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Domino Elimination/Nucleophilic Addition in the Synthesis of Chiral Pyrrolidines

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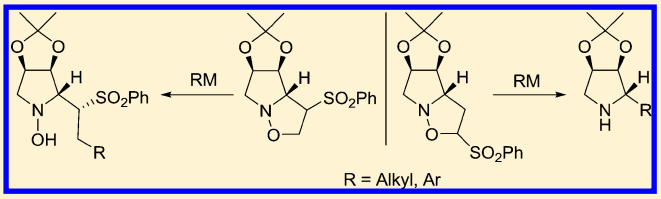
Supporting Information

ABSTRACT: Polyhydroxylated pyrrolidines have been synthesized in a one-pot procedure by the addition of an organometallic reagent to isoxazolidines obtained by a 1,3-dipolar cycloaddition between nitrones and vinylsulfones. This method highlights sulfone reactivity and provides an easy approach for the preparation of chiral pyrrolidines using cyclic imines as key intermediates.



INTRODUCTION

Polyhydroxylated pyrrolidines are among the most active glycosidase inhibitors. They display either glycosidase-[1] or glycosyltransferase-inhibition activity.[2] Therefore, these compounds could be used as tools in the treatment of cancer,[3] diabetes,[4] and infectious diseases.[5]

In Figure 1, several representative polyhydroxylated pyrrolidines are depicted. DAB-1 (1,4-dideoxy-1,4-imino-D-arabinitol), **1**, has been isolated from *Angylocalyx boutiqueanus*[6] and shows a potent inhibition of glycogen phosphorylase.[7] DIM (1,4-dideoxy-1,4-imino-D-mannitol), **2**, is an effective α-mannosidase inhibitor,[8] and several authors have reported on its synthesis.[9] (−)-Anisomycin, **3**, is a peptidyl-transferase inhibitor with activity against protozoa and fungi.[10] The biological activity of the latter has caught the interest of many synthetic chemists.[11] Recently, a review on the synthesis of pyrrolidine-containing iminosugars has been published[12] in which substitution reactions and organometallic additions to nitrones and cyclic imines were the most used methods, including the harnessing of sulfone-group reactivity. Domino reactions are highly appealing for the synthesis of biologically active compounds[13,14] because they enable the formation of elaborated products in a step-economy manner with the avoidance of the often tedious isolation of synthesis intermediates. In this regard, we have developed a method for the synthesis of chiral polyhydroxylated pyrrolidines by means of a domino elimination/imine addition or elimination/Michael addition,[15] which is herein documented.

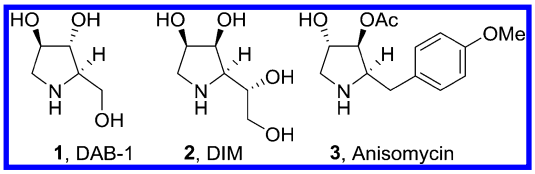


Figure 1. Biologically active polyhydroxylated pyrrolidines.

RESULTS AND DISCUSSION

1,3-Dipolar cycloaddition is one of the most versatile reactions to date.[16] Many dipoles and dipolarophiles have been employed to obtain either carbocycles or heterocycles of biological importance. It is worth mentioning that nitrone dipoles have been successfully employed to produce aza-heterocycles such as chiral pyrrolidines,[17] pyrrolizidines, and indolizidines.[18] Nitrone **4** is a versatile starting material[19] that has been used for the synthesis of biologically active compounds and structurally complex molecules with a high degree of selectivity.[20] Recently, we reported the 1,3-dipolar cycloaddition of nitrone **4** with phenylvinylsulfone[21] (Scheme 1). In our case, four isoxazolidines, **5**−**8**, were obtained in good yield. The stereochemistry of the addition occurs anti with respect to the acetonide group. In the absence of additives, isoxazolidines **7** and **8** are obtained as the major regioisomeric system. However, the proportion of the pair **5**, **6** increases if a coordinating agent (HMPA) is present in the reaction.[21] Although several conditions were tested, no special endo/exo selectivity was observed, and only the ratios of the different isoxazolidines were slightly effected.

As shown in Scheme 1, there are two pairs of regiosiomeric isoxazolidines, **5**, **6** and **7**, **8**, that can be easily separated by chromatography. As illustrated below, each pair of regiosiomeric isoxazolidines displays different reactivity because of the position of the sulfone group.

First, we started to explore the reactivity of **5** and **6**. Tetrahydropiranylsulfones are known to stabilize an anion

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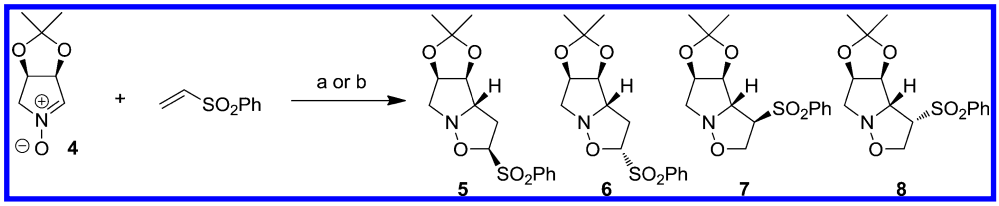
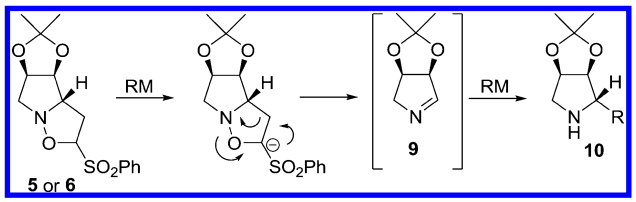
Scheme 1. 1,3-Dipolar Cycloaddition of Nitrone 4 with Phenylvinylsulfone[a]



[a]Conditions for a: $PhCH_3$, rt, 6 h, 98% combined yield, ratio of isoxazolidines **5**/**6**/**7**/**8**: 12/12/38/38. Conditions for b: $PhCH_3$, HMPA, rt, 24 h, 80% combined yield, ratio of isoxazolidines **5**/**6**/**7**/**8**: 31/19/23/27.

when they are treated with a base. These anionic intermediates have been employed in the synthesis of many spiroketal natural compounds by Ley et al.[22] via their reaction with an adequate electrophile, sulfone group loss, and treatment under acidic conditions. Herein, we envisioned that an organometallic reagent could behave as a base and nucleophile with these compounds, making it possible to perform a domino elimination/addition reaction, as shown in Scheme 2. Thus,

Scheme 2. Proposed Mechanism for the Reaction of Isoxazolidines 5 and 6 with an Organometallic Reagent



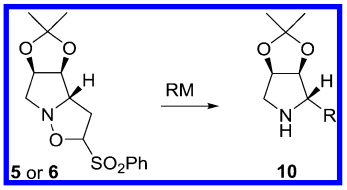
when **5** or **6** were treated with 3 equiv of an organometallic reagent, pyrroline **9** was formed in situ, which will subsequently undergo the addition of the organometallic reagent (Scheme 2).

