D-Mannitol as the Chiral Source for the EPC Synthesis of Both Enantiomers of 3-Ethoxycarbonyl-4-hydroxy-2-isoxazolines and Highly Functionalized Tricyclic Systems

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The EPC preparation of both enantiomers of cis- and trans 5-substituted 4-hydroxy-2-isoxazoline 2-oxides has been achieved in an enantiodivergent fashion starting from D-mannitol through the application of the tandem nitroaldol-cyclization reaction to enantiomerically pure α-mesyloxyaldehydes. These stereochemically labile aldehydes have been generated in situ and reacted under very mild domino conditions. Enantiomeric purity of the products has been assessed by ^{1}H NMR and HPLC analyses of the corresponding Mosher's esters. The enantiomerically pure 4-hydroxy-2-isoxazoline 2-oxides have been employed as pivotal intermediates for the EPC preparation of the corresponding deoxygenated derivatives and highly functionalized tricyclic systems (HFTS) **1**, useful for the preparation of 2-aminopolyols and α,α-disubstituted polyhydroxy amino acids.

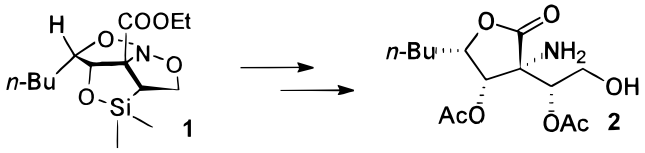
Introduction

A major challenge in contemporary organic synthesis is to devise methods and strategies for the rapid and economic preparation of enantiomerically pure complex molecules from simple starting materials. In fact, despite the fact that the synthesis of complex molecules seems to be a relatively advanced and successful science, most synthetic problems have not been solved in a practical fashion, and yet, there is a need for improving the efficiency. The control of the regio- and stereochemistry in the synthesis of linear structures containing many chirality centers and several hydroxy or amino groups on adjacent carbon atoms is of particular interest. Many research groups have oriented their efforts to develop practical methods to prepare these kind of compounds in a predictable way,[2] eventually for commercial production.

Along these lines, we have recently developed a new methodology[3] for rapid assembly of stereochemically defined and functionally rich tricyclic systems such as **1** (Scheme 1). The easy conversion of **1** into the polyhydroxylated amino acid derivatives **2** through simple manipulations makes these compounds important intermediates in our synthetic strategy based on the "folding and unfolding approach".

The synthesis of the tricyclic system (**1**) has been achieved by two consecutive tandem sequences developed

Scheme 1



in our group. The first tandem sequence consists of a nitroaldol (Henry) reaction[4−7] of a substrate (**3**) having two different and contiguous electrophilic centers, such as α-bromoaldehydes[8] or α,β-epoxyaldehydes,[9] with an activated nitromethane able to act twice as a nucleophile, for instance ethyl nitroacetate (**4**), followed by a ring closure to generate 5-substituted *cis*- and *trans*-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-oxides (**6**). (Scheme 2).

The vinylsilicon derivatization of the newly formed 4-hydroxyl group of **6** is followed by a spontaneous intramolecular 1,3-dipolar cycloaddition to generate a new class of highly functionalized tricyclic structures **1** (HFTS)[10] in almost quantitative yields and in regio- and stereospecific fashion[3] (Scheme 3). The preparation of these fused triheteroatomic tricyclic compounds has

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(1) Taken in part from the Tesi di Laurea of L. Maini (March 1997) and M. Baravelli (March 1998) at the Università di Bologna, Facoltà di Chimica Industriale.

(2) For a review on biologically active aminopolyols or hydroxylated amino acids, see: Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075−1091. For some other examples, see: (a) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887−7890. (b) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301−303. (c) Kobayashi, S.; Hayashi, T.; Iwamoto, S.; Furuta, T.; Matsumura, M. *Synlett* **1996**, 672−674. (d) Mori, K.; Otaka, K. *Tetrahedron Lett.* **1994**, *35*, 9207−9210.

(3) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446−9447.

(4) Henry, L. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265−1268. Rosini, G. The Henry (Nitroaldol) Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 321 and references therein.

(5) For an excellent review on the lanthanum-catalysed asymmetric Henry reaction, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

(6) Studies concerning ab initio models for the nitroaldol (Henry) reaction were reported recently, see: Lecea, B.; Arrieta, A.; Morao, I.; Cossio, F. *Chem.—Eur. J.* **1997**, *3*, 20−28.

(7) For reviews on the versatility of nitro compounds in organic synthesis, see: (a) *Nitro Compounds, Recent Advances in Synthesis and Chemistry*; Fever, H., Nielsen, A. T., Eds.; VCH: Weinheim, 1990. (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (d) Seebach, D.; Colvin, E. W.; Leher, F.; Weller, T. *Chimia* **1979**, *33*, 1−18.

(8) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J.-P. *J. Org. Chem.* **1991**, *56*, 6258−6260.

(9) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781−783.

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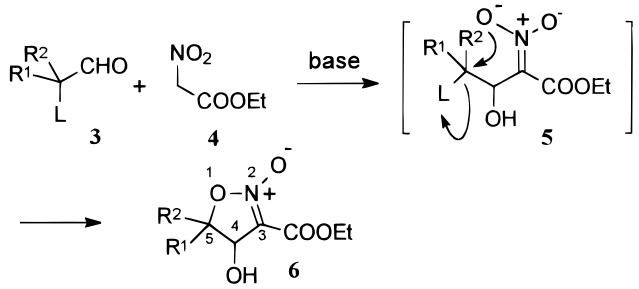
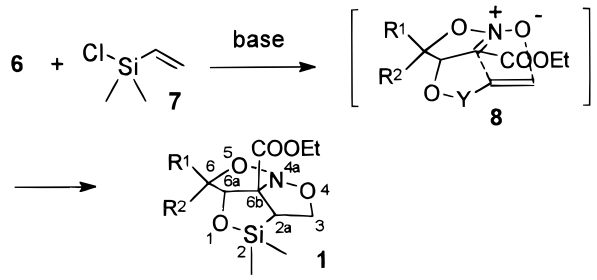
Scheme 2



Scheme 3

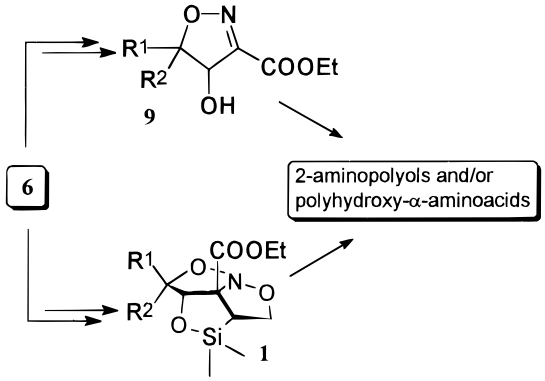


recently been accomplished in consecutive and domino conditions[11] starting, in some cases, from nonracemic aldehydes.

The main aspects concerning the chemio-, regio-, ambido-, and stereoselectivity of each step have been considered in previous communications.[3,8,9] In particular, it is important to stress that only the first step of the overall process, the nitroaldol (Henry) reaction, is stereoselective, while all the successive steps occur stereospecifically. We therefore explored the possibility of preparing the target compounds in nonracemic form by the use of optically active aldehydes of type **3**. We chose α-hydroxyaldehydes because of their easy availability from cheap starting materials by many multigram methods[12,13] that afford, in most cases, both enantiomerically pure forms. In addition, the hydroxy group can be activated by reaction with acid chlorides for its nucleophilic displacement.

A preliminary screening study[1] revealed that only α-mesyloxyaldehydes and α-tosyloxyaldehydes afford the corresponding 4-hydroxy-2-isoxazoline 2-oxides in high yields and under mild reaction conditions with a trans/cis ratio of 1:1. The same study showed that aldehydes bearing acetoxy, benzoyloxy, chloroacetoxy, trichloroacetoxy, or a trifluoroacetoxy group on the α-carbon gave only the nitroaldol reaction; the corresponding nitroalkanols **5** were isolated, and no product arising from the ring closure was observed.

Scheme 4



Scheme 4 shows the pivotal role that cis and trans 5-substituted 3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-oxides (**6**) play in the global synthetic project. In fact, these compounds can be considered as key intermediates both for the preparation of the tricyclic derivatives **1**, which can be unfolded to obtain the target linear products, as well as for the preparation of linear 2-aminopolyols or polyhydroxylated α-amino acid derivatives by deoxygenation, followed by stereoselective reduction of the C=N[14] and the reductive cleavage of the heteroatomic ring.[15]

This paper reports the results obtained in preparing nonracemic chiral cis and trans 5-substituted 3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-oxides (**6**) and their separation and conversion into the corresponding deoxygenated forms (**9**) and tricyclic compounds (**1**).

Results and Discussion

The approach we used to prepare chiral nonracemic 2-sulfonyloxyaldehydes is depicted in Scheme 5. It is known that both D-mannitol diepoxide **10** and L-iditol diepoxide **11** can be prepared from D-mannitol and that they can be used as convenient chiral building blocks to prepare, respectively, suitably O-derivatized (2*R*)- and (2*S*)-2-hydroxyaldehydes in an enantiodivergent fashion.

(10) We found that one of the possible IUPAC names of tricyclic compounds of type **1** is ethyl 2,2-dimethyltetrahydro-2H,6bH-1,4,5-trioxa-4a-aza-2-silacyclopenta[*cd*]pentalene-6b-carboxylate. (*ACD/IUPAC* Name, version 3.00; Advanced Chemistry Development, Inc.: Toronto, Nov. 1997.) We suggest the use of the acronym HFTS in place of this awkward IUPAC name.

(11) Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett.* **1998**, *39*, 1041−1044.

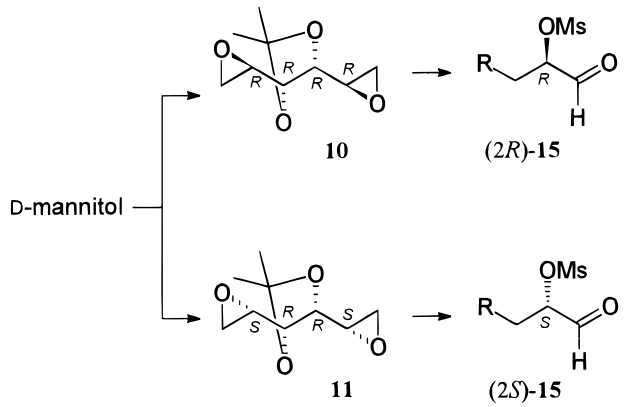
(12) Among the classical procedures for the EPC synthesis of 2-hydroxy aldehydes, see: (a) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937−2942. (b) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943−2948. (c) Frye, St. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402−3404. (d) Eliel, E. L. in *Asymmetric Synthesis-Stereodifferentiating Addition Reactions*; Morrison, J. D., Ed.; Academic Press Inc.: Orlando, FL; Vol. 2. (e) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988−989. (f) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989−990. (g) Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111. (h) O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1995**, *36*, 2681−2684 and literature therein cited. (i) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693−702. (j) Dondoni, A. *Pure Appl. Chem.* **1990**, *62*, 643−652. (k) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275−277. (l) Dondoni, A.; Merino, P. *Org. Synth.* **1993**, *72*, 21−31. (m) Kirshning, A.; Dräger, G.; Jung, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 253−255. All these procedures are potentially useful for the preparation of optically active 2-mesyloxy or 2-tosyloxy aldelhydes if the hydrolysis of the corresponding acetals or aminals does not compromise the chemical and/or stereochemical integrity of the products.

(13) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983. 2-Hydroxy aldehydes, O-protected 2-hydroxy aldehydes, as well as 2-mesyloxy and 2-tosyloxy-aldehydes may be obtained by reduction of the methyl or ethyl esters of 2-hydroxy acid derivatives with DIBAH: Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Syntheses*; VCH: Weinheim, 1997. Ho, T.-L. *Enantioselective Synthesis: Natural Products from Chiral Terpenes*; John Wiley & Sons: New York, 1992. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules using Amino Acids*; John Wiley & Sons: New York, 1987.

