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Design and Synthesis of CB1 Receptor Ligands and Synthesis of Amphibian Alkaloids

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Design and Synthesis of CB1 Receptor Ligands and Synthesis of Amphibian Alkaloids

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
The Department of Chemistry

by

Hong Shu

B.S., Chemistry, Wuhan University
M.S., Chemistry, University of New Orleans

December 2009

To my family, my advisor, my colleagues, and my friends.

ACKNOWLEDGMENTS

I sincerely thank my advisor, Professor Mark L. Trudell, for his guidance, his support, and his patience. His trust and encouragement brought us where we are and will always lead our way in the future.

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I want to thank my parents for their unconditional love and support!

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ABSTRACT

Our project was aimed at the development of novel CB1 cannabinoid receptor antagonists that may have clinical applications for the treatment of cannabinoid and psychostimulant addiction. In this study, we designed, synthesized, and established the CB1 affinity for the 1,5-diaryl-1,2,3-triazole esters, a series of 4,5-diaryl-1-substituted-1,2,3-triazole analogues and a series of 4,5-diaryl-2-substituted-1,2,3-triazoles.

Our research group has been interested in the synthesis of amphibian alkaloids due to their interesting biological activities. We have recently developed a general synthetic strategy which can rapidly prepare a few amphibian alkaloids simply from the abundant natural product (-)-cocaine This strategy was first successfully applied to the synthesis of (-)-monomorine. More recently, this strategy has also been utilized in the syntheses of both of the enantiomers of *cis*-pyrrolidine 225H and (+)-gephyrotoxin 287C.

Keywords: endocannabinoid system, CB1 receptors, antagonists, drug abuse, binding affinity, amphibian alkaloid, formal synthesis, neuronal nicotinic acetylcholine receptor.

CHAPTER 1

DESIGN AND SYNTHESIS OF CB1 RECEPTOR LIGANDS

1.1 ABSTRACT

This study was aimed at the development of novel CB1 cannabinoid receptor antagonists that may have clinical applications for the treatment of cannabinoid and psychostimulant addiction. Our original target molecule was carboxamide. The rationale was to incorporate a bioisosteric 1,2,3-triazole ring into the vicinal diaryl group revealed in the prototypical antagonist/inverse agonist SR141716 (Rimonabant) that was presumed to interact with a unique region in the CB1 receptors.

Based on our preliminary results we identified a novel series of 1,2,3-triazole ester derivatives as lead compounds for for biological evaluation.

Herein the design rationale, synthesis and CB1 receptor affinity for the 1,5-diaryl-1,2,3-triazole esters, a series of 4,5-diaryl-1-substituted-1,2,3-triazole analogues and a series of 4,5-diaryl-2-substituted-1,2,3-triazoles is described.

1.2 INTRODUCTION

The Endocannabinoid System

The endocannabinoid system is a physiological system that is believed to regulate body weight, glucose and lipid metabolism, and tobacco dependence. The endocannabinoid system consists of three components: cannabinoid receptors, their endogenous ligands

(endocannabinoids), and the enzymes, proteins, and transporters involved in the synthesis and degradation of endocannabinoids. [1]

The research on cannabinoid receptors was stimulated by the identification of the chemical structure of Δ^9-tetrahydrocannabinol (**1**, Δ^9-THC), the major active component of marijuana. Although, the central and peripheral actions of marijuana have been studied for over half a century and marijuana has been used in medical and recreational applications throughout the ages, it has taken many years to understand the action mechanisms.[2] The effects of Δ^9-THC have been assumed to be mediated by the binding of this drug to a certain type of receptors located throughout the body, defined as cannabinoid receptors.

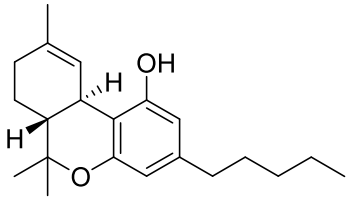
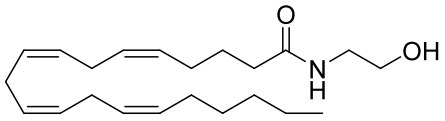


Figure 1.1 Δ^9-Tetrahydrocannabinol (**1**, Δ^9-THC)

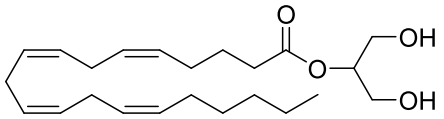
Endocannabinoids are endogenous compounds that bind to and functionally activate the same receptors Δ^9-THC binds to. A tremendous number of studies have contributed to the comprehension of the endocannabinoid regulation and function. Unlike many other neuromodulators or hormones, endocannabinoids are not synthesized in advance and stored in vesicles, they are released "on demand" from their phospholipid precursors in cell membranes.[2,3] To date, five endocannabinoids have been identified. Anandamide (AEA, **2**) was the first endogenous ligand identified and reported in the early 1990's. Anandamide together with 2-arachidonoyl glycerol (2-AG, **3**) are the two most studied endocannabinoids.[4]

Anandamide and 2-arachidonoyl glycerol are biosynthesized "on demand" from their membrane lipid precursors, N-arachidonoyl-phosphatidylethanolamine (N-ArPE) and *sn*-1-acyl-

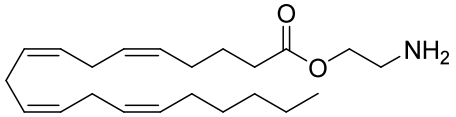
2-arachidonoylglycerols (DAGs) respectively.[5] Most of the proteins involved in the metabolism of Anandamide and 2-arachidonoyl glycerol have been fully characterized, especially the enzymes responsible for their biosynthesis and degradation. However, the route for the synthesis and inactivation of Virhodamine (**4**), *N*-arachidonoyldopanime (NADA, **5**), and noladin ether (**6**) still remains unclear. And further efforts are necessary to understand the signaling system of the endocannabinoid system.



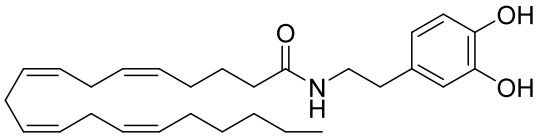
Anandamide **2**



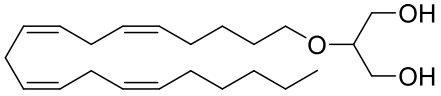
2-Arachidonoyl-glycerol **3**



Virodhamine **4**



N-arachidonoyl-dopamine **5**



Noladin ether **6**

Figure 1.2 Endocannabinoids

Cannabinoid Receptors

The identification of the cannabinoid receptors was stimulated by the desire to understand the pharmacological and biochemical effects of the psychoactive effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of cannabis. It was believed that the effects of Δ^9-

tetrahydrocannabinol (Δ^9-THC) are mediated by occupation of receptors located throughout the body.

Although the existence of protein receptors for Δ^9-tetrahydrocannabinol (Δ^9-THC) had been indicated for a long time, Allyn Howlett *et al*., for the first time, provided definitive evidence for a cannabinoid receptor. They developed a binding assay established that cannabinoids activated a G protein-coupled receptor (GPCR) that inhibited adenylyl cyclase. Their work further showed this receptor was present in certain brain regions with a high expression level.[4] Furthermore, the cannabinoid receptor distribution was successfully mapped with the development of highly active cannabinoid receptor agonists.[6,7] The existence of cannabinoid receptor was ultimately proved by the cloning of a cannabinoid receptor in 1990 by Matsuda et al.[8] which was followed by the cloning of a second type of cannabinoid receptors three years later in 1993.[9]

Much has been learned about the cannabinoid receptors by determining its localization. The localization of cannabinoid receptors was mainly determined using quantitative autoradiography, *in situ* hybridization and immunocytochemsitry.[10] The autoradiographic studies performed by Herkenham *et al*. demonstrated significant results about CB1 receptors: a) The CB1 cannabinoid receptors are mainly expressed in the central nervous system with high density in the cerebellum, hippocampus, and striatum. The CB1 cannabinoid receptors were highly abundant in the brain regions that are affected by psychoactive effects of Δ^9-tetrahydrocannabinol (Δ^9-THC); b) the concentration was low in the brain regions unaffected by tetrahydrocannabinol (Δ^9-THC); c) CB1 receptors were expressed abundantly on axon terminals. The expression of CB1 receptors has also been described with high resolution from immunoctyochemical studies. It was revealed that CB1 receptors are expressed at very high levels in a subset of GABAergnic interneurones, the cholecystokinin (CCK) containing basket cells and at lower levels on many glutamatergic

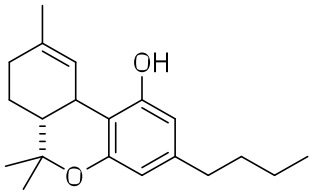
terminals throughout the brain. CB1 receptors are largely present on the preterminal axonal segment and axons but very little on more proximal axons, dendrites, or the cell body. CB1 receptors are also found in fat, liver, pancreas, skeletal muscles, and a number of other peripheral tissues.[11] Conversely, the CB2 cannabinoid receptors are exclusively present in the immune system. It has been found in the periphery of the spleen and cells associated with immune system. The presence of a third type of cannabinoid receptor has been indicated recently.

Cannabinoid receptors (CB1, CB2) belong to the Class A, rhodospin-like family of G protein-coupled receptors (GPCRs). The cannabinoid receptors signals primarily through the inhibitory G proteins G_i and G_o, to a less extend via Gs and $Gq/_{11}$ with certain agonists. Both the CB1 cannabinoid receptor and the CB2 cannabinoid receptors share the similar signaling sequence. Upon the binding of cannabinoid ligands on cannabinoid receptors, the cannabinoid receptors were stimulated which leads to the activation of adenylyl acyclase, the activation of mitogen-activated protein kinases, the inhibition of certain voltage-gated calcium channels and the activation of G protein-linked inwardly rectifying potassium channels. The modulation of ion channels by CB2 cannabinoid receptors is more variable than that of CB1 cannabinoid receptors. CB1 was originally believed to be the "brain type" of receptors because it is among the most abundant G protein-coupled receptors in the central nervous system of mammalians. Now it is clear that CB1 is predominantly expressed in the central nervous system but also, to a lesser extent, in various peripheral organs, while CB2 receptors are mostly expressed in the immune system. "The endocannabinoid system appears to be involved in a rising number of pathological conditions and hence represents an exciting target for drug discovery."[12]

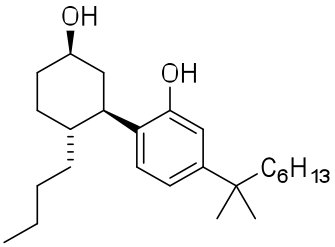
CB1 Receptor Ligands

The CB1 receptor is pharmacologically activated upon small molecule occupation of the binding sites. Based on structural features, cannabinoid receptor ligands fall into four classes[4]:

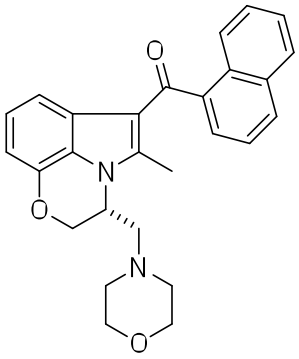
1. "Classical" Cannabinoids typified by tetrahydrocannabinol (Δ^9-THC, **1**);
2. "Non-classical" cannabinoids [e.g. CP55,940, **7**];
3. "Aminoalkylindoles" [e.g. WIN55212-2, **8**];
4. "Endocannabinoids" [e.g. anandamide, **9**].



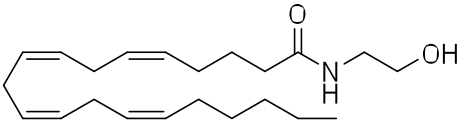
Δ^9-THC (**1**)



CP55,940 (**7**)



WIN55,212-2 (**8**)



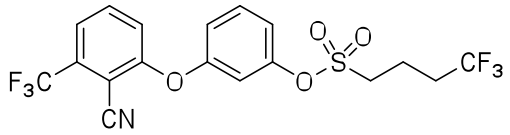
Anandamide (**9**)

Figure 1.3 Cannabinoid receptor ligands

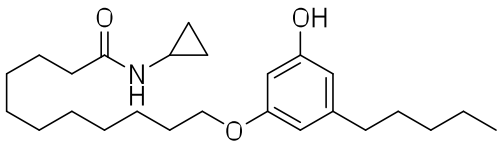
These ligands typically exhibit low nanomolar binding affinity for CB1 receptors and generally do not exhibit significant differential in binding affinity between the two subtypes of

the cannabinoid receptors, CB1 and CB2. Of these ligands, anandamide has been reported to exhibit selectivity for CB1 over CB2 with K_i = 61 nM (CB1) and K_i = 1930 nM (CB2). CB1 receptor agonists inhibit cAMP production through inhibition of adenlyl cyclase, inhibit Ca^{+2} influx, activate K^+ channels and activate MAP kinase pathways. One of the many indications of CB1 receptor agonists is to increase intracellular dopamine levels in brain (striatum) similar to cocaine. It is believed that CB1 agonist modulation of dopamine levels in the central nervous system is responsible partially for the abuse liability observed for cannabinoid agonists.

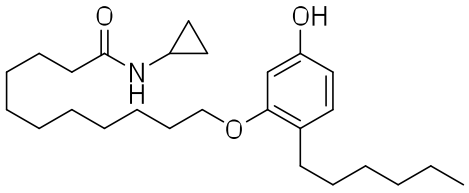
The CB1 cannabinoid receptor agonists have a great variety of potential pharmacological applications including nausea, glaucoma, cancer, stroke, pain, cachexia, and neuronal disorders such as multiple sclerosis and Parkinson's disease.[13]



BAY 59-3704 (**10**)



CB-25 (**11**)



CB-52 (**12**)

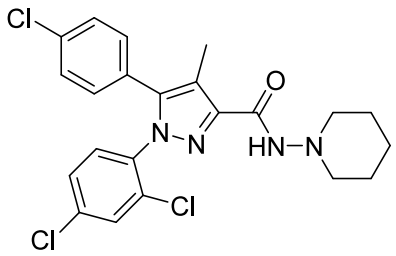
Figure 1.4 Cannabinoid receptor partial agonists

Among known cannabinoid receptor agonists there are several compounds exhibiting low efficacy agonist profiles in vitro and in vivo. Like the potent cannabinoid receptor ligand CP-

55,940 (**7**) and WIN 55212-2 (**8**), they stimulated [^{35}S]GTPγS binding but were significantly less potent and hence they have been designated as partial agonists.[14,15] The partial agonists include tetrahydrocannabinol (Δ^9-THC), BAY59-3704 (**10**), CB-25 (**11**) and CB-52 (**12**).

CB1 Receptor Antagonists

The CB1 cannabinoid receptor antagonists bind to CB1 receptors and block the effects of CB1 agonists. CB1 antagonists block stimulation of [^{35}S]GTPγS binding and block the inhibition of adenlyl cyclase activity. The CB1 cannabinoid antagonists have potential applications in the treatment of obesity and nicotine dependence. The CB1 receptor antagonists known so far are diarylpyrazoles, or aminoalkylidoles or triazole drivatives.[16]



Firgure 1.5 SR141716A (Rimonabant, **13**)

SR141716A (Rimonabant, **13**), the first CB1 receptor antagonist synthesized, was tested in humans and then approved as a drug for the treatment of obesity and related comorbidities.

Bioisosterism is an important approach frequently used in medicinal chemistry to discover new lead compounds based on existing key ligands. It plays a significant role in attenuating toxicity, optimizing binding, and altering pharmacokinetics of a lead compound. The three dimensional structures of thiazoles, triazoles, and imidazoles and the structure of pyrazole

exhibit a high degree of similarity. Consequently, the pyrazole ring in Rimanabant can be replaced by such heterocyclic five-membered rings in order to discover bioisosteres, compounds that have similar chemical or physical properties and therefore similar biological properties.

Based on the structure of Rimonabant, numerous analogues have been synthesized to elucidate the structure-activity relationship information and the biological mechanisms. Most of those analogues were designed and synthesized based on the 1,5-diarylpyrazole ring as structural template, which was believed to be the molecular region binding to CB1 receptors. Various structural modifications of the prototype Rimonabant were undertaken and led to new series of cannabinoid compounds. Some of those compounds turned out to be CB1 antagonists with good potency, CB1/CB2 selectivity, and improved lipophilicity.

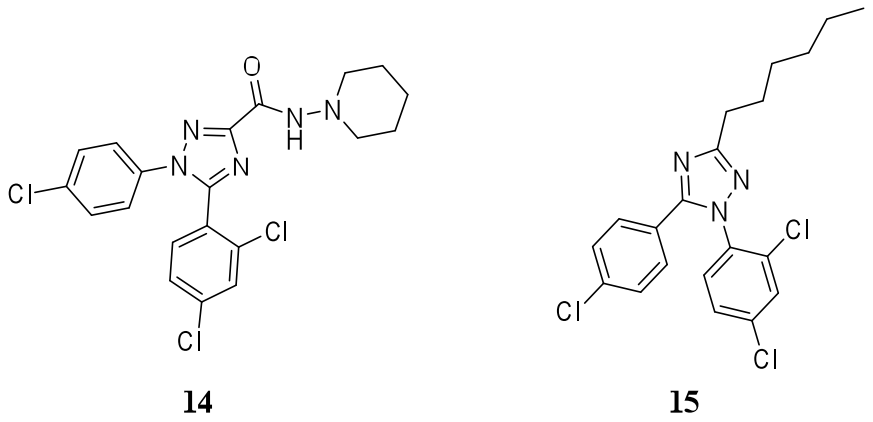
One of the most important structural modifications was focused on the changes of the C-3 acyl group. Analogues have been synthesized and evaluated to establish the influence of the presence of the carboxamide oxygen from the C-3 position on the binding affinity.[17] The carboxamide group was replaced by heterocyclic carboxamide bioisosteres, amino alcohols, ketones. It was discovered that the potency was diminished relative to Rimonabant when the carboxamide oxygen was absent from the pyrazole ring. It was explained by the hypothesis that the carboxamide oxygen forms a hydrogen bond with the CB1 receptor binding region. However, the functional assay results of those analogues suggested that the carboxamide group contributes to the inverse agonist property. Analogues without the carboxamide oxygen were identified as neutral antagonists in efficacy evaluations. Moreover, the analogues of Rimonabant consisting of long-chain alkyl amide have been synthesized and reported to exhibit good affinity for CB1 receptors.[18] Analogues with alkyl chain longer than six carbons exhibited decreased binding

affinity at CB1 receptors. Branched alkyl amides were generally more potent than the corresponding straight alkyl amides same number of carbon atoms.[19]

Based on the experimental and computational studies, the pharmacophoric requirements were concluded for the potency of the pyrazole analogues in CB1 binding: a *para*-substitute phenyl ring at the pyrazole C-5 position, a 2,4-dichlorophenyl ring at pyrazole N-1 position, and a carboxamide moiety at pyrazole C-3 position.[20]

SAR studies revealed that the C-5 phenyl group was essential for the CB1 binding. Substitution at the *p*-position of the phenyl with a halogen atom or an alkyl chain can effectively increase the binding affinity. In a recent study, pentyl chains with a variety of groups attached to the terminal carbon were used as the substituents at that position. The resulting analogues exhibited excellent binding affinity to CB1 receptors.[19]

Based on Rimonabant as the prototype, ring bioisosterism has been the most widely used strategy to design and synthesize cannabinoid antagonists with optimal pharmacological properties. The first reported bioisosteric analogues of Rimonabant were 4,5-diarylimidazole-2-carboxamides synthesized by replacing the pyrazole core with an imidazole ring.[21] A series of 1,2-diarylimidazole-4-carboxamides were also described and structural modifications were conducted to established SAR information.[22] The biological data clearly demonstrated that for both of those two isomeric series of imidazole analogues, the most potent ligands were those possessing substitution pattern very similar to that of SR141716A. In addition, most of those imidazole analogues showed antagonistic properties in functional assay studies. Some compounds displayed affinities for CB1 receptors comparative to that of SR141716A and had good oral bioavailability and brain penetration.



14 **15**

Figure 1.6 Rimonabant bioisosteric analogues

The pyrazole core in SR141716A was also replaced by other five-membered bioisosteric rings. These included thiazole, oxazole and 1,2,4-triazole derivatives. Those analogues were reported to be less potent than the methyl-diarylimidazoles discussed earlier. This difference in binding affinity may be attributed to the absence of methyl group which was believed to play a very important role in properly orienting the carbonyl group for molecular recognition at the CB1 binding pocket. Despite the moderate binding affinity associated with the 1,2,4-triazole derivatives, this series provided interesting compounds. The analogue bearing the same substituents as SR141716A was found to be an antagonist (**14**). Another 1,2,4-triazole derivative (**15**) bearing a *n*-hexyl instead of a carboxamide was reported to be an antagonist both in vitro and in vivo. In addition, it was one of the few known CB1 receptor antagonists without inverse agonistic properties.[23] Tremendous amount of work has also been done researching on the structure-activity relationship of the imidazole bioisosteric analogue of SR141716A (**16**, **17**).

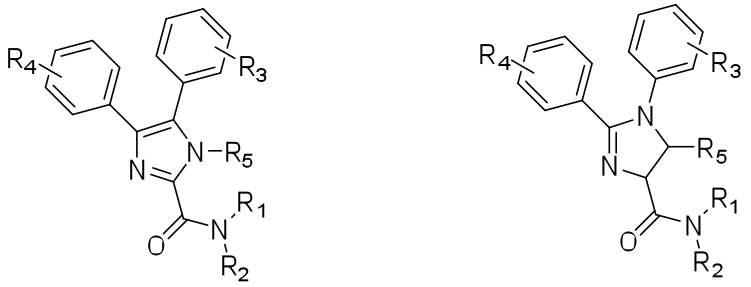
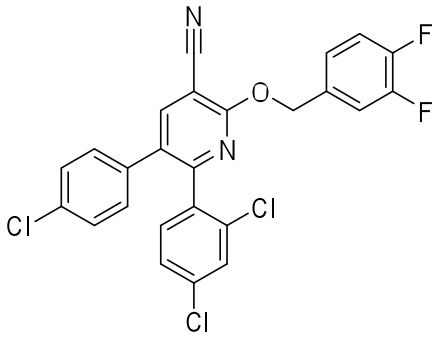


Figure 1.7 Rimonabant bioisosteric analogues

In addition to the analogues with five-membered bioisosteric rings, six-membered ring replacement of the pyrazole ring in SR141716A has afforded a number of pyridine, pyrimidine and pyrazine derivatives. Diarylpyridine analogues with or without the carboxamide group were all synthesized and evaluated in binding assay studies. The ether **18**, a potent and selective CB1 agonist, demonstrated that the presence of amide moiety was not necessary for this category of compounds. It could be replaced by other functional groups combination with the substituent at the pyridine C-5 position, such as the nitrile in **19**, to optimize pharmacological profiles.[24] The introduction of a polar substituent to the pyrazine ring provided analogues **20** that were less lipophilic and more bioavailable. Compound with phenyl group **21** as the central ring still exhibited good binding to CB1 receptor. It indicated that the presence of a heterocycle is not strictly required for a CB1 antagonist.[25]



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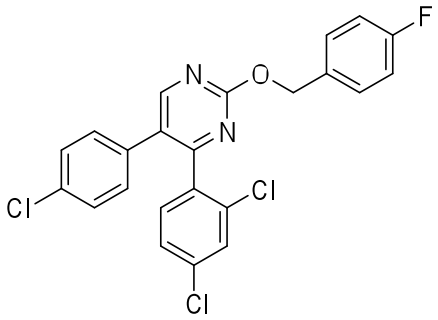

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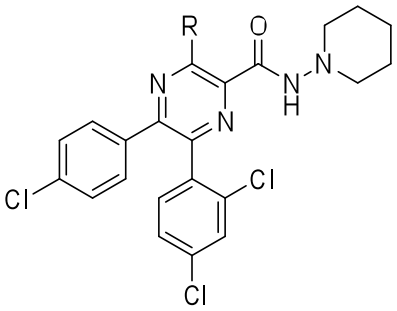

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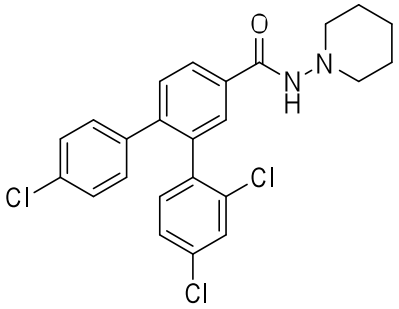


21

Figure 1.8 Six-membered bioisosteric analogues of Rimonabant

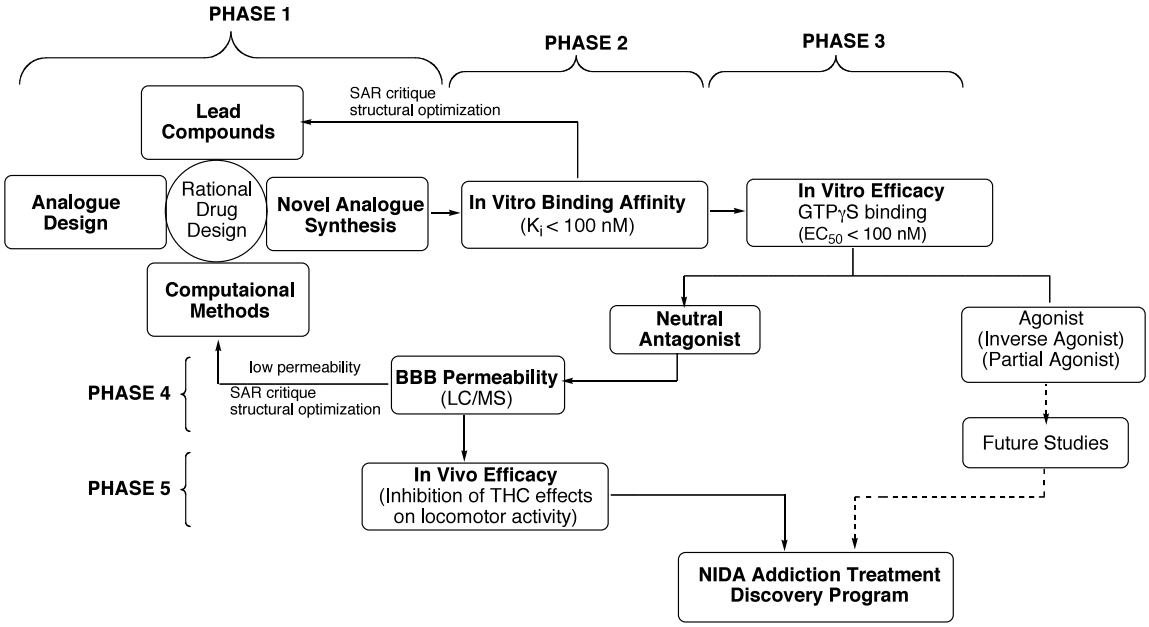
Drug Abuse

Behavioral pharmacologists are particularly interested in the roles of CB1 receptors because of their selective presence in the central nervous system and their association with brain-reward circuitry.[14] The mesocorticolimbic dopamine system has been implicated in mediating the effects of several drugs. The mesocorticolimbic dopamine system is believed to be the primary region of the brain mediating the effects of several drugs and is closely associated with brain-reward circuitry mechanisms. The mesocorticolimbic dopamine system includes neurons in the ventral tegmental areaand corresponding projections into the forebrain regions.[15] Even though CB1 receptors do not reside on the mesencephalic dopaminergic neurons, they are located in these regions.[2] CB1 receptor agonists elevate dopamine levels, while CB1 receptor antagonists or

inverse agonists can attenuate the dopamine level elevations associated with drug abuse and diminish the stimulation of dopaminergic activity in the reward circuitry of the brain and attenuate the effects of drug abuse. Therefore, the development of CB1 antagonists as potential therapeutic agents for drug abuse is straightforward. While the CB1 antagonist Rimonabant did not show to have an effect on cocaine and amphetamine self-administration, it has been reported to reduce rat cocaine-primed and cue-induced reinstatement studies with CB1 antagonist CB1 antagonists have been shown to block the effects of Δ^9-THC and appear to be devoid of abuse liability.[16]

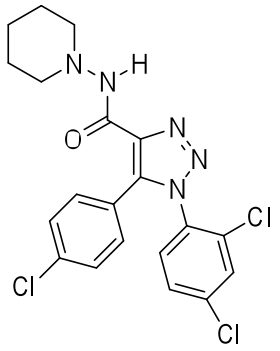
1.3 RESULTS AND DISCUSSION

The program, illustrated in **Scheme 1.1**, includes chemical synthesis, in vitro biological evaluation, and in vivo biological evaluation. Phase 1 of the study will consist of rational drug design and synthesis. Novel analogues will be designed based upon lead structures identified in our preliminary studies and supported by computational studies. In phase 2, compounds will be evaluated in vitro studies to identify structural requirements for high affinity binding. The binding affinity results will be used to advance compounds to in vitro efficacy studies as well as provide feedback information for the optimization of compound structures to identify more potent ligands. Phase 3 of the study will consist of in vitro characterization of compound efficacy and identify CB1 antagonists, agonists, or inverse agonists. Because of their different action mechanisms and potential therapeutic values, inverse agonists and partial agonists will be directed to another program. Compounds that elicit neutral antagonist efficacy will be advanced to the blood-brain barrier permeability evaluations. Compounds that exhibit good blood-brain barrier permeability will be advanced to in vivo evaluation of antagonist efficacy.



Scheme 1.9 Flowscheme of CB1 receptor rug discovery program

Compounds with poor blood-brain permeability will be re-evaluated in the rational drug design process to improve their physical properties to improve permeability. Finally, phase 5 will establish in vivo antagonist activity for compounds that have met the goals of in vitro efficacy and blood brain permeability. Those compounds that exhibit good in vivo antagonist efficacy will be submitted to the National Institute of Drug Abuse and serve as a lead compounds in future studies aimed at developing them further as drug abuse medications. The various phases of the program all go simultaneously with each phase contributing to the refinement of the ligand structure.



22

Figure 1.9 Initial target

In reviewing the literature about CB1 receptor antagonists, we noticed that the 1,2,3-triazole analogues were absent from the pool of SR141716A bioisosteric analogues. Our initial design of the target compound was based upon prototypical structure of SR141617A and its related compounds discussed in the literature. The design rationale was to incorporate the 1,2,3-triazole ring with the vicinal diaryl system. This led to the compound **22**. This design was supported by preliminary computational study. As illustrated in **Figure 1.10**, for the AM1 geometry optimized structures, a 1,2,3-triazole ring in **2** could replace the pyrazole ring and provide good overlap with SR141716A in the diaryl groups which was believed to be the molecular region binding to CB1 receptors. It was not clear at that time how the juxtaposition of the alignment of the carboxamide moieties of **22** relative to SR141716A would affect molecular recognition at CB1 receptors. Molecular modeling studies reported for analogues of SR141716A had suggested that increased steric bulk at C4 could be tolerated. This suggested that the carboxamide at C4 of **22** may not have detrimental effect on CB1 binding. Furthermore important to the target selection was that computational logP (clogP) values for the 1,2,3-triazole derivatives typically exhibited a trend of improved lipophilicity over corresponding pyrazole or 1,2,4-triazole isomers of similar substitution and functionality. Although the ClogP values may vary from actual logP values, this

trend of decreased lipophilicity was encouraging for us to move forward. Based on this analysis, we identified the 1,5-diaryl-1,2,3-triazole as our initial target for synthesis.

