Synthesis of a Novel Multicyclic Organic Scaffold via a Photoinitiated Intramolecular Ylide-Alkene Cycloaddition Reaction

A Major Qualifying Project Report
submitted to the Faculty
of the
WORCESTER POLYTECHNIC INSTITUTE
In partial fulfillment of the requirements for the Degree of Bachelor of Science

by

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Submitted: April 30, 2009

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Abstract

Access to a diverse array of druglike organic molecules via efficient total synthesis is of critical importance for the exploration of new compounds of biological and medicinal interest. In particular, any viable synthetic route to such molecules must incorporate precise control of stereochemistry as well as the ability to tune medicinally relevant parameters such as acidity, lipophilicity, and the incorporation of bioisosteres. Synthesis of a bioisosteric analog of the opiate analgesic morphine was pursued using an intramolecular ylide-alkene cycloaddition as the key step which would establish the configuration of the six stereocenters of the molecule in a single operation. The novel structure of the target analog is expected to produce a compound with compelling biological activity from a brief, diversifiable synthesis.
Acknowledgments

I would like to thank Worcester Polytechnic Institute, the Department of Chemistry and Biochemistry, Professor James P. Dittami, Ilie Fishtik, and Victor Kiryak.
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Introduction

During the drug discovery and development process, useful products sometimes arise from the interchange of groups that are closely related both chemically and structurally. These groups, which tend to produce similar therapeutic effects in biological systems, are referred to as bioisosteres.1 Catechol 1, for example, is seen in different forms in several different biologically active compounds, including the opiate analgesic drug morphine 2 and the neurotransmitter dopamine 3.

One bioisostere of catechol is the molecule benzothiazole, 4. Benzothiazole derivatives have in the past been studied for their potentially useful biological activity as antimicrobials.2 Others have shown moderate anti-inflammatory activity,3,4 while others still have been researched as potential antitumor agents.5,6

The replacement of pharmacophores, the parts of molecules responsible for their biological or pharmacological interactions, in existing biologically active compounds is therefore often done
in the hopes of generating new and potentially useful molecules that may lead to new pharmaceuticals.

The objective of this project is to generate a multicyclic organic scaffold that somewhat resembles morphine and incorporates the benzothiazole bioisostere in place of catechol. This novel scaffold 5 is to be generated via a method developed in our laboratory. The cycloaddition product will then be submitted for biological testing. We are particular interested in using the bioassay known as “Biospectra Analysis” developed by R.A. Volkmann.⁷

![Chemical Structure](image)

Our synthetic plan for the construction of 5 is an extension of work pioneered by A.G. Schultz et al. in his Heteroatom Directed Photoarylation Reaction.⁸ Their investigations showed that various 2-aryloxyenones generated by the reaction of aromatic alcohols with isophorone epoxide under basic conditions could be photocyclized to their respective dihydrofurans, as exemplified by the photocyclization of 7 to 9 shown below.⁹ This photocyclization reportedly proceeds via the carbonyl ylide intermediate 8, which then rearranges to the dihydrofuran product. Similar results were reported for aryl vinyl sulfides.¹⁰
Our interest in this work stemmed from a well-known [3+2] cycloaddition of ylide systems such as 8 with alkenes.\textsuperscript{11,12} Thus, we proposed incorporation of pendant dipolarophiles in aryl vinyl X systems such as I where X = S, O, or N-R. We anticipated that upon photolysis these would cyclize to ylide systems II which could then undergo [3+2] cycloaddition to form the multicyclic scaffold III. Indeed preliminary studies demonstrated that this was a feasible approach to construct complex frameworks in a single experimental operation.

During the course of our research we observed that the kinds and ratios of photoproducts obtained was dependent on reaction temperature, solvent, and substituents. Following is a brief summary of some of our findings.

Photolysis of naphthyl vinyl sulfide 10 incorporating a 3-butenyl side chain was observed to produce different major products as a consequence of different reaction temperatures.\textsuperscript{13}
Photolysis at room temperature or below in toluene resulted in the formation of ring-closed product 11 in which no interaction of the side chain olefin with the ylide was observed. Conversely, when the photoreaction was conducted at reflux temperature in toluene intramolecular addition product 12 was observed. Control experiments demonstrated that both light and heat were required to produce 12. Furthermore, these experiments demonstrated that 11 is not an intermediate in the formation of 12.

