) of **21** as colorless liquids.

1-(Methoxymethyl)-2-phenylimidazole (20): bp 138–141 °C (0.7 Torr); ^1H NMR δ ($CDCl_3$) 3.38 (s, 3 H), 5.25 (s, 2 H), 7.18 (s, 2 H), 7.40–7.63 (m, 3 H), 7.70–7.95 (m, 2 H); exact mass, *m/z* 188.0951 (calcd for $C_{11}H_{12}N_2O$ 188.0950). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.28; H, 6.36; N, 14.63.

1-(Methoxymethyl)imidazole (21): bp 77–80 °C (1.0 Torr); ^1H NMR δ ($CDCl_3$) 3.25 (s, 3 H), 5.20 (s, 2 H), 7.03 (s, 1 H), 7.05 (s, 1 H), 7.58 (s, 1 H); exact mass, *m/z* 112.0641 (calcd for $C_5H_8N_2O$ 112.0637). Anal. Calcd for $C_5H_8N_2O$: C, 53.55; H, 7.19; N, 24.98. Found: C, 53.43; H, 7.20; N, 24.75.

(11) MacPhee, J. A.; Dubois, J. E. *J. Chem. Soc., Perkin Trans. 1* **1977**, 694.
(12) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.
(13) Representative examples of tris alkylations have been reported. (a) CH_3I: Krüger, C. R.; Rochow, E. G. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 617. (b) CH_3CH_2Br: Sperber, N.; Papa, D.; Schwenk, E. *J. Am. Chem. Soc.* **1948**, *70*, 3091. (c) *n*-PrBr: Larcheveque, M.; Debal, A.; Cuvigny, T. *C. R. Acad. Sci., Ser. C* **1975**, *280*, 889. (d) *i*-PrI: Newman, M. S.; Fukunaga, T.; Miwa, T. *J. Am. Chem. Soc.* **1960**, *82*, 873. (e) Benzyl chloride: Gornowicz, G. A.; West, R. *Ibid.* **1971**, *93*, 1714.
(14) Manoharan, T. S.; Brown, R. S. *J. Org. Chem.* **1988**, *53*, 1107.
(15) VanderStelt, C.; Hofmann, P. S.; Funcke, A. B. H. *Eur. J. Med. Chem.* **1978**, *13*, 251.

General Procedure for the Preparation of (Hydroxymethyl)imidazoles. The appropriate 1-(methoxymethyl)-imidazole (**20** or **21**) was dissolved in dry THF (0.15 mol of **20** or 0.22 mol of **21** in 550 mL of THF) and cooled to −40 °C with stirring under Ar. *sec*-BuLi (1.1 equiv of 1.5 M in hexane) in the case of **20** or *n*-BuLi (1.1 equiv of 2.5 M in hexane) in the case of **21** was added via syringe or double-ended needle at such a rate that the temperature did not rise above −35 °C. The resulting pink slury (**20**) or pale yellow solution (**21**) was stirred for 30 min at −40 °C to −35 °C, and then dry DMF (1.1 equiv) was added. The system was allowed to warm to room temperature and stirred overnight. After that period, water (70–90 mL) was added, and the solution was stirred for 10 min and then THF was evaporated. Usual workup with methylene chloride for extractions (3 × 250 mL) yielded the crude aldehyde, which was directly reduced to the (hydroxymethyl)imidazole as follows. The crude aldehyde was dissolved in 100 mL of methanol with stirring in a flask protected by a $CaCl_2$ drying tube and cooled to 0 °C with ice. Sodium borohydride (2 equiv) was slowly added at such a rate that the reaction was not too vigorous. The system was allowed to warm to room temperature and stirred overnight. Methanol was evaporated, water (50 mL) was added, and the product was extracted with $CHCl_3$ (3 × 250 mL) to yield the crude desired alcohol (**22** or **23**).

5-(Hydroxymethyl)-1-(methoxymethyl)-2-phenylimidazole (22) was recrystallized from ethyl acetate–benzene to give 19.3 g of pure **22** (59%) as a colorless compound: mp 97–99 °C; ^{1}H NMR δ ($CDCl_3$) 3.25 (s, 3 H), 4.68 (s, 2 H), 4.90–5.15 (br, 1 H, OH), 5.30 (s, 2 H), 6.98 (s, 1 H), 7.40–7.83 (m, 5 H); exact mass, m/z 218.1053 (calcd for $C_{12}H_{14}N_2O_2$ 218.1055).

