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Polyketide Building Blocks via Diastereoselective Nitrile Oxide Cycloadditions with Homoallylic Alcohols and Monoprotected Homoallylic Diols

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Abstract: A modular approach to Δ^2-isoxazolines, latent aldol adducts and polyketide building blocks, is reported. The magnesium-mediated, hydroxyl-directed method allows for the diastereoselective access to a wide variety of masked β-hydroxy ketones, starting from readily available aliphatic and aromatic oximes, homoallylic alcohols and monoprotected homoallylic diols. The utility of the prepared Δ^2-isoxazolines as polyketide building blocks is demonstrated by their ready conversion into the corresponding β-hydroxy ketones. The *anti*-diastereoselectivity of the reaction was established by derivatization, NOE studies and comparison of known compounds. A rationale for the observed diastereoselectivity is proposed.

Keywords: allylic alcohols · cycloaddition · nitrile oxide · polyketides · synthetic methods

Introduction

Polyketide natural products are attractive synthetic targets due to their potent biological activity and their stereochemical complexity. The modular synthesis of relevant building blocks is a major challenge in organic chemistry, as it would emulate the biosynthetic strategies.[1] Although the most widely used strategies for addressing this objective are aldol additions, allylation, crotylation and allenylmetal reactions,[2] other methodologies have been reported.[3] We have recently disclosed an alternative approach to polyketide building blocks via Kanemasa nitrile oxide cycloadditions[4] with allylic alcohols.[5] Following a single reaction protocol and using easily accessible optically active oximes and allylic alcohols, this method allows for the direct synthesis of an entire palette of stereochemical permutations found in dipropionate subunits and represents a novel approach to polyketide building blocks. This magnesium-mediated nitrile oxide cycloaddition was successfully applied in total syntheses of complex polyketide natural products[6,7] and for the preparation of stereochemically rich pentaketides.[8]

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Results and Discussion

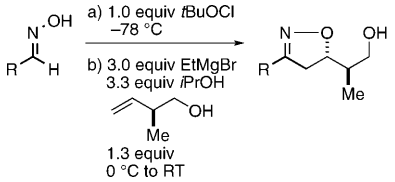
Within this article we document in full detail[9] the successful extension of the magnesium-mediated, hydroxyl-directed nitrile oxide cycloaddition methodology from allylic alcohols to homoallylic alcohols and monoprotected homoallylic diols. A wide variety of highly functionalized polyketide building blocks can be synthesized from a readily available set of starting materials due to the modular nature of this protocol. The utility of the prepared Δ^2-isoxazolines as masked aldol adducts is demonstrated by their facile transformation into the corresponding β-hydroxy ketones. The *anti*-relationship found in these cycloadducts was confirmed by conversion of a cycloadduct into a known isoxazoline for which the relative configuration had been previously established. Additionally, derivatization of two additional cycloadducts and subsequent NOE experiments provided further strong evidence for the proposed *anti*-relationship. The requisite starting materials—oximes, homoallylic alcohol (*S*)-2-methyl-3-butenol and monoprotected homoallylic alcohols—were readily prepared, as described below and in the Supporting Information.

Magnesium-mediated nitrile oxide cycloadditions with (*S*)-2-methyl-3-butenol: The preliminary prospecting cycloaddition reaction was performed with 1 equiv of oxime **1** and 2 equiv of homoallylic alcohol (*S*)-2-methyl-3-butenol[10] in the presence of 3.3 equiv of *i*PrOH and 3.0 equiv of EtMgBr in CH_2Cl_2, in parallel to the conditions initially developed

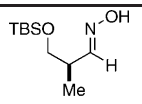
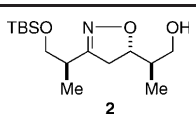
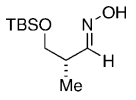
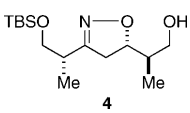
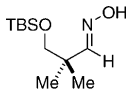
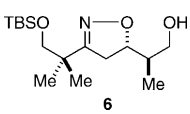
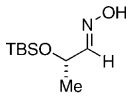
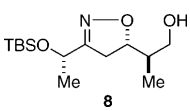
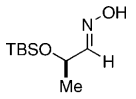
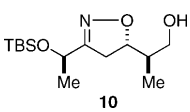
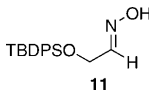
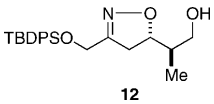
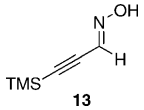
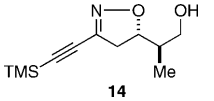
for allylic alcohols.[5a] Chlorination of the oxime to the corresponding hydroximinoyl chloride was achieved using 1.0 equiv of *t*BuOCl. The reaction proceeded in a completely regioselective manner, in 83% yield and with dr of 7:1 in favor of the *anti*-diastereomer.[11] Slow addition of the hydroximinoyl chloride to the magnesium alkoxides solution proved to be advantageous with respect to the observed diastereoselectivity. The optimal time was found to be 1 to 1.5 h; longer addition times did not result in further improvement of the diastereoselectivity. Lowering the reaction temperature, varying the solvent (CH_2Cl_2, toluene and hexane)[12] or the addition order of the reactants did not increase the diastereomeric ratio but in some cases resulted in a decrease in the isolated yield. While the initial reactions were performed with 2.0 equiv of the homoallylic alcohol, it was observed that identical results could be obtained with only 1.3 equiv of the dipolarophile. With these optimized conditions in hand, different aliphatic as well as aromatic oximes were examined in the magnesium-mediated cycloaddition with (*S*)-2-methyl-3-butenol in the presence of *i*PrOH and EtMgBr in either CH_2Cl_2 or toluene. As shown herein, the protocol proved successful for a broad range of aliphatic and aromatic nitrile oxides. Unless otherwise stated the nitrile oxides were generated in situ according to standard procedures using *t*BuOCl. The hydroximinoyl chloride solutions were generally added over 1 to 1.5 h to the solution of magnesium alkoxides at 0°C. After 6 h at 0°C the reaction mixture was gradually warmed to RT over 12 h.

The 1,3-dipolar cycloaddition of the nitrile oxide derived from oxime **1** and (*S*)-2-methyl-3-butenol in toluene afforded cycloadduct **2** in a dr of 7:1 and in 78% yield (Table 1, entry 1). When the reaction was performed in CH_2Cl_2, isoxazoline **2** was formed with the same diastereoselectivity and in slightly better yield (83%, entry 2). With the enantiomeric oxime **3** under identical reaction conditions, the cycloaddition took place in a similar yield (83% in toluene, 85% in CH_2Cl_2) but with slightly better diastereoselectivity (9:1) (entries 3 and 4). However, to consider this result as a matched/mismatched case, more detailed studies and experiments would be necessary. Oxime **5**, quaternary at the α-position, underwent cycloaddition in toluene in 89% yield and the diastereoselectivity of this reaction was found to be 4:1 (entry 5). During the course of related studies in the area of nitrile oxide cycloadditions with allylic alcohols it was found that in some cases a large excess of *t*BuOH instead of 3.3 equiv of *i*PrOH as additive in the reaction can dramatically improve the diastereoselectivity.[13] In the case of homoallylic alcohols these conditions proved unsuccessful; when 25 equiv of *t*BuOH were used instead of 3.3 equiv of *i*PrOH both the diastereoselectivity (2:1 vs. 4:1) and the yield (54% vs. 89%) decreased (entry 6). Oximes **7**[14] and **9**, derived from (+)- and (−)-lactates, respectively, were submitted to standard reaction conditions in toluene (entries 7 and 8). The resulting yields were similar to those of oximes **1** and **3** (82 and 83% vs. 78 and 83%), while the diastereoselectivities were slightly

Table 1. Nitrile oxide cycloadditions with (*S*)-2-methyl-3-butenol.



(1)

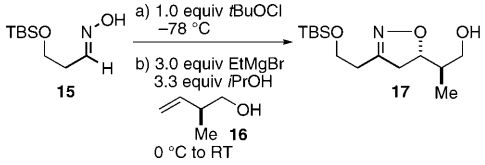
Entry	Oxime	Solvent	Cycloadduct	dr[a]	Yield [%][b]
1	 **1**	toluene	 **2**	7:1	78
2		CH_2Cl_2		7:1	83
3	 **3**	toluene	 **4**	9:1	83
4		CH_2Cl_2		9:1	85
5	 **5**	toluene	 **6**	4:1[c]	89
6				2:1[d]	54[d]
7	 **7**	toluene	 **8**	6:1[e]	82
8	 **9**	toluene	 **10**	5:1[e]	83
9	 **11**	toluene	 **12**	10:1[e]	87
10	 **13**	toluene	 **14**	5:1[c]	66[f,g]

[a] Determined by ^{1}H NMR analysis of the crude material. [b] Isolated yield. [c] Determined after filtration over silica gel. [d] 25 equiv of *t*BuOH instead of 3.3 equiv of *i*PrOH. [e] Determined by ^{13}C NMR analysis of the crude material. [f] NCS used instead of *t*BuOCl. [g] Isolation of the hydroximinoyl chloride.

lower (6:1 and 5:1 vs. 7:1 and 9:1). In the reaction with the nitrile oxide derived from oxime **11**,[8] unbranched at the α-position, cycloadduct **12** was formed in 87% yield and with a diastereomeric ratio of 10:1 (entry 9). The *C*-alkynyl nitrile oxide **13**[15] underwent cycloaddition in toluene in 66% yield and in 5:1 diastereoselectivity. As previously reported, chlorination of this substrate was achieved using 1 equiv of NCS instead of the generally used *t*BuOCl.[5]

Under the same conditions in toluene, oxime **15**, unbranched at the α-position, exhibited a drastically lower yield (45%) than the substituted oximes **1** and **3** (78% and 83%), albeit in the same diastereoselectivity range (8:1) (Table 2, entry 1).[16] In order to improve the yield of the reaction with oxime **15**, the reaction in toluene was performed under slightly different conditions: the oxime was used in excess and the homoallylic alcohol as the limiting reagent (entry 2). Under these conditions the yield could be slightly improved (52% vs. 45%), nonetheless, it remained below a satisfactory level. However, when the cycloaddition was conducted in CH_2Cl_2 with the oxime as the limiting reagent and excess homoallylic alcohol, the yield obtained was 67%, and the diastereomeric ratio of 8:1 remained unchanged (entry 3).

Table 2. Nitrile oxide cycloadditions with (*S*)-2-methyl-3-butenol (**16**).



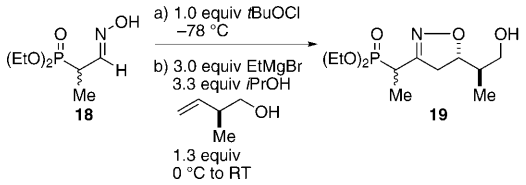
(2)

Entry	equiv oxime	equiv *t*BuOCl	equiv **16**	Solvent	dr[a]	Yield [%][b]
1	1.0	1.0	1.3	toluene	8:1	45
2	1.3	1.3	1.0	toluene	7:1	52
3	1.0	1.3	1.3	CH_2Cl_2	8:1[c]	67

[a] Determined by 1H NMR analysis of the crude material. [b] Isolated yield. [c] Determined after filtration over silica gel.

The phosphonate in cycloadduct **19** provides an excellent starting point for further synthetic transformations.[6] When oxime **18**[6] was chlorinated in either toluene or CH_2Cl_2, and the in situ prepared hydroximinoyl solution, as generally done, was added slowly to the magnesium alkoxides solution, the isolated yields of the corresponding cycloadduct were less then desirable—38 and 36%, respectively—while the diastereoselectivity was excellent (12:1 and 11:1) (Table 3, entries 1 and 2). The hydroximinoyl chloride **20**, derived from oxime **18**, can be isolated and purified before being used in nitrile oxide cycloadditions [Eq. (4)].[6] With 1 equiv of the purified hydroximinoyl chloride and 1.3 equiv of (*S*)-2-methyl-3-butenol in either toluene or CH_2Cl_2, the corresponding cycloadduct **19** could be isolated in 68 and 71% yield, respectively (Table 4), a significant improvement compared to the conditions with the in situ generated hydroximinoyl chloride, and diastereoselectivity of 8:1 and 12:1, respectively.

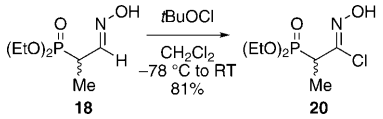
Table 3. Reaction with oxime **18**.



(3)

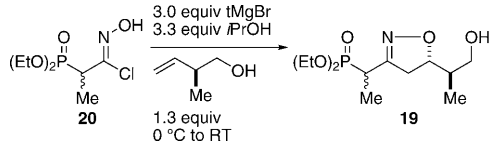
Entry	Solvent	dr[a]	Yield [%][b]
1	toluene	12:1	38
2	CH_2Cl_2	11.1	36

[a] Determined after derivatization with benzaldehyde, see Equation (6). [b] Isolated yield.



(4)

Table 4. Reaction with hydroximinoyl chloride **20**.

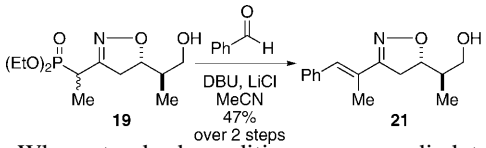


(5)

Entry	Solvent	dr[a]	Yield [%][b]
1	toluene	8:1	68
2	CH_2Cl_2	13.1	71

[a] Determined after derivatization with benzaldehyde, see Equation (6). [b] Isolated yield.

As a consequence of overlapping peaks in the ^{1}H NMR as well as in the ^{13}C NMR spectra of cycloadduct **19**, the diastereoselectivity could not be determined from these data. Condensation of the unpurified material with benzaldehyde, LiCl and DBU in MeCN afforded alkene **21** as a single olefin diastereomer [determined by ^{1}H NMR, Eq. (6)], as expected from the use of a stabilized phosphonate reagent.[5a]

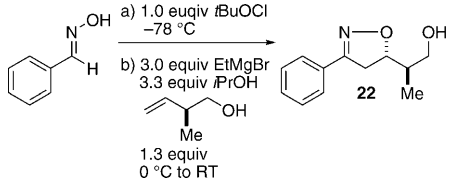


(6)

When standard conditions were applied to the reaction with benzaldehyde oxime[17] in toluene, the isolated yield of 38% was poor, however, the observed diastereoselectivity was excellent (14:1) (Table 5, entry 1). We suspected that part of the problem could be found in the chlorination step. In a next experiment, the chlorination was carried out in CH_2Cl_2 instead of toluene, with 1.1 equiv of *t*BuOCl instead of 1 equiv and at 0°C instead of −78°C. After 30 min the hydroximinoyl chloride could be isolated as an off-white solid. Excess *t*BuOCl was removed under high vacuum and the crude product was directly used without further purifica-

tion in the next step. In the reaction with the isolated hydroximinoyl chloride in toluene, the yield could be improved from 38 to 56%, whereas the diastereoselectivity was found to be slightly lower (10:1 vs. 14:1) (entry 2). When the cycloaddition reaction with the previously isolated hydroximinoyl chloride was carried out under otherwise standard conditions in CH_2Cl_2, the resulting isoxazoline could be isolated in 87% yield, while the diastereoselectivity was found to be 7:1 (entry 3).

Table 5. Reaction with benzonitrile oxide.

