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4-Alkoxycarbonyl- and Aminocarbonyl-Substituted Isoxazoles as Masked Acrylates and Acrylamides in the Asymmetric Synthesis of Δ^2-Isoxazolines

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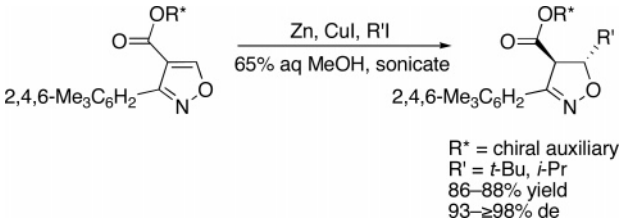
Received February 7, 2006

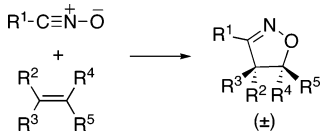


4-Alkoxycarbonyl and aminocarbonyl-substituted isoxazoles undergo conjugate reduction to give Δ^2-isoxazolines on treatment with sodium borohydride and sodium trifluoroacetoxyborohydride, respectively. They are also alkylated at C5 through sonication with secondary and tertiary alkyl iodides in the presence of zinc dust and copper(I) iodide. These reactions are analogous to those observed with acrylates and acrylamides. The behavior is characteristic of the 4-substituted isoxazoles but not the 5-substituted regioisomers. The reductions of 4,5-disubstituted isoxazoles and the C5 alkylations of 4-substituted isoxazoles generally afford *trans*-4,5-disubstituted isoxazolines. Incorporating chiral auxiliaries into the alkoxycarbonyl group maintains this relative stereoselectivity. It does not provide significant levels of asymmetric induction in the reductions, but the alkylations occur with good levels of stereocontrol at both C4 and C5. Because both enantiomers of the auxiliaries are available, this provides access to either enantiomer of the products, in 93 to ≥98% de. The methodology, therefore, provides a complementary approach to nitrile oxide cycloadditions to alkenes for the asymmetric synthesis of Δ^2-isoxazolines.

Introduction

Δ^2-Isoxazolines are of interest as precursors of 1,3-diols, β-hydroxy ketones, α,β-unsaturated ketones, γ-amino alcohols, β-hydroxy nitriles, and related compounds,[1] and in this context, they have been employed in numerous natural product syntheses.[2] The conventional method for their synthesis is via cycloaddition of nitrile oxides and alkenes (Scheme 1). These reactions are generally highly regioselective, and the configuration of the alkenes is retained in the cycloadducts; however, developing stereoselective syntheses of isoxazolines continues to be a challenge.[3] The asymmetric induction observed in the

SCHEME 1



cycloadditions of optically active nitrile oxides with alkenes is typically poor.[4] More promising results have been obtained using chiral alkenes, such as allylic ethers,[5] allylic amines,[6] allyl

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10.1021/jo0602569 CCC: $33.50
Published on Web 03/23/2006

silanes,[7] vinyl sulfoxides,[8] vinyl phosphine oxides,[9] vinyl ethers,[10] acrylates,[11,12] and acrylamides.[11,13] With compounds of these types, the stereoselectivity varies widely, but of particular note, reactions of acrylamide derivatives of Oppolzer's chiral sultam,[13] a novel camphor derivative,[14] and Kemp's diacid[15] have afforded isoxazolines with 98% de. Chiral metal chelates have also been exploited to accomplish highly asymmetric cycloadditions of nitrile oxides with allylic alcohols[16] and acrylamides.[17]

Recently, we reported some unusual substituent effects in reactions of acyl- and alkoxycarbonyl-substituted isoxazoles.[18,19] Isoxazoles substituted at the 4-position underwent efficient electrochemical and yeast-catalyzed ring opening via cleavage of the N−O bond. By contrast, the regioisomers substituted at the 5-position did not. The basis of these substituent effects was investigated through X-ray crystallographic and theoretical structural analyses.[19] These showed that the 4-substituted isoxazoles are conjugated and polarized like Michael acceptors, with C5 being more electropositive than C4, in a manner analogous to the β- and α-carbons of an acrylate, respectively (Figure 1). The 5-substituted isoxazoles lack this type of conjugation and polarization. Accordingly, the 4-methoxycarbonyl-substituted isoxazole **1a** was found to react by conjugate reduction with sodium borohydride, to form the 4-hydroxymethylisoxazoline **2a** (Scheme 2), while the 5-substituted isoxazole **4a** gave only the 5-hydroxymethylisoxazole **5a** under analogous conditions (Scheme 3).[19] A similar pattern of reactivity was seen with the isoxazoles **1b** and **4b**.

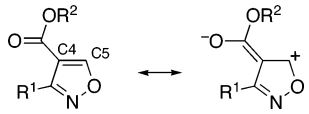

FIGURE 1. Resonance contributors illustrating the acrylate-type polarization of a 4-alkoxycarbonyl-substituted isoxazole.

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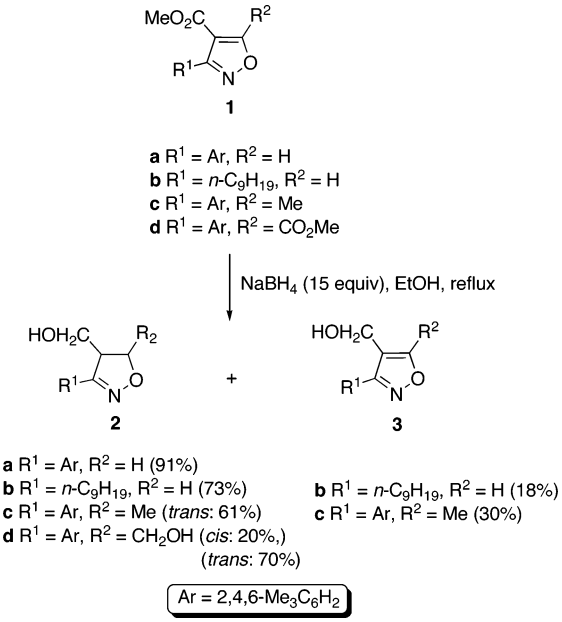
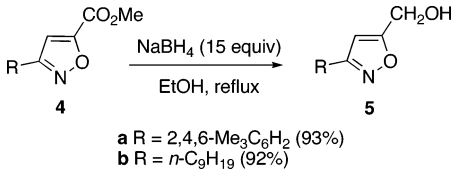


SCHEME 3



We have now examined the scope and limitations of the use of 4-alkoxycarbonylisoxazoles and the corresponding amides, as masked acrylates and acrylamides, in alkylations as well as reductions. Of particular significance, we have found that, by incorporating chiral auxiliaries into the alkoxycarbonyl group, alkylation affords isoxazolines with a high degree of stereocontrol at both C4 and C5, providing an efficient and complementary method to nitrile oxide cycloadditions to alkenes for the asymmetric synthesis of these compounds.

Results and Discussion

A variety of 4- and 5-substituted isoxazoles were required for this study. The syntheses of the 4-methoxycarbonylisoxazoles **1a**,**b** and their corresponding 5-substituted regioisomers **4a**,**b** were carried out as reported recently.[19] The isoxazoles **1c** and **1d**[20] were prepared via cycloaddition of mesitonitrile oxide (**7**) with methyl tetrolate (**6d**) and dimethyl acetylenedicarboxy-

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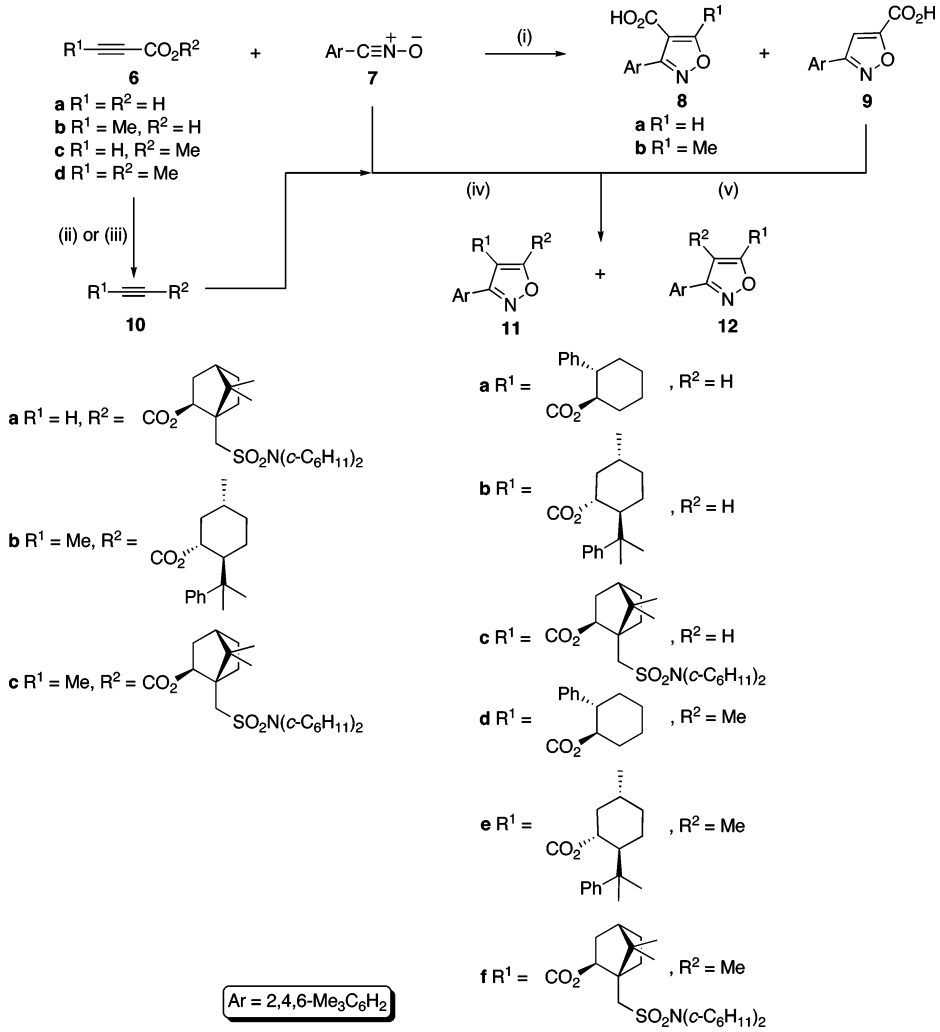
SCHEME 4[a]



[a] Reagents and conditions: (i) THF, reflux, **6a** gave **8a** and **9** (quantitative), **6b** gave **8b** (quantitative). (ii) DCC/DMAP, Et_2O, 18 °C, **6b** and (−)-8-phenylmenthol gave **10b** (86%). (iii) Me_3Al, toluene, reflux, **6c** and (+)-10-dicyclohexylsulfamoyl-*L*-isoborneol gave **10a** (95%), **6d** and (+)-10-dicyclohexylsulfamoyl-*L*-isoborneol gave **10c** (95%). (iv) THF, reflux, **10a** gave **11c** (19%) and **12c** (56%), **10b** gave **11e** (93%), **10c** gave **11f** (13%) and **12f** (81%). (v) DCC/DMAP, Et_2O, 18 °C, **8a** and **9** and Whitesell's auxiliary gave **11a** (50%) and **12a** (38%), **8a** and **9** and (−)-8-phenylmenthol gave **11b** (48%) and **12b** (37%), **8b** and Whitesell's auxiliary gave **11d** (87%).

late, respectively. The isoxazoles **13a**−**c** and **15** were synthesized through the reaction of mesitonitrile oxide (**7**) with propiolamide, tetrolamide, and 3-phenylpropiolamide. The latter two reactions were completely regioselective, while that of propiolamide afforded a 1:2 mixture of the 4- and 5-substituted regioisomers **13a** and **15**.