2-(Hydroxymethyl)-1-(methoxymethyl)imidazole (23) was recrystallized from benzene to give pure 12.8 g of **23** (41%) as a colorless compound: mp 78–80 °C; ^{1}H NMR δ ($CDCl_3$) 3.33 (s, 3 H), 4.70 (s, 2 H), 5.38 (s, 2 H), 5.63–5.93 (br s, 1 H, OH), 6.93 (s, 1 H), 7.00 (s, 1 H); exact mass, m/z 142.0741 (calcd for $C_6H_{10}N_2O_2$ 142.0742).

General Procedure for the Preparation of (Chloromethyl)imidazole Hydrochlorides (13·HCl and 16b). A solution of the appropriate (hydroxymethyl)imidazole (**22** or **23**) (0.04 mol) in 20 mL of chloroform was slowly dropped into a stirring solution of thionyl chloride (0.12 mol) in 100 mL of chloroform at 0 °C under dry conditions over a period of 45 min in the case of **22** and 5 min in the case of **23**. The system was allowed to warm to room temperature and stirred overnight. Then it was warmed at 40–45 °C for 30 min. Most of the volatiles were removed at 40–45 °C with a water suction pump connected to the flask with a protecting calcium chloride guard tube. Toward the end, 20 mL of dry benzene was added, and the volatiles were fully evaporated. The residue was dried in vacuum to yield the desired moisture-sensitive (chloromethyl)imidazole hydrochloride (**13**·HCl or **16b**) in quantitative yield.

13·HCl: mp 96–98 °C; ^{1}H NMR δ ($CDCl_3$) 3.40 (s, 3 H), 4.90 (s, 2 H), 5.58 (s, 2 H), 7.58–7.78 (m, 4 H), 7.80–8.00 (m, 2H). Anal. Calcd for $C_{12}H_{14}Cl_2N_2O$: C, 52.76; H, 5.17; N, 10.26. Found: C, 52.85; H, 5.09; N, 10.20.

16b: mp 137–139 °C; ^{1}H NMR δ (DMSO-d_6) 3.30 (s, 3 H), 5.18 (s, 2 H), 5.63 (s, 2 H), 7.73 (d, J = 2 Hz, 1 H), 7.93 (d, J = 2 Hz 1 H). Anal. Calcd for $C_6H_{10}N_2Cl_2O$: C, 36.57; H, 5.12; N, 14.22. Found: C, 36.15; H, 5.09; N, 13.89.

5-(Chloromethyl)-1-(methoxymethyl)-2-phenylimidazole (13). In ~20 mL of $CHCl_3$ was dissolved imidazole hydrochloride **13**·HCl (3.5 g, 0.013 mol), and excess $NaHCO_3$ solid was added followed by stirring under an inert atmosphere until CO_2 evolution ceased completely. The $CHCl_3$ layer was filtered through Na_2SO_4, and the volatiles were evaporated at low temperature (5–10 °C) in vacuum to yield 2.8 g (92%) of the free **13** as a thick liquid (the latter operations must be carried out as quickly as possible and the final compound can be stored at low temperature for a few minutes): ^{1}H NMR δ ($CDCl_3$) 3.30 (s, 3 H), 4.83 (s, 2 H), 5.40 (s, 2 H), 7.25 (s, 1 H), 7.40–7.88 (m, 5 H).

General Procedure for the Preparation of Tris(imidazolylmethyl)acetonitriles (17a, 17b, 18). The desired (chloromethyl)imidazole hydrochloride (**16a,b** or **13**·HCl) (0.021 mol), powdered with a pestle and a mortor in a glovebag, was stirred as a slurry in dry THF (150 mL) under Ar at −40 °C, and acetonitrile (0.007 mol) was added. LDA (0.047 mol) (prepared according to a reported[10] procedure) in 50 mL of dry THF was allowed to drop slowly into this slurry through a double-ended needle over a period of 1.5 h at −40 °C to −30 °C. The mixture was allowed to warm to room temperature and stirred overnight (~20 h) and then quenched with 25 mL of water and extracted with $CHCl_3$ (250 mL + 2 × 100 mL). If the pH of the aqueous layer was not alkaline, it was basified with NH_4OH to pH ≃11 before extraction. Workup involving drying of the $CHCl_3$ extracts (Na_2SO_4) followed by removal of the volatiles yielded the crude material.

