A Stereoselective Intramolecular 1,3-Dipolar Nitrone Cycloaddition for the Synthesis of Substituted Chromanes

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A stereoselective intramolecular 1,3-dipolar nitrone cycloaddition useful in the synthesis of chromanes is described. The reaction relies on the use of a chiral auxiliary on the nitrone partner. Key to the success of the reaction is the choice of auxiliary and the choice of Lewis acid catalyst. Utilizing an auxiliary with a pendant coordinating group, and $Zn(OTf)_2$ as the Lewis acid, diastereoselectivities up to 22:1 could be achieved.

Introduction

Chromane **1** (commercially available from Bionet Research Ltd.) was one of a number of compounds which showed modest antibacterial activity against *S. aureus* in a whole-cell screen of Pharmacia's compound collection. Since **1** possesses an interesting structure with a number of handles available for further modification, we undertook the design of an enantioselective synthesis to provide access to the core template. Retrosynthetic analysis led to the design of a route based on an intramolecular dipolar nitrone cycloaddition where the stereochemistry would be established in the cycloaddition step (Scheme 1). The objective of this work is to develop an effective method to produce the requisite chromane ring system[1] via a stereoselective intramolecular 1,3-dipolar nitrone cycloaddition reaction.

Preparation of enantiopure 3-hydroxymethyl chromanes was first reported[1b] in 1996. However, this methodology provided diastereoselectivities of only 3:2, and separation of the diastereomers was difficult. In addition, the chiral auxiliary could not be removed selectively. To circumvent these problems, we elected to utilize a chiral auxiliary with a pendant coordinating group, such as a *β*-hydroxy group, which would restrict rotation around the carbon−nitrogen single bond via intramolecular chelation to the nitrone oxygen (Figure 1). In practice, stereoselectivity would be achieved by coordination of a Lewis acid to both the nitrone oxygen and the *β*-oxygen of the chiral auxiliary, which would result in a six-membered chairlike chelate (*Z*-nitrone preferred[2]), where the phenyl group would adopt an axial orientation to avoid an eclipsing interaction with the nitrone C=N bond. Thus, the axial phenyl group would effectively shield the top face of the nitrone from the approach of the dipolarphile (**A** preferred over **B**).

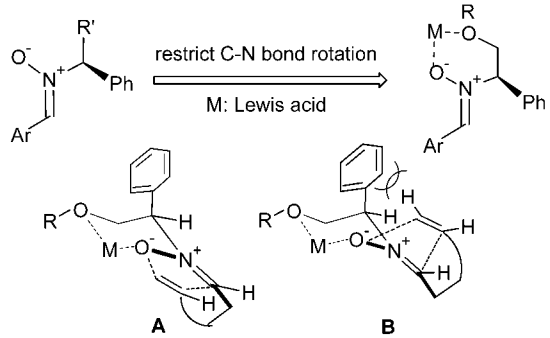
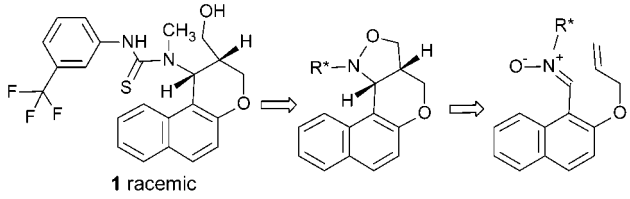
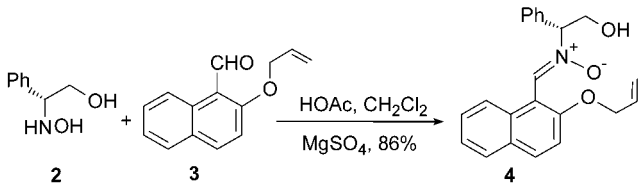


Figure 1. Design of chiral auxiliary.

Scheme 1



Scheme 2



Results and Discussion

The requisite nitrones were prepared by condensation of chiral N-hydroxyamines (e.g. **2**)[3] with 2-allyloxy-1-naphthaldehyde (Scheme 2). The addition of 5 mol % glacial acetic acid was found to be necessary in order for reaction to occur.

Subjection of each nitrone to refluxing in CH_2Cl_2 led to desired cyclized products as a mixture of two diastereomers (Scheme 3) in good yields. The stereochemistry

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(1) (a) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A.; Albinati, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1711. (b) Broggini, G.; Folcio, F.; Sardone, N.; Sonzogni, M.; Zeechi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 797.

(2) (a) Jennings, W. B.; Boyd, D. R.; Waring, L. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 610. (b) Bjorgo, J.; Boyd, D. R.; Neill, D. C. *J. Chem. Soc., Chem. Commun.* **1974**, 478.

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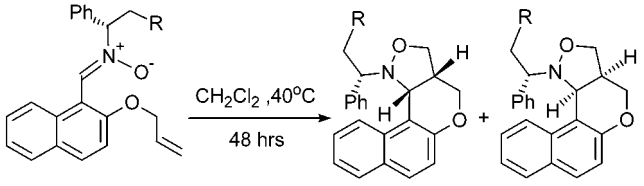
Scheme 3



4, R = OH — **8**, 82% (X-ray) — **9**, 12% (X-ray)
5, R = OBn — **10**, 54% (X-ray) — **11**, 40%
6, R = OMe — **12**, 53% (X-ray) — **13**, 40%
7, R = H — **14**[1], 51% — **15**[1], 42%

Table 1. Role of Protic Acid in the Nitrone Cyclization (4 to 8 and 9)

entry	conditions[a]	time (h)	yield, %	ratio[b] (**8**:**9**)
1	2 equiv of $ZnCl_2$	48	92	5:1
2	2 equiv of $ZnCl_2$[c]	48	95	6:1
3	2 equiv of $ZnCl_2$[d]	96	90	9:1

[a] Experiments at 40 °C in CH_2Cl_2 unless otherwise noted; $ZnCl_2$ was dried by heating to 400 °C in a stream of N_2; isolated overall yield. [b] Ratio determined from HPLC. [c] 5 equiv of 2,6-di-*tert*-butylpyridine was added. [d] 5 equiv of Et_3N was added.

of the cyclized products was determined by X-ray crystallography and ^1H NMR analysis, and by comparison to literature data[1] (for **14** and **15**). It was very encouraging that a selectivity of ~7:1 was observed under the thermal conditions in the case where R was a free hydroxyl group (**4**). It was also noteworthy that the *O*-benzyl and *O*-methyl substituted nitrones exhibited no selectivity under the thermal conditions.

Next, the effect of Lewis acid on the diastereoselectivity was explored. Thus, anhydrous $ZnCl_2$ was added to each solution of nitrone in CH_2Cl_2 at 40 °C (Table 1). As expected, nitrone **4** afforded the same cyclized products as under the thermal conditions, but unfortunately, a similar diastereoselectivity was obtained (Table 1, entry 1). Next, addition of a proton sponge to sop up adventitious acid was investigated. Thus, 2,6-di-*tert*-butylpyridine (entry 2) was added to the solution of nitrone and $ZnCl_2$ in refluxing CH_2Cl_2, and a slight increase in selectivity from 5:1 to 6:1 was observed. A further improvement (9:1) in stereoselectivity was observed when 5 eq. of Et_3N was added (entry 3).