4-Alkoxycarbonylisoxazoles esterified with the chiral auxiliaries (−)-(1*R*,2*S*)-2-phenylcyclohexanol (Whitesell's auxiliary),[21] (−)-8-phenylmenthol [(−)-(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol], and (+)-10-dicyclohexylsulfamoyl-*L*-isoborneol [(+)−(1*R*,2*S*,4*S*)-*N*,*N*-dicyclohexyl-7,7-dimethyl-2-hydroxybicyclo[2.2.1]heptane-1-methanesulfonamide][22] were also prepared (Scheme 4). The reaction of mesitonitrile oxide (**7**) and propiolic acid (**6a**) gave a 1.3:1 mixture of the acids **8a** and **9**, which were coupled with Whitesell's auxiliary and (−)-8-phenylmenthol, using DCC/DMAP,[23] to produce mixtures of **11a**,**b** and **12a**,**b** that were separated using chromatography. For the sterically more encumbered isobornyl auxiliary, a trimethylaluminum-catalyzed transesterification[24] of methyl propiolate (**6c**), followed by the cycloaddition of the resulting chiral alkyne **10a** with mesitonitrile oxide (**7**), gave rise to the chiral acylisoxazoles **11c** and **12c**, which were separated by chromatography. The 5-methyl-substituted isoxazole **11d** bearing Whitesell's auxiliary was synthesized in two steps by the cycloaddition of mesitonitrile oxide (**7**) and tetrolic acid (**6b**), followed by a DCC/DMAP-mediated esterification of the resulting cycloadduct **8b**. The other 5-methyl-substituted isoxazoles **11e**,**f** were formed, as a separable mixture, with the regioisomer **12f** in the case of **11f** by the reaction of mesitonitrile oxide (**7**) with the corresponding chiral dipolarophiles **10b**,**c**. The dipolarophiles **10b** and **10c**[25]

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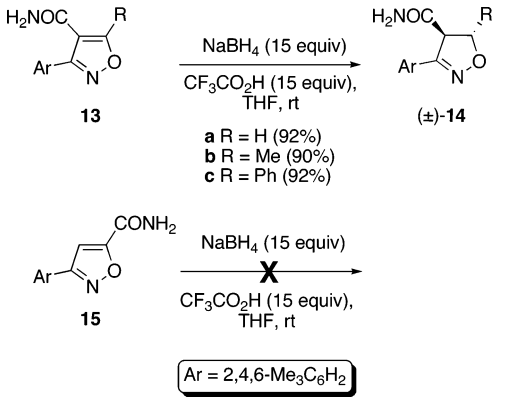
SCHEME 5

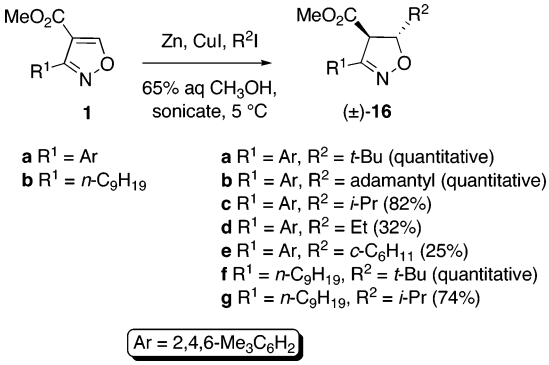


had been prepared by esterification of tetrolic acid (**6b**), mediated with DCC/DMAP, and by transesterification of methyl tetrolate (**6d**) with trimethylaluminum, respectively.

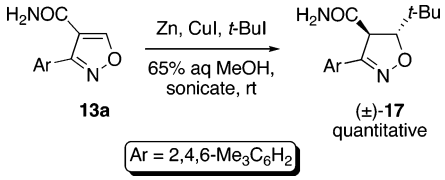
In a fashion similar to the reactions of the 4-methoxycarbonyl-substituted isoxazoles **1a**,**b**,[19] treatment of **1c** with excess sodium borohydride in ethanol at reflux afforded the trans isomer of the isoxazoline **2c**[26] and the isoxazole **3c**[26] in yields of 61 and 30%, respectively (Scheme 2). Under identical conditions, the diester **1d** gave only the trans and cis isomers of the isoxazoline **2d** in yields of 70 and 20%, respectively. The aminocarbonyl-isoxazoles **13a**−**c** and **15** were unreactive toward sodium borohydride. However, with sodium trifluoroacetoxyborohydride,[27] which was prepared in situ by the treatment of sodium borohydride with trifluoroacetic acid, the 4-aminocarbonylisoxazoles **13a**−**c** were efficiently converted to the corresponding isoxazolines (±)-**14a**, (±)-**14b**,[28] and (±)-**14c**,[28] while the 5-aminocarbonylisoxazole **15** remained inert (Scheme 5). Thus, conjugate reduction is the major reaction pathway for the 4-alkoxycarbonyl- and aminocarbonyl-substituted isoxazoles **1a**−**d** and **13a**−**c**. The isoxazole **1a** was also efficiently converted to the isoxazoline **2a** through a reaction with lithium borohydride in THF at reflux, although it was unreactive toward either sodium cyanoborohydride, potassium borohydride, sodium borohydride/15-crown-5, or lithium borohydride/12-crown-4. The isoxazole **1c** also reacted with lithium borohydride to give the cis and trans isomers of the isoxazoline **2c**, in a 1:2 ratio.

Having observed conjugate reduction in the reactions of the 4-alkoxycarbonyl- and aminocarbonyl-substituted isoxazoles **1a**−**d** and **13a**−**c**, we next investigated the possibility of alkylations of compounds of these types. Treatment of the 4-methoxycarbonylisoxazole **1a** with lithium dimethylcopper, a reagent commonly used for conjugate additions to α,β-unsaturated carbonyl compounds,[29] was not successful. Instead, mesitonitrile was produced, presumably via anionic cleavage of the isoxazole ring.[30] Likewise, no alkylation of the 4-methoxycarbonylisoxazole **1a** was observed on treatment with nitroalkanes under basic conditions,[31] no free radical addition occurred using either alkyl iodides, tributyltin hydride, and 2,2′-azobisisobutyronitrile[32] or alkylmercuric iodides and sodium borohydride,[33] and no Diels−Alder cycloaddition resulted from treatment with either cyclopentadiene or Danishefsky's diene.[34]

SCHEME 6



SCHEME 7



Success was eventually realized with the methodology of Luche et al.,[35] whereby conjugate additions of alkyl halides to α,β-unsaturated carbonyl compounds are effected via a radical mechanism, in the presence of zinc dust and cuprous iodide, with sonication. The C5 alkylations of the 4-alkoxycarbonyl- and aminocarbonyl-substituted isoxazoles **1a**,**b** and **13a** with a range of alkyl iodides that were performed using this procedure are summarized in Schemes 6 and 7. Those involving *tert*-butyl iodide, 1-iodoadamantane, and isopropyl iodide were highly stereoselective and afforded good to excellent yields of the *trans*-isoxazolines (±)-**16a**−**c**, (±)-**16f**,**g**, and (±)-**17**. The relative configuration of these compounds was confirmed through their lack of epimerization at C4 on treatment with base (cis isomers would be expected to convert to their thermodynamically more stable trans forms)[36] and by X-ray crystallographic analysis in the case of (±)-**16b**. The corresponding *cis*-isoxazolines were

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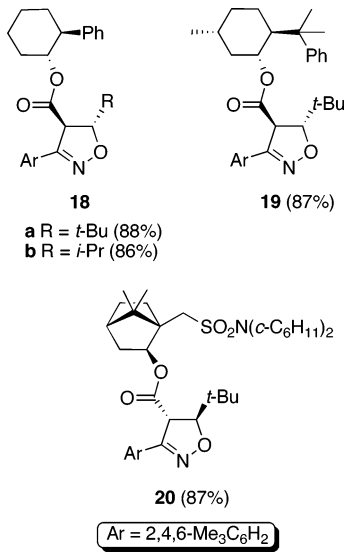
not detected, except in the reaction of **1a** with cyclohexyl iodide that afforded a 5:4 mixture of (±)-**16e** and the corresponding cis isomer. In contrast to the facile reactions of tertiary and secondary alkyl iodides, treatment of the isoxazole **1a** with ethyl iodide as a representative primary iodide gave only a 32% yield of the *trans*-isoxazoline (±)-**16d**, and the starting material was recovered in a 63% yield, even after extended periods of reaction and repeated additions of the alkyl iodide, zinc powder, and cuprous iodide. Under similar conditions, no reaction was observed between the isoxazole **1a** and methyl iodide. This is consistent with the pattern of reactivity reported by Luche et al.,[35] for the utility of various classes of alkyl halides in alkylations of this type. The 5-methoxycarbonyl-substituted isoxazole **4a** was inert to a reaction with isopropyl iodide under the conditions used to alkylate the 4-substituted regioisomer **1a**, confirming that the reactivity of isoxazoles as masked acrylates and acrylamides is characteristic of those substituted at C4 with alkoxycarbonyl and aminocarbonyl groups.

The reductions of the isoxazoles **1c**,**d** and **13b**,**c** and the alkylations of **1a**,**b** and **13a** generally showed a strong preference for the formation of *trans*-4,5-disubstituted isoxazolines, but the products are racemic. To determine whether chiral auxiliaries attached to isoxazoles could be exploited to control the absolute as well as the relative stereochemistry in 4,5-disubstituted isoxazolines, reductions of **11d**−**f** and alkylations of **11a**−**c** were also investigated. The reactions of **11d**−**f** with sodium borohydride were impractically slow. After extended reaction times, in each case the trans isomer of the isoxazoline **2c**[26] and the corresponding 4-hydroxymethylisoxazole **3c** were produced but in yields of only about 10−15 and 5−10%, respectively. There was no evidence of formation of the cis isomer of the isoxazoline **2c**. The lack of enantioselectivity in the reactions to give the isoxazoline **2c** was determined by DCC/DMAP-mediated coupling with (*S*)-2-phenylpropionic acid and analysis of the product diastereomeric esters using ^{1}H NMR spectroscopy. In each case, this showed a de of approximately 10%, indicating that the conjugate reductions of **11d**−**f** were not only inefficient, but also that they occurred with little asymmetric induction. The alkylations of **11a**−**c** with *tert*-butyl iodide and of **11a** with isopropyl iodide gave the *trans*-isoxazolines **18a**,**b**, **19**, and **20** in variable yields up to 86−88% and with de values of 95, 93, 94, and ≥98%, respectively. The relative and absolute stereochemistries of **18a** and **20** were determined through X-ray crystallographic analysis. That of **18b** and **19** was assigned by analogy with **18a** and **20** on the basis of MM2 calculations and the examination of models that show the re face of the isoxazoles **11a**,**b** and the si face of **11c** to be hindered such that alkylation from the opposite face is favored. The de values were calculated on the basis of analysis of ^{1}H NMR spectra of crude samples of **18a**,**b**, **19**, and **20**. Minor resonances attributable to the other *trans*-4,5-disubstituted isoxazoline diastereomers were observed with **18a**,**b** and **19**, but there was no evidence of this with **20**. However, small amounts of the cis isomer of **20** were sometimes observed in the alkylations of **11c**.

