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Enantioselective Synthesis of Cocaine C-1 Analogues using Sulfinimines (*N*-Sulfinyl Imines)

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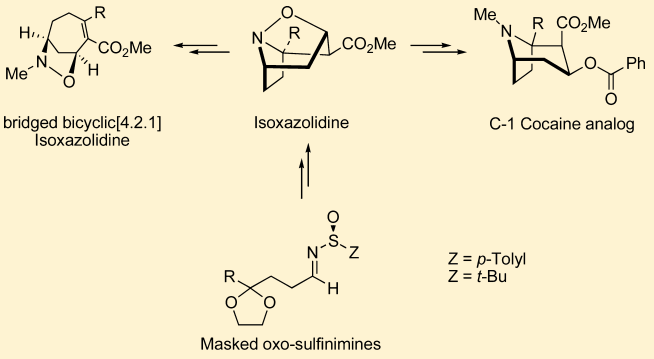
Supporting Information

ABSTRACT: The first examples of cocaine analogues having substituents (methyl, ethyl, *n*-propyl, *n*-pentyl, and phenyl) at the C-1 position of the cocaine tropane skeleton were prepared by heating sulfinimine-derived α,β-unsaturated pyrrolidine nitrones. In the presence of the Lewis acid $Al(O^tBu)_3$ the nitrones undergo an intramolecular [3 + 2] cycloaddition to give tricyclic isoxazolidines that were transformed in three steps to the cocaine analogues. In the absence of the Lewis acid, lactams were formed resulting from rearrangement of the nitrone to an oxaziridine. A novel Pd- and base-promoted rearrangement of methanesulfonate salts of isoxazolidine to bridge bicyclic[4.2.1]isoxazolidines was discovered.



INTRODUCTION

Tropane alkaloids such as (*R*)-(−)-cocaine (**1**) have often served as lead compounds in drug discovery (Figure 1). This is

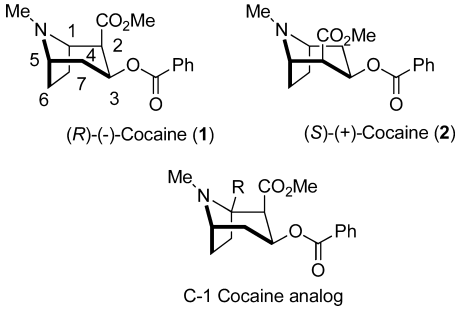


Figure 1. Cocaine and C-1 cocaine analogues.

because cocaine targets the three monoamine transporters: dopamine (DAT), serotonin (SERT), and norepinephrin (NET).[1] Modification in the dopamine transporter function may have a role in Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, aging, depression, and cocaine's powerful stimulator and addictive properties.[2,3] For these reasons there is continuing interest in the asymmetric synthesis of cocaine-like compounds that can selectively target the monoamine transporters and DAT in particular.[3,4]

The difficulty encountered in the stereoselective synthesis of cocaine analogues is the requirement that the C-2 and C-3 substituents have a *cis* relationship. Additionally, of cocaine's eight stereoisomers only the *R*-isomer (−)-**1** is addictive.[3,5,6] For these reasons most nonracemic analogues of cocaine have focused on modifications of the C-2 and C-3 substituents, which are prepared from (−)-**1**. Although useful information on the cocaine-binding site has resulted from these studies, to date there are no therapeutically useful cocaine analogues.[3] The introduction of groups at other positions of the cocaine tropane skeleton is much more problematic, often requiring multistep syntheses and resolutions to access enantiopure materials.[3] Recently Shing et al. described the enantioselective synthesis of C-6,7 and C-7 cocaine analogues from D-(−)-ribose.[6e] In 2010 we disclosed the first synthesis of enantiopure cocaine analogues having substituents at the C-1 or bridgehead position of the cocaine tropane skeleton in addition to (*S*)-(+)-**2** the enantiomer of cocaine (*R*)-(−)-**1** (Figure 1).[7] Here we describe full details of the enantioselective synthesis of C-1 substituted cocaine analogues and their related chemistries.

Our synthesis of C-1 cocaine analogues builds on Tufariello's synthesis of racemic cocaine described in the late 1970s.[8] His procedure employed a novel [3 + 2] cycloaddition reaction of a pyrrolidine nitrone to give a tricyclic isoxazolidine, which determines the *cis* relationship of the C-2 and C-3 substituents in the tropane skeleton. Unfortunately, an enantioselective route could not be adapted to this method, and the introduction of functionality at other positions of the skeleton was impractical. Our asymmetric synthesis of C-1 cocaine analogues, which employs an enantiopure-masked oxo-sulfinimine, is given in Figure 2. Here the tricyclic isoxazolidine and the enantiopure nitrone are prepared from an *N*-sulfinyl β-amino ketal ester derived from a masked oxo-sulfinimine.[9,10]

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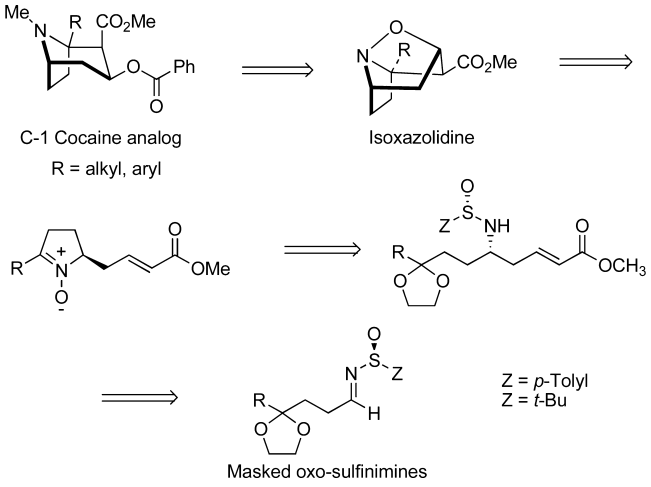
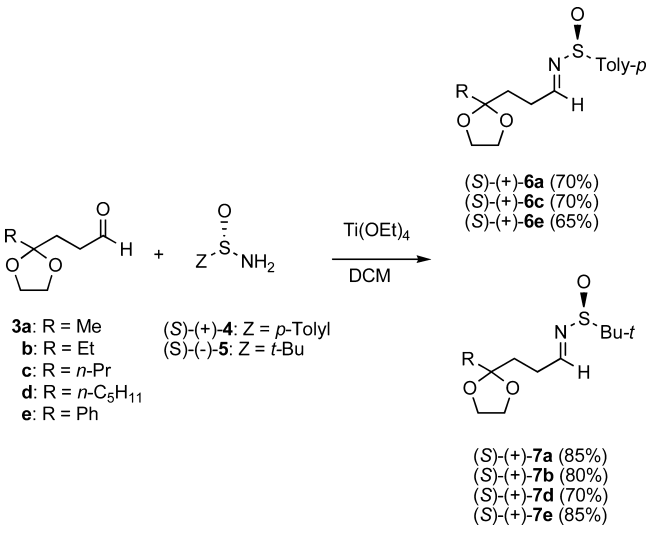


Figure 2. Retrosynthetic analysis of C-1 cocaine analogues from masked oxo-sulfinimines.

RESULTS AND DISCUSSION

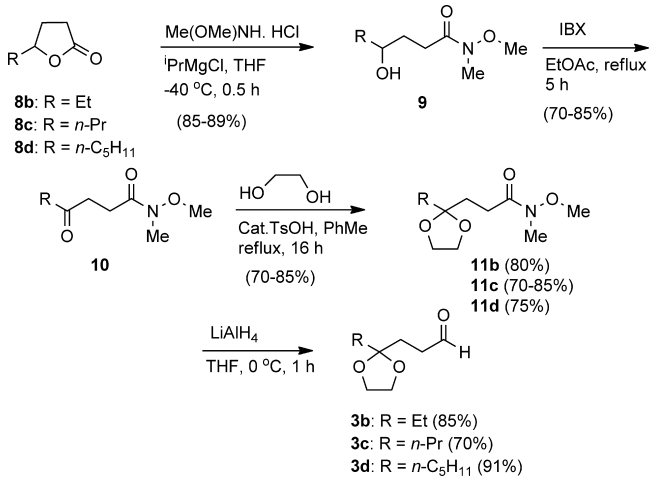
Masked Oxo-sulfinimines. Our synthesis of C-1 cocaine analogues begins with the preparation of the masked oxo-sulfinimine, a sulfinimine-derived chiral building block.[11] The sulfinimines were prepared in the usual manner by condensing (*S*)-(+)-*p*-toluenesulfinamide (**4**) or (*S*)-(−)-*tert*-butanesulfinamide (**5**) with the appropriate ketal aldehyde **3** in the presence of excess $Ti(OEt)_4$ as shown in Scheme 1.[10] The bulkier and more nucleophilic (*S*)-(−)-*tert*-butanesulfinamide (**5**) gave the product within 24 h, but (*S*)-(+)-**4** required longer times (24 to 48 h). In general yields using (*S*)-(−)-**5** were also improved compared to (*S*)-(+)-**4** (Scheme 1).

Scheme 1



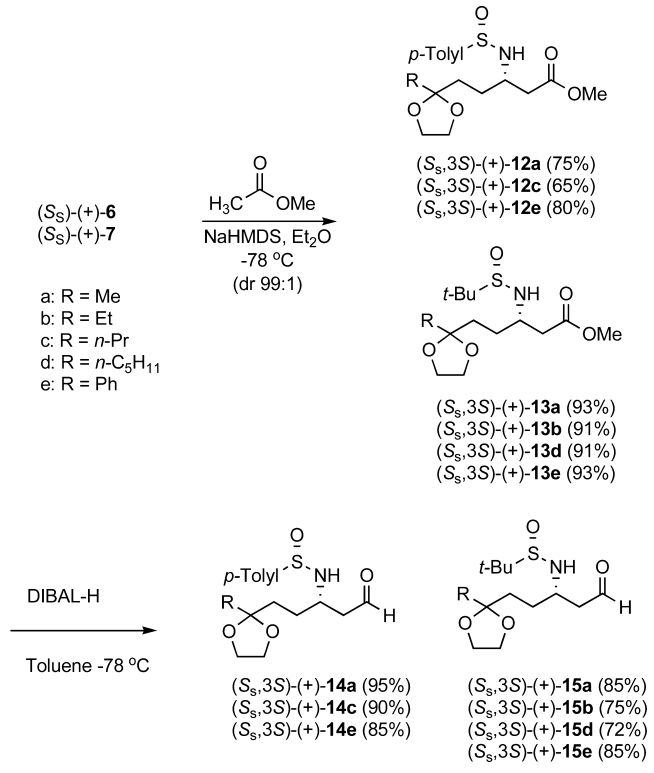
The ketal aldehydes **3a** (R = Me) and **3e** (R = Ph) were prepared as previously described.[11a,12] Ketal aldehydes **3b** (R = Et), **3c** (R = *n*-Pr), and **3d** (R = n-C_5H_{11}) were prepared from the corresponding commercially available lactones **8** as shown in Scheme 2. Reaction of lactone **8** with *in situ* generated magnesium *N*,*O*-dimethyhydroxylamine[13] afforded the corresponding Weinreb amides **9** in 85−89% yields. Swern oxidation of **9c** (R = *n*-Pr) failed to give the ketone, but oxidation using iodoxybenzoic acid (IBX) gave the ketones **10** in 70−85% yields. Acid-catalyzed ketalization followed by reduction of the Weinreb amides using lithium aluminum hydride ($LiAlH_4$) gave the desired aldehydes **3** in good yields (Scheme 2).

Scheme 2



(*S*)-(+)-Dehydropyrrolidines. Treatment of sulfinimines (*S*)-(+)-**6** and (*S*)-(+)-**7** with an excess of the sodium enolate of methyl acetate in Et_2O at −78 °C afforded the corresponding β-amino esters (S_S,3*S*)-(+)-**12** and (S_S,3*S*)-(+)-**13** as single diastereoisomers in good to excellent yields (Scheme 3). Reduction of (+)-**12** and (+)-**13** with DIBAL-H in toluene at −78 °C gave the desired aldehydes (S_S,3*S*)-(+)-**14** and (S_S,3*S*)-(+)-**15** in good yield, but over-reduction to the alcohols was problematic. Careful control of the reaction time and equivalents of DIBAL-H were necessary to minimize over-reduction. Best yields were observed using 1.8 equiv of DIBAL-

Scheme 3



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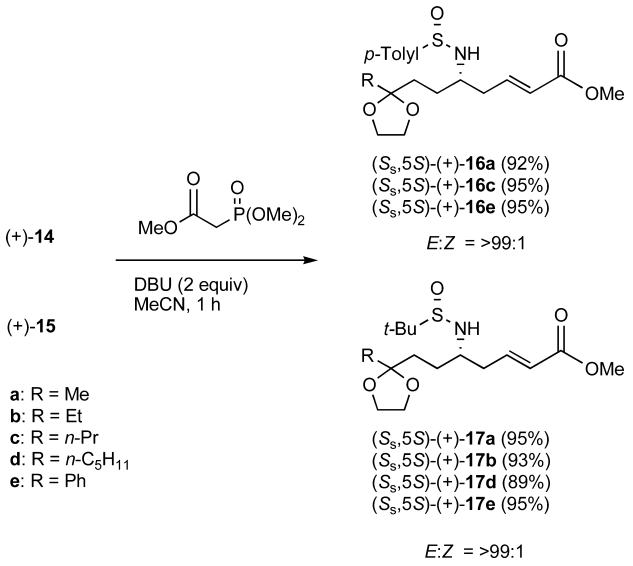
H and a time of approximately 45 min for (+)-**12** and only 10 min for (+)-**13** (Scheme 3). Importantly, epimerization at the C−N chiral center in (+)-**14** and (+)-**15** was not observed.

Conversion of (+)-**14** and (+)-**15** into the (*E*)-α,β-unsaturated *N*-sulfinyl β-amino ketals was next explored. Reaction of aldehyde (+)-**14a** with methyl (triphenylphosphoranylidene) acetate for 10 h gave the α,β-unsaturated *N*-sulfinyl δ-amino ketal (S_S,5*S*)-(+)-**16a** in 92% yield (Scheme 4). The

Scheme 4



16 Hz coupling constant observed for the olefinic protons in (+)-**16a** is consistent with the major isomer having the desired (*E*)-geometry.[14] To overcome the longer reaction times, β-amino aldehyde (+)-**14a** (R = Me) was subjected to the Roush−Masamune modification of the Horner−Wadsworth−Emmons (HWE) reaction with nucleophilic trimethylphosphonoacetate and DBU-LiCl.[12] However, these conditions resulted in the formation of (S_S,5*S*)-(+)-**16a** as an inseparable 9:1 *E*:*Z* mixture of isomers in 80% yield within 5−6 h. Prolonged reaction times and the presence of LiCl were thought to be causing isomerization of olefin geometry. Importantly, only the (*E*)-isomer (+)-**16a** was obtained in >90% yield when LiCl was omitted from the HWE reaction.

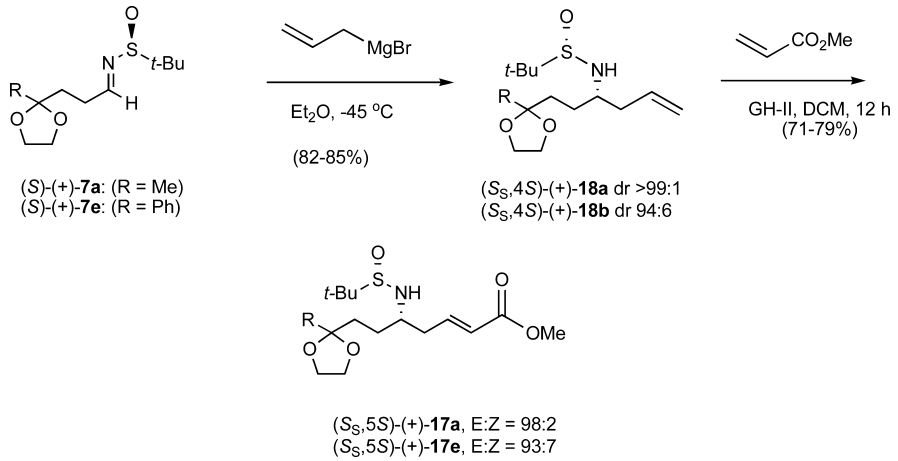
In the absence of LiCl with 2 equiv of trimethyl phosphonoacetate/DBU, *N*-*p*-toluenesulfinyl aldehydes (+)-**14a** (R = Me), (+)-**14c** (R = *n*-Pr), and (+)-**14e** (R = Ph) were converted into α,β-unsaturated esters (+)-**16a**, (+)-**16c**, and (+)-**16e** in less than 1 h and in >90% yield with exclusive (*E*)-geometry for the olefin. Olefination of the *N*-*tert*-butanesulfinyl β-amino aldehydes (+)-**15** under similar reaction conditions resulted in formation of the α,β-unsaturated ester ketals (+)-**17a** (R = Me), (+)-**17b** (R = Et), and (+)-**17d** (R = n-C_5H_{11}) in excellent yield without isomerization. However, ester (+)-**17e** (R = Ph) was isolated as 95:5 mixture of inseparable *E*:*Z* isomers.

