CONCISE SYNTHESIS OF (±)-ROELACTAMINE AND STRUCTURAL ANALOGS

Honors Thesis by

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First and foremost, I would like to think Professor Stephen F. Martin, who has been an outstanding advisor and mentor. His extensive knowledge and passion for chemistry has been a great encouragement. Throughout our many communications, I have learned a great deal about the field of organic chemistry, including (but certainly not limited to) new ideas to try and ways to become a better experimentalist. I appreciate the freedom he has given me to explore and the direction he has given me when I needed it. Steve has certainly prepared me for my future graduate career!

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ABSTRACT

Multicomponent reactions (MCRs) provide a facile means for the preparation of diverse chemical structures that can be elaborated into both natural product libraries and druglike molecules. Recently, our group has developed a novel 4CR involving the sequential reaction of a primary amine, an aldehyde, an acyl chloride, and a nucleophile, to produce a general intermediate which is then subjected to cyclizations and functional group transformations to afford a highly-functionalized heterocyclic scaffold. A notable

advantage of this 4CR is the commercial availability of a wide variety of starting materials, allowing diverse structures to be created in a small number of steps.

To illustrate our 4CR in natural product synthesis, the first total synthesis of the isopavine alkaloid (±)-roelactamine has recently been completed in just four steps from commercially available starting materials. Roelactamine is the only known naturally occurring isopavine alkaloid with a lactam moiety. Having completed (±)-roelactamine, the synthesis was further shortened to just two steps. Pleased by this result, an alternative 2-3 step route to the amine-containing isopavine alkaloids was developed. This route was used in a synthesis of several isopavine analogs.

Synthetic isopavine alkaloids have been shown to act as potent NMDA receptor antagonists. Since overstimulation of the NMDA receptor by glutamate has been shown to result in neuronal degeneration in several diseases, a selective NMDA receptor antagonist may provide a neuroprotective effect.

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Chapter 1: Multicomponent Reactions and Diversity-Oriented Synthesis

1.1 Introduction

The field of organic synthesis has experienced a revolution over the past several decades: The question of whether a target molecule can be constructed has been supplanted by the question of how efficiently the target structure can be generated (both in step count and overall chemical yield). Indeed, the facile generation of molecular complexity is an ongoing challenge for synthetic chemists around the world. Despite the great strides made toward this end, we are still far from approximating the efficiency of nature.

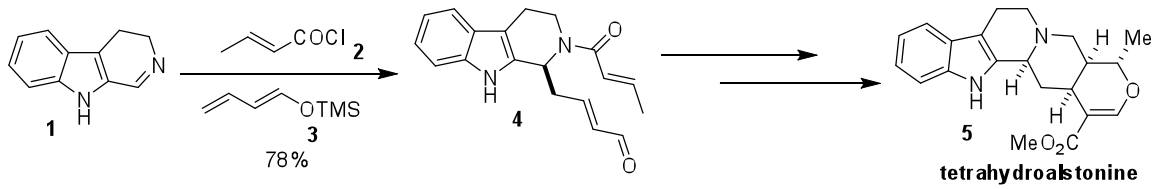
The total synthesis of natural products has long provided an avenue for testing current synthetic methods as well as an inspiration for the development of new synthetic methods, but natural products also play an important role in the development of new medicines.[1] Natural products with known biological activities are often used as "lead structures" from which combinatorial libraries are generated. Due to the large numbers of diverse compounds that must be generated, chemical efficiency is especially important in combinatorial synthesis. Multicomponent reactions (MCRs) provide a facile means for the preparation of diverse chemical structures that can be elaborated into both natural product libraries and druglike molecules.

1.2 The Four-Component Reaction

Several years ago, Martin and coworkers discovered a vinylogous Mannich three-component reaction during a formal synthesis of the heteroyohimboid alkaloid tetrahydroalstonine (Scheme 1).[2] In an effort to develop a concise route to the natural product, compound **1** (prepared in two steps from tryptamine) was treated with crotonyl

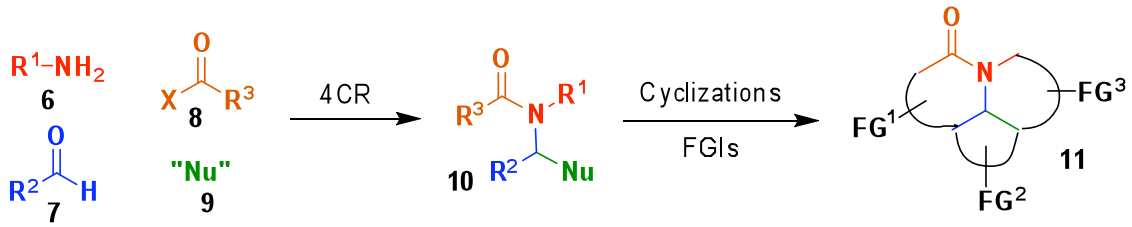
chloride (**2**) and 1-trimethylsilyloxybutadiene (**3**) to furnish **4** in 78% yield. The reaction presumably proceeds via nucleophilic attack of an N-acyl iminium intermediate formed by acylation of **1** with **2**. Compound **4** was subsequently elaborated into tetrahydroalstonine (**5**) in three steps.

Scheme 1



In subsequent years, several alkaloid natural products were prepared by the Martin group using a generalized form of the vinylogous Mannich reaction, including an exceptionally concise formal synthesis of strychnine in 17 total steps.[3] In recent years, the vinylogous Mannich reaction has been expanded into a novel four-component reaction (4CR).[4-6] This generalized reaction (Scheme 2) involves the sequential reaction of a primary amine (**6**), an aldehyde (**7**), an acyl chloride (**8**), and a nucleophile (**9**), to produce a general intermediate (**10**) which is then subjected to cyclizations and functional group transformations to afford a highly-functionalized heterocyclic scaffold (**11**).

Scheme 2



This reaction proceeds via condensation of the primary amine with the aldehyde to form an imine. The imine can then be acylated and the resulting acyl iminium ion trapped by the nucleophile. Alternatively, the imine intermediate can be allowed to react with the nucleophile; the resulting amine can subsequently be acylated. The former

pathway is typically better with moderately powerful nucleophiles such as silyl enol ethers, while the latter alternative may be used with more powerful nucleophiles such as organolithium or Grignard reagents. A notable advantage of this 4CR is the commercial availability of a wide variety of starting materials, allowing a diverse array of structures to be created in a small number of steps.

A large number of compounds has already been prepared using the 4CR,[4-6] and many more heterocyclic compound libraries based on biologically active natural products are currently being prepared in the Martin group. In addition to efforts in diversity oriented synthesis, the 4CR has also been used toward the synthesis of natural products. In 2007, Sunderhaus and Martin published a 4 step synthesis of (±)-roelactamine using the 4CR (more details to follow).[4] In addition, a generalized route to the *Aspidosperma* alkaloids employing the 4CR has been envisaged, and substantial progress has been made.[7,8]

1.3 Conclusion

As the discipline of organic synthesis rapidly progresses toward the achievement of more complexity in fewer chemical steps, new synthetic methodologies are required to keep pace. Multicomponent reactions are an excellent strategy for both target-oriented and diversity-oriented synthesis, and the Martin group 4CR has demonstrated excellent utility in both areas.

