Synthesis of Novel Materials Containing Catechol Bioisosteres

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by

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Abstract

The “photoinitiated intramolecular ylide-alkene cycloaddition reaction” which was developed in our laboratory provides a method for construction of up to three rings and six chiral centers in a single experimental operation from relatively simple starting materials. This project has attempted to utilize this reaction to quickly synthesize novel materials which incorporate catechol bioisosteres into the organic scaffold in the hopes of imparting potentially useful bioactivity to the new molecules.
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**Introduction**

Catechol 1 is a commonly seen motif in many active medicinal compounds such as Morphine 2, and Dopamine 3.

Bioisosteres of catechol, including benzoazole 4 and benzothiazole 5 also commonly occur as motifs in a wide range of antibacterial, antifungal, non-narcotic analgesic, anti-inflammatory, anticancer, anti-HIV-1, and antimicrobial agents\(^1\).\(^2\).
A common method used for development of new drugs from known active compounds is via the introduction of bioisosteres. Bioisosteres are groups or molecules that have chemical and physical similarities producing broadly similar biological properties. Thus if one knows the pharmacophores, or groups in a molecule which are responsible for biological activity, one could systematically replace these with bioisosteric groups to generate new compounds with potentially improved therapeutic profiles. Thus novel compounds 6, 7, and 8 are logical targets for the development of new medicines.

Our group has actively pursued development of procedures to build multicyclic scaffolds similar to those found in natural products\(^3,4\). The method is based on a photoarylation procedure pioneered by A.G. Schultz and exemplified via the conversion 13→15\(^5\).

![Chemical diagram showing the photoarylation reaction](image)

We sought to take advantage of the reactive ylide intermediate by appending a dipolarophile to the enone system as in 22. Synthesis of 22 is representative of the methods used in preparation of all photoprecursors used in this study.
Upon photolysis it was observed that 22 underwent ring closure and subsequent intramolecular ylide alkene addition. At room temperature the predominant product 25 was consistent with ring closure to provide an ylide which underwent hydrogen shift as in Schultz's model $13\rightarrow 14\rightarrow 15$. A second product 24 arising from ylide alkene addition was also observed. At higher temperature we observed exclusively ylide alkene addition products 26 and 24 in a 4:1 ratio$^{3,4}$. 
Formation of the [3+2] products can be enhanced by addition of electron withdrawing groups on the side chain of 22. Therefore, photolysis of 22b in toluene (0.001 M) provides 28 as the only product, even at room temperature. Compound 22b was prepared from the acetal derivative of 22 via (1) acetal hydrolysis followed by (2) Wittig addition to the resulting aldehyde\textsuperscript{3,4}.

![](image)

With this established precedent, we predicted photolysis of 9 would provide carbonyl ylide intermediate 10 which would be expected to undergo a [3+2] intramolecular ylide-alkene cycloaddition to give 6\textsuperscript{3,4}.

![](image)

Similarly, precursors 11 and 12 are expected to undergo the same transition to give products 7 and 8 respectively.
Former researchers in our lab have prepared substrates 29 and 32, which both contain heteroaromatic groups, in order to test the feasibility of performing a [3+2] ylide alkene cycloaddition on compounds similar to the target benzoxazole and benzothiazole derivatives. Photolysis of 29 in toluene at room temperature provided 30 in 60% yield and 31 in 30%. Similarly, photolysis of 32 in xylene at reflux gave 33 in 10% yield and 34 in 60%.
The successful formation of 30 and 33 shows the feasibility of using heteroaromatic systems to promote the photoinitiated intramolecular [3+2] cycloaddition reaction. With this demonstrated precedent, it is likely that photoprecursors 9, 11, and 12 will undergo similar transformations to give the desired [3+2] cycloaddition products 6, 7 and 8 respectively.
Results and Discussion

As noted in our introduction, this project addresses the synthesis and photochemical reactions of products 9, 11 and 12 as a means to prepare complex multi-cyclic scaffolds.

In order to achieve maximum versatility in substrates for our studies, we selected the following general method of synthesis.