Under similar conditions, isoxazolidines **5** and **6** led to the same pyrroline. For example, when **5** or **6** were treated individually with *n*-BuLi, pyrrolidine **10a** was obtained in excellent yield (94%) from both isoxazolidines (Table 1, entries 1 and 2). The addition of the organometallic species took place at the α-side because of the steric inherence of the acetonide group. Because we were encouraged by these results, we decided to test different organometallic compounds with both isoxazolidines **5** and **6**. In all cases, the protected dihydroxylated pyrrolidines were obtained in good yields (Table 1) and with excellent diastereoselectivity of >95%; no minor diastereoisomer was observed by ^{1}H NMR.

As can be seen in Table 1, pyrrolidines **10** were formed in higher yields when using less hindered bases (entries 1, 2 vs 3, 4). Grignard reagents also provided excellent yields (entries 5, 6), which exhibited a similar steric effect (entries 5, 6 vs 7, 8). When aromatic Grignards were employed, a reduction in the yield was observed (entries 9−12, 19, and 20) with no appreciable variations in the substitution pattern on the aromatic ring (entries 9−12, 19, and 20). However, the lithium derivative of the phenylvinylsulfone (entries 17, 18) afforded the product in acceptable yields considering the two consecutive steps that have occurred.

The configuration of the addition product was established as the enantiomer of compound **10e**, which has been previously reported by Davis et al.[23] Furthermore, derivative **10i** has been previously prepared by us[24] using another methodology.

Table 1. Synthesis of Dihydroxylated Pyrrolidines by Treatment of Isoxazolidines 5 and 6 with Organometallic Reagenst[a]



entry	SM	RM	product	yield (%)
1	**5**	*n*-BuLi	**10a**, R = *n*-Bu	94
2	**6**	*n*-BuLi	**10a**, R = *n*-Bu	94
3	**5**	*s*-BuLi	**10b**, R = *s*-Bu	55
4	**6**	*s*-BuLi	**10b**, R = *s*-Bu	67
5	**5**	allylMgBr	**10c**, R = allyl	90
6	**6**	allylMgBr	**10c**, R = allyl	91
7	**5**	2-methylallylMgBr	**10d**, R = 2-methylallyl	65
8	**6**	2-methylallylMgBr	**10d**, R = 2-methylallyl	68
9	**5**	PhMgBr	**10e**, R = Ph	72
10	**6**	PhMgBr	**10e**, R = Ph	70
11	**5**	*p*-FC_6H_4MgCl	**10f**, R = *p*-FC_6H_4	73
12	**6**	*p*-FC_6H_4MgCl	**10f**, R = *p*-FC_6H_4	75
13	**5**	2-NaphCH_2MgBr	**10g**, R = 2-NaphCH_2	78
14	**6**	2-NaphCH_2MgBr	**10g**, R = 2-NaphCH_2	80
15	**5**	BnMgCl	**10h**, R = Bn	70
16	**6**	BnMgCl	**10h**, R = Bn	70
17	**5**	$PhSO_2CH_2Li$	**10i**, R = CH_2SO_2Ph	48
18	**6**	$PhSO_2CH_2Li$	**10i**, R = CH_2SO_2Ph	45
19	**5**	*p*-$MeOC_6H_4CH_2MgCl$	**10j**, R = *p*-$MeOC_6H_4CH_2$	70
20	**6**	*p*-$MeOC_6H_4CH_2MgCl$	**10j**, R = *p*-$MeOC_6H_4CH_2$	70

[a]Isoxazolidine **5** or **6** (1 equiv) in THF (0.1 M). RM (3 equiv) was added at −78 °C, and the solution was stirred for 1 h.

To demonstrate the versatility of the procedure, isoxazolidines **5** and **6** were treated with the magnesium derivative of *p*-MeO-benzylchloride (Table 1, entries 19, 20). As expected, starting materials **5** and **6** both gave the same protected dihydroxylated pyrrolidine **10j** in good yield. Compound **10j** is the enantiomer of one described by Davis et al. in their synthesis of unnatural analogue 1-epidesacetylanisomycin.[23] They managed to prepare it by the addition of *p*-$MeOC_6H_4CH_2MgCl$ to the enantiomer of pyrroline **9**. In this manner, we corroborated the stereochemistry attained in the pyrrolidines, proving the usefulness of this new methodology for the synthesis of this kind of compound. As can be seen in Table 1, isoxazolidines **5** and **6** behave as masked cyclic imines (Δ^1 pyrrolines), which are compounds that have recently been an area of focused interest in the scientific community. They have been synthesized in a few ways,[25] including from nitrones[26] and oxazines,[27] by a Staudinger/aza-Wittig reac-

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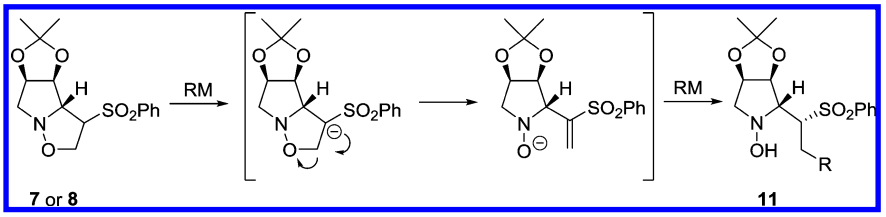
Scheme 3. Proposed Mechanism for the Reaction of Isoxazolidines 7 and 8 with an Organometallic Reagent



tion,[28] by the addition of an organometallic to an adequately functionalized nitrile,[29] by the elimination of an *N*-chloropyrrolidine derivative,[30] and by the biocatalytic oxidative desymmetrization of symmetric pyrrolidines using MAO-N.[31]

As shown earlier in Scheme 1, the 1,3-dipolar reaction between nitrone **4** and phenylvinylsulfone not only afforded isoxazolidines **5** and **6** but also resulted in the isolation of two regioisomeric isoxazolidines **7** and **8**. With the aim of exploiting the versatility of the sulfone group[32] in these compounds, **7** and **8** were also treated with an organometallic reagent. In this case, they led to the formation of hydroxylamines as expected and followed the proposed mechanism depicted in Scheme 3.

When isoxazolidines **7** and **8** were submitted to the same conditions as before, the expected hydroxylamines were obtained albeit in diminished yield (Table 2). This observation can be understood because of the competitive recyclization of the intermediate to afford the starting materials.