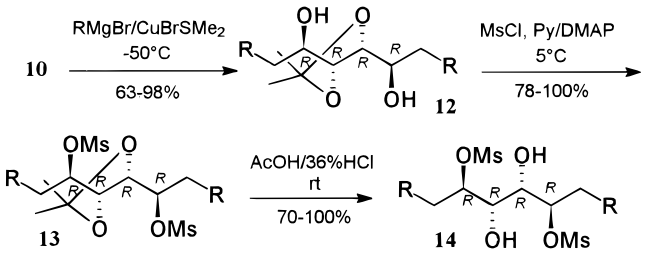
(14) $LiAlH_4$ is reported to reduce 4-hydroxy-2-isoxazolines to aminopolyols by introduction of the hydride ion syn to the C4 hydroxyl group and anti when this has been protected with a group bulky enough: Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601−603.

(15) Jäger et al. have shown 4-hydroxy-2-isoxazolines are versatile intermediates for the synthesis of amino sugars and other biologically important molecules, see: (a) Jäger, V.; Schone, R. *Tetrahedron* **1984**, *40*, 2199−2210. (b) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heter. Chem.* **1985**, *6*, 79−98 and references therein.

Scheme 5



Scheme 6



a: R = *n*-Pr; **b**: R = *n*-Bu; **c**: R = 3-Butenyl; **d**: R = Cyclohexyl; **e**: R = (2*S*)-Methylbutyl.

Thus, D-mannitol was converted into the diepoxide **10** through a simple sequence of well-known reactions.[16,17] The regiospecific opening of this diepoxide was performed by means of alkylmagnesium bromides in the presence of cuprous bromide−dimethyl sulfide[18] (Scheme 6). The reaction of **10** with a variety of organocopper compounds allowed us to prepare symmetric alkylated diols **12**, which were successively converted into the corresponding bismethanesulfonate derivatives **13**, which upon deprotection afforded the diols **14**.

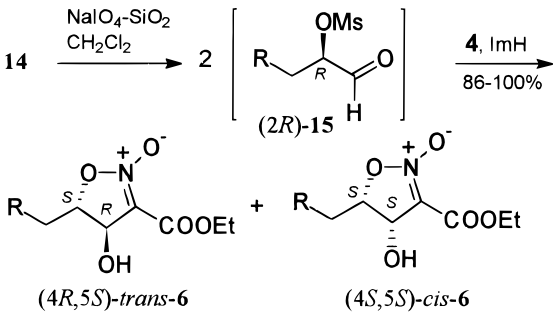
The symmetry of the starting material is preserved during the chemical transformations and, as a consequence, the oxidative cleavage of compounds **14** led to 2 equiv of identical enantiopure (2*R*)-2-methanesulfonyloxyaldehydes **15**. Moreover, **15** can be generated in the presence of ethyl nitroacetate (**4**) and imidazole, working in domino conditions, without any need to isolate or even manipulate the stereochemically labile[19] aldehyde (Scheme 7). After 6−10 h of reaction at room temperature and a simple workup, the mixtures of *cis*- and *trans*-4-hydroxy-2-isoxazoline 2-oxides **6** were isolated from the other reaction products and small amounts of unreacted starting materials by flash column chromatography (Table 1).

To verify if the stereochemical integrity of the starting material was preserved, we made the Mosher's ester

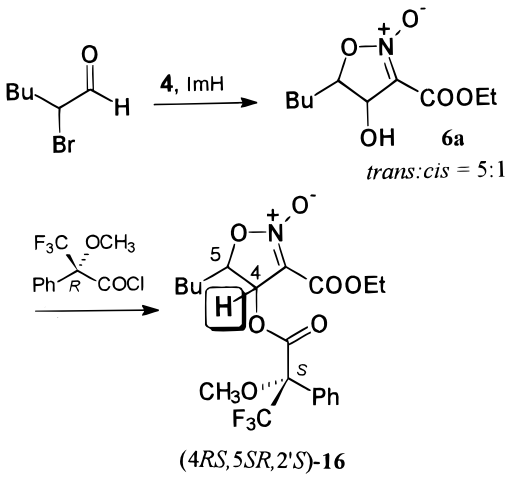
Table 1. Yields of the Formation of 6

	R	yield (%)
a	*n*-Pr	93
b	*n*-Bu	86
c	3-butenyl	90
d	cyclohexyl	quant
e	(2*S*)-2-methylbutyl	95

Scheme 7



Scheme 8



analysis of the mixture of products (4*RS*,5*R*)-**6a**. First, racemic **6a** was prepared from the corresponding racemic bromoaldehyde, which gave the products in a trans/cis 5:1 ratio. These racemic and isomeric substrates were converted into the Mosher's esters (Scheme 8) and the ^{1}H NMR spectrum was recorded focusing on the proton attached to C4, which appears as a doublet since it couples only with the proton on C5.

The analysis of the spectrum (Figure 1a) revealed that all four stereoisomers are distinguishable by this method. The doublets of the pair of diastereoisomers derived from two enantiomers of the *cis*-isoxazoline 2-oxide have larger coupling constants (J = 5.8 Hz and J = 5.8 Hz) and are in the 6.7 ppm region, while the doublets deriving from the two enantiomers of the trans isomers are in the 6.3 ppm region with a smaller coupling constant (J = 1.4 Hz and J = 1.4 Hz).

Next, the 2-isoxazoline 2-oxides **6a**, prepared from the pure enantiomer **14**, were converted into the corresponding Mosher's esters (4*RS*,5*S*,2′*S*)-**16** (Scheme 9).

From the ^{1}H NMR spectra (Figure 1b), we could verify that in this case only one enantiomer for both the *cis*- and *trans*-isoxazolines was seen, confirming that the isoxazoline 2-oxides obtained from **14** were enantiomerically pure and that the intramolecular cyclization occurred stereospecifically with the complete inversion of the original chirality.

(16) Le Merrer, Y.; Duréault, A.; Greck, C.; Micos-Lauguin, D.; Gravier, G.; Depazay, J. C. *Heterocycles* **1987**, *25*, 541−548.
(17) (a) Le Merrer, Y.; Gravier-Pelletier, C.; Micos-Lauguin, D.; Mestre, F.; Duréault, A.; Depazay, J. C. *J. Org. Chem.* **1989**, *54*, 2409−2416. (b) Tranchpain, I.; Le Berre, F.; Duréault, A.; Le Merrer, Y.; Depazay, J. C. *Tetrahedron* **1989**, *45*, 2057−2065. (c) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron: Asymmetry* **1994**, *5*, 927−934.
(18) House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. *J. Org. Chem.* **1975**, *40*, 1460−1469.
(19) Morpain, C.; Tisserand, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1379−1383.

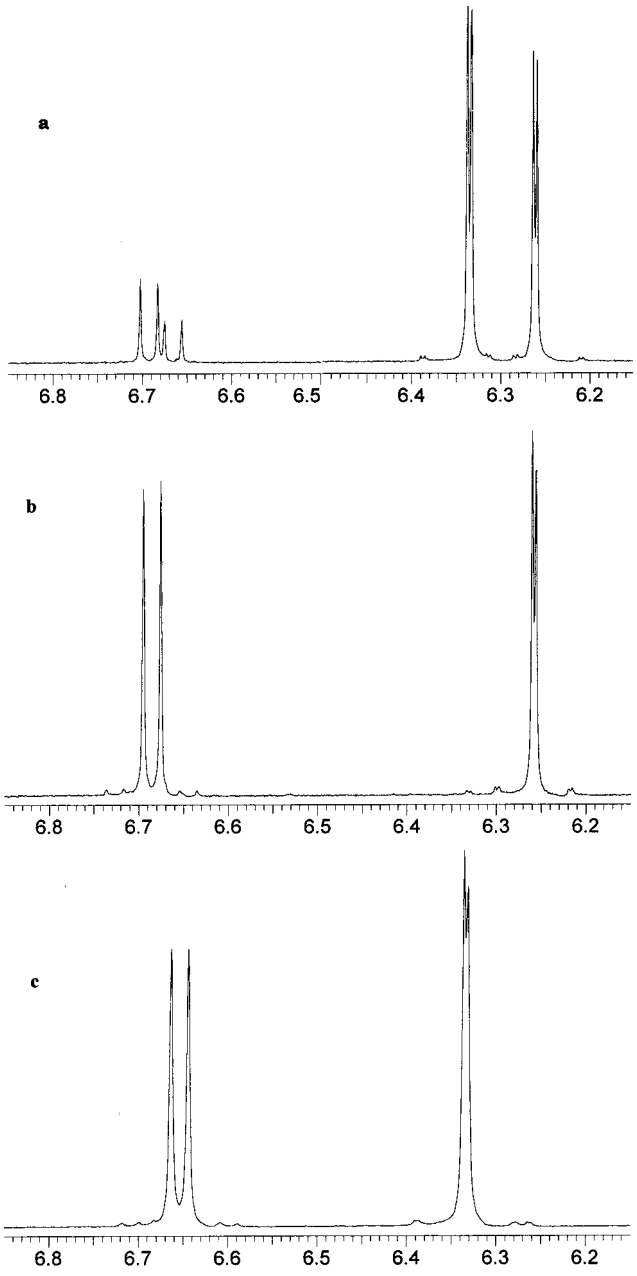
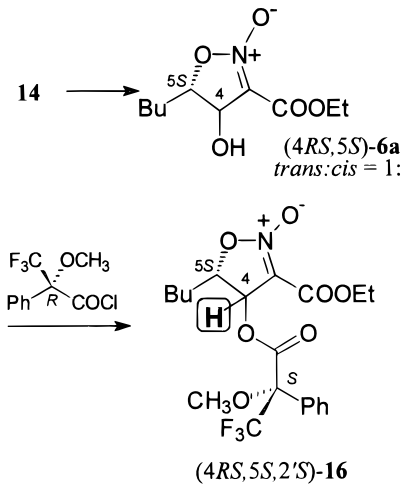


Figure 1.

To further confirm this important result, the enantiomers of the isoxazolines **6a** were prepared from the diepoxyacetal **11**, by the same procedure used for the diastereoisomer **10** and previously depicted in Scheme 6 (Scheme 10). Again, the ^{1}H NMR analysis of the Mosher's esters (Figure 1c) confirmed the enantiomeric purity of the isoxazolines; this time the other two signals for the C4 H were observed.

Each pair of the diastereomeric Mosher's esters **16** was separated and for each one the ^{1}H NMR spectrum was recorded again as a single pure diastereoisomer. The differences in the chemical shifts observed in the spectra allowed us to assign the absolute configuration to both chiral centers of all four stereoisomeric 2-isoxazoline 2-oxides **6a**, according to Mosher's method for the elucidation of the structure of secondary alcohols.[20] In particular, it was possible to assign the 4S configuration to the two isomers that showed an upfield shift of the signals relative to the ethyl group of the ester and the

Scheme 9



(4*RS*,5*S*,2′*S*)-**16**

4R configuration to the two isomers that showed an upfield shift of the C5 H and C1′ H_2 signals.[21] This assignment confirmed that the isoxazoline ring closure occurs with complete inversion of the configuration of the chiral center of the starting aldehyde. Finally, the enantiomeric excesses of the isoxazolines **6a** were determined also by HPLC analysis of the Mosher's esters **16** and were found to be in the range of 98.0−99.2%.[22]

It is noteworthy that this synthesis employs only 1 equiv of sodium periodate to generate 2 equiv of products without any loss of the carbon atoms of the starting mannitol. Both of the three-carbon fragments from D-mannitol were embedded into the structure of 2-activated aldehydes, preserving the chirality of C2 and C5 of the intermediate diepoxide **10**. Moreover, the possibility of using the mesyl group for the activation of the α-hydroxy aldehyde, in place of the tosyl group, reduces the waste production. All these achievements greatly contribute to increasing the atom economy of the overall process. An additional advantage of the synthesis is that the antipodal enantiomer of the target compounds **6** can be obtained by using the diastereoisomeric diepoxyacetal **11** as a chiral template in lieu of **10**.

Separation of Cis- and Trans Isomers of 5-Alkyl-4-hydroxy-2-isoxazoline 2-Oxides. Any attempt to separate the cis- and trans-isomers of the 5-substituted 4-hydroxy-2-isoxazoline 2-oxides **6a**−**e** was unsuccessful. To achieve a good and practical separation of the enantiopure *cis*- and *trans*-**6a**−**e**, we performed a simple derivatization of the hydroxyl group on C4 with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in dichloromethane in the presence of triethylamine and a catalytic amount of (dimethylamino)pyridine (DMAP). (Scheme 11).