Thus, synthesis of either epoxide 20 or 21 can give rise to a variety of substituted or non-substituted alkene systems such as:
Coupling of either epoxide with one of the three aromatic systems as shown gives rise to an array of aryl-vinyl ether photo precursors for use in our studies.

Synthesis of epoxide 20 was achieved as follows. Reaction of 16 with \( p \)-toluene sulfonic acid (\( p \)-TsOH) in ethanol-benzene provided 17\(^6\). Grignard addition of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide and subsequent acid workup yielded 18. Facile epoxidation of 18
under basic conditions gave 20 in a 54% yield. Compound 20 shows peaks in the $^1$H NMR at δ 1.17-1.39 (2 H), 1.72-2.41 (10 H), 3.68-3.80 (2 H), 4.02-4.15 (2 H), 4.45-4.53 (1 H), and 5.80-5.88 (1 H).

Similarly, epoxide 21 was prepared via Grignard addition of but-3-enylmagnesium bromide to 17 followed by acid catalyzed hydrolysis to give 19 and subsequent treatment with basic hydrogen peroxide provided 21 in 74% yield. 21 showed peaks in the $^1$H NMR at δ 1.87-2.45 (10 H), 4.87-5.10 (2 H), and 5.68-5.90 (2 H).
Epoxide 21 incorporates a simple alkene side chain. Epoxide 20 incorporates a protected aldehyde which can subsequently be converted to a substituted alkene, where R can be electron withdrawing or electron donating (e.g. CO$_2$Et or OMe respectively, illustrated below).

Much of the prior successful work on building scaffolds similar to 6, 7 and 8 in our lab was conducted using the ethyl buteionate side chain. Accordingly, we selected the series of compounds 9, 11 and 12 as initial synthesis targets.
It was noted that benzoxazoles hydrolyzed under acidic conditions. Given the instability of benzoxazole toward acid and the need for an acid workup of 39 to form aldehyde 40, we turned our attention to an alternative approach to 40 via epoxide 21. This approach takes advantage of ozonolysis of the side chain olefin late in the synthesis to provide aldehyde 40 as shown\textsuperscript{7,8}.

![Chemical diagram](attachment:image.png)

Synthesis of the bioisostere containing aryl groups 35, 36, and 37 was easily accomplished from commercially available materials. Compound 35 was synthesized via a two-step published procedure\textsuperscript{9,10}. Thus, addition of 42 to a mixture of hydroxylamine hydrochloride and sodium acetate in water provided 43. Treatment of 43 with phosphorous oxychloride (POCl\textsubscript{3}) in acetonitrile and dimethylformamide, followed by aqueous sodium acetate gave rise to 35 in 43% yield. Compound 35 displays \textsuperscript{1}H NMR peaks at $\delta$ 2.57 (3 H), 6.75 (1 H), 6.97 (1 H), 7.37 (1 H), and 9.67 (1 H).
Similarly, 36 was obtained in 85% yield via the same procedure starting with commercially available 44 and shows $^1$H NMR peaks at δ 2.53 (3 H), 6.65 – 6.75 (1 H), 6.82 – 6.84 (1 H), 7.43 – 7.42 (1 H), and 9.48 (1 H).

Benzothiazole 37 was obtained in a 70% yield from the commercially-available 46 upon treatment with 4 equivalents of BBr$_3$ in methylene chloride, followed by slow addition of methanol and neutralization with sodium bicarbonate. Previous research in our laboratory found a temperature of -12°C was essential for the reaction to proceed in high yield$^{11}$. Benzothiazole 37 exhibits $^1$H NMR peaks at δ 2.42 – 2.48 (2 H), 6.64 – 6.66 (1 H), 7.02 – 7.22 (2 H), and 9.17 (1 H).

