Regio- and Stereoselective Ring Openings of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene Systems with Copper Catalyst-Modified Grignard Reagents: Application to the Synthesis of an Inhibitor of 5-Lipoxygenase

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Treatment of acylnitroso hetero Diels−Alder cycloadducts **2** with organomagnesium reagents in the presence of a catalytic amount of copper induces ring opening to afford predominantly monocyclic *anti*-1,2-hydroxamic acids **12**. Alkylmagnesium reagents were found to give superior regio- and stereoselectivities compared with vinyl and arylmagnesium reagents. This cycloadduct ring opening methodology was applied to the synthesis of a unique cyclopentenyl hydroxamic acid-based inhibitor of 5-lipoxygenase.

Introduction

3-Aza-2-oxabicyclo[2.2.1]hept-5-enes (**2**), derived from the hetero Diels−Alder reaction between transient acylnitroso species and cyclopentadiene,[1] continue to hold a tremendous amount of synthetic potential as intermediates in the construction of a variety of biologically interesting molecules. Most commonly, the acylnitroso Diels−Alder cycloadducts (**2**) are elaborated through cleavage of the N−O bond to form 1,4-aminocyclopentenols (**3**) (Scheme 1). These amino alcohols are highly valuable intermediates in the synthesis of carbocyclic nucleosides,[2] prostaglandins,[3] and other natural products.[4] Alternatively, the cycloadducts (**2**) can be opened through oxidative cleavage of the olefin to form diacids (**4**),[5] which can be carried on to give novel amino acids. A less commonly employed approach to the elaboration of acylnitroso Diels−Alder cycloadducts involves the cleavage of the C−O bond. This approach is of particular interest because it generates a hydroxamic acid, which is an important functionality found in a wide range of biologically active compounds.[6] We and others have shown that this ring opening can be induced by Brønsted acid,[7] Lewis acids,[7c,8] or palladium(0)[9,7c] to selectively provide *syn*-1,2-, *anti*-1,4-, or *syn*-1,4-disubstituted cyclopentenes (**5**−**7**), respectively.

In our investigation of cycloadduct ring opening reactions through C−O bond cleavage, we desired to induce ring opening in conjunction with C−C bond formation. In this way, the carbon framework of the molecules could be expanded directly from the cycloadduct. Thus, the synthetic versatility of the cycloadducts would be greatly enhanced. One method that proved to be successful for this transformation involved the treatment of cycloadducts with palladium(0) and a carbon nucleophile such as dimethyl malonate[9a] or methyl nitroacetate.[9c] Another intriguing possibility was the use of organometallic carbon nucleophiles, such as Grignard reagents. Initial inspection of the *N*-acetyl cycloadducts might arouse a certain level of skepticism, however, as the cycloadducts are, in fact, bicyclic forms of Weinreb amides.[10] Therefore,

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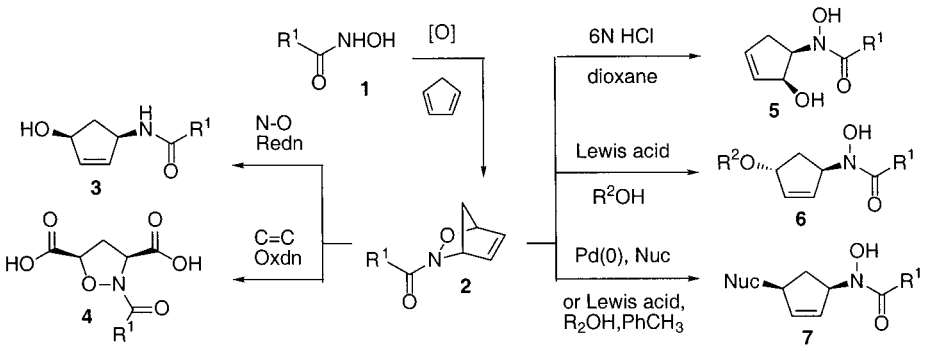
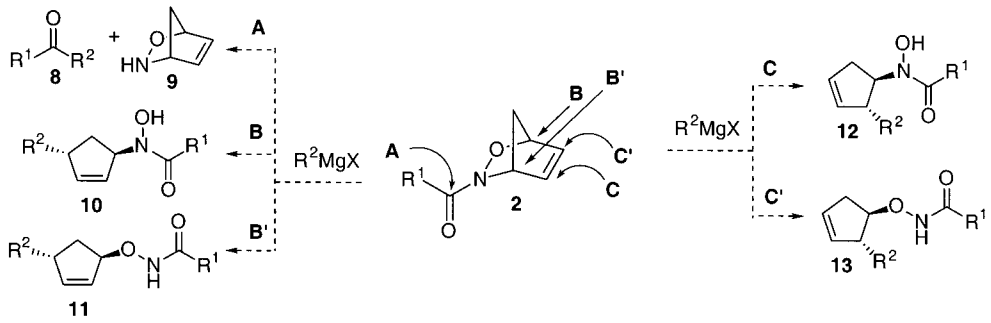
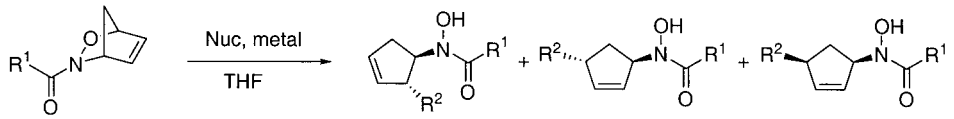
Scheme 1