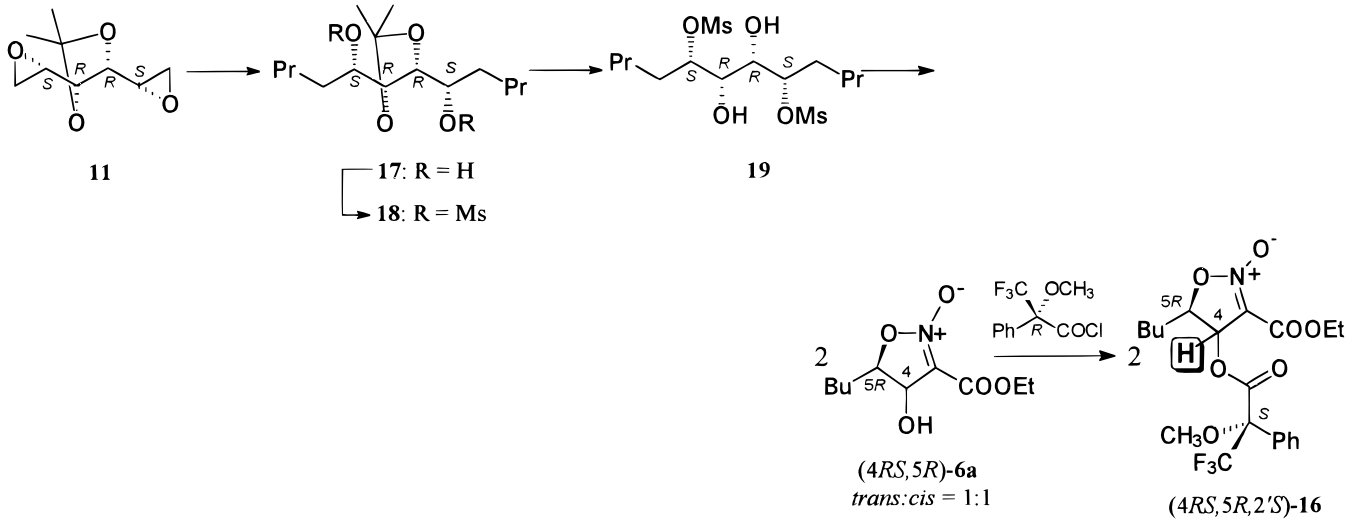
The derivatization of *cis*- and *trans*-**6** occurred with different rates as reported in Table 2. While the trans isomers reacted faster to give the protected compounds **20**, the cis isomers reacted much more slowly and after 24 h of reaction at room temperature remained mainly unprotected. In addition, the *tert*-butyldiphenylsilyl

(20) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. For a more recent application with high-field FT NMR, see: Ohtani, I.; Jusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(21) For a more detailed discussion see the Supporting Information.

(22) For more details and actual chromatograms, see the Experimental Section and Supporting Information.

Scheme 10



Scheme 11

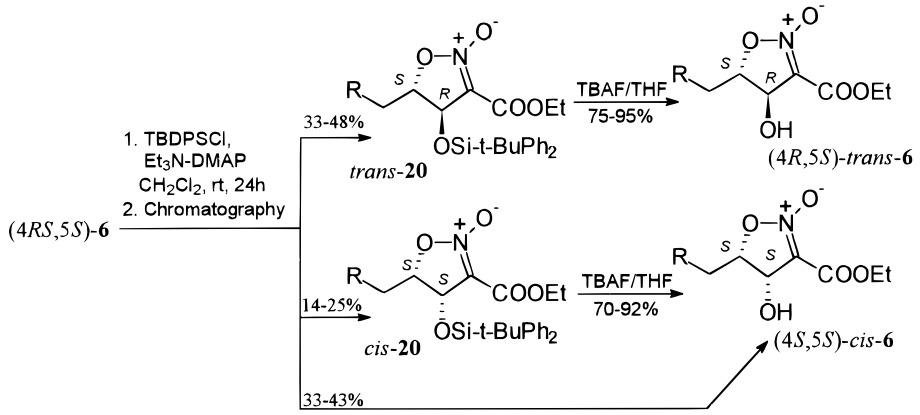


Table 2. Yields of Isolated Components of the Reaction Mixtures after Derivatization

	R	trans/cis ratio of starting **6**	(4*R*,5*S*-*trans*)-**20** (%)	(4*S*,5*S*-*cis*)-**20** (%)	(4*S*,5*S*-*cis*)-**6** (%)
a	*n*-Pr	43/57	33	19	36
b	*n*-Bu	44/56	34	25	33
c	3-butenyl	42/58	39	15	43
d	cyclohexyl	48/52	48	14	36
e	(2*S*)-2-methylbutyl	44/56	39	17	39

derivatives of the trans isomers were eluted first in flash column chromatography (SiO_2, petroleum ether/diethyl ether 4:1) and were well differentiated from the cis isomers. Finally, the unreacted compounds *cis*-**6** were recovered by elution with diethyl ether or ethyl acetate. The deprotection of the separated enantiopure *trans*- and *cis*-4-*tert*-butyldiphenylsilyl derivatives **20** was performed by treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF, which gave the enantiopure 4-hydroxy-2-isoxazoline 2-oxides **6** in fairly good yields.

Deoxygenation of 2-Isoxazolines 2-Oxide 6. In addition to opening an efficient route for the separation of the isomers (**6**), the derivatization with TBDPSCl was useful to accomplish the deoxygenation reaction to generate the corresponding enantiopure *cis*- and *trans*-4-hydroxy-2-isoxazolines **9**. Some selected examples illustrating the viability of this procedure are shown in Scheme 12.

Compounds *trans*- and *cis*-**20a**,**c**,**e** were easily converted into the deoxygenated derivatives when treated with trimethyl phosphite at 100 °C for half an hour. The deprotection promoted by the fluoride anion gave enantiopure (4*R*,5*S*)- and (4*S*,5*S*)-5-alkyl-4-hydroxy-2-isoxazolines **9**. It is necessary to stress that the sequence takes place without epimerization and/or decomposition of substrates and that the same deoxygenation step failed when the unprotected substrates were used. To the best of our knowledge, this is the first general route to obtain enantiomerically pure *cis*- and *trans*-3-ethoxycarbonyl-5-alkyl-4-hydroxy-2-isoxazolines.[23] The previously described procedures for the synthesis of optically active 4-hydroxy-2-isoxazolines are all based on the general methodology first depicted by Jäger et al.[24] for racemic compounds by which the hydroxylation of C4 was achieved

(23) For methods that yield optically active 4-hydroxy-2-isoxazolines, see: (a) Liu, J.; Eddings, A.; Wallace, R. H. *Tetrahedron Lett.* **1997**, *38*, 6795−6798. (b) Wade, P. A.; Shah, S. S.; Govindarajian, *J. Org. Chem.* **1994**, *59*, 7199−7200. (c) Davis, F. A.; Kumar, A.; Reddy, R. E.; Chen, B.; Wade, P. A.; Shah, S. W. *J. Org. Chem.* **1993**, *58*, 7591−7593. (d) Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898−7899.

Scheme 12

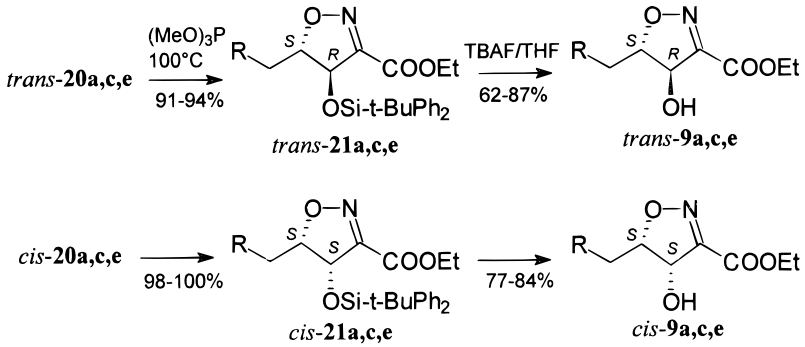


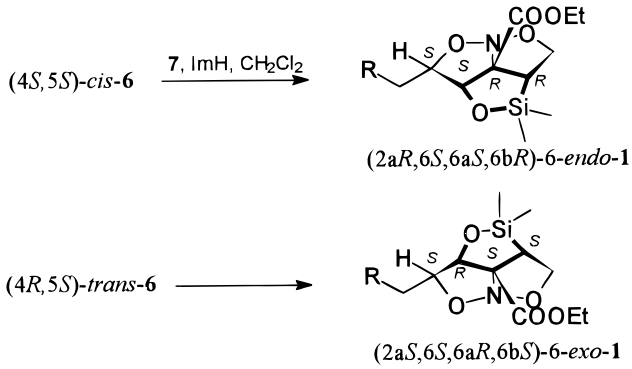
Table 3. Yields of the Tricyclization Reactions

starting material	product	yield (%)
(4*R*,5*S*-*trans*)-**6a**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*exo*-**1a**	93
(4*S*,5*S*-*cis*)-**6a**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*endo*-**1a**	93
(4*R*,5*S*-*trans*)- and (4*S*,5*S*-*cis*)-**6b**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*exo*-**1b** and (2a*R*,6*S*,6a*S*,6b*R*)−6-*endo*-**1b**	85
(4*R*,5*S*-*trans*)-**6c** and (4*S*,5*S*-*cis*)-**6c**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*exo*-**1c** and (2a*R*,6*S*,6a*S*,6b*R*)−6-*endo*-**1c**	89
(4*R*,5*S*-*trans*)-**6d**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*exo*-**1d**	76
(4*S*,5*S*-*cis*)-**6d**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*endo*-**1d**	73
(4R,5S-*trans*)-**6e**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*exo*-**1e**	81
(4*S*,5*S*-*cis*)-**6e**	(2a*R*,6*S*,6a*S*,6b*R*)−6-*endo*-**1e**	83

through (a) the generation of azaenolate anions of 5-alkyl-2-isoxazolines at very low temperature, (b) selective enolate treatment with borates, and (c) subsequent oxidative workup. The asymmetric hydroxylation performed by Davis and Wade et al.[23b] with chiral *N*-sulfonyloxyaziridines gave low yields and low ee of only the *trans*-4-hydroxy-2-isoxazolines. The procedure developed by Wallace[23a] stems from the utilization of vinylboronic esters derivatized with an optically active sultam in a cascade of (a) nitrile oxide cycloaddition, (b) oxidative cleavage of the intermediate boronic ester and, finally, (c) hydrolysis of the amide. However, notwithstanding the higher yields and better ee, both of these procedures are restricted to the preparation of the trans isomers only.

Preparation of Enantiomerically Pure Highly Functionalized Tricyclic Systems (HFTS). The synthesis of enantiomerically pure *endo*- and *exo*-6-alkyl-HFTS (**1**) was accomplished through the utilization of the same conditions we developed for the racemic compounds.[3] The *trans*-3-ethoxycarbonyl-5-alkyl-4-hydroxy-2-isoxazoline 2-oxides (**6**) furnished exclusively the 6-*exo*-alkyl-HFTS **1** and the cis isomers gave the 6-*endo*-**1**. In general, the endo and exo diastereoisomers can be easily separated and purified by flash column chromatography with silica gel. This methodology made it possible to perform the tricyclization reaction directly with the mixtures of *cis*- and *trans*- 4-hydroxy-2-isoxazoline 2-oxides **6**, maintaining the same diastereoisomeric ratio (Scheme 13, Table 3).

Scheme 13



Conclusions

In this paper, we have shown a general and efficient procedure to prepare enantiomerically pure 3-ethoxycarbonyl-5-alkyl-4-hydroxy-2-isoxazoline 2-oxides (**6**) and their conversion into the deoxygenated forms **9** and the highly functionalized tricyclic systems **1**.

The "folding" sequence we have devised and developed highly implements the chirality of enantiomerically pure 2-methanesulfonyloxy aldehydes and allows one to quickly achieve the molecular complexity associated with the target structures **9** and **1**, useful intermediates for the preparation of linear 2-amino polyols and polyhydroxylated 2-amino acids by practical "unfolding" sequences.[2,3,8]

The optically active 2-activated aldehydes are available in both enantiomeric forms by chirality transfer[25] from D-mannitol by two enantiodivergent synthetic sequences.

The general procedures here depicted are particularly attractive and efficient since they utilize enantiopure 2-activated aldehydes and their conversion into the corresponding enantiopure target compounds **6**, and then **9** and **1,** through a sequence of stereospecific reactions, except the nitroaldol reaction. The criteria of selectivity and atom economy have been the guidelines for our efforts in achieving practicality in the procedures we have developed.

Experimental Section

General. Proton and ^{13}C NMR were recorded at 300.08 MHz and at 75.46 MHz, respectively, in $CDCl_3$ at 20 °C with either tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm for ^{1}H NMR, 77.00 for ^{13}C NMR) as the internal standard.