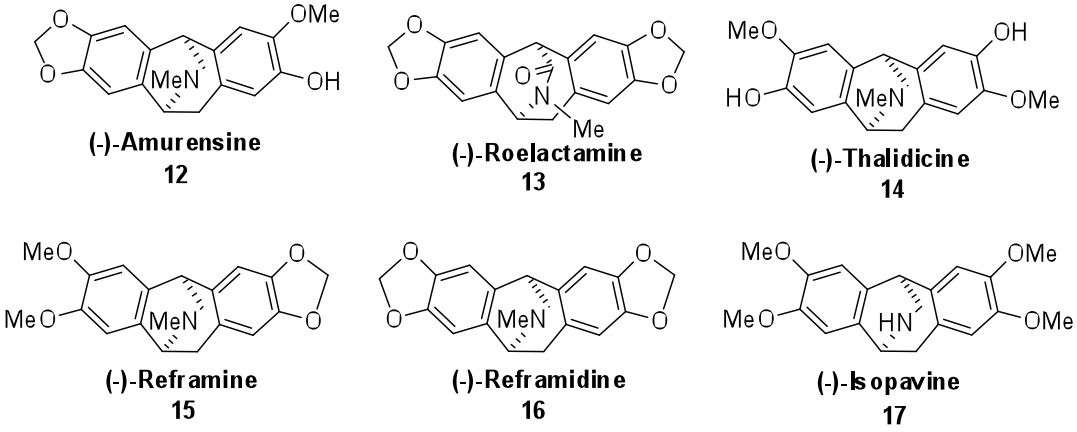
Chapter 2: The Isopavine Alkaloids

2.1 Introduction

The isopavines are a relatively small family of tetracyclic natural products (approximately 12 members) isolated from several plants in the Papaveraceae and

Ranunculaceae families (Figure 1).[9] All isopavines that have been isolated from nature are in enantiomerically pure (levorotatory) form. Structurally, the isopavines share a doubly benzanulated azabicyclo[3.2.2]nonane core structure.

Figure 1

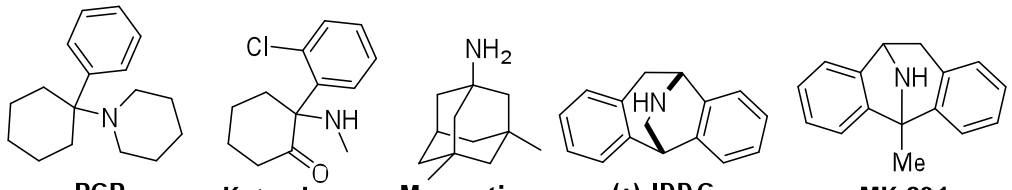


Amurensine (**12**), the first isopavine alkaloid found in nature, was isolated by Boit and Flentje in 1960.[10] Since then, several other isopavines have been isolated and synthesized. In recent years, synthetic isopavine derivatives have garnered much interest due to their interactions with receptors in the central nervous system.[11-13] Specifically, synthetic isopavines have been shown to act as noncompetitive NMDA receptor antagonists by blocking the receptor's associated ion channel.[11] This activity is potentially useful, since excessive calcium ion influx into the neuron via the NMDA receptor-associated ion channel has been linked to neuronal degeneration during prolonged hypoxic events and in a number of diseases (Alzheimer's, Parkinson's, Huntington's, etc.).[11-12]

This mode of action is not specific to the isopavines: The compounds PCP (**18**), ketamine (**19**), and memantine (**20**) (Figure 2) all interact with the NMDA receptor ion channel in the same manner, differing primarily in their binding affinities.[14] PCP and ketamine are high affinity channel blockers, while memantine is a relatively low affinity,

voltage-dependent channel blocker. While PCP and ketamine are known to induce psychotomimetic effects, memantine produces no such effects due to its lower affinity for the ion channel. Memantine, FDA approved for the treatment of Alzheimer's disease, is the only drug that has made it into the clinic that interacts specifically with the NMDA receptor.[14]

Figure 2



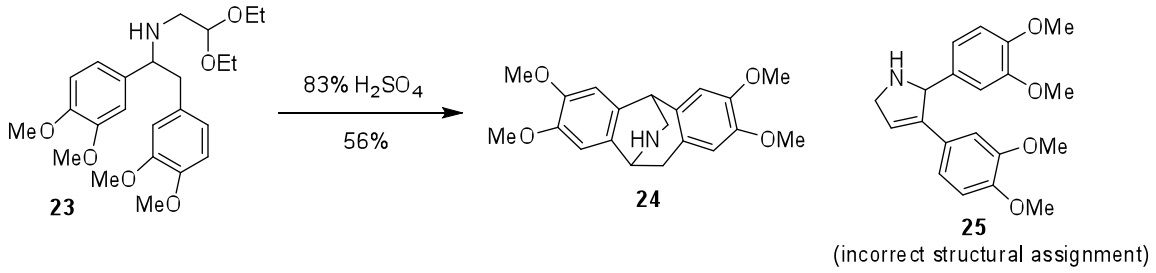
PCP 18 **Ketamine 19** **Memantine 20** **(+)-IDDC 21** **MK-801 22**

Although the synthetic isopavine (+)-IDDC (**21**) and structurally related MK-801 (**22**) have been shown to possess exceptionally high binding affinities for the NMDA receptor ion channel,[11] the clinical and commercial success of memantine suggests that compounds with more moderated affinity may be the most useful. Another (less explored) area of isopavine biological activity is in pain management. Specifically, Hanessian and coworkers have reported on a class of synthetic isopavines that bind strongly to opioid receptors.[13] Due to the interesting structures and biological profiles of the isopavine alkaloids, a significant number of synthetic approaches have previously been developed.

2.2 Synthetic Approaches

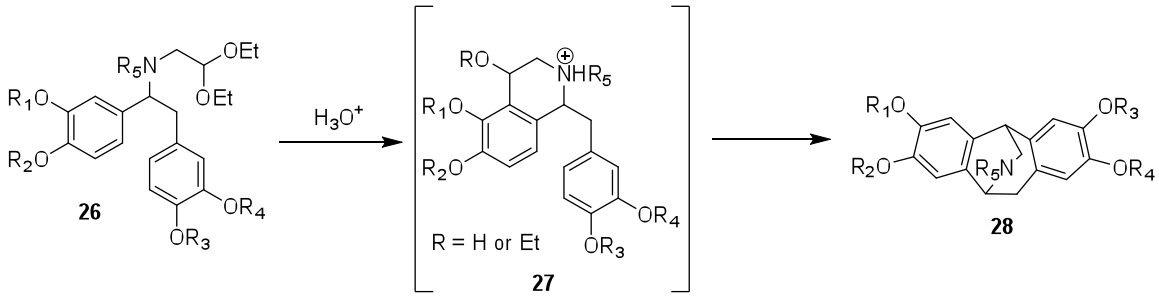
Although there have been several distinct syntheses of isopavines, the most commonly utilized approach to access the isopavine core has been the double Friedel-Crafts type cyclization of benzylaminoacetaldehyde dialkyl acetals as pioneered by Guthrie's synthesis of (±)-isopavine in 1955 (Scheme 3).[15]

Scheme 3



Upon treatment of **23** with sulfuric acid, Guthrie obtained isopavine (**24**) in 56% yield, although he incorrectly assigned the structure as **25**. This structural misassignment was later corrected by Battersby and Yoewell.[16] The general mechanism of this cyclization reaction (Scheme 4) is thought to proceed stepwise, with electrophilic aromatic substitution of the acetal **26** or its corresponding aldehyde intermediate to **27**. Ionization of the secondary alcohol or alkoxy group followed by a second electrophilic aromatic substitution event furnishes the core isopavine structure **28**.