Conclusion

Thus, all of the results discussed above show that isoxazoles substituted at the 4-position with alkoxycarbonyl and aminocarbonyl groups undergo unusual conjugate reductions and alkylations to give Δ^2-isoxazolines and, as such, they may be regarded as masked acrylates and acrylamides. This behavior is not observed with the regioisomeric 5-substituted isoxazoles. The reductions of 4,5-disubstituted isoxazoles generally show a strong preference for the formation of *trans*-4,5-disubstituted isoxazolines, but this stereocontrol was not augmented by the chiral auxiliaries of **11d**−**f**, which failed to provide significant levels of asymmetric induction. By contrast, the C5 alkylations of 4-substituted isoxazoles gave good yields of *trans*-4,5-disubstituted isoxazolines and, in the cases of the chiral isoxazoles **11a**−**c**, with control of the absolute stereochemistry at both C4 and C5. This methodology, therefore, provides an alternative and complementary approach to nitrile oxide cycloadditions to alkenes for the asymmetric synthesis of Δ^2−isoxazolines. It is versatile in that the auxiliaries of **11a**−**c** are each available in either enantiomeric form and the alkylations of **11a**,**b** and **11c** give the opposite stereoselectivity. This method is likely to be particularly useful for accessing isoxazoles substituted at C5 with secondary and tertiary alkyl groups, which are well-suited to incorporation, using the alkylation procedure, and where the alkenes required for the corresponding cycloaddition method are not readily available.



Experimental Section

Methyl 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylate (1c). A mixture of mesitonitrile oxide (**7**; 0.50 g, 3.1 mmol) and methyl tetrolate (**6d**; 0.30 g, 3.1 mmol) in THF (25 mL) was heated at reflux for 4 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazole **1c** (0.79 g, 98%) as colorless blocks after recrystallization through vapor diffusion of hexanes into Et_2O at room temperature: mp 76−78 °C; IR 2952, 2923, 2858, 1730, 1719, 1603, 1441, 1409, 1311, 1297, 1250, 1191, 1096, 1035, 994, 980, 851, 806, 770 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.05 (s, 6H), 2.31 (s, 3H), 2.77 (s, 3H), 3.67 (s, 3H), 6.91 (s, 2H); ^{13}C NMR (75.4 MHz) δ 13.6, 19.9, 21.2, 51.6, 109.1, 124.2, 128.0, 136.8, 138.6, 161.9, 162.2, 175.4; LRMS (%) *m*/*z* 259 (M^+, 100), 244 (28), 228 (42), 212 (65), 200 (24), 185 (92), 171 (57), 157 (59), 144 (17), 130 (22), 115 (30), 103 (20), 91 (28), 77 (31). HRMS (*m*/*z*): (M^+) calcd for $C_{15}H_{17}NO_3$, 259.1208; found, 259.1213.. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.40; H, 6.41; N, 5.68. The structure of the isoxazole **1c** was confirmed using X-ray crystallographic analysis (CCDC-261167).

Dimethyl 3-(2,4,6-Trimethylphenyl)isoxazole-4,5-dicarboxylate (1d). A mixture of mesitonitrile oxide (**7**; 0.50 g, 3.1 mmol)

(36) Alberola, A.; Gonzalez, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis* **1983**, 413.

and dimethyl acetylenedicarboxylate (0.44 g, 3.1 mmol) in THF (40 mL) was heated at reflux for 2 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazole **1d** (0.91 g, quantitative) as a colorless solid, mp 56−57 °C, with physical and spectral data consistent with reported values.[20]

***trans*-4-Hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline (*trans*-2c) and 4-Hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)isoxazole (3c).** Sodium borohydride (0.22 g, 5.8 mmol) was added slowly to a solution of the isoxazole **1c** (0.10 g, 0.39 mmol) in EtOH (10 mL) at 0−5 °C. The mixture was then heated at reflux for 24 h before it was cooled to 0−5 °C and adjusted to pH 2 through the dropwise addition of 1 M aq HCl. The resultant solution was concentrated under reduced pressure, and the residue was taken up in Et_2O and washed with H_2O. The aqueous washings were extracted with Et_2O. The organic solutions were combined, washed with H_2O and saturated brine, dried (anhyd $MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazoline **2c** (55 mg, 61%) and the isoxazole **3c** (27 mg, 30%) as colorless oils with physical and spectral data consistent with reported values.[26]

***trans*-4,5-Di(hydroxymethyl)-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline (*trans*-2d) and *cis*-4,5-Di(hydroxymethyl)-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline (*cis*-2d).** The procedure described above for the reaction of the isoxazole **1c** with sodium borohydride was followed in the treatment of the isoxazole **1d** (0.10 g, 0.33 mmol) with sodium borohydride (0.19 g, 5.0 mmol), which afforded the *trans*-disubstituted isoxazoline ***trans*-2d** (57 mg, 70%) as a colorless solid: mp 102−103 °C; IR 3332, 2953, 2925, 1612, 1438, 1118, 1031 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.60 (br s, 2H), 2.27 (s, 6H), 2.29 (s, 3H), 3.65 (m, 1H), 3.90 (m, 2H), 4.05 (m, 1H), 4.13 (m, 1H), 4.89 (ddd, J = 10.0, 6.0, 3.5 Hz, 1H), 6.90 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.0, 21.0, 55.4, 57.8, 59.8, 81.7, 124.8, 128.2, 136.8, 139.1, 159.0; LRMS (%) *m*/*z* 249 (M$^+$, 48), 229 (14), 218 (77), 188 (100), 172 (61), 158 (52), 146 (42), 130 (38), 119 (53), 103 (20), 91 (58), 77 (31), 65 (13). HRMS (*m*/*z*): (M$^+$) calcd for $C_{14}H_{19}NO_3$, 249.1365; found, 249.1360. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.42; H, 7.62; N, 5.60. The cis isomer, ***cis*-2d** (16 mg, 20%), was obtained as a colorless solid: mp 85−86 °C; IR 3369, 2921, 2874, 1611, 1453, 1081, 1042, 851 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.61 (br s, 2H), 2.26 (s, 6H), 2.28 (s, 3H), 3.62−3.77 (m, 3H), 3.81 (m, 1H), 3.97 (m, 1H), 4.72 (dt, J = 7.5, 3.5 Hz), 6.91 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.2, 21.2, 56.1, 61.4, 63.5, 84.4, 124.7, 128.7, 136.8, 138.9, 158.4; LRMS (%) *m*/*z* 249 (M$^+$, 45), 218 (100), 205 (21), 188 (80), 172 (54), 158 (47), 145 (42), 130 (44), 119 (34), 103 (17), 91 (41), 77 (29), 57 (48). HRMS (*m*/*z*): (M$^+$) calcd for $C_{14}H_{19}NO_3$, 249.1365; found, 249.1366. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.40; H, 7.65; N, 5.61.

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid (8a) and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid (9). A mixture of mesitonitrile oxide (**7**;[37] 1.0 g, 6.2 mmol) and propiolic acid (**6a**; 0.44 g, 6.3 mmol) in THF (60 mL) was heated at reflux for 2 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded an inseparable mixture of **8a** and **9** in a 1.3:1 ratio (colorless oil, 1.4 g, quantitative): IR 2924, 2361, 2338, 1700, 1652, 1576, 1506, 1457, 1295, 1140, 910, 851, 732, 667 cm^{-1}. **8a**: ^{1}H NMR (300 MHz) δ 2.06 (s, 6H), 2.33 (s, 3H), 6.94 (s, 2H), 8.40−9.10 (br s, 1H), 9.16 (s, 1H). **9**: ^{1}H NMR (300 MHz) δ 2.13 (s, 6H), 2.33 (s, 3H), 6.96 (s, 2H), 6.98 (s, 1H), 8.40−9.10 (br s, 1H). LRMS (%) *m*/*z* 231 (M$^+$, 100), 213 (5), 203 (10), 186 (84), 170 (31), 158 (100), 144 (34), 130 (27), 115 (40), 103 (23), 91 (53), 77 (44), 65 (22). HRMS (*m*/*z*): (M$^+$) calcd for $C_{13}H_{13}NO_3$, 231.0895; found, 231.0898.

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid (8b). A mixture of mesitonitrile oxide (**7**; 0.81 g, 5.0 mmol) and tetrolic acid (**6b**; 0.42 g, 5.0 mmol) in THF (55 mL) was heated at reflux for 2 days, then cooled, and concentrated under reduced pressure. The residue was recrystallized from a mixture of hexanes and Et_2O to afford **8b** (1.2 g, quantitative) as a colorless solid: mp 205−207 °C; IR 2922, 1688, 1595, 1453, 1313, 1145, 1093, 1035, 979, 944, 849, 796, 772, 735 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.02 (br s, 1H), 2.08 (s, 6H), 2.34 (s, 3H), 2.80 (s, 3H), 6.91 (s, 2H); ^{13}C NMR (75.4 MHz) δ 13.8, 19.9, 21.2, 108.5, 124.8, 128.1, 136.9, 138.8, 161.8, 166.8, 177.5; LRMS (%) *m*/*z* 245 (M$^+$, 100), 228 (9), 212 (32), 201 (17), 186 (52), 170 (15), 158 (77), 142 (10), 128 (10), 115 (19), 103 (11), 91 (27), 77 (21), 65 (9). HRMS (*m*/*z*): (M$^+$) calcd for $C_{14}H_{15}NO_3$, 245.1052; found, 245.1051. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.31; H, 6.21; N, 5.69.

(+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-propynoyloxybicyclo[2.2.1]heptane-1-methanesulfonamide (10a). Trimethylaluminum (2 M in hexanes, 0.35 mL, 0.70 mmol) was added dropwise to a solution of methyl propiolate (**6c**; 65 μL, 0.73 mmol) in dry toluene (3 mL) at 18 °C, and the mixture was stirred at that temperature for 20 min. A solution of (+)-(1*R*,2*S*,4*S*)-*N*,*N*-dicyclohexyl-7,7-dimethyl-2-hydroxybicyclo[2.2.1]heptane-1-methanesulfonamide (0.25 g, 0.63 mmol) in dry toluene (0.5 mL) was then added, and the mixture was heated at reflux for 72 h. After cooling to 0−5 °C (ice bath), the reaction was quenched by the addition of aq NH_4Cl. The solvent was then evaporated under reduced pressure, and the residue was taken up in EtOAc (50 mL). The organic solution was washed with H_2O (30 mL). The aq washings were extracted with EtOAc (3 × 30 mL). The combined organic solutions were washed with brine (30 mL), dried (anhyd Na_2SO_4), and then concentrated under reduced pressure. Chromatography of the residue afforded the ester **10a** (0.27 g, 95%) as a colorless solid: mp 225−230 °C; $[\alpha]_D$ +45.4 (*c* 0.5); IR 3233, 2935, 2856, 2115, 1713, 1452, 1321, 1165, 1141, 1123, 1109, 1049, 982, 894, 858, 733, 641 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.89 (s, 3H), 1.00 (s, 3H), 1.01−1.40 (m, 9H), 1.50−1.66 (m, 2H), 1.67−1.88 (m, 16H), 1.90−2.08 (m, 2H), 2.67 (d, J = 13.5 Hz, 1H), 2.80 (s, 1H), 3.20−3.34 (m, 2H), 3.27 (d, J = 13.5 Hz, 1H), 5.10 (dd, J = 7.6, 2.7 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 19.9, 20.3, 25.1, 26.4, 26.8, 29.8, 32.6, 32.7, 39.0, 44.4, 49.0, 49.4, 53.3, 57.4, 73.7, 80.4, 151.3; LRMS (%) *m*/*z* 449 (M$^+$, 30), 406 (19), 298 (87), 272 (9), 259 (6), 244 (80), 205 (17), 180 (64), 162 (13), 135 (100), 121 (16), 107 (42), 83 (49). HRMS (*m*/*z*): (M$^+$) calcd for $C_{25}H_{39}NO_4S$, 449.2600; found, 449.2601. Anal. Calcd for $C_{25}H_{39}NO_4S$: C, 66.78; H, 8.74; N, 3.12. Found: C, 66.08; H, 8.02; N, 2.93.