(24) Schwab, W.; Jager, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603−605.

(25) (a) Joullie, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887−889. (b) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1997**, 2251−2257.

Solvents were reagent grade and used as received; anhydrous solvents were prepared according to standard methodologies. Melting points are uncorrected. Unless otherwise stated, the solution of the crude product obtained at the end of each workup procedure was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. All chromatographic separations were performed with flash column chromatography using Silica gel Merck 60 (70−230 mesh ASTM). Diepoxides **10** and **11** were prepared according to ref 16.

Bisalkylation of Diepoxide 10. A three-necked round-bottomed flask with a internal stirring and equipped with a thermometer, addition funnel, and reflux cooler was kept under a positive pressure of nitrogen. The flask was charged with magnesium turnings (2.05 equiv), which were barely covered with anhydrous diethyl ether, and a catalytic amount of 1,2-dibromoethane (10 μL) was added. Stirring was started very slowly, and the mixture was heated to reflux for about 15 min until spontaneous gas evolution was observed. A solution of the corresponding alkyl bromide in anhydrous diethyl ether (2 M, 2 equiv) was added dropwise at room temperature, and the mixture was kept stirring until most of the magnesium was consumed. The dark solution was then cooled to −50 °C, and a catalytic amount of $CuBr\cdot SMe_2$ (0.5 equiv) was added to the mixture that was kept stirring for another 2 h. After that, a solution of the diepoxide **10** in anhydrous THF (0.33 M, 1 equiv) was added dropwise to the mixture. The cooling bath was removed, and the temperature was allowed to reach the ambient value in about 30 min. The mixture was quenched by the careful addition of a saturated solution of NH_4Cl and extracted several times with ethyl acetate. The crude product was purified by flash chromatography.

a. (5*R*,6*R*,7*R*,8*R*)-6,7-*O*-Isopropylidene-5,6,7,8-dodecanetetraol (12a). The reaction was performed on 10.8 mmol of **10**. Yield 79% of a white solid. mp 36−38 °C. ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 6), 1.20−1.65 (m, 16), 1.80 (m, 2), 3.45−3.70 (m, 4), 4.36 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 108.7, 83.8, 73.6, 34.4, 27.8, 27.4, 23.2, 14.5 ppm. $[\alpha]^{26}_D$ = +26.81 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{15}H_{30}O_4$: C, 65.66; H, 11.02. Found: C, 65.52 H, 11.08.

b. (6*R*,7*R*,8*R*,9*R*)-7,8-*O*-Isopropylidene-6,7,8,9-tetradecanetetraol (12b). The reaction was performed on 5 mmol of **10**. Yield 75% of a white solid. mp 41−44 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6), 1.20−1.65 (m, 20), 1.80 (m, 2), 3.55 (bs, 2), 3.65 (m, 2), 4.35 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 108.7, 83.3, 73.2, 34.2, 31.9, 26.9, 24.9, 14.1 ppm. $[\alpha]^{33}_D$ = +25.43 (*c* 0.93, $CHCl_3$). Anal. Calcd for $C_{17}H_{34}O_4$: C, 67.51; H, 11.33. Found: C, 67.58; H, 11.29.

c. (6*R*,7*R*,8*R*,9*R*)-7,8-*O*-Isopropylidenetetradecane-1,-13-dien-6,7,8,9-tetraol (12c). The reaction was performed on 8.06 mmol of **10**. Yield 95% of a clear oil. ^{1}H NMR ($CDCl_3$) δ 1.20−1.95 (m, 14), 2.10 (m, 4), 3.55 (m, 4), 4.40 (m, 2), 5.00 (m, 4), 5.80 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 139.0, 115.0, 109.3, 83.7, 73.5, 34.2, 27.4, 24.9 ppm. $[\alpha]^{27}_D$ = +25.86 (*c* 1.14, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.53; H, 10.20.

d. (2*R*,3*R*,4*R*,5*R*)-1,6-Dicyclohexyl-3,4-*O*-isopropilidene-2,3,4,5-hexanetetraol (12d). The reaction was performed on 1.61 mmol of **10**. Yield 63% of a white waxy solid. ^{1}H NMR ($CDCl_3$) δ 0.75−1.90 (m, 30), 3.70 (m, 4), 4.05 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 109.3, 83.9, 70.9, 42.3, 35.1, 33.9, 32.7, 27.5, 27.1, 26.9, 26.6 ppm. $[\alpha]^{30}_D$ = +37.38 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.03; H, 10.78.

e. (3*S*,6*R*,7*R*,8*R*,9*R*,12*S*)-7,8-*O*-Isopropylidene-3,12-dimethyl-6,7,8,9-tetradecanetetraol (12e). The reaction was performed on 6.77 mmol of **10**. Yield 80% of a white solid. mp 54−57 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 12), 1.00−1.55 (m, 18), 1.75 (m, 2), 3.52 (m, 2), 3.65 (dt, 2), 4.15 (d, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 109.2, 83.7, 73.9, 35.0, 32.4, 32.2, 30.1, 27.4, 19.5, 11.9 ppm. $[\alpha]^{22}_D$ = +35.36 (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 69.12; H, 11.63.

Bismesylation of Diols 12. To a solution of the starting diol **12** in dry pyridine (0.3 M, 1 equiv) was added DMAP (0.1 equiv). The solution was cooled to 0 °C, and methanesulfonyl chloride (1.25 equiv) was slowly added via a syringe. The flask was stoppered and kept in a refrigerator at 4 °C overnight. The solution was carefully poured onto a 3:1 mixture of 10% HCl and crushed ice and extracted several times with ethyl acetate. The organic layer was subsequently washed with a saturated solution of $CuSO_4$ and brine, and the crude product was used without further purification.

a. (5*R*,6*S*,7*S*,8*R*)-6,7-*O*-Isopropylidene-5,8-di-*O*-methanesulfonyl-5,6,7,8-dodecanetetraol (13a). The reaction was performed on 7.81 mmol of **12a**. Quantitative yield of a clear oil. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6), 1.20−1.65 (m, 14), 1.80 (m, 4), 3.10 (s, 6), 4.29 (m, 2), 4.77 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 111.4, 82.2, 79.3, 39.3, 30.8, 27.5, 27.1, 22.9, 14.4 ppm. $[\alpha]^{25}_D$ = +28.70 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{17}H_{34}O_8S_2$: C, 47.42; H, 7.96. Found: C, 47.53; H, 8.01.

b. (6*R*,7*S*,8*S*,9*R*)-7,8-*O*-Isopropylidene-6,9-di-*O*-methansulfonyl-6,7,8,9-tetradecanetetraol (13b). The reaction was performed on 3.31 mmol of **12b**. Quantitative yield of a clear oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6), 1.20−1.65 (m, 18), 1.82 (m, 2), 3.10 (s, 6), 4.15 (m, 2), 4.75 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 111.4, 82.1, 79.3, 39.3, 31.9, 31.0, 27.5, 24.6, 22.8, 14.4 ppm. $[\alpha]^{30}_D$ = +25.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{38}O_8S_2$: C, 49.76; H, 8.35. Found: C, 49.61; H, 8.30.

c. (6*R*,7*S*,8*S*,9*R*)-7,8-*O*-Isopropylidene-6,9-di-*O*-(methanesulfonyl)tetradecane-1,13-diene-6,7,8,9-tetraol (13c). The reaction was performed on 3.02 mmol of **12c**. Yield 90% of a clear oil. ^{1}H NMR ($CDCl_3$) δ 1.30−1.95 (m, 14), 2.10 (m, 4), 3.10 (s, 6), 4.16 (m, 2), 4.75 (m, 2), 5.00 (m, 4), 5.80 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 138.3, 115.7, 111.5, 81.8, 79.4, 39.3, 33.7, 30.4, 27.5, 24.1 ppm. $[\alpha]^{27}_D$ = +24.70 (*c* 1.12, $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_8S_2$: C, 50.20; H, 7.54. Found: C, 50.35; H, 7.59.

d. (2*R*,3*S*,4*S*,5*R*)-1,6-Dicyclohexyl-3,4-*O*-Isopropylidene-2,5-di-*O*-(methanesulfonyl)-2,3,4,5-hexanetetraol (13d). The reaction was performed on 1.86 mmol of **12d**. Quantitative yield of a clear oil. ^{1}H NMR ($CDCl_3$) δ 0.75−2.00 (m, 32), 3.10 (s, 6), 4.15 (m, 2), 4.88 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 111.4, 79.7, 39.4, 38.5, 34.5, 33.5, 32.8, 27.5, 26.8, 26.6, 26.3 ppm. $[\alpha]^{29}_D$ = +53.67 (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{23}H_{42}O_8S_2$: C, 54.09; H, 8.29. Found: C, 53.91; H, 8.34.

e. (3*S*,6*R*,7*S*,8*S*,9*R*,12*S*)-7,8-*O*-Isopropylidene-3,12-dimethyl-6,9-di-*O*-(methanesulfonyl)-6,7,8,9-tetradecanetetraol (13e). The reaction was performed on 5.94 mmol of **12e**. Quantitative yield of a clear oil. ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 12), 1.05−1.55 (m, 16), 1.80 (m, 4), 3.12 (s, 6), 4.17 (dd, 2), 4.72 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 111.6, 82.5, 79.3, 39.3, 34.6, 31.5, 29.8, 28.6, 27.6, 19.3, 11.8 ppm. $[\alpha]^{25}_D$ = +31.29 (*c* 1.08, $CHCl_3$). Anal. Calcd for $C_{21}H_{42}O_8S_2$: C, 51.83; H, 8.70. Found: C, 51.99; H, 8.77.

Hydrolysis of Acetals 13. Concentrated hydrochloric acid (ca. 10 equiv) was added dropwise to a stirred solution of the starting acetal **13** in acetic acid (0.1 M). During the addition, the solution turned deep-blue, and after 1 h of being stirred at room temperature, the reaction was diluted with water and extracted several times with ethyl acetate. The combined organic layers were subsequently washed with saturated sodium carbonate and brine. The crude product was used without further purifications.

a. (5*R*,6*S*,7*S*,8*R*)-5,8-Di-*O*-methanesulfonyl-5,6,7,8-dodecanetetraol (14a). The reaction was performed on 7.81 mmol of **13a**. Yield 82% of a white solid. mp 64−66 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6), 1.20−1.60 (m, 8), 1.85 (m, 4), 3.12 (s, 8), 3.88 (d, 2), 4.72 (dt, 2) ppm. ^{13}C NMR δ 82.1, 69.5, 38.5, 30.8, 26.6, 22.5, 13.9 ppm. $[\alpha]^{26}_D$ = −3.65 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{14}H_{30}O_8S_2$: C, 43.06; H, 7.74. Found: C, 42.90; H, 7.78.

b. (6*R*,7*S*,8*S*,9*R*)-6,9-Di-*O*-methanesulfonyl-6,7,8,9-tetradecanetetraol (14b). The reaction was performed on 3.27 mmol of **13b**. Quantitative yield of a greenish oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6), 1.20−1.60 (m, 12), 1.85 (m, 4), 2.90 (bs, 2), 3.10 (s, 6), 3.88 (d, 2), 4.66 (ddd, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 82.0, 69.5, 38.5, 31.6, 31.1, 24.2, 22.4, 14.0 ppm. $[\alpha]^{31}_D$ = −0.86 (*c* 1.12, $CHCl_3$). Anal. Calcd for $C_{16}H_{34}O_8S_2$: C, 45.91; H, 8.19. Found: C, 46.10; H, 8.15.

c. (6*R*,7*S*,8*S*,9*R*)-6,9-Di-*O*-(methanesulfonyl)tetradecane-1,13-diene-6,7,8,9-tetraol (14c). The reaction was performed on 1.03 mmol of **13c**. Yield 85% of a clear oil. ^{1}H NMR δ 1.60 (m, 4), 1.85 (m, 4), 2.15 (m, 4), 3.12 (s, 6), 3.22 (bs, 2), 3.85 (d, 2), 4.75 (ddd, 2), 5.00 (m, 4), 5.80 (m, 2) ppm. ^{13}C NMR δ 138.0, 115.2, 81.7, 69.5, 38.5, 33.3, 30.5, 23.7 ppm. $[\alpha]^{28}_D = -6.77$ (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{16}H_{30}O_8S_2$: C, 46.36; H, 7.29. Found: C, 46.18; H, 7.34.

d. (2*R*,3*S*,4*S*,5*R*)-1,6-Dicyclohexyl-2,5-di-*O*-(methanesulfonyl)-2,3,4,5-hexanetetraol (14d). The reaction was performed on 1.86 mmol of **13d**. Yield 70% of a white solid. mp 114−115 °C. ^{1}H NMR δ 0.80−2.00 (m, 26), 3.01 (d, 2), 3.10 (s, 6), 3.88 (dd, 2), 4.82 (dt, 2) ppm. ^{13}C NMR δ 81.2, 70.9, 39.0, 38.9, 34.6, 33.8, 32.8, 26.8, 26.7, 26.4 ppm. $[\alpha]^{28}_D = +34.67$ (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{20}H_{38}O_8S_2$: C, 51.04; H, 8.14. Found: C, 51.18; H, 8.15.

e. (3*S*,6*R*,7*S*,8*S*,9*R*,12*S*)-3,12-Dimethyl-6,9-di-*O*-(methanesulfonyl)-6,7,8,9-tetradecanetetraol (14e). The reaction was performed on 5.94 mmol of **13e**. Yield 98% of a clear oil. ^{1}H NMR δ 0.90 (m, 12), 1.10−1.62 (m, 10), 1.85 (m, 4), 3.10 (s, 8), 3.88 (d, 2), 4.66 (ddd, 2) ppm. ^{13}C NMR δ 82.4, 69.4, 38.5, 34.2, 31.1, 29.4, 28.6, 18.9, 11.4 ppm. $[\alpha]^{27}_D = +0.60$ (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{18}H_{38}O_8S_2$: C, 48.41; H, 8.58. Found: C, 48.20; H, 8.53.