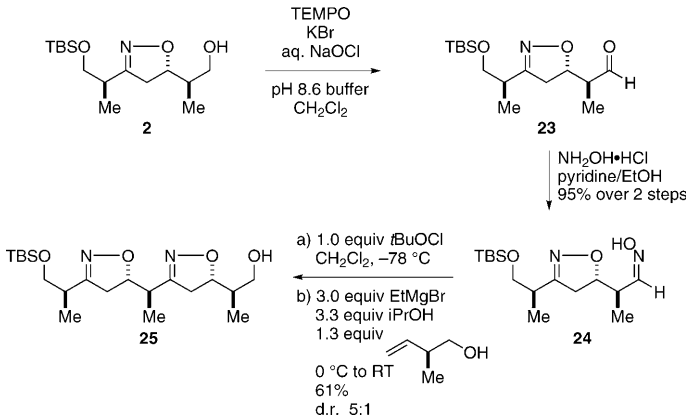


(7)

Entry	equiv *t*BuOCl	Solvent	dr[a]	Yield [%][b]
1	1.0	toluene	14:1	38
2	1.1[c]	toluene[d]	10:1	56
3	1.1[c]	CH_2Cl_2	7:1	87

[a] Determined by ^{1}H NMR analysis of the crude material. [b] Isolated yield. [c] Isolation of the hydroximinoyl chloride. [d] Chlorination in CH_2Cl_2.

The primary alcohol in cycloadducts arising from 1,3-dipolar reactions between nitrile oxides and homoallylic alcohols provides a very useful starting point for further functionalization. The 1,3-relationship generally found in polyketides is—unlike in products arising from nitrile oxide cycloadditions with allylic alcohols—already installed after the cycloaddition reaction. Accordingly, the primary alcohol in diastereomerically pure cycloadduct **2**[18] was conveniently oxidized with the biphasic NaOCl/TEMPO/KBr system[19] to the corresponding aldehyde **23**. Further reaction of the unpurified aldehyde with hydroxylamine hydrochloride in a pyridine/EtOH mixture allowed access to oxime **24** in 95% yield over two steps (Scheme 1). When the 1,3-dipolar cycloaddition was performed with diastereomerically pure oxime **24** and 1.3 equiv of (*S*)-2-methyl-3-butenol under the optimized conditions, the reaction proceeded in 61% yield to afford bis(isoxazoline) **25** in a dr of 5:1. The diastereomers could easily be separated by flash chromatography. Compound **25** is a masked pentaketide adduct comprised of alternating propionate and acetate subunits. It includes five stereocenters, is densely functionalized and might serve as a useful building block for polyketide synthesis. The primary alcohol, as well as the primary silyl ether, provide the necessary functionality for further chemical transformations. The two isoxazolines in **25** can potentially be cleaved to the corresponding β-hydroxy ketones and subsequently further elaborated to the corresponding *syn*- or *anti*-diols.[20]

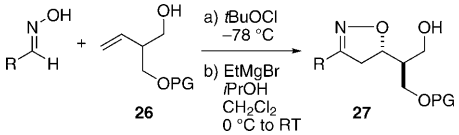


Scheme 1. Synthesis of a small polyketide fragment.

During the course of our studies, magnesium-mediated nitrile oxide cycloadditions with homoallylic alcohols have been communicated.[21] Although the influence of different substituents on the homoallylic alcohol was examined, these studies were limited to the use of benzonitrile oxide. Aliphatic nitrile oxides, known to be more susceptible towards dimerization, were not investigated.

The limitations of the Kanemasa nitrile oxide cycloaddition with homoallylic alcohols were found to preclude the use of 1,2-disubstituted and secondary homoallylic alcohols. In both cases the isolated yields of the desired cycloadducts were poor due to the diminished reactivity of the dipolarophile. Moreover, in reactions with secondary homoallylic alcohols, both *syn*- and *anti*-diastereomers were recovered from the reaction mixture in nearly equal amounts.

Magnesium-mediated nitrile oxide cycloadditions with monoprotected homoallylic diols: Like other isoxazolines derived from diastereoselective nitrile oxide cycloadditions with allylic and homoallylic alcohols, cycloadducts **27**, arising from monoprotected homoallylic diols **26**, serve as useful, densely functionalized building blocks for polyketide synthesis [Eq. (8)].

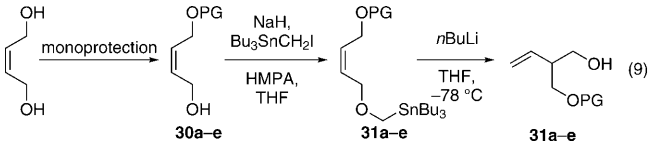


(8)

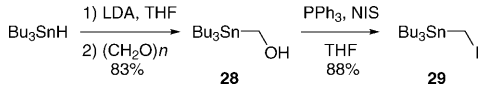
The monoprotected homoallylic diols were readily prepared as illustrated in Table 6 via a Wittig rearrangement.[22] For the synthesis of iodomethyltributyltin **29**, tributyltinhydride was in a first step alkylated with paraformaldehyde to afford hydroxymethyltributyltin **28** in 83% yield. The primary alcohol was readily converted via Appel reaction[23] to the corresponding iodide in 88% yield (Scheme 2).[24]

The precursors for the Wittig rearrangement were prepared in excellent yields by *O*-alkylation of 2 equiv of the monoprotected (*Z*)-butenediol[25] with iodomethyltributyltin in a THF/HMPA mixture at RT (Table 6). The presence of HMPA was crucial to achieve high yields in this reaction. Wittig rearrangement using 3 equiv of *n*BuLi at −78°C in THF smoothly afforded the desired monoprotected homoallylic alcohols. Although Still and co-workers reported that

Table 6. Synthesis of monoprotected homoallylic diols.



Entry	PG	Product	Isolated yield [%]	Product	Yield [%][a]	Product	Isolated yield [%]
1	Tr	**30a**	96	**31a**	86	**32a**	83
2	TBDPS	**30b**	90	**31b**	88	**32b**	63
3	TIPS	**30c**	87	**31c**	93	**32c**	73
4	TBS	**30d**	89	**31d**	89	**32d**	78
5	TES	**30e**	58	**31e**	53	**32e**	43



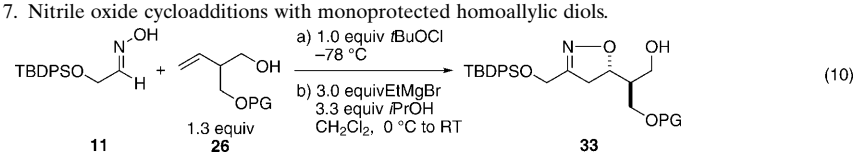
Scheme 2. Preparation of **29**.

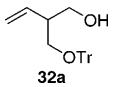
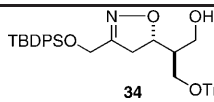
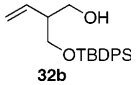
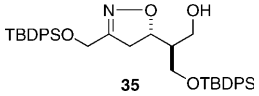
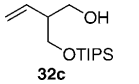
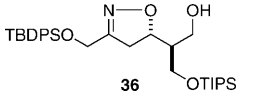
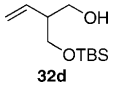
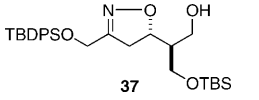
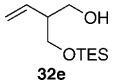
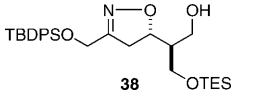
these two reactions can be carried out in a one-pot procedure,[26] we found it to be advantageous to isolate the stannane intermediates.

In an initial series of experiments the cycloaddition between the nitrile oxide derived from oxime **11** and differently monoprotected homoallylic diols **26** was examined. The results in Table 7 clearly reveal the dependence of the diastereomeric ratio in the corresponding cycloadduct on the chosen protective group in the dipolarophile. With sterically demanding protective groups, such as Tr or TBDPS, excellent diastereoselectivities up to 21:1 could be obtained. However, with less bulky substituents, such as TBS or TES ethers, the observed diastereoselectivity decreased (10:1, entry 4, and 6:1, entry 5). The yields of the reaction were generally high (73% to 85%) except for the reaction with mono-TES-protected diol **32e** (53%) (entry 5). The lower yield in the reaction with TES derivative **32e** might be due to the relative instability of this silyl ether under the reaction conditions. The diastereoselectivities of nitrile oxide cycloadditions with monoprotected homoallylic diols were generally determined by integration of the differently shifted diastereotopic signals for the hydrogen atom at C_5 of the isoxazoline in the crude ^{1}H NMR spectrum or—in cases when this method could not be applied due to overlapping peaks—by comparison of the differently shifted diastereotopic signals of C_5 of the isoxazoline in the crude ^{13}C NMR spectrum after prolonged measurement times.

In a similar fashion the cycloaddition with optically active oxime **1** as nitrile oxide precursor and different monoprotected homoallylic diols was examined. Again, as the results summarized in Table 8 indicate, the same trends as outlined above could be observed. Cycloadducts arising from monoprotected homoallylic diols with bulkier protective groups showed better *anti*/*syn* diastereoselectivity than their counterparts derived from dipolarophiles with less sterically demanding substituents. As in the above described series of experiments, the yields of the 1,3-dipolar reactions were all good (79 to 86%). With trityl ether **32a** the cycloaddition was performed both in CH_2Cl_2 and toluene under otherwise identical conditions. By employing the chlorinated solvent both yield (86 vs. 79%) and diastereoselectivity (25:1 vs. 12:1) were superior compared to the reaction in toluene (entries 1 and 2). The diastereoselectivity of cycloadduct **40** was determined by ^{1}H NMR analysis of the mixture. As in similar cases with silicon protective groups described above, this method of analysis could not be applied to the other cycloaddition products in Table 8 due to overlapping signals. The diastereomeric ratios of the cycloadducts given in entries 3 and 4 were determined after protection of the crude primary alcohols as the corresponding trityl ethers. In these derivatives, the differently shifted diastereotopic signals of the hydrogen atom at C_5 of the isoxazoline in the ^{1}H NMR spectrum allowed for the determination of the diastereoselectivity of the previous cycloaddition.[27] For the determination of both yield and diastereoselectivity of these cycloaddition re-

Table 7. Nitrile oxide cycloadditions with monoprotected homoallylic diols.

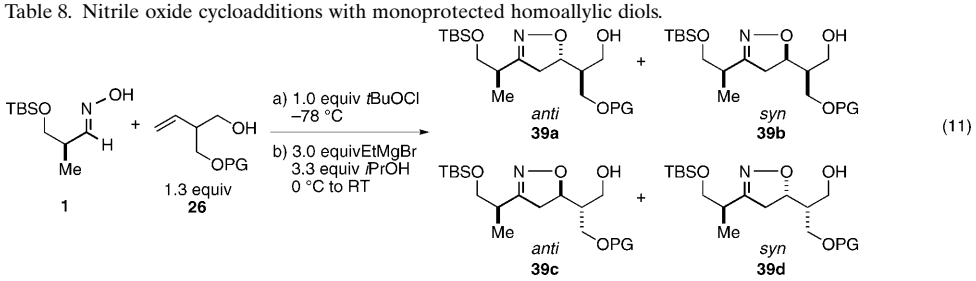


Entry	Homoallylic alcohol	Cycloadduct	dr *anti*/*syn*[a]	Yield [%][b]
1	 **32a**	 **34**	19:1[c]	82
2	 **32b**	 **35**	21:1	85
3	 **32c**	 **36**	14:1	73
4	 **32d**	 **37**	10:1	78
5	 **32e**	 **38**	6:1	53

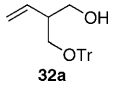
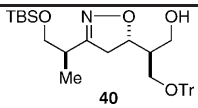
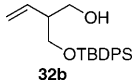
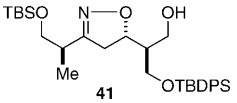
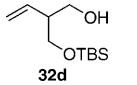
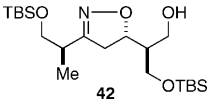
[a] Determined by ^{13}C NMR analysis of the crude material. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude material.

actions, equal amounts of the crude material were used for derivatization and purification. Cycloadducts arising from reactions with monoprotected homoallylic alcohols inherit an *anti*-relationship (see below). A simple orthogonal protection–deprotection of the primary alcohols would allow ready access to the corresponding *syn*-diastereomers.

Table 8. Nitrile oxide cycloadditions with monoprotected homoallylic diols.



(11)

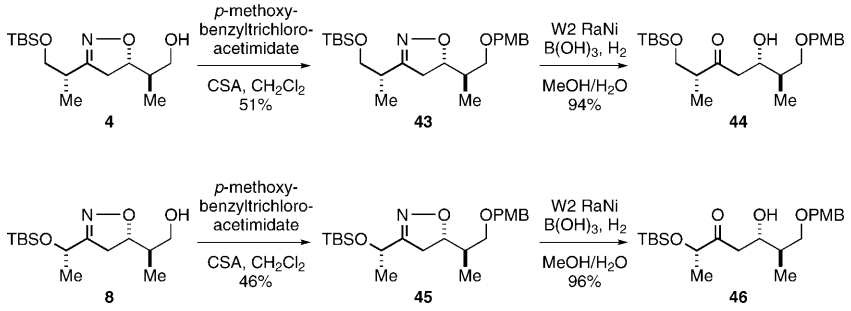
Entry	Homoallylic alcohol	Solvent	Cycloadduct	dr *anti*/*syn*[a] **39a+39c/39b+39d**	Yield [%][b]
1	 **32a**	CH_2Cl_2	 **40**	25:1	86
2		toluene		12:1	79
3	 **32b**	CH_2Cl_2	 **41**	20:1[c]	83
4	 **32d**	CH_2Cl_2	 **42**	6:1[c]	84

[a] Determined by ^{1}H NMR analysis of the crude material. [b] Isolated yield of combined diastereomeric products. [c] Determined by ^{1}H NMR analysis of the material after protection of the primary alcohol as trityl ether.

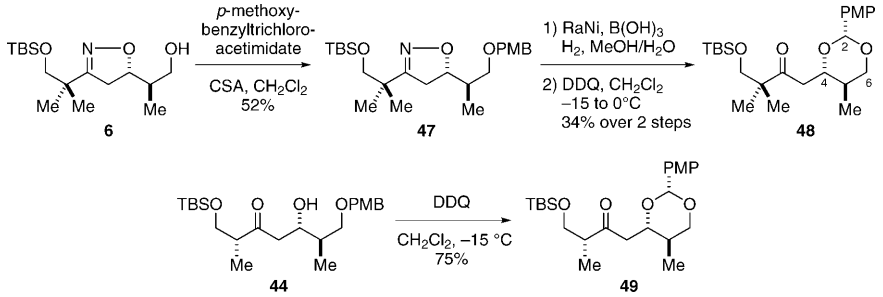
Isoxazoline reduction to β-hydroxyketones: The utility of cycloadducts arising from reactions with homoallylic alcohols as latent aldol adducts and polyketide building blocks was demonstrated by their straightforward transformation into the corresponding β-hydroxy ketones. The N–O bond cleavage of the isoxazoline can be effected by reduction with Raney nickel and subsequent hydrolysis of the resulting imine to afford the corresponding β-hydroxy ketone.[28] The primary alcohols in cycloadducts **4** and **8** were protected as their *p*-methoxybenzyl ethers under mild conditions. Reduction with Raney nickel, accompanied by boric acid, in a methanol/water mixture under hydrogen atmosphere lead to the desired β-hydroxy ketones **44** and **46** in 94 and 96% yield (Scheme 3).