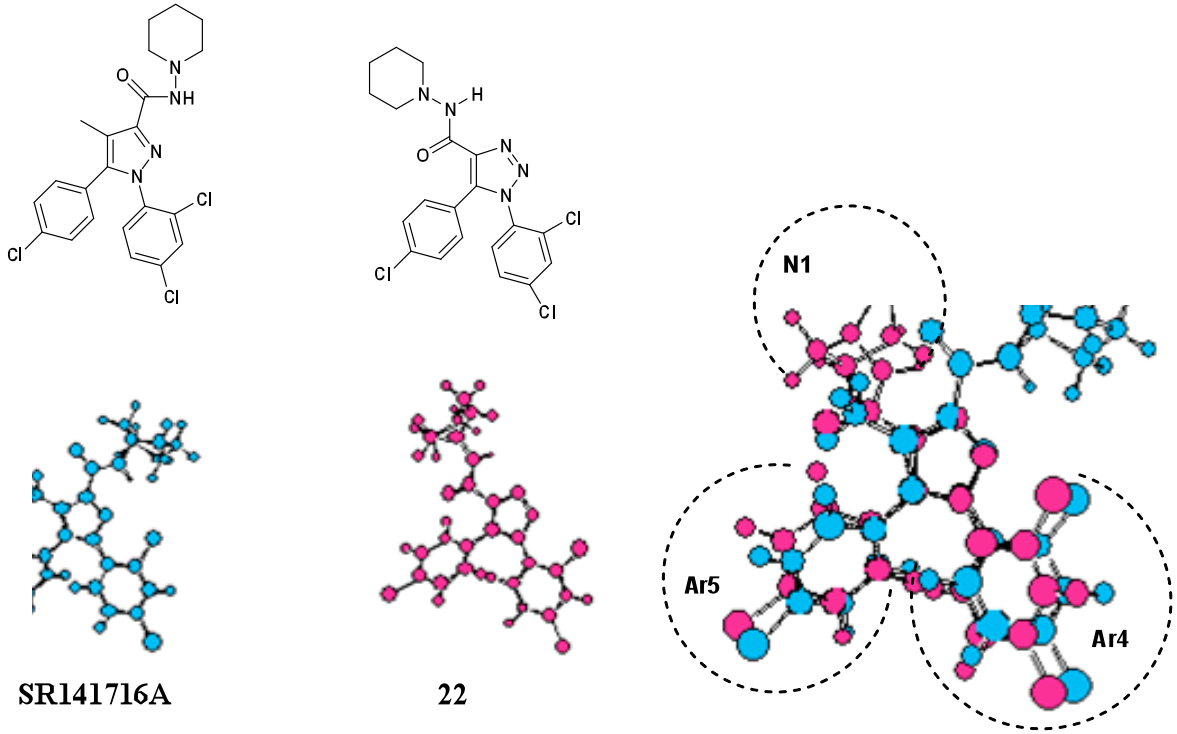
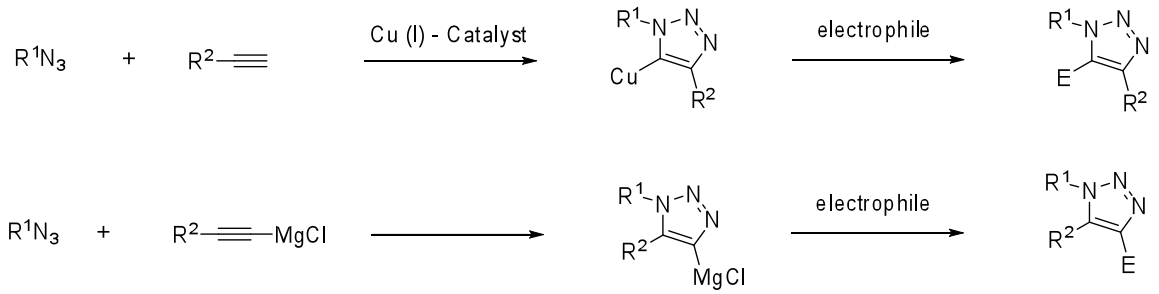


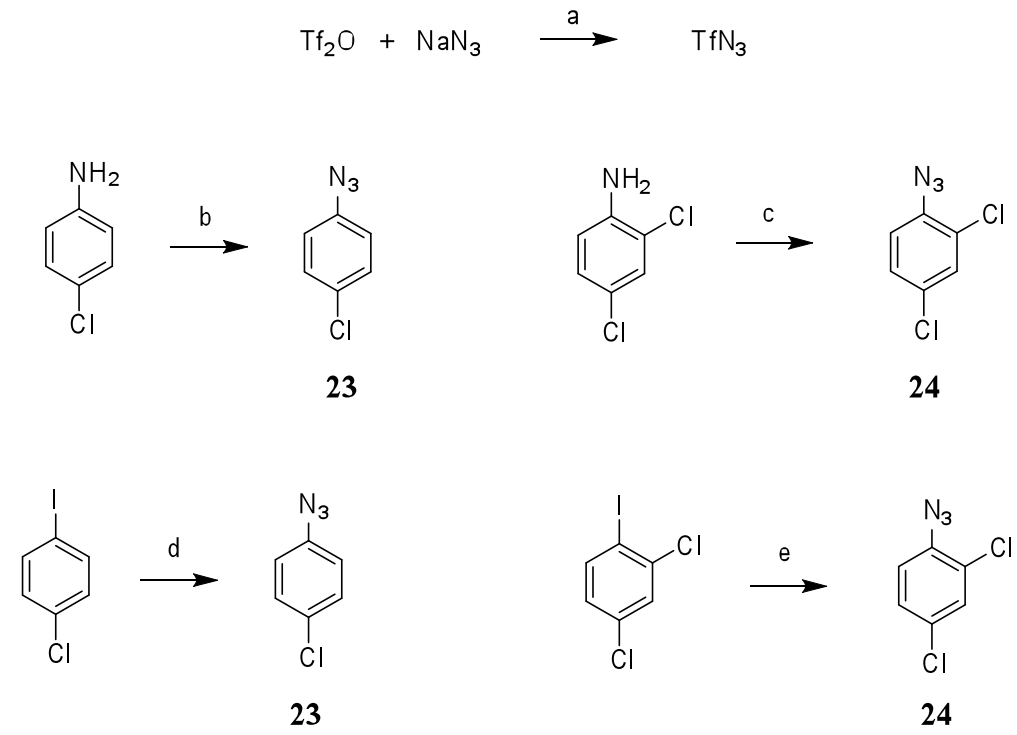
Figure 1.10 Preliminary computational study

To synthesize the target molecule, the key was to construct the 1,2,3-triazole ring with the right regiochemistry. One of the most attractive strategy was the 1,2,3-triazole ring system was to exploit the 1,3-dipolar cycloaddition reaction of an azide and a terminal alkyne (**Scheme 1.2**).[26, 27] When Cu(I) salt was used as catalyst for this reaction, the product was 1,4-disubstituted-1,2,3-triazole. However the reaction of magnesium actylide and terminal alkyne give the 1,5-disubstituted-1,2,3-triazole exclusively. This strategy would allow rapid regioselective ring construction of the target molecules and provide suitable intermediates for parallel synthesis of potential analogues.



Scheme 1.2 The strategy to synthesize 1,2,3-triazoles

As one the building blocks for the cycloaddition reaction, 2,4-dichloropheynlazide **24** was required to be synthesized. Unlike the preparation of alkyl azides, there are only few effective methods available for the synthesis of aryl azides. Aryl azides were generally synthesized by diazotization of aryl amine followed by the treatment of sodium azide. An alternative method developed recently was to treat the corresponding amines with triflyl azide.[28] As illustrated in **Scheme 1.3**, this reaction worked well on 4-chloroaniline to provide 4-chlorophenyl azide **23** in a 82% yield. It did not furnish useful quantities of the 2,4-dichlorophenyl azide. Moreover, triflyl azide was not commercially available nor could it be stored for a long time. It needed to be freshly prepared every time to synthesize phenyl azide. Fortunately, the Ullmann-type of conversion iodobenzene catalyzed by CuI with *trans*-1,2-di(aminomethyl)-cyclohexane as ligand worked efficiently on both 4-chloroiodobenzene and 2,4-dichloroiodobenzend.[30] 4-Chlorophenyl azide was prepared in a 89% yield and 2,4-dichloropheny benzene in a 54% yield from 2,4-dichloroiodobenzene. All the reagents required for the synthesis of azide in this reaction were commercially available and the reaction could be conducted in a gram-scale.

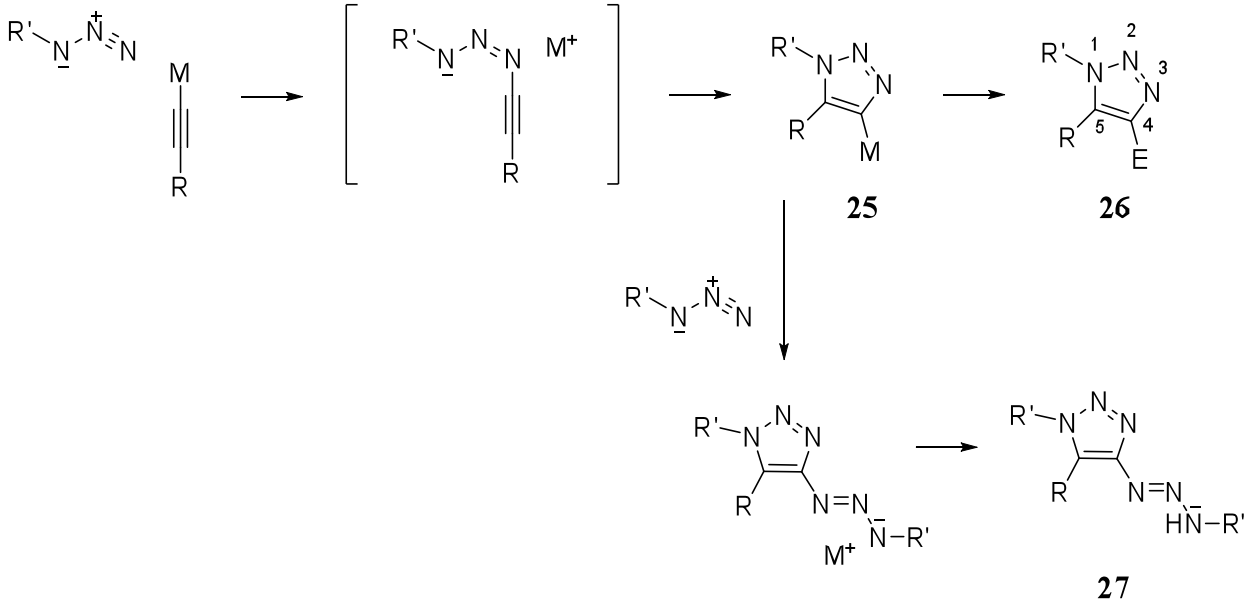


Scheme 1.3 Synthesis of azide

Reagents and conditions: a) H_2O/CH_2Cl_2, 0 º Cb) TfN_3, aq. $CuSO_4$, Et_3N, CH_2Cl_2/MeOH, rt, 2 h; c) TfN_3, aq. CuSO4, Et_3N, CH_2Cl_2/MeOH, rt, 2 h; d) NaN_3, Sodium ascorbate, CuI (10% mol), Ligand (15 mol%), DMSO/H_2O, 50 ºC, 1 h; e) NaN_3, Sodium ascorbate, CuI (10% mol), Ligand (15 mol%), DMSO/H_2O, 100 ºC, 2 h

Since the mono-chlorophenyl azide **23** was more readily available by the synthesis, it was employed as the model to explore the potential of the cycloaddition approach and to examine the reaction conditions. Additionally, the resulting analogues with monochloro-substituted phenyl at N-1 position could be evaluated for CB1 binding and provide SAR information about substitution at this position. The proposed mechanism of the cycloaddition reaction was illustrated in **Scheme 1.4**.[27] The reaction started with the nucleophilic attack of the acetylide on the terminal nitrogen of the azide to form a linear intermediate which spontaneously closed to give the 4-metallotriazole **25** which leads to 1,5-disubstituted-1,2,3-triazole **26** when treated with

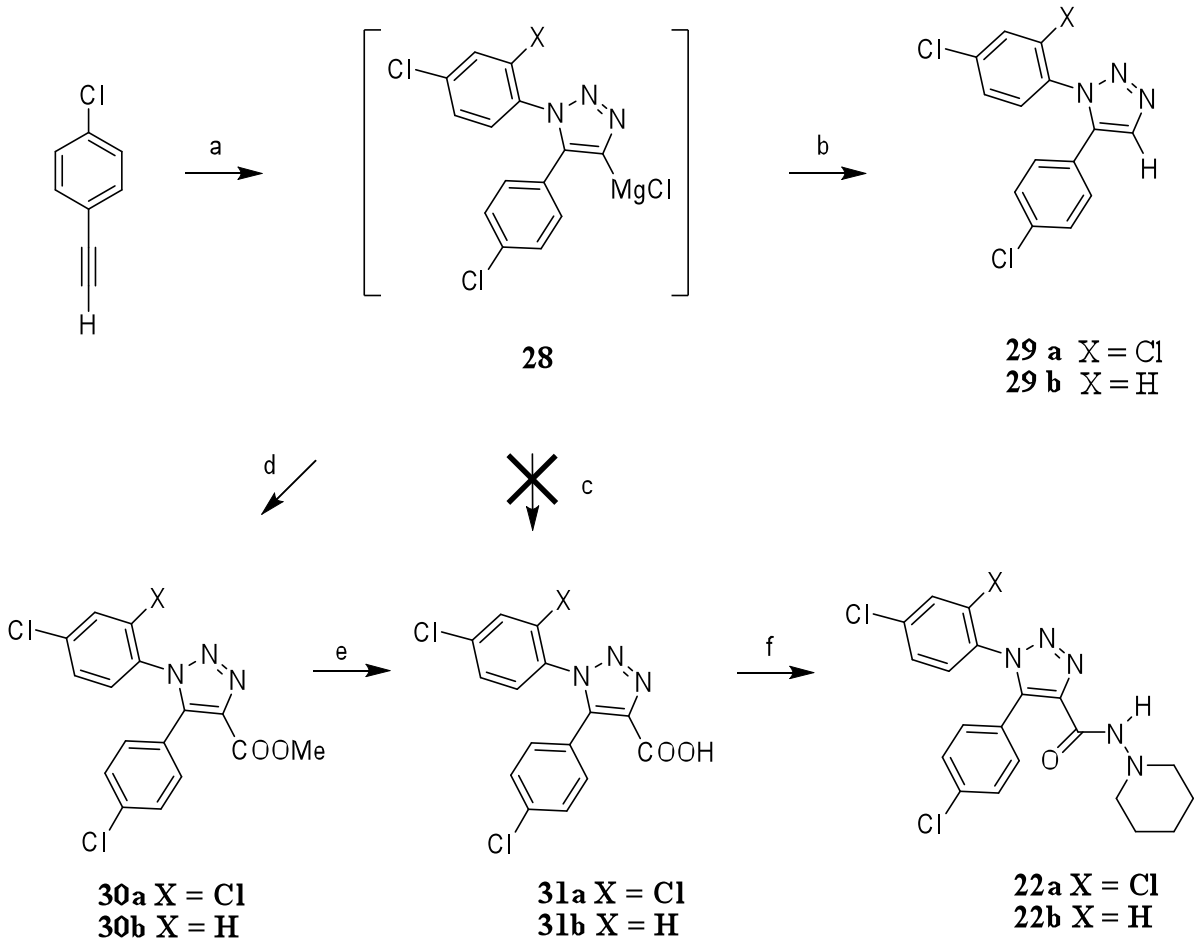
an electrophile. In the excess of azide, the intermediate 4-metallotriazole **25** reacts with the second azide and gives the side product **27**.



Scheme 1.4 Proposed mechanisms of 1,2,3-triazole formation

To monitor the process of the one-pot three-step reaction and to optimize the yield for this reaction, the cycloaddition adduct was first directly treated with aqueous NH_4Cl solution. The evaluation of the resultant 4-unsubstitute analogues would provide important SAR information about the effects of substitution at this position on the binding of 1,2,3-triazoles to CB1 receptors. The best yield (85%) was obtained when freshly made azide in THF was added to the acetylide and was heated for 2 hours at 50 °C with a small amount of acetylene remaining unreacted. Excessive azide or extended reaction time led to decreased yield due to the addition of a second molecule of azide to the 4-magnesio-1,2,3-triazole. To synthesize the target carboxamide analogue **22**, the carboxylic acid **31** was proposed as an intermediate from which the carboxamide could be synthesized through a straightforward amidation. When the cycloaddtion

intermediate **28** was treated with CO_2, only the hydrolyzed product 4-unsubstituted-1,2,3-triazole **29** was obtained because of the moisture introduced by CO_2 stream. As an alternative synthetic route, methyl ester **30** was synthesized and concomitant hydrolysis gave the carboxylic acid **31** in a good yield. The methyl ester **30** was prepared by capturing the 4-magnesio-1,2,3-triazole with methyl chloroformate.



Scheme 1.5 Synthesis of target compound

Reagents and conditions: a) 1. EtMgCl, THF, rt, 1 h; 2. **23** or **24**, THF, 50 ^{o}C, 2 h; b) 1 N NH_4Cl; c) CO_2, 0 ^{o}C; d) ClCOOMe, THF, 0 ^{o}C; e) KOH, MeOH, reflux; f) DIPEA, HBTU, CH_3CN, 1-aminopiperidine.

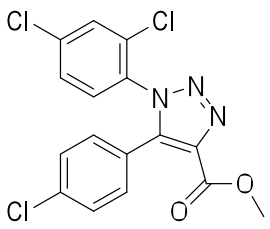
Cmpd[a]	Code	*ClogP*[b]	K_i (nM)[c]
22a	HS69	5.33	590 ± 170
22b	HS60	4.69	54%[d]
29b	HS53-2	4.46	6,900 ± 1,300
29a	HS57-2	5.11	1,420 ± 266
30b	HS53-1	4.68	4,400 ± 760
30a	HS57-1	5.32	66 ± 7.0

[a]All compounds were tested as the freebase.
[b] See Ref. 30.
[c]All values are the mean ± SEM of three experiments performed in triplicate.
[d]Percent inhibition at 100μM.

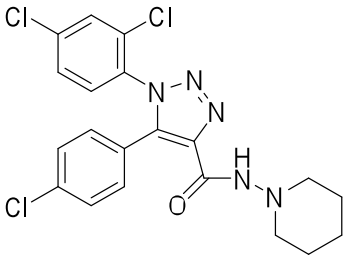
Table 1.1 Inhibition of [^{3}H]SR141716A at CB1 Receptors

As illustrated in **Table 1.1**, the binding affinities for CB1 receptors of the three 1,5-diaryl-1,2,3-triazoles were determined in vitro by displacement of [^{3}H]SR141716A for CB1 receptors in rat brain. The K_i values summarized in **Table 1.1** indicate that the initial SR141716A analogue carboxamide **22a** exhibited only modest binding for CB1 receptors (K_i =590 nM). The C4-unsubstituted analogue exhibited only micromolar affinity for CB1 receptors. It was even less potent than the bulky carboxamide. It suggested that substitution at this position of the 1,2,3-triazole ring is favorable for CB1 receptor binding and structural modification at this position may lead to compounds with optimal pharmacological profiles. The N-1 monochloro phenyl analogues **29b**, **30b**, and **22b** were less potent than the corresponding N-1 dichloro phenyl analogues **29a**, **30a**, and **22a**. However, it was serendipitous to find that the simple ester analogue **30a** exhibited potent affinity for CB1 receptors. This result validated the previous hypothesis that 1,2,3-triazole ring was suitable replacement for pyrazole ring in SR141716A. It also indicated that an amide moiety at C4-position was not essential for high binding at CB1 receptors, which updated the SAR information based on previous studies on other bioisosteric SR141716A analogues. More important for the future studies, it provided a very promising compound as a new lead compound.

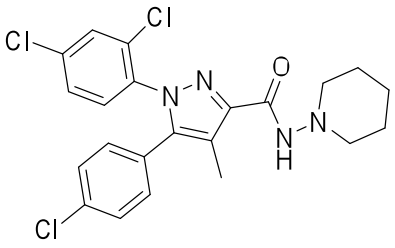
Compared with the target analogue and even SR141716A (**Table 1.2**), methyl ester **30a** had a few desirable pharmacological features. First of all, it is near one order of magnitude more potent than the target compound and its K_i value was already in the same range with that of SR141716A. It also has a significantly smaller molecular weight than those of **30a** and SR141716A. It has a much lower *ClogP* value than that of SR141716A.



30a



22a



SR141617A

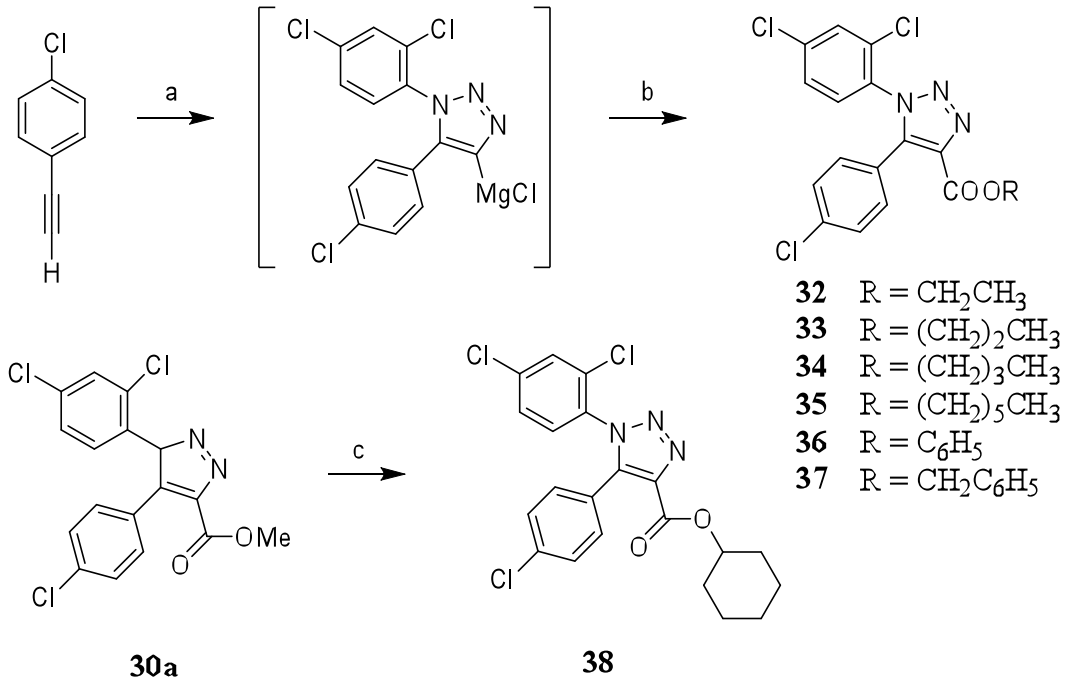
Cmpd	K_i (CB1) nM	*ClogP*	MW
30a	66	5.32	383
22a	590	5.33	451
SR141617A	11.5[a]	6.26	464

[a]Taken form reference 31.

Table 1.2 The properties of lead compound

More importantly, the ester moiety may lead to a significant increase in compound metabolism since esters are typically more readily hydrolyzed than amides in vivo. This is extremely important in lieu of the long half-lives typically observed for cannabinoids. Ester derivatives will undoubtedly be more susceptible to metabolism and have shorter duration of action than amide or hydrazide analogues. Although the measurement of ligand half-lives is not

part of this study, the development of an ester-based ligand would be an important step toward the development of shorter acting cannabinoids with better safety profiles. Therefore, methyl ester was identified as a new lead compound for further studies in the development of 1,2,3-triazoles as CB1 antagonists.



Scheme 1.6 Synthesis of esters

Reagents and conditions: a) 1. EtMgCl (2 N in THF), THF, rt, 1 h; 2. 2,4-dichlorophenyl azide, 50 ºC, 2 h; b) ClCOOR, THF, 0 ºC; c) cyclohexanol, *n*-BuLi, THF, 0 ºC, 2 h.

As illustrated in **Scheme 1.6**, a series of 1,2,3-triazole analogues with varying ester groups were prepared to investigate how lipophilicity and steric effects affect the binding of the ester to CB1 receptors. They were synthesized using the procedures described earlier for the methyl esters. The 4-magnesio-1,2,3-triazole intermediate was captured with a number of alkyl chloroformates. Each of the analogues could be synthesized in gram-scale. But since only a small quantity of product was required for the binding assay studies, only the cycloaddition reaction

was conducted in a gram-scale. Then the solution of cycloaddition adduct in THF was separated into a number of portions and each portion was treated with a different commercially available chloroformate to provide the corresponding 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazole. The cyclohexyl ester derivative **38** was prepared by a simple transesterification from the methyl ester **30a**.

As shown in **Figure 1.11**, the X-ray crystallographic analysis of 4-methoxycarbonyl-1,5-diaryl-1,2,3-triazole served to confirm the regioselectivity of the cycloaddition reaction and unequivocally established the regiochemistry of the 1,2,3-triazole ring system.

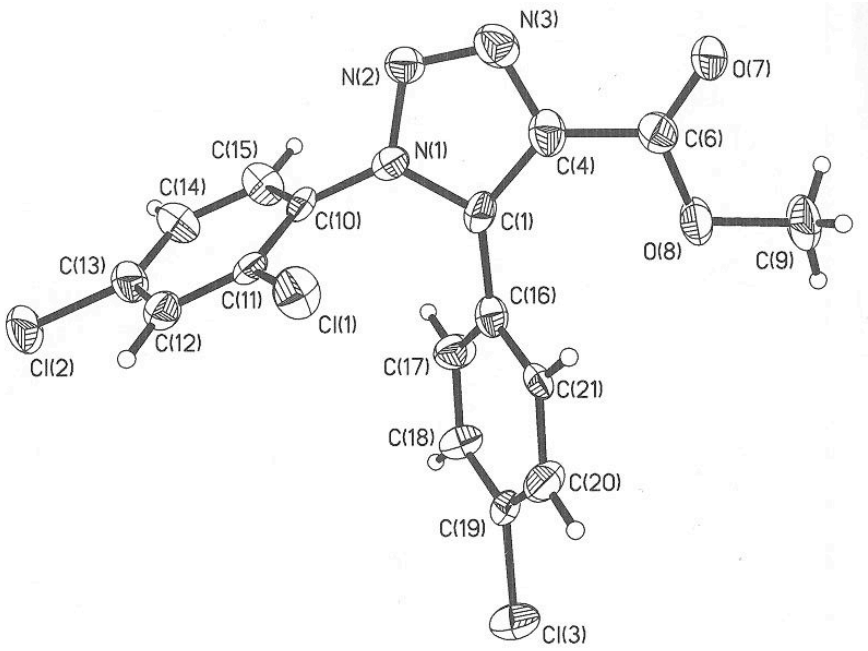
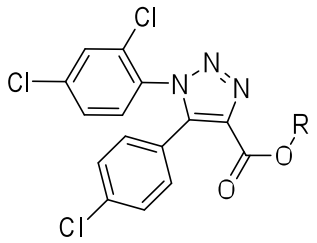


Figure 1.11 ORTEP Drawing of 4-methoxycarbonyl-1-(4-chlorophenyl)-5-(2,4-dichlorphenyl)-1,2,3triazole **30a**.[32]

The esters were evaluated in vitro for binding affinity at CB1 receptors (**Table 1.3**). The *n*-propyl ester **33**, with a K_i value slightly higher than SR141716A, was the most potent derivative of the series. We noticed that it exhibited similar lipophilicity to that of SR141716A. The phenyl ester **36** also exhibited high affinity for CB1 receptors, but the affinity of the benzyl ester **37** was

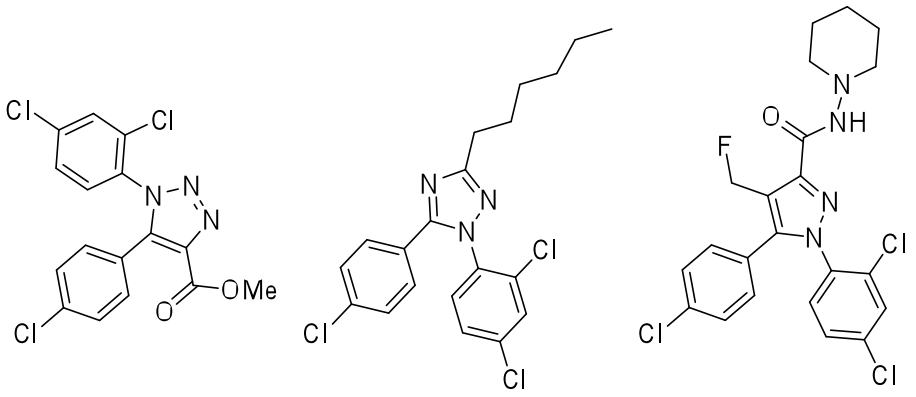
somehow diminished, even though they share very similar lipophilicity. The larger alkyl esters exhibited high lipophilicity and were difficult to handle in the binding assay. Preliminary binding studies indicated diminished binding affinity relative to propyl ester. In general, analogues with either decreased or increased lipophilicity relative to SR141716A exhibited diminished affinity. It seems to suggest that a narrow window of lipophilic character may exist for binding of these triazoles at CB1 receptors.



Cmpd[a]	Code	R	ClogP[b]	K_i (nM)
SR141716A			6.26	11.5[c]
30a	HS57-1	Methyl	5.32	66
32	HS57-3	Ethyl	5.68	180
33	HS57-4	*n*-Propyl	6.21	4.6
34	HS57-5	*n*-Butyl	6.70	I.R.[d]
35	HS57-6	*n*-Hexyl	7.62	I. R.
36	HS57-8	Phenyl	6.83	11
37	HS57-9	Benzyl	6.85	97
38	HS57-7	*c*-Hexyl	7.23	240

[a]All compounds were tested as the freebase.
[b] See Ref. 30.
[c]All values are the mean ± SEM of three experiments performed in triplicate.
[d] Inconsistent results.

Table 1.3 Inhibition of [^{3}H]SR141716A at CB1 Receptors



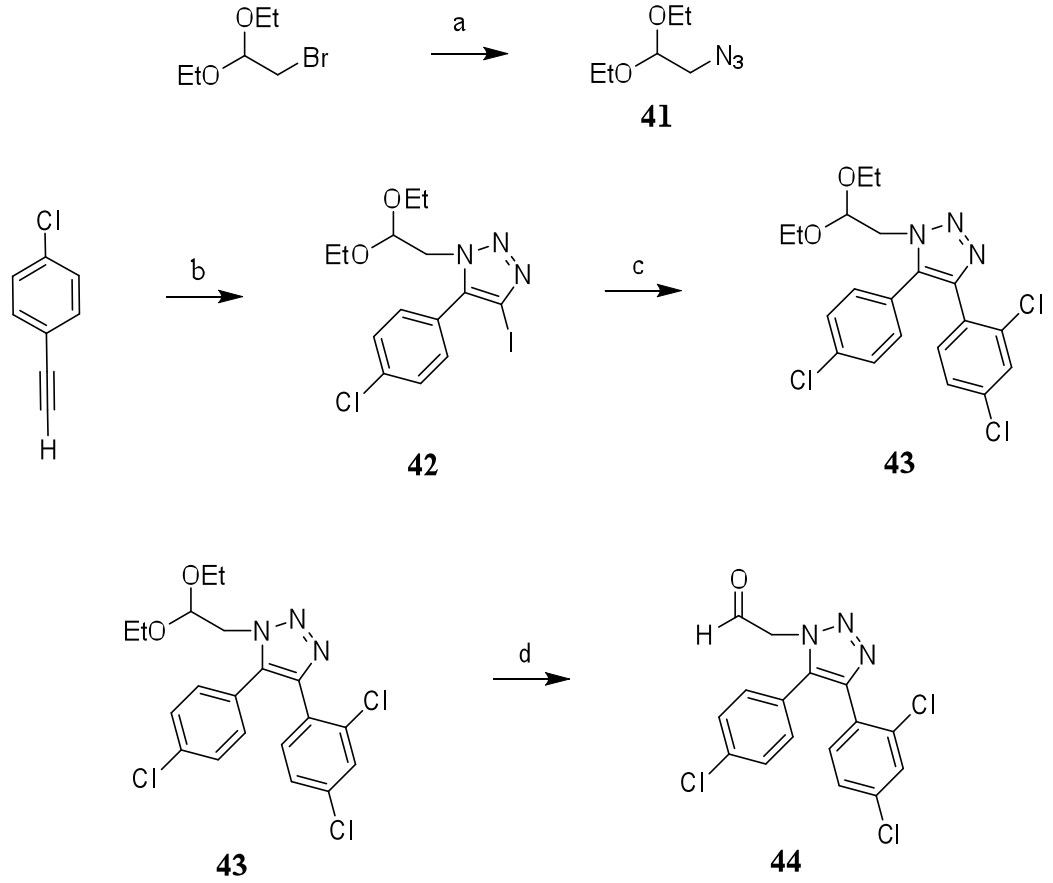
30a **39** **40**

Figure 1.12

The second class of compounds prepared were based on the 4,5-diaryltriazole ring system. They were prepared to investigate the effects of the orientation of triazole system on CB1 receptor affinity. Preliminary computational study confirmed that 4,5-diaryltriazole could also provide good overlap with SR141716A. In this vein, the 4,5-diarytriazoles would be expected to be equipotent to 1,5-diaryltriazoles. In addition, the 4,5-diaryltriazoles typically offer the advantage of lower lipophilicity over the corresponding 1,5-diarytriazoles. A series of 4,5-diaryltriazole derivatives were designed and synthesized with three very interesting compounds as structure stereotype: our lead compound **30a**, triazole **39** has been the only reported neutral antagonists. **40** exhibited a nanomolar binding potency.

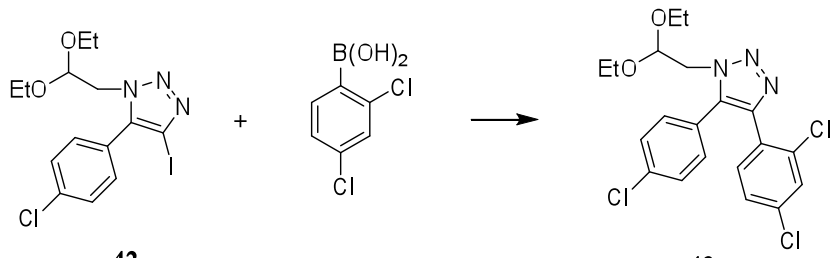
In the synthesis of 4,5-diphenyl-1,2,3-triazoles (**Scheme 1.7**), the acetal azide was selected to be the reaction partner of the 1,3-dipolar cylcoaddition reaction for the consideration of further functionalization at a later stage. The acetal group was stable in the early stage reactions, but when transformed to the aldehyde, it can react with a number of reagents to prepare a variety of analogues.

The 1,3-dipolar cycloadditon reaction of azide **41** and the alkyne gave a 4-magnesio-1,2,3-triazole intermediate which was treated with elemental iodine giving **42**. The heterocyclic aromatic iodide **42** was converted into the 4,5-diphenyl-1,2,3-triazole through Suzuki cross coupling reaction with 2,4-dichlorophenylboronic acid.



Scheme 1.7

Reagents and conditions: a) NaN_3, $DMSO/H_2O$, 100 ºC, 2 h; b) 1. EtMgCl (2 M in THF), THF, rt, 1 h; 2. 2,4-dichlorophenyl azide, 50 ºC, 2 h; 3. I_2, THF, 10 min; c) 2,4-Dichlorophenylboronic acid, $Pd_2(dba)_3$ (5%mol), PCy_3 (12%mol), K_3PO_4 (1.7 equiv), THF/H_2O, 110 ºC, 16 h; d) Me_3SiI, $CHCl_3$, rt, 1 h.