The effect of altering the reaction solvent (CH_2Cl_2, PhH, $CHCl_3$, Et_2O, THF, and CH_3CN) was then explored. The reaction occurred more quickly in polar solvents (Et_2O, THF, and CH_3CN), but it proceeded with poorer selectivity (3−5:1). In terms of achieving selectivity with a reasonable rate of reaction, methylene chloride seemed to be the solvent of choice for this reaction.

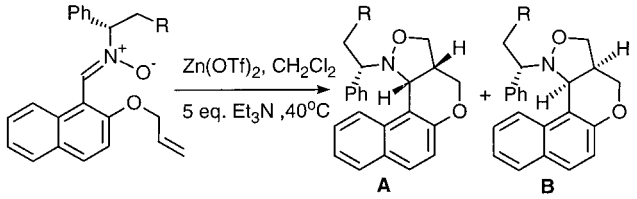
To further improve the reaction selectivity, the choice of Lewis acid was also extensively surveyed (Table 2, entries 1−7). A strong Lewis acid such as Et_2AlCl led only to decomposition products. The use of either Bu_2BOTf or $TiCl_4$ afforded cyclized products, but with poor stereoselectivity. The use of a weaker Lewis acid such as $Ti(OiPr)_4$ resulted in a sluggish reaction with poor stereoselectivity. Improvements in stereoselectivity were obtained with $Cu(OTf)_2$ and $Yb(OTf)_3$, but the reactions were slow. Of the Lewis acids surveyed at this point, only $MgCl_2$ and $ZnCl_2$ gave good conversions and good selectivities (9:1). Therefore, we focused on further exploration of a variety of zinc and magnesium containing Lewis acids with differing counterions (Table 2, entries 8−12). The same trends were observed for both zinc and

Table 2. Lewis Acid Effected Nitrone Cyclization (4 to 8 and 9)

entry	Lewis acid[a]	time (h)	yield, %	ratio[b] (**8**:**9**)
1	$EtAlCl_2$[c]	6	0	N/A
2	Bu_2BOTf[d]	36	90	2:1
3	$TiCl_4$	36	72	3:2
4	$Ti(OiPr)_4$	96	*e*	3:1
5	$Cu(OTf)_2$	96	*e*	16:1
6	$Yb(OTf)_3$	96	*e*	10:1
7	$MgCl_2$	96	73	9:1
8	$MgBr_2$	82	61	15:1
9	$Mg(OTf)_2$	66	93	20:1
10	$ZnCl_2$	96	90	9:1
11	$ZnBr_2$	82	93	12:1
12	$Zn(OTf)_2$	68	92	22:1

[a] Experiments at 40 °C in CH_2Cl_2 with 5 equiv of Et_3N unless otherwise noted; isolated overall yield. [b] Ratio determined from HPLC. [c] No Et_3N added. [d] 1 equiv of Et_3N added. [e] Conversions were in the 5−10% range as determined by HPLC.

Table 3



R	nitrones	time (h)	yield, %[a]	ratio[b] (**A**:**B**)
OH	**4**	72	93	22:1 (**8**:**9**)
OBn	**5**	72	93	7:1 (**10**:**11**)
OMe	**6**	72	90	10:1 (**12**:**13**)
H	**7**	36	92	3:2 (**14**:**15**)[1]

[a] Isolated overall yield. [b] Ratio determined from HPLC.

magnesium containing Lewis acids. Going from Cl^- to Br^- to OTf^- resulted in increases in both reaction rate and selectivity. It seemed that weakly coordinated counterions afforded better selectivity and faster reaction to the point where the use of $Zn(OTf)_2$ afforded a 92% yield of the desired cyclized product in a 22:1 ratio!

To further support the proposed bidentate chelation of the Lewis acid, the nitrone β-alkoxy functionality on the nitrone was varied while keeping the Lewis acid constant as $Zn(OTf)_2$ (Table 3). As anticipated, removal of the hydroxyl group on the chiral auxiliary as in nitrone **7** led to erosion of stereoselectivity (3:2). While OBn and OMe β-substituted nitrones (**5** and **6**) afforded reasonably good selectivities (7−10:1), by far the best selectivity was observed when the β-functionality was a free hydroxy group (22:1).

Both of the observed products from this cycloaddition are derived from exo-cycloaddition of the dipolarphile to the nitrone. Stereoselectivity is achieved by controlling approach of the dipolarophile to the nitrone from either the top or the bottom face (Figure 2). In this case, we hypothesize that the Lewis acid coordinates to both the nitrone oxygen and the β-oxygen of the auxiliary to afford a chairlike chelate. (footnote: The phenyl group adopts axial orientation to avoid eclipsing interaction with nitrone C═N bond. There is no 1,3-diaxial interaction that would disfavor the orientation of the axial phenyl group.) Thus, approach of the olefin from the top face would result in severe steric interactions with the axial phenyl group. Therefore, the approach of the dipolarophile from the bottom face is preferred since this results in only a slight steric interaction with the counterion of

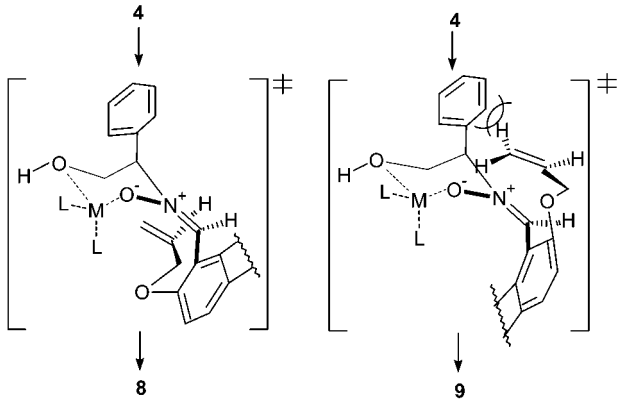
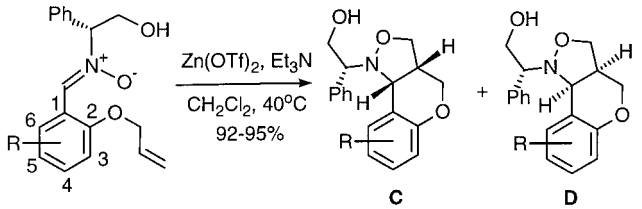


Figure 2. Rationale for diastereoselectivity.