Tris[(1-methyl-2-imidazolyl)methyl]acetonitrile (17a) crystallizes from benzene. A second crystallization from benzene yields 0.36 g of pure **17** (16%) as pale brown needles: mp 201–202 °C; IR (Nujol) 2220 cm^{-1} (CN); ^{1}H NMR δ ($CDCl_3$) 3.58 (s, 9 H), 3.60 (s, 6 H), 6.83 (s, 3 H), 7.00 (s, 3 H); exact mass, m/z (relative intensity) 323.1862 (0.15) (calcd for $C_{17}H_{21}N_7$ 323.1858), 228.1242 (100) ($M^+ - C_5H_7N_2$); mass spectrum (CI, NH_3) 324 (M^+ + 1, base peak). Anal. Calcd for $C_{17}H_{21}N_7$: C, 63.14; H, 6.55; N, 30.32. Found: C, 62.90; H, 6.64; N, 29.95.

Tris[[1-(methoxymethyl)-2-imidazolyl]methyl]acetonitrile (17b). The crude material was chromatographed on neutral alumina column (15 × 2.4 cm) and eluted with 50% $CHCl_3$ in petroleum ether. An impurity (1,2-bis[1-(methoxymethyl)-2-imidazolyl]ethane), was removed from the eluted material by crystallization from benzene. The product was then purified by preparative TLC on neutral alumina with CH_3OH–NH_4OH (30% aqueous solution)–EtOAc (4:7:89, v/v) as the solvent system (R_f = 0.52) to yield 0.40 g (14%) of pure **17b** as a hygroscopic pale brown waxy material: IR (Nujol) 2240 cm^{-1} (CN); ^{1}H NMR δ ($CDCl_3$) 3.25 (s, 9 H), 3.68 (s, 6 H), 5.25 (s, 6 H), 6.98 (δ_A), 7.06 (δ_B) (AB q, 6 H); exact mass, m/z (relative intensity) 413.2187 (0.27) (calcd for $C_{20}H_{27}N_7O_3$ 413.2175), 288.1460 (100) ($M^+ - C_6H_9N_2O$); mass spectrum (CI, NH_3) 414 (M^+ + 1, base peak). Anal. Calcd for $C_{20}H_{27}N_7O_3$: C, 58.09; H, 6.58; N, 23.71. Found: C, 57.88; H, 6.53; N, 23.53.

Tris[[1-(methoxymethyl)-2-phenyl-5-imidazolyl]-methyl]acetonitrile (18). The crude material was chromatographed on neutral alumina column (30 × 2.4 cm) and eluted with 50–80% $CHCl_3$ in petroleum ether. The eluted material was crystallized from $CHCl_3$–diethyl ether to give 0.80 g (18%) of pure **18** as pale yellow crystals: mp 146–148 °C; ^{1}H NMR δ ($CDCl_3$) 3.20 (s, 9 H), 3.33 (s, 6 H), 5.20 (s, 6 H), 7.35 (s, 3 H), 7.45–7.85 (m, 15 H); exact mass, m/z 641.3118 (calcd for $C_{38}H_{39}N_7O_3$ 641.3114); mass spectrum (CI, NH_3) 642 (M^+ + 1, base peak). Anal. Calcd for $C_{38}H_{39}N_7O_3$: C, 71.11; H, 6.13; N, 15.28. Found: C, 70.77; H, 5.99; N, 15.27.