An alternative strategy was briefly explored to access α,β-unsaturated ester ketals (+)-**17a** (R = Me) and **17e** (R = Ph) (Scheme 5).[15] This procedure treats oxo-sulfinimines (+)-**7a** and (+)-**7e** with 2 equiv of allylmagnesium bromide at −50 °C to give allyl amines (S_S4*S*)-(+)-**18a** and (S_S4*S*)-(+)-**18b** in 82% and 85% yields, respectively. Cross metathesis (CM) using Hoveyda−Grubbs catalyst II for 12 h in DCM afforded the desired α,β-unsaturated ester ketals (+)-**17a** and (+)-**17e** in 79% and 71% yields, respectively, but the *E*:*Z* ratios were 92:8 and 93:7, respectively. All attempts to improve the ratios by using Grubbs I or Grubbs II were unsuccessful.

Hydrolysis of the α,β-unsaturated δ-amino ester ketals (+)-**16** and (+)-**17** with 3 N HCl in THF/MeOH (1:1) gave the corresponding dehydropyrrolidines (*S*)-(+)-**19a−e** in excellent yields without *E*:*Z* isomerization (Scheme 6). However, with excess methanol/THF (3:1) isomerization of the α,β-unsaturated ester was observed, and in THF hydrolysis of the ester functionality was noted in addition to isomerization. Importantly, even when the α,β-unsaturated δ-amino ester ketals were not single isomers, after purification the dehydropyrrolidines (*S*)-(+)-**19a−e** were obtained as single isomers (Scheme 6).

Preparation of Nitrones. With the dehydropyrrolidines (+)-**19** in hand it was next necessary to selectively oxidize them to the corresponding nitrones (*S*)-**20** (Scheme 6). Oxidation of imines with reagents such as *m*-CPBA can give nitrones or oxaziridines.[16] The selective oxidation of imines to nitrones by urea hydrogen peroxide (UHP) catalyzed by methyltrioxorhenium (MTO) has recently been described by Goti and coworkers.[17] Oxidation of (+)-**19a** (R = Me) with 3.3 equiv of UHP and cat. MTO (2 mol %) in anhydrous MeOH for 1 h resulted in no reaction and recovery of starting material.

Scheme 5



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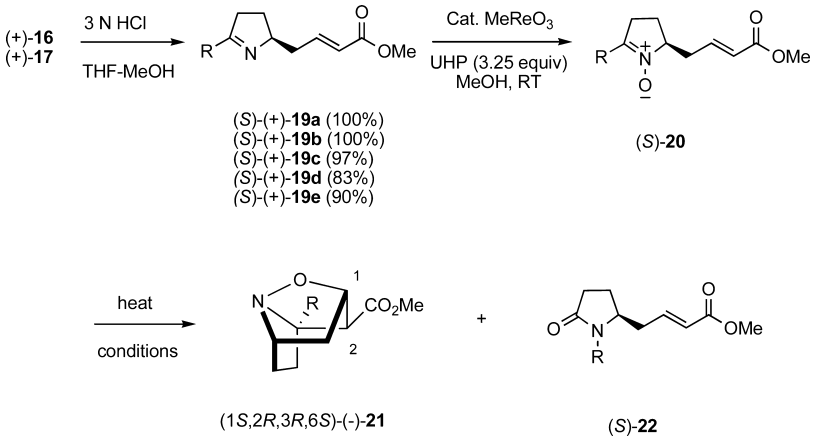
Scheme 6



a: R = Me; **b**: R =Et: **c**: R = *n*-Pr: **d**: R = *n*-C_5H_{11}, **e**: R = Ph

Increasing the amount of catalyst from 2 to 6 mol % and the reaction time to 16 h resulted in conversion of the imine to the nitrone (*S*)-**20a** (R = Me) in quantitative yield. Nitrone formation was confirmed by ^{1}H NMR analysis of crude reaction mixture in which the C-2 hydrogen of the pyrrole ring was shifted downfield to δ 4.20 ppm as compared to δ 4.05 ppm in the imine. In the ^{13}C NMR the C-5 carbon in **20a** was shifted upfield to δ 150.5 ppm as compared to δ 175.0 ppm for the imine. Using the optimized conditions, dehydropyrrolidines (+)-**19b−e** were converted to the corresponding nitrones (*S*)-**20b−e** in quantitative yield. While the ^{1}H NMR results of the crude nitrones were clean, attempts to purify them by chromatography resulted in decomposition. For this reason the nitrones were used without purification in the [3 + 2] cycloaddition reactions discussed below.

Formation of Isoxazolidines and Lactams. Heating nitrone **20a** (R = Me) in toluene for 24 h gave less than 20% yield of tricyclic isoxazolidines (1*S*,2*R*,3*R*,6*S*)-(−)-**21a** (Scheme 6, Table 1, entry 1). The yield improved to 45−50% on heating for 48 h (Table 1, entry 2). In xylene at 143 °C **20a** decomposed (Table 1, entry 3). In these experiments a considerable amount of a dark residue was produced. Since it was shown that (−)-**21a** was stable under these reaction conditions, it suggests that the nitrone was decomposing. Due to the difficulty associated with isolation of the volatile isoxazolidine (−)-**21a** (R = Me), it was converted into a water-soluble hydrochloride salt by treating with aqueous 5% HCl. Neutralization of the aqueous phase with solid sodium carbonate and extraction into diethyl ether afforded isoxazolidine (−)-**21a** in moderate yield (Table 1, entries 1−8). The structure of (1*S*,2*R*,3*R*,6*S*)-(−)-**21a** is supported by characteristic proton resonances at δ 4.93 ppm for the C-1 proton (doublet) and at δ 2.44 ppm for the C-2 proton (singlet) in the ^{1}H NMR spectra.[8]

Heating nitrone **20b** (R = Et) under the optimized conditions, toluene at 110 °C for 48 h, resulted in formation of both the tricyclic isoxazolidine (−)-**21b** and the lactam (−)-**22b** in a 1:1 ratio. Upon purification only the lactam (−)-**22b** was isolated in 32% yield (Scheme 6, Table 1, entry 9). Under similar conditions nitrones (*S*)-**20c** (R = *n*-Pr) and (*S*)-**20d** (R = *n*-C_5H_{11}) gave only the corresponding lactams (−)-**22c,d** (Table 1, entries 11, and 13). Interestingly nitrone (*S*)-**20e** (R = Ph) afforded a 1:3 mixture of isoxazolidine and lactam (Table 1, entry 15). The olefin protons at δ 6.9 and 5.90 ppm in the ^{1}H NMR and the carboxylic carbons at approximately 179−178 ppm in the ^{13}C NMR support the lactam structures (see below).

Table 1. Intramolecular [3 + 2] Cycloaddition of Nitrones 20 to Isoxazolidines (−)-21 and Lactam (*S*)-(−)-22

entry	nitrone **20** (R =)	solvent, °C	time, h	Al(O^{t}Bu)$_3$, mol %	products (% yield) isoxazoline **21**, lactam **22**
1	**20a** (Me)	PhMe, 110	24	none	**21a** (20)
2			48		**21a** (45−50)
3		xylene, 143	24		decomp
4		PhH	24	10	**21a** (<10)
5		PhMe, 110	24	10	**21a** (25)
6		PhMe, 110	72	50	**21a** (70)
7		PhMe, 110	72	100	**21a** (40)
8		xylene, 143	24	10	decomp
9	**20b** (Et)	PhMe, 110	48		**21b**:**22b** 1:1[a] **22b** (32)
10		PhMe, 110	96	50	**21b** (64)
11	**20c** (*n*-Pr)	PhMe, 110	48		**22c** (40)
12		PhMe, 110	72	50	**21c** (65)
13	**20d** (*n*-C_5H_{11})	PhMe, 110	48		**22d** (62)
14		PhMe, 110	96	50	**21d** (68)
15	**20e** (Ph)	PhMe, 110	48		**21e**:**22e** 1:3[a] **22e** (50)
16		PhMe, 110	72	50	**21e** (50), **22e** (40)

[a]Ratio of isoxazolidine:amide determined by ^{1}H NMR on the crude reaction mixture.

Nitrones on heating can rearrange to oxaziridines, and oxaziridines can rearrange to amides.[17] To verify the source of the lactams, the corresponding oxaziridines, oxaziridine **23c** (R = *n*-Pr) and **23d** (R = *n*-C_5H_{11}) were prepared as mixtures of isomers by oxidation of dehydropyrrolidines (+)-**19c** and

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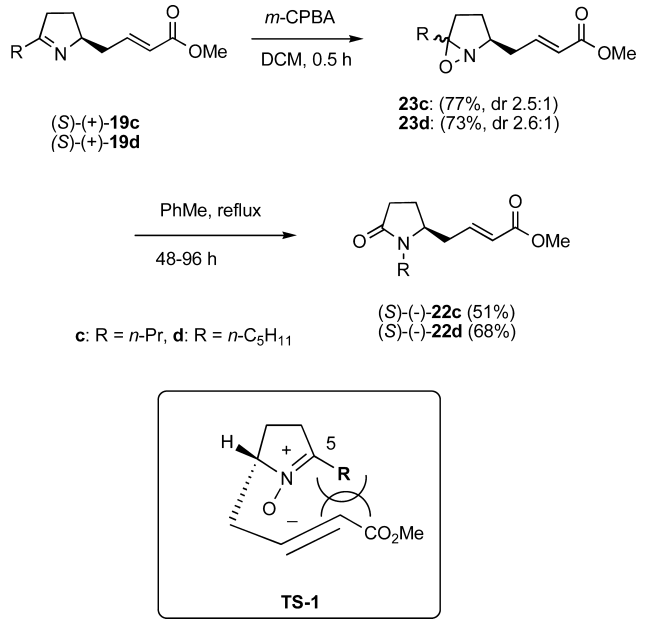
(+)-**19d** with *m*-CPBA (Scheme 7). However, heating oxaziridine **23c** under the cycloaddition reaction conditions

Scheme 7



resulted in no reaction. When **23c** was refluxed in toluene for 96 h in the presence of a catalytic amount of peroxorhenium complex, prepared by reacting 2 mol % MTO with UHP, lactam (*S*)-(−)-**22c** was obtained in 51% yield (Scheme 7). By contrast oxaziridine **23d** afforded the lactam (−)-**22d** in 68% yield after 48 h in the absence of the catalyst. Both lactams were identical to those obtained on heating nitrones **20c** and **20d** (Table 1, entries 11 and 13).

As shown in transition state **TS-1** in Scheme 7 a possible rationale for the formation of amide rather than isoxazolidine assumes a steric interaction between the substituent at C-5 in the cyclic nitrones and the carbomethoxy group inhibiting cycloaddition and leading to oxaziridine formation. If this is correct, the amount of the amide formed should increase with increasing size of the C-5 substituent. Indeed nitrone **20a** (R = Me) gave only the isoxazolidine, while nitrone **20b** (R = Et) gave mixtures of isoxazolidine and amide. Nitrones **20c** (*n*-Pr) and **20d** (R = *n*-C_5H_{11}) gave only the amides (Table 1, entries 2, 9, 11, and 13). However, nitrone **20e** (R = Ph) having the bulky C-5 phenyl group gave both isoxazolidine and amide (Table 1, entry 15). The reason for this is not readily apparent but may be related to a stabilizing interaction between the phenyl group and the antibonding orbital of the carbonyl in the carbomethoxy group at C-2.[20]

Nitrone 1,3-dipolar cycloadditions are favored by Lewis acids that can coordinate to the α,β-unsaturated carbonyl moiety.[20] Initial attempts using 10 mol % of Lewis acids such as $BF_3{\cdot}OEt_2$ and $Ti(O^iPr)_4$ to catalyze the reaction of nitrone **20d** (R = C_5H_{11}) in toluene at 110 °C resulted in decomposition. However, 10 mol % of $La(OTf)_3$, $Cu(OTf)_3$, or $Sc(OTf)_3$ under similar conditions resulted in the formation of both isoxazolidine (−)-**21d** and amide (−)-**22d** in about equal amounts, but only the amide could be isolated in poor yield, i.e., <30%. Higher amounts of these Lewis acids, 20 mol %, resulted in decomposition. Attempts to improve the yield of (−)-**21d** by variation of the temperature and time were also unsuccessful.

Because the Lewis acid can also coordinate to the nitrone, it was thought that a bulky Lewis acid might preferentially activate the α,β-unsaturated ester group in the nitrone. Indeed, heating nitrone **20a** (R = Me) with 10 mol % of commercially available aluminum *tert*-butoxide [$Al(O^tBu)_3$] for 24 h gave the desired tricyclic isoxazolidine (−)-**21a** in 25% yield (Table 1, entry 5). The optimum conditions were heating for 72 h with 50 mol % of $Al(O^tBu)_3$ affording a 70% yield of (−)-**21a**, (Table 1, entry 6). Significantly, when these conditions were applied to nitrones **20b** (R = Et), **20c** (R = *n*-Pr), and **20d** (R = *n*-C_5H_{11}), none of the corresponding lactams **22** were detected, but 72 to 96 h of heating was required (Table 1, entries 10, 12, and 14). However, even under these conditions phenyl nitrone **20e** gave about equal amounts of the isoxazolidine (−)-**21e** and lactam (+)-**22e** (Table 1, entry 16).

The reaction mixtures were treated with 5% HCl and neutralization of the aqueous phase to give isoxazolidines (−)-**21a**−**c**. Isoxazolidine (−)-**21d** (R = *n*-C_5H_{11}) failed to be extracted into the aqueous phase and was isolated from the toluene solution. Isoxazolidine (−)-**21e** (R^1 = Ph) with aqueous 5% HCl resulted in decomposition. Repeated washings of the reaction mixture with water to remove the $Al(O^tBu)_3$, resulted in a 1:1 mixture of (−)-**21e** and amide (+)-**22d** in 95% combined yield, which were separated by chromatography affording the isoxazolidine (−)-**21e** as a white solid in 50% yield.

The X-ray crystallographic structure of (−)-**21e** (see Supporting Information) reveals that the molecule is best described as a C_7ON tricyclic core with a pendant phenyl group on C(3), and a carbomethoxy group on C(2). These groups are both oriented "vertically" such that the C(10)−C(2)−C(3)−C(12) dihedral angle is nearly zero (2.1°), and the phenyl and carbomethoxy groups are oriented approximately parallel such that planar faces of the carbomethoxy and the phenyl group are oriented toward one another. The angle between the least-squares fitted planes defined by the phenyl ring and by the carbomethoxy group is 41.6° and is entirely the result of the angle between the C(3)−C(12) and C(2)−C(10) bond vectors. The planes defined by the phenyl and carbomethoxy groups are nearly perpendicular to the C(2)−C(3) bond vector (82.2° and 82.0°, respectively). The proximity of the carbomethoxy group to the phenyl ring is further supported by the upfield shift of the methyl protons of the carbomethoxy group to δ 3.04 ppm compared to δ 3.68 ppm for this group in isoxazolidines (−)-**21a**−**d**.

Heating isoxazolidine (−)-**21a**−**d** with 10 equiv of methylmethanesulfonate in DCM for 48 h gave the quaternary ammonium salts **24** in quantitative yield (Scheme 8). However, (−)-**21e** (R = Ph) required 72 h. Attempts to increase the reaction rate using higher boiling solvents such as benzene resulted in decomposition. The salts were dissolved in water to separate the excess methylmethanesulfonate from the isoxazolidinium salts **24**, and the latter were recovered from the aqueous solution by lyophilized. Cleavage of the N−O bond in **24** was accomplished by hydrogenolysis with palladium on charcoal (5% Pd−C) to give ecgonine methyl ester derivatives **25** in excellent yield (Table 2). As can be seen from the results summarized in Table 2, at 1 atm of H_2 **24a**−**c** took 48 h for completion (Table 2, entries 1, 3 and 5) and at 4 atm for 15−30 h (Table 3, entries 2 and 4). Isoxazolidinium salt **24e** (R = Ph) at 1 atm of H_2 for 48 h gave a complex mixture of products

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Scheme 8

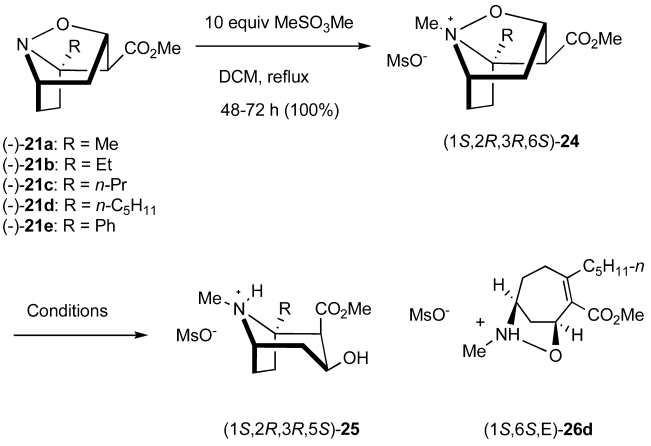

Table 2. Hydrogenolysis of Isoxazolidinium Salts 24 with 5% Pd–C in MeOH

entry	24 (R =)	H_2, atm	time, h	25 (% yield)
1	**24a** (Me)	1	48	**25a** (100)
2		4	30	**25a** (100)
3	**24b** (Et)	1	48	**25b** (100)
4		4	15	**25b** (100)
5	**24c** (*n*-Pr)	1	48	**25c** (100)
6	**24d** (*n*-C_5H_{11})	1	48	(+)-**24d** [**27**, (32%)][a]
7	**24d** (*n*-C_5H_{11})	4	6	**25d** (100)
8	**24e** (Ph)	1	48	complex mixture
9		1	10	**25e** (<80)[b]

[a]See Table 3 and discussion below. [b]Mixture containing predominantly **25e** and other unidentified materials.

and less than 20% of **25e** was formed (Table 2, entry 8). Hydrogenation for 10 h (Table 2, entry 9) gave mostly **25e**, but it could not be purified and was taken on to the next step without additional purification. Unexpectedly isoxazolidinium salt **24d** (R = *n*-C_5H_{11}) at 1 atm of H_2 and 48 h gave bridged bicyclo[4.2.1]isoxazolidine salt **26d** (Table 2, entry 6). Its formation will be discussed in detail below. Fortunately, at 4 atm of H_2 and 6 h **24d** gave a quantitative yield of alcohol (+)-**25d** (Table 2, entry 7).