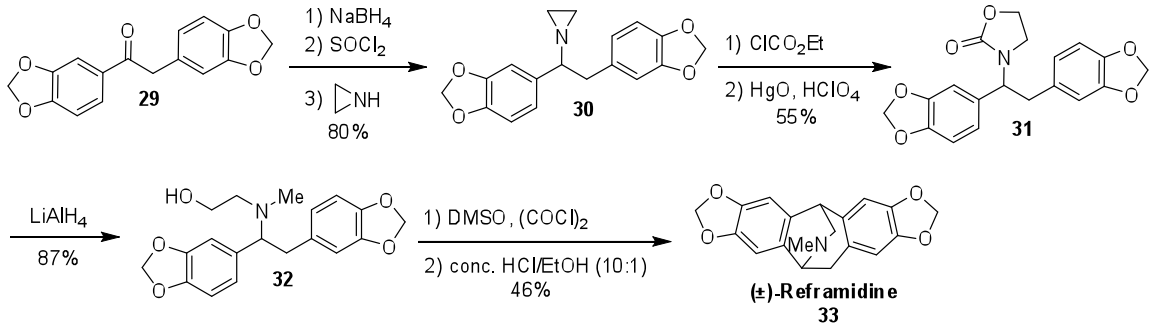
Scheme 4



As stated previously, this type of double cyclization has been utilized in a number of syntheses of both natural and unnatural isopavines. In their work on aziridines in alkaloid synthesis, Kametani and coworkers reported a total synthesis of (±)-reframidine in 1984 (Scheme 5).[17] Deoxypiperoin **29** was reduced with sodium borohydride, and the resulting alcohol was treated sequentially with thionyl chloride and

aziridine to furnish compound **30** in 80% yield over the three steps. The aziridine ring in **30** was opened with ethyl chlorocarbonate, and the ring-opened product was treated with mercuric oxide in 60% aqueous perchloric acid to afford oxazolidinone **31** in 55% yield (2 steps) after chromatography on neutral alumina. Reduction of **31** with lithium aluminum hydride afforded β-amino alcohol **32** in 87% yield. Swern oxidation of **32** followed by acid cyclization of the aldehyde product gave (±)-reframidine (**33**) in 46% yield. Interestingly, a tertiary amine such as triethylamine was not used in the Swern oxidation. Presumably, the tertiary amine in substrate **32** acted as the base necessary for the decomposition of the alkoxysulfonium salt intermediate.

Scheme 5



As mentioned above, Martin and Sunderhaus published the first synthesis of (±)-roelactamine in 2007 (Scheme 6).[4] Utilizing the 4CR, piperonal (**34**) was treated sequentially with condensed methylamine, Grignard reagent **35**, and acyl chloride **36** in THF with molecular sieves to afford amide **37** in 61% yield. Acyl chloride **36** was prepared in two steps from glyoxylic acid by reaction with acetic anhydride followed by thionyl chloride.[18] Amide **37** was cyclized in a solution of hydrochloric acid and methanol to provide (±)-roelactamine in 71% yield along with elimination product **39**. As only two products were detected by thin layer chromatography, it is assumed that **39**

was produced to a large extent. This was the first synthesis of roelactamine as well as the shortest reported synthesis of an isopavine alkaloid.

Scheme 6

2.3 Conclusion

Due to the interesting structures and biological activities of the isopavines, a number of syntheses have been reported. Although some medicinal chemistry with the isopavine core structure has been reported,[11,13] a more concise route to access isopavines would provide a means for diversity oriented synthesis. The route reported by Martin and Sunderhaus is exceptionally concise, and it may be used for the preparation of both lactam- and amine-containing (via reduction) structural analogs. Furthermore, shortening their 4 step synthesis would make the construction of a library even more accessible.

Chapter 3: Concise Syntheses of Roelactamine, Reframidine, and Analogs Thereof

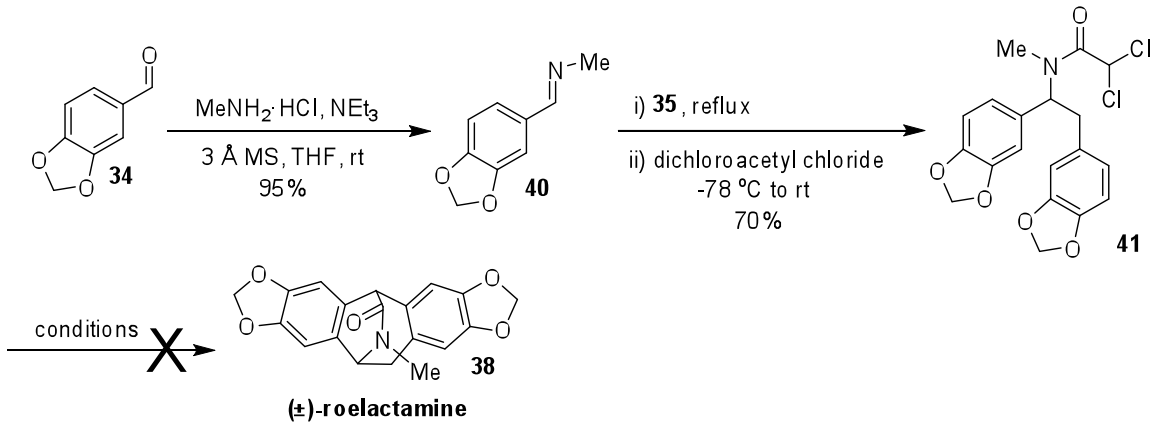
3.1 Introduction

(-)-Roelactamine (**13**) was isolated by Gözler and Hesse from *Roemeria refracta* DC, a plant in the Papaveraceae family, in 1992.[19] Roelactamine is the only reported naturally occurring isopavine alkaloid that possesses a lactam moiety. It's amine counterpart, (-)-Reframidine (**16**), was first reported by Pfeifer and Thomas in 1967.[20]

3.2 Synthesis of Roelactamine

In an effort to achieve a shorter synthesis of roelactamine, we opted to synthesize compound **41** by using commercially available dichloroacetyl chloride rather than diacetoxyacetyl chloride (**36**) (Scheme 7). Compound **41** was first synthesized stepwise. Thus, piperonal (**34**) was treated with methylamine hydrochloride to afford imine **40** in 95% yield. The imine was treated sequentially with Grignard **35** and dichloroacetyl chloride, providing **41** in 70% yield.

Scheme 7

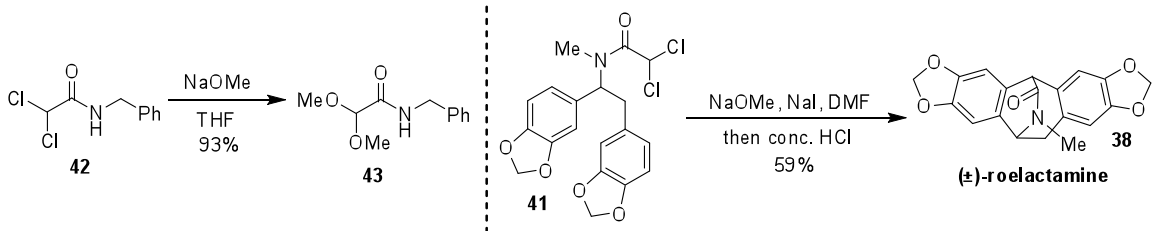


Unfortunately, numerous attempts to convert **41** into roelactamine were unsuccessful. Several conditions were tried, including treatment with several protic acids at a variety of temperatures, co-treatment with acid and sodium iodide or silver nitrate, and treatment with acid and microwave irradiation. Water, nitromethane, and dimethyl sulfoxide were all used as co-solvents. Hydrolysis of the gem-dichloride under basic conditions was also attempted without success. In most cases, starting material, elimination product **39**, or a mixture of the two were the only products.