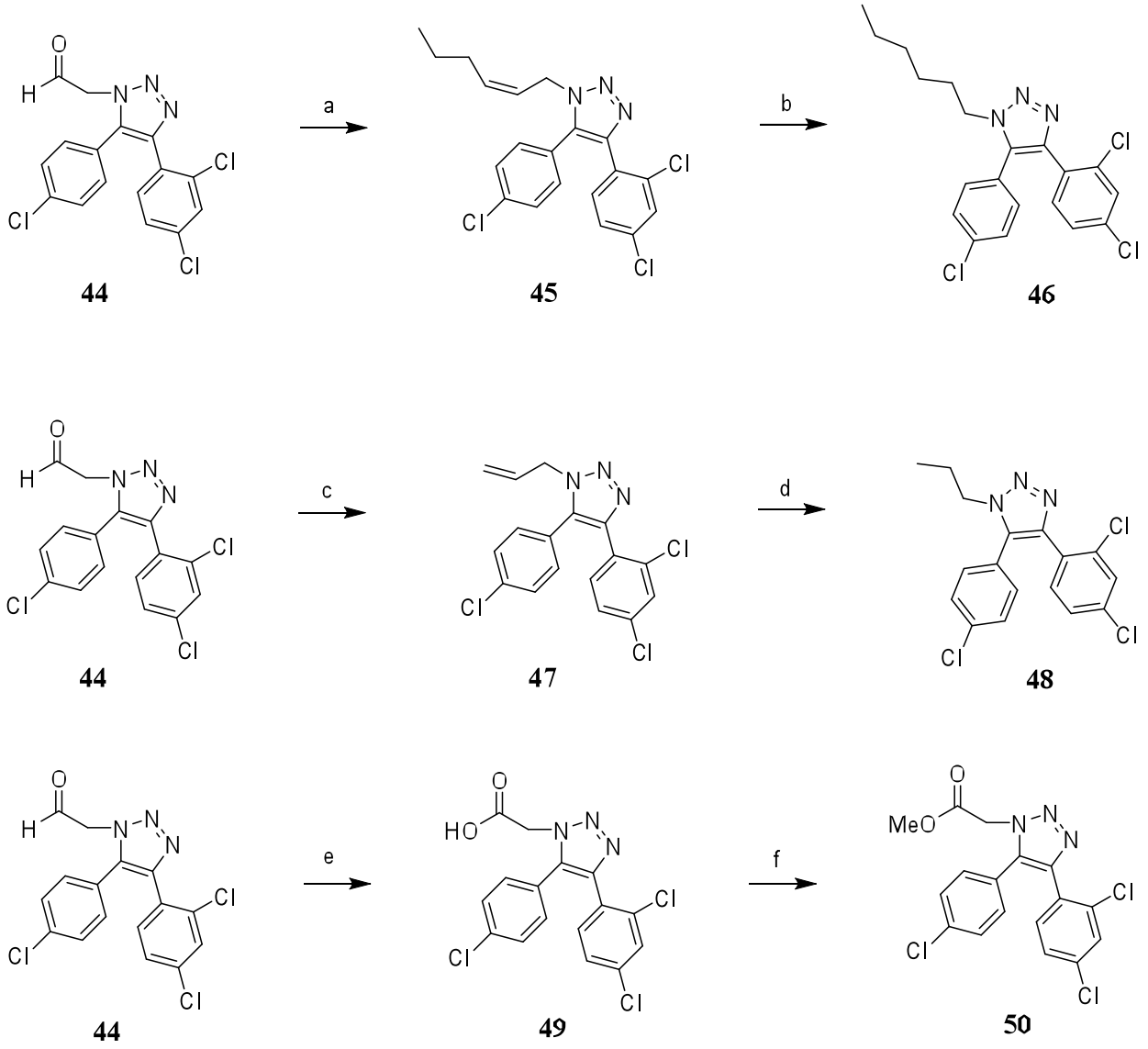


42 **43**

Entry	Catalyst	Solvent	Temperature	Time	Yield
1	$Pd(PPh_3)_4$, K_2CO_3	THF	rt/50°C	24 hr.	NR
2	$Pd_2(dba)_3$ (1.5%) $P(t\text{-}Bu)_3$ (4.2%) KF (3.3 equiv)	THF	rt/50°C	24 hr.	NR
3	$Pd_2(dba)_3$ (1.0%) PCy_3 (2.4 %) K_3PO_4(1.7 equiv)	Dioxane/H_2O (2:1)	100°C	18 hr.	62%
4	$Pd_2(dba)_3$ (1.0%) PCy_3 (2.4 %) K_3PO_4(1.7 equiv)	THF/H_2O (2:1)	70°C	20 hr.	75%
5	$Pd_2(dba)_3$ (5%) PCy_3 (12 %) K_3PO_4(1.7 equiv)	THF/H_2O (4:1)	110°C	16 hr.	98%

Table 1.4 Suzuki Cross Coupling

As demonstrated in **Table 1.4**, we focused on the protocols that have been reported to successfully work on heterocyclic substrates especially the nitrogen containing heterocycles. Although essentially no desired product was determined from the first two reaction we ran (**Entry 1, Entry 2**), the methodology developed by Fu and coworkers gave the product in a 62% for the first run. With a simple screening of the reaction conditions, the desired product was obtained in an excellent yield (98%).

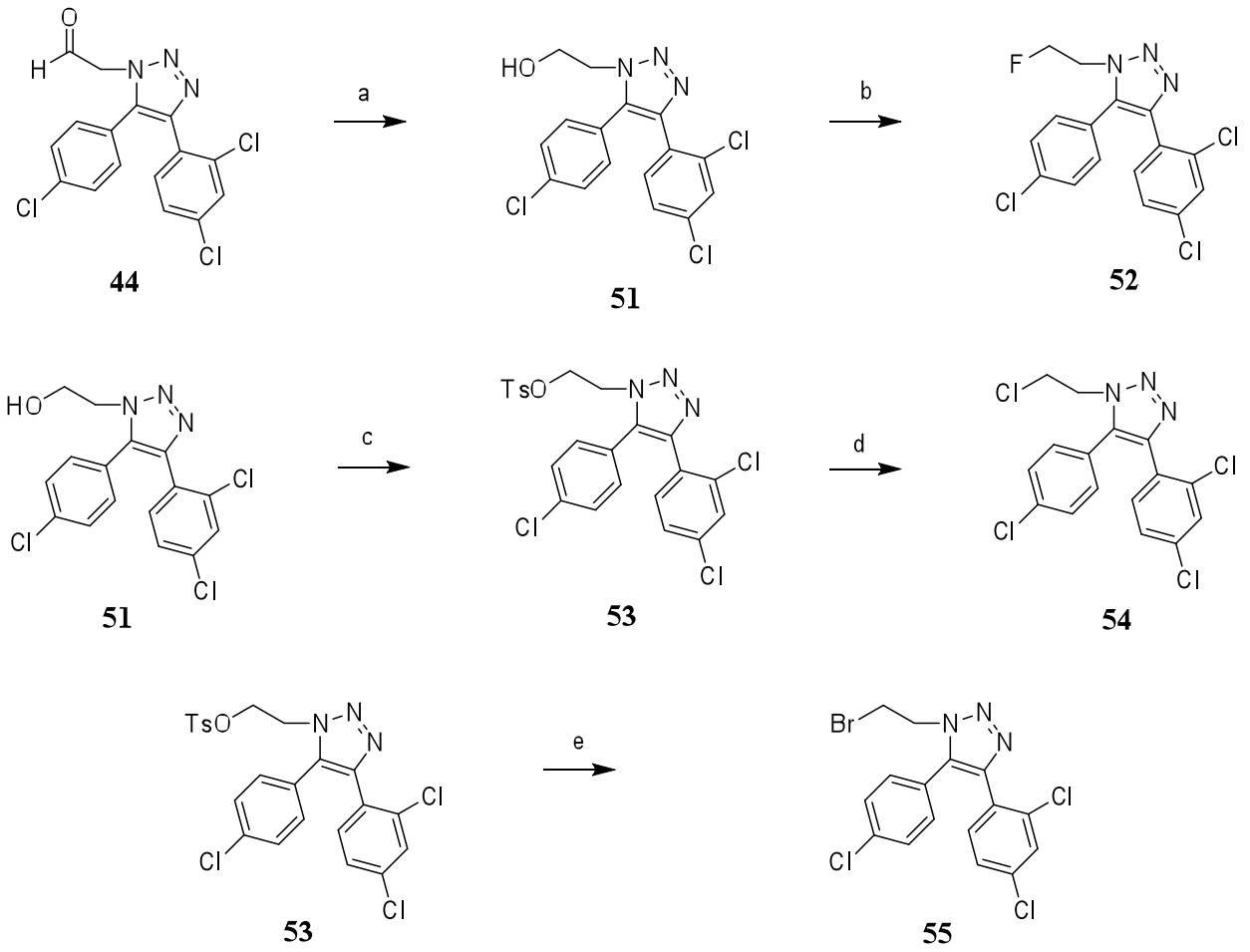


Scheme 1.8

Reagents and conditions: a) $Ph_3P(Br)(CH_2)_3CH_3$, *t*-BuOK, THF, 0 ºC, 1.5 h; b) H_2, 10% Pd/C, MeOH, rt, overnight; c) $Ph_3P(Br)CH_2CH_3$, t-BuOK, THF, 0 ºC, 1.5 h; d) H_2, 10% Pd/C, MeOH, rt; e) $NaClO_2$, NaH_2PO_4, 2-Methyl-2-butene, Acetone/H_2O, rt, 2 h, overnight; f) $TMSCHN_2$, toluene/MeOH, rt, 10 min.

With aldehyde **44** at hand, a number of analogues with different groups at N-1 position were synthesized. Wittig olefination reaction of **44** with $Ph_3P(Br)(CH_2)_3CH_3$ or $Ph_3P(Br)CH_2CH_3$ gave **45** and **47** respectively which were reduced to **46** and **48** by a simple hydrogenation. Aldehyde

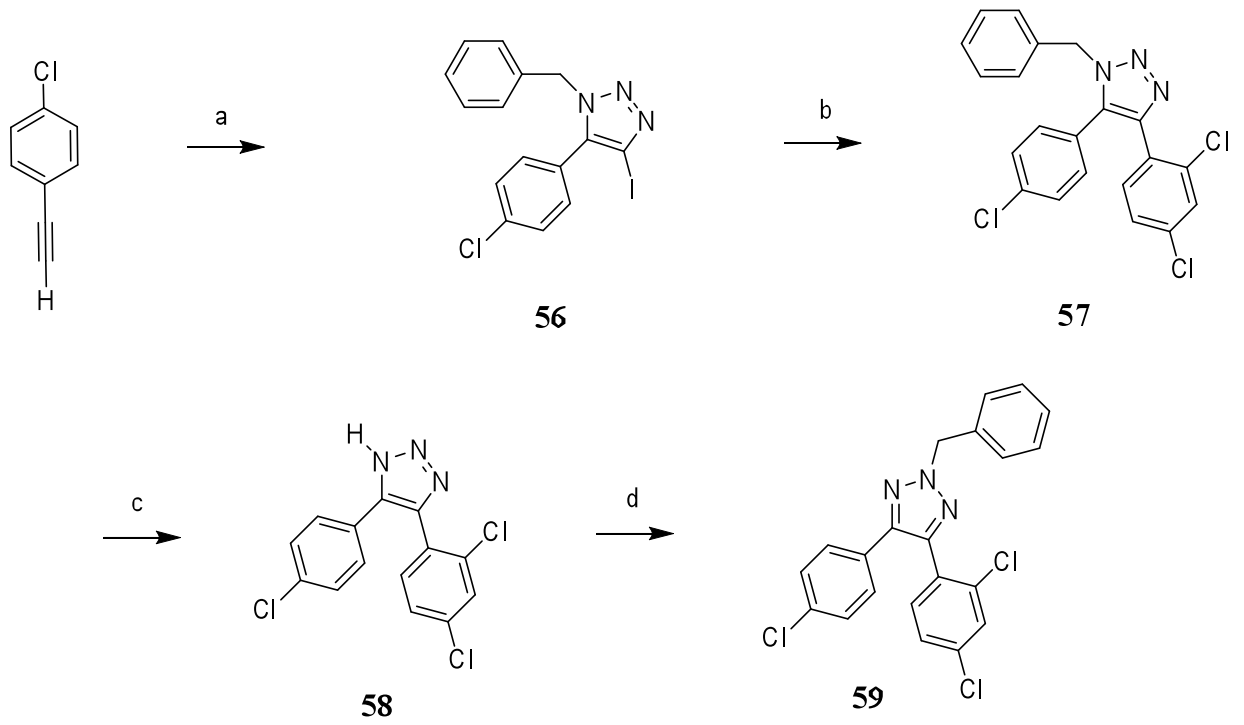
44 was efficiently oxidized to carboxylic acid **49** using sodium chlorite as oxidizing agent. Carboxylic **50** was then methylated giving ester **50**.



Scheme 1.9

Reagents and conditions: a) $NaBH_4$, MeOH, 0 ºC; b) DAST, CH_2Cl_2, -78 ºC to rt; c) TsCl, Pyridine, rt, 15 min; d) LiCl, Ethanol, reflux, 12 h; e) LiBr, Acetone, reflux, 16 h.

Aldehyde **44** was reduced to alcohol **51** which was also converted into fluoride **53**. When the hydroxyl group in **51** was transformed to tosylate, a better leaving group, chloride **54** and bromide **56** were prepared from tosylate **53**.



Scheme 1.10

Reagents and conditions: a) 1. EtMgCl (2 M in THF), THF, rt, 1 h; 2. Benzyl azide, 50 ºC, 2 h; 3. I_2, THF, 10 min; b) 2,4-Dichlorophenylboronic acid, $Pd_2(dba)_3$ (5%mol), PCy_3 (12%mol), K_3PO_4 (1.7 equiv), THF/H_2O, 110 ºC, 16 h; c) t-BuOK (1 M in THF), O_2, DMSO, rt, 2 h; d) NaH, DMF, Benzyl bromide.

The N2-substituted-4,5-diphenyl-1,2,3-triazole analogues were synthesized from the intermediate N1-H-4,5-diphenyl-1,2-3-triazole **58**. No methodology available to prepare **58** directly and it had to obtained from the deprotection of a N1-substituted-4,5-diphenyl-1,2,3-triazole. Therefore, the selection of the azide for the 1,3-dipolar reaction was important. The azide functional groups associated with the azide had to be stable enough through the Grignard ring closure reaction and the following Suzuki cross coupling. At a later stage, the functional group should be removed readily to release an active hydrogen. Commercially available benzyl azide was a great candidate for our synthesis.

The 4-magnesio-1,2,3-triazole intermediate was trapped with elemental iodine giving **56** which served as the coupling partner for the following Suzuki reaction under the reaction conditions described previously. Although the most employed hydrogenation could not remove the benzyl group from triazole **57,** a novel methodology reported by Aubrey A. Haddach *et. al*. successfully worked on our substrate and gave **58** in a high yield.[35]

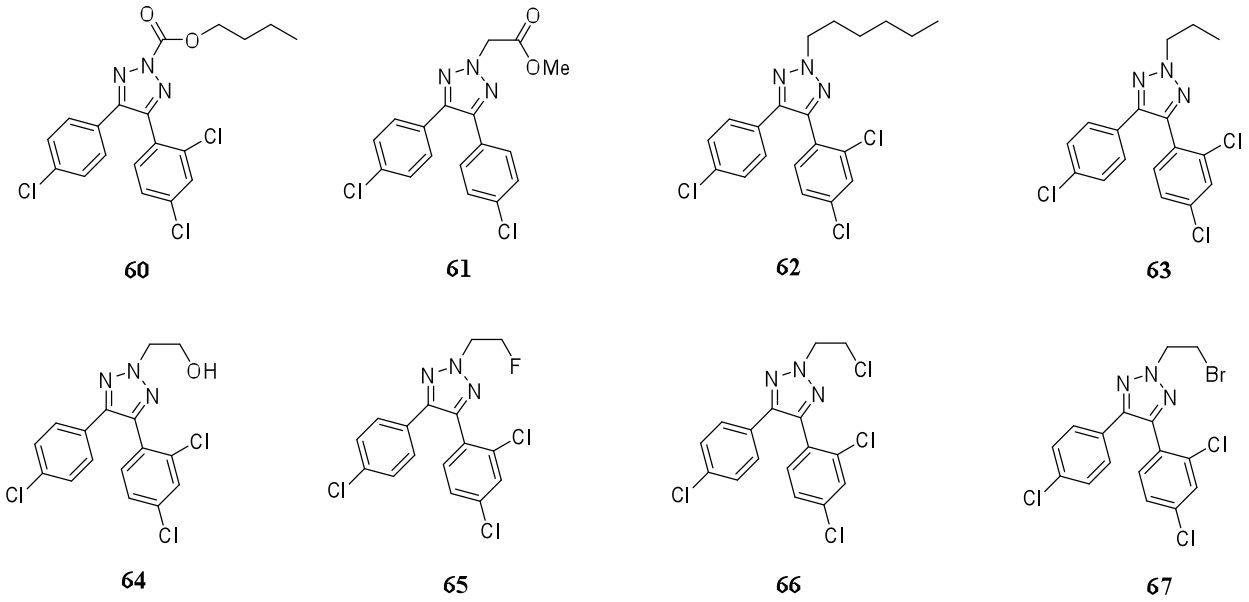
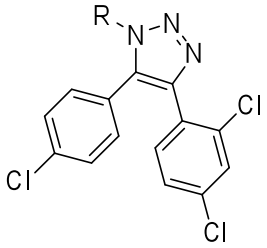
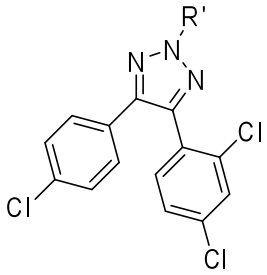


Figure 1.13

With the active hydrogen, **58** was treated with sodium hydride and reacted straightforwardly with a variety of electronphilic groups giving nine N2-substituted-4,5-diphenyl-1,2,3-triazole analogues. They are **59**, butyl ester **60**, methyl ester **61**, hexyl analogue **62**, propyl analogue **63**, alcohol **64**, fluoride **65**, chloride **66**, and bromide **67**.

The binding affinity results of N1-substituted-4,5-diphenyl-1,2,3-triazoles and N2-substituted-4,5-diphenyl-1,2,3-triazoles were summarized in **Table 1.5**. Although most of the analogues only exhibited modest potency, the fluoride **65** (K_i = 72 nM) and the chloride **66** (K_i = 80 nM) were potent enough to be advanced into further biological evaluations

Cmpd[a]	Code	R or R'	ClogP[b]	K_i (nM)
SR141716A			6.26	11.5[c]
45	HS179	R = C_6H_{11}	6.66	I.R.[d]
48	HS192	R = C_3H_7	5.58	152
50	HS183	R = CH_2COOMe	4.34	247
51	HS184	R = CH_2CH_2OH	4.03	163
52	HS193	R = CH_2CH_2F	4.93	420
57	HS142	R = $CH_2C_6H_5$	6.55	187
59	HS216	R' = $CH_2C_6H_5$	7.44	230
60	HS147	R' = COOBu	5.55	30% inhibition[e]
61	HS226	R' = CH_2COOMe	5.23	855
64	HS 230	R' = CH_2CH_2OH	4.92	660
65	HS232	R' = CH_2CH_2F	5.82	72
66	HS251	R' = CH_2CH_2Cl	6.37	80
67	HS265	R' = CH_2CH_2Br	6.43	I.R.[d]

[a]All compounds were tested as the freebase.
[b] See Ref. 30.
[c]All values are the mean ± SEM of three experiments performed in triplicate.
[d] Inconsistent results.
ePercent inhibition at 100 μM

Table 1.5 Inhibition of [^{3}H]SR141716A at CB1 Receptors

1.4 CONLUSIONS

We started with designing the SR141716A derivative **22a** as our target molecule and developed chemical synthesis to prepare this compound. Our preliminary binding assay results revealed the ester **30a** was 10-fold more potent than **22a**. Better potency, together with other more optimal drug-like properties, ester **30a** was chosen to be our lead compound. With this lead compound, a series of esters (**32-38)**, N1-substituted-4,5-diphenyl-1,2,3-triazoles (**45-55**), and

N2-substituted-4,5-diphenyl-1,2-3-triazoles (**59-67**) were synthesized. Six compounds (**30a**, **33**, **36**, **37**, **65**, **66**) exhibited good potency binding to CB1 receptors (K_i <100 nM) and they are currently being evaluated to determine efficacy. Based on these results, an extensive study is undergoing in our research laboratory searching for novel selective CB1 receptor antagonists.

1.5 EXPERIMENTAL SECTION

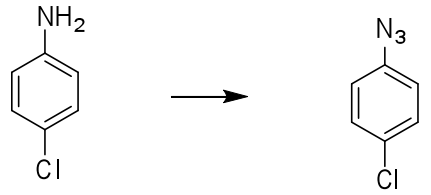
General Experimental Methods

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous dichloromethane was purchased from Mallinckrodt Baker, Inc. Research Technology Branch, National Institute on Drug Abuse. Proton and carbon NMR were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in deuterated chloroform ($CDCl_3$) from Cambridge Isotope Laboratories, Inc. ^{1}H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to chloroform-*d* (77.0 ppm). Melting points (mp) were measured with an Electrothermal R Mel-Temp apparatus and are uncorrected.

$$Tf_2O + NaN_3 \xrightarrow[0\,^\circ C]{H_2O/CH_2Cl_2} TfN_3$$

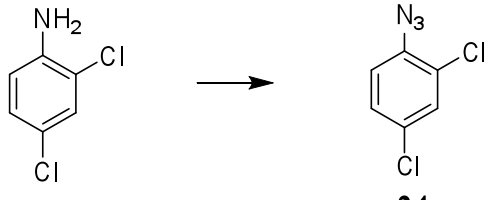
Triflyl azide Sodium azide (1.17 g, 18 mmol) was dissolved in a mixture of 4 mL water and 1.5 mL CH_2Cl_2 in a 20 mL glass vial. The mixture was cooled to 0 °C in an ice-water cold bath and trifluorosulfanic anhydride (0.85 g, 0.51 mL, 3 mmol) was added dropwise. Upon the completion of addition, the vial was sealed by a screw cap. The reaction was stirred at 0 °C for 2.5 hours. The mixture was poured into 10 mL of ice water and extracted with CH_2Cl_2.

Combined organic portions were washed by sat. $NaHCO_3$ aqueous solution. This triflyl azide solution was directly introduced to the following step.



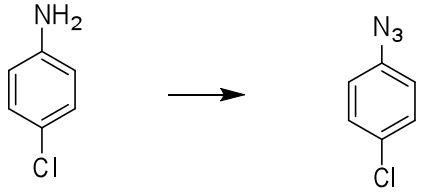
23

4-Chlorophenyl azide (**23**) Aniline (130 mg, 1.02 mmol) was dissolved in 1 mL of CH_2Cl_2 in a 20-mL glass vial. Triethylamine (0.42 mL) was added by one portion, followed by the addition of a solution of $CuSO_4.5H_2O$ (13 mg in 0.25 mL H_2O). To this solution was added the freshly made triflyl azide described above. MeOH was added dropwise until the solution was made homogeneous and the color of the reaction changed from light blue to dark. The reaction vial was sealed by a screw cap. The stirring continued for 2.5 hours until the process of reaction stopped indicated by TLC. The mixture was partitioned between 10 mL sat. $NaHCO_3$ and 10 mL CH_2Cl_2. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). Combined organic fractions were washed by sat. NaCl, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The dark brown oily residue was purified by a silica gel column eluting with hexanes affording 4-chlorophenyl azide **23** (125 mg, 82%) as a slightly yellowish oil. $R_f = 0.58$ (CH_2Cl_2/hexanes = 1:9).



24

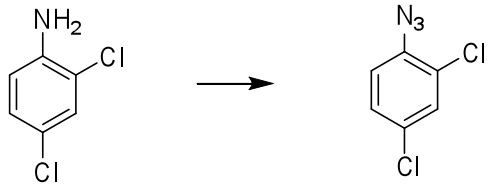
2,4-dichlorophenyl azide (**24**) 2,4-Dichloroaniline (172 mg, 1 mmol) was dissolved in 1 mL of CH_2Cl_2 in a 20-mL glass vial. Triethylamine (0.42 mL) was added by one portion, followed by the addition of a solution of $CuSO_4.5H_2O$ (13 mg in 0.25 mL H_2O). To this solution was added the freshly made triflyl azide from trifluorosulfanic anhydride (0.85 g, 0.51 mL, 3 mmol) by the procedure described above. MeOH was added dropwise until the solution was made homogeneous and the color of the reaction changed from light blue to dark. The reaction vial was sealed by a screw cap. The stirring continued at room and reaction process was monitored by TLC. After 2 hours, only a small amount of product was observed and longer reaction time up to 24 hours did not seem to drive the reaction. The mixture was partitioned between 10 mL sat. $NaHCO_3$ and 10 mL CH_2Cl_2. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). Combined organic fractions were washed by sat. NaCl, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The dark brown oily residue was purified by a silica gel column eluting with hexanes affording 2,4-dichlorophenyl azide **24** (15 mg, 8%) as a slightly yellowish oil. $R_f = 0.2$ (CH_2Cl_2/hexanes = 1:9).



23

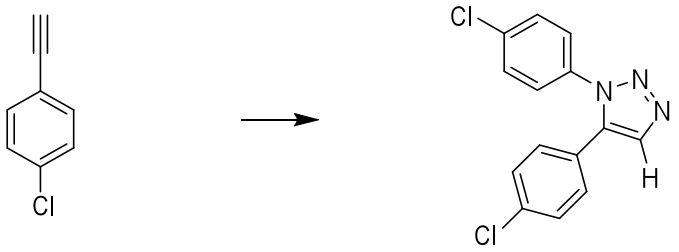
4-Chlorophenyl azide (**23**) NaN_3 (3.25g, 50 mmol) was suspended in the mixture of DMSO (25 mL) and H_2O (5 mL). The reaction apparatus was degassed and then filled with N_2. Sodium ascorbate (99.0 mg, 0.5 mmol) and CuI (190 mg, 1 mmol), the ligand (S, S)-(+)-N,N'-Dimethyl-1,2-cyclohexanediamine (213 mg, 1.5 mmol), and 4-chloro-iodobenzene (2.38 g, 10 mmol) were added to the flask consecutively. The mixture was heated at 100 °C. When the progress of the

reaction was stopped, it was worked up by a mixture of brine (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL × 2). The combined organic phases were washed with brine (30 mL × 3), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by a short flash chromatography (SiO_2, Hexanes) affording 4-chlorophenyl azide **23** (1.41g, 9.2 mmol). R_f = 0.5 (Hexanes).



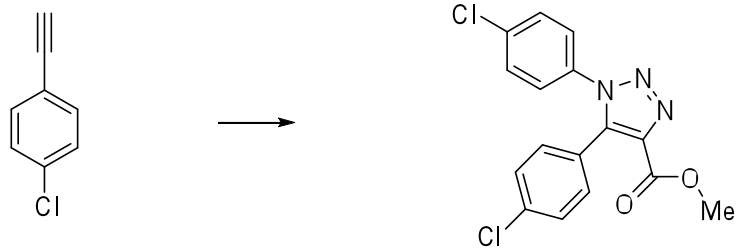
24

2,4-Dichlorophenyl azide (**24**) NaN_3 (3.25g, 50 mmol) was suspended in the mixture of DMSO (25 mL) and H_2O (5 mL). The reaction apparatus was degassed and then filled with Argon. Sodium ascorbate (99.0 mg, 0.5 mmol) and CuI (190 mg, 1 mmol), the ligand (S, S)-(+)-N,N'-Dimethyl-1,2-cyclohexanediamine (213 mg, 1.5 mmol), and 2,4-dichloro-iodobenzene (2.73 g, 10 mmol)were added to the flask consecutively. The mixture was heated at 100 °C. When the progress of the reaction was stopped, it was worked up by a mixture of brine (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL × 2). The combined organic phases were washed with brine (30 mL × 3), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by a short flash chromatography (SiO_2, Hexanes) affording 2,4-dichlorophenyl azide (**24**) (0.846 g, 4.5 mmol). R_f = 0.2 (Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.27 (dd, *J* = 22, *JJ* = 6), 7.105 (d, *J* = 22). ^{13}C NMR ($CDCl_3$) δ 136.2, 130.8, 130.6, 128.3, 120.6, 102.6.



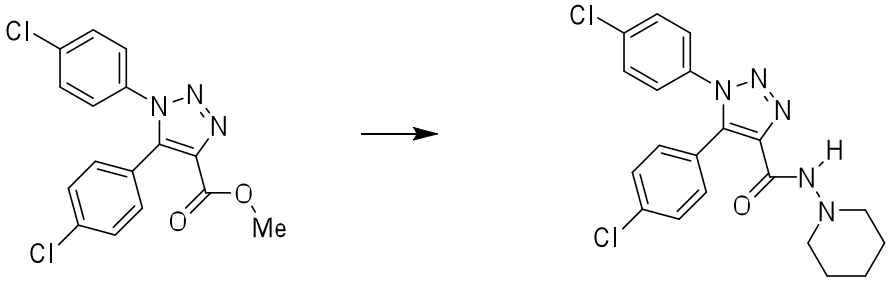
29b

1,5-bis(4-Chlorophenyl)-1H-1,2,3-triazole Under N_2, a solution of 4-chlorophenyl azide **23** (69 mg, 0.50 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.25 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made chlorophenyl azide (76 mg, 0.50 mmol) in 1 mL of THF was added dropwise. The mixture was stirred at room temperature for 2 hr. and then heated to 50 °C for 1 hr. The reaction was cooled down to 0 °C quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/Hexanes = 1/5) affording **29b** (126 mg, 87%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.64-7.30 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 136.8, 135.8, 135.5, 134.9, 133.7, 130.0, 129.8, 129.5, 126.4, 125.0. Anal. Calcd for $C_{14}H_9Cl_2N_3$: C, 57.95; H, 3.13; N, 14.48. Found: C, 58.08; H, 3.14; N, 14.35.



30b

Methyl 1,5-bis(4-chlorophenyl)-1H-1,2,3-triazole-4-carboxylate (30b) Under N_2, a solution of 4-chlorophenyl azide **23** (205 mg, 1.50 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.75 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made chlorophenyl azide (230 mg, 1.50 mmol) in 2 mL of THF was added dropwise. The mixture was stirred at room temperature for 2 hr. and then heated to 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of methyl Chloroformate (184 mg,1.95 mmol) in 5 mL THF at -20 °C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/Hexanes = 1/5) affording **30b** (350 mg, 67%) as a white solid. Mp: 172-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.40 (m, 8H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 140.0, 137.0, 136.8, 136.0, 135.4, 134.1, 131.7, 139.9, 139.2, 126.5, 123.8, 52.4. Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 55.19; H, 3.18; N, 12.07. Found: C, 55.43; H, 3.21; N, 12.07.

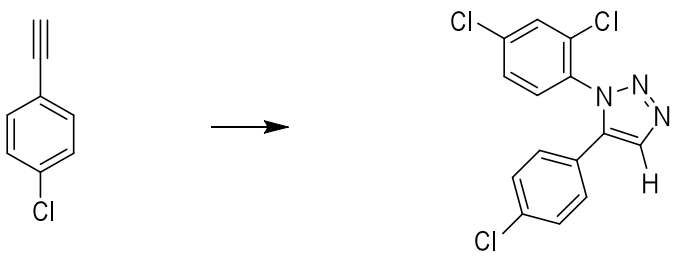


30b **22b**

1,5-bis(4-Chlorophenyl)-N-(piperidin-1-yl)-1H-1,2,3-triazole-4-carboxamide (22b) Methyl ester **30b** (306 mg, 0.88 mmol) was taken up in KOH (45 wt% in water, 2 mL) + 20 mL

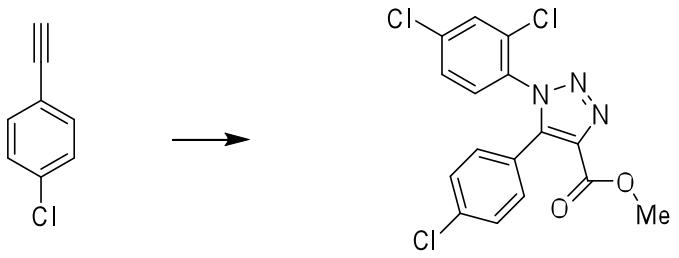
MeOH and heated to reflux for 2 hours. The reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in 3 mL of water and acidified by hydrochloric acid (1 N in water) to pH =2. White precipitate was extracted out with CH_2Cl_2 (2 x 20 mL). Combined organic fractions were washed by sat. NH_4Cl, dried over Na_2SO_4, filtered, and concentrated in vacuo.

The carboxylic acid was then dissolved in 10 mL of CH_3CN and cooled to 0 °C. To this solution diisopropylethylamine (DIPEA, 239 mg, 1.85 mmol) was added dropwise. HBTU (367 mg, 0.97 mmol) in 4 mL of CH_3CN was added one portion followed by the slow addition of 1-aminopiperidine (97 mg, 0.97 mmol). After the addition was complete, cold bath was removed and the reaction was stirred at room temperature for 16 hours. The mixture was then partitioned between 5% $NaHCO_3$ (20 mL) + CH_2Cl_2 (50 mL). The organic fraction was separated and the aqueous fraction was extracted with CH_2Cl_2 (2 x 30 mL). Combined organic portions were washed by sat. NaCl, filtered, and concentrated in vacuo. The residue was purified by a column chromatography (SiO_2, eluting with EtOAc/hexanes = 1:3) affording **22b** (344 mg, 0.82 mmol, 94%) as a white solid. R_f = 0.25 (EtOAc/hexanes = 1:2). Mp: 172-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.59-7.34 (m, 8H), 2.78 (t, 4H), 1.58-1.53 (m, 4H), 1.36-1.32 (m, 2H). ^{13}C NMR ($CDCl_3$) δ157.3, 138.2, 138.1, 136.2, 135.7, 134.2, 132.0, 129.7, 128.5, 126.5, 123.4, 56.9, 25.3, 23.2. Anal. Calcd for $C_{20}H_{19}Cl_2N_5O$: C, 57.70; H, 4.60; N, 16.82. Found: C, 57.66; H, 4.68; N, 16.67.



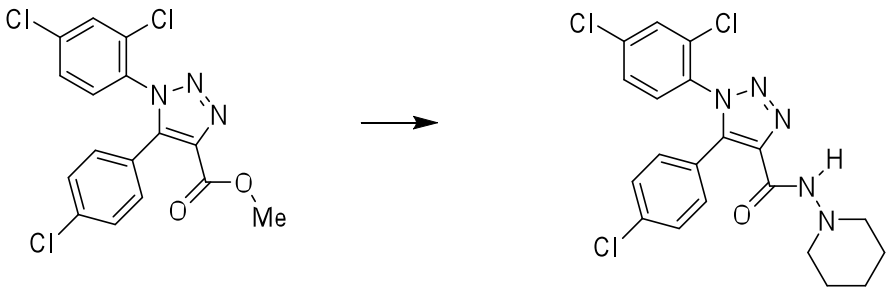
29a

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole Under N_2, a solution of 2,4-dichlorophenyl azide **24** (69 mg, 0.50 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.25 mL, 2 M in THF). Stirring was continued at 50 °C for 1 h. Then a solution of freshly made 2,4-dichlorophenyl azide (94 mg, 0.50 mmol) in 1 mL of THF was added dropwise. The mixture was stirred at room temperature for 2 hr. and then heated to 50 °C for 1 hr. The reaction was cooled down to 0 °C quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/Hexanes = 1/5) affording **29a** (138 mg, 85%) as a light yellow solid. Mp: 140-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.96-7.28 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 138.6, 135.8, 137.4, 136.0, 133.2, 132.7, 132.6, 130.9, 130.3, 129.6, 129.2, 128.6, 124.9. Anal. Calcd for $C_{14}H_8Cl_3N_3$: C, 51.80; H, 2.48; N, 12.95. Found: C, 51.80; H, 2.48; N, 12.79.