The mechanism for formation of 12 likely involves ylide intermediate 13a or b. Orbital symmetry rules favor formation of 13a. However, spectroscopic studies in our laboratory support the formation of at least two different ylides in similar photoreactions.\textsuperscript{14}

Surprisingly, neither set of reaction conditions (low or high temperature) resulted in the anticipated [3+2] product. We reasoned that this could be the result of the low reactivity of the thiocarbonyl ylide toward simple unsubstituted alkenes.\textsuperscript{11,12,15} Accordingly, we examined aryl vinyl photoprecursors which incorporated a more reactive electron-deficient alkene, as in 13c. Indeed, these yielded intramolecular addition products at lower temperature. However, in all cases where we used an aryl vinyl sulfide to generate a thiocarbonyl ylide, no [3+2] products (such as 13d) were observed.\textsuperscript{17}
We thus turned our attention to carbonyl ylide systems derived from aryl vinyl ethers, such as 14 and 17. These were expected to be more reactive than the corresponding sulfur ylides.

As expected, photolysis of the corresponding aryl vinyl ether 14 produced the intramolecular addition product 15 as the major product at room temperature. This result contrasts that of aryl vinyl sulfide 10 which yielded the intramolecular addition product 12 only at 110°C.

Interestingly, when 14 was subjected to high temperature photolysis products 16 and 15 were observed in a 4:1 ratio. Formation of 16 can be rationalized by photochemical ring closure to provide ylide 14b followed by intramolecular [3+2] cycloaddition.
Subsequent studies with 17, which incorporates an ethyl butenoate side chain, provided [3+2] adduct 18 in 87% isolated yield upon photolysis at room temperature.\textsuperscript{16} This conversion provides an effective method to assemble three rings and six chiral centers in a single experimental operation.

With a method in hand to assemble scaffolds with topology similar to the morphine series, we turned our attention to targets incorporating bioisosteric replacements for the aromatic ring in morphine. Two such targets Va and Vb could be derived by photocyclization and subsequent intramolecular addition of aryl vinyl ethers IVa and IVb. These in turn should be available via methods developed in our lab for preparation of 14 and 17.\textsuperscript{16,17}
IVa, $R = H$

b, $R = \text{CO}_2\text{Et}$

Va, $R = H$

Vb, $R = \text{CO}_2\text{Et}$
Results and Discussion

As described in the Introduction, we hoped to synthesize the photoprecursors 29a and b, which have the catechol bioisostere benzothiazole included in it. Subjection to photolysis should then yield the [3+2] cycloaddition products 5a and b via a photoinitiated intramolecular ylide-alkene cycloaddition reaction.

Our approach to synthesis of 29 utilized the same strategy for preparation of 14 and 17.\textsuperscript{16,17} Thus commercially available 19 was converted to 3-ethoxy-2-cyclohexenone 20 in the presence of p-toluenesulfonic acid monohydrate (pTsOH•H\textsubscript{2}O) in ethanol/toluene with refluxing.\textsuperscript{18} Purification by fractional distillation afforded 20 as a clear oil. Reaction with the appropriate Grignard reagents followed by acid hydrolysis in aqueous HCl/ethanol yielded the corresponding enones 21a and b. Epoxidation under basic conditions provided 22a,b.

The requisite aminohydroxybenzothiazole 34 was prepared by treatment of commercially available 2-amino-6-methoxybenzothiazole 33 with BBr\textsubscript{3} in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (4 equiv.) at -10 to -12°C for 3 hours. This provided the HCl salt of 34. The free base was obtained in 59% yield by neutralization of an aqueous solution of the salt with saturated aqueous NaHCO\textsubscript{3}, providing 34 as a grey solid with 97% purity by \textsuperscript{1}H NMR.
Base-catalyzed epoxide opening of 22a with 2-amino-6-hydroxybenzothiazole 34 while refluxing in tetrahydrofuran in the presence of N,N’-dimethylpropyleneurea gave rise to aryl vinyl ether 31a in only 5% yield. When performed with epoxide 22b, the same procedure did not yield any of the desired coupled product 31b.
After repeated failed attempts at performing the base-catalyzed epoxide opening, the procedure was modified slightly with the hope the more favorable results could be obtained. It was hypothesized that running a microwave-assisted coupling reaction would produce cleaner product in less time and in greater yield. To test this, a model system was chosen in the form of β-naphthol 35. The aryl vinyl ether 36 was synthesized by two methods. “Method A” refers to the traditional procedure while “Method B” refers to the microwave-assisted synthesis. See Table 1 below for results.
As indicated by Table 1, the microwave-assisted synthesis afforded the desired aryl vinyl ether in greater yield and in higher purity by NMR. Synthesis of 31b was then attempted by the same procedure. Unfortunately, NMR of the crude material showed that this method only afforded 31b in a negligible amount. Future work demands adjusting the conditions of the microwave-assisted coupling reaction so that 31b can be synthesized in greater yield.

