

Synthesis of Detomidine and Medetomidine Metabolites: 1,2,3-Trisubstituted Arenes with 4'(5')-Imidazolylmethyl Groups

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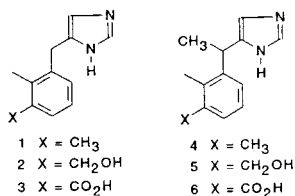
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Two synthetic strategies permitted the synthesis of various metabolites of detomidine (**1**) and medetomidine (**4**), potent α_2 adrenoceptor agonists that undergo rapid oxidative metabolism at the aromatic methyl group distal to the imidazole ring. In the detomidine series, the addition of a Grignard reagent prepared from 2-((3',4'-dimethoxyphenyl)methoxymethyl)-6-bromotoluene (**13**) to imidazole-4(5)-carboxaldehyde (**7**) provided 2-(((3',4'-dimethoxyphenyl)methoxymethyl)-6-(1'-hydroxy-1'-(5''-imidazolyl)methyl)toluene (**14**). In a subsequent reduction, it was possible to differentiate between the secondary benzylic hydroxyl group and the primary benzylic hydroxyl group protected as a 3,4-dimethoxybenzyl ether. Removal of the protecting group provided 3-(hydroxymethyl)detomidine (3-HD) (**2**) and an oxidation furnished 3-carboxydetomidine (3-CD) (**3**). However, in the medetomidine series, a similar hydrogenolysis of 2-(((3',4'-dimethoxyphenyl)methoxymethyl)-6-(1'-hydroxy-1'-methyl-1'-(5''-imidazolyl)methyl)toluene (**17**) failed, and an alternate, longer route involving dehydration and reduction was necessary to secure 3-(hydroxymethyl)medetomidine (3-HM) (**5**) and following an oxidation, 3-carboxymedetomidine (3-CM) (**6**). Finally, an expeditious route to 3-CM (**6**) involved the addition of the Grignard reagent prepared from 2-(3-bromo-2-methylphenyl)-4,4-dimethyl-2-oxazoline (**22**) to 4-acetyl-1*H*-imidazole and the hydrogenolysis and hydrolysis of 2-(1-(4,4-dimethyl-2-oxazolyl))-6-(1'-oxo-1'-(5'-imidazolyl)methyl)toluene (**23**).

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Detomidine (**1**) (4-((2,3-dimethylphenyl)methyl)-1*H*-imidazole, Domosedan, Figure 1) is a potent α_2 adrenoceptor agonist used clinically as an analgesic sedative for horses and cattle in veterinary medicine [1]. Unfortunately, detomidine (**1**) and a new analog, medetomidine (**4**) [2] are also suspected of illegitimate use in racing and show horses where a subtherapeutic dose is sufficient to alter the outcome of a performance [3]. The development of detection and confirmation protocols required access to authentic samples of the metabolites or potential metabolites in the case of medetomidine (**4**) where the metabolic fate in the horse was uncertain. We report a synthesis of the oxidative metabolites of detomidine (**1**) and medetomidine (**4**) in which the construction of a 1,2,3-trisubstituted arene bearing an 4'(5')-imidazolylmethyl group proved particularly challenging.

Figure 1

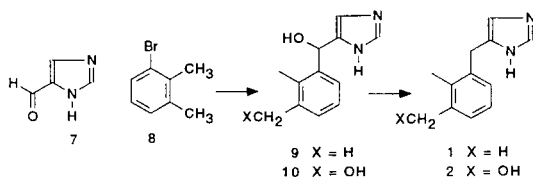


The major metabolites of detomidine (**1**) derive from the sequential benzylic oxidation of the C-3 methyl group leading to the 3-hydroxymethyl derivative (3-HD) (**2**) and the 3-carboxy derivative (3-CD) (**3**) shown in Figure 1. These compounds are formed in the rat [4,5] and in the horse [6]. In the rat, 3-CD (**3**) appears to be the major metabolite excreted in the urine (*ca.* 27%) together with a small amount of 3-HD (**2**) (*ca.* 6%) that is excreted as the α -glucuronide conjugate. Another metabolite, 4-hydroxydetomidine, arising from the oxidation of the C-4 aromatic position *para* to the 4(5)-imidazolylmethyl group was also detected at late post-dosing times using hplc [7] but will not be considered here. The metabolism of medetomidine (**4**) in the rat was reported to produce *ca.* 35% of the glucuronide of 3-HM (**5**) and *ca.* 40% of 3-CM (**6**) [8]. No information is available on the presumed 4-hydroxymedetomidine metabolite arising from the oxidation at the C-4 aromatic position.

Although there are patents [1a,2] that describe the synthesis of the parent drugs, the preparation of the detomidine and medetomidine metabolites have not been described. In the published approach [1a] to detomidine (**1**) in Figure 2, the addition of the Grignard reagent prepared from 2,3-dimethylbromobenzene (**8**) to imidazole-4(5)-carboxaldehyde (**7**) [9] provided the benzylic alcohol **9**,

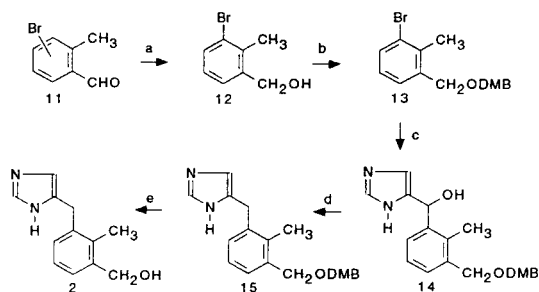
and the hydrogenolysis of **9** furnished detomidine (**1**). This route was unsuitable, however, for the preparation of the hydroxymethyl metabolite, 3-HD (**2**), where application of the putative hydrogenolysis reaction to **10** would eliminate *both* benzylic hydroxyl groups. To solve this problem and still utilize imidazole-4(5)-carboxaldehyde (**7**), a synthetic route to the 3-HD metabolite (**2**) was needed that would differentiate between these benzylic hydroxyl groups and preserve the benzylic hydroxyl group of 3-HD (**2**).