In the preceding section hydrogenolysis of isoxazolidinium salt **24d** (R = *n*-C_5H_{11}) at 1 atm gave a new compound tentatively identified as salt **26d**. In the crude ^{1}H NMR two new doubles appeared at δ 5.2 (J = 8.8 Hz) and δ 1.88 (J = 12 Hz). The ratio of **24d**:**26d** determined by ^{1}H NMR was estimated to be 1:0.5 (Table 2, entry 6). Treatment of the mixture with satd K_2CO_3 solution gave a 32% isolated yield of an oil identified as bridged bicyclo[4.2.1]isoxazolidine (*E*,1*S*,6*S*)-(+)-**27d** based on 2D NMR analysis (Scheme 9). The ^{1}H NMR of (+)-**27d** is characterized by doublets at δ 5.2 ppm (J = 8.8 Hz) and at 1.88 ppm (J = 2 Hz) for the C-1 proton and C-9 protons. In the ^{13}C NMR the C-2 and C-3 olefinic carbons are at δ 157.4 and δ 131.8 ppm, respectively, and there were seven methylene carbons and two methine units (see Experimental Section).

A reasonable mechanism for the formation of (+)-**27d** is base-catalyzed elimination of the C-2 carbomethoxy proton as shown in Scheme 9. The driving force for this reaction is relief of ring strain and formation of the C–C double bond. When (+)-**24d** (R = *n*-C_5H_{11}) was treated with pyridine or K_2CO_3

Table 3. Rearrangement of Isoxazolidinium Salts 24 to 26 and 27 in MeOH at 25 °C

entry	(R =)	conditions[a]	time, h	ratio **24**:**26**[a]	**27** (% yield)
1	**24a** (Me)	5% Pd–C	48	NR	
2		1:1 MeOH/Et_3N	18		**27a** (95)
3		1:1 MeOH/pyridine	18	NR	
4	**24b** (Et)	1:1 MeOH/pyridine	48	NR	
6	**24d** (*n*-C_5H_{11})	5% Pd–C/MeOH	48	1:0.48	**27d** (32)[b]
7		5% Pd–C	96	1:0.52	
8		5% Pd–C	48 (reflux)	1:0.5	
9		5% Pd–C	48 and 48[c]	1:0.5	**27d**
9		MeOH	48	NR	
10		pyridine[d]	48	NR	
11		1:1 MeOH/pyridine	48	NR	
12		MeOH/satd K_2CO_3	48	NR	
13		1:1 MeOH/Et_3N	18		**27d** (83)
14		1:1 MeOH/Et_3N	4		
15		5% Pd–C, 4 atm H_2	6		**27d** (100)[e]
16		MeCN, DABCO[f]	18		**27d** (84)
17		5% Pd–C, 4 atm H_2/1 atm H_2[g]	6		**25d** (99)
18	**24e** (Ph)	5% Pd–C	48	NR	
19		1:1 MeOH/pyridine	18		**27e** (84)
20		1:1 MeOH/Et_3N	18		**27e** (81)

[a]Determined by ^{1}H NMR on the crude reaction mixture by integration of the protons at δ 5.2 ppm for **26** and δ 5.29 ppm for **24d**. [b]Isolated by treatment of the crude reaction mixture with satd K_2CO_3. [c]Reaction run for 48 h and a second addition of 5% Pd. [d]Pyridine as the solvent. [e]See Table 2. [f]DABCO, 4 equiv. [g]Pd saturated with H_2 at 4 atm followed by addition of **24d** at 1 atm H_2.

there was no reaction (Table 3, entries 10, 11 and 12). However, with Et_3N an 83% isolated yield of (+)-**27d** was obtained (Table 2, entries 13 and 14). Similar results were observed for (−)-**24a** (R = Me) (Table 3, entry 2). Whereas isoxazolidinium salts **24a** (R = Me) and **24b** (R = Et) did not react with pyridine, (+)-**24e** (R = Ph) did affording (+)-**27e** in 84% yield (Table 3, entries 3. Four and 15). Isoxazolidines are important intermediates in the synthesis of natural product and other biologically important compounds.[21] Bridged bicyclo[4.2.1]isoxazolidines such as (+)-**27** are rare, with the few known examples being employed in the synthesis of glycoside inhibitors[22,23] and cocaine analogues.[6e]

The reason that (+)-**24d** (R = *n*-C_5H_{11}) is the only isoxazolidinum salt to form bridged bicyclo[4.2.1]isoxazolidine (+)-**27d** under the hydrogenolysis conditions, 5% Pd–C at 1 atm of H_2 but cleavage of the N–O bond to give alcohol (+)-**25d** at 4 atm of H_2 is not readily apparent (Table 1, entries 6 and 7). Furthermore, as can be seen from Table 3, entry 6, this transformation does not require hydrogen. Palladium-catalyzed dehydrogenation of secondary alcohols to ketones,[24] oximes to nitriles,[25] amines to imines,[26] and aromatization of cyclic dienes[27] is well-known. We speculate that the C-1 *n*-pentyl group in (+)-**24d** sterically inhibits coordination of the Pd–H_2 species with the N–O bond favoring coordination at

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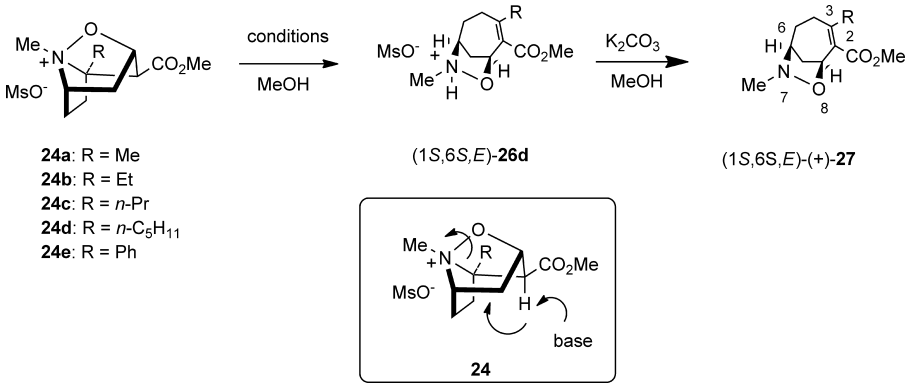
Scheme 9



24a: R = Me
24b: R = Et
24c: R = *n*-Pr
24d: R = *n*-C_5H_{11}
24e: R = Ph

(1*S*,6*S*,*E*)-**26d**

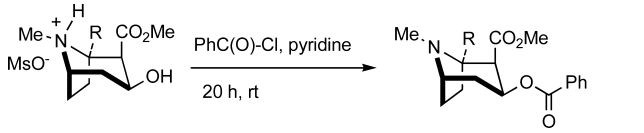
(1*S*,6*S*,*E*)-(+)-**27**

24

the C-2 carbomethoxy group leading to (+)-**27d**. At higher pressures of H_2 Pd is likely to be completely saturated, preventing coordination with the CO_2Me group resulting in N−O bond cleavage to give alcohol (+)-**25d**. Indeed when the catalyst was hydrogenated in MeOH at 4 atm for 12 h to saturate the Pd and the reaction vessel exposed to the atmosphere, followed by addition of (+)-**24d** and hydrogenation at 1 atm of H_2 for 6 h, a quantitative isolated yield of alcohol (+)-**25d** was realized (Table 3, entry 17).

Cocaine C-1 Analogues. The first examples of C-1 substituted cocaine analogues were prepared by benzoylation of the secondary alcohol in tropanes **25** with 1.5 equiv of benzoyl chloride in pyridine at rt affording (−)-**28a** (R = Me), (−)-**28b** (R = Et), (−)-**28c** (R = *n*-Pr), (+)-**28d** (R = *n*-C_5H_{11}), and (+)-**28e** (R = Ph) as pale yellow oils in good to excellent yields (Scheme 10).

Scheme 10



25

(1*R*,2*R*,3*S*,5*S*)-(-)-**28a**: (94%)
(-)-**28b**: (75%)
(-)-**28c**: (92%)
(+)-**28d**: (82%)
(+)-**28e**: (80%)

a: R = Me; **b**: R = Et; **c**: R = *n*-Pr; **d** R = *n*-C_5H_{11}; **e**: R = Ph

SUMMARY AND CONCLUSIONS

The first examples of cocaine analogues **28** having methyl, ethyl, *n*-propyl, *n*-pentyl, and phenyl at the bridgehead or C-1 position of the cocaine tropane skeleton were prepared in nine steps from sulfinimine-derived masked oxo-sulfinimines (+)-**6** and (+)-**7**. The key step in the synthesis was a highly stereoselective [3 + 2] cycloaddition reaction of α,β-unsaturated pyrrolidine nitrones (*S*)-**20**. In the presence of the Lewis acid Al(O^tBu)$_3$ the nitrones gave tricyclic isoxazolidines (−)-**21**, which were transformed in three steps to the cocaine analogues. In the absence of the Lewis acid the nitrones gave lactams resulting from rearrangement of the nitrone to an intermediate oxaziridine, which rearranged on heating to the lactam. An unusual Pd- and base-promoted rearrangement of methanesulfonate salts of isoxazolidine **24** to bridge bicyclic[4.2.1] isoxazolidines (+)-**27** was discovered in studies of the hydrogenation of isoxazolidine (+)-**24d**. These heterocycles are potentially useful new chiral scaffolds for enantioselective synthesis. Our new methodology has the potential for the enantioselective syntheses of a wide variety of new and novel cocaine analogues not only having varied substituents at the C-1 position, but at other positions as well because of the diverse groups that can be introduced using sulfinimine chemistry.

EXPERMENTAL SECTION

Ketal aldehydes 3-(2-methyl-1,3-dioxolan-2-yl)propanal (**3a**),[11a] 3-(2-propyl-1,3-dioxolan-2-yl)propanal (**3c**),[28] 3-(2-phenyl-1,3-dioxolan-2-yl)propanal (**3e**),[12] and (S_S)-(+)-3-(2-methyl-1,3-dioxolan-2-yl)-propylidene-*p*-toluenesulfinamide (**6a**)[11c] were prepared as previously described.

4-Hydroxy-*N*-methoxy-*N*-methylhexanamide (9b). Typical Procedure. In a 100 mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed *N*,*O*-dimethyl hydroxylamine hydrochloride (2.9 g, 29.8 mmol) and dihydro-5-ethyllfuran-2(3*H*)-one (**8b**) (2.2 g, 19.3 mmol) in THF (96 mL), and the solution was cooled to −15 °C in an salt−ice mixture. Isopropylmagnesuim chloride (2.0 M solution in THF, 28.8 mL, 57.6 mmol) was added slowly *via* syringe, and the reaction mixture was stirred at −20 °C for 20 min. At this time the solution was quenched with satd NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (60% EtOAc/hexanes) gave 2.87 g (85%) of a colorless oil: IR (neat) 3418, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.943 (t, J = 7.2 Hz, 3H), 1.49 (m, 2H), 1.72 (m, 1H), 1.85 (m, 1H), 2.58 (m, 3H), 3.18 (s, 3H), 3.54 (b, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 9.9, 28.5, 30.4, 31.1, 61.2, 72.9, 82.0, 175.1. HRMS calcd for $C_8H_{18}NO_3$ (M + H) 176.1287, found 176.1279.

4-Hydroxy-*N*-methoxy *N*-methylheptamide (9c). Prepared from γ-heptalactone. Flash chromatography (50% EtOAc in hexanes) afforded a clear oil: IR (film) 3440, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.1 Hz, 3H), 1.45 (m, 4H), 1.72 (m, 1H), 1.84 (m, 1H), 2.57 (m, 3H), 3.18 (s, 3H), 3.64 (m, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.8, 28.5, 31.6, 32.2, 39.9, 61.2, 71.3, 175.1. HRMS calcd for $C_9H_{20}NO_3$ (M + H) 190.1443, found 190.1436.

4-Hydroxy-*N*-methoxy-*N*-methylnonanamide (9d). Prepared from dihydro-5-pentylfuran-2(3*H*)-one. Flash chromatography (40% EtOAc/hexanes) gave a colorless oil: IR (neat) 3418, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.31 (b, 5H), 14.3(b, 3H), 1.70 (m, 1H), 1.86 (m, 1H), 2.56 (m, 3H), 3.18 (s, 3H), 3.62 (b, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 25.3, 28.4, 31.5, 31.8, 32.1, 37.6, 175.0. HRMS calcd for $C_{11}H_{24}NO_3$ (M + H) 218.1756, found 218.1753.

***N*-Methoxy-*N*-methyl-4-oxonohexanamide (10b). Typical Procedure.** In a 250 mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon

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inlet were placed IBX (13.44 g, 48 mmol) in dry EtOAc (80 mL, and the mixture was cooled to 0 °C. A solution of **9b** (2.8 g, 16 mmol) in EtOAc (80 mL) was added, and the reaction mixture was refluxed for 3 h, cooled to rt, and filtered. The filter cake was washed with EtOAc (2 × 30 mL), and the combined organic phase combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (40% EtOAc/hexanes) gave 2.07 g (75%) of a colorless oil: IR (neat) 1698, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 3H), 2.50 (q, J = 7.3 Hz, 2H), 2.72 (b, 4H), 3.16 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 7.6, 25.7, 32.0. 35.9, 36.0, 61.0, 173.1, 210.3. HRMS calcd for $C_8H_{16}NO_3$ (M + H) 174.1130, found 174.1123.

***N*-Methoxy-*N*-methyl-4-oxoheptamide (10c).** Flash chromatography (50% EtOAc in hexanes) afforded a clear oil: IR (film) 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.58 (m, 2H), 2.42 (t, J = 7.3 Hz, 2H), 2.71 (bm, 4H), 3.13 (s, 3H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.6, 17.1, 25.6, 32.1, 36.3, 44.7, 61.0, 173.1, 209.8. HRMS calcd for $C_9H_{18}NO_3$ (M + H) 188.1287, found 188.1279.

***N*-Methoxy-*N*-methyl-4-oxononanamide (10d).** Flash chromatography (20% EtOAc/hexanes) gave a colorless oil: IR (neat) 1698, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.29 (m, 4H), 1.57 (m, 2H), 2.46 (t, J = 7.6 Hz, 2H), 2.73 (s, 4H), 3.16 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.4, 23.4, 25.7, 31.3, 32.1, 36.5, 42.9, 61.1, 173.2, 210.1. HRMS calcd for $C_{11}H_{22}NO_3$ (M + H) 216.1600, found 216.1595

***N*-Methoxy-*N*-methyl-3-(2-ethyl-1,3-dioxolan-2-yl)-propanamide (11b). Typical Procedure.** In a 250 mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar and rubber septum were placed **10b** (2.0 g, 11.56 mmol), ethylene glycol (1.07 g, 17.34 mmol), PTSA.H_2O (0.0679 g, 0.34 mmol), and benzene (140 mL). The reaction mixture was refluxed using a Dean–Stark column for 12 h and concentrated, and the residue was diluted with EtOAc (100 mL). The organic phase was washed with satd $NaHCO_3$ (3 × 30 mL), H_2O (2 × 20 mL), and brine (2 × 25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (40% EtOAc/hexanes) gave 2.00 g (80%) of a colorless oil: IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ (t, J = 7.6 Hz, 3H), 1.63 (q, J = 7.6 Hz, 2H), 1.96 (m, 2H), 2.47 (m, 2H), 3.15 (s, 3H), 3.67 (s, 3H), 3.93 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 7.9, 26.4, 29.8, 30.9, 32.3, 35.9, 36.1, 61.2, 64.4, 111.3, 174.4. HRMS calcd for $C_{10}H_{20}NO_4$ (M + H) 218.1392, found 218.1386.

***N*-Methoxy-*N*-methyl-3-(2-propyl-1,3-dioxolan-2-yl)-propanamide (11c).** Flash chromatography (70% EtOAc in hexanes) afforded a clear oil: IR (film) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 1.35 (m, 2H), 1.55 (m, 2H), 1.93 (m, 2H), 2.44 (t, J = 7.6 Hz, 2H), 3.12 (s, 3H), 3.64 (s, 3H), 3.89 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.2, 16.9, 26.3, 31.3, 32.2, 39.3, 61.1, 64.7, 110.9, 174.3. HRMS calcd for $C_{11}H_{22}NO_4$ (M + H) 232.1549, found 232.1544.

