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Conversion of L-Cysteine into D-α-Amino Acids and Related Transformations

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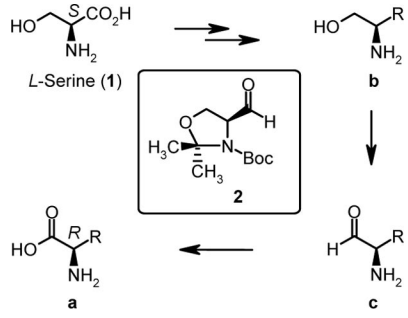
Naturally configured cysteine is converted into 4-substituted thiazolidines via the 4-carbaldehyde corresponding to the serine derived Garner's aldehyde. The key transformation is the conversion into 5-thiazolidinones by $^1O_2$ oxidation, and fragmentation of the primary 5-hydroperoxides under in situ acetylating conditions. Whereas the reagent couple trimethylsilyl halides/phenol selectively cleaves the *N*-Boc group, $LiOH/H_2O_2$ transforms the thiol lactones into lactones by an unknown mechanism, and, subsequently, also cleaves the acetonide affording *N*-Boc-protected D-amino acids without loss of optical activity. This sequence tolerates unsaturated residues with sensitive allylic functions. In some cases, double bond isomerization is, however, observed. The thiazolidine intermediates can be cleaved with 3-nitro-2-pyridinesulfenyl chloride, giving reactive mixed disulfides.

Introduction

α-Amino acids are important natural products in terms of occurrence, biological function, building components for other natural products, and metabolism. In addition to the large number of naturally occurring representatives, artificial structures are designed and synthesized for various purposes, notably also as pharmaceuticals. Not surprisingly, many synthetic strategies have been developed with emphasis on stereoselectivity because, with few exceptions, α-amino acids are chiral.[1] An appealing possibility that is often used relies on transformations of proteinogenic α-amino acids, most of which are readily available in the L-configuration. A useful synthon for the D-configured enantiomers **a** is (*S*)-serine (**1**), which can be converted by transformation of the carboxylic acid into the desired side chain R (→**b**), and oxidation of the hydroxymethyl side chain to the carboxylic acid (Scheme 1).[1b] A versatile and configurationally stable intermediate that can be used for conversion into intermediates **b** is Garner's aldehyde **2**,[2,3] which is most conveniently prepared by $LiAlH_4$ mediated reduction of the corresponding Weinreb *N*-methoxy-*N*-methyl amide.[2b]

Potentially problematic steps of this sequence are, in the case of Garner's aldehyde **2**, selective acetonide cleavage without affecting the *tert*-butyl carbamate, and, in general, the oxidation of alcohol **b** to the carboxylate **a** with a racemisation-prone aldehyde intermediate **c**. If applicable, the reagents of choice are Dess–Martin periodinane (2 equiv.) – a potentially dangerous reagent – for the conversion of **b** into aldehyde **c**, followed by $NaClO_2$ (7 equiv.)/$Na[H_2PO_4]$ (4 equiv.) with bulk amounts of 2-methyl-2-butene (used in a 1:4 ratio as solvent as a radical trap) for the conversion into acid **a**.[3a]



Scheme 1. Conversion of (*S*)-serine (**1**) into (*R*)-α-amino acids **a**.

Some time ago we speculated that (*R*)-cysteine (**3**) might offer advantages with respect to the final oxidation, because it was known that *N*-acylated thiazolidine derivatives **d** can be oxidized at C(5) by various methods, giving hemiacetal-like structures **e** (Scheme 2). Pioneering work was done by Woodward, who introduced a 5-hydrazino residue with azodicarboxylate in his cephalosporin synthesis.[4] Transformation into the 5-acetoxy derivative was achieved with $Pb(OAc)_4$. Later Baldwin and co-workers introduced a 5-benzoyloxy group using benzoyl peroxide.[5] Problems were, however, encountered with the Pummerer rearrangement of sulfoxide **f**.[6] In contrast to conventional Ac_2O treatment,[6a] reaction with silyl triflates induced rearrangement to **e**, but this was accompanied by elimination.[6b,6c] The most elegant method is oxidation with $^1O_2$, which was described by Ando and co-workers.[7] With a catalytic amount of a sensitizing dye, daylight, and air, a 5-hydroperoxy group is smoothly generated. In situ reduction with a sulfide or phosphane gives hemiacetal **e**.