Confirmation of the relative configuration: The primary alcohols in isoxazolines **6** and **4** were protected as *p*-methoxybenzyl ethers under mild conditions (Schemes 3 and 4). Reductive N–O bond cleavage and subsequent imine hydrolysis, followed by DDQ oxidation, afforded *p*-methoxybenzylidene acetals **48** and **49**. Isoxazolines **6** and **4** were both submitted to the reaction conditions as a mixture of diastereomers. The same diastereomeric ratios were observed again in the corresponding acetals. NOE analysis with selective irradiation on the major diastereomer revealed an *anti*-relationship. Strong NOEs were observed between all three hydrogen atoms at C_2, C_4 and C_6, providing strong evidence for this relative configuration as illustrated in Figure 1.

In a second approach to confirm the *anti*-diastereoselectivity of magnesium-mediated nitrile oxide cycloadditions with homoallylic alcohols, cycloadduct **12** was converted into known isoxazoline **52**



Scheme 3. Reductive opening of cycloadducts.



Scheme 4. Structural determination of relative configuration.

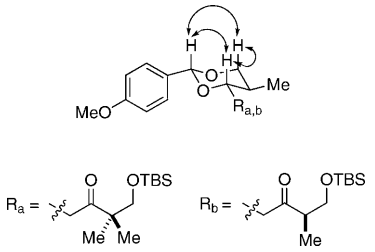
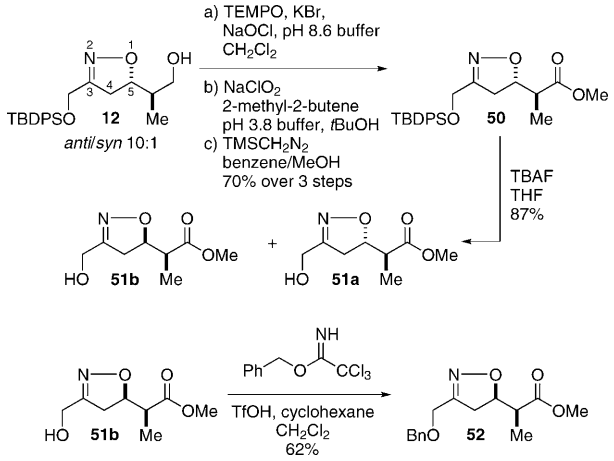


Figure 1. Observation of strong NOEs in *p*-methoxybenzylidene acetals **48** and **49**.

(Scheme 5). Panek et al. had previously established the relative stereochemistry for this class of compounds by derivatization and subsequent coupling constant analysis.[29] The primary alcohol in isoxazoline **12** was conveniently oxidized to the corresponding aldehyde with the biphasic TEMPO/NaOCl/KBr system.[19] Lindgren oxidation[30] to the carboxylic acid, followed by methylation with $TMSCH_2N_2$ afforded methyl ester **50** in 70% yield over three steps. Deprotection of the silyl ether with TBAF in THF lead to alcohol **51** in 87% yield. At this point the diastereomers were separated and the synthesis was continued with exclusively the minor *syn*-isomer **51b**. Protection of the primary alcohol as benzyl ether provided isoxazoline **52**. The spectral characteristics (^1H and ^{13}C NMR, HRMS) of isoxazoline **52** were in all respects identical to those previously reported, providing further strong evidence for the *syn*-relationship in this minor diastereomer and therefore for an *anti*-relationship in the major diastereomer.



Scheme 5. Structural confirmation of relative configuration.

Kociolek and Hongfa assigned the relative configuration of the products of 1,3-dipolar cycloadditions between nitrile oxides and homoallylic alcohols as *syn*.[21] Their assignment of the relative stereochemistry of β-hydroxy isoxazolines is based on the comparison of the chemical shifts of the C_5 hydrogen atom in the ^1H NMR spectrum with analogous β-methyl ester isoxazolines, compounds described by Panek et al.[29] who demonstrated that the chemical shift of the C_5 hydrogen atom of the *syn*-diastereomer of the examined β-methyl ester isoxazolines occurs at slightly higher field than the corresponding signal of the *anti*-diastereomer. In ^1H NMR spectra of β-hydroxy isoxazolines we found the major diastereotopic signal for the C_5 hydrogen atom shifted slightly upfield compared to the analogous minor diastereotopic signal. As is illustrated in Scheme 5, β-hydroxy isoxazoline **12** was converted to the corresponding methyl ester. After this transformation, the chemical shifts of the C_5 hydrogen atoms of the heterocycle had inverted; the signal of the major diastereomer occurred now more downfield than the corresponding signal of the minor diastereomer. We therefore propose an *anti*-diastereoselectivity of magnesium-mediated nitrile oxide cycloadditions with homoallylic alcohols.

Model for the *anti*-diastereoselectivity: A rationale for the observed *anti*-diastereoselectivity arises from the comparison of the possible transition states depicted in Figure 2. In

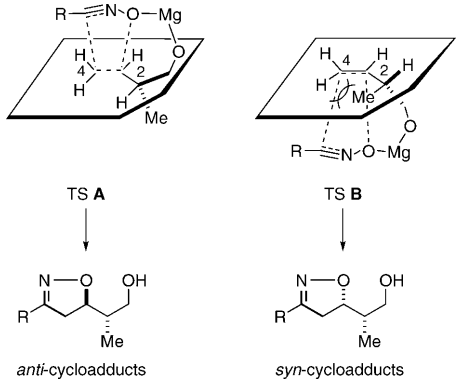


Figure 2. Proposed transition states leading to *anti*- or *syn*-cycloadducts.

analogy to the generally accepted transition state model for Kanemasa nitrile oxide cycloadditions with allylic alcohols,[12] the comparison of the two chelated transitions states provides a possible explanation for the observed diastereoselectivity in 1,3-dipolar reactions between nitrile oxides and homoallylic alcohols. Transition state **B** (TS **B**) suffers from a somewhat higher energy of formation as a consequence of 1,3-allylic interactions (H ↔ Me) which are absent in transition state **A** (TS **A**). The reaction is thus suggested to proceed through a transition-state similar to TS **A**, resulting in the observed preference for the formation of the *anti*-diastereomer. However, the energetic difference between the two reaction transition states leading to *anti*- and *syn*-products cannot solely arise from the energetic differential arising from simple analysis of allylic interactions, which can be estimated to be at best as 0.5 kcal mol^{-1}. We suggest that the eclipsing interaction between C-2 Me and C-4 is magnified as C-4 undergoes rehybridization from Csp^2 in the starting material to C_{sp^3} in the product, wherein the costly interaction can be estimated by comparison of eclipsed gauche butane ($E = 4.5$–6 kcal mol^{-1}).

Conclusion

We have described diastereoselective magnesium-mediated, hydroxyl-directed nitrile oxide cycloadditions with homoallylic alcohols and monoprotected homoallylic diols. These reactions represent an alternative approach to masked polyketide building blocks. While the reaction is *anti*-diastereoselective, the corresponding *syn*-diastereomers of reactions with monoprotected homoallylic diols are likewise accessible by a simple orthogonal protection-deprotection sequence. The value of the presented nitrile oxide cycloaddition approach to polyketide building blocks was demonstrated by the ready transformation of different isoxazolines to the corresponding β-hydroxy ketones. The observed *anti*-diastereoselectivity was confirmed by NOE studies as well as by the conversion of a cycloadduct into a previously described isoxazoline, for which the relative configuration had been established.

Experimental Section

General methods: All non-aqueous reactions were carried out using oven-dried (135 °C) or flame-dried glassware under a positive pressure of dry argon unless otherwise stated. Tetrahydrofuran, diethyl ether, toluene, acetonitrile, and methylene chloride were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content <30 ppm, Karl-Fischer titration).[31] Pyridine was distilled from KOH under an atmosphere of dry nitrogen. *n*-Butyl lithium was titrated with *s*BuOH/phenanthroline.[32] All other commercially available reagents were used without further purification. The reactions were all magnetically stirred and monitored by thin-layer chromatography using Merck silica gel 60 F_{254} plates and visualized using ceric ammonium molybdate or potassium permanganate stain. Chromatographic purification of products (flash chromatography) was performed on E. Merck silica gel 60 (230–400 mesh) using a forced flow of eluant at 0.3–0.5 bar.[33] Concentration under reduced pressure was performed by rotary evaporation at 30 °C at the appropriate pressure, unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated. Melting points were measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected. Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]^T_D$, concentration (g per 100 mL), and solvent. NMR spectra were recorded either on a Varian Mercury 300 spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C acquisitions, respectively, or on a Bruker DRX500 spectrometer operating at 500 MHz for ^1H acquisitions. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) for ^1H, and (δ 77.0) ^{13}C. All ^{13}C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz. IR spectra were recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm^{-1}). Mass spectra were recorded by the MS service at ETH Zürich. EI-MS (*m*/*z*): VG-TRIBRID spectrometer. MALDI-MS and ESI-MS (*m*/*z*): IonSpec Ultima Fourier Transform Mass Spectrometer. Elemental analyses were performed at the Mikrolabor der ETH Zürich.

(*R*)-2-{(*S*)-3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (2): To a solution of oxime **1** (109 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59.0 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting deep blue solution was stirred 1 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 60 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) provided isoxazoline **2** (125 mg, 83 %, dr 7:1 by integration of the signals at 4.40 ppm (major) and 4.65 ppm (minor) in the crude ^1H NMR spectrum) as a clear, colorless oil. $[\alpha]^{34}_D$ (c = 0.50, $CHCl_3$) = +37.3°; ^1H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.65* (ddd, 1H, J = 12.5, 8.1, 4.4 Hz), 4.40 (ddd, 1H, J = 10.3, 8.4, 8.4 Hz), 3.71–3.58 (m, 2H), 3.68 (d, 2H, J = 6.2 Hz), 3.02 (dd, 1H, J = 17.8, 10.9 Hz), 3.00* (dd, 1H, J = 17.1, 10.6 Hz), 2.85* (dd, 1H, J = 16.8, 8.1 Hz), 2.82–2.71 (m, 1H), 2.79 (dd, 1H, J = 17.1, 8.7 Hz), 2.33 (brs, 1H), 1.95–1.82 (m, 1H), 1.17 (d, 3H, J = 7.2 Hz), 1.14* (d, 3H, J = 7.1 Hz), 0.95* (d, 3H, J = 7.2 Hz), 0.90 (d, 3H, J = 6.8 Hz), 0.90* (s, 9H), 0.89 (s, 9H), 0.06* (s, 6H), 0.05 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 161.8, 84.0, 81.5*, 66.4, 66.2, 65.0*, 40.4, 40.3, 39.7*, 38.2*, 36.0, 26.1, 18.4, 14.8, 13.5, 11.4*, −5.2 ppm; IR (thin film): $\tilde{\nu}$ = 3428, 2957, 2930, 2884, 2858, 2740, 2710, 2243, 1621, 1472, 1434, 1390, 1362, 1298, 1257, 1213, 1182, 1097, 1046, 1007, 974, 939, 909, 838, 815, 777, 734, 678, 646 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{31}NO_3Si$: C 59.76, H 10.36, N 4.65; found: C 59.67, H 10.41, N 4.82; HRMS (MALDI): *m*/*z*: calcd for $C_{15}H_{32}NO_3Si$ $[M+H]^+$: 302.2146; found: 302.2142.

(*R*)-2-{(*S*)-3-[(*S*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (4): To a solution of oxime **3** (109 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59.0 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting deep blue solution was stirred 1 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 60 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 20 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) provided isoxazoline **4** (128 mg, 85 %, dr 9:1 by integration of the signals at 4.41 ppm (major) and 4.64 ppm (minor) in the crude ^1H NMR spectrum) as a clear, colorless oil. $[\alpha]^{25}_D$ (c = 0.98, $CHCl_3$) = +36.0°; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.41 (ddd, 1H, J = 10.3, 8.1, 8.1 Hz), 3.69–3.56 (m, 4H), 3.03 (dd, 1H, J = 16.8, 10.3 Hz), 2.84–2.72 (m, 1H), 2.78 (dd, 1H, J = 16.8, 7.8 Hz), 2.41 (brs, 1H), 1.94–1.81 (m, 1H), 1.14 (d, 3H, J = 7.2 Hz), 0.88 (d, 3H, J = 6.9 Hz), 0.87 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 83.7, 66.1, 66.0, 40.2, 39.6, 35.7, 25.9, 18.3, 14.6, 13.4, 5.3, −5.4 ppm; IR (thin film): $\tilde{\nu}$ = 3421, 2957, 2930, 2884, 2858, 2739, 2360, 2341, 1622, 1472, 1463, 1389, 1362, 1297, 1257, 1098, 1045, 1007, 972, 939, 897, 838, 815, 782, 754, 678, 668 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{31}NO_3Si$: C 59.76, H 10.36, N 4.65; found: C 59.58, H 10.16, N 4.85; HRMS (MALDI): *m*/*z*: calcd for $C_{15}H_{31}NO_3SiNa$ $[M+Na]^+$: 324.1965; found: 324.1962.

(*R*)-2-{(*S*)-3-[2-(*tert*-Butyldimethylsilanyloxy)-1,1-dimethylethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (6): To a solution of oxime **5** (118 mg,

0.500 mmol, 1.00 equiv) in toluene (5 mL) at −78 °C was added *t*BuOCl (59.0 μL, 0.500 mmol, 1.00 equiv) dropwise over 15 min. The solution was stirred at −78 °C for 4 h. After 1 h the solution was still colorless and turned light blue and cloudy over the course of 4 h. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in toluene (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. At this time, about 2/3 of the cloudy hydroximinoyl chloride mixture was added to the reaction dropwise via cannula over 60 min. Then the light blue, turbid hydroximinoyl chloride mixture was allowed to warm to RT for 1 min, whereupon it turned deep blue and clear. The solution was cooled again to −78 °C and the addition via cannula was continued over 30 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 14 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. After filtration over silica gel (hexane/EtOAc 3:1) isoxazoline **6** (141 mg, 89%, dr 4:1 by integration of the signals at 4.39 ppm (major) and 4.64 ppm (minor) in the ^{1}H NMR spectrum) was isolated as a pale, colorless oil. $[\alpha]_D^{30}$ (c = 1.08, $CHCl_3$) = +17.1°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.64* (ddd, 1H, J= 12.8, 8.4, 4.4 Hz), 4.39 (ddd, 1H, J=10.0, 8.1, 8.1 Hz), 3.74–3.3.56 (m, 2H), 3.51* (s, 2H), 3.50 (s, 2H), 3.05 (dd, 1H, J=16.8, 10.3 Hz), 3.02* (dd, 1H, J=16.8, 10.6 Hz), 2.85* (dd, 1H, J=16.8, 8.4 Hz), 2.80 (dd, 1H, J=16.8, 8.4 Hz), 2.37 (dd, 1H, J=7.5, 4.1 Hz), 1.95–1.81 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H), 0.93* (d, 3H, J=7.2 Hz), 0.89 (s, 9H), 0.88 (d, 3H, J= 7.2 Hz), 0.05 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 164.6, 164.3*, 83.9, 81.5*, 70.9, 66, 0, 65.1*, 40.2, 39.9*, 39.2, 38.6, 38.2*, 26.0, 23.0, 18.4*, 13.3, 11.3*, −5.4 ppm; IR (thin film): $\tilde{\nu}$ = 3414, 2957, 2931, 2886, 2858, 2246, 1611, 1472, 1392, 1363, 1282, 1254, 1217, 1186, 1099, 1046, 1006, 939, 838, 815, 757, 668 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{33}NO_3Si$: C 60.91, H 10.54, N 4.44; found: C 61.16, H 10.71, N 4.36; HRMS (MALDI): m/z: calcd for $C_{16}H_{33}NO_3SiNa$ $[M+Na]^+$: 338.2122; found: 338.2121.