30a

Methyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (**30a**) Under N_2, a solution of 2,4-dichlorophenyl azide (205 mg, 1.50 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.75 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (282 mg, 1.60 mmol) in 2 mL THF was added dropwise. The mixture was stirred at room temperature for 2 hr. and then heated to 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of methyl Chloroformate (184 mg,1.95 mmol) in 5 mL THF at -20°C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/Hexanes = 1/5) affording **30a** (0.35 g, 61%). R_f = 0.28 (EtOAc/Hexanes = 1:4). Mp: 158-160 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93-7.40 (m, 7H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 142.0, 137.9, 136.9, 136.3, 132.8, 132.1, 131.4, 130.8, 130.4, 129.0, 128.5, 123.3, 52.5. Anal. Calcd for $C_{16}H_{10}Cl_3N_3O_2$: C, 50.22; H, 2.63; N, 10.98. Found: C, 49.95; H, 2.68; N, 10.70.

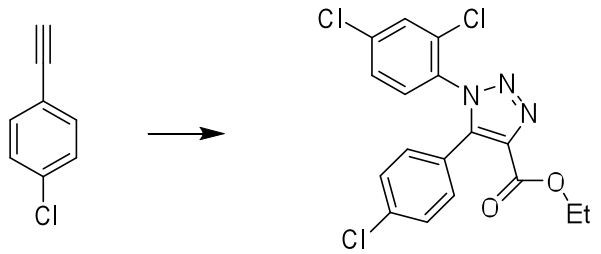


30a **22a**

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-1,2,3-triazole-4-carboxamide (**22a**) Methyl ester **30a** (210 mg, 0.55 mmol) was taken up in KOH (45 wt% in

water, 2 mL) + 20 mL MeOH and heated to reflux for 2 hours. The reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in 3 mL of water and acidified by hydrochloric acid (1 N in water) to pH =2. White precipitate was extracted out with CH_2Cl_2 (2 x 20 mL). Combined organic fractions were washed by sat. NH_4Cl, dried over Na_2SO_4, filtered, and concentrated in vacuo.

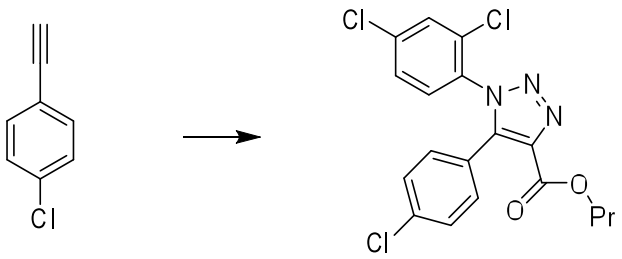
The carboxylic acid was then dissolved in 10 mL of CH_3CN and cooled to 0 °C. To this solution diisopropylethylamine (DIPEA, 149 mg, 1.16 mmol) was added dropwise. HBTU (227 mg, 0.61 mmol) in 4 mL of CH_3CN was added one portion followed by the slow addition of 1-aminopiperidine (61 mg, 0.61 mmol). After the addition was complete, cold bath was removed and the reaction was stirred at room temperature for 16 hours. The mixture was then partitioned between 5% $NaHCO_3$ (20 mL) + CH_2Cl_2 (50 mL). The organic fraction was separated and the aqueous fraction was extracted with CH_2Cl_2 (2 x 30 mL). Combined organic portions were washed by sat. NaCl, filtered, and concentrated in vacuo. The residue was purified by a column chromatography (SiO_2, eluting with EtOAc/hexanes = 1:3) affording **30a** (234 mg, 0.52 mmol, 94%) as a white solid. R_f = 0.2 (EtOAc/hexanes = 1:3). Mp: 209-212 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.88-7.31 (m, 7H), 2.78 (t, 4H), 1.55-1.52 (m, 4H), 1.35-1.31 (m, 2H). ^{13}C NMR ($CDCl_3$) δ157.2, 140.1, 137.5, 137.3, 136.2, 132.5, 132.2, 131.6, 130.6, 130.5, 129.7, 128.4, 128.3, 123.1, 56.9, 25.4, 23.2. Anal. Calcd for $C_{20}H_{18}Cl_3N_5O$: C, 53.29; H, 4.03; N, 15.54. Found: C, 53.01; H, 4.10; N, 15.30.



32

Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (32a)

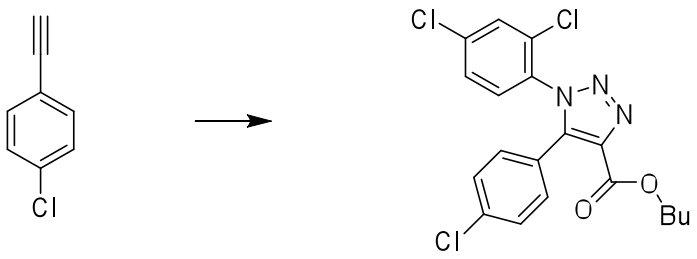
Under N_2, a solution of 1-chloro-4-ethynyl-benzene (232 mg, 1.70 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.85 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (320 mg, 1.70 mmol) in 2 mL THF was added by dropwise. The mixture was heated at room temperature for 2 hr. and then at 50 °C for 1 hr. The reaction mixture was cooled down to room temperature and added dropwise to the solution of ethyl chloroformate (221 mg,2.04 mmol) in 5 mL THF at -20 °C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/Hexanes = 1/5) affording **32** (370 mg, 55%) as a white solid. Mp: 135-136 °C. R_f = 0.5 (Acetone: $CHCl_3$:hexanes = 1:4:5). Mp: 135-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.36 (m, 7H), 4.246 (q, 2H), 1.167 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 160.9, 137.9, 136.9, 133.0, 132.2, 132.4, 130.8, 130.4, 129.0, 128.5, 123.5, 61.7, 14.4. Anal. Calcd for $C_{17}H_{12}Cl_3N_3O_2$: C, 51.48; H, 3.05; N, 10.59. Found: C, 51.75; H, 3.07; N, 10.66.



33

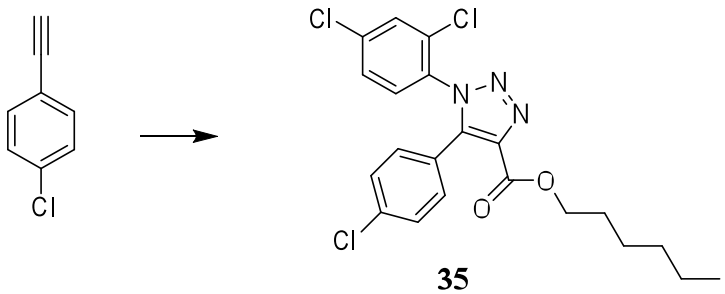
Propyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (33)

Under N_2, a solution of 1-chloro-4-ethynyl-benzene (109 mg, 0.8 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.4 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (75 mg, 0.4 mmol) in 2 mL THF was added by dropwise. The mixture was heated at room temperature for 2 hr. and then at 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of propyl chloroformate (63.4 mg, 0.52 mmol) in 5 mL THF at -20°C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by running a flash chromatography (SiO_2, EtOAc/Hexanes = 1/5) affording **33** (93.4 mg, 57%). R_f = 0.3 (EtOAc/Hexanes = 1:5). Mp: 117-118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.39 (m, 7H), 4.145 (t, 2H), 1.539 (m, 2H), 0.747 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 160.9, 141.8, 137.8, 136.7, 136.6, 132.8, 132.1, 131.4 130.7, 130.4, 128.9, 128.4, 123.6, 67.2, 22.0, 10.4. Anal. Calcd for $C_{18}H_{14}Cl_3N_3O_2$: C, 52.62; H, 3.44; N, 10.23. Found: C, 52.90; H, 3.47; N, 10.25.



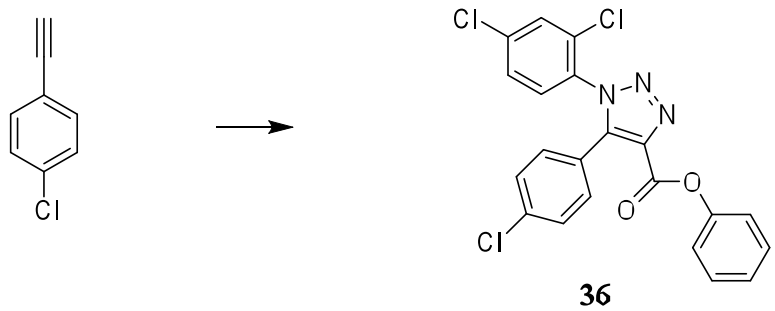
34

Butyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (**34**) Under N_2, a solution of 1-chloro-4-ethynyl-benzene (68 mg, 0.5 mmol) in 2 mL was added dropwise to Ethyl magnesium chloride (0.25 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (94 mg, 0.5 mmol) in 1 mL THF was added by dropwise. The mixture was heated at room temperature for 2 hr. and then at 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of butyl chloroformate (88 mg, 0.65 mmol) in 5 mL THF at -20°C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/Hexanes = 1:5) affording **34** (127 mg, 60%) as a white solid. R_f = 0.34 (EtOAc/Hexanes = 1:4). Mp: 108-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.39 (m, 7H), 4.17 (t, 2H), 1.48 (m, 2H), 1.10 (m, 2H), 0.80 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 160.9, 141.8, 137.8, 136.7, 132.8, 132.1, 131.4 130.7, 130.4, 128.9, 128.4, 123.6, 65.5, 30.6, 19.2, 13.8. Anal. Calcd for $C_{19}H_{16}Cl_3N_3O_2$: C, 53.73; H, 3.80; N, 9.89. Found: C, 53.95; H, 3.81; N, 9.89.



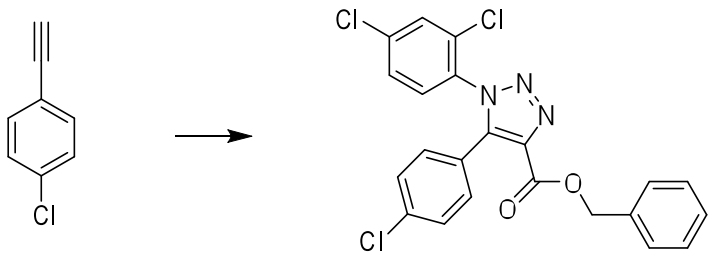
35

Hexyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (35) Under N_2, a solution of 1-chloro-4-ethynyl-benzene (82 mg, 0.6 mmol) in 2 mL was added dropwise to Ethyl magnesium chloride (0.30 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (113 mg, 0.60 mmol) in 2 mL THF was added by dropwise. The mixture was heated at room temperature for 2 hr. and then at 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of hexyl chloroformate (129 mg, 0.78 mmol) in 5 mL THF at -20 °C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/Hexanes = 1:5) affording **35** (163 mg, 60%) as a white solid. R_f = 0.33 (EtOAc/Hexanes = 1:5). Mp: 89-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.39 (m, 7H), 4.16 (t, 2H), 1.47 (m, 2H), 1.22-1.02 (m, 6H), 0.83 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 160.9, 141.8, 137.8, 136.8, 135.4, 132.8, 132.1, 131.4 130.7, 130.4, 128.9, 128.4, 123.6, 65.8, 31.6, 28.6, 25.7, 22.7, 14.1. Anal. Calcd for $C_{21}H_{20}Cl_3N_3O_2$: C, 55.71; H, 4.45; N, 9.28. Found: C, 55.62; H, 4.52; N, 9.06.



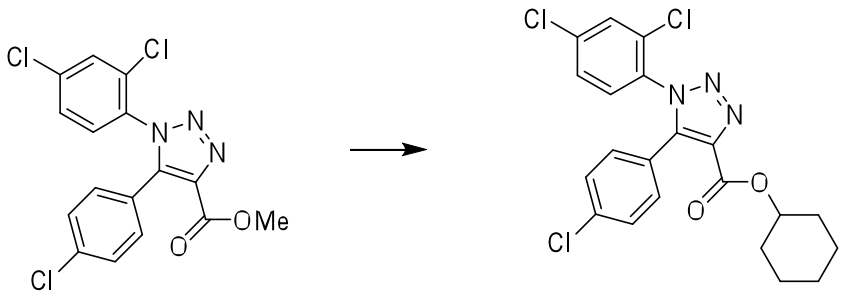
36

Phenyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate Under N_2, a solution of 1-chloro-4-ethynyl-benzene (150 mg, 1.10 mmol) in 2 mL was added dropwise to ethyl magnesium chloride (0.55 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (207 mg, 1.10 mmol) in 2 mL THF was added by dropwise. The mixture was heated at room temperature for 2 hr. and then at 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of phenyl chloroformate (206 mg,1.43 mmol) in 5 mL THF at -20°C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/Hexanes = 1:4) affording phenyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (352 mg, 72%). R_f = 0.29 (EtOAc/Hexanes = 1:4). Mp: 205-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.21 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 169.4, 150.4, 142.9, 138.0, 137.0, 135.9, 132.8, 132.0, 131.4, 130.8, 130.4, 129.7, 129.0, 128.6, 126.4, 123.1, 121.7. Anal. Calcd for $C_{21}H_{12}Cl_3N_3O_2$: C, 56.72; H, 2.72; N, 9.45. Found: C, 55.57; H, 2.79; N, 9.47.



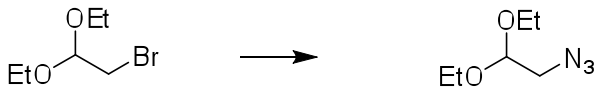
37

Benzyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (**37**) Under N_2, a solution of 1-chloro-4-ethynyl-benzene (41 mg, 0.3 mmol) in 2 mL was added dropwise to Ethyl magnesium chloride (0.15 mL, 2 M in THF). Stirring was continued at 50 °C for 1 hr. Then a solution of freshly made 2,4-dichlorophenyl azide (56 mg, 0.3 mmol) in 2 mL THF was added by dropwise. The mixture was heated at room temperature for 2 hr. and then at 50 °C for 1 hr. The solution was cooled down to room temperature and added dropwise to the solution of benzyl chloroformate (67 mg, 0.39 mmol) in 5 mL THF at -20°C. After stirring for 10 minutes, the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with EtOAc (30 mL). The organic fraction was separated. The aqueous fraction was extracted with EtOAc (30 mL × 2). Combined organic fractions were washed with brine (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/CH_2Cl_2/hexanes = 1:4:5) affording **37** (105 mg, 76%) as a white solid. R_f = 0.43 (EtOAc/CH_2Cl_2/hexanes = 1:4:5). Mp: 148-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.21 (m, 12H), 5.27 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 160.6, 142.0, 137.8, 136.7, 136.5, 135.2, 132.8, 132.0, 131.3, 130.7, 130.3, 128.9, 128.7, 128.6, 128.5, 128.4, 123.4, 67.1. Anal. Calcd for $C_{22}H_{14}Cl_3N_3O_2$: C, 57.64; H, 3.08; N, 9.16. Found: C, 57.84; H, 3.21; N, 9.08.



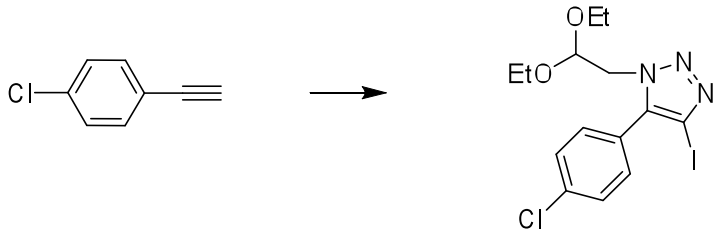
30a **38**

Cyclohexyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (**38**) A flame dried 50-mL round bottomed flask was vacuumed and backfilled with N_2. The flask was charged with cyclohexanol (20 mg, 0.2 mmol) in 10 mL of anhydrous THF. The solution was cooled to 0 °C and *n*-butyl lithium (2.5 M in hexanes, 0.18 mmol) was added slowly. After stirring for 10 minutes, methyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (77 mg, 0.2 mmol) in 2 mL of anhydrous THF was added dropwise. The resultant solution was stirred for 1 hour and poured into 30 mL ice water in a separatory funnel and extracted with EtOAc (2 x 30 mL). The combined organic fractions were washed by sat. NaCl, dried on anhydrous $MgSO_4$, filtered, and purified by running through a thin pad of silica gel. The solution was concentrated in vacuo affording **38** (89 mg, 99%) as a white solid. Mp: 138-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.40 (m, 7H), 4.89 (m, 1 H), 1.73 (m, 1H), 1.42-1.17 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 160.3, 141.6, 137.8, 137.1, 136.7, 132.9, 132.2, 131.4, 130.8, 130.4, 128.9, 128.4, 123.8, 74.4, 31.6, 25.3, 23.8. Anal. Calcd for $C_{21}H_{18}Cl_3N_3O_2$: C, 55.96; H, 4.03; N, 9.32. Found: C, 55.96; H, 3.98; N, 9.22.



41

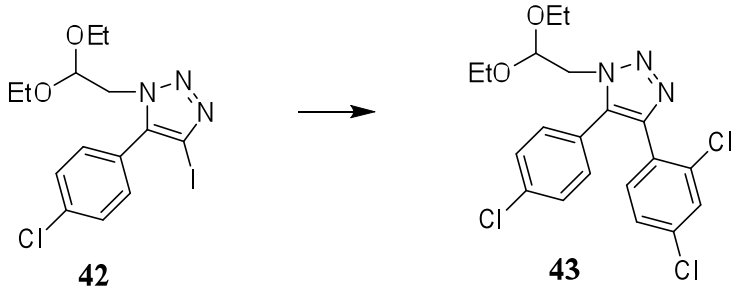
2-Azido-1,1-diethoxyethane (41) A 50-mL round-bottomed flask was charged with 2-bromo-1,1-diethoxyethane (1.97 g, 10 mmol) in 15 mL of DMSO. Sodium azide (1.95 g, 30 mmol) was added. The reaction was heated to 100 °C for 2 hours until the starting material spot disappeared on TLC. The reaction was cooled to room temperature, poured into 20 mL of ice water, and extracted with CH_2Cl_2 (2 x 50 mL). Combined organic fractions were washed by sat. NaCl (3 x 30 mL), dried on anhydrous Na_2SO_4, filtered, and concentrated in vacuo affording **41** (1.55 g, 97%) as a slightly yellowish oil. R_f = 0.2 (EtOAc/hexanes = 1:4).



42

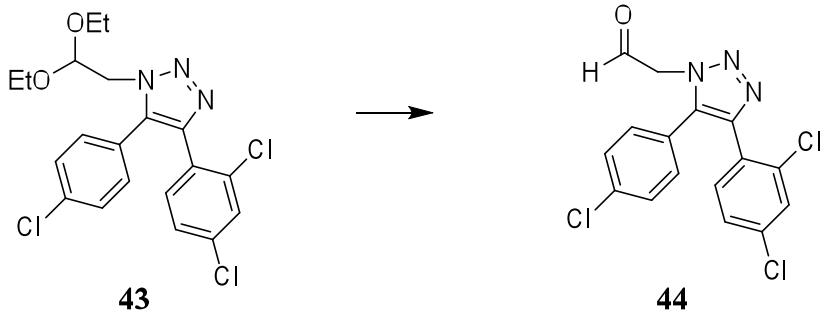
5-(4-Chlorophenyl)-1-(2,2-diethoxyethyl)-4-iodo-1H-1,2,3-triazole (42) A flame dried flash was filled with N_2 and charged with 1-chloro-4-ethynylbenzene (0.82 g, 6 mmol) in 10 mL of anhydrous THF. At room temperature ethylmagnesium chloride (2 M in THF, 3 mL) was added slowly. The reaction was stirred at room temperature for 1 hour before 2-azido-1,1-diethoxyethane (1.05 g, 6.6 mmol) in 3 mL of THF was added dropwise. The reaction was heated to 55 °C for 2 hours. Iodine (1.82 g, 7.2 mmol) in 4 mL of THF was added and stirring continued for 10 minutes. The reaction was cooled to room temperature and quenched by the addition of 10 mL of sat. NH_4Cl aqueous solution. The reaction mixture was partitioned between $Na_2S_2O_3$ solution (2 N in water, 20 mL) and EtOAc (50 mL). The organic fraction was separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). Combined organic fractions were washed by sat. NaCl, dried on anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The

residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:4) affording **42** (1.99 g, 4.7 mmol, 79%) as a yellowish oil. R_f = 0.4 (EtOAc/hexanes = 1:4). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.39 (m, 4H), 4.82 (t, 1H), 4.33 (d, 2H), 3.35 (t, 4H), 1.03 (q, 6H). ^{13}C NMR ($CDCl_3$) δ 140.2, 136.6, 131.7, 129.6, 124.6, 103.2, 90.2, 63.0, 55.8, 50.7, 16.1.



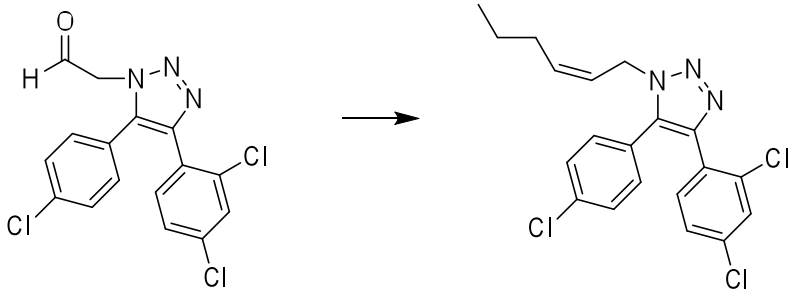
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-(2,2-diethoxyethyl)-1H-1,2,3-triazole (43)

42 (211 mg, 0.5 mmol), 2,4-dichlorophenyl boronic acid (105 mg, 0.55 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol), tricyclohexylphosphine (17 mg, 0.06 mmol), and K_3PO_4 (180 mg, 0.85 mmol)were suspended in 8 mL THF + 2 mL H_2O in a 30 mL pressure tube. The reaction vessel was purged with N_2, sealed, and heated to 120 °C for 16 hours in a oil bath. The reaction mixture was partitioned between water (40 mL) and EtOAc (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 40 mL). Combined organic fractions were washed by sat. NaCl, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/Hexanes = 1:3) affording **43** (216 mg, 0.49 mmol, 98%). ^1H NMR (400 MHz, $CDCl_3$) δ ^{13}C NMR ($CDCl_3$) δ 7.53-7.30 (m, 7H), 4.81 (t, 1H), 4.30 (d, 2H), 3.35 (t, 4H), 1.02 (q, 6H).



43 **44**

2-(5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazol-1-yl)acetaldehyde Under N_2**, 43** (661 mg, 1.5 mmol) was taken up in anhydrous chloroform (20 mL). Iodotrimethylsilane (360 mg, 0.245 mL, 1.8 mmol) was added to the solution and the reaction was stirred at room temperature for 1hours. Solvent was removed in vacuo and the residue was purified on a flash chromatography (SiO_2, EtOAc/Hexanes = 1:1) affording **44** (297 mg, 0.81 mmol) with 30% of starting material recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (S, 1H), 7.53-7.30 (m, 7H), 5.54 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 192.8, 142.7, 136.5, 135.7, 134.6, 133.1, 131.3, 131.2, 130.5, 130.0, 129.9, 129.6, 129.5, 128.0, 127.5, 124.7, 57.3.

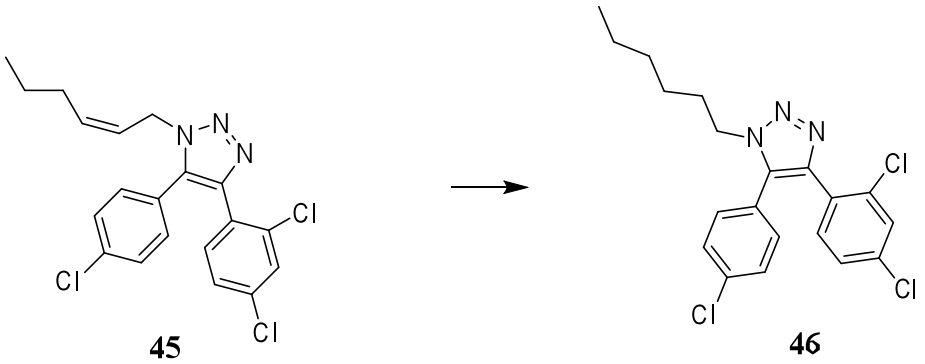


44 **45**

(Z)-5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-(hex-2-enyl)-1H-1,2,3-triazole (45) A oven dried 25-mL round bottomed flask was flushed with N_2 and charged with $Ph_3P(Br)(CH_2)_3CH_3$ (186 mg, 0.47 mmol) in 5 mL of anhydrous THF. At 0 °C, *t*-BuOK (1 M in THF, 0.47 mL) was added dropwise. To the resultant bright orange solution was slowly added **44** (114 mg, 0.31 mmol) dissolved in 1 mL of THF. The reaction was warmed up to room

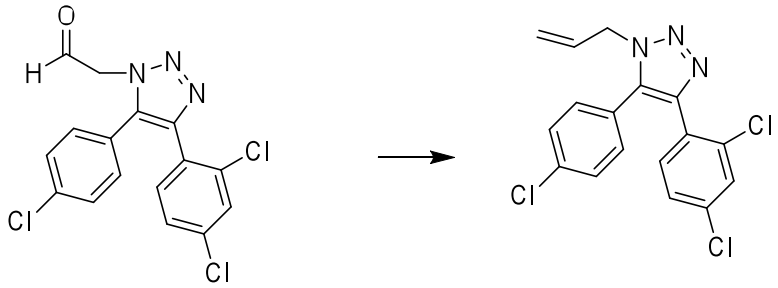
temperature and stirred for 1 hour before sat. NH_4Cl was added to quench the reaction. The reaction mixture was taken up in water (30 mL) + EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). Combined organic portions were washed by sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, EtOAc/hexanes = 1:6) affording **45** (93 mg, 74%) as a clear oil. Mp: 143-146 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.36 (m, 7H), 5.62-5.49 (m, 2H), 5.12 (d, 2H), 2.05 (m, 1H), 1.98 (q, 1H), 1.34 (m, 2H), 0.85 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 142.5, 135.9, 135.3, 135.2, 134.6, 133.2, 130.7, 129.9, 129.6, 129.5, 128.7, 127.4, 125.9, 123.1, 46.4, 29.6, 22.4, 13.8.

Anal. Calcd for $C_{20}H_{18}Cl_3N_3$: C, 59.06; H, 4.46; N, 10.33. Found: C, 58.52; H, 4.54; N, 10.02.



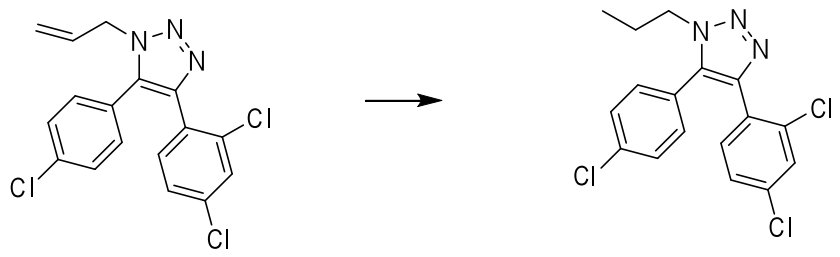
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-hexyl-1H-1,2,3-triazole (46) A 25-mL round-bottomed flask was charged with **45** (81 mg, 0.2 mmol). The flask was vacuumed and backfilled with H_2. 10 wt.% Pd on activated carbon (8 mg) and 10 mL MeOH was added. The reaction was stirred at room temperature for 4 hours. The reaction solution was filtered through a thin pad of celite and washed with 20 mL of EtOAc and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/hexanes = 1:7) affording **46** (76 mg, 0.18 mmol, 93%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.32 (m, 7H), 4.26 (t, 2H), 1.76

(m, 2H), 1.29-1.17 (m, 6H), 0.82 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 143.6, 136.4, 133.9, 131.5, 131.4, 130.1, 129.9, 129.4, 128.9, 128.8, 128.7, 128.2, 126.5, 48.6, 31.2, 30.2, 26.2, 22.5, 14.1.



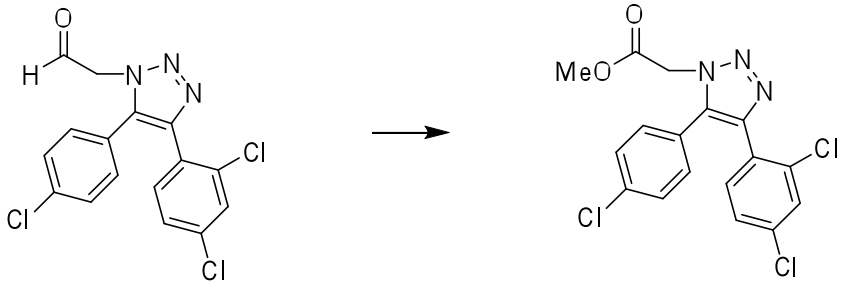
44 **47**

1-Allyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazole (47) A oven dried 50-mL round-bottomed flask was charged with $Ph_3(Br)CH_3$ (157 mg, 0.44 mmol) in 10 mL anhydrous THF. At 0 ^{0}C, *t*-BuOK (1 M in THF, 0.44 mL) was added dropwise. To the resultant bright orange solution was slowly added **44** (107 mg, 0.29 mmol) dissolved in 1 mL of THF. The reaction was warmed up to room temperature and stirred for 1 hour before sat. NH_4Cl was added to quench the reaction. The reaction mixture was taken up in water (30 mL) + EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). Combined organic portions were washed by sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:4) affording **47** (88 mg, 0.24 mmol, 83%) as a clear oil. R_f = 0.3 (EtOAc/hexanes = 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.11 (m, 7H), 6.06-5.86 (m, 1H), 5.28 (dd, *J* = 24, *JJ* = 1, 1H), 5.05 (dd, *J* = 41, *JJ* = 2, 1H), 4.96-4.94 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 136.1, 135.5, 134.6, 133.2, 132.0, 130.6, 130.0, 129.6, 129.1, 128.6, 128.3, 127.4, 125.6, 119.2, 51.1.



47 **48**

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-propyl-1H-1,2,3-triazole (48) A 25-mL round-bottomed flask was charged with **47** (80 mg, 0.22 mmol). The flask was vacuumed and backfilled with H_2. 10 wt.% Pd on activated carbon (8 mg) and 10 mL MeOH was added. The reaction was stirred at room temperature for 4 hours. The reaction solution was filtered through a thin pad of celite and washed with 20 mL of EtOAc and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/hexanes = 1:6) affording **48** (77 mg, 0.21 mmol, 97%) as a clear oil. Mp: 132 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.38 (m, 7H), 4.39 (t, 2H), 1.84 (m, 2H), 0.85 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 142.5, 135.9, 135.3, 134.9, 134.7, 133.2, 131.4, 130.6, 130.1, 129.9, 129.7, 128.9, 128.8, 128.2, 127.4, 126.0, 50.5, 23.6, 11.2. Anal. Calcd for $C_{17}H_{14}Cl_3N_3$: C, 55.69; H, 3.85; N, 11.46. Found: C, 55.77; H, 3.85; N, 11.16.

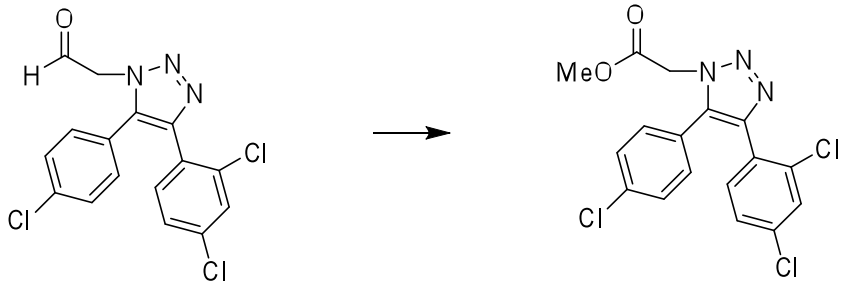


44 **50**

Methyl 2-(5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazol-1-yl)acetate (49) **44** (135 mg, 0.37 mmol) was taken up in 4 mL acetone followed by the addition of 2-methyl-2-butene (0.15 mL). At 0 ^{0}C, to this solution was added a solution of $NaClO_2$ (262 mg, 2.9 mmol) + NaH_2PO_4 (348 mg, 2.9 mmol). The reaction was stirred at room temperature for 1 hour.

Solvent was removed under reduced pressure. The residue was dissolved 1 N hydrochloric acid (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). Combined organic fractions were washed with sat. NaCl, dried on anhydrous Na_2SO_4, filtered, and concentrated affording the carboxylic acid **49** (141 mg, 99%) as a white solid.

The carboxylic acid prepared above was dissolved in 3 mL toluene + 0.6 mL MeOH. At 0 ^{0}C, $TMSCHN_2$ (2 M in hexanes, 0.19 mL) was added dropwise. The reaction stirred at room temperature until the evolution of gas was ceased. The solvent was removed under reduced pressure. The residue was taken up in water (20 mL) + CH_2Cl_2 (20 mL). The organic layer was separated. The aqueous layer was extracted with (20 mL). Combined organic layers were washed by sat. NaCl, dried on anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc:hexanes = 1:3) affording **50** (147mg, 93%) as a white solid. Mp: 145-146 ^{0}C. Anal. Calcd for $C_{17}H_{12}Cl_3N_3O_2$: C, 51.48; H, 3.05; N, 10.59. Found: C, 51.64; H, 3.15; N, 10.39.

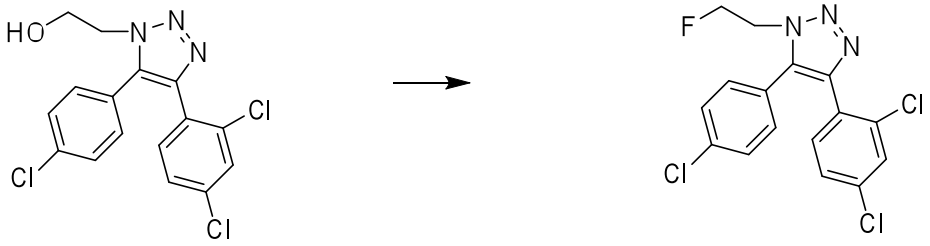


44 **51**

2-(5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazol-1-yl)ethanol (51)

Aldehyde **44** (204 mg, 0.56 mmol) was dissolved in 15 mL MeOH. At 0 ^{0}C, $NaBH_4$ (21 mg, 1.2 mmol) was added by three portions. After stirring for 10 minutes, reaction was warmed to room temperature and continued stirring for 30 minutes. The solvent was removed and residue was taken up in sat. NH_4Cl (aqueous, 20 mL) + CH_2Cl_2 (20 mL). The aqueous layer was extracted

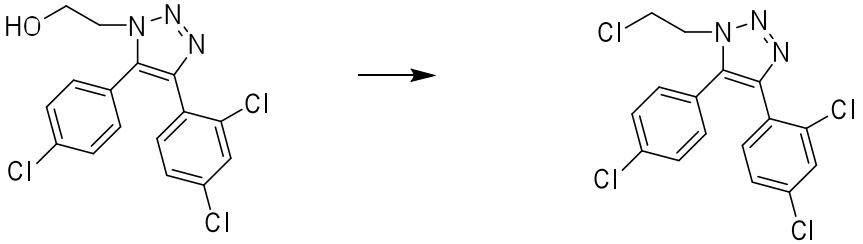
with CH_2Cl_2 (2 x 20 mL). Combined organic portions were washed by sat. NaCl, dried on Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/hexanes = 1:1) affording **51** (196 mg, 95%) as a clear oil. ^{1}H NMR (400 MHz, acetone-d6) δ 7.50-7.40 (m, 7H), 4.48 (t, 2H), 4.04 (t, 2H), 1.96 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 142.0, 136.1, 136.0, 135.4, 134.5, 133.0, 131.0, 129.9, 129.5, 128.2, 127.3, 125.2, 60.8, 50.9. Calcd for $C_{16}H_{12}Cl_3N_3O$: C, 52.13; H, 3.28; N, 11.40. Found: C, 51.98; H, 3.46; N, 10.95.



