The Vinylogous Aldol Reaction of Furoate Esters and the Synthesis of Unnatural Enantiomer Morphinans as TLR4 Inhibitors

By

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This thesis entitled:

The Vinylogous Aldol Reaction of Furoate Esters and the Synthesis of Unnatural Enantiomer Morphinans as TLR4 Inhibitors

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has been approved for the Department of Chemistry and Biochemistry

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Tarek Sammakia

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

Hartwig, William Theodore (Ph.D., Chemistry)

The Vinylogous Aldol Reaction of Furoate Esters and the Synthesis of Unnatural Enantiomer Morphinans as TLR4 Inhibitors

Thesis directed by Professor Tarek Sammakia

Abstract

While in the Sammakia Lab, I have focused on developing and applying new approaches to organic synthesis and the creation of novel cell-signaling inhibitors. My research efforts can be classified into (i) the development and application of new methods for the synthesis of novel chemical motifs, and (ii) the use of organic molecules as probes for problems in chemical biology. The use of the Lewis acid, ATNP, which promotes the vinylogous aldol reaction of enolizable aldehydes and ketones with furoate esters, and the design and synthesis of unnatural enantiomer morphinans as inhibitors of Toll-Like Receptor 4 will be discussed.

Acknowledgements

Graduate school is a challenge that I could not have completed without support from many mentors, colleagues, and family members. Without my advisor (for both undergraduate and graduate school) Professor Tarek Sammakia, I would never have started my doctorate, much less finish it. He has always provided encouragement and pushed me to be a better chemist and person. Thank you for being my advisor for the last 10 years.

Professor Kateri Ahrendt, who mentored me while I was at Array, helped me decide to go to graduate school, and provided me great advice while I was here.

My colleagues in the Sammakia group: first Aaron, Joe, Matt and Greg, and later Carolynn, Mai, Jeff, Ryan, Katelyn, and Jake, I could never have finished without you. Whether it was commiserating over research not going as planned, celebrating a new result, or discussing new chemistry ideas, you were always there to keep me going. Thank you.

Finally my family: my mom and dad, my sister, and my grandparents. Thank you for encouraging me and helping me when research or graduate school wasn't going the way I'd hoped. Your support while I've been at CU means more than I can say. Thank you.

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The Vinylogous Aldol of Furoate Esters

1.1 Lewis Acids in Organic Synthesis

Lewis acids play an important role in organic synthesis. Chemists have studied the interactions of Lewis acids and bases for decades. The studies have led to a deep understanding of the synthetic utility of Lewis acids in dozens of reaction. Examples include reactions that form carbon-carbon bonds, such as the Diels-Alder and Aldol reactions. Within this area, the activation of carbonyls to nucleophilic addition by Lewis acids has been fertile.[1] After decades of work, chemists continue to find new ways to improve catalytic activity and chemo-, regio-, and stereoselectivity of reactions using Lewis acids.

Aluminum Lewis acids have been widely used in synthetic chemistry due to low cost, widespread availability, and diverse reactivity. Aluminum trichloride, for example, is used in Friedel-Crafts and ene reactions.[2] The ligands on aluminum Lewis acids are easily varied allowing tuning of reactivity and access to a range of reactions. Replacing the halides with alkoxide ligands attenuates the Lewis acidity creating opportunities for the catalysis of multiple reactions.

Yamamoto's Bulky Lewis Acids

Aluminum alkoxide Lewis acids, like those in the Oppenauer xxidation, are known to adopt complicated macro structures in solution.[3] These structures may affect reactivity and introduce undesired variability in reactions. These higher-order structures can be minimized by selecting bulky alkoxide substituents, such as large phenoxides, for the aluminum, allowing monomeric aluminum Lewis acids to dominate. Their monomeric nature means these aluminum

[1] Yamamoto, H.; Editor *Lewis Acids in Organic Synthesis*, Volume *2*, **2000**.
[2] (a) Olah, G. A.; Editor; *Friedel-Crafts and Related Reactions*, Volumes *1-4*, Wiley-Interscience: New York, **1963-1965**. (b) Snider, B.B.; *Acc. Chem. Res*., **1980**, *13*, 426-432
[3] Elschenbroich, C.; Salzer, A.; Eds. *Organometallics*, VCH, Weinheim, **1992**, Ch. 7.2.

Lewis acids are more Lewis acidic despite having a less available metal center than traditional alkoxide aluminium Lewis acids such as aluminum isopropoxide. Yamamoto and coworkers have developed a series of bulky aluminum Lewis acids using these phenoxide ligands that allow astonishing reactions to take place at carbonyls (Figure 1.1).[4]

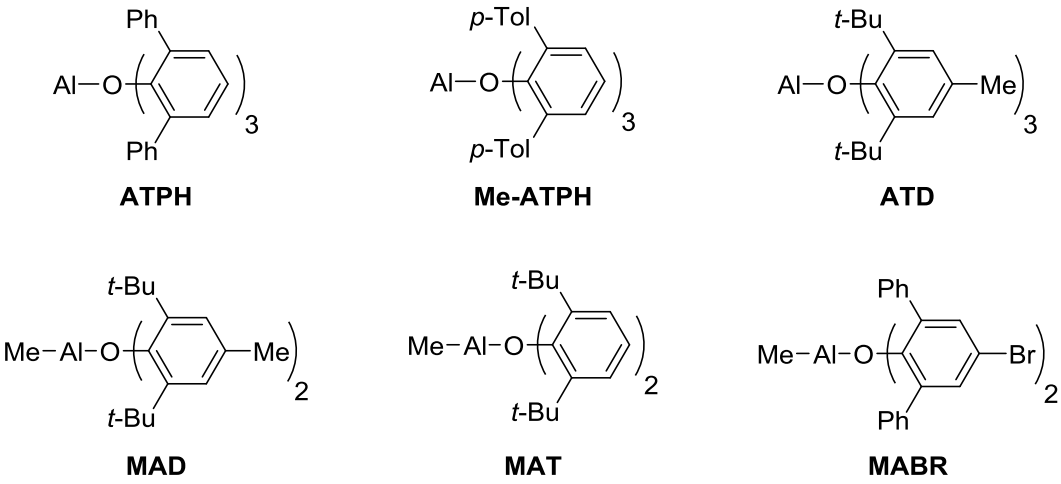
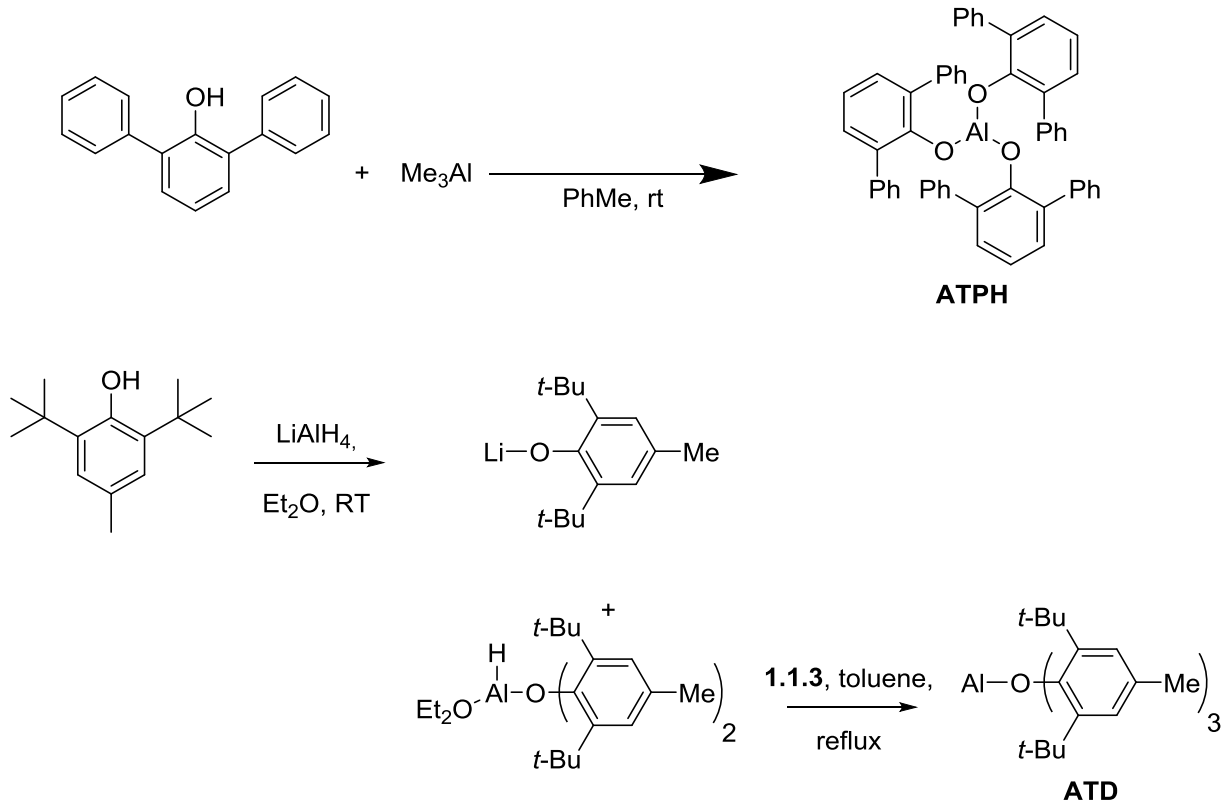


Figure 1.1 Yamamoto's Bulky Aluminum Lewis acids

Yamamoto's bulky Lewis acids are prepared by the reaction of trimethyl aluminum and the desired phenol and are used without purification. For example, aluminum tris(2,6-diphenylphenoxide) (ATPH) is prepared by adding trimethyl aluminum (1 equiv) to a solution of 2,6-diphenylphenol (3 equiv) in toluene at room temperature with the rigorous exclusion of air and moisture (Scheme 1.1).[5] Exceptionally bulky Lewis acids, such as aluminum tris(2,6-di-tert-butyl-4-methylphenoxide) (ATD) require a more elaborate preparation.[6] In order to create this sterically challenging acid, three equivalents of the 2,6-di-*tert*-butyl-4-methylphenol are added to lithium aluminum hydride in ether. After liberation of H_2 and removal of $Li[AlH_2(OC_6H_3t\text{-}Bu,\text{-}2,6)_2]$ by fractional crystallization, the resulting $[AlH(OC_6H_3tBu\text{-}2,6)_2,(OEt_2)]$ is reacted with an

[4] Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585–1592.
[5] Saito, S.; Shiozawa, M. *J. Am. Chem. Soc.* **1998**, *120*, 813–814.
[6] Healy, M. D.; Barron, A. R. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 921-922.

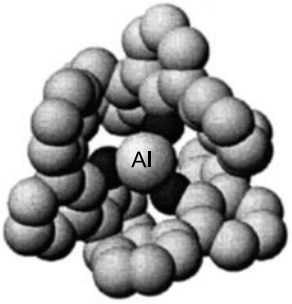
additional equivalent of 2,6-di-*tert*-butyl-4-methylphenol in refluxing toluene to provide the desired Lewis acid (Scheme 1.1).



Scheme 1.1 Preparation of ATPH and ATD

ATPH is perhaps the most intriguing of Yamamoto's bulky aluminum Lewis acids. It owes its unusual reactivity to its three dimensional structure. Crystal structures of APTH bound to dimethylformamide show a pseudo C_3 symmetric, cup-shaped cavity with a propeller-like ligand array around the central aluminum atom (Figure 1.2).[7a] The oxygen of a bound carbonyl is enclosed within this cavity, creating a sterically hindered environment adjacent to the binding site.

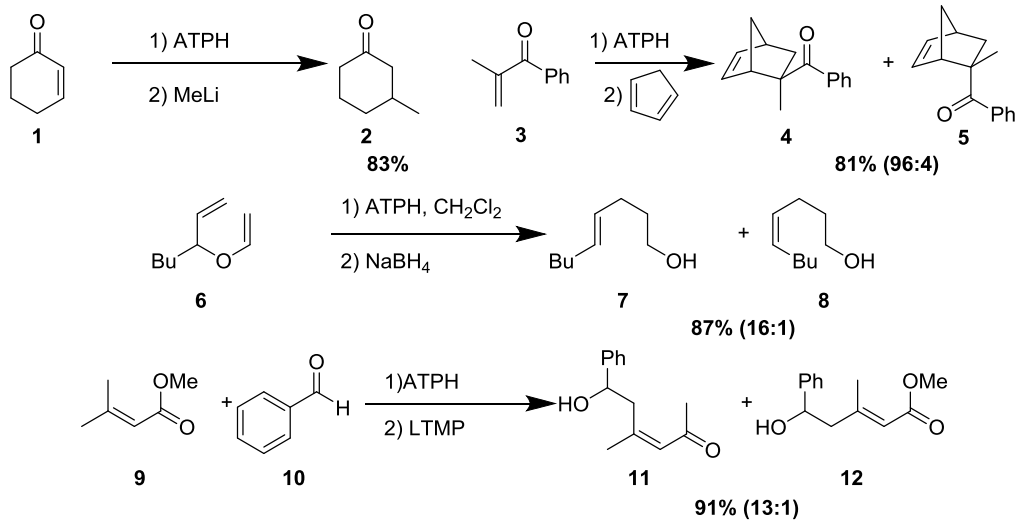
[7] (a) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto,H. *J. Am. Chem. Soc*. **1998**, *120*, 813-814. (b) Saito, S.; Shiozawa, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 17691771. (c) Saito, S.; Shiozawa, M.; Nagahara, T.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc*. **2000**, *122*, 7847-7848. (d) Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200-6210. (e) Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett* **2004**, 732-734.



(CPK model based on the X-ray crystal structure of the ATPH-DMF complex)

Figure 1.2 CPK model of ATPH based on a crystal structure[7a]

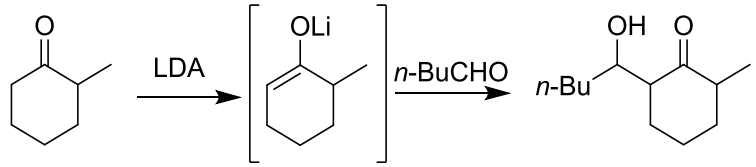
ATPH promotes a number of reactions such as 1,4-addition of nucleophiles to α,β-unsaturated carbonyl compounds, promotion of stereoselective Claisen rearrangements, and exo-selective Diels-Alder reactions.[4] Our group thought its ability to access δ-hydroxy-α,β-unsaturated esters via the vinylogous aldol reaction of α,β-unsaturated esters and aldehydes would be of great utility in the synthesis of natural products, particularly polyketides and macrolides (Scheme 1.2).[7]



Scheme 1.2 Select reactions using ATPH (1,4 addition of MeLi; Diels-Alder; Claisen Rearrangement; Vinylogous Aldol)

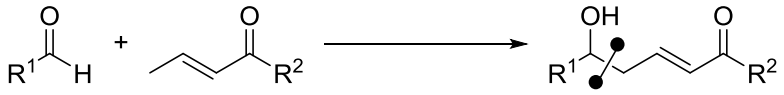
1.2 The Yamamoto Vinylogous Aldol

It is difficult to imagine modern organic synthesis without the widely used and synthetically powerful aldol reaction.[8] Controlling the direction of the mixed aldol reaction between two different carbonyl compounds which exhibit multiple sites of potential enolization presents difficulties for synthetic chemists and numerous methods have been developed to circumnavigate this challenge. Such reactions are best carried out by converting the carbonyl compound, which is to serve as a nucleophile, to an enolate. This reactive nucleophile is then added to the second, electrophilic, carbonyl compound (Scheme 1.3).



Scheme 1.3 Typical Procedure for Aldol Reactions

The extension of the aldol reaction to its vinylog (i.e., the vinylogous aldol reaction) is well known, and in its simplest form, proceeds via a dienolate derived from an α, β-unsaturated carbonyl and an aldehyde.[9] The prototypical transformation produces a functionally dense δ-hydroxy-α,β-unsaturated carbonyl compound, and as this bond construction occurs in an uncommon position (between the γ- and δ-carbons of the product), it offers a novel strategic disconnection in synthetic planning (Scheme 1.4).

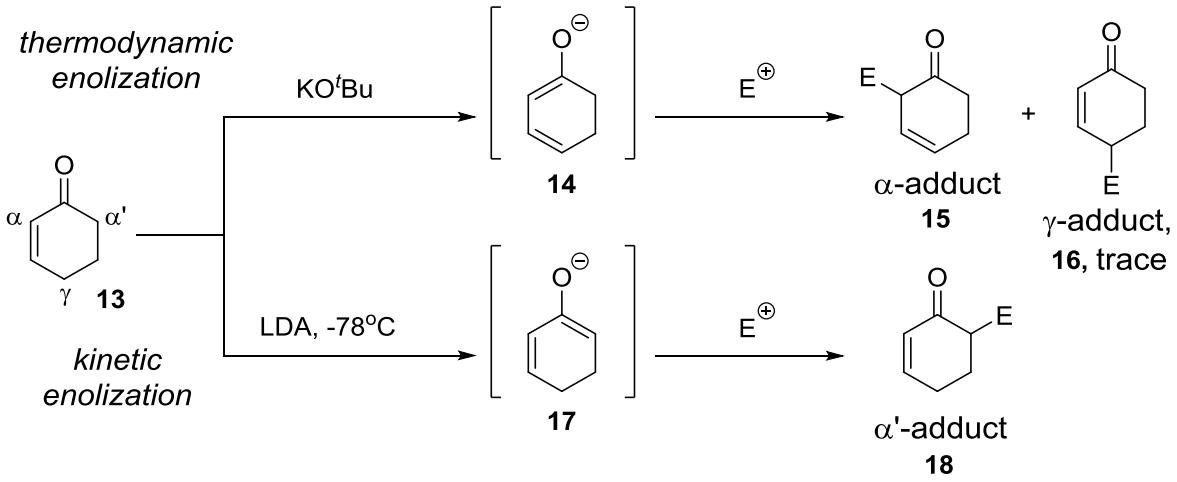


[8] For recent reviews on the aldol reaction, see: (a) Modern Aldol Reactions; Mahrwald, R., Ed.;Wiley-VCH:Weinheim, **2004**. (b) Paterson, I. Total Synthesis of Polyketides using Asymmetric Aldol Reactions. In Asymmetric Synthesis, 2nd ed.; Christmann, M., Brase, S., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, **2008**; pp 293-298.

[9] (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *11*, 3076-3154. (b) Denmark, S.E.; Heemstra, J.R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682-4698.

Scheme 1.4 The Vinylogous Aldol Reaction

Given the challenges of directing traditional aldol reactions, one would expect the complications of the vinylogous derivative to be greater with more potential sites of reactivity. The ability to selectively form the more distal γ-adduct, such as **16**, would be useful extension of this reaction. Traditional methods entail the treatment of cyclohexenone (**13**) with a thermodynamic base, such as a hydroxide or alkoxide, and yields the extended dienolate **14** via deprotonation at the γ-position. Quenching of this enolate with an electrophile leads primarily to addition at the α-position and product **15** (Scheme 1.5).[10] Reaction of the same cyclohexenone with a kinetic base, such as lithium diisopropylamide, leads to deprotonation at the α-position opposite the double bond providing enolate **17**. Trapping of this enolate with an electrophile leads to the α'-adduct, **18** (Scheme 1.5).



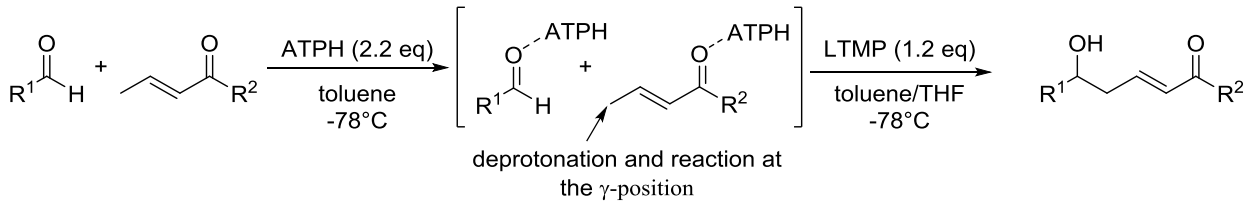
Scheme 1.5 Enolization/Trapping Strategies of Cyclohexenone[10]

ATPH-mediated Vinylogous Aldol Reaction

Yamamoto described an important advancement in the vinylogous aldol with the use of the very bulky Lewis acid, ATPH.[7] ATPH can be used in reactions of lithium enolates with

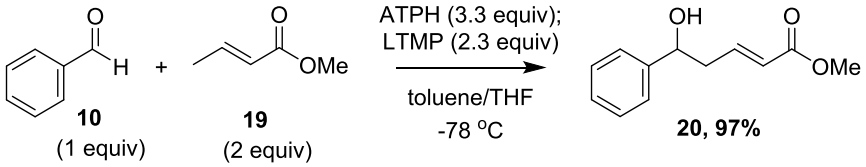
[10] Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 3, Chapter 1.1 pp. 21–25 and references therein.

aldehydes, and is thought to bind to both the nucleophilic and electrophilic components of the reaction. ATPH causes addition to occur at the more distant γ-carbon by blocking reaction at the α-carbon with its bulk and reach (Scheme 1.6). Remarkably, ATPH has proven capable of directing reactivity to the terminal carbon in substrates as long as hexaenolates derived from pentaenoates.[7b]



Scheme 1.6 The Yamamoto Vinylogous Aldol Reaction

The reaction begins with pre-complexation of methyl crotonate **1.7.2** (2.0 equiv) and benzaldehyde **1.7.1** (1.0 equiv) with ATPH (3.3 equiv). LTMP (2.3 equiv) in THF is added to the complexed substrates at -78 ºC under an argon atmosphere. The mixture is stirred for a half-hour at -78 ºC and then quenched by the addition of saturated aqueous ammonium chloride. Purification by column chromatography with silica gel provides aldol adduct **1.7.3** with exclusive (E)-configuration at the olefin in 97% yield (Scheme 1.8).[7b]



Scheme 1.7 Yamamoto Vinylogous Aldol Reaction of Benzaldehyde and Methyl Crotonate

Yamamoto found that this reaction proceeds well in most cases where α,β-unsaturated aldehydes, ketones, and esters are used as nucleophiles with aldehydes.[7a,b] Unfortunately α,β-unsaturated esters reacting with unbranched, enolizable aldehydes are a notable exception, with the vinylogous aldol reaction between methyl crotonate and valeraldehyde providing 22% of the desired product (Table 1.1).[7b] The complicated mixture of products isolated in this reaction

suggests that competitive deprotonation at the α-position of the aldehyde is the culprit (Table 1.1).

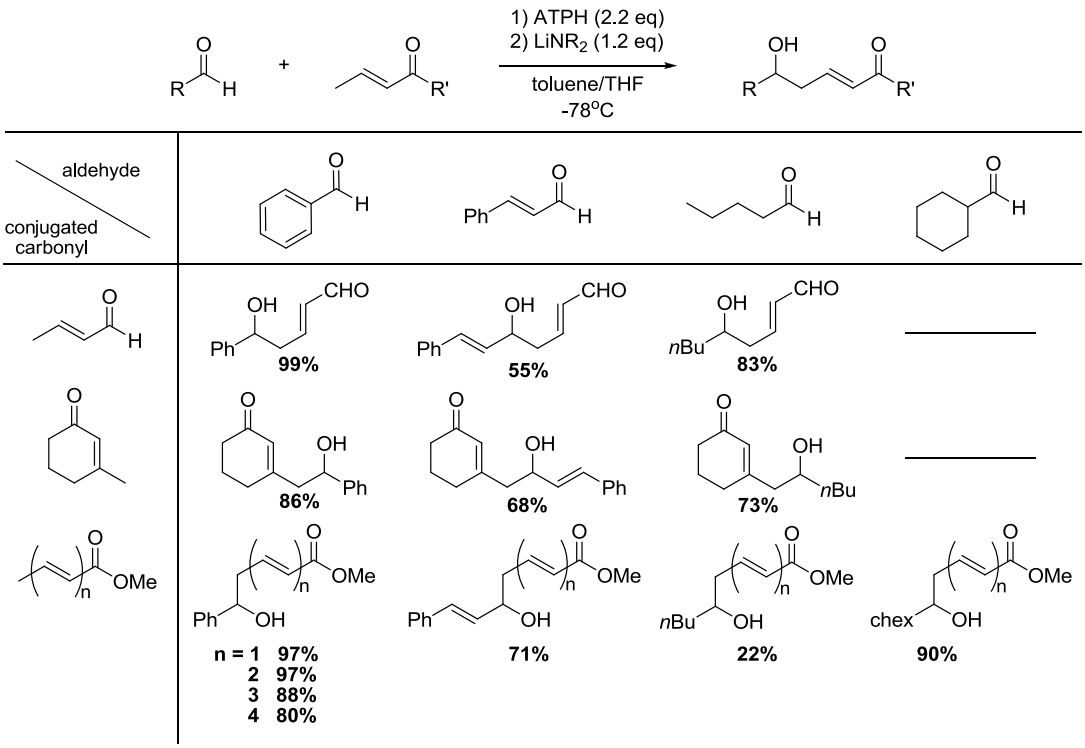
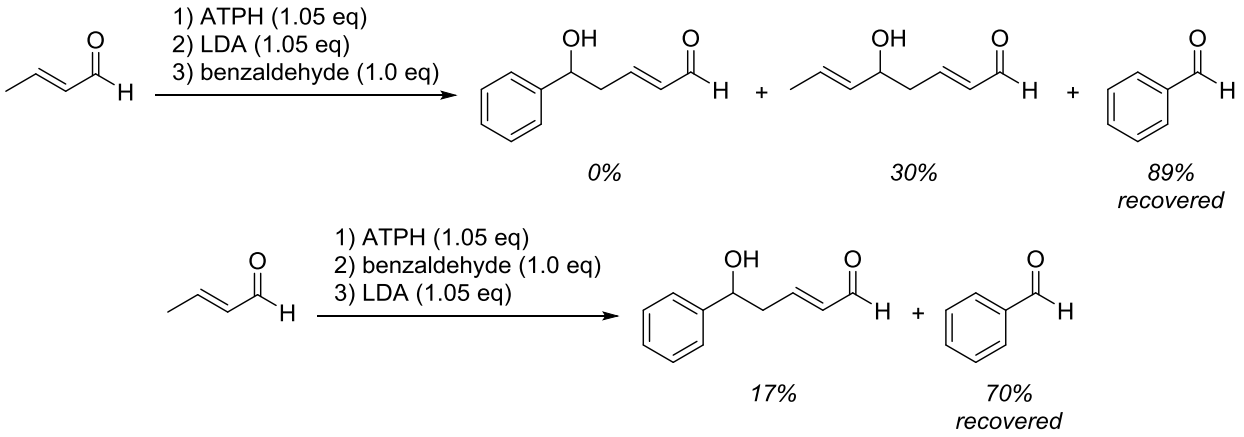


Table 1.1 Scope of the Yamamoto Vinylogous Aldol Reaction

The Yamamoto protocol forms ATPH *in situ* after which both the nucleophile and electrophile are added prior to the addition of the base. Attempts to conduct the reaction in a stepwise fashion wherein the complexed enolate is first formed and then unbound aldehyde is added provides no desired product (Scheme 1.8).[7a] Adding the uncomplexed benzaldehyde prior to the LTMP provided only slightly better results with 17% yield of the desired adduct and 70% recovered benzaldehyde.[7a] Thus the reaction requires stoichiometric ATPH with respect to both nucleophile and electrophile and these must be complexed prior to addition of base for the reaction to be successful.



Scheme 1.8 Unsuccessful Stepwise Yamamoto Vinylogous Aldol Protocols

The Intramolecular Yamamoto Vinylogous Aldol Reaction

An intramolecular vinylogous aldol reaction would lend itself to the construction of biologically-active, macrocycle-containing natural products such as arenolide, RK-397, peloruside A, and laulimalide (Figure 1.3). The functional group placement and possibility of hexaenolates being tolerated in the reaction lead to intriguing possible retrosynthetic disconnections shown in Figure 1.3. Dr. Mark Mitton-Fry and Dr. Joseph Abramite, former graduate students in the Sammakia lab,

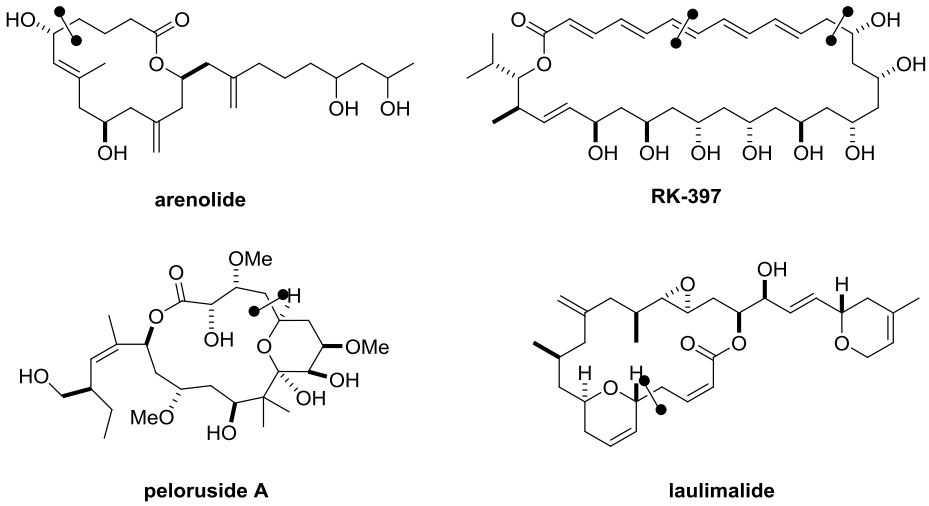


Figure 1.3 Possible Target Molecules Utilizing an Intramolecular Vinylogous Aldol Reaction

hypothesized that the necessity of pre-complexing both the ester and the aldehyde with ATPH would make the vinylogous aldol reaction well suited to intramolecular reactions where both nucleophile and electrophile would be present from the start. An intramolecular variation of the vinylogous aldol reaction would be readily applied in the macroaldolization of crotonate esters to form rings of various sizes. Medium-membered rings formed by such a reaction would be valuable synthetic motifs as rings of this size possess difficult entropic and enthalpic energy barriers to their formation as compared to larger or smaller rings. Prior syntheses of compounds containing such medium-membered rings have been accomplished by ring closure with macrolactonizations such as the Yamuguchi[11] or Mitsunobu[12] esterification or ring-closing metathesis,[13] but these methods often provide only moderate yields and lack the opportunity of forming additional asymmetric carbons in the course of the reaction, other methods are also known.[14] Dr. Abramite, however, successfully made 10- to 14-membered macrolides in good yields (up to 90%) and excellent remote diastereoselection simultaneously (~20:1 dr) (Table 1.2) using an intramolecular variation of the Yamamoto vinylogous aldol reaction.[15] While useful and high yielding, the reactions is limited to non-enolizable aldehydes.

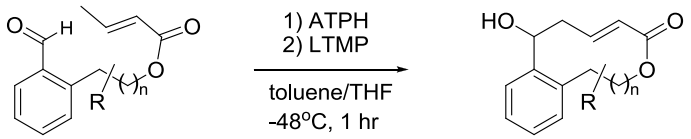
[11] (a) Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303–1305.; (b) Ghosh, A. K.; Xu, X.; Kim, J.-H.; Xu, C.-X. *Org. Lett.* **2008**, *10*, 1001–1004.; (c) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194–9204.

[12] Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed*. **2003**, *42*, 1648-1652.

[13] (a) Wang, B.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 5223–5226.; (b) Wullschleger, C. W.; Gertsch, J.; Altmann, K.-H. *Org. Lett.* **2010**, *12*, 1120–1123.; (c) Oh, H.-S.; Kang, H.-Y. *J. Org. Chem.* **2012**, *77*, 1125–1130.; (d) Willwacher, J.; Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 4217–4221.

[14] For selected examples see: (a) Sammakia, T. The Lewis Acid Mediated Version of the Nicholas Reaction: Investigations on the Stereochemistry and Mechanism The Effects of Local Conformational Control in the Epoxidation of Unsaturated Macrolides: Stererocontrolled Routes to Ionophore Subunits Class C , Yale University, 1988. (b) Wessjohan, L. A.; Ruijter, E. In *Topics in Current Chemistry*; Springer Berlin Heidelberg, 2005; pp. 137–184.

[15] Abramite, J. A.; Sammakia, T. *Org. Lett*. **2007**, *9*, 2103-2106.



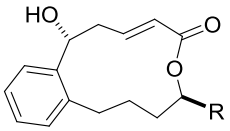
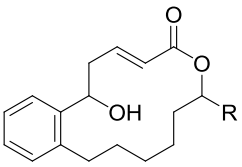
entry	product	R	yield	alkene geometry	dr
1		H (**6**)	81%	*E*	—
2		Me (**7**)	84%	*E*	> 25:1
3		*i*-Pr (**8**)	83%	*E*	> 25:1
4		H (**9**)	90%	*E*	—
5		Me (**10**)	89%	*E*	20:1
6		*i*-Pr (**11**)	88%	*E*	23:1

Table 1.2 The Intramolecular Vinylogous Aldol Reaction

Dr. Abramite wished to demonstrate the utility of the intramolecular vinylogous aldol reaction for constructing macrolide-containing natural products. The polyoxygenated, 16-membered macrolide (+)-peloruside A **1.4.1** was chosen as the target because a synthesis using the intramolecular vinylogous aldol method developed by Dr. Abramite could be envisioned that was plausible and step economical. In addition, the synthesis of peloruside A is of interest as it displays antimitotic activity against several cancer cell lines via tubulin inhibition.[16]

1.3 Isolation, Characterization, and Biological Activity of (+)-Peloruside A

Isolation and Characterization

Marine organisms are a rich source of natural products, with potent activity and intriguing structures. In 2000, the lab of Peter Northcote isolated the polyoxygenated 16-membered macrolide natural product Peloruside A from *Mycale hentscheli,* a marine sponge, found in the Pelorus Sound off the coast of the coast of New Zeland.[17] The absolute configuration was

[16] (a) Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridge, M. V; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356–3360. (b) Gaitanos, T. N.; Buey, R. M.; Díaz, J. F.; Northcote, P. T.; Teesdale-Spittle, P.; Andreu, J. M.; Miller, J. H. *Cancer Res.* **2004**, *64*, 5063–5067. (c) Miller, J. H.; Rouwé, B.; Gaitanos, T. N.; Hood, K. A.; Crume, K. P.; Bäckström, B. T.; La Flamme, A. C.; Berridge, M. V; Northcote, P. T. *Apoptosis* **2004**, *9*, 785–796. (d) Page, M.; West, L.; Northcote, P.; Battershill, C.; Kelly, M. *J. Chem. Ecol.* **2005**, *31*, 1161–1174.