Table 4



R	nitrones	time (h)	yield[a]	ratio[b] (**C**:**D**)
H	**16**	72	92	16:1 (**21**:**22**)
5-nitro	**17**	66	95	18:1 (**23**:**24**)
4,6-dichloro	**18**	24	91	20:1(**25**:**26**)
5-methoxy	**19**	72	90	16:1 (**27**:**28**)
4-methoxy	**20**	72	0	N/A

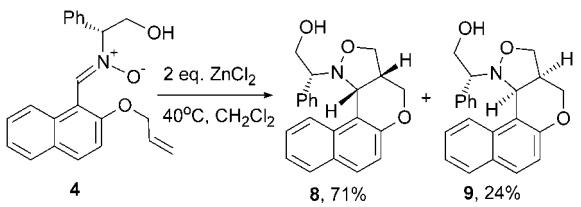
[a] Isolated overall yield. [b] Ratio determined from HPLC.

the Lewis acid, leading to the major product observed in this reaction.

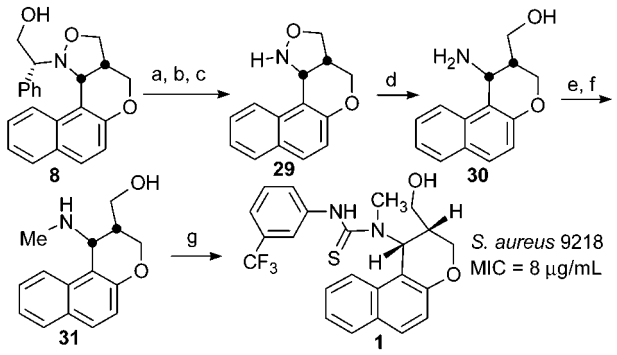
To expand this methodology further, a series of nitrones derived from substituted aromatic substrates was investigated (Table 4). As anticipated when substitution on the ring was tolerated, it did not substantially affect the yield or stereoselectivity. In one case, when R was 4-methoxy, only starting material was recovered. Pushing the reaction to elevated temperature (110 °C) caused decomposition of the nitrone and 3,3-sigmatropic rearrangement of the phenyl allyl ether. Thus it appears that placement of electron-donating substituents on the phenyl ring is not tolerated. Likewise, judicious placement of electron-withdrawing substituents, such as the 4,6-dichloro-substituted substrate, facilitates the rate of this 1,3-dipolar nitrone cycloaddition.

It is noteworthy that the reaction of 1,3-dipolar nitrone cycloaddition effected by Lewis acids is slower than the thermal reaction. For cycloadditions of nitrones, interactions of either $HOMO_{nitrone}-LUMO_{alkene}$ or $LUMO_{nitrone}-HOMO_{alkene}$ can occur.[4] $HOMO_{nitrone}-LUMO_{alkene}$ interaction dominates in most cases, especially when the dipolarphile is an electron-deficient alkene. However, coordination of a Lewis acid to the nitrone could lower $LUMO_{nitrone}$ so that the reaction might be controlled by the $LUMO_{nitrone}-HOMO_{alkene}$ interaction. This hypothesis is supported by the fact that the reaction effected by weakly coordinated Lewis acids was faster (OTf^- vs Cl^- and Br^-). It is also supported by the observation that the Lewis acid effected reaction was faster with electron-withdrawing substituents on the phenyl of the nitrone (4,6-dichloro vs H, 5-nitro, and 5-methoxy), while the presence of an electron-donating substituent such as 4-methoxy on the phenyl nitrone shut down the reaction completely.

Scheme 4



Scheme 5[a]



[a] Reagents: (a) MsCl, Et_3N, CH_2Cl_2; (b) ^{t}BuOK, ^{t}BuOH, 40 °C; (c) 3 N HCl, THF, 85% for three steps; (d) Zn dust, HOAc, 55 °C, THF, H_2O, 89%; (e) $ClCO_2Me$, Et_3N, THF; (f) $LiAlH_4$, THF, reflux, 86% for two steps; (g) α,α,α-trifluoro-*m*-tolyl isothiocyanate, THF, 92%.

The target molecule was synthesized by removal of the chiral auxiliary on nitrogen in a three-step sequence (mesylation, elimination, and hydrolysis[5]) affording **29** as shown in Scheme 4, followed by reductive cleavage[6] of the N−O bond and N-methylation to produce **31**. Treatment of **31** with α,α,α -trifluoro-*m*-tolyl isothiocyanate afforded **1**.

Conclusion

A novel method was developed for stereoselective intramolecular 1,3-dipolar nitrone cycloadditions. The good diastereoselectivity observed in the nitrone cycloaddition reaction facilitated by Lewis acids $Mg(OTf)_2$ or $Zn(OTf)_2$ and Et_3N could be explained by the proposed metal-chelated nitrone complex. The synthesis of enantiomerically pure chromane **1** was completed utilizing this methodology.

Experimental Section

General. Proton and carbon magnetic resonance spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz or 400 and 100 MHz, respectively, and are reported in ppm on the δ scale. Infrared spectra, mass spectra, optical rotation values, and combustion analyses were determined by Structural and Analytical Chemistry, Pharmacia Corp. Anhydrous THF and Et_2O were distilled prior to use from sodium metal/benzophenone ketyl. Dry benzene and acetonitrile were purchased from Aldrich in Sure-Seal bottles. CH_2Cl_2 and Et_3N were distilled from calcium hydride prior to use. $CHCl_3$ was passed through activated alumina and distilled from P_2O_5. Unless otherwise noted, all nonaqueous reactions were carried out under a nitrogen atmosphere using oven-dried glassware.

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General Procedure for Preparation of Nitrones. (2*R*)-2-[(*Z*)-{[2-(Allyloxy)-1-naphthyl]methylene}(oxido)amino]-2-phenylethanol (4). To a solution of *N*-hydroxyamine **2** (153 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added 2-allyloxy-1-naphthaldehyde (233 mg, 1.1 mmol), glacial acetic acid (0.003 mL), and $MgSO_4$ (140 mg). The mixture was stirred at room temperature for 5 h. The mixture was filtered at room temperature and washed with CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution, H_2O, and brine. The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (33% ethyl acetate in hexanes) afforded nitrone **4** (300 mg, 86%) as a white solid: R_f 0.3 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −28.5 (*c* 0.778, CH_2Cl_2); IR (thin film) 3295, 1591, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (1 H, s), 7.9 (d, 1 H, J = 9 Hz), 7.79 (d, 1H, J = 8.1 Hz), 7.64−7.35 (m, 8H), 7.24 (d, 1H, J = 9 Hz), 6.0 (m, 1H), 5.4−5.25 (m, 3H), 4.68 (dd, 2H, J = 4, 1.5 Hz), 4.59 (dd, 1H, J = 12, 9 Hz), 4.02 (dd, 1H, J = 12, 3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.63, 135.33, 133.62, 132.95, 132.37, 131.09, 129.11, 129.04, 128.89, 128.37, 127.75, 127.22, 124.97, 124.21, 117.97, 113.86, 112.6, 79.07, 77.26, 70.05, 64.3; HRMS HRMS (FAB) *m/e* 348.1589 ($C_{22}H_{21}NO_3$ + H requires 348.1599). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06%; H, 6.09%; N, 4.03%. Found: C, 75.69%; H, 6.21%; N, 4.00%.