Scheme 2



Scheme 3



2a (R^1=CH_3)
2b (R^1=CH_2Ph)
2c (R^1=O-*t*-Bu)
2d (R^1=OMe)

one might expect the nucleophile to attack the carbonyl carbon, giving rise to a ketone (**8**) after acidic workup (Scheme 2, path A). There are, however, several other potential electrophilic sites on the cycloadducts. One could envision direct nucleophilic displacement of either the oxygen (path B) or nitrogen (path B′) to give rise to *anti*-1,4-disubstituted hydroxamic acids (**10**) or hydroxamates (**11**). Alternatively, an S_N2' attack might also be possible to indirectly displace either the oxygen (path **C**) or nitrogen (path **C**′) and give rise to *anti*-1,2-products (**12** and **13**). In order for the desired transformation to be synthetically useful, two criteria must be met. First, one of the many possible reaction pathways must be favored over the others, and second, that pathway must not be path A.

Results and Discussion

Our investigation began with the treatment of *N*-acetyl cycloadduct **2a**[11] with vinylmagnesium bromide. A low yield (11%) of an essentially 1:1 mixture of *anti*-1,2-:*anti*-1,4-hydroxamic acids (**14a**:**15a**) was obtained (Table 1, entry 1). While the yield and selectivity were not particularly impressive, two encouraging points were noted. First, of all the possible reaction pathways, only two products were isolated, and second, none of the products arising from attack at the carbonyl were detected. Therefore, attention was turned to optimization of the reaction conditions. Copper is often used to affect the reactivity of organomagnesium reagents. Thus, the reaction was repeated with the addition of a catalytic amount (10 mol %) of copper(II) chloride.[12,13] A dramatic effect on the yield and selectivity of the reaction was observed, providing an 89% yield of a 7:3:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**14a**:**15a**:**16a**) (Table 1, entry 2).[14] The major *anti*-1,2-product could be isolated cleanly by silica gel chromatography. Therefore, through the addition of copper, not only was the yield significantly increased, the reaction pathway leading to the separable *anti*-1,2-product **14a** also was shown to be favored. Thus, according to the original criteria, the reaction could be considered a synthetically useful route to *anti*-1,2-cyclopentenyl hydroxamic acids (**14**).

While encouraged by the result of the addition of copper(II), questions remained as to the role of the copper in the reaction. Our previous studies of Lewis acid-mediated ring openings of acylnitroso Diels−Alder cyclo-

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Table 1. Ring Openings of Cycloadduct 2 with Organometallic Reagents

entry	R^1	Nuc	R^2	metal	products	yield, %	product ratios, **14**:**15**:**16**
1	CH_3	vinylMgBr	CH_2CH	none	**14a**−**16a**	11	1:1:trace
2	CH_3	vinylMgBr	CH_2CH	$CuCl_2$	**14a**−**16a**	89	7:3:1
3	CH_3	vinylMgBr	CH_2CH	$FeCl_3$	**14a**−**16a**	−	complex mixture
4	CH_3	vinylMgBr	CH_2CH	$Ga(acac)_3$	**14a**−**16a**	−	complex mixture
5	CH_3	vinylMgBr	CH_2CH	CuCl	**14a**−**16a**	77	3:3:1
6	$PhCH_2$	Bu_2CuLi	$CH_3(CH_2)_3$	none	**14b**−**16b**	73	2:1:0
7	$PhCH_2$	PhMgBr	C_6H_5	none	**14c**−**16c**	−	no hydroxamic acid products
8	$PhCH_2$	PhMgBr	C_6H_5	$CuCl_2$	**14c**−**16c**	96	1.9:1.6:1
9	t-BuO	vinylMgBr	CH_2CH	$CuCl_2$	**14d**−**16d**	71	8.4:3:1
10	t-BuO	EtMgBr	CH_3CH_2	$CuCl_2$	**14e**−**16e**	93	18:2:1
11	t-BuO	EtMgBr	CH_3CH_2	none	**14e**−**16e**	87	38:2:1
12	t-BuO	PhMgBr	C_6H_5	$CuCl_2$	**14f**−**16f**	50	3.5:1:0
13	t-BuO	EtMgBr	CH_3CH_2	$MgBr_2{\cdot}OEt_2$	**14e**−**16e**	89	5.7:3:1

Table 2. Ring Openings of Cycloadduct 2 with Lewis Acids

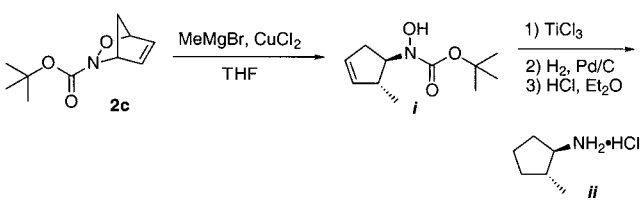
entry	R^1	Nuc	R^2	Lewis acid	products	yield, %	product ratios, **14**:**15**:**16**
1	CH_2Ph	MeOH	OCH_3	$CuCl_2$	**14g**−**16g**	78	1:14:5
2	CH_2Ph	MeOH	OCH_3	$FeCl_3$	**14g**−**16g**	74	1:7:1.7
3	CH_2Ph	MeOH	OCH_3	$Ga(acac)_3$	**14g**−**16g**	−	no reaction
4	t-BuO	MeOH	OCH_3	$CuCl_2$	**14g**−**16g**	41	1:2.4:1.4
5	t-BuO	MeOH	OCH_3	$FeCl_3$	**14g**−**16g**	72	1:1.8:1.2