[17] West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem*. **2000**, *65*, 445-449.

established in 2003 when De Brabander and coworkers synthesized the unnatural enantiomer, (-)-peloruside A.[12]

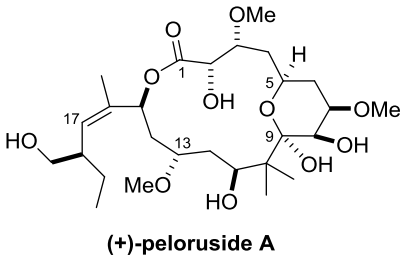


Figure 1.4 (+)-Peloruside A

Biological Activity

Northcote and coworkers found (+)-peloruside A to be cytotoxic in P388 murine leukemia cells at approximately 10 ng/mL (18 nM).[17] Following the isolation, Miller and coworkers confirmed that (+)-peloruside A is indeed a potent cytotoxin against a variety of other cancer cell lines at low nanomolar concentrations (4-15 nM).[16c] It is hypothesized that (+)-peloruside A stabilizes microtubules during mitosis, preventing breakdown of tubulin polymers and causing cells to stop mitosis and leading to apoptosis. Inducing apoptosis by stopping mitosis via microtubule stabilization is a known mechanism of action for several drugs on the market including paclitaxel, vincristine, vinorelbine, and vinblastine.[16]

(+)-Peloruside A was found to be effective against paclitaxel-resistant mutants.[18] Competition binding experiments show that peloruside A binds to a different site than members of the taxane family (Figure 1.5), hence its effectiveness against some drug-resistant cancer cells.

[18] Giannakakou, P.; Gussio, R.; Nogales, E.; Downing, K. H.; Zaharevitz, D.; Bollbuck, B.; Poy, G.; Sackett, D.; Nicolaou, K. C.; Fojo, T. *PNAS*, **2000**, *97*, 2904-2909.

(+)-Peloruside A was discovered to have synergistic effects with taxane drugs in polymerizing purified tubulin as well as *in vivo* assays.[19]

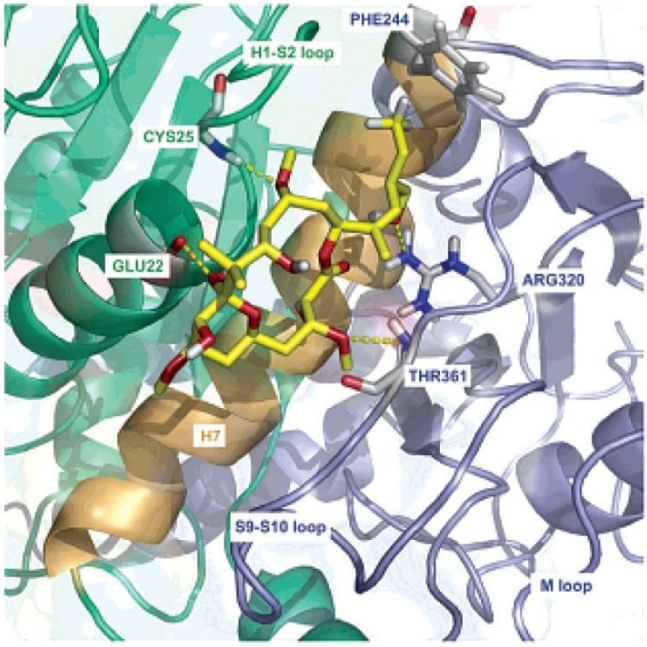


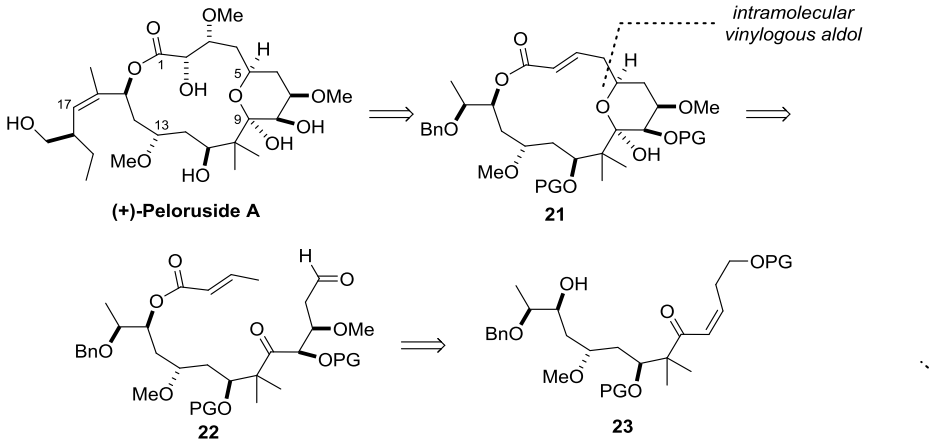
Figure 1.5 Proposed Binding Site of (+)-Peloruside A[16]

1.4 (+)-Peloruside A Synthesis

Retrosynthetic analysis

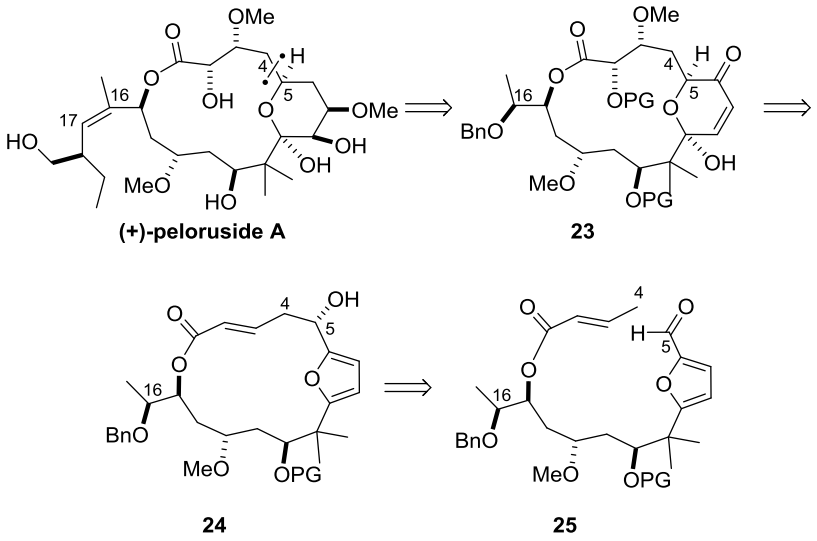
Our efforts towards the synthesis of (+)-peloruside A have focused on the use of the intramolecular vinylogous aldol reaction.[20] Dr. Abramite envisioned using the vinylogous aldol reaction for a disconnection between carbons 4 and 5 to provide crontonyl ester **22** as a key intermediate (Scheme 1.9). Removal of the crontonyl group and proection of the aldehyde yielded highly functionalized ketone **23** (Scheme 1.9). Unfortunately intermediate **22**

[19] Altmann, K. H. *Curr. Opin. Chem. Biol.* **2001**, *5*, 424-431.
[20] Gazaille, J. A.; Abramite, J. A.; Sammakia, T. *Org. Lett.* **2012**, *14*, 178–181.



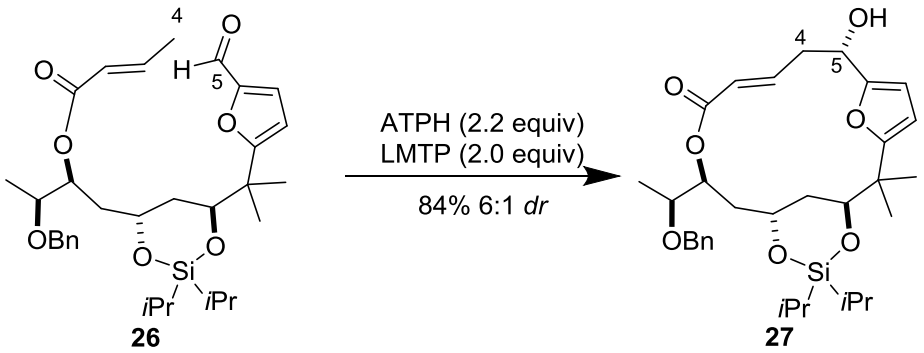
Scheme 1.9 Initial Retrosynthesis of (+)-Peloruside A

possesses an enolizable aldehyde rendering it unsuitable for a vinylogous aldol reaction using ATPH. This necessitated an alternative route, using non-enolizable aldehyde **25**, taking advantage of the Achmatowicz rearrangement of a furan ring containing intermediate **24** to conduct the vinylogous aldol on a furfural derivative which was then subjected to oxidative rearrangement to provide the requisite pyranone ring compound **23**.



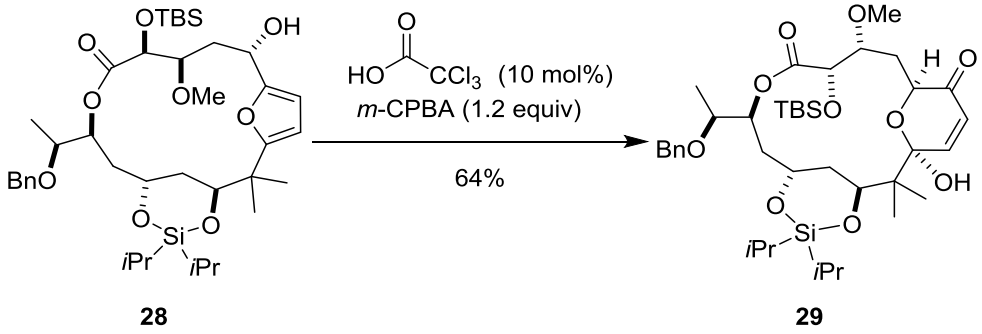
Scheme 1.10 Modified (+)-Peloruside A Retrosynthesis

This new strategy led to crontonyl ester **26**, wherein the key intramolecular vinylogous aldol reaction was successfully conducted to provide macrolide **27** in 86% yield with a 6:1 *dr* (Scheme 1.11). This



Scheme 1.11 Intramolecular vinylogous aldol in (+)-peloruside A synthesis

intermediate was carried forward to the Achmatowicz rearrangement which provided the highly functionalized pyranone **29** in 64% yield (scheme 1.12). Unfortunately the pyranone was resistant to dihydroxylation from the necessary face to complete the synthesis of (+)-peloruside A.



Scheme 1.12 Achmatowicz rearrangement in (+)-peloruside A synthesis

We, therefore, investigated ways in which the vinylogous aldol of ester enolates could be expanded to include enolizable aldehydes and provide an alternative route to (+)-peloruside that would avoid the pyranone intermediate.

1.5 Vinylogous Aldol of Crotonate Esters with Enolizable Aldehydes

As previously mentioned, a key limitation of the vinylogous aldol reaction of ester-derived enolates using the Yamamoto protocol is their incompatibility with enolizable aldehyde electrophiles. Yamamoto found that vinylogous aldol reactions of enolizable aldehydes, such as valeraldehyde, provided diminished yields (Table 1.1).[7b] This limitation had required the use of

the furfural derivative en route to (+)-peloruside A, which led to the pyran intermediate that could not be carried forward.[20] Devising a way to expand the compatibility of the vinylogous aldol reaction of esters to include enolizable aldehydes could provide access to an alternative route to (+)-peloruside A, and broaden the utility of the vinylogous aldol reaction further.

Aluminum tris(2,6-di-2-naphthylphenoxide) (ATNP)

The use of enolizable aldehydes necessitates a Lewis acid with sufficiently bulk and reach to prevent deprotonation of α-protons of bound aldehydes by bulky amide bases such as LTMP and LDA. A screen of bulky Lewis acids – ATPH,[7a] MAD,[21] MABR,[22] MAT,[22] ATD,[6] and MeATPH[7e] (Table 1.3) by Dr. Jeff Gazaille failed to find a Lewis acid with the necessary spread to prevent

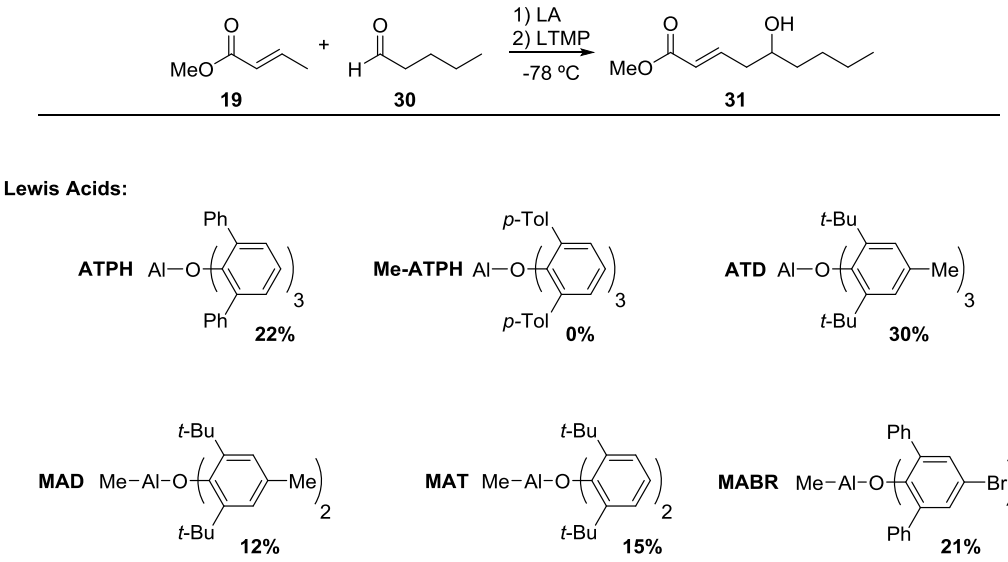
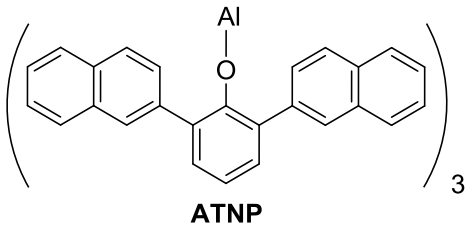


Table 1.3 Bulky Lewis Acid Screen

deprotonation at the α-position.[23] Dr. Gazaille hypothesized that a Lewis acid with longer reach than ATPH might block deprotonation of the α-protons and allow the reaction to proceed with improved yield. To test this hypothesis the new Lewis acid aluminum tris(2,6-di-2-

[21] Starowieyski, K. B.; Pasynkiewicz, S.; Skowrońska-Ptasińska, M. *J. Organomet. Chem.* **1975**, *90*, C43–C44.
[22] Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 7922–7924.
[23] Gazaille, J. A.; Sammakia, T. *Org. Lett.* **2012**, *14*, 2678–2681.

napthylphenoxide) (ATNP), was synthesized (Figure 1.6). ATNP features 2-napthyl arms on either side of the phenol and it was expected that these longer arms would block access to the site of enolization on the aldehydes where tert-butyl (MAD, ATD, MAT) or *p*-tolyl (Me-ATPH) groups had failed.



ATNP

Figure 1.6 Aluminum tris(2,6-di-2-napthylphenoxide) (ATNP)

Gratifyingly, ATNP successfully mediated the reaction of methyl crotonate (**19**) with valeraldehyde (**30**), providing product **31** in 82% yield after optimization compared to 22% with the same conditions using ATPH. Following this excellent initial result, the substrate scope was explored with a variety of enolizable aldehydes with diverse functionalities. Heptanal (**32**) and hydrocinnamaldehyde (**34**) reacted similarly to valeraldehyde (**30**) and provided products in yields of 76% and 82%, respectively (Table 1.4, entries 2-3). Cyclohexanecarboxaldehyde (**36**) reacted similarly and provided the product in 96% yield, moderately improving on the ATPH yield of 90% (Table 1.4, entry 4).[7b] Yields as high as 97% were found for pivaldehyde (**38**) and benzaldehyde (**10**) (Table 1.4, entries 5 and 6). Oxygenation at the α- and β-position was well-tolerated and provided products in yields ranging from 65-77% depending on the protecting group and position (Table 1.4, entries 7-11). Cinnamaldehyde (**51**) proved to be a less efficient reaction partner and provided the product in a moderate yield of 43% (Table 1.4, entry 12). This low yield is due to a competing reaction wherein the enolate adds in a conjugate fashion to the aldehyde.

entry	aldehyde	product	yield (%) dr

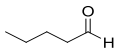
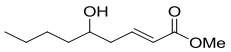
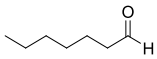
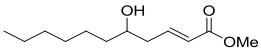
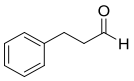
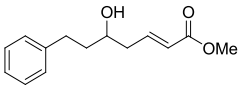
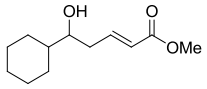
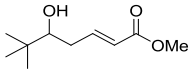
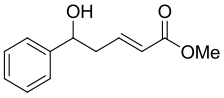
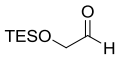
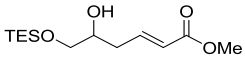
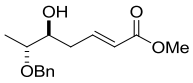
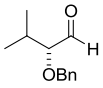
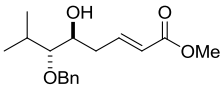
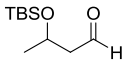
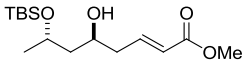
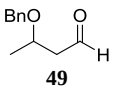
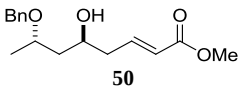
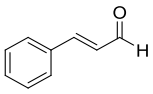
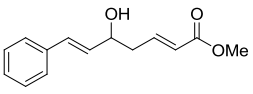
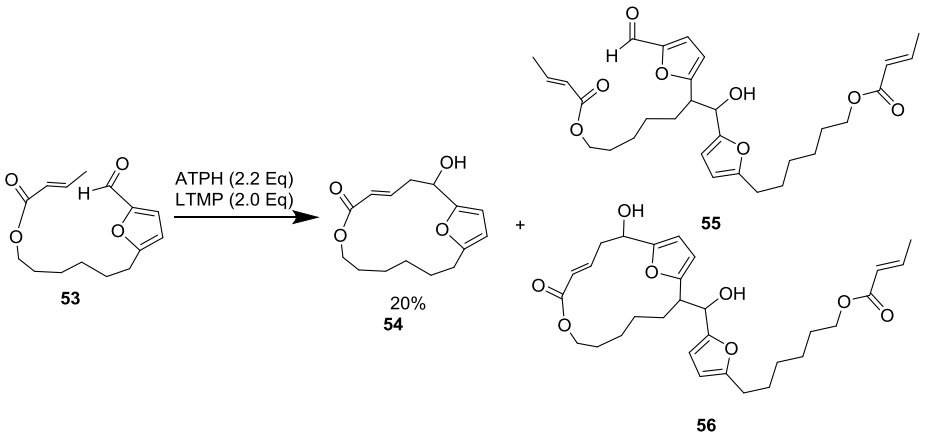
1	 **30**	 **31**	82
2	 **32**	 **33**	76
3	 **34**	 **35**	82
4	 **36**	 **37**	96
5	 **38**	 **39**	97
6	 **10**	 **40**	97
7	 **41**	 **42**	77
8	 **43**	 **44**	77 2.4:1 dr
9	 **45**	 **46**	87 10:1 dr
10	 **47**	 **48**	65 1.3:1 dr
11	 **49**	 **50**	78 3.4:1 dr
12	 **51**	 **52**	43

Table 1.4 Substrate scope of vinylogous aldol with ATNP and methyl crotonate[23]

1.6 Vinylogous Aldol of Furoate Esters with Enolizable Aldehydes and Ketones

With the successful application of ATNP to the vinylogous aldol reaction of enolizable aldehydes with methyl crotonate, we decided to revisit a reaction that had been observed during research towards the synthesis of (+)-peloruside A.[24] Compound **53** had been prepared as a model system and was subjected to the optimized intramolecular vinylogous aldol reaction conditions devised by Dr. Abaramite.[15] Surprisingly the desired macrolide **54** was isolated in only 20% yield with side products **55** and **56** comprising the bulk of the crude product. It was hypothesized that deprotonation at the benzylic position of the furfural competitively formed an extended enolate that was able to react with the furfural of compound **53** leading to the side products.

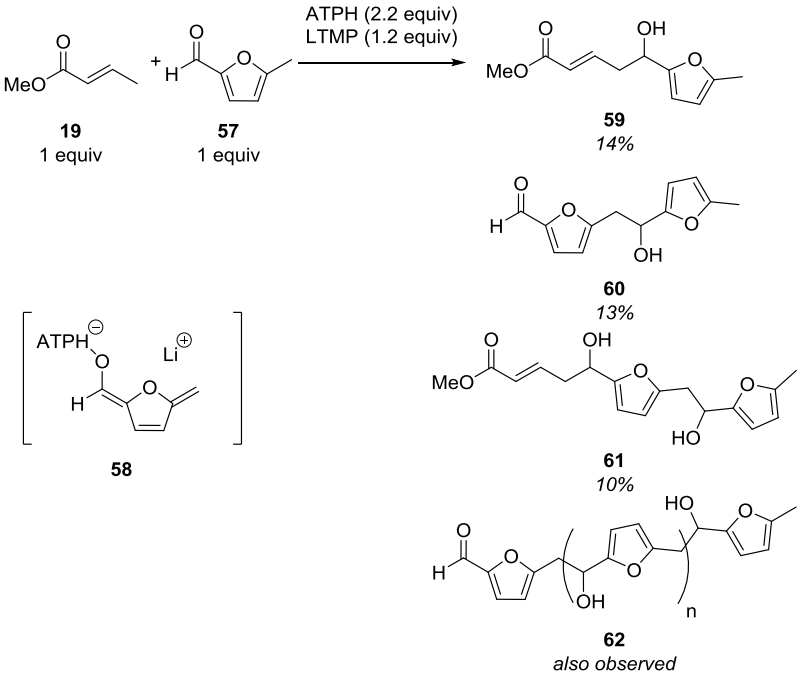


Scheme 1.13 Observed side reaction[24]

To test this hypothesis, Dr. Abramite carried out the vinylogous aldol reaction between methyl crotonate (**19**) and 5-methylfurfural (**57**). Unfortunately, several other products were formed in addition to desired product **59** including: **60**, **61**, and **62**.[24] This formation of an

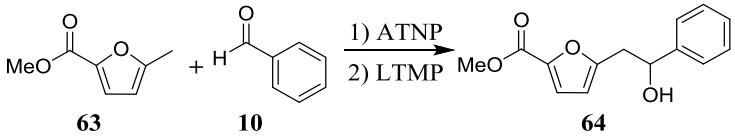
[24]Abramite, J. A. The Intramolecular Vinylogous Aldol Reaction and Its Application in the Total Synthesis of (+)-Peloruside A, University of Colorado, 2008.

extended enolate through an aromatic system was not unprecedented, as Yamamoto had previously reported forming an enolate through a *p*-methylacetophenone.[7a]



Scheme 1.14 Intermolecular Vinylogous Aldol Reaction of 5-Methylfurfural[24]

With hopes of building on the work of Yamamoto and Dr. Abramite, we decided to explore the potential of methyl-5-methylfuroate (**63)** to undergo the vinylogous aldol reaction with benzaldehyde using ATNP (Scheme 1.15). The initial experiment, using the optimized



Scheme 1.15 Vinylogous Aldol Reaction of Methyl-5-methylfuroate and benzaldehyde.

conditions developed by Dr. Gazaille in his studies of ATNP proved variable and provided modest yields. The low and inconsistent yield was initially thought to stem from adventitious moisture. Numerous iterations of the reaction failed to increase this yield even with rigorous exclusion of moisture by using only freshly distilled solvents and reagents, transferring solvents via dried cannulas, storing substrates over molecular sieves, and using dry, gas-tight syringes.

We hypothesized that perhaps a small amount of moisture was in fact necessary for the reaction, perhaps by forming a di-aluminum oxo-bridged Lewis acid (Figure 1.7). These species are not

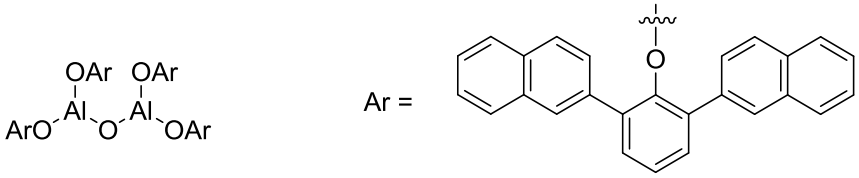


Figure 1.7 Proposed oxo-bridged aluminum Lewis acid

unknown and it was decided to synthesize an ATNP-derived complex and observe the effects on the reaction.[25] The oxo-bridged Lewis acid failed to mediate the reaction. Finally it was decided to increase the scale of the reaction from 0.076 mmol to 0.471 mmol to reduce the effect of any water contamination. Drying of the 2,6-dinaphthylphenol, used to make ATNP, by azeotropic distillation with toluene was found to improve the reliability of the reaction as well. These additional measures, while using the optimized conditions of Dr. Gazaille, provided desired product 1.15.2 in 56% yield.

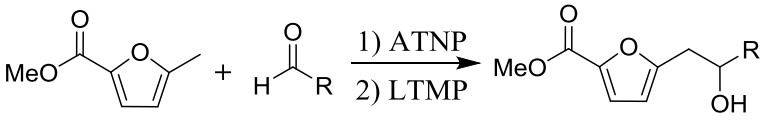
We rationalized that the enolate derived from methyl-5-methylfuroate was more difficult to form due to the increased basicity of the parent ester relative to methyl crotonate leading to the diminished yield relative to the methyl crotonate reactions. We, therefore, experimented with increasing the amount of base used in the reaction (table 1.5, entries 2-4) and found that 3.5 equivalents of LTMP provided the desired product in 78% yield (table 1.5, entry 3) which was within experimental error of 5.0 equivalents of LTMP.

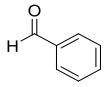
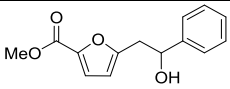
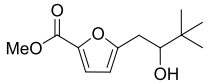
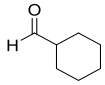
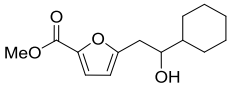
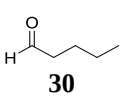
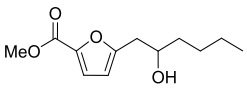
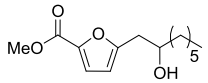
entry	ester (equiv)	ATNP (equiv)	LTMP (equiv)	temp (°C)	yield (%)
1	2	3.3	2.3	-78	56
2	2	3.3	3.0	-78	55
3	2	3.3	3.5	-78	78
4	2	3.3	5.0	-78	80

[25] Kissin, Y. V. *Macromolecules* **2003**, *36*, 7413–7421.

Table 1.5 Optimization of furoate ester vinylogous aldol reaction with ATNP

With optimized conditions in hand, we decided to explore the scope of the reaction (Table 1.6). We found that both branched (pivaldehyde **38** and cyclohexanecarboxaldehyde **36**) and unbranched (valeraldehyde **30** and heptanal **32**) aliphatic aldehydes are good reaction partners and provide the products in yields ranging from 71-81% (Table 1.6, entries 2-5). Aldehydes with oxygenation at the α- or β-positions were also studied and provided moderate to high yields (46-85%, Table 1, entries 6-8). Triethylsiloxyacetaldehyde (**41**), an α-oxygenated aldehyde, provided the desired product in a modest yield of 52% (Table 1.6, entry 6). Aldehyde (**47)**, which bears a β-tertbutyldimethylsilyloxy group, provided a relatively low yield of 46% and a diastereoselectivity of 1.5:1 (Table 1.6, entry 8). The cause of the reduced yield with silyl protected substrates remains unclear. Oxygenation at the β-position was well-tolerated in the case of β-benzyloxy aldehyde (**71)** which provided the product in a high yield of 85% but with a moderate diastereoselectivity of 3.4:1 favoring the *syn* isomer (Table 1.6, entry 7).



entry	aldehyde	product	yield (%) dr
1	 **10**	 **65**	78
2	 **38**	 **66**	81
3	 **36**	 **67**	78
4	 **30**	 **68**	72
5			71

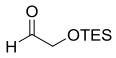
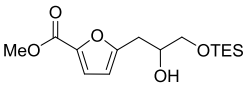
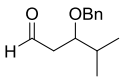
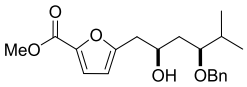
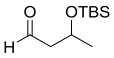
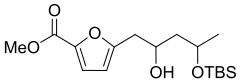
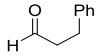
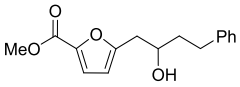
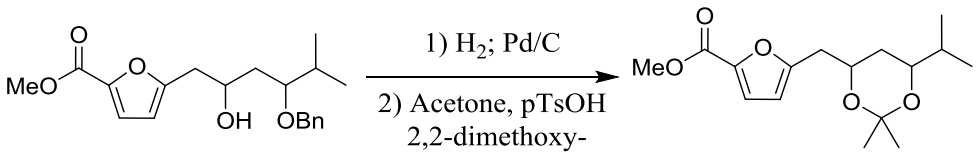
	32		**69**	
6	 **41**		 **70**	52
7	 **71**		 **72**	85 3.4:1
8	 **47**		 **73**	46 1.5:1
9	 **34**		 **74**	27

Table 1.6 Substrate scope of vinylogous aldol reaction of aldehydes

The major stereoisomer was identified using the ^{13}C NMR analysis method of Rychnovsky.[26] This method first required the cleavage of the benzyl group by hydrogenolysis, followed by the formation of the dimethyl acetonide (scheme 1.16). The ^{13}C spectrum of **75** had large peaks at 19.77 and 30.06 corresponding to the *gem*-dimethyl groups of the chair conformer of the acetonide indicative of *syn* stereochemistry. Smaller resonances at 24.68 and 24.22 ppm were consistent with the *anti*-product.



73 **75**

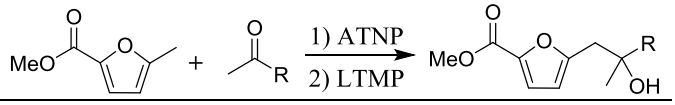
Scheme 1.16 Synthesis of acetonide for Rychnovsky's method

A peculiar outlier was hydrocinnamaldehyde (**34**) which provided the desired product in a low yield of 27% (Table 1.6, entry 9). This low yield could be due to hydrocinnamaldehyde being a poor substrate for the reaction or it inhibiting the reactivity of the enolate by an unknown mechanism. In order to distinguish between these possibilities, we performed a competition

[26] Rychnovsky, S.D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.

experiment using 4 equiv of furoate and 1 equiv each of valeraldehyde and hydrocinnamaldehyde. We observed that the two desired products were formed in a 10:1 ratio with the valeraldehyde-derived product, **68**, predominating, indicating that hydrocinnamaldehyde is indeed a poor substrate, but does not interfere with the vinylogous aldol reaction of other aldehydes.

Having observed the substrate scope of the reaction with aldehydes, we decided to explore the ability of the furoate ester / ATNP system to reaction with ketones. Our initial results, utilizing the optimized conditions from our aldehyde experiments, with 2-butanone (**76**) were promising providing product **77** in 68% yield (table 1.7, entry 1). This was an exciting result as ketones had not previously been used as electrophiles in ATPH or ATNP mediated reactions. We found that ATNP was necessary for this reaction to proceed in good yield as an experiment with ATPH replacing ATNP provided a diminished yield of 27%



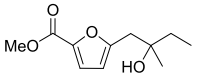
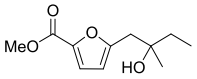
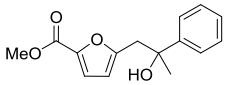
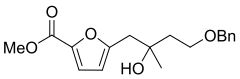
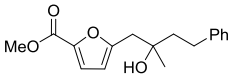
entry	ketone	product	yield (%)
1	 **76**	 **77**	68
2	 **76**	 **77**	27[b]
3	 **78**	 **79**	50
4	 **80**	 **81**	51
5	 **82**	 **83**	58

Table 1.7 Substrate scope of reaction with ketones [b] Reaction was run with ATPH

(table 1.7, entry 2). This result is to be expected given that enolizable aldehydes were previously established to be incompatible with the ATPH-mediated vinylogous aldol reaction of ester-derived enolates.[7b,23] We decided to test the scope of this reaction with a variety of ketones and found that aryl groups and β-benzyloxy groups were tolerated with yields of 50-51% (Table 1.7, entries 3-4). Most intriguingly, we found that 4-phenyl-2-butanone (**82**), the methyl ketone analogue of hydrocinnamaldehyde, was a relatively good reaction partner providing product in 58% yield (Table 1.7, entry 5). This contrasts starkly with hydrocinnamaldehyde (**34**) (Table 1.6, entry 9, 27% yield). This result was unexpected given the more sterically-challenging and less electrophilic nature of ketones compared to aldehydes. This was rationalized as being due to a cation-π interaction between the phenyl ring and the partially positively charged carbon of the

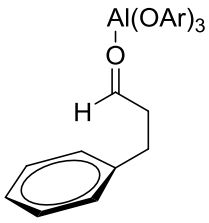


Figure 1.8 Hypothesized cation-π interaction of hydrocinnamaldehyde

aldehyde (figure 1.8). We hypothesize that the greater reactivity of the 4-phenyl-2-butanone (**82**) is due to the greater bulk of methyl group attenuating this interaction and disfavoring this conformation, thereby allowing the reaction to proceed. A competition experiment between hydrocinnamaldehyde (**34**) and 4-phenyl-2-butanone (**82**) is consistent with this hypothesis as we observed greater conversion of the ketone compared to the aldehyde with the ketone-derived product predominating over the hydrocinnamaldehyde product by a ratio of 3.7:1 by NMR. This further corroborates the hypothesis that hydrocinnamaldehyde is intrinsically less reactive in our reaction system. Examining the effect of electron-withdrawing substituents on the phenyl ring of hydrocinnamaldehyde in the ATNP system could elucidate the importance of the cation-π

interaction. Electron withdrawing groups (such as trifluoromethyl or nitro) would be expected to attenuate the interaction between the phenyl ring and the ATNP-bound aldehyde, which would lead to improved yield compared to the parent hydrocinnamaldehyde.

The ability of the furoate ester to react with ketone electrophiles prompted us to study the reactions of crotonate esters with ketone electrophiles. In the event, the reaction of methyl crotonate (**19**) with 4-phenyl-2-butanone (**82**) proceeded in a disappointing yield of 13%. In order to establish that this was due to the ketone substrate, a series of competition experiments were conducted between methyl furoate (**63**), methyl crotonate (**19**), and two ketones – 4-phenyl-2-butanone (**82**) and acetophenone (**78**). In each case, the furoate ester reacted much more readily than the crotonate ester. In the case of acetophenone, the ratio of furoate-derived product to crotonate-derived product was 10:1, while with 4-phenyl-2-butanone the ratio of furoate-derived product to crotonate-derived product was 5:1. We hypothesize that this difference is due to the increased reactivity (both basicity and nucleophilicity) of the furoate ester-derived enolate, allowing it to react with the less electrophilic ketones in higher yields.