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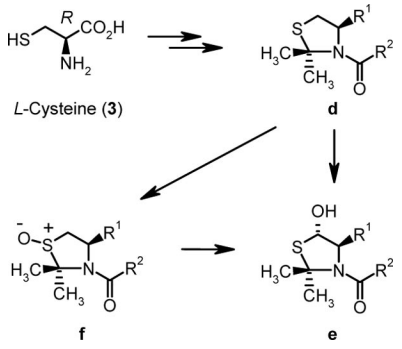
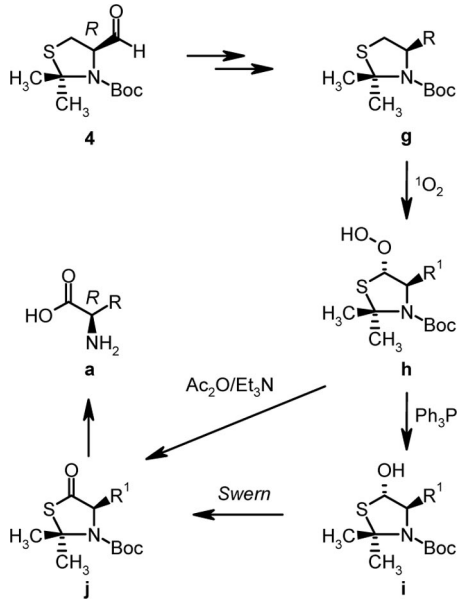


Scheme 2. Oxidation of (*R*)-cysteine-derived *N*-acylthiazolidines **d**.

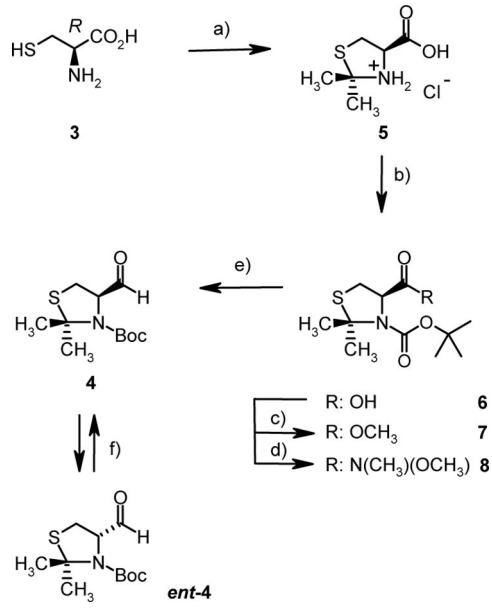
Following these lines, we have transformed L-cysteine (**3**) into the protected aldehyde **4**, which, like Garner's serine aldehyde **2**,[2] can be transformed into various 4-substituted thiazolidines **g** (Scheme 3). The $^1O_2$ oxidation gives hydroperoxides **h**, which are reduced to hemiacetals **i** with triphenyl phosphane. As opposed to the aldehydes **c** – intermediates in the route from serine (**1**, Scheme 1) – these masked aldehydes are configurationally stable and can be oxidized readily to the thiol lactones **j**. These 5-thiazolidinones **j** can be obtained directly from the hydroperoxides **h** by treatment with acetic anhydride/triethylamine at low temperatures. Deprotection under acidic conditions finally gives the target α-amino acids **a**. This sequence was successfully applied to a series with olefinic residues R, thus giving access to (*R*)-configured β,γ-unsaturated amino acids.[8] This manuscript describes these transformation in full detail, adds additional methods for the final deprotection, exemplifies the method with an exceptionally delicate example with an allylic mono-phosphate function, and includes further transformations of intermediates, for example, the cleavage of the *N*-Boc-thiazolidine ring with 3-nitro-2-pyridinesulfenyl chloride.