For this particular domino procedure, it was observed that a lower temperature resulted in a decreased yield (Table 2, entries 1, 2 vs 3, 4), which made 0 °C the temperature of choice. The employment of Grignard reagents proved beneficial in comparison to the use of lithium derivatives, allowing product formation in higher yields (entry 5 vs 6, 7). As noted before, the use of more-hindered bases led to a reduction of the yield (entries 1, 2 vs 8, 9). Aryl and benzyl organometallics are also allowed (entries 12−19), and different substituents on the aromatic ring showed no alteration in the reaction performance (entries 14, 15, 18, and 19). Furthermore, propargyl lithium derivatives behaved in the same manner, forming the desired hydroxylamine with similar efficacy (entry 20).

The stereochemistry of the sulfone group for compounds **11** was easily established by NMR on the basis of the NOE experiments and the corresponding coupling constants of H2, which was confirmed by X-ray analysis of compound **11f** (see the Supporting Information).

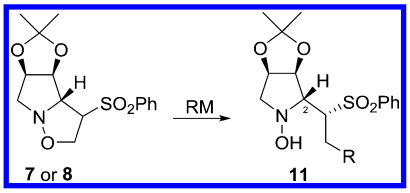
As depicted in Table 2, several highly functionalized polyhydroxylated pyrrolidines were prepared by means of this method, affording unique building blocks that could be used in further transformations. *N*-Hydroxylamines have been extensively transformed into their corresponding nitrones by oxidation[33] or pyrrolidines by reductive cleavage.[34] To extend the reactivity of these compounds, as an example we oxidized compound **11e** with MnO_2 to obtain compound **12** in high yield (Scheme 4).

In recent years, compounds with a nitrone and sulfone group have increased in interest for many chemists because of their applications.[35]

CONCLUSIONS

A new procedure involving a masked cyclic imine (Δ^1 pyrroline) has been developed, facilitating the addition reaction of organometallic reagents to nitrone compounds. This method affords highly functionalized pyrrolidines with complete diastereoselection; furthermore, a subsequent reduction step is avoided. The isoxazolidines derived from the 1,3-dipolar cycloaddition of a nitrone and a vinyl sulfone have been transformed into chiral polyhydroxylated pyrrolidines and hydroxylamines. This methodology can be considered an example of domino elimination/addition reactions for the diversity-oriented synthesis of chiral biologically active pyrrolidines.

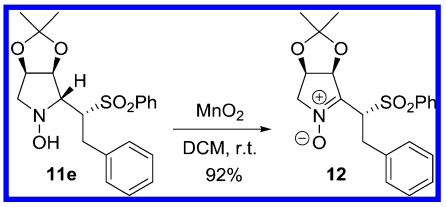
Table 2. Synthesis of Polyhydroxylated *N*-Hydroxypyrrolidines by Treatment of Isoxazolidines 7 and 8 with Organometallic Reagents[a]



entry	SM	RM	product	yield (%)
1	7	*n*-BuLi	**11a**, R = *n*-Bu	55
2	8	*n*-BuLi	**11a**, R = *n*-Bu	58
3[b]	7	*n*-BuLi	**11a**, R = *n*-Bu	42
4[b]	8	*n*-BuLi	**11a**, R = *n*-Bu	40
5	7	MeLi	**11b**, R = Me	60
6	7	MeMgBr	**11b**, R = Me	78
7	8	MeMgBr	**11b**, R = Me	74
8	7	*s*-BuLi	**11c**, R = *s*-Bu	35
9	8	*s*-BuLi	**11c**, R = *s*-Bu	35
10	7	2-MethylallylMgBr	**11d**, R = 2-Methylallyl	55
11	8	2-MethylallylMgBr	**11d**, R = 2-Methylallyl	55
12	7	PhMgBr	**11e**, R = Ph	50
13	8	PhMgBr	**11e**, R = Ph	52
14	7	*p*-FC_6H_4MgCl	**11f**, R = *p*-FC_6H_4	48
15	8	*p*-FC_6H_4MgCl	**11f**, R = *p*-FC_6H_4	50
16	7	BnMgCl	**11g**, R = Bn	45
17	8	BnMgCl	**11g**, R = Bn	42
18	7	*p*-$MeOC_6H_4CH_2MgCl$	**11h**, R = *p*-$MeOC_6H_4CH_2$	42
19	8	*p*-$MeOC_6H_4CH_2MgCl$	**11h**, R= *p*-$MeOC_6H_4CH_2$	40
20	8	$LiCCCH_2OTHP$	**11i**, R = $CCCH_2OTHP$	40

[a]Isoxazolidine **7** or **8** (1 equiv) in THF (0.1M). RM (3 equiv) was added at 0 °C, and the solution was stirred continued for 1 h. [b]The reaction was carried out at −78 °C.

Scheme 4



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EXPERIMENTAL SECTION

General Methods. Single crystal X-ray diffraction data for **12f** were collected at room temperature (see Supporting Information). NMR spectra were recorded on 200, 400, and 600 MHz spectrometers. The NMR peaks were assigned by taking into consideration HMQC, HSQC, COSY, NOESY, and ROESY experiments of compounds **10f**, **10i**, and **11a**. FTIR spectra were recorded as films. HRMS spectra were recorded with a Q-TOF apparatus using the electrospray ionization method.

Addition of Organometallic Reagents: Standard Procedure (Isoxazolidines 5 and 6). To a stirred solution of isoxazolidine **5** or **6** (1 equiv) in THF (0.1 M) was added dropwise RMg (Br or Cl) or RLi (3 equiv) at −78 °C. The solution was stirred at −78 °C for 1 h, and the mixture was allowed to warm slowly to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:9) to obtain pyrrolidines.

*(2S,3S,4R)-2-Butyl-3,4-isopropylidenedioxypyrrolidine (**10a**).* (a) To a stirred solution of isoxazolidine **5** (50 mg, 0.15 mmol) in 1.50 mL of THF was added dropwise a 1.6 M hexane solution of *n*-BuLi (0.30 mL, 0.45 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h, and the mixture was allowed to warm slowly to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford **10a** (28 mg, 94%): $[\alpha]_D^{20}$ −8.4 (*c* = 0.7, $CHCl_3$); IR (film) 3313, 2956, 2931, 2860, 1627, 1446, 1083, 867 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.63 (1H, t, *J* = 5.0 Hz), 4.33 (1H, d, *J* = 6.0 Hz), 3.02 (1H, dd, *J* = 7.4 and 13.6 Hz), 2.80 (1H, s), 2.78 (1H, dd, *J* = 4.4 and 13.6 Hz), 1.37 (3H, s), 1.32−1.14 (6H, m), 1.25 (3H, s), 0.87−0.85 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.9, 86.1, 81.9, 65.0, 51.9, 30.5, 29.2, 26.4, 24.1, 22.7, 14.2; HRMS (EI) $[M + H]^+$ calcd for $C_{11}H_{22}NO_2$, 200.1645; found, 200.1633. (b) Following the general procedures, 60 mg (0.18 mmol) of isoxazolidine **6**, 1.90 mL of THF, and 0.35 mL (0.55 mmol) of 1.6 M hexane solution of *n*-BuLi were used, affording **10a** (34 mg, 94%).