adducts (**2**) showed that the cycloadducts were susceptible to ring opening with copper(II) chloride (Table 2, entry 1).[8] Therefore, the copper could have acted as a Lewis acid and assisted in the opening of the cycloadducts. To test this hypothesis, reactions were run in which the copper(II) chloride was replaced with other Lewis acids. Iron(III) chloride and gallium(III) acetylacetonate were chosen as being toward opposite ends of the spectrum of reactivity with acylnitroso Diels−Alder cycloadducts. In alcohol solvent, iron(III) chloride affords a significantly more facile ring opening than copper(II) chloride and gallium(III) acetylacetonate is essentially ineffective at inducing any cycloadduct ring opening (Table 2, entries 2 and 3). When *N*-acetyl cycloadduct **2a** was treated with vinylmagnesium bromide and each of the alternative Lewis acids, the reactions were unsuccessful, giving rise to complex mixtures of products (Table 1, entries 3 and 4). From this brief study, the copper(II) chloride did not appear to act as a simple Lewis acid. Another possible role of the copper was in a reaction with the vinylmagnesium bromide to form an organocopper reagent. If this was the case, then a copper(I) salt should also effectively catalyze the ring opening reaction. Indeed, treatment of *N*-acetyl cycloadduct **2a** with vinylmagnesium bromide and copper(I) chloride (10 mol %) did provide hydroxamic acid products in good yield (77%) (Table 1, entry 5). However, the selectivity of the reaction suffered significantly, giving a 3:3:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**14a**:**15a**:**16a**). These studies indicated that the role of the copper(II) chloride was a bit more complex than just a simple Lewis acid or in the catalytic generation of the organocopper reagent. However, further evidence of an organocopper reagent being responsible for the cycloadduct ring opening came from the treatment of *N*-phenylacetyl cycloadduct **2b** with preformed dibutylhomocuprate. The reaction resulted in a 73% yield of a 2:1 mixture of *anti*-1,2-:*anti*-1,4-hydroxamic acids (**14b**:**15b**) (Table 1, entry 6).

Aryl Grignard reagents were found to offer poorer product selectivity than vinylmagnesium bromide. Not surprisingly, when *N*-phenylacetyl cycloadduct **2b** was initially reacted with phenylmagnesium bromide in the absence of any copper salts, no hydroxamic acid products were formed (Table 1, entry 7). Once again, however, the addition of a catalytic amount of copper(II) chloride had a dramatic effect on the outcome of the reaction. When copper was added, the reaction provided a 96% yield of 1.9:1.6:1 ratio of *anti*-1,2-:*anti*-1,4:*syn*-1,4-hydroxamic acids (**14c**:**15c**:**16c**) (Table 1, entry 8).

The copper-catalyzed reactions of *N*-carbamate cycloadducts with organomagnesium reagents also were investigated. Previous studies showed that Lewis acid-mediated ring openings of *N*-carbamate cycloadducts provided compromised product selectivities in comparison with *N*-acetyl cycloadducts (Table 2, entries 4 and 5).[8] Therefore, we were pleased to find that reaction of *N*-Boc cycloadduct **2c** with vinylmagnesium bromide and copper(II) chloride gave a comparable yield (71%) and selectivity [8.4:3:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**14d**:**15d**:**16d**)] to the treatment of *N*-acetyl cycloadduct under the same reaction conditions (Table 1, entry 9). This improved selectivity might be due to the decreased leaving group abilities of the *N*-hydroxycarbamate relative to the hydroxamate. Improved yields

(14) The *syn*-1,4- and *anti*-1,4-stereochemical assignments were based upon the ^1H NMR coupling pattern. The C(5) methylene protons of 1,4-disubstituted cyclopentene systems have a very characteristic coupling pattern. The C(5) protons of *syn*-1,4-aminocyclopentenols have a characteristic overlapping ddd pattern, with approximate *J* values of 3.9, 3.9, and 14.7 Hz and 7.8, 7.8, and 14.7 Hz for the *cis*- and *trans*-methylene protons, respectively. There is normally a difference in chemical shift ranging from 0.8 to 1.3 ppm between each respective C(5) proton. The C(5) protons of *anti*-1,4-aminocyclopentenols have a characteristic ddd pattern, with approximate *J* values of 3.9, 7.1, and 13.6 Hz with a smaller chemical shift, ranging from 0.2 to 0.35 ppm between the two C(5) protons. The *anti*-1,2-stereochemical assignment was proven through the synthesis of known *anti*-2-methylcyclopentylamine hydrochloride (**ii**) from cycloadduct **2c**. Cycloadduct **2c** was treated with methylmagnesium bromide and a catalytic amount of copper(II) chloride to give *anti*-1,2-hydroxamic acid **i**. Reduction of the N−O bond followed by reduction of the cyclopentenyl olefin and removal of the Boc group provided *anti*-2-methylcyclopentylamine hydrochloride (**ii**). The melting point of **ii** (196−197 °C) was consistent with the literature value (196−198 °C).[15] The melting point of *syn*-2-methylcyclopentylamine hydrochloride is 256−257 °C.[16]