(−)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Tetrolate (10b). DMAP (21 mg, 0.17 mmol) was added to a stirred mixture of (−)-(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (0.46 g, 2.0 mmol) and tetrolic acid (**6b**; 0.15 g, 1.8 mmol) in Et_2O (15 mL) at 0−5 °C (ice bath). After 10 min, DCC (0.40 g, 1.9 mmol) was added and stirring was continued at 18 °C for an additional 48 h. The mixture was then diluted with Et_2O (50 mL) and filtered through a pad of Celite. The filter cake was washed with Et_2O (6 × 100 mL), and the combined filtrates were evaporated under reduced pressure to about 50 mL. The residual solution was washed with 1 M aq HCl (3 × 30 mL), aq $NaHCO_3$ (2 × 30 mL), H_2O (1 × 30 mL), and brine (1 × 30 mL), and then it was dried (anhyd $MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue afforded the ester **10b** (0.46 g, 86%) as a colorless solid with physical and spectral data consistent with reported values.[25]

(+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-tetrolyloxybicyclo[2.2.1]heptane-1-methanesulfonamide (10c). The procedure described above for the synthesis of the propiolate **10a** was followed for the reaction of trimethylaluminum (2 M in hexanes, 0.35 mL, 0.70 mmol), methyl tetrolate (**6d**; 56 mg, 0.57 mmol), and (+)-(1*R*,2*S*,4*S*)-*N*,*N*-dicyclohexyl-7,7-dimethyl-2-hydroxybicyclo-[2.2.1]heptane-1-methanesulfonamide (0.25 g, 0.63 mmol), which afforded **10c** (0.25 g, 95%) as a colorless solid: mp 132−134 °C; $[\alpha]_D$ +51.7 (*c* 0.12); IR 2929, 2854, 1708, 1452, 1325, 1258, 1165,

(37) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.

1143, 1110, 1048, 982, 854, 824 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (s, 3H), 0.99 (s, 3H), 1.01−1.40 (m, 7H), 1.50−1.62 (m, 2H), 1.65−1.84 (m, 16H), 1.85−2.04 (m, 2H), 1.92 (s, 3H), 2.64 (d, J = 13.5 Hz, 1H), 3.15−3.35 (m, 2H), 3.27 (d, J = 13.5 Hz, 1H), 5.04 (dd, J = 8.0, 3.0 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 3.7, 20.0, 20.4, 25.0, 26.3, 26.4, 26.8, 29.8, 32.5, 32.7, 39.2, 44.4, 49.0, 49.3, 53.3, 57.6, 73.1, 79.8, 84.1, 151.3; LRMS (%) m/z 463 (M^+, 11), 420 (3), 315 (3), 298 (32), 272 (7), 244 (27), 216 (5), 180 (36), 153 (8), 135 (44), 110 (6), 93 (24). HRMS (m/z): (M^+) calcd for $C_{26}H_{41}NO_4S$, 463.2756; found, 463.2746. Anal. Calcd for $C_{26}H_{41}NO_4S$: C, 67.35; H, 8.91; N, 3.02. Found: C, 67.17; H, 8.94; N, 2.90.

(−)-(1*R*,2*S*)-2-Phenylcyclohexyl 3-(2,4,6-Trimethylphenyl)-isoxazole-4-carboxylate (11a) and (−)-(1*R*,2*S*)-2-Phenylcyclohexyl 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylate (12a). The procedure described above was followed for the synthesis of the tetrolate **10b**. A reaction of DMAP (16 mg, 0.13 mmol), DCC (0.30 g, 1.4 mmol), (−)-(1*R*,2*S*)-2-phenylcyclohexanol (0.25 g, 1.4 mmol), and a 1.3:1 mixture of the acids **8a** and **9** (0.30 g, 1.3 mmol) afforded the ester **11a** (0.25 g, 50%) as colorless plates after chromatography and recrystallization from hexanes/Et_2O: mp 119−121 °C; $[\alpha]_D$ −22.6 (*c* 0.5); IR 2930, 2858, 1717, 1583, 1449, 1390, 1288, 1172, 1134, 1120, 1015, 851, 776, 699, 531 cm^{-1}; ^1H NMR (300 MHz) δ 1.10−1.66 (m, 4H), 1.80 (s, 3H), 1.68−2.00 (m, 2H), 1.91 (s, 3H), 2.04−2.16 (m, 2H), 2.26−2.38 (m, 1H), 2.37 (s, 3H), 5.06 (td, J = 10.5, 4.5 Hz, 1H), 6.89 (s, 1H), 6.92 (s, 1H), 6.98 (s, 1H), 7.01 (s, 1H), 7.10−7.25 (m, 3H), 8.87 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.6, 19.7, 21.2, 24.2, 25.5, 32.0, 33.9, 49.4, 76.6, 114.3, 124.2, 126.3, 127.2, 127.7, 128.1, 128.6, 136.9, 138.6, 142.5, 159.9, 160.4, 163.3; LRMS (%) m/z 389 (M^+, 5), 279 (1), 231 (12), 186 (9), 130 (17), 91 (93). HRMS (m/z): (M^+) calcd for $C_{25}H_{27}NO_3$, 389.1991; found, 389.2003. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.90; H, 6.89; N, 3.51. The regioisomer, **12a** (0.19 g, 38%), was obtained as a colorless oil: $[\alpha]_D$ −116.1 (*c* 0.3); IR 2930, 2856, 2118, 1739, 1450, 1294, 1280, 1216, 1119, 1007, 851, 768, 755, 699, 532 cm^{-1}; ^1H NMR (300 MHz) δ 1.11−1.78 (m, 4H), 1.78−2.13 (m, 2H), 2.07 (s, 6H), 2.25−2.38 (m, 2H), 2.31 (s, 3H), 2.85 (td, J = 11.5, 4.0 Hz, 1H), 5.20 (td, J = 10.5, 4.0 Hz, 1H), 6.63 (s, 1H), 6.92 (s, 2H), 7.12−7.28 (m, 5H); ^{13}C NMR (75.4 MHz) δ 20.2, 21.1, 24.7, 25.6, 32.1, 33.3, 49.5, 78.7, 110.5, 124.8, 126.6, 127.5, 128.3, 128.4, 137.1, 139.2, 142.3, 156.1, 160.2, 162.4; LRMS (%) m/z 389 (M^+, 6), 224 (4), 206 (2), 186 (20), 158 (100), 130 (14), 91 (44). HRMS (m/z): (M^+) calcd for $C_{25}H_{27}NO_3$, 389.1991; found, 389.1999. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.93; H, 6.92; N, 3.52. The structure of the isoxazole **11a** was confirmed using X-ray crystallographic analysis (CCDC-261168).

(−)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylate (11b) and (+)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylate (12b). The procedure described above was used for the synthesis of the tetrolate **10b**. A reaction of DMAP (14 mg, 0.12 mmol), DCC (0.27 g, 1.3 mmol), (−)-(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (0.30 g, 1.3 mmol), and a 1.3:1 mixture of the isoxazoles **8a** and **9** (0.27 g, 1.2 mmol) afforded the ester **11b** (0.25 g, 48%) as a colorless oil: $[\alpha]_D$ −77.3 (*c* 0.8); IR 2954, 2922, 1723, 1573, 1457, 1392, 1304, 1295, 1172, 1129, 1012, 849, 778, 700 cm^{-1}; ^1H NMR (300 MHz) δ 0.86 (d, J = 6.5 Hz, 3H), 0.90−1.10 (m, 1H), 1.14 (s, 3H), 1.20 (s, 3H), 1.24−1.54 (m, 3H), 1.61−1.74 (m, 1H), 1.78−1.92 (m, 2H), 1.97 (s, 3H), 2.10 (s, 3H), 2.28 (m, 1H), 2.32 (s, 3H), 4.86 (td, J = 11.0, 4.5 Hz, 1H), 6.91 (s, 1H), 6.95 (s, 1H), 7.08−7.18 (m, 1H), 7.19−7.25 (m, 4H), 7.74 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.8, 21.1, 21.5, 22.7, 26.3, 29.5, 31.1, 34.3, 39.2, 41.1, 49.7, 74.5, 113.1, 123.9, 124.8, 125.0, 127.8, 127.9, 128.0, 136.6, 136.7, 138.7, 152.2, 159.4, 160.4, 162.8; LRMS (%) m/z 445 (M^+, 9), 327 (17), 232 (60), 214 (31), 199 (6), 186 (9), 158 (18), 143 (8), 119 (100), 105 (38), 91 (42), 77 (11). HRMS (m/z): (M^+) calcd for $C_{29}H_{35}NO_3$, 445.2617; found, 445.2619. Anal. Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.01; H, 7.88; N, 3.10. The regioisomer, **12b** (0.19 g, 37%), was obtained as a colorless oil: $[\alpha]_D$ +0.20 (*c* 0.6); IR 2956, 2923, 2869, 1733, 1613, 1583, 1495, 1456, 1388, 1378, 1296, 1218, 1173, 1121, 1050, 994, 850, 763, 700 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (d, J = 6.5 Hz, 3H), 0.91−1.02 (m, 1H), 1.10−1.38 (m, 2H), 1.25 (s, 3H), 1.38 (s, 3H), 1.48−1.60 (m, 1H), 1.66−1.78 (m, 1H), 1.79−1.92 (m, 1H), 1.93−2.05 (m, 1H), 2.11 (s, 6H), 2.21 (td, J = 10.5, 4.0 Hz, 1H), 2.33 (s, 3H), 5.12 (td, J = 10.5, 4.0 Hz, 1H), 6.29 (s, 1H), 6.91−6.94 (m, 3H), 7.15−7.18 (m, 2H), 7.26−7.32 (m, 2H); ^{13}C NMR (75.4 MHz) δ 20.2, 21.1, 21.7, 24.0, 26.4, 28.8, 31.3, 34.3, 39.5, 41.4, 50.2, 65.8, 110.2, 124.9, 125.1, 125.2, 127.9, 128.4, 137.0, 139.1, 151.1, 156.0, 160.1, 162.3; LRMS (%) m/z 445 (M^+, 10), 326 (10), 283 (33), 232 (92), 214 (8), 186 (20), 158 (18), 143 (8), 119 (100), 105 (17), 91 (38). HRMS (m/z): (M^+) calcd for $C_{29}H_{35}NO_3$, 445.2617; found, 445.2617. Anal. Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.28; H, 7.87; N, 3.11.