Realizing that substrate **41** was more prone to elimination than cyclization, we explored the possibility of a one-pot nucleophilic substitution/cyclization reaction sequence. A literature search revealed the work of Katritzky and coworkers, in which

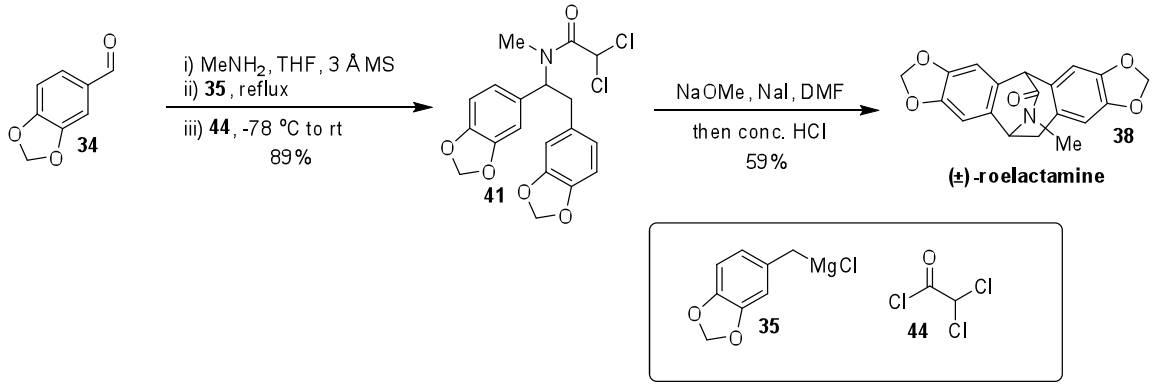
acetal **43** was prepared from gem-dichloride **42** by treatment with sodium methoxide in THF (Scheme 8, left).[21] After some experimentation, we found that substitution of gem-dichloride **41** with sodium methoxide occurred in under 30 minutes in DMF with 0.5 equivalents of sodium iodide. Interestingly, substitution was unsuccessful in THF and methanol and in the absence of sodium iodide. This result is not surprising, as **41** is clearly more sterically congested than **42**. This reaction was combined with the cyclization, and (±)-roelactamine was prepared in 59% yield (Scheme 8, right). The only detectable byproduct was stilbenoid **39**.

Scheme 8



Pleased with this result, we proceeded to prepare **41** using the 4CR strategy (Scheme 9). Sequential treatment of piperonal (**34**) with condensed methylamine, Grignard **35**, and dichloroacetyl chloride (**44**) afforded **41** in 89% yield. Thus, a synthesis of (±)-roelactamine was accomplished in only two steps and 53% overall yield.

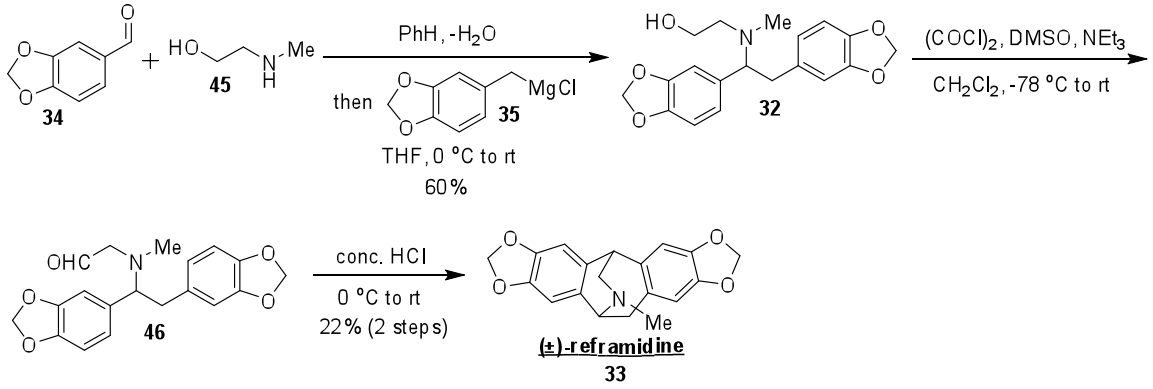
Scheme 9



3.3 Synthesis of Reframidine

While pleased with our shortened synthesis of (±)-roelactamine, a number of reasons led us to develop another route to the isopavines. Perhaps the most pressing reason was our desire to design a more direct route to amine-containing isopavines. In addition, we were concerned with the facile elimination of **41** when exposed to acid. We reasoned that less electron-rich substrates would likely be more prone to elimination because electrophilic aromatic substitution would be significantly slower. Thus, we developed a synthesis of (±)-reframidine that intercepted synthetic intermediate **32** in Kametani's synthesis (Scheme 10).[17]