Scheme 3. Conversion of cysteine aldehyde **4** into (*R*)-α-amino acids **a**.

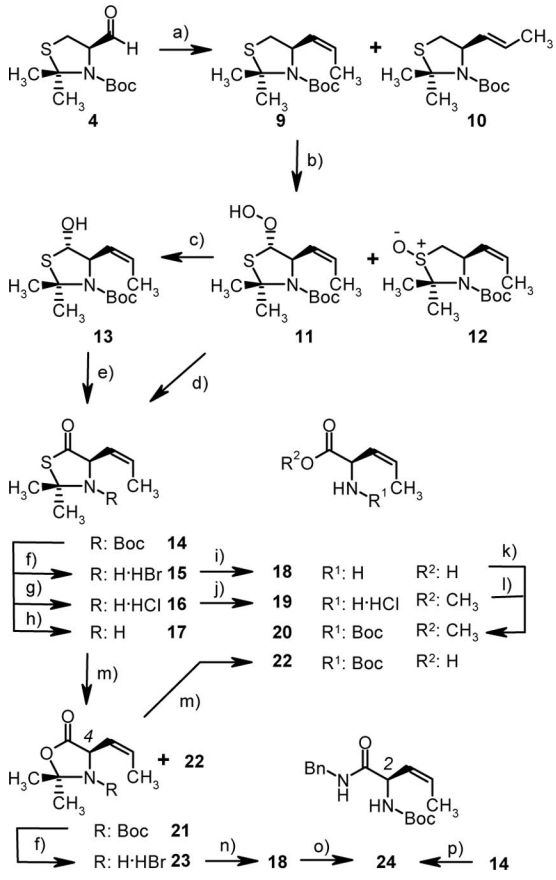
Results and Discussion

As previously described,[9a] cysteine hydrochloride (**3**) was transformed into thiazolidine **5** upon treatment with dimethoxypropane in boiling acetone. The *N*-*tert*-butyl carbamoylation to give **6** was effected with a slight excess of di-*tert*-butyl dicarbonate (Boc_2O) in pyridine with cooling during addition of the reagent.[10] To assess the optical purity of **6**, the known methyl ester **7**[4a] was prepared by methylation with 3-methyl-1-tolyltriazene.[11] Conversion into *N*-methoxy-*N*-methyl amide **8** could be effected by activation of acid **7** with *N*,*N*-dicyclohexylcarbodiimide (DCC). Alternatively, conversion into the acid chloride with 1-chloro-1-dimethylamino-2-methylpropene[12] followed by treatment with *N*-methoxy-*N*-methylamine/pyridine was also successful. The use of thionyl chloride or oxalyl chloride was not suitable for conversion into the acid chloride, nor was formation of a mixed anhydride with isobutyl chloroformate/*N*-methylmorpholine. Reduction of **8** to aldehyde **4** was performed with $LiAlH_4$ in ether. Purification by distillation gave **4** with 95–98% *ee* (Scheme 4). Occasionally, loss of optical purity was observed during distillation. Aldehyde **4** can readily be racemized with Et_3N in boiling dichloromethane, thus also giving access to racemic reference compounds for the determination of optical purity. After our initial report,[8] several authors prepared aldehyde **4** either following our route or with minor modifications.[13]



Scheme 4. Synthesis of 4-formylthiazolidine **4** from (*R*)-cysteine (**3**). Reagents and conditions: (a) 2,2-dimethoxypropane/acetone, reflux, 20 h, 82%; (b) $(Boc)_2O$ (1.1 equiv.)/pyridine, –23 °C to room temp., 2–3 d, 78%; (c) 3-methyl-1-(*p*-tolyl)triacene/CH_2Cl_2, 20 °C, 69%; (d) DCC/*N*-methoxy-*N*-methylamine/EtOAc, room temperature, 4 d, 74%; (e) $LiAlH_4/Et_2O$, 5 °C, 95%; (f) Et_3N/CH_2Cl_2, reflux, 18 h.