and selectivities could be achieved by substituting the vinylmagnesium bromide with an alkylmagnesium reagent. Treatment of *N*-Boc cycloadduct **2c** with ethylmagnesium bromide resulted in a 93% yield of an 18:2:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**14e**:**15e**:**16e**) (Table 1, entry 10). Interestingly, when the *N*-carbamate cycloadducts were used, the use of catalytic copper was not always necessary. For example, when *N*-Boc cycloadduct **2c** was treated with ethylmagnesium bromide in the absence of any copper salts, a 38:2:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**14e**:**15e**:**16e**) was obtained in 87% yield (Table 1, entry 11). Furthermore, the reactions of *N*-carbamate cycloadducts often appeared to be influenced more by the Lewis acidity of the reaction media than by the specific presence of copper(II). When *N*-Boc cycloadduct **2c** was treated with ethylmagnesium bromide and 0.5 equiv of $MgBr_2 \cdot OEt_2$, a reduction in selectivity was observed. The reaction gave an 89% yield of a 5.7:2:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**14e**:**15e**:**16e**) (Table 1, entry 13). As seen previously with *N*-phenylacetyl cycloadduct **2b**, reaction of *N*-Boc cycloadduct **2c** with arylmagnesium reagents resulted in compromised selectivity. Treatment of *N*-Boc cycloadduct **2c** with phenylmagnesium bromide and copper(II) chloride resulted in a 50% yield of a 3.5:1 ratio of *anti*-1,2-:*anti*-1,4-hydroxamic acids (**14f**:**15f**) (Table 1, entry 12).

The results of these studies showed that *acylnitroso Diels−Alder cycloadducts **2** could be opened with organomagnesium reagents in the presence of a catalytic amount of copper to provide hydroxamic acids in up to 93% yield and with selectivities of up to 18:2:1 for the anti-1,2-:anti-1,4-:syn-1,4-products (**14**:**15**:**16**).* This constitutes a novel and synthetically useful cycloadduct ring opening and allows for the direct elaboration of the cyclopentene carbon framework while regenerating a hydroxamic acid moiety.

As mentioned previously, hydroxamic acids represent an important functionality found in a variety of biologically active compounds.[6] The activity of these compounds often relies on the hydroxamic acid's ability to effectively bind metals such as iron(III), nickel(II), and zinc(II).[17] Thus, hydroxamates often act as inhibitors of metal-containing enzymes such as 5-lipoxygenase.[18] 5-Lipoxygenase (5-LO) is an iron(III) containing enzyme that is the first in a cascade of enzymes that metabolize arachidonic acid (**17**) into inflammatory-mediating leukotrienes. Elevated levels of leukotrienes have been associated with a variety of disease states including asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and allergy. Compounds that inhibit 5-lipoxygenase show promise in treating such inflammatory diseases.[19] Many known inhibitors of 5-LO contain hydroxamic acids, which are thought to bind to the iron(III) within the enzyme. These inhibitors also typically contain an aromatic portion, which is thought to interact with the hydrophobic regions of the enzyme. An example of a potent class of such 5-LO inhibitors is the 3,4-dihydronaphthyl hydroxamic acids.[20] Extensive SAR studies revealed that a phenoxy group at the 5 position of the 3,4-dihydronaphthalene ring produced the most potent compounds.

Table 3. 5-LO Inhibitory Activity of Compounds 18 and 19a

entry	compd	5-LO source	IC_{50}, nM
1	**18**	rat polymorphonuclear leukocytes	46
2	**19a**	human peripheral blood mononuclear cells	51

We envisioned using our newly developed acylnitroso Diels−Alder cycloadduct ring opening methodology with copper-catalyzed organomagnesium reagents to produce analogues of known 5-LO inhibitors. Importantly, these analogues would be accessible in a single synthetic transformation from the cycloadduct. To demonstrate our vision, we designed an analogue of potent inhibitor 5-phenoxy-3,4-dihydronaphthyl hydroxamic acid **18** (IC_{50} = 46 nM against 5-LO in intact rat polymorphonuclear leukocyts, Table 3, entry 1). Figure 1 shows how hydroxamic acid **18** was thought to sit in the active site of the 5-LO enzyme in alignment with the natural substrate, arachidonic acid (**17**). While the hydroxamic acid moiety was bound to the iron(III), the aromatic portions of **18** were proposed to overlap with the sites of the enzyme that interact with the C5−C15 portions of arachidonic acid (**17**). Similarly, proposed analogue **19a** contains hydroxamic acid and aromatic portions that could interact with the 5-lipoxygenase enzyme in a comparable fashion.

Formation of analogue **19** was anticipated to involve treatment of *N*-methyl carbamate cycloadduct **2d** with an appropriate organomagnesium reagent (Scheme 4). The required bromide precursor (**21**) was obtained after treatment of 3-phenoxybenzyl alcohol (**20**) with carbon tetrabromide and triphenylphosphine.[21] Accordingly, bromide **21** was converted to the corresponding organomagnesium reagent and used to open cycloadduct **2d** in the presence of a catalytic amount of copper(II) chloride. Initial attempts using THF as the solvent were unsuccessful, leading only to decomposition and polymerization products. However, when the solvent was changed to diethyl ether, a 60% yield of a 8.8:4:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acids (**19a**:**19b**:**19c**) was obtained.