Scheme 10

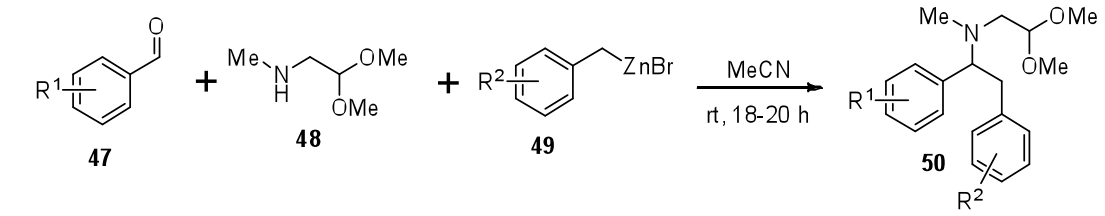


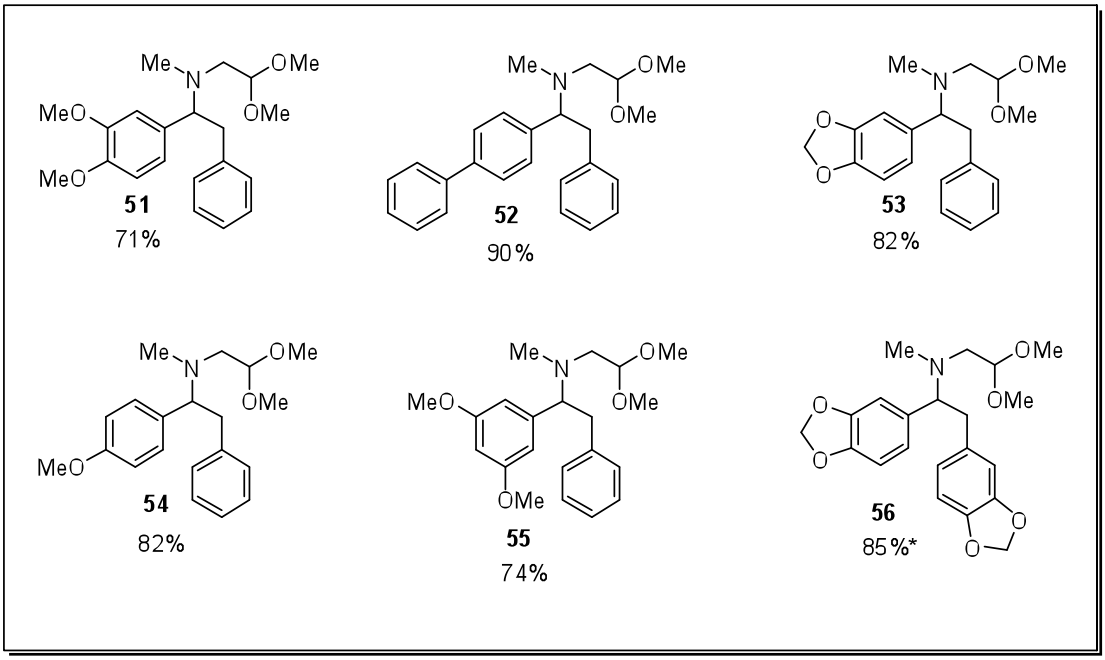
According to precedent set forth by Goodson and Christopher,[22] piperonal (**34**) was heated under Dean-Stark conditions with aminoalcohol **45** to form a 2-aryloxazolidine intermediate, which was opened with Grignard **35** to afford Kametani's intermediate (**32**) in 60% yield. The synthesis of (±)-reframidine was completed in 22% yield by Swern oxidation of **32** followed by cyclization in concentrated hydrochloric acid. Because this yield is substantially lower than that reported by Kametani, yet another (more direct) route was developed.

3.4 A General Isopavine Synthesis

In an effort to prepare double cyclization substrates **50** in one step, we combined benzaldehydes **47** (commercial), aminoacetal **48** (commercial), and organozinc reagents **49** in acetonitrile for 18-20 h (Scheme 11). We were thrilled to discover that simple acid-base extraction of the crude products afforded pure products **50** in good to excellent yields.

Scheme 11



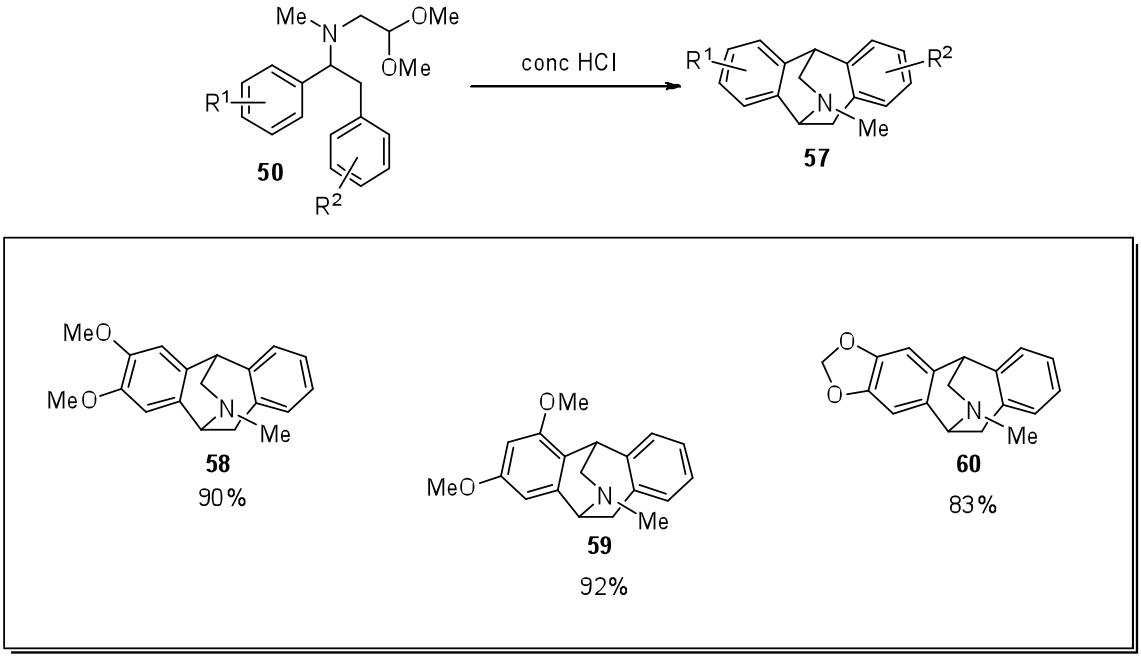


*Reaction was carried out in THF with 10 mol% $LiClO_4$

The organozinc reagents were prepared from the corresponding bromides via direct zinc insertion. Interestingly, the yield of compound **56** was greatly improved by the addition

of 10 mol% lithium perchlorate. This compound was prepared in THF because the corresponding organozinc compound was unstable as an acetonitrile solution.

After some experimentation, we found that double cyclization substrates **50** afforded isopavines **57** in excellent yield upon treatment with concentrated hydrochloric acid (Scheme 12).



In the near future, this method for preparing the isopavine core will be used to synthesize several isopavine analogs.

3.5 Conclusion

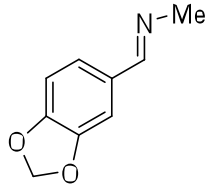
In summary, a synthesis of (±)-roelactamine was accomplished in 53% overall yield and only two steps from commercially available materials. This syntheses showcases the utility of our 4CR in natural product synthesis. In addition, a synthesis of (±)-reframidine was completed in three steps from commercially available materials. Furthermore, a simple, high yielding route for the synthesis of several isopavine analogs

was developed and used to prepare a few examples. This library will be submitted to an NIH small molecule repository.

EXPERIMENTAL

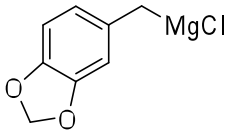
General Methods: Nuclear magnetic resonance spectra were recorded on a 300 MHz spectrometer unless otherwise indicated. Chemical shifts are reported in parts per million (δ) and are referenced to TMS (if present) or the indicated deuterated solvent. Coupling constants (*J*) are reported in Hertz (Hz) and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; ddd, doublet of doublets of doublets; dtd, doublet of triplets of doublets; dq, doublet of quartets; m, multiplet; comp, overlapping multiplets; br, broad. Infrared (IR) spectra were obtained with a Perkin-Elmer FTIR 1600 series spectrometer, neat on sodium chloride plates. Band positions are given in reciprocal centimeters (cm^{-1}). Thin layer chromatography (TLC) was performed on glass-backed precoated silica gel plates (0.25 mm thick with 60 F_{254}) and were visualized using one or both of the following manners: UV light (254 nm) and staining with basic aqueous $KMnO_4$ or *p*-anisaldehyde. Column chromatography was performed using glass columns and "medium pressure" silica gel (Sorbent Technologies, 45-70μ). Tetrahydrofuran and acetonitrile were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996**, *15*, 1518-1520). Triethylamine and dichloromethane were distilled from CaH_2 prior to use. All reagents were purchased and used as received unless otherwise stated. Glassware used in the reactions was used without extra drying

procedures unless otherwise indicated. All reactions were performed under an atmosphere of argon unless otherwise noted.