We wished to compare the breadth of the ATNP-mediated reaction with that of ATPH-mediated reaction (Table 1.8). The results are consistent with

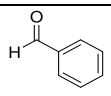
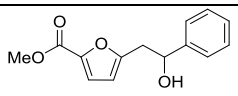
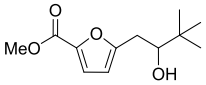
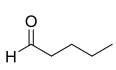
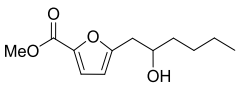
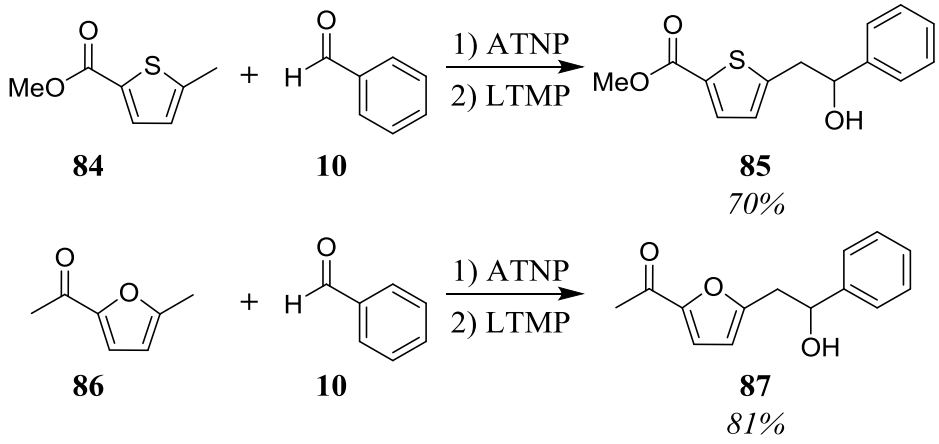
entry	substrate	product	yield ATPH (%)	yield ATNP (%)
1	 **10**	 **65**	78	78
2	 **38**	 **66**	82	81
3	 **30**	 **68**	25	72

Table 1.8 Substrate scope of reaction with ATPH

previous work, with ATPH successfully mediating reaction with non-enolizable aldehydes such as benzaldehyde and pivaldehyde (Table 1.8; entries 1, 2; yields 78 and 82% respectively), and providing yields comparable to the reaction mediated by ATNP (Table 1.6, entries 1, 2; yields 78 and 81%, respectively). Unsurprisingly the reaction proceeded in diminished yield with valeraldehyde (**30**) where enolizable protons are present, also consistent with prior work (Table 1.8; entry 3; 25% yield).

1.7 Vinylogous Aldol with Other Furoate Derivatives

Seeking to further expand the scope of this reaction, we sought additional related derivatives to study including methyl-5-methyl-2-thiophenoate (**84**) and 2-acetyl-5-methylfuran (**86**). Utilizing our optimized



Scheme 1.17 Vinylogous Aldol with Novel Heterocycle-containing Compounds

reaction conditions from the furoate experiments we subjected both substrates to a vinylogous aldol reaction with benzaldehyde (**10**). We found that methyl-5-methyl-2-thiophenoate reacted in comparable yield to the methyl furoate (70%). This result was consistent with our expectations. A comparable yield might have been predicted given the similar aromaticity of the thiophene ring to the furoate (though we recognize the thiophene has more aromatic stabilization than the

furan ring).[27] The extent of the scope of this reaction remains to be defined, but is expected to be comparable to the furoate ester.

Satisfyingly, ketone **86** reacted with good selectivity to provide desired product **87** in 81% yield. In this reaction, bulky ATNP prevented any competing enolate formation at the α-position, and resulted in selective formation of the extended enolate via deprotonation of the methyl group attached to the furan ring. This was not an unexpected result as Yamamoto reported a similar reaction between 4'-methylacetophenone and benzaldehyde.[7a] The ability to use a ketone nucleophile raises the possibility of using an intramolecular vinylogous aldol to for carbocycles in addition to macrolide-like structures, which opens up the possibilty of accessing furan-containing carbocycles found in natural products.

1.8 Future Directions

Exploring the exact mechanism by which ATNP allows reaction of ester derived enolates with enolizable aldehydes would provide useful insight to the reaction. Deuterated aldehydes could be used to verify that the novel reactivity provided by ATNP stems from blocking deprotonation of the aldehyde. Deuteration could be accomplished using 4-dimethylaminopyridine or triethylamine in deuterium oxide.[28] This deuterated aldehyde would be used in reactions with ATNP and ATPH. If deprotonation is occurring at the α-position when ATPH is used, deuterium incorporation will be observed in the extended enolate whereas it will not be observed with ATPH (Figure 1.10).

[27] a) Horner, K. E.; Karadakov, P. B. *J. Org. Chem.* **2013**, *78*, 8037–8043. b) Katrizky, A.R.; Ramsden, C.A.; Zhdankin, V. V. In *Handbook of Heterocyclic Chemistry*; Elsevier: Amsterdam, 2010; pp. 126–128.
[28] Ariza, X.; Asins, G.; Garcia, J.; Hegardt, F. G.; Makowski, K.; Serra, D.; Velasco, J. *J. Label. Compd. Radiopharm.* **2010**, *53*, 556–558.

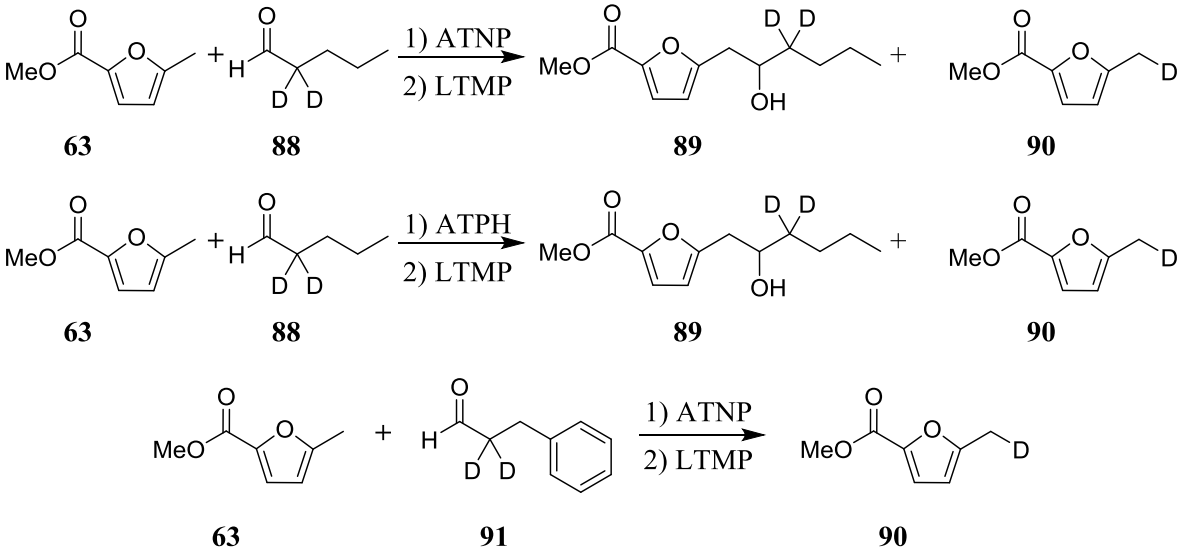


Figure 1.9 Proposed Deuterium Labeling Experiments

Furthermore, incorporation of deuterium in the methyl group of recovered furoate would support the hypothesis that at least part of the challenge of hydrocinnamaldehyde stems from its increased acidity combined with the increased basicity of the furoate leading to quenching of the furoate-derived enolate.

Studies of the scope of the vinylogous aldol of heterocycle-containing enolates would also be valuable. The range of reactivity for both the thiophenoate **84** and keto furan **86** compounds remains unexplored, and beyond these heterocycles, the possibility of using oxazoles such as those in figure 1.11 is enticing as oxazoles are a common motif in natural products.

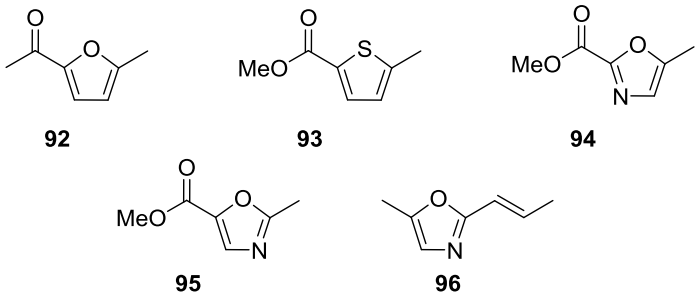
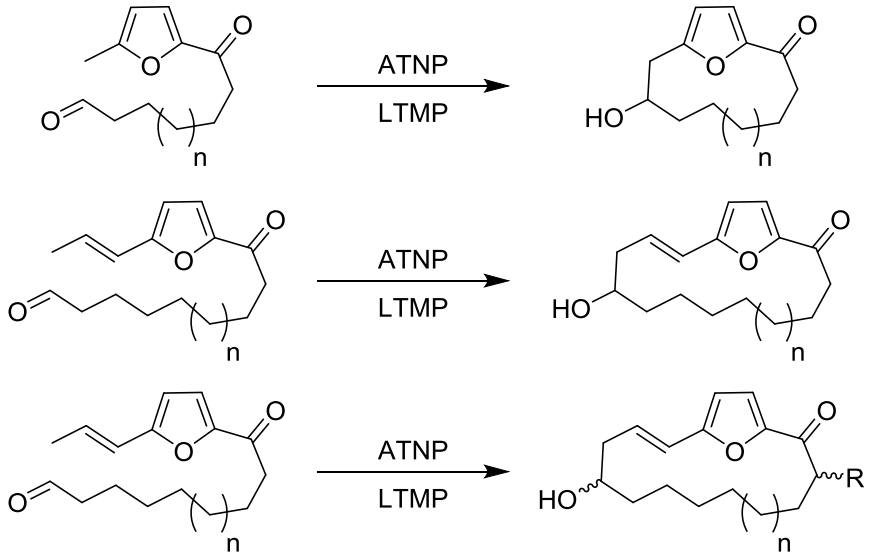


Figure 1.10 Heterocycles to explore reaction scope

Another intriguing possible avenue to explore is the intramolecular heterocyclic vinylogous aldol (Scheme 1.18). If these reactions prove practical, application of the ATNP-mediated vinylogous aldol of the furoate ketone to natural product synthesis would provide a more efficient and high-yielding route to a range of natural products.



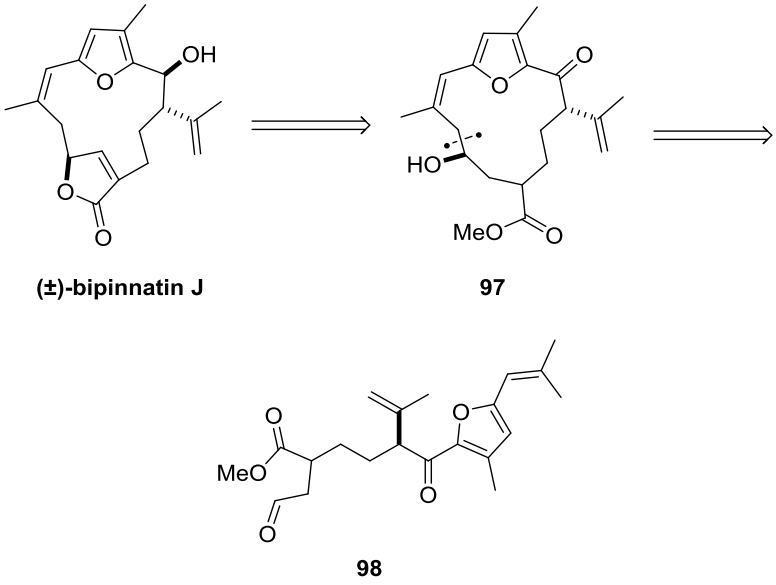
Scheme 1.18 Intramolecular vinylogous aldol reactions

Building upon the favorable intermolecular results of 2-acetyl-5-methylfuran (**86**), initial work would focus on the methylfuran ketone. We would aim to build on this gradually introducing an extended system as in Scheme 1.18, and finally exploring the potential for remote stereo induction as preparation for a synthesis of bipinnatin J (Scheme 1.19).

Bipinnatin J (Scheme 1.19) is an intriguing pseudoterane compound first isolated in 1998 from the Gorgon coral *Pseudopterogorgia bipinnata* by Rodriguez and Shi.[29] The structure lends itself to an intramolecular vinylogous aldol with the functionally-dense, 13-membered carbocycle that contains a furan ring (Scheme 1.19). Previous syntheses by Trauner and Rawal both relied on a Nozaki-Hiyama-Kishi reaction to form the secondary alcohol adjacent to the

[29] Rodríguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420–421.

furan ring and close the macrocycle.[30] The retrosynthetic route shown below relies on the vinylogous aldol reaction to form the carbocycle and set the stereochemistry of the future lactone in one step from linear aldehyde **98** via an unexplored disconnection. If the intramolecular model studies are fruitful, the synthesis of bipinnatin J would provide an excellent demonstration of the utility of the heterocyclic intramolecular vinylogous aldol reaction.



Scheme 1.19 bipinnatin J retrosynthesis

[30] (a) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347. (b) Huang, Q.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 543–545.

1.9 Experimental Section

General Information

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. 2,2,6,6-Tetramethylpiperdine was distilled from sodium metal prior to use. Toluene and dichloromethane were distilled from calcium hydride prior to use. Acetone was dried by storage over 4Å sieves for 2 days. Solvents were transferred via cannula. Commercially available aldehydes **10**, **30**, **32**, **34**, **36**, and **38** were distilled prior to use. Aldehydes **41**[31] and **47**[32] were prepared according to literature procedures. Aldehyde **71** was synthesized as described below. Commercially available ketones **76**, **78**, **80** and **82** were distilled prior to use. Me_3Al (2.0M solution in hexanes) was used as received from Sigma Aldrich. n-BuLi was purchased from Acros and titrated prior to use with 2,2'-bipyridine/menthol. 2,6-Di-2-napthylphenol was prepared according to a literature procedure.[23] This material was recovered from reactions and purified by recrystallization from hexanes/chloroform and dried by azeotropic distillation using distilled toluene. Residual toluene was removed by stirring under vacuum overnight. Methyl 5-methyl-2-furoate (**63**) was prepared from commercially available 5-methylfurfural purchased from Aldrich.[33]

^1H NMR spectroscopy was performed at 500 MHz in $CDCl_3$ using residual chloroform as an internal standard (7.27 ppm). ^{13}C NMR spectroscopy was performed at 75 MHz or at 100 MHz in $CDCl_3$ using residual chloroform as an internal standard (77.26 ppm for the central peak). FT-IR spectra were collected as thin films on sodium chloride plates. Exact mass was determined using electrospray ionization.

[31] Angle, S. R.; Choi, I.; Tham, F. S. *J. Org. Chem.* **2008**, *73*, 6268-6278.
[32] Ishiyama, H.; Ishibashi, M.; Ogawa, A.; Yoshida, S.; Kobayashi, J. *J. Org. Chem.* **1997**, *62*, 3831-3836.
[33] Reddy, K.R.; Venkasteshwar, M.; Maheswari, C.U.; Prashanthi, S. *Synth. Commun*. **2009**, *40*, 186-195.

General Vinylogous aldol procedure with ATNP:

Preparation of ATNP: Me_3Al (0.777 ml, 1.554 mmol, 2M solution in hexanes) was added via syringe to a stirred solution of 2,6-dinapthylphenol (1.615 g, 4.66 mmol) in freshly distilled toluene (40 ml) at room temperature. Vigorous bubbling was observed and the solution turned yellow. After 20 min the solution was cooled to -78°C in a dry ice/acetone bath and used as described below.

Preparation of LTMP: To a stirred solution of 2,2,6,6-tetramethylpiperdine (0.278 mL, 1.649 mmol) in freshly distilled THF (4 mL) cooled to -78°C in a dry ice/acetone bath was added n-BuLi (1.03 ml,1.649 mmol, 1.6M solution in hexanes) via syringe. The dry ice bath was removed and the reaction was allowed to warm to 0°C over a 20 min period. The solution was then re-cooled in a dry ice/ acetone bath to -78°C and allowed to stir 20 min longer then used as described below.

Methyl 5-methyl-2-furoate (0.118 mL, 0.942 mmol) and the aldehyde (0.471 mmol) were added via syringe to the stirred solution of ATNP (prepared above) at -78°C. After 20 min the solution of LTMP (prepared above) was added dropwise via cannula to the ATNP complex over ~ 2 minute period. The solution turned opaque immediately. The reaction was allowed to stir for 3 hrs at -78°C then quenched by the addition of 1M hydrochloric acid, diluted with hexanes (10 mL), and stirred while being allowed to warm to room temperature. The biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide the desired compound plus

recovered 2,6-dinapthylphenol as a solid. The resulting solid was suspended in hexanes and warmed to reflux. Chloroform was added until the solution cleared. The resulting yellow solution was cooled to room temperature, and then chilled in an ice bath for 30 minutes. The resulting solid filtered to recover the majority of the 2,6-dinapthylphenol. The mother liquor was then concentrated and purified by Flash Chromatography (10:1 hexanes : ethyl acetate to elute residual phenol then 3:1 hexanes : ethyl acetate to elute the substrate) to provide the desired product.

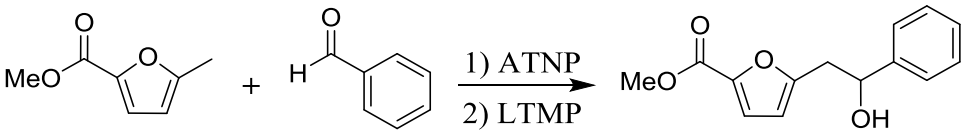
General Vinylogous aldol procedure with ATPH:

Preparation of ATPH: Me_3Al (0.777 ml, 1.554 mmol, 2M solution in hexanes) was added via syringe to a stirred solution of 2,6-diphenylphenol (1.149 g, 4.66 mmol) in freshly distilled toluene (40 ml) at room temperature. Vigorous bubbling was observed and the solution turned yellow. After 20 min the solution was cooled to -78°C in a dry ice/acetone bath and used as described below.

Preparation of LTMP: To a stirred solution of 2,2,6,6-tetramethylpiperdine (0.278 mL, 1.649 mmol) in freshly distilled THF (4 mL) cooled to -78°C in a dry ice/acetone bath was added n-BuLi (1.03 ml, 1.649 mmol, 1.6M solution in hexanes) via syringe. The dry ice bath was removed and the reaction was allowed to warm to 0°C over a 20 min period. The solution was then re-cooled in a dry ice/ acetone bath to -78°C and allowed to stir 20 min longer then used as described below.

Methyl 5-methyl-2-furoate (0.118 mL, 0.942 mmol) and the aldehyde (0.471 mmol) were added to the stirred solution of ATPH (prepared above) at -78°C. After 20 min the solution of LTMP (prepared above) was added dropwise via cannula to the ATPH complex over ~ 2 minute period.

The solution turned opaque immediately. The reaction was allowed to stir for 3 hrs at -78°C then quenched by the addition of 1M Hydrochloric acid, diluted with hexanes (10 mL), and stirred while being allowed to warm to room temperature. The biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide the desired compound plus recovered 2,6-diphenylphenol as a solid. This material was purified by Flash Chromatography (10:1 hexanes : ethyl acetate to elute the phenol, then 3:1 hexanes : ethyl acetate to elute the substrate).

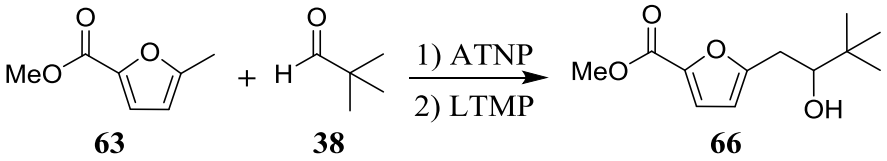


63 **10** **65**

Methyl 5-(2-hydroxy-2-phenylethyl)-2-furoate (65)

Compound **65** was prepared from benzaldehyde **10** and methyl 5-methyl-2-furoate **63** in 78% yield after purification according to the general procedure.

R*f* = 0.26 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.37-7.25 (m, 5H), 7.13-7.10 (d, *J* = 3.4Hz, 1H), 6.22-6.19 (d, *J* = 3.4Hz, 1H), 5.13-5.08 (dd, *J* = 8.4, 4.9Hz, 1H), 3.91-3.87 (s, 3H), 3.19-3.13 (dd, *J* = 15.1, 8.5, 1H), 3.13-3.07 (dd, *J* = 15.1, 4.9, 1H), 2.16-2.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.21, 157.39, 143.39, 143.15, 128.56, 127.93, 125.70, 119.29, 109.94, 51.83, 38.39.; IR (thin film) 3442, 3030, 2951, 1720, 1519, 1437, 1383 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{28}H_{28}O_8Na$ $[2M+Na]^+$: 515.1677 ; found 515.1684.

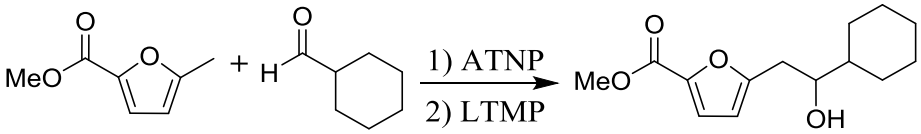


63 **38** **66**

Methyl 5-(2-hydroxy-3,3-dimethylbutyl)-2-furoate (66)

Compound **66** was prepared from pivaldehyde **38** and methyl 5-methyl-2-furoate **63** in 81% yield after purification according to the general procedure.

R*f* = 0.34 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.07-7.05 (d, J = 3.4Hz, 1H), 6.23-6.21 (d, *J* = 3.4Hz, 1H), 3.82-3.79 (s, 3H), 3.62-3.56 (d, *J* = 10.7Hz, 1H), 2.91-2.87 (dd, *J* = 15.2, 1.9Hz, 1H), 2.66-2.59 (dd, *J* = 15.2, 10.7Hz, 1H), 2.06-2.01 (s, 1H) 0.93-0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.35, 159.19, 143.20, 119.38, 109.35, 77.40, 51.74, 34.91, 31.31, 25.58.; IR 3473, 2956, 2907, 2870, 1722, 1595, 1531, 1518, 1437, 1363 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$: 249.1278; found 249.1284.



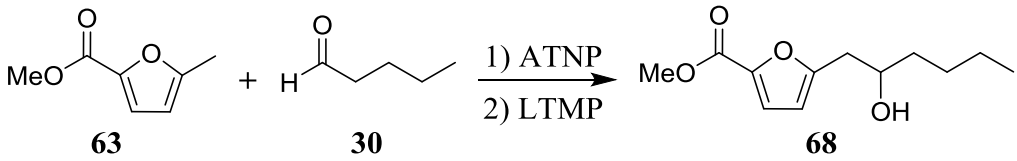
63 **36** **67**

Methyl 5-(2-cyclohexyl-2-hydroxyethyl)-2-furoate (67)

Compound **67** was prepared from cyclohexanecarbaldehyde **36** and methyl 5-methyl-2-furoate **63** in 78% yield after purification according to the general procedure.

R*f* = 0.37 (hexanes: ethyl acetae 2:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.15-7.11 (d, *J* = 3.4Hz, 1H), 6.29-6.25 (d, *J* = 3.4Hz, 1H), 3.90-3.87 (s, 3H), 3.80-3.74 (m, 1H), 2.96-2.90 (dd, *J* = 15.2, 3.3Hz, 1H), 2.82-2.76 (dd, *J* = 15.2, 9.3Hz, 1H), 1.90-1.84 (d, *J* = 12.7Hz, 1H), 1.83-1.75 (m,

1H), 1.75-1.64 (m, 5H), 1.43-1.34 (m, 1H), 1.32-1.00 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.18, 158.66, 143.32, 119.32, 109.52, 74.07, 51.78, 43.34, 33.56, 29.09, 27.72, 26.38, 26.18, 26.04.; IR 3448, 2926, 2852, 1720, 1519, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}O_4Na$ $[M+Na]^+$: 275.1254; found 275.1260.

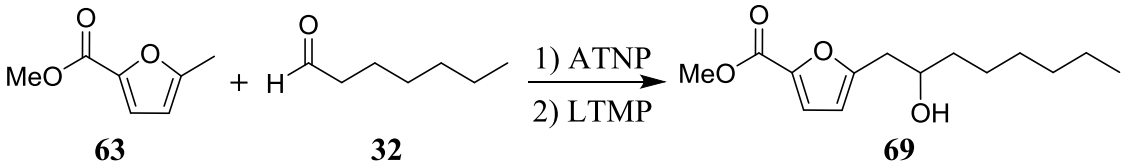


63 **30** **68**

Methyl 5-(2-hydroxyhexyl)-2-furoate (68)

Compound **68** was prepared from valeraldehyde **30** and methyl 5-methyl-2-furoate **63** in 72% yield after purification according to the general procedure.

R*f* = 0.24 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.08-7.05 (d, *J* = 3.4Hz, 1H), 6.22-6.19 (d, *J* = 3.4Hz, 1H) 3.96-3.89 (m, 1H), 3.84-3.80 (s, 3H), 2.87-2.81 (dd, *J* = 15.1, 4.1, 1H), 2.78-2.71 (dd, *J* = 15.1, 8.1, 1H), 2.16-2.05 (s, 1H), 1.5-1.22 (m, 6H), 0.88-0.82 (t, *J* = 7.1Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.20, 158.18, 143.33, 119.29, 109.55, 70.03, 51.78, 36.65, 36.52, 27.70, 22.58, 13.99; IR 3435, 2955, 2931, 2860, 1721, 1519, 1437, 1382, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$: 249.1098; found 249.1106.

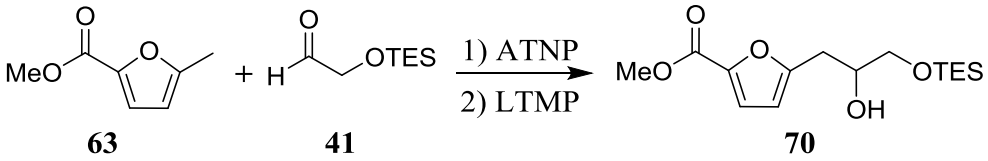


63 **32** **69**

Methyl 5-(2-hydroxyoctyl)-2-furoate (69)

Compound **69** was prepared from heptaldehyde **32** and methyl 5-methyl-2-furoate **63** in 71% yield after purification according to the general procedure.

R*f* = 0.31 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.10-7.07 (d, *J* = 3.4Hz, 1H), 6.23-6.20 (d, *J* = 3.4Hz, 1H), 3.97-3.90 (m, 1H), 3.85-3.82 (s, 3H), 2.89-2.83 (dd, *J* = 15.1, 4.1Hz, 1H), 2.79-2.73 (dd, *J* = 15.1, 8.1Hz, 1H), 1.50-1.19 (m, 10H), 0.88-0.81 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.16, 158.11, 143.41, 119.26, 109.57, 70.09, 51.79, 36.98, 36.54, 31.75, 29.19, 25.50, 22.57, 14.06; IR 3434, 2929, 2857, 1723, 1595, 1519, 1437, 1382, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{22}O_4Na$ $[M+Na]^+$: 277.1411; found 277.1411.

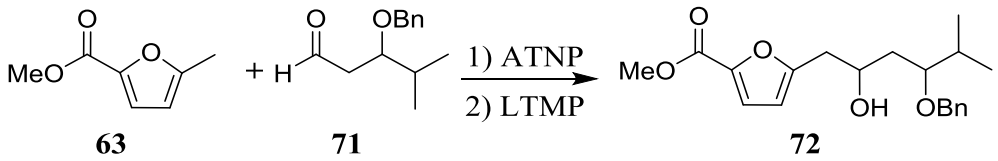


63 **41** **70**

Methyl 5-(2-hydroxy-3-triethylsilyloxy-propyl)-2-furoate(70)

Compound **70** was prepared from aldehyde **41** and methyl 5-methyl-2-furoate **63** in 52% yield after purification according to the general procedure.

R*f* = 0.29 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.11-7.09 (d, *J* = 3.4Hz, 1H), 6.27-6.24 (d, *J* = 3.4Hz, 1H), 4.04-3.97 (m, 1H), 3.87-3.84 (s, 3H), 3.67-3.63 (dd, *J* = 10.0, 3.7Hz, 1H), 3.50-3.45 (dd, *J* = 10.0, 6.4Hz, 1H), 2.87-2.84 (d, *J* = 6.5Hz, 2H), 2.56-2.52 (d, *J* = 4.4Hz, 1H), 0.96-0.90 (t, *J* = 8.0Hz, 9H), 0.63-0.56 (q, *J* = 8.0Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.16, 157.63, 143.30, 119.33, 109.45, 70.11, 65.92, 51.77, 32.34, 6.69, 4.29.; IR 3457, 2954, 2912, 2876, 1724, 1595, 1520 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{30}H_{52}O_{10}Si_2Na$ $[2M+Na]^+$: 651.2992; found 651.3000.

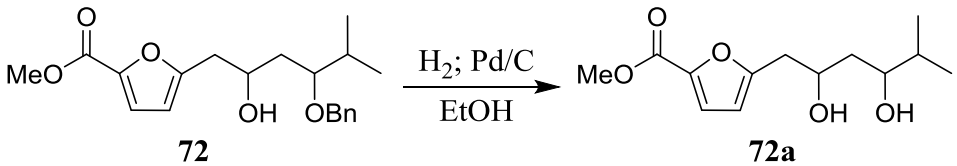


63 **71** **72**

Methyl 5-[4-(benzyloxy)-2-hydroxy-5-methylhexyl]-2-furoate (72)

Compound **72** was prepared from aldehyde **71** and methyl 5-methyl-2-furoate **63** in 85% yield after purification according to the general procedure. This material was found to be a 3.4:1 mixture of diastereomers.

R*f* = 0.21 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38-7.28 (m, 5H, major and minor) 7.12 (d, *J* = 3.4 Hz, 1H, major and minor), 6.25 (d, *J* = 3.4 Hz, 1H, major), 6.23 (d, *J* = 3.4 Hz, 1H, minor), 4.68 (d, *J* = 11.1 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H, minor), 4.53 (d, *J* = 11.3 Hz, 1H, minor) ,4.42 (d, *J* = 11.1 Hz, 1H, major), 4.26-4.20 (m, 1H, minor), 4.19-4.12 (m, 1H, major), 3.94 (s, 3H, minor), 3.88 (s, 3H, major), 3.62-3.57 (m, 1H, major), 3.52-3.47 (m, 1H, minor), 2.97-2.91 (m, 1H, minor), 2.90-2.78 (m, 2H, major and minor), 2.21-2.12 (m, 1H, major), 2.10-2.01 (m, 1H, minor), 1.74-1.59 (m, 2H, major and minor), 0.96 (d, *J* = 6.8 Hz, 3H, minor), 0.93 (d, *J* = 7.0 Hz, 3H, major), 0.91-0.87 (m, 3H, major and minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.48, 158.29, 143.43, 137.98, 128.81, 128.73, 128.28, 128.12, 128.06, 119.62, 119.57, 109.80, 109.67, 84.95, 81.98, 72.08, 71.17, 70.67, 67.68, 52.03, 36.91, 36.84, 35.43, 35.01, 30.29, 29.19, 19.34, 18.80, 17.65, 15.99; IR 3468, 2958, 1727, 1519, 1454, 1436 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{26}O_5Na$ $[M+Na]^+$: 369.1673; found 369.1672.

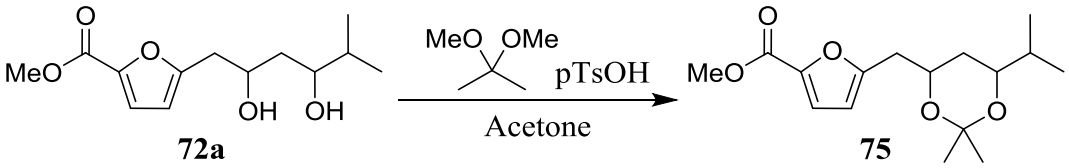


72 **72a**

Methyl 5-(2,4-dihydroxy-5-methylhexyl)-2-furoate (72a)

Compound **72** (0.185g, 0.534mmol) was taken up in 5 ml of methanol and 5% palladium on carbon (0.057 g, 0.027 mmol) was added. The reaction was placed under H_2 atm using a balloon to deliver the H_2 and stirred for 16 hr, filtered and concentrated, to give compound **72a** (0.133g, 519 mmol, 97% yield).

R*f* = 0.31 (hexanes: ethyl acetate 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 3.5 Hz, 1H, major and minor), 6.28 (d, *J* = 3.5 Hz, 1H, major and minor), 4.36-4.28 (m, 1H, minor) 4.26-4.19 (m, 1H, major), 3.88 (s, 3H, major and minor), 3.73-3.65 (m, 1H, major and minor), 2.90-2.86 (m, 2H), 1.74-1.49 (m, 3h, major and minor), 0.99-0.88 (m, 6H, major and minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.43, 158.14, 157.86, 143.66, 119.53, 109.95, 109.79, 77.96, 74.09, 71.49, 68.11, 39.19, 39.15, 37.23, 36.67, 34.45, 34.01, 18.78, 18.47, 18.10, 17.52; IR 3402, 2957, 1721, 1519, 1437, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 257.1387; found 257.1389.



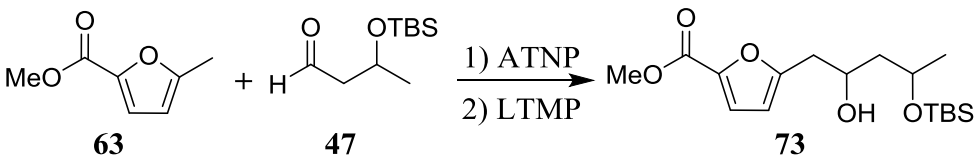
Methyl 5-[(6-isopropyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl]-2-furoate (75)

Compound **72a** (0.390 mmol) was taken up in a 1:1 mixture of dry acetone, 2,2-dimethoxypropane (0.790 ml; 0.5M) over 4Å molecular sieves. *p*-Toluenesulfonic acid (0.020 mmol, 0.05 equiv) was then added, the reaction was stirred for 2 hours. The reaction was diluted

with 1:1 hexanes: ethyl acetate and washed with saturated sodium bicarbonate. The aqueous layer was back extracted with 1:1 hexanes: ethyl acetate, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The crude material was purified using Flash Chromatography with a solvent gradient from 50:1 to 2:1 to isolate **75** (0.077mg, 0.260mmol, 67% yield).

The major stereoisomer was assigned as *syn* using ^{13}C NMR analysis of Rychnovsky[26] with resonances at 19.77 and 30.06 ppm. The minor diastereomer displayed resonances at 24.68 and 24.22 ppm consistent with *anti*-product.