(*Z*)-{[2-(Allyloxy)-1-naphthyl]methylene}[(1*R*)-2-(benzyloxy)-1-phenylethyl]azane oxide (5): 85% yield; R_f 0.46 (40% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −23.6 (*c* 0.63, CH_2Cl_2); IR (thin film) 3088, 1591, 1509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.84 (d, 1H, J = 9 Hz), 7.75 (d, 1H, J = 7.5 Hz), 7.72−7.6 (m, 4H), 7.45−7.2 (m, 9H), 7.19 (d, 1H, J = 9 Hz), 5.92 (m, 1H), 5.4 (dd, 1H, J = 9, 3 Hz), 5.3 (dd, 1H, J = 16, 1.5 Hz), 5.17 (d, 1H, J = 10.5 Hz), 4.82 (A of ABq, J_{AB}=12 Hz), 4.75−4.5 (m, 4H), 3.9 (dd, 1H, J = 10, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.78, 138.02, 135.03, 133.13, 131.96, 131.66, 131.11, 128.98, 128.91, 128.67, 128.47, 128.08, 128.03, 127.83, 127.76, 126.88, 125.91, 124.02, 117.27, 113.95, 113.5478.7, 73.73, 69.97, 69.94; HRMS (FAB) *m/e* 438.2080 ($C_{29}H_{27}NO_3$ + H requires 438.2069). Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.61%; H, 6.22%; N, 3.20%. Found: C, 79.19%; H, 6.43%; N, 3.20%.

(*Z*)-{[2-(Allyloxy)-1-naphthyl]methylene}[(1*R*)-2-methoxy-1-phenylethyl]azane oxide (6): 86% yield; R_f 0.38 (40% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −19.2 (*c* 0.68, CH_2Cl_2); IR (thin film) 1608, 1598, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 (d, 1H, J = 9 Hz), 7.75 (d, 1H, J = 8.2 Hz), 7.72−7.6 (m, 2H), 7.57 (d, 1H, J = 8.4 Hz), 7.48 (dd, 1H, J = 6.6, 1 Hz), 7.45−7.3 (m, 4H), 7.18 (d, 1H, J = 9 Hz), 5.96 (m, 1H), 5.4−5.26 (m, 2H), 5.21 (dd, 1H, J = 10.5, 2 Hz), 4.7−4.5 (m, 3H), 3.81 (dd, 1H, J = 10, 3.6 Hz), 3.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.78, 135.05, 133.17, 132, 131.6, 131.09, 129, 128.91, 128.69, 128.1, 128.04, 126.92, 125.83, 124, 117.25, 113.92, 113.49, 78.5, 72.04, 69.95, 59.28; HRMS (FAB) *m/e* 362.1751 ($C_{22}H_{23}NO_3$ + H requires 362.1756).

(2*R*)-2-[(*Z*)-[2-(Allyloxy)benzylidene](oxido)amino]-2-phenylethanol (16): 85% yield; R_f 0.38 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −27.2 (*c* 0.78, CH_2Cl_2); IR (thin film) 3395, 1595, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.3 (d, 1H, J = 8 Hz), 8.02 (s, 1H), 7.6−7.3 (m, 6H), 7.02 (t, 1H, J = 8.2 Hz), 6.86 (d, 1H, J = 8 Hz), 6.02 (m, 1H), 5.4−5.1 (m, 3H), 4.7−4.4 (m, 3H), 4.0 (dd, 1H, J = 12, 3 Hz), 4.78 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.63, 135.8, 133.08, 133.03, 132.27, 131.4, 130.37, 129.51, 129.24, 128.82, 121.22, 120.3, 119.3, 111.87, 80.91, 77.87, 69.26, 64.79; HRMS (FAB) *m/e* 298.1441 ($C_{18}H_{19}NO_3$ + H requires 298.1443). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71%; H, 6.44%; N, 4.71%. Found: C, 72.33%; H, 6.44%; N, 4.74%.

(2*R*)-2-[(*Z*)-[2-(Allyloxy)-5-nitrobenzylidene](oxido)amino]-2-phenylethanol (17): 89% yield; R_f 0.28 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −31.2 (*c* 0.75, CH_2Cl_2); IR (thin film) 3347, 1608, 1574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.1 (d, 1H, J = 3 Hz), 8.2 (dd, 1H, J = 9, 3 Hz), 7.89 (s, 1H), 7.55−7.2 (m, 5 H), 6.8 (d, 1H, J = 9 Hz), 5.93 (m, 1H), 5.35−5.2 (m, 2H), 5.15 (dd, 1H, J = 9, 3 Hz), 4.65−4.5 (m, 2H), 3.86 (dd, 1H, J = 12, 3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.51, 141.52, 135.22, 131.68, 129.61, 129.25, 128.95, 127.9, 127.6, 124.67, 120.24, 119.6, 111.19, 81.58, 77.76, 77.44, 69.63, 64.07; HRMS (FAB) *m/e* 343.1289 ($C_{18}H_{18}N_2O_5$ + H requires 343.1294).

(2*R*)-2-[(*Z*)-[2-(Allyloxy)-4,6-dichlorobenzylidene](oxido)amino]-2-phenylethanol (18): 88% yield; R_f 0.56 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −21.2 (*c* 0.65, CH_2Cl_2); IR (thin film) 3392, 1570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, 1H, J = 3 Hz), 7.82 (s, 1H), 7.49−7.3 (m, 6 H), 5.89 (m, 1H), 5.4−5.1 (m, 3H), 4.6 (dd, 1H, J = 12, 9 Hz), 4.42 (A of ABX, 1H, J_{AB} = 12 Hz, J_{AX} = 6 Hz), 4.3 (B of ABX, 1H, J_{AB} = 12 Hz, J_{BX} = 6 Hz), 3.91 (dd, 1H, J = 12, 3 Hz), 3.8 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.05, 136.27, 133.66, 131.59, 131.09, 130.61, 129.84, 129.15, 128.48, 127.67, 127.08, 121.05, 82.83, 78.98, 78.67, 77.1, 65.94; HRMS (FAB) *m/e* 366.0667 ($C_{18}H_{17}NO_3Cl_2$ + H requires 366.0663). Anal. Calcd for $C_{18}H_{17}NO_3Cl_2$: C, 59.03%; H, 4.68%; N, 3.82%; Cl, 19.36%. Found: C, 59.89%; H, 5.06%; N, 3.62%; Cl, 17.61%.

(2*R*)-2-[(*Z*)-[2-(Allyloxy)-5-methoxybenzylidene](oxido)amino]-2-phenylethanol (19): 85% yield; R_f 0.34 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −18.8 (*c* 0.68, CH_2Cl_2); IR (thin film) 3225, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, 1H, J = 3 Hz), 7.91 (s, 1H), 7.49−7.42 (m, 5 H), 6.84 (dd, 1H, J = 9, 3 Hz), 6.71 (d, 1H, J = 9 Hz), 5.85 (m, 1H), 5.2−5.1 (m, 3 H), 4.69 (dd, 1 H, J = 9.2, 9 Hz), 4.38 (m, 2H), 3.92 (dd, 1H, J = 9.4, 3 Hz), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.74, 151.47, 135.46, 133.21, 132.76, 129.53, 128.1, 120.1, 119.62, 118.1, 113.37, 113.17, 80.53, 77.65, 70.4, 68.6, 56.22; HRMS (FAB) *m/e* 328.1552 ($C_{18}H_{21}NO_4$ + H requires 328.1548).