*(2S,3S,4R)-2-(1-Methylpropyl)-3,4-isopropylidenedioxypyrrolidine (**10b**).* (a) Following the general procedures, isoxazolidine **5** (59 mg, 0.18 mmol) in 1.80 mL of THF and a 1.4 M cyclohexane solution of *s*-BuLi (0.38 mL, 0.54 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:9) to obtain **10b** (40 mg, 55%): $[\alpha]_D^{20}$ −10.0 (*c* = 0.9, $CHCl_3$); IR (film) 2983, 2933, 1375, 1207, 1043, 813, 752 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.67−4.61 (1H, m), 4.47−4.42 (1H, m), 2.98−2.92 (2H, m), 2.85 (1H, d, *J* = 10.6 Hz), 1.48 (3H, s), 1.30−1.24 (3H, m), 1.32 (3H, s), 0.92−0.84 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 111.7, 84.8, 81.7, 60.8, 52.3, 35.6, 26.8, 26.7, 24.5, 16.3, 11.6; HRMS (EI) $[M + H]^+$ calcd for $C_{11}H_{22}NO_2$, 200.1645; found, 200.1644. (b) Following the general procedures, 75 mg (0.23 mmol) of isoxazolidine **6**, 2.30 mL of THF, and a 0.50 mL (0.69 mmol) of 1.4 M cyclohexane solution of *s*-BuLi were used, affording **10b** (30.5 mg, 67%).

*(2S,3S,4R)-2-Propenyl-3,4-isopropylidenedioxypyrrolidine (**10c**).* (a) Following the general procedures, isoxazolidine **5** (40 mg, 0.12 mmol) in 1.30 mL of THF and a 1.0 M Et_2O solution of allylMgBr (0.36 mL, 0.36 mmol) were used to afford **10c** (19.5 mg, 90%): $[\alpha]_D^{20}$ −14.9 (*c* = 1.0, $CHCl_3$); IR (film) 3396, 2980, 2931, 2854, 1375, 1261, 1083, 802 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.91−5.70 (1H, m), 5.18−5.05 (2H, m), 4.68 (1H, t, *J* = 4.8 Hz), 4.33 (1H, d, *J* = 6.0 Hz), 3.22 (1H, t, *J* = 8.0 Hz), 3.00 (1H, d, *J* = 13.2 Hz), 2.85 (1H, dd, *J* = 4.0 and 13.2 Hz), 2.20−2.04 (2H, m), 1.46 (3H, s), 1.30 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.5, 117.3, 111.1, 85.3, 81.9, 64.5, 51.9, 35.4, 26.5, 24.2; HRMS (EI) $[M + H]^+$ calcd for $C_{10}H_{18}NO_2$, 184.1332; found, 184.1321. (b) Following the general procedures, 30 mg (0.09 mmol) of isoxazolidine **6**, 1 mL of THF, and 0.28 mL (0.28 mmol) of a 1.0 M Et_2O solution of allylMgBr were used, affording **10c** (15 mg, 91%).

*(2S,3S,4R)-2-(2-Methylpropenyl)-3,4-isopropylidenedioxypyrrolidine (**10d**).* (a) Following the general procedures, isoxazolidine **5** (60 mg, 0.18 mmol) in 1.80 mL of THF and a 0.5 M THF solution of 2-methallylMgCl (1.10 mL, 0.54 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:9) to obtain **10d** (46 mg, 65%): $[\alpha]_D^{20}$ −16.5 (*c* = 0.8, $CHCl_3$); IR (film) 3396, 2980, 2931, 2854, 1375, 1261, 1083, 802 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.84 (1H, sa), 4.72 (1H, sa), 4.69 (1H, t, *J* = 4.6 Hz), 4.40 (1H, d, *J* = 6.0 Hz), 3.35 (1H, t, *J* = 8.2 Hz), 3.05 (1H, d, *J* = 13.6 Hz), 2.84 (1H, dd, *J* = 4.0 and 13.6 Hz), 2.03 (2H, d, *J* = 8.2 Hz), 1.76 (3H, s), 1.47 (3H, s), 1.30 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.3, 113.1, 111.4, 84.9, 81.2, 62.6, 51.5, 38.6, 26.5, 24.3, 22.4; HRMS (EI) $[M + H]^+$ calcd for $C_{11}H_{20}NO_2$, 198.1488; found, 198.1484. (b) Following the general procedures, 35 mg (0.11 mmol) of isoxazolidine **6**, 1.10 mL of THF, and 0.66 mL (0.33 mmol) of a solution of 2-methallylMgCl were used, affording **10d** (18 mg, 68%).

*(2S,3S,4R)-2-Phenyl-3,4-isopropylidenedioxypyrrolidine (**10e**).* (a) Following the general procedures, isoxazolidine **5** (35 mg, 0.11 mmol) in 1.10 mL of THF and a 2.8 M Et_2O solution of PhMgBr (0.12 mL, 0.33 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:9) to obtain **10e** (17 mg, 72%): $[\alpha]_D^{20}$ −15.0 (*c* = 0.3, $CHCl_3$); IR (film) 3348, 2983, 2927, 2852, 1446, 1309, 1051, 603 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38−7.23 (5H, m), 4.63−4.71 (1H, m), 4.86 (1H, d, *J* = 5.4 Hz), 4.37 (1H, s), 3.09 (1H, d, *J* = 13.0 Hz), 2.92 (1H, dd, *J* = 4.4 and 13.0 Hz), 1.54 (3H, s), 1.35 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.5, 128.7, 127.3, 127.0, 111.5, 88.3, 82.2, 67.8, 52.8, 26.6, 24.3; HRMS (EI) $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$, 220.1332; found, 220.1335. (b) Following the general procedures, 20 mg (0.06 mmol) of isoxazolidine **6**, 1 mL of THF, and 65 μL (0.18 mmol) of a 2.8 M Et_2O solution of PhMgBr were used, affording **10e** (9.2 mg, 70%).