Figure 2



An approach to 3-HD (**2**) was first explored in which the two benzylic hydroxyl groups in the putative intermediate **10** (Figure 2) were differentiated by a suitable protecting group. As shown in Figure 3, the bromination [10] of 2-tolualdehyde provided an inseparable mixture of 3-bromo- and the 5-bromo-2-tolualdehyde regioisomers **11**. However, the reduction of this mixture with sodium borohydride provided the corresponding benzylic alcohols from which the desired benzylic alcohol **12** was readily separated by crystallization. Protection of the benzylic hydroxyl group in **12** with 3,4-dimethoxybenzyl bromide [11] furnished the 3,4-dimethoxybenzyl (DMB) ether **13**. The direct addition [1a,12] of the Grignard reagent of **13** to the imidazole-4(5)-carboxaldehyde (**7**) in refluxing THF afforded the adduct **14**. Remarkably, the selective hydrogenolysis of the benzylic alcohol functionality in **14** in the presence of the DMB ether was possible using hydrogen and palladium on carbon in acetic acid [1a] to give the desired DMB ether **15** in addition to some detomidine (**1**) derived from the reduction of both groups. The oxidative deprotection [11] of the DMB ether **15** provided 3-HD (**2**).

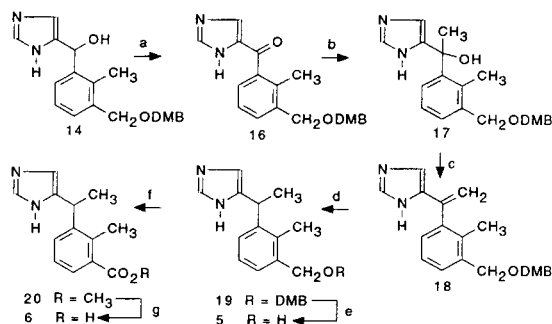
Figure 3



Reagents: a, NaBH₄; b, 3,4-dimethoxybenzyl bromide; c, Mg, Et₂O followed by imidazole-4(5)-carboxaldehyde (**7**); d, H₂, 10% Pd-C; EtOAc; e, DDQ.

This selective hydrogenolysis procedure was next applied to the preparation of the medetomidine metabolite, 3-HM (**5**). As shown in Figure 4, an oxidation of the benzylic alcohol **14** with nitric acid, a reagent recommended for such oxidations [12], led to undesired nitration products; an oxidation with lead tetraacetate [13] failed for steric reasons; but, the pyridinium chlorochromate oxidation of **14** furnished the ketone **16** in good yield. The addition of methyl lithium to the ketone **16**, without protection of the imidazole ring, furnished the tertiary benzylic alcohol **17**. Unfortunately, the selective hydrogenolysis that served well for the removal of the benzylic hydroxyl group in the detomidine series in Figure 3 failed in this particular case. The reduction of the benzylic alcohol **17** using hydrogen and palladium on carbon in acetic acid [1a] led to an undesired hydrogenolysis of the (3,4-dimethoxybenzyloxy)methyl group to a methyl group. The reduction of the benzylic alcohol **17** using triphenylsilane [14] in trifluoroacetic acid led to the selective deprotection of the (3,4-dimethoxybenzyloxy)methyl group to a hydroxymethyl group. Neither reaction appeared to affect the tertiary hydroxyl group in **17**.

Figure 4



Reagents: a, PCC; b, CH₃Li; c, POCl₃, Py; d, H₂, 10% Pd-C; e, DDQ; f, ((n-Bu₄N)MnO₄, Py followed by HCl, MeOH; g, 4N HCl.

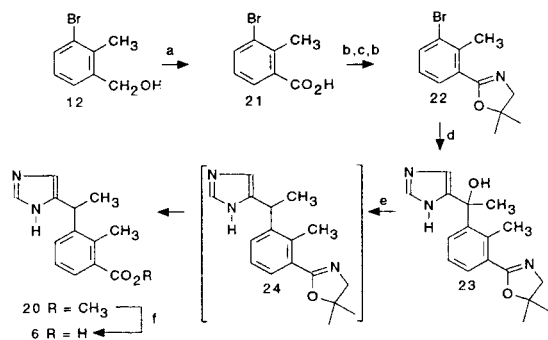
An alternate route was devised, however, that circumvented this inability to effect the selective reduction of the tertiary benzylic alcohol in **17**. As shown in Figure 4, the dehydration [15] of **17** secured the olefin **18**, and the selective reduction [16] of the olefinic bond in **18** using hydrogen over palladium on carbon furnished the desired DMB ether **19**. The deprotection [11] of **19** using 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) provided the desired 3-HM metabolite (**5**). Finally, the tetra-*n*-butylammonium permanganate oxidation [17] of **5** and subsequent esterification provided the methyl ester **20**. The preparation of the methyl ester **20** was necessary in order to separate the oxidized product from the permanganate salts. A final acid-catalyzed hydrolysis of **20** furnished 3-CM (**6**) as its hydrochloride salt.