R*f* = 0.29 (hexanes: ethyl acetate 10:1); ^{1}H NMR (500 MHz $CDCl_3$) δ7.08 (d, *J* = 3.4Hz, 1H, major and minor), 6.21(d, *J* = 3.4Hz, 1H, major and minor), 4.17-4.06 (m, 1H, major and minor), 3.84 (s, 3H, major and minor), 3.45 (ddd, *J* = 11.6, 6.7, 2.31Hz, 1H, major), 3.42-3.38 (m, 1H, minor), 2.91 (dd, *J* = 15.2, 6.73Hz, 1H, major), 2.75 (dd, *J* = 15.17, 6.2 Hz, 1H, major), 1.63-1.52 (m, 1H, major and minor), 1.43 (dt, *J* =12.7, 2.5, 2.5 Hz, 1H, major and minor) ,1.38 (s, 3H, major), 1.35 (s, 3H, major), 1.30 (d, *J* = 3.5 Hz, 6H, minor) 1.14 (q, *J* = 11.6, 11.6, 11.6 Hz, 1H, major), 0.90-0.85 (m, 3H, major and minor), 0.81 (d, *J* = 6.8 Hz, 3H, major and minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.17, 157.76, 157.41, 143.11, 119.24, 109.53, 109.09, 100.48, 98.57, 73.72, 71.56, 67.47, 65.01, 51.70, 35.90, 35.59, 34.72, 33.21, 32.94, 30.06, 24.68, 24.22, 19.78, 18.60, 18.28, 17.63, 17.54; IR 3422, 2989, 2956, 2873, 1732, 1531, 1519, 1436, 1379, 1307 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}O_5Na$ $[M+Na]^+$: 319.1522; found 319.1521.

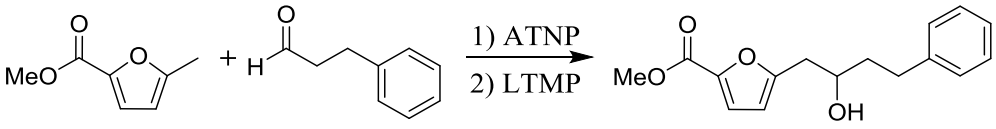


63 **47** **73**

Methyl 5-[3-[tert-butyl(dimethyl)silyl]oxy-2-hydroxy-4-methyl-pentyl]-2-furoate (73)

Compound **73** was prepared as a mixture of diastereomers from aldehyde **47** and methyl 5-methyl-2-furoate **63** in 46% yield and 1.5:1 *dr* after purification according to the general procedure.

R*f* = 0.14 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.14-7.11 (m,1H, major and minor), 6.29-6.26 (m, 1H, major and minor), 4.40-4.33 (m, 1H, minor), 4.27-4.20 (m, 1H, minor), 4.18-4.05 (m, 2H, major), 3.88 (s, 3H, major and minor), 3.77 (m, 1H, major and minor), 2.89 (dd, *J* = 15.1, 6.9 Hz, 1H, major and minor), 2.80 (dd, *J* = 15.0, 6.3 Hz, 1H, major and minor), 1.75-1.68 (m, 1H, major and minor), 1.63-1.53 (m, 1H, major and minor), 1.23 (d, *J* = 6.3, 3H, minor), 1.18 (d, *J* = 6.1Hz, 3H, major), 0.91 – 0.86 (m, 9H, major and minor), 0.11 (d, *J* = 7.1 Hz, 6H, major), 0.09 (d, *J* = 5.0 Hz, 6H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.20, 158.12, 157.96, 143.23, 143.20, 119.34, 119.32, 109.57, 109.40, 70.00, 69.87, 67.61, 66.89, 51.74, 44.95, 43.39, 36.76, 36.51, 25.79, 25.76, 24.55, 22.55, 17.90, 17.86, -3.86, -4.56, -4.81, -5.09; IR 3495, 2955, 2930, 2856, 1724, 1519 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{30}O_5SiNa$ $[M+Na]^+$: 365.1755; found 365.1757.

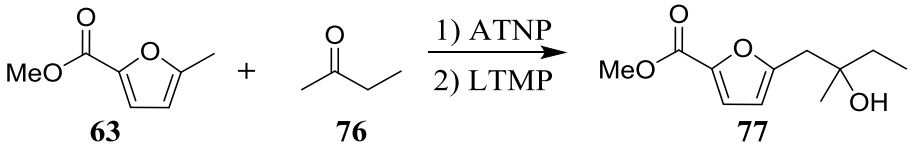


63 **34** **74**

Methyl 5-(2-hydroxy-4-phenylbutyl)-2-furoate (74)

Compound **74** was prepared from hydrocinnamaldehyde **34** and methyl 5-methyl-2-furoate **63** in 27% yield after purification according to the general procedure.

R*f* = 0.29 (hexanes: ethyl acetate 2:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.22-7.18 (m, 3H), 7.12 (d, *J* = 3.4 Hz, 1H), 6.25 (d, *J* = 3.4 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.88 (s, 3H), 2.92 (dd, *J* = 15.1, 4.3 Hz, 1H), 2.88-2.80 (m, 2H), 2.75-2.67 (m, 1H), 2.05 (s, 1H), 1.89 – 1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.35, 157.94, 143.70, 141.82, 128.65, 128.61, 126.14, 119.45, 109.90, 77.68, 77.26, 76.84, 69.64, 52.02, 38.73, 36.82, 32.10; IR 3449, 2946, 1718, 1518, 1437, 1309 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}O_5Na$ $[M+Na]^+$: 297.1103; found 297.1109.

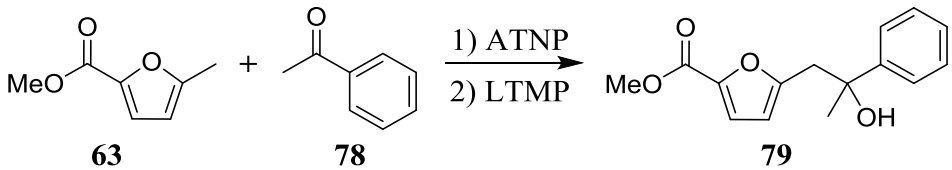


63 **76** **77**

Methyl 5-(2-hydroxy-2-methylbutyl)-2-furoate (77)

Compound **77** was prepared from 2-butanone **76** and methyl 5-methyl-2-furoate **63** in 68% yield after purification according to the general procedure.

R*f* = 0.20 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 3.4 Hz, 1H), 6.28 (d, *J* = 3.6, 1H), 3.88 (s, 3H), 2.87 (d, *J* = 2.9 Hz, 2H), 2.18 (s, 1H), 1.53 (q, *J* = 7.5 Hz, 2H), 1.20 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.41, 157.86, 143.76, 119.48, 110.66, 73.00, 52.06, 40.52, 34.68, 26.34, 8.49; IR 3492, 2969, 1719, 1517, 1437, 1309 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{16}O_4Li$ $[M+Li]^+$: 218.1195; found 218.1196.

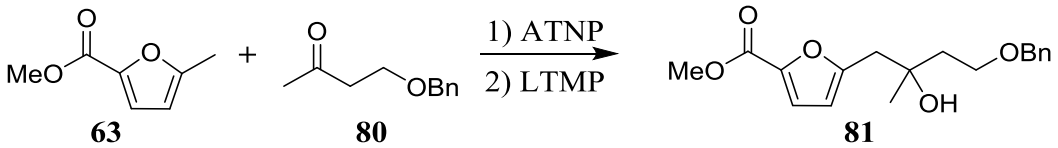


63 **78** **79**

Methyl 5-[4-(benzyloxy)-2-hydroxy-2-methylbutyl]-2-furoate (79)

Compound **79** was prepared from acetophenone **78** and methyl 5-methyl-2-furoate **63** in 50% yield after purification according to the general procedure.

R*f* = 0.32 (hexanes: ethyl acetate 3:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.48-7.33 (m, 5H), 7.06 (d, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 3.4 Hz, 1H), 3.88 (s, 3H), 3.21 (d, *J* = 3.8 Hz, 2H), 2.18 (s, b, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.15, 156.96, 146.82, 143.52, 128.60, 128.31, 127.06, 124.72, 119.20, 110.67, 74.21, 51.85, 43.07, 29.65, 29.40; IR 3474, 2976, 1720, 1593, 1517, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{16}O_4Li$ $[M+Li]^+$: 266.1200; found 266.1199.

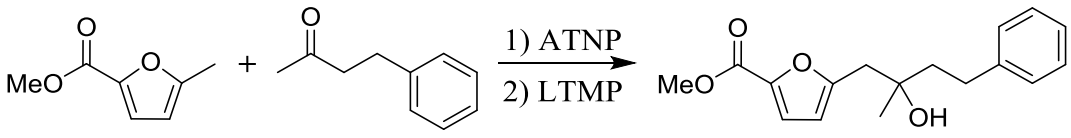


63 **80** **81**

Methyl 5-[4-(benzyloxy)-2-hydroxy-2-methylbutyl]-2-furoate (81)

Compound **81** was prepared from ketone **80** and methyl 5-methyl-2-furoate **63** in 51% yield after purification according to the general procedure.

R*f* = 0.31 (hexanes: ethyl acetate 2:1); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.39-7.28 (m, 5H), 7.13 (d, *J* = 3.4 Hz, 1H), 6.27 (d, *J* = 3.4 Hz, 1H), 4.53 (s, 1H), 3.87 (s, 3H), 3.77 (t, *J* = 5.8 Hz, 2H), 2.91 (s, 2H), 1.93-1.76 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.30, 157.85, 143.39, 137.72, 128.62, 128.00, 127.91, 119.43, 110.61, 73.60, 72.45, 67.41, 51.86, 41.35, 39.65, 26.98; IR 3485, 2949, 2869, 1720, 1593, 1517, 1454, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{22}O_5Li$ $[M+Li]^+$: 324.1618; found 324.1620.

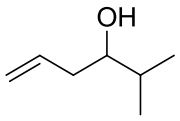


63 **82** **83**

Methyl 5-(2-hydroxy-2-methyl-4-phenylbutyl)-2-furoate (83)

Compound **83** was prepared from 4-phenyl-2-butanone **82** and methyl 5-methyl-2-furoate **63** in 58% yield after purification according to the general procedure.

R*f* = 0.31 (hexanes: ethyl acetate 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 7.16 (d, *J* = 3.4 Hz, 1H), 6.30 (d, *J* = 3.4 Hz, 1H), 3.90 (s, 3H), 2.96 (d, *J* = 3.4 Hz, 2H), 2.82 – 2.72 (m, 2H), 1.83-1.79 (m, 2H), 1.78 (s, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.06, 157.21, 143.69, 142.06, 128.42, 128.35, 125.84, 119.18, 110.55, 77.42, 77.00, 76.58, 72.36, 51.78, 43.84, 40.71, 30.39, 26.87; IR 3466, 2950, 1720, 1517, 1436, 1310 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{20}O_4Li$ $[M+Li]^+$: 295.0772; found 295.1529.

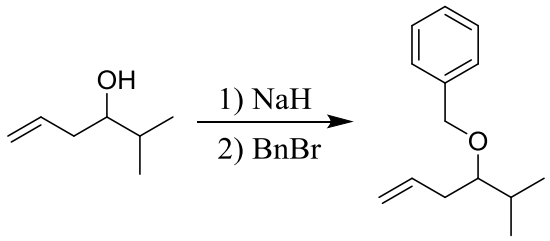


S1

2-Methyl-5-hexen-3-ol (S1)

Compound S1 was prepared using a literature procedure.[34]

[34] Cleary, P.A.; Woerpel K.A. *Org. Lett.* **2005**, *7*, 5531-5533



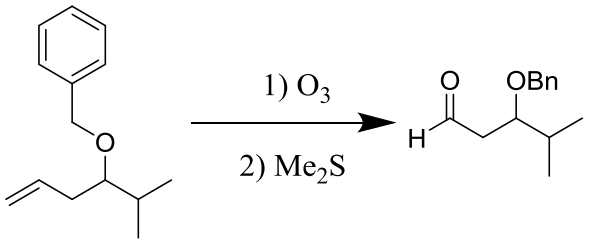
S1 **S2**

4-(Benzyloxy)-5-methyl-1-hexene (S2)

NaH (60% in mineral oil dispersion; 11.73 mmol; 1.48 equiv) was weighed into a flame dried flask with a stir bar. NaH was stirred with distilled cyclohexane (10 mL), allowed to settle and the cyclohexane decanted off with a cannula. The dry NaH was taken up in freshly distilled THF (26 mL; 0.3M) and cooled in an ice bath. To the stirring suspension was added alcohol **S1** in THF (0.903g; 5 mL) dropwise. The suspension was allowed to stir for one hour and benzyl bromide (1.035 mL, 1.1 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 24 hr. The reaction was quenched with water and extracted with ether. Purification via Flash Chromatography (30:1 hexanes: ethyl acetate) provided the product as an oil which was spectroscopically identical to that reported in the literature (0.601g, 37% yield).[35]

^{1}H NMR (500MHz $CDCl_3$) 7.39-7.27 (m, 5H), 5.95-5.85 (m, 1H), 5.15-5.05 (m, 2H) 4.59 (d, *J* = 11.5Hz, 1H), (4.51 (d, *J* = 11.5Hz, 1H) δ 3.22 (q, *J* = 5.7Hz, 1H), 2.35-2.31 (m, 2h), 1.94-1.86 (m, 1H), 0.97 (d, *J* = 6.9Hz, 3H), (0.94 (d, *J* = 6.9Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.30, 135.93, 128.49, 127.95, 127.62, 116.70, 84.14, 72.05, 35.48, 31.17, 18.70, 18.42.

[35] Murugan, K.; Srimurugan, S.; Chen, C. *Tetrahedron* **2011**, *67*, 5621–5629.

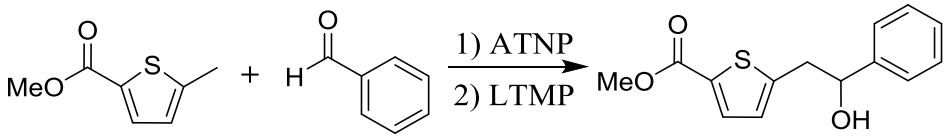


S2 **71**

4-methyl-3-(phenylmethoxy)-valeraldehyde (**71**)

Compound **S2** (1.95g, 7.64 mmol, 1 equiv) was taken up in freshly distilled CH_2Cl_2 and cooled to -78°C in a dry ice/acetone bath. A stream of ozone from a Welsbach ozone generator was bubbled through for 20 min until solution turned blue. Nitrogen was bubbled through until the blue color dissipated. Dimethylsulfide (2.82 mL, 38.2 mmol, 5 equiv) was added and the reaction allowed to stir overnight. The reaction was concentrated under reduced pressure and the crude product was purified by Flash Chromatography (10:1 hexanes: ethyl acetate) to provide aldehyde **71** as a clear oil (1.164g, 74% yield). Spectral data matched reported literature.[36]

^{1}H NMR (500 MHz $CDCl_3$) δ 9.82 (dd, *J* = 2.7, 1.7 Hz, 1H), 7.38-7.27 (m, 5H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 3.81 (ddd, *J* = 8.6, 5.1, 3.8 Hz, 1H), 2.65 (ddd, *J* = 16.4, 8.3, 2.7 Hz, 1H), 2.51 (ddd, *J* = 16.4, 3.8, 1.8 Hz, 1H), 2.09-2.01 (m, 1H), 0.96 (d, *J* = 2.9 Hz, 3H), 0.95 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.34, 138.54, 128.63, 127.97, 127.91, 79.30, 72.00, 45.13, 31.10, 18.64, 17.51.



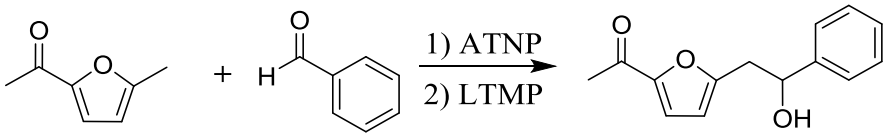
84 **10** **85**

[36] Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *Tetrahedron*, **1994**, *50*, 12853-12882

Ester (85)

Ester **85** was prepared from benzaldehyde **10** and methyl 5-methyl-2-thiophenoate **84** in 70% yield after purification according to the general procedure.

R*f* = 0.26 (hexanes: ethyl acetate 4:1); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 3.8 Hz, 1H), 7.39 – 7.28 (m, 5H), 6.79 (d, *J* = 3.8 Hz, 1H), 4.94-4.89 (m, 1H), 3.85 (s, 3H), 3.30 – 3.19 (m, 2H), 2.47 – 2.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.90, 148.49, 143.16, 133.78, 132.12, 128.79, 128.23, 127.37, 126.04, 74.97, 52.26, 40.45; IR 3449, 3030, 2951, 1711, 1538, 1458, 1273, 1051 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{14}O_3S$ $[M+H]^+$: 262.0740; found 263.0742.



86 **10** **87**

Ketone (87)

Ketone **87** was prepared from benzaldehyde **10** and 2-acetyl-5-methylfuran **86** in 81% yield after purification according to the general procedure.

R*f* = 0.43 (hexanes: ethyl acetate 1:1); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.29 (m, 5H), 7.12 (d, *J* = 3.5 Hz, 1H), 6.26 (d, *J* = 3.5 Hz, 1H), 5.12 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.19 (dd, *J* = 15.1, 8.4 Hz, 1H), 3.13 (dd, *J* = 15.1, 4.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.50, 158.13, 152.03, 143.30, 128.83, 128.25, 125.93, 119.46, 110.62, 72.72, 38.61, 26.00; IR 3425, 3031, 2922, 1764, 1720, 1668, 1514, 1358, 1029 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{14}O_4$ $[M+Li]^+$: 237.0350; found 237.1109.

Chapter 2
Synthesis of Unnatural Enantiomer Morphinans as TLR4 Inhibitors

2.1 Role of Glial Cell Activation in Pain and Opioid Tolerance

Glial Cells

The term "neuroglia" was coined in 1856 by Rudolph Virchow in reference to the interstitial space between cells in the central nervous system.[37] In the intervening century and a half, neuroglia has come to encompass a wide variety of non-neuronal support cells including macroglia, microglia, astrocytes, and ependymal cells.[38] Glia is Greek for "glue" and glial cells were so named because they were initially thought to merely provide structural support for neurons. More recently it was discovered that glial cells fulfill a variety of roles including responding to the nervous system's response to injury, for example.[39] In a normal state, microglia migrate around the nervous system searching for damage or disease.[39] In response to injury or pathogens, microglia proliferate, congregate at the site of injury or disease, and finally become macrophages and ingest the target.[39]

Neuropathic pain is a pathological type of pain that can present in a variety of ways including unexplainable widespread pain, allodynia, burning sensations, sensory deficit, or acute pain without a proximate cause which has been hypothesized to have a microglial cell component.[40,41] Glial cells have been thought to play another role in pain regulation since 1988 when it was hypothesized that they may be a root cause of developing tolerance to morphine.[42] Work by Hutchinson and Watkins demonstrated that opioids, such as morphine, induce a pro-

[37] Kettemann, H.; Ransom, B. R. *Neuroglia*; Kettenmann, H.; Ransom, B. R., Eds.; Second.; Oxford University Press: New York, New York, 2005; pp. 1–16.
[38] Patesta, M. A.; Gertner, L. P. In *A Textbook of Neuroanatomy*; Blackwell Science LTD: Malden, MA, 2006; pp. 3–9.
[39] Nolte, J. In *The Human Brain: An Introduction to Its Functional Anatomy*; Mosby Elsevier: Philadelphia, PA, 2009; pp. 1–36.
[40] Tanga, F. Y.; Nutile-McMenemy, N.; DeLeo, J. A. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 5856–5861.
[41] Milligan, E. D.; Watkins, L. R. *Nat. Rev. Neurosci.* **2009**, *10*, 23–36.
[42] Rönnböck, B.; Hansson, E. *Neurochem. Res.* **1988**, *13*, 87–103.

inflammatory response in glial cells, which opposes the analgesic action of the opioid and implicates glia in the development of opioid tolerance.[43]

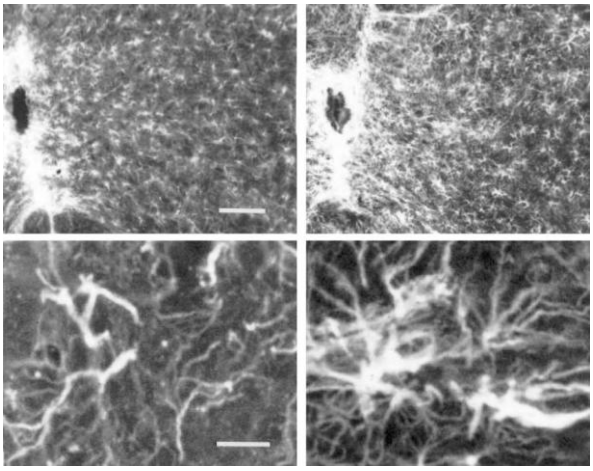


Figure 2.1 Glial activation in response to morphine: control left; morphine treated right.[43a]

In vivo evidence of this opioid pro-inflammatory link includes upregulation of microglia formation by morphine,[44] upregulation and release of pro-inflammatory cytokines induced by morphine,[45] potentiation of morphine analgesia by administering minocycline or AV411 (known microglial attenuators),[45,46] blockage of pro-inflammatory cytokine action potentiating morphine analgesia,[45,47] and selective activation of the p38 MAPK pathway in microglia.[48] Work by Ruzicka and Akil established that microglia and astrocytes both express mRNA for opioid receptors,[49] and it was once thought that this was the avenue through which the opioids acted on

[43] (a) Watkins, L. R.; Hutchinson, M. R.; Johnston, I. N.; Maier, S. F. *Trends Neurosci.* **2005**, *28*, 661–669. (b) Hutchinson, M. R.; Bland, S. T.; Johnson, K. W.; Rice, K. C.; Maier, S. F.; Watkins, L. R. *Sci. World J.* **2007**, *7*, 98–111.
[44] (a) Cui, Y.; Chen, Y.; Zhi, J.-L.; Guo, R.-X.; Feng, J.-Q.; Chen, P.-X. *Brain Res.* **2006**, *1069*, 235–243. (b) Hutchinson, M. R.; Lewis, S. S.; Coats, B. D.; Skyba, D. a; Crysdale, N. Y.; Berkelhammer, D. L.; Brzeski, A.; Northcutt, A.; Vietz, C. M.; Judd, C. M.; Maier, S. F.; Watkins, L. R.; Johnson, K. W. *Brain. Behav. Immun.* **2009**, *23*, 240–250.
[45] (a) Hutchinson, M. R.; Coats, B. D.; Lewis, S. S.; Zhang, Y.; Sprunger, D. B.; Rezvani, N.; Baker, E. M.; Jekich, B. M.; Wieseler, J. L.; Somogyi, A. a; Martin, D.; Poole, S.; Judd, C. M.; Maier, S. F.; Watkins, L. R. *Brain. Behav. Immun.* **2008**, *22*, 1178–1189. (b) Hutchinson, M. R.; Northcutt, A. L.; Chao, L. W.; Kearney, J. J.; Zhang, Y.; Berkelhammer, D. L.; Loram, L. C.; Rozeske, R. R.; Bland, S. T.; Maier, S. F.; Gleeson, T. T.; Watkins, L. R. *Brain. Behav. Immun.* **2008**, *22*, 1248–1256. (c) Hutchinson, M. R.; Zhang, Y.; Brown, K.; Coats, B. D.; Shridhar, M.; Sholar, P. W.; Patel, S. J.; Crysdale, N. Y.; Harrison, J. a; Maier, S. F.; Rice, K. C.; Watkins, L. R. *Eur. J. Neurosci.* **2008**, *28*, 20–29.
[46] Cui, Y.; Liao, X.-X.; Liu, W.; Guo, R.-X.; Wu, Z.-Z.; Zhao, C.-M.; Chen, P.-X.; Feng, J.-Q. *Brain. Behav. Immun.* **2008**, *22*, 114–123.
[47] Shavit, Y.; Wolf, G.; Goshen, I.; Livshits, D.; Yirmiya, R. *Pain* **2005**, *115*, 50–59.
[48] Cui, Y.; Chen, Y.; Zhi, J.-L.; Guo, R.-X.; Feng, J.-Q.; Chen, P.-X. *Brain Res.* **2006**, *1069*, 235–243.
[49] Ruzicka, B. .; Akil, H. *Neuroscience* **1997**, *79*, 517–524.

the glial cells. However, work with opioid-receptor knockout mice by Gaveriaux-Ruff indicated that there are also opioid receptor independent pathways.[50] Work by Kest found that opioid administration to triple opioid receptor (μ, δ, and κ) knockout mice increased nociception, further indication of an opioid-receptor independent pathway.[51]

Toll-like Receptor 4

Toll-like receptor 4 (TLR4) is an innate immune system receptor that is expressed by glial cells.[52] As part of the innate immune system TLR4 is responsible for detecting lipopolysaccharide (LPS) particularly the lipid A portion (Figure 2.2).[53] TLR4 has been

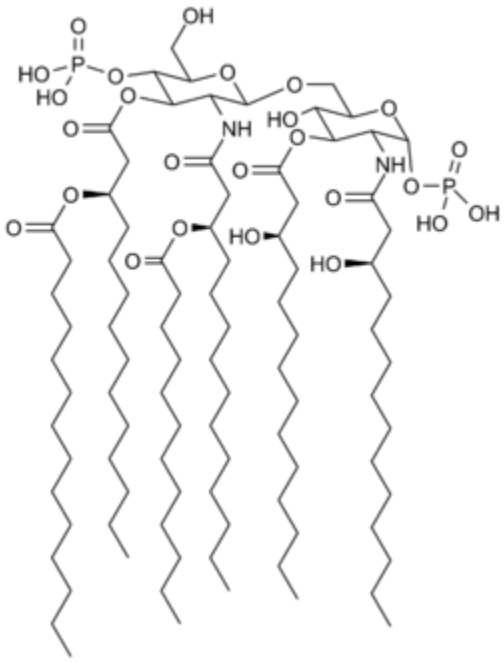
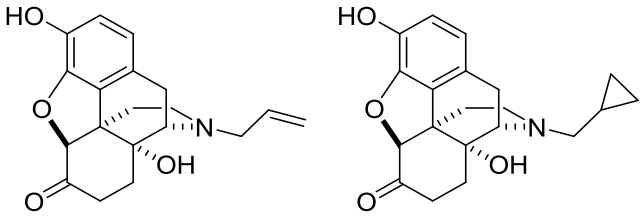


Figure 2.2 Lipid A.[54]

implicated in neuropathic pain development, with TLR4 knockout and point-mutant mice both displaying reduced allodynia compared to wild-type mice when neuropathy was induced by

[50] (a) Gaveriaux-Ruff, C.; Matthes, H. W. D.; Peluso, J.; Kieffer, B. L. *Proc. Natl. Acad. Sci.* **1998**, *95*, 6326–6330. (b) Gaveriaux-Ruff, C.; Filliol, D.; Simonin, F.; Matthes, H. W. D.; Kieffer, B. L. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 1193–1198.
[51] Juni, A.; Klein, G.; Pintar, J. E.; Kest, B. *Neuroscience* **2007**, *147*, 439–444.
[52] Watkins, L. R.; Hutchinson, M. R.; Rice, K. C.; Maier, S. F. *Trends Pharmacol. Sci.* **2009**, *30*, 581–591.
[53] (a) Aderem, A.; Ulevitch, R. J. *Nature* **2000**, *406*, 782–787. (b) Akira, S.; Takeda, K.; Kaisho, T. *Nat. Immunol.* **2001**, *2*, 675–680. (c) Underhill, D. M.; Ozinsky, A. *Curr. Opin. Immunol.* **2002**, *14*, 103–110.
[54] Raetz, C. R. H.; Guan, Z.; Ingram, B. O.; Six, D. A.; Song, F.; Wang, X.; Zhao, J. *J. Lipid Res.* **2009**, *50 Suppl*, S103–8.

transection of the L5 spinal nerve.[40] Unnatural enantiomers of opioid antagonists, (+)-naloxone and (+)-naltrexone (Figure 2.3) were found to improve opioid analgesia in cases where glial cells had been activated by LPS.[55] Since LPS is the ligand for TLR4, Hutchinson and Watkins hypothesized



(+)-naloxone, 99 **(+)-naltrexone 100**

Figure 2.3 (+)-naloxone and (+)-naltrexone.

that the unnatural enantiomers of naloxone and naltrexone might be interacting with TLR4, for which they found evidence in 2010.[56] This work indicated both the natural (-) and unnatural (+) enantiomers of the opioid antagonist naloxone binds TLR4 and inhibits activation by other opioids and LPS. This opens up the exciting possibility of using other novel (+)-morphinans as TLR4 antagonists.

[55] Wu, H.; Sun, H.-S.; Terashivili, M.; Schwasinger, E.; Sora, I.; Hall, F. S.; Uhl, G. R.; Tseng, L. F. *Eur. J. Pharmacol.* **2006**, *531*, 103–107.

[56] Hutchinson, M. R.; Zhang, Y.; Shridhar, M.; Evans, J. H.; Buchanan, M. M.; Zhao, T. X.; Slivka, P. F.; Coats, B. D.; Rezvani, N.; Wieseler, J.; Hughes, T. S.; Landgraf, K. E.; Chan, S.; Fong, S.; Phipps, S.; Falke, J. J.; Leinwand, L. a; Maier, S. F.; Yin, H.; Rice, K. C.; Watkins, L. R. *Brain. Behav. Immun.* **2010**, *24*, 83–95.

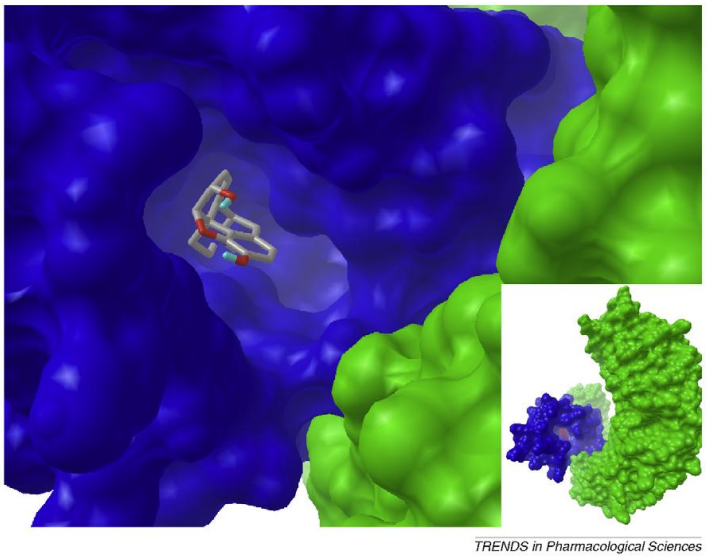
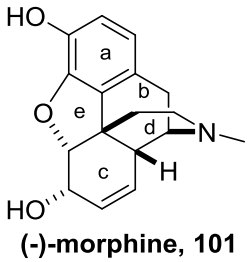


Figure 2.4 Docking model of (-)-morphine in TLR4-MD2 complex.[52]

Metabolism of Morphinans

Morphine and related compounds are metabolized via many routes. In the case of morphine, glucuronidation at the 3 position is the most common pathway (50%). In addition, morphine can be glucuronidated at the 6 position, *N*-demethylated, and glucuronidated at both the 3- and 6-positions.[57]



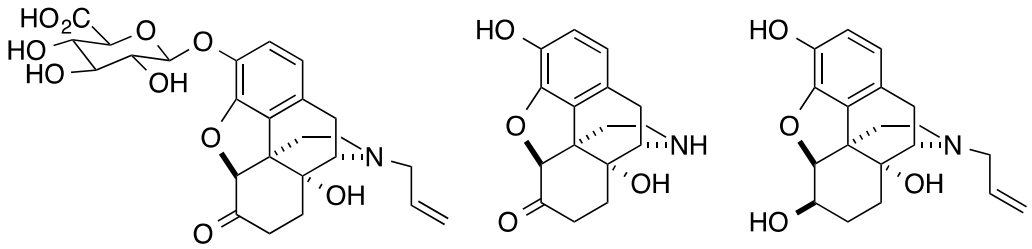
(-)-morphine, 101

Figure 2.5 (-)-morphine with rings labeled.

Glucuronidation allows the morphinan to be rapidly cleared. The half-life of (-)-naloxone (the natural enantiomer) is 0.5-0.67 hours[58] while that of the (+)-naloxone (the unnatural enantiomer)

[57] Coleman, M. D. *Human Drug Metabolism*; Second.; Wiley-Blackwell: Chichester, England, 2010; pp. 285–292.
[58] (a) Hussain, M. A.; Aungst, B. J.; Kearney, A.; Shefter, E. *Int. J. Pharm.* **1987**, *36*, 127–130. (b) Ngai, S. H.; Berkowitz, B. A.; Yang, J. C.; Hempstead, J.; Spector, S. *Anesthesiology* **1976**, *44*, 398–401.

has a longer half-life of 1.57 ± 0.784 hours for subcutaneous administration.[59] The limited half-life and oral bioavailability offer areas that could be improved along with potency. In humans and rabbits, the primary metabolite formed is the 3-glucuronated compound **102** with a small amount of the de-allylated compound **103** and the reduced (at the 6 position) naloxonol (**104**).[60]



102 **103** **104**

Figure 2.6 Naloxone metabolites

2.2 Biological Data

In order to find a better TLR4 inhibitor, a reliable biological assay was necessary. For this project, an assay using BV-2 murine glial cells was developed by our collaborators in the Yin and Watkins labs. These cells natively express TLR4 and are a good model system for human glial cells.[61] The assay relies on nitric oxide (NO) reporting. Nitric oxide is a normal part of TLR4 signaling, making it an excellent reporter. Results from the assay are provided in Tables 2.1 and 2.4. All of the cell assays were run by Dr. Xiaohui Wang of the Yin lab at the University of Colorado.

Entry	Structure	IC_{50} (μM) of inhibiting LPS induced NO	IC_{50} (μM)of cell viability

[59] Lewis, S. S.; Loram, L. C.; Hutchinson, M. R.; Li, C.-M.; Zhang, Y.; Maier, S. F.; Huang, Y.; Rice, K. C.; Watkins, L. R. *J. Pain* **2012**, *13*, 498–506.
[60] Weinstein, S. H.; Pfeffer, M.; Schor, J. M. In *Advances in Biochemical Pschopharmacology, Vol. 8 Narcotic Antagonists*; Braude, M. C.; Harris, L. S.; May, E. L.; Smith, J. P.; Villarreal, J. E., Eds.; Raven Press: New York, New York, 1974; pp. 525–535.
[61] Henn, A.; Lund, S.; Hedtjärn, M.; Schrattenholz, A.; Pörzgen, P.; Leist, M. *ALTEX* **2009**, *26*, 83–94.