The desired analogue **19a** was isolated and submitted for testing against human 5-LO enzyme.[22] The test results indicated complete (100%) enzyme inhibition at the testing concentrations of 10, 5, and 1 μM and an IC_{50} value of 51 nM (Table 3, entry 2). Thus, compound **19a** was shown to be a potent inhibitor of 5-LO with comparable activity to known inhibitor **18**. One could envision rapidly generating libraries of such cyclopentenyl hydroxamic acid-based 5-LO inhibitors from acylnitroso Diels−Alder adducts and a variety of aromatic Grignard reagents.

Conclusions

Acylnitroso Diels−Alder cycloadducts **2** were shown to be susceptible to ring opening with organomagnesium

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(22) Biological testing was performed by MDS Pharma Services.

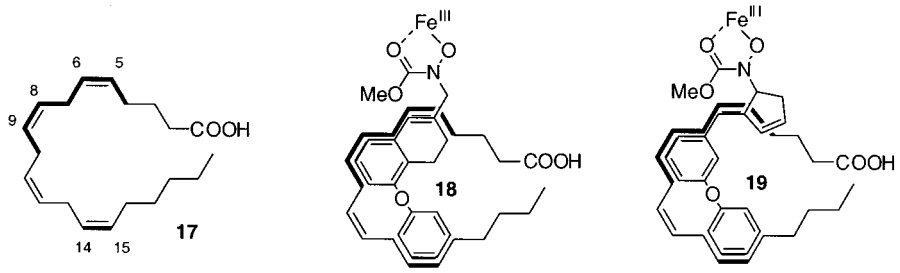
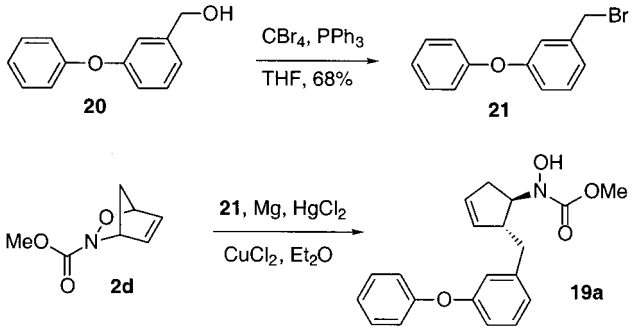


Figure 1.

Scheme 4



reagents in the presence of a catalytic amount of copper to provide hydroxamic acids in up to 93% yield and with selectivities of up to 18:2:1 for the *anti*-1,2-:*anti*-1,4-:*syn*-1,4-products (**14**:**15**:**16**). This novel ring opening methodology was shown to have synthetic utility in the construction of a unique cyclopentenyl hydroxamic acid that demonstrated potent 5-LO inhibitory activity.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian 300 spectrometer and were referenced to residual DMSO or $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer, and TF refers to thin film. Analytical TLC was carried out using Merck aluminum-backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using Merck silica gel 60 (230−400) mesh.

All reactions were periodically monitored by TLC and worked up after the complete consumption of starting materials unless specified otherwise. Anhydrous tetrahydrofuran was freshly distilled from sodium and stored under argon. All purchased reagents were of reagent grade quality and were used without further purification.

All product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. The major products (**14a**, **14b**, **14c**, **14e**, **21**, and **19**) were isolated and fully characterized as follows. The minor products (**15a**, **15b**, **15c**, **16c**, and **19b**) and major products **14d** and **14f** were characterized from the crude reaction mixtures.

1,2-*anti*-Hydroxamic Acid (14a). A solution of *N*-acetyl cycloadduct **2a**[11] (112 mg, 0.803 mmol) in THF (2 mL) was cooled to 0 °C in an ice bath and treated with $CuCl_2$ (11 mg, 0.0833 mmol). The resulting mixture was slowly treated with a 1 M solution of vinylmagnesium bromide (1.0 mL, 1.0 mmol) in THF over the course of 15 min and stirred under argon for 1 h. The mixture was diluted with EtOAc and washed with 1 M HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with a saturated solution of Na_2EDTA, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (silica gel; eluted with 3% MeOH−CH_2Cl_2) provided 120 mg (89%) of a 7:3:1 mixture of hydroxamic acids **14a**:**15a**:**16a** as an orange solid. Recrystallization from EtOAc and hexanes provided *anti*-1,2-product (**14a**) as a white solid: mp 87−88 °C; IR (TF) 3127, 2764, 2675, 1562, 1474, 1421, 1242, 1187, 933, 725; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.98 (s, 3H), 2.43 (d, J = 6.9 Hz, 2H), 3.45 (m, 1H), 4.88 (m, 1H), 4.96 (d, J = 9.6 Hz, 1H), 5.05 (d, J = 17.4 Hz, 1H), 5.58 (d, J = 4.5 Hz, 1H), 5.72 (m, 1H), 5.79 (dd, J = 7.2, 9.9 Hz, 1H), 9.58 (s, 1H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.99 (s, 3H), 2.43 (bs, 2H), 3.44 (m, 1H), 4.88 (dm, J = 7.5 Hz, 1H), 4.96 (d, J = 9.5 Hz, 1H), 5.05 (d, J = 17.0 Hz, 1H), 5.58 (dm, J = 4.5 Hz, 1H), 5.72 (m, 1H), 5.78 (m, 1H), 9.60 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.77, 34.04, 50.59, 59.63, 114.67, 129.43, 131.80, 139.87, 170.50; HRMS (FAB) calcd for $C_9H_{13}NO_2$ (M + H)$^+$ 168.1025, found 168.1036.