Efforts described thus far focused on the preparation of

the hydroxymethyl metabolites, 3-HD (**2**) or 3-HM (**5**) as key intermediates and required a final oxidation to prepare the 3-CD (**3**) or 3-CM (**5**) metabolites, respectively. In these approaches, a suitable protecting group for the benzylic hydroxyl group of 3-HD or 3-HM was required, and although a satisfactory solution to this problem was found, the routes to 3-HD and 3-HM using this protecting group were relatively inefficient. As an alternative to this strategy, the carboxy metabolites, 3-CD (**3**) or 3-CM (**5**) were targeted as the key intermediates in which a final reduction would afford the corresponding 3-HD or 3-HM metabolites.

As shown in Figure 5, investigations along these lines led to a very efficient route to the 3-CM metabolite. 3-Bromo-2-methylbenzyl alcohol (**12**), that was prepared as shown in Figure 3, served as a suitable starting material. Oxidation [17] of **12** to the benzoic acid **21** and condensation of **21** with 2-amino-2-methyl-1-propanol and thionyl chloride according to the procedure of Meyers [18] delivered the oxazoline-protected bromobenzene **22**. The condensation of the Grignard of **22** with 5-acetyl-1*H*-imidazole [19] gave the tertiary alcohol **23**. The selective hydrogenolysis of the tertiary alcohol in **23** using hydrogen and palladium on carbon and methanolysis of the intermediate oxazoline **24** led, without isolation of **24**, directly to the methyl ester **20** in good yield. The hydrolysis of **20** gave 3-CM (**6**). The substitution of imidazole-4(5)-carboxaldehyde (**7**) for 5-acetyl-1*H*-imidazole would presumably afford the corresponding detomidine metabolite, although this particular sequence was never in fact reduced to practice. Nevertheless, the route in Figure 5 holds considerable promise for the synthesis of not only metabolites but also other analogs in the detomidine or medetomidine series.

Figure 5



Reagents: a, [(*n*-Bu₄N)MnO₄]; b, SOCl₂; c, H₂NC(CH₃)₂CH₂OH, d, Mg followed by 4-acetyl-1*H*-imidazole; e, H₂, Pd-C, 4*N* HCl followed by HCl, MeOH; f, H₃O⁺

EXPERIMENTAL

General Chemical Procedures.

Chemicals were purchased from Aldrich or Sigma. Infrared spectra were recorded on a Perkin Elmer Model 357 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian 400 MHz or Gemini 200 MHz NMR spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra of synthetic compounds were determined on a Kratos Concept 1H spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Column chromatography using Macherey Nagel silica gel 60 is referred to as "chromatography on silica gel".

3-Bromo- and 5-Bromo-2-tolualdehyde (**11**).

To 11.6 g (87.5 mmoles, 1.75 equivalents) of aluminum chloride in 15 ml of anhydrous dichloromethane at 30-40° was added 5.77 ml (6 g, 50 mmoles, 1 equivalent) of 2-tolualdehyde *via* a syringe in small portions. To this solution was added 8 g (50 mmoles, 1 equivalent) of bromine in 10 ml of anhydrous dichloromethane in five 2 ml portions. The mixture was stirred for 30 minutes at 40°, and the solution was cooled to 25°. The product was poured over 150 g of ice with stirring in order to hydrolyze the aluminum chloride complex. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic solutions were washed successively with 2*N* hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, dried over anhydrous magnesium sulfate, and concentrated to afford an inseparable mixture of the two monobrominated isomers and some dibrominated material. The inseparable mixture had ¹H nmr (deuteriochloroform): data consistent with the presence of the monobrominated isomers **11**: for the 3-bromo isomer; ¹H nmr (deuteriochloroform): δ 2.76 (s, 3, ArCH₃), 7.0-8.0 (m, 3, ArH), 10.27 (s, 1, CHO) and for the 5-bromo isomer; ¹H nmr (deuteriochloroform): δ 2.63 (s, 3, ArCH₃), 7.0-8.0 (m, 3, ArH), 10.23 (s, 1, CHO).

3-Bromo-2-methylbenzyl Alcohol (**12**).

To a suspension of 1.82 g (0.048 mole, 1.2 equivalents) of sodium borohydride in 50 ml of anhydrous methanol at 0° under a nitrogen atmosphere was added 31.8 g (0.159 mole, 1 equivalent) of a mixture of 3-bromo- and 5-bromo-2-tolualdehyde (**11**) in small portions in order to control the exothermic reaction. The mixture was stirred for 2 hours and diluted slowly with 50 ml of water and subsequently with 50 ml of 1:1 diethyl ether-hexane. The organic layer was separated, and the aqueous layer was extracted with 1:1 diethyl ether-hexane. The combined organic extracts were washed with 5% aqueous hydrochloric acid solution, water, and brine, dried over anhydrous magnesium sulfate, and concentrated. The mixture of isomers was crystallized from 15 ml of anhydrous dichloromethane at -5°. The crystals were collected, washed twice with 2 ml portions of cold anhydrous dichloromethane, and dried at 60° for 2 hours to afford a first crop of 9.8 g (31%) of **12** (95% pure) according to ¹H nmr analysis, mp 100-101°. This material was recrystallized from dichloromethane to afford 7.7 g (24%) of **12**, mp 101-102°; ir (chloroform): 3620 (OH), 3020, 1565, 1440, 1380, 1170, 1130, 1000, 710, 630 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.43 (s, 3, CH₃), 4.73 (s, 2, CH₂OH), 7.07 (dd, J = 7.8 and 7.8 Hz, 1, C-5 ArH), 7.33 (d, J = 7.6 Hz, 1, C-6 ArH), 7.52 (d, J = 7.8 Hz, 1, C-4 ArH); ¹³C nmr (deuteriochloroform): δ 18.7, 64.4, 126.9, 127.4, 127.8, 132.7, 136.6, 141.3.

Anal. Calcd. for C₈H₉BrO: C, 47.79; H, 4.51. Found: C, 47.69; H, 4.48.