(*R*)-2-{(*S*)-3-[(*S*)-1-(*tert*-Butyldimethylsilanyloxy)-ethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (8): To a solution of oxime **7** (102 mg, 0.500 mmol, 1.00 equiv) in toluene (5 mL) at −78 °C was added *t*BuOCl (59.0 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The mixture turned yellow, then green and finally blue over the course of 15 min and was stirred total 105 min at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in toluene (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. At this time, the hydroximinoyl chloride in toluene was added to the reaction dropwise via cannula over 2 h, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) provided isoxazoline **8** (114 mg, 82%, dr 6:1 by integration of the signals at 83.9 ppm (major) and 81.7 ppm (minor) in the crude ^{13}C NMR spectrum (12 h measurement time)) as a clear, colorless oil. $[\alpha]_D^{28}$ (c = 0.99, $CHCl_3$) = −10.9°; ^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.73 (q, 1H, J=6.4 Hz), 4.67* (ddd, 1H, J=13.2, 8.6, 4.5 Hz), 4.46 (ddd, 1H, J=10.4, 8.3, 8.3 Hz), 3.70–3.59 (m, 2H), 3.07 (dd, 1H, J= 17.1, 10.4 Hz), 3.05* (dd, 1H, J=17.4, 10.9 Hz), 2.84* (dd, 1H, J=17.3, 8.6 Hz), 2.81 (dd, 1H, J=17.2, 8.3 Hz), 2.15 (brs, 1H), 1.94–1.86 (m, 1H), 1.35 (d, 3H, J=6.451 Hz), 0.95* (d, 3H, J=6.9 Hz), 0.92 (d, 3H, J=7.0 Hz), 0.89 (s, 9H), 0.88* (s, 9H), 0.10 (s, 3H), 0.10* (s, 3H), 0.07 (s, 3H), 0.07* ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 162.1, 83.9, 81.7*, 65.8, 65.1*, 64.7*, 64.5, 40.3, 40.0*, 36.6, 36.0*, 25.9, 22.4, 18.2*, 13.0, 11.3*, −4.6, −4.7 ppm; IR (thin film): $\tilde{\nu}$ = 3435, 2957, 2931, 2887, 2858, 1627, 1472, 1464, 1408, 1389, 1372, 1362, 1340, 1312, 1294, 1258, 1216, 1116, 1086, 1026, 954, 881, 834, 778, 664 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{29}NO_3Si$: C 58.49, H 10.17, N 4.87; found: C 58.56, H 10.41, N 5.05; HRMS (MALDI): m/z: calcd for $C_{14}H_{29}NO_3SiNa$ $[M+Na]^+$: 310.1809; found: 310.1813.

(*R*)-2-{(*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-ethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (10): To a solution of oxime **9** (102 mg, 0.500 mmol, 1.00 equiv) in toluene (5 mL) at −78 °C was added *t*BuOCl (59.0 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The mixture turned yellow, then green and finally blue over the course of 15 min and was stirred total 105 min −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in toluene (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. At this time, the hydroximinoyl chloride in toluene was added to the reaction dropwise via cannula over 2 h, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) provided isoxazoline **10** (119 mg, 83%, dr 5:1 by integration of the signals at 84.0 ppm (major) and 81.6 ppm (minor) in the crude ^{13}C NMR spectrum (12 h measurement time)) as a clear, colorless oil. $[\alpha]_D^{26}$ (c = 1.27, $CHCl_3$) = +59.5°; ^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.73 (q, 1H, J=6.4 Hz), 4.70* (ddd, 1H, J=10.9, 8.5, 4.4 Hz), 4.45 (ddd, 1H, J=10.3, 8.6, 8.6 Hz), 3.71–3.59 (m, 2H), 3.07 (dd, 1H, J=17.5, 10.3 Hz), 3.06* (dd, 1H, J=17.8, 10.5 Hz), 2.86* (dd, 1H, J=17.3, 8.4 Hz), 2.79 (dd, 1H, J=17.1, 8.8 Hz), 2.14 (brs, 1H), 1.95–1.86 (m, 1H), 1.36* (d, 3H, J=6.4), 1.35 (d, 3H, J=6.5 Hz), 0.95* (d, 3H, J= 6.9 Hz), 0.92 (d, 3H, J=6.4 Hz), 0.90* (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 162.3, 161.8*, 84.0, 81.6*, 65.8, 65.1*, 64.6, 64.5*, 40.3, 40.0*, 36.9, 35.8*, 25.9, 22.4, 18.2, 13.2, 11.1*, −4.6, −4.7 ppm; IR (thin film): $\tilde{\nu}$ = 3414, 2957, 2931, 2887, 2859, 1680, 1627, 1472, 1464, 1409, 1389, 1372, 1362, 1339, 1313, 1294, 1259, 1217, 116, 1094, 1042, 1025, 953, 880, 835, 813, 778, 757, 667 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{29}NO_3Si$: C 58.49, H 10.17, N 4.87; found: C 58.47, H 10.24, N 5.15; HRMS (MALDI): m/z: calcd for $C_{14}H_{29}NO_3SiNa$ $[M+Na]^+$: 310.1809; found: 310.1811.

(*R*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-4,5-dihydroisoxazol-5-yl]-propan-1-ol (12): To a solution of oxime **11** (314 mg, 1.00 mmol, 1.00 equiv) in toluene (10 mL) at −78 °C was added *t*BuOCl (118 μL, 1.00 mmol, 1.00 equiv) dropwise over 15 min. The mixture turned yellow, then green and finally blue over the course of 2.5 h and was stirred total 2.5 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 1.00 mL, 3.00 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (112.0 mg, 1.30 mmol, 1.30 equiv) and *i*PrOH (252 μL, 3.30 mmol, 3.30 equiv) in toluene (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. At this time, the hydroximinoyl chloride in toluene was added to the reaction dropwise via cannula over 2 h 15 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 16 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (30 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1 to 2:1) provided isoxazoline **12** (345 mg, 87%, dr 10:1 by integration of the signals at 84.1 ppm (major) and 81.9 ppm (minor) in the crude ^{13}C NMR spectrum

(12 h measurement time)) as a clear, slightly yellow oil. $[\alpha]_D^{30}$ (c = 0.46, $CHCl_3$) = +22.8°; ^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.67–7.64 (m, 4H), 7.49–7.38 (m, 6H), 4.71* (ddd, 1H, J = 10.9, 8.5, 4.5 Hz), 4.48 (ddd, 1H, J = 10.4, 8.4, 8.4 Hz), 4.44 (s, 2H), 3.70–3.59 (m, 2H), 3.08 (dd, 1H, J = 17.1, 10.4 Hz), 3.07* (dd, 1H, J = 17.2, 10.9 Hz), 2.87* (dd, 1H, J = 17.3, 8.5 Hz), 2.80 (dd, 1H, J = 17.2, 8.6 Hz), 2.17 (brs, 1H), 1.94–1.86 (m, 1H), 1.11* (s, 9H), 1.07 (s, 9H), 0.95* (d, 3H, J = 6.9 Hz), 0.91 ppm (d, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 158.4, 158.2*, 135.5, 132.6, 130.0, 127.8, 84.1, 81.9*, 65.7, 65.0*, 59.3, 40.2, 40.0*, 38.8, 38.1*, 26.9, 19.4, 13.1, 11.2* ppm; IR (thin film): $\tilde{\nu}$ = 3436, 3071, 3041, 2947, 2932, 2885, 2858, 2363, 1628, 1589, 1472, 1428, 1390, 1363,, 1334, 1301, 1259, 1211, 1113, 1083, 1000, 878, 824, 800,, 741, 702 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{31}NO_3Si$: C 69.48, H 7.86, N 3.52; found: C 69.38, H 7.90, N 3.43; HRMS (MALDI): m/z: calcd for $C_{23}H_{31}NO_3SiNa$ $[M+Na]^+$: 420.1965; found: 420.1960.

(*R*)-2-((*S*)-3-Trimethylsilanylethynyl-4,5-dihydroisoxazol-5-yl)-propan-1-ol (14): To a solution of trimethylsilanylpropynal oxime[34] (70.6 mg, 0.500 mmol, 1.00 equiv) in $CHCl_3$ (0.75 mL) at RT was added pyridine (one drop), followed by NCS (66.8 mg, 0.500 mmol, 1.00 equiv). The solution was stirred 1.5 h at RT before Et_2O (10 mL) was added. After filtration over Celite the mixture was concentrated, diluted with Et_2O (10 mL), filtered again over Celite and concentrated. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in toluene (10 mL) at 0°C. The mixture was stirred at 0°C for 1 h. At this time, the previously prepared hydroximinoyl chloride in toluene (5 mL) was added to the reaction dropwise via cannula over 3.5 h, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0°C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 2.5 d the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was filtered over a shot pad of silica gel (hexane/EtOAc 1:2). The analysis of the ^{1}H NMR spectrum (integration of the signals at 4.60 ppm (major) and 4.79 ppm (minor)) revealed a diastereomeric ratio of 5:1. Purification by flash chromatography (hexane/EtOAc 3:1) provided isoxazoline **14** (63 mg, 66%) as a clear, colorless oil. $[\alpha]_D^{26}$ (c = 0.37, $CHCl_3$) = +53.4°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.79* (ddd, 1H, J = 13.8, 9.0, 4.8 Hz), 4.60 (ddd, 1H, J = 17.2, 9.1, 8.1 Hz), 3.68 (brs, 2H), 3.11* (dd, 1H, J = 17.1, 11.1 Hz), 3.10 (dd, 1H, J = 17.0, 10.7 Hz), 2.89* (dd, 1H, J = 17.0, 9.0 Hz), 2.86 (dd, 1H, J = 17.0, 9.1 Hz), 2.01–1.89 (m, 1H), 1.85 (brs, 1H), 0.97* (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 7.0 Hz), 0.24 (s, 9H), 0.23* ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 143.3, 143.2*, 104.6, 104.3*, 93.2*, 93.1, 85.3, 83.5*, 65.3, 64.9*, 41.3, 40.9*, 40.0, 39.8*, 12.8, 11.1*, −0.4 ppm; IR (thin film): $\tilde{\nu}$ = 3401, 2963, 2895, 2361, 2160, 1594, 1555, 1462, 1437, 1321, 1252, 1085, 1045, 995, 921, 846, 761 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{19}NO_2Si$: C 58.63, H 8.50, N 6.22; found: C 58.44, H 8.47, N 6.49; HRMS (MALDI): m/z: calcd for $C_{11}H_{19}NO_2SiNa$ $[M+Na]^+$: 248.1077; found: 248.1073.

(*R*)-2-{(*S*)-3-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (17): To a solution of oxime **15** (102 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78°C was added *t*BuOCl (59.0 μL, 0.500 mmol, 1.00 equiv) dropwise over 15 min. The resulting deep blue solution was stirred 50 min at −78°C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0°C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0°C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 75 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0°C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 48 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3× 15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. After filtration over silica gel (hexane/EtOAc 2:1) isoxazoline **17** (96 mg, 67%, dr 8:1 by integration of the signals at 4.37 ppm (major) and 4.60 ppm (minor) in the crude ^{1}H NMR spectrum) was isolated as a pale, colorless oil. $[\alpha]_D^{28}$ (c = 0.75, $CHCl_3$) = +27.7°; ^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.60* (ddd, 1H, J = 12.9, 8.4, 4.5), 4.37 (ddd, 1H, J = 10.3, 8.3, 8.3 Hz), 3.78 (t, 2H, J = 6.4 Hz), 3.64–3.54 (m, 2H), 2.98 (dd, 1H, J = 17.1, 10.3 Hz), 2.94* (dd, 1H, J = 17.1, 10.8 Hz), 2.80* (dd, 1H, J = 17.2, 8.4 Hz), 2.75 (dd, 1H, J = 17.1, 8.4 Hz), 2.55–2.45 (m, 2H), 2.22 (brdd, 1H, J = 4.0 Hz), 1.87–1.78 (m, 1H), 0.89* (d, 3H, J = 7.0 Hz), 0.85* (s, 9H), 0.84 (d, 3H, J = 6.9 Hz), 0.83 (s, 9H), 0.01 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 157.9, 83.7, 81.5*, 65.9, 64.9*, 60.6, 59.3*, 41.6, 40.2, 39.7*, 31.2, 25.9, 25.7*, 18.2, 13.2, 11.2, −5.3, −5.4 ppm; IR (thin film): $\tilde{\nu}$ = 3413, 2956, 2930, 2884, 2858, 2362, 1626, 1472, 1434, 1388, 1361, 1313, 1257, 1223, 1103, 1049, 1007, 962, 939, 838, 811, 778, 719, 662 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{29}NO_3Si$: C 58.49, H 10.17, N 4.87; found: C 58.56, H 10.27, N 5.05; HRMS (MALDI): m/z: calcd for $C_{14}H_{29}NO_3SiNa$ $[M+Na]^+$: 310.1809; found: 310.1812.

{1-[(*S*)-5-((*R*)-2-Hydroxy-1-methylethyl)-4,5-dihydroisoxazol-3-yl]ethyl}-phosphonic acid diethyl ester (19): EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0°C. The mixture was stirred at 0°C for 30 min. At this time, previously prepared hydroximinoyl chloride **20** (122 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) was added to the reaction dropwise via cannula over 2 h, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0°C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 24 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Half of the crude material was used for the determination of the dr by derivatization with benzaldehyde to alkene **21** (see below). Analysis of the corresponding crude ^{1}H NMR spectrum (integration of the signals at 4.60 ppm (major) and 4.81 ppm (minor)) revealed a diastereomeric ratio of 13:1. Purification of half of the crude material by flash chromatography (15% acetone in EtOAc) provided isoxazoline **19** (52 mg, 71%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.56–4.45 (m, 1H), 4.20–4.09 (m, 4H), 3.72–3.57 (m, 2H), 3.25–2.87 (m, 3H), 2.41–2.33 (m, 1H), 1.96–1.87 (m, 1H), 1.50–1.40 (m, 3H), 1.36–1.31 (m, 6H), 0.93–0.90 ppm (m, 3H, J = 7.2 Hz) (includes both diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 156.8, 85.1, 84.6, 65.7, 62.8, 62.7, 65.7, 62.8, 62.7, 40.2, 33.4, 33.2, 31.5, 31.3, 29.8, 21.6, 21.5, 16.6, 16.5, 13.3, 13.3, 12.4, 12.3 ppm (includes both diastereomers); IR (thin film): $\tilde{\nu}$ = 3412, 2982, 2927, 1646, 1617, 1458, 1392, 1333, 1250, 1218, 1164, 1093, 1047, 1021, 968, 900, 860, 799, 725 cm^{-1}; HRMS (MALDI): m/z: calcd for $C_{12}H_{24}NO_5PNa$ $[M+Na]^+$: 316.1284; found: 316.1282.