Domino Preparation of 2-Isoxazolines 2-Oxides (4*RS*,-5*S*)-6. A 1 M aqueous solution of sodium periodate (1 equiv) was added to a stirred solution of the diol **14** in ethanol (0.1 M, 1 equiv). Imidazole (1.1 equiv) and ethyl nitroacetate (1 equiv) were immediately added, and the mixture was kept stirring at room temperature until the reaction was complete. The mixture was filtered over a glass sintered filter, and the solution was concentrated in vacuo. The residue was taken up with a 10% solution of sodium carbonate and extracted several times with ethyl acetate. The combined organic layers were washed with brine, and the crude product was obtained as a mixture of (4S,5S) and (4R,5S) diastereoisomers. Sometimes, the products required purification by flash chromatography. For the spectroscopical characterization of the single diastereoisomers, see below.

a. (4*RS*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-Oxide (6a). The reaction was performed on 6.41 mmol of diol **14a**. No chromatographic purification was needed. Yield 93% of a clear oil.

b. (4*RS*,5*S*)-3-Ethoxycarbonyl-5-pentyl-4-hydroxy-2-isoxazoline 2-Oxide (6b). The reaction was performed on 3.28 mmol of diol **14b**. Yield 86% of a clear oil.

c. (4*RS*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-(4-pentenyl)-2-isoxazoline 2-Oxide (6c). The reaction was performed on 0.87 mmol of diol **14c**. No chromatographic purification was needed. Yield 90% of a clear oil.

d. (4*RS*,5*S*)-5-Cyclohexylmethyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-Oxide (6d). The reaction was performed on 1.25 mmol of diol **14d**. No chromatographic purification was needed. Quantitative yield of a clear oil.

e. (4*RS*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-[(3*S*)-3-methylpentyl]-2-isoxazoline 2-Oxide (6e). The reaction was performed on 5.04 mmol of diol **14e**. No chromatographic purification was needed. Yield 95% of a clear oil.

Bisalkylation of Diepoxide 11. The reaction was performed as described above for diepoxide **10** on 4.14 mmol of starting material **11**, obtaining 0.84 g (74% yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6), 1.20−1.65 (m, 12), 1.41 (s, 6), 2.10 (d, 2), 3.50 (m, 2), 3.93 (dd, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 110.1, 80.94, 71.08, 35.55, 28.96, 28.30, 23.61, 15.00 ppm. $[\alpha]^{28}_D = +8.58$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{15}H_{30}O_4$: C, 65.66; H, 11.02. Found: C, 65.80 H, 10.94.

Bismesylation of Diol 17. The reaction was performed as described above for diol **12**, in this case on 3.02 mmol of starting material obtaining 1.12 g (87% yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6), 1.41 (m, 14), 1.71−1.95 (m, 4), 3.10 (s, 6), 4.12 (s, 2H), 4.75 (t, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 110.2, 80.40, 77.57, 39.31, 31.98, 27.85, 27.37, 22.83, 14.31 ppm. $[\alpha]^{28}_D = -10.03$ (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{17}H_{34}O_8S_2$: C, 47.42; H, 7.96. Found: C, 47.55; H, 8.02.

Hydrolysis of Acetal 18. The reaction was performed as described above for acetal **13**, in this case on 3.02 mmol of starting material, obtaining 1.08 g (92% yield) of a waxy white solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6), 1.45 (m, 8), 1.60−1.83 (m, 4), 3.07 (s, 2), 3.10 (s, 6), 3.75 (d, 2), 4.83 (m, 2) ppm. ^{13}C NMR ($CDCl_3$) δ 85.53, 72.78, 39.70, 31.74, 28.10, 23.45, 14.92 ppm. $[\alpha]^{24}_D = -25.51$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{14}H_{30}O_8S_2$: C, 43.06; H, 7.74. Found: C, 42.89; H, 7.79.

Domino Preparation of 2-Isoxazolines 2-Oxides (4*RS*,-5*R*)-6a. The reaction was performed as described above for the preparation of the (4RS,5S) isomers, in this case on 2.59 mmol of diol **19**, obtaining a 92% yield of a clear oil.

Preparation and Analysis of Mosher's Esters of 6a. The preparation of the Mosher's esters was performed according to Sharpless et al.,[26] using (*R*)-2-methoxy-2-phenyl-3,3,3-trifuoropropanoyl chloride [(*R*)-MTPA-Cl, which is obtained from the corresponding (S) acid]. The reactions were performed on a 0.1 mmol scale for (i) *rac*-**6a** obtained from racemic 2-bromohexanal as a 5:1 mixture of the trans and cis isomers, (ii) (4*RS*,5*S*)-**6a** obtained from **14** as a 1:1 mixture of the trans and cis isomers, and (iii) (4*RS*,5*R*)-**6a** obtained from **19** as a 1:1 mixture of the trans and cis isomers. ^{1}H NMR analysis in $CDCl_3$ at 300 MHz focused on the proton on C4 of the isoxazoline ring (doublet) that is found in the region 6.2−6.8 ppm. After determination of the enantiomeric excess, the diastereoisomer pairs were separated by column chromatography eluting with petroleum ether/diethyl ether = 4:1.

Alternatively, in each case (i, ii, and iii) *trans*- and *cis*-**6a** were separated and derivatized with (*R*)-MTPA-Cl. The crude mixture of the esters was analyzed by HPLC (column, Lichrospher 100 RP-18 (5 μm) 4 mm ID × 250 mm with a 4 mm ID × 4 mm precolumn (Merck); mobile phase, 80% methanol in water; flow rate, 1 mL/min; detector, UV 254 nm; sample, An aliquot of the crude esterification mixture dissolved in the mobile phase (20 μL). The measured enantiomeric excesses were always in the range 98.0−99.5%.

a. (4*R*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyloxy]-2-isoxazoline 2-Oxide [(4*R*,5*S*,2′*S*)-*trans*-16]. ^{1}H NMR δ 0.93 (t, 3), 1.30 (t, 3), 1.35−1.55 (m, 4), 1.83 (dt, 2), 3.56 (s, 3), 4,30 (q, 2), 4.40 (dt, 1), 6.36 (d, 1), 7.35−7.45 (m, 3), 7,36−7,55 (m, 2) ppm. ^{13}C NMR δ 166.06, 157.88, 131.52, 130.02, 128.66, 127.01, 124.97, 121.14, 106.09, 82.02, 79.78, 62.17, 55.65, 31.66, 26.47, 22.19, 14.04, 13.73 ppm.

b. (4*S*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyloxy]-2-isoxazoline 2-Oxide [(4*S*,5*S*,2′*S*)-*cis*-16]. ^{1}H NMR δ 0.88 (t, 3), 1.24 (t, 3), 1.30−1.50 (m, 4), 1.55−1.80 (m, 2), 3.44 (s, 3), 4.24 (q, 2), 4.76 (dt, 1), 6.69 (d, 1), 7.35−7.45 (m, 3), 7.50−7.60 (m, 2) ppm. ^{13}C NMR δ 165.69, 157.61, 130.81, 130.02, 128.66, 127.62, 125.05, 121.22, 108.54, 80.16, 75.59, 62.02, 55.28, 27.52, 26.42, 22.28, 13.97, 13.65 ppm.

c. (4*S*,5*R*)-5-Butyl-3-ethoxycarbonyl-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyloxy]-2-isoxazoline 2-Oxide [(4*S*,5*R*,2′*S*)-*trans*-16]. ^{1}H NMR δ 0.95 (t, 3), 1.18 (t, 3), 1.30−1.60 (m, 4), 1.65−1.95 (m, 2), 3.53 (s, 3), 4.22 (q, 2), 4.56 (dt, 1), 6.28 (d, 1), 7.30−7.60 (m, 5) ppm. ^{13}C NMR δ 166.40, 157.95, 131.51, 130.35, 129.48, 128.96, 128.56, 127.68, 126.27, 120.52, 106.46, 82.55, 80.52, 62.38, 56.83, 31.97, 26.88, 22.58, 14.27, 14.09, 12.46, 12.27 ppm.

d. (4*R*,5*R*)-5-Butyl-3-ethoxycarbonyl-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyloxy]-2-isoxazoline 2-Oxide [(4*R*,5*R*,2′*S*)-*cis*-16]. ^{1}H NMR δ 0.85 (t, 3), 1.28 (t, 3), 1.30−1.50 (m, 6), 3.55 (s, 3), 4.28 (q, 2), 4.73 (dt, 1), 6.71 (d, 1), 7.35−7.45 (m, 3), 7.50−7.65 (m, 2) ppm. ^{13}C NMR δ 165.63, 157.83, 131.59, 129.97, 128.51, 127.10, 125.05, 121.21, 108.57, 80.41, 62.19, 55.73, 27.61, 26.15, 22.23, 13.99, 13.70 ppm.

Protection of 2-Isoxazolines 2-Oxides 6. To a stirred solution of the starting 2-isoxazoline 2-oxide (**6**) in dichloromethane (0.5 M, 1 equiv) was added triethylamine (1.1

(26) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

equiv), DMAP (0.3 equiv), and *tert*-butyldiphenylsilyl chloride (1.1 equiv). The mixture was kept stirring at room temperature for 24 h, and then it was partitioned between saturated NH_4Cl and dichloromethane. The aqueous layer was extracted 3 times with dichloromethane, and the products were separated by flash chromatography eluting with petroleum ether/diethyl ether, 4:1, for the protected derivatives **20** and then with diethyl ether alone for unreacted *cis*-**6**.

a. Protection of 6a. The reaction was performed on 11.9 mmol. Overall yield 88%.

a.1. (4*R*,5*S*)-5-Butyl-4-(*t*-butyldiphenylsilyloxy)-3-ethoxycarbonyl-2-isoxazoline 2-Oxide (*trans*-20a). Yield 33% of a white solid. mp 58−60 °C. ^{1}H NMR δ 0.67 (t, 3), 0.80−1.40 (m, 16), 4.01 (dq, 1), 4.24 (dq, 1), 4.29 (ddd, 1), 5.06 (d, 1), 7.40 (m, 6), 7.70 (m, 4), ^{13}C NMR δ 159.2, 136.3−128.3, 111.1, 85.2, 79.3, 62.1, 31.5, 27.1, 27.0, 22.6, 19.7, 14.4, 14.2 ppm. $[\alpha]^{27}_D = -42.64$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{27}H_{37}NO_5Si$: C, 67.05; H, 7.71; N, 2.90. Found: C, 67.20; H, 7.76; N, 2.87.

a.2. (4*S*,5*S*)-5-Butyl-4-(*t*-butyldiphenylsilyloxy)-3-ethoxycarbonyl-2-isoxazoline 2-Oxide (*cis*-20a). Yield 19% of a white solid. mp 90−92 °C. ^{1}H NMR δ 0.86 (t, 3), 0.92 (t, 3), 1.05 (s, 9), 1.40 (m, 4), 1.90 (m, 1), 2.10 (m, 1), 3.26 (dq, 1), 3.87 (dq, 1), 4.40 (ddd, 1), 5.20 (d, 1), 7.90−7.30 (m, 10) ppm. ^{13}C NMR δ 158.1, 136.0−127.6, 113.2, 83.2, 74.3, 61.1, 27.6, 26.8, 26.3, 22.5, 19.7, 14.0, 13.6 ppm. $[\alpha]^{27}_D = +6.61$ (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{27}H_{37}NO_5Si$: C, 67.05; H, 7.71; N, 2.90. Found: C, 66.88; H, 7.67; N, 2.95.