(2*R*)-2-[(*Z*)-[2-(Allyloxy)-4-methoxybenzylidene](oxido)amino]-2-phenylethanol (20): 89% yield; R_f 0.35 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −25.5 (*c* 0.88, CH_2Cl_2); IR (thin film) 3100, 1601, 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, 1H, J = 9 Hz), 8.2 (s, 1H), 7.55−7.52 (m, 2H), 7.36−7.34 (m, 3H), 6.49 (dd, 1H, J = 9, 2.4 Hz), 6.31 (d, 1H, J = 2.4 Hz), 5.9 (m, 1H), 5.54 (dd, 1H, J = 9, 3 Hz), 5.23−5.18 (m, 3H), 4.64 (dd, 1H, J = 12, 9 Hz), 4.45 (d, 2H, J = 4 Hz), 4.17 (dd, 1H, J = 12, 3 Hz), 3.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 160.67, 141.2, 134.56, 132.38, 129.77, 129.49, 128.71, 118.64, 110.94, 106.09, 99.58, 79.04, 77.65, 69.86, 69.61, 63.08, 56.12; HRMS (FAB) *m/e* 328.1553 ($C_{18}H_{21}NO_4$ + H requires 328.1548).

General Procedure for Cyclization of Nitrones. (2*R*)-2-((3a*S*,11c*R*)-3a,11c-Dihydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (8). $Zn(OTf)_2$ (363 mg, 1 mmol) was added to a solution of **4** (173 mg, 0.5 mmol) and Et_3N (0.35 mL, 2.5 mmol) in CH_2Cl_2 (3 mL). The reaction was then heated to 40 °C and stirred for 68 h. The reaction was then analyzed by HPLC, and the ratio of products was determined. The reaction was then diluted with CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2, and the organic phases were combined, dried (Na_2SO_4), and concentrated. Purification via flash chromatography (50% ethyl acetate in hexanes) afforded **8** (156 mg, 89%) and **9** (6 mg, 3%): R_f 0.56 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −32.6 (*c* 0.69, CH_2Cl_2); IR (thin film) 3592, 1599, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, J = 9 Hz), 7.63 (d, 1H, J = 9 Hz), 7.6−7.48 (m, 5H), 7.27 (t, 1H, J = 7.8 Hz), 7.14 (t, 1H, J = 7.8 Hz), 7.01 (d, 1H, J = 9 Hz), 6.96 (d, 1H, J = 9 Hz), 4.87 (d, 1H, J = 8 Hz), 4.6 (dd, 1H, J = 9.6, 7.8 Hz), 4.4−4.2 (m, 3H), 4.12 (dd, 1H, J = 6.6, 3.6 Hz), 4.06 (dd, 1H, J = 11, 2 Hz), 3.9 (m, 1H), 3.58 (m, 1H), 2.9 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.67, 137.43, 132.49, 129.99, 129.76, 129.24, 128.93, 128.31, 125.62, 124.13, 123.54, 118.55, 114.37, 68.84, 68.3, 67.07, 65.5, 58.96, 41.17; HRMS (FAB) *m/e* 348.1597 ($C_{22}H_{21}NO_3$ + H requires 348.1599). Anal. Calcd $C_{22}H_{21}NO_3$: C, 76.06%; H, 6.09%; N, 4.03%. Found: C, 74.44%; H, 6.05%; N, 3.96%. Single crystals of **8** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **8** (complete crystallographic data can be found in the Supporting Information).

(2*R*)-2-((3a*R*,11c*S*)-3a,11c-Dihydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (9): R_f 0.38 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −26.6 (*c* 0.75, CH_2Cl_2); IR (thin film) 3418, 1600, 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 9 Hz), 7.78 (d, 1H, J = 7.8 Hz), 7.68 (d, 1H, J = 9 Hz), 7.58 (td, 1H, J = 7.2, 1.5 Hz), 7.52−7.3 (m, 6H), 7.02 (d, 1H, J = 9 Hz), 5.13 (d, 1H, J = 8.1 Hz), 4.27−4.2

(m, 2H), 4.05 (dd, 1H, J = 10, 3 Hz), 3.96 (dd, 1H, J = 10, 3 Hz), 3.91 (d, 1H, J = 7.2 Hz), 3.72 (m, 1H), 2.87 (br, 1H), 2.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.18, 137.64, 133.24, 130.14, 129.96, 129.31, 128.82, 128.78, 128.66, 126.49, 123.76, 123.68, 118.72, 114.73, 71.86, 69.72, 64.11, 63.96, 59.31, 41.62; HRMS (FAB) *m/e* 348.1591 ($C_{22}H_{21}NO_3$ + H requires 348.1599). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06%; H, 6.09%; N, 4.03%. Found: C, 75.71%; H, 6.08%; N, 4.02%. Single crystals of **9** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **9** (complete crystallographic data can be found in the Supporting Information).

(2*R*)-2-((3a*S*,9b*R*)-8-Methoxy-3a,9b-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (27): R_f 0.45 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −19.5 (*c* 0.72, CH_2Cl_2); IR (thin film) 3505, 1499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.25 (m, 5H), 6.66−6.57 (m, 2H), 6.53 (d, 1H, J = 3 Hz), 5.42 (dd, 1H, J = 9.6, 6 Hz), 4.15−4.05 (m, 4H), 3.97−3.91 (m, 2H), 3.69 (m, 1H), 3.63 (s, 3H), 3.17 (m, 1H), 3.07 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.54, 150.36, 138.79, 130.35, 129.53, 129.38, 129.33, 129.06, 128.78, 127.87, 123.53, 118.28, 117.97, 115.7, 114.05, 69.85, 68.64, 68.51, 65.38, 61.21, 55.86, 40.39; HRMS (FAB) *m/e* 328.1551 ($C_{18}H_{21}NO_4$ + H requires 328.1548). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71%; H, 6.47%; N, 4.28%. Found: C, 68.74%; H, 6.44%; N, 4.29%. Single crystals of **27** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **27** (complete crystallographic data can be found in the Supporting Information).

(2*R*)-2-((3a*R*,9b*S*)-8-Methoxy-3a,9b-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (28): R_f 0.58 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −21.5 (*c* 0.76, CH_2Cl_2); IR (thin film) 3584, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6−7.5 (m, 2H), 7.45−7.35 (m, 3H), 6.9−6.75 (m, 3H), 4.2−4.02 (m, 3H), 4.01 (m, 2H), 3.97 (t, H, J = 7.7 Hz), 3.81 (s, 3H), 3.78−3.68 (m, 2H), 2.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.93, 149.5, 136.22, 130.01, 128.64, 128.41, 121.45, 117.92, 115.13, 69.37, 68.1, 65.51, 64.13, 58.28, 55.77, 40.71; HRMS (FAB) *m/e* 328.1546 ($C_{18}H_{21}NO_4$ + H requires 328.1548). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71%; H, 6.47%; N, 4.28%. Found: C, 68.75%; H, 6.48%; N, 4.22%.