(+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-(3-(2,4,6-trimethylphenyl)isoxazole-4-carboxy)bicyclo[2.2.1]heptane-1-methanesulfonamide (11c) and (+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-(3-(2,4,6-trimethylphenyl)isoxazole-5-carboxy)bicyclo[2.2.1]heptane-1-methanesulfonamide (12c). A mixture of the propiolate **10a** (0.27 g, 0.60 mmol) and mesitonitrile oxide (**7**; 97 mg, 0.60 mmol) in THF (15 mL) was heated at reflux for 7 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded the cycloadduct **11c** (70 mg, 19%) as a colorless oil: $[\alpha]_D$ +34.0 (*c* 0.48); IR 2931, 2855, 1731, 1612, 1454, 1324, 1282, 1236, 1166, 1143, 1111, 1048, 982, 910, 894, 853, 770, 732, 654, 515 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (s, 3H), 0.90 (s, 3H), 1.14−1.39 (m, 7H), 1.50−1.84 (m, 18H), 1.86−2.00 (m, 2H), 2.06 (s, 3H), 2.09 (s, 3H), 2.30 (s, 3H), 2.68 (d, J = 13.5 Hz, 1H), 3.08−3.30 (m, 2H), 3.17 (d, J = 13.5 Hz, 1H), 5.14 (dd, J = 8.0, 3.0 Hz, 1H), 6.92 (s, 2H), 8.90 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.7, 19.9, 20.0, 20.3, 21.1, 25.0, 26.2, 26.3, 26.9, 30.3, 32.6, 32.7, 39.2, 44.3, 48.9, 49.4, 53.8, 57.4, 78.7, 114.6, 123.5, 128.2, 136.6, 137.0, 139.0, 158.8, 161.0, 161.7; LRMS (%) m/z 610 (M^+, 23), 439 (7), 421 (2), 380 (100), 316 (7), 298 (12), 246 (14), 214 (43), 180 (21), 158 (18), 135 (76), 107 (20), 83 (35). HRMS (m/z): (M^+) calcd for $C_{35}H_{50}N_2O_5S$, 610.3440; found, 610.3435. Anal. Calcd for $C_{35}H_{50}N_2O_5S$: C, 68.82; H, 8.25; N, 4.59. Found: C, 69.07; H, 8.12; N, 4.11. The regioisomer, **12c** (0.21 g, 56%), was obtained as a colorless solid: mp 200−202 °C; $[\alpha]_D$ +36.1 (*c* 0.48); IR 3769, 2929, 2855, 1731, 1612, 1453, 1325, 1282, 1165, 1143, 1111, 1048, 1029, 982, 894, 853, 769, 732 cm^{-1}; ^1H NMR (300 MHz) δ 0.94 (s, 3H), 1.13 (s, 3H), 1.20−1.39 (m, 7H), 1.46−1.58 (m, 2H), 1.62−2.20 (m, 18H), 2.12 (s, 6H), 2.33 (s, 3H), 2.73 (d, J = 13.5 Hz, 1H), 3.22 (m, 2H), 3.49 (d, J = 13.5 Hz, 1H), 5.31 (dd, J = 7.5, 3.0 Hz, 1H), 6.95 (s, 2H), 6.97 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.9, 20.1, 20.2, 20.9, 24.9, 26.0, 26.1, 26.8, 29.9, 32.4, 32.7, 39.1, 44.3, 49.0, 49.4, 53.2, 57.3, 80.1, 111.3, 124.7, 128.3, 136.8, 139.1, 155.2, 160.8, 162.4; LRMS (%) m/z 610 (M^+, 9), 380 (22), 323 (11), 298 (14), 259 (11), 232 (23), 214 (14), 180 (100), 158 (23), 135 (89), 107 (42), 83 (70). HRMS (m/z): (M^+) calcd for $C_{35}H_{50}N_2O_5S$, 610.3440; found, 610.3433. Anal. Calcd for $C_{35}H_{50}N_2O_5S$: C, 68.82; H, 8.25; N, 4.59. Found: C, 68.57; H, 8.03; N, 4.92.

(−)-(1*R*,2*S*)-2-Phenylcyclohexyl 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylate (11d). The procedure described above was followed for the synthesis of the tetrolate **10b**. A reaction of DMAP (12 mg, 96 μmol), DCC (0.22 g, 1.1 mmol), (−)-(1*R*,2*S*)-2-phenylcyclohexanol (0.19 g, 1.1 mmol), and the isoxazole **8b** (0.24 g, 0.96 mmol) afforded the ester **11d** (0.34 g, 87%) as a colorless oil: $[\alpha]_D$ −53.3 (*c* 0.9); IR 2929, 1716, 1611, 1434, 1308, 1296, 1285, 1181, 1134, 1096, 1070, 1033, 1016, 980, 851, 790 cm^{-1}; ^1H NMR (300 MHz) δ 1.10−2.60 (m, 9H), 1.73 (s, 3H), 1.95 (s, 3H), 2.37 (s, 3H), 2.59 (s, 3H), 5.05 (td, J = 10.5, 4.5 Hz, 1H), 6.86−6.97 (m, 4H), 7.10−7.23 (m, 3H); ^{13}C NMR (75.4 MHz) δ 13.3, 19.8, 19.9, 21.3, 24.6, 25.7, 32.1, 34.5, 49.3, 75.5, 109.1,

125.6, 126.3, 127.2, 127.4, 127.6, 128.1, 128.2, 128.3, 136.7, 136.8, 138.3, 142.5, 153.0, 161.1, 161.6; LRMS (%) *m*/*z* 403 (M^+, 13), 273 (1), 246 (37), 228 (21), 212 (17), 201 (13), 186 (59), 171 (6), 158 (100), 129 (13), 117 (20), 104 (8), 91 (85), 67 (9). HRMS (*m*/*z*): (M^+) calcd for $C_{26}H_{29}NO_3$, 403.2147; found, 403.2151. Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.16; H, 7.28; N, 3.46.

(−)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylate (11e). The procedure described above for the synthesis of the isoxazoles **11c** and **12c** was followed for the reaction of mesitonitrile oxide (**7**; 0.25 g, 1.5 mmol) and the alkyne **10b** (0.46 g, 1.5 mmol), which afforded the isoxazole **11e** (0.65 g, 93%) as a colorless oil: $[\alpha]_D$ −40.4 (*c* 0.6); IR 2953, 2922, 2869, 1712, 1599, 1436, 1307, 1136, 1089, 986, 849, 700 cm^{-1}; ^1H NMR (300 MHz) δ 0.85 (d, J = 6.5 Hz, 3H), 1.06 (m, 1H), 1.08 (s, 3H), 1.17 (s, 3H), 1.24−1.60 (m, 4H), 1.72 (td, J = 11.0, 4.0 Hz, 1H), 1.77−1.88 (m, 2H), 2.04 (s, 3H), 2.11 (s, 3H), 2.36 (s, 3H), 2.43 (s, 3H), 4.98 (td, J = 11.0, 4.0 Hz, 1H), 6.94 (s, 1H), 6.96 (s, 1H), 7.07−7.17 (m, 3H), 7.19−7.24 (m, 2H); ^{13}C NMR (75.4 MHz) δ 13.2, 19.9, 20.0, 21.1, 21.6, 25.6, 26.6, 26.8, 31.1, 34.1, 39.7, 41.9, 50.2, 74.3, 109.3, 125.1, 125.3, 127.8, 128.0, 136.6, 136.7, 138.7, 151.1, 160.8, 161.7, 175.3; LRMS (%) *m*/*z* 459 (M^+, 7), 341 (9), 246 (74), 228 (8), 214 (2), 201 (6), 186 (31), 158 (22), 119 (100), 105 (38), 91 (48). HRMS (*m*/*z*): (M^+) calcd for $C_{30}H_{37}NO_3$, 459.2773; found, 459.2779. Anal. Calcd for $C_{30}H_{37}NO_3$: C, 78.40; H, 8.11; N, 3.05. Found: C, 78.58; H, 8.05; N, 3.01.

(+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-(5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxy)bicyclo[2.2.1]heptane-1-methanesulfonamide (11f) and (+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-(5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-5-carboxy)bicyclo[2.2.1]heptane-1-methanesulfonamide (12f). The procedure described above for the synthesis of the isoxazoles **11c** and **12c** was followed for the reaction of mesitonitrile oxide (**7**; 0.12 g, 0.72 mmol) and the alkyne **10c** (0.22 g, 0.48 mmol), which afforded the isoxazole **11f** (40 mg, 13%) as a colorless solid: mp 200−202 °C; $[\alpha]_D$ +32.2 (*c* 0.35); IR 2929, 2855, 1723, 1614, 1454, 1326, 1291, 1165, 1144, 1048, 982, 854, 776 cm^{-1}; ^1H NMR (300 MHz) δ 0.95 (s, 3H), 1.13 (s, 3H), 1.00−1.40 (m, 7H), 1.48−2.01 (m, 20H), 2.01 (s, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 2.33 (s, 3H), 2.72 (d, J = 13.5 Hz, 1H), 3.22 (m, 2H), 3.53 (d, J = 13.5 Hz, 1H), 5.27 (dd, J = 8.0, 3.0 Hz, 1H), 6.95 (s, 2H); ^{13}C NMR (75.4 MHz) δ 7.9, 19.8, 19.9, 20.2, 20.4, 21.1, 25.2, 26.2, 26.3, 27.0, 29.6, 30.1, 32.5, 33.0, 39.4, 44.5, 49.2, 49.5, 53.3, 57.4, 79.8, 122.2, 124.2, 128.3, 128.4, 137.1, 137.3, 139.3, 155.6, 156.4, 164.3; LRMS (%) *m*/*z* 624 (M^+, 15), 337 (25), 298 (12), 272 (7), 246 (42), 200 (34), 180 (100), 136 (37), 107 (15), 83 (22). HRMS (*m*/*z*): (M^+) calcd for $C_{36}H_{52}N_2O_5S$, 624.3597; found, 624.3595. Anal. Calcd for $C_{36}H_{52}N_2O_5S$: C, 69.20; H, 8.39; N, 4.48. Found: C, 69.23; H, 8.21; N, 4.06. The regioisomer, **12f** (0.24 g, 81%), was obtained as a colorless solid: mp 205−208 °C; $[\alpha]_D$ +33.3 (*c* 0.60); IR 2931, 2856, 1725, 1613, 1452, 1326, 1255, 1165, 1143, 1144, 1048, 982, 853, 774, 643 cm^{-1}; ^1H NMR (300 MHz) δ 0.61 (s, 3H), 0.82 (s, 3H), 1.05−1.40 (m, 7H), 1.50−1.84 (m, 18H), 1.85−2.00 (m, 2H), 2.04 (s, 3H), 2.12 (s, 3H), 2.29 (s, 3H), 2.63 (d, J = 13.5 Hz, 1H), 2.74 (s, 3H), 3.05 (d, J = 13.5 Hz, 1H), 3.09−3.21 (m, 2H), 5.22 (dd, J = 8.0, 3.5 Hz, 1H), 6.87 (s, 2H); ^{13}C NMR (75.4 MHz) δ 13.2, 19.6, 19.7, 19.9, 20.0, 20.9, 24.7, 24.9, 26.1, 26.3, 26.7, 30.5, 32.6, 32.7, 39.0, 44.1, 48.6, 49.3, 53.6, 57.2, 57.3, 78.2, 110.1, 124.8, 127.9, 128.0, 136.4, 136.5, 138.4, 160.4, 161.7, 173.1; LRMS (%) *m*/*z* 624 (M^+, 2), 380 (100), 316 (16), 298 (22), 246 (36), 228 (96), 186 (72), 158 (24), 146 (12), 135 (100), 119 (6), 107 (22), 93 (28), 83 (32), 67 (10). HRMS (*m*/*z*): (M^+) calcd for $C_{36}H_{52}N_2O_5S$, 624.3597; found, 624.3595. Anal. Calcd for $C_{36}H_{52}N_2O_5S$: C, 69.20; H, 8.39; N, 4.48. Found: C, 69.47; H, 8.37; N, 4.38.