(*R*)-2-[(*S*)-3-((*E*)-1-Methyl-2-phenylvinyl)-4,5-dihydroisoxazol-5-yl]propan-1-ol (21): To flame dried LiCl (12.7 mg, 0.300 mmol, 1.20 equiv) was added azeotropically dried unpurified cycloadduct **19** (0.250 mmol, 1.00 equiv) in MeCN (3 mL) at RT, followed by dropwise addition of DBU (41.1 μL, 0.275 mmol, 1.10 equiv). The yellow, slightly cloudy mixture was stirred 15 min at RT, before freshly distilled benzaldehyde (37.2 μL, 0.375 mmol, 1.50 equiv) was added dropwise. After the mixture was stirred at RT for 15 h, H_2O (3 mL) and brine (3 mL) were added and the resulting solution extracted with EtOAc (3×10 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) provided isoxazoline **21** (29 mg, 47% yield over two steps, dr 13:1 by integration of the signals at 4.60 ppm (major) and 4.81 ppm (minor) in the crude ^{1}H NMR spectrum)

as a white solid. M.p. 86 °C; $[\alpha]_D^{28}$ (c = 0.28, $CHCl_3$) = +55.4°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.42–7.27 (m, 5H), 6.70 (s, 1H), 4.81* (ddd, 1H, J = 13.7, 9.0, 5.0 Hz), 4.60 (ddd, 1H, J = 10.3, 8.7, 8.7 Hz), 3.78–3.63 (m, 2H), 3.31 (dd, 1H, J = 15.9, 10.3 Hz), 3.29* (dd, 1H, J = 16.2, 10.6 Hz), 3.06* (dd, 1H, J = 16.5, 9.0 Hz), 3.02 (dd, 1H, J = 16.2, 8.7 Hz), 2.22 (d, 3H, J = 1.3 Hz), 2.17* (d, 3H, J = 1.6 Hz), 2.07–1.94 (m, 1H), 1.00* (d, 3H, J = 6.9 Hz), 0.98 ppm (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 136.3, 133.4, 129.4, 129.1, 128.4, 127.7, 85.6, 66.3, 40.6, 38.6, 14.9, 13.5 ppm; IR (thin film): $\tilde{\nu}$ = 3402, 2962, 2924, 1560, 1490, 1442, 1372, 1239, 1086, 1028, 918, 864, 814, 758, 698, 618, 581 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{19}NO_2$: C 73.44, H 7.81, N 5.71; found: C 72.93, H 7.32, N 5.21; HRMS (MALDI): m/z: calcd for $C_{14}H_{19}NO_2$ $[M-H]^+$: 244.1332; found: 244.1335.

(*R*)-2-[(*S*)-3-((*E*)-1-Methyl-2-phenylvinyl)-4,5-dihydroisoxazol-5-yl]propan-1-ol (22): To a solution of *syn*-benzaldehyde oxime (60.6 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added *t*BuOCl (62.2 μL, 0.550 mmol, 1.10 equiv) dropwise. After 1.5 h the solution was concentrated under reduced pressure. The resulting off-white solid was dried azeotropically with toluene (3×5 mL). Last traces of *t*BuOCl were removed under high vacuum for 10 min. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (56.0 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 (5 mL) at RT was added to the reaction dropwise via cannula over 1 h 45 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 14 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:1 to 1:1) provided isoxazoline **22** (89 mg, 87 %, dr 7:1 by integration of the signals at 4.66 ppm (major) and 4.85 ppm (minor) in the crude ^{1}H NMR spectrum) as a white solid. M.p. 61 °C; $[\alpha]_D^{22}$ (c = 0.89, $CHCl_3$) = +63.5°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.70–7.63 (m, 2H), 7.43–7.37 (m, 3H), 4.85* (ddd, 1H, J = 13.4, 8.6, 4.7 Hz), 4.66 (ddd, 1H, J = 10.3, 8.4, 8.4 Hz), 3.77–3.66 (m, 2H), 3.40 (dd, 1H, J = 16.5, 10.3 Hz), 3.39* (dd, 1H, J = 16.8, 10.9 Hz), 3.17* (dd, 1H, J = 16.8, 8.7 Hz), 3.13 (dd, 1H, J = 16.5, 8.7 Hz), 2.26 (br s, 1H), 2.09–1.85 (m, 1H), 0.99* (d, 3H, J = 6.8 Hz), 0.98 ppm (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 156.8, 130.2, 129.5, 128.7, 126.7, 84.9, 82.8*, 65.9, 65.3*, 40.4, 40.0*, 38.9, 38.0*, 13.3, 11.5* ppm; IR (thin film): $\tilde{\nu}$ = 3401, 3062, 2964, 2931, 2881, 1597, 1570, 1498, 1447, 1357, 1235, 1181, 1077, 1041, 996, 908, 855, 761, 692, 674 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{15}NO_2$: C 70.22, H 7.37, N 6.82; found: C 70.09, H 7.45, N 6.65; HRMS (MALDI): m/z: calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176; found: 206.1179.

(*S*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-4,5-dihydroisoxazol-5-yl]-3-trityloxy-propan-1-ol (34): To a solution of oxime **11** (157 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting deep blue solution was stirred 2.5 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32a** (224 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 90 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 5:1 to 2:1) provided isoxazoline **34** (269 mg, 82 %, dr 19:1 by integration of the signals at 4.70 ppm (major) and 4.79 ppm (minor) in the crude ^{1}H NMR spectrum) as a pale, thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 4H), 7.48–7.22 (m, 21H), 4.70 (ddd, 1H, J = 10.2, 8.8, 8.8 Hz), 4.41 (dd, 2H, J = 15.7, 12.9 Hz), 3.96–3.83 (m, 2H), 3.33 (dd, 1H, J = 9.6, 4.9 Hz), 3.19 (dd, 1H, J = 9.6, 5.5 Hz), 3.00 (dd, 1H, J = 17.3, 10.4), 2.71 (dd, 1H, J = 17.3, 8.8 Hz), 2.29 (br s, 1H), 2.00–1.91 (m, 1H), 1.07 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 143.7, 135.6, 132.7, 130.1, 128.7, 128.1, 128.0, 127.3, 87.2, 81.0, 62.8, 62.5, 59.3, 46.4, 39.5, 26.9, 19.3 ppm; IR (thin film): $\tilde{\nu}$ = 3436, 3067, 3020, 2947, 2931, 2858, 2361, 1960, 1898, 1825, 1590, 1490, 1472, 1449, 1428, 1391, 1363, 1333, 1254, 1217, 1151, 1113, 1088, 1026, 933, 899, 876, 824, 798, 761, 745, 702, 668 cm^{-1}; HRMS (MALDI): m/z: calcd for $C_{42}H_{45}NO_4SiNa$ $[M+Na]^+$: 678.3010; found: 678.3001.

(*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxymethyl)-4,5-dihydroisoxazol-5-yl]-propan-1-ol (35): To a solution of oxime **11** (157 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting green solution was stirred 2.5 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32b** (221 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 60 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1) provided isoxazoline **35** (277 mg, 85 %, dr 21:1 by integration of the signals at 80.6 ppm (major) and 79.4 ppm (minor) in the crude ^{13}C NMR spectrum (12 h measurement time)) as a pale, thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.61 (m, 8H), 7.47–7.35 (m, 12H), 4.67 (ddd, 1H, J = 10.3, 8,7, 8.7 Hz), 4.40 (dd, 2H, J = 15.3, 12.8 Hz), 3.95–3.81 (m, 2H), 3.81–3.69 (m, 2H), 3.04 (dd, 1H, J = 17.1, 10.6 Hz), 2.77 (dd, 1H, J = 17.1, 9.0 Hz), 2.30 (dd, 1H, J = 5.6, 6.5 Hz), 1.97–1.87 (m, 1H), 1.07 (s, 9H), 1.06 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 135.5, 135.5, 132.9, 132.9, 132.6, 130.0, 129.9, 127.9, 80.6, 63.3, 62.3, 59.4, 47.8, 39.6, 27.1, 27.0, 19.4, 19.4 ppm; IR (thin film): $\tilde{\nu}$ = 34.36, 3071, 3050, 3014, 2958, 2931, 2891, 2858, 2361, 1962, 1891, 1825, 1773, 1654, 1628, 1590, 1472, 1428, 1391, 1362, 1334, 1306, 1260, 1216, 1189, 1113, 1000, 998, 938, 880,, 824, 803, 741, 702, 668, 613 cm^{-1}; elemental analysis calcd (%) for $C_{39}H_{49}NO_4Si_2$: C,71.85, H 7.57, N 2.15; found: C 71.69, H 7.71, N 2.29; HRMS (MALDI): m/z: calcd for $C_{39}H_{49}NO_4Si_2Na$ $[M+Na]^+$: 674.3092; found: 674.3100.

(*S*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-4,5-dihydroisoxazol-5-yl]-3-triisopropylsilanyloxypropan-1-ol (36): To a solution of oxime **11** (157 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting green solution was stirred 2.5 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32c** (168 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 90 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by

addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1) provided isoxazoline **36** (209 mg, 73%, dr 14:1 by integration of the signals at 80.6 ppm (major) and 79.0 ppm (minor) in the crude ^{13}C NMR spectrum (12 h measurement time)) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 4H), 7.48–7.37 (m, 6H), 4.70 (ddd, 1H; J=16.5, 9.0, 7.5 Hz), 4.44 (s, 2H), 3.93–3.80 (m, 4H), 3.16 (dd, 1H, J=17.4, 10.6), 2.95 (dd, 1H, J=17.1, 9.0 Hz), 2.52 (t, 1H, J=5.9 Hz), 1.99–1.90 (m, 1H), 1.11–1.04 ppm (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 135.6, 132.7, 130.1, 127.9, 80.6, 63.7, 62.9, 59.4, 47.6, 39.5, 27.0, 19.5, 18.2, 12.1 ppm; IR (thin film): $\tilde{\nu}$ =3436, 3072, 3051, 2942, 2892, 2865, 2717, 2247, 1961, 1891, 1822, 1773, 1656, 1628, 1590, 1464, 1428, 1383, 1363, 1334, 1307, 1257, 1208, 1156, 1113, 1013, 998, 910, 883, 824, 795, 739, 702, 690, 660, 612 cm^{-1}; HRMS (MALDI): m/z: calcd for $C_{32}H_{51}NO_4Si_2Na$ $[M+Na]^+$: 592.3249; found: 592.3241.

(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxymethyl)-4,5-dihydroisoxazol-5-yl]-propan-1-ol (37): To a solution of the oxime **11** (107 mg, 0.340 mmol, 1.00 equiv) in CH_2Cl_2 (3.5 mL) at −78 °C was added *t*BuOCl (40 μL, 0.340 mmol, 1.00 equiv) dropwise over 10 min. The resulting green solution was stirred 2.5 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 340 μL, 1.02 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32d** (98.0 mg, 0.450 mmol, 1.30 equiv) and *i*PrOH (86.0 μL, 1.12 mmol, 3.30 equiv) in CH_2Cl_2 (7 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 90 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1 to 4:1) provided isoxazoline **37** (141 mg, 78%, dr 10:1 by integration of the signals at 80.6 ppm (major) and 79.0 ppm (minor) in the crude ^{13}C NMR spectrum (12 h measurement time)) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.65 (4H), 7.49–7.38 (m, 6H), 4.66 (ddd, 1H, J=16.5, 9.1, 7.4 Hz), 4.45 (s, 2H), 3.83 (brs, 2H), 3.76 (dd, 2H, J=5.5, 1.9 Hz), 3.14 (dd, 1H, J=17.3, 10.7 Hz), 2.93 (dd, 1H, J=17.3, 9.1 Hz), 2.47 (brs, 1H), 1.97–1.88 (m, 1H), 1.07 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 135.5, 132.6, 130.0, 127.9, 80.6, 63.1, 62.6, 59.4, 47.4, 39.4, 27.0, 26.1, 19.5, 18.4, −5.3, −5.3 ppm; IR (thin film): $\tilde{\nu}$ =3430, 3072, 3050, 2855, 2931, 2889, 2858, 2247, 1958, 1893, 1827, 1712, 1662, 1624, 1585, 1470, 1426, 1390, 1362, 1334, 1255, 1209, 1113, 1007, 938, 910, 838, 779, 739, 702, 611 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{45}NO_4Si_2$: C 65.99, H 8.59, N 2.65; found: C 66.13, H 8.50, N 2.67; HRMS (MALDI): m/z: calcd for $C_{29}H_{45}NO_4Si_2Na$ $[M+Na]^+$: 550.2779; found: 550.2772.

(*S*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-4,5-dihydro-isoxazol-5-yl]-3-triethylsilanyloxy-propan-1-ol (38): To a solution of oxime **11** (157 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting green solution was stirred 2.5 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32e** (141 mg, 0.650 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 90 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1) provided isoxazoline **38** (139 mg, 53%, dr 6:1 by integration of the signals at 79.2 ppm (major) and 78.8 ppm (minor) in the crude ^{13}C NMR spectrum (12 h measurement time)) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4H), 7.48–7.35 (m, 6H), 4.70 (ddd, 1H, J=16.6, 9.2, 7.3 Hz), 4.55 (d, 2H, J=1.2 Hz), 4.14–4.04 (m, 2H), 3.74 (dd, 2H, J=5.4, 0.9 Hz), 3.15–2.97 (m, 2H), 2.18–2.04 (m, 1H), 1.07 (s, 9H), 0.94 (t, 9H, J=8.0 Hz), 0.58 ppm (q, 6H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 135.6, 133.0, 130.0, 127.9, 79.2, 60.5, 59.5, 57.4, 45.2, 38.7, 27.0, 19.5, 7.1, 4.5 ppm; IR (thin film): $\tilde{\nu}$ =3338, 3072, 3050, 2956, 2932, 2876, 2859, 1960, 1889, 1822, 1768, 1657, 1590, 1472, 1428, 1390, 1362, 1308, 1258, 1240, 1209, 1186, 1114, 1006, 939, 909, 881, 823, 802, 740, 702, 612 ppm; HRMS (MALDI): m/z: calcd for $C_{29}H_{45}NO_4Si_2Na$ $[M+Na]^+$: 550.2779; found: 550.2772.