N-(benzo[d][1,3]dioxol-5-ylmethylene)methanamine (40) (TCT 1-68)

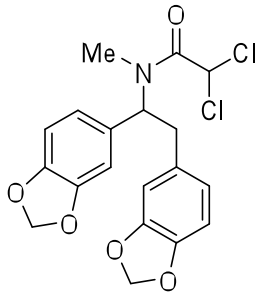
Molecular sieves (3 Å) were added to a round bottom flask, and the flask was flame dried under vacuum. Piperonal (20 g, 133 mmol), Methylamine hydrochloride (18 g, 266 mmol), CH_2Cl_2 (250 mL), and triethylamine (37 mL, 266 mmol) were added sequentially, and the reaction was stirred at rt for 26 h. The solvent was evaporated under reduced pressure, and Et_2O (300 mL) was added. The mixture was vacuum filtered, and the filtrate was concentrated to afford 20.68 g (95%) of **40** as a yellow oil that solidified upon standing. 1H-NMR data were consistent with published spectral data.[23]



(benzo[d][1,3]dioxol-5-ylmethyl)magnesium chloride (35) (TCT 3-82)

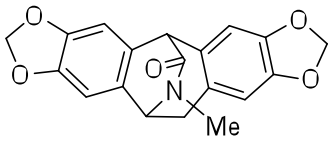
Concentrated hydrochloric acid (60 mL) was added to piperonyl alcohol (7.0 g), and the mixture was stirred for 1 h. The mixture was extracted with CH_2Cl_2 (2 x 40 mL). The combined extracts were washed with sat. aqueous $NaHCO_3$ (40 mL), dried (Na_2SO_4), and concentrated. Distillation under high vacuum afforded 6.53 g (83%) of the chloride as a clear oil. A solution of the chloride in THF (30 mL) was added dropwise over 1.5 h to a stirred suspension of freshly acid-washed magnesium turnings (1.7 g, 70 mmol) in THF

(8 mL) at 0 °C. The resulting dark green solution of the Grignard was stirred for an additional hour and titrated against iodine, indicating a 0.78 M solution.



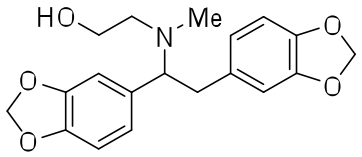
2,2-dichloro-N-(1,2-di(benzo[d][1,3]dioxol-5-yl)ethyl)-N-methylacetamide (41) (TCT 3-81)

Molecular sieves (3 Å pellets, ca 4 g) were added to a round bottom and flame dried under vacuum. Piperonal (0.50 g, 3.33 mmol), THF (8 mL), and freshly condensed methylamine (0.22 mL, 5.00 mmol) were added sequentially, and the solution was stirred for 8 h. The Grignard reagent **35** (12.8 mL, 9.99 mmol, 0.78 M solution in THF) was added, and the reaction was stirred for 18 h at rt. The reaction was cooled to -78 °C, and dichloroacetyl chloride (2.6 mL, 26.6 mmol) was added. After stirring for 2 h, the reaction was warmed to rt, quenched with sat. aqueous NH_4Cl (30 mL), and vacuum filtered. The filtrate was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Purification via flash chromatography, eluting with 1:4 → 1:3 ethyl acetate:hexanes, afforded 1.218 g (89%) of product **41** as a light yellow solid; ^{1}H NMR (300 MHz) δ 6.87-6.58 (comp, 6 H), 6.11 (s, 1 H), 6.02-5.90 (comp, 5 H), 3.21 (dd, 1 H), 3.11-3.00 (m, 1 H), 2.79 (d, 3 H); ^{13}C NMR (300 MHz) δ 163.8, 148.2, 147.8, 147.4, 131.9, 130.7, 121.9, 121.1, 109.3, 109.1, 108.5, 108.3, 101.3, 65.7, 64.3, 35.7, 30.1; HRMS (CI) *m/z* calculated for $C_{19}H_{18}NO_5Cl_2$, 410.0562; found, 410.0562; IR (cm^{-1}) 2895, 1667, 1490, 1443, 1248, 1039, 810.



(±)-Roelactamine (38) (TCT 2-78)

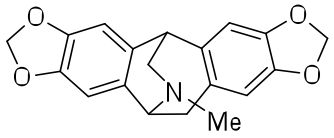
Amide **41** (300 mg, 0.73 mmol), sodium iodide (54 mg, 0.37 mmol), sodium methoxide (320 mg, 5.9 mmol) and DMF (6 mL) were added sequentially to a dry round bottom flask, and the reaction was stirred at rt for 45 min. The reaction was cooled to 0 ^{o}C in an ice-water bath, and concentrated hydrochloric acid (18 mL) was added dropwise. The reaction was stirred for 10 min at 0 ^{o}C and 12 h at rt. Sat. aq. $NaHCO_3$ was added to neutralize the acid, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via flash chromatography, eluting with ethyl acetate:hexanes (1:1) to afford **38** (145 mg, 59%). Spectral data were identical to those reported in the literature.[6]



2-((1,2-di(benzo[d][1,3]dioxol-5-yl)ethyl)(methyl)amino)ethanol (32) (TCT 2-81)

Aminoethanol **45** (0.8 mL, 10 mmol) was added to a solution of piperonal (1.5 g, 10 mmol) in benzene (20 mL). The solution was heated to reflux under Dean-Stark conditions with continuous removal of water for 2 h. The trap was emptied, and the benzene was allowed to distill from the flask. The reaction was cooled to rt, and THF (4 mL) was added. The reaction was cooled to 0 ^{o}C in an ice-water bath, and Grignard **35**

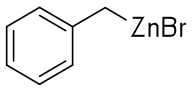
(60 mL, 30 mmol as a solution in THF) was added. The reaction was stirred for 1 h at 0 ^{o}C and 11 h at rt. Sat. NH_4Cl (40 mL) and CH_2Cl_2 (40 mL) were added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic fractions were concentrated under reduced pressure and then dissolved in Et_2O (30 mL). The ethereal solution was extracted with 1 M HCl (3 x 30 mL). The acidic aqueous solution was cooled to 0 ^{o}C, and solid sodium hydroxide was added until the pH reached 12. The product was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford **32** (2.06 g, 60%).



(±)-Reframidine (33) (TCT 2-92)

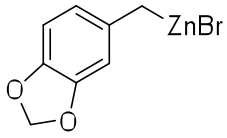
A solution of oxalyl chloride (0.37 mL, 4.35 mmol) in CH_2Cl_2 (4 mL) was cooled to -78 ^{o}C. A solution of dimethyl sulfoxide (0.37 mL, 5.22 mmol) in CH_2Cl_2 (3.3 mL) was added dropwise, and the reaction was stirred for 10 min. A solution of alcohol **32** (300 mg, 0.87 mmol) in CH_2Cl_2 (1.74 mL) was added dropwise, and the reaction was stirred for 1 h. Triethylamine (1.21 mL, 8.70 mmol) was added, and the reaction was stirred for 20 min at -78 ^{o}C and for 40 min at rt. CH_2Cl_2 (10 mL, water (5 mL), and sat. $NaHCO_3$ (10 mL) were added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude aldehyde **46** was dissolved in methanol (2 mL), and the solution was added dropwise to a stirred solution of concentrated hydrochloric acid at 0 ^{o}C. The reaction was warmed to rt

and stirred for 17 h. The reaction was poured into water (20 mL), and CH_2Cl_2 (20 mL) was added. The mixture was cooled to 0 ^oC, and concentrated NH_4OH was added until the pH of the solution reached 8. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via flash chromatography, eluting with 1 to 4% methanol in CH_2Cl_2 to afford **33** (59 mg, 22%).