(2*R*)-2-((3a*S*,9b*R*)-7,9-Dichloro-3a,9b-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (25): R_f 0.38 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −26.6 (*c* 0.86, CH_2Cl_2); IR (thin film) 3425, 1493 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.35 (m, 5H), 7.16 (d, 1H, J = 2 Hz), 6.96 (d, 1H, J = 2 Hz), 4.5 (dd,1 H, J = 9.6, 8.1 Hz), 4.38 (dd, 1H, J = 12, 2 Hz), 4.2−4.05 (m, 4H), 3.99 (dd, 1H, J = 6.6, 3.3 Hz), 3.76 (brd, 1H, J = 11 Hz), 3.28 (m, 1H), 2.96 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.42, 137.86, 129.39, 128.98, 128.93, 128.33, 128.27, 126.16, 125.51, 122.31, 69.45, 67.89, 65.58, 60.32, 53.51, 39.3; HRMS (FAB) *m/e* 366.0674 ($C_{18}H_{17}NO_3Cl_2$ + H requires 366.0663). Anal. Calcd for $C_{18}H_{17}NO_3Cl_2$: C, 59.03%; H, 4.68%; N, 3.82%; Cl, 19.36%. Found: C, 58.90%; H, 4.62%; N, 3.63%; Cl, 21.47%.

(2*R*)-2-((3a*R*,9b*S*)-7,9-Dichloro-3a,9b-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (26): R_f 0.58 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −33.6 (*c* 0.63, CH_2Cl_2); IR (thin film) 3429, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6−7.4 (m, 5H), 7.33 (d, 1H, J = 2 Hz), 7.23 (d, 1H, J = 2 Hz), 4.3−4.08 (m, 5H), 3.99 (t,1 H, J = 8 Hz), 3.85−3.75 (m, 2H), 2.6 (m, 1H), 2.65 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.43, 136.43, 130.11, 129.87, 129.21, 129.14, 128.99, 126.21, 124.22, 123.34, 77.62, 70.17, 68.31, 66.34, 64.7, 58.5, 40.53; HRMS (FAB) *m/e* 366.0657 ($C_{18}H_{17}NO_3Cl_2$ + H requires 366.0663). Anal. Calcd for $C_{18}H_{17}NO_3Cl_2$: C, 59.03%; H, 4.68%; N, 3.82%; Cl, 19.36%. Found: C, 59.79%; H, 4.90%; N, 3.71%; Cl, 21.47%.

(2*R*)-2-((3a*S*,9b*R*)-8-Nitro-3a,9b-dihydro-3*H*-chromeno-[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (23): R_f 0.36 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −26.1 (*c* 0.78, CH_2Cl_2); IR (thin film) 3551, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, 1H, J = 2 Hz), 7.92 (dd, 1H, J = 10, 8 Hz), 7.42 (d, 4H, J = 4 Hz), 7.33 (m, 1H), 6.79 (d, 1H, J = 8.8 Hz), 4.48 (dd, 1H, J = 8, 2 Hz), 4.3 (dd, 1H, J = 12, 2 Hz), 4.2 (d, 1H, J = 8 Hz), 4.15−4.1 (m, 2H), 4.05 (t,1 H, J = 6.8 Hz), 3.97 (dd, 1H, J = 7.2, 3.6 Hz), 3.72 (brd, 1H, J = 10 Hz), 3.28 (m, 1H), 2.81 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.18, 142.55, 138.13, 129.89, 129.42, 128.63, 127.12, 124.85, 123.62, 117.98, 77.63, 70.1, 68.41, 68.35, 65.69, 60.43, 39.34; HRMS (FAB) *m/e* 343.1301 ($C_{18}H_{18}N_2O_5$ + H requires 343.1294). Single crystals of **23** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **23** (complete crystallographic data can be found in the Supporting Information).

(2*R*)-2-((3a*R*,9b*S*)-8-Nitro-3a,9b-dihydro-3*H*-chromeno-[4,3-*c*]isoxazol-1(4*H*)-yl)-2-phenylethanol (24): R_f 0.55 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −35.2 (*c* 0.56, CH_2Cl_2); IR (thin film) 3551, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, J = 2 Hz), 8.04 (dd, 1H, J = 8, 2.8 Hz), 7.48 (d, 1H, J = 8 Hz), 7.47 (d, 1H, J = 8 Hz), 7.4−7.2 (m, 3H), 6.9 (d, 1H, J = 8.8 Hz), 4.25−4.05 (m, 5H), 3.98 (t, 1H, J = 8 Hz),), 3.8−3.6 (m, 2H), 2.68 (m, 1H), 2.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.02, 141.11, 135.43, 129.23, 128.34, 128.07, 126.63, 124.52, 120.29, 117.37, 76.67, 68.66, 67.08, 65.1, 93.91, 57.01, 38.66; HRMS (FAB) *m/e* 343.1293 ($C_{18}H_{18}N_2O_5$ + H requires 343.1294).

(2*R*)-2-((3a*S*,9b*R*)-3a,9b-Dihydro-3*H*-chromeno[4,3-*c*]-isoxazol-1(4*H*)-yl)-2-phenylethanol (21): R_f 0.35 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −31.5 (*c* 0.55, CH_2Cl_2); IR (thin film) 3437, 1608, 1586 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.35 (m, 6H), 7.2−7.05 (m, 2H), 6.92 (t, 1H, J = 7.5 Hz), 6.78 (d, 1H, J = 8 Hz), 4.5 (dd, 1H, J = 9.6, 7.8 Hz), 4.35−4.0 (m, 6H), 3.77 (brd, 1H, J = 9 Hz), 3.4−3.1 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 138.38, 129.93, 129.18, 128.67, 128.61, 128.35, 122.64, 121.84, 116.77, 69.33, 68.2, 68.09, 64.69, 60.46, 39.74; HRMS (FAB) *m/e* 298.1436 ($C_{18}H_{19}NO_3$ + H requires 298.1443). Single crystals of **21** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **21** (complete crystallographic data can be found in the Supporting Information).

(2*R*)-2-((3a*R*,9b*S*)-3a,9b-Dihydro-3*H*-chromeno[4,3-*c*]-isoxazol-1(4*H*)-yl)-2-phenylethanol (22): R_f 0.46 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −25.5 (*c* 0.65, CH_2Cl_2); IR (thin film) 3295, 1610, 1582 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6−7.5 (m, 2H), 7.45−7.5 (m, 6H), 6.98 (t, 1H, J = 7.5 Hz), 6.89 (d, 1H, J = 8.5 Hz), 4.25−4.05 (m, 5H), 3.95 (t, 1H, J = 7.8 Hz), 3.76−3.67 (m, 2H), 2.78 (br, 1H), 2.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.34, 136.1, 130.61, 130.18, 129.28, 128.62, 128.39, 121.32, 120.58, 117.29, 69.2, 67.98, 65.27, 64.03, 57.75, 40.34; HRMS (FAB) *m/e* 298.1440 ($C_{18}H_{19}NO_3$ + H requires 298.1443). Single crystals of **22** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **22** (complete crystallographic data can be found in the Supporting Information).