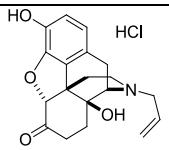
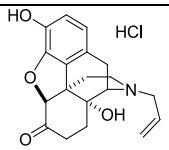
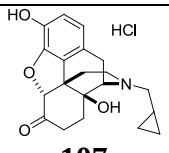
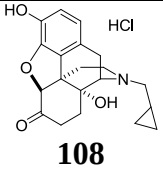
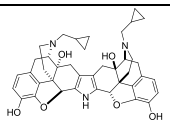
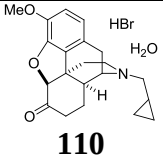
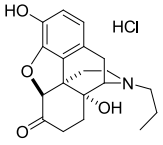
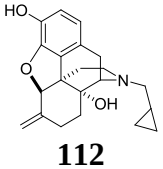
1	 **105**	101.5±8.4	>400
2	 **106**	94.4±11.2	>400
3	 **107**	107.2±14.3	>400
4	 **108**	105.5±10.1	>400
5	 **109**	6.4±0.4	37.1±5.7
6	 **110**	>400	>400
7	 **111**	179.1±19.9	>400
8	 **112**	12.3±2.9	394.0±39.3

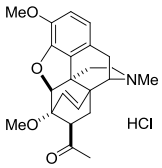
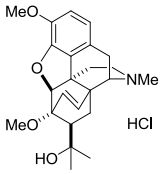
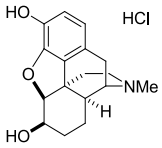
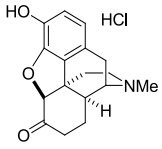
Table 2.1 *In vitro* TLR4 Inhibition Data.

Table 2.1 are selected compounds synthesized by Dr. Kenner Rice and provided to the Watkins lab in an earlier phase of the project. Entries 1-4 of Table 2.1 are the natural (**105, 107**) and unnatural (**106, 108**) enantiomers of naloxone and naltrexone. The similar IC_{50} of each enantiomer supports the hypothesis that TLR4 is sufficiently promiscuous to bind the

enantiomers of the morphinans with comparable affinity. While (+)-norbinaltorphimine (**109**) is a potent inhibitor with an IC_{50} of 6.4 μM, is also very toxic with an IC_{50} of cell viability of 37 μM (Table2.1, entry 5). The naltrexone-like compound (+)-*N*-cyclopropyl methylnordihydrocodeinone (**110**) had no detectable activity, most likely due to the methoxy group in the three position (Table 2.1, entry 6). (+)-Dihydronaloxone (**111**), which bears a propyl group rather than the allyl group of naloxone, displayed an increase in IC50 compared to (+)-naloxone (179 μM vs 94 μM) which leads us to believe that the alkene moiety of the allyl group is advantageous to potency (Table 2.1, entry 7). (+)-Nalmefene (**112**) is a most interesting compound, the alkene analog of naltrexone, with an exceedingly low IC_{50} TLR4 inhibition of 12.3 μM and a very good IC50 of cell viability of nearly 400 μM (Table 2.1, entry 8). Unfortunately the cell assay results do not correlate well with its activity in animals where no potentiation of opioid analgesia is observed.[56] The origin of the difference in *in vitro* and *in vivo* activity is unclear.

Table 2.2 consists of compounds that were synthesized as part of this dissertation in the Sammakia lab and have been tested. (+)-Thevinone (**113**) tested favorably with an IC_{50} of 53 μM, approximately half that of (+)-naloxone (Table 2.2, entry 1). (+)-Thevinone has functionality that could be easily modified to enhance the potency, namely the 3-methoxy group and the *N*-methyl group, both of which have been liabilities in other scaffolds. Compound **114**, a derivative of (+)-thevinone, displayed comparable potency to (+)-naloxone with an IC_{50} of 93 μM (Table 2.2, entry 2). (+)-Dihydromorphine (**115**), (+)-hydromorphone (**116**), and (+)-oxymorphone (**117**) were tested to determine their behavior with TLR-4 (Table 2.2, entries 3-5). (+)-Dihydromorphine (**115**) exhibited no detectable inhibition of NO production suggesting that it is not an TLR4 antagonist (Table 2.2, entry 3), while (+)-hydromorphone (**116**) displayed

inconsistent behavior in the assay: Hydromorphone (**116**) provided by the us displayed an IC_{50} of 30 μM, while that provided by the Rice lab had no measureable inhibitory effect (Table 2.2, entries 4a and 4b respectively). Similarly, (+)-oxymorphone (**117**) provided by our lab demonstrated greater potency than that of (+)-oxymorphone provided by the Rice lab (Table 2.2, entries 5a and 5b respectively). These results are consistent, yet the cause of these discrepancies is not understood and remains under investigation by our collaborators.

Entry	Structure	IC_{50} (μM) of inhibiting LPS induced NO	IC_{50} (μM)of cell viability
1	 **113**	52.5±2.5	>400
2	 **114**	92.9±3.9	~ 400
3	 **115**	>400	>400
4a	 **116**	30.5±19.2 Synthesized by Sammakia Lab	>400

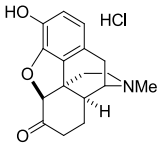
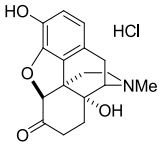
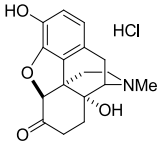
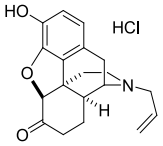
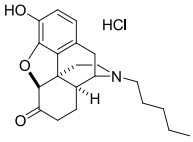
4b	 **116**	>400 Synthesized by Rice	>400
5a	 **117**	57.1±5.2 Synthesized by Sammakia Lab	>400
5b	 **117**	179.1±19.9 Synthesized by Rice	>400
6	 **118**	135.4±11.0	252.1±10.0
7	 **119**	26.2±3.4	307.6±20.1

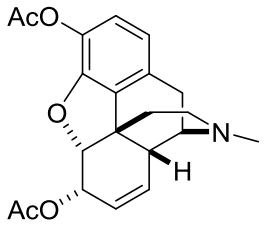
Table 2.2 In vitro TLR4 inhibition data

(+)-14-Deshydroxynalxone (**118**), which lacks the tertiary hydroxyl group at the 14-position, was synthesized to probe the contribution of this group to TLR4 inhibition. This compound proved slightly less potent and displayed an IC_{50} of 135 μM versus 94 μM (Table 2.2 entry 6 and Table 2.1 entry 2 respectively). Intriguingly compound **119**, bearing a 5-carbon alkyl chain, proved to be strongly potent with an IC_{50} of 26 μM even without the 14-hydroxyl group installed (Table

2.2, entry 7). This positive result piqued our interest in the impact of alkyl chain length on potency. In order to explore the relationship, we have synthesized a series of compounds bearing crotyl, butyl, and hexyl chains on the nitrogen and are in the process of studying their activity.

2.3 Synthesis of Opioids

(-)-Morphine (**101**, figure 2.5) has been used medicinally for several thousand years, beginning with cultivation of the opium poppy in ancient Mesopotamia.[62] Morphine is one of the active ingredient in opium, and was isolated in 1806 by Seturner.[63] Heroin (**120**, figure 2.7), the diacylated derivative, was synthesized by Wright in 1875 in an attempt to find a more potent and less addictive compound. The first total synthesis of morphine was accomplished by Gates and Tschudi in 1952.[64]



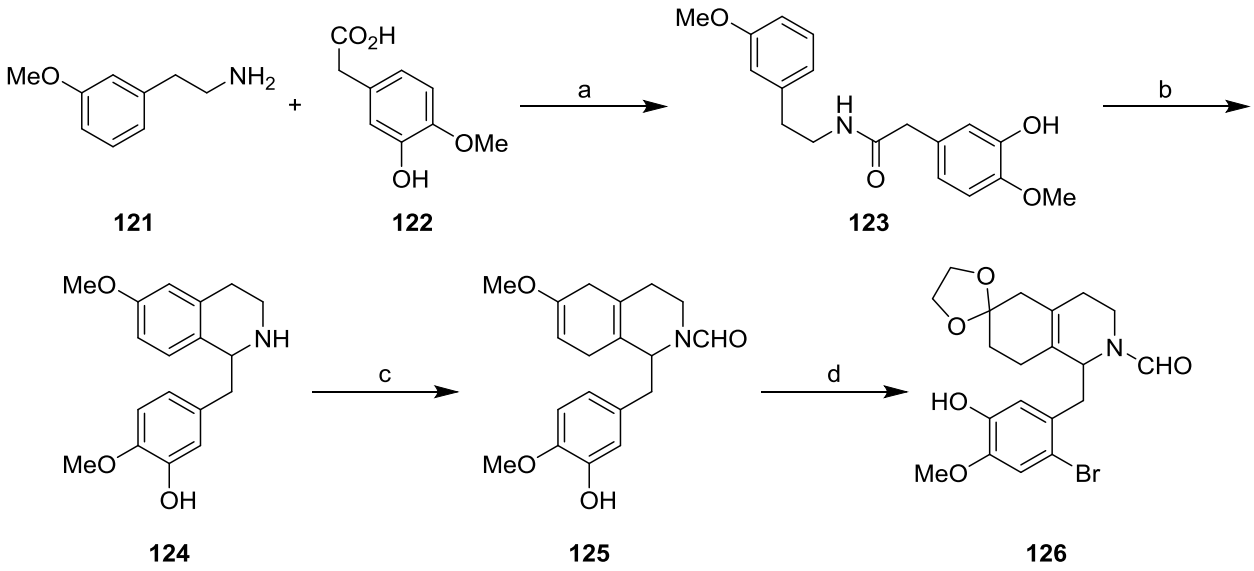
heroin, 120

Figure 2.7 Heroin.

In the time since Gate's synthesis, there have been numerous syntheses of morphine and related morphinans. Interest in these compounds was spurred by the synthetic challenge and the utility of having a supply of morphinans independent of opium poppies.[65] Of these, the synthesis of Rice stands out as short, efficient, and versatile.[65d] Rice successfully sythensized (±)-dihydrocodeinone (hydrocodone) in 29% overall yield starting from commercially available

[62] Brownstein, M. J. *Proc. Natl. Acad. Sci.* **1993**, *90*, 5391–5393.
[63] Serturner, F. *Ann. Phys.* **1817**, *55*, 56–89.
[64] Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109–1110.
[65] (a) Geffe, M.; Opatz, T. *Org. Lett.* **2014**, *16*, 5282-5285. For reviews of morphine syntheses see: (b) Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 1159–1168. (c) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388–405. (d) Rinner, U.; Hudlicky, T. *Top. Curr. Chem.* **2012**, *309*, 33–66.

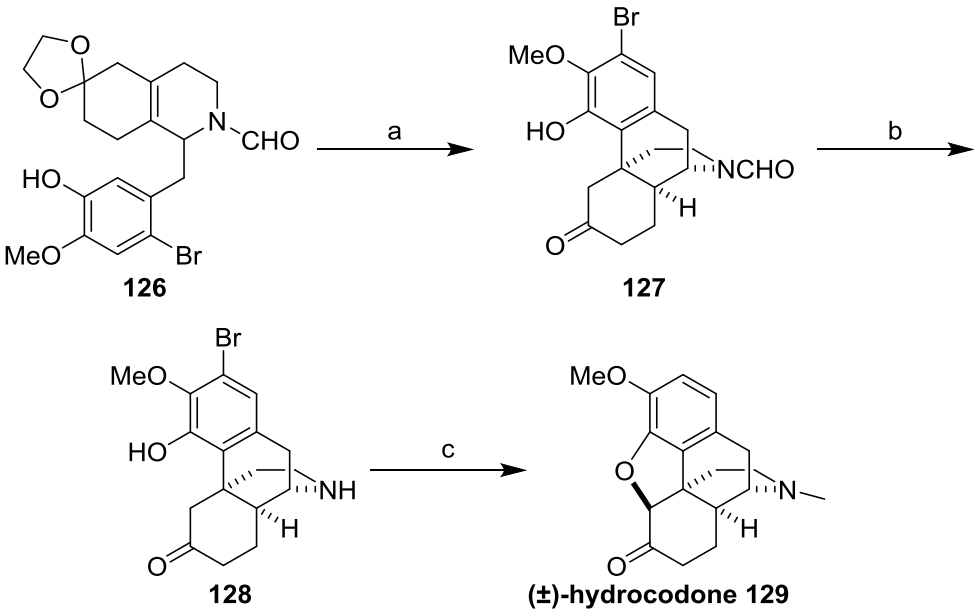
mterials as shown in Scheme 2.1.[66] His synthesis begins with the condensation of amine **121** and acid **122** (scheme 2.1) to provide amide **123**. The amide is then subjected to a Bischler-Napieralski reaction followed by a sodium cyanoborohydride reduction to provide tetrahydroquinoline **124**. Birch reduction with lithium metal in ammonia followed by *N*-formylation with phenylformate lead to methyl enol ether **125**. The enol ether was protected as a ketal and the aryl ring brominated using *N*-bromoacetamide to yield the important intermediate **126**, a substrate for the key step in the synthesis, a Grewe cyclization.



a) 200°C, 2 hours b) $POCl_3$, MeCN; $NaCNBH_3$, MeOH c) Li, NH_3, *t*BuOH; PhOCHO, EtOAc, Δ d) ethylene glycol, THF, $MeSO_3H$; $CH_3CONHBr$, 0°C

Scheme 2.1 Initial steps of the Rice Synthesis

[66] Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135–3137.



a) Formic acid, H_2O; NH_4F, HF, triflic acid b) HCl/MeOH, reflux c) Br_2, AcOH; NaOH, $CHCl_3$; Pd/C, H_2, AcOH, HCHO

Scheme 2.2 Grewe cyclization and terminal steps of synthesis

Ketal **126** was cleaved using formic acid and water to reveal the β, γ-unsaturated ketone which underwent the Grewe cyclization with ammonium fluoride/ hydrofluoric acid in triflic acid to form the B ring of the morphinan and provide ketone **127** (Scheme 2.2). The formamide was removed using refluxing HCl in methanol to provide the deprotected secondary amine **128**. The synthesis of racemic dihydrocodeinone was completed by α-bromination of the ketone with bromine in acetic acid followed by attack of the phenol to form the 5-membered ring. Hydrogenolysis of the aryl bromide was accomplished by hydrogenation in the presence of formaldehyde to provide the desired product (±)-hydrocodone (**129**) in 29% overall yield.

In the Rice synthesis, an early intermediate, the dihydroquinoline (**130,** Figure 2.8), provides an opportunity for an enantioselective synthesis via asymmetric reduced to provide non-racemic material.

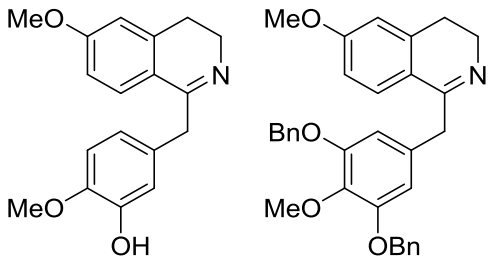
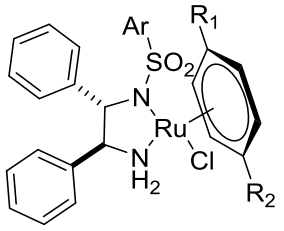


Figure 2.8 Dihydroisoquinoline intermediate from Rice (**130**) and Beyerman (**131**)

A similar dihydroisoquinoline (**131**, figure 2.8) was described in an earlier morphinan synthesis by Beyerman.[67] An asymmetric reduction of these compounds was first reported by Meuzelaar[68] who found that the Rice dihydroisoquinoline (**130**) could be reduced in an excellent *ee* of 99% and a good yield of 73% following crystallization when chiral ruthenium(II) catalyst **134**, the Noyori catalyst, was used. Unfortunately, the Beyerman dihydroisoquinoline



132: Ar = 4-MePh, R_1 = Me, R_2 = *i*Pr
133: Ar = 4-MePh, R_1 = R_2 = H
134: Ar = 2,4,6-(Me)Ph, R_1 = Me, R_2 = *i*Pr
135: Ar = 1-naphthyl, R_1 = Me, R_2 = iPr
136: Ar = 2,4,6-(*i*Pr)Ph, R_1 = Me, R_2 = *i*Pr

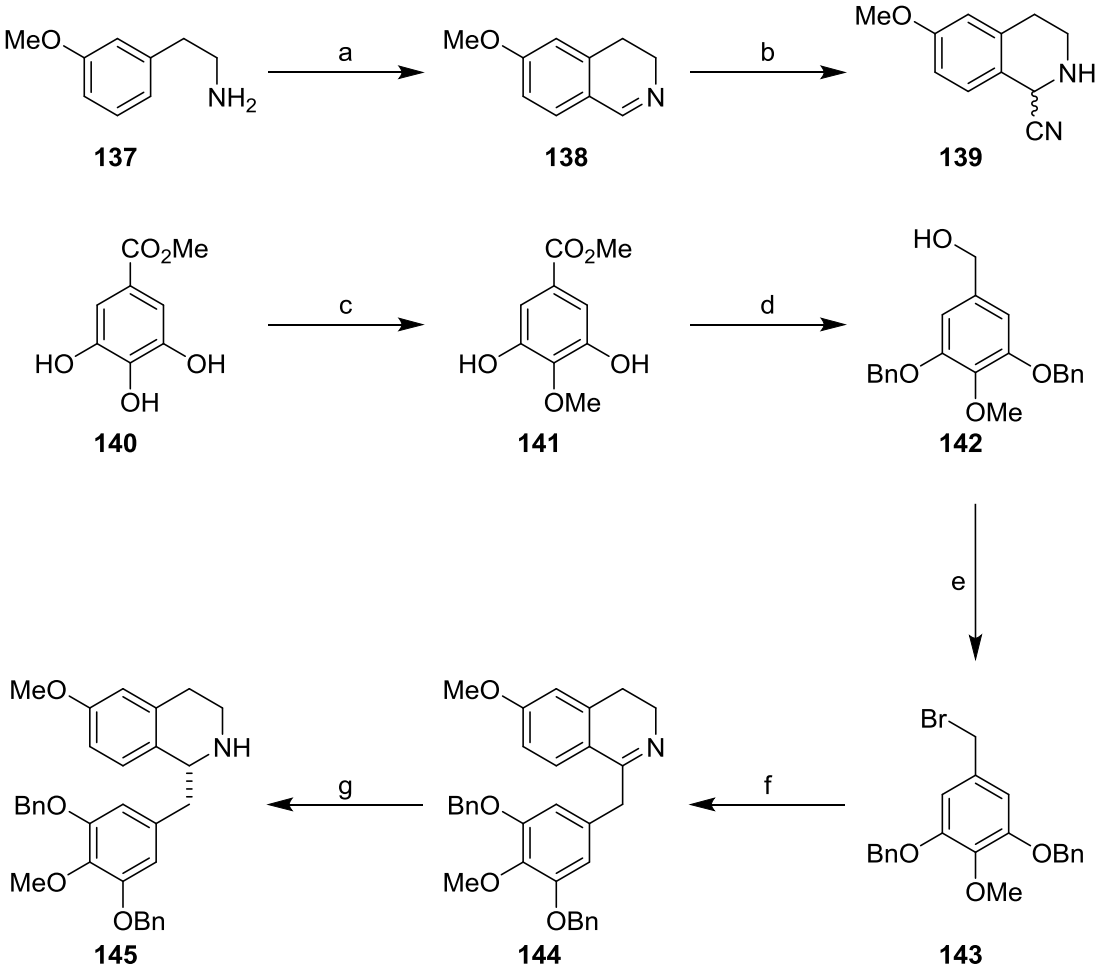
Figure 2.9 Noyori Catalysts used by Meuzelaar[68]

product was difficult to isolate and could only be obtained in 23% yield and 81% *ee* when catalyst **132** was used.

In 2014, Geffe and Opatz successfully used the Noyori catalyst in the total synthesis of (-)-dihydrocodeine and the formal synthesis of (-)-thebaine, (-)-codeine, and (-)-morphine.[65a] Geffe

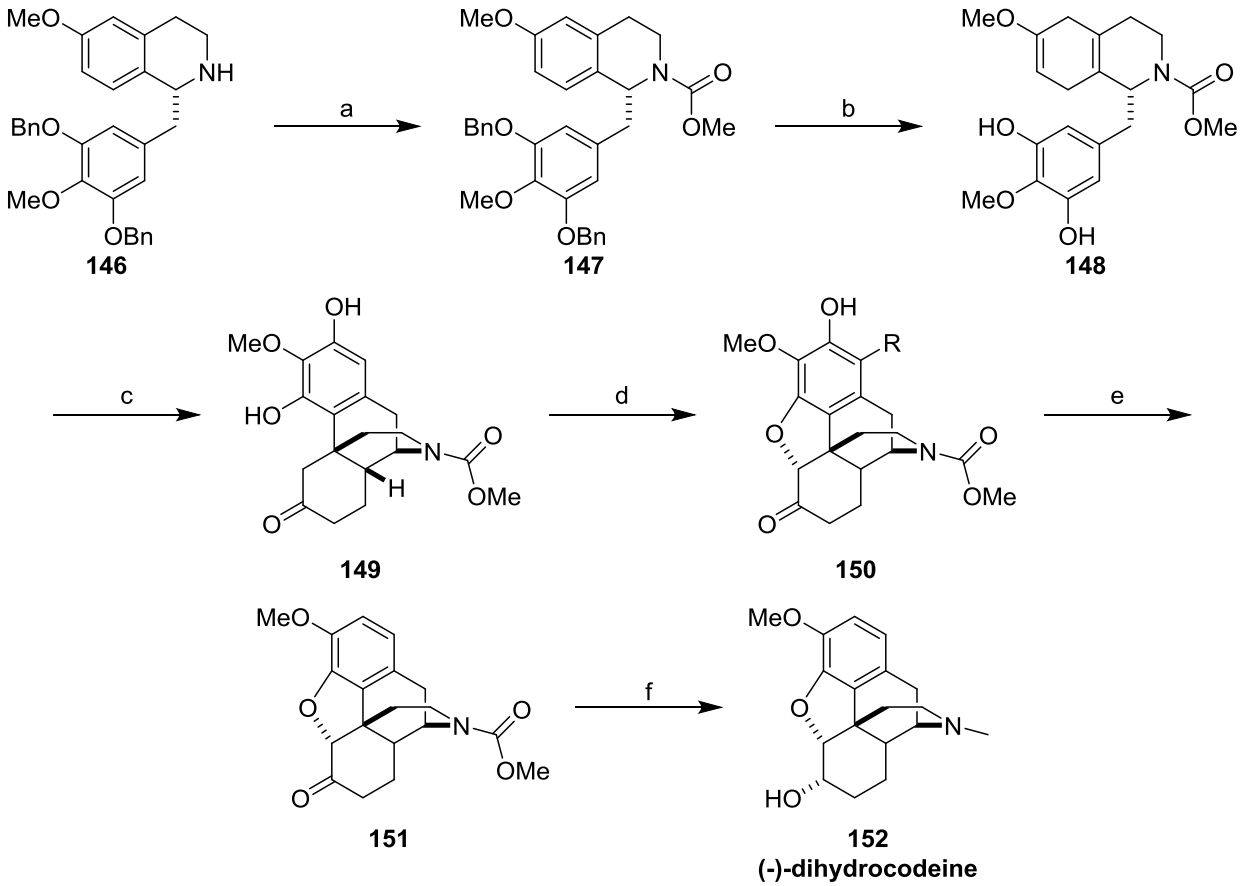
[67] (a) Beyerman, H. C.; Lie, T. S.; Maat, L.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M.; Sinnige, H. J. M. *Recl. des Trav. Chim. des Pays-Bas* **1976**, *95*, 24–25. (b) Beyerman, H. C.; van Berkel, J.; Lie, T. S.; Maat, L.; Wessels, J. C. M.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M.; Sinnige, H. J. M. *Recl. des Trav. Chim. des Pays-Bas* **1978**, *97*, 127–130.
[68] Meuzelaar, G. J.; van Vliet, M. C. A.; Maat, L.; Sheldon, R. A. *European J. Org. Chem.* **1999**, *1999*, 2315–2321.

and Opatz were able to synthesize (-)-dihydrocodeine in 31% overall yield, making the synthesis comparable to Rice's in yield, yet it is asymmetric.



a) HCO_2Et; PCl_5 b) acetone cyanohydrin c) MeI, K_2CO_3 d) BnCl, K_2CO_3; LAH
e) NBS, PPh_3 f) **139**, KHMDS g) **132,** HCO_2H, NEt_3

Scheme 2.3 Synthesis of enantioselective tetrahydroisoquinoline.[65a]



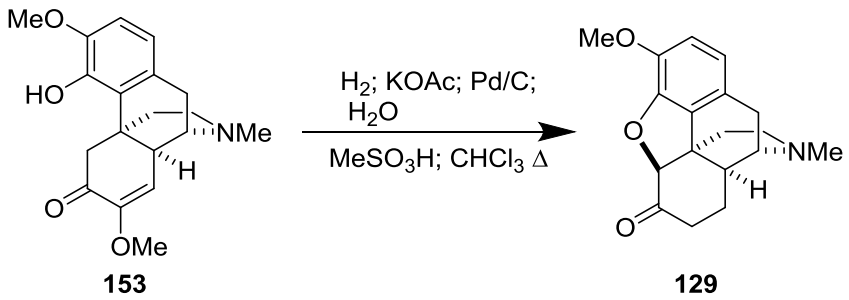
a) $ClCO_2Me$, THF, NEt_3 b) Li, NH_3, *t*BuOH c) HCl, Et_2O, reflux d) $CuBr_2$, $CHCl_3$/ EtOAc; 0.5M NaOH e) Tf_2O, pyridine; cat. $Pd(Ph_3)_4$, HCO_2H, NEt_3, DMF 60°C f) DIBAL, THF

Scheme 2.4 Completion of Geffe Synthesis[65a]

2.4 Synthesis of (+)-naloxone analogs

Since our goal was to access the unnatural enantiomers of naloxone-like compounds, an enantioselective synthesis was necessary. Fortunately Ikuo Iijima, Ju-ichi Minamikawa , Arthur Jacobson, Arnold Brossi and Kenner Rice had devised a semi-synthesis to access unnatural enantiomers of morphinans using (-)-sinomenine (**153**) as the starting material (scheme 2.5).[69] (-)-sinomenine is commercially available in bulk and was purchased at the start of this project at a cost of $200/kg.

[69] (a) Iijima, I.; Minamikawa, J.; Jacobson, A. E.; Brossi, A.; Rice, K. C. *J. Med. Chem.* **1978**, *21*, 1462–1463. (b) unpublished notes



Scheme 2.5 Synthesis of (+)-hydrocodone.

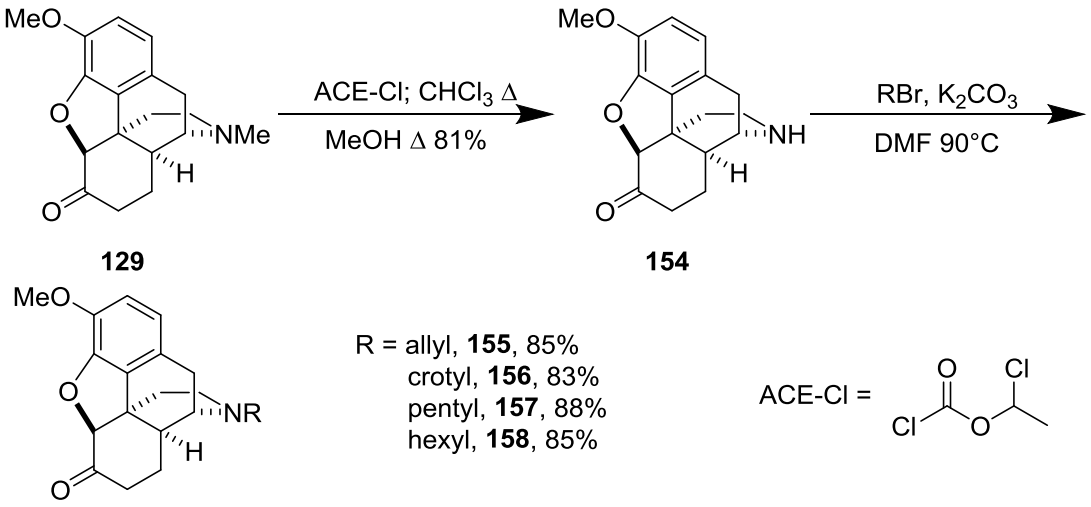
Starting with (-)-sinomenine, a hydrogenation was carried out using palladium on carbon to provide (-)-dihydrosinomeine, which was not isolated but instead carried forward in an S_N2' ring closure catalyzed by methanesulfonic acid giving (+)-hydrocodone (**129**). This material was isolated as the tartrate salt in 55% yield over two steps on scale as large as 130 grams. The (+)-hydrocodone intermediate was used for the synthesis of all analogs and provided a useful point for derivatization.

Variation of N-alkyl chain

The first structure activity relationship we decided to explore was the length *N*-alkyl chain. In naloxone, which is a μ-opioid/TLR4 antagonist, this is an *N*-allyl group. In several opioid/TLR4 agonists, such as morphine or oxycodone, it is an *N*-methyl group. We were curious about the relationship between chain length, agonism/antagonism, and potency. We hypothesized that a longer *N*-alkyl chain might emulate the tails of the lipid A (Figure 2.2) thereby improving potency. To that end we needed to remove the methyl group on the nitrogen. Numerous methods were attempted using cyanogen bromide[70] and various chloroformates such as methyl[71], ethyl[72], and 2,2,2-trichloroethyl chloroformate.[73] Formation of the quaternary salt,

[70] Park, H. S.; Lee, H. Y.; Kim, Y. H.; Park, J. K.; Zvartau, E. E.; Lee, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3609–3613.
[71] Coop, A.; Janetka, J. W.; Lewis, J. W.; Rice, K. C. *J. Org. Chem.* **1998**, *63*, 4392–4396.
[72] Wright, W. B.; Brabander, H. J. *J. Org. Chem.* **1961**, *26*, 4057–4060.
[73] Bellingham, R. K.; Carey, J. S.; Hussain, N.; Morgan, D. O.; Oxley, P.; Powling, L. C. *Org. Process Res. Dev.* **2004**, *8*, 279–282.

followed by removal of the methyl group with thiolate base was also studied.[74] The method of Olofson, which utilized alpha chloroethylchloroformate followed by cleavage of the resulting carbamate in refluxing methanol to provide the *N*-nor hydrocodone **154** in 81% yield over two steps and was by far the cleanest and most effective demethylation method, and was amenable to a one pot procedure.[75] The (+)-norhydrocodone was then alkylated with the desired bromoalkane



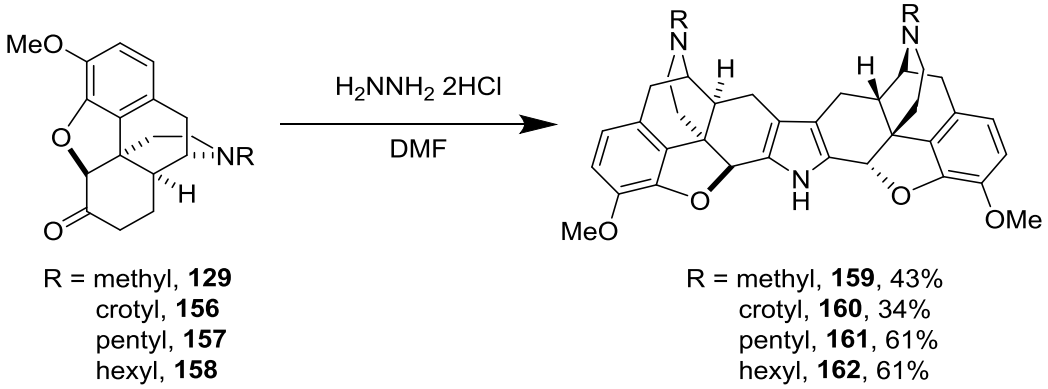
Scheme 2.6 *N*-Demethylation alkylation.

in warm dimethylformamide with potassium carbonate to give the alkylated product in 60-70% yield. A variety of alkyl groups were used in this alkylaton including crotyl, *n*-pentyl, and *n*-hexyl. The crotyl group was targeted because of the loss of potency observed between (+)-naloxone and (+)-dihydronaloxone (Table 2.1, entries 2 and 7), leading to the hypothesis that an alkene bond allylic to the nitrogen might improve potency compared to a saturated compound alkyl group.[76] The promising results of the *N*-pentyl analog (Table 2.2, entry 7) indicate alkyl chain length merits further exploration.