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxamide (13a) and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxamide (15). A mixture of mesitonitrile oxide (**7**; 0.50 g, 3.1 mmol) and propiolamide (0.21 g, 3.1 mmol) in THF (25 mL) was heated at reflux for 3 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazole **13a** (0.23 g, 32%) as colorless rods after recrystallization from acetone/hexanes: mp 195−200 °C; IR 3422, 3324, 2922, 2392, 1662, 1583, 1401, 1378, 1136, 1034, 855, 775, 739 cm^{-1}; ^1H NMR (300 MHz) δ 2.10 (s, 6H), 2.35 (s, 3H), 5.28 (br s, 1H), 5.44 (br s, 1H), 7.02 (s, 2H), 9.16 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.9, 21.3, 116.5, 122.7, 129.1, 137.5, 140.5, 158.2, 158.3, 163.8; LRMS (%) *m*/*z* 230 (M^+, 37), 213 (49), 186 (27), 170 (13), 157 (100), 142 (16), 130 (14), 115 (18), 103 (10), 91 (24), 77 (21), 65 (11). HRMS (*m*/*z*): (M^+) calcd for $C_{13}H_{14}N_2O_2$, 230.1055; found, 230.1057. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.65; H, 6.15; N, 12.09. The regioisomer, **15** (0.45 g, 64%), was obtained as colorless plates after recrystallization from acetone/hexanes: mp 135−137 °C; IR 3391, 3185, 2923, 1672, 1613, 1460, 1364, 1244, 1118, 1033, 851 cm^{-1}; ^1H NMR (300 MHz) δ 2.14 (s, 6H), 2.33 (s, 3H), 5.27 (br s, 1H), 6.55 (br s, 1H), 6.91 (s, 1H), 6.96 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.3, 21.2, 109.3, 124.6, 128.4, 136.9, 139.3, 157.8, 162.5, 163.1; LRMS (%) *m*/*z* 230 (M^+, 70), 186 (100), 171 (6), 158 (60), 143 (16), 130 (9), 115 (16), 103 (9), 91 (24), 77 (18), 65 (8). HRMS (*m*/*z*): (M^+) calcd for $C_{13}H_{14}N_2O_2$, 230.1055; found, 230.1054. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 6.09; N, 12.21. The structures of the isoxazoles **13a** and **15** were confirmed using X-ray crystallographic analysis (CCDC-261169 for **13a** and CCDC-261172 for **15**).

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxamide (13b). A mixture of mesitonitrile oxide (**7**; 0.50 g, 3.1 mmol) and tetrolamide (0.26 g, 3.1 mmol) in THF (25 mL) was heated at reflux for 6 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazole **13b** (0.72 g, 95%) as colorless needles after recrystallization from acetone/hexanes: mp 214−215 °C; IR 3439, 1683, 1601, 1449, 1353, 1183, 1155, 902, 873, 767, 750, 711, 689, 502 cm^{-1}; ^1H NMR (300 MHz) δ 2.11 (s, 6H), 2.34 (s, 3H), 2.83 (s, 3H), 5.02 (br s, 1H), 5.21 (br s, 1H), 7.00 (s, 2H); ^{13}C NMR (75.4 MHz) δ 13.6, 19.8, 21.2, 109.9, 124.1, 129.1, 137.5, 140.3, 159.3, 163.5, 176.0; LRMS (%) *m*/*z* 244 (M^+, 89), 227 (49), 212 (42), 202 (5), 185 (100), 171 (50), 157 (100), 142 (15), 130 (19), 115 (31), 103 (18), 91 (45), 77 (35), 63 (7). HRMS (*m*/*z*): (M^+) calcd for $C_{14}H_{16}N_2O_2$, 244.1212; found, 244.1216. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.55; N, 11.41. The structure of the isoxazole **13b** was confirmed using X-ray crystallographic analysis (CCDC-261170).

5-Phenyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxamide (13c). A mixture of mesitonitrile oxide (**7**; 0.10 g, 0.62 mmol) and phenylpropiolamide (90 mg, 0.62 mmol) in THF (6 mL) was heated at reflux for 6 days, then cooled, and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazole **13c** (0.18 g, 93%) as colorless blocks after recrystallization from acetone/hexanes: mp 192−193 °C; IR 3304, 2921, 2853, 1677, 1611, 1422, 1363, 1131, 1035, 853, 691 cm^{-1}; ^1H NMR (300 MHz) δ 2.18 (s, 6H), 2.36 (s, 3H), 5.15 (br s, 1H), 5.35 (br s, 1H), 7.02 (s, 2H), 7.51−7.56 (m, 3H), 8.10−8.14 (m, 2H); ^{13}C NMR (75.4 MHz) δ 19.8, 21.1, 110.3, 124.1, 126.8, 128.2, 128.3, 128.9, 131.1, 137.4, 140.0, 160.6, 163.1, 172.2; LRMS (%) *m*/*z* 306 (M^+, 50), 289 (30), 277 (2), 262 (5), 233 (100), 218 (4), 184 (2), 158 (4), 130 (3), 105 (100), 91 (7), 77 (41), 65 (2). HRMS (*m*/*z*): (M^+) calcd for $C_{19}H_{18}N_2O_2$, 306.1369; found, 306.1368. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.38; H, 5.86; N, 9.16. The structure of the isoxazole **13c** was confirmed using X-ray crystallographic analysis (CCDC-261171).

3-(2,4,6-Trimethylphenyl)-Δ^2-isoxazoline-4-carboxamide [(±)-14a]. Trifluoroacetic acid (0.17 mL, 2.2 mmol) was added dropwise to a stirred solution of sodium borohydride (82 mg, 2.2 mmol) in dry THF (2.5 mL), and the mixture was stirred at room temperature for 0.5 h. A solution of the isoxazole **13a** (33 mg, 0.14 mmol) in dry THF (2.5 mL) was then added, and the mixture was stirred at

room temperature for 30 h before it was cooled to 0−5 °C and adjusted to pH 2 through the dropwise addition of 1 M aq HCl. The resultant solution was concentrated under reduced pressure, and the residue was taken up in EtOAc and washed with H_2O. The aq washings were extracted with EtOAc. The organic solutions were combined, washed with saturated brine, dried (anhyd $MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazoline (±)-**14a** (31 mg, 92%) as a colorless solid: mp 175−176 °C; IR 3334, 3194, 2923, 1677, 1611, 1455, 1394, 1337, 1306, 1289, 1195, 1118, 1035, 943, 908, 852, 730 cm^{-1}; ^1H NMR (300 MHz) δ 2.27 (s, 6H), 2.30 (s, 3H), 4.25 (dd, $J = 11.0$, 8.0 Hz, 1H), 4.64 (m, 1H), 5.01 (m, 1H), 5.10 (br s, 1H), 5.29 (br s, 1H), 6.92 (s, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.9, 21.2, 58.6, 73.2, 125.8, 129.5, 138.6, 140.3, 157.1, 172.1; LRMS (%) *m*/*z* 232 (M^+, 67), 214 (26), 201 (33), 185 (90), 171 (31), 158 (83), 144 (100), 130 (55), 121 (5), 115 (48), 103 (27), 91 (63), 77 (45), 71 (32), 65 (20), 59 (5). HRMS (*m*/*z*): (M^+) calcd for $C_{13}H_{16}N_2O_2$, 232.1212; found, 232.1210. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.28; H, 6.97; N, 12.07.

***trans*-5-Methyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxamide [(±)-14b].** The procedure described above for the reaction of the isoxazole **13a** with sodium trifluoroacetoxyborohydride was followed for the treatment of the isoxazole **13b** (0.10 g, 0.41 mmol) with sodium borohydride (0.23 g, 6.1 mmol) that had been pretreated with trifluoroacetic acid (0.46 mL, 6.1 mmol), which afforded the isoxazoline (±)-**14b** (90 mg, 90%) as a colorless solid, with physical and spectral data consistent with reported values.[28]

***trans*-5-Phenyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxamide [(±)-14c].** The procedure described above for the reaction of the isoxazole **13a** with sodium trifluoroacetoxyborohydride was followed for the treatment of the isoxazole **13c** (0.10 g, 0.33 mmol) with sodium borohydride (0.19 g, 4.9 mmol) that had been pretreated with trifluoroacetic acid (0.38 mL, 4.9 mmol), which afforded the isoxazoline (±)-**14c** (93 mg, 92%) as a colorless solid, with physical and spectral data consistent with reported values.[28]

Methyl *trans*-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate [(±)-16a]. A suspension of zinc dust (35 mg, 0.54 mmol) and cuprous iodide (31 mg, 0.16 mmol) in 65% aq MeOH (3 mL) was sonicated at 5 °C for 5−10 min until it turned black. The isoxazole **1a** (50 mg, 0.20 mmol) was then added, followed by the slow addition of a solution of *tert*-butyl iodide (70 μL, 0.60 mmol) in 65% aq MeOH (3 mL) over 2 h, while the solution was maintained at 5 °C and sonication was continued. After an additional 9 h, saturated aq NH_4Cl (1 mL) was added, and the mixture was filtered through a pad of Celite. The filter cake was washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O, and the solution was washed with H_2O. The aq layer was extracted with Et_2O. The organic solutions were combined, washed with saturated aq $Na_2S_2O_4$, H_2O, and brine, dried (anhyd $MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue afforded the isoxazoline (±)-**16a** (59 mg, quantitative) as a colorless solid: mp 59−62 °C; IR 2956, 2871, 1743, 1610, 1434, 1398, 1367, 1306, 1292, 1199, 1026, 1000, 906, 851, 781 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (s, 9H), 2.23 (s, 6H), 2.27 (s, 3H), 3.54 (s, 3H), 4.20 (d, $J = 11.0$ Hz, 1H), 4.85 (d, $J = 11.0$ Hz, 1H), 6.86 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.0, 21.2, 25.3, 33.7, 52.7, 57.4, 92.7, 124.7, 128.4, 136.9, 138.7, 153.4, 169.3; LRMS (%) *m*/*z* 303 (M^+, 31), 246 (100), 218 (59), 186 (68), 158 (54), 146 (24), 119 (10), 91 (10), 77 (6). HRMS (*m*/*z*): (M^+) calcd for $C_{18}H_{25}NO_3$, 303.1834; found, 303.1835. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.14; H, 8.28; N, 4.66.

Methyl *trans*-5-(Adamantan-1-yl)-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate [(±)-16b]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 14 h, in the reaction of zinc dust (70 mg, 1.08 mmol), cuprous iodide (62 mg, 0.32 mmol), the isoxazole **1a** (50 mg, 0.20 mmol), and 1-iodoadamantane (0.32 g, 1.20 mmol), which afforded the isoxazoline (±)-**16b** (74 mg, quantitative) as colorless plates after recrystallization from hexanes/Et_2O: mp 82−84 °C; IR 2904, 2849, 1743, 1612, 1434, 1306, 1289, 1198, 1168, 1003, 897, 867, 850 cm^{-1}; ^1H NMR (300 MHz) δ 1.18−1.37 (m, 6H), 1.51−1.62 (m, 6H), 2.00−2.09 (m, 3H), 2.22 (s, 6H), 2.27 (s, 3H), 3.53 (s, 3H), 4.27 (d, $J = 11.0$ Hz, 1H), 4.69 (d, $J = 11.0$ Hz, 1H), 6.85 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.4, 21.5, 28.3, 30.8, 35.3, 36.5, 36.7, 36.9, 37.8, 38.4, 41.0, 53.0, 56.0, 93.1, 125.1, 128.8, 137.2, 139.0, 153.3, 170.0; LRMS (%) *m*/*z* 381 (M^+, 18), 246 (100), 218 (9), 186 (34), 158 (12), 135 (69), 108 (7), 93 (13), 79 (19), 66 (10). HRMS (*m*/*z*): (M^+) calcd for $C_{24}H_{31}NO_3$, 381.2304; found, 381.2303. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.49; H, 8.14; N, 3.63. The structure of the isoxazoline (±)-**16b** was confirmed using X-ray crystallographic analysis (CCDC-261173).