51 **52**

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-(2-fluoroethyl)-1H-1,2,3-triazole (52)

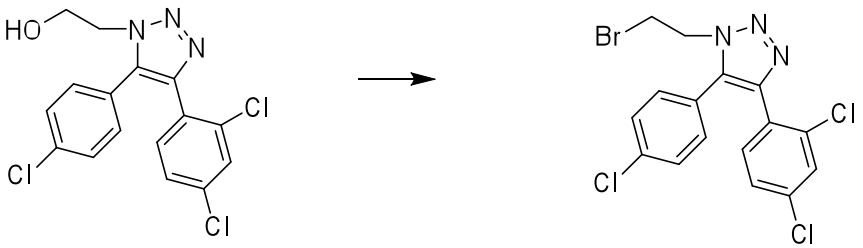
(Diethylamino)sulfur trifluoride (DAST, 131 mg, 0.81 mmol) was taken up in 10 mL anhydrous CH_2Cl_2 and cooled to -78 ^{0}C. The solution of **51** (100 mg, 0.27 mmol) in 2 mL CH_2Cl_2 was added dropwise. Upon completion of addition, the reaction was warmed to room temperature and stirred overnight. The reaction mixture was then washed with sat. NaCl, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, CH_2Cl_2/EtOAc/hexanes = 5:1:4) affording **52** (85 mg, 85%) as a white solid. Mp: 98-103^{0}C. ^{1}H NMR (400 MHz, acetone-d6) δ 7.57-7.36 (m, 7H), 5.01-4.73 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 136.2, 135.5, 134.7, 133.2, 131.1, 131.0, 130.0, 129.7, 128.5, 127.4, 125.3, 82.6, 80.8, 48.9, 48.7. Calcd for $C_{16}H_{11}Cl_3FN_3$: C, 51.85; H, 2.99; N: 11.34. Found: C, 52.07; H, 2.81; N, 11.25.



51 **54**

1-(2-Chloroethyl)-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazole (54) A 10-mL round-bottomed flask was charged with a stirring bar and 1 mL of pyridine. **51** (75 mg, 0.20 mmol) was added followed by the addition of TsCl (194 mg, 1.0 mmol). The reaction was stirred at room temperature for 30 minutes. The solvent pyridine was removed under reduced pressure. The residue was taken up in sat. $NaHCO_3$ (5 mL) + CH_2Cl_2 (10 mL). The organic fraction was separated, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo.

Anhydrous LiCl (34 mg, 0.8 mmol) and the tosylate prepared from above were taken up in 20 mL of absolute ethanol. The reaction was heated to reflux for 15 hours. The solvent was removed. The residue was dissolved in CH_2Cl_2 (10 mL), washed by sat. NaCl (10 mL), dried on anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:8) affording **54** (56 mg, 72%). R_f = 0.5 (EtOAc/hexanes = 1:6).

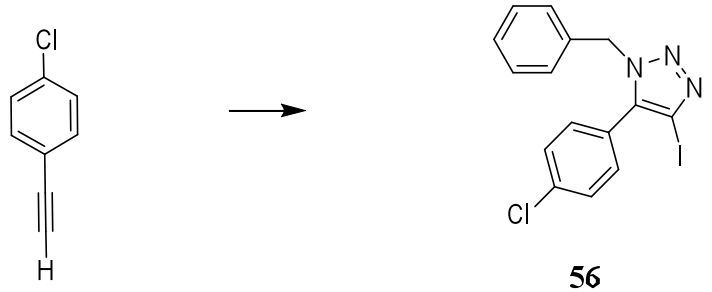


51 **55**

1-(2-Bromoethyl)-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazole (55) A 10-mL round-bottomed flask was charged with a stirring bar and 1 mL of pyridine. **51** (75 mg, 0.20

mmol) was added followed by the addition of TsCl (194 mg, 1.0 mmol). The reaction was stirred at room temperature for 30 minutes. The solvent pyridine was removed under reduced pressure. The residue was taken up in sat. $NaHCO_3$ (5 mL) + CH_2Cl_2 (10 mL). The organic fraction was separated, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo.

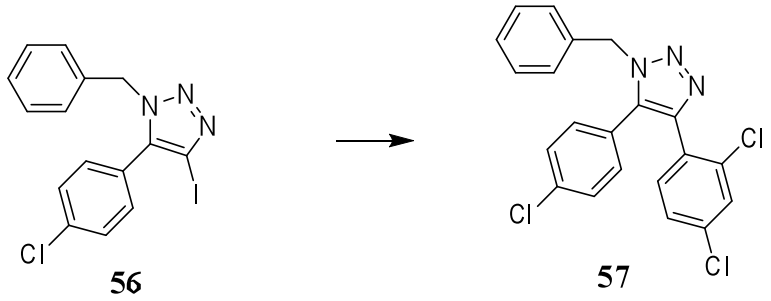
Anhydrous LiBr (60 mg, 0.8 mmol) and the tosylate prepared from above were taken up in 20 mL of anhydrous acetone. The suspension was heated to reflux for 15 hours. The solvent was removed. The residue was dissolved in CH_2Cl_2 (10 mL), washed by sat. NaCl (10 mL), dried on anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:8) affording **55** (54 mg, 63%). R_f = 0.5 (EtOAc/hexanes = 1:6).



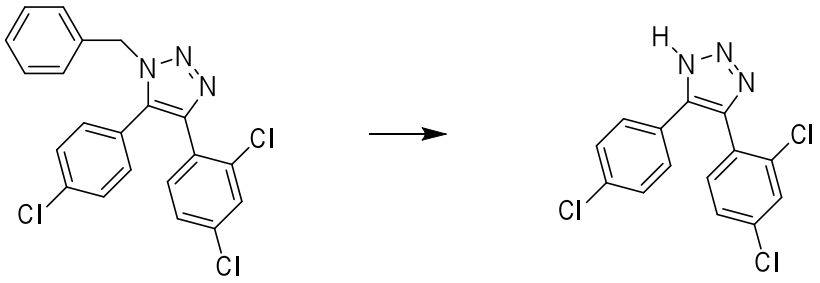
56

1-Benzyl-5-(4-chlorophenyl)-4-iodo-1H-1,2,3-triazole (56) A flame dried flash was filled with N_2 and charged with 1-chloro-4-ethynylbenzene (0.274 g, 2 mmol) in 5 mL of anhydrous THF. At room temperature ethylmagnesium chloride (2 M in THF, 1 mL) was added slowly. The reaction was stirred at room temperature for 1 hour before benzyl azide (293 mg, 0.25 mL, 2.2 mmol) was added dropwise. The reaction was heated to 55 ^{0}C for 2 hours. Iodine (1.82 g, 7.2 mmol) in 2 mL of THF was added and stirring continued for 10 minutes. The reaction was cooled to room tempearature and quenched by the addition of 10 mL of sat. NH_4Cl aqueous solution. The reaction mixture was partitioned between $Na_2S_2O_3$ solution (2 N in water, 10 mL) and EtOAc (30 mL). The organic fraction was separated. The aqueous layer was extracted with

EtOAc (2 x 30 mL). Combined organic fractions were washed by sat. NaCl, dried on anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:6) affording **56** (554 mg, 70%) as a white solid.

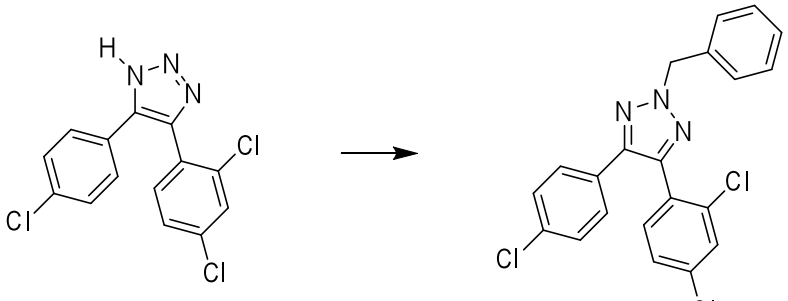


1-Benzyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazole (57) 56 (829 mg, 2 mmol), 2,4-dichlorophenyl boronic acid (420 mg, 2.2 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), tricyclohexylphosphine (68 mg, 0.24 mmol), and K_3PO_4 (721 mg, 3.4 mmol) were suspended in 16 mL THF + 4 mL H_2O in a 50 mL pressure tube. The reaction vessel was purged with N_2, sealed, and heated to 120 ^{0}C for 16 hours in a oil bath. The reaction mixture was partitioned between water (40 mL) and EtOAc (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 40 mL). Combined organic fractions were washed by sat. NaCl, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/Hexanes = 1:4) affording **57** (827 mg, 99%) as a white solid. R_f = 0.3 (EtOAc/Hexanes = 1:4). Mp: 146-149 ^{0}C. ^{1}H NMR (400 MHz, acetone-d6) δ 7.38-6.96 (m, 12H), 5.53 (s, 2H).^{13}C NMR ($CDCl_3$) δ 146.3, 135.8, 135.3, 135.2, 134.5, 133.1, 130.6, 129.8, 129.4, 129.0, 128.5, 128.4, 127.3, 127.2, 125.5, 52.9. Calcd for $C_{21}H_{14}Cl_3N_3$: C, 60.82; H, 3.40; N, 10.13. Found: C, 60.53; H, 3.40; N, 9.89.



57 **58**

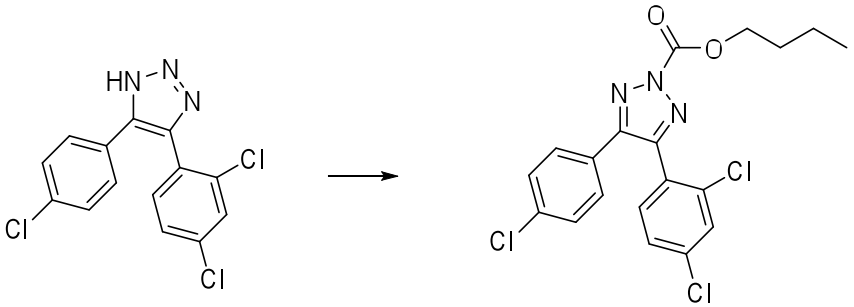
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazole (58) **57** (40 mg, 0.1 mmol) was dissolved in 0.5 mL anhydrous DMSO and 1.5 mL anhydrous THF and cooled to 0 ^{0}C. To this solution was slowly added *t*-BuOK (1 M in THF, 1 mL). Upon the completion of addition, O_2 was bubbled through the resultant dark blue mixture for 15 minutes until the blue color disappeared and TLC indicated no starting material remained. The reaction was portioned between sat. NaCl (20 mL) + CH_2Cl_2 (30 mL). The organic fraction was separated. The aqueous fraction was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic portions were washed by sat. NaCl (30 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 2:3) affording **58** (32 mg, 99%) as a clear oil.



58 **59**

2-Benzyl-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazole (59) Under N_2, **58** (145 mg, 0.45 mmol) was dissolved in 2 mL anhydrous DMF. NaH (40% in mineral oil, 21.4 mg,

0.54 mmol) was added by one portion and stirred for 15 minutes at room temperature. Benzyl bromide (81 mg, 0.056 mL, 0.47 mmol) was added dropwise and stirred overnight. The reaction was then quenched with aqueous NH_4Cl (1 N) and diluted with water (10 mL) + EtOAc (15 mL). The organic portion was separated. The aqueous portion was extracted with EtOAc (2 x 20 mL). Combined organic fractions were washed by sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:3) affording **59** (112 mg, 60%) as a white solid. R_f = 0.4 (EtOAc/Hexanes = 1:3). ^1H NMR (400 MHz, acetone-d6) δ 7.66-7.37 (m, 12H), 5.75 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 144.9, 141.7, 135.9, 135.1, 134.5, 133.0, 130.1, 129.2, 129.0, 128.7, 128.6, 128.3, 127.6, 126.5, 59.2. Calcd for $C_{21}H_{14}Cl_3N_3$: C, 60.82; H, 3.40; N, 10.13. Found: C, 60.97; H, 3.56; N, 9.92.

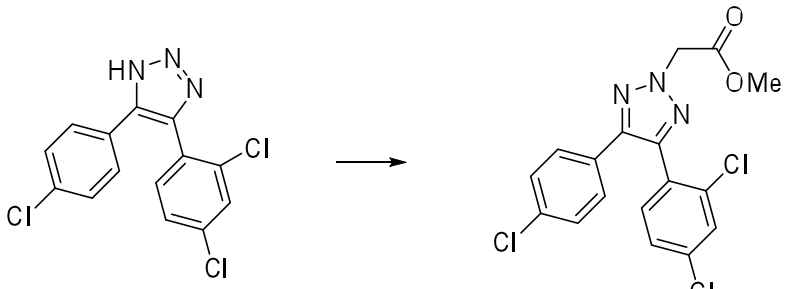


58 **60**

Butyl 4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazole-2-carboxylate (60)

Under N_2, **58** (94 mg, 0.29 mmol) was dissolved in 4 mL anhydrous THF. NaH (40% in mineral oil, 14 mg, 0.35 mmol) was added by one portion and stirred for 15 minutes at room temperature. The solution was then added dropwise to another flask that was charged with butyl chloroformate (48 mg, 0.35 mmol) in 2 mL anhydrous THF. The reaction was stirred at room temperature for 2 hours and quenched with aqueous NH_4Cl (1 N) and diluted with water (10 mL) + EtOAc (15 mL). The organic portion was separated. The aqueous portion was extracted with EtOAc (2 x 20 mL). Combined organic fractions were washed by sat. NaCl, dried on $MgSO_4$,

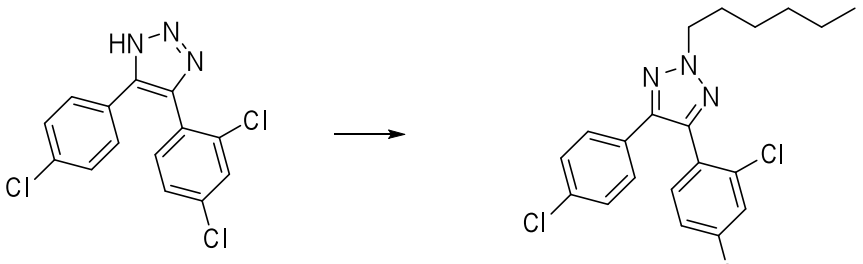
filtered, and concentrated in vacuo affording **60** (123 mg, 0.29 mmol) as a white solid. ^{1}H NMR (400 MHz, acetone-d6) δ 7.50-7.30 (m, 7H), 4.62 (t, 2H), 1.89 (m, 2H), 1.52 (m, 2H), 0.11 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 147.6, 136.9, 136.0, 135.0, 132.8, 130.2, 129.3, 128.8, 127.8, 127.6 70.1, 30.6, 19.0, 13.8. Calcd for $C_{19}H_{16}Cl_3N_3O_2$: C, 53.73; H, 3.80; N, 9.89. Found: C, 53.74; H, 3.85; N, 9.77.



58 **61**

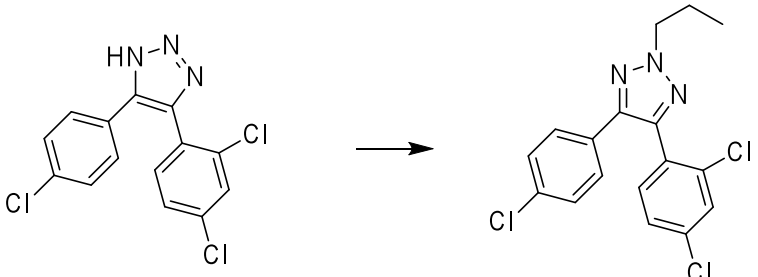
Methyl 2-(4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-2-yl)acetate (61) **58** (200 mg, 0.62 mmol) was dissolved in 3 mL anhydrous DMF in a flask backfilled with N_2. NaH (40% in mineral oil, 29.6 mg, 0.65 mmol) was added. The reaction was stirred at room temperature for 15 minutes before methyl 2-bromoacetate (99 mg, 0.65 mmol) was added dropwise. After stirring for 20 hours at room temperature, the reaction was quenched by 1 N NH_4Cl in water (1 mL). The mixture was diluted with water (15 mL) + EtOAc (15 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 15 mL). Combined organic portions were washed with sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:3) affording **61** (147 mg, 0.37 mmol, 60%). R_f = 0.47 (EtOAc/hexanes = 1:3). Mp: 121-123 ^{0}C. ^{1}H NMR (400 MHz, acetone-d6) δ 7.67-7.39 (m, 7H), 5.47 (s, 2H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 167.1, 145.7, 142.4, 136.1, 135.0, 134.7, 132.9, 130.2, 129.1, 129.0,

128.9, 128.3, 127.6, 55.8, 53.1. Calcd for $C_{17}H_{12}Cl_2N_3O_2$: C, 51.48; H, 3.05; N, 10.59. Found: C, 51.58; H, 3.05; N, 10.40.



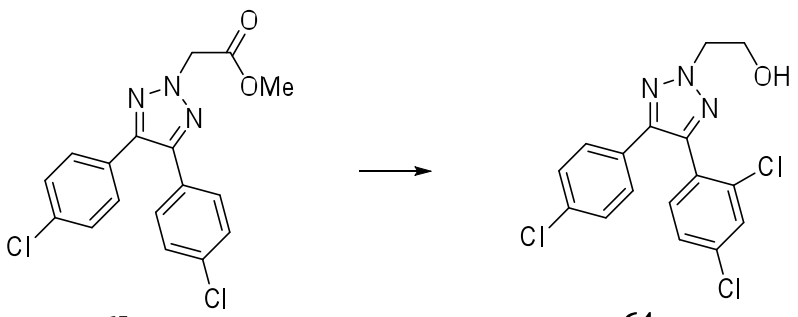
58 **62**

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-hexyl-2H-1,2,3-triazole (62) 58 (65 mg, 0.2 mmol) was dissolved in 3 mL anhydrous DMF in a flask backfilled with N_2. NaH (40% in mineral oil, 13.2 mg, 0.22 mmol) was added. The reaction was stirred at room temperature for 15 minutes before hexyl bromide (41 mg, 0.25 mmol) was added dropwise. After stirring for 12 hours at room temperature, the reaction was quenched by 1 N NH_4Cl in water (1 mL). The mixture was diluted with water (10 mL) + EtOAc (10 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). Combined organic portions were washed with sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:8) affording **62** (49 mg, 60%) as a clear oil.



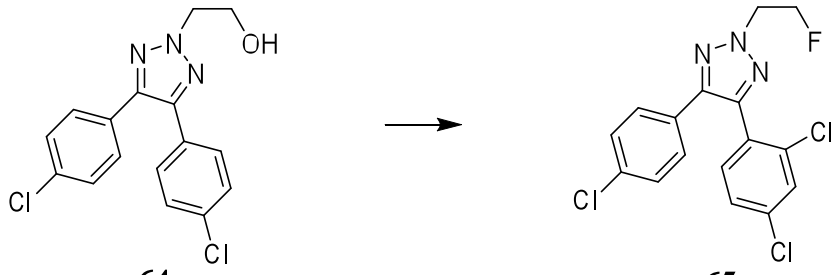
58 **63**

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-propyl-2H-1,2,3-triazole (63) 58 (88 mg, 0.27 mmol) was dissolved in 3 mL anhydrous DMF in a flask backfilled with N_2. NaH (40% in mineral oil, 18 mg, 0.3 mmol) was added. The reaction was stirred at room temperature for 15 minutes before bromopropane (40 mg, 0.32 mmol) was added dropwise. After stirring for 12 hours at room temperature, the reaction was quenched by 1 N NH_4Cl in water (1 mL). The mixture was diluted with water (10 mL) + EtOAc (10 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). Combined organic portions were washed with sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, eluting with EtOAc/hexanes = 1:8) affording **63** (50 mg, 50%) as a yellowish oil.



2-(4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-2-yl)ethanol (64) Methyl ester **61** (320 mg, 0.81 mmol) was dissolved in 10 mL anhydrous THF. To the resultant solution $LiAlH_4$ (2 M in THF, 1.22 mL) was added dropwise at -40 ^{0}C. Upon the completion of addition, the reaction was brought up to 0 ^{0}C and stirred for 15 minutes. The reaction was then quenched with 1 M NH_4Cl in water (0.3 mL). After vigorously stirring for 5 minutes, anhydrous $MgSO_4$ was added and the slurry was filtered. The filtrate was concentrated in vacuo. The residue was purified by running through a short pad of silica gel affording **64** (298 mg, 99%) as a clear oil. R_f

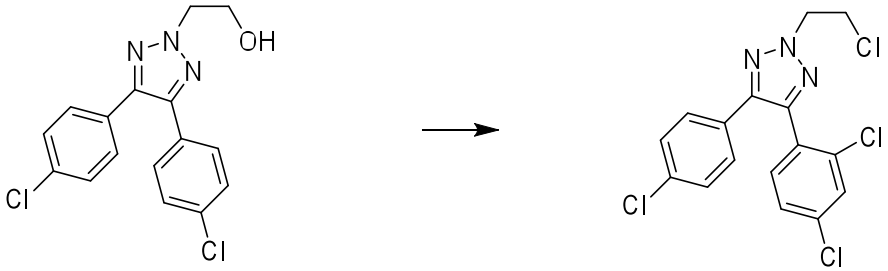
= 0.36 (EtOAc/hexanes = 1:1). ^{1}H NMR (400 MHz, acetone-d6) δ 7.67-7.36 (m, 7H), 4.59 (t, 2H), 4.23 (s, 1H), 4.15 (t, 2H). ^{13}C NMR ($CDCl_3$) δ 144.7, 143.7, 141.3, 135.9, 134.9, 134.7, 134.5, 132.8, 130.1, 129.6, 129.1, 129.0, 128.9, 128.8, 128.7, 127.6, 60.9, 57.2.



64 65

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-(2-fluoroethyl)-2H-1,2,3-triazole (65)

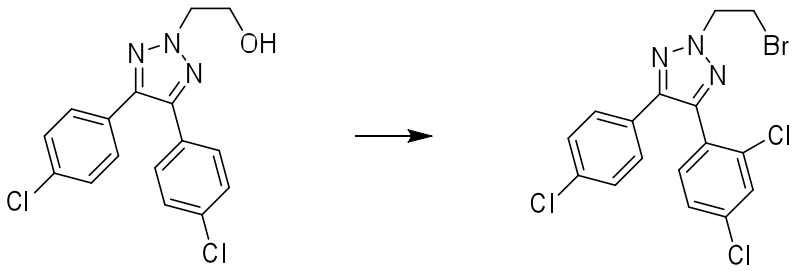
DAST (223 mg, 0.183 mL, 1.38 mmol) was taken up in 15 mL anhydrous CH_2Cl_2. At -78 °C, **64** (170 mg, 0.46 mmol) in 3 mL of CH_2Cl_2 was added to the DAST solution dropwise. After the addition was complete, the cold bath was removed and the reaction was brought up to room temperature and stirred overnight. The reaction mixture was washed by sat. NaCl (20 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, EtOAc/hexanes = 1:4) affording **65** (140 mg, 82%) as a clear oil. R_f = 0.4 (EtOAc/hexanes = 1:4). ^{1}H NMR (400 MHz, acetone-d6) δ 7.65-7.36 (m, 7H), 5.11-4.80 (m, 4H).



64 66

2-(2-Chloroethyl)-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazole (66)

Alcohol **64** (163 mg, 0.44 mmol), pyridine (168 mg, 0.88 mmol), and toluene sulphonyl chloride (70 mg, 0.88 mmol) were taken up in 5 mL of CH_2Cl_2 and stirred at room temperature for 4 hours. The solvent was removed and the residue was purified by running through a thin pad of silica gel. The concentrate together with lithium chloride (186 mg, 4.4 mmol) was taken up in 20 mL of absolute ethanol. The reaction was refluxed for 15 hours. The solvent was removed and the residue was dissolved in 20 mL water and extracted with EtOAc (2 x 20 mL). Combined organic portions were washed with sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, EtOAc/hexanes = 1:6) affording **66** (153 mg, 90%) as a white solid. Mp: 115-118 °C. R_f = 0.55 (EtOAc/hexanes = 1:4). ^{1}H NMR (400 MHz, acetone-d6) δ 7.52-7.27 (m, 7H), 4.81 (t, 2H), 4.08 (t, 2H). ^{13}C NMR ($CDCl_3$) δ245.1, 141.9, 136.0, 135.1, 134.6, 132.9, 130.2, 129.7, 129.2, 129.1, 129.0, 128.3, 127.7,56.3, 41.5.



64 **67**

2-(2-Bromoethyl)-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazole (67)

Alcohol **64** (111 mg, 0.3 mmol), pyridine (114 mg, 0.6 mmol), and TsCl (48 mg, 0.6 mmol) were taken up in 5 mL of CH_2Cl_2 and stirred at room temperature for 4 hours. The solvent was removed and the residue was purified by running through a thin pad of silica gel. The concentrate together with LiBr (260 mg, 3 mmol) was taken up in 20 mL of acetone. The

reaction was refluxed for 15 hours. The solvent was removed and the residue was dissolved in 20 mL water and extracted with EtOAc (2 x 20 mL). Combined organic portions were washed with sat. NaCl, dried on $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on a flash chromatography (SiO_2, EtOAc/hexanes = 1:6) affording **67** (102 mg, 79%) as a white solid. R_f = 0.5 (EtOAc/hexanes = 1:6).

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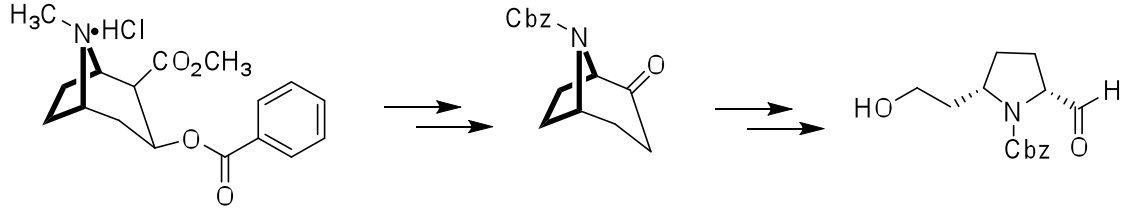
CHAPTER 2

SYNTHESIS OF PYRROLIDINE 225H AND A FORMAL SYNTHESIS OF (+)-GEPHYROTOXIN

2.1 ABSTRACT

Neuronal nicotinic acetylcholine receptors have long been the target for the development of a large number of central nervous system diseases and disorders. In an effort to develop new neuronal nicotinic acetylcholine receptor ligands as therapeutic agents, we have been very interested in amphibian alkaloids.

To effectively synthesize amphibian alkaloids, our research group has recently developed a general synthetic strategy which can rapidly prepare a few amphibian alkaloids simply from the abundant natural product (-)-cocaine **1** as a starting material (**Scheme 2.1**). This strategy was first successfully applied to the synthesis of (-)-monomorine. More recently, this strategy has also been utilized in the syntheses of both of the enantiomers of *cis*-pyrrolidine 225H and (+)-gephyrotoxin 287C.



(-)-Cocaine hydrochloride **1** **2** **3**

Scheme 2.1 Synthesis of amphibian from 2,5-cis-pyrrolidine building block

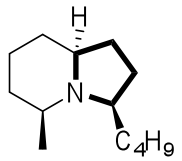
2.2 INTRODUCTION

Amphibians have produced a great number of biologically active compounds as a chemical defense against predators. These compounds are mostly present in the skin or venom of amphibians. Lipophilic alkaloids are one of the largest categories of chemicals detected in amphibian skin. Through 2005, over 800 hundred amphibian alkaloids of over 20 structural classes have been reviewed.[1] The structural diversity and biological activity of amphibian alkaloids have aroused tremendous academic and pharmaceutical interest. However, the presence of alkaloids in amphibian species is very scarce. Dependence on the supply from natural sources is very limited. Therefore, total synthesis is the most used method to provide sufficient material for intensive structure and biological activity studies. An ongoing project in our laboratory has been to develop synthetic strategies for the construction of amphibian alkaloids that exhibit pharmacological activities mediated by nicotinic receptor ion channels.

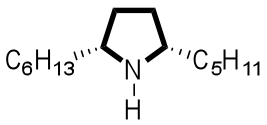
Neuronal nicotinic acetylcholine receptors (nAChRs) are members of a super family of central nervous system synapses and the neuromuscular endplate. Neuronal nicotinic acetylcholine receptors respond to physiological signal of the neurotransmitter acetylcholine. They can also be activated by nicotine.[2] Neuronal nicotinic acetylcholine receptors have been the target for the drug development for tobacco addiction, smoking cessation, muscle relaxation, and anti-hypertension.[3,4] More recently, neuronal nicotinic acetylcholine receptors have been the target for the development of new therapeutic agents for the treatment of a number of other central nervous system disease and disorders such as Alzheimer's Disease, Parkinson's Disease, Tourettes syndrome, anxiety, and depression. Scientific findings have also indicated that nicotine receptors are involved in memories and learning activities. It is now widely believed that

neuronal nicotinic acetylcholine receptor agonists and antagonists have great potential for the treatment of a variety of diseases and disorders.

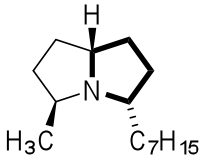
Unfortunately, most of the neuronal nicotinic acetylcholine receptor agents available up to date have adverse side effects which severely prevent them from being applied as drug therapy. Therefore, it is of great interest and benefit to discover and search novel nicotinic receptor ligands and develop them to provide therapeutic agents and medications for the treatment of a variety of neurological diseases and disorders.



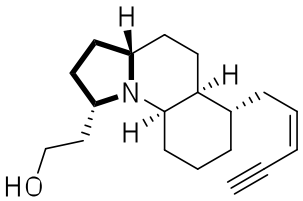
(+)-Monomorine **4**



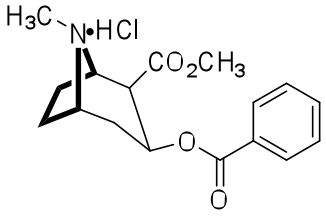
cis-Pyrrolidine 225H **5**



trans-pyrrolizidine 223H **6**



(+)-Gephyrotoxin **7**



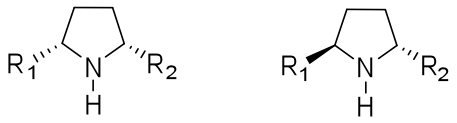
(-)-Cocaine hydrochloride **1**

Figure 2.1 Structures of Amphibian Alkaloids and Cocaine

Several classes of the amphibian alkaloids have been found to be non-competitive blockers at nicotinic receptor ion channels. Among these alkaloids, at least four classes share the common skeletal structure. They are the pyrrolidine, pyrrolizidine, indolizidine, and gephyrotoxin. As illustrated in **Figure 2.1**, they are respectively represented by four natural products, (+)-monomorine **4**, *cis*-pyrrolidine 225H **5**, *trans*-pyrrolizidine 223H **6** and (+)-gephyrotoxin **7**. A *cis*-2,5-disubstituted pyrrolidine-ring structural feature was observed in all of those four natural

products. Meanwhile, this ring system can also be found in the abundant natural product (-)-cocaine•HCl. Seeing this prominent similarity, we were encouraged to develop an enantioselective and general synthetic strategy preparing sample amphibian alkaloids and analogues for further structure-activity studies.

Pyrrolidine 225H

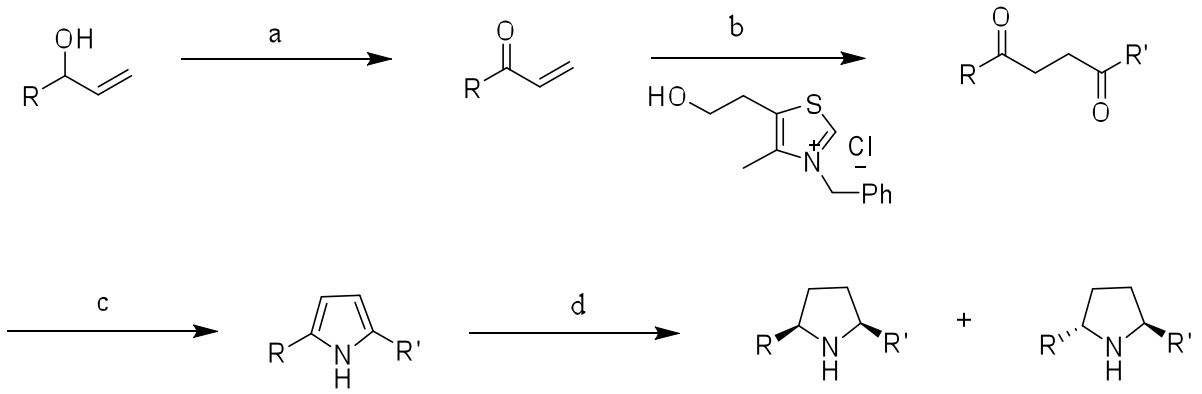


	2,5-Pyr	R_1	R_2
	183B	*n*-C_4H_9	*n*-C_4H_9
	*197B	*n*-C_4H_9	*n*-C_5H_{11}
trans	223N	C_6H_{11}	*n*-C_5H_{11}
	225C	*n*-C_4H_9	*n*-C_7H_{15}
	225H	*n*-C_6H_{13}	*n*-C_5H_{11}
cis/trans	235F	C_7H_{13}	C_5H_9
	253I	*n*-C_6H_{13}	*n*-C_7H_{15}
trans	277D	C_6H_{11}	C_9H_{17}
	279G	*n*-C_6H_{13}	*n*-C_9H_{17}

Table 2.1 Pyrrolidines

A 2,5-disubstituted pyrrolidine has been identified as the major alkaloid in skin extracts of *Dendrobates histrionicus*, a population of a Colombian dendrobatid frog. Such 2,5-disubstituted pyrrolidines (**Table 2.1**) were also detected in myrmicine ant venoms. These 2,5-disubstituted pyrrolidines were found to exhibit insecticidal activity serving as a defensive repellant.[5] Synthetic compound, 197B, acted as a noncompetitive blocker of nicotinic receptor exhibiting interesting biological activities.[6] Yet very little is known about this class of alkaloids. Up to date, there is only one pyrrolidine structure was firmly established with organic synthesis as a tool. We were pleased to find that most of *cis*-2,5-disubstituted pyrrolidines in the chart can be synthesized from (-)-cocaine with two chiral centers directly introduced from (-)-cocaine. We selected pyrrolidine 225H as an example to interpret the application of this strategy.