Once the aryl vinyl ether synthesis is worked out, compound 31b could be tested directly in a photoreaction whereas 31a will require conversion to the aldehyde 32 and subsequent Wittig olefination to provide 29. An alternate route to 29 could potentially involve ozonolysis of 31b to provide 32, followed by Wittig olefination as before.
Experimental

General Methods

Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica plates (0.25 mm thickness with a 254 nm fluorescent indicator). Visualization was performed using a UV lamp (254 nm) and by staining with a $p$-anisaldehyde solution. Melting points were determined on a TA Instruments DSC 2920 Modulated DSC. Infrared spectra (IR) were recorded on a Bruker Vertex 70 Infrared Spectrometer with a 4 cm$^{-1}$ resolution, scanning from 4000 to 650 cm$^{-1}$ over 16 scans. $^1$H NMR spectra were recorded on a Bruker Avance III (500 MHz) NMR Spectrometer. Chemical shifts ($\delta$) are reported in ppm relative to tetramethylsilane (TMS) at 0.00. Carbon nuclear magnetic resonance spectra were recorded at 50.3 MHz. LC/MS data was obtained on an Agilent Technologies 6130 Quadrupole LC/MS using an SB-C18 Rapid Resolution 3.5 $\mu$m, 2.1x30 mm Zorbax HPLC cartridge column. Microwave-assisted reactions were performed on a Personal Chemistry Emrys Optimizer Workstation in Emrys Process Vials (2-5 mL). Flash chromatography was performed on an AnaLogix IntelliFlash 280 using 40-63 $\mu$m silica gel. Triethylamine-deactivated silica gel columns were prepared by washing the silica gel with a mixture of hexane and triethylamine (10:1). The column was then rinsed with three column volumes of hexane and one column volume of elution solvent to purge excess triethylamine.
3-Ethoxy-2-cyclohexenone (20)

[See notebook page BCC-I-001. $^1$H NMR spectrum: Sep24-2008-MQP (10)]. To a solution of 1,3-cyclohexanedione (10.0 g, 89 mmol) in absolute ethanol (47 mL) was added p-toluenesulfonic acid monohydrate (0.444 g, 2.33 mmol) in toluene (170 mL). A Dean-Stark trap fitted with a reflux condenser was attached to the reaction flask and the reaction mixture was heated at reflux with stirring. The ethanol/water/toluene azeotrope was removed periodically over a period of one hour. The reaction was allowed to cool and stirred overnight at room temperature. The following day, ethanol (60 mL) was added to the mixture and distillation was resumed. Distillation was ceased when thin-layer chromatography (TLC) analysis indicated consumption of the starting cyclohexanedione. The resulting dark brown reaction mixture was washed with 4 x 25 mL portions of 10% aqueous sodium hydroxide in brine, water (until neutral), and brine. The organic layer was dried (MgSO$_4$). Solvent was removed under reduced pressure to yield a dark amber oil. The same procedure was then repeated on a larger scale of 1,3-cyclohexanedione (57.543 g, 513 mmol). See notebook page BCC-I-002. The two crude products were combined for a total 60.150 g of the dark amber oil. Purification via short-path distillation yielded 20 as a clear oil (28.5 g, 33%): $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.08 (t, 3 H, $J$ = 7.0 Hz), 1.7 (q, 2 H, $J$ = 6.6 Hz), 2.04 (t, 2 H, $J$ = 6.9 Hz), 2.13 (t, 2 H, $J$ = 6.3 Hz), 3.63 (q, 2 H, $J$ = 7.07 Hz), 5.04 (s, 1 H).
3-(3-Butenyl)-2-cyclohexenone (21b)