Once both the epoxide and the aryl-oxy systems were synthesized, we turned our attention to determine methods to couple the two systems together via an epoxide-opening reaction. Although procedures for preparing aryl-vinyl ether systems from epoxide 21 and various phenols had been developed in our laboratory, we chose to investigate some other attractive procedures.
in the hopes of attaining higher yields. In one published report, epoxides were successfully coupled with phenols to provide aryl-vinyl ether systems as shown below:\textsuperscript{12,13}.

\[
\begin{align*}
\text{O} & \quad \text{HO} \quad \text{R} \\
\text{47} & \quad + \quad \text{48} \\
\text{R}_4N^+OH^- \quad \text{CH}_2\text{Cl}_2/H_2O & \quad \text{16-24 h} \\
\text{O} & \quad \text{O} \quad \text{R} \\
\text{49} &
\end{align*}
\]

In our trials however, this approach failed to provide product under a variety of concentrations and conditions.

\[
\begin{align*}
\text{O} & \quad \text{HO} \quad \text{48} \\
\text{47} & \quad + \quad \text{3 Reactions} \\
\text{O} & \quad \text{O} \quad \text{49} \\
\text{Reaction 1: (CH3)4NI, NaOH, CH2Cl2 / H2O, 0.1 M, 5 d} \\
\text{Reaction 2: (CH3)4NI, NaOH, CH2Cl2 / H2O, 1.0 M, 5 d} \\
\text{Reaction 3: NaOH, CH2Cl2, 1.0 M, 5 d}
\end{align*}
\]

In another approach, we attempted to affect the coupling between 47 and 48 with potassium hydride (30\% by weight in mineral oil) and dimethylformamide.

\[
\begin{align*}
\text{O} & \quad \text{HO} \quad \text{48} \\
\text{47} & \quad + \quad \text{KH, DMF} \\
\text{O} & \quad \text{O} \quad \text{49}
\end{align*}
\]
When this attempt failed, we turned our attention to the method previously developed in our laboratory and typified by the scheme below\textsuperscript{5}.

![Reaction scheme](image)

In order to evaluate this method for use with heterocyclic aromatic systems, we tested the conditions for synthesis of 51 from the readily available 47 and 50.

![Relevant reactions](image)

After heating at reflux temperature for one day, followed by standard workup, aryl-vinyl ether 51 was collected in 47\% yield. Following this success, coupling was done using epoxide 21 with the two benzoazoles and one benzothiazole under the same conditions.
Epoxide 21 and benzoxazole 35 were allowed to heat at reflux temperature for two days, after which, a standard workup and a wash with 1 N sodium hydroxide were performed to afford aryl-vinyl ether 38 in a 35% yield. Compound 38 shows $^1$H NMR peaks at $\delta$ 2.05 – 2.14 (10 H), 2.57 (3 H), 4.99 – 5.04 (2 H), 5.75 – 5.80 (1 H), 6.87 – 6.89 (1 H), 6.93 – 6.95 (1 H), and 7.65 – 7.69 (1 H). This same procedure was used to couple epoxide 21 and benzoxazole 36 to afford aryl-vinyl ether 52 in 40% yield. Compound 52 displays $^1$H NMR peaks at $\delta$ 1.54-2.17 (10 H), 2.53 (3 H), 4.88-5.01 (2 H), 5.65-5.78 (1 H), 6.74-6.79 (1 H), 7.04-7.07 (1 H), and 7.18-7.25 (1 H).
Epoxide 21 and benzothiazole 37 were heated at reflux temperature for two days using the standardized procedure of KH and DMPU in THF. A standard workup and purification by column chromatography on silica gel (methylene chloride : methanol (98:2)) afforded pure aryl-vinyl ether 53 in 45% yield. Aryl-vinyl ether 53 showed peaks in the $^1$H NMR at $\delta$ 2.06-2.12 (2 H), 2.22-2.28 (2 H), 2.42 (2 H), 2.54-2.58 (4 H), 4.98 (1 H), 5.03 (1 H), 5.09 (2 H), 5.70-5.79 (1 H), 6.86 (1 H), 7.07 (1 H), and 7.42 (1 H).

The next step in the synthesis is to oxidize the simple alkene side-chain to an aldehyde via ozonolysis followed by a reductive workup using dimethylsulfide. Compounds 38 and 52 may be converted to compounds 54 and 55 through simple ozonolysis at -78 °C.