***N*-Methoxy-*N*-methyl-3-(2-pentyl-1,3-dioxolan-2-yl)-propanamide (11d).** Flash chromatography (15% EtOAc/hexanes) afforded 75% of a colorless oil: IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.6 Hz, 3H), 1.31 (b, 6H), 1.61 (m, 2H), 1.97 (m, 2H), 2.48 (m, 2H), 3.17 (s, 3H), 3.68 (s, 3H), 3.94 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.5, 23.3, 26.4, 31.3, 32.0, 32.2, 37.0, 61.1, 64.8, 111.1, 174.4. HRMS calcd for $C_{13}H_{26}NO_4$ (M + H) 260.1862, found 260.1860.

3-(2-ethyl-1,3-dixoxlan-2-yl)propanal (3b).[29] Typical Procedure. In a 100 mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet, was placed $LiAlH_4$ (0.525 g, 13.82 mmol) in THF (40 mL), and the reaction mixture was cooled to −78 °C. A solution of **11b** (2.0 g, 9.21 mmol) in THF (52 mL) was added slowly, and the reaction mixture was stirred at −78 °C for 1 h, quenched with H_2O (50 mL), and extracted with EtOAc (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 50 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc/hexanes) gave 1.23 g (85%) of a colorless oil: IR (neat) 1704, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.6 Hz, 3H), 1.57 (m, 2H), 2.00 (m, 2H), 2.41 (m, 2H), 3.90 (s, 4H), 9.67 (t, J = 1.6, 1H); ^{13}C NMR($CDCl_3$) δ 7.8, 29.1, 30.0, 37.9, 64.7, 110.8, 201,6. HRMS calcd for $C_8H_{15}O_3$ (M + H) 159.1021, found 159.1014.

3-(2-Pentyl-1,3-dixoxlan-2-yl)propanal (3d). Flash chromatography (10% EtOAc/hexanes) gave a colorless oil: IR (neat) 1704, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 6.8 Hz, 3H), 1.26 (m, 6H), 1.56 (m, 2H), 2.01 (t, J = 6.8 Hz, 2H), 2.42 (m, 2H), 3.90 (m, 4H), 9.69 (t, J = 2.72 Hz, 1H); ^{13}C NMR($CDCl_3$) δ 14.0, 22.6, 23.6, 29.8, 32.0, 37.6, 38.3, 65.0, 111.0, 202.2. HRMS calcd for $C_{11}H_{21}O_3$ (M + H) 201.1491, found 201.1482.

(*S*)-(+)-3-(2-Propyl-1,3-dioxalan-2-yl)propylidene-*p*-toluenesulfinamide (6c). Typical Procedure. To a 500 mL round-bottomed flask equipped with magnetic stirring bar and argon inlet was placed **3c** (2.22 g, 12.88 mmol) in dry CH_2Cl_2 (100 mL). (*S*)-(+)-*p*-Toluenesulfinamide (1.99 g, 12.88 mmol) was added followed by $Ti(OEt)_4$ (14.71 g, 64.45 mmol), and the reaction was stirred at rt for 24–48 h until complete. At this time, the reaction mixture was cooled to 0 °C and then quenched with H_2O (6 mL). After 5 min of stirring, the solids were filtered, the filter cake was washed with DCM (3 × 50 mL), and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc/hexanes) gave 2.79 g (70%) of slightly yellow oil: IR (film) 1625 cm^{-1}; $[\alpha]^{20}_D$ +230.2 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.36 (m, 2H), 1.55 (m, 2H), 1.96 (m, 2H), 2.39 (s, 3H), 2.55 (m, 2H), 3.86 (m, 4H), 7.29 (bd, J = 7.8 Hz, 2H), 7.56 (bd, J = 8.1 Hz, 2H), 8.23 (t, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.1, 30.5, 32.5, 39.7, 64.9, 65.0, 110.8, 124.6, 129.7, 141.6, 141.8, 167.3; HRMS calcd for $C_{16}H_{24}NO_3S$ (M + H) 310.1477, found 310.1473.

(*S*)-(+)-3-(2-Phenyl-1,3-dioxolan-2-yl)propylidene-*p*-toluenesulfinamide (6e). Flash chromatography (12% EtOAc/hexanes) yielded 0.710 g (65%) of a slightly yellow oil: $[\alpha]^{20}_D$ +206.0 (*c* 1.30, $CHCl_3$); IR (neat) 3051, 1635, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (m, 2H) 2.33 (s, 3H), 2.53 (dt, J = 7.6 Hz, 4.4 Hz, 2H), 3.66 (m, 2H), 3.88 (m, 2H), 7.24 (m, 5H), 7.35 (m, 2H), 7.48 (d, J = 10.0 Hz, 2H), 8.18 (t, J = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 30.6, 35.9, 64.5, 109.5, 124.6, 125.6, 128.0, 128.2, 129.7, 141.5, 142.1, 167.1. HRMS calcd for $C_{19}H_{21}NNaO_3S$ (M + Na) 366.1140, found 366.1139

(*S*)-(+)-3-(2-Ethyl-1,3-dioxolan-2-yl)propylidene-*tert*-butylsulfinamide (7b). Typical Procedure. In a 250 mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed **3b** (1.2 g, 7.59 mmol) in THF (76 mL) and (*S*)-(+)-*tert*-butylsulfinamide (0.919 g, 7.59 mmol), and $Ti(OEt)_4$ (5.19 g, 22.78 mmol) were added. The reaction mixture was stirred at rt for 24 h, cooled to 0 °C, and quenched by addition of brine solution (75 mL). The solution was filtered through Celite, the filter cake was washed with EtOAc (2 × 75 mL), and the combined organic phases were washed with brine (75 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc/hexanes) gave 1.58 g (80%) of a colorless oil: $[\alpha]^{20}_D$ +163.4 (*c* 2.085, $CHCl_3$); IR (neat) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) 0.917 (t, J = 7.6 Hz, 3H), 1.18 (s, 9H), 1.64 (m, 3H), 1.97 (m, 2H), 2.57 (m, 2H), 3.94 (s, 4H), 8.08 (t, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 8.0, 22.1, 30.0, 30.5, 31.9, 56.3, 64.9, 65.0, 111.0, 169.3. HRMS calcd for $C_{12}H_{24}NO_3S$ (M + H) 262.1477, found 262.1477

(*S*)-(+)-3-(2-Methyl-1,3-dioxalan-2-yl)propylidene-*tert*-butylsulfinamide (7a). Flash chromatography (40% EtOAc/hexanes) gave 85% of a clear oil: $[\alpha]^{20}_D$ +228.9 (*c* 1.59, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.35 (s, 3H), 2.01 (m, 2H), 2.61 (m, 2H), 3.95 (m, 4H), 8.09 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2, 23.9, 30.7, 34.4, 56.3, 64.5, 64.6, 109.0, 169.1. HRMS calcd for $C_{11}H_{22}NO_3S$ (M + H) 248.3623, found 248.3620.

(*S*)-(+)-3-(2-Pentyl-1,3-dioxolan-2-yl)propylidene-*tert*-butylsulfinamide (7d). Flash chromatography (25% EtOAc/hexanes) gave 1.59 g (70%) of a colorless oil: $[\alpha]^{20}_D$ +156.6 (*c* 3.56, $CHCl_3$); IR (neat) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.18 (s, 9H), 1.31 (m, 6H), 1.59 (m, 2H), 1.98 (m, 2H), 2.57 (m, 2H), 3.94 (m, 4H), 8.08 (t, J = 4.4 Hz, 1H); ^{13}C NMR($CDCl_3$) δ 13.9, 22.2, 22.4, 23.4, 30.6, 31.9, 32.4, 37.2, 56.4, 64.8, 64.9, 110.8, 169.3. HRMS calcd for $C_{15}H_{30}NO_3S$ (M + H) 304.1946, found 304.1945.

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(*S*)-(+)-3-(2-Phenyl-1,3-dioxalan-2-yl)propylidene-*tert*-butylsulfinamide (7e). Flash chromatography (40% EtOAc/hexanes) gave 85% of a white solid: mp 60−61 °C; $[\alpha]^{20}_{D}$ +155.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 2.24 (m, 2H), 2.60 (m, 2H), 3.78 (m, 2H), 4.02 (m, 2H), 7.35 (m, 3H), 7.45 (m, 2H), 8.08 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 30.7, 35.9, 56.5, 64.5, 64.6, 109.6, 125.6, 128.1, 128.2, 142.1, 169.2. HRMS calcd for $C_{16}H_{24}NO_3S$ (M + H) 310.1477, found 310.1477.

(S_S,3*S*)-(+)-Methyl *N*-(*p*-Toluenesulfinyl)-3-amino-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate (12a). Typical Procedure. To a 500 mL round-bottomed flask equipped with magnetic stirring bar and argon inlet was added NaHMDS (53.63 mL, 53.63 mmol, 1.0 M solution in THF) in anhydrous ether (300 mL). To this solution methyl acetate (3.61 g, 48.75 mmol) was added dropwise at −78 °C slowly via syringe, and the reaction mixture was stirred at this temperature for 1 h. At this time (+)-**6a** (5.48 g, 19.50 mmol) in THF (20 mL) was added to the above solution slowly via cannula. After 2 h of stirring at −78 °C, the reaction mixture was quenched by adding satd NH_4Cl solution (30 mL), and H_2O (100 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes/EtOAc, 50:50) gave 6.92 g (75%) of a clear oil (dr >99:1): IR (film) 3230, 1740 cm^{-1}; $[\alpha]^{20}_{D}$ +80.4 (*c* 1.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.73 (m, 3H), 1.87 (m, 1H), 2.40 (s, 3H), 2.60 (dq, *J* = 5.4 Hz, *J* = 16.4 Hz, 2H), 3.65 (s, 3H), 3.68 (m, 1H), 3.94 (m, 4H), 4.62 (d, *J* = 8.8 Hz, 1H), 7.28 (bd, *J* = 8.4 Hz, 2H), 7.57 (td, *J* = 1.6 Hz, *J* = 8.0 Hz, 2H); ^{13}C NMR($CDCl_3$) δ 21.3,23.9, 30.0, 35.4, 40.5, 51.7, 52.6, 64.6, 64.7, 109.7, 125.4, 129.5, 41.3, 142.4, 171.9. HRMS calcd for $C_{17}H_{25}NNaO_5S$ (M + Na) 378.1351, found 378.1333.

(S_S,3*S*)-(+)-Methyl *N*-(*p*-Toluenesulfinyl)-3-amino-5-(2-propyl-1,3-dioxolan-2-yl)pentanoate (12c). Flash chromatography (hexanes/EtOAc, 50:50) gave a clear oil (dr >99:1): IR (film) 3226, 1736, cm^{-1}; $[\alpha]^{20}_{D}$ +66.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.38 (m, 2H), 1.58 (m, 2H), 1.69 (m, 3H), 1.83 (m, 1H), 2.40 (s, 3H), 2.60 (dq, *J* = 16.6 Hz, *J* = 5.6 Hz, 2H), 3.65 (s, 3H), 3.68 (m, 1H), 3.92 (bs, 4H), 4.61 (d, *J* = 9.0 Hz, 1H), 7.28 (bd, *J* = 8.1 Hz, 2H), 7.58 (td, *J* = 8.1 Hz, *J* = 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.1, 21.3, 29.8, 33.3, 39.4, 40.5, 51.6, 52.7, 64.9 (2C), 111.4, 125.4, 129.5, 141.3, 142.4, 171.9. HRMS calcd for $C_{19}H_{29}NNaO_5S$ (M + Na) 406.1664, found 406.1665.

(S_S,3*S*)-(+)-Methyl *N*-(*p*-Toluenesulfinyl)-3-amino-5-(2-phenyl-1,3-dioxolan-2-yl)pentanoate (12e). Flash chromatography (hexanes/EtOAc, 50:50) gave a clear oil (dr >99:1): IR (film) 3230, 1740 cm^{-1}; $[\alpha]^{20}_{D}$ +62.6 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 1H), 1.94 (m, 1H), 2.01 (m, 1H), 2.32 (s, 3H), 2.49 (m, 2H), 3.54 (s, 3H), 3.61 (m, 1H), 3.67 (m, 2H), 3.92 (m, 2H), 4.50 (d, *J* = 9.2 Hz, 1H), 7.23 (m, 5H), 7.37 (m, 3H), 7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 29.5, 36.6, 40.6, 51.5, 52.5, 64.4, 64.5, 109.9, 125.4, 125.5, 127.8, 128.1, 129.4, 141.1, 142.3, 142.4, 171.7. HRMS calcd for $C_{22}H_{28}NO_5S$ (M + H) 418.1688, found 418.1687.

(S_S,3*S*)-(+)-Methyl *N*-(*tert*-Butylsulfinyl)-3-amino-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate (13a). Flash chromatography (hexanes/EtOAc, 50:50) gave a clear oil (dr >99:1): IR (film) 3235, 1730 cm^{-1}; $[\alpha]^{20}_{D}$ +44.0 (*c* 1.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.27 (s, 3H), 1.63 (m, 3H), 1.78 (m, 1H), 2.68 (m, 2H), 3.54 (m, 1H), 3.66 (s, 3H), 3.91 (m, 4H), 4.16 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 23.6, 29.9, 35.3, 40.2, 51.5, 53.8, 55.7, 64.4, 64.5, 109.5, 172.1. HRMS calcd for (M + H) $C_{14}H_{28}NO_5S$ 322.1688, found 322.1682.

(S_S,3*S*)-(+)-Methyl *N*-(*tert*-butylsulfinyl)-3-amino-5-(2-ethyl-1,3-dioxolan-2-yl)pentanoate (13b). Flash chromatography (80% EtOAc/hexanes) gave a colorless oil: $[\alpha]^{20}_{D}$ +29.2 (*c* 1.60, $CHCl_3$); IR (neat) 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 9H), 1.60 (m, 5H), 1.79 (m, 1H), 2.62 (dd, *J* = 16.0, 5.2 Hz, 1H), 2.79 (dd, J = 16.0, 5.2 Hz, 1H), 3.53 (b, 1H), 3.68 (s, 3H), 3.92 (s, 4H), 4.17 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0, 22.6, 29.7, 32.8, 40.3, 51.6, 54.0, 55.8, 64.8, 64.9, 111.6, 172.2. HRMS calcd for $C_{15}H_{30}NO_5S$ (M + H) 336.1845, found 336.1837.

(S_S,3*S*)-(+)-Methyl *N*-(*tert*-Butylsulfinyl)-3-amino-5-(2-pentyl-1,3-dioxolan-2-yl)pentanoate (13d). Flash chromatography (70% EtOAc/hexanes) gave a colorless oil: $[\alpha]^{20}_{D}$ +34.8 (*c* 1.375, $CHCl_3$); IR (neat) 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.21 (s, 9H), 1.27 (m, 6H), 1.55 (m, 3H), 1.62 (m, 1H), 2.61 (dd, *J* = 16.1, 5.6 Hz, 1H), 2.79 (dd, *J* = 16.1, 5.6 Hz, 1H), 3.53 (b, 1H), 3.68 (s, 3H), 3.92 (m, 4H), 4.18 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR($CDCl_3$) δ 13.9. 22.5, 22.6, 23.4, 29.8, 31.9, 33.2, 37.0, 40.3, 51.6, 54.0, 55.8, 64.8 (2 C's), 111.4, 172.2. HRMS calcd for $C_{18}H_{36}NO_5S$ (M + H) 378.2314, found 378.2314.

(S_S,3*S*)-(+)-Methyl *N*-(*tert*-Butylsulfinyl)-3-amino-5-(2-phenyl-1,3-dioxolan-2- yl)pentanoate (13e). Flash chromatography (hexanes/EtOAc, 50:50) gave 0.60 g (93%) of a clear oil (dr >99:1): IR (film) 3230, 1740 cm^{-1}; $[\alpha]^{20}_{D}$ +31.3 (*c* 2.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.62 (m, 2H), 1.94 (m, 1H), 2.03 (m, 1H), 2.65 (m, 2H), 3.55 (m, 1H), 3.65 (s, 3H), 3.75 (m, 2H), 4.00 (m, 2H), 4.09 (d, *J* = 8.8 Hz, 1H), 7.32 (m, 3H), 7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.5, 29.4, 36.5, 40.2, 51.5, 53.7, 55.7, 64.3, 64.4, 109.9, 125.4, 127.7, 128.0, 142.2, 172.1. HRMS calcd for $C_{19}H_{30}NO_5S$ 384.1845, found 384.1842.

(S_S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-5-(2-methyl-1,3-dioxolan-2-yl)pentanal (14a). Typical Procedure. In a 250 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar, and a rubber septum was placed (S_S,3*S*)-(+)-**12a** (2.64 g, 7.42 mmol) in toluene (75 mL). The solution was cooled to −78 °C, and diisobutylaluminumhydride (13.36 mL, 13.36 mmol, 1.0 M solution in toluene) was added slowly via syringe. After 1 h of stirring, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) at −78 °C and warmed to rt. The reaction mixture was diluted with EtOAc (50 mL) and water (40 mL). This mixture was filtered through a Celite pad, and the aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Chromatography (80% EtOAc/hexanes) afforded 2.3 g (95%) of a clear oil: IR (film) 3424, 1725 cm^{-1}; $[\alpha]^{20}_{D}$ +78.3 (*c* 1.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.75 (m, 4H), 2.39 (s, 3H), 2.68 (m, 1H), 3.76 (m, 1H), 3.93 (m, 4H), 4.43 (d, *J* = 8.8 Hz, 1H), 7.27 (bd, *J* = 8.0 Hz, 2H), 7.54 (td, *J* = 2.0 Hz, *J* = 8.0 Hz, 2H), 9.61 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.8, 30.5, 35.4, 49.9, 50.6, 64.6, 64.7, 109.6, 125.4, 129.5, 141.5, 141.9, 200.7. HRMS calcd for $C_{16}H_{24}NO_4S$ (M + H) 326.1421, found 326.1424.