[See notebook page BCC-I-014. "H NMR spectrum: BCC-I-014b (10)]. To a dry three-neck round bottom flask fitted with a Claisen adapter and a reflux condenser was added freshly cut magnesium turnings (2.52 g, 104 mmol). The apparatus was dried under vacuum and purged with nitrogen. THF (18 mL) was added to the flask, followed by the slow addition of 4-bromo-1-butene (9.24 g, 68.4 mmol). Upon the initiation of an exothermic reaction, anhydrous THF (18 mL) was added and the reaction mixture was allowed to reflux. After the exothermic reaction subsided, 3-ethoxy-2-cyclohexenone (9.00 g, 64.2 mmol) was added slowly, resulting in the evolution of heat. Anhydrous THF (10 mL) was added and the mixture was stirred for three hours, after which saturated aqueous ammonium chloride (180 mL) was added. The resulting yellow organic phase was extracted with dichloromethane. The combined organic phases were washed with water and brine. Solvent was removed under reduced pressure. The resulting yellow oil was combined with a solution of 1M HCl (18 mL) in ethanol (45 mL) and stirred for 1 hour. Solvent was removed under reduced pressure. The crude product was extracted with dichloromethane. The combined organic phases were washed with water and brine and then dried (MgSO4). Removal of solvent under reduced pressure yielded the crude product 21b as an orange oil (7.1 g, 73%); "H NMR (CDCl3, 500 MHz) δ 1.99 (q, 2 H, J = 6.5 Hz), 2.17-2.30 (m, 8 H), 4.91-5.00 (m, 2 H), 5.66-5.76 (m, 1 H), 5.88 (s, 1 H).
2-Amino-6-hydroxybenzothiazole (34)

![Chemical structure diagram]

[See notebook page BCC-I-010. \(^1\)H NMR spectrum: BCC-I-017a (12). \(^{13}\)C CPD spectrum: Oct22-2008-jpdMQP (30). \(^{13}\)C DEPT-135 spectrum: Oct22-2008-jpdMQP (22)]. In a dried 100-mL round bottom flask under nitrogen, 2-amino-6-methoxybenzothiazole (1.00 g, 5.55 mmol) was suspended in anhydrous DCM (5.6 mL) with continuous stirring. The mixture was cooled to approximately -12°C, at which time a 1 M solution of boron tribromide (28 mL, 28 mmol) was added slowly. After stirring for three hours at -12°C, thin-layer chromatography (hexanes/ethyl acetate (1:1)) showed consumption of starting material. The reaction was quenched with methanol (2.8 mL) and allowed to warm to room temperature. After 2.5 hours, the precipitate was collected by suction filtration, dissolved in water, and washed with ethyl acetate. Neutralization of the aqueous phase with saturated aqueous NaHCO\(_3\) yielded 34 as a grey solid (546 mg, 59%) that was collected by suction filtration and dried under vacuum. \(^1\)H NMR (DMSO-d6, 500 MHz) \(\delta\) 6.64 (d, 1 H, \(J = 8.4\) Hz), 7.02 (d, 1 H), 7.08 (s, 2 H), 7.13 (d, 1 H, \(J = 8.5\)), 9.08 (s, 1 H); \(^{13}\)C NMR (DMSO-d6, 50.3 MHz) \(\delta\) 107.4 (CH), 114.0 (CH), 118.5 (CH), 132.3 (C), 146.1 (C), 152.3 (C), 164.3 (C); LC/MS (ESI/APCI) \(m/e\) 167 [MH]\(^+\).
6-(But-3-enyl)-7-oxabicyclo[4.1.0]heptan-2-one (22b)

[See notebook page BCC-I-016. ¹H NMR spectrum: BCC-I-016a (10)]. Enone 21b (1.00 g, 6.657 mmol) was dissolved in methanol (6.30 mL), and hydrogen peroxide (35%, 1.57 mL) was added. The solution was cooled to 0°C, and a solution of NaOH (6N, 0.571 mL) was added slowly. The resulting mixture was stirred at room temperature for 1 h after which the solvent was removed. The mixture was then partitioned between DCM and water. The organic phase was washed with water and brine and dried (MgSO₄). Removal of solvent under reduced pressure yielded 22b as a clear oil (0.85 g, 76%): ¹H NMR (CDCl₃, 500 MHz) δ 1.63-2.23 (m, 10 H), 2.51 (d, 1 H, J = 17.9), 3.10 (s, 1 H), 4.98-5.08 (m, 2 H), 5.75-5.85 (m, 1 H).
3-(2-(1,3-Dioxan-2-yl)ethyl)-2-(2-aminobenzo[d]thiazol-6-yloxy)cyclohex-2-enone (31a)