***Anti*-1,4-product (15a):** ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75 (ddd, J = 4.8, 8.7, 13.2 Hz, 1H), 1.96 (s, 1H), 2.04 (ddd, J = 4.8, 8.4, 13.2 Hz, 1H), 3.44 (bm, 1H), 4.92 (dm, J = 9.9 Hz, 1H), 5.03 (dm, J = 17.1 Hz, 1H), 5.50 (bs, 1H), 5.59 (m, 1H), 5.71 (m, 1H), 5.86 (dm, J = 5.4 Hz, 1H), 9.39 (s, 1H

1,2-*anti*-Hydroxamic Acid (14b). A solution of butyllithium (0.43 mL, 2.3 M) in THF was added over the course of 10 min to a suspension of CuI (94 mg, 0.491 mmol) in THF (3 mL) at 0 °C. The resulting dark mixture was stirred for 30 min and then treated with a solution of *N*-phenylacetyl cycloadduct **2b**[11] (105 mg, 0.489 mmol) in THF (3 mL). After the mixture was stirred for 30 min at 0 °C, the ice bath was removed, and the mixture was stirred at room temperature for 45 min. The reaction mixture was partitioned between a saturated solution of NH_4Cl and ethyl acetate, and the organic phase was washed with the NH_4Cl solution, a saturated solution of Na_2EDTA, and brine. The combined aqueous layers were extracted with ethyl acetate, and the combined organics were dried with Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel; eluted with hexanes−ethyl acetate, 2:1) provided 97 mg (73%) of a 2:1 mixture of hydroxamic acids **14b**:**15b** as an oil. Chromatography (silica gel; eluted with 1% AcOH, 1%MeOH−CH_2Cl_2) provided *anti*-1,2-product (**14b**) as an oil: IR (TF) 3176, 2960, 2921, 2862, 1597, 1494, 1450, 1268, 1234, 1175, 1032 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (t, J = 6.3 Hz, 3H), 1.23 (m, 6H), 2.41 (bd, J = 6.9 Hz, 2H), 2.77 (m, 1H), 3.66 (d, J = 14.7 Hz, 1H), 3.76 (d, J = 15 Hz, 1H), 4.75 (dd, J = 7.2 Hz, 1H), 5.63 (s, 2H), 7.25 (m, 5H), 9.64 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.87, 22.25, 28.93, 33.44, 34.31, 38.80, 46.93, 59.65, 126.16, 128.03, 128.10, 129.30, 133.54, 135.94, 170.66; HRMS (FAB) calcd for $C_{17}H_{24}NO_2$ (M + H)$^+$ 274.1808, found 274.1827.

***Anti*-1,4-product (15b):** ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 6.6 Hz, 1H), 1.26 (m, 6H), 1.59 (m, 1H), 1.97 (ddd, J = 4.2, 8.1, 13.2 Hz, 1H), 2.76 (bs, 1H), 3.68 (s, 2H), 5.49 (m, 2H), 5.94 (m, 1H), 7.24 (m, 5H), 9.46 (s, 1H).). HRMS (FAB) calcd for $C_{17}H_{23}NO_2$ (M + H)$^+$ 274.1807, found 274.1807.

1,2-*anti*-Hydroxamic Acid (14c). A solution of *N*-phenylacetyl cycloadduct **2b**[11] (106 mg, 0.493 mmol) in THF (2 mL) was cooled to 0 °C in an ice bath and treated with $CuCl_2$ (7 mg, 0.0528 mmol). The resulting mixture was slowly treated with a 1 M solution of phenylmagnesium bromide (1.0 mL, 1.0 mmol) in THF over the course of 15 min and stirred under argon for 1 h. The mixture was diluted with EtOAc and washed with 1 M HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with a saturated solution of Na_2EDTA, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (silica gel; eluted with 3% MeOH−CH_2Cl_2) provided 140 mg

(96%) of a 1.9:1.6:1 mixture of hydroxamic acids **14c**:**15c**:**16c** as an oil. Chromatography (silica gel; eluted with 5% EtOAc−CH_2Cl_2) followed by recrystallization from EtOAc−hexanes provided **14c** as a white solid: mp 123−124 °C; IR (TF) 3153, 3061, 3030, 2885, 1600, 1494, 1453, 1236, 1176, 1031, 699; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.53 (m, 2H), 3.67 (d, J = 15.3 Hz, 1H), 3.77 (d, J = 15.9 Hz, 1H), 4.03 (m, 1H), 4.96 (dd, J = 7.5 Hz, 1H), 5.73 (dm, J = 5.7 Hz, 1H), 5.88 (dm, J = 6.3 Hz, 1H), 7.18 (m, 5H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.43, 38.82, 52.02, 63.09, 126.18, 126.29, 127.10, 128.03, 128.33, 129.31, 129.83, 132.60, 135.76, 143.55, 171.03; HRMS (FAB) calcd for $C_{19}H_{20}NO_2$ (M + H)$^+$ 294.1494, found 294.1483.