2-(3',4'-Dimethoxyphenyl)methoxy)methyl-6-bromotoluene (**13**).

To 4.5 g (112 mmoles, 3 equivalents) of sodium hydride (60% suspension in oil) under a nitrogen atmosphere at 0° was added 10 ml of anhydrous DMF. The mixture was stirred for 15 minutes. To this mixture was added 7.5 g (37 mmoles) of **12** dropwise in 20 ml of anhydrous DMF. The mixture was stirred for 30 minutes. To this solution was added *via* cannula 7.6 g (41 mmoles, 1.1 equivalents) of 3,4-dimethoxybenzyl chloride [11] in 15 ml of anhydrous DMF. The mixture was allowed to warm to 25°, and the solution was stirred for an additional 3 hours. The reaction was quenched with water, and the product was extracted with 1:1 diethyl ether-hexane. The combined organic layers were washed with 10% aqueous hydrochloric solution, water, brine, dried over anhydrous magnesium sulfate, and concentrated to afford the product contaminated with mineral oil from the sodium hydride suspension. The mixture was crystallized twice from hexane and once from ethanol to give 9.84 g (75%) of **13**, mp 101-102°; ir (chloroform) 3020, 2970, 2950, 2920, 2870, 2850, 1600, 1510, 1460, 1440, 1420, 1360, 1270, 1160, 1140, 1070, 1030, 860, 810, 660, 630 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.39 (s, 3, CH₃), 3.87 and 3.88 (two s, 6, OCH₃), 4.49 (s, 2, CH₂OCH₂DMP), 4.51 (s, 2, CH₂OCH₂DMP), 6.80-6.95 (m, 3, C-2', C-5', C-6' ArH), 7.02 (dd, J = 7.8, 7.8 Hz, 1, C-4 ArH), 7.28 (d, J = 7.6 Hz, 1, C-3 ArH), 7.49 (d, J = 7.8 Hz, 1, C-5 ArH); ¹³C nmr (deuteriochloroform): δ 23.1, 60.4, 60.5, 75.5, 77.0, 115.6, 115.9, 125.3, 131.0, 131.7, 132.9, 135.4, 137.0, 141.5, 143.1, 153.6, 154.0.

Anal. Calcd. for C₁₇H₁₅BrO₃: C, 58.12; H, 5.55. Found: C, 58.13; H, 5.38.

2-((3',4'-Dimethoxyphenyl)methoxy)methyl-6-(1'-hydroxy-1'-(5''-imidazolyl)methyl)toluene (**14**).

A mixture of 9.0 g (28 mmoles, 2.4 equivalents) of **13** and 676 mg (28 mmoles, 2.4 equivalents) of Mg turnings in 25 ml of anhydrous THF was refluxed for 2.5 hours. To the Grignard solution was added 1.14 g (12 mmoles, 1 equivalent) of imidazole-4(5)-carboxaldehyde (**7**) [9]. The mixture was refluxed for an additional 3 hours, cooled to 25°, and quenched with 50 ml of saturated ammonium chloride solution. The mixture was poured into 50 ml of ethyl acetate and stirred for 3 hours. A thick white precipitate formed. The precipitate was collected and washed with water, 1:1 hexane-ethyl acetate, and dried at 60° for 3 hours to give 3.95 g (90%) of **14** as a white crystalline product: mp 169-171°. An analytical sample was prepared by a combination of chromatography on silica gel using 1:8 methanol-dichloromethane and recrystallization from methanol, mp 170-172°; ir (potassium bromide): 3600-2600 (br OH), 1600, 1510, 1470, 1450, 1420, 1410, 1360, 1260, 1230, 1160, 1140, 1120, 1030, 945, 815, 780, 645 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.22 (s, 3, CH₃), 3.80 (s, 1, OCH₃), 3.81 (s, 3, OCH₃), 4.47 (s, 2, CH₂OCH₂DMP), 4.54 (s, 2, CH₂OCH₂DMP), 6.04 (s, 1, CHOH), 6.66 (s, 1, C-4 imidazole H), 6.89-6.94 (m, 3, C-2'', C-5'', C-6'' ArH), 7.15-7.29 (m, 2, C-4', C-5' ArH), 7.53 (d, J = 7.6 Hz, 1, C-3' ArH), 7.61 (s, 1, C-2 imidazole H); ¹H nmr (pyridine-d₅): δ 2.45 (s, 3, CH₃), 3.72 (s, 3, OCH₃), 3.73 (s, 3, OCH₃), 4.58 (s, 2, CH₂OCH₂DMP), 4.62 (s, 2, CH₂OCH₂DMP), 6.66 (s, 1, CHOH), 6.91-7.19 (m, 5, C-2'', C-5'', C-6'' ArH), 7.37 (dd, J = 7.6, 7.6 Hz, 1, C-4' ArH), 7.50 (d, J = 7.4 Hz, 1, C-3' ArH), 8.01 (s, 1, C-4 imidazole H), 8.22 (d, J = 7.6 Hz, 1, C-5' ArH); ¹³C nmr (pyridine-d₅): δ 14.5, 56.0, 56.1, 67.7, 71.5, 72.7, 112.6, 112.8, 119.1, 121.3, 126.3, 127.6, 128.7, 132.3, 135.2, 136.4, 137.7, 142.9, 144.6, 150.1, 150.4.

Anal. Calcd. for C₂₁H₂₄N₂O₄: C, 68.46; H, 6.57. Found: C, 68.18; H, 6.61.

2-(((3',4'-Dimethoxyphenyl)methoxy)methyl)-6-((5'-imidazolyl)methyl)toluene (**15**).