Compound 53 may be converted to compound 56 through ozonolysis; however, the primary amine group on 53 must first be protected as the amine salt using perchloric acid.

![Chemical structures and reactions]

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Following the formation of aldehydes 54, 55, and 56, Wittig addition may provide a convenient path to photolysis precursors, 9, 11, and 12 respectively.
Before attempting photocyclization of our precursors, and in order to gain experience, aryl-vinyl ether $57$ was dissolved in toluene and irradiated for thirty minutes. $^1$H-NMR shows that the compound formed from the photoreaction was the trans-product, $58$.

The photo precursors synthesized in our lab will be irradiated in toluene according to conditions used previously and are expected to undergo photocyclization followed by an intramolecular [3+2] cycloaddition to form products 6, 7 and 8.
In conclusion, aryl-vinyl ether systems 38, 52, and 53 were successfully synthesized. Future work will entail conversion of these substrates to photoprecursors 9, 11, and 12, which will be employed to construct multi-cyclic scaffolds via photochemical methods developed in our laboratory to provide 6, 7, and 8.
Experimental

General Methods

$^1$H NMR spectra were recorded on a Bruker 400 (400 MHz) NMR Spectrometer or a Bruker 500 (500 MHz) NMR Spectrometer. Chemical shifts ($\delta$) are reported in ppm relative to tetramethylsilane (TMS) at 0.00. $^{13}$C NMR spectra were recorded at 100.61 MHz.

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 4 scans.

Analytical thin-layer chromatography were done on precoated silica gel plates (0.25 mm thickness) with a 254 nm fluorescent indicator and were visualized under a UV lamp and/or by staining with either iodine or a $p$-anisaldehyde stain.
3-ethoxy-2-cyclohexenone (17)

To a 500-mL two-neck flask equipped with a reflux condenser and Dean Stark trap was added 3-hydroxycyclohex-2-enone 16 (10.3 g, 91.6 mmol), ethanol (50 mL), benzene (175 mL) and p-toluene sulfonic acid monohydrate (441 mg, 2.3 mmol). The resulting solution was stirred at room temperature for 4 h. The resulting clear, amber solution was heated at reflux temperature for 2 h after which it was allowed to cool to room temperature. Solvent was removed under reduced pressure and the resulting oil was dissolved in ethyl acetate, washed with a sodium hydroxide solution (10% aqueous saturated with sodium chloride), followed by water until neutral and then washed with brine. The organic layer was collected, dried (Na₂SO₄) and the solvent was removed under reduced pressure to yield 17 as an amber colored oil (8.66 g, 67.5%):

$^1$H NMR (CDCl₃, 400 MHz) δ 1.40 (t, 3 H), 1.89-2.42 (m, 6 H), 3.91 (q, 2 H), 5.37 (s, 1 H); $^{13}$C NMR (CDCl₃, 100.6 MHz) δ 14.5, 21.6, 29.5, 37.1, 64.6, 103.1, 178.4, 200.4.
3-(2-(1,3-dioxan-2-yI)ethyl)cyclohex-2-enone (18)

Magnesium turnings (2.31 g, 95.2 mmol) were added to a dry 250-mL three-neck flask under nitrogen. Anhydrous tetrahydrofuran (THF, 10 mL) followed by 2-(2-bromoethyl)-1,3-dioxane (9.26 mL, 13.3 g, 68.3 mmol) was added along with additional THF (40 mL). The reaction mixture was allowed to reflux under exothermic heat for 10 min and the resulting mixture was refluxed with heating for an additional 30 min. The reaction mixture was cooled to 0 °C and a solution of 17 (8.25 g, 58.8 mmol) in THF (40 mL) was added dropwise over 30 min. The resulting solution was allowed to stir at room temperature over the weekend and was neutralized with saturated aqueous ammonium chloride, and the solvent removed under reduced pressure. The resulting oil was dissolved in ethyl acetate, washed with water and brine and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to yield an amber oil, which was diluted in ethanol, cooled to 0 °C, and slowly treated with aqueous hydrochloric acid (3.7%, 13.3 mL). The resulting solution was allowed to warm to room temperature and stirred for 4 h. The resulting solution was neutralized with saturated aqueous sodium bicarbonate and concentrated under reduced pressure. The resulting oil was diluted with ethyl acetate and washed with water, brine, and dried (Na$_2$SO$_4$). Removal of solvent under reduced pressure yielded 18 as an amber oil.
(9.31 g, 75.3%): $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.17-1.39 (m, 2 H), 1.72-2.41 (m, 10 H), 3.68-3.80 (m, 2 H), 4.02-4.15 (m, 2 H), 4.45-4.53 (m, 1 H), 5.80-5.88 (m, 1 H).
3-(but-3-enyl)cyclohex-2-enone (19)