(*S*)-2-{(*S*)-3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-4,5-dihydroisoxazol-5-yl}-3-trityloxypropan-1-ol (40): To a solution of oxime **1** (326 mg, 1.50 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at −78 °C was added *t*BuOCl (177 μL, 1.50 mmol, 1.00 equiv) dropwise over 10 min. The resulting deep blue solution was stirred 1 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 1.50 mL, 4.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32a** (672 mg, 1.95 mmol, 1.30 equiv) and *i*PrOH (378 μL, 4.95 mmol, 3.30 equiv) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 60 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 8:1 to 6:1) provided isoxazoline **40** (721 mg, 86%, dr 25:1 by integration of the signals at 4.64 ppm (major) and 4.79 ppm (minor) in the crude ^1H NMR spectrum) as a pale, thick oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 6H), 7.34–7.21 (m, 9H), 4.70–4.58 (m, 1H), 3.2–3.77 (m, 2H), 3.64–3.62 (m, 2H), 3.31–3.26 (m, 1H), 3.20–3.13 (m, 1H), 3.01–2.82 (m, 1H), 2.80–2.63 (m, 2H), 2.48 (brt, 0.5H, J= 6.1 Hz), 2.38 (brt, 0.5H, J=6.0 Hz), 2.00–1.90 (m, 1H), 1.12 (d, 1.5H, J= 7.0 Hz), 1.11 (d, 1.5H, J=7.0 Hz), 0.87 (s, 9H), 0.04 ppm (s, 6H) (includes both *anti*-diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 161.6, 143.5, 128.5, 127.8, 127.0, 87.0, 86.9, 80.2, 80.0, 66.0, 62.7, 62.5, 46.4, 46.3, 40.2, 39.9, 35.8, 25.9, 18.3, 14.7, 14.6, −5.2, −5.3, −5.4 ppm (includes both *anti*-diastereomers); IR (thin film): $\tilde{\nu}$ =3468, 3061, 3030, 2958, 2930, 2886, 2857, 2361, 2342, 1955, 1815, 1721, 1654, 1623, 1598, 1490, 1472, 1446, 1390, 1358, 1325, 1256, 1210, 1176, 1158, 1088, 1032, 1012, 969, 939, 912, 896, 838, 777, 760, 700, 668, 638 cm^{-1}; HRMS (MALDI): m/z: calcd for $C_{34}H_{45}NO_4SiNa$ $[M+Na]^+$: 583.3010; found: 578.3004.

(*S*)-2-{(*S*)-3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-4,5-dihydroisoxazol-5-yl}-3-(*tert*-butyldiphenylsilanyloxy)-propan-1-ol (41): To a solution of oxime **1** (109 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting deep blue solution was stirred 1 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32b** (221 mg, 0.65 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 60 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was

quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Half of the crude material was used for the determination of the dr by derivatization to the corresponding trityl ether (protection of the primary alcohol with TrCl, see below). Analysis of the corresponding crude ^{1}H NMR spectrum (integration of the signals at 4.63 ppm (major) and 4.40 ppm (minor)) revealed a diastereomeric ratio of 20:1. Purification of half of the crude material by flash chromatography (hexane/EtOAc 6:1) provided isoxazoline **41** (115 mg, 83%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.61 (m, 4H), 7.48–7.36 (m, 6H), 4.68–4.56 (m, 1H), 3.95–3.58 (m, 6H), 2.98–2.83 (m, 1H), 2.81–2.68 (m, 2H), 2.53 (br s, 0.5H), 2.43 (br s, 0.5H), 1.95–1.86 (m, 1H), 1.12 (d, 1.5H, J=7.2 Hz), 1.11 (d, 1.5H, J=6.9 Hz), 1.06 (s, 9H), 0.87 (s, 9H), 0.04 ppm (s, 6H) (includes both *anti*-diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 161.6, 135.4, 132.8, 129.8, 127.7, 79.7, 79.6, 66.0, 65.9, 63.3, 63.2, 62.4, 62.2, 47.8, 47.7, 40.2, 39.9, 35.8, 26.9, 25.9, 19.3, 18.3, 14.7, 14.6, −5.3, −5.4 ppm (includes both *anti*-diastereomers); IR (thin film): $\tilde{\nu}$ =3436, 2956, 2930, 2858, 2361, 1958, 1895, 1818, 1660, 1590, 1472, 1428, 1390, 1362, 1307, 1257, 1212, 1190, 1113, 1004, 936, 837, 778, 740, 702 cm^{-1}; HRMS (MALDI): m/z: calcd for $C_{31}H_{49}NO_4Si_2Na$ $[M+Na]^+$: 578.3092; found: 578.3096.

(*S*)-3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-5-[(*S*)-1-(*tert*-butyldiphenylsilanyloxymethyl)-2-trityloxyethyl]-4,5-dihydroisoxazole (55): To unpurified primary alcohol **41** (0.250 mmol, 1.00 equivalent) in dry pyridine (2 mL) at RT was added TrCl (209 mg, 0.750 mmol, 3.00 equiv). The mixture was stirred at RT for 20 h before all volatiles were removed under reduced pressure. Last traces of pyridine were removed by azeotropic coevaporation with cyclohexane (3×4 mL). Purification by flash chromatography (hexane/EtOAc 10:1) provided **55** (134 mg, 67% over two steps, dr 20:1 by integration of the signals at 4.63 ppm (major) and 4.40 ppm (minor) in the crude ^{1}H NMR spectrum) as a pale, thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.58 (m 4H), 7.43–7.17 (m,, 21H), 4.68–4.58 (m, 1H), 3.92–3.83 (m, 1H), 3.78–3.72 (m, 1H), 3.64–3.49 (m, 2H), 3.33 (d, 1H, J=5.9 Hz), 3.32 (d, 1H, J=6.2 Hz), 2.82–2.56 (m, 3H), 2.10–2.00 (m, 1H), 1.07 (d, 1.5H, J=6.9 Hz), 1.02 (d, 1.5H, J=6.9 Hz), 0.96 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 ppm (s, 3H) (includes both *anti*-diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 144.2, 135.7, 135.6, 133.5, 133.3, 129.7, 128.7, 127.8, 127.3, 126.9, 86.8, 79.0, 66.0, 65.9, 61.9, 61.8, 61.0, 46.4, 39.5, 39.0, 36.1, 36.0, 27.0, 26.1, 19.4, 18.5, 14.9, 14.8, −5.1 ppm (includes both *anti*-diastereomers); IR (thin film): $\tilde{\nu}$ =3088, 3058, 3015, 2953, 2929, 2880, 2856, 2361, 2341, 2320, 1958, 1818, 1776, 1656, 1597, 1568, 1542, 1490, 1472, 1447, 1428, 1390, 1361, 1325, 1256, 1216, 1185, 1157, 1113, 1081, 1032, 1010, 935, 898, 837, 775, 762, 744, 700, 633 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{50}H_{63}NO_4Si_2Na$ $[M+Na]^+$: 820.4188; found: 820.4176.

(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-{(*S*)-3-[(*R*)-2-(*tert*-butyldimethylsilanyloxy)-1-methyl-ethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (42): To a solution of oxime **1** (109 mg, 0.500 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added *t*BuOCl (59 μL, 0.500 mmol, 1.00 equiv) dropwise over 10 min. The resulting deep blue solution was stirred 1 h at −78 °C. In a separate flask EtMgBr (3.0 M in Et_2O, 500 μL, 1.50 mmol, 3.00 equiv) was added dropwise to a solution of monoprotected homoallylic diol **32d** (141 mg, 0.65 mmol, 1.30 equiv) and *i*PrOH (126 μL, 1.65 mmol, 3.30 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 60 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0 °C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 18 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Half of the crude material was used for the determination of the dr by derivatization to the corresponding trityl ether (protection of the primary alcohol with TrCl, see below). Analysis of the corresponding crude ^{1}H NMR spectrum (integration of the signals at 4.62 ppm (major) and 4.55 ppm (minor)) revealed a diastereomeric ratio of 6:1. Purification of half of the crude material by flash chromatography (hexane/EtOAc 10:1) provided isoxazoline **42** (91 mg, 84%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.66–4.55 (m, 1H), 3.82–3.66 (m, 6H), 3.12–2.98 (m, 1H), 2.93–2.72 (m, 2H), 2.66 (br s, 0.5H), 2.57 (br s, 0.5H), 1.93–1.85 (m, 1H), 1.16 (d, 1.5H, J=7.2 Hz), 1.14 (d, 1.5H, J=7.2 Hz), 0.89 (s, 18H), 0.06 (s, 3H), 0.06 (s, 6H), 0.05 ppm (s, 3H) (includes both *anti*-diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 162.0, 79.8, 79.6, 66.2, 63.1, 63.0, 62.7, 62.5, 47.5, 47.4, 40.2, 39.8, 35.9, 26.0, 18.4, 18.3, 14.8, 14.7, −5.4, −5.5 ppm (includes both *anti*-diastereomers); IR (thin film): $\tilde{\nu}$ =3436, 2957, 2930, 2886, 2858, 2246, 1620, 1579, 1472, 1434, 1390, 1362, 1310, 1257, 1216, 1095, 1006, 939, 911, 838, 814, 777, 734, 668 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{45}NO_4Si_2Na$ $[M+Na]^+$: 454.2779; found: 454.2773.

(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-{(*R*)-3-[(*R*)-2-(*tert*-butyldimethylsilanyloxy)-1-methyl-ethyl]-4,5-dihydroisoxazol-5-yl}-propan-1-ol (56): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.73–4.62 (m, 1H), 3.99–3.84 (m, 2H), 3.76–3.62 (m, 4H), 3.10–2.99 (m, 1H), 2.94–2.71 (m, 3H), 1.90–1.80 (m, 1H), 1.16 (d, 1.5H, J=6.9 Hz), 1.15 (d, 1.5H, J=7.2 Hz), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 ppm (s, 6H) (includes both *syn*-diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.9, 161.8, 78.1, 77.4, 66.2, 64.0, 63.8, 46.3, 46.2, 39.5, 39.0, 36.2, 36.1, 26.1, 18.5, 18.4, 14.9, −5.2, −5.3 ppm (includes both *syn*-diastereomers); IR (thin film): $\tilde{\nu}$ =3436, 2955, 2930, 2892, 2858, 1586, 1472, 1408, 1390, 1361, 1256, 1211, 1093, 1045, 1003, 972, 936, 837, 776 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{45}NO_4Si_2Na$ $[M+Na]^+$: 454.2779; found: 454.2770.

(*S*)-3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-5-[(*S*)-1-(*tert*-butyldimethylsilanyloxymethyl)-2-trityloxyethyl]-4,5-dihydroisoxazole (57): To unpurified primary alcohol **42** (0.250 mmol, 1.00 equivalent) in dry pyridine (2 mL) at RT was added TrCl (209 mg, 0.750 mmol, 3.00 equiv). The mixture was stirred at RT for 20 h before all volatiles were removed under reduced pressure. Last traces of pyridine were removed by azeotropic coevaporation with cyclohexane (3×4 mL). Purification by flash chromatography (hexane/EtOAc 10:1) provided **57** (104 mg, 62% over two steps, dr 6:1 by integration of the signals at 4.62 ppm (major) and 4.55 ppm (minor) in the crude ^{1}H NMR spectrum) as a pale, thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 6H), 7.31–7.18 (m, 9H), 4.62 (ddd, 1H, J=9.3, 9.3, 7.2 Hz), 3.77–3.55 (m, 4H), 3.25 (d, 2H, J=5.6 Hz), 2.95–2.77 (m, 2H), 2.76–2.59 (m, 1H), 2.09–1.99 (m, 1H), 1.11 (d, 1.5H, J=6.9 Hz), 1.08 (d, 1.5H, 7.2 Hz), 0.88 (s, 9H), 0.82 (s, 9H), 0.04 (s, 6H), −0.02 ppm (s, 6H) (includes both *anti*-diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 144.2, 128.8, 127.8, 126.9, 86.7, 79.2, 66.2, 66.1, 61.2, 46.2, 39.4, 38.9, 36.2, 36.0, 26.1, 18.4, 14.9, 14.4, −5.1, −5.2 ppm (includes both *anti*-diastereomers); IR (thin film): $\tilde{\nu}$ =3089, 3068, 3034, 2955, 2929, 2884, 2857, 2735, 2247, 1958, 1812, 1598, 1491, 1472, 1462, 1449, 1389, 1362, 1316, 1255, 1218, 1184, 1088, 1006, 977, 910, 837, 814, 776, 734, 706, 668, 648, 632 cm^{-1}; HRMS (MALDI): m/z: calcd for $C_{40}H_{59}NO_4Si_2Na$ $[M+Na]^+$: 696.3875; found: 696.3868.

(*R*)-2-{(*S*)-3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methyl-ethyl]-4,5-dihydroisoxazol-5-yl}-propionaldehyde oxime (24): To the diastereomerically pure primary alcohol **2** (85.1 mg, 0.282 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C was added TEMPO (0.900 mg, 5.60 μmol, 2.00 mol%) and KBr (3.40 mg, 28.2 μmol, 10.0 mol%). The mixture was vigorously stirred and NaOCl (0.61 M in H_2O, 509 μL, 0.310 mmol, 1.10 equiv) in pH 8.6 buffer (1.8 mL) was added in portions. After 15 min TLC analysis indicated complete consumption of the starting material. The reaction was quenched by addition of MeOH (100 μL). CH_2Cl_2 (10 mL) and brine (10 mL) were added. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate aldehyde. The resulting colorless oil was used immediately without further purification. To a solution of the unpurified aldehyde in EtOH (2.2 mL) at RT was added $NH_2OH{\cdot}HCl$ (29.4 g, 0.423 mmol, 1.50 equiv) in pyridine (0.3 mL).

The mixture was stirred at RT for 12 h and subsequently concentrated under reduced pressure. To the resulting residue was added EtOAc (20 mL) and H_2O (10 mL). The layers were separated and the organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The pyridine was removed by azetropical coevaporation with cyclohexane (3×10 mL). Purification by flash chromatography (hexane/EtOAc 4:1) gave oxime **24** (84 mg, 95% over two steps) as a clear, colorless oil. $[\alpha]_D^{25}$ (c = 0.64, $CHCl_3$) = +77.4°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ = 9.04* (br s, 1H), 8.54 (br s, 1H), 7.29 (d, 1H, J = 7.2 Hz), 6.62 (d, 1H, J = 7.8 Hz), 4.56 (ddd, 1H, J = 10.6, 7.2, 4.7 Hz), 3.68–3.58 (m, 2H), 3.41–3.30* (m, 1H), 3.00 (dd, 1H, J = 17.4, 10.6 Hz), 2.82–2.70 (m, 1H), 2.73 (dd, 1H, J = 16.8, 6.9 Hz), 2.57–2.46 (m, 1H), 1.13 (d, 3H, J = 7.2 Hz), 1.11 (d, 3H, J = 7.2 Hz), 0.87 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ = 161.4*, 161.2, 152.2*. 152.0, 81.5, 81.3*, 66.0, 39.4, 39.3*, 38.9, 35.8, 34.4*, 26.0, 18.4, 14.8, 14.7*, 14.3*, 14.1, −5.2, −5.3 ppm; IR (thin film): $\tilde{\nu}$ = 3324, 2955, 2930, 2886, 2857, 2368, 2360, 2341, 1648, 1624, 1587, 1462, 1436, 1408, 1389, 1356, 1300, 1256, 1220, 1182, 1098, 1046, 1007, 980, 938, 837, 815, 777, 668 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{31}N_2O_3Si$ $[M+H]^+$: 315.2099; found: 315.2094.