(3a*S*,11c*R*)-1-[(1*R*)-2-Methoxy-1-phenylethyl]-1,3a,4,-11c-tetrahydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazole (12): R_f 0.45 (40% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −32.6 (*c* 0.69, CH_2Cl_2); IR (thin film) 1599, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 7.6 Hz), 7.7−7.5 (m, 6H), 7.31 (t, 1H, J = 7.6 Hz), 7.16 (t, 1H, J = 8 Hz), 7.07 (d, 1H, J = 8 Hz), 6.98 (d, 1H, J = 8 Hz), 4.91 (d, 1H, J = 8 Hz), 4.54 (dd, 1H, J = 9.5, 8 Hz), 4.35−4.25 (m, 2H), 4.21 (dd, 1H, J = 8, 4.8 Hz), 4.1−4.0 (m, 2H), 3.92 (dd, 1H, J = 9.6, 8 Hz), 3.54 (m, 1H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.18, 138.96, 133.08, 130.43, 130.0, 128.98, 128.88, 128.78, 127.33, 125.43, 123.86, 118.98, 115.35, 77.81, 74.94, 68.73, 67.96, 66.35, 59.5, 58.08, 41.54; HRMS (FAB) *m/e* 362.1756 ($C_{22}H_{23}NO_3$ + H requires 362.1756). Single crystals of **12** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **12** (complete crystallographic data can be found in the Supporting Information).

(3a*R*,11c*S*)-1-[(1*R*)-2-Methoxy-1-phenylethyl]-1,3a,4,-11c-tetrahydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazole (13): R_f 0.66 (40% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −32.6 (*c* 0.69, CH_2Cl_2); IR (thin film) 1599, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 1H, J = 8 Hz), 7.8 (d, 1H, J = 7.8 Hz), 7.69 (d, 1H, J = 8.8 Hz), 7.58 (t, 1H, J = 8 Hz), 7.5−7.38 (m, 3H), 7.36−7.25 (m, 3H), 7.05 (d, 1H, J = 8 Hz), 5.69 (d, 1H, J

= 8 Hz), 4.35 (dd, 1H, *J* = 8.5, 3.5 Hz), 4.3 (dd, 1H, *J* = 12, 2 Hz), 4.2−4.1 (m, 5H), 4.04 (t, 1H, *J* = 7 Hz), 3.7 (dd, 1H, *J* = 8.5, 3 Hz), 3.52 (s, 3H), 3.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.36, 139.61, 133.8, 130.67, 129.95, 128.93, 128.84, 128.37, 128.16, 126.31, 124.47, 123.82, 119.11, 115.93, 77.68, 76.86, 68.38, 68.27, 65.7, 59.47, 59.37, 41.81; HRMS (FAB) *m/e* 362.1759 ($C_{22}H_{23}NO_3$ + H requires 362.1756).

(3a*S*,11c*R*)-1-[(1*R*)-2-(Benzyloxy)-1-phenylethyl]-1,3a,4,-11c-tetrahydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazole (10): R_f 0.57 (40% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −16.7 (*c* 0.87, CH_2Cl_2); IR (thin film) 1598, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J* = 8 Hz), 7.6 (d, 1H, *J* = 9 Hz), 7.6−7.56 (m, 4H), 7.4−7.2 (m, 7H), 7.1 (t, 1H, *J* = 8 Hz), 7.02 (d, 1H, *J* = 10 Hz), 6.85 (d, 1H, *J* = 8.5 Hz), 4.89 (d, 1H, *J* = 8 Hz), 4.6−4.4 (m, 3H), 4.38−4.1 (m, 4H), 4.04 (dd, 1H, *J* = 11, 2 Hz), 3.95 (dd, 1H, *J* = 9, 7.5 Hz), 3.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.75, 138.61, 138.23, 132.63, 130.08, 130.01, 129.61, 128.83, 128.71, 128.34, 128.22, 127.81, 127.62, 125.67, 124.13, 123.44,118.55, 114.9, 73.45, 42.29, 68.4, 37.83, 65.98, 58.41, 41.18; HRMS (FAB) *m/e* 438.2062 ($C_{29}H_{27}NO_3$ + H requires 438.2069). Single crystals of **10** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 CH_2Cl_2/hexanes solution of **10** (complete crystallographic data can be found in the Supporting Information).

(3a*R*,11c*S*)-1-[(1*R*)-2-(Benzyloxy)-1-phenylethyl]-1,3a,4,-11c-tetrahydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazole (11): R_f 0.62 (40% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −23.5 (*c* 0.91, CH_2Cl_2); IR (thin film) 3088, 1598, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 1H, *J* = 8.5 Hz), 7.79 (d, 1H, *J* = 8 Hz), 7.69 (d, 1H, *J* = 8.8 Hz), 7.48 (dd, 1H, *J* = 8, 4.8 Hz), 7.41−7.28 (m, 11H), 7.04 (d, 1H, *J* = 8 Hz), 5.72 (d, 1H, *J* = 8 Hz), 4.73 (A of ABq, J_{AB}=12 Hz, ΔV_{AB} = 40 Hz), 4.62 (B of ABq, J_{AB}=12 Hz, ΔV_{AB} = 40 Hz), 4.38 (dd, 1H, *J* = 8, 3 Hz), 4.35−4.2 (m, 2H), 4.2−4.1 (m, 2H), 4.03 (t, 1H, *J* = 7 Hz), 3.8 (dd, 1H, *J* = 8, 3 Hz), 3.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.54, 138.99, 137.23, 133.01, 129.89, 129.22, 128.19, 128.14, 128.08, 127.73, 127.65, 127.58, 127.38, 125.64, 123.82, 123.09, 118.33, 115.1, 76.91, 73.77, 73.53, 67.85, 67.48, 64.84, 58.69, 41.02; HRMS (FAB) *m/e* 438.2060 ($C_{29}H_{27}NO_3$ + H requires 438.2069). Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.61%; H, 6.22%; N, 3.20%. Found: C, 78.67%; H, 6.42%; N, 3.15%.