To a mixture of magnesium turnings (0.28 g, 12 mmol) in dry THF (2 mL) under nitrogen was added 4-bromo-1-butene (0.85 mL, 8.3 mmol) in THF (4 mL). The mixture was maintained at reflux temperature for 45 min, after which it was cooled to 0 °C and compound 17 (0.96 mL, 7.12 mmol) in THF (5 mL) was added. The solution was stirred at room temperature for 22 h and then was filtered. To the filtrate was added saturated aqueous ammonium chloride (5 mL) and the solvent was removed under reduced pressure. The crude product was taken up in ethyl acetate, washed with water, brine, and dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure. The resulting oil was taken up in ethanol and cooled to 0 °C. Aqueous hydrochloric acid (3.7%, 1.7 mL) was added dropwise and the mixture was stirred at 0 °C for 3 h, allowed to warm to room temperature, neutralized with saturated aqueous sodium bicarbonate and concentrated under reduced pressure. Product was extracted from the resulting liquid with ethyl acetate and the organic layer was washed with water, brine and dried (Na$_2$SO$_4$). Solvent was removed under reduced pressure to yield 19 as a yellow oil (638 mg, 62 %): $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.87-2.45 (m, 10 H), 4.87-5.10 (m, 2 H), 5.68-5.90 (m, 2 H).
6-(2-(1,3-dioxan-2-yl)ethyl)-7-oxabicyclo[4.1.0]heptan-2-one (20)

To a 500-mL flask containing methanol (147 mL) at 10 °C was added 18 (9.28 g, 44.1 mmol) and hydrogen peroxide (35%, 9.9 mL, 115 mmol). Aqueous sodium hydroxide (0.5 M, 98 mL) was added over 75 min and the temperature was maintained at 10-12 °C. The resulting solution was allowed to stir an additional 50 min at 10-12 °C, after which it was extracted with dichloromethane. The combined organic layers were washed with brine and dried (Na$_2$SO$_4$). Solvent was removed under reduced pressure to yield 20 as a yellow colored oil (5.38 g, 53.9%):

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.18-1.38 (m, 2 H), 1.75-2.38 (m, 10 H), 3.12 (s, 1 H), 3.68-3.80 (m, 2 H), 4.03-4.16 (m, 2 H), 4.45-4.52 (m, 1 H).
6-(but-3-enyl)-7-oxabicyclo[4.1.0]heptan-2-one (21)

A solution of 19 (638 mg, 4.3 mmol) in methanol was cooled to 10 °C and hydrogen peroxide (35%, 0.98 mL, 11 mmol) was added dropwise. Aqueous sodium hydroxide (0.5 M, 10 mL) was added over 16 min via addition funnel and stirring was continued for 1 h at 10-12 °C. The reaction mixture was extracted with dichloromethane and the combined organic layers were washed with brine and dried (Na₂SO₄). Solvent was removed under reduced pressure to yield 21 as an oil (540 mg, 74 %): ¹H NMR (CDCl₃, 400 MHz) δ 1.45-2.57 (m, 10 H), 3.11 (s, 1 H), 4.89-5.10 (m, 2 H), 5.69-5.92 (m, 1 H).
3,5,5-trimethyl-2-(6-methylpyridin-3-yloxy)cyclohex-2-enone (51)