(*R*)-2-[(*S*)-3-((*R*)-1-{3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-4,5-dihydroisoxazol-5-yl}-ethyl)-4,5-dihydroisoxazol-5-yl]-propan-1-ol (25): To a solution of oxime **24** (118 mg, 0.374 mmol, 1.00 equiv) in CH_2Cl_2 (3.7 mL) at −78°C was added *t*BuOCl (47.0 μL, 0.412 mmol, 1.10 equiv) dropwise over 10 min. The resulting green solution was stirred 3 h at −78°C. In a separate flask EtMgBr (3.0 M in Et_2O, 374 μL, 1.12 mmol, 3.00 equiv) was added dropwise to a solution of (*S*)-2-methyl-3-butenol (41.9 mg, 0.487 mmol, 1.30 equiv) and *i*PrOH (95.0 μL, 1.23 mmol, 3.30 equiv) in CH_2Cl_2 (7.4 mL) at 0°C. The reaction mixture turned momentarily cloudy and became clear and colorless upon stirring at 0°C for 30 min. At this time, the hydroximinoyl chloride in CH_2Cl_2 was added to the reaction dropwise via cannula over 90 min, followed by two rinses (1 mL each). The slightly yellow solution was stirred at 0°C for 6 h and was slowly allowed to warm to room temperature overnight (large Dewar with ice, covered with aluminum foil). After 15 h the reaction was quenched by addition of saturated, aqueous NH_4Cl (15 mL). The mixture was vigorously stirred for 20 min, then the layers were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1 to 1:1) provided isoxazoline **25** (90 mg, 61%, dr 5:1 by integration of the signals at 0.90 ppm (major) and 0.96 ppm (minor) in the ^{1}H NMR spectrum) as a pale, colorless oil. $[\alpha]_D^{27}$ (c = 0.17, $CHCl_3$) = +125.6°; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.64 (ddd, 1H, J = 12.5, 7.5, 5.0 Hz), 4.37 (ddd, 1H, J = 10.0, 9.0, 9.0 Hz), 3.70–3.58 (m, 4H), 3.08 (dd, 1H, J = 17.4, 10.0 Hz), 3.05 (dd, 1H, J = 17.1, 10.6 Hz), 2.87 (dd, 1H, J = 17.4, 7.5 Hz), 2.77 (dd, 1H, J = 17.1, 9.3 Hz), 2.84–2.71 (m, 2H), 2.27 (br s, 1H), 1.97–1.83 (m, 1H), 1.23 (d, 3H, J = 7.2 Hz), 1.14 (d, 3H, J = 6.9 Hz), 0.90 (d, 3H, J = 7.4 Hz), 0.88 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 160.3, 84.4, 82.0, 66.3, 66.0, 40.4, 40.1, 39.1, 37.7, 35.9, 26.0, 18.3, 14.8, 14.4, 13.4, −5.3, −5.4 ppm; IR (thin film): $\tilde{\nu}$ = 3430, 2956, 2929, 2872, 2857, 1720, 1621, 1582, 1462, 1435, 1388, 1357, 1322, 1293, 1257, 1219, 1093, 1046, 1013, 974, 940, 838, 812, 777, 670 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{38}N_2O_4SiNa$ $[M+Na]^+$: 421.2493; found: 421.2486.

(*S*)-3-[(*S*)-2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-5-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-4,5-dihydroisoxazole (43): To isoxazoline **4** (310 mg, 1.03 mmol, 1.00 equiv) and CSA (23.8 mg, 0.103 mmol, 0.100 equiv) in CH_2Cl_2 (9 mL) at RT was added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (466 mg, 1.65 mmol, 1.60 equiv). The mixture was stirred for 18 h at RT before additional *p*-methoxybenzyl 2,2,2-trichloroacetimidate (291 mg, 1.03 mmol, 1.00 equiv) was added. After a total of 64 h H_2O (10 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 15:1 to 10:1) afforded *p*-methoxybenzyl ether **43** (22 mg, 51%) as a colorless oil. $[\alpha]_D^{30}$ (c = 1.26, $CHCl_3$) = +17.4°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.32–7.18 (m, 2H), 6.93–6.82 (m, 2H), 4.59* (ddd, 1H, J = 13.1, 8.1, 5.0 Hz), 4.49 (ddd, 1H, J = 15.9, 8.4, 6.9 Hz), 4.42 (s, 2H), 3.81* (s, 3H), 3.80 (s, 3H), 3.70–3.56 (m, 2H), 3.48* (dd, 1H, J = 9.3, 5.3 Hz), 3.47 (dd, 1H, J = 9.4, 5.6 Hz), 3.40 (dd, 1H, J = 9.0, 5.9 Hz), 3.39* (dd, 1H, J = 9.3, 6.2 Hz), 2.91 (dd, 1H, J = 17.1, 10.6 Hz), 2.73 (dd, 1H, J = 17.4, 8.7 Hz), 2.82–2.68 (m, 1H), 2.12–1.98 (m, 1H), 1.14 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.8 Hz), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 161.3, 159.0, 130.6, 129.1, 113.7, 81.5, 80.7*, 72.9, 72.5*, 71.9, 66.2, 55.4, 38.7*, 38.4*, 38.2, 37.9, 36.0*, 35.9, 26.0, 18.4, 14.9, 13.1*, 13.0, −5.2, −5.3 ppm; IR (thin film): $\tilde{\nu}$ = 2956, 2931, 2901, 2857, 2740, 2547, 2362, 2062, 1882, 1715, 1613, 1586, 1514, 1464, 1442, 1389, 1361, 1302, 1249, 1174, 1096, 1037, 1008, 981, 939, 900, 874, 837, 778, 705, 679, 637 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{39}NO_4Si$: C 65.52, H 9.32, N 3.32; found: C 65.36, H 9.48, N 3.60; HRMS (ESI): m/z: calcd for $C_{23}H_{40}NO_4Si$ $[M+H]^+$: 422.2721; found: 422.2715.

(2*R*,5*S*,6*S*)-1-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-7-(4-methoxybenzyloxy)-2,6-dimethylheptan-3-one (44): To a solution of isoxazoline **43** (200 mg, 0.474 mmol) in 5:1 MeOH/H_2O (18 mL) was added boric acid (445 mg, 7.20 mmol) and W-2 Raney Nickel (20 mg). The reaction was purged with H_2 and vigorously stirred for 45 min. The mixture was filtered through Celite, concentrated under reduced pressure and immediately purified by flash chromatography (hexane/EtOAc 15:1 to 10:1) to afford β-hydroxy ketone **44** (189 mg, 94%) as a colorless oil. $[\alpha]_D^{30}$ (c = 0.97, $CHCl_3$) = −32.7°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.26–7.21 (m, 2H), 6.88–6.84 (m, 2H), 4.42 (s, 2H), 4.07–3.98 (br s, 1H), 3.79 (s, 3H), 3.73* (dd, 1H, J = 9.7, 7.8 Hz), 3.72 (dd, 1H, J = 9.7, 7.5 Hz), 3.62 (dd, 1H, J = 10.0, 5.3 Hz), 3.61* (dd, 1H, J = 9.7, 5.3 Hz), 3.53–3.39 (m, 2H), 2.84–2.71 (m, 1H), 2.68–2.53 (m, 2H), 1.94–1.81 (m, 1H), 1.02* (d, 3H, J = 7.2 Hz), 1.01 (d, 3H, J = 7.2 Hz), 0.92 (d, 3H, J = 7.2 Hz), 0.91* (d, 3H, J = 7.5 Hz), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 214.6*, 214.4, 159.1, 130.3, 129.2, 113.8, 73.1, 73.0, 70.8*, 70.7, 69.0*, 65.7, 55.4, 49.3, 47.5, 47.0*, 38.6, 38.3*, 26.0, 18.4, 14.0, 13.9*, 13.0, 11.5*, −5.3 ppm; IR (thin film): $\tilde{\nu}$ = 3500, 2955, 2929, 2904, 2884, 2856, 1706, 1612, 1586, 1513, 1462, 1407, 1386, 1361, 1301, 1246, 1088, 1035, 1006, 939, 834, 775, 667 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{40}O_5Si$: C 65.05, H 9.49; found: C 64.94, H 9.48; HRMS (ESI): m/z: calcd for $C_{23}H_{40}O_5SiNa$ $[M+Na]^+$: 447.2537; found: 447.2531.

(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-1-[(2*R*,4*S*,5*R*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3-methylbutan-2-one (49): To β-hydroxy ketone **44** (123 mg, 0.289 mmol, 1.00 equiv) and 4 Å molecular sieves (300 mg) in CH_2Cl_2 (3 mL) at −15°C was added DDQ (78.8 mg, 0.347 mmol, 1.20 equiv). The mixture was stirred at −15°C for 20 h before the suspension was filtered over silica gel, and concentrated under reduced pressure. Purification by chromatotron (hexane/EtOAc 30:1) afforded **49** (92 mg, 75%) as a colorless oil. $[\alpha]_D^{26}$ (c = 0.40, $CHCl_3$) = −52.2°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.40–7.33 (m, 2H), 6.88–6.83 (m, 2H), 5.49* (s, 1H), 5.46 (s, 1H), 4.15–3.97 (m, 2H), 3.79* (s, 3H), 3.79 (s, 3H), 3.78–3.49 (m, 3H), 2.93–2.76 (m, 1H), 2.88 (dd, 1H, J = 16.2, 8.1 Hz), 2.71* (dd, 1H, J = 16.1, 4.1 Hz), 2.70 (dd, 1H, J = 16.3, 3.4 Hz), 1.94–1.78 (m, 1H), 1.18* (d, 3H, J = 6.9 Hz), 1.05* (d, 3H, J = 7.2 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.87 (s, 9H), 0.86* (s, 9H), 0.77 (d, 3H, J = 6.9 Hz), 0.04 (s, 3H), 0.02 (s, 3H), 0.02* (s, 3H), 0.01* ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 211.5, 211.1*, 159.8*, 159.7, 131.3*, 131.0, 127.4*, 127.3, 113.6*, 113.5, 101.8*, 100.9, 79.2, 75.5*, 73.6*, 73.0, 65.6, 65.3*, 55.4, 49.7, 49.5*, 46.8, 45.9*, 34.4, 31.4*, 26.1, 18.5, 13.2*, 13.1*, 12.8, 12.6, −5.3 ppm; IR (thin film): $\tilde{\nu}$ = 3400, 2956, 2930, 2901, 2856, 2360, 2342, 2028, 1891, 1793, 1715, 1615, 1590, 1518, 1463, 1391, 1366, 1303, 1250, 1214, 1172, 1141, 1114, 1077, 1035, 1008, 979, 949, 938, 910, 891, 836, 777, 668 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{23}H_{38}O_5SiNa$ $[M+Na]^+$: 423.2561; found: 423.2555. NOE-experiments: Irradiation at 5.46 ppm: enhanced signals at 4.05 ppm (strong), 3.79 (weak), 3.54 (strong). Irradiation at 0.77 ppm: enhanced signals at 4.10 ppm

(medium), 4.04 ppm (medium), 3.53 ppm (medium), 2.70 ppm (medium), 1.86 ppm (strong).

(*S*)-3-[(*S*)-1-(*tert*-Butyldimethylsilanyloxy)-ethyl]-5-[(*R*)-2-(4-methoxybenzyloxy)-1-methylethyl]-4,5-dihydroisoxazole (45): To isoxazoline **8** (87 mg, 0.303 mmol, 1.00 equiv) and CSA (7.00 mg, 0.0303 mmol, 0.100 equiv) in CH_2Cl_2 (2.7 mL) at RT was added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (137 mg, 0.484 mmol, 1.60 equiv). The mixture was stirred for 20 h at RT before additional *p*-methoxybenzyl 2,2,2-trichloroacetimidate (137 mg, 0.484 mmol, 1.60 equiv) was added. After a total of 3 d, additional *p*-methoxybenzyl 2,2,2-trichloroacetimidate (137 mg, 0.484 mmol, 1.60 equiv) was added. After a total of seven days H_2O (10 mL) and CH_2Cl_2 (10 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Filtration over a short pad of silica gel (hexane/EtOAc 2:1), followed by purification by flash chromatography (hexane/EtOAc 12:1) afforded *p*-methoxybenzyl ether **45** (56 mg, 46%) as a colorless oil. $[\alpha]_D^{30}$ (c = 0.33, $CHCl_3$) = −11.2°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak) δ7.32–7.22 (m, 2H), 6.90–6.82 (m, 2H), 4.69 (q, 1H, J = 5.9 Hz), 4.65–4.51 (m, 1H), 4.43 (s, 2H), 4.39* (s, 2H), 3.81* (s, 3H), 3.80 (s, 3H), 3.48 (dd, 1H, J = 9.0, 5.3 Hz), 3.42* (dd, 1H, J = 9.0, 5.3 Hz), 3.41 (dd, 1H, J = 9.3, 5.9 Hz), 3.35* (dd, 1H, J = 9.0, 5.6 Hz), 3.02* (dd, 1H, J = 17.4, 10.9 Hz), 2.95 (dd, 1H, J = 17.1, 10.6 Hz), 2.80* (dd, 1H, J = 17.1, 8.1 Hz), 2.79 (dd, 1H, J = 17.4, 8.7 Hz), 2.13–2.00 (m, 1H), 1.99–1.86* (m, 1H), 1.34 (d, 3H, J = 6.5 Hz), 1.32* (d, 3H, J = 6.2 Hz), 0.94 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak) δ161.8, 159.1, 130.6, 129.2, 113.8, 82.0, 81.4*, 73.1*, 73.0, 72.5*, 71.9, 64.8*, 64.7, 55.4, 38.8*, 38.0, 36.4*, 35.2, 25.9, 22.5, 18.3, 12.8, 11.9*, −4.5, −4.6 ppm; IR (thin film): $\tilde{\nu}$ = 2954, 2930, 2892, 2856, 1739, 1612, 1586, 1512, 1463, 1441, 1370, 1362, 1301, 1246, 1217, 1172, 1111, 1085, 1034, 1006, 980, 952, 881, 865, 826, 812, 776, 753, 707, 666, 636 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{37}NO_4Si$: C 64.82, H 9.15, N 3.44; found: C 64.85, H 9.25, N 3.64; HRMS (ESI): m/z: calcd for $C_{22}H_{38}NO_4Si$ $[M+H]^+$: 408.2565; found: 408.2559.

(2*S*,5*S*,6*R*)-2-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-7-(4-methoxybenzyloxy)-6-methyl-heptan-3-one (46): To a solution of isoxazoline **45** (50.0 mg, 0.123 mmol) in 5:1 MeOH/H_2O (5 mL) was added boric acid (124 mg, 2.00 mmol) and W-2 Raney Nickel (5 mg). The reaction was purged with H_2 and vigorously stirred for 60 min. The mixture was filtered through Celite, concentrated under reduced pressure and immediately purified by flash chromatography (hexane/EtOAc 15:1 to 10:1) to afford β-hydroxy ketone **46** (49 mg, 96%) as a colorless oil. $[\alpha]_D^{26}$ (c = 0.46, $CHCl_3$) = −23.3°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.26–7.21 (m, 2H), 6.89–6.84 (m, 2H), 4.43 (s, 2H), 4.20* (ddd, 1H, J = 12.8, 6.9, 3.4 Hz), 4.14 (q, 1H, J = 6.8 Hz), 4.03 (ddd, 1H, J = 12.5, 6.2, 3.1 Hz), 3.80 (s, 3H), 3.49–3.45 (m, 2H), 2.84 (dd, 1H, J = 17.7, 3.1 Hz), 2.83* (dd, 1H, J = 17.7, 9.3 Hz), 2.68 (dd, 1H, J = 17.7, 9.3 Hz), 2.64* (dd, 1H, J = 17.7, 2.8 Hz), 1.97–1.82 (m, 1H), 1.28 (d, 3H, J = 6.5 Hz), 0.95* (d, 3H, J = 6.8 Hz), 0.93 (d, 3H, J = 6.9 Hz), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 214.6, 159.2, 130.3, 129.3, 113.8, 75.1, 73.5*, 73.2, 73.1, 70.7, 68.9*, 55.4, 42.0, 41.6*, 38.6, 38.4*, 26.0, 20.9, 18.3, 14.0, 11.6*, −4.4, −4.7 ppm; IR (thin film): $\tilde{\nu}$ = 3500, 2954, 2930, 2888, 2856, 1713, 1612, 1586, 1513, 1463, 1443, 1407, 1389, 1363, 1336, 1301, 1247, 1204, 1172, 1114, 1087, 1036, 1006, 937, 831, 777, 705, 668, 636 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{38}O_5SiNa$ $[M+Na]^+$: 433.2381; found: 433.2374.