As a model system, we decided to introduce an unsaturated chain at C(4) of thiazolidine **4**. Wittig olefination with ethyl triphenylphosphonium bromide and butyllithium gave the (*Z*)-propenyl derivative **9** containing 10% of the (*E*)-isomer **10**, in 80% yield. Crystallization gave isomerically pure **9** (27%) and a 7:1 mixture of **9** and **10** (32%; Scheme 5). According to analysis by chiral capillary GLC and NMR [in the presence of the chiral shift reagent (2,2,2-trifluoro-1-anthracen-9-yl)ethanol (TFAE)[14]] the optical purity remained intact. Treatment with $^1O_2$ converted thiazolidine **9** into hydroperoxide **11**, which was stable in solution up to 0 °C, and various amounts of sulfoxide **12** (see Table 1 below). The mechanism of this rather clean conversion has been studied by Ando and co-workers.[7] When a solution of **9** and a catalytic amount of a sensitizing dye were exposed to daylight and air, formation of hydroperoxide **11** could be detected by TLC. Preparative runs were best performed at –78 °C in a cylindrical vessel with a water-cooled and insulated insert for a halogen lamp. About 0.25 wt-% *meso*-tetraphenylporphyrin was found to be sufficient sensitizer. Suitable solvents were tetrahydrofuran (THF), *tert*-butyl methyl ether, and toluene (Table 1). In dichloromethane, formation of sulfoxide **12** prevailed. Other dyes – bengal rose or methylene blue – in ethanol were found to be unsuitable. In situ reduction gave hemiacetal **13**, which was isolated in 66% yield together with 23% of **12**. The target 5-thiazolidinone **14** should be obtainable directly from hydroperoxide **11** by fragmentation (formal water elimination), which is a well-documented process for other hydroperoxides.[15] Whereas most documented conditions, including acylation with various acid chlorides or imidazolides,[15b] and also cobalt-catalysis,[15g] failed, treatment with acetic anhydride/triethylamine[15d] at –78 °C was successful, affording **14** with 66% yield based on thiazolidine **9**. However, the use of acetic anhydride with other bases, e.g., pyridine or diisopropylethylamine, was not successful. According to NMR analysis with the chiral shift reagent TFAE,[14] the optical purity of **14** was at least 95%. Complete racemization of **14** in dichloromethane containing 5% Et_3N occurred in 65 h at room temperature. At 0 °C, the optical purity dropped to 25% within 24 h. Only a slow loss of optical activity was observed with Et_3N/CH_2Cl_2 at –25 °C (86% *ee* after 48 h), and racemization was negligible at –78 °C or with diisopropylethylamine at 0 °C (24 h). Thiol lactone **14** of comparable quality could also be obtained in 81% yield by oxidation of hemi-thioacetal **13** under Swern conditions.[16] The remaining task – deprotection to give the free amino acid or suitably protected derivatives – was solved in various ways (Scheme 5). Treatment of **14** with either bromo- or chlorotrimethylsilane and phenol in dichloromethane at 0 °C[17] cleanly cleaved only the *tert*-butyl carbamate to give the crystalline hydrobromide **15** (98%) or the hydrochloride **16** (96%). The free base **17** could be liberated with aqueous Na_2CO_3 in 70% yield. The 5-thiazolidinone ring was slowly cleaved in 1 N hydrochloric acid, giving the hydrochloride salt of amino acid **18**. Ion exchange chromatography (Dowex 50W × 8, H^+) gave free **18** in 64% yield.[18,19] Similarly, the hydrochloride was transformed in dry methanol/chlorotrimethylsilane into methyl ester hydrochloride **19** (87%). Both, amino acid **18** and ester **19**, were converted into *N*-Boc methyl ester **20** with 94% *ee*, and 98.8% *ee*, respectively. More demanding was cleavage of the 5-thiazolidinone ring without losing the *tert*-butyl carbamate. Treatment with LiOH in THF/water gave the desired product **22** but only with 78% *ee*. With the more nucleophilic LiOH/H_2O_2 couple,[20] we stumbled on an unexpected and puzzling conversion of thiol lactone **14** into lactone **21**, which was isolated in 56% yield in addition to starting material **14** (13%) and 4% of desired **22**, which was isolated as the methyl ester **20** in 99% *ee*. Prolonged exposure of lactone **21** to LiOH/H_2O_2 afforded **22** in 65% yield and 98% optical purity.[18,19] Similar to thiol-lactone **14**, the *N*-Boc-group of lactone **21** could be cleaved with bromotrimethylsilane and phenol.[17] The product **23**, which