Tris[(2-phenyl-5-imidazolyl)methyl]acetonitrile (19). Nitrile **18** (1.0 g, 1.56 mmol) and 30 mL of glacial AcOH–concentrated HCl–H_2O (10:1:1 v/v) were mixed and refluxed for 7 h. The volatiles were distilled under vacuum, and a solid residue was obtained. This was dissolved in 30 mL of water and basified with 20% aqueous sodium hydroxide solution to pH = 11. A solid precipitated, and the mixture was filtered after cooling in ice. The precipitate was washed with ice-cold water (3 × 10 mL) and dried in vacuo. This was dissolved in methanol and acidified to pH = 1 with dilute HCl. The volatiles were evaporated, and the solid was dried in vacuo at 60 °C. This was recrystallized from 98% EtOH–diethyl ether. The crystallized material was filtered and dried in vacuo at 60 °C for 30 h to get 0.52 g (53%) of pure tris hydrochloride **19**·HCl: mp 256 °C dec; ^{1}H NMR δ (D_2O–CD_3OD) 3.63 (s, 6 H), 7.63–7.98 (m, 12 H), 8.00–8.28 (m, 6 H). Anal. Calcd for $C_{32}H_{30}N_7Cl_3 \cdot {}^1/_2H_2O$: C, 61.20; H, 4.98; N, 15.61. Found: C, 61.40; H, 4.89; N, 15.55.

This tris hydrochloride salt (0.1 g, 0.159 mmol) was dissolved in 10 mL water and basified to pH = 11 with 20% aqueous sodium hydroxide solution. A white precipitate was formed. This was stirred well, cooled with ice for 30 min, and then filtered. The filtered precipitate was washed well with small portions of cold water (~20 mL) and then dried under vacuum at 60 °C for 24 h to give 0.08 g (0.157 mmol) of pure **19**: mp 176 °C dec; IR (Nujol) 2240 cm^{-1} (CN); ^{1}H NMR δ (300 MHz, CD_3OD) 3.18 (s, 6 H), 7.30 (s, 3 H), 7.42–7.54 (m, 9 H), 7.94–8.02 (m, 6 H); mass spectrum (FAB) m/z (relative intensity) 510 (72) (M^+ + 1), 158 (100).

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Supplementary Material Available: Syntheses of diethyl [[1-(methoxymethyl)-2-phenyl-5-imidazolyl]methyl]malonate (**24**), **14**, and **15** (3 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of the 4a-Aryl-6-oxodecahydroisoquinolines

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The synthesis of part structures of the morphine molecule and structural modification of these fragments has led to the discovery of many important medicinal agents and research tools. Consequently, the efficient synthesis of morphine base structures has been a goal of organic chemists for many years.

Recently the metalated enamines **1** (Figure 1) have proven to be useful in the synthesis of morphine part structures,[1-4] and we have reported that the *trans*-4a-aryldecahydroisoquinoline **2** can be readily synthesized in just two steps from **1**[1,4] by using the metalated enamine approach. Pharmacological evaluation of compound **2** and its *m*-hydroxy and N-substituted analogues identified potent opioid analgesic activities within this series,[4] and further modification of the aryldecahydroisoquinoline molecule was deemed appropriate.

Because several important opioid receptor ligands have been discovered through further functionalization of the 6-keto group in oxycodone (Figure 1) and related molecules,[5-8] the *trans*-4a-aryl-6-oxodecahydroisoquinoline **3** appeared to be a logical intermediate for new analogue synthesis. Though the synthesis of the isoquinoline **3** has been previously reported,[9] we sought a more direct route, which would make the synthesis of large quantities of **3** practical. In this paper we describe an efficient route to the *trans*-4a-aryl-6-oxodecahydroisoquinolines, employing as a key step the use of a metalated enamine. In addition, practical synthesis of the *cis*-4a-aryl-6-oxodecahydroisoquinoline **4** and the *cis*- and *trans*-4a-aryl-6-decahydroisoquinols **5**-**8** (Schemes I and II) was discovered.

Results and Discussion

The synthetic route employed for the synthesis of the oxodecahydroisoquinoline **3** is depicted in Schemes I and II. Alkylation of the metalated enamine **10**[10] with the oxirane derivative **22**, followed by spontaneous addition of the alcohol generated to the immonium moiety, gave in good yield a mixture of the oxa-8-azabicyclononanes **11** and **12**. Separation was achieved by using preparative HPLC,