Methyl *trans*-5-(Prop-2-yl)-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate [(±)-16c]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 60 h, in the reaction of zinc dust (245 mg, 3.78 mmol), cuprous iodide (217 mg, 1.12 mmol), the isoxazole **1a** (50 mg, 0.20 mmol), and 2-iodopropane (420 μL, 4.20 mmol), which afforded the isoxazoline (±)-**16c** (48 mg, 82%) as a colorless oil: IR 2960, 2926, 2875, 1742, 1611, 1595, 1435, 1266, 1198, 1168, 1031, 897, 851 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (d, $J = 6.5$ Hz, 3H), 1.09 (d, $J = 6.5$ Hz, 3H), 2.05 (m, 1H), 2.24 (s, 6H), 2.28 (s, 3H), 3.56 (s, 3H), 4.16 (d, $J = 10.0$ Hz, 1H), 4.86 (dd, $J = 10.0$, 7.0 Hz, 1H), 6.87 (s, 2H); ^{13}C NMR (75.4 MHz) δ 17.6, 18.1, 19.7, 20.9, 31.6, 52.4, 58.8, 89.6, 124.6, 128.4, 136.8, 138.6, 153.6, 169.0; LRMS (%) *m*/*z* 289 (M^+, 34), 246 (100), 218 (17), 186 (95), 158 (52), 146 (24), 119 (12), 101 (7), 91 (12). HRMS (*m*/*z*): (M^+) calcd for $C_{17}H_{23}NO_3$, 289.1678; found, 289.1678. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.36; H, 8.06; N, 4.80.

Methyl *trans*-5-Ethyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate [(±)-16d]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 8 days, in the reaction of zinc dust (840 mg, 13.0 mmol), cuprous iodide (744 mg, 3.84 mmol), the isoxazole **1a** (50 mg, 0.20 mmol), and iodoethane (1.15 mL, 14.4 mmol), which afforded the isoxazoline (±)-**16d** (18 mg, 32%) as a colorless oil: IR 1741, 1611, 1434, 1378, 1309, 1151, 1033, 893, 852 cm^{-1}; ^1H NMR (300 MHz) δ 1.08 (t, $J = 7.5$ Hz, 3H), 1.79 (m, 1H), 1.92 (m, 1H), 2.24 (s, 6H), 2.29 (s, 3H), 3.58 (s, 3H), 4.08 (d, $J = 9.0$ Hz, 1H), 5.02 (dt, $J = 9.0$, 6.5 Hz, 1H), 6.88 (s, 2H); ^{13}C NMR (75.4 MHz) δ 9.3, 20.0, 21.2, 27.4, 52.6, 60.9, 85.7, 124.6, 128.5, 136.9, 138.8, 153.7, 168.8; LRMS (%) *m*/*z* 275 (M^+, 49), 256 (27), 246 (95), 230 (7), 214 (19), 202 (7), 186 (100), 170 (12), 158 (65), 144 (20), 130 (27), 115 (24), 103 (14), 91 (38), 77 (23), 65 (10), 57 (14). HRMS (*m*/*z*): (M^+) calcd for $C_{16}H_{21}NO_3$, 275.1521; found, 275.1518. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.71; H, 7.63; N, 5.04.

Methyl *cis*-5-Cyclohexyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate and Methyl *trans*-5-Cyclohexyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate [(±)-16e]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 6 days, in the reaction of zinc dust (630 mg, 9.72 mmol), cuprous iodide (558 mg, 2.88 mmol), the isoxazole **1a** (50 mg, 0.20 mmol), and cyclohexyl iodide (1.40 mL, 10.8 mmol), which afforded methyl *cis*-5-cyclohexyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate (13 mg, 20%) as a colorless oil: IR 2925, 2853, 1742, 1611, 1449, 1378, 1309, 1275, 1208, 1171, 1032, 999, 906, 886, 851, 782, 576 cm^{-1}; ^1H NMR (300 MHz) δ 1.00−1.50 (m, 6H), 1.60−1.94 (m, 4H), 1.97−2.09 (m, 1H), 2.22 (s, 6H), 2.27 (s, 3H), 3.53 (s, 3H), 4.18 (d, $J = 10.5$ Hz, 1H), 4.83 (dd, $J = 10.5$, 7.5 Hz, 1H), 6.86 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.0,

21.1, 25.6, 25.8, 26.3, 28.4, 29.0, 41.6, 52.6, 59.1, 89.1, 124.6, 128.5, 136.9, 138.7, 153.8, 169.1; LRMS (%) *m*/*z* 329 (M^+, 45), 270 (2), 246 (100), 218 (31), 202 (4), 186 (67), 158 (34), 145 (20), 130 (25), 119 (24), 101 (12), 91 (25), 67 (8). HRMS (*m*/*z*): (M^+) calcd for $C_{20}H_{27}NO_3$, 329.1991; found, 329.1994. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.73; H, 8.24; N, 4.23. The trans isomer, (±)-**16e** (16 mg, 25%), was obtained as a colorless oil: IR 2925, 2853, 1740, 1611, 1450, 1434, 1311, 1245, 1202, 1173, 1152, 1034, 888, 850 cm^{-1}; ^1H NMR (300 MHz) δ 1.00−1.40 (m, 6H), 1.58−1.87 (m, 4H), 1.88−2.09 (m, 1H), 2.27 (s, 6H), 2.31 (s, 3H), 3.64 (s, 3H), 4.15 (d, J = 9.5 Hz, 1H), 4.43 (app. t, J = 9.5 Hz, 1H), 6.88 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.1, 21.1, 25.4, 25.7, 26.2, 30.1, 30.3, 37.9, 52.1, 58.2, 88.5, 124.9, 128.7, 137.0, 138.9, 155.7, 167.7; LRMS (%) *m*/*z* 329 (M^+, 51), 312 (2), 270 (6), 246 (100), 201 (5), 186 (79), 168 (10), 158 (66), 145 (25), 130 (30), 119 (22), 103 (11), 91 (30), 67 (10). HRMS (*m*/*z*): (M^+) calcd for $C_{20}H_{27}NO_3$, 329.1991; found, 329.1990. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.75; H, 8.30; N, 4.21.

Methyl *trans*-5-*tert*-Butyl-3-nonyl-Δ²-isoxazoline-4-carboxylate [(±)-16f]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed in the reaction of zinc dust (35 mg, 0.54 mmol), cuprous iodide (31 mg, 0.16 mmol), the isoxazole **1b** (52 mg, 0.20 mmol), and *tert*-butyl iodide (72 μL, 0.60 mmol), which afforded the isoxazoline (±)-**16f** (60 mg, quantitative) as a colorless oil: IR 2955, 2926, 2855, 1743, 1466, 1435, 1366, 1292, 1164, 1026, 907 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H), 1.20−1.38 (m, 12H), 1.42−1.68 (m, 2H), 2.18−2.32 (m, 1H), 2.33−2.48 (m, 1H), 3.76 (s, 3H), 3.77 (d, J = 8.5 Hz, 1H), 4.54 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 14.2, 22.7, 25.0, 26.1, 26.9, 29.1, 29.2, 29.3, 29.5, 31.9, 34.1, 52.8, 56.0, 91.8, 154.8, 169.8; LRMS (%) *m*/*z* 311 (M^+, 34), 282 (3), 268 (7), 254 (40), 236 (3), 226 (23), 212 (34), 199 (66), 182 (7), 167 (5), 154 (25), 141 (22), 128 (13), 110 (8), 100 (24), 85 (31), 72 (42), 57 (100). HRMS (*m*/*z*): (M^+) calcd for $C_{18}H_{33}NO_3$, 311.2460; found, 311.2462. Anal. Calcd for $C_{18}H_{33}NO_3$: C, 69.41; H, 10.68; N, 4.50. Found: C, 69.26; H, 10.61; N, 4.56.

Methyl *trans*-3-Nonyl-5-(prop-2-yl)-Δ²-isoxazoline-4-carboxylate [(±)-16g]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the time allowed for alkylation was 2.5 days, in the reaction of zinc dust (35 mg, 0.54 mmol), cuprous iodide (31 mg, 0.16 mmol), the isoxazole **1b** (52 mg, 0.20 mmol), and 2-iodopropane (60 μL, 0.60 mmol), which afforded the isoxazoline (±)-**16g** (44 mg, 74%) as a colorless oil: IR 2956, 2926, 2855, 1743, 1466, 1435, 1369, 1267, 1201, 1167, 1027, 905 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (t, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 1.18−1.38 (m, 12H), 1.42−1.64 (m, 2H), 1.87 (m, 1H), 2.26 (m, 1H), 2.42 (m, 1H), 3.74 (d, J = 8.0 Hz, 1H), 3.77 (s, 3H), 4.59 (dd, J = 8.0, 6.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 14.2, 17.7, 17.9, 22.7, 26.2, 27.0, 29.1, 29.2, 29.3, 29.5, 31.9, 32.9, 52.8, 57.6, 88.9, 155.1, 169.6; LRMS (%) *m*/*z* 297 (M^+, 19), 268 (3), 254 (65), 240 (5), 226 (10), 210 (3), 198 (53), 185 (100), 168 (11), 154 (13), 141 (11), 126 (19), 110 (9), 101 (30), 85 (21), 71 (37), 57 (42). HRMS (*m*/*z*): (M^+) calcd for $C_{17}H_{31}NO_3$, 297.2304; found, 297.2311. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.68. Found: C, 68.43; H, 10.48; N, 4.73.

Methyl *trans*-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxamide [(±)-17]. The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 48 h, in the reaction of zinc dust (228 mg, 3.54 mmol), cuprous iodide (198 mg, 1.02 mmol), the isoxazole **13a** (50 mg, 0.22 mmol), and *tert*-butyl iodide (450 μL, 3.9 mmol), which afforded the isoxazoline (±)-**17** (61 mg, quantitative) as a colorless solid: mp 143−146 °C; IR 3369, 3175, 1693, 1601, 1400, 1365, 1349, 1307, 1247, 1039, 895, 845, 728 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (s, 9H), 2.24 (s, 6H), 2.28 (s, 3H), 3.96 (d, J = 10.0 Hz, 1H), 4.20 (br s, 1H), 5.02 (d, J = 10.0 Hz, 1H), 6.00 (br s, 1H), 6.89 (s, 2H); ^{13}C NMR (75.4 MHz) δ 20.1, 21.2, 25.4, 33.7, 58.0, 91.6, 124.9, 128.8, 137.2, 139.1, 152.9, 168.7; LRMS (%) *m*/*z* 288 (M^+, 14), 255 (2), 231 (24), 214 (14), 203 (17), 185 (39), 146 (30), 130 (20), 119 (16), 103 (8), 86 (100), 77 (12), 65 (5), 57 (37). HRMS (*m*/*z*): (M^+) calcd for $C_{17}H_{24}N_2O_2$, 288.1838; found, 288.1843. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.76; H, 8.32; N, 9.70.