[See notebook page BCC-0-018. ¹H and ¹³C NMR spectrum: BCC-I-018q (10-14)]. To a solution of epoxide 22a (2.26 g, 9.99 mmol) in anhydrous THF (20 mL) was added potassium hydride (35% in mineral oil (0.11 g, 0.84 mmol) and 2-amino-6-hydroxybenzothiazole (1.99 g, 12.0 mmol) in anhydrous THF (25 mL). N,N’-Dimethylpropyleneurea, DMPU (1.7 mL, 14.06 mmol), was added, and the mixture was stirred at reflux temperature for 48 h. The solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane and water. The aqueous phase was further extracted with dichloromethane, and the combined extracts were washed with water and brine and dried (MgSO₄). Removal of solvent at reduced pressure, recrystallization from hexanes/ethyl acetate, and chromatography on silica gel deactivated with triethylamine (100% ethyl acetate) gave 31a as a white solid (174 mg, 5% yield) which requires further purification: mp 170.2 °C; IR (ATR) 3370, 2942, 1732, 1670, 1626, 1543, 1455 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.23-1.34 (m, 2.3 H), 1.66 (s, 1.8 H), 1.74-1.80 (m, 2.1 H), 1.98-2.11 (m, 3.9 H), 2.40 (t, 2 H, J = 8.07 Hz), 2.52-2.58 (m, 4 H), 3.65-3.72 (m, 2 H), 4.02-4.07 (m, 2 H), 4.46 (t, 1 H, J = 5.07 Hz), 5.09 (s, 2 H), 6.84 (dd, 1 H, J = 3.05 Hz, 2.53 Hz), 7.05 (d, 1 H, J = 2.54), 7.40 (d, 1 H, J = 9.00 Hz); ¹³C NMR (CDCl₃, 125.8 MHz) δ 22.3 (CH₂), 25.7 (CH₂), 26.1 (CH₂), 29.6 (CH₂), 32.4 (CH₂), 38.5 (CH₂), 66.8 (CH₂) (double
intensity), 101.4 (CH), 106.9 (CH), 113.8 (CH), 119.7 (CH), 132.7 (C), 144.3 (C), 147.0 (C),
151.9 (C), 153.7 (C), 164.1 (C), 193.3 (C); LC/MS (ESI/APCI) m/e 375 [MH]$^+$. 
3-(But-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone (36a)

[See notebook page BCC-I-025. $^1$H NMR spectrum: DJS-I-022a (10)]. Potassium hydride (30 wt% dispersion in mineral oil, 0.04 g) was measured into a dried 25 mL round bottom flask. Under nitrogen, a solution of β-napthol (0.09 g, 0.602 mmol) in anhydrous THF (2 mL) was added. A solution of epoxide 22a (0.10 g, 0.602 mmol) in anhydrous THF (2 mL) was added, followed by DMPU (0.1 mL, 0.827 mmol). The reaction mixture was stirred at reflux temperature for 48 h. The solvent was removed under reduced pressure, and the resulting oil was partitioned between diethyl ether and 10% NaOH in saturated aqueous sodium hydroxide. The organic phase was washed with the 10% NaOH solution, water, and brine. The organic phase was dried (MgSO$_4$). Removal of the solvent at reduced pressure yielded 36a as a yellow oil (120 mg, 68% crude yield).
3-(But-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone (36b)

[See notebook page BCC-I-028. ¹H NMR spectrum: BCC-I-028a (10)]. Potassium hydride (30 wt% dispersion in mineral oil, 0.04 g) was measured into a microwave reaction vial. Under nitrogen, a solution of β-naphthol (0.09 g, 0.602 mmol) in anhydrous THF (2 mL) was added. A solution of epoxide 22a (0.10 g, 0.602 mmol) in anhydrous THF (2 mL) was added, followed by DMPU (0.1 mL, 0.827 mmol). The vial was placed in the microwave, which was run for 2 h at a constant temperature of 110°C with a maximum power setting of 200 W and a fixed hold time. The solvent was removed under reduced pressure, and the resulting oil was partitioned between diethyl ether and 10% NaOH in saturated aqueous sodium hydroxide. The organic phase was washed with the 10% NaOH solution, water, and brine. The organic phase was dried (MgSO₄). Removal of the solvent at reduced pressure yielded 36b as a yellow oil (167 mg, 95% crude yield).
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