Benzylzinc bromide (TCT 2-120)

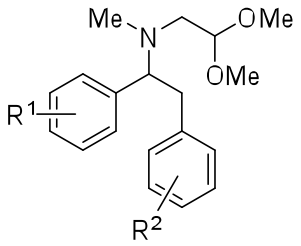
Benzylzinc bromide was prepared from benzyl bromide according to the literature procedure.[24] Benzyl bromide (1.18 mL, 10 mmol) was flushed through a basic alumina plug and added to a stirred suspension of zinc shavings (1.3 g, 20 mmol) in acetonitrile (10 mL) over ca 5 min. The reaction was stirred for 1 h. Titration against iodine indicated a 0.87 M solution.



Piperonylzinc bromide (TCT 3-75/3-76)

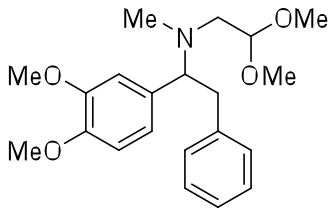
Phosphorus tribromide (3.8 mL, 39 mmol) was added dropwise to a stirred solution of piperonyl alcohol (5.0 g, 33 mmol) in diethyl ether (100 mL) at 0 ^oC. The reaction was warmed to rt and stirred for 5 h. The reaction was quenched with water (100 mL) at 0 ^oC (SLOWLY) and extracted with CH_2Cl_2 (50 mL). The organic fractions were dried (Na_2SO_4) and concentrated. Recrystallization from hexanes afforded 5.7 g (81%) of the bromide as a white solid. A solution of the bromide (5.0 g, 23.3 mmol) in THF (30 mL)

was added dropwise to a stirred suspension of zinc shavings (3.0 g, 46.5 mmol) in THF (10 mL) at 0 °C over 3 h. The reaction was stirred for an additional 1.5 h. Titration against iodine indicated a 0.47 M solution.



General preparation of aminoacetals (50) (See TCT 3-24 for example)

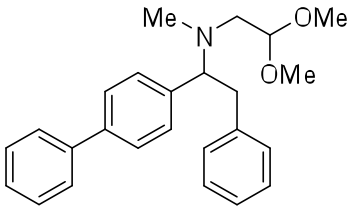
A substituted benzaldehyde **47** (2.5 mmol), aminoacetal **48** (0.49 mL, 3.8 mmol), acetonitrile (5 mL), and benzylzinc bromide (9 mL, 7.5 mmol, 0.83 M solution in MeCN) were added sequentially, and the reaction was stirred for 18 h. The reaction was poured into sat. aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was dissolved in diethyl ether (30 mL) and extracted with 1 M HCl (30 mL). The aqueous layer was washed with diethyl ether (30 mL), basified with 4 M NaOH to pH 12 at 0 °C, and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic fractions were washed with water (2 x 30 mL) to remove aminoacetal starting material, dried (Na_2SO_4), and concentrated to afford pure aminoacetal **50**.



N-(2,2-dimethoxyethyl)-1-(3,4-dimethoxyphenyl)-N-methyl-2-phenylethanamine (51) (TCT 3-24)

Aminoacetal **51** was prepared in 71% yield using the general procedure.

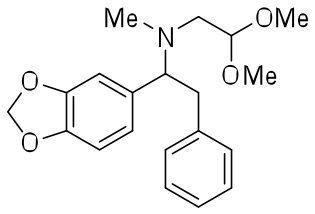
^{1}H NMR (300 MHz) δ 7.19 – 6.99 (comp, 5 H), 6.76 – 6.65 (comp, 3 H), 4.41 (t, *J* = 5.2 Hz, 1 H), 3.82 (d, *J* = 4.2 Hz, 6 H), 3.72 (dd, *J* = 9.2, 5.5 Hz, 1 H), 3.26 (comp, 7 H), 2.95 (dd, *J* = 13.4, 9.2 Hz, 1 H), 2.67 (dd, *J* = 13.5, 5.5 Hz, 1 H), 2.45 (dd, *J* = 13.5, 5.0 Hz, 1 H), 2.35 (s, 3 H); ^{13}C NMR (300 MHz) δ 148.4, 147.9, 139.8, 132.2, 129.3, 128.0, 125.8, 121.0, 112.0, 110.4, 103.5, 70.8, 55.9, 55.8, 53.5, 39.8, 39.1; HRMS (CI) *m/z* calculated for $C_{21}H_{30}NO_4$, 360.2175; found, 360.2173; IR (cm^{-1}) 2936, 2833, 1514, 1453, 1259, 1236, 1142, 1074, 1030.



1-(biphenyl-4-yl)-N-(2,2-dimethoxyethyl)-N-methyl-2-phenylethanamine (52) (TCT 3-73)

Aminoacetal **52** was prepared in 90% yield using the general procedure. Since the hydrochloride salt of **52** was insoluble in water, **52** was purified via flash chromatography, eluting with 0-10% methanol in CH_2Cl_2.

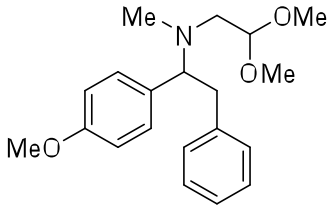
^{1}H NMR (300 MHz) δ 7.70 – 7.11 (comp, 14 H), 4.48 (t, *J* = 5.2 Hz, 1 H), 3.94 (dd, *J* = 8.8, 6.0 Hz, 1 H), 3.38 (comp, 7 H), 3.12 (dd, *J* = 13.5, 8.9 Hz, 1 H), 2.76 (dd, *J* = 13.5, 5.4 Hz, 1 H), 2.55 (dd, *J* = 13.4, 5.1 Hz, 1 H), 2.41 (s, 3 H); ^{13}C NMR (300 MHz) δ 140.9, 139.9, 138.3, 129.4, 128.8, 128.1, 127.3, 127.1, 126.7, 125.9, 103.6, 70.5, 56.0, 53.6, 39.6, 38.7; HRMS (CI) *m/z* calculated for $C_{25}H_{30}NO_2$, 376.2277; found, 376.2273; IR (cm^{-1}) 2945, 2830, 1487, 1453, 1125, 1075, 838, 766, 739, 699.



1-(benzo[d][1,3]dioxol-5-yl)-N-(2,2-dimethoxyethyl)-N-methyl-2-phenylethanamine (53) (TCT 3-28)

Aminoacetal **53** was prepared in 75% yield using the general procedure.

^{1}H NMR (300 MHz) δ 7.21 – 7.01 (comp, 5 H), 6.74 (s, 1 H), 6.67 (d, *J* = 7.9 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 5.94 – 5.85 (s, 2 H), 4.40 (t, *J* = 5.2 Hz, 1 H), 3.73 (dd, *J* = 9.1, 5.6 Hz, 1 H), 3.33 – 3.19 (comp, 7 H), 2.94 (dd, *J* = 13.5, 9.2 Hz, 1 H), 2.65 (dd, *J* = 13.5, 5.4 Hz, 1 H), 2.44 (dd, *J* = 13.4, 5.1 Hz, 1 H), 2.31 (s, 3 H); ^{13}C NMR (300 MHz) δ 147.5, 146.5, 139.8, 133.2, 129.4, 128.1, 125.9, 122.3, 109.0, 107.6, 103.5, 100.9, 70.6, 55.9, 53.5, 39.6, 39.0; HRMS (CI) *m/z* calculated for $C_{20}H_{26}NO_4$, 344.1862; found, 344.1861; IR (cm^{-1}) 2941, 1487, 1440, 1370, 1242, 1126, 1040, 969, 935, 812, 742, 670.