To a solution of 3-hydroxy-6-methylpyridine 50 (600 mg, 5.5 mmol) in anhydrous THF (10 mL) was added potassium hydride (30% by weight in mineral oil, 6 drops). The resulting mixture was stirred for 10 min after which isophorone oxide 47 (0.78 mL, 5.0 mmol) was added followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, 0.66 mL, 5.5 mmol). The resulting solution was stirred at reflux temperature for 25 h. The resulting mixture was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure. The resulting oil was dissolved in hexane, filtered, and washed with sodium hydroxide (1 N), water, and brine. The organic layer was collected, dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to yield 51 as an amber colored oil (0.58 g, 47.4%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.91 (s, 6 H), 1.63 (s, 3 H), 2.14 (s, 2 H), 2.18 (s, 2 H), 2.25 (s, 3 H), 6.86 (m, 2 H), 7.88 (m, 1 H).
To a 100-mL round-bottom flask was added compound 46 (1.002 g, 5.56 mmol) in anhydrous dichloromethane (5.6 mL). The resulting solution was stirred at -12 °C. Boron tribromide (1.0 M in methylene chloride, ~28 mL, 28 mmol) was added dropwise under nitrogen and the resulting reaction mixture was stirred at -9 to -12 °C for 3 h, at which point, starting material was no longer visible by thin layer chromatography (TLC) analysis (Hexanes : Ethyl Acetate (50:50)). Methanol (2.8 mL, 69.1 mmol) was slowly added, resulting in formation of a white gas. A light colored solid slowly formed and the flask was allowed to warm to room temperature with stirring. After 2.5 h, the solid was collected, dissolved in water and washed with ethyl acetate. The aqueous layer was collected and neutralized with saturated aqueous sodium bicarbonate. Evolution of gas was observed with concomitant formation of light grey solid. The mixture was filtered to yield 37 as a light grey solid (0.6454 g, 69.8%): $^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 2.42 – 2.48 (m, 2 H), 6.64 – 6.66 (m, 1 H), 7.02 – 7.22 (m, 2 H), 9.17 (s, 1 H).
(E)-1-(2,5-dihydroxyphenyl)ethanone oxime (45)

To a mixture of hydroxylamine hydrochloride (5.14 g, 73.9 mmol) and sodium acetate (10.2 g, 125 mmol) in water (15 mL) was added a solution of 2',5'-dihydroxyacetophenone 44 (3.00 g, 19.7 mmol) in water (15 mL). The mixture was heated at reflux temperature for 2 h, and the crude mixture was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried (Na₂SO₄). The solvent was removed under reduced pressure to yield 45 as a brown solid (3.20 g, 97%): ¹H NMR (CDCl₃, 400 MHz) δ 2.19 (s, 3 H), 6.68 (d, 2 H), 6.83 (s, 1 H), 8.96 (s, 1 H), 10.86 (dd, 1 H), 11.53 (d, 1 H).
(E)-1-(2,4-dihydroxyphenyl)ethanone oxime (43)

To a solution of hydroxylamine hydrochloride (4.61 g, 66 mmol) and sodium acetate (9.18 g, 112 mmol) in water (15 mL) was added 2’,4’-dihydroxyacetophenone 42 (3.00 g, 20 mmol) and water (20 mL). The solution was heated at reflux temperature for 75 min after which product was extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried (Na$_2$SO$_4$). Removal of solvent provided 43 as a light orange solid (3.10 g, 94%): $^1$H NMR (DMSO-d$_6$, 400 MHz) δ 2.19 (s, 3 H), 6.24 (t, $J$=2.78 Hz, 1 H), 6.31 (m, 1 H), 7.28 (m, 1 H), 9.82 (broad s, 1 H), 11.26 (broad s, 1 H), 11.78 (s, 1 H).
2-methylbenzo[d]oxazol-5-ol (36)

![Chemical structure diagram]