A mixture of 67 mg (0.18 mmole) of **14** in 1.5 ml of acetic acid and 30 mg of 10% Pd/C at 25° was hydrogenated in a Parr apparatus under 60 psi of hydrogen. The mixture was stirred for 6 hours at 25° with no change, and subsequently, the temperature was increased to 60°. Tlc analysis indicated the absence of starting material, and the appearance of the desired product. The solution was cooled and filtered. The acetic acid was evaporated, and the residue was chromatographed to give 15 mg (22%) of **15**; ¹H nmr (deuteriochloroform): δ 2.24 (s, 3, ArCH₃), 3.88 (two overlapping s, 6, OCH₃), 3.97 (s, 2, ArCH₂), 4.53 (two overlapping s, 4, CH₂OCH₂), 6.57 (s, 1, C-4 imidazole H), 6.82-6.95 (m, 3, ArH), 7.10-7.45 (m, 3, ArH), 7.50 (s, 1, C-2 imidazole H); ¹³C nmr (deuteriochloroform): δ 14.3 (ArCH₃), 31.4 (ArCH₂), 55.7 and 55.8 (OCH₃), 70.9 (CH₂OCH₂DMP), 72.3 (CH₂OCH₂DMP), 110.9, 111.3, 117.9, 120.6, 125.8, 127.9, 128.1, 129.8, 130.9, 134.8, 135.8, 136.8, 138.2, 148.8, 149.2.

2-(Hydroxymethyl)-6-((5'-imidazolyl)methyl)toluene or 3-HD (**2**).

To 14 mg (0.039 mmole) of **15** in 5 ml of dichloromethane was added 14 mg (0.063 mmole, 1.5 equivalents) of DDQ. The mixture was stirred for 1 hour, and the solvent was evaporated. The residue was chromatographed on silica gel with 1:10 methanol-dichloromethane. The fraction containing the deprotected product was treated with 1 ml of 10M hydrogen chloride in dimethyl ether, and the solvent was evaporated to afford 7 mg (70%) of the hydrochloride of **2** having ¹H nmr identical to an authentic sample provided by Farnos; ¹H nmr (deuterium oxide): δ 2.05 (s, 3, ArCH₃Ar), 3.95 (s, 2, ArCH₂), 4.51 (s, 2, ArCH₂OH), 6.86 (s, 1, C-4 imidazole H), 7.05-7.20 (m, 3H, ArH), 8.39 (s, 1, C-2 imidazole H); ms: m/z (assignment, expected composition, error) 202.1110 (M⁺ (base peak), C₁₂H₁₄N₂O, 0.4 mmu), 201.1051 ([M-H]⁺, C₁₂H₁₃N₂O, 2.3 mmu), 187.0883 ([M-CH₃]⁺, C₁₁H₁₁N₂O, 1.2 mmu), 184.1014 ([M-H₂O]⁺, C₁₂H₁₂N₂, 1.4 mmu), 169.0770 ([M-CH₃-H₂O]⁺, 0.4 mmu).

2-(((3',4'-Dimethoxyphenyl)methoxy)methyl)-6-(1'-oxo-1'-(5''-imidazolyl)methyl)toluene (**16**).

To 3.85 g (10.5 mmoles, 1 equivalent) of **14** suspended in 100 ml of anhydrous dichloromethane under a nitrogen atmosphere was added 2.71 g (12.6 mmoles, 1.2 equivalents) of pyridinium chlorochromate (PCC). Approximately 15 minutes after the addition of PCC, the alcohol had dissolved. The dark orange-brown solution was stirred 36 hours at 25°. The solution was concentrated. To the dark-colored residue was added 40 ml of 10% aqueous sodium hydroxide solution (105 mmoles, 10 equivalents). The mixture was heated at 80° for 15 minutes, cooled, and extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to give 3.14 g (82%) of **16** as a pale yellow oil. An analytical sample was prepared by column chromatography on silica gel using 1:15 methanol-dichloromethane, mp 132-133°; ir (chloroform): 3440, 2250, 1635, 1590, 1545, 1510, 1355, 1265, 1240, 1160, 1140, 1030, 855, 810 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.33 (s, 3, CH₃), 3.87 (two s, 6, OCH₃), 4.55 (s, 2, CH₂OCH₂DMP), 4.57 (s, 2, CH₂OCH₂DMP), 6.82-6.94 (m, 3, C-2'', C-5'', C-6'' ArH), 7.25 (dd, J = 7.6, 7.6 Hz, 1, C-4' ArH), 7.38-7.52 (m, 2, C-3' and C-5' ArH), 7.94 (s, 1, C-2 imidazole H); ¹H nmr (perdeuteriomethanol): δ 2.26 (s, 3, CH₃), 3.81 (two s, 6, OCH₃), 4.53 (s, 2, CH₂OCH₂DMP), 4.59 (s, 2, CH₂OCH₂DMP), 6.91-6.97 (m, 3, C-2'', C-5'', C-6'' ArH),

7.25-7.55 (m, 4, C-4 imidazole H, C-3', C-4', C-5' ArH), 7.91 (s, 1, C-2 imidazole H); ^{13}C nmr (deuteriochloroform): δ 19.8, 60.2, 60.3, 74.6, 77.0, 115.4, 115.7, 125.2, 129.8, 132.2, 134.9, 135.1, 135.4, 139.7, 141.9, 142.2, 144.0, 144.3, 153.3, 153.6, 194.8.

Anal. Calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4$: C, 68.86; H, 6.06. Found: C, 68.81; H, 6.16.

2-(((3',4'-Dimethoxyphenyl)methoxy)methyl)-6-(1'-hydroxy-1'-methyl-1'-(5''-imidazolyl)methyl)toluene (**17**).