[74] Werner, L.; Machara, A.; Adams, D. R.; Cox, D. P.; Hudlicky, T. *J. Org. Chem.* **2011**, *76*, 4628–4634.
[75] Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082.
[76] Unpublished biological data

(+)-Norbinaltorphimine analogs

(-)-Norbinaltorphimine is a known κ-opioid receptor antagonist, the enantiomer of which displayed excellent activity in BV-2 cells as previously mentioned (Table 2.1 entry 5).[77] Inspired by a solid-phase synthesis of norbinaltorphimine analogs from Takahashi, we decided to make a series of analogs by heating hydrocodone analogs with hydrazine hydrochloride in dimethylformamide (scheme 2.7).[78] Ketones **129** and **157** both reacted in good yield to provide pyrroles **161** and **162** (61%, Scheme 2.7) while the ketones **129** and **156** provided diminished yields of pyrrole **159** and **160** (43% and 34% respectively, Scheme 2.7)



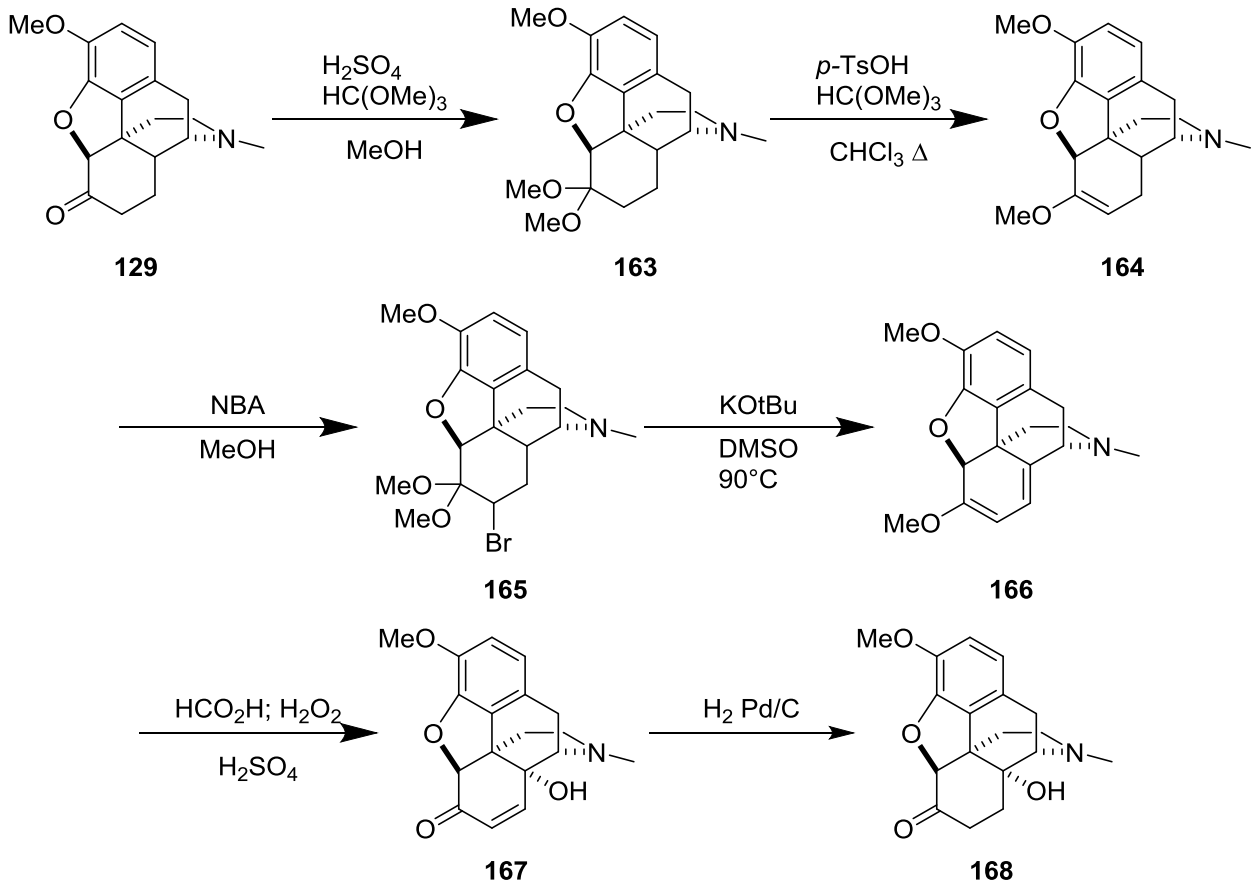
Scheme 2.7 Formation of (+)-norbinaltorphimine analogs

Installation of 14-hydroxy group

The importance of the 14-hydroxy group of naloxone to the inhibition of TLR4 was also known, so a method to install the hydroxyl group was necessary. Following on previous work by Rice, our route consisted of five steps. We began with previously synthesized (+)-hydrocodone (**129**) and formed the dimethyl ketal **163** in near quantitative yield using sulfuric acid and trimethylorthoformate in methanol (Scheme 2.8). Methanol was eliminated using *p*-toluene sulfonic acid to provide the enol ether **164** in 66% after recrystallization (Scheme 2.7). The most challenging step of the sequence was the formation of the α-bromo ketal **165** using *N*-

[77] Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. *Life Sci.* **1987**, *40*, 1287–1292.
[78] Tanaka, H.; Moriwaki, M.; Takahashi, T. *Org. Lett.* **2003**, *5*, 3807–3809.

bromoacetamide in methanol. This was due to unavoidable formation of an over-brominated side product wherein the aryl ring was also brominated leading to a dibromo compound (not shown). This result is not surprising given the electron rich nature of the aromatic ring which bears two alkyl groups and two alkoxy groups. Eventually it was decided that this second bromo group could be removed in subsequent steps via hydrogenation, as per recent literature precedent.[65a] The subsequent double elimination of HBr and methanol proceeded cleanly to provide (+)-thebaine (**166**) in 83% yield. This lead to the final step of 14-hydroxyl group installation-oxidation of (+)-thebaine using formic acid and hydrogen peroxide in sulfuric acid providing (+)-14-hydroxycodeinon (**167**) in 70% yield. Hydrogenation of (+)-14-hydroxycodeinone (**167**) using palladium on carbon provided (+)-oxycodone (**168**) in 84% yield.



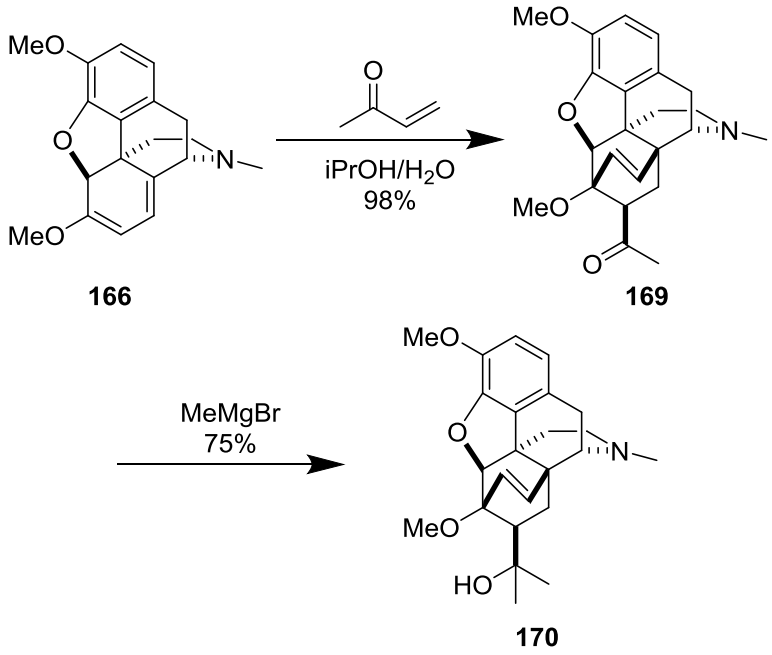
129 **163** **164** **165** **166** **167** **168**

Scheme 2.8 Installation of 14-hydroxyl group

Upon installation of the hydroxyl group, this compound could be carried forward in a manner similar to the (+)-hydrocodone: *N*-demethylation, alkylation, and *O*-demethylation to provide the 14-hydroxy series of compounds. Preliminary biological results led us to focus on the deshydroxy compounds initially as the difference in potency was relatively small (135mM vs 95mM IC_{50} for (+)-14-deshydroxynaloxone and (+)-naloxone respectively), with plans to return to install the hydroxyl group once other areas of scaffold have been optimized.

Thebaine-derived Compounds

(+)-Thebaine (**166**), an intermediate in the synthesis of the 14-hydroxy class of compounds, is an important synthetic intermediate in opioid research.[79] The diene of (+)-thebaine readily undergoes Diels-Alder reactions with suitable dienophiles to provide structurally interesting compounds known to have opioid receptor activity. The ease of access led us to synthesize two such compounds. The first compound, (+)-thevinone (**169**), was made in 98% yield in from (+)-



[79] Berényi, S.; Csutorás, C.; Sipos, A. *Curr. Med. Chem.* **2009**, *16*, 3215–3242.

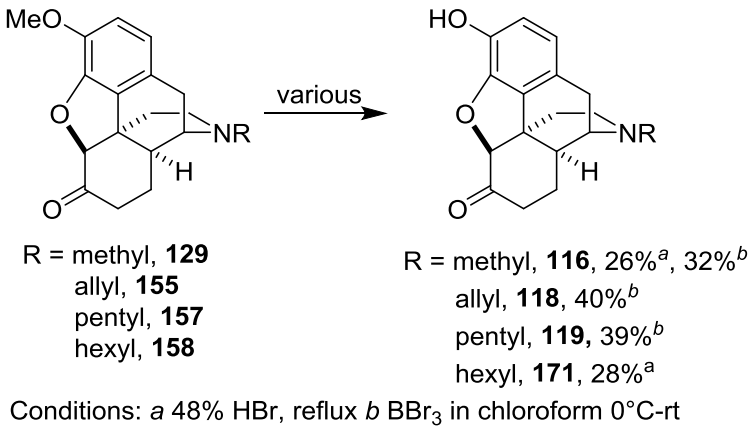
Scheme 2.9 Thebaine Derivatives

thebaine.[80] A second compound was made by the addition of methyl Grignard to the ketone provide compound **170**, in 75% yield. As previously discussed, (+)-thevinone (**169**) proved to be more potent that (+)-naloxone, while the alcohol **170** was of comparable potency (Table 2.2, entries 1, 2). Further exploration of the thevinone scaffold, including varying the *N*-alkyl chain and altering the phenol at the 3-position, is a particularly exciting avenue for the future direction of this work.

Altering the 3-position functionality

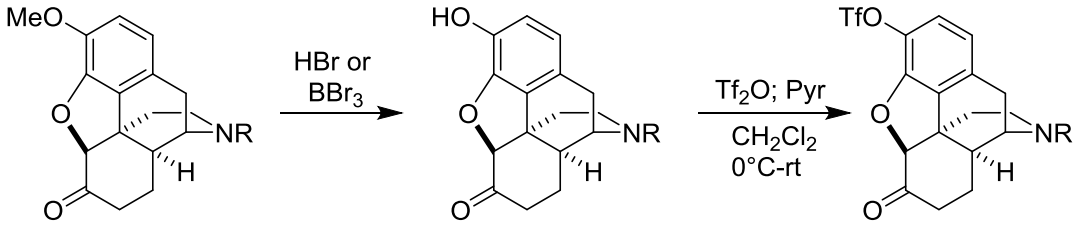
As previously mentioned, the 3- methoxy group has proven to be a liability in terms of potency, and the corresponding phenol, while more potent, is known to be vulnerable to rapid metabolic clearance, therefore altering the 3-position so that compounds are less rapidly cleared while maintaining potency is highly desirable. We chose to functionalize this position with other polar groups and targeted the triflate as our intermediate as it is easily accessed from the phenol previously synthesized. Since the starting material had the methoxy group in the 3-position a reliable method of cleaving the methyl group was necessary. This step proved difficult to carry out in a reliable manner with numerous methods, including trimethyl silyl iodide generated *in situ*, hydrogen bromide in acetic acid,[81] and potassium hydroxide in diethylene glycol,[82] proving unproductive. The two methods that proved most reliable were boron tribromide in chloroform[83] and refluxing concentrated hydrobromic acid.[84]

[80] Bentley, K. W.; Hardy, D. G.; Crocker, H. P.; Haddlesey, D. I.; Mayor, P. A. *J. Am. Chem. Soc.* **1967**, *89*, 3312–3321.
[81] Przybyl, A. K.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *J. Org. Chem.* **2003**, *68*, 2010–2013.
[82] Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3281–3292.
[83] Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164–165.
[84] Spetea, M.; Schüllner, F.; Moisa, R. C.; Berzetei-Gurske, I. P.; Schraml, B.; Dörfler, C.; Aceto, M. D.; Harris, L. S.; Coop, A.; Schmidhammer, H. *J. Med. Chem.* **2004**, *47*, 3242–3247.



Scheme 2.10 Methyl Aryl Ether Clevage

Once the phenol was successfully isolated, the triflation was carried out in good yield using triflic anhydride with pyridine in dichloromethane. Literature precedent indicated that the triflate was a useful intermediate to access different functionalities.[85]



Scheme 2.11 Varying the 3-position.

We chose a nitrile as our first target. Unfortunately cyanation using palladium tetrakis triphenylphosphine with zinc (II) cyanide in dimethylformamide failed to furnish the desired product despite related literature precedence.[85] Alternative conditions were attempted with metal, ligand, cyanide source, and solvent being altered to no avail (Table 2.5). Changing from palladium to nickel did not improve conversion (Table 2.5, entry 8), and potassium cyanide was used in place of zinc (II) cyanide in the hopes that a more anionic cyanide source would improve transmetalation but this uniformly resulted in cleavage of the triflate instead (Table 2.1, entries 6,

[85] (a) Kubota, H.; Rice, K. C. *Tetrahedron Lett.* **1998**, *39*, 2907–2910. (b) Wentland, M.; Lou, R.; Ye, Y.; Cohen, D. J.; Richardson, G. P.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 623–626.

8, 10, 11). The chelating ligands 1,1′-bis(diphenylphosphino)ferrocene and 1,2-bis(diphenylphosphino)ethane were tested, but no improvement in the reaction was discernable (Table 2.10, entries 5,11). Triphenyl arsine was used in the place of more standard phosphine ligands with the hope that this would encourage oxidative addition (Table 2.10, entries 3, 4); but, again, no improvement was observed.

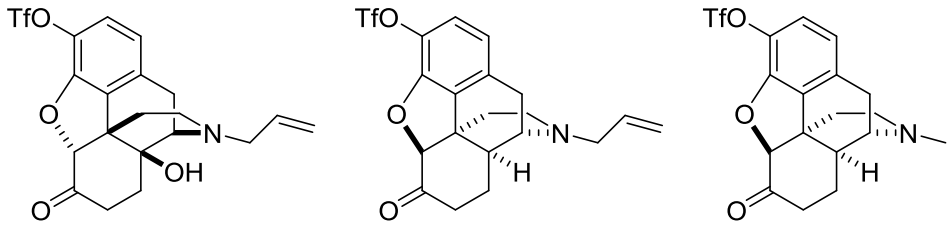


Figure 2.10 Cyanation Substrates

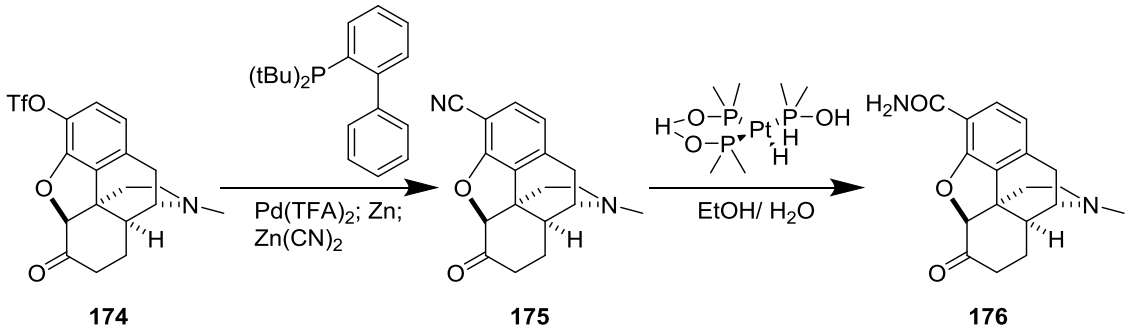
Entry	Substrate	Palladium Source	Ligand	Cyanide source	Solvent	Result
1	**172**	$Pd(PPh_3)_4$		$Zn(CN)_2$	DMF	NR or trace product
2	**172**	$Pd(PPh_3)_4$		$Zn(CN)_2$	NMP	NR
3	**172**	$Pd(dba)_2$	$AsPh_3$	$Zn(CN)_2$	NMP	NR
4	**172**	$Pd(dba)_2$	$AsPh_3$	$Zn(CN)_2$	DMF	NR
5	**172**	$Pd(dba)_2$	dppf	$Zn(CN)_2$	DMF	NR
6	**172**	$Pd(PPh_3)_4$		KCN	PhMe	Triflate cleaved
7	**172**	$Pd(PPH_3)_4$, $Pd_2(dba)_3$		$Zn(CN)_2$	DMF	NR
8	**172**	$NiCl_2(PPh_3)_2$	PPh_3	KCN	DMF	Triflate cleaved
9	**172**	$Pd(dba)_2$	PPh_3	KCN CuI	THF	Triflate Cleaved
10	**172**	$Pd_2(dba)_3$	dppe	KCN	NMP	Triflate Cleaved
11	**172**	$Pd(dba)_2$	PPh_3	$Zn(CN)_2$	DMF	NR
12	**172**	$Pd(dba)_2$	dppe	$Zn(CN)_2$	NMP	NR
13	**172**	$Pd(dba)_2$	dppe	$Zn(CN)_2$	DMF	NR
14	**173**	$Pd(TFA)_2$	2-di-tertbutylphosphino-1,1'-	$Zn(CN)_2$	DMA	44%

			binapthyl	Zn		
15	**174**	$Pd(PPh_3)_4$		$Zn(CN)_2$	DMF	26%[a]
16	**174**	$Pd(TFA)_2$	2-di-tertbutylphosphino-1,1'-binapthyl	$Zn(CN)_2$ Zn	DMA	45%
17	**174**	$Pd(TFA)_2$	PCy_3	$Zn(CN)_2$ Zn	DMA	NR
18	**174**	$Pd(OAc)_2$	2-di-tertbutylphosphino-1,1'-binapthyl	$Zn(CN)_2$ Zn	DMA	40%
19	**172**	$Pd(TFA)_2$	2-di-tertbutylphosphino-1,1'-binapthyl	$Zn(CN)_2$ Zn	DMA	33%

Table 2.3 Cyanation conditions [a]by NMR

The cyanation was successfully carried out on a model, 2-naphthyl triflate, leading to the conclusion that the naloxone triflate was a more challenging substrate for an unclear reason. The cyanation was attempted with (+)-hydromorphone triflate (**174**) as it is quickly accessed from (+)-hydrocodone. In the case of the hydromorphone derivative the standard literature conditions of zinc (II) cyanide with palladium-tetrakis(triphenyl phosphine) in dimethylformamide was found to provide 26% conversion of starting material to product by NMR. We then decided to study the conditionS of Littke and coworkers on the cyanation of aryl chlorides.[86] We hypothesized that conditions that worked for aryl chlorides might prove applicable to the aryl triflate in our compounds. Gratifyingly the cyanation was successfully carried out to complete conversion with these conditions using palladium(II) trifluoroacetate, 2-di-*tert*-butylphosphino-1,1'-binapthyl, zinc cyanide, and zinc dust in dimethyl acetamide. These conditions consistently provided desired cyano compound in ~40% isolated yield. The zinc metal provides a reductant to form the desired Pd(0) *in situ*, and the reaction is sensitive to perturbation with replacement of the

[86] Littke, A.; Soumeillant, M.; Kaltenbach III, R. F.; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711–1714.

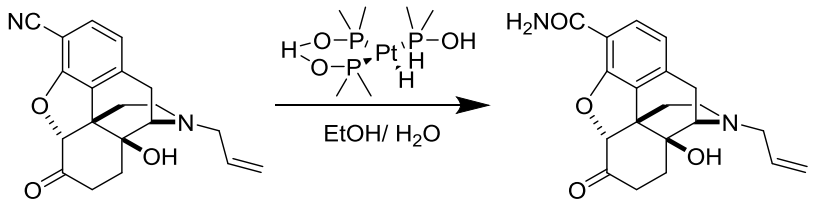


Scheme 2.12 Successful Cyanation Reaction and Hydrolysis

2-di-tertbutylphosphino-1,1'-binapthyl ligand with tricyclohexylphosphine ligand resulting in no reaction, implying that a large bulky phosphine ligand is necessary for the reaction to proceed. Work by Buchwald and Barder indicates that the 2-di-*tert*-butylphosphino-1,1'-binapthyl ligand is substantially more resistant to oxidation than ligands wherein the phosphorous is more accesible, such as triphenyl or tricyclohexyl phosphine, and we hypothesize that this oxidation resistance is the root of the importance of the ligand to the stability of the complex and a successful reaction.[87] Replacement of palladium (II) trifluoroacetate with palladium (II) acetate was found to have negligible impact on yield (Table 2.5, entry 18) with a small amount of side product formed that is not observed in the palladium (II) trifluoroacetate reaction. Given the experience of the potassium cyanide cleaving the triflate and the report of inferior yields with other cyanide sources by Littke et al,[86] zinc(II) cyanide was deemed the best choice. In addition to experimenting with the ligand and palladium source, we also studied a competition experiment between (-)-naloxone triflate and (+)-hydromorphone triflate in order to elucidate the nature of (-)-naloxone triflate resistance to coupling. In this experiment, we found that contrary to expectation, the (-)-naloxone triflate successfully reacted with 85% conversion by NMR. The reaction was then run with (-)-naloxone triflate alone which provided the nitrile compound in 33% isolated yield (Table 2.5, entry 19).

[87] Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

The resulting nitriles were then hydrolyzed catalytically using Parkin's platinum catalyst (Scheme 2.12).[88] In the case of nitrile **175** the hydrolysis was slow, but the starting nitrile was easily recovered, and the reaction was stopped at 40% conversion after two weeks. Hypothesizing that a large excess of water would speed the reaction, the reaction was run again with nitrile **177** in 1:1 ethanol : water which led to completion of the hydrolysis in 4 hours and provided carboxamide **178** in 78% yield.



177 **178**

Scheme 2.13 Hydrolysis of (+)-naloxone nitrile

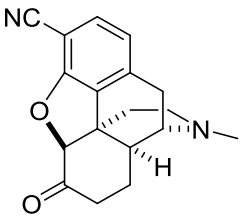
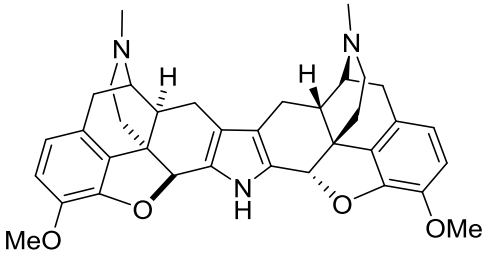
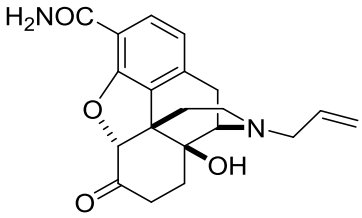
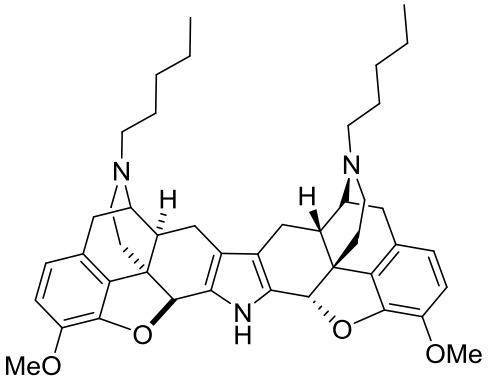
Biological testing of these compounds is on progress, and a comparison of the biological activity of the carboxamide **176** to hydromorphone (**117**) and that of (-)-naloxone to (-)-naloxone derivative **178** will provide insight into whether the amide is a suitable replacement for the 3-phenol.

2.5 Conclusions

We have synthesized a variety of morphinan derivatives and while we have some promising lead structures that appear to be TLR4 antagonists, we are interested in a better understanding of the structure-activity relationship of this class of molecules. One of the important issues that we wish to address is the reproducibility of the biological data. Given that the assay used requires agonism to induce a TLR4 response followed by antagonism with our potential inhibitors, one strategy we could pursue for future research is the development of

[88] (a) Parkins, A. W. *Platin. Met. Rev.* **1996**, *40*, 169–174. (b) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657–8660.

morphinan agonists for use in the assay. The structural difference between lipid A and the morphinans is striking and it could be that TLR4 agonism by the morphinans occurs in a substantially different manner than that with lipid A. In addition, the synthesis of other polar groups, such as amines, at the 3-position of the morphinan skeleton is another potentially fruitful avenue to pursue as such groups could mimic the polarity of the hydroxyl group yet not have the same metabolic profile. Further, the (+)-thevinone skeleton is a promising platform for further optimization, as are the (+)-naloxone-like compounds with longer *N*-alkyl chains. Once an optimized assay is developed, we will test these as well as compounds currently synthesized that are yet untested as shown in Table 2.4.

Entry	Structure	Entry	Structure
1		5	
2		6	

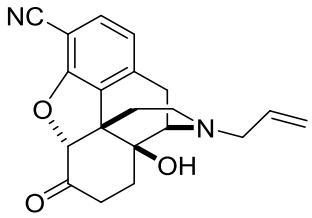
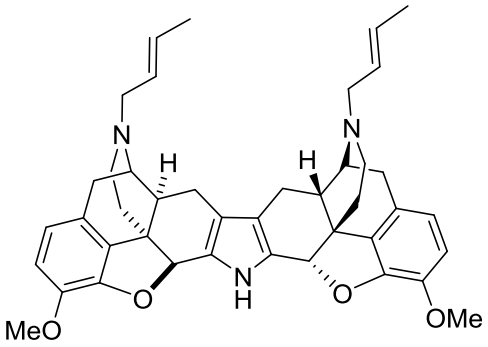
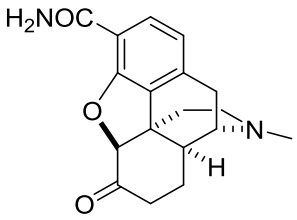
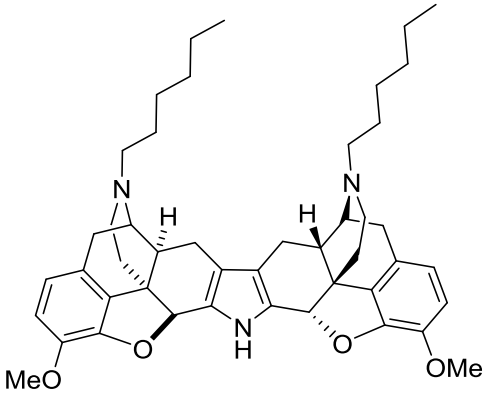
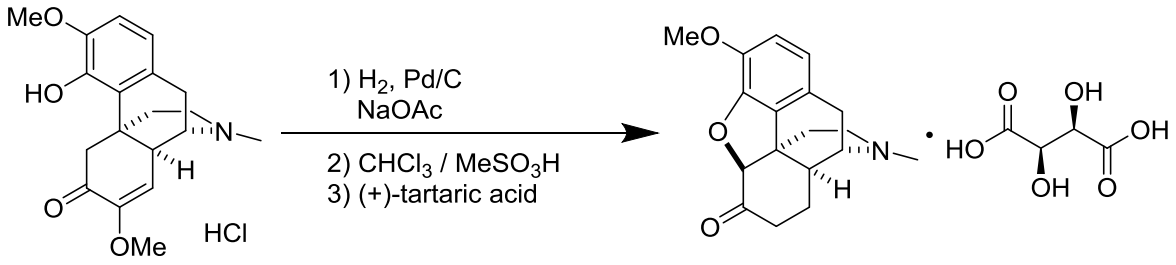
3		7	
4		8	

Table 2.4 Untested compounds

2.6 Experimental Section

General Information

^{1}H NMR spectroscopy was performed at 500 MHz in $CDCl_3$ using residual chloroform as an internal standard (7.27 ppm). ^{13}C NMR spectroscopy was performed at 75 MHz or at 100 MHz in $CDCl_3$ using residual chloroform as an internal standard (77.26 ppm for the central peak).**Error! Bookmark not defined.** FT-IR spectra were collected as thin films on sodium chloride plates. Exact mass was determined using electrospray ionization. Dichloromethane, dimethylformamide, methanol, and chloroform were distilled from calcium hydride when needed. Dimethylacetamide was distilled from barium oxide and stored over 4Å molecular sieves. Alkyl halides were distilled from calcium hydride and stored over 4Å molecular sieves.



153 **129**

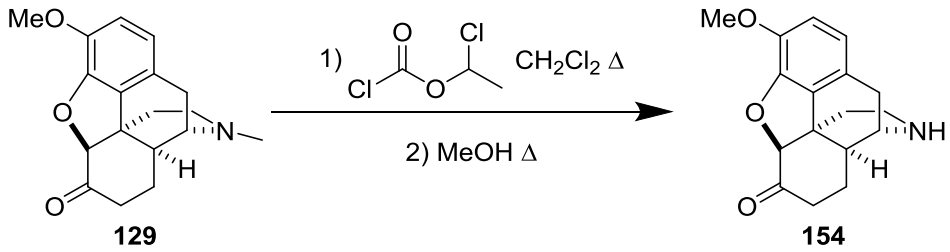
(+)-hydrocodone (129)

(+)-Hydrocodone **129** was prepared from commercially available (-)-sinomenine (**153**) over two steps using the Rice procedure.[69] (-)-Sinomenine (137.3g, 342mmol), 5% Pd/C (3.64g, 1.708mmmol, 0.05 equivs), and NaOAc (28.0g, 342mmol, 1 equiv) were combined in a 2 l Parr Shaker bottle and water added (0.7 l). The bottle was placed in the Parr and vacuum/ H_2 purged by placing under vacuum and then filling with H_2 (2x) and then placed under a 30 psi H_2 atmosphere. The Parr Shaker was turned on and the reaction shaken until H_2 uptake ceased (~2.5

hours). The Parr Shaker was turned off and the bottle removed. The solution was filtered through a Celite plug, neutralized with 47 ml concentrated ammonium hydroxide, and extracted with chloroform (4x 75 ml). The combined organic extracts were washed with water (1x 125 ml), and the water layer was back-extracted with chloroform (75 ml). The combined organic layers were concentrated to a viscous oil then taken up in 700 ml of chloroform. Methanesulfonic acid (450 ml) was slowly poured into the stirring chloroform at a rate such that slight warming was observed (~5 min). Once the addition was complete, a reflux condenser was added and the biphasic solution was warmed to 60° C for two hours. After two hours the reaction was allowed to cool. The solution was then poured over 800 g of ice, which melts as the addition proceeds. The resulting biphasic mixture was poured slowly into 700 ml concentrated ammonium hydroxide and 140 ml chloroform chilled in a dry ice bath with overhead mechanical stirring. The dry ice bath was removed upon completion of the addition and the mixture was stirred for 1 hour and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with chloroform (2x 100 ml). The combined organic layers were washed with 1M sodium hydroxide (270 ml). The sodium hydroxide layer was back-extracted with chloroform (50 ml). The organic layers were combined and washed with water (2x 130 ml). The combined organic layers were filtered through Celite and partially concentrated. The resulting solution was diluted with ethanol and then concentrated to yield a light-brown solid material. The solid was taken up in 400 ml of 70% ethanol : water with 51.2 g (341mmol) of (+)-tartaric acid and heated to dissolution while being stirred. This homogenous solution was then allowed to cool to room temperature with stirring, then placed in a cold room (~4° C) and the stirring continued overnight. The resulting solid was filtered and the solid material was rinsed with ethanol then diethylether to provide white solid (75 g). The mother liquor was recrystallized and yielded an

additional 10 g of material as the tartrate salt (85 g total, 55% yield over two steps). The material was characterized as the free base by taking up a sample in chloroform, washing with sodium hydroxide (1M), then water, drying over magnesium sulfate, filtering and concentrating to provide the freebase.

R*f* = 0.28 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 4.67 (s, 1H), 3.90 (s, 3H), 3.18 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.03 (d, *J* = 18.4 Hz, 1H), 2.61-2.53 (m, 2H), 2.46-2.27 (m, 4H), 2.43 (s 3H), 2.19 (td, *J* = 12.1, 3.6 Hz, 1H), 2.07 (td, *J* = 12.2, 4.8 Hz, 1H), 1.90-1.77, (m, 3H) 1.26 (qd, *J* = 13.3, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.12, 145.62, 143.06, 127.47, 126.52, 119.99, 114.70, 91.64, 59.43, 56.97, 47.15, 47.06, 43.14, 42.98, 40.48, 35.79, 25.81, 20.18; IR (thin film) 2929, 2838, 2799, 1726, 1636, 1609, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^{+}$: 300.1595; found 300.1600.



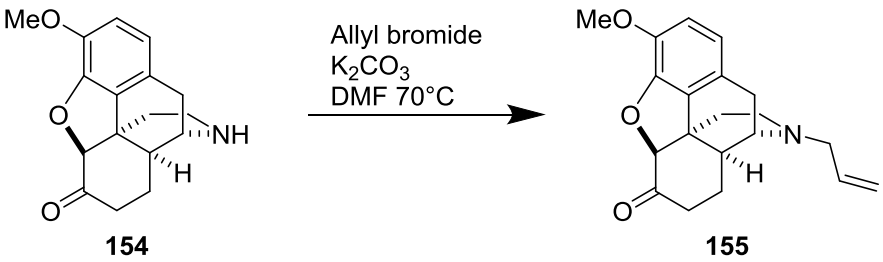
129 **154**

(+)-Norhydrocodone (154)

To a stirring suspension of (+)-hydrocodone (**129**) (15.67 g, 52.3 mmol) in distilled dichloromethane (374 ml) was added 1-chloroethylchloroformate (25.7 ml, 236 mmol). Once addition was complete, the reaction was warmed to reflux. After 42 hours, all (+)-hydrocodone had been consumed as indicated by TLC. The clear solution was concentrated to a yellow

viscous oil. This was taken up in methanol and gently refluxed overnight. The reaction was concentrated at reduced pressure to one third the original volume and chloroform added. The organic layer was washed with saturated sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate and concentrated to yield a yellow foam. The product was taken up in isopropanol (~200 ml, sufficient to completely dissolve the material). Concentrated HCl was added dropwise (4.9 ml, ~1.1 equiv) with stirring. Crystals formed almost immediately and the suspension was chilled and stirred overnight in a cold room (~4° C). The crystals were filtered and rinsed with chilled isopropanol followed by diethyl ether. The resulting solid was dried by suction, followed by high vac to provid (+)-norhydrocodone (**154**) as an off-white solid (13.61 g, 81% yield). The material was characterized as the free base by taking up a sample in chloroform, washing with sodium hydroxide (1M), then water, drying over magnesium sulfate, filtering and concentrating to provide the freebase.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.72 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.65 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.64 (s, 1H), 3.91 (s, 3H), 3.47-3.42 (m, 1H), 2.92-2.8 (m, 2H), 2.78-2.68 (m, 2H), 2.51 (dt, *J* = 12.8, 3.6 Hz, 1H), 2.46-2.33 (m, 2H) 1.93 (td, *J* = 12.2, 4.9 Hz, 1H), 1.89-1.78 (m, 4H), 1.20 (qdd, *J* = 13.1, 3.7, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.94, 145.64, 143.07, 127.54, 126.66, 120.03, 114.74, 91.81, 56.96, 52.57, 48.01, 43.38, 40.53, 39.24, 36.33, 31.20, 26.09; IR (thin film): 2916, 2840, 1727, 1607, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 286.1438; found 286.1443.

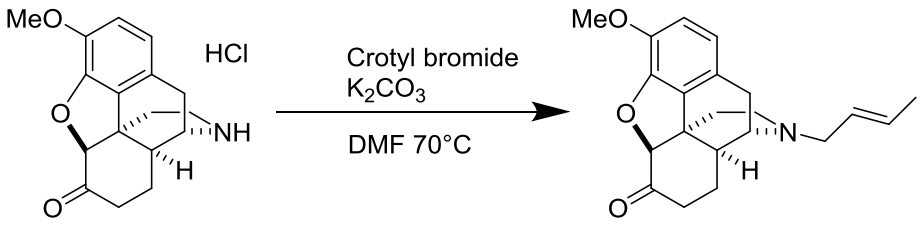


154 **155**

Ketone (155)

A solution of allyl bromide (1.264 ml, 14.61 mmol), (+)-norhydrocodone (**154**) (3.79 g, 13.28 mmol), and potassium carbonate (2.019 g, 14.61 mmol, as a suspension) in dimethylformamide (66.4 ml) was warmed to 70° C and stirred for 17 hours. The reaction was cooled, diluted with water, and extracted with chloroform (3x). The organic layers were combined, washed with brine, and dried over magnesium sulfate. The crude material was purified by flash Chromatography (gradient of 5-10% methanol : 1% ammonium hydroxide : chloroform) to provide ketone **155** as an oil (3.68 g, 85% yield).