(S_S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-5-(2-propyl-1,3-dioxolan-2-yl)pentanal (14c). Chromatography (80% EtOAc/hexanes) afforded a clear oil: IR (film) 3440, 1721 cm^{-1}; $[\alpha]^{20}_{D}$ +73.7 (*c* 1.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.37 (m, 2H), 1.57 (m, 2H), 1.69 (m, 3H), 1.83 (m, 1H), 2.40 (s, 3H), 2.67 (m, 2H), 3.75 (m, 1H), 3.92 (bs, 4H), 4.41 (d, *J* = 8.8 Hz, 1H), 7.28 (bd, *J* = 7.8 Hz, 2H), 7.55 (td, *J* = 8.1 Hz, *J* = 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.1, 21.3, 30.3, 33.2, 39.4, 49.9, 50.7, 64.9(2C), 111.3, 125.4, 129.5, 141.4, 142.0, 200.7; HRMS calcd for $C_{18}H_{27}NNaO_4S$ (M + Na) 376.1558, found 376.1557.

(S_S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-5-(2-phenyl-1,3-dioxolan-2-yl)pentanal (14e). Chromatography afforded a clear oil: IR (film) 3430, 1730 cm^{-1}; $[\alpha]^{20}_{D}$ +69.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.88 (m, 1H), 2.15 (m, 1H), 2.32 (s, 3H), 2.56 (dt, J = 5.4 Hz, J = 1.2 Hz, 2H), 3.67 (m, 3H), 3.93 (m, 2H), 4.33 (d, J = 8.8 Hz, 1H), 7.18 − 7.28 (m, 5H), 7.36 (m, 2H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 30.1, 36.6, 49.9, 50.5, 64.4, 64.5, 109.9, 125.4, 125.5, 127.9, 128.1, 129.5, 141.3, 141.9, 142.2, 200.7. HRMS calcd for $C_{21}H_{26}NO_4S$ (M + H) 388.1583. A satisfactory HRMS could not be obtained due to decomposition.

(S_S,3*S*)-(+)-*N*-(*tert*-Butylsulfinyl)-3-amino-5-(2-ethyl-1,3-dioxolan-2yl)pentanal (15b). Typical Procedure. In a 100 mL, oven-dried, single-necked round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (+)-7 (1.84 g, 5.49 mmol) in toluene (55 mL), and the solution was cooled to −78 °C. DIBAL-H in toluene (1.0 M solution in toluene, 9.9 mL, 9.88 mmol) was added slowly via syringe, and the solution was stirred for 10 min at −78 °C, and quenched by the addition of satd NH_4Cl (30 mL). The solution was extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), and

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concentrated. Flash chromatography (90% EtOAc/hexanes) provided 1.25 g (75%) of colorless oil: $[\alpha]^{20}_D$ +35.5 (*c* 1.46, $CHCl_3$); IR (film) 3435, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.6 Hz, 3H), 1.20 (s, 9H), 1.65 (m, 5H), 1.80 (m, 1H), 2.89 (d, *J* = 5.6 Hz, 2H), 3.62 (b, 1H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 4H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0, 22.5, 29.7, 30.0, 32.7, 49.8, 52.8, 55.8, 64.8 (2 C's), 111.5, 200.9; HRMS calcd for $C_{14}H_{28}NO_4S$ (M + H) 306.1739, found 306.1737.

(*S*$_S$,3*S*)-(+)-*N*-(*tert*-Butylsulfinyl)-3-amino-5-(2-methyl-1,3-dioxolan-2-yl)pentanal (15a). Chromatography (80% EtOAc/hexanes) afforded a clear oil: IR (film) 3435, 1725 cm^{-1}; $[\alpha]^{20}_D$ +43.0 (*c* 1.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.28 (s, 3H), 1.67 (m, 3H), 1.81 (m, 1H), 2.86 (dd, *J* = 5.4 Hz, *J* = 1.0 Hz, 2H), 3.62 (m, 1H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.91 (m, 4H), 9.76 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 23.8, 30.3, 35.5, 49.9, 52.8, 55.9, 64.5, 64.6, 109.6, 200.9. HRMS calcd for $C_{13}H_{26}NO_4S$ (M + H) 292.1583, found 292.1580.

(*S*$_S$,3*S*)-(+)-*N*-(-*tert*-Butylsulfinyl)-3-amino-5-(2-pentyl-1,3-dioxolan-2yl)pentanal (15d). Flash chromatography (90% EtOAc/hexanes) gave a colorless oil: $[\alpha]^{20}_D$ +32.5 (*c* 1.64, $CHCl_3$); IR (film) 3435, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 9H), 1.28 (m, 6H), 1.63 (b, 5H), 1.772 (b, 1H), 2.89 (d, *J* = 5.6 Hz, 2H), 3.62 (b, 1H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.92 (m, 4H), 9.78 (s, 1H); ^{13}C NMR($CDCl_3$) δ 13.9, 22.6, 23.5, 30.1, 32.0, 33.3, 37.1, 50.0, 53.0, 56.0, 64.8, 64.9, 111.4, 201.0. HRMS calcd for $C_{17}H_{34}NO_4S$ (M + H) 348.2209, found 348.2208.

(*S*$_S$,3*S*)-(+)-*N*-(*tert*-Butylsulfinyl)-3-amino-5-(2-phenyl-1,3-dioxolan-2-yl)pentanal (15e). Chromatography (80% EtOAc/hexanes) afforded a clear oil: $[\alpha]^{20}_D$ +32.5 (*c* 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.66 (m, 1H), 1.93 (m, 1H), 2.06 (m, 1H), 2.83 (dd, *J* = 5.4 Hz, *J* = 1.0 Hz, 2H), 3.63 (m, 1H), 3.68 (d, *J* = 8.4 Hz, 1H), 3.76 (m, 2H), 3.99 (m, 2H), 7.33 (m, 3H), 7.41 (m, 2H), 9.74 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 29.9, 36.7, 49.9, 52.7, 55.9, 64.4, 64.5, 109.9, 125.5, 127.9, 128.1, 142.2, 200.9. HRMS calcd for (M + H) $C_{18}H_{28}NO_4S$ 354.1739. A satisfactory HRMS could not be obtained due to decomposition.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(*p*-toluenesulfinyl)-5-amino-7-(2-methyl-1,3-dioxolan-2-yl)-hept-2-enoate (16a). Typical Procedure. In a 50 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar, and a rubber septum was placed trimethylphosphonoacetate (2.11 g, 11.60 mmol) in anhydrous acetonitrile (20 mL) under argon. To this solution was added DBU (1.76 g, 11.60 mmol) at rt, and the solution was stirred for 15 min. At this time, a solution of (+)-**14a** (1.89 g, 5.80 mmol) in dry acetonitrile (20 mL) was added to the mixture via cannula, and the reaction mixture was monitored for completion by TLC (typically 2 h). At this time the reaction mixture was quenched by addition of water (80 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (4 × 60 mL). The combined organic phases were washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated. Chromatography (80% EtOAc/hexanes) afforded 2.10 g (95%) of a colorless oil: IR (film) 3440, 1720,1660 cm^{-1}; $[\alpha]^{20}_D$ +34.9 (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.57 (m, 1H), 1.74 (m, 2H), 1.84 (m, 1H), 2.30 (m, 1H), 2.39 (s, 3H), 3.49 (m, 1H), 3.71 (s, 3H), 3.94 (m, 4H), 4.07 (d, *J* = 8.0 Hz, 1H), 5.80 (td, *J* = 1.6 Hz, *J* = 15.2 Hz, 1H), 6.80 (td, *J* = 7.2 Hz, *J* = 15.6 Hz, 1H), 7.27 (bd, *J* = 8.0 Hz, 2H), 7.56 (td, *J* = 2.0 Hz, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 23.8, 29.7, 35.0, 39.0, 51.4, 53.2, 64.5, 64.6, 109.6, 123.9, 125.5, 129.4, 141.2, 141.9, 144.2, 166.4. HRMS calcd for $C_{19}H_{28}NO_5S$ (M + H) 382.1683, found 382.1695.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(*p*-toluenesulfinyl)-5-amino-7-(2-propyl-1,3-dioxolan-2yl)-hept-2-enoate (16c). Chromatography (50% EtOAc/hexanes) afforded 95% of a colorless oi: IR (film) 3431, 1722, 1657 cm^{-1}; $[\alpha]^{20}_D$ +26.6 (*c* 2.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.40 (m, 2H), 1.56 (m, 3H), 1.66 (m, 2H), 1.84 (m, 1H), 2.26 (m, 1H), 2.36 (m, 1H), 2.39 (s, 3H), 3.48 (m, 1H), 3.71 (s, 3H), 3.92 (bs, 4H), 4.07 (d, *J* = 8.1 Hz, 1H), 5.81 (td, J = 15.7 Hz, *J* = 1.2 Hz, 1H), 6.80 (td, *J* = 15.7 Hz, *J* = 7.6 Hz, 1H), 7.27 (bd, *J* = 8.1 Hz, 2H), 7.56 (td, *J* = 8.1 Hz, *J* = 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.1, 21.3, 29.5, 32.9, 39.1, 39.4, 51.4, 53.3, 64.8(2C), 111.3, 124.0, 125.5, 129.5, 141.3, 141.9, 144.2, 166.4. HRMS calcd for $C_{21}H_{31}NNaO_5S$ (M + Na) 432.1821, found 432.1820.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(*p*-toluenesulfinyl)-5-amino-7-(2-phenyl-1,3-dioxolan-2-yl)-hept-2-enoate (16e). Chromatography (50% EtOAc/hexanes) afforded 95% of a colorless oil: IR (film) 3440, 1725, 1660 cm^{-1}; $[\alpha]^{20}_D$ +35.4 (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.56 (m, 1H), 1.67 (m, 1H), 1.98 (m, 1H), 2.05 (m, 1H), 2.26 (m, 1H), 2.34 (m, 1H), 2.39 (s, 3H), 3.49 (m, 1H), 3.71 (s, 3H), 3.75 (m, 2H), 4.00 (m, 2H), 4.04 (d, J = 8.0 Hz, 1H), 5.77 (td, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H), 6.77 (td, J = 15.7 Hz, J = 7.6 Hz, 1H), 7.26 − 7.35 (m, 5H), 7.43 (m, 2H), 7.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ δ 21.3, 29.3, 36.3, 39.1, 51.4, 53.3, 64.4, 64.5, 110.0, 123.9, 125.5, 125.6, 127.9, 128.1, 129.4, 141.3, 141.9, 142.2, 144.2, 166.4. HRMS calcd for $C_{24}H_{30}NO_5S$ (M + H) 444.1845, found 444.1841.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(*tert*-butylsulfinyl)-5-amino-7-(2-methyl-1,3-dioxolan-2-yl)-hept-2-enoate (17a). Chromatography (80% EtOAc/hexanes) afforded 95% of a clear oil. The product was isolated as 95:5 mixture of *E*:*Z* isomers: IR (film) 3430, 1720, 1650 cm^{-1}; $[\alpha]^{20}_D$ +20.3 (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.16 (s, 9H), 1.25 (s, 3H), 1.51 (m, 1H), 1.63 (m, 2H), 1.76 (m, 1H), 2.54 (m, 2H), 3.17 (d, *J* = 7.6 Hz, 1 H), 3.35 (m, 1H), 3.68 (s, 3H), 3.89 (m, 4H), 5.89 (bd, *J* = 16.0 Hz, 1H), 6.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 23.7, 29.5, 35.1, 39.2, 51.4, 55.7, 55.9, 64.5, 64.6, 109.6, 124.3, 144.0, 166.4. HRMS calcd for (M + H) $C_{16}H_{30}NO_5S$ 348.1845, found 348.1841.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(-*tert*-butylsulfinyl)-5-amino-7-(2-ethyl-1,3-dioxolan-2yl)-hept-2-enoate (17b). Flash chromatography (80% EtOAc/hexanes) afforded 93% of a colorless oil: $[\alpha]^{20}_D$ +20.0 (*c* 1.74, $CHCl_3$); IR (film) 3428, 1716, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.6 Hz, 3H), 1.20 (s, 9H), 1.61 (m, 5H), 1.70 (b, 1H), 2.54 (m, 1H), 2.61 (m, 1H), 3.16 (d, *J* = 8.0 Hz, 1H), 3.39 (b, 1H), 3.73 (s, 3H), 3.92 (m, 4H), 5.94 (td, *J* = 1.5 Hz, 15.7 Hz, 1H), 6.82 (td, *J* = 7.1 Hz, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.30. HRMS calcd for $C_{17}H_{32}NO_5S$ (M + H) 362.2001, found 362.1997.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(-*tert*-butylsulfinyl)-5-amino-7-(2-pentyl-1,3-dioxolan-2yl)-hept-2-enoate (17d). Flash chromatography (75% EtOAc/hexanes) afforded 89% of a colorless oil: $[\alpha]^{20}_D$ +16.9 (*c* 1.31, $CHCl_3$); IR (film) 3428, 1716, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 9H), 1.28 (m, 6H), 1.596 (m, 5H), 1.76 (m, 1H), 2.57 (m, 2H), 3.15 (d, *J* = 8.0 Hz, 1H), 3.38 (bm, 1H), 3.73 (s, 3H), 3.92 (m, 4H), 5.94 (td, *J* = 1.5 Hz, 15.7 Hz, 1H), 6.91 (td, *J* = 7.1 Hz, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.5, 22.6, 23.4, 29.3, 31.9, 32.9, 37.0, 39.0, 51.4, 55.8, 56.0, 64.8 (2 C's), 111.4, 124.4, 144.0, 166.4. HRMS calcd for $C_{20}H_{38}NO_5S$ (M + H) 404.2471, found 404.2470.

(*S*$_S$,5*S*,2*E*)-(+)-Methyl-*N*-(*tert*-butylsulfinyl)-5-amino-7-(2-phenyl-1,3-dioxolan-2-yl)-hept-2-enoate (17e). Chromatography (60% EtOAc/hexanes) afforded 90% of clear oil. The product was isolated as a 95:5 mixture of *E*:*Z* isomers: IR (film) 3430, 1730, 1665 cm^{-1}; $[\alpha]^{20}_D$ +14.4 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.42 (m, 1H), 1.58 (m, 1H), 1.87 (m, 1H), 1.95 (m, 1H), 2.40 (m, 1H), 2.51 (m, 1H), 3.03 (d, *J* = 7.6 Hz, 1H), 3.29 (m, 1H), 3.65 (s, 3H), 3.68 (m, 2H), 3.92 (m, 2H), 5.82 (td, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H), 6.79 (td, *J* = 15.7 Hz, *J* = 7.1 Hz, 1H), 7.24 (m, 3H), 7.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.6, 29.1, 36.3, 39.3, 51.4, 55.6, 56.0, 64.3, 64.4, 110.0, 124.3, 125.5, 127.9, 128.1, 142.2, 144.1, 166.4. HRMS calcd for (M + H) $C_{21}H_{32}NO_5S$ 410.2001, found 410.1997.

(*S*$_S$,4*S*)-(+)-*N*-(*tert*-Butylsulfinyl)-4-amine 6-(2-methyl-1,3-dioxolan-2-yl)hex-1-ene (18a). Typical Procedure. To a 500 mL round-bottom flask equipped with magnetic stirring bar and argon inlet was added (*S*)-(+)-**7a** (1.903 g, 7.693 mmol) in anhydrous ether (256 mL). The solution was cooled to −50 °C, and allylmagnesium bromide (15.4 mL, 15.39 mmol, 1.0 M solution in ether) was added dropwise via syringe. After 1 h of stirring at this temperature the reaction mixture was quenched with satd aqueous NH_4Cl (18 mL) at −50 °C and warmed to rt. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (50% EtOAc/hexanes) afforded 1.83 g (82%) of a clear oil: IR (film) 3385 cm^{-1}; $[\alpha]^{20}_D$ +48.9 (*c* 1.69,

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$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.30 (s, 3H), 1.66 (m, 4H), 2.36 (m, 2H), 3.24 (d, J = 6.3 Hz, 1H), 3.32 (m, 1H), 3.92 (m, 4H), 5.15 (dd, J = 2.3 Hz, J = 14.4 Hz, 2H), 5.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.7, 23.8, 29.3, 34.9, 40.4, 54.9, 55.8, 64.6 (2C), 109.8, 119.0, 134.0. HRMS calcd for $C_{14}H_{27}NO_3S$ (M + H) 290.1790, found 290.1788

(S_S,4*S*)-(+)-*N*-(*tert*-Butylsulfinyl)-4-amino-6-(2-phenyl-1,3-dioxolan-2-yl)hex-1-ene (18b). Flash chromatography (40% EtOAc/hexanes) afforded 85% of a colorless oil that crystallized to a white solid, mp 33 °C, on cooling to −20 °C: IR (film) 854 cm^{-1}, 1059 cm^{-1}, 3233 cm^{-1}; $[\alpha]^{20}_D$ +42.0 (c 1.37, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.51 (m, 1H), 1.62 (m, 1H), 1.96 (m, 2H), 2.32 (m, 2H), 3.17 (d, J = 6.6 Hz, 1H), 3.30 (m, 1H), 3.76 (m, 2H), 4.00 (m, 2H), 5.09 (d, J = 3.9 Hz, 1H), 5.13 (s, 1H), 5.73 (m, 1H), 7.31 (m, 3H), 7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.7, 28.8, 36.2, 40.5, 54.9, 55.8, 64.5 (2C), 110.2, 119.0, 125.6, 127.9, 128.1, 134.0, 142.4. HRMS calcd for $C_{14}H_{27}NO_3S$ (M + H) 352.1946, found 352.1944.