A solution of oxime 45 (1.50 g, 9 mmol) in dry acetonitrile (1.8 mL) and dry dimethylformide (5.4 mL) was treated with phosphorous oxychloride (0.85 mL, 9.1 mmol) over a period of 3 min. During the addition, the temperature was maintained below 30 °C. The resulting mixture was stirred at room temperature for 60 min. Aqueous sodium acetate (1.75 M, 15 mL) was added and stirring was continued for 5 min. The crude product was extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried (Na$_2$SO$_4$). Removal of solvent provided 36 as a tan solid (1.14 g, 85 %): $^1$H NMR (DMSO-d$_6$, 400 MHz) δ 2.53 (s, 3 H), 6.65 – 6.75 (m, 1 H), 6.82 – 6.84 (m, 1 H), 7.43 – 7.42 (m, 1 H), 9.48 (s, 1 H).
A solution of oxime 43 (1.50 g, 9 mmol) in dry acetonitrile (1.8 mL) and dry dimethylformide (5.4 mL) was treated with phosphorous oxychloride (0.84 mL, 9 mmol) over a period of 2 min. During the addition, the temperature was maintained below 30 °C. The resulting mixture was stirred at room temperature for 75 min. Aqueous sodium acetate (1.32 M, 20 mL) was added and stirring was continued for 5 min. The crude product was extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried (Na₂SO₄). Removal of solvent provided a brown solid (2.07 g) and recrystallization from acetonitrile yielded 35 as a light brown solid (.582 g, 43%): ¹H NMR (DMSO-d₆, 400 MHz) δ 2.57 (s, 3 H), 6.75 (m, 1 H), 6.97 (m, 1 H), 7.37 (m, 1 H), 9.67 (s, 1 H).
To a solution of phenol 37 (0.2205 g, 1.33 mmol) in dry THF (2.4 mL) at 0 °C was added potassium hydride (30% by weight in mineral oil, 2 drops), resulting in a green cloudy reaction mixture. Compound 21 (0.20 mL, 1.20 mmol) and DMPU (0.16 mL, 1.32 mmol) were added and the mixture was stirred for 10 min at 0 °C. The reaction mixture was heated at reflux temperature for 63 h. The resulting dark brown reaction mixture was cooled to room temperature, after which the solvent was removed under reduced pressure. The resulting dark oil was dissolved in ethyl acetate, washed with water, brine, and dried (Na$_2$SO$_4$). Solvent was removed under reduced pressure to yield a viscous brown oil (0.5709 g), which was dissolved in chloroform and filtered (solid 0.0590 g). The brown filtrate was concentrated under reduced pressure to yield a brown-orange residue (0.4259 g). Purification by column chromatography over silica gel (methylene chloride : methanol (98:2)) provided 53 as a brown solid (0.161 g, 44.7%): IR (film) 3382, 3107, 2954, 1676, 1633 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 2.06-2.12 (m, 2 H), 2.22-2.28 (m, 2 H), 2.42 (t, 2 H), 2.54-2.58 (m, 4 H), 4.98 (dq, 1 H), 5.03 (dq, 1 H), 5.09 (broad s, 2 H), 5.70-5.79 (m, 1 H), 6.86 (dd, 1 H), 7.07 (d, 1 H), 7.42 (d, 1 H).
3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-5-yloxy)cyclohex-2-enone (52)

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\begin{array}{c}
\text{21} \\
1.54-2.17 (m, 10 H), 2.53 (s, 3 H), 4.88-5.01 (m, 2 H), 5.65-5.78 (m, 1 H), 6.74-6.79 (m, 1 H), 7.04-7.07 (m, 1 H), 7.18-7.25 (m, 1 H).
\end{array}
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A solution of alcohol 36 (155.6 mg, 1.05 mmol), dry tetrahydrofuran (1.5 mL) and potassium hydride (35% in mineral oil, 222 mg, 0.14 mmol) was stirred at ice-bath temperature under a nitrogen environment while a solution of epoxide 21 (156.0 mg, 0.95 mmol) in dry THF (0.4 mL) was added over 2 min. The mixture was heated at reflux temperature for 24 h after which product was extracted with ethyl acetate. The organic phase was washed with water, brine and dried (Na$_2$SO$_4$). Removal of solvent yielded 52 as an impure dark brown solid (263.5 mg, 85%): IR (film) 3076, 2927, 1680, 1618 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.54-2.17 (m, 10 H), 2.53 (s, 3 H), 4.88-5.01 (m, 2 H), 5.65-5.78 (m, 1 H), 6.74-6.79 (m, 1 H), 7.04-7.07 (m, 1 H), 7.18-7.25 (m, 1 H).
3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone (38)