(*S*)-3-[2-(*tert*-Butyldimethylsilanyloxy)-1,1-dimethylethyl]-5-[(*R*)-2-(4-methoxybenzyloxy)-1-methylethyl]-4,5-dihydroisoxazole (47): To primary alcohol **6** (135 mg, 0.428 mmol, 1.00 equiv) and CSA (9.90 mg, 0.0428 mmol, 0.100 equiv) in CH_2Cl_2 (2.7 mL) at RT was added *p*-methoxybenzyl 2,2,2-trichloroacetimidate (242 mg, 0.856 mmol, 2.00 equiv). The mixture was stirred for 63 h at RT before H_2O (10 mL) and CH_2Cl_2 (10 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 15:1) afforded *p*-methoxybenzyl ether **47** (97 mg, 52%) as a colorless oil. $[\alpha]_D^{28}$ (c = 0.92, $CHCl_3$) = +16.0°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.29–7.23 (m, 2H), 6.88–6.85 (m, 2H), 4.58* (ddd, 1H, J = 12.8, 8.1, 4.7 Hz), 4.47 (ddd, 1H, J = 15.9, 8.7, 7.2 Hz), 4.42 (s, 2H), 3.80 (s, 3H), 3.49 (s, 2H), 3.48 (dd, 1H, J = 9.3, 5.3 Hz), 3.34 (dd, 1H, J = 9.0, 6.2 Hz), 3.33* (dd, 1H, J = 9.3, 5.9 Hz), 3.00* (dd, 1H, J = 17.1, 10.9 Hz), 2.92 (dd, 1H, J = 16.8, 10.3 Hz), 2.78* (dd, 1H, J = 16.8, 7.8 Hz), 2.76 (dd, 1H, J = 16.8, 8.7 Hz), 2.10–1.98 (m, 1H), 1.95–1.82* (m, 1H), 1.15 (s, 6H), 0.94 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 164.2, 164.1*, 159.0, 130.7, 129.1, 113.7, 81.7, 80.9*, 72.9, 72.6*, 71.9, 71.0, 55.4, 38.6, 38.0, 37.8, 26.0, 23.2, 23.1, 18.4, 13.1, 11.8*, −5.3 ppm; IR (thin film): $\tilde{\nu}$ = 2956, 2991, 2857, 1613, 1586, 1514, 1464, 1391, 1362, 1302, 1249, 1173, 1097, 1037, 1007, 887, 837, 777, 670 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{41}NO_4Si$: C 66.16, H 9.48, N 3.21; found: C 66.32, H 9.50, N 3.34; HRMS (MALDI): m/z: calcd for $C_{24}H_{41}NO_4SiNa$ $[M+Na]^+$: 458.2697; found: 458.2694.

4-(*tert*-Butyldimethylsilanyloxy)-1-[(2*R*,4*S*,5*R*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3,3-dimethylbutan-2-one (48): To a solution of isoxazoline **47** (90.0 mg, 0.207 mmol) in 5:1 MeOH/H_2O (8.2 mL) was added boric acid (203 mg, 3.28 mmol) and W-2 Raney Nickel (10 mg). The reaction was purged with H_2 and vigorously stirred for 50 min. The mixture was filtered through Celite into a separating funnel containing H_2O (5 mL) and CH_2Cl_2 (10 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate β-hydroxy ketone which was used without further purification. To the unpurified β-hydroxy ketone (43.2 mg, 98.5 μmol, 1.00 equiv) and 4 Å molecular sieves (100 mg) in CH_2Cl_2 (1 mL) at −15°C was added DDQ (26.8 mg, 0.118 mmol, 1.20 equiv). The mixture was stirred at −15°C for 5 h and 3 h at 0°C before the suspension was filtered over silica gel and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 5:1) afforded **48** (30 mg, 34% over two steps) as a colorless oil. $[\alpha]_D^{31}$ (c = 0.35, $CHCl_3$) = −32.9°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.41–7.32 (m, 2H), 6.89–6.82 (m, 2H), 5.49* (s, 1H), 5.46 (s, 1H), 4.48* (ddd, 1H, J = 6.8, 6.8, 2.5 Hz), 4.16–3.97 (m, 2H), 3.79* (s, 3H), 3.78 (s, 3H), 3.66–3.50 (m, 3H), 2.98 (dd, 1H, J = 17.1, 7.8 Hz), 2.92* (dd, 1H, J = 11.8, 5.9 Hz), 2.64* (dd, 1H, J = 17.7, 6.9 Hz), 2.61 (dd, 1H, J = 17.1, 3.4 Hz), 1.93–1.78 (m, 1H), 1.79–1.70* (m, 1H), 1.17* (d, 3H, J = 7.2 Hz), 1.10 (s, 3H), 1.09 (s, 3H),0.87 (s, 9H), 0.76 (d, 3H, J = 6.5 Hz), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 212.4, 159.9, 131.6*, 131.3, 127.5*, 127.4, 113.8*, 113.6, 101.9*, 101.0, 79.0, 75.9*, 73.7*, 73.0, 70.1*, 69.9, 55.4, 49.9, 42.1, 41.2*, 34.4, 31.3*, 25.9, 21.5*, 21.4, 21.3, 18.3, 12.6, 11.5*, −5.5 ppm; IR (thin film): $\tilde{\nu}$ = 2957, 2930, 2895, 2857, 2719, 2361, 2034, 1711, 1616, 1590, 1519, 1464, 1393, 1365, 1343, 1303, 1251, 1171, 1143, 1114, 1036, 1010, 984, 938, 912, 837, 777, 668 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{40}O_5SiNa$ $[M+Na]^+$: 459.2537; found: 459.2530. NOE-experiments: Irradiation at 5.49 ppm: enhanced signals at 4.48 ppm (strong), 3.78 ppm (medium) and 3.53 ppm (strong). Irradiation at 5.46 ppm: enhanced signals at 4.10 ppm (strong), 3.78 ppm (weak) and 3.53 ppm (strong). Irradiation at 4.48 ppm: enhanced signals at 5.49 ppm (strong), 3.78 ppm (weak) and 3.53 ppm (weak). Irradiation at 2.98 ppm: enhanced signals at 3.62 ppm (medium), 2.61 ppm (strong) and 1.10 (weak). Irradiation at 1.75 ppm: enhanced signals at 4.48 ppm (medium), 4.10 (medium), 3.97 (medium), 3.79 (weak), 1.17 (medium). Irradiation at 1.86 ppm: 4.10 (weak), 2.98 (weak), 2.61 (weak), 1.10 (weak), 0.76 (medium). Irradiation at 0.76 ppm: enhanced signals at 4.10 ppm (medium), 3.53 ppm (medium), 2.61 ppm (medium), 1.93 ppm (strong). Irradiation at 1.17 ppm: 3.97 (weak), 3.65 ppm (weak), 3.53 ppm (weak), 2.92 ppm (weak), 2.64 ppm (weak).

(*S*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-4,5-dihydroisoxazol-5-yl]-propionic acid methyl ester (50): To primary alcohol **12** (152 mg, 0.382 mmol, 1.00 equiv) in CH_2Cl_2 (4 mL) at 0°C was added TEMPO (1.20 mg, 7.60 μmol, 2.00 mol%) and KBr (4.50 mg, 38.2 μmol, 10.0 mol%). The mixture was vigorously stirred and NaOCl (approx 1.5 M in H_2O, 382 μL, 0.573 mmol, 1.50 equiv) in pH 8.6 buffer (3 mL) was added in portions. Additional aq. NaOCl solution (400 μL,

0.600 mmol, 1.57 equiv) was added after 10 min. After a total of 1.5 h TLC analysis indicated complete consumption of the starting material. The reaction was quenched by addition of MeOH (200 μL). H_2O (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate aldehyde which was used without further purification. A solution of $NaClO_2$ (207 mg, 2.29 mmol, 6.00 equiv) and 2-methyl-2-butene (404 μL, 3.82 mmol, 10.0 equiv) in pH 3.8 buffer (2.3 mL) and *t*BuOH (11.1 mL) was added at 0 °C to the unpurified aldehyde. The mixture was stirred at 0 °C for 50 min, before pH 3.8 buffer (6 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic solutions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate carboxylic acid which was used without further purification. To the unpurified carboxylic acid in benzene/MeOH 7:1 (16 mL) at 0 °C was added dropwise $TMSCH_2N_2$ (2.0 M in hexane, 1.53 mL, 3.06 mmol, 8.00 equiv). The yellow solution was stirred for 15 min at 0 °C before being quenched with acetic acid (dropwise addition until solution stayed colorless). The volatiles were removed under reduced pressure. Purification by flash chromatography (hexane/EtOAc 8:1) provided methyl ester **50** (113 mg, 70% yield over three steps) as a colorless oil. $[\alpha]_D^{34}$ (c = 0.58, $CHCl_3$) = +29.8°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 7.67–7.64 (m, 4H), 7.45–7.37 (m, 6H), 4.85 (ddd, 1H, J = 10.9, 7.5, 7.5 Hz), 4.72* (ddd, 1H, J = 10.6, 7.5, 7.5 Hz), 4.43 (s, 2H), 3.72 (s, 3H), 3.71* (s, 3H), 3.17* (dd, 1H, J = 17.4, 10.6), 3.10 (dd, 1H, J = 17.7, 10.9), 2.86* (dd, 1H, J = 17.4, 7.5 Hz), 2.85 (dd, 1H, J = 17.4, 7.8 Hz), 2.77 (dq, 1H, J = 7.0, 7.0 Hz), 2.64* (dq, 1H, J = 7.0, 7.0 Hz), 1.28* (d, 3H, J = 7.2 Hz), 1.15 (d, 3H, J = 7.2 Hz), 1.07 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 173.9*, 173.8, 158.2*, 157.9, 135.5, 132.6, 130.0, 127.9, 81.1*, 81.0, 59.2, 52.1, 44.3*, 43.6, 39.1*, 37.5, 29.9, 19.4, 13.6*, 12.1 ppm; IR (thin film): $\tilde{\nu}$ = 3437, 3072, 3049, 2954, 2933, 2892, 2859, 1963, 1893, 1831, 1740, 1629, 1606, 1594, 1502, 1472, 1462, 1429. 1379, 1362, 1338, 1263, 1203, 1166, 1113, 998, 939, 873, 824, 800, 742, 703, 612 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{31}NO_4Si$: C 67.73, H 7.34, N 3.29; found: C; 67.58 H, 7.57, N 3.54; HRMS (MALDI): m/z: calcd for $C_{24}H_{31}NO_4SiNa$ $[M+Na]^+$: 448.1915; found: 448.1914.

(*S*)-2-((*S*)-3-Hydroxymethyl-4,5-dihydroisoxazol-5-yl)-propionic acid methyl ester (51): To TBDPS ether **50** (111 mg, 0.260 mmol, 1.00 equiv) in THF (2.5 mL) was added at 0 °C TBAF (1.0 M in THF, 0.780 mL, 0.780 mmol, 3.00 equiv). The mixture was stirred at 0 °C for 4 h before additional TBAF (1.0 M in THF, 0.780 mL, 0.780 mmol, 3.00 equiv) was added. The mixture was stirred for 12 h at RT. The reaction was quenched by the addition of saturated, aqueous $NaHCO_3$ solution (10 mL) and Et_2O (10 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic solutions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) provided **51** (128 mg, 85%) as a clear, colorless oil. A second purification by flash chromatography (hexane/EtOAc 5:1) resulted in separation of the diastereomers. $[\alpha]_D^{34}$ (c = 0.61, $CHCl_3$) = +13.5°; ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 4.88 (ddd, 1H, J = 10.6, 7.5, 7.5 Hz), 4.76* (ddd, 1H, J = 10.6, 7.5, 7.5 Hz), 4.40 (s, 2H), 3.71 (s, 3H), 3.70* (s, 3H), 3.19* (dd, 1H, J = 17.4, 10.6 Hz), 3.12 (dd, 1H, J = 17.4, 10.9 Hz), 2.93* (dd, 1H, J = 17.4, 7.5 Hz), 2.88 (dd, 1H, J = 17.4, 7.8 Hz), 2.79 (dq, 1H, J = 7.2, 7.2 Hz), 2.71* (dq, 1H, J = 7.2, 7.2 Hz), 2.18 (br s, 1H), 1.28* (d, 3H, J = 7.2 Hz), 1.17 ppm (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor diastereomeric peak): δ = 174.0*, 173.8, 158.6*, 158.2, 81.7*, 81.5, 58.3, 52.2, 44.2*, 43.7, 38.8*, 37.6, 13.8*, 12.4 ppm; IR (thin film): $\tilde{\nu}$ = 3419, 2978, 2954, 2885, 2361, 2342, 1734, 1629, 1460, 1437, 1380, 1337, 1266, 1206, 1168, 1051, 991, 922, 867, 668 cm^{-1}; elemental analysis calcd (%) for $C_8H_{13}NO_4$: C 51.33, H 7.00, N 7.48; found: C 51.40, H 7.10, N 7.62; HRMS (MALDI): m/z: calcd for $C_8H_{13}NO_4Na$ $[M+Na]^+$: 210.0737; found: 210.0733.

(*S*)-2-((*R*)-3-Benzyloxymethyl-4,5-dihydroisoxazol-5-yl)-propionic acid methyl ester (52): To a solution of alcohol **51b** (22.0 mg, 0.118 mmol, 1.00 equiv) and benzyl 2,2,2-trichloroacetimidate (44.0 μL, 0.235 mmol, 2.00 equiv) in cyclohexane (0.5 mL) and CH_2Cl_2 (0.25 mL) at RT was added trifluoromethanesulfonic acid (5.00 μL, 0.0572 mmol, 0.487 equiv). The mixture was stirred for 15 h at RT. The crystalline trichloroacetamide was removed by filtration (washings with pentane (10 mL), Et_2O dissolves the amide). The filtrate was washed with saturated, aqueous $NaHCO_3$ solution (5 mL) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) provided isoxazoline **52** (20 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5H), 4.74 (ddd, 1H, J = 10.6, 7.5, 7.5 Hz), 4.53 (s, 2H), 4.30 (s, 2H), 3.70 (s, 3H), 3.17 (dd, 1H, J = 17.4, 10.6 Hz), 2.89 (dd, 1H, J = 17.4, 7.5 Hz), 2.73–2.63 (m, 1H), 1.29 ppm (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 156.7, 137.3, 128.6, 128.1, 128.0, 81.5, 72.9, 64.7, 52.2, 44.4, 39.4, 13.8 ppm; HRMS (MALDI): m/z: calcd for $C_{15}H_{19}NO_4Na$ $[M+Na]^+$: 278.1387; found: 278.1393. These spectral characteristics are identical in all respects to those previously reported.[35]

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