*(2S,3S,4R)-2-(4-Fluoro)phenyl-3,4-isopropylidenedioxypyrrolidine (**10f**).* (a) Following the general procedures, isoxazolidine **5** (40 mg, 0.12 mmol) in 1.20 mL of THF and a 0.8 M THF solution of *p*-FC_6H_4MgCl (0.45 mL, 0.36 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 3:7) to obtain **10f** (20 mg, 73%): $[\alpha]_D^{20}$ −3.0 (*c* = 0.4, $CHCl_3$); IR (film) 2985, 2935, 2858, 1637, 1508, 1219, 1085, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41−7.34 (2H, m, H*meta*), 7.05−6.97 (2H, m, H*ortho*), 4.80 (1H, dd, *J* = 5.6 Hz, H-3), 4.67 (1H, t, *J* = 4.4 Hz, H-4), 4.32 (1H, s, H-2), 3.08 (1H, d, *J* = 13.6 Hz, H_A-5), 2.92 (1H, dd, *J* = 4.0 and 13.6 Hz, H_B-5), 1.54 (3H, s, Me-acetonide), 1.34 (3H, s, Me-acetonide); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 161.2, 135.2, 128.4, 115.5, 111.5, 88.1, 82.2, 67.2, 52.7, 26.6, 24.3; HRMS (EI) $[M + H]^+$ calcd for $C_{13}H_{17}NO_2F$, 238.1237; found, 238.1235. (b) Following the general procedures, 80 mg (0.25 mmol) of isoxazolidine **6**, 2.40 mL of THF, and 0.95 mL (0.75 mmol) of a 0.8 M THF solution of *p*-FC_6H_4MgCl were used, affording **10f** (44.4 mg, 75%).

*(2S,3S,4R)-2-Naphthalenylmethyl-3,4-isopropylidenedioxypyrrolidine (**10g**).* (a) Following the general procedures, isoxazolidine **5** (68 mg, 0.20 mmol) in 2 mL of THF and a 0.25 M Et_2O solution of (2-naphthalenylmethyl)magnesium bromide (2.40 mL, 0.6 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:9) to obtain **10g** (44 mg, 78%): $[\alpha]_D^{20}$ −27.9 (*c* = 0.6, $CHCl_3$); IR (film) 2983, 2933, 1375, 1207, 1043, 813, 752 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81−7.25 (7H, m), 4.79−4.75 (1H, m), 4.50 (1H, dd, *J* = 5.6 Hz), 3.59 (1H, t, *J* = 8.2 Hz), 3.10 (1H, d, *J* = 13.2 Hz), 3.00 (1H, dd, *J* = 4.0 and 13.2 Hz), 2.84−2.70 (2H, m), 1.46 (3H, s), 1.24 (3H, s,); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.5, 132.4, 133.7, 128.5, 127.8, 128.7, 126.3, 125.7, 111.2, 85.1, 81.9, 66.2, 52.1, 37.3, 26.5, 24.3; HRMS (EI) $[M + H]^+$ calcd for $C_{18}H_{22}NO_2$, 284.1645; found, 284.1650. (b) Following the general procedures, 40 mg (0.12 mmol) of isoxazolidine **6**, 1.20 mL of THF, and 1.50 mL (0.37 mmol) of a 0.25 M Et_2O solution of (2-naphthalenylmethyl)magnesium bromide were used, affording **10g** (27 mg, 80%).

*(2S,3S,4R)-2-Benzyl-3,4-isopropylidenedioxypyrrolidine (**10h**).* (a) Following the general procedures, isoxazolidine **5** (86 mg, 0.26 mmol) in 2.60 mL of THF and a 1.5 M THF solution of BnMgCl (0.52 mL,

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0.78) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/Et_2O 1:9) to obtain **10h** (42 mg, 70%): $[\alpha]_D^{20}$ −28.4 (*c* = 0.3, CH_2Cl_2); IR (film) 2981, 2927, 2854, 1654, 1448, 1209, 1045, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32−7.18 (5H, m), 4.77−4.73 (1H, m), 4.45 (1H, d, *J* = 5.6 Hz), 3.50 (1H, t, *J* = 7.8 Hz), 3.08 (1H, d, *J* = 13.2 Hz), 2.92 (1H, dd, *J* = 4.1 and 13.2 Hz), 2.73−2.57 (2H, m), 1.46 (3H, s), 1.28 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 129.3, 128.9, 126.9, 111.5, 84.4, 81.1, 66.1, 51.7, 36.5, 26.4, 24.2; HRMS (EI) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1488; found, 234.1478. (b) Following the general procedures, 40 mg (0.12 mmol) of isoxazolidine **6**, 1.20 mL of THF, and 0.25 mL (0.37 mmol) of a 1.5 M THF solution of BnMgCl were used, affording **10h** (19.5 mg, 70%).

*(2R,3S,4R)-2-Phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (**10i**).* (a) To a stirred solution of $MeSO_2Ph$ (86 mg, 0.55 mmol) in THF (2 mL) was added slowly a 1.6 M hexane solution of *n*-BuLi (0.53 mL, 0.33 mmol), and the mixture was reacted at 0 °C for 10 min. The reaction mixture was cooled to −78 °C, stirred for 10 min, and added to a solution of isoxazolidine **5** (60 mg, 0.19 mmol) in 1.50 mL of THF. The mixture was stirred at −78 °C for 1 h and then allowed to warm slowly to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to obtain **10i** (27 mg, 48%): $[\alpha]_D^{20}$ −13.1 (*c* = 1.7, $CHCl_3$); IR (film) 3317, 2985, 2936, 1448, 1375, 1306, 1209, 1144, 1083, 1046, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.65−7.54 (3H, m, H*meta* and H*para*), 4.67 (1H, dd, *J* = 4.4 and 5.3 Hz, H-4), 4.57 (1H, dd, *J* = 5.3 Hz, H-3), 3.57 (1H, t, *J* = 6.4 Hz, H-2), 3.13 (2H, d, *J* = 13.2 Hz, CH_2-1′), 3.05 (1H, d, *J* = 13.6 Hz, H_A-5), 2.69 (1H, dd, *J* = 4.4 and 13.2 Hz, H_B-5), 1.44 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 133.8, 129.3, 128.1, 111.6, 85.0, 84.9, 60.3, 57.2, 51.8, 26.2, 24.1; HRMS (EI) $[M + H]^+$ calcd for $C_{14}H_{20}NO_4S$, 298.1113; found, 298.1115. (b) Following the general procedures, 50 mg (0.15 mmol) of isoxazolidine **6**, 1.50 mL of THF, 70.3 mg (0.45 mmol) of $MeSO_2Ph$ in 2 mL of THF, and 0.26 mL (0.42 mmol) of a 1.6 M hexane solution of *n*-BuLi were used, affording **10i** (20 mg, 45%).