(S_S,5*S*,2*E*)-(+)-Methyl-*N*-(*tert*-butylsulfinyl)-5-amino-7-(2-methyl-1,3-dioxolan-2-yl)-hept-2-enoate (17a). Typical Procedure Using Cross-Metathesis. To a 100 mL round-bottomed flask equipped with magnetic stirring bar and argon inlet were placed (*S*)-(+)-**18a** (0.182 g, 0.629 mmol) and methyl acrylate (283 μL, 3.14 mmol) in DCM (62.9 mL), followed by a solution of Hoveyda−Grubbs II catalyst (19.7 mg, 0.0314 mmol) in DCM (2 mL) added dropwise via cannula. The reaction mixture was refluxed for 12 h and concentrated. Chromatography (60% EtOAc/hexanes) afforded 0.173 g (79%) of a colorless oil identical to (+)-**17a** prepared above; $[\alpha]^{20}_D$ +20.5 (c 2.02, $CHCl_3$).

(S_S,5*S*,2*E*)-(+)-Methyl-*N*-(*tert*-butylsulfinyl)-5-amino-7-(2-phenyl-1,3-dioxolan-2-yl)-hept-2-enoate (17e). Prepared using cross metathesis to give (+)-**17e** with properties identical to (+)-**17e** prepared above; $[\alpha]^{20}_D$ +14.2 (c 1.21, $CHCl_3$).

(5*S*,2*E*)-(+)-Methyl-(3,4-dihydro-5-methyl-2*H*-pyrrol-2-yl)-but-2-enoate (19a). Typical Procedure. In a 250 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar, and a rubber septum was placed (+)-**16a** (0.12 g, 0.31 mmol) in MeOH (15 mL) and THF (15 mL). To this solution was added 3.0 N HCl (1.05 mL) slowly via syringe at rt. This reaction mixture was stirred at rt for 16 h, concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), brine (30 mL), dried ($MgSO_4$), and concentrated. Chromatography (70% EtOAc/hexanes) gave 0.55 g (100%) of a clear oil: IR (film) 1720, 1655, 1650 cm^{-1}; $[\alpha]^{20}_D$ +39.7 (c 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45 (m, 1H), 2.00 (d, J = 1.6 Hz, 3H), 2.02 (m, 1H), 2.33 (m, 1H), 2.45 (m, 2H), 2.58 (m, 1H), 3.69 (s, 3H), 4.05 (m, 1H), 5.87 (td, J = 1.6 Hz, J = 16.0 Hz, 1H), 6.95 (td, J = 7.2 Hz, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 28.4, 38.9, 39.0, 51.3, 71.2, 122.6, 146.3, 166.8, 175.0. HRMS calcd for $C_{10}H_{16}NO_2$ (M + H) 182.1176, found 182.1172.

(5*S*,2*E*)-(+)-Methyl-(3,4-dihydro-5-ethyl-2*H*-pyrrol-2-yl)-but-2-enoate (19b). Flash chromatography (60% EtOAc/hexanes) afforded 100% of a oil: $[\alpha]^{20}_D$ +43.4 (c 1.9, $CHCl_3$); IR (neat) 1636, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.6 Hz, 3H), 1.46 (m, 1H), 2.04 (m, 1H), 2.33 (m, 3H), 2.49 (m, 2H), 2.65 (m, 1H), 3.72 (s, 3H), 4.09 (m, 1H), 5.89 (td, J = 1.6, 15.7 Hz, 1H), 6.96 (td, J = 7.6, 15.7 Hz, 1H); ^{13}H NMR ($CDCl_3$) δ 10.6, 26.7, 27.7, 36.7, 38.8, 51.1, 70.7, 122.5, 146.1, 166.6, 179.2. HRMS calcd for $C_{11}H_{18}NO_2$ (M + H) 196.1338, found 196.1334.

(5*S*,2*E*)-(+)-Methyl-(3,4-dihydro-5-propyl-2*H*-pyrrol-2-yl)-but-2-enoate (19c). Flash chromatography (60% EtOAc/hexanes) afforded 93% of a clear oil: IR (film) 1730, 1660, 1653 cm^{-1}; $[\alpha]^{20}_D$ +39.1 (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.46 (m, 1H), 1.59 (m, 1H), 2.03 (m, 1H), 2.33 (m, 3H), 2.46 (m, 2H), 2.65 (m, 1H), 3.70 (s, 3H), 4.09 (m, 1H), 5.88 (td, J = 15.7 Hz, J = 1.5 Hz, 1H), 6.95 (td, J = 15.7 Hz, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.8, 27.9, 35.7, 37.1, 39.0, 51.4, 70.9, 122.7, 146.3, 166.8, 178.3. HRMS calcd for $C_{12}H_{20}NO_2$ (M + H) 210.1494, found 210.1489.

(5*S*,2*E*)-(+)-Methyl-(3,4-dihydro-5-pentyl-2*H*-pyrrol-2-yl)-but-2-enoate (19d). Flash chromatography (50% EtOAc/hexanes) afforded 83% of an oil: $[\alpha]^{20}_D$ +31.1 (c 3.15, $CHCl_3$); IR (neat) 1636, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.31 (m, 4H), 1.50 (m, 3H), 2.03 (m, 1H), 2.40 (m, 5H), 2.63 (m, 1H), 3.72 (s, 3H), 4.09 (m, 1H), 5.88 (td, J = 1.5, 15.7 Hz, 1H), 6.96 (td, J = 7.3, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.9, 22.4, 26.2, 27.9, 31.6, 33.8 37.2, 39.0, 51.3, 71.0, 122.7, 146.3, 166.8, 178.5; HRMS calcd for $C_{14}H_{24}NO_2$ (M + H) 238.1807, found 238.1805.

(5*S*,2*E*)-(+)-Methyl-(3,4-dihydro-5-phenyl-2*H*-pyrrol-2-yl)-but-2-enoate (19e). Chromatography (30% EtOAc/hexanes) gave 90) of a clear oil: IR (film) 1735, 1663, 1650 cm^{-1}; $[\alpha]^{20}_D$ +27.5 (c 1.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.65 (m, 1H), 2.20 (m, 1H), 2.45 (m, 1H), 2.75 (m, 1H), 2.94 (m, 1H), 3.01 (m, 1H), 3.72 (s, 3H), 4.33 (m, 1H), 5.93 (td, J = 15.6 Hz, J = 1.6 Hz, 1H), 7.04 (td, J = 15.6 Hz, J = 7.6 Hz, 1H), 7.41 (m, 3H), 7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.0, 35.1, 39.1, 51.4, 71.7, 122.8, 127.7, 128.4, 130.5, 134.3, 146.3, 166.8, 172.9. HRMS calcd for $C_{15}H_{18}NO_2$ (M + H) 244.1338, found 244.1329.

(5*S*,2*E*)-Methyl-(3,4-dihydro-5-methyl-2*H*-pyrrol-2-yl)-but-2-enoate-*N*-oxide (20a). In a 50 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar, and a rubber septum was placed urea hydrogen peroxide (0.743 g, 7.898 mmol) in anhydrous MeOH (30 mL) under argon. Methyltrioxorhenium (0.041 g, 0.165 mmol) was added, the solution was stirred for 15 min, and (*S*)-**18a** (0.440 g, 2.43 mmol) in MeOH (20 mL) was added via cannula. The yellow solution was stirred at rt for 15 h, concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL). The suspended urea crystals were filtered; the filtrate was concentrated to give 0.47 g (98%) of a yellow oil, which was taken to the next step without further purification. The C-2 hydrogen in the nitrone was shifted downfield to δ 4.20 ppm as compared to 4.06 ppm in the dehydropyrrolidine. The C-5 carbon in the nitrone was shifted upfield to δ 150.5 ppm as compared to 175.0 ppm for its precursor. This procedure was followed in the synthesis of nitrones **20b−e**.

General Procedure for the Synthesis of (1*S*,2*R*,3*R*,6*S*)-(−)-Methyl-3-methyl-7-aza-8-oxatricyclo[4.2.1.0]nonane-2-carboxylate (21a) by Heating. In a 500 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed nitrone **20a** (0.400 g, 2.028 mmol) in anhydrous toluene (400 mL,) and the solution was refluxed (while maintaining the oil bath temperature at 150 °C for 48 h and concentrated. Purification by flash column chromatography gave 0.180 g (45%) of a low melting solid: IR (film) 1740 cm^{-1}; $[\alpha]^{20}_D$ −56.5 (c 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.81 (m, 3H), 2.18 (m, 3H), 2.44 (s, 1H), 3.61 (m, 1H), 3.68 (s, 3H), 4.94 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 26.0, 33.8, 42.0, 51.5, 61.2, 62.7, 75.7, 81.5, 171.6. HRMS calcd for $C_{10}H_{16}NO_3$ (M + H) 198.1130, found 198.1124.

(1*S*,2*R*,3*R*,6*S*)-(−)-Methyl-3-methyl-7-aza-8-oxatricyclo-[4.2.1.0]nonane-2-carboxylate (21a) using the Lewis Acid Aluminum *tert*-Butoxide. Typical Procedure. In a 500 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed nitrone **20a** (0.370 g, 1.876 mmol) in anhydrous toluene (200 mL). To this solution was added $Al(O^tBu)_3$ (0.230 g, 0.938 mmol), and the solution was stirred at rt for 6 h. At this time the reaction mixture was refluxed for 96 h, cooled to rt, and extracted with aqueous 5% HCl solution (4 × 50 mL). The combined aqueous phases were carefully neutralized by slow addition of solid Na_2CO_3 until the solution became slightly basic (pH 8). This aqueous solution was extracted with DCM (4 × 50 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography gave 0.260 g (70%) of a low melting white solid: IR (film) 1740 cm^{-1}; $[\alpha]^{20}_D$ −56.47 (c 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.81 (m, 3H), 2.18 (m, 3H), 2.44 (s, 1H), 3.61 (m, 1H), 3.68 (s, 3H), 4.94 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 26.0, 33.8, 42.0, 51.5, 61.2, 62.7, 75.7, 81.5, 171.6. HRMS calcd for $C_{10}H_{16}NO_3$ (M + H) 198.1130, found 198.1124.

(1*S*,2*R*,3*R*,6*S*)-(−)-Methyl-3-ethyl-7-aza-8-oxatricyclo-[4.2.1.0]nonane-2-carboxylate (21b). The toluene solution was extracted with 5% HCl solution (4 × 50 mL, the combined aqueous phases were neutralized by slow addition of solid Na_2CO_3 until the solution was slightly basic. At this time the aqueous solution was

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extracted with DCM (4 × 50 mL), and the combined organic phases were washed with brine, dried, and concentrated to give 0.192 g (52%) of a clear oil: $[\alpha]^{20}_{D}$ −27.3 (*c* 0.495, $CHCl_3$); IR (film) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) 0.95 (t, *J* = 7.6 Hz, 3H), 1.26 (dd, *J* = 11.8, 2.4 Hz, 1H), 1.57 (q, *J* = 7.6 Hz, 3H), 1.85 (m, 1H), 1.98 (m, 2H), 2.14 (m, 2H), 2.48 (s, 1H), 3.619 (m, 1H), 3.69 (s, 3H), 4.90 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 8.7, 25.8, 26.1, 29.3, 41.9, 51.5, 62.2, 62.8, 77.3 81.6, 171.8. HRMS calcd for $C_{11}H_{18}NO_3$ (M + H) 212.1287, found 212.1282.

(1*S*,2*R*,3*R*,6*S*)-(−)-Methyl-3-propyl-7-aza-8-oxatricyclo-[4.2.1.0]nonane-2-carboxylate (21c). Clear oil; IR (film) 1738 cm^{-1}; $[\alpha]^{20}_{D}$ −56.6 (*c* 0.71, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ* 0.88 (t, *J* = 7.1 Hz, 3H), 1.25 (dd, *J* = 11.5 Hz, *J* = 2.2 Hz, 1H), 1.31 (m, 1H), 1.49 (m, 3H), 1.80 (m, 1H), 1.99 (m, 2H), 2.15 (m, 2H), 2.46 (s, 1H), 3.60 (m, 1H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 14.6, 17.7, 25.9, 30.1, 35.9, 42.0, 51.6, 62.3, 62.8, 79.0, 81.6, 171.9. HRMS calcd for $C_{12}H_{19}NNaO_3$ (M + Na) 248.1263, found 248.1260.

(1*S*,2*R*,3*R*,6*S*)-(−)-Methyl-3-pentyl-7-aza-8-oxatricyclo-[4.2.1.0]nonane-2-carboxylate (21d). At this time the toluene solution was extracted with 5% HCl solution (4 × 50 mL), and the organic layer was washed satd Na_2CO_3 solution (2 × 30 mL), brine (40 mL), dried ($MgSO_4$) and concentrated to give 0.328 g (58%) of clear oil: $[\alpha]^{20}_{D}$ −45.6 (*c* 1.275, $CHCl_3$); IR (film) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.86 (t, *J* = 6.8 Hz, 3H), 1.25 (b, 6H), 1.49 (b, 4H), 1.81 (m, 1H), 2.0 (m, 2H), 2.18 (m, 2H), 2.46 (s, 1H), 3.60 (m, 1H), 3.69 (s, 3H), 4.89 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 14.0, 22.6, 24.2, 25.9, 30.1, 32.4, 33.7, 42.0, 51.5, 62.2, 62.8, 79.1, 81.6, 171.8. HRMS calcd for $C_{14}H_{24}NO_3$ (M + H) 254.1756, found 254.1752.

(1*S*,2*R*,3*R*,6*S*)-(−)-Methyl-3-phenyl-7-aza-8-oxatricyclo-[4.2.1.0]nonane-2-carboxylate (21e). The crude reaction mixture was washed with H_2O (3 × 20 mL), and the organic phase was dried ($MgSO_4$) and concentrated. Chromatography (35% EtOAc/hexanes) gave 0.31 g (40%) of a white solid, mp 136−138 °C, and 0.30 g (38%) of lactam (*S*)-(+)-**22e** (see below): IR (film) 1750 cm^{-1}; $[\alpha]^{20}_{D}$ −54.7 (*c* 0.88, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ* 1.38 (dd, *J* = 11.7 Hz, *J* = 2.4 Hz, 1H), 1.93 (m, 1H), 2.22 (m, 2H), 2.28 (m, 1H), 2.73 (m, 1H), 2.81 (s, 1H), 3.04 (s, 3H), 3.75 (m, 1H), 4.95 (d, *J* = 4.9 Hz, 1H), 7.14 (m, 1H), 7.23 (m, 2H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) *δ* 25.4, 34.1, 42.2, 50.9, 63.0, 64.5, 80.7, 81.2, 126.6, 126.8, 127.3, 141.5, 170.6. HRMS calcd for (M + H) $C_{15}H_{18}NO_3$ 260.1287, found 260.1281.

(*E*)-(*S*)-(+)-Methyl-4-(5-oxo-1ethylpyrrolidini-2-yl)-but-2-enoate (22b). Typical Procedure. In a 100 mL round-bottom flask equipped with magnetic stirring bar and argon inlet was placed nitrone **20b** (0.05 g, 0.226 mmol) in anhydrous toluene (23 mL), and the solution was refluxed for 96 h. At this time, the reaction mixture was cooled to rt and concentrated. Flash chromatography (90% EtOAc/hexanes) gave 0.016 g (32%) of slightly brownish oil: IR (film) 1726, 1651, 1640 cm^{-1}; $[\alpha]^{20}_{D}$ +36.0 (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ* 1.14 (t, *J* = 7.6 Hz, 3H), 2.04 (m, 2H), 2.35 (m, 3H), 2.51 (m, 2H), 2.65 (m, 1H), 3.72 (s, 3H), 4.10 (m, 1H), 5.89 (td, *J* = 1.6, 15.7 Hz, 1H), 6.97 (td, *J* = 7.6, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 10.8, 26.9, 28.0, 37.0, 39.0, 51.3, 71.1, 122.8, 146.3, 166.8, 179.8. HRMS calcd for $C_{11}H_{18}NO_3$ (M + H) 212.1287, found 212.1280

(*E*)-(*S*)-(+)-Methyl-4-(5-oxo-1-propylpyrrolidin-2-yl)-but-2-enoate (22c). Typical Procedure. In a 100 mL round-bottomed flask equipped with magnetic stirring bar and argon inlet was placed nitrone **20c** (0.100 g, 0.444 mmol) in anhydrous toluene (45.0 mL), and the solution was refluxed for 96 h. At this time, the reaction mixture was cooled to rt and concentrated. Flash chromatography (25% EtOAc/hexanes) yielded 0.04 g (40%) of slightly yellow oil: IR (film) 1724, 1657, 1642 cm^{-1}; $[\alpha]^{20}_{D}$ +25.1 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ* 0.95 (t, *J* = 7.1 Hz, 3H), 1.49 (m, 1H), 1.61 (m, 2H), 2.06 (m, 1H), 2.35 (m, 3H), 2.51 (m, 2H), 2.66 (m, 1H), 3.72 (s, 3H), 4.15 (m, 1H), 5.90 (bd, *J* = 15.7 Hz, 1H), 6.96 (td, *J* = 15.7 Hz, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 13.9, 19.8, 27.7, 35.6, 37.1, 38.8, 51.4, 70.6, 122.9, 146.0, 166.8, 179.5. HRMS calcd for $C_{12}H_{20}NO_3$ (M + H) 226.1443, found 226.1436.