b. Protection of 6b. The reaction was performed on 2.45 mmol. Overall yield 92%.

b.1. (4*R*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-pentyl-2-isoxazoline 2-Oxide (*trans*-20b). Yield 34% of a clear oil. ^{1}H NMR δ 0.80 (t, 3), 1.06 (m, 17), 1.16 (t, 3), 4.02 (dq, 1), 4.24 (dq, 1), 4.28 (ddd, 1), 5.05 (d, 1), 7.40 (m, 6), 7.70 (m, 4) ppm. ^{13}C NMR δ 159.2, 136.3−128.2, 111.1, 85.1, 79.3, 62.1, 31.8, 31.6, 27.1, 24.6, 22.7, 19.8, 14.4, 14.3 ppm. $[\alpha]^{36}_D = -34.45$ (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{28}H_{39}NO_5Si$: C, 67.57; H, 7.90; N, 2.81. Found: C, 67.71; H, 7.92; N, 2.83.

b.2. (4*S*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-pentyl-2-isoxazoline 2-Oxide (*cis*-20b). Yield 25% of a white solid. mp 99−101 °C. ^{1}H NMR 0.86 (t, 3), 0.93 (t, 3), 1.08 (s, 9), 1.40 (m, 6), 1.90 (m, 1), 2.10 (m, 1), 3.32 (dq, 1) 3.87 (dq, 1), 4.40 (ddd, 1), 5.20 (d, 1), 7.45 (m, 6), 7.84 (m, 4) ppm. ^{13}C NMR δ 158.6, 136.4−128.1, 113.7, 83.6, 74.7, 61.5, 32.0, 27.2, 27.0, 25.6, 23.0, 20.2, 14.4, 14.0 ppm. $[\alpha]^{33}_D = +2.24$ (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{28}H_{39}NO_5Si$: C, 67.57; H, 7.90; N, 2.81. Found: C, 67.48; H, 7.92; N, 2.82.

c. Protection of 6c. The reaction was performed on 10.9 mmol. Overall yield 97%.

c.1. (4*R*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-(4-pentenyl)-2-isoxazoline 2-Oxide (*trans*-20c). Yield 39% of a clear oil. ^{1}H NMR δ 0.45−1.40 (m, 4), 1.06 (s, 9), 1.15 (t, 3), 1.85 (m, 2), 4.03 (dq, 1), 4.23 (dq, 1), 4.30 (ddd, 1), 4.90 (m, 2), 5.05 (d, 1), 5.60 (m, 1), 7.42 (m, 6), 7.70 (m, 4) ppm. ^{13}C NMR δ 158.8, 137.6, 135.9−127.7, 115.3, 110.6, 84.5, 78.9, 61.6, 33.0, 30.8, 26.7, 23.7, 19.3, 14.0 ppm. $[\alpha]^{28}_D = -31.79$ (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{27}H_{35}NO_5Si$: C, 67.33; H, 7.32; N, 2.91. Found: C, 67.23; H, 7.30; N, 2.92.

c.2. (4*S*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-(4-pentenyl)-2-isoxazoline 2-Oxide (*cis*-20c). Yield 15% of a white solid. mp 94−96 °C. ^{1}H NMR δ 0.86 (t, 3), 1.05 (s, 9), 1.50−1.90 (m, 4), 2.20 (m, 2), 3.26 (dq, 1), 3.82 (dq, 1), 4.39 (ddd, 1), 5.00 (m, 2), 5.17 (d, 1), 5.78 (m, 1), 7.42 (m, 8), 7.70 (m, 2) ppm. ^{13}C NMR δ 158.6, 138.2, 136.4−128.1, 115.8, 113.6, 83.4, 74.8, 61.5, 33.9, 27.2, 26.5, 25.1, 20.2, 14.0 ppm. $[\alpha]^{31}_D = +1.20$ (*c* 1.10, $CHCl_3$). Anal. Calcd for $C_{27}H_{35}NO_5Si$: C, 67.33; H, 7.32; N, 2.91. Found: C, 67.22; H, 7.33; N, 2.92.

d. Protection of 6d. The reaction was performed on 2.50 mmol. Overall yield 98%.

d.1. (4*R*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-5-cyclohexylmethyl-3-ethoxycarbonyl-2-isoxazoline 2-Oxide (*trans*-20d). Yield 48% of a clear oil. ^{1}H NMR δ 0.50−1.70 (m, 25), 4.01 (dq, 1), 4.21 (dq, 1), 4.43 (ddd, 1), 5.04 (d, 1), 7.40 (m, 6), 7.70 (m, 4) ppm. ^{13}C NMR δ 159.2, 136.3−128.2, 111.1, 83.1, 79.8, 62.0, 39.2, 34.0, 33.7, 32.6, 27.0, 26.7, 26.4, 26.3, 19.8, 14.5 ppm. $[\alpha]^{25}_D = -27.98$ (*c* 1.02, $CHCl_3$). Anal. Calcd $C_{29}H_{39}NO_5Si$: C, 68.34; H, 7.71; N, 2.75. Found: C, 68.21; H, 7.72; N, 2.78.

(4*S*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-5-cyclohexylmethyl-3-ethoxycarbonyl-2-isoxazoline 2-Oxide (*cis*-20d). Yield 14% of a white solid. mp 140−142 °C. ^{1}H NMR δ 0.85 (t, 3), 1.05 (s, 9), 1.20 (m, 6), 1.70 (m, 6), 2.00 (m, 1), 3.25 (dq, 1), 3.82 (dq, 1), 4.45 (ddd, 1), 5.15 (d, 1), 7.30−7.90 (m, 10) ppm. ^{13}C NMR δ 158.6, 136.5−128.0, 113.7, 81.6, 75.1, 61.6, 34.6, 34.5, 34.0, 33.4, 27.3, 26.8, 26.6, 20.2, 14.0 ppm. $[\alpha]^{23}_D = -7.89$ (*c* 0.95, $CHCl_3$). Anal. Calcd $C_{29}H_{39}NO_5Si$: C, 68.34; H, 7.71; N, 2.75. Found: C, 68.39; H, 7.68; N, 2.74.

e. Protection of 6e. The reaction was performed on 9.81 mmol. Overall yield 95%.

e.1. (4*R*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-[(3*S*)-3-methylpentyl]-2-isoxazoline 2-Oxide (*trans*-20e). Yield 39% of a clear oil. ^{1}H NMR δ 0.68 (d, 3), 0.75 (t, 3), 0.80−1.40 (m, 19), 4.02 (dq, 1), 4.14−4.32 (m, 2), 5.07 (d, 1), 7.40 (m, 6), 7.70 (m, 4) ppm. ^{13}C NMR δ 159.2, 136.3−128.3, 111.1, 85.6, 79.3, 62.0, 34.4, 31.5, 29.6, 29.5, 27.2, 19.7, 19.3, 14.4, 11.7 ppm. $[\alpha]^{23}_D = -35.87$ (*c* 1.01, $CHCl_3$). Anal-.Calcd $C_{28}H_{39}NO_5Si$: C, 67.57; H, 7.90; N, 2.81. Found: C, 67.48; H, 7.90; N, 2.82.

(4*S*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-[(3*S*)-3-methylpentyl]-2-isoxazoline 2-Oxide (*cis*-20e). Yield 17% of a white solid. mp 100−101 °C. ^{1}H NMR δ 0.80 (m, 9), 1.05 (s, 9), 1.10−1.50 (m, 5), 1.85 (m, 2), 3.32 (dq, 1), 3.85 (dq, 1), 4.34 (ddd, 1), 5.18 (d, 1), 7.30−7.90 (m, 10) ppm. ^{13}C NMR δ 158.6, 136.4−128.1, 113.7, 84.1, 74.7, 61.5, 34.7, 32.6, 29.6, 27.2, 25.0, 20.2, 19.5, 14.0, 11.7 ppm. $[\alpha]^{26}_D = +0.60$ (*c* 1.00, $CHCl_3$). Anal. Calcd $C_{28}H_{39}NO_5Si$: C, 67.57; H, 7.90; N, 2.81. Found: C, 67.65; H, 7.93; N, 2.79.

Deprotection of Silyl Ethers 20. A flask fitted with a calcium chloride tube was charged with a solution of the starting ether **20** in anhydrous THF (0.2 M, 1 equiv). To the stirred solution was added a solution of tetrabutylammonium fluoride in THF (1 M, 2 equiv). After 30 min, the reaction was quenched by the addition of a saturated solution of NH_4Cl. The aqueous layer was extracted several times with dichloromethane. The crude product was purified by filtration over a 5 cm pad of silica gel eluting with ethyl acetate/petroleum ether, 4:1.

a. (4*R*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-Oxide (*trans*-6a). The reaction was performed on 1.28 mmol of *trans*-**20a**. Yield 94% of a clear oil. ^{1}H NMR δ 0.94 (t, 3), 1.40 (m, 7), 1.72 (m, 2), 3.98 (d, 1), 4.34 (q, 2), 4.53 (ddd, 1), 5.16 (dd, 1) ppm. ^{13}C NMR δ 159.8, 111.5, 84.7, 77.4, 62.5, 32.5, 27.1, 22.7, 14.6, 14.2 ppm. $[\alpha]^{24}_D = -158.63$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.79; H, 7.38; N, 6.05.

b. (4*S*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-Oxide (*cis*-6a). ^{1}H NMR δ 0.92 (t, 3), 1.30−1.50 (m, 7), 1.87 (m, 2), 3.21 (bs, 1), 4.36 (dq, 1), 4.37 (dq, 1), 4.56 (dt, 1), 5.25 (d, 1) ppm. ^{13}C NMR δ 159.3, 112.5, 81.6, 72.8, 62.0, 27.5, 25.8, 22.5, 14.2, 13.9 ppm. $[\alpha]^{27}_D = -15.66$ (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.85; H, 7.44; N, 6.09.

c. (4*R*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-pentyl-2-isoxazoline 2-Oxide (*trans*-6b). The reaction was performed on 0.83 mmol of *trans*-**20b**. Yield 60% of a clear oil. ^{1}H NMR δ 0.88 (t, 3), 1.36 (t, 3), 1.50−1.26 (m, 6), 1.70 (m, 2), 3.45 (bs, 1), 4.32 (dq, 1), 4.36 (dq, 1), 4.53 (ddd, 1), 5.15 (d, 1) ppm. ^{13}C NMR δ 159.4, 111.0, 84.2, 77.0, 62.1, 32.3, 31.3, 24.3, 22.4, 14.1, 13.9 ppm. $[\alpha]^{35}_D = -122.21$ (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 54.01; H, 7.78; N, 5.73.

d. (4*S*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-pentyl-2-isoxazoline 2-Oxide (*cis*-6b). The reaction was performed on 0.60 mmol of *cis*-**20b**. Yield 61% of a clear oil. ^{1}H NMR 0.90 (m, 3), 1.34 (t, 3), 1.50−1.26 (m, 6), 1.88 (dt, 2), 3.45 (bs, 1), 4.32 (dq, 1), 4.36 (dq, 1), 4.57 (dt, 1), 5.26 (d, 1) ppm. ^{13}C NMR δ 159.3, 112.7, 81.8, 72.8, 62.1, 31.6, 26.0, 25.1, 22.4,

14.2, 13.9 ppm. $[\alpha]^{33}_D = -17.47$ (*c* 0.83, $CHCl_3$). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.95; H, 7.82; N, 5.73.

e. (4*R*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-(4-pentenyl)-2-isoxazoline 2-oxide (*trans*-6c). The reaction was performed on 1.25 mmol of *trans*-**20c**. Yield 75% of a clear oil. ^{1}H NMR δ 1.35 (t, 3), 1.45−1.81 (m, 4), 2.11 (m, 2), 3.85 (bs, 1), 4.26 (q, 2), 4.52 (ddd, 1), 4.89 (m, 2), 5.14 (d, 1), 5.76 (m, 1) ppm. ^{13}C NMR δ 159.7, 138.0, 115.9, 111.4, 84.5, 77.4, 62.5, 33.5, 32.1, 24.3, 14.6 ppm. $[\alpha]^{27}_D = -141.14$ (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.42; H, 7.05; N, 5.77.