To 366 mg (1 mmole, 1 equivalent) of the ketone **16** in 20 ml of anhydrous THF at -78° was added 3.1 ml (5 mmoles, 5 equivalents) of methylolithium (1.6 M in hexane). The mixture was stirred at -78° for 1 hour and warmed for ca. 1 hour to 0° . The reaction was quenched with 10 ml of water. The product was extracted with three 30 ml portions of ethyl acetate. The combined extracts were washed twice with 10 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel using 1:15 methanol-chloroform to give 344 mg (90%) of **17** as an oil; ir (chloroform): 3460 (imidazole NH), 3020, 2590, 1510, 1460, 1440, 1420, 1260, 1220, 1160, 1140, 1030, 930 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.82 (s, 3, C(CH₃)OH), 2.06 (s, 3, ArCH₃), 3.82 and 3.84 (two s, 6, OCH₃), 4.47 (s, 2, CH₂OCH₂C₆H₃(OCH₃)₂), 4.49 (s, 2, CH₂OCH₂C₆H₃(OCH₃)₂), 6.38 (s, 1, C-4 imidazole H), 6.78-6.89 (m, 3, ArH), 7.05 (s, 1, C-2 imidazole H), 7.10 (dd, 1, J = 7.6 Hz, C-4 ArH), 7.26 (d, 1, J = 6.8 Hz, C-3 ArH), 7.52 (d, 1, J = 7.8 Hz, C-5 ArH).

Anal. Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4$: C, 69.09; H, 6.85. Found: C, 69.18; H, 6.97.

2-(((3',4'-Dimethoxyphenyl)methoxy)methyl)-6-(1'-methylene-1'-(5''-imidazolyl)methyl)toluene (**18**).

To 236 mg (0.62 mmole, 1 equivalent) of the **17** in 10 ml of anhydrous dichloromethane at 0° under a nitrogen atmosphere was added 181 mg (110 μl , 1.2 mmoles, 2 equivalents) of phosphoryl chloride. The ice bath was removed, and the mixture was warmed to 25° . The reaction was complete in 1 hour at 25° , and the product was poured over ice. The product was extracted with dichloromethane. The combined extracts were washed successively with 10% sodium carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel using 1:20 methanol-dichloromethane to afford 226 mg (100%) of **18** as an oil; ir (chloroform): 3460 (imidazole NH), 3010, 1590, 1510, 1465, 1420, 1265, 1160, 1140, 1030, 660, 630 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.16 (s, 3, ArCH₃), 3.84 (two overlapping s, 6, OCH₃), 4.54 (two overlapping s, 4, CH₂OCH₂C₆H₃(OCH₃)₂), 4.93 (s, 1, vinylic H), 5.90 (s, 1, vinylic H), 6.40 (s, 1, C-4 imidazole H), 6.80-6.93 (m, 3, ArH), 7.18-7.39 (m, 3, ArH), 7.46 (s, 1, C-2 imidazole H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$: C, 72.50; H, 6.64. Found: C, 72.61; H, 6.62.

2-(((3',4'-Dimethoxyphenyl)methoxy)methyl)-6-(1'-methyl-1'-(5''-imidazolyl)methyl)toluene (**19**).

To 200 mg (0.55 mmole, 1 equivalent) of **18** in 10 ml of ethyl acetate was hydrogenated using 50 mg of 10% Pd/C at 60 psi for 48 hours. The catalyst was removed by filtration, and the filtrate was concentrated. The crude product was chromatographed on silica gel using 1:20 methanol-dichloromethane to furnish 181 mg (91%) of **19** as an oil; ir (chloroform): 3460 (imidazole NH), 3010, 1590, 1510, 1460, 1440, 1420, 1260, 1240, 1160, 1140, 1030, 940,

660, 630 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.51 (d, 3, J = 7.0 Hz, CHCH₃), 2.24 (s, 3, ArCH₃), 3.85 (two overlapping s, 6, OCH₃), 4.31 (q, 1, J = 7.0 Hz, CHCH₃), 4.50 (two overlapping s, 4, CH₂OCH₂C₆H₃(OCH₃)₂), 6.57 (s, 1, C-4 imidazole H), 6.80-6.92 (m, 3, ArH), 7.02-7.19 (m, 4, ArH and C-2 imidazole H); ^{13}C nmr (deuteriochloroform): δ 14.0 (CHCH₃), 20.8 (ArCH₃), 34.0 (CHCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 71.6 (CH₂OCH₂C₆H₃(OCH₃)₂), 72.6 (CH₂OCH₂C₆H₃(OCH₃)₂), 111.2, 111.6, 117.5, 120.9, 126.1, 127.3, 127.9, 131.2, 135.1, 135.3, 136.6, 141.7, 144.6, 149.1, 149.4.

Anal. Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3$: C, 72.10; H, 7.15. Found: C, 72.19; H, 7.03.

2-(Hydroxymethyl)-6-(1'-methyl-1'-(5''-imidazolyl)methyl)toluene or 3-HM (**5**).