The only laboratory synthesis of unsymmetrical 2,5-pyrrolidines was reported about 30 years ago.[7] As demonstrated in **Scheme 2.2**, a complexity of multiple isomers occurred in the reaction sequence as a result of harsh reaction conditions in the reaction sequences.

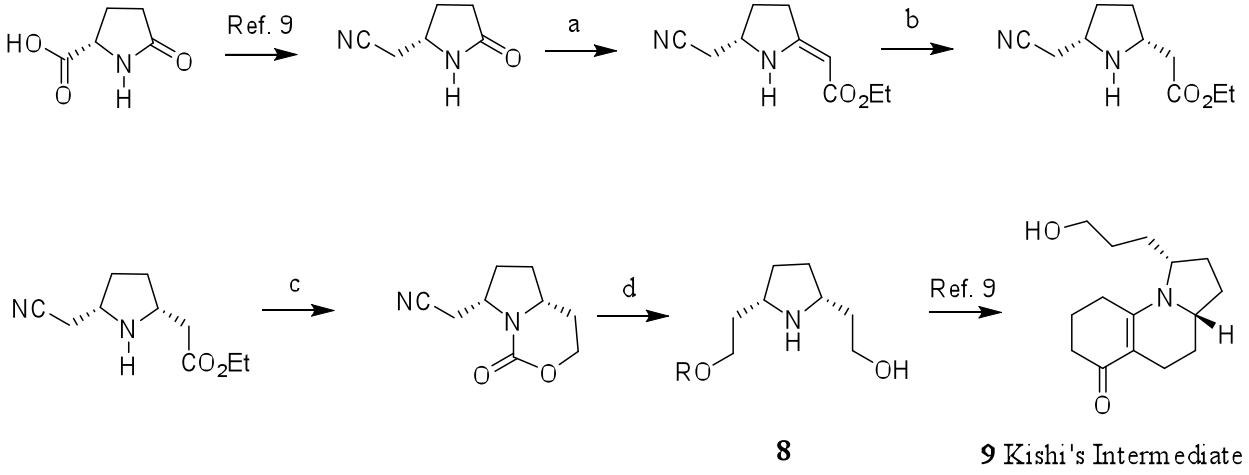


Scheme 2.2 Review of the synthesis of Pyrrolidine 225H

Reagents and conditions: a) PCC; b) R'CHO, Et_3N; c) $(NH_4)_2CO_3$; d) H_2, Rh/Al_2O_3.

(+)-Gephyrotoxin

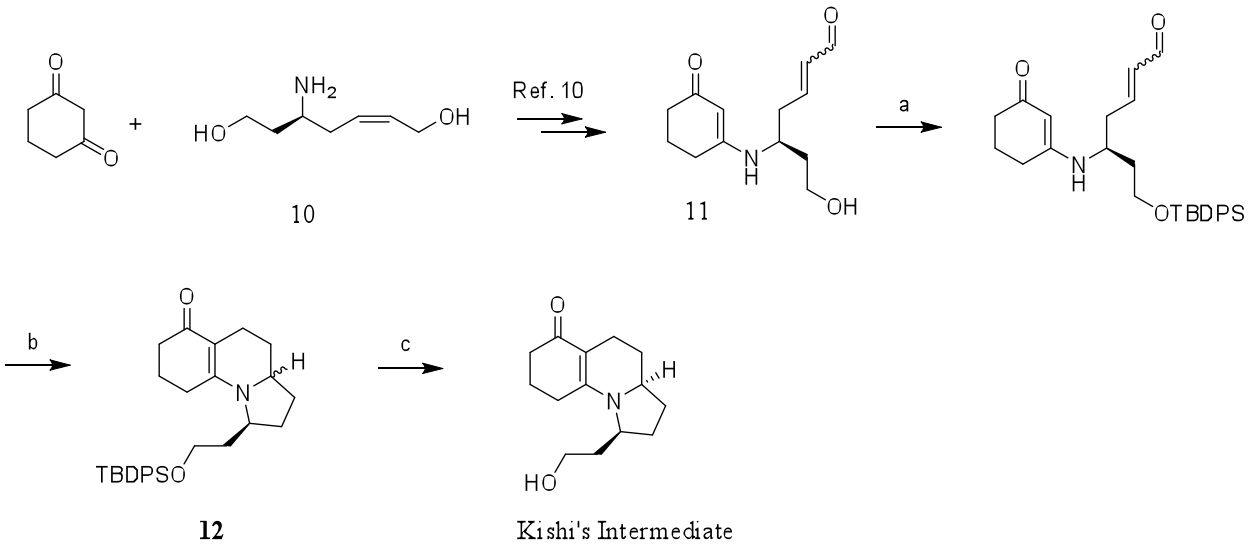
Four classes of tricyclic alkaloids have been detected in amphibians. Gephyrotoxin was the first tricyclic alkaloid that has been structurally defined. It was isolated from the skin secretion of tropical frog Dendrobates histrionicus and characterized by Daly and co-workers in 1977.[8] Although controversy still remains as to the absolute configuration of the major component from the *Dendrobates histrionicus*, this compound has aroused increasing pharmacological interest due to its observed biological activities. (+)-Gephyrotoxin was relatively nontoxic. It exhibited weak muscarinic antagonist activities and neurological activities. It acted as a noncompetitive blocker of nicotinic receptor-channels of muscle, electric ray electroplax, and pheochromocytoma cells.[8] Due to its extreme scarcity in nature, (+)-Gephyrotoxin and analogues have been an interesting synthetic target for several organic synthetic groups.



Scheme 2.3 Review of synthesis of Kishi's Intermediate I

Reagents and conditions: a) 1. P_2S_5, pyridine, 80 °C; 2. $MeCOCH(Br)CO_2Et$, $NaHCO_3$, reflux; 3. 0.1 N KOH, EtOH, 80 °C; b) H_2 (1 atm), 5 % Pd/C, $HClO_4$, MeOH, rt; c) 1. C_6H_5OCOCl, pyridine, CH_2Cl_2, rt; 2. $LiBH_4$, THF, rt; 3. KH, THF, rt; d) 1. DIBAL-H, THF/toluene, -105 °C; 2. 3 N HCl; 3. $NaBH_4$, DME, rt; 4. $MeOCH_2Br$, DIPEA, CH_2Cl_2, rt; 5. $Ba(OH)_2$, H_2O, reflux.

Among the different approaches, only one total synthesis and two formal syntheses have been reported for the enantioselective preparation of (+)-Gephyrotoxin. The first and only enantioselective total synthesis of (+)-Gephyrotoxin was reported by Kishi and coworkers.[9] In their synthesis (**Scheme 2.3**), *L*-pyroglutamic acid was converted into the enantiopure *cis*-2,5-disubstituted pyrrolidine **8** in 15 step and another 3 steps led to the tricyclic intermediate **9** which is called Kishi's intermediate. Kishi's intermediate is a tricyclic compound with two chiral centers and a *cis*-2,5-disubstituted pyrrolidine ring system. Kishi's strategy provided Kishi's intermediate in 18 steps from *L*-pyroglutamic acid and it included a hydrogenation step which afforded a 2.3:1 mixture of *cis*- and *trans*-pyrrolidine.

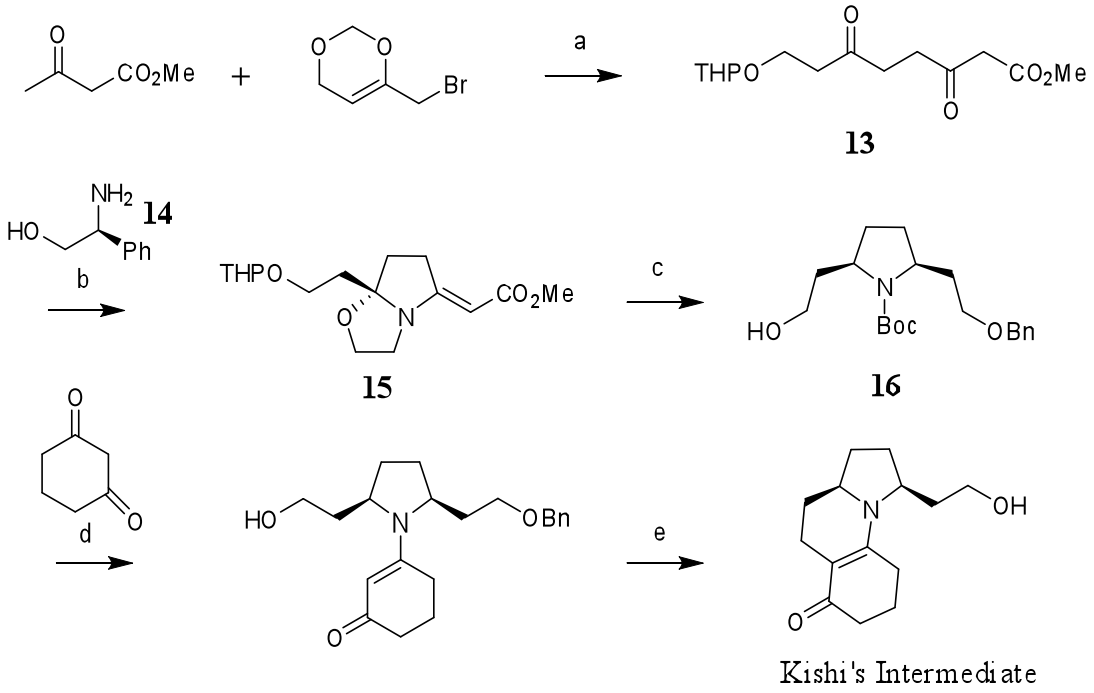


Scheme 2.4 Review of synthesis of Kishi's Intermediate II

Reagents and conditions: a) TBDPSCl, imidazole; b) 1. toluene/EtOH, Na_2SO_4, piperidinium acetate, 100 °C; 2. 5% Pd/C, H_2 (1 atm), EtOAc/EtOH; c) TBAF, CH_2Cl_2, 0 °C.

Hsung and coworkers reported a shorter access to Kishi's intermediate (**Scheme 2.4**). The key step of Hsung's strategy was the stereoselective intramolecular formal [3+3] cycloaddition reaction of vinylogous amide with α,β-unsaturated aldehyde **11** which was obtained by

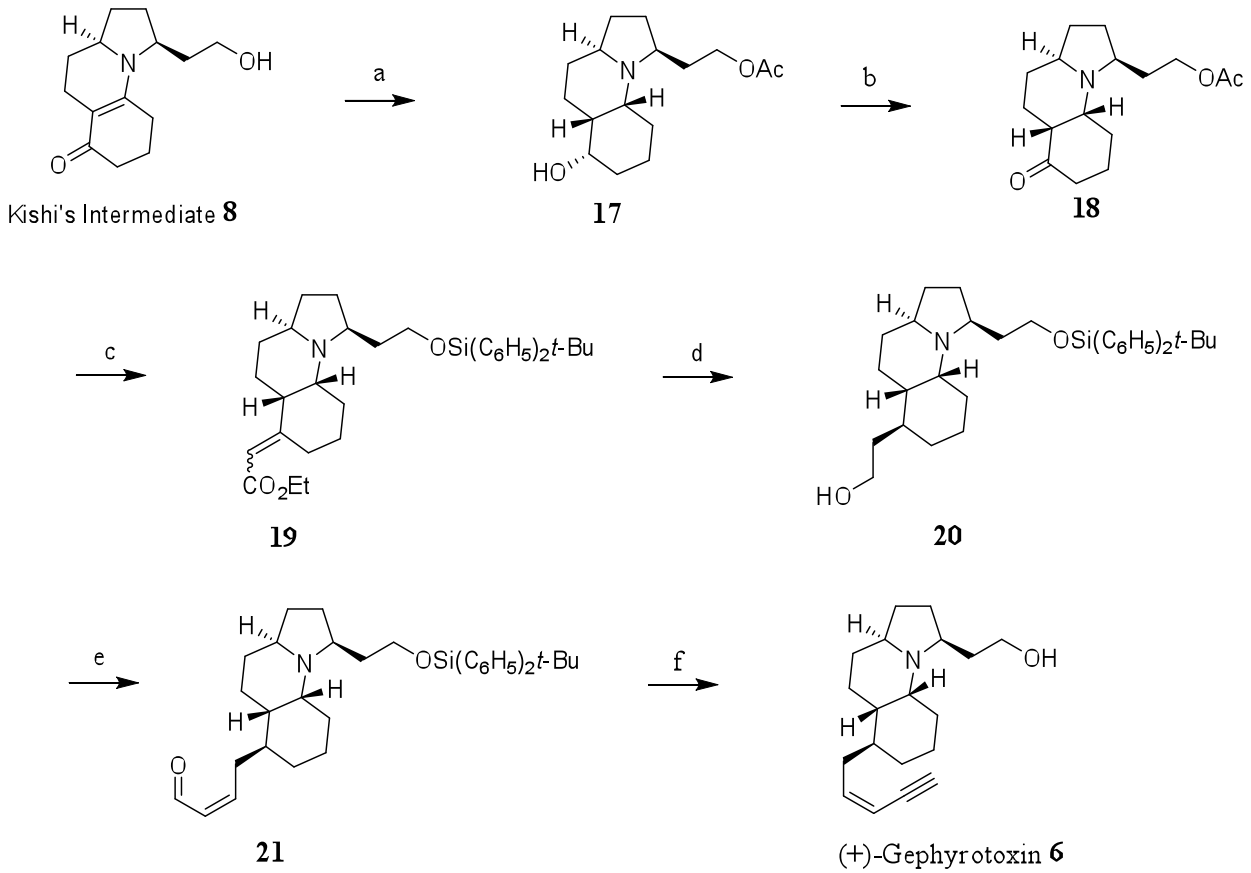
condensation of the chiral amino diol **10** with 1,3-cyclo-hexanedione. This synthesis afforded Kishi's intermediate in 10 steps from commercially available starting material. However the intramolecular cycloaddition gave the tricyclic precursor **12** in a low yield (50%) and a poor diastereoselectivity.[10]



Scheme 2.5 Review of synthesis of Kishi's Intermediate III

Reagents and conditions: a) 1. LDA; 2. *p*-TsOH, DHP, CH_2Cl_2; b) $Zn(ClO_4)_2 \bullet 6H_2O$, $MgSO_4$, CH_2Cl_2; c) 1. $NaBH_4$, AcOH, CH_3CN; 2. H_2, $Pd(OH)_2/C$, Boc_2O, AcOMe; 3. $LiAlH_4$, THF, 0 °C; 4. NaH, BnBr, TBAI, DMF; 5. HCl, MeOH; d) *p*-TsOH, toluene; e) 1. PBr_3, CH_2Cl_2; 2. NaI, CH_3CN; 3. H_2, Pd/C, $HClO_4$, MeOH.

More recently, Vanucci-Bacqué and coworkers reported a more diastereocontrolled synthesis of Kishi's intermediate (**Scheme 2.5**). In this strategy, Vanucci-Bacqué synthesized the enantiopure *cis*-2,5-disubstituted pyrrolidine **15** from the diastereocontrolled reduction of the chiral bicyclic pyrrolidine β-enamino ester **14** which was obtained by condensation of the chiral amine (*S*)-phenylglycinol **13** on a protected *ω*-oxo *β*-keto ester **12**.[11]



Scheme 2.6 Review of the synthesis of (+)-Gephyrotoxin from Kishi's Intermediate

Reagents and conditions: a) H_2 (60 psi), 5% Pt/Al, EtOAc; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; c) 1.EtOCCMgCl, THF; 2.MeMgBr; 3. H_3O^+; 4. *t*-Bu$(C_6H_5)_2$SiCl, imidazole; d) 1. H_2 (1 atm), 5% Rh/Al_2O_3, hexanes; 2. $LiAlH_4$; e) 1. PCC; 2. $Ph_3P(CH{=}CHOEt)Br$; 3. TSA, acetone/H_2O; f) 1. $Ph_3P(CH_2Cl)Cl$, BuLi, THF; 2. MeLi, Me_3SiCl, THF; 3. TBAF, DMF.

As demonstrated in **Scheme 2.6**, Kishi's intermediate was diastereoselectively converted into (+)-gephyrotoxin by Kishi *et. al*.[12] The unique and key aspect of the synthesis was that all three remaining asymmetric centers on the tricylic ring were stereoselectively introduced through hydrogenation reactions with specific catalysts and additives. When the hydrogenation of the vinylogous amide **8** was carried out with the presence of 10% Pd/C in ethyl acetate under 60 psi hydrogen pressure, the hydrogenation product along with hydrogenolysis side product were found to be the product with reversed stereochemical outcome. However, when the reaction

proceeded using 5% Platinum on an alumina support in anhydrous ethyl acetate at 60 psi hydrogen pressure at room temperature, the desired product **16** was obtained with the best result of a 12:1 ratio of the amino alcohol favoring the product with the right asymmetrical centers. For the purpose of purification and protection, the amino alcohol was isolated as its monoacetate. Swern oxidation of the alcohol **16** gave the ketone **17** which reacted with ethoxyacetylenemagnesium chloride in THF giving a mixture of the Z and E isomers **18**. Addition of methylmagnesium bromide to the acetate ester and acid workup followed by the silylation afforded the unsaturated ester **19**. The introduction of the bulky silyl group dramatically controlled the stereoselectivity of the last hydrogenation. With the directing effect of the silyl group, dissolving metal reduction by lithium in liquid ammonium followed by lithium aluminum hydride reduction gave the equatorial isomer with a 35:1 selectivity disfavoring the desired product. On the other hand, hydrogenation with 5% Rhodium on Al_2O_3 support in hexanes with 1 atm hydrogen atmosphere followed by lithium aluminum hydride reduction gave the axial isomer favoring the desired product with a 10:1 ratio. The stereochemistry of this synthesis was further proved by the comparison of the synthetic compound with authentic sample derived from natural source.

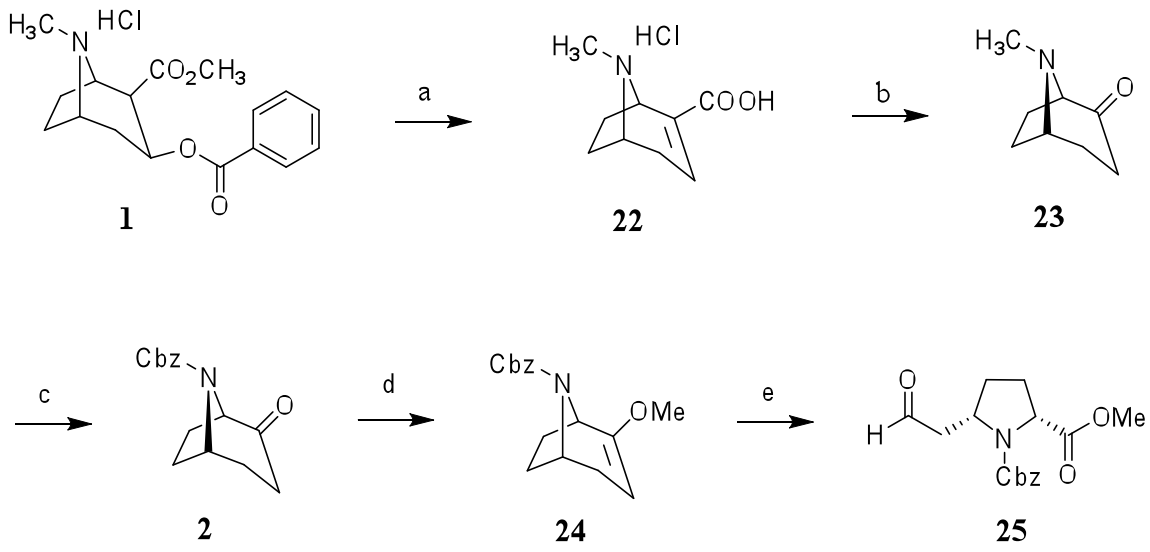
2.3 RESULTS AND DISCUSSION

Synthesis of (-)-Monomorine

As discussed earlier, (+)-monomorine **3**, *cis*-pyrrolidine 225H **4**, pyrrilizidine 233H **5** and (+)-gephyrotoxin **6** all share the common structural feature of a *cis*-2,5-disubstituted pyrrolidine ring system. This structural similarity encouraged us to develop a general synthetic sequence to

enantioselectively prepare those natural products. The building block in this strategy is *cis*-2,5-disubstituted pyrrolidine **2** which can be easily obtained from (+)-2-tropinone **22**. (+)-2-Tropinone **22** was selected as the early stage intermediate due to its availability and relative ease of preparation in our research laboratory.

This chemical and stereochemical efficiency of this approach was first successfully tested in the synthesis of (-)-Monomorine since this is a compound that has been enantioselectively synthesized and well chracterized.[13] The aldehyde **25** was selected as the building block due to its desired flexibility for a good chiral building block. It has the orthogonal reactivity of the aldehyde, ester and the N-Cbz protecting group as well as the asymmetry of *cis*-2,5-appendages which can all be developed into a diversity of functional groups.

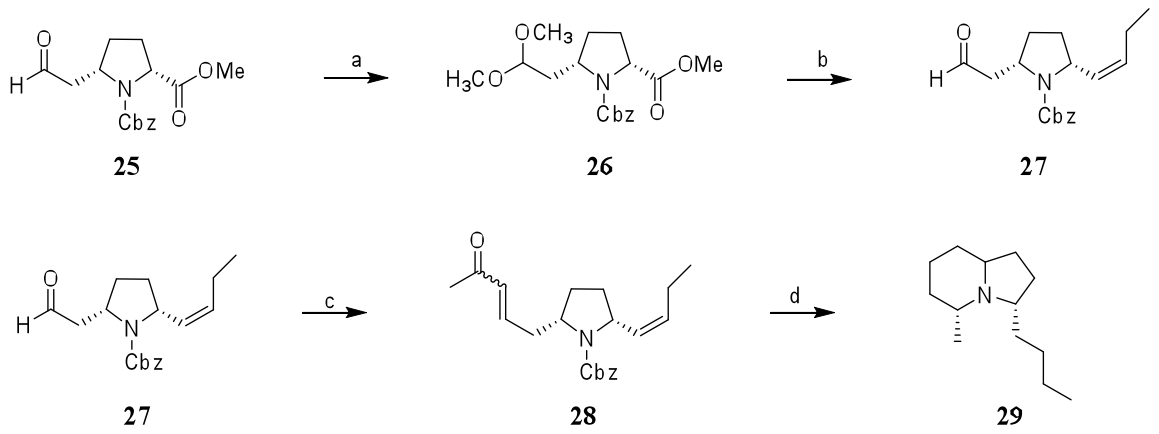


Scheme 2.7 Synthesis of pyrrolidine building block

Reagents and conditions: a) 37% HCl, reflux, 24 h; b) 1. $(PhO)_2P(O)N_3$, DMAP, Na_2CO_3, CH_2Cl_2, rt, 48 h; 2. 1 N HCl, reflux, 1 h; c) Cbz-Cl, K_2CO_3, toluene, reflux, 48 h; d) $HC(OCH_3)_3$, PTSA•H_2O; e) 1. O_3, CH_2Cl_2, – 78 °C; 2. Ph_3P, rt.

Confiscated grade (-)-cocaine was used as the starting material in sufficient quantities to provide the chiral building block for the syntheses. Although it is not commercially available, confiscated (-)-cocaine can be obtained from the National Institute on Drug Abuse with appropriate DEA licensing. As illustrated in **Scheme 2.7**, (-)-cocaine hydrochloride was treated with concentrated hydrochloric acid and reflux. Hydrolysis and condensation provided (-)-anhydroecgonine hydrochloride **22** in a quantitative yield. A suspension of the carboxylic acid **22** in dichloromethane was treated with diphenylphosphoryl azide (DPPA) and a catalytic amount of DMAP. The reaction took 48 hours at room temperature and it afforded the corresponding acyl azide. Without purification, the residue of acyl azide was taken up in hydrochloric acid and refluxed. This step converted the acyl azide to the desired (+)-2-tropinone **23** via a Curtius rearrangement.

The 2-tropinone **23** was demethylated and simultaneously the nitrogen was protected as the Cbz-carbamate. This reaction was done by heating the mixture of Cbz-Cl and K_2CO_3 in toluene to 120 °C for 48 hours when the progress of the reaction stopped indicated by TLC. This step reduced the basicity associated with the nitrogen atom and protected it from oxidation during the ozonolysis step. The *N*-Cbz-2-tropinone **2** was then treated with trimethyl orthoformate in the presence of PTSA•H_2O as catalyst. This step converted *N*-Cbz-2-tropanone into the methyl enol **24** which was unstable on silica gel and had a very short shelf life. Without further purification, the methyl enol ether was brought to ozonolysis. At -78 °C, ozone was bubbled through the solution of methyl enol ether in dichloromethane till the solution turned light blue and the blue color persisted which indicated the complete cleavage of the double bond. The addition of triphenylphosphine subsequently reduced the intermediate to the enantiopure tricarbonyl derivative **25**.



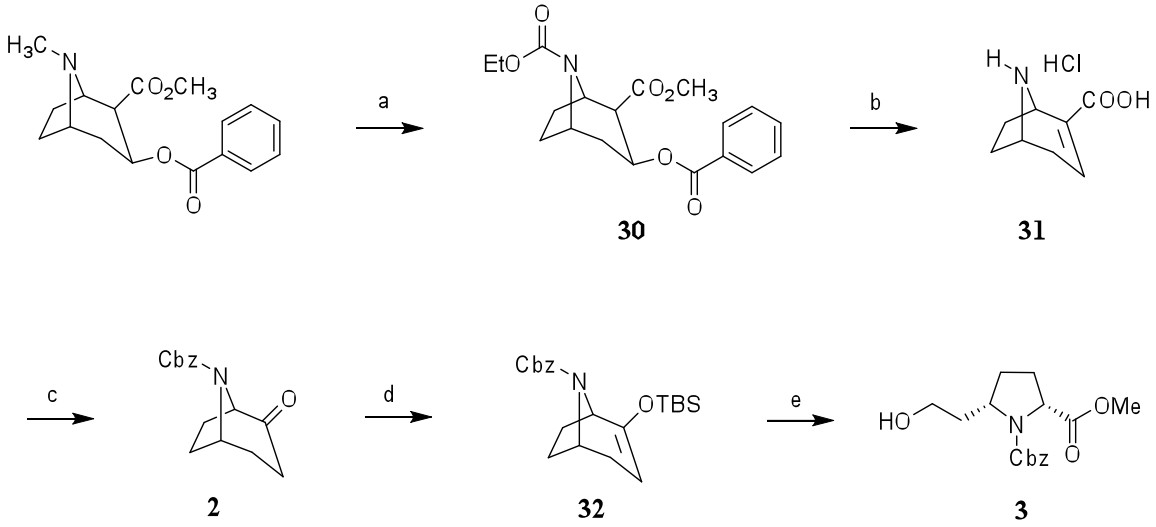
Scheme 2.8 Synthesis of (-)-Monomorine

Reagents and conditions: a) $CH(OCH_3)_3$, $CeCl_3 \bullet 7H_2O$; b) 1. DIBAL-H, toluene, -78 °C; 2. $Ph_3PCH_2CCH_2CH_3Br$, *t*-BuOK, toluene; 3. $PTSA.H_2O$, Acetone; c) $(CH_3O)_2POCH_2COCH_3$, LiCl, DBU, CH_3CN; d) H_2 (55 psi), 10% Pd/C, CH_3OH.

In the synthesis of (-)-monomorine **3** (**Scheme 2.8**), the right butyl side chain was initially built from the ester moiety. This approach avoided the protection and deprotection of this ester functional group at a later stage. Thus, the aldehyde moiety was protected as the acetal **26** (in a 92% yield) with trimethyl orthoformate catalyzed by cerric chloride. When the solution of DIBAL-H in THF was added slowly at a low temperature of -78°C, the ester group was cleanly reduced to aldehyde **27** which was directly introduced to the Wittig olefination reaction adding a four-carbon unit for the side-chain. Hydrogenation of the olefin at this point was not necessary since it could be done concomitantly with the ring closure step at the last step. The acetal group was subjected to hydrolysis when it was treated with $PTSA \bullet H_2O$ at room temperature affording the aldehyde **27** in a 55% overall yield for three steps. Olefination of **27** with trimethylphosphonoacetate, lithiumchloride, and DBU gave the diene **28** in a form of the mixture of two isomers in an 80% yield. The construction of the indolizidine ring system was the key step for the synthesis of (-)-monomorine. It was completed with a simultaneous hydrogenation/reductive animation of **28**. The hydrogenation of the side olefin moieties,

deprotection of the pyrrolidine nitrogen, and reductive animation/ring closure all ran smoothly with the application of hydrogen (55 psi) over 10% Pd/carbon. During the sequence of the reactions, Z/E olefinations isomers were not separated since the later hydrogenation step would lead all to the same compound. The relative stereochemistry and absolute configuration of the synthesized (-)-monomorine product was confirmed by a good match of our collected analytical data of compound **29** with the published analytical data for (+)-monomorine in literature.

Synthesis of (+)-*cis*-pyrrolidine 225H



Scheme 2.9 Revised synthetic route of building block

Reagents and conditions: a) EtOOCCl, K_2CO_3, toluene, reflux, 12 h; b) 37% HCl, reflux, 10 h; c) 1. $(PhO)_2P(O)N_3$, DMAP, Na_2CO_3, CH_2Cl_2, rt, 24 h; 2. 1 N HCl, reflux, 1 h; 3. Cbz-Cl, CH_2Cl_2; d) 1. KH, THF, 0 °C, 1 h; 2. TBDMS-Cl, rt, overnight; e) 1. O_3, MeOH/CH_2Cl_2, – 78 °C; 2. $NaBH_4$, 0 °C; 3. CH_2N_2, Et_2O, 0 °C, 30 min.

We were pleased to see the chemical and stereochemical efficiency of our new synthetic strategy in the preparation of (-)-monomorine. To further apply this methodology to synthesize other amphibian alkaloids and the general synthesis of natural products and drug candidates, we

felt the need to optimize our reaction sequences to prepare the building block more rapidly and more efficiently.

Building block **25** (**Scheme 2.8**) was synthesized in a moderate yield of 31% over five steps and it took a long cycle to prepare **25** from our starting material natural product (-)-cocaine with 24 hours and 48 hours reaction time for the first step and the second step respectively. The demethylation/protection step provided the product in a moderate yield (56%). The overall yield was also limited by the ozonolysis step where the low yield was believed to have caused by impurities brought from the previous step.

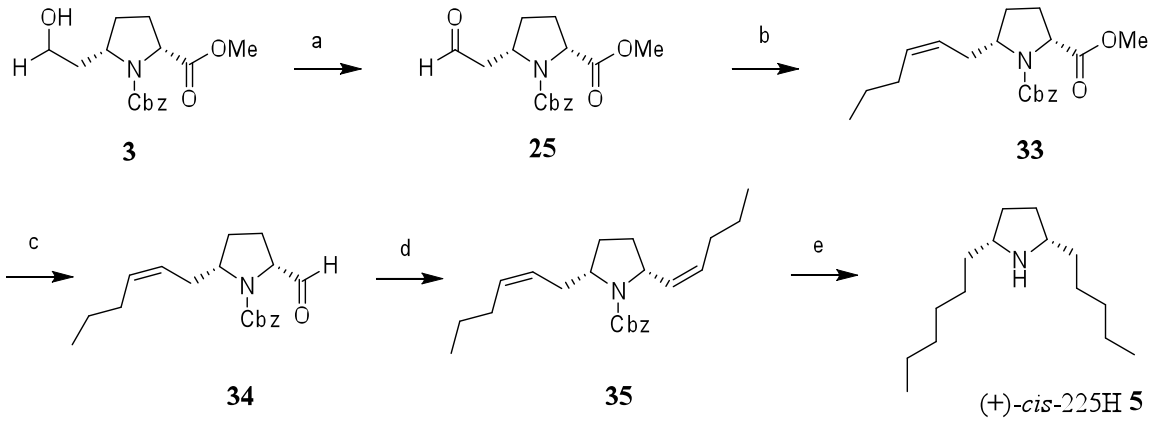
Targeting at the resolution of these problems, we designed a different synthetic route to make the building block **25**. In our previous synthesis, we noticed that the overall yield of the (+)-2-tropinone **23** varied with the quality of the confiscated (-)-cocaine. To minimize this influence, we simply purified the (-)-cocaine by extraction. The confiscated (-)-cocaine hydrochloride salt was first dissolved in water and the aqueous solution was washed by ethyl ether to removed trace of organic impurities. The aqueous solution was then basified to pH =10 with saturated sodium carbonate aqueous solution and extracted by dichloromethane. This procedure eliminated potential water-soluble inorganic impurities. We realized that the difficulty of the Cbz-protection on the nitrogen could be caused by the *β*-carbonyl group on **23**. The β-carbonyl group made the nitrogen more hindered and the lone pair electrons on nitrogen less reactive with the chloroformate reagent. But if the demethylation/deprotection step was done before the *β*-carbonyl was introduced, the difficulty of reaction could then be avoided. In the revised building block synthetic route (**Scheme 2.10**), demethylation was done as the first step accompanied by protection with ethyl chloroformate. This provided **30** in almost a quantitative yield and chromatography purification provided a clean intermediate for the next two steps. The carbamate

30 was refluxed in concentrated hydrochloric acid for 12 hours. Hydrolysis of two ester groups, one amide, and dehydrogenation all proceeded concomitantly giving the *α,β*-unsaturated carboxylic acid **31**. The acid **31** reacted with diphenylphosphoryl azide catalyzed by DMAP in dichloromethane giving the intermediate acyl azide which then underwent Curtius rearrangement releasing nitrogen gas and carbon dioxide gas upon decomposition.[14] It was not easy and not necessary to separate the intermediate (*1R,5S*)-8-azabicyclo[3.2.1]octan-2-one from DMAP since they share similar chemical and physical properties. The crude mixture reacted with benzyl chloroformate to protect the nitrogen and reduce its basicity. Since this was a heterogenous reaction, the yield of this one-pot three-step reaction was closely related to the dryness of the reactant carboxylic **31**. Completely drying and finely grinding the acid **30** was found to greatly facilitate conversion of the carboxylic acid **31** into acyl azide and as a result could favor the yield for those steps giving ketone **2**.