(3a*S*,11c*R*)-1,3a,4,11c-Tetrahydro-3*H*-benzo[5,6]-chromeno[4,3-*c*]isoxazole (29). To a solution of **8** (347 mg, 1 mmol) and methanesulfonyl chloride (0.085 mL, 1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise Et_3N (0.16 mL, 1.2 mmol). The solution was allowed to stir at room temperature for 3 h, solvent was removed via rotoevaporator, and the residue was dissolved in 10 mL of anhydrous *t*BuOH followed by addition of KH (200 mg, 5 mmol). The solution was then heated to 40 °C and stirred for 18 h. Et_2O (10 mL) and H_2O were added to the reaction mixture, and the aqueous phase was extracted with Et_2O. The organic phase was dried (Na_2SO_4) and concentrated. The residue was dissolved in THF (10 mL), and 5 mL of 3 M HCl was added. The reaction was allowed to stir for 6 h. Saturated Na_2CO_3 solution (10 mL) and Et_2O were added successively. Phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (20% ethyl acetate in hexanes) afforded **29** (184 mg, 85% yield) as a colorless oil: R_f 0.35 (34% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −27.7 (*c* 0.43, CH_2Cl_2); IR (thin film) 3057, 1621, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1H, *J* = 8 Hz), 7.78 (d, 1H, *J* = 8 Hz), 7.75 (d, 1H, *J* = 8 Hz), 7.56 (t, 1H, *J* = 8 Hz), 7.41 (t, 1H, *J* = 8 Hz), 7.14 (d, 1H, *J* = 8 Hz), 4.7 (d, 1H, *J* = 6 Hz), 4.46 (t, 1H, *J* = 8 Hz), 4.36 (dd, 1H, *J* = 11, 5 Hz), 3.82 (t, 1H, *J* = 11 Hz), 3.8−3.7 (m, 2H), 3.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 134.44, 130.68, 129.67, 128.58, 127.57, 124.56, 124.47, 118.85, 110.98, 77.62, 65.26, 55.99, 39.88; HRMS (FAB) *m/e* 228.1027 ($C_{14}H_{13}NO_2$ + H requires 228.1024).

[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-benzo[*f*]chromen-2-yl]methanol (30). A solution of **29** (108 mg, 0.5 mmol) in glacial acetic acid (3 mL), THF (1.5 mL), and H_2O (1.5 mL) was preheated to 55 °C. Zinc dust (163 mg, 2.5 mmol) was added to the above solution. The reaction was stirred at 55 °C, and an additional amount of zinc was added until starting material disappeared. The reaction was cooled to room temperature, and saturated Na_2CO_3 solution and Et_2O were added successively. Phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (5% CH_2Cl_2 in MeOH) afforded **30** (101 mg, 92% yield) as a colorless oil: R_f 0.25 (10% CH_2Cl_2 in MeOH); $[\alpha]^{23}_D$ −32.3 (*c* 0.33, CH_2Cl_2); IR (thin film) 3357, 1622, 1586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H, *J* = 8 Hz), 7.8 (d, 1H, *J* = 8 Hz), 7.69 (d, 1H, *J* = 8 Hz), 7.55 (t, 1H, *J* = 8 Hz), 7.38 (t, 1H, *J* = 8 Hz), 7.05 (d, 1H, *J* = 8 Hz), 4.73 (d, 1H, *J* = 4 Hz), 4.45−4.3 (m, 2H), 4.23 (dd, 1H, *J* = 9, 3 Hz), 3.97 (dd, 1H, *J* = 9, 5 Hz), 2.9 (br, 3H), 2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.33, 131.71, 129.46, 129.2, 128.89, 126.94, 123.3, 120.96, 119.06, 117.23, 77.12, 63.39, 44.9, 37.89; HRMS (FAB) *m/e* 230.1177 ($C_{14}H_{15}NO_2$ + H requires 230.1181).

[(1*R*,2*R*)-1-(Methylamino)-2,3-dihydro-1*H*-benzo[*f*]-chromen-2-yl]methanol (31). To a solution of **30** (90 mg, 0.41 mmol) and Et_3N (0.06 mL, 0.45 mmol) in THF (5 mL) at 0 °C was added methyl chloroformate (0.035 mL, 0.45 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. $LiAlH_4$ (1.5 mL, 1 M in THF) was then added, and the reaction mixture was heated to reflux and stirred for 4 h. The mixture was cooled to room temperature, Et_2O and H_2O were added to the reaction mixture, and the aqueous phase was extracted with Et_2O. The combined organic phase was dried (Na_2SO_4) and concentrated. Purification by flash chromatography (40% ethyl acetate in hexanes) afforded **31** (84 mg, 88% yield) as a colorless oil: R_f 0.27 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −11.5 (*c* 0.62, CH_2Cl_2); IR (thin film) 3400, 1622 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 1H, *J* = 8 Hz), 7.7 (d, 1H, *J* = 8 Hz), 7.6 (d, 1H, *J* = 8 Hz), 7.45 (t, 1H, *J* = 8 Hz), 7.28 (t, 1H, *J* = 8 Hz), 6.98 (d, 1H, *J* = 8 Hz), 4.44 (t, 1H, *J* = 12 Hz), 4.4−4.3 (m, 2H), 4.15 (dd, 1H, *J* = 9, 3 Hz), 3.9 (dd, 1H, *J* = 9, 3 Hz), 2.62 (s, 3H), 2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.56, 132.96, 130.25, 129.51, 129.27, 127.27, 123.73, 122.0, 119.63, 115.9, 77.64, 68.57, 67.25, 60.81, 54.01, 38.85, 37.44; HRMS (FAB) *m/e* 244.1337 ($C_{15}H_{17}NO_2$ + H requires 244.1337).

***N*-[(1*R*,2*R*)-2-(Hydroxymethyl)-2,3-dihydro-1*H*-benzo-[*f*]chromen-1-yl]-*N*-methyl-*N*′-[3-(trifluoromethyl)phenyl]-thiourea (1).** To a solution of **31** (50 mg, 0.21 mmol) in THF (2 mL) at room temperature was added α,α,α-trifluoro-*m*-tolyl isothiocyanate (47 mg, 0.23 mmol). The reaction was stirred for 15 h and then concentrated. Flash chromatography (40% ethyl acetate in hexanes) afforded **1** (87 mg, 95% yield) as a colorless oil: R_f 0.35 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −36.9 (*c* 0.26, CH_2Cl_2); IR (thin film) 3279, 1626 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 9.7 (s, 1H), 8.09 (d, 1H, *J* = 8 Hz), 7.9−7.8 (m, 2H), 7.8−7.8 (m, 2H), 7.59 (t, 1H, *J* = 8 Hz), 7.55−7.45 (m, 2H), 7.38 (t, 1H, *J* = 8 Hz), 7.26 (d, 1H, *J* = 6 Hz), 7.16 (d, 1H, *J* = 8 Hz), 4.7 (t, 1H, *J* = 5 Hz), 4.49 (dd, 1H, *J* = 8, 5 Hz), 4.3−4.2 (m, 2H), 3.46 (m, 1H), 2.56 (m, 1H), 2.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 182.9, 154.8, 142.56, 133.7, 131.4, 131.1, 129.9, 129.7, 129.4, 128.1, 214.5, 123.7, 122.1, 119.8, 112.3, 65.6, 59.3, 52.7, 41.6, 36.6, 34.1, 23.5, 15.6; HRMS (FAB) *m/e* 447.1351 ($C_{23}H_{21}F_3N_2O_2S$ + H requires 447.1354).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**, **5**, **6**, **8**, **10**, **11**, **12**, **13**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, and **31.** X-ray crystal structures and tables of supporting data for compounds **8**, **9**, **10**, **12**, **21**, **22**, **23**, and **27**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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