***Anti*-1,4-product (15c):** ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88 (ddd, J = 5.1, 8.1, 13.5 Hz, 1H), 2.35 (ddd, J = 4.2, 8.7, 12.9 Hz, 1H), 3.73 (s, 2H), 4.07 (bm, 1H), 5.67 (bm, 1H), 5.74 (m, 1H), 6.02 (m, 1H), 7.24 (m, 10H), 9.65 (s, 1H). HRMS (FAB) calcd for $C_{19}H_{19}NO_2$ (M + H)$^+$ 294.1494, found 294.1489.

***Syn*-1,4-product (16c):** ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.73 (overlapping ddd, J = 7.8, 7.8, 12.9 Hz, 1H), 2.58 (overlapping ddd, J = 8.1, 8.1, 12.3 Hz, 1H), 3.73 (s, 2H), 3.80 (m, 1H), 5.59 (bm, 1H), 5.74 (m, 1H), 5.90 (m, 1H), 7.24 (m, 10H), 9.67 (s, 1H).

1,2-*anti*-Hydroxamic Acid (14d). A solution of *N*-Boc cycloadduct **2c**[11] (140 mg, 0.711 mmol) in THF (2 mL) was cooled to 0 °C in an ice bath and treated with $CuCl_2$ (10 mg, 0.0758 mmol). The resulting mixture was slowly treated with a 1 M solution of vinylmagnesium bromide (1.0 mL, 1.0 mmol) in THF over the course of 15 min and stirred under argon for 1 h. The mixture was diluted with EtOAc and washed with 1 M HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with a saturated solution of Na_2EDTA, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (silica gel; eluted with 1% MeOH−CH_2Cl_2) provided 114 mg (71%) of a 8.4:3:1 mixture of hydroxamic acids **14d**:**15d**:**16d** as an oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (s, 9H), 2.43 (dm, J = 8.1 Hz, 2H), 3.43 (m, 1H), 4.46 (dd, J = 8.1 Hz, 1H), 5.01 (m, 2H), 5.67 (m, 3H), 9.10 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.95, 34.02, 50.55, 63.82, 79.52, 114.68, 129.37, 131.75, 140.17, 155.78.

1,2-*anti*-Hydroxamic Acid (14e). A mixture of freshly ground magnesium (253 mg, 10.4 mmol) and a catalytic amount of $HgCl_2$ in THF (6.7 mL) was treated with bromoethane (0.5 mL, 6.70 mmol) and refluxed in an oil bath (50 °C) for 20 min. The resulting gray mixture was allowed to cool to room temperature. A mixture of *N*-Boc cycloadduct **2c**[11] (102 mg, 0.516 mmol) and $CuCl_2$ (7 mg, 0.084 mmol) in diethyl ether (2 mL) was cooled in an ice bath and slowly treated with the freshly prepared ethylmagnesium bromide (0.8 mL, 0.8 mmol) over the course of 15 min. After stirring in the ice bath for 1 h, the reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with a saturated solution of Na_2EDTA, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (silica gel; eluted with hexanes−ethyl acetate, 2:1) provided 110 mg (93%) of an 18:2:1 ratio of hydroxamic acids **14e**:**15e**:**16e** as a clear oil. Chromatography (silica gel; eluted with 3% MeOH−CH_2Cl_2) provided 1,2-anti product (**14e**) as an oil: IR (TF) 3225, 2966, 2932, 16.94, 1456, 1368, 1250, 1165, 1110, 865, 757, 712 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, J = 7.5 Hz, 3H), 1.34 (m, 2H), 1.40 (s, 9H), 2.40 (d, J = 8.1 Hz, 2H), 2.71 (m, 1H), 4.34 (q, J = 7.5 Hz, 1H), 5.60 (s, 2H), 8.98 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.25, 26.05, 28.01, 34.32, 48.13, 62.57, 79.30, 128.22, 133.07, 155.54; HRMS (FAB) calcd for $C_{12}H_{22}NO_3$ (M + H)$^+$ 228.1601, found 228.1612.

1,2-*anti*-Hydroxamic Acid (14f). A solution of *N*-Boc cycloadduct **2c**[11] (101 mg, 0.512 mmol) in THF (2 mL) was cooled to 0 °C in an ice bath and treated with $CuCl_2$ (8 mg, 0.0565 mmol). The resulting mixture was slowly treated with a 1 M solution of phenylmagnesium bromide (1.0 mL, 1.0 mmol) in THF over the course of 15 min and stirred under argon for 1 h. The mixture was diluted with EtOAc and washed with 1 M HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with a saturated solution of Na_2EDTA, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (silica gel; eluted with hexanes−ethyl acetate, 2:1) provided 70 mg (50%) of a 3.5:1 mixture of hydroxamic acids **14f**:**15f** as an oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (s, 9H), 2.53 (dm, J = 7.2 Hz, 2H), 3.98 (m, 1H), 4.55 (dd, J = 8.1 Hz, 1H), 5.65 (m, 1H), 5.84 (m, 1H), 7.22 (m, 5H), 9.23 (s, 1H); HRMS (FAB) calcd for $C_{16}H_{21}NO_3$ (M + H)$^+$ 276.15997, found 276.15933.