Ketone **2** was treated with NaH followed by the addition of *t*-buytldimethylsilyl chloride to furnish silyl enol ether **32** according to the procedure reported by Rassat and coworkers.[15] Compared with methyl enol ether, silyl enol ether was more stable to acid conditions. Ether **32** could be purified by silica gel chromatography. The clean product resulted in a significantly increased yield for the ozonolysis step. Ozone was freshly generated in our laboratory from oxygen. Ozone was slowly and steadily bubbled through the solution of enol ether **32** in the mixture of dichloromethane and methanol at a low temperature of -78 °C. When all the enol ether was converted and no more ozone was consumed, the solution turned light blue and the blue color persisted. The ozonide was formed as the oxidation product but it could only exist in solvent at low temperature. Different reducing agents could result in different reduction products of the ozonide. When sodium borohydride was used, the two functional groups introduced were

carboxylic acid and alcohol. This product was not purified since it was highly polar. Therefore, the crude product residue was directly treated with diazomethane to convert the carboxylic acid to methyl ester. The new pyrrolidine building block **3** was furnished with 67% yield over three steps.[4,14]

Diazomethane is a highly explosive material. Diazomethane frequently employed in routine work is generally prepared from precursors by dangerous and time-consuming distillation and collection. The diazomethane used in the reaction was freshly prepared by simply reacting toluenesulphonylmethylnitrosamide (Diazald) with sodium hydroxide in methanol in a simplified apparatus designed for this reaction. The stream of diazomethane was bubbled through the solution of intermediate carboxylic acid in ethyl ether and the reaction was done in minutes to afford **3** in a good yield. This revised synthetic route gave the new building block **3** in a 51% yield from (-)-cocaine.



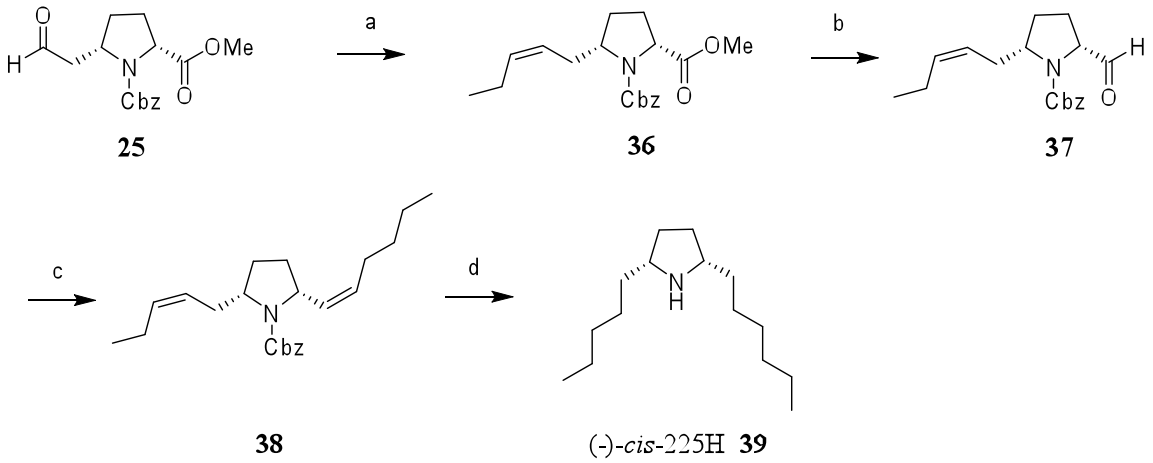
Scheme 2.10 Synthesis of (+)-Pyrrolidine 225H

Reagents and conditions: a) 1. Oxalyl chloride, DMSO, Et_3N, -78 ºC; b) $(Ph_3PCH_2CH_2CH_2CH_3)Br$, KH, THF, rt; c) DIBAL-H, CH_2Cl_2, -78 ºC; d) $(Ph_3PCH_2CH_2CH_2CH_3)Br$, KH, THF, rt; e) H_2, Pd/C, MeOH, rt, overnight.

In the synthesis of pyrrolidine 225H, no protection of either the alcohol functional group or the ester moiety was necessary when the reactions were under taken in the right sequence. The alcohol **3** was oxidized to aldehyde **25** following the Swern oxidation. The aldehyde **25** coupled with triphenylphosphoniumbutyl bromide gave a mixture of Z/E olefin with the ration of 5:1. The Z isomer was isolated and reduced by DIBAL-H. Although alcohol usually appeared as over-reduction product, the reaction ran cleanly to give aldehyde as the exclusively only reduction product with a very small amount starting material remained, when the DIBAL-H solution was added dropwise at a strictly controlled low temperature. Wittig reaction of the aldehyde **34** coupled again with triphenylphosphoniumbutyl bromide furnishing **35**. This step produced four products, likely the isomers of *Z-cis*-pyrrolidine, *E-cis*-pyrrolidine, *Z-trans*-pyrrolidine and *E-trans*-pyrrolidine as the result of epimerization associated with the Wittig basic reaction conditions. Fortunately, all those four isomers were easily separated on silica gel column chromatography. At that point we assume that the predominantly major product was *Z-cis*-pyrrolidine isomer and it was exposed to hydrogen (1 atm) with 10% Pd/carbon. Hydrogenation of the two double bonds and the removal of Cbz protection group went simultaneously giving (+)-pyrrolidine 225H.

The absolute configuration of *cis*-pyrrolidine 225H has yet to be established and there is no reported spectroscopic data or optical rotation data of this compound that we could compare with our product. With the asymmetry of the appendages, the intermediates existed as a complex mixture of two conformers (rotomers) due to hindered rotation of the *N*-Cbz bond. The existence of rotomers significantly complicated the NMR spectroscopy of late stage intermediates and made it difficult to fully and accurately characterize intermediate compounds spectroscopically. As a result, we decided to synthesize the other enantiomer of *cis*-pyrrolidine 225H and to

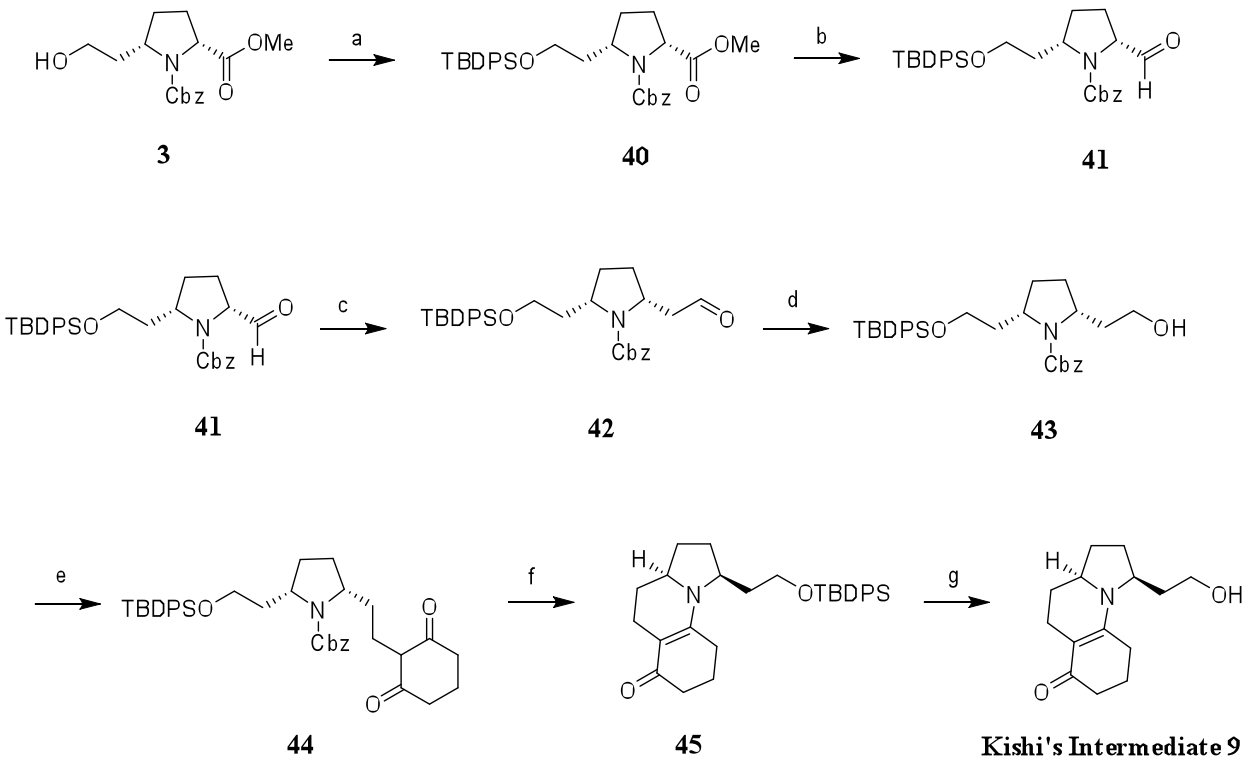
compare the optical rotation data collected from both of the synthetic enantiomers. If our synthetic route especially the last hydrogenation step did not cause eperimerization of any asymmetric center, the optical rotation of the two enantiomers should be opposite to each other. The synthesis was completed following steps in described in **Scheme 2.12** affording (-)-*cis*-pyrrolidine 225 **39**. The spectroscopic data of **39** (NMR) was identical with that of **5**. The optical rotation of **39** ($[\alpha]_D^{25}$ -19.6 (*c* 0.5, CH_3OH)) was determined to be nearly opposite to that of **5** ($[\alpha]_D^{25}$ +21.9 (*c* 1.0, CH_3OH)). This supported that both of the enantiomers of *cis*-pyrrolidine 225H have been synthesized in our laboratory from the building block in a stereocontrolled manner.



Scheme 2.11 Synthesis of (-)-Pyrrolidine 225H

Reagents and conditions: a) 1. Oxalyl chloride, DMSO, Et_3N, -78 ºC; b) $(Ph_3PCH_2CH_2CH_3)Br$, KH, THF, rt; c) 1. DIBAL-H, CH_2Cl_2, -78 ºC; 2. $(Ph_3PCH_2CH_2CH_2CH_2CH_3)Br$, KH, THF, rt; c) H_2, Pd/C, MeOH, rt, overnight.

Formal Synthesis of (+)-Gephyrotoxin



Scheme 2.12 Synthesis of Kishi's Intermediate

Reagents and conditions: a) 1. TBDPS-Cl, imidazole, DMF; b) DIBAL-H, toluene, -78 ºC; c) 1. $(Ph_3PCH_2OCH_3)Cl$, *t*-BuOK, THF; 2. PTSA•H_2O, acetone; d) 1. $NaBH_4$, MeOH; e) 1. TsCl, pyridine, rt; 2. 1,3-Cyclohexanedione, *t*-BuOK, THF, 0 ºC; f) H_2 (1 atm), Pd/C, MeOH, rt, overnight; g) TBAF, DMF.

As demonstrated in **Scheme 2.13**, Kishi's intermediate has two asymmetric centers which can be directly introduced from our building block **3**. With the *cis*-2,5-disubstituted pyrrolidine **3** in hand, our attention was directed toward the construction of the remaining rings of tricyclic ketone **9**. To this end, a one-carbon homologation sequence was used to install the C5 atom of the tricyclic system **9**. The alcohol **3** was initially converted into silyl ether **40** using TBDPS-Cl in a 93% yield.[16] The ester unit of **40** was then reduced using DIBAL-H to furnish the corresponding aldehyde **41** in an 83% yield. Wittig olefination of **41** using a preformed ylide

generated from $Ph_3PCH_2OCH_3Cl$ and *t*-BuOK gave the methyl enol ether. Subsequent hydrolysis of the enol moiety with PTSA·H_2O in acetone furnished the desired aldehyde **42** in a 79% yield over the two-step sequence. Although we only observed one compound with the right NMR spectrum, there was the potential for epimerization at C5 of **41**. We continued on with the intention of characterizing any diastereoisomers at a later stage in the synthesis.

Aldehyde **42** was reduced carefully with DIBAL-H. The product alcohol **43** was converted to its tosylate and then coupled with 1,3-cyclohexanedione .[16] This one-step coupling method afforded the dione **44** in a 93 % yield. Subsequent hydrogenation of the dione **44** catalyzed by 10% Pd/C furnished the tricyclic amine as a mixture of diastereoisomers (9:1) in 75% yield via sequential Cbz removal, cyclization and enolamine elimination. Two isomers were observed as products with very similar NMR spectrum.

The rigid nature of the tricyclic ring system facilitated the structural characterization of the diastereoisomers. The two diastereoisomers were readily distinguished by ^{13}C and ^{1}H NMR but were not easily separated by column chromatography. Presumably the minor isomer resulted from epimerization of C5 during the ozonolysis, the DIBAL-H reduction or the Wittig olefination steps. Nevertheless, the minor diastereoisomer could be readily removed after the subsequent step. Removal of the silyl-protecting group with TBAF gave a separable mixture of diastereoisomers and furnished Kishi's intermediate **9** in an 87% yield in its enantiopure form. The NMR spectra were consistent with previously reported data[9-12] and the absolute configuration of **9** was unequivocally established by X-ray crystallography.

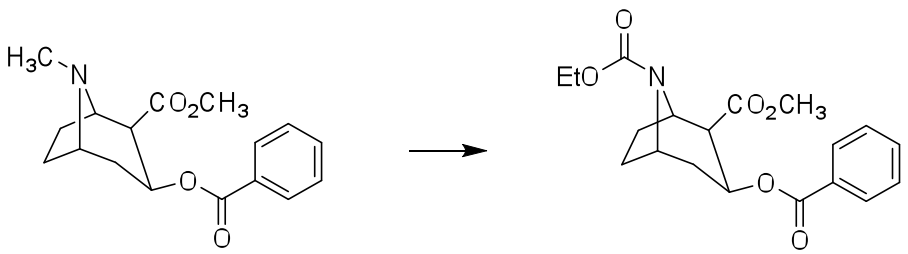
2.4 CONCLUSIONS

Our efficient and expeditious approach exploits the inherent stereochemistry of a (*1R*)-2-tropinone derivative **2** prepared from (-)-cocaine **1** for the construction of the core *cis*-2,5-disubstuted pyrrolidine ring system. Utilizing this intermediate as a building block, the enantioselective syntheses of both of the (+)-*cis*-pyrrolidine 225H in a 31% yield and (-)-*cis*-pyrrolidine 225H in a 29% yield were achieved. An enantioselective synthesis of the tricyclic gephyrotoxin skeleton was also successfully conducted. The synthesis provided Kishi's intermediate in an enantiopure form in a 19% overall yield and constitutes a formal synthesis of (+)-gephyrotoxin 287C.

2.5 EXPERIMENTAL SECTION

General Experimental Methods

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous dichloromethane was purchased from Mallinckrodt Baker, Inc. Confiscated grade (-)-cocaine hydrochloride was provided by NIDA Drug Supply System, Research Technology Branch, National Institute on Drug Abuse. Proton and carbon NMR were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in $CDCl_3$ from Cambridge Isotope Laboratories, Inc. ^1H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to chloroform-*d* (77.0 ppm). Optical rotations were measured on Autopol III polarimeter at the sodium D line (2 mL sample cell). Melting points (mp) were measured with an Electrothermal R Mel-Temp apparatus and are uncorrected.

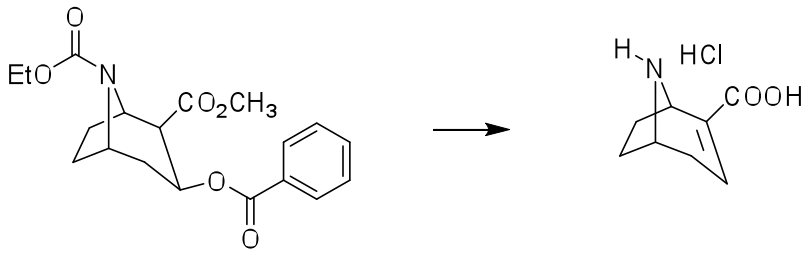


30

(1R,2R,3S,5S)-8-Ethyl 2-methyl 3-(benzoyloxy)-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate (30) Confiscated (-)-cocaine hydrochloride salt (20 g) was dissolved in water (50 mL). The aqueous solution was washed by ether to remove the trace of organic impurity. The saturated Na_2CO_3 in water was added till pH=10. The resultant slurry of white solid was treated with dichloromethane (100 mL). The aqueous portion was discarded. The organic solution was dried on anhydrous Na_2SO_4, filtered, and concentrated in vacuo giving the pure (-)-cocaine (18.1 g, 100%)

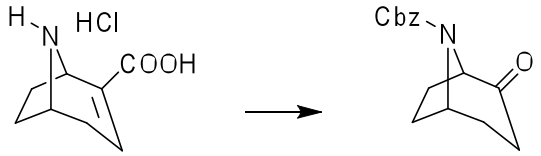
Pure (-)-Cocaine (9.76 g, 32.1 mmol) and $NaHCO_3$ (4.05 g, 48.3 mmol) were taken up in 100 mL of anhydrous toluene. To the suspension was added ethyl chloroformate (17.45 g, 15.30 mL, 160.8 mmol). The reaction mixture was heated to reflux at 120 °C. After 12 hours, another portion of ethyl chloroformate (10.47 g, 9.18 mL, 96.5 mmol) was added. The stirring and refluxing continued for additional 12 hours till the TLC indicated the complete conversion of the starting material. Toluene was removed under reduced pressure. The residue was portioned between EtOAc (100 mL) and water (100 mL). The aqueous layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). Combined organic portions were washed by saturated Na_2CO_3 in water (100 mL), brine (100 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/hexanes = 1:2) affording **30** (11.37 g, 31.46 mmol, 98%) as a slightly yellow oil. R_f = 0.34 (EtOAc/hexanes = 1:2). $[\alpha]_D^{25}$ -30.4 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-

7.90 (m, 2H), 7.59-7.51 (m, 1H), 7.42-7.37 (m, 2H), 5.50-5.41 (m, 1H), 4.76-4.41 (m, 2H), 4.20-4.00 (m, 2H), 3.63 (s, 3H), 3.09 (brs, 1H), 2.61-2.56 (m, 1H), 2.18-1.72 (m, 5H), 1.30-1.19 (m, 3H). ^{13}C NMR ($CDCl_3$) δ170.4, 166.0, 153.9, 133.3, 129.7, 128.5, 66.7, 61.23, 61.12, 54.89, 54.60, 52.55, 52.37, 51.95, 51.63, 49.38, 48.92, 33.67, 33.28, 28.91, 28.20, 27.94, 27.32, 14.75. Anal. Calcd. for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.22; H, 6.49; N, 3.91.



30 **31**

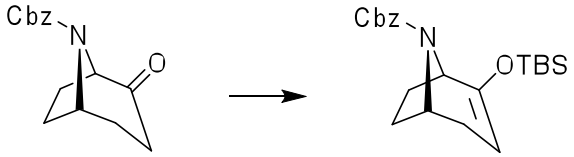
(1R,5S)-8-Azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid hydrochloride (31) 30 (10.14 g, 28.5 mmol) was taken up in 100 mL of concentrated hydrochloric acid (12 N). The reaction was heated to reflux at 120 °C for 6 hours. After being cooled to room temperature, the aqueous solution was washed by ether (2 x 50 mL). Most of the water was removed under high vacuum at elevated temperature. Then the slurry was azeotropic distilled with toluene twice to remove the remaining water. The resultant solid was dried in a oven under vacuum (30 torr, 80 °C) for 12 hours. The solid was ground into fine powder and heated again in the oven for 12 hours giving the desired product **31** (5.41 g, 28.5 mmol) as a white powder. Mp/Dec. 260-262°C. Anal. Calcd for $C_8H_{12}ClNO_2$: C, 50.67; H, 6.38; N, 7.39. Found: C, 50.38; H, 6.39; N, 7.27.



31 **2**

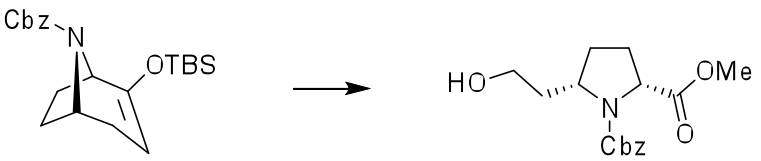
(**1R,5S)-Benzyl 2-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2)** The finely powdered **31** (3.216 g, 17.0 mmol) and sodium carbonate (4.50 g, 42.50 mmol) ware suspended in 100 mL of anhydrous dichloromethane followed by the addition of 4-dimethylaminopyridine (104 mg, 0.84 mmol). The suspension was purged with N_2, sealed, and stirred for 15 minutes before diphenylphosphoryl azide (5.71 g, 4.48 mL, 20.74 mmol) was added dropwise. The stirring was continued for 48 hours. Solvent was removed in vacuo. The mixture slurry was taken up in 40 mL of water. At 0 °C, 120 mL of hydrochloric acid (1 N in water) was added slowly and carefully with the evolution of gas. The aqueous solution was then heated in a preheated oil bath (120 °C) for 40 minutes until the carbon dioxide and nitrogen gas evolution ceased. The aqueous hydrochloric acid solution was removed under reduced pressure. The residue was basified (pH 9.5-10) by the addition of saturated Na_2CO_3. The aqueous solution was then extracted with CH_2Cl_2 (2 x 50 mL). The combined organic portions were washed by brine (50 mL), dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue without further purification was dissolved in the mixture of 108 mL of MeOH and 12 mL of water. At 0 °C, sodium bicarbonate (4.6 g) was added followed by the addition of benzyl chloroformate (2.4 mL). The reaction mixture was stirred at room temperature for 5 hours. The solvent methanol was removed under reduced pressure. The aqueous solution was diluted with 50 mL of water and extracted with CH_2Cl_2 (2 x 50 mL). Combined organic fractions were washed by brine, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, EtOAc/hexanes = 1:2) affording **2** (3.84 g, 14.79 mmol, 87%) as a clear oil. 1H NMR

(400 MHz, $CDCl_3$) δ7.39-7.27 (m, 5H), 5.19-5.07 (m, 2H), 4.54-4.44 (m, 2H), 2.48-2.42 (m, 2H), 2.38-2.32 (m, 2H), 2.25-2.18 (m, 2H), 1.86-1.77 (m, 2H). ^{13}C NMR ($CDCl_3$) δ205.5, 154.0, 136.5, 128.6, 128.2, 128.0, 67.2, 64.3, 53.0, 32.6, 30.6, 28.0, 27.2. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.65; H, 6.65; N, 5.29.



2 **32**

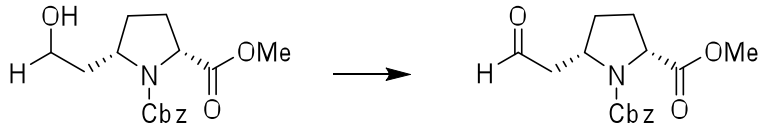
(1R,5S)-benzyl 2-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (32) Under nitrogen atmosphere, NaH (60 mg, 2.5 mmol) was suspended in anhydrous THF (4 mL). At 0 °C, a solution of compound **2** (130 mg, 5 mmol) in dry THF (2 mL) was added dropwise and stirred for 2 hours. Then TBDMSCl (1.0 M in THF, 1 mL) was added dropwise and stirred overnight at room temperature. At 0 °C, the reaction was quenched by a slow addition of water (10 mL) and diluted with ethyl ether (20 mL). The organic fraction was separated and the aqueous was extracted with ethyl ether (2 x 20 mL). Combined organic portions were dried on $MgSO_4$, filtered, and concentrated. The crude product was purified by a flash chromatography (SiO_2, eluting with EtOAc/Hexanes = 5:95) to afford **32** (166 mg, 89% yield) as a colorless oil. $[\alpha]_D^{25}$ -43.5 (*c* 1.2, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.35 (m, 5H), 5.09-5.19 (m, 2H), 4.11-4.49 (m, 2.5H), 2.61-2.79 (m, 0.5H), 1.94-2.18 (m, 3H), 1.74 (dd, *J* = 16.4, 4.6, 1H), 1.58-1.67 (m, 2H), 0.90 (s, 9H), 0.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8., 154.4, 137.1, 128.6, 128.1, 128.0, 97.3, 66.8, 57.7, 52.5, 34.4, 33.7, 32.4, 31.4, 30.2, 29.4, 25.8, 18.2, -4.5, -4.1, Anal. Calcd for $C_{21}H_{31}NO_3Si$: C, 67.52; H, 8.36; N, 3.79. Found: C, 67.73; H, 8.58; N, 3.79.



32 **3**

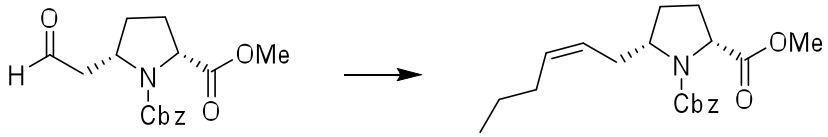
(2R,5S)-1-benzyl 2-methyl 5-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate (3) Silyl ether **32** (781 mg, 2.1 mmol, 1.0 equiv) was dissolved in the solution of CH_2Cl_2 (50 mL) + CH_3OH (5 mL). At -78 °C, O_3 was bubbled into the solution till a light blue color was observed and persisted. A stream of N_2 was bubbled through for 10 minutes. At -78 °C, $NaBH_4$ (250 mg) was added by one portion. After 30 minutes, another portion of $NaBH_4$ (300 mg) was added and the reaction was warmed to room temperature. The solvent was removed under reduced pressure. The residue was triturated with 2N HCl (25 mL) to pH<1. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). Combined organic portions were dried on anhydrous $MgSO_4$, filtered, and concentrated affording a slightly yellow oil.

CH_2N_2 gas was freshly prepared from *p*-toluenesulphonylmethylnitrosamide (Diazald) and bubbled through the solution of the previous oil in Et_2O (20 mL) at 0°C. When a yellow color was observed in the solution, CH_2N_2 stream was removed and N_2 was bubbled through the solution for 5 minutes. The reaction was warmed to room temperature and the solvent was removed in vacuo. The residue was purified by a flash chromatography (SiO_2, eluting with hexanes/EtOAc = 4:6) affording ester **3** (430 mg, 67% yield, 3 steps) as a colorless oil. $[\alpha]_D^{25}$ +52 (*c* 0.6, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.37 (m, 5H), 5.03-5.22 (m, 2H), 4.37 (t, *J* = 8.3, 1H), 3.93 (dd, *J* = 9.8, 4.6, 1H), 3.64-3.82 (m, 3H), 3.60 (s, 3H), 2.30-2.37 (m, 1H), 1.95-2.11 (m, 2H), 1.61-1.82 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 156.1, 136.4, 128.7, 128.3, 127.9, 67.8, 59.9, 59.1, 55.8, 52.4, 37.8, 30.9, 29.2. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.28; H, 7.00; N, 4.49.



3 **25**

(2R,5S)-1-benzyl 2-methyl 5-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (25) Under N_2, oxalyl chloride (150 mg, 0.1 mL, 1.18 mmol) was taken up in 30 mL of CH_2Cl_2 and cooled to -78 °C in a dry ice/acetone bath. Dimethyl sulfoxide (184 mg, 0.17 mL, 2.25 mmol) was added dropwise. The mixture was stirred at -78 °C for 10 minutes before a solution of the alcohol **3** (300 mg, 1.07 mmol) in 2 mL CH_2Cl_2 was added slowly. The mixture again was stirred for 15 minutes. Then triethyl amine (541 mg, 0.75 mL, 5.35 mmol) was added and the reaction was warmed to room temperature. Water (30 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). Combined organic portions were washed by brine, dried on anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by a silica gel column eluting with 1:1 EtOAc/hexanes affording the product (294 mg, 90%) as a clear oil. $[\alpha]_D^{25}$ +23.6 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 0.6H), 9.71 (s, 0.4H), 7.35-7.27 (m, 5H), 5.19-5.03 (m, 2H), 4.50-4.32 (m, 2H), 3.74 (s, 1.2H), 3.61 (s, 1.8H), 3.24 (dd, J = 20, 3.7, 0.6H), 3.05 (dd, J = 20, 3.7, 0.4H), 2.72-2.62 (m, 1H), 2.27-2.16 (m, 2H), 2.03-1.94 (m, 1H), 1.75-1.66 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 200.9, 200.7, 173.2, 173.0, 154.3, 153.9, 136.3, 136.1, 128.5, 128.4, 128.2, 128.1, 128.0, 127.6, 67.3, 67.0, 59.9, 59.5, 54.0, 53.2, 52.3, 52.1, 48.9, 48.2, 31.0, 30.2, 28.9, 28.0, 22.2. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.51; H, 6.53; N, 4.49.

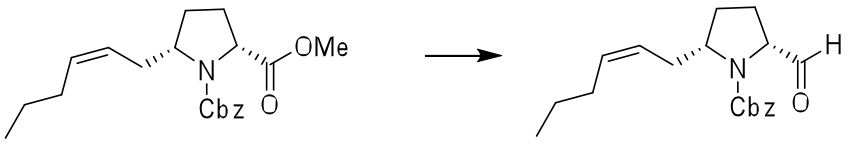


25 **33**

(2R,5S)-1-benzyl 2-methyl 5-((Z)-hex-2-enyl)pyrrolidine-1,2-dicarboxylate (33)

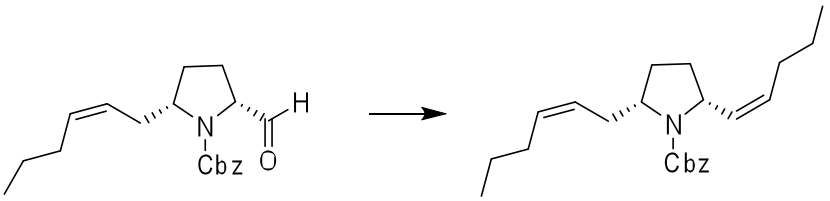
Potassium hydride (40% in mineral oil) was washed by anhydrous hexanes and dried by a stream of argon. Potassium hydride (47.3 mg, 1.18 mmol) and $Ph_3P(CH_2)_3CH_3Br$ (628 mg, 1.572 mmol) were suspended in 10 mL of anhydrous THF. The reaction was stirred under the atmosphere of N_2 at room temperature for 30 minutes and then cooled to 0 °C in an ice water cold bath. At 0 °C, the solution of aldehyde **25** (120 mg, 0.393 mmol) in 1 mL of THF was added dropwise. Upon the completion of addition, the cold bath was removed and the reaction mixture was stirred at room temperature for one hour. The reaction was quenched by the addition of 1 mL of saturated ammonium chloride aqueous solution. The reaction was then partitioned between EtOAc (20 mL) and water (20 mL). The top organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). Combined organics were washed by brine, dried on anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 1:4 EtOAc/hexanes affording the Z-alkene (85 mg, 85%) as the predominant major isomer. R_f = 0.44 (EtOAc:Hexanes = 1:4). $[\alpha]_D^{25}$ +15.6 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 5.53-5.44 (m, 2H), 5.43-5.29 (m, 2H), 4.41-4.30 (m, 1H), 4.00-3.83 (m, 1H), 3.77 (s, 1.4H), 3.61 (s, 1.6H), 2.84-2.62 (m, 1H), 2.31-2.13 (m, 2H), 2.10-1.87 (m, 4H), 1.84-1.70 (m, 1H), 1.42-1.34 (m, 2H), 0.93 (t, *J* = 0.68, 1.6H), 0.84 (t, *J* = 0.68, 1.4H). ^{13}C NMR ($CDCl_3$) δ 173.5, 173.3, 154.9, 154.1, 136.6, 136.5, 132.4, 132.2, 128.4, 128.3, 128.0, 127.8, 127.6, 125.6, 125.3, 67.2, 66.8, 60.2, 59.8, 59.2, 58.6,

52.1, 52.0, 32.0, 31.2, 29.4, 29.3, 29.0, 28.7, 28.0, 22.7, 22.6, 13.7, 13.6. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.34; H, 8.01; N, 4.21.



33 **34**

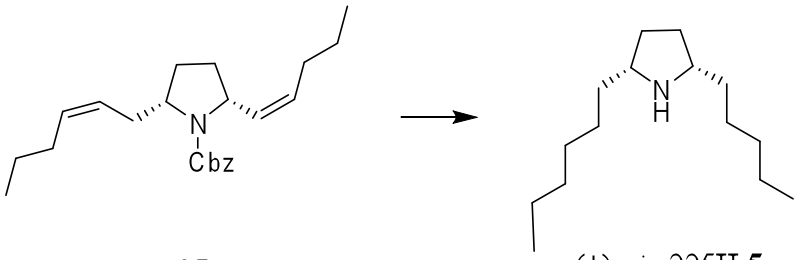
(**2R,5S)-benzyl 2-formyl-5-((Z)-hex-2-enyl)pyrrolidine-1-carboxylate (34)** Methyl ester **33** (100 mg, 0.289 mmol) was taken up in 15 mL of anhydrous CH_2Cl_2 and cooled to -78 °C in a dry ice/acetone bath. At -78°C, diisobutylaluminium hydride (DIBAL-H, 1 M in toluene, 0.376 mL) was added dropwise in a period of 30 minutes. After the completion of addition, the reaction mixture was stirred at -78 °C for two hours till the starting material disappeared monitored by TLC. The reaction was quenched by the addition of 0.5 mL of MeOH and warmed up to room temperature. The mixture was poured into ice-cold hydrochloric acid solution in water (1 N). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic portions were washed by brine, dried on anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 1:4 EtOAc/Hexanes affording the aldehyde (86 mg, 95%). $[\alpha]_D^{25}$ +4.6 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 0.5H), 9.74 (s, 0.5H), 7.39-7.22 (m, 5H), 5.53-5.44 (m, 2H), 5.43-5.29 (m, 2H), 4.45-4.39 (m, 1H), 4.00-3.83 (m, 1H), 2.84-2.62 (m, 1H), 2.31-2.13 (m, 2H), 2.08-1.78 (m, 4H), 1.84-1.70 (m, 1H), 1.42-1.34 (m, 2H), 0.93 (t, *J* = 0.68, 1.6H), 0.84 (t, *J* = 0.68, 1.4H). ^{13}C NMR ($CDCl_3$) δ 200.6, 156.0, 154.8, 136.4, 133.1, 128.9, , 128.0, 127.2, 67.9, 67.7, 66.3, 66.1, 59.9, 58.7, 32.5, 31.9, 29.8, 28.3, 26.0, 24.8, 22.9. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.09; H, 8.07; N, 4.19.