(*E*)-(S)-Methyl-4-(5-oxo-1-pentylpyrrolidin-2-yl)-but-2-enoate (22d). Flash chromatography (50% EtOAc/hexanes) gave 45% of an oil: $[\alpha]^{20}_{D}$ −33.9 (*c* 1.28, $CHCl_3$); IR (film) 1720, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (t, *J* = 6.8 Hz, 3H), 1.35 (m, 4H), 15.6 (m, 2H), 2.03 (m, 1H), 2.39 (m, 6H), 2.64 (m, 1H), 3.71 (s, 3H), 4.1 (m, 1H), 5.88 (td, *J* = 1.5, 17.7 Hz, 1H), 6.95 (td, *J* = 7.3, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.9, 22.4, 26.2, 27. 9, 31.6, 33.7, 37.2, 39.0, 51.4, 70.8, 122.78, 146.3, 166.8, 178.7. HRMS calcd for $C_{14}H_{24}NO_3$(M + H) 254.1756, found 254.1752.

(*E*)-(*S*)-(+)-Methyl-4-(5-oxo-1-phenylpyrrolidin-2-yl)-but-2-enoate (22e). Flash chromatography (35% EtOAc/hexanes) gave a brown oil: $[\alpha]^{20}_{D}$ +27.9 (*c* 1.53, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ* 1.65 (m, 1H), 2.21 (m, 1H), 2.45 (m, 1H), 2.75 (m, 1H), 2.93 (m, 1H), 3.01 (m, 1H), 3.73 (s, 3H), 4.34 (m, 1H), 5.94 (td, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H), 7.04 (td, *J* = 15.6 Hz, *J* = 7.6 Hz, 1H), 7.41 (m, 3H), 7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) *δ* 28.1, 35.1, 39.1, 51.4, 71.7, 122.8, 127.7, 128.4, 130.5, 134.4, 146.3, 166.8, 172.8. HRMS calcd for (M + H) $C_{15}H_{18}NO_3$ 260.1287, found 260.1281.

(*E*)-Methyl-4((2*S*)-(+)-5-propyl-6-oxa-1-aza-bicyclo[3.1.0]-hexan-2-yl)-but-2-enoate (23c). Typical Procedure. In a 25 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed (+)-**19c** (0.054 g, 0.259 mmol) in anhydrous dichloromethane (5.0 mL) under argon. To this solution was added *m*-CPBA (0.067 g, 0.388 mmol, ≥77%) at 0 °C, and the reaction mixture was stirred for 0.5 h and quenched by adding a saturated solution of $NaHCO_3/Na_2S_2O_3$ (1:1) (10 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL), and the combined organic phases were washed with satd $NaHCO_3$ solution (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (30% EtOAc in hexanes) afforded 0.045 g (77%) of a yellow oil as 2.5:1 mixture of isomers: IR (film) 1724, 1650 cm^{-1}; $[\alpha]^{20}_{D}$ +60.3 (*c* 1.53, $CHCl_3$); major isomer ^1H NMR ($CDCl_3$) *δ* 0.93 (t, *J* = 7.4 Hz, 3H), 1.45 (m, 3H), 1.81 (m, 4H), 2.29 (m, 1H), 2.39 (m, 1H), 2.70 (m, 1H), 3.19 (m, 1H), 3.70 (s, 3H), 5.92 (td, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 7.01 (td, *J* = 15.6 Hz, *J* = 7.3 Hz, 1H); *δ* minor isomer 0.94 (t, *J* = 7.3 Hz, 3H), 1.28 (m, 3H), *1.67* (m, 4H), 2.10−2.24 (m, 2H), 2.39 (m, 1H), 3.58 (m, 1H), 3.71 (s, 3H), 5.87 (td, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 6.91 (td, *J* = 15.6 Hz, *J* = 7.3 Hz, 1H); major isomer ^{13}C NMR ($CDCl_3$) *δ* 14.1, 17.9, 25.3, 29.3, 34.6, 35.3, 51.4, 65.8, 90.2, 122.7, 145.6, 166.7; *δ* minor isomer 14.2, 17.9, 24.4, 27.5, 34.7, 35.3, 51.5, 64.5, 90.3, 123.3, 144.8, 166.5. HRMS calcd for $C_{12}H_{20}NO_3$ (M + H) 226.1443, found 226.1441.

(*E*)-Methyl-4((2*S*)-(+)-5-pentyl-6-oxa-1-aza-bicyclo[3.1.0]-hexan-2-yl)-but-2-enoate (23d). Flash chromatography (50% EtOAc/hexanes) provided a colorless oil as a 2.6:1 mixture of oxaziridines isomers: $[\alpha]^{20}_{D}$ +46.2 (c 2.03, $CHCl_3$); IR (film) 1728, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) major isomer: *δ* 0.87 (t, *J* = 6.7 Hz, 3H), 1.29 (m, 5H), 1.45 (m, 2H), 1.74 (m, 1H), 2.43 (m, 6H), 2.71 (m, 1H), 3.71 (s, 3H), 4.2 (b, 1H), 5.92 (td, *J* = 1.5, 15.7 Hz, 1H), 7.06 (td, *J* = 7.6, 15.7 Hz, 1H); minor isomer: *δ* (t, *J* = 6.7 Hz, 3H), 1.29 (m, 5H), 1.74 (m, 1H), 2.39 (m, 6H), 2.71 (m, 1H), 3.72 (s, 3H), 5.86 (td, J = 1.5, 15.7 Hz, 1H), 6.92 (td, J = 7.6, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) major isomer: *δ* 13.9, 22.5, 22.3, 24.8, 25.3, 27.5, 29.4, 31.8, 32.6, 35.4, 51.4, 65.9, 90.3, 122.8, 145.7, 166.8; minor isomer: *δ* 15.2, 23.3, 24.4, 24.7, 29.7, 32.5, 34.7, 51.5, 64.5, 90.5, 123.3, 144.8, 166.5. HRMS: calcd for $C_{14}H_{24}NO_3$ (M + H) 254.1756, found 254.1750.

(*E*)-(*S*)-(+)-Methyl-4-(5-oxo-1-propylpyrrolidin-2-yl)-but-2-enoate (22c) from Oxaziridine 23c. In a 50 mL single-necked round-bottom flask were added $MeReO_3$ (0.001 g, 0.005 mmol) and UHP (0.021 g, 0.224 mmol) in methanol (2.0 mL). The reaction mixture was stirred for 0.5 h under an argon atmosphere and concentrated, and the residue was dissolved in CH_2Cl_2 (10 mL). The solids were removed by filtration, and the filtrate was concentrated to give the methylperoxorhenium complex. The complex was dissolved in anhydrous toluene (4.0 mL) and added to a solution of (+)-**23c** (0.015 g, 0.069 mmol) in anhydrous toluene (4.0 mL). The solution was refluxed for 96 h, and concentrated. Flash chromatography (25% EtOAc/hexanes) gave 0.008 g (51%) of slightly yellow oil with spectral properties identical to that prepared from **20c**; $[\alpha]^{20}_{D}$ +27.5 (*c* 0.4, $CHCl_3$).

Methane Sulfonate Salt of Methyl (1*S*,2*R*,3*R*,6*S*)-(−)-3-Methyl-7-aza-8-oxatricyclo[4.2.1.0]nonane-2-carboxylate

(24a). Typical Procedure. In a 50 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a reflux condenser was placed (−)-**21a** (0.06 g, 0.304 mmol) in anhydrous benzene (20 mL) under argon. Methylmethanesulfonate (0.335 g, 3.04 mmol) was added via syringe, and the solution was heated at refluxed for 24 h. At this time the solution was concentrated, the residue was dissolved in H_2O (20 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL), to the aqueous phase was added acetonitrile/water (2:1, 20 mL), and the solution was lyophilized to give 0.92 g (98%) of a white sticky material: IR (film) 1745 cm^{-1}; $[\alpha]^{20}_D$ −2.9 (*c* 0.7, $CHCl_3$); ^1H NMR (CD_3OD) δ 1.45 (s, 3H), 2.12 (dd, *J* = 2.4 Hz, *J* = 12.7 Hz, 1H), 2.28 (m, 2H), 2.50 (m, 1H), 2.58 (m, 1H), 2.62 (s, 3H), 2.77 (m, 1H), 3.42 (s, 3H), 3.50 (s, 1H), 3.71 (s, 3H), 4.43 (tq, *J* = 8.6 Hz, *J* = 2.0 Hz, 1H), 5.36 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 18.2, 25.6, 34.1, 39.7, 41.6, 41.7, 53.1, 60.8, 78.3, 84.0, 88.1, 170.2. HRMS calcd for $C_{11}H_{18}NO_3$ (M^+) 212.1281, found 212.1279.

Methanesulfonate Salt of Methyl (1*S*,2*R*,3*R*,6*S*)-(+)- 3-Ethyl-7-methyl-7-aza-8-oxatricyclo[4.2.1.0]nonane-2-carboxylate (24b). Sticky material: $[\alpha]^{20}_D$ +10.7 (*c* 3.975, MeOH); IR (film) 1748 cm^{-1}; ^1H NMR (CD_3OD) δ 0.617 (t, *J* = 7.6 Hz, 3H), 1.69 (m, 2H), 1.87 (dd, *J* = 12.8, 2.8 Hz, 1H), 2.02 (m, 2H), 2.18 (m, 1H), 2.33 (m, 1H), 2.38 (s, 3H), 2.51 (m, 1H), 3.01 (s, 1H), 3.16 (s, 3H), 3.22 (s, 1H), 3.41 (s, 3H), 4.14 (m, 1H), 5.02 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 8.98, 25.2, 25.75, 32.64, 39.65, 41.54, 42.0, 53.20, 59.8, 79.10, 84.97, 92.0, 171.0. HRMS calcd for $C_{12}H_{20}NO_3$ (M^+) 226.1443, found 226. 1438.

Methanesulfonate Salt of Methyl (1*S*,2*R*,3*R*,6*S*)-(+)-3-Propyl-7-aza-8-oxatricyclo[4.2.1.0]nonane-2-carboxylate (24c). Sticky solid: IR (film) 1750 cm^{-1}; $[\alpha]^{20}_D$ +14.3 (*c* 0.77, $CHCl_3$); ^1H NMR (CD_3OD) δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.13 (m, 1H), 1.28 (m, 1H), 1.82 (m, 2H), 2.08 (dd, *J* = 12.5 Hz, *J* = 2.7 Hz, 1H), 2.25 (m, 2H), 2.41 (m, 1H), 2.52 (m, 1H), 2.58 (m, 1H), 2.59 (s, 3H), 2.74 (m, 1H), 3.41 (s, 3H), 3.42 (s, 1H), 3.66 (s, 3H), 4.36 (m, 1H), 5.26 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (CD_3OD) δ 14.8, 19.0, 25.4, 32.9, 34.7, 39.6, 41.7, 41.9, 53.2, 60.0, 78.9, 85.0, 91.5, 171.1. HRMS calcd for $C_{13}H_{22}NO_3$ (M^+) 240.1594, found 240.1598.

Methanesulfonate Salt of Methyl (1*S*,2*R*,3*R*,6*S*)-(+)-3-Pentyl-7-methyl-7-aza-8-oxatricyclo[4.2.1.0]nonane-2-carboxylate (24d). Sticky material: $[\alpha]^{20}_D$ +13.9 (*c* 1.06, MeOH); IR (film) 1748 cm^{-1}; ^1H NMR (CD_3OD) δ 0.82 (t, *J* = 7.2 Hz, 3H), 1.20 (m, 6H), 1.81 (dt, *J* = 4.4, 12.4 Hz, 1H), 1.94 (m, 1H), 2.08 (dd, *J* = 2.7, 12.5 Hz, 1H), 2.23 (m, 2H), 2.39 (m, 1H), 2.55 (m, 1H), 2.60 (s, 3H), 2.73 (m, 1H), 3.41 (s, 3H), 3.42 (s, 1H), 3.66 (s, 3H), 4.36 (m, 1H), 5.26 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 14.3, 23.4, 25.2, 25.4, 32.7, 33.0, 33.3 39.6, 41.6, 41.9, 53.2, 60.0. 78.9, 85.0, 91.6, 171.1. HRMS calcd for $C_{15}H_{26}NO_3$ (M+) 268.1907, found 268.1912.

Methanesulfonate Salt of Methyl (1*S*,2*R*,3*R*,6*S*)-(+)-3-Phenyl-7-aza-8-oxatricyclo[4.2.1.0]nonane-2-carboxylate (24e). Isolated as a white sticky material: IR (film) 1760 cm^{-1}; $[\alpha]^{20}_D$ +38.9 (*c* 1.62, CH_3OH); ^1H NMR (CD_3OD) δ 2.21 (dd, *J* = 12.5 Hz, *J* = 1.7 Hz, 1H), 2.40 (m, 1H), 2.55 (s, 3H), 2.65 (m, 1H), 2.77 (m, 1H), 2.88 (m, 1H), 2.91 (s, 3H), 2.99 (m, 1H), 3.21 (s, 3H), 3.85 (s, 1H), 4.59 (m, 1H), 5.60 (d, J = 4.6 Hz, 1H), 7.36 (m, 3H), 7.45 (m, 2H); ^{13}C NMR (CD_3OD) δ 25.8, 31.3, 39.7, 42.7, 42.9, 52.7, 62.9, 80.1, 83.8, 91.8, 129.6, 130.2, 131.9, 133.5, 169.7. HRMS calcd for $C_{16}H_{20}NO_3$ (M^+) 274.1443, found 274.1440.

Methanesulfonate Salt of Methyl (1*R*,2*R*,3*S*,5*S*)-(−)-3-(Hydroxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-2-carboxylate (25a). Typical Procedure. In a 50 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed (−)-**24a** (0.030 g, 0.097 mmol) in anhydrous MeOH (10 mL), and Pd−C (0.01 g, 5% Pd on carbon) was added. A hydrogen atmosphere (1 atm) was maintained using a balloon, and the reaction mixture was stirred at rt for 48 h. At this time the solution was filtered through a short pad of Celite and concentrated to give 0.03 g (99%) of a white sticky solid: IR (film) 3400, 1750, cm^{-1}; $[\alpha]^{20}_D$ −24.2 (*c* 1.17, MeOH); ^1H NMR (CD_3OD) δ 1.38 (s, 3H), 1.99 (m, 1H), 2.07 (m, 4H), 2.28 (m, 1H), 2.63 (s, 3H), 2.71 (s, 3H), 3.12 (d, *J* = 6.8 Hz, 1H), 3.73 (s, 3H), 3.84 (m, 1H), 4.28 (td, *J* = 6.6 Hz, *J* = 11.0 Hz, 1H); ^{13}C NMR (CD_3OD) δ 20.8, 25.3, 32.4, 36.4, 36.5, 39.6, 53.2, 57.0, 63.1, 66.8, 71.8, 175.7. HRMS calcd for $C_{11}H_{20}NO_3$ 214.1434, found 214.1434.

Methanesulfonate Salt of Methyl (1*R*,2*R*,3*S*,5*S*)-(−)-1-Ethyl-3-(hydroxyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (25b). Sticky solid: $[\alpha]^{20}_D$ −7.6 (*c* 4.055, MeOH); IR (film) 3380, 1749 cm^{-1}; ^1H NMR (CD_3OD) 0.89 (t, *J* = 7.6 Hz, 3H), 1.56 (m, 1H), 1.80 (m, 1H), 1.99 (m, 3H), 2.10 (m, 2H), 2.25 (m, 1H), 2.59 (s, 3H), 2.62 (s, 3H), 3.22 (s, 1H), 3.27 (d, *J* = 6.8 Hz, 1H), 3.68 (s, 3H), 3.81 (b, 1H), 4.22 (m, 1H); ^{13}C NMR (CD_3OD) 9.4, 25.0, 28.1, 30.4, 36.4, 39.7, 52.8, 53.2, 63.1, 67.0, 75.3, 175.4. HRMS calcd for $C_{12}H_{22}NO_3$(M+) 228.16, found 228.1592.

Methanesulfonate Salt of Methyl (1*R*,2*R*,3*S*,5*S*)-(+)-1-Propyl-3-(hydroxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (25c). Sticky solid: IR (film) 3340, 1745 cm^{-1}; $[\alpha]^{20}_D$ +1.7 (*c* 0.82, MeOH); ^1H NMR (CD_3OD) δ 0.85 (t, *J* = 7.3 Hz, 3H), 1.15 (m, 1H), 1.35−1.71 (m, 7H), 1.97 (m, 1H), 2.10 (m, 1H), 2.12 (s, 3H), 2.60 (s, 3H), 2.89 (d, *J* = 6.6 Hz, 1H), 3.17 (m, 1H), 3.57 (s, 3H), 3.88 (m, 1H); ^{13}C NMR (CD_3OD) δ 15.4, 19.5, 27.2, 33.7, 36.6, 37.7, 39.6, 39.9, 51.6, 55.6, 64.3, 65.7, 69.1, 173.6. HRMS calcd for $C_{13}H_{24}NO_3$ (M^+) 242.1751, found 242.1751.