(−)-(1*R*,2*S*)-2-Phenylcyclohexyl (4*R*,5*R*)-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate (18a). The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 8 days, in the reaction of zinc dust (384 mg, 5.76 mmol), cuprous iodide (336 mg, 1.73 mmol), the isoxazole **11a** (35 mg, 90 μmol), and *tert*-butyl iodide (768 μL, 6.48 mmol), which afforded the isoxazoline **18a** (35 mg, 88%) as colorless blocks after recrystallization from hexanes/Et_2O: mp 92−93 °C; $[\alpha]_D$ −116.5 (*c* 0.2); IR 2934, 2860, 1734, 1611, 1448, 1398, 1367, 1293, 1191, 1170, 1124, 1026, 960, 899, 851 cm^{-1}; ^1H NMR (300 MHz) δ 0.68 (s, 9H), 1.10−1.91 (m, 8H), 2.20 (s, 6H), 2.29 (s, 3H), 2.42 (m, 1H), 3.96 (d, J = 11.5, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.85 (td, J = 11.0, 4.5 Hz, 1H), 6.86 (s, 2H), 6.90−7.27 (m, 5H); ^{13}C NMR (75.4 MHz) δ 20.1, 20.7, 24.6, 25.1, 25.6, 31.0, 33.1, 33.2, 49.6, 56.9, 76.9, 92.1, 124.9, 126.4, 127.2, 128.2, 128.3, 128.4, 128.7, 137.0, 138.6, 142.5, 153.7, 168.0; LRMS (%) *m*/*z* 447 (M^+, 46), 424 (3), 390 (72), 346 (3), 290 (16), 270 (2), 232 (43), 204 (28), 188 (55), 159 (66), 130 (19), 117 (25), 91 (100). HRMS (*m*/*z*): (M^+) calcd for $C_{29}H_{37}NO_3$, 447.2773; found, 447.2770. Anal. Calcd for $C_{29}H_{37}NO_3$: C, 77.82; H, 8.33; N, 3.13. Found: C, 77.76; H, 8.30; N, 3.18. The structure of the isoxazoline **18a** was confirmed using X-ray crystallographic analysis (CCDC-261174). Analysis of the crude product mixture by ^1H NMR spectroscopy showed that **18a** was produced in 95% de. Separate resonances of a minor diastereomer were observed as follows: ^1H NMR (300 MHz) δ 0.73 (s, 9H), 3.77 (d, J = 11.0 Hz, 1H), 4.59 (d, J = 11.0 Hz, 1H), 5.05 (td, J = 10.5, 4.0 Hz, 1H).

(−)-(1*R*,2*S*)-2-Phenylcyclohexyl (4*R*,5*S*)-5-(Prop-2-yl)-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate (18b). The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 12 days, in the reaction of zinc dust (576 mg, 8.64 mmol), cuprous iodide (504 mg, 2.59 mmol), the isoxazole **11a** (35 mg, 90 μmol), and 2-iodopropane (936 μL, 9.72 mmol), which afforded the isoxazoline **18b** (34 mg, 86%) as a colorless oil: $[\alpha]_D$ −110.2 (*c* 0.1); IR 2930, 2858, 1734, 1611, 1492, 1448, 1378, 1271, 1123, 1032, 894, 851, 756, 699 cm^{-1}; ^1H NMR (300 MHz) δ 0.80 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H), 1.05−2.10 (m, 9H), 2.19 (s, 6H), 2.29 (s, 3H), 2.42 (m, 1H), 3.90 (d, J = 11.0 Hz, 1H), 4.49 (dd, J = 11.0, 7.5 Hz, 1H), 4.85 (td, J = 11.0, 4.5 Hz, 1H), 6.85 (s, 2H), 7.02−7.30 (m, 5H); ^{13}C NMR (125 MHz) δ 17.3, 18.4, 20.1, 21.1, 24.5, 25.5, 31.0, 31.5, 33.8, 49.6, 58.5, 77.9, 89.6, 125.0, 126.6, 128.4, 128.5, 128.8, 137.1, 138.7, 142.6, 154.4, 167.9; LRMS (%) *m*/*z* 433 (M^+, 31), 390 (60), 274 (10), 232 (33), 203 (11), 188 (27), 158 (53), 171 (16), 91 (100). HRMS (*m*/*z*): (M^+) calcd for $C_{28}H_{35}NO_3$, 433.2617; found, 433.2621. Anal. Calcd for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14; N, 3.23. Found: C, 77.48; H, 8.17; N, 3.25. Analysis of the crude product mixture by ^1H NMR spectroscopy showed that **18b** was produced in 93% de. Separate resonances of a minor diastereomer were observed as follows: ^1H NMR (300 MHz) δ 3.65 (d, J = 11.0 Hz, 1H), 5.06 (td, J = 11.0, 4.0 Hz, 1H).

(−)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4*R*,5*R*)-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ²-isoxazoline-4-carboxylate (19). The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 8 days, in the reaction of zinc dust (384 mg, 5.76 mmol), cuprous iodide (336 mg, 1.73 mmol), the isoxazole **11b** (40 mg, 90 μmol), and *tert*-butyl iodide (744 μL, 6.48 mmol), which afforded the isoxazoline **19** (39 mg, 87%) as a

colorless oil: $[\alpha]_D$ −53.8 (*c* 1.7); IR 2954, 2919, 1730, 1611, 1455, 1367, 1294, 1191, 1170, 1031, 850, 764, 700 cm^{-1}; ^1H NMR (300 MHz) δ 0.65 (d, J = 6.5 Hz, 3H), 0.70−1.85 (m, 6H), 1.00 (s, 9H), 1.14 (s, 3H), 1.22 (s, 3H), 1.44 (m, 1H), 1.73 (m, 1H), 2.13 (s, 6H), 2.27 (s, 3H), 3.78 (d, J = 11.5 Hz, 1H), 4.59 (td, J = 10.5, 4.5 Hz, 1H), 4.83 (d, J = 11.5 Hz, 1H), 6.82 (s, 2H), 7.08−7.32 (m, 5H); ^{13}C NMR (75.4 MHz) δ 15.4, 18.0, 20.3, 21.1, 21.6, 25.6, 26.6, 26.8, 29.8, 30.8, 33.2, 34.2, 39.8, 49.7, 56.6, 76.4, 91.8, 124.9, 125.1, 125.3, 125.5, 127.9, 128.0, 128.4, 128.7, 137.3, 138.7, 151.0, 153.7, 167.9; LRMS (%) *m*/*z* 503 (M^+, 34), 446 (27), 385 (4), 328 (4), 290 (47), 232 (46), 214 (12), 188 (89), 158 (19), 119 (100). HRMS (*m*/*z*): (M^+) calcd for $C_{33}H_{45}NO_3$, 503.3399; found, 503.3404. Anal. Calcd for $C_{33}H_{45}NO_3$: C, 78.69; H, 9.00; N, 2.78. Found: C, 78.59; H, 8.97; N, 2.81. Analysis of the crude product mixture by ^1H NMR spectroscopy showed that **19** was produced in 94% de. Separate resonances of a minor diastereomer were observed as follows: ^1H NMR (300 MHz) δ 4.19 (d, J = 11.5 Hz, 1H), δ 4.69 (d, J = 11.5 Hz, 1H).

(+)-(1*R*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-7,7-dimethyl-2-((4*S*,5*S*)-5-*tert*-butyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxy)-bicyclo[2.2.1]heptane-1-methanesulfonamide (20). The procedure described above for the synthesis of the isoxazoline (±)-**16a** was followed, except that the reagents were added in aliquots over 13 days, in the reaction of zinc dust (576 mg, 8.64 mmol), cuprous iodide (504 mg, 2.59 mmol), the isoxazole **11c** (55 mg, 90 μmol), and *tert*-butyl iodide (1.12 mL, 9.72 mmol), which afforded the isoxazoline **20** (52 mg, 87%) as colorless plates after recrystallization from hexanes/Et_2O: mp 245−246 °C; $[\alpha]_D$ +141.9 (*c* 0.69); IR 2929, 2856, 1737, 1613, 1372, 1327, 1280, 1190, 1166, 1144, 1109, 1049, 1028, 981, 908, 853, 775, 741, 643 cm^{-1}; ^1H NMR (300 MHz) δ 0.02 (s, 3H), 0.72 (s, 3H), 0.80−1.90 (m, 27H), 1.06 (s, 9H), 2.20 (s, 6H), 2.25 (s, 3H), 2.51 (d, J = 13.5 Hz, 1H), 3.00 (d, J = 13.5 Hz, 1H), 3.21 (p, J = 7.5 Hz, 2H), 4.19 (d, J = 11.0 Hz, 1H), 4.75 (dd, J = 8.0, 3.5 Hz, 1H), 5.03 (d, J = 11.0 Hz, 1H), 6.81 (s, 2H); ^{13}C NMR (150 MHz) δ 18.6, 19.8, 20.2, 21.0, 25.0, 25.5, 26.4, 26.5, 26.8, 29.7, 31.2, 32.5, 32.9, 33.4, 38.9, 44.2, 48.7, 49.1, 53.9, 56.6, 57.6, 80.3, 92.4, 125.4, 128.7, 136.9, 139.0, 153.2, 167.7; LRMS (%) *m*/*z* 668 (M^+, 0.2), 611 (4), 425 (2), 414 (0.4), 397 (2), 380 (56), 316 (8), 298 (20), 259 (6), 246 (18), 228 (34), 203 (10), 180 (32), 158.1 (12), 146 (18), 135 (100), 107 (30), 93 (36), 83 (46), 67 (16). HRMS (*m*/*z*): (M^+) calcd for $C_{39}H_{60}N_2O_5S$, 668.4223; found, 668.4219. Anal. Calcd for $C_{39}H_{60}N_2O_5S$: C, 70.02; H, 9.04; N, 4.19. Found: C, 70.02; H, 8.92; N, 3.86. The structure of the isoxazoline **20** was confirmed using X-ray crystallographic analysis (CCDC-261175). Analysis of the crude product mixture by ^1H NMR spectroscopy showed no separate resonances attributable to the other *trans*-4,5-disubstituted diastereomer of the isoxazoline **20** and, on this basis, it was calculated that **20** was produced in ≥98% de. However, the yields from repeated alkylations of the isoxazole **11c** were variable, and small amounts of one of the *cis*-diastereomers of **20** were sometimes formed. For this compound, $[\alpha]_D$ −69.3 (*c* 0.15); ^1H NMR (300 MHz) δ 0.72 (s, 3H), 0.82 (s, 3H), 1.11−1.96 (m, 27H), 1.06 (s, 9H), 2.25 (s, 6H), 2.35 (s, 3H), 2.62 (d, J = 13.0 Hz, 1H), 3.17 (d, J = 13.0 Hz, 1H), 3.25 (p, J = 7.5 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 4.69 (dd, J = 3.5, 8.0 Hz, 1H), 4.76 (d, J = 9.0 Hz, 1H), 6.83 (s, 2H); LRMS (%) *m*/*z* 668 (M^+, 5), 611 (15), 425 (3), 380 (45), 316 (5), 298 (13), 259 (2), 246 (18), 228 (28), 203 (5), 180 (24), 158 (11), 146 (12), 135 (100), 107 (23).

Acknowledgment. The authors acknowledge the receipt of an Australian Postgraduate Award (Industry) for C.K.Y.L and are grateful for financial support provided by CSIRO Molecular & Health Technologies, Dunlena Pty., Ltd., and the Australian Research Council.

Supporting Information Available: General experimental details as well as atomic displacement plots and cifs for compounds **1c**, **11a**, **13a**−**c**, **15**, (±)-**16b**, **18a**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0602569