34 **35**

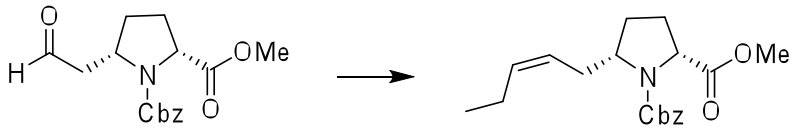
(2S,5R)-benzyl 2-((Z)-hex-2-enyl)-5-((Z)-pent-1-enyl)pyrrolidine-1-carboxylate (35)

Potassium hydride (40% in mineral oil) was washed by anhydrous hexanes and dried by a stream of argon. Potassium hydride (50 mg, 1.25 mmol) and $Ph_3P(CH_2)_3CH_3Br$ (663 mg, 1.66 mmol) were suspended in 10 mL of anhydrous THF. The reaction was stirred under the atmosphere of N_2 at room temperature for 30 minutes and then cooled to 0 °C in an ice/water cold bath. At 0 °C, the solution of aldehyde (131 mg, 0.415 mmol) in 1 mL of THF was added dropwise. Upon the completion of addition, the cold bath was removed and the reaction mixture was stirred at room temperature for one hour. The reaction was quenched by the addition of 1 mL of saturated ammonium chloride aqueous solution. The reaction was then partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). Combined organic fractions were washed by brine, dried on anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 1:11 EtOAc/hexanes affording the Z-alkene (116 mg, 0.328 mmol, 85%) as the predominant major isomer. $[\alpha]_D^{25}$ -117.7 (*c* 1.5, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 5.55-5.30 (m, 4H), 5.12 (s, 2H), 4.61-4.57 (m, 1H), 3.95-3.85 (m, 1H), 2.62-2.51 (m, 2H), 2.20-1.80 (m, 6H), 1.80-1.60 (m, 4H), 1.51-1.18 (m, 4H), 1.00-0.85 (m, 4H) ^{13}C NMR ($CDCl_3$) δ 155.5, 137.1, 133.2, 130.5, 130.1, 128.4, 128.1, 128.0, 125.9, 67.7, 59.0, 56.2, 32.9, 31.7, 30.0, 22.8, 14.3. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.66; H, 9.49; N, 4.08.



35 (+)-*cis*-225H **5**

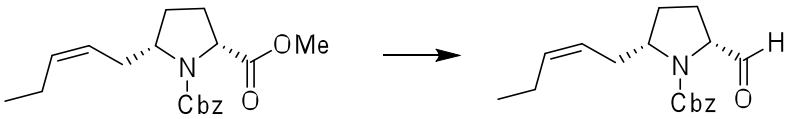
(+)-*cis*-Pyrrolidine 225H (5) Diene **35** (45 mg, 0.126 mmol) was taken up in 10 mL of MeOH and 10 mg of 10% Palladium on activated carbon was added. The reaction vessel was vacuumed and backfilled with hydrogen. This procedure was repeated three times and a balloon filled with H_2 was connected to the reaction vessel. The solution was stirred overnight. The reaction solution was filtered through a thin pad of celite and washed with 20 mL of EtOAc and concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:10) affording (+)-*cis*-pyrrolidine 225H (31.8 mg, 0.124 mmol, 99%) as a slightly yellow oil. $[\alpha]_D^{25}$ +21.9 (*c* 1.0, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98-2.88 (m, 2H), 1.87-1.79 (m, 2H) 1.54-1.21 (m, 22H), 0.92-0.84 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 59.6, 36.98, 36.94, 32.27, 32.04, 31.54, 29.72, 27.69, 27.42, 22.83, 22.82, 14.29, 14.25. Anal. Calcd for $C_{15}H_{31}N$: C, 79.92; H, 13.86; N, 6.21. Found: C, 79.68; H, 13.97; N, 6.18.



25 **36**

(2R,5S)-1-Benzyl 2-methyl 5-((Z)-pent-2-enyl)pyrrolidine-1,2-dicarboxylate (36) Potassium hydride (40% in mineral oil) was washed by anhydrous hexanes and dried by a stream of argon. Potassium hydride (60.1 mg, 1.50 mmol) and $Ph_3P(CH_2)_2CH_3Br$ (770 mg, 2.0 mmol) were suspended in 10 mL of anhydrous THF. The reaction was stirred under the atmosphere of

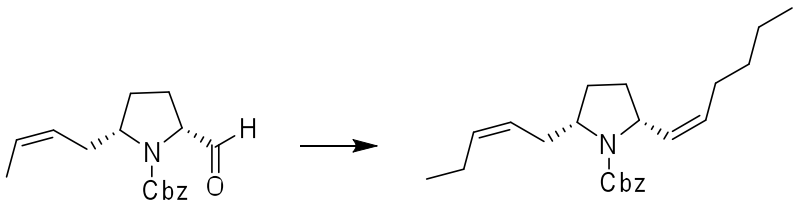
N_2 at room temperature for 30 minutes and then cooled to 0 °C in an ice water cold bath. At 0 °C, the solution of aldehyde (152.7 mg, 0.50 mmol) in 1 mL of THF was added dropwise. Upon the completion of addition, the cold bath was removed and the reaction mixture was stirred at room temperature for one hour. The reaction was quenched by the addition of 1 mL of saturated ammonium chloride aqueous solution. The reaction was then partitioned between EtOAc (20 mL) and water (20 mL). The top organic layer was separated. The aqueous layer was extracted with EtOAc(2 x 20 mL). Combined organics were washed by brine, dried on anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 1:4 EtOAc/hexanes affording the Z-alkene (146 mg, 0.44 mmol, 87%) as the predominant major isomer. R_f = 0.4 (EtOAc:Hexanes = 1:4). $[\alpha]_D^{25}$ +13.0 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 5.55-5.44 (m, 2H), 5.33-5.27 (m, 2H), 4.41-4.30 (m, 1H), 4.00-3.83 (m, 1H), 3.77 (s, 1.4H), 3.61 (s, 1.6H), 2.84-2.62 (m, 1H), 2.31-2.13 (m, 2H), 2.13-1.87 (m, 4H), 1.78-1.70 (m, 1H), 2.32-2.14 (m, 2H), 1.23 (t, *J* = 0.62, 1.6H), 1.19 (t, *J* = 0.62, 1.4H). ^{13}C NMR ($CDCl_3$) δ 173.5, 173.3, 154.9, 154.1, 136.6, 136.5, 132.4, 132.2, 128.4, 128.3, 128.0, 127.8, 127.6, 125.6, 125.3, 67.2, 66.8, 60.2, 59.8, 59.2, 58.6, 52.1, 52.0, 32.0, 31.2, 29.4, 28.7, 28.0, 20.7, 20.6, 13.9, 13.7. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.04; H, 7.44; N, 4.21.



36 **37**

(2R,5S)-Benzyl 2-formyl-5-((Z)-pent-2-enyl)pyrrolidine-1-carboxylate (37) Ester **36** (76 mg, 0.23 mmol) was taken up in 15 mL of anhydrous CH_2Cl_2 and cooled to -78°C in a dry ice/acetone bath. At -78 °C, diisobutylaluminium hydride (DIBAL-H, 1 M in toluene, 0.276 mL)

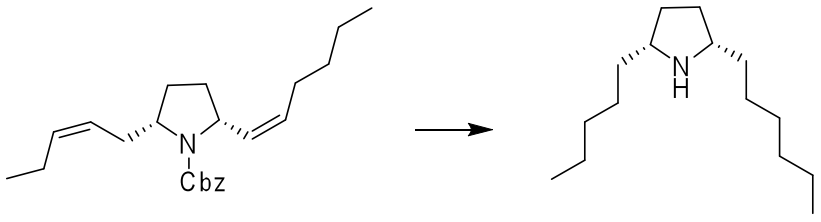
was added dropwise in 30 minutes. After the completion of addition, the reaction mixture was stirred at -78 °C for two hours till the starting material disappeared monitored by TLC. The reaction was quenched by the addition of 0.5 mL of MeOH and warmed up to room temperature. The mixture was poured into ice-cold hydrochloric acid solution in water (1 N). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic portions were washed by brine, dried on anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 1:4 EtOAc/Hexanes affording the aldehyde (62.3 mg, 0.207 mmol, 90%). $[\alpha]_D^{25}$ +9.8 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 5.55-5.44 (m, 2H), 5.33-5.27 (m, 2H), 4.41-4.30 (m, 1H), 4.00-3.83 (m, 1H), 2.84-2.62 (m, 1H), 2.31-2.13 (m, 2H), 2.13-1.87 (m, 4H), 1.78-1.70 (m, 1H), 2.32-2.14 (m, 2H), 1.23 (t, *J* = 0.62, 1.6H), 1.19 (t, *J* = 0.62, 1.4H). ^{13}C NMR ($CDCl_3$) δ 200.6, 156.0, 154.8, 136.4, 133.1, 128.9, , 128.0, 127.2, 67.9, 67.7, 66.3, 66.1, 32.5, 31.9, 29.8, 28.3, 26.0, 24.8, 22.9. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.36; H, 7.83; N, 4.69.



37 **38**

Potassium hydride (40% in mineral oil) was washed by anhydrous hexanes and dried by a stream of argon. Potassium hydride (28.8 mg, 0.72 mmol) and $Ph_3P(CH_2)_4CH_3Br$ (409 mg, 0.96 mmol) were suspended in 10 mL of anhydrous THF. The reaction was stirred under the atmosphere of N_2 at room temperature for 30 minutes and then cooled to 0°C in an ice water cold bath. At 0°C, the solution of aldehyde (72.2 mg, 0.24 mmol) in 1 mL of THF was added dropwise. Upon the

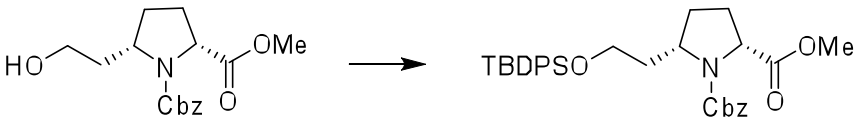
completion of addition, the cold bath was removed and the reaction mixture was stirred at room temperature for one hour. The reaction was quenched by the addition of 1 mL of saturated ammonium chloride aqueous solution. The reaction was then partitioned between EtOAc (20 mL) and water (20 mL). The top organic layer was separated. The aqueous layer was extracted with EtOAc(2 x 20 mL). Combined organics were washed by brine, dried on anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 1:4 EtOAc/hexanes affording the Z-alkene (74.7 mg, 0.21 mmol, 86%) as the predominant major isomer. R_f = 0.4 (EtOAc:Hexanes = 1:4). $[\alpha]_D^{25}$ +42.6 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 5.65-5.40 (m, 4H), 5.17 (s, 1H), 5.12 (s, 1H), 4.61-4.57 (m, 1H), 3.79-3.85 (m, 1H), 2.62-2.51 (m, 2H), 2.20-1.80 (m, 4H), 1.77-1.62 (m, 4H), 1.51-1.11 (m, 4H), 1.11-0.83 (m, 6H) ^{13}C NMR ($CDCl_3$) δ 155.5, 137.1, 133.2, 130.5, 130.1, 128.4, 128.1, 128.0, 125.9, 67.7, 59.0, 56.2, 32.9, 31.7, 30.0, 22.8, 14.3. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.66; H, 9.49; N, 4.08.



38 (-)-*cis*-225H **39**

(-)-*cis*-Pyrrolidine 225H (39) Diene **38** (56.8 mg, 0.08 mmol) was taken up in 10 mL of MeOH and 10 mg of 10% Palladium on activated carbon was added. The reaction vessel was vacuumed and backfilled with hydrogen. This procedure was repeated three times and a balloon filled with H_2 was connected to the reaction vessel. The solution was stirred overnight. The reaction solution was filtered through a thin pad of celite and washed with 20 mL of EtOAc and

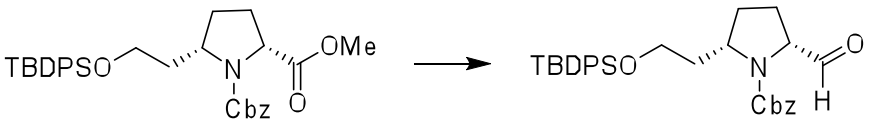
concentrated in vacuo. The residue was purified by a flash chromatography (SiO_2, $MeOH/CH_2Cl_2$ = 1:10) affording (17 mg, 0.076 mmol, 95%) as a slightly yellow oil. $[\alpha]_D^{25}$ -19.6 (*c* 0.5, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 2.96-2.88 (m, 2H), 1.80-1.70 (m, 2H) 1.59-1.21 (m, 22H), 0.95-0.85 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 58.9, 36.98, 36.94, 32.27, 32.04, 31.54, 29.72, 27.69, 27.42, 22.83, 22.82, 14.29, 14.25. Anal. Calcd for $C_{15}H_{31}N$: C, 79.92; H, 13.86; N, 6.21. Found: C, 79.84; H, 14.20; N, 6.05.



3 **40**

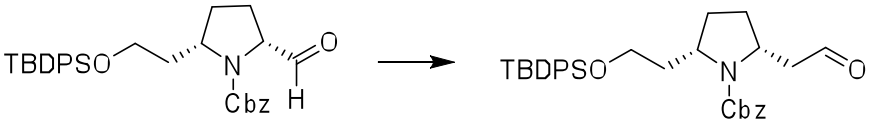
(2R,5S)-1-Benzyl 2-methyl 5-(2-(tert-butyldiphenylsilyloxy)ethyl)pyrrolidine-1,2-dicarboxylate (40) Under the atmosphere of nitrogen, alcohol **3** (374 mg, 1.22 mmol) and imidazole (166 mg, 2.44 mmol) were taken up in dry DMF (15 mL). At 0 °C, TBDPS-Cl (402 mg, 1.46 mmol) was added dropwise. The reaction was warmed to room temperature and stirred overnight. At 0 °C, the reaction was quenched by water (15 mL) and extracted with Et_2O (2 × 30 mL). The combined organic portions were dried on $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a flash column chromatography (SiO_2, eluting with EtOAc/Hexane = 15:85) affording silyl ether **40** (617 mg, 93% yield) as a colorless oil. $[\alpha]_D^{25}$ +22.1 (*c* 0.73, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 6.4, 4H), 7.26-7.44 (m, 11H), 5.01-5.20 (m, 2H), 4.31-4.41 (m, 1H), 4.09-4.16 (m, 1H), 3.65-3.79 (m, 4H), 3.58 (s, 1H), 2.15-2.40 (m, 2H), 1.61-2.02 (m, 4H), 1.03 (d, *J* = 11.0, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 155.1, 136.9, 135.8, 134.0, 129.8, 128.7, 128.6, 128.1, 127.9, 67.3, 67.0, 62.1, 61.7, 60.2, 59.9, 57.7, 56.5, 52.4,

52.2, 37.2, 36.5, 30.2, 29.9, 29.4, 28.4, 27.0, 19.4. Anal. Calcd for $C_{32}H_{39}NO_5Si$: C, 70.43; H, 7.20; N, 2.57. Found: C, 70.64; H, 7.23; N, 2.56.



40 **41**

(2S,5R)-benzyl 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5-formylpyrrolidine-1-carboxylate (41). Under nitrogen, ester **40** (547 mg, 1 mmol) was dissolved in toluene (6 mL). At -78 °C, DIBAL-H (1.0 M in toluene, 1.5 mL) was added dropwise over a period of 45 minutes. The reaction was stirred at -78 °C for 30 minutes and warmed to -40 °C. The reaction mixture was diluted with Et_2O (10 mL) and reaction was quenched by the addion of 1 N NH_4Cl (1 mL). Anhydrous $MgSO_4$ was added till the solution became clear. The solution was filtered through a thin pad of celite and concentrated in vacuo. The residue was purified by a flash column chromatography (SiO_2, eluting with EtOAc/hexanes = 1:4) affording aldehyde **41** (431 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ +17.3 (*c* 0.95, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 0.5H), 9.35 (s, 0.5H), 7.67 (s, 4H), 7.26-7.46 (m, 11H), 4.13-4.27 (m, 2H), 4.13-4.27 (m, 2H), 3.59-3.80 (m, 2H), 1.43-2.45 (m, 6H), 1.06 (d, *J* = 6.7, 9H). ^{13}C NMR ($CDCl_3$) δ 200.5, 155.9, 154.7, 136.5, 135.8, 133.9, 129.9, 128.8, 128.3, 128.1, 127.9, 67.6, 67.4, 66.3, 65.9, 61.8, 61.6, 57.7, 56.5, 37.8, 37.3, 30.1, 29.8, 27.1, 26.0, 24.9, 19.4. Anal. Calcd for $C_{31}H_{37}NO_4Si$: C, 72.20; H, 7.23; N, 2.72. Found: C, 71.88; H, 7.37; N, 2.61.

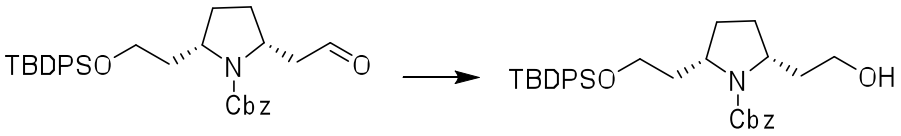


41 **42**

(2S,5R)-benzyl 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5-(2-oxoethyl)pyrrolidine-1-carboxylate (42) Under N_2, $(Ph_3PCH_2OCH_3)Cl$ (2.50 g, 7.28 mmol) was suspended in dry THF (50 mL) in a round-bottomed flask. At 0 °C, *t*-BuOK (1.0 M in THF, 6.84 mmol) was added dropwise. The solution was stirred at room temperature for 15 minutes and was added dropwise to the solution of aldehyde **41** (1.412 g, 2.74 mmol) in dry THF (10 mL) till an orange color persisted. Then reaction mixture was stirred at room temperature for additional 15 minutes before it was diluted by EtOAc (30 mL) and quenched by the addition of 1 N NH_4Cl (20 mL). The organic fraction was separated and the aqueous was extracted with EtOAc (2 x 20 mL). Combined organic fractions were washed by saturated NaCl, dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording the methyl enol ether which was used in next step without further purification.

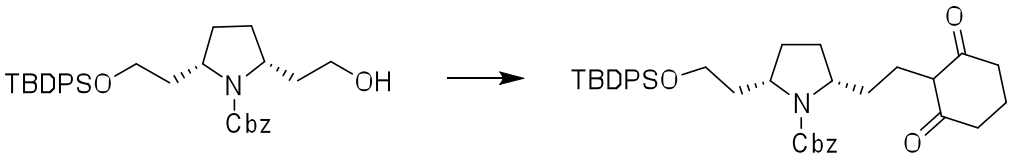
To the solution of methyl enol ether prepared above in acetone (50 mL), PTSA·H_2O (260 mg, 1.37 mmol) was added one portion at 0 °C. The reaction was stirred at room temperature for 30 minutes and solvent was removed in vacuo. The residue was taken up in water (20 mL) + CH_2Cl_2 (20 mL). The organic fraction was separated and the aqueous was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic portions were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by a flash column chromatography (SiO_2, eluting with EtOAc/hexanes = 1:4) affording aldehyde **42** (1.145 g, 79%, 2 steps) as a colorless oil. $[\alpha]_D^{25}$ +2.44 (*c* 1.31, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 52.8, 1H), 9.71 (d, *J* = 52.8, 1H), 7.63 (s, 4H), 7.25-7.44 (m, 11H), 5.10 (d, *J* = 6.2, 2H), 4.22-4.36 (m, 1H), 4.04 (s, 1H),

3.69 (s, 2H), 2.78-3.11 (m, 1H), 2.36-2.45 (m, 1H), 1.39-2.27 (m, 6H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 136.8, 135.8, 133.9, 129.9, 128.7, 128.1, 127.9, 127.2, 67.1, 67.0, 61.8, 56.4, 55.8, 54.2, 52.9, 50.3, 48.1, 38.4, 36.5, 30.4, 29.7, 28.5, 27.7, 27.1, 19.4. Anal. Calcd for $C_{32}H_{39}NO_4Si$: C, 72.55; H, 7.42; N, 2.64. Found: C, 72.55; H, 7.39; N, 2.57.



42 **43**

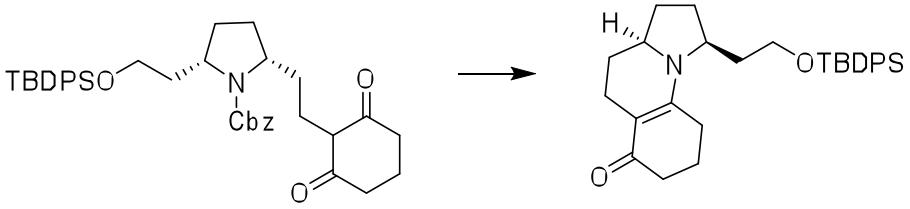
(2S,5R)-benzyl 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5-(2-hydroxyethyl)pyrrolidine-1-carboxylate (43) Aldehyde **42** (530 mg, 1 mmol) was dissolved in 15 mL MeOH. At 0 °C, $NaBH_4$ (80 mg, 2 mmol) was added by three portions and stirred for 30 minutes. The reaction was warmed to room temperature and stirred for 15 minutes. The solvent was removed under reduced pressure. The residue was portioned between sat. NaCl (20 mL) and DCM (30 mL). The organic fraction was separated and the aqueous was extracted with DCM (30 mL). Combined organic portions were dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a flash chromatography.



43 **44**

(2S,5S)-benzyl 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5-(2-(2,6-dioxocyclohexyl)ethyl)pyrrolidine-1-carboxylate (44) Aldehyde **43** (462 mg, 0.872 mmol, 1.0

equiv) was dissolved in CH_2Cl_2 (1.75 mL). Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (221 mg, 0.872 mmol, 1.0 equiv) and cyclohexane-1,3-dione (98 mg, 0.872 mmol, 1.0 equiv) were added subsequently. Then L-proline (20 mg, 0.175 mmol, 0.2 equiv) was added to the mixture. The stirring was continued for 1 hour. The resulting mixture was directly subjected to purify by a flush column chromatography (SiO_2, 50:50 hexanes/EtOAc) to afford 509 mg (93% yield) of **44** as a colorless oil. $[\alpha]_D^{25}$ +42.1 (*c* 0.4, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.64 (m, 4H), 7.26-7.45 (m, 11H), 5.15 (d, *J* = 2.0, 2H), 4.00-4.09 (m, 1H), 3.60-3.81 (m, 3H), 2.15-2.54 (m, 6H), 1.35-1.97 (m, 11H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 135.7, 133.8, 129.9, 128.7, 128.3, 128.2, 127.9, 114.7, 67.8, 61.7, 58.7, 56.9, 39.2, 37.2, 37.0, 31.7, 30.0, 29.7, 27.0, 21.1, 19.4, 19.2, 14.4. Anal. Calcd for $C_{38}H_{47}NO_5Si \cdot H_2O$: C, 70.88; H, 7.67; N, 2.18. Found: C, 70.98; H, 7.46; N, 2.18.



44 **45**

(1S,3aS)-1-(2-(tert-butyldiphenylsilyloxy)ethyl)-1,2,3,3a,4,5,8,9-octahydropyrrolo[1,2-a]quinolin-6(7H)-one (45) Compound **44** (473 mg, 0.756 mmol, 1.0 equiv) was dissolved in methanol (100 mL). 10% Pd/C (245 mg) was added to the solution. The mixture was subjected to hydrogenation with hydrogen balloon at room temperature for 24 hours. The resulting mixture was filtered through celite 545 (5 g) and rinsed with methanol (2 × 50 mL). All the combined filtrates were concentrated under vacuum. The residue was purified by **preparative TLC** (SiO_2, 95:5 EtOAc/CH_3OH) to afford 270 mg (75% yield) of **45** as a yellow oil. $[\alpha]_D^{25}$ +317 (*c* 0.31,

CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 8.0, 1.6, 4H), 7.37-7.47 (m, 6H), 4.03 (t, J = 8.6, 1H), 3.58-3.78 (m, 2H), 3.20-3.28 (m, 1H), 2.60-2.75 (m, 2H), 2.26-2.43 (m, 3H), 1.38-2.20 (m, 10H), 1.13-1.28 (m, 1H), 1.06 (d, *J* = 7.7, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 158.9, 135.8, 135.7, 133.6, 130.1, 128.0, 107.3, 61.4, 61.0, 59.4, 57.3, 56.4, 55.7, 38.9, 38.5, 36.6, 36.3, 30.7, 29.8, 29.1, 28.6, 27.8, 27.6, 27.4, 27.1, 22.1, 21.6, 20.3, 19.4. Anal. Calcd for $C_{30}H_{39}NO_2Si \cdot 0.5H_2O$: C, 74.64; H, 8.35; N, 2.90. Found: C, 74.51; H, 8.28; N, 2.95.

45 **Kishi's Intermediate 9**

(1S,3aS)-1-(2-hydroxyethyl)-1,2,3,3a,4,5,8,9-octahydropyrrolo[1,2-a]quinolin-6(7H)-one (9) Silyl ether **45** (174 mg, 0.367 mmol) was dissolved in THF (5 mL). At 0 °C, Tetrabutylammoniumfluoride (1.0 M in THF, 0.55 mL) was added dropwise to the solution. The reaction was stirred at room temperature for 3 hours and quenched by the addition of satuarted Na_2CO_3 solution (0.5 mL). The reaction mixture was partitioned in EtOAc (20 mL) + brine (20 mL). The organic fraction was separated and the aqueous was extracted with EtOAc (2 x 20 mL). Combined organic fractions were dried on anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, eluting with CH_3OH/CH_2Cl_2 = 8:92) affording Kishi's Intermediate **9** (75 mg, 87% yield) as a white solid, mp 178-180 °C (recrystallization from EtOAc/cyclohexane, 1:1) {lit.[10]: mp 176-179 °C }. $[\alpha]_D^{25}$ +798 (*c* 0.29, EtOH) {lit.[10]: $[\alpha]_D^{25}$ +538 (*c* 1.40, EtOH)}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (t, *J* = 8.0, 1H), 3.61-3.78 (m, 2H), 3.23-3.31 (m, 1H), 2.61- 2.68 (m, 2H), 2.40-2.48 (m, 1H), 2.32 (t, *J* = 6.5,

2H), 1.49-2.20 (m, 11H), 1.18-1.29 (m, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 193.7, 158.9, 107.1, 60.0, 59.3, 55.6, 38.5, 36.3, 29.6, 29.0, 28.4, 27.3, 21.9, 21.4.

2.6 REFERENCES AND NOTES

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APPENDIX

Crystal Structure of
(1*S*,3a*S*)-1-(2-hydroxyethyl)-1,2,3,3a,4,5,8,9-octahydropyrrolo[1,2-a]quinolin-6(7*H*)-one (**6**)-Kishi's intermediate

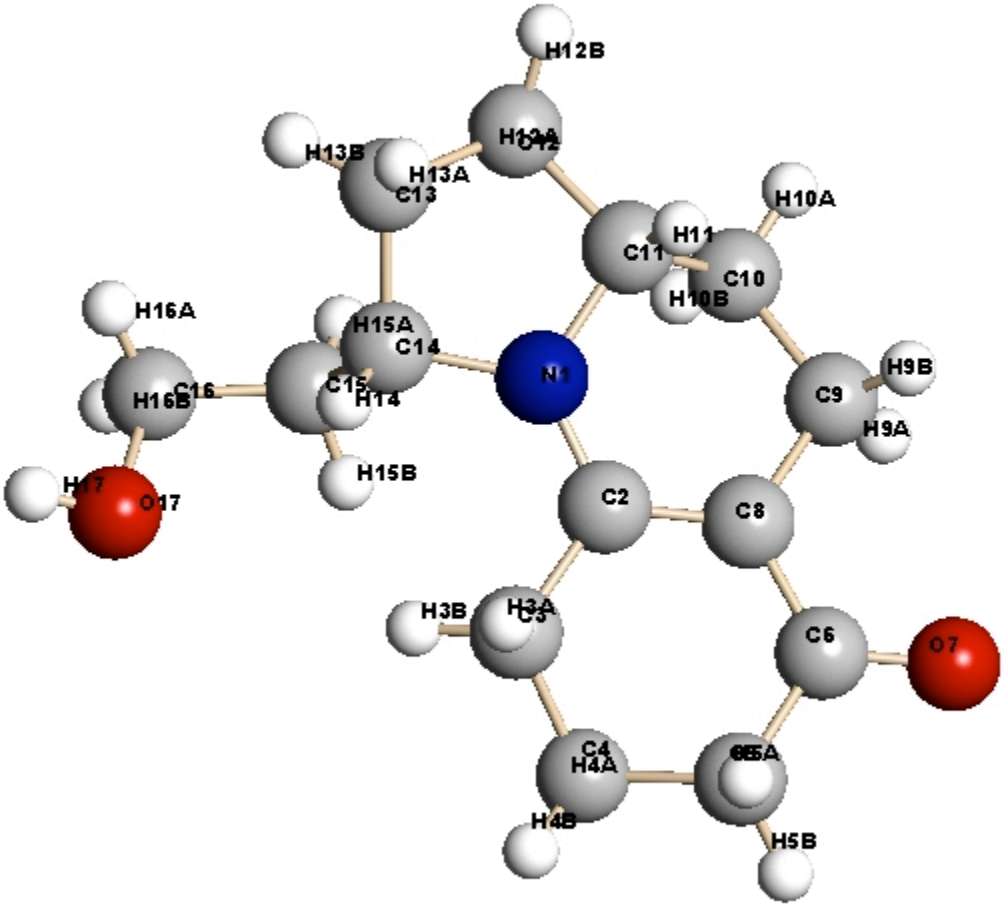

Table 1. Crystal data and structure refinement for Kishi's intermediate (**6**)

Empirical formula	$C_{14}H_{21}NO_2$	
Formula weight	235.32	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.83600(10) Å	aα= 90°.
	b = 10.49690(10) Å	bβ= 90°.
	c = 13.3180(2) Å	gγ= 90°.
Volume	1235.25(3) $Å^3$	
Z	4	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	512	
Crystal size	0.80 x 0.40 x 0.20 mm^3	
Theta range for data collection	2.47 to 32.49°.	
Index ranges	-13<=h<=13, -15<=k<=15, -20<=l<=20	
Reflections collected	52997	
Independent reflections	4454 [R(int) = 0.0208]	
Completeness to theta = 32.49°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9834 and 0.9360	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4454 / 0 / 238	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0285, wR2 = 0.0805	
R indices (all data)	R1 = 0.0291, wR2 = 0.0814	
Absolute structure parameter	-0.4(6)	
Largest diff. peak and hole	0.371 and -0.182 e. $Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for Kishi's intermediate (**6**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	4153(1)	1342(1)	10115(1)	17(1)
C(2)	3935(1)	2114(1)	9329(1)	15(1)
C(3)	4005(1)	1532(1)	8296(1)	18(1)
C(4)	3347(1)	2399(1)	7496(1)	22(1)
C(5)	3991(1)	3732(1)	7589(1)	23(1)
C(6)	3814(1)	4264(1)	8634(1)	19(1)
O(7)	3770(1)	5442(1)	8756(1)	30(1)
C(8)	3741(1)	3415(1)	9468(1)	17(1)
C(9)	3499(1)	3977(1)	10499(1)	21(1)
C(10)	3235(1)	2945(1)	11285(1)	23(1)
C(11)	4368(1)	1876(1)	11127(1)	20(1)
C(12)	4237(1)	717(1)	11810(1)	28(1)
C(13)	4756(1)	-383(1)	11141(1)	25(1)
C(14)	4075(1)	-59(1)	10114(1)	18(1)
C(15)	2438(1)	-520(1)	10005(1)	20(1)
C(16)	2333(1)	-1923(1)	9743(1)	25(1)
O(17)	2895(1)	-2090(1)	8753(1)	30(1)

Table 3. Bond lengths [Å] and angles [°] for Kishi's intermediate (**6**).

N(1)-C(2)	1.3386(8)
N(1)-C(11)	1.4716(8)
N(1)-C(14)	1.4719(8)
C(2)-C(8)	1.3881(8)
C(2)-C(3)	1.5069(8)
C(3)-C(4)	1.5174(10)
C(4)-C(5)	1.5161(11)
C(5)-C(6)	1.5079(10)
C(6)-O(7)	1.2480(8)
C(6)-C(8)	1.4257(9)
C(8)-C(9)	1.5093(9)
C(9)-C(10)	1.5238(11)
C(10)-C(11)	1.5185(10)
C(11)-C(12)	1.5236(11)
C(12)-C(13)	1.5287(12)
C(13)-C(14)	1.5328(10)
C(14)-C(15)	1.5323(9)
C(15)-C(16)	1.5154(10)
C(16)-O(17)	1.4202(10)
C(2)-N(1)-C(11)	120.27(5)
C(2)-N(1)-C(14)	126.66(6)
C(11)-N(1)-C(14)	112.84(5)
N(1)-C(2)-C(8)	120.59(6)
N(1)-C(2)-C(3)	117.54(5)
C(8)-C(2)-C(3)	121.75(5)
C(2)-C(3)-C(4)	112.46(5)
C(5)-C(4)-C(3)	110.61(6)
C(6)-C(5)-C(4)	112.26(6)
O(7)-C(6)-C(8)	121.18(7)
O(7)-C(6)-C(5)	119.32(7)
C(8)-C(6)-C(5)	119.48(6)
C(2)-C(8)-C(6)	120.35(6)
C(2)-C(8)-C(9)	121.56(6)

Table 3 (Continued). Bond lengths [Å] and angles [^{o}] for Kishi's intermediate (**6**).

C(6)-C(8)-C(9)	118.06(6)
C(8)-C(9)-C(10)	111.63(6)
C(11)-C(10)-C(9)	109.21(6)
N(1)-C(11)-C(10)	108.87(6)
N(1)-C(11)-C(12)	103.45(6)
C(10)-C(11)-C(12)	117.22(6)
C(11)-C(12)-C(13)	103.40(6)
C(12)-C(13)-C(14)	103.61(6)
N(1)-C(14)-C(15)	111.12(5)
N(1)-C(14)-C(13)	101.62(6)
C(15)-C(14)-C(13)	112.63(6)
C(16)-C(15)-C(14)	112.74(6)
O(17)-C(16)-C(15)	108.17(6)

Symmetry transformations used to generate equivalent atoms:

VITA

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