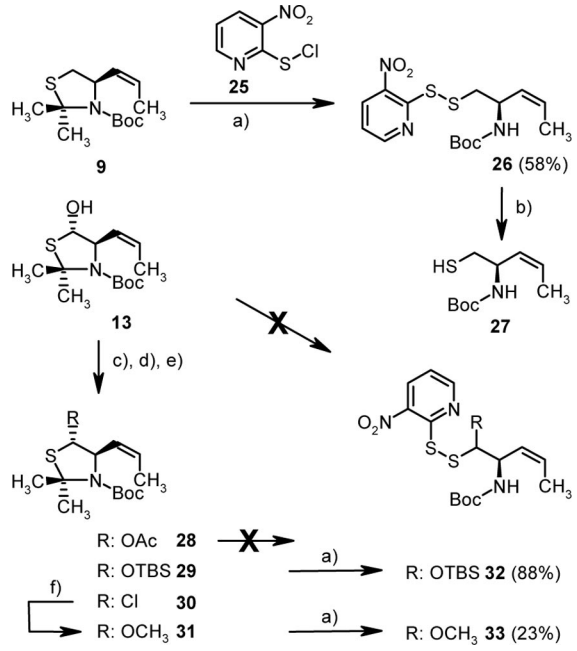


Scheme 5. Synthesis and transformations of (*R*)-4-propenylthiazolidine **9**. Reagents and conditions: (a) ethyl triphenylphosphonium bromide/BuLi, THF, 5–10 °C, 80%; (b) O_2/*meso*-tetraphenylporphyrin (cat.)/light, THF, –78 °C; (c) Ph_3P, room temp., 66%; (d) Ac_2O/Et_3N, –78 °C, (66%); (e) DMSO/oxalyl chloride/Et(*i*Pr)$_2$N, CH_2Cl_2, –70 °C to room temp., 81%; (f) TMSBr/phenol, CH_2Cl_2, 0 °C, 98%; (g) TMSCl/phenol, CH_2Cl_2, 0 °C, 96%; (h) 10% Na_2CO_3, 70%; (i) 1 N HCl, room temp., 18 days, ion exchange resin, 64%; (j) TMSCl/MeOH, 6 d, 87%; (k) (*i*) $Boc_2O/NaHCO_3$, H_2O/dioxane; (*ii*) CH_2N_2/ether; (l) $Boc_2O/NaHCO_3$, H_2O/dioxane; (m) LiOH/H_2O_2, THF/H_2O, 0 °C, 30 min, 56%; (n) methanol, room temp., 3 d, 99%; (o) (*i*) $Boc_2O/NaHCO_3$, H_2O/dioxane (→ **22**, 74%); (*ii*) HOBT/DCC, $BnNH_2$, DMF, room temp., 3 h, 71%; (p) $Me_2AlNHBn$, toluene, room temp., 57%.