3-Phenoxybenzyl Bromide (21). A solution of CBr_4 (1.09 g, 3.28 mmol) in THF (17 mL) was cooled to 0 °C in an ice bath and treated with 3-phenoxybenzyl alcohol (0.44 mL, 2.52 mmol). The resulting mixture was slowly treated with a solution of PPh_3 in THF (8 mL) over the course of 5 min and stirred under argon at 0 °C for 1 h and at room temperature for 20 h. The mixture was concentrated under reduced pressure. Flash chromatography (silica gel; eluted with 100% hexanes to hexanes−ethyl acetate, 1:1) provided 452 mg (68%) of 3-phenoxybenzyl bromide (**21**) as an oil: IR (TF) 3039, 1584, 1487, 1445, 1258, 1220, 1162, 959, 886, 778, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (s, 2H), 6.96 (m, 1H), 7.05 (m, 3H), 7.16 (m, 2H), 7.35 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.87, 118.55, 119.07, 119.13, 123.57, 123.65, 129.81, 130.05, 139.55, 156.66, 157.55; HRMS (FAB) calcd for $C_{13}H_{12}BrO$ (M + H)$^+$ 168.1025, found 168.1036.

***N*-Hydroxycarbamate 19.** A mixture of freshly ground magnesium (105 mg, 4.33 mmol) and a catalytic amount of $HgCl_2$ in diethyl ether (1 mL) was treated with a solution of bromide **21** (518 mg, 1.97 mmol) in diethyl ether (3 mL) and refluxed in an oil bath (50 °C) for 30 min. A mixture of *N*-methyl carbamate cycloadduct **2d**[11] (119 mg, 0.766 mmol) and $CuCl_2$ (11 mg, 0.084 mmol) in diethyl ether (2.5 mL) was cooled in an ice bath and treated with the Grignard reagent (2.0 mL, 0.983 mmol). After stirring in the ice bath for 1.5 h, the reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with a saturated solution of Na_2EDTA, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (silica gel; eluted with hexanes−ethyl acetate, 2:1) provided 88 mg (34%) of *anti*-1,2-product **19a** as a clear oil, as well as 68 mg (26%) of a 1:4:1 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-hydroxamic acid products (**19**) as a clear oil. *anti*-1,2-product **19a**: IR (TF) 3272, 3061, 2921, 1695, 1582, 1487, 1447, 1340, 1252, 1109, 946, 755, 692 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (m, 2H), 2.52 (dd, J = 8.4, 13.5 Hz, 1H), 2.75 (dd, J = 6.0, 13.5 Hz, 1H), 3.10 (m, 1H), 3.56 (s, 3H), 4.43 (m, 1H), 5.49 (dm, J = 2.1, 6.3 Hz, 1H), 5.60 (dm, J = 2.1, 6.3 Hz, 1H), 6.80 (dm, J = 7.5 Hz, 1H), 6.86 (m, 1H), 6.97 (m, 3H), 7.10 (tm, J = 7.2 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.36 (m, 2H), 9.27 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (m, 1H), 2.60 (m, 1H), 2.62 (dd, J = 8.7, 13.5 Hz, 1H), 2.82 (dd, J = 6.0, 13.5 Hz, 1H), 3.29 (dm, J = 6.3 Hz, 1H), 3.68 (s, 3H), 4.47 (q, J = 7.5 Hz, 1H), 5.58 (m, 1H), 5.67 (m, 1H), 6.83−7.35 (m, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.10, 38.78, 48.10, 52.33, 62.48, 116.30, 118.28, 119.52, 123.15, 124.38, 128.75, 129.64, 129.95, 132.45, 142.15, 156.29, 156.83, 156.90; ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.45, 39.85, 48.51, 53.30, 63.39, 116.58, 118.62, 119.71, 123.03, 124.06, 128.66, 129.43, 129.67, 132.59, 142.09, 157.04, 157.38, 157.56; HRMS (FAB) calcd for $C_{20}H_{22}NO_4$ (M + H)$^+$ 340.1549, found 340.1546.

***Anti*-1,4-product 19b:** ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67 (ddd, J = 4.8, 8.7, 13.5 Hz, 1H), 1.90 (ddd, J = 4.5, 8.1, 13.2 Hz, 1H), 2.51 (dd, J = 7.8, 13.2 Hz, 1H), 2.64 (dd, J = 6.9, 13.2 Hz, 1H), 3.03 (m, 1H), 3.58 (s, 3H), 5.05 (m, 1H), 5.55 (m, 1H), 5.83 (m, 1H), 6.83 (m, 2H), 6.97 (dm, J = 7.5 Hz, 3H), 7.11 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.36 (m, 2H).

5-LO Inhibition Testing Procedure.[22] Human peripheral blood mononuclear cells were isolated through a Ficoll-Paque density gradient. Compound **19a** (10 μM) was incubated with A 23187 (30 μM)-stimulated human peripheral blood mononuclear ($\approx 5 \times 10^6$ cells/mL) in HBBS for 15 min at 37 °C. Following neutralization with NaOH and centrifugation, the supernatant LTB_4 was measured using an EIA kit (Assay Design Inc.).

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Supporting Information Available: NMR data for products **14a**−**c**, **14e**, **21**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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