*(2S,3S,4R)-2-(4-Methoxybenzyl)-3,4-isopropylidenedioxypyrrolidine (**10j**).* (a) Following the general procedures, isoxazolidine **5** (150 mg, 0.46 mmol) in 4.60 mL of THF and a 0.25 M THF solution of *p*-$MeOC_6H_4CH_2MgCl$ (5.50 mL, 1.38 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/Et_2O 1:9) to obtain **10j** (84 mg, 70%): $[\alpha]_D^{20}$ −18.0 (*c* = 0.4, $CHCl_3$); IR (film) 2985, 2935, 1629, 1512, 1458, 1247, 1037, 864 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.12 (2H, d, *J* = 8.2 Hz), 6.85 (2H, d, *J* = 8.2 Hz), 4.73 (1H, t, *J* = 5.6 Hz), 4.43 (1H, dd, *J* = 6.0 Hz), 3.79 (3H, s), 3.43 (1H, t, *J* = 8.0 Hz), 3.08 (1H, d, *J* = 13.6 Hz), 2.97 (1H, dd, *J* = 4.0 and 13.6 Hz), 2.68−2.47 (2H, m), 1.46 (3H, s), 1.28 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.4, 130.8, 130.2, 114.3, 111.3, 84.8, 81.6, 66.4, 55.5, 51.9, 36.0, 26.5, 24.3; HRMS (EI) $[M + H]^+$ calcd for $C_{15}H_{22}NO_3$, 264.1594; found, 264.1600. (b) Following the general procedures, 50 mg (0.15 mmol) of isoxazolidine **6**, 1.50 mL of THF, and 1.80 mL (0.45 mmol) of a 0.25 M THF solution of *p*-$MeOC_6H_4CH_2MgCl$ were used, affording **10h** (27.50 mg, 70%).

Addition of Organometallic Reagents: Standard Procedure (Isoxazolidines 7 and 8). To a stirred solution of isoxazolidine **7** or **8** (1 equiv) in THF (0.1 M) was added dropwise RMg (Br or Cl) or RLi (3 equiv) at 0 °C. The solution was stirred at 0 °C for 1 h, and the mixture was allowed to warm slowly to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain *N*-hydroxylamines.

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)hexyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11a**).* (a) To a stirred solution of isoxazolidine **7** (60 mg, 0.19 mmol) in 1.90 mL of THF was added dropwise a 1.6 M hexane solution of *n*-BuLi (0.24 mL, 0.38 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h, and the mixture was allowed to warm slowly to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford **11a** (36.4 mg, 55%): $[\alpha]_D^{20}$ −6.8 (*c* = 1.2, $CHCl_3$); IR (film) 3455, 2955, 2933, 1447, 1304, 1145, 726 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.67−7.52 (3H, m, H*meta* and H*para*), 5.61 (1H, bs, −OH), 4.79 (1H, dd, *J* = 6.2 and 12.8 Hz, H-4), 4.57 (1H, t, *J* = 6.2 Hz, H-3), 3.70 (1H, dd, *J* = 6.2 and 12.2 Hz, H_A-5), 3.50−3.41 (1H, m, H-1′), 3.18 (1H, t, *J* = 6.2 Hz, H-2), 2.99 (1H, dd, *J* = 5.8 and 12.2 Hz, H_B-5), 1.80−1.71 (2H, m, CH_2-2′), 1.47 (3H, s, Me-acetonide), 1.31 (3H, s, Me-acetonide), 1.21−1.17 (6H, m, CH_2-3′, CH_2-4′ and CH_2-5′), 0.82 (3H, t, *J* = 7.0 Hz, CH_3-6′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 134.1, 129.4, 129.3, 114.9, 82.5, 77.8, 72.5, 64.9, 63.1, 31.6, 27.5, 27.1, 26.9, 25.3, 22.4, 14.1; HRMS (EI) $[M + H]^+$ calcd for $C_{19}H_{30}NO_5S$, 384.1845; found, 384.1834. (b) Following the general procedures at −78 °C, 62 mg (0.19 mmol) of isoxazolidine **7**, 2 mL of THF, and 0.35 mL (0.57 mmol) of a 1.6 M hexane solution of *n*-BuLi were used, affording **11a** (30.5 mg, 42%). (c) Following the general procedures at 0 °C, 70 mg (0.22 mmol) of isoxazolidine **8**, 2.20 mL of THF, and 0.40 mL (0.65 mmol) of a 1.6 M hexane solution of *n*-BuLi were used, affording **11a** (50 mg, 58%). (d) Following the general procedures at −78 °C, 40 mg (0.13 mmol) of isoxazolidine **8**, 1.30 mL of THF, and 0.23 mL (0.37 mmol) of a 1.6 M hexane solution of *n*-BuLi were used, affording **11a** (20 mg, 40%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)propyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11b**).* (a) Following the general procedures, isoxazolidine **7** (112 mg, 0.34 mmol) in 3.40 mL of THF and 3.0 M Et_20 solution of MeMgBr (0.34 mL, 1.02 mmol) were used to afford **11b** (72 mg, 78%): $[\alpha]_D^{20}$ −152.9 (*c* = 6.8, $CHCl_3$); IR (film) 3448, 2983, 2937, 2877, 2858, 1585, 1448, 1247, 914 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98 (2H, d, *J* = 8.0 Hz), 7.68−7.54 (3H, m), 5.85 (1H, bs), 4.82−4.77 (1H, m), 4.60 (1H, t, *J* = 6.6 Hz), 3.71−3.64 (1H, m), 3.43−3.39 (1H, m), 3.22−3.16 (1H, m), 2.98 (1H, dd, *J* = 5.8 and 12.0 Hz), 1.85−1.78 (2H, m), 1.45 (3H, s), 1.25 (3H, s), 0.94 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 134.0, 129.3, 129.3, 114.9, 82.7, 78.5, 72.1, 66.3, 63.2, 27.5, 25.3, 20.5, 12.0; HRMS (EI) [M + Na] calcd for $C_{16}H_{23}NO_5NaS$, 364.1189; found, 364.1188. (b) Following the general procedures, 112 mg (0.34 mmol) of isoxazolidine **7**, 3.5 mL of THF, and 0.65 mL (1.02 mmol) of a 1.6 M Et_2O solution of MeLi were used, affording **11b** (70 mg, 60%). (c) Following the general procedures, 50 mg (0.15 mmol) of isoxazolidine **8**, 1.5 mL of THF, and 0.15 mL (0.45 mmol) of a 3.0 M Et_2O solution of MeMgBr were used, affording **11b** (37 mg, 74%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(3′-methyl)pentyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11c**).* (a) Following the general procedures, isoxazolidine **7** (50 mg, 0.15 mmol) in 1.50 mL of THF and a 1.4 M cyclohexane solution of *s*-BuLi (0.35 mL, 0.46 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11c** (20 mg, 35%): $[\alpha]_D^{20}$ −11.2 (*c* = 0.5, $CHCl_3$); IR (film) 3336, 2962, 2933, 2875, 1560, 1448, 1381, 1209, 1083, 685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* = 8.2 Hz), 7.67−7.52 (3H, m), 5.60 (1H, bs), 4.77−4.60 (2H, m), 4.41 (1H, s), 3.70 (1H, dd, *J* = 6.2 and 11.8 Hz), 3.55−3.48 (1H, m), 3.12−2.99 (1H, m), 2.93 (1H, dd, *J* = 5.8 and 11.8 Hz), 2.40 (2H, d, *J* = 3.2 Hz), 1.47 (3H, s), 1.30 (3H, s), 0.92−0.74 (5H, m), 0.74−0.65 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 134.0, 129.6, 128.5, 114.5, 82.1, 77.8, 73.3, 62.9, 32.6, 29.9, 29.2, 27.5, 25.3, 18.7; HRMS (EI) calcd for $C_{19}H_{29}NO_5NaS$, 406.1658; found, 406.1651. (b) Following the general procedures, 58 mg (0.18 mmol) of isoxazolidine **8**, 1.80 mL of THF, and 0.40 mL (0.54 mmol) of a 1.4 M cyclohexane solution of *s*-BuLi were used, affording **11c** (24 mg, 35%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(4′-methyl)pent-4′-enyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11d**).* (a) Following the general procedures, isoxazolidine **7** (60 mg, 0.18 mmol) in 1.80 mL of