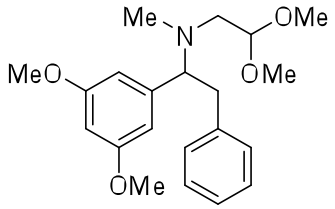


N-(2,2-dimethoxyethyl)-1-(4-methoxyphenyl)-N-methyl-2-phenylethanamine (54) (TCT 3-74)

Aminoacetal **54** was prepared in 82% yield using the general procedure.

^{1}H NMR (300 MHz) δ 7.21 – 7.00 (comp, 7 H), 6.85 – 6.76 (m, 2 H), 4.41 (t, *J* = 5.3 Hz, 1 H), 3.84 – 3.74 (comp, 4 H), 3.34 – 3.21 (comp, 7 H), 3.00 (dd, *J* = 13.5, 9.1 Hz, 1 H), 2.66 (dd, *J* = 13.4, 5.4 Hz, 1 H), 2.44 (dd, *J* = 13.4, 5.1 Hz, 1 H), 2.32 (s, 3 H); ^{13}C NMR (300 MHz) δ 158.6, 140.0, 131.2, 129.9, 129.4, 128.1, 125.8, 113.3, 103.5, 70.2, 55.8,

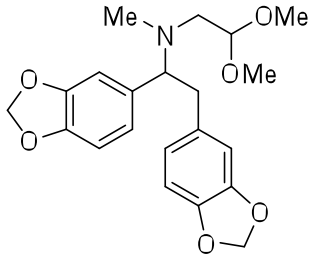
55.2, 53.5, 39.6, 38.9; HRMS (CI) *m/z* calculated for $C_{20}H_{28}NO_3$, 330.2069; found, 330.2063; IR (cm^{-1}) 2937, 2834, 1609, 1511, 1455, 1248, 1179, 1125, 1074, 832, 700.



N-(2,2-dimethoxyethyl)-1-(3,5-dimethoxyphenyl)-N-methyl-2-phenylethanamine (55) (TCT 3-25)

Aminoacetal **55** was prepared in 74% yield using the general procedure.

^{1}H NMR (300 MHz) δ 7.21 – 7.03 (comp, 5 H), 6.33 (comp, 3 H), 4.39 (t, *J* = 5.2 Hz, 1 H), 3.77 – 3.68 (comp, 7 H), 3.31 – 3.20 (comp, 7 H), 2.95 (dd, *J* = 13.5, 8.8 Hz, 1 H), 2.68 (dd, *J* = 13.5, 5.4 Hz, 1 H), 2.47 (dd, *J* = 13.5, 5.1 Hz, 1 H), 2.35 (s, 3 H); ^{13}C NMR (300 MHz) δ 160.4, 142.0, 139.8, 129.4, 128.0, 125.9, 107.0, 103.6, 99.0, 71.1, 56.1, 55.3, 53.6, 39.7, 39.0; HRMS (CI) *m/z* calculated for $C_{21}H_{30}NO_4$, 360.2175; found, 360.2174; IR (cm^{-1}) 2939, 2835, 1597, 1456, 1348, 1291, 1204, 1155, 1068, 835, 700.



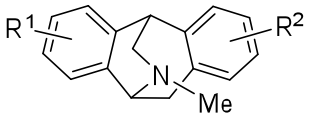
1,2-di(benzo[d][1,3]dioxol-5-yl)-N-(2,2-dimethoxyethyl)-N-methylethanamine (56) (TCT 3-77)

Lithium perchlorate (53 mg, 0.5 mmol), piperonal (0.75 g, 5.0 mmol), THF (10 mL), aminoacetal **48** (1.3 mL, 10.0 mmol), and piperonylzinc bromide (32 mL, 15.0 mmol, 0.47 M solution in THF) were added sequentially, and the reaction was stirred for 20 h.

The reaction was poured into sat. aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The reside was dissolved in 1 M HCl (50 mL) and washed with diethyl ether (3 x 50 mL). The aqueous layer was basified with 6 M NaOH to pH 12 at 0 ^oC and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated to afford 1.647 g (85%) of **56** as a pale yellow semisolid.

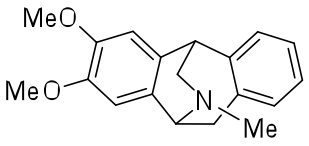
^1H NMR (300 MHz) δ 6.73-6.47 (comp, 6 H), 5.93-5.86 (m, 4 H), 5.30 (s, 2 H), 4.44 (s, 1 H), 3.75-3.63 (m, 1 H), 3.32 (d, *J* = 3.7 Hz, 1 H), 2.97-2.81 (m, 1 H), 2.65 (dd, *J* = 12.8, 5.9 Hz, 1 H), 2.51-2.35 (m, 1 H), 2.31 (s, 3 H).

*Due to time constraints, other characterization data were not obtained for this compound!



General synthesis of isopavines (57) (See TCT 3-67 for example)

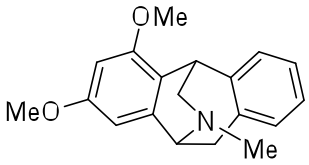
Concentrated HCl (2 mL) was added to the neat aminoacetal **50** (0.5 mmol), and the reaction was stirred at rt for 18 h. The reaction was diluted with water (10 mL), basified with 6 M NaOH to pH 12 at 0 ^oC, and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried (Na_2SO_4), concentrated, and flashed through a basic alumina plug to afford the pure isopavine.



(58) (TCT 3-67)

Isopavine **58** was prepared in 90% yield using the general procedure.

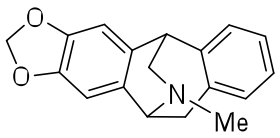
^{1}H NMR (300 MHz) δ 7.40 – 7.15 (comp, 4 H), 7.11 – 7.01 (comp, 2 H), 6.35 (d, *J* = 2.2 Hz, 1 H), 6.10 (dd, *J* = 7.3, 1.3 Hz, 1 H), 5.66 (dd, *J* = 9.3, 4.8 Hz, 2 H), 4.37 (t, *J* = 6.6 Hz, 1H), 3.87 (s, 3 H), 3.58 (s, 3 H), 3.08 (dd, *J* = 12.7, 6.1 Hz, 1 H), 2.95 – 2.77 (comp, 4 H); ^{13}C NMR (300 MHz) δ 148.1, 145.5, 138.7, 134.8, 130.1, 128.1, 125.9, 120.3, 110.7, 105.9, 96.7, 64.5, 55.8, 40.7, 36.6; HRMS (CI) *m/z* calculated for $C_{19}H_{22}NO_2$, 296.1651; found, 296.1656; IR (cm^{-1}) 2936, 1616, 1508, 1267, 1228, 1191, 1050, 701.



(59) (TCT 3-69)

Isopavine **59** was prepared in ca 92% yield using the general procedure.

The ^{1}H NMR spectrum of this compound is messier than the others – this compound should be prepared again and characterized.



(60) (TCT 3-78)

Isopavine **60** was prepared in ca 83% yield using the general procedure.

The ^{1}H NMR spectrum of this compound is messier than the others – this compound should be prepared again and characterized.

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