R*f* = 0.26 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 5.87 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H), 5.23 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.16 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.66 (s, 1H), 3.90 (s, 3H), 3.29 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.24 – 3.12 (m, 2H), 2.96 (d, *J* = 18.4 Hz, 1H), 2.66 (ddd, *J* = 12.1, 4.7, 1.8 Hz, 1H), 2.58 (dt, *J* = 12.8, 3.5 Hz, 1H), 2.45 – 2.27 (m, 3H), 2.15 (td, *J* = 12.0, 3.2 Hz, 1H), 2.05 (td, *J* = 12.1, 4.6 Hz, 1H), 1.87 – 1.77 (m, 2H), 1.25 (qd, *J* = 13.3, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.14, 145.65, 143.06, 136.00, 127.67, 126.56, 119.96, 117.79, 114.77, 91.67, 58.45, 57.15, 57.00, 47.65, 45.20, 42.86, 40.48, 35.75, 25.85, 20.88; IR (thin film) 2918, 2836, 1730, 1640, 1611, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 326.1751; found 326.1756.



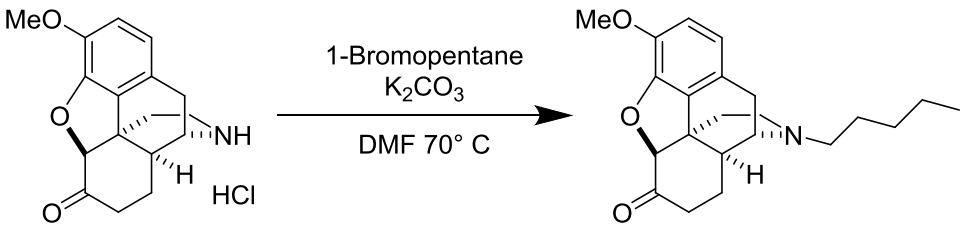
154 **156**

Ketone (156)

A solution of crotyl bromide (0.740 ml, 7.19 mmol), (+)-norhydrocodone HCl (**154**) (2.104 g, 6.54 mmol), and potassium carbonate (1.898 g, 13.73 mmol, as a suspension) in dimethylformamide (32.7 ml) was warmed to 70 °C and stirred for 17 hours. The reaction was diluted with ethyl acetate and washed with water (3x) to remove dimethylformamide. The organic layer was then washed with brine and dried over magnesium sulfate. Filtration and concentration under reduced pressure provided a brown oil. This material was purified by Flash Chromatography (5% methanol : 0.2% ammonium hydroxide : chloroform) to provide ketone **156** as a yellow oil (1.846 g, 83% yield; 5 : 1 mixture of alkene diasteromers).

R*f* = 0.34 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.73-6.69 (m, 1H, major + minor), 6.68-6.61 (m, 1H, major + minor), 5.70-5.61 (m, 1H, major + minor), 5.57-5.48 (m, 1H, major + minor), 4.67 (s, 1H, major + minor), 3.91 (s, 3H), 3.34-3.28 (m, 1H, major + minor), 3.25-3.07 (m, 2H, major + minor), 2.96 (d, *J* = 18.4 Hz, 1H major + minor), 2.72-2.65 (m, 1H, major + minor), 2.63-2.55 (m, 1H, major + minor), 2.48-2.27 (m, 3H, major + minor), 2.22-2.03 (m, 2H, major + minor), 1.73 (d, *J* = 6.2 Hz, 2.22H, major), 1.70 (d, *J* = 6.9 Hz, 0.81H, minor); ^{13}C NMR (101 MHz, $cdcl_3$) (major + minor) δ 208.18, 145.60, 143.05, 127.64, 119.94, 114.61, 91.67, 57.48, 57.14, 56.94, 56.91, 53.68, 51.38, 47.68, 47.62, 45.29, 45.18, 42.79, 40.48, 35.67, 25.84, 20.95, 20.71, 18.13, 13.47; IR (thin film):

2918, 2834, 1728, 1636, 1609, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 340.1908; found 340.1922.



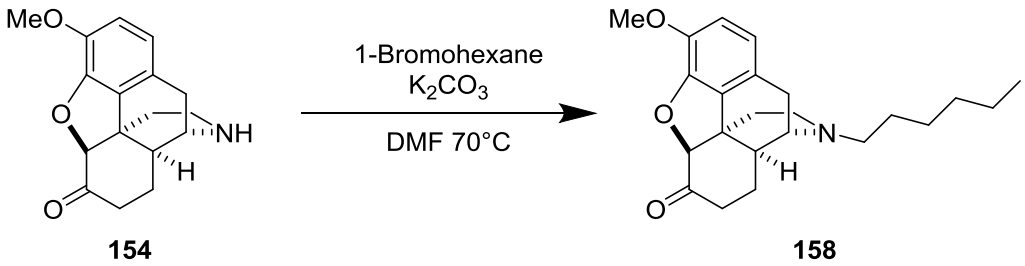
154 **157**

Ketone (157)

A solution of bromopentane (0.915 ml, 7.38 mmol, 1.1 equiv), (+)-norhydrocodone HCl (**154**) (2.158 g, 6.71 mmol), and potassium carbonate (1.946 g, 14.08 mmol, as a suspension) in dimethylformamide (33.5 ml) was warmed to 70 °C and stirred for 17 hours. The reaction was diluted with ethyl acetate and washed with water (3x) to remove dimethylformamide. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a brown oil. The crude material was purified by Flash Chromatography (3% methanol : 0.2% ammonium hydroxide : chloroform) to provide ketone **157** as an oil (2.089 g, 88% yield).

R*f* = 0.32 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.69 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.65 (s, 1H), 3.89 (s, 3H), 3.28 – 3.23 (m, 1H), 2.96 (d, *J* = 18.2 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.60 – 2.53 (m, 1H), 2.53 – 2.26 (m, 5H), 2.13 (tt, *J* = 11.9, 2.3 Hz, 1H), 2.05 (tdd, *J* = 12.2, 4.5, 1.8 Hz, 1H), 1.81 (m, 2H), 1.49 (p, *J* = 7.7 Hz, 2H), 1.39 – 1.18 (m, 5H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.18, 145.62, 142.99, 127.70, 126.68, 119.90, 114.69, 91.68, 57.30, 56.98, 55.24,

47.71, 45.42, 42.87, 40.49, 35.86, 30.03, 27.77, 25.91, 22.87, 20.85, 14.32; IR (thin film) 2929, 2866, 1730, 1637, 1611, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 356.2221; found 356.2226.



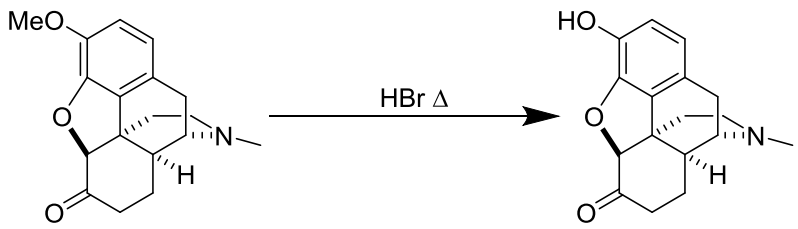
154 **158**

Ketone (158)

A solution of bromohexane (1.010 ml, 7.19 mmol), (+)-norhydrocodone (**154**) (2.104 g, 6.54 mmol), and potassium carbonate (1.898 g, 13.73 mmol, as a suspension) in dimethylformamide (32.7 ml) was warmed to 70 °C and stirred for 48 hours. The reaction was diluted with ethyl acetate and washed with water (3x) to remove dimethylformamide. The organic layer was washed with brine and dried over magnesium sulfate. Filtration and concentration under reduced pressure provided a brown oil. This material was purified by Flash Chromatography (5% methanol : 0.2% ammonium hydroxide : chloroform) to provide ketone **158** as a yellow oil (2.06 g, 85% yield).

R*f* = 0.32 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 4.66 (s, 1H), 3.91 (s, 3H), 3.29-3.25 (m, 1H), 2.97 (d, *J* = 18.4 Hz, 1H), 2.68-2.63 (m, 1H), 2.61-2.55 (m, 1H), 2.54-2.28 (m, 5H), 2.14 (td, *J* = 12.0, 3.2 Hz, 1H), 2.06 (td, *J* = 12.0, 4.4 Hz, 1H), 1.88-1.78 (m, 2H), 1.53-1.46 (m, 2H), 1.37-1.20 (m, 7H), 0.90 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.25,

145.63, 143.03, 127.70, 126.66, 119.94, 114.67, 91.70, 57.30, 56.99, 55.29, 47.73, 45.48, 42.85, 40.51, 35.85, 32.06, 28.03, 27.54, 25.93, 22.90, 20.85, 14.33; IR (thin film) 2929, 2856, 1726, 1635, 1608, 1502, 1438 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 370.2377; found 370.2382.



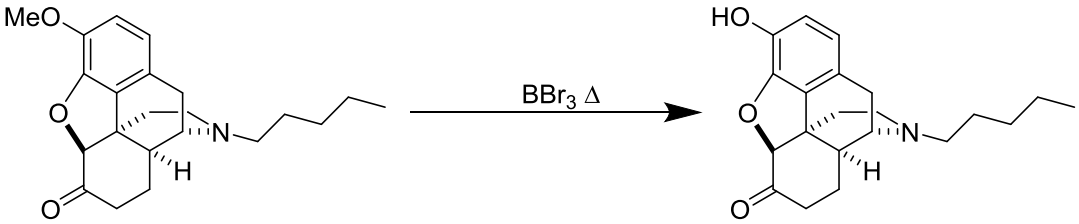
129 **116**

(+)-Hydromorphone (116)

A solution of (+)-hydrocodone (**129**) (6.836 g, 22.84 mmol) in concentrated hydrobromic acid (48%, 45.7 ml) was warmed to reflux. The reaction was cooled to room temperature after 2 hours and chilled in an ice bath. Ammonium hydroxide was added to bring the pH to ~9. Sodium chloride was added to the solution and the solution transferred to a separatory funnel. The aqueous layer was extracted with chloroform (3x) followed by 3:1 chloroform : isopropanol. The combined organic layers were dried over magnesium sulfate and concentrated to dryness under reduced pressure. The material was dissolved in minimal ethanol and hydrogen chloride (1.25M in ethanol) was added dropwise. A solid precipitated out and the suspension was warmed to reflux. Absolute ethanol added until the solid went into solution. The suspension was allowed to cool to room temperature with stirring and then placed in a -20° C freezer for two days. Filtration provided an off-white solid. The solid material was freebased using sodium bicarbonate and the resulting freebase was purified by Flash chromatography (gradient of 5%-15% methanol : 0.2%

ammonium hydroxide : chloroform) to provide (+)-hydromorphone (**116**) as a white amorphous solid (1.776 g, 27% yield).

R*f* = 0.20 (10% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.64 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 4.59 (s, 1H), 3.18 (dd, *J* = 5.7, 2.9 Hz, 1H), 2.97 (d, *J* = 18.4 Hz, 1H), 2.56 (ddt, *J* = 12.3, 7.8, 2.7 Hz, 3H), 2.40 (s, 3H), 2.37 – 2.31 (m, 2H), 2.27 (dd, *J* = 18.5, 5.6 Hz, 1H), 2.18 (td, *J* = 12.1, 3.6 Hz, 1H), 2.06 (td, *J* = 12.2, 4.8 Hz, 1H), 1.84 – 1.73 (m, 2H), 1.28 – 1.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.60, 144.32, 139.62, 126.92, 124.84, 120.04, 117.86, 100.15, 91.30, 59.30, 47.04, 46.99, 42.93, 42.69, 40.44, 35.56, 25.55, 20.12; IR (thin film): 3059, 2928, 1725, 1610, 1502 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 286.1438 found 286.1438.



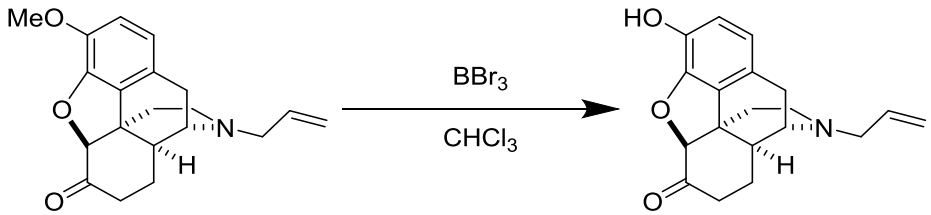
157 **119**

Ketone (119)

To a stirring solution of boron tribromide (0.442 ml, 4.68 mmol) in chloroform (2.3ml, 2.1M) chilled in an ice bath was added ketone **157** (0.396 g, 1.114 mmol) in chloroform (2.79 ml) dropwise over 10 minutes. A yellow precipitate formed upon the addition of the substrate. After 1 hour the reaction was quenched by pouring it slowly into a chilled (0 C) solution of saturated tris base. The layers were separated and the aqueous layer extracted with chloroform (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, and

concentrated under reduced pressure to yield crude material as a yellow foam. The crude material was purified by Flash Chromatography (1% triethyl amine : 1% methanol : chloroform) to provide ketone **119** as a yellow foam (147 mg, 39% yield).

R*f* = 0.27 (2% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.64 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 1H), 3.27 (dd, *J* = 5.5, 2.8 Hz, 1H), 2.91 (d, *J* = 18.3 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.60 – 2.52 (m, 1H), 2.52 – 2.41 (m, 2H), 2.40 – 2.22 (m, 3H), 2.09 (dtd, *J* = 35.6, 12.2, 3.9 Hz, 2H), 1.83 – 1.70 (m, 2H), 1.47 (p, *J* = 7.5 Hz, 2H), 1.35 – 1.15 (m, 5H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101MHz, $CDCl_3$) δ 208.75, 144.34, 139.48, 127.11, 124.96, 119.96, 117.81, 91.32, 57.06, 55.08, 47.57, 45.43, 42.50, 40.45, 35.56, 29.93, 27.38, 25.63, 22.73, 20.63, 14.22; IR (thin film) 3447, 2933, 2817, 1726, 1622 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 342.2064; found 342.2069.



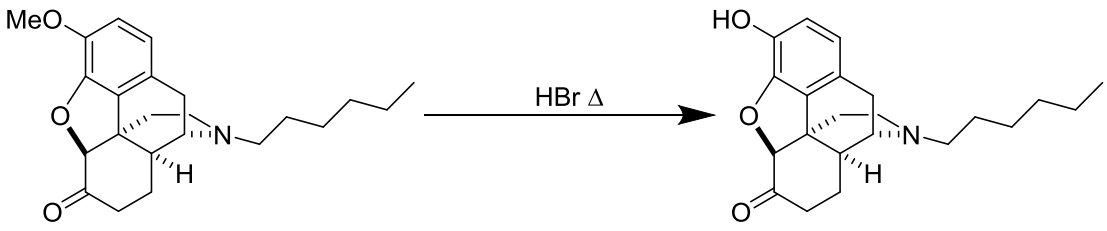
155 **118**

(+)-14-Deshydroxynaloxone (118)

To a solution of boron tribromide (0.609 ml, 6.44 mmol) in chloroform (3.1 ml, 2.1M), chilled in an ice bath, was added ketone **155** (.699 g, 2.148 mmol) in chloroform (5.37 ml) dropwise. Once addition was complete, the reaction was quenched by slow addition of chilled water, basified with concentrated ammonium hydroxide, and saturated with sodium chloride. The reaction mixture was extracted with chloroform (3x), the combined organic layers were dried over

magnesium sulfate and concentrated under reduced pressure to yield a yellow solid. The solid was purified by Flash Chromatography (gradient of 1-20% methanol : 1% triethylamine : chloroform) to provide (+)-14-deshydroxynaloxone (**118**) as a white foam (190 mg, 28.4% yield).

R*f* = 0.3 (5% methanol : 1% trithethylamine : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.71 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 5.96-5.85 (m, 1H), 5.28 – 5.20 (m, 1H), 5.17 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.67 (s, 1H), 3.38-3.33 (m, 1H), 3.22 (qd, *J* = 13.4, 6.6 Hz, 2H), 2.97 (d, *J* = 18.5 Hz, 1H), 2.76-2.71 (m, 1H), 2.68-2.62 (m, 1H), 2.42-2.27 (m, 3H), 2.22-2.09 (m, 2H), 1.87-1.75 (m, 2H), 1.29-1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.94, 145.64, 143.07, 127.54, 126.66, 120.03, 114.74, 91.81, 56.96, 52.57, 48.01, 43.38, 40.53, 39.24, 36.33, 31.20, 26.09; IR (thin film) 2921, 1425, 1612, 1502, 1450 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^{+}$: 312.1601; found 312.1595.



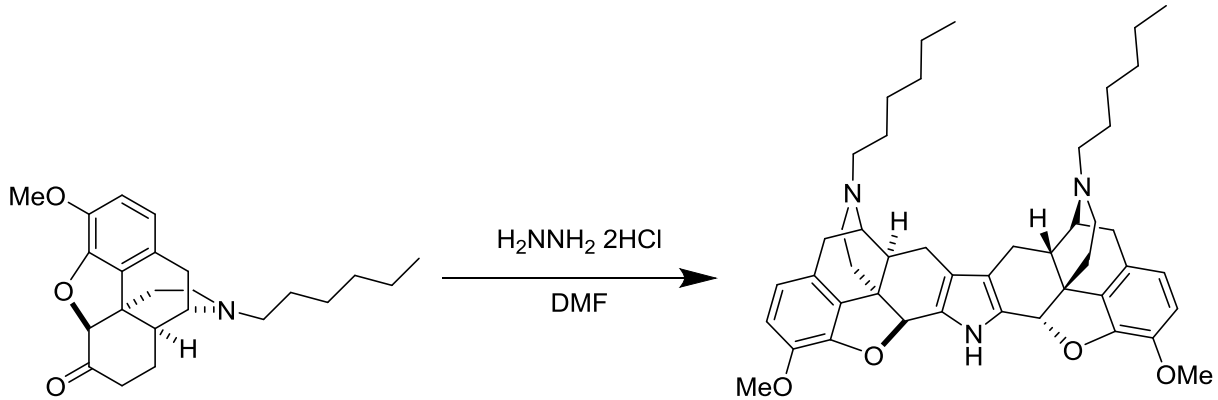
158 **171**

Ketone (171)

A solution of ketone **158** (0.191 g, 0.470 mmol) in concentrated hydrobromic acid (2.83 ml) was warmed to reflux. After 30 minutes the reaction was cooled to room temperature. The reaction mixture was diluted with methanol and concentrated under reduced pressure (2x) to yield a brown oil. The oil was dissolved in chloroform and washed with saturated sodium bicarbonate.

The aqueous layer was back extracted with chloroform (2x), and the organic layers were combined and dried over magnesium sulfate. Concentration under reduced pressure provided crude material which was purified by Flash Chromatography (gradient from 1-5% methanol : 0.2% ammonium hydroxide : chloroform) to provide ketone **171** as a yellow film (46 mg, 28% yield).

R*f* = 0.29 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 4.66 (s, 1H), 3.35 – 3.30 (m, 1H), 2.97 (d, *J* = 18.3 Hz, 1H), 2.75 – 2.69 (m, 1H), 2.66 – 2.59 (m, 1H), 2.52 (td, *J* = 7.3, 3.7 Hz, 3H), 2.43 – 2.38 (m, 2H), 2.38 – 2.28 (m, 1H), 2.22 – 2.08 (m, 2H), 1.88 – 1.80 (m, 1H), 1.80 – 1.75 (m, 1H), 1.55-1.45 (m, 3H), 1.35 – 1.20 (m, 6H), 0.92 – 0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.81, 144.27, 139.01, 127.23, 120.30, 117.74, 91.70, 57.26, 56.34, 55.25, 47.77, 45.54, 42.65, 40.53, 35.67, 32.01, 27.79, 27.52, 25.70, 22.87, 20.83, 14.30; IR (thin film): 2918, 2836, 1730, 1640, 1611, 1503, 1439 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 356.2221; found 356.2226.

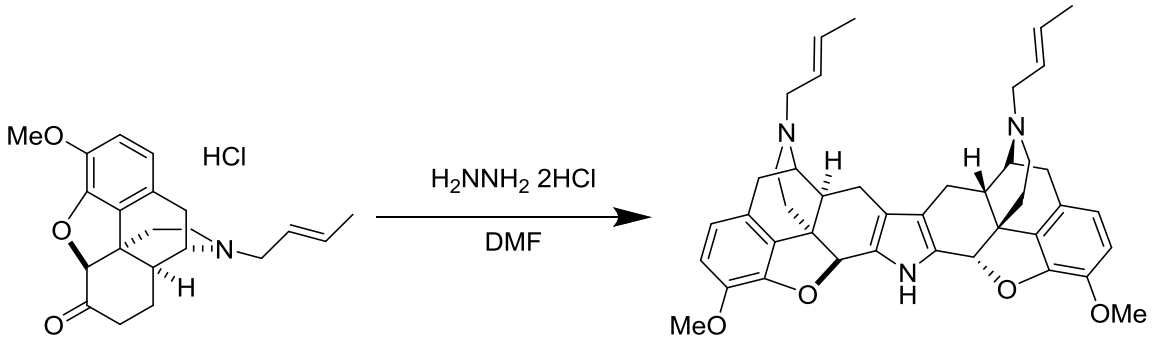


158 **162**

Pyrrole (162)

To a stirring solution of ketone **158** (0.209 g, 0.556 mmol) in dimethylformamide was added hydrazine dihydrochloride (0.146 g, 1.390 mmol). The resulting solution was warmed to 50° C. After three days the starting material had been consumed as, indicated by TLC, and the reaction was allowed to cool to room temperature, diluted with ethyl acetate, and washed with saturated sodium bicarbonate, water (3x), and brine. The crude material was purified by flash Chromatography (5% methanol : 0.2% ammonium hydroxide : chloroform) to provide pyrrole **162** as a yellow film (112 mg, 61% yield).

R*f* = 0.31 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.58 (d, *J* = 8.3 Hz, 2H), 5.40 (s, 2H), 3.80 (s, 6H), 3.22 (d, *J* = 5.8 Hz, 2H), 2.99 – 2.86 (m, 2H), 2.64 – 2.30 (m, 10H), 2.28 – 2.10 (m, 4H), 1.98 – 1.74 (m, 10H), 1.45 (d, *J* = 8.1 Hz, 4H), 1.35 – 1.23 (m, 12H), 0.91 – 0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.75, 143.03, 129.50, 127.58, 125.90, 118.54, 118.23, 112.56, 86.21, 57.47, 56.26, 55.19, 45.54, 44.41, 41.42, 36.14, 32.06, 27.94, 27.55, 22.90, 21.61, 21.26, 14.32; IR (thin film) 3394, 2925, 2851, 1637, 1611, 1506, 1443 cm^{-1}; HRMS (ESI) *m/z* calc'd for C46H57N3O4 $[M+H]^{+}$: 718.4579; found 718.4584.

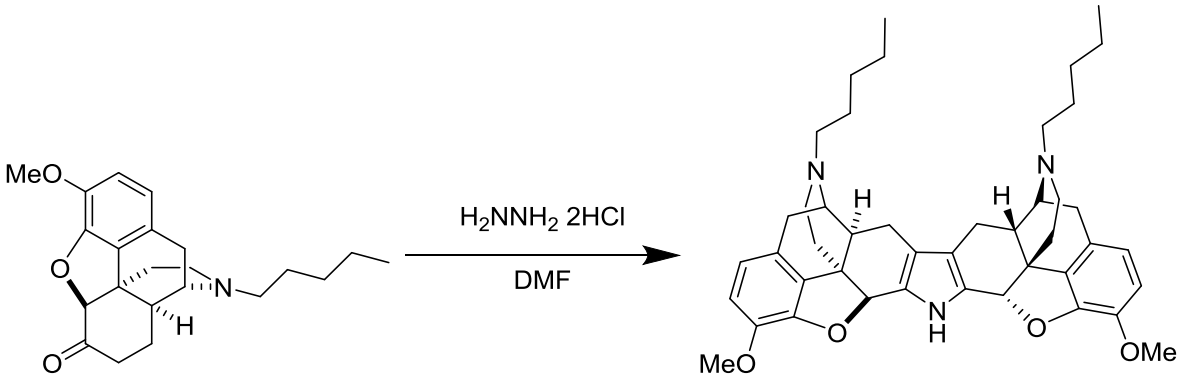


156 **160**

Pyrrole (160)

To a stirring solution of ketone **156** (0.209 g, 0.556 mmol) in dimethylformamide was added hydrazine dihydrochloride (0.146 g, 1.390 mmol). The resulting solution was warmed to 50° C. After three days the starting material had been consumed, as indicated by TLC, and the reaction was cooled to room temperature. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water (3x), and brine. The crude material was purified by Flash Chromatography (5% methanol : 0.2% ammonium hydroxide : chloroform) to provide pyrrole **160** as a yellow film (61 mg, 34% yield; mixture of cis / trans diastereomers).

R*f* = 0.28 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) (major + minor) δ 8.12 (s, 1H), 6.70-6.65 (m, 2H, major + minor), 6.64-6.59 (m, 2H, major + minor), 5.67-5.58 (m, 2H, major + minor), 5.55-5.46 (m, 2H, major + minor), 5.41 (s, 2H, major + minor), 3.82 (s, 6H, major + minor), 3.30-2.87 (m, 8H, major + minor), 2.66-2.58 (m, 2H, major + minor), 2.52-2.11 (m, 4H, major + minor), 1.98-1.74 (m, 6H, major + minor), 1.73-1.66 (m, 6H, major + minor); ^{13}C NMR (75 MHz, $CDCl_3$) (major + minor) δ 144.74, 143.06, 129.47, 127.45, 125.87, 118.57, 118.21, 112.65, 86.18, 57.44, 57.34, 56.27, 51.34, 45.10, 44.36, 44.31, 41.22, 35.92, 21.55, 21.31, 18.09, 13.44; IR (thin film) 3387, 3022, 2914, 2836, 1637, 1611, 1506, 1443 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^{+}$: 340.1914; found 340.1908.



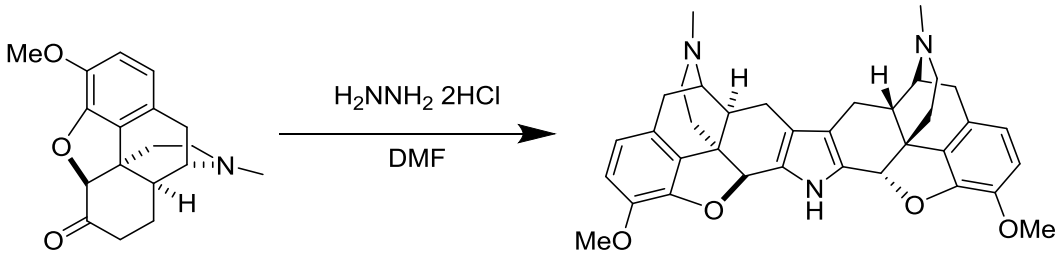
157 **161**

Pyrrole (161)

To a stirring solution of ketone **157** (0.224 g, 0.572 mmol) in dimethylformamide was added hydrazine dihydrochloride (0.150 g, 1.429 mmol). The resulting solution was warmed to 50° C. After three days the starting material had been consumed according to TLC. The reaction was cooled to room temperature, diluted with ethyl acetate, and washed with saturated sodium bicarbonate, water (3x), and brine. The crude material was purified by Flash Chromatography (5% methanol : 0.2% ammonium hydroxide : chloroform) to provide pyrrole **161** as a yellow amorphous solid (120 mg, 61% yield).

R*f* = 0.35 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz CDCl3) δ 8.12 (s, 1H), 6.67 (d, *J* = 8.2 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 5.41 (s, 2H), 3.81 (s, 6H), 3.27 – 3.21 (m, 2H), 3.01 – 2.88 (m, 2H), 2.64 – 2.56 (m, 2H), 2.55 – 2.42 (m, 6H), 2.37 (ddd, *J* = 11.9, 5.6, 2.7 Hz, 2H), 2.24 (td, *J* = 12.2, 3.7 Hz, 2H), 2.17 (dd, *J* = 15.0, 5.7 Hz, 2H), 1.92 (td, *J* = 12.4, 4.9 Hz, 2H), 1.87 – 1.77 (m, 4H), 1.53 – 1.43 (m, 4H), 1.39 – 1.24 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.75, 143.01, 129.51, 127.59, 125.89, 118.52, 118.22, 112.59, 86.20, 57.48, 56.25, 55.15, 45.51, 44.41, 41.42, 36.15, 30.08, 27.68,

22.87, 21.60, 21.28, 14.33; IR (thin film) 3394, 2925, 2851, 1637, 1611, 1506, 1443 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 690.4266; found 690.4271.



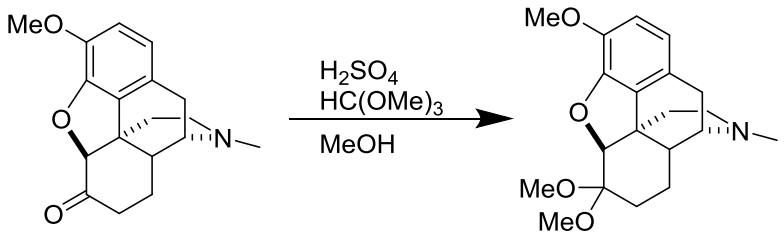
129 **159**

Pyrrole (159)

To a stirring solution of ketone **129** (0.163g, 0.544mmol) in dimethylformamide was added hydrazine dihydrochloride (0.143 g, 1.361 mmol). The resulting solution was warmed to 50° C. After three days TLC indicated the starting material had been consumed. The reaction was allowed to cool, diluted with ethyl acetate, and washed with saturated sodium bicarbonate, water (3x), and brine. The chloroform was removed under reduced pressure to provide a solid that was was purified by Flash Chromatography (5% methanol : 0.2% ammonium hydroxide : chloroform) to provide pyrrole **159** as an amorphous yellow solid (67 mg, 43% yield).

R*f* = 0.37 (10% : methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 6.67 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.2 Hz, 2H), 5.42 (s, 2H), 3.81 (s, 6H), 3.16 (dd, *J* = 6.1, 2.9 Hz, 2H), 3.04 (d, *J* = 18.5 Hz, 2H), 2.60 – 2.38 (m, 14H), 2.28 (td, *J* = 12.2, 3.7 Hz, 2H), 2.22 – 2.14 (m, 2H), 1.94 (td, *J* = 12.3, 4.8 Hz, 2H), 1.89 – 1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.75, 143.11, 129.26, 127.34, 125.88, 118.62, 118.13, 112.72, 86.11, 60.11, 56.27, 46.97, 43.76, 43.23, 41.52, 36.13, 21.52, 20.61; IR (thin film): 3123,

3046, 2928, 2844, 1699, 1632, cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 578.7206; found 578.3023.



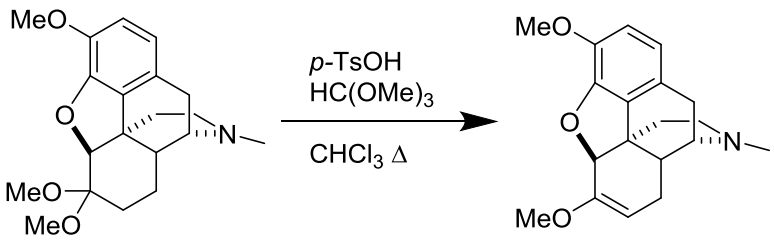
129 **163**

Ketal (163)

Concentrated sulfuric acid (1.913ml , 35.9 mmol) was added dropwise to a stirring mixture of (+)-hydrocodone (**129**) (6.32 g, 21.11 mmol) and trimethyl orthoformate (10.17 ml, 92 mmol) in distilled methanol (106 ml). The solution was then refluxed for 18 hours, after which it was cooled to ambient temperature and poured into saturated sodium carbonate. The solution was extracted with chloroform (3x) and the combined organic layers washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide ketal **163** as a yellow foam (7.27 g, 98% yield). Ketal **163** was used crude in following reactions.

R*f* = 0.33 (10% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.72 (d, *J* = 8.1 Hz, 1H), 6.63 – 6.57 (m, 1H), 4.47 (d, *J* = 1.2 Hz, 1H), 3.90 – 3.83 (m, 3H), 3.31 – 3.26 (m, 6H), 3.09 (dd, *J* = 6.2, 2.9 Hz, 1H), 2.98 (d, *J* = 18.6 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.41 (s, 4H), 2.25 (td, *J* = 12.3, 3.7 Hz, 1H), 1.94 (td, *J* = 12.4, 5.0 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.58 – 1.49 (m, 2H), 1.30 – 1.22 (m, 1H), 0.97 – 0.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.79, 141.97, 130.46, 127.85, 118.94, 114.65, 99.97, 90.03, 59.90, 57.14,

48.54, 48.44, 46.68, 43.40, 43.32, 38.40, 38.25, 24.56, 20.18, 20.03; IR (thin film): 2935, 2833, 1605, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 346.2020; found 346.2013.



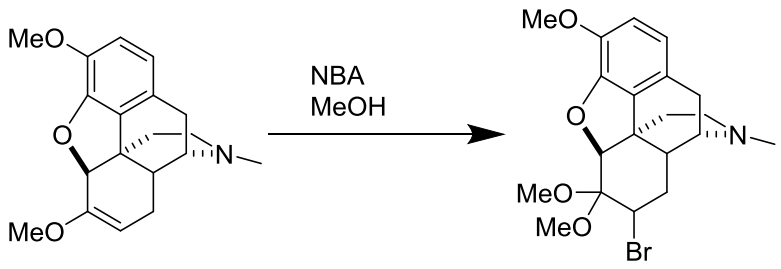
163 **164**

(+)-Dihydrothebaine (164)

To a solution of dimethyl ketal **163** (1.00 g, 2.89 mmol) and trimethyl orthoformate (0.576 ml, 5.21 mmol) in dichloroethane (28.9 ml) was added p-toluenesulfonic acid monohydrate (0.744 g, 3.91 mmol). The reaction was warmed to distilled slowly until it was reduced to half initial volume, then cooled to ambient temperature and poured into 1M potassium carbonate. The layers were separated and the aqueous layer was back extracted with chloroform (2x). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was recrystallized from ethyl acetate to provide (+)-dihydrothebaine **164** as a white solid (600mg, 66% yield).