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THF and a 0.5 M THF solution of 2-methylallylMgCl (1.10 mL, 0.54 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11d** (35 mg, 55%): $[\alpha]_D^{20}$ −8.7 (c = 1.1, $CHCl_3$); IR (film) 3448, 3062, 3030, 2987, 2935, 1663, 1496, 1448, 1029, 734, 596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.01 (2H, d, J = 7.8 Hz), 7.67−7.53 (3H, m), 5.59 (1H, bs), 4.79−4.72 (1H, m), 4.75 (1H, s), 4.64−4.57 (1H, m), 4.60 (1H, s), 3.70 (1H, dd, J = 5.4 and 11.6 Hz), 3.50 (1H, dt, J = 5.0 and 6.8 Hz), 3.14 (1H, t, J = 5.6 Hz), 2.98 (1H, dd, J = 5.0 and 11.6 Hz), 2.10−1.95 (2H, m), 1.95−1.92 (2H, m), 1.47 (3H, s), 1.55 (3H, s), 1.30 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 134.1, 129.5, 129.3, 144.2, 112.1, 114.8, 82.3, 77.3, 72.5, 63.6, 62.9, 35.3, 27.5, 24.8, 25.2, 22.0; HRMS (EI) calcd for $C_{19}H_{28}NO_5S$, 382.1682; found, 382.1699. (b) Following the general procedures, 61 mg (0.19 mmol) of isoxazolidine **8**, 1.90 mL of THF, and 1.12 mL (0.56 mmol) of a 0.5 M THF solution of 2-methylallylMgCl were used, affording **11d** (40 mg, 55%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(2′-phenyl)ethyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11e**).* (a) Following the general procedures, isoxazolidine **7** (88 mg, 0.27 mmol) in 2.70 mL of THF and a 2.8 M Et_2O solution of PhMgBr (0.30 mL, 0.81 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11e** (54 mg, 50%): $[\alpha]_D^{20}$ −3.2 (c = 1.7, $CHCl_3$); IR (film) 3448, 3062, 3030, 2987, 2935, 1663, 1496, 1448, 1029, 734, 596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 7.8 Hz), 7.64−7.48 (3H, m), 7.26−7.06 (5H, m), 4.71−4.73 (2H, m), 3.83 (1H, dd, J = 6.0 and 11.2 Hz), 3.40−3.42 (1H, dd, J = 6.0 and 11.0 Hz), 3.25 (1H, t, J = 5.4 Hz, H-2), 3.15 (2H, d, J = 6.0 Hz, CH_2-2′), 2.95 (1H, dd, J = 5.0 and 11.0 Hz), 1.34 (3H, s), 1.26 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 137.9, 134.1, 129.4, 129.2, 128.8, 126.9, 114.4, 81.4, 77.3, 71.9, 65.9, 62.7, 32.9, 27.4, 25.4; HRMS (EI) calcd for $C_{21}H_{25}NO_5NaS$, 426.1345; found, 426.1342. (b) Following the general procedures, 60 mg (0.18 mmol) of isoxazolidine **8**, 1.80 mL of THF, and 0.20 mL (0.54 mmol) of a 2.8 M Et_2O solution of PhMgBr were used, affording **11e** (38 mg, 52%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(2′-(4-fluorophenyl))ethyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11f**).* (a) Following the general procedures, isoxazolidine **7** (100 mg, 0.30 mmol) in 3 mL of THF and a 0.8 M THF solution of p-FC_6H_4MgCl (1.15 mL, 0.90 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11f** (60 mg, 48%): $[\alpha]_D^{20}$ −8.7 (c = 0.4, $CHCl_3$); IR (film) 3423, 3066, 2987, 2926, 2868, 1600, 1508, 1375, 1249, 1157, 1024, 864 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 (2H, d, J = 8.0 Hz), 7.58 (1H, t, J = 8.0 Hz), 7.47 (2H, t, J = 8.0 Hz), 6.97−6.94 (2H, m), 6.85−6.80 (2H, m), 5.45 (1H, bs), 4.68−4.58 (1H, m), 4.57 (1H, t, J = 5.8 Hz), 3.72−3.68 (1H, m), 3.64 (1H, dd, J = 6.0 and 11.8 Hz), 3.12 (1H, t, J = 5.4 Hz), 3.10 (1H, d, J = 6.2 Hz), 3.08 (1H, d, J = 6.2 Hz), 2.90 (1H, dd, J = 5.4 and 11.8 Hz), 1.29 (3H, s), 1.20 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.8, 160.4, 138.3, 133.9, 133.4, 130.6, 129.2, 128.7, 115.2, 114.3, 81.3, 77.9, 71.9, 66.0, 62.6, 32.0, 27.2, 25.1; HRMS (EI) calcd for $C_{21}H_{24}NO_5FNaS$, 444.1251; found, 444.1261. (b) Following the general procedures, 58 mg (0.18 mmol) of isoxazolidine **8**, 1.80 mL of THF, and 0.67 mL (0.54 mmol) of a 0.8 M THF solution of p-FC_6H_4MgCl were used, affording **11f** (38 mg, 50%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(3′-phenyl)propyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11g**).* (a) Following the general procedures, isoxazolidine **7** (80 mg, 0.30 mmol) in 3 mL of THF and a 1.5 M THF solution of BnMgCl (0.60 mL, 0.90 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11g** (50 mg, 45%): $[\alpha]_D^{20}$ −7.8 (c = 1.4, $CHCl_3$); IR (film) 3448, 3062, 2987, 2937, 2862, 1558, 1442, 1305, 1085, 864 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98 (2H, d, J = 7.8 Hz), 7.68−7.52 (3H, m), 7.26−7.06 (5H, m), 5.15 (1H, bs), 4.77−4.68 (1H, m), 4.45 (1H, t, J = 6.2 Hz), 3.65 (1H, dd, J = 6.0 and 11.8 Hz), 3.50−3.41 (1H, m), 3.11 (1H, t, J = 6.2 Hz), 2.94 (1H, dd, J = 6.0 and 11.8 Hz), 2.77−2.60 (2H, m), 2.25−2.04 (2H, m), 1.50 (3H, s), 1.31 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6, 138.2, 134.0, 129.5, 129.1, 128.7, 128.9, 126.6, 114.8, 81.8, 77.3, 73.1, 71.9, 62.9, 33.2, 28.1, 27.4, 25.2; HRMS (EI) calcd for $C_{22}H_{27}NO_5NaS$, 440.1502; found, 440.1502. (b) Following the general procedures, 50 mg (0.15 mmol) of isoxazolidine **8**, 1.50 mL of THF, and 0.30 mL (0.45 mmol) of a 1.5 M THF solution of BnMgCl were used, affording **11g** (26 mg, 42%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(3′-(4-methoxyphenyl))-propyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11h**).* (a) Following the general procedures, isoxazolidine **7** (150 mg, 0.45 mmol) in 4.50 mL of THF and a 0.25 M THF solution of p-$MeOC_6H_4CH_2MgCl$ (5.40 mL, 1.35 mmol) were used. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11h** (83 mg, 42%): $[\alpha]_D^{20}$ −5.2 (c = 1.4, $CHCl_3$); IR (film) 3456, 2989, 1610, 1512, 14461, 1301, 1247, 1033, 864 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 8.2 Hz), 7.71−7.52 (3H, m), 6.98 (2H, d, J = 6.2 Hz), 6.77 (2H, d, J = 6.2 Hz), 5.26 (1H, bs), 4.74 (1H, dd, J = 6.2 and 6.0 Hz), 4.46 (1H, t, J = 6.0 Hz), 3.77 (3H, s), 3.66 (1H, dd, J = 6.2 and 11.6 Hz), 3.48−3.37 (1H, m), 3.10 (1H, t, J = 6.6 Hz,), 2.92 (1H, dd, J = 6.2 and 11.6 Hz), 2.66 (2H, t, J = 8.4 Hz), 2.16−2.02 (2H, m), 1.50 (3H, s), 1.31 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.3, 138.3, 134.1, 132.4, 129.6, 129.5, 129.3, 129.1, 126.8, 114.2, 81.8, 77.3, 72.3, 62.9, 55.5, 32.3, 28.1, 27.5, 25.2; HRMS (EI) calcd for $C_{23}H_{29}NO_6NaS$, 470.1607; found, 470.1614. (b) Following the general procedures, 50 mg (0.15 mmol) of isoxazolidine **8**, 1.90 mL of THF, and 1.80 mL (0.45 mmol) of a 0.25 M THF solution of p-$MeOC_6H_4CH_2MgCl$ were used, affording **11h** (27 mg, 40%).