f. (4*S*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-(4-pentenyl)-2-isoxazoline 2-Oxide (*cis*-6c). The reaction was performed on 0.33 mmol of *cis*-**20c**. Yield 62% of a clear oil. ^{1}H NMR δ 1.35 (t, 3), 1.57 (m, 2), 1.91 (m, 2), 2.14 (m, 2), 3.25 (bs, 1), 4.34 (q, 1), 4.35 (q, 1), 4.59 (ddd, 1), 5.02 (m, 2), 5.27 (d, 1), 5.80 (m, 1) ppm. ^{13}C NMR δ 159.3, 137.8, 115.3, 112.4, 81.3, 79.9, 62.0, 33.3, 25.6, 24.6, 14.2 ppm. $[\alpha]^{31}_D = -18.70$ (*c* 0.94, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.29; H, 7.00; N, 5.72.

g. (4*R*,5*S*)-5-Cyclohexylmethyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-Oxide (*trans*-6d). The reaction was performed on 1.16 mmol of *trans*-**20d**. mp 73−75 °C. Yield 70% of a white solid. ^{1}H NMR δ 0.80−1.80 (m, 16), 3.80 (bs, 1), 4.32 (q, 1), 4.65 (ddd, 1), 5.10 (d, 1) ppm. ^{13}C NMR δ 159.8, 111.4, 82.9, 77.9, 62.5, 40.3, 34.2, 34.0, 32.9, 26.7, 26.5, 14.6 ppm. $[\alpha]^{30}_D = -134.47$ (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.40; H, 7.82; N, 5.18.

h. (4*S*,5*S*)-5-Cyclohexylmethyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline 2-Oxide (*cis*-6d). The reaction was performed on 0.35 mmol of *cis*-**20d**. Yield 64% of a white solid. mp 85−87 °C. ^{1}H NMR δ 0.80−1.90 (m, 16), 3.30 (bs, 1), 4.32 (q, 1), 4.32 (q, 1), 4.70 (ddd, 1), 5.24 (d, 1) ppm. ^{13}C NMR δ 159.8, 113.1, 80.3, 73.6, 62.5, 34.7, 34.1, 33.8, 33.3, 26.7, 26.6, 26.5, 14.6 ppm. $[\alpha]^{23}_D = -20.94$ (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.62; H, 7.85; N, 5.16.

i. (4*R*,5*S*)-3-Ethoxycarbonyl-5-[(3*S*)-3-methylpentyl]-4-hydroxy-2-isoxazoline 2-Oxide (*trans*-6e). The reaction was performed on 1.41 mmol of *trans*-**20e**. Yield 92% of a clear oil. ^{1}H NMR δ 0.80 (m, 6), 1.04−1.60 (m, 8), 1.70 (m, 2), 3.70 (bs, 1), 4.36 (q, 1), 4.50 (dt, 1), 5.18 (d, 1) ppm. ^{13}C NMR δ 159.8, 111.4, 85.0, 77.4, 62.6, 34.5, 31.6, 30.5, 29.6, 19.4, 14.6, 11.7 ppm. $[\alpha]^{21}_D = -140.55$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.70; H, 8.16; N, 5.44.

j. (4*S*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-[(3*S*)-3-methylpentyl]-2-isoxazoline 2-Oxide (*cis*-6e). Clear oil. ^{1}H NMR δ 0.85 (m, 6), 1.10−1.55 (m, 8), 1.85 (m, 2), 3.40 (m, 1), 4.35 (dq, 2), 4.55 (ddd, 1), 5.26 (d, 1) ppm. ^{13}C NMR δ 159.8, 113.1, 82.5, 73.1, 62.4, 34.8, 32.4, 29.7, 24.1, 19.4, 14.6, 11.7 ppm. $[\alpha]^{26}_D$ −9.94 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.61; H, 8.17; N, 5.42.

Deoxygenation of 2-Isoxazolines 2-Oxides 20. A solution of the *N*-oxide **20** in trimethyl phosphite (0.25 M) was heated to reflux until disappearance of the starting material was observed by TLC. The reaction mixture was allowed to cool to room temperature and taken up in diethyl ether. The mixture was washed 4 times with 5% HCl, and the combined aqueous layers were back extracted with a small portion of diethyl ether. The crude product needed no further purification.

a. (4*R*,5*S*)-5-Butyl-4-(*t*-butyldiphenylsilyloxy)-3-ethoxycarbonyl-2-isoxazoline (*trans*-21a). The reaction was performed on 0.21 mmol of *trans*-**20a**. Yield 94% of a clear oil. ^{1}H NMR δ 0.70 (t, 3), 0.80 (m, 15), 1.30 (t, 3), 4.22 (dq, 1), 4.26 (dq, 1), 4.40 (ddd, 1), 4.95(d, 1), 7.40 (m, 6), 7.70 (m, 4) ppm. ^{13}C NMR δ 160.9, 152.9, 136.1−128.2, 91.8, 80.7, 62.4, 31.4, 27.4, 27.3, 22.8, 19.8, 14.5, 14.2 ppm. $[\alpha]^{24}_D = -64.05$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.97; H, 7.81; N, 3.11.

b. (4*S*,5*S*)-5-Butyl-4-(*t*-butyldiphenylsilyloxy)-3-ethoxycarbonyl-2-isoxazoline (*cis*-21a). The reaction was performed on 1.83 mmol of *cis*-**20a**. Yield 97% of a clear oil. ^{1}H NMR δ 0.90 (t, 3), 1.02 (s, 9), 1.09 (t, 3), 1.35 (m, 4), 1.95 (m, 2), 3.70 (dq, 1), 3.89 (dq, 1), 4.06 (ddd, 1), 4.95 (d, 1), 7.40 (m, 8), 7.85 (m, 2) ppm. ^{13}C NMR δ 160.6, 155.1, 136.1−127.9, 89.5, 74.7, 62.1, 28.6, 27.3, 26.4, 23.1, 20.1, 14.4, 14.3 ppm. $[\alpha]^{24}_D = -57.89$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.71; H, 7.78; N, 3.11.

c. (4*R*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-(4-pentenyl)-2-isoxazoline (*trans*-21c). The reaction was performed on 3.24 mmol of *trans*-**20c**. Yield 91% of a clear oil. ^{1}H NMR δ 0.80−1.20 (m, 13), 1.30 (t, 3), 1.80 (m, 2), 4.23 (dq, 1), 4.27 (dq, 1), 4.40 (ddd, 1), 4.86 (m, 2), 4.92 (d, 1), 5.59 (m, 1), 7.40 (m, 6), 7.52 (m, 4) ppm. ^{13}C NMR δ 160.8, 152.9, 138.3, 136.1−128.1, 115.5, 91.5, 80.8, 62.4, 36.3, 31.1, 27.2, 24.6, 19.8, 14.6 ppm. $[\alpha]^{24}_D = -62.34$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{27}H_{35}NO_4Si$: C, 69.64; H, 7.58; N, 3.01. Found: C, 69.75; H, 7.57; N, 3.02.

d. (4*S*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-(4-pentenyl)-2-isoxazoline (*cis*-21c). The reaction was performed on 2.16 mmol of *cis*-**20c**. Quantitative yield of a white solid. mp 48−50 °C. ^{1}H NMR δ 1.03 (s, 9), 1.10 (t, 3), 1.55 (m, 2), 1.80−2.20 (m, 4), 3.72 (dq, 1), 3.89 (dq, 1), 4.06 (ddd, 1), 4.97 (d, 1), 5.04 (m, 2), 5.80 (m, 1), 7.45 (m, 2), 7.88 (m, 8) ppm. ^{13}C NMR δ 160.6, 155.1, 138.3, 136.7−127.9, 115.6, 88.2, 74.9, 62.1, 34.1, 27.3, 26.3, 20.1, 14.3 ppm. $[\alpha]^{26}_D = -58.48$ (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{27}H_{35}NO_4Si$: C, 69.64; H, 7.58; N, 3.01. Found: C, 69.55; H, 7.55; N, 2.99.

e. (4*R*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-[(3*S*)-3-methylpentyl]-2-isoxazoline (*trans*-21e). The reaction was performed on 2.25 mmol of *trans*-**20e**. Yield 92% of a clear oil. ^{1}H NMR δ 0.64 (d, 3), 0.76 (t, 3), 0.82−1.20 (m, 15), 1.30 (t, 3), 4.20 (dq, 1), 4.31 (dq, 1), 4.37 (ddd, 1), 4.94(d, 1), 7.40 (m, 6), 7.70 (m, 4) ppm. ^{13}C NMR δ 160.4, 152.5, 136.0−127.8, 91.8, 80.3, 61.9, 34.0, 31.5, 29.1, 28.9, 26.7, 19.3, 18.9, 14.1, 11.3 ppm. $[\alpha]^{25}_D = -73.49$ (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.82; H, 8.16; N, 2.91. Found: C, 69.71; H, 8.15; N, 2.93.

f. (4*S*,5*S*)-4-(*t*-Butyldiphenylsilyloxy)-3-ethoxycarbonyl-5-[(3*S*)-3-methylpentyl]-2-isoxazoline (*cis*-21e). The reaction was performed on 1.99 mmol of *cis*-**20e**. Yield 98% of a clear oil. ^{1}H NMR δ 0.83 (m, 6), 0.90−1.60, (m, 17), 1.90 (m, 2), 3.72 (dq, 1), 3.90 (dq, 1), 4.02 (ddd, 1), 4.97 (d, 1), 7.30−7.90 (m, 10) ppm. ^{13}C NMR δ 160.7, 155.1, 136.7−127.9, 89.9, 74.8, 62.1, 34.8, 33.4, 29.6, 27.3, 24.6, 20.1, 19.5, 14.3, 11.7 ppm. $[\alpha]^{25}_D = -58.72$ (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.82; H, 8.16; N, 2.91. Found: C, 69.88; H, 8.18; N, 2.90.

Deprotection of Silyl Ethers 21. The reactions were performed as described above for silyl ethers **20**.

a. (4*R*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline (*trans*-9a). The reaction was performed on 1.96 mmol of *cis*-**21a**. Yield 62% of a clear oil. ^{1}H NMR δ 0.92 (t, 3), 1.50−1.78 (m, 9), 3.92 (bs, 1), 4.36 (q, 2), 4.57 (ddd, 1), 5.03 (d, 1) ppm. ^{13}C NMR δ 160.9, 152.4, 90.9, 78.8, 62.2, 31.8, 26.9, 22.3, 14.0, 13.8 ppm. $[\alpha]^{25}_D = -216.57$ (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.87; H, 7.99; N, 6.50.

b. (4*S*,5*S*)-5-Butyl-3-ethoxycarbonyl-4-hydroxy-2-isoxazoline (*cis*-9a). The reaction was performed on 1.83 mmol of cis-**21a**. Yield 84% of a waxy solid. ^{1}H NMR δ 0.90 (t, 3), 1.20−1.65 (m, 7), 1.90 (m, 2), 3.20 (bs, 1), 4.40 (m, 3), 5.15 (d, 1) ppm. ^{13}C NMR δ 161.2, 153.5, 87.7, 73.5, 62.3, 28.3, 25.6, 22.7, 14.1, 13.9 ppm. $[\alpha]^{23}_D = -114.54$ (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.72; H, 7.99; N, 6.52.

c. (4*R*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-(4-pentenyl)-2-isoxazoline (*trans*-9c). the reaction was performed on 1.39 mmol of *trans*-**21c**. Yield 87% of a clear oil. ^{1}H NMR δ 1.40 (t, 3), 1.60 (m, 4), 2.12 (m, 2), 3.70 (bs, 1), 4.38 (q, 2), 4.60 (m, 1), 5.02 (m, 3), 5.80 (m, 1) ppm. ^{13}C NMR δ 161.4, 152.6, 138.3, 115.7, 91.1, 79.3, 62.8, 33.7, 32.0, 24.6, 14.5 ppm. $[\alpha]^{24}_D =$

−198.29 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.22; H, 7.56; N, 6.13.

(4*S*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-(4-pentenyl)-2-isoxazoline (*cis*-9c). The reaction was performed on 2.04 mmol of *cis*-**21c**. Yield 80% of a white solid. mp 32−35 °C. ^{1}H NMR δ 1.38 (t, 3), 1.64 (m, 2), 1.90 (m, 2), 2.15 (m, 2), 3.30 (bs, 1), 4.35 (m, 1), 4.60 (q, 2), 5.02 (m, 2), 5.15 (d, 1), 5.83 (m, 1) ppm. ^{13}C NMR δ 161.2, 153.5, 138.1, 115.0, 87.5, 73.5, 62.3, 33.6, 25.4, 14.1 ppm. $[\alpha]^{21}_D = -106.08$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.08; H, 7.51; N, 6.15.