was isolated in 80% yield, was, however, more labile than either **15** or **16**. Thus, an NMR sample in CD_3OD was cleaved quantitatively to the hydrobromide of **18** in three days. In D_2O, this cleavage was almost instantaneous, and was much faster than the corresponding deprotection of the thiol-analogue **15** in 1 N hydrochloric acid (see above).[21] Hydrobromide **18** could be protected as the *tert*-butyl carbamate to give **22** (74%), and coupled through standard *N*-hydroxy-benztriazol (HOBT)/DCC methodology with benzylamine to give amide **24** in 71% yield. The same derivative was also obtained directly from thiol lactone **14** by treatment with *N*-benzyl-dimethylaluminum amide.[22]

In addition to the transformations described above for 5-thiazolidinone **14** (Scheme 5), it was also of interest to find methods for cleaving either the parent thiazolidine **9** or the C(5)-hydroxylated derivative **13**, which is an aldehyde equivalent. Of special value would be removal of the acetonide without affecting the *tert*-butyl carbamate. This has been achieved under strictly controlled and optimized conditions either with trifluoroacetic acid in wet dichloromethane,[13a] or with 1 equiv. *p*-toluenesulfonic acid in methanol.[13b] An interesting alternative is the use of methoxycarbonyl-sulfenyl chloride in acetate-buffered *N*,*N*-dimethylformamide (DMF)/water, followed by reductive disulfide cleavage with trimethylphosphane in wet THF.[13d] We were, on the other hand, intrigued by the versatility of 3-nitro-2-pyridinesulfenyl protection/activation of cysteine residues.[23] The reagent 3-nitro-2-pyridinesulfenyl chloride (**25**)[24] cleaves other thiol protecting groups such as *p*-methoxybenzyl and *tert*-butyl cleanly,[24b,25] and is also expected to cleave the C–S bonds of acetonides such as **9** and **13** (Scheme 6). The target disulfide **26** could indeed be obtained from **9** in moderate yield in ethanol in the presence of solid $NaHCO_3$ to quench hydrochloric acid formed by solvolysis. An excess of sulfenyl chloride **25** is required because a side reaction is formation of the ethyl sulfenate derived from chloride **25**. Other solvents (CF_3CH_2OH, AcOH) or ethanol alone gave lower yields of **26**, and other products were formed when dichloromethane or DMF were used as solvent. Reduction with trioctylphosphane in dioxane/water readily gave mercaptan **27**. When applied to hemiacetal **13**, an intractable mixture was formed under the conditions described above. Therefore, the hydroxyl group was protected as either acetate **28** or *tert*-butyldimethylsilyl ether **29**. The labile chloride **30** could be readily prepared with Ghosez's chlorenamine reagent.[12] Solvolysis of **30** in methanol gave the methyl ether **31**, which was accompanied by 15% of the *N*-Boc-cleaved product. Whereas the acetate was unreactive, sulfenyl chloride **25** cleaved silyl ether **29** cleanly to give the masked aldehyde **32**. The corresponding methoxy derivative **33** was, however, obtained in low yield only.

The scope and limitations of this $^1O_2$-mediated oxidation is outlined in Figure 1 and Table 1. In general, bulkier 4-substituents (R) facilitate this reaction, and rather moderate yields are observed for the parent compound (R = H; Table 1, entry 1) and R = CH_2OH (Table 1, entry 5; $NaBH_4$ reduction of aldehyde **4** gave racemic thiazolidine **g** in this



Scheme 6. Cleavage of thiazolidine **9** and 5-hydroxylated derivatives. Reagents and conditions: (a) 3-nitro-2-pyridinesulfenyl chloride, EtOH/$NaHCO_3$, 0 °C, 5.5 h; (b) trioctylphosphane/dioxane – water, room temp. 30 min, 78%; (c) Ac_2O/pyridine, room temp., 18 h, 84%; (d) *tert*-butylchlorodimethylsilane/imidazol, DMF, room temp., 18 h, 85%; (e) 1-chloro-1-dimethylamino-2-methylpropene, CH_2Cl_2, 0 °C, 18 h, 78%; (f) CH_3OH, room temp., 2 h, 54%.