*(1′R,2R,3S,4R)-2-[(1′-Phenylsulfonyl)(2′-(2-propynyloxytetrahydropirane))ethyl]-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (**11i**).* (a) To a stirred solution of 2-propynylloxytetrahydropirane (75 μL, 0.54 mmol) in THF (1.50 mL) was slowly added a 1.6 M hexane solution of n-BuLi (0.30 mL, 0.50 mmol), and the mixture was reacted at 0 °C for 10 min. The reaction was added to a solution of isoxazolidine **8** (60 mg, 0.18 mmol) in 1.50 mL of THF, and the mixture was stirred at 0 °C for 1 h. The reaction was allowed to warm slowly to room temperature, quenched with a saturated aqueous solution of NH_4Cl, and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 7:3) to obtain **11i** (33 mg, 40%): $[\alpha]_D^{20}$ −22.3 (c = 0.6, $CHCl_3$); IR (film) 3410, 2937, 2854, 1448, 1375, 1149, 731, 721 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98 (2H, d, J = 8.0 Hz), 7.68−7.54 (3H, m), 5.85 (1H, bs), 4.99−4.95 (1H, m), 4.91−4.75 (4H, m), 4.03−3.34 (7H, m), 3.05 (1H, dd, J = 5.2 and 11.8 Hz), 2.87−2.80 (2H, m), 1.75−1.54 (4H, m), 1.48 (3H, s), 1.32 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 134.6, 129.8, 129.3, 112.7, 97.1, 82.2, 81.9, 79.9, 79.8, 77.3, 63.7, 63.1, 62.2, 54.6, 30.4, 29.9, 27.5, 25.5, 25.4, 19.2; HRMS (EI) calcd for $C_{23}H_{31}NO_7NaS$, 488.1713; found, 488.1715.

*(1′R,3S,4R)-3,4-Isopropylidenedioxy-5-[(1′-phenylsulfonyl)(2′-phenyl)ethyl]-3,4-dihydro-2H-pyrrole 1-Oxide (**12**).* To a stirred solution of hydroxylamine **11e** (71 mg, 0.18 mmol) in 1 mL of DCM at 0 °C was added 30 mg (0.27 mmol) of activated MnO_2 (90% purity). The resulting dispersion was stirred for 2 h at rt, filtered through a short pad of Celite and Na_2SO_4, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 3:7) to obtain **12** (69 mg, 92%): $[\alpha]_D^{20}$ +35.6 (c = 0.3, $CHCl_3$); IR (film) 2978, 2937, 1577, 1560, 1375, 1209, 1085, 688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 8.0 Hz), 7.65−7.53 (3H, m), 7.27−7.11 (5H, m), 5.15 (1H, d, J = 6.8 Hz), 4.87 (1H, dt, J = 6.8 and 12.0 Hz), 4.74−4.67 (1H, m), 3.96 (2H, bs), 3.80 (1H, dd, J = 12.2 and 14 Hz), 3.36 (1H, dd, J = 4.2 and 14 Hz), 1.30 (3H, s), 1.17 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.1, 135.9, 135.8, 134.4, 129.4, 129.1, 128.6, 128.3, 127.4, 112.9, 81.0, 71.3, 68.3, 64.4, 30.6, 26.2, 25.5; HRMS (EI) calcd for $C_{21}H_{23}NO_5NaS$, 424.1189; found, 424.1184.

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■ ASSOCIATED CONTENT

Supporting Information

IR, NMR, and HRMS spectra and crystallographic information (data and CIF-format data) for **11f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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