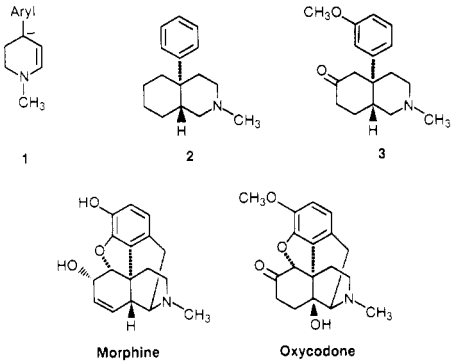
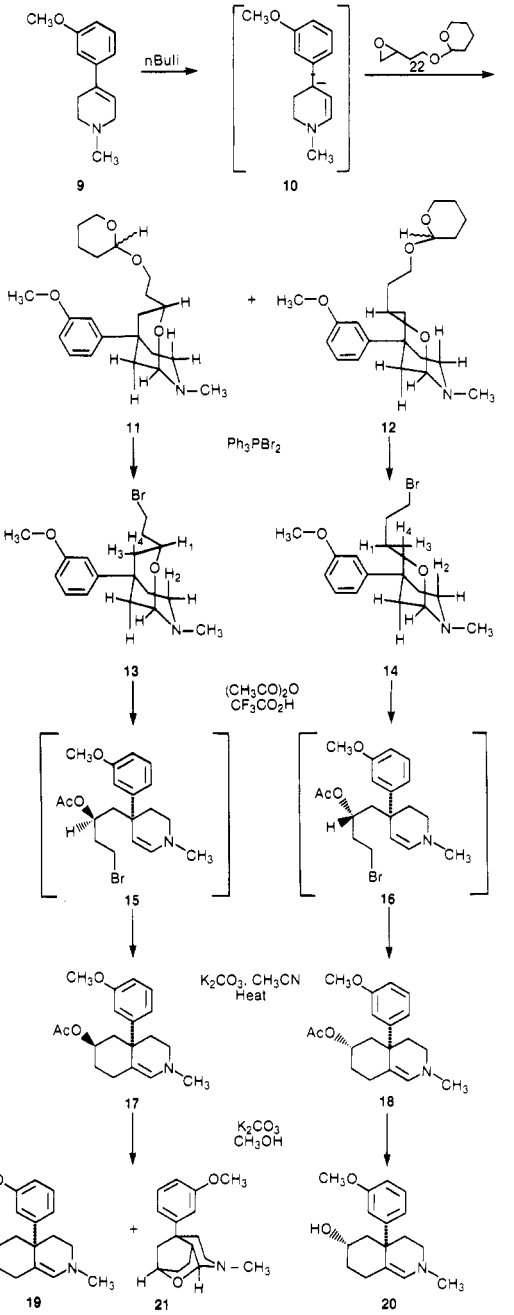


Figure 1.

Scheme I



(1) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955-5956.
(2) Shenvi, A. B.; Ciganek, E. *J. Org. Chem.* **1984**, *49*, 2942-2947.
(3) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, 285-288.
(4) Zimmerman, D. M.; Cantrell, B. E.; Swartzendruber, J. K.; Jones, N. D.; Mendelsohn, L. G.; Leander, J. D.; Nickander, R. C. *J. Med. Chem.* **1988**, *31*, 555-560.
(5) Portoghese, P. S.; Takemori, A. E. In *The Chemical Regulation of Biological Mechanisms*; Creighton, A. M., Turner, S., Eds.; Whitstable Litho Ltd: Whitstable, England, 1982; p 181.
(6) Portoghese, P. S.; Takemori, A. E. *Life Sci.* **1985**, *36*, 801-805.
(7) Lipkowski, A. W.; Tam, S. W.; Portoghese, P. S. *J. Med. Chem.* **1986**, *29*, 1222-1225.
(8) Portoghese, P. S.; Ronsisualle, G.; Larson, D. L.; Takemori, A. E. *J. Med. Chem.* **1986**, *29*, 1650-1653 and references cited therein.
(9) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485-1496.
(10) We have since shown that **9**, which is the 3-methoxy analogue of the Parkinsonian-causing agent MPTP, is, like MPTP, highly neurotoxic. We now recommend using the *N*-ethyl derivative as described in Zimmerman, D. M.; Cantrell, B. E.; Reel, J. K.; Hemrick-Luecke, S. K.; Fuller, R. W. *J. Med. Chem.* **1986**, *29*, 1517-1520.

0022-3263/89/1954-1442$01.50/0