R*f* = 0.24 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.71 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 4.85 (s, 1H), 4.74 (d, *J* = 4.8 Hz, 1H), 3.85 (s, 3H), 3.50 (s, 3H), 3.13 (dd, *J* = 6.2, 2.9 Hz, 1H), 3.02 (d, *J* = 18.5 Hz, 1H), 2.53 (dd, J = 12.3, 3.9, 1H), 2.42 (s, 3H), 2.37 (d, *J* = 6.1 Hz, 1H), 2.32 (ddd, *J* = 11.6, 5.6, 2.9 Hz, 1H), 2.26 (td, *J* = 12.2, 3.7 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.87 – 1.77 (m, 1H), 1.61 – 1.53 (m,

1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.55, 145.44, 143.32, 129.57, 127.29, 118.78, 113.85, 98.33, 88.83, 59.27, 56.76, 54.61, 46.75, 43.35, 42.77, 40.10, 36.03, 23.89, 20.48; IR (thin film): cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 314.1760; found 314.1751.



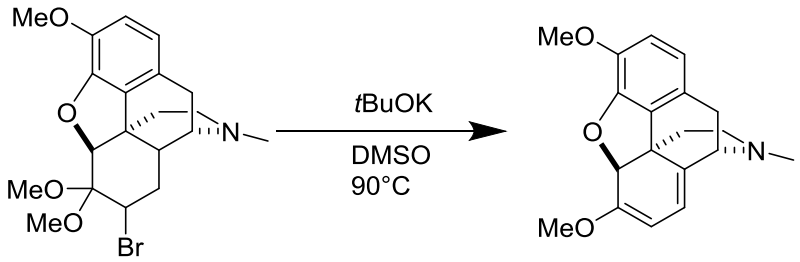
164 **165**

Ketal (165)

To a solution of 4.14 g (10.5 mmol) of (+)-dihydrothebaine (**164**) in chilled chloroform (330 ml) was added 1.6 ml of concentrated hydrobromic acid (14.31 mmol; 1.36 equiv). The mixture was shaken in a separatory funnel for 2 minutes. Chilled saturated sodium bromide solution was added and the layers separated. The aqueous was back-extracted with chloroform (2x) and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. The resulting solid was taken up in distilled methanol (70.0 ml, 0.15M) and chilled in an ethanol/ethylene glycol bath to -25 °C. Trimethyl orthoformate (2.32 ml, 21.00 mmol) was added to scavenge any residual water. A solution of N-bromoacetamide (1.449 g, 10.50 mmol) in methanol (70.0 ml) was added dropwise over 45 minutes. After 3.5 hours, the reaction was allowed to warm to room temperature and concentrated under reduced pressure. The solid was taken up in chloroform and washed with sodium hydroxide (1M). The aqueous was back extracted with chloroform (2x) and the combined organic layers were washed with water, then

brine, and dried over magnesium sulfate. Concentration provided crude material as a pale yellow foam that was purified by Flash chromatography (5% methanol : chloroform) to provide ketal **165** as an white amorphous solid (3.79 g, 79% yield).

R*f* = 0.32 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.72 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 8.2, 1H), 4.72 (s, 1H), 4.08 (s, 1H), 3.88 (s, 3H), 3.51 (s, 3H), 3.23 (s, 3H), 3.12 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.04 (d, *J* = 18.4 Hz, 1H), 2.91 (ddd, *J* = 11.3, 6.5, 2.8 Hz, 1H), 2.58 – 2.48 (m, 1H), 2.42 (s, 3H), 2.37 (dd, *J* = 18.5, 5.7 Hz, 1H), 2.22 (td, *J* = 12.2, 3.7 Hz, 1H), 1.98 (td, *J* = 12.3, 5.0 Hz, 2H), 1.71 – 1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.27, 142.21, 130.01, 126.82, 119.18, 114.96, 98.57, 91.42, 77.46, 59.33, 57.26, 51.00, 49.55, 47.09, 43.20, 43.01, 38.71, 37.07, 31.02, 20.32; IR (thin film): 2939, 2836, 1608, 1508, 1441 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 424.1124; found 424.1118.



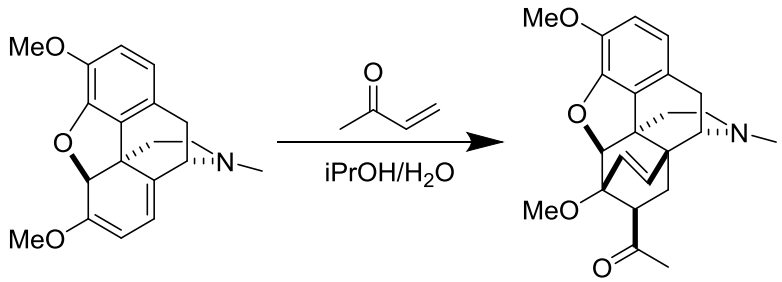
165 **166**

(+)-Thebaine (166)

A mixture of ketal **165** (1.23 g, 2.90 mmol) and potassium *t*-butoxide (1.006 g, 8.70 mmol) in distilled DMSO (30.8 ml) was warmed to 100 °C. The reaction was cooled to room temperature after 5 hours and partitioned between chloroform and brine. The aqueous layer was back extracted with chloroform (2x), and the combined organic layers were dried over magnesium

sulfate and concentrated under reduced pressure to yield a brown powder. Recrystallization from methanol : water provided (+)-thebaine (**166**) as a brown powder (600 mg, 66% yield)

R*f* = 0.28 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.67 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 5.57 (d, *J* = 6.4 Hz, 1H), 5.31 (s, 1H), 5.05 (d, *J* = 6.4 Hz, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.32 (d, *J* = 17.9 Hz, 1H), 2.82 (td, *J* = 12.8, 3.6 Hz, 1H), 2.72 – 2.56 (m, 2H), 2.47 (s, 3H), 2.21 (td, *J* = 12.6, 5.1 Hz, 1H), 1.74 (ddd, *J* = 12.6, 3.7, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.29, 144.18, 142.06, 128.31, 126.03, 117.52, 112.59, 97.07, 87.57, 58.01, 55.50, 53.35, 45.49, 42.09, 41.51, 38.84, 34.77, 22.63, 19.22; IR (thin film): 2930, 2836, 2796, 1608, 1605 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 312.1595; found 312.1609.



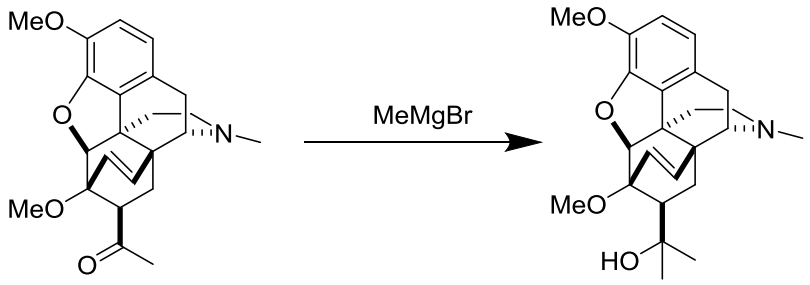
166 **169**

(+)-Thevinone (169)

(+)-Thebaine (**166**)(1.00 g, 3.21 mmol) was suspended in 2-propanol (2.318 ml) with stirring. Distilled methyl vinyl ketone (0.647 ml, 7.07 mmol, 2.2 equiv) was added followed by water (0.993 ml). The mixture was then gently warmed to reflux over 30 minutes. The reaction turned clear yellow after 1 hour at reflux and was then cooled to room temperature and stirred overnight. It was then diluted with chloroform and washed with brine. The organic layer was

dried over magnesium sulfate and concentrated under reduced pressure to yield a brown oil which was purified by Flash Chromatography (gradient of 0-1% methanol : 0.5% triethylamine : chloroform) to provide (+)-thevinone (**169**) as a clear oil (1.20 g, 98% yield).

R*f* = 0.19 (2% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.64 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.91 (d, *J* = 8.8 Hz, 1H), 5.59 (d, *J* = 8.8 Hz, 1H), 4.59 (s, 1H), 3.83 (s, 3H), 3.60 (s, 3H), 3.27-3.19 (m, 2H), 2.97-2.89 (m, 2H), 2.55-2.49 (m, 1H), 2.47-2.38 (m, 2H), 2.37 (s, 3H), 2.15 (s, 3H), 1.98 (td, *J* = 12.7, 5.6 Hz, 1H), 1.86 (ddd, *J* = 13.1, 3.9, 1.6 Hz, 1H), 1.42 – 1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.33, 148.26, 136.15, 134.28, 128.46, 126.28, 119.63, 113.75, 100.67, 95.47, 81.48, 60.21, 56.88, 53.74, 50.92, 47.74, 45.73, 43.77, 43.47, 33.73, 30.79, 30.22, 22.67; IR (thin film): 2930, 2837, 1701, 1500, 1442 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 382.2020; found 382.2018.



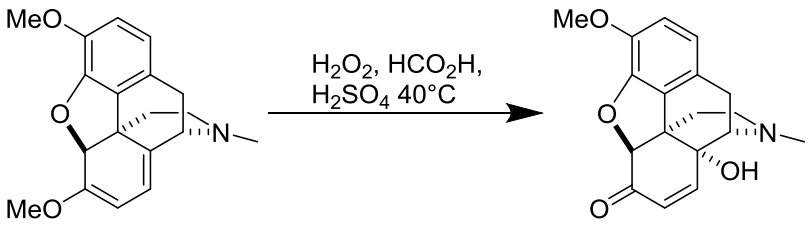
169 **170**

Alcohol (170)

A solution of methyl magnesium bromide (3M in diethylether, 0.516 ml, 1.547 mmol) was diluted with 1.5 ml of distilled diethyl ether to a concentration of 0.69M. The solution was warmed to reflux and (+)-thevinone (**169**) (0.236 g, 0.619 mmol) in 12 ml distilled diethyl ether

was added dropwise. After 24 hours, the reaction was diluted with chloroform and washed with saturated ammonium chloride solution. The pH of the aqueous layer was adjusted to ~11 with a small amount of sodium hydroxide (1M) and the layers separated. The aqueous layer was back extracted with chloroform (2x) and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to yield an off-white solid. Crude material was crystalized as the HCl salt from 2% water in isopropanol, providing alcohol **170** as a white solid (201 mg, 75% yield). Compound was characterized as free base by taking up a sample in chloroform, washing with sodium hydroxide (1M), then water, drying over magnesium sulfate, filtering and concentrating to provide the freebase.

R*f* = 0.2 (3% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.63 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 8.9 Hz, 1H), 5.45 (d, *J* = 8.9 Hz, 1H), 4.90 (s, 1H), 4.56 (d, *J* = 1.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.23 (d, *J* = 18.5 Hz, 2H), 3.14 (d, *J* = 6.4 Hz, 1H), 2.86 (dd, *J* = 12.7, 9.1 Hz, 1H), 2.57 – 2.48 (m, 1H), 2.45 – 2.31 (m, 5H), 2.04 – 1.94 (m, 2H), 1.85 (ddd, *J* = 13.2, 3.9, 1.6 Hz, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.78 (dd, *J* = 12.7, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.31, 141.97, 135.46, 134.53, 128.61, 125.11, 119.45, 114.01, 99.02, 84.40, 73.72, 60.24, 57.08, 55.47, 48.85, 47.43, 45.78, 43.80, 43.12, 33.82, 31.26, 29.00, 25.52, 22.49; IR (thin film): 3494, 2970, 2931, 1630, 1500, 1450 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 398.2333; found 398.2326

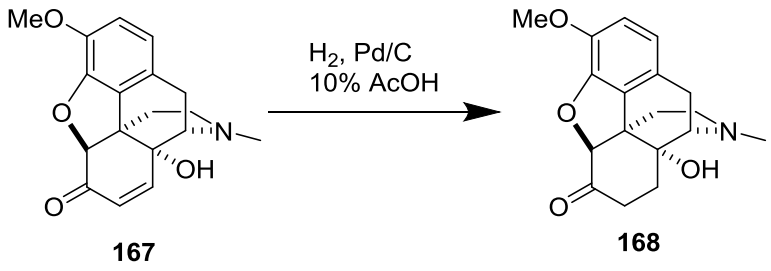


166 167

(+)-14-Hydroxycodeinone (167)

(+)-Thebaine (**166**) (0.106 g, 0.340 mmol) was taken up in a 3:1 mixture of sulfuric acid (0.143 ml) and formic acid (0.046 ml). Hydrogen peroxide 30% (0.014 ml, 0.443 mmol, 1.3 equiv) was added and the mixture was warmed to 40° C. After completion of the reaction, the reaction was diluted with 1 ml water. The reaction was basified with concentrated ammonium hydroxide and the resulting precipitate filtered. The crude material was recrystallized from chloroform/ethanol to provide (+)-14-hydroxycodeinone (**167**) as a white powder (75 mg, 70% yield). (+)-14-hydroxycodeinone was characterized as free base by taking up a sample in chloroform, washing with sodium hydroxide (1M), then water, drying over magnesium sulfate, filtering and concentrating to provide the freebase.

R*f* = 0.19 (2% methanol : 0.2% ammonium hydroxide : chloroform) ; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 10.2 Hz, 2H), 6.20 (d, *J* = 10.0 Hz, 1H), 5.16 (s, 1H), 4.72 (s, 1H), 3.85 (s, 3H), 3.24 (d, *J* = 18.6 Hz, 1H), 3.05 (d, *J* = 5.9 Hz, 1H), 2.59 – 2.50 (m, 2H), 2.46 (s, 4H), 2.29 (td, *J* = 12.0, 3.7 Hz, 1H), 1.74 – 1.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.49, 147.58, 144.65, 142.98, 134.95, 130.78, 125.22, 119.80, 115.40, 87.34, 68.06, 64.46, 57.13, 46.90, 45.43, 42.83, 29.72, 22.66; IR (thin film) 3268, 2944, 2925, 2813, 1730, 1678, 1611 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 314.1387; found 314.1392.

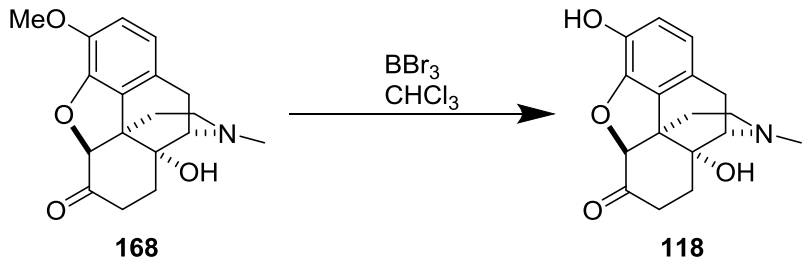


167 **168**

(+)-Oxycodone (168)

(+)-14-Hydroxycodeinone (**167**) (0.100 g, 0.319 mmol) was taken up in 10% acetic acid (2.00 ml) and 5% palladium on carbon (0.051mg, 0.024mmol, 0.075 equiv) added. The reaction mixture was placed under an H_2 balloon. After two hours the reaction was filtered and basified using concentrated ammonium hydroxide. The solution was saturated with sodium chloride and extracted with chloroform. Solvent was removed to provide (+)-oxycodone (**168**) as a white solid (85 mg, 84% yield). (+)-oxycodone was characterized as free base by taking up a sample in chloroform, washing with sodium hydroxide (1M), then water, drying over magnesium sulfate, filtering and concentrating to provide the freebase.

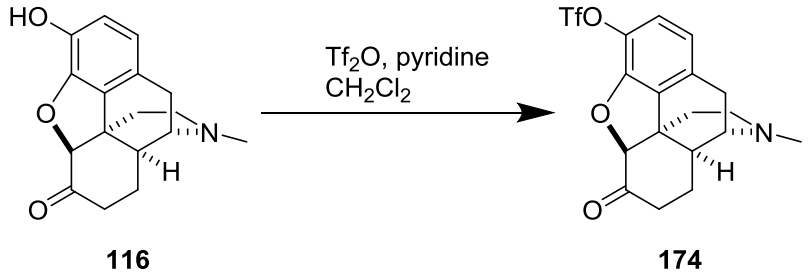
R*f* = 0.19 (2% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.71 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 5.09 (s, 1H), 4.67 (s, 1H), 3.90 (s, 3H), 3.16 (d, *J* = 18.5 Hz, 1H), 3.03 (td, *J* = 14.4, 5.0 Hz, 1H), 2.87 (d, *J* = 5.9 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.50 – 2.35 (m, 5H), 2.31 (dt, *J* = 14.4, 3.2 Hz, 1H), 2.17 (td, *J* = 11.6, 3.9 Hz, 1H), 1.88 (ddd, *J* = 13.4, 5.0, 3.0 Hz, 1H), 1.67 – 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.75, 145.26, 143.22, 129.64, 125.18, 119.67, 115.15, 90.64, 70.62, 64.85, 57.09, 50.50, 45.49, 42.99, 36.39, 31.68, 30.78, 22.16.; IR (thin film) 3212, 2936, 2907, 2843, 1730, 1607, 1503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 316.1544; found 316.1549.



168 **118**

(+)-Oxymorphone (118)

(+)-Oxycodone (**168**) (0.100 g, 0.317 mmol) in chloroform (0.793 ml) was added dropwise to a chilled solution of boron tribromide (0.090 ml, 0.951 mmol) in 0.45 ml chloroform (2.1M). After three hours the reaction was poured into saturated tris base, the resulting mixture was saturated with sodium chloride, and the layers separated. The aqueous layer was back extracted with chloroform (3x), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to provide a crude solid which was purified by Flash Chromatography (5% methanol : 1% ammonium hydroxide : chloroform) to provide (+)-oxymorphone (**118**) as amorphous white solid (51 mg, 53% yield). Spectral data was consistent with reported literature values.[89]



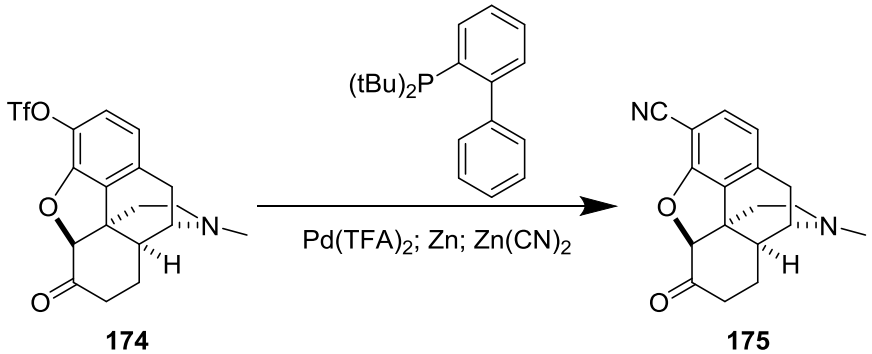
116 **174**

Triflate (174)

[89] Kok, G. B.; Scammells, P. J. *RSC Adv.* **2012**, *2*, 11318-11325.

To a stirring solution of (+)-hydromorphone (**116**) (1.776 g, 6.22 mmol) and pyridine (1.994 ml, 24.90 mmol, 4 equiv) in dichloromethane (30 ml), chilled to 0° C in an ice bath, was added trifluoromethanesulfonic anhydride (2.103 ml, 12.45 mmol, 2 equiv) dropwise via syringe. After 45 minutes, the reaction was diluted to double initial volume with 1:1 hexanes : ethyl acetate and washed with saturated sodium bicarbonate. The layers were separated and the aqueous back extracted with chloroform. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to yield a brown-orange oil. The crude material was purified by Flash Chromatography (gradient of 5-10% methanol : 0.2% ammonium hydroxide : chloroform) to provide triflate **174** as a pale yellow foam (1.885 g, 73% yield).

R*f* = 0.23 (5% methanol : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 4.80 (s, 1H), 3.23 (dd, *J* = 5.5, 2.8 Hz, 1H), 3.08 (d, *J* = 18.9 Hz, 1H), 2.69 – 2.54 (m, 2H), 2.50 – 2.31 (m, 6H), 2.18 – 2.07 (m, 2H), 1.89 (dq, *J* = 12.8, 4.1 Hz, 1H), 1.81 – 1.75 (m, 1H), 1.28 – 1.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.86, 148.29, 134.89, 131.34, 129.69, 122.67, 120.52, 118.66 (q, *J*= 321 Hz), 92.52, 59.12, 47.33, 46.71, 43.07, 42.63, 40.30, 35.70, 25.58, 20.65; IR (thin film): 2933, 2802, 1730, 1631, 1448, 1425 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 418.0931; found 418.0936.



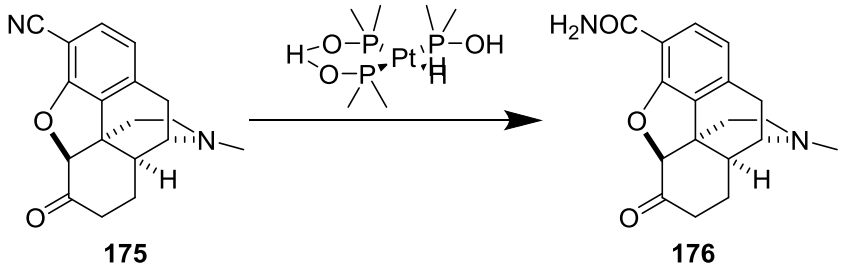
174 **175**

Nitrile (175)

To a mixture of zinc cyanide (0.024 g, 0.208 mmol), zinc dust (4.62 mg, 0.071 mmol), palladium II trifluoroacetate (5.31 mg, 0.016 mmol), 2-(di-*t*-butylphosphino)biphenyl (9.75 mg, 0.033 mmol), and triflate **174** (0.155 g, 0.371 mmol) in a sealed tube under nitrogen was cannulated dry, degassed dimethyl acetamide (22.34 ml). The resulting solution was placed under vacuum and back filled with N_2 (6x) and then sealed. The reaction was warmed to 100 °C over 95 min. After 20 hours, the reaction mixture was cooled to room temperature and filtered through a Celite. The sealed tube was rinsed several times with chloroform and the Celite rinsed with the chloroform. The solution was reduced in volume to ~1 ml under vacuum. The resulting brown oil was brought to a pH of 11 with 0.5 ml of 3M ammonium hydroxide. The suspension was filtered and the cake rinsed with water. The resulting solid was a yellow, sticky powder and massed 55 mg. The filtrate was back extracted with chloroform and concentrated under reduced pressure to yield a yellow oil. This was desired nitrile with a large amount of dimethylacetamide. The two separate materials were combined and purified by Flash Chromatography (gradient of 3-10% methanol : 0.2% ammonium hydroxide : chloroform) to provide nitrile **175** as an off-white solid (45 mg, 41% yield).

R*f* = 0.25 (5% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 1H), 3.24 (dd, *J* = 5.3, 2.8 Hz, 1H), 3.11 (d, *J* = 19.4 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.63 – 2.57 (m, 1H), 2.52 – 2.45 (m, 1H), 2.44 (s, 3H), 2.41 (t, *J* = 5.0 Hz, 1H), 2.38 (dd, *J* = 10.5, 5.1 Hz, 1H), 2.18 – 2.04 (m, 2H), 1.91 (dq, *J* = 12.6, 4.2 Hz, 1H), 1.80 – 1.75 (m, 1H), 1.20 (qd, *J* = 13.4, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.84, 159.90, 140.55, 131.96, 127.64, 120.15, 115.44, 92.86, 92.41, 58.95, 46.56, 46.52, 43.06, 42.71, 40.29, 35.60, 25.62, 21.26; IR (thin film) 2912.83, 2797.39,

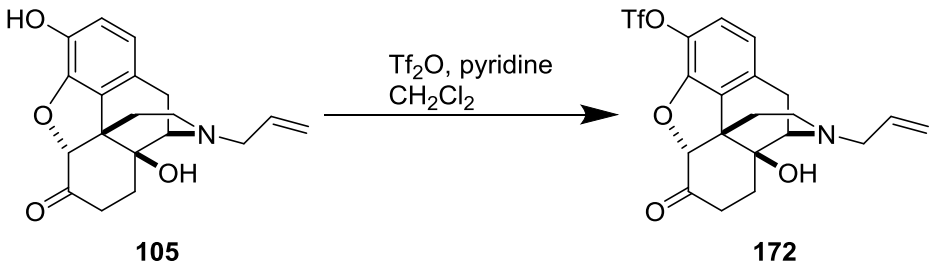
2226.24, 1729.48, 1600.72, 1428.35, 1036.00, 955.42; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 295.1442; found 295.1447.



Amide (176)

A mixture of nitrile **175** (0.050 g, 0.170 mmol), Parkin's catalyst (0.004 g, 9.30 µmol), water (2.500 ml), and ethanol (2.5 ml) was warmed to reflux in a cold finger. After 4 hours, the reaction was concentrated under reduced pressure to yield a yellow foam. The crude material was purified by Flash Chromatography (gradient of 10-15% methanol : 0.2% ammonium hydroxide : chloroform) to provide amide **176** as a clear yellow film (46 mg, 87% yield).

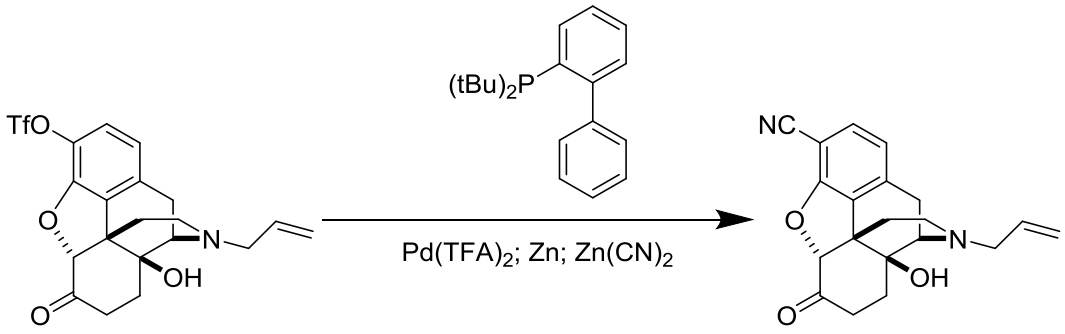
R*f* = 0.25 (10% methanol : 0.2% ammonium hydroxide : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 5.85 (s, 1H), 4.81 (s, 1H), 3.22 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.10 (d, *J* = 19.2 Hz, 1H), 2.69 – 2.54 (m, 2H), 2.48 – 2.32 (m, 5H), 2.19 – 2.07 (m, 2H), 1.93 – 1.84 (m, 1H), 1.81 – 1.74 (m, 1H), 1.28 – 1.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.94, 166.02, 155.98, 139.20, 130.04, 126.35, 120.39, 114.52, 92.27, 58.99, 46.64, 46.34, 43.03, 42.73, 40.22, 35.50, 25.61, 21.13; IR (thin film) 3443, 2933, 2802, 173, 1670, 1637, 1614 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 313.1547; found 313.1552.



Triflate (172)

To a stirring solution of (–)-naloxone hydrochloride (**105**) (0.500 g, 1.374 mmol) in dichloromethane (6.87 ml), chilled to 0 °C in an ice bath, was added pyridine (0.667 ml, 8.25 mmol) via syringe. After stirring for a few minutes, triflic anhydride (0.462 ml, 2.75 mmol) was added dropwise via syringe. The reaction turned orange rapidly after addition was complete. After 4 hours indicated the starting material had been consumed, as indicated by NMR. The reaction was diluted with 1:1 hexanes : ethyl acetate and washed with saturated sodium bicarbonate. The layers were separated and the aqueous back extracted with chloroform. Concentration under reduced pressure provided crude material that was purified by Flash Chromatography (chloroform) to provide triflate **172** as an amorphous white solid (435 mg, 69% yield).

R*f* = 0.3 (chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.82 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.26 – 5.19 (m, 2H), 4.79 (s, 1H), 3.22 – 3.11 (m, 3H), 3.08 – 2.96 (m, 2H), 2.67 – 2.58 (m, 2H), 2.43 (td, *J* = 12.7, 5.2 Hz, 1H), 2.32 (dt, *J* = 14.6, 3.2 Hz, 1H), 2.09 (td, *J* = 12.3, 3.8 Hz, 1H), 1.90 (ddd, *J* = 13.5, 5.1, 2.9 Hz, 1H), 1.63 – 1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.44, 147.92, 134.95, 133.50, 131.73, 131.44, 122.99, 118.90 (q, *J* = 321.1 Hz), 120.10, 118.73, 91.53, 70.17, 62.01, 57.81, 51.08, 43.21, 36.16, 31.40, 30.85, 23.31; IR (thin film) 3394, 2929, 2825, 1730, 1631 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+Li]^+$: 466.0373; found 466.1124.



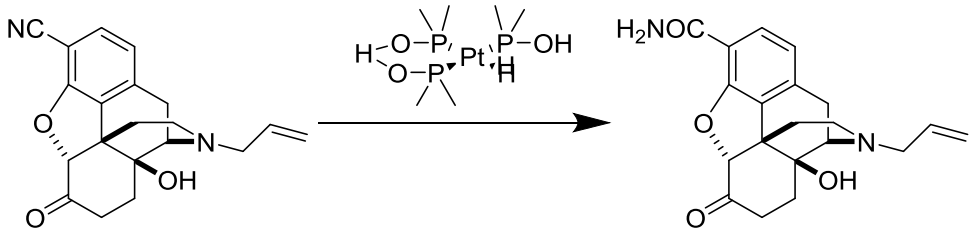
172 **177**

Nitrile (177)

To a mixture of the zinc cyanide (0.043 g, 0.366 mmol, 0.58 equiv), zinc dust (8.12 mg, 0.124 mmol, 0.19 equiv), palladium (II) trifluoroacetate (9.33 mg, 0.028 mmol, 4.3% loading), 2-(Di-t-butylphosphino)biphenyl (0.017 g, 0.057 mmol, 8.8% loading), and triflate **172** (0.300 g, 0.653 mmol) under nitrogen was cannulated dry, degassed dimethylacetamide (3.26 ml). The resulting solution was placed under vacuum and back-filled with N_2 (6x) and then sealed. The reaction was warmed to 100 °C over 90 minutes. After 24 hours, the reaction was allowed to cool to room temperature. The reaction mixture was filtered through a Celite plug. The sealed tube was rinsed several times with chloroform and the Celite rinsed with the chloroform. The filtrate was concentrated under reduced pressure. The resulting oil was diluted with chloroform and washed with 1M ammonium hydroxide, then water 3x, and finally brine. The organic layer was dried over magnesium sulfate. Concentration under reduced pressure provided an orange oil that was purified by Flash Chromatography (2:1 hexanes : ethyl acetate) to provide nitrile **177** as a white amorphous solid.(73 mg, 33% yield).

R*f* = 0.27 (2:1 hexanes: ethyl acetate); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.82 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.28 – 5.20 (m, 2H), 5.02 (s,

1H), 4.84 (s, 1H), 3.23 – 3.12 (m, 3H), 3.09 – 3.00 (m, 2H), 2.69 – 2.61 (m, 2H), 2.45 (td, *J* = 12.6, 5.2 Hz, 1H), 2.35 (dt, *J* = 14.6, 3.2 Hz, 1H), 2.05 (td, *J* = 12.4, 3.8 Hz, 1H), 1.92 (ddd, *J* = 13.5, 5.1, 3.0 Hz, 1H), 1.58 – 1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.40, 159.49, 139.00, 134.87, 132.33, 129.67, 119.74, 118.87, 115.25, 93.10, 91.48, 70.16, 61.90, 57.84, 50.34, 43.10, 36.16, 31.47, 30.76, 23.99; IR (thin film) 3391, 2928, 2823, 2228, 1728, 1634, 1602 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 337.1547; found 337.1552.



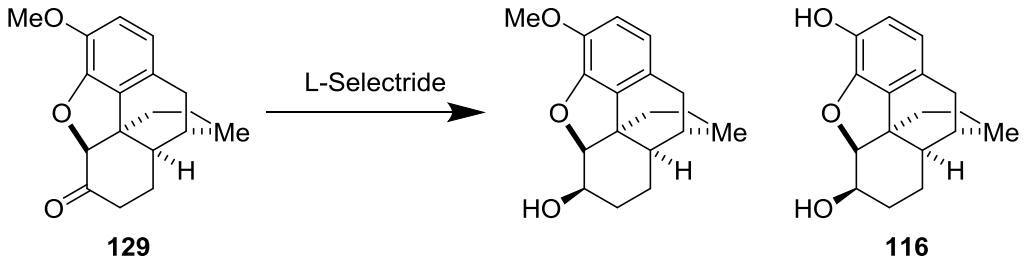
177 **178**

Amide (178)

Nitrile **177** (0.073 g, 0.217 mmol) and Parson's Catalyst (9.34 mg, 0.022 mmol) was suspended in 1:1 ethanol : water (2 ml) and warmed to reflux in a coldfinger. The reaction was cooled to room temperature after 4 hours. Solvent was removed via reduced pressure to provide crude solid material that was purified by Flash Chromatography (5% methanol : chloroform) to provide amide **178** isolated as a white amorphous solid (60 mg, 78% yield).

R*f* = 0.28 (5% methanol : chloroform); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.83 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.71 (s, 1H), 5.29 – 5.18 (m, 2H), 5.07 (s, 1H), 4.82 (s, 1H), 3.23 – 3.14 (m, 3H), 3.11 – 3.02 (m, 2H), 2.69 – 2.60 (m, 2H), 2.45 (td, *J* = 12.6, 5.2 Hz, 1H), 2.33 (dt, *J* = 14.4, 3.1 Hz, 1H), 2.11 (td, *J* = 12.3, 3.8 Hz, 1H), 1.92 (ddd, *J* = 13.5, 5.0, 2.9 Hz, 1H), 1.63 – 1.52 (m, 2H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 207.57, 165.77, 155.58, 137.69, 135.04, 130.55, 128.48, 120.05, 118.74, 114.75, 91.41, 70.37, 62.05, 57.86, 50.30, 43.23, 36.19, 31.59, 30.67, 23.85; IR (thin film) 3460, 3289, 3187, 2925, 1728, 1674, 1636, 1612, cm^{-1}; HRMS (ESI) *m/z* calc'd for $[M+H]^+$: 355.1653; found 355.1658.



129 **116**

(+)-Dihydromorphine (116)

To a solution of (+)-hydrocodone (**129**) (1.363 g, 4.55 mmol) in THF (45.5 ml) was added L-Selectride (1M in THF) (13.66 ml, 13.66 mmol). The reaction was stirred at room temperature for 30 minutes and brought to reflux for 17 hours. The reaction was cooled to room temperature and quenched by slow addition of methanol, after which 15 ml of 2:1 methanol : 30% hydrogen peroxide was added and the reaction stirred for 30 minutes. The reaction was concentrated under reduced pressure and the resulting slurry diluted with 1M sodium hydroxide and back extracted with methylene chloride (2x). The organic layers were combined, washed with water, brine, and dried over magnesium sulfate and concentrated under reduced pressure to yield 743 mg of (+)-dihydrocodeine as a yellow oil (54% yield).

The aqueous layer was acidified with hydrochloric acid, brought to a pH of 11 with ammonium hydroxide, and extracted with chloroform (4x). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduce pressure to provide (+)-

dihydromorphine as a yellow foam (164 mg, 13% yield). Spectral data of (+)-dihydromorphine was consistent with that reported in the literature.[81]

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