A solution of alcohol 35 (302.8 mg, 1.82 mmol), dry tetrahydrofuran (THF, 3 mL) and potassium hydride (35% in mineral oil, 11.07 mg, 0.28 mmol) was stirred at ice-bath temperature under a nitrogen environment while a solution of epoxide 21 (304.7 mg, 0.95 mmol) in dry THF (0.6 mL) was added over 2 min. The mixture was heated at reflux temperature for 48 h after which product was extracted with ethyl acetate. The organic phase was washed with water, sodium hydroxide (1 N), brine and dried (Na$_2$SO$_4$). Removal of solvent followed by purification by column chromatography over silica gel (methylene chloride : methanol (99:1)) yielded 38 as a viscous yellow liquid (188 mg, 35%): IR (film) 3078, 2945, 2859, 1711, 1613 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.05 – 2.14 (m, 10 H), 2.57 (s, 3 H), 4.99 – 5.04 (m, 2 H), 5.75 – 5.80 (m, 1 H), 6.87 – 6.89 (m, 1 H), 6.93 – 6.95 (m, 1 H), 7.65 – 7.69 (m, 1 H).
References


11. Conditions developed by Brian Costa during summer 2007 fellowship work.

Figure 1 $^1$H NMR Spectra of 3-ethoxy-2-cyclohexenone (17)
Figure 2 $^1$H NMR Spectra of 3-(2-(1,3-dioxan-2-yl)ethyl)cyclohex-2-enone (18)
Figure 3 $^1$H NMR Spectra of 3-(but-3-enyl)cyclohex-2-enone (19)
Figure 4 $^1$H NMR Spectra of 6-(2-(1,3-dioxan-2-yl)ethyl)-7-oxabicyclo[4.1.0]heptan-2-one (20)
Figure 5 $^1$H NMR Spectra of 6-(but-3-enyl)-7-oxabicyclo[4.1.0]heptan-2-one (21)
Figure 6 $^1$H NMR Spectra of 3,5,5-trimethyl-2-(6-methylpyridin-3-yloxy)cyclohex-2-enone (51)
Figure 7 $^1$H NMR Spectra of 2-aminobenzod[thiazol-6-ol (37)
Figure 8 $^1$H NMR Spectra of (E)-1-(2,5-dihydroxyphenyl)ethanone oxime (45) (-1 to 11 ppm)
Figure 9 $^1$H NMR Spectra of (E)-1-(2,5-dihydroxyphenyl)ethanone oxime (45) (0 to 12 ppm)
Figure 10 $^1$H NMR Spectra of (E)-1-(2,4-dihydroxyphenyl)ethanone oxime (43) (-1 to 11 ppm)
Figure 11 $^1$H NMR Spectra of (E)-1-(2,4-dihydroxyphenyl)ethanone oxime (43) (0 to 12 ppm)
Figure 12 $^1$H NMR Spectra of 2-methylbenzo[d]oxazol-5-ol (36)
Figure 13 $^1$H NMR Spectra of 2-methylbenzo[d]oxazol-6-ol (35)
Figure 14 $^1$H NMR Spectra of 2-(2-aminobenzo[d]thiazol-6-ylxy)-3-(but-3-enyl)cyclohex-2-enone (53)
Figure 15 IR Spectra of 2-(2-aminobenzod/thiazol-6-yloxy)-3-(but-3-enyl)cyclohex-2-enone (53)
Figure 16 $^1$H NMR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-5-yloxy)cyclohex-2-enone (52)
Figure 17 IR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-5-yloxy)cyclohex-2-enone (52)
Figure 18 $^1$H NMR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-ylxy)cyclohex-2-ene (38)
Figure 19 IR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cy clohex-2-enone (38)