case). The effect of the substituent R is also evident in the propensity of the 5-thiazolidinones **j** to undergo racemization. The methyl ester (Table 1, entry 2) was isolated only in racemic form, the *tert*-butyl ester (Table 1, entry 3) shows low optical activity, and the bulky Weinreb amide (Table 1, entry 4) was obtained in optically pure form. With triethylamine in dichloromethane at reflux, this β-dicarbonyl derivative retained 70% of its optical activity after 24 h, whereas the propenyl-substituted analogue **14** (Table 1, entry 6) underwent racemization even at 0 °C (see above, Scheme 5). Solvent effects were studied with the propenylthiazolidine (Table 1, entries 6–9). High yield of C(5) oxidation (to give **13**, **14**) and low sulfoxide formation (to give **12**) was observed in toluene and *tert*-butyl methyl ether (Table 1, entries 7 and 8); THF (Table 1, entry 6) was intermediate, and, in dichloromethane, only sulfoxide **12** was isolated (Table 1, entry 9). Interestingly, $^1O_2$ attack on the allylic positions was never observed, not even for the allylsilanes **34** and **35** (Table 1, entries 11 and 12), which should be especially sensitive towards allylic oxidation.[26] The 5-thiazolidinones **j** were generally obtained in higher yield by the direct conversion of primary hydroperoxides **h** with Ac_2O/Et_3N, than by the two-step sequence with reduction to hemiacetal **i** and Swern oxidation (Table 1, columns 4 vs. 5). Amino acids with relatively complex side-chains can be prepared (Table 1, entries 19–21). To avoid acetylation and oxidation, respectively, alcohol functions required protection (Table 1, entry 16). However, whereas some base-sensitive functions such as a primary allyl bromide, were tolerated (Table 1,

entry 17), double bond isomerizations were observed when the acidity of the allylic protons reached a limit (governed by stereo-electronic effects). Thus, the 4-ethynyl derivative is smoothly oxidized as seen by the high yielding conversion into hemiacetal **i** (Table 1, entry 13), however, Ac_2O/Et_3N treatment was accompanied by isomerization to allene **37**, which was isolated as a dimer in low yield. Similarly, an acryl ester side-chain survived reduction to **i**, but isomerized to **38** upon exposure to Ac_2O/Et_3N (Table 1, entry 14). Gratifyingly, this isomerization was not a problem for the methacryl analogue **39** (Table 1, entry 15). In the case of an allylic nitrile (Table 1, entry 18), the expected product, which was isolated in moderate yield (42%), was accompanied by the formation of isomer **42** (10%). It is still possible that some of these rather delicate 5-thiazolidinones can be prepared from the hemiacetals **i** by using milder oxidation methods that avoid the need for strong bases.