To 170 mg (0.46 mmole, 1 equivalent) of **19** in 5 ml of dichloromethane was added 273 mg (1.61 mmoles, 3.5 equivalents) of DDQ to give an immediate dark red-brown color. After stirring for 1 hour, the mixture was extracted with five 2 ml portions of water. The combined aqueous extracts were washed with an aqueous sodium thiosulfate solution. The mixture was evaporated to dryness, and the residue was chromatographed on silica gel using 1:10 methanol-dichloromethane to obtain 68 mg (68%) of **5** as an oil which solidified on standing. This solid was recrystallized from ethyl acetate to give white crystals, mp 194-195 $^\circ$; ir (potassium bromide): 3600-2300 (br), 1580, 1480, 1440, 1370, 1290, 1230, 1110, 1050, 990, 840, 800, 660, 630 cm^{-1} ; ^1H nmr (perdeuteriomethanol): δ 1.53 (d, 3, J = 7.2 Hz, CHCH₃), 2.32 (s, 3, ArCH₃), 4.42 (q, 1, J = 7.2 Hz, CHCH₃), 4.63 (s, 2, CH₂OH), 6.74 (s, 1, C-4 imidazole H), 6.90-7.22 (m, 6, ArH), 7.63 (s, 1, C-2 imidazole H); ^{13}C nmr (perdeuteriomethanol): δ 13.9 (CHCH₃), 21.1 (ArCH₃), 34.8 (CHCH₃), 64.2 (ArCH₂OH), 118.3, 127.0, 127.5, 127.6, 135.2, 136.2, 140.9, 142.7, 145.1; ms: m/z (assignment, expected composition, error) 216.1263 (M^+ , $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$, 0.03 mmu), 201.1052 ($[\text{M}-\text{CH}_3]^+$ (base peak), $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}$, 2.4 mmu), 198.1175 ($[\text{M}-\text{H}_2\text{O}]^+$, $\text{C}_{13}\text{H}_{14}\text{N}_2$, 1.8 mmu), 197.1102 ($[\text{M}-\text{H}_2\text{O}-\text{H}]^+$, $\text{C}_{13}\text{H}_{13}\text{N}_2$, 2.3 mmu), 183.0885 ($[\text{M}-\text{H}_2\text{O}-\text{CH}_3]^+$, $\text{C}_{12}\text{H}_{11}\text{N}_2$, -3.7 mmu).

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$: C, 72.19; H, 7.46. Found: C, 71.94; H, 7.57.

Methyl 2-Methyl-3-(1'-methyl-1'-(5''-imidazolyl)methyl)benzoate (**20**) from **5**.

To 10 mg (0.05 mmole, 1 equivalent) of **5** in 0.5 ml of pyridine at 25° was added 31 mg (0.08 mmole, 1.6 equivalents) of [(*n*-Bu)₄N]MnO₄ [17] in 0.5 ml of pyridine. After 1 hour, the mixture was evaporated to dryness, resuspended in 2 ml of toluene, and again evaporated to dryness. To the residue was added 1 ml of methanol saturated with hydrogen chloride gas. The mixture was refluxed for 30 minutes. The solution was evaporated to dryness. The crude product was chromatographed on silica gel using 1:20 methanol-dichloromethane to afford 4 mg (36%) of **20**. An analytical sample was prepared by recrystallization from ethyl acetate or 1:1 dichloromethane-hexane, mp 149-150 $^\circ$; ir (chloroform): 3460 (NH of imidazole), 2970, 1705 (ArCOOCH₃), 1430, 1285, 1140, 1075, 1025, 990, 960 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.60 (d, J = 7 Hz, 3, CHCH₃), 2.52 (s, 3, ArCH₃), 3.89 (s, 3, CO₂CH₃), 6.74 (s, 1, C-4 imidazole H), 7.15-7.32 (m, 2, C-5 and C-6 ArH), 7.56 (s, 1, C-2 imidazole H), 7.61 (d, J = 6 Hz, 1, C-4 ArH); ^{13}C nmr (deuteriochloroform): δ 15.6 (CHCH₃), 20.4 (ArCH₃), 33.8 (CHCH₃), 51.9 (CO₂CH₃), 117.1, 125.8, 128.0, 130.4, 131.9, 135.0, 136.0, 141.5, 145.1, 169.7 (CO₂CH₃); ms: m/z (assign-

ment, expected composition, error) 244.1210 (M^+ , $C_{14}H_{16}N_2O_2$, -0.2 mmu), 243.1140 ($[M-H]^+$, $C_{14}H_{15}N_2O_2$, 0.7 mmu), 229.0990 ($[M-CH_3]^+$ (base peak), $C_{13}H_{13}N_2O_2$, 1.3 mmu), 213.1024 ($[M-OCH_3]^+$, $C_{13}H_{13}N_2O$, -0.4 mmu), 212.0965 ($[M-CH_3OH]^+$, $C_{13}H_{12}N_2O$, 1.6 mmu), 211.0898 ($[M-CH_3OH-H]^+$, $C_{13}H_{11}N_2O$, 2.7 mmu), 197.0719 ($[M-CH_3-CH_3OH]^+$, $C_{12}H_9N_2O$, 0.4 mmu), 176.0833 ($[M-imidazole]^+$, $C_{11}H_{12}O_2$, -0.4 mmu).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60. Found: C, 68.75; H, 6.60.

Methyl 2-Methyl-3-(1'-methyl-1''-(5''-imidazolyl)methyl)benzoate (**20**) from **23**.

A mixture of 458 mg (1.5 mmoles, 1 equivalent) of **23** in 15 ml of 4*N* hydrochloric acid and 450 mg of 10% Pd/C was hydrogenated at 60 psi and 65° for 6 hours. The mixture was cooled, and the catalyst was removed by filtration. The filtrate was refluxed for an additional 3 hours, concentrated, and refluxed for another 1 hour with 15 ml of 10*N* hydrochloric acid in methanol. The methanol was evaporated, and the residue was neutralized with a saturated solution of potassium carbonate. The product was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, concentrated, and chromatographed on silica gel using 1:15 methanol-dichloromethane to afford 263 mg (70%) of **20** having spectral data in agreement with that reported earlier.

2-Methyl-3-(1'-methyl-1''-(5''-imidazolyl)methyl)benzoic Acid Hydrochloride or 3-CM (**6**).