Methanesulfonate Salt of Methyl (1*R*,2*R*,3*S*,5*S*)-(+)-1-Pentyl-3-(hydroxyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (25d). A hydrogen atmosphere (50 atm) was applied, and the reaction mixture was stirred at rt for 6 h. At this time the solution was filtered through a short pad of Celite, and the Celite was washed with MeOH (2 × 5 mL) and concentrated to give 0.295 g (98%) of a sticky solid: $[\alpha]^{20}_D$ +3.5 (*c* 0.43, MeOH); IR (film) 3380, 1749 cm^{-1}; ^1H NMR (CD_3OD) δ 0.82 (t, *J* = 7.2 Hz, 3H), 1.20 (b, 6H), 1.48 (m, 8H), 1.94 (m, 1H), 2.09 (3, 3H), 2.60 (s, 3H), 2.88 (d, *J* = 6.4 Hz, 1H), 3.14 (m, 1H), 3.24 (s, 1H), 3.55 ((s, 3H), 3.87 (m, 1H); ^{13}C NMR (CD_3OD) δ 14.4, 23.6, 25.7, 27.2, 33.8, 33.9, 36.6, 36.3, 37.5, 37.7, 39.5, 51.5, 55.6, 64.2, 65.7, 68.9, 173.5. HRMS calcd for $C_{15}H_{28}NO_3$ (M+) 270.2064, found 270.2066.

Methanesulfonate Salt of Methyl (1*R*,2*R*,3*S*,5*S*)-(−)-3-(Hydroxy)-1-phenyl-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (25e). In a 50 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed (1*S*,2*R*,3*R*,6*S*)-(+)-**23e** (0.160 g, 0.433 mmol) in anhydrous MeOH (10 mL), and Pd−C (0.01 g, 5% Pd on carbon) was added. A hydrogen atmosphere (1 atm) was maintained using a balloon, and the reaction mixture was stirred at rt for 10 h. At this time the solution was filtered through a short pad of Celite, and concentrated to give 0.159 g (99%) of sticky material. This crude reaction mixture was taken further in the synthesis because it could not be purified.

(1*S*,6*S*,*E*)-(+)-Methyl 7-methyl-3-pentyl-8-oxa-7-aza-bicyclo-[4.2.1]non-2-ene-2-carboxylate (27d) from Palladium. In a 25 mL, oven-dried, single-necked round-bottom flask equipped with magnetic stirring bar and rubber septum was placed **24d** (0.030 g, 0.083 mmol) and 5% Pd/C (20% w/w) in methanol (10 mL). The reaction mixture was stirred at rt for 48 h, the solution was filtered through Celite, washed using methanol (2 × 7 mL), and concentrated. The residue was dissolved in anhydrous pyridine (5 mL) and stirred at rt for 20 h under an argon atmosphere. At this time the solution was concentrated, the residue was dissolved in satd K_2CO_3 (10 mL) and extracted with DCM (2 × 7 mL), and the combined organic phases were washed with brine (8 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (60% EtOAC in hexanes) yielded 0.014 g (63%) of oil: $[\alpha]^{20}_D$ +66.5 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.28 (m, 4H), 1.46 (m, 3H), 1.98 (m, 3H), 2.20 (m, 1H), 2.40 (m, 1H), 2.65 (m, 4H), 3.17 (m, 1H), 3.45 (t, *J* = 6.0 Hz, 1H), 3.70 (s, 3H), 5.20 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 27.5, 31.1, 31.8, 33.1, 37.8, 39.3, 46.5, 51.3, 64.4, 76.8, 131.8, 157.4, 168.4. HRMS calcd for $C_{15}H_{26}NO_3$ (M + H) 268.1913, found 268.1909.

(1*S*,6*S*,*E*)-(+)-Methyl 7-Methyl-3-pentyl-8-oxa-7-aza-bicyclo-[4.2.1]non-2-ene-2-carboxylate (27d). Typical Procedure from Triethylamine. In a 25 mL, oven-dried, single-necked round-bottom flask equipped with magnetic stirring bar and rubber septum was placed salt **24d** (0.020 g, 0.055 mmol) in methanol (1 mL), and triethylamine was added (1 mL). The reaction mixture was stirred at rt for 12 h, and the solution was concentrated. The residue was taken

into satd K_2CO_3 (5 mL) and extracted with DCM (2 × 5 mL), the combined organic phases were washed with brine (8 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (60% EtOAC in hexanes) gave 0.0132 g (90%) of oil identical to that prepared above.

(1*S*,6*S*,*E*)-(+)-Methyl 3,7-Dimethyl-8-oxa-7-aza-bicyclo-[4.2.1]non-2-ene-2-carboxylate (27a). Flash chromatography (70% EtOAC in hexanes) yielded 0.013 g (95%) of oil: $[\alpha]^{20}_D$ +73.7 (*c* 2.195, $CHCl_3$); IR ($CHCl_3$) 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (m, 1H), 1.95 (m, 3H), 2.04 (s, 3H), 2.65 (m, 4H), 3.22 (m, 1H), 3.44 (t, *J* = 6.0 Hz, 1H), 3.71 (s, 3H), 5.24 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 29.6, 32.6, 33.0, 39.1, 46.5, 51.3, 64.3, 77.2, 131.9, 154.2, 168.3. HRMS calcd for $C_{11}H_{18}NO_3$ (M + H) 211.1208, found 212.1284.

(1*S*,6*S*,*E*)-(+)-Methyl-7-methyl-3-phenyl-8-oxa-7-aza-bicyclo-[4.2.1]non-2-ene-2-carboxylate (27e). In a 50 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed **24e** (0.028 g, 0.076 mmol) in anhydrous MeOH (1.0 mL) under argon. To this solution was added pyridine (1.0 mL), and the mixture was stirred at rt for 16 h. At this time, the solvent was removed, satd aqueous potassium carbonate (30 mL) was added, and the solution was stirred for 10 min. At this time the aqueous solution was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (50% EtOAc/hexanes) gave 0.019 g (96%) of a syrupy oil: $[\alpha]^{20}_D$ +97.1 (*c* 0.38, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.74 (ddt, *J* = 13.4 Hz, *J* = 3.4 Hz, *J* = 1.0 Hz, 1H), 2.04 (m, 1H), 2.15 (d, *J* = 12.4 Hz, 1H), 2.33 (td, *J* = 16.4 Hz, *J* = 3.9 Hz, 1H), 2.71 (s, 3H), 2.76 (m, 1H), 3.36 (s, 3H), 3.50 (m, 2H), 5.26 (d, *J* = 9.2 Hz, 1H), 7.08 (m, 2H), 7.27 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 32.7, 33.2, 39.1, 46.6, 51.2, 64.5, 77.2, 126.4, 127.1, 127.9, 134.9, 144.5, 153.1, 169.2. HRMS calcd for $C_{16}H_{20}NO_3$ (M + H) 274.1443, found 274.1440.

Methyl (1*R*,2*R*,3*S*,5*S*)-(−)-3-(Benzyloxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-2-carboxylate (28a). Typical Procedure. In a 25 mL, oven-dried, single-neck round-bottomed flask equipped with magnetic stirring bar and a rubber septum was placed (−)-**25a** (0.03 g, 0.097 mmol) in anhydrous pyridine (1.0 mL) under argon. Benzoyl chloride (0.020 g, 0.145 mmol) was slowly added, and the solution was stirred at rt for 20 h. At this time the solvent was removed, satd aqueous potassium carbonate (30 mL) was added, and the solution was stirred for 10 min. At this time the mixture was extracted with $CHCl_3$ (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (1% NH_4OH in 40% EtOAc/hexanes) gave 0.029 g (94%) of a syrupy oil: IR (film) 1720, 1645 cm^{-1}; $[\alpha]^{20}_D$ −8.3 (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.72 (m, 1H), 1.81 (m, 2H), 1.89 (m, 1H), 2.14 (m, 1H), 2.26 (s, 3H), 2.50 (dt, *J* = 2.7 Hz, *J* = 12.0 Hz, 1H), 2.94 (d, *J* = 6.8 Hz, 1H), 3.36 (m, 1H), 3.64 (s, 3H), 5.36 (td, *J* = 6.4 Hz, *J* = 11.7 Hz, 1H), 7.40 (m, 2H), 7.54 (m, 1H), 7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.7, 26.7, 34.2, 34.5, 36.8, 51.1, 55.5, 62.8, 64.9, 68.4, 128.3, 129.5, 130.1, 132.9, 165.9, 170.4. HRMS calcd for $C_{18}H_{24}NO_4$ (M + H) 318.1705, found 318.1701.

Methyl (1*R*,2*R*,3*S*,5*S*)-(−)-1-Ethyl-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (28b). Flash chromatography (1% NH_4OH on EtOAc) gave 75% of an oil: $[\alpha]^{20}_D$ −1.8 (*c* 1.365, $CHCl_3$); IR (film) 1721, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.61 (m, 3H), 1.75 (m, 2H), 1.84 (m, 1H), 2.07 (m, 1H), 2.28 (s, 3H), 2.53 (td, *J* = 11.7, 2.7 Hz, 1H), 3.17 (d, *J* = 6.4 Hz, 1H), 3.39 (m, 1H), 3.62 (s, 3H), 5.34 (m, 1H), 7.4 (m, 2H), 7.53 (m, 1H), 7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) 9.2, 26.1, 28.5, 29.6, 32.4, 33.2, 35.9, 50.7, 51.0, 62.5, 68.1, 68.5, 128.2, 129.5, 130.1, 132.9, 165.8, 170.5. HRMS calcd for $C_{19}H_{26}NO_4$ (M + H) 332.1862, found 332.1858.

Methyl (1*R*,2*R*,3*S*,5*S*)-(−)-1-Propyl-3-(benzyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (28c). Chromatography (1% NH_4OH in 40% EtOAc/hexanes) gave 92% of a syrupy oil: IR (film) 1719, 1641 cm^{-1}; $[\alpha]^{20}_D$ −3.0 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.23 (m, 1H), 1.44 (m, 1H), 1.66 (m, 2H), 1.76 (m, 1H), 1.84 (m, 1H), 2.08 (m, 1H), 2.30 (s, 3H), 2.53 (dt, *J* = 12.0 Hz, *J* = 2.4 Hz, 1H), 3.15 (d, *J* = 6.6 Hz, 1H), 3.39 (m, 1H), 3.63 (s, 3H), 5.33 (m, 1H), 7.40 (m, 2H), 7.53 (m, 1H), 7.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.0, 18.2, 26.3, 32.9, 33.4, 36.1, 38.5, 51.1, 51.4, 62.4, 67.8, 68.6, 128.3, 129.6, 130.2, 132.9, 165.9, 170.6. HRMS calcd for $C_{20}H_{28}NO_4$ (M + H) 346.2018, found 346.2019.

Methyl (1*R*,2*R*,3*S*,5*S*)-(+)-1-Pentyl-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (28d). Flash chromatography (1% NH4OH:EtOAc) gave 82% of an oil: $[\alpha]^{20}_D$ +6.7 (*c* 1.2, $CHCl_3$); IR (film) 1721, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.37 (b, 4H), 1.62 (b, 5H), 1.77 (m, 2H), 1.84 (b, 1H), 2.09 (b, 1H), 2.30 (s, 3H), 2.54 (dt, *J* = 2.7, 12.2 Hz, 1H), 3.16 (d, *J* = 6.8 Hz, 1H), 3.39 (b, 1H), 3.62 (s, 3H), 5.34 (m, 1H), 7.41 (m, 2H), 7.52 (m, 1H), 7.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 24.4, 26.2, 32.6, 32.9, 33.2, 36.0, 36.1, 51.0, 51.3, 62.4, 67.7, 68.6, 128.2, 129.5, 130.1, 132.9, 165.8, 170.5; HRMS calcd for $C_{22}H_{32}NO_4$ (M + H) 374.2331, found 374.2327.

Methyl (1*R*,2*R*,3*S*,5*S*)-(+)-1-Phenyl-3-(benzyloxy)-1-phenyl-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (28e). Chromatography (40% EtOAc/hexanes) gave 80% of a syrupy oil: IR (film) 1710, 1635 cm^{-1}; $[\alpha]^{20}_D$ +33.1 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.81 (m, 1H), 1.97 (m, 1H), 2.09 (s, 3H), 2.21 (m, 2H), 2.34 (m, 1H), 2.58 (m, 1H), 2.98 (d, *J* = 6.8 Hz, 1H), 3.22 (s, 3H), 3.52 (m, 1H), 5.38 (td, *J* = 11.6 Hz, *J* = 6.3 Hz, 1H), 7.17 (m, 2H), 7.27 (m, 5H), 7.45 (m, 1H), 7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 32.3, 34.3, 38.4, 50.9, 58.1, 62.9, 68.3, 73.1. 127.1, 127.7, 128.1, 128.3, 128.4, 129.5, 129.9, 133.0, 133.3, 165.7, 169.7. HRMS calcd for $C_{23}H_{26}NO_4$ (M + H) 380.1862, found 380.1859.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental general procedures and ^1H and ^{13}C NMR spectroscopic data for all new compounds; ORTEP/X-ray structure of tricyclic isoxazolidine (−)-**21e** in CIF format. 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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■ REFERENCES

(1) (a) Carroll, F. I. *J. Med. Chem.* **2003**, *46* (10), 1775. (b) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.

(2) Runyon, S. P.; Carroll, F. I. *Curr. Top. Med. Chem.* **2006**, *6*, 1825.

(3) Singh, S. *Chem. Rev.* **2000**, *100*, 925.

(4) Pollini, G. P.; Benetti, S.; De Risi, C.; Zanirato, V. *Chem. Rev.* **2006**, *106*, 2434.

(5) Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883.

(6) For earlier asymmetric syntheses of cocaine, see: (a) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069. (b) Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773. (c) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305. (d) Cheng, G.; Wang, X.; Zhu, R.; Shao, C.; Xu, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 2694. (e) Shing, T. K. M.; So, K. H. *Org. Lett.* **2011**, *13*, 2916.

(7) Davis, F. A.; Theddu, N.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 4118.

(8) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali., S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435.

(9) For a review on S-N chemistry, which includes sulfinimines and sulfinimine-derived chiral building blocks, see: Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
(10) For recent reviews on the chemistry of sulfinimines, see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (e) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
(11) For applications of masked oxo-sulfinimines in asymmetric synthesis of nitrogen heterocycles see the following. (a) Proline and pipecolic acid derivatives: Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759. (b) Cyclic α-amino phosphonates: Davis, F. A.; Lee, S. H.; Xu, H. *J. Org. Chem.* **2004**, *69*, 3774. (c) Piperidines: Davis, F. A.; Gaspari, P. M.; Nolt, B.; Xu, P. *J. Org. Chem.* **2008**, *73*, 9619. (d) Tropinones: Davis, F. A.; Theddu, N.; Gaspari, P. M. *Org. Lett.* **2009**, *11*, 1647. (e) Tropanes: ref 7. (f) Homotropinones: Davis, F. A.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 848.
(12) Johnson, S. J.; Kesten, S. R.; Wise, L. D. *J. Org. Chem.* **1992**, *57*, 4746.
(13) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G. *Tetrahedron Lett.* **1995**, *36*, 5461.
(14) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(15) Gonzalez-Gomez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.
(16) Davis, F. A.; Chen, B.-C.; Zhou, P. Oxaziridines and Oxazirines. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol.*1*, p 559.
(17) Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473.
(18) Davis, F. A.; Chen, B.-C.; Zhou, P. Oxaziridines and Oxazirines. In *Comprehensive Heterocyclic Chemistry III*, Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. *1*, p 559.
(19) Joucla, M.; Gree, D.; Hamelin, J. *Tetrahedron* **1973**, *29*, 2315.
(20) Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449.
(21) (a) Roy, A.; Chakrabarty, K.; Dutta, P. K.; Bar, N. C.; Basu, N.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1999**, *64*, 2304. (b) Patra, R.; Bar, N. C.; Roy, A.; Achari, B.; Ghoshal, N.; Mandal, S. B. *Tetrahedron* **1996**, *52*, 11265. (c) Shing, T. K. M.; So, K. H. *Org. Lett.* **2011**, *13*, 2916.
(22) For leading references, see: (a) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Chem. Eur. J.* **2009**, *15*, 2693. (b) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585. (c) Reference 7.
(23) Gravier-Pelletier, C.; Maton, W.; Dintinger, T.; Tellier, C.; Merrer, Y. L. *Tetrahedron* **2003**, *59*, 8705.
(24) (a) Hayashi, M.; Yamada, K.; Nakayama, S. *Synthesis* **1999**, 1869. (b) Stolz, B. M. *Chem. Lett.* **2004**, *33*, 362. (c) Zhang, Q.; Deng, W.; Wang, Y. *Chem. Commun.* **2011**, *47*, 9275.
(25) Kim, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1717.
(26) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 8771.
(27) (a) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955. (b) Kulkarni, A.; Abid, M.; Torok, B.; Huang, X. *Tetrahedron Lett.* **2009**, *50*, 1791. (c) Tanaka, T.; Okunaga, K-i.; Hayashi, M. *Tetrahedron Lett.* **2010**, *51*, 4633.
(28) Brown, E.; Lavoue, J.; Dhal, R. *Tetrahedron* **1973**, *29*, 455.
(29) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.