(4*R*,5*S*)-3-Ethoxycarbonyl-5-[(3*S*)-3-methylpentyl]-4-hydroxy-2-isoxazoline (*trans*-9e). The reaction was performed on 2.06 mmol of *trans*-**21e**. Yield 78% of a clear oil. ^{1}H NMR δ 0.82 (d, 3), 0.83 (t, 3), 1.05−1.65 (m, 10), 3.40 (bs, 1), 4.35 (q, 1), 4.52 (ddd, 1), 5.01 (d, 1) ppm. ^{13}C NMR δ 161.5, 152.9, 91.6, 79.1, 62.7, 34.6, 31.9, 30.2, 29.4, 19.5, 14.5, 11.7 ppm. $[\alpha]^{21}_D = -194.98$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.12; H, 8.66; N, 5.75.

(4*S*,5*S*)-3-Ethoxycarbonyl-4-hydroxy-5-[(3*S*)-3-methylpentyl]-2-isoxazoline (*cis*-9e). The reaction was performed on 1.93 mmol of *cis*-**21e**. Yield 92% of a white solid. mp 33−35 °C. ^{1}H NMR δ 0.90 (t, 3), 0.91 (d, 3), 1.00−1.70 (m, 8), 1.85 (m, 2), 3.28 (bs, 1), 4.32 (ddd, 1), 4.37 (q, 1), 5.15 (d, 1) ppm. ^{13}C NMR δ 161.6, 154.0, 88.6, 73.9, 62.7, 34.9, 33.3, 29.9, 23.9, 19.3, 14.5, 11.8 ppm. $[\alpha]^{21}_D = -100.90$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.29; H, 8.73; N, 5.79.

Tricyclization of 2-Isoxazolines 2-Oxide 6. A solution of the starting 2-isoxazoline 2-oxide **6** in anhydrous dichloromethane (0.3 M, 1 equiv) was placed in a flask under a nitrogen atmosphere. Imidazole (2.5 equiv) and chlorodimethylvinylsilane (1.2 equiv) were added to the stirred mixture. After 24 h, the mixture was partitioned between water and dichloromethane. The aqueous layer was extracted 4 times with dichloromethane. The crude product needed no further purification.

a. 6-*exo*-Butyl-HFTS (6-*exo*-1a). The reaction was performed on 1.12 mmol of *trans*-**6a**. Yield 93% of a clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.40 (s, 3), 0.90 (t, 3), 1.28−1.80 (m, 9), 2.46 (dd, 1), 4.07 (ddd, 1), 4.29 (q, 1), 4.30 (q, 1), 4.34 (dd, 1), 4.41 (dd, 1), 4.80 (d, 1) ppm. ^{13}C NMR δ 170.8, 93.6, 90.2, 87.1, 72.8, 62.8, 36.9, 31.7, 28.1, 22.9, 14.5, 14.4, 0.4, −2.0 ppm. $[\alpha]^{27}_D = -14.88$ (*c* 1.11, $CHCl_3$). Anal. Calcd for $C_{14}H_{25}NO_5Si$: C, 53.31; H, 7.99; N, 4.44. Found: C, 53.44; H, 7.95; N, 4.45.

b. 6-*endo*-Butyl-HFTS (6-*endo*-1a). The reaction was performed on 1.30 mmol of *cis*-**6a**. Yield 93% of a clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.39 (s, 3), 0.70 (t, 3), 1.30−1.46 (m, 7), 1.65 (m, 2), 2.44 (dd, 1), 3.87 (dt, 1), 4.28 (q, 1), 4.29 (q, 1), 4.38 (dd, 1), 4.49 (dd, 1), 4.78 (d, 1) ppm. ^{13}C NMR δ 170.8, 95.8, 86.3, 79.0, 74.5, 62.7, 35.8, 28.4, 26.4, 23.2, 14.5, 14.3, 0.2, −2.7 ppm. $[\alpha]^{26}_D = +33.31$ (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{14}H_{25}NO_5Si$: C, 53.31; H, 7.99; N, 4.44. Found: C, 53.18; H, 7.95; N, 4.42.

c. Tricyclization of 6b. The reaction was performed on 5.35 mmol of the mixture of *trans*- and *cis*-**6b**. The corresponding two products, 6-*exo*-**1b** and 6-*endo*-**1b**, were separated by column chromatography eluting with ethyl acetate/petroleum ether, 3:7. Overall yield 85%.

c.1. 6-*exo*-Pentyl-HFTS (6-*exo*-1b). Clear oil. ^{1}H NMR $CDCl_3$ δ 0.32 (s, 3), 0.40 (s, 3), 0.90 (t, 3), 1.20−1.80 (m, 11), 2.45 (dd, 1), 4.07 (ddd, 1), 4.27 (dq, 1), 4.28 (dq, 1), 4.38 (dd, 1), 4.47 (dd, 1), 4.75 (d, 1) ppm. ^{13}C NMR δ 170.4, 93.2, 89.8, 86.6, 72.4, 62.3, 36.5, 31.5, 25.2, 22.5, 14.0; 13.9, 0.0, −2.4 ppm. $[\alpha]^{34}_D = -8.71$ (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{15}H_{27}NO_5Si$: C, 54.68; H, 8.26; N, 4.25. Found: C, 54.81; H, 8.28; N, 4.23.

c.2. 6-*endo*-Pentyl-HFTS (6-*endo*-1b). Clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.38 (s, 3), 0.90 (t, 3), 1.25−1.50 (m, 9), 1.63 (m, 2), 2.44 (dd, 1), 3.86 (dt, 1), 4.26 (dq, 1), 4.27 (dq, 1), 4.38 (dd, 1), 4.47 (dd, 1), 4.75 (d, 1) ppm. ^{13}C NMR δ 170.4, 95.4, 85.9, 78.6, 74.0, 62.3, 35.3, 31.8−26.3, 25.6, 22.5, 14.1, 14.0, 0.2, −3.1 ppm. $[\alpha]^{34}_D = +34.51$ (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{15}H_{27}NO_5Si$: C, 54.68; H, 8.26; N, 4.25. Found: C, 54.78; H, 8.27; N, 4.25.

d. Tricyclization of 6c. The reaction was performed on 1.57 mmol of the mixture of *trans*- and *cis*-**6c**. The corresponding two products, 6-*exo*-**1c** and 6-*endo*-**1c**, were separated by column chromatography eluting with ethyl acetate/petroleum ether, 3:7. Overall yield 89%.

d.1. 6-*exo*-(4-Pentenyl)-HFTS (6-*exo*-1c). Clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.40 (s, 3), 1.32 (t, 3), 1.30−1.80 (m, 4), 2.10 (m, 2), 2.45 (dd, 1), 4.07 (ddd, 1), 4.27 (q, 1), 4.28 (q, 1), 4.31 (dd, 1), 4.41 (dd, 1), 4.79 (d, 1), 4.98 (m, 2), 5.79 (m, 1) ppm. ^{13}C NMR δ 170.8, 138.7, 115.3, 93.6, 90.1, 86.9, 72.8, 62.8, 36.9, 33.8, 31.4, 25.2, 22.5, 14.5, 0.4, −2.0 ppm. $[\alpha]^{34}_D = -16.30$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}NO_5Si$: C, 55.02; H, 7.70; N, 4.28. Found: C, 55.16; H, 7.72; N, 4.29.

d.2. 6-*endo*-(4-Pentenyl)-HFTS (6-*endo*-1c). Clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.38 (s, 3), 1.32 (t, 3), 1.40−1.72 (m, 4), 2.09 (m, 2), 2.44 (dd, 1), 3.87 (dt, 1), 4.27 (dq, 2), 4.37 (dd, 1), 4.47 (dd, 1), 4.75 (d, 1), 4.97 (m, 2), 5.79 (m, 1) ppm. ^{13}C NMR δ 170.7, 138.7, 115.1, 95.8, 86.2, 76.8, 74.5, 62.6, 35.7, 34.0, 26.2, 25.4, 14.4, 0.1, −2.8 ppm. $[\alpha]^{28}_D = +32.58$ (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}NO_5Si$: C, 55.02; H, 7.70; N, 4.28. Found: C, 55.09; H, 7.71; N, 4.29.

e. 6-*exo*-Cyclohexylmethyl-HFTS (6-*exo*-1d). The reaction was performed on 0.74 mmol of *trans*-**6d**. Yield 76% of a clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.40 (s, 3), 0.80−1.87 (m, 16), 2.45 (dd, 1), 4.20 (ddd, 1), 4.28 (q, 1), 4.29 (q, 1), 4.32 (dd, 1), 4.41 (dd, 1), 4.76 (d, 1) ppm. ^{13}C NMR δ 170.8, 93.6, 90.5, 84.8, 72.9, 62.7, 39.5, 36.9, 34.5, 34.1, 33.1, 26.9, 26.6, 26.5, 14.5, 0.4, −2.0 ppm. $[\alpha]^{26}_D = -18.26$ (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{17}H_{29}NO_5Si$: C, 57.43; H, 8.22; N, 3.94. Found: C, 57.58; H, 8.25; N, 3.93.

f. 6-*endo*-Cyclohexylmethyl-HFTS (6-*endo*-1d). The reaction was performed on 1.00 mmol of *cis*-**6d**. Yield 73% of a clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.38 (s, 3), 0.80−1.85 (m, 16), 2.42 (dd, 1), 3.90 (ddd, 1), 4.19 (q, 2), 4.29 (dd, 1), 4.39 (dd, 1), 4.67 (d, 1) ppm. ^{13}C NMR δ 170.8, 95.8, 86.8, 76.8, 74.5, 62.7, 35.8, 35.0, 34.2, 33.6, 26.9, 26.6, 26.5, 14.5, 0.2, −2.7 ppm. $[\alpha]^{24}_D = +21.65$ (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{17}H_{29}NO_5Si$: C, 57.43; H, 8.22; N, 3.94. Found: C, 57.31; H, 8.20; N, 3.92.

g. 6-*exo*-[(3*S*)-3-Methylpentyl]-HFTS (6-*exo*-1e). The reaction was performed on 3.86 mmol of *trans*-**6e**. Yield 81% of a clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.38 (s, 3), 0.85 (m, 6), 1.05−1.75 (m, 10), 2.45 (dd, 1), 4.05 (dt, 1), 4.28 (q, 1), 4.29 (q, 1), 4.31 (dd, 1), 4.41 (dd, 1), 4.80 (d, 1) ppm. ^{13}C NMR δ 170.9, 93.6, 90.2, 87.5, 72.8, 62.8, 35.8, 34.6, 32.6, 29.8, 29.7, 19.4, 14.5, 11.8, 0.4, −1.9 ppm. $[\alpha]^{25}_D = -6.75$ (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{16}H_{29}NO_5Si$: C, 55.95; H, 8.51; N, 4.08. Found: C, 56.09; H, 8.49; N, 4.10.

h. 6-*endo*-[(3*S*)-3-Methylpentyl]-HFTS (6-*endo*-1e). The reaction was performed on 3.86 mmol of *cis*-**6e**. Yield 83% of a clear oil. ^{1}H NMR δ 0.32 (s, 3), 0.38 (s, 3), 0.70 (m, 6), 0.80−1.40 (m, 8), 1.63 (m, 2), 2.29 (dd, 1), 3.68 (dt, 1), 4.12 (dq, 1), 4.13 (dq, 1), 4.24 (dd, 1), 4.36 (dd, 1), 4.62 (d, 1) ppm. ^{13}C NMR δ 170.8, 95.9, 86.3, 79.4, 74.5, 62.7, 35.7, 34.8, 32.9, 29.7, 24.3, 19.4, 14.5, 11.8, 0.2, −2.7 ppm. $[\alpha]^{22}_D = +37.10$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{16}H_{29}NO_5Si$: C, 55.95; H, 8.51; N, 4.08. Found: C, 55.86; H, 8.48; N, 4.07.

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Supporting Information Available: Actual ^{1}H NMR and HPLC chromatograms of the Mosher's esters **16** and details about the assignment of their absolute configuration as well as actual ^{13}C NMR of compounds **6a**−**e**, **9a**,**c**,**e**, and **1a**−**e** (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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