A solution of 29 mg (0.117 mmole) of **20** and 0.5 ml of 4*N* hydrochloric acid was refluxed for 2 hours. The solution was evaporated to dryness. The product was crystallized from diethyl ether-methanol to afford 29 mg (94%) of **6** as the hydrochloride salt, mp 228-230°; 1H nmr (perdeuteriomethanol): δ 1.64 (d, $J = 7.2$ Hz, 3, $CHCH_3$), 2.58 (s, 3, $ArCH_3$), 4.65 (q, $J = 7$ Hz, 1, $CHCH_3$), 4.98 (br s, 3, NH_2^+ , CO_2H), 7.20-7.30 (m, 2, C-5 and C-6 ArH), 7.43 (s, 1, C-4 imidazole H), 7.66 (d, $J = 7.4$ Hz, 1, C-4 ArH); ms; m/z (assignment, expected composition, error) 230.1047 (M^+ , $C_{13}H_{14}N_2O_2$, -0.8 mmu).

3-Bromo-2-methylbenzoic Acid (**21**).

The procedure of Sargent [17] was repeated using 4.24 g (21 moles) of **12** and 16.7 g (43 mmoles, 2 equivalents) of $[(n-Bu_4)N]MnO_4$ to afford, after recrystallization from 1:4 acetone-dichloromethane, 4.17 g (92%) of **21**, mp 152-153°; lit [20] mp 151-152°; ir (deuteriochloroform): 2800-3400 (OH), 1695 (C=O), 1590, 1560, 1440, 1400, 1290, 1260, 1010, 685 cm^{-1} ; 1H nmr (deuteriochloroform): δ 2.73 (s, 3, $ArCH_3$), 7.16 (t, $J = 7.8$ Hz, 1, C-5 ArH), 7.78 (d, $J = 7.8$ Hz, 1, C-6 ArH), 7.95 (d, $J = 7.8$ Hz, 1, C-4 ArH); ^{13}C nmr (deuteriochloroform): δ 20.7, ($ArCH_3$), 127.0, 127.6, 130.5, 131.2, 137.2, 140.1, 173.2 (CO_2H).

Anal. Calcd. for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 44.73; H, 3.28.

2-(3-Bromo-2-methylphenyl)-4,4-dimethyl-2-oxazoline (**22**).

The procedure of Meyers [18] was repeated using 3 g (14 mmoles) of **21** and 4.98 g (41.9 mmoles, 3 equivalents) of thionyl chloride and 2.48 g (27.9 mmoles, 2 equivalents) of 2-amino-2-methyl-1-propanol to afford, after chromatography on silica gel using 1:3 ethyl acetate-hexane, 2.77 g (74%) of **22**, mp 36.5-37.5°; ir (chloroform): 2980, 1650, 1560, 1460, 1435, 1350, 1310, 1200,

1065, 1010, 970, 880, 710, 660 cm^{-1} ; 1H nmr (deuteriochloroform): δ 1.39 (s, 6, $C(CH_3)_2$), 2.61 (s, 3, $ArCH_3$), 4.09 (s, 2, OCH_2), 7.06 (t, $J = 8$ Hz, 1, C-5, ArH), 7.62 (two overlapping d, $J = 7.8$ Hz, 2, C-4 and C-6 ArH); ^{13}C nmr (deuteriochloroform): δ 20.9 ($ArCH_3$), 28.5 ($C(CH_3)_2$), 68.4 ($C(CH_3)_2$), 79.2 (OCH_2), 127.0, 127.1, 129.4, 130.6, 135.0, 138.2, 162.8 ($OC=N$).

Anal. Calcd. for $C_{12}H_{14}NBrO$: C, 53.75; H, 5.26. Found: C, 53.62; H, 5.30.

2-(1'-(4,4-Dimethyl-2-oxazolyl))-6-(1''-oxo-1''-(5''-imidazolyl)methyl)toluene (**23**).

A Grignard reagent was prepared from 1.51 g (5.6 mmoles, 2.6 equivalents) of **25** and 104 mg (4.3 mmoles, 2.0 equivalents) of Mg in 30 ml of anhydrous THF at reflux for 2 hours under a nitrogen atmosphere. To this solution was added 239 mg (2.2 mmoles, 1 equivalent) of 4-acetyl-1*H*-imidazole [19]. The mixture was refluxed for 2 hours, cooled, and quenched with 3 ml of saturated ammonium chloride solution. The product was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, concentrated, and chromatographed on silica gel using 1:10 methanol-dichloromethane to afford 468 mg (72%) of **23** as a low melting solid; ir (chloroform): 2600-3400 (br OH), 1650 ($OC=N$), 1585, 1460, 1440, 1370, 1350, 1310, 1140, 1070, 1060, 1020, 1010, 660, 630 cm^{-1} ; 1H nmr (deuteriochloroform): δ 1.34 (s, 6, $C(CH_3)_2$), 1.82 (s, 3, $C(CH_3)OH$), 2.12 (s, 3, $ArCH_3$), 4.06 (s, 2, CH_2O), 6.45 (s, 1, C-4 imidazole H), 7.04 (s, 1, C-2 imidazole H), 7.12 (t, $J = 7.8$ Hz, 1, C-4 ArH), 7.37 (d, $J = 7.8$ Hz, 1, C-3 ArH), 7.71 (d, $J = 7.8$ Hz, 1, C-5 ArH); ^{13}C nmr (deuteriochloroform): δ 17.4 ($ArCH_3$), 27.9 ($C(CH_3)_2$), 28.4 ($C(CH_3)OH$), 67.4 ($C(CH_3)_2$), 72.0 ($C(CH_3)OH$), 78.8 (OCH_2), 115.9, 125.0, 128.4, 128.5, 130.2, 134.8, 135.6, 143.9, 145.7, 164.7 ($OC=N$).

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