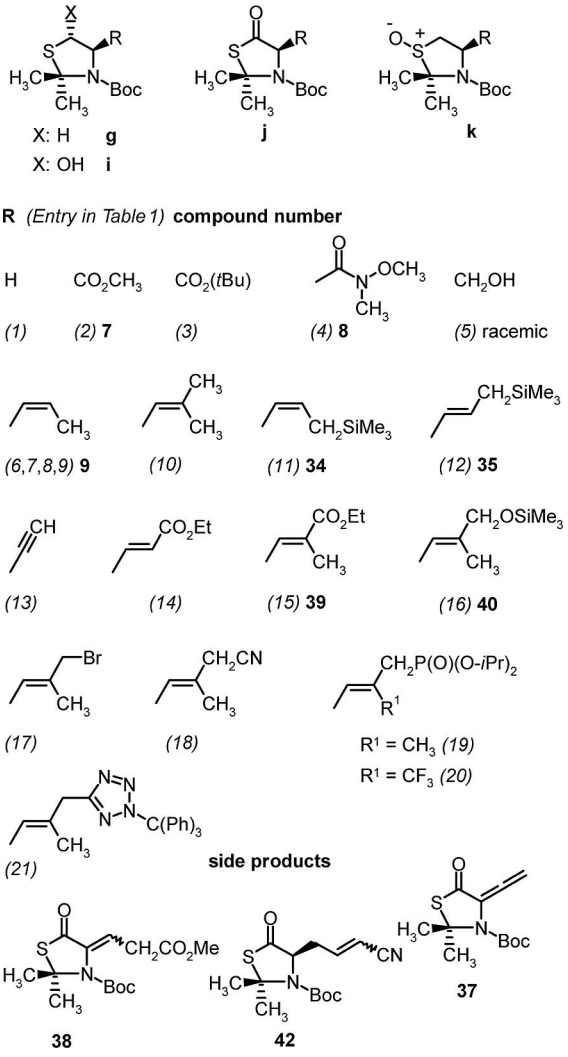


Figure 1. Compound structures for Table 1. Compounds with numbers are described in the Exp. Section (with the exception of side products **37**, **38**, and **42**).

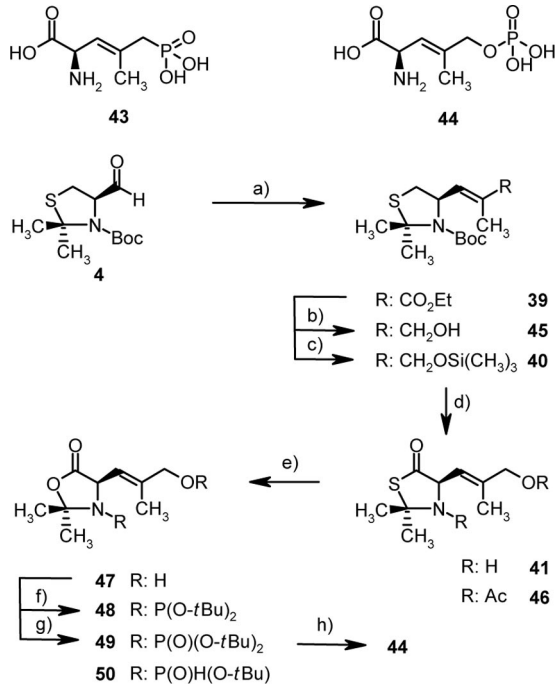
This method has been developed to prepare analogues of (*R*)-2-amino-5-phosphonopentanoic acid (AP5), a competitive antagonist of the excitatory neurotransmitter L-glutamate that is specific for the *N*-methyl-D-aspartate (NMDA) receptor subtype. The main therapeutic use envisaged was treatment of epileptic seizures and prevention of ischemic brain damage after strokes.[27] A promising compound still considered an experimental drug is (*E*)-(*R*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (**43**; CGP-40116),[28] which could also be prepared from cysteine (**3**) using $^1O_2$-mediated oxidation of the corresponding thiazolidine **g** (Table 1, entry 19). It has been found that, for mono-phosphate processing enzymes, directly connected phosphonates (non-isosteric analogs shortened by one atom) are as good or even better than the isosteric methylene-phosphonates.[29] In this context, we were interested in establishing the potency of the non-isosteric phosphate analogue **44** as a NMDA antagonist in comparison to phosphonate **43**. The synthesis of the former is depicted in Scheme 7.

Table 1. The $^1O_2$-mediated oxidation of *N*-(*tert*-butoxycarbonyl)-thiazolidines [THF, *meso*-tetraphenylporphyrin (cat.)/O_2/light, –78 °C]; see Figure 1 for structures.

Entry	g	i [%][a]	k [%][b]	j [%][c]	j [%][d]
1		40[e]	23[e]		
2	**7**	57		73[f]	4[f]
3		74		71[g]	49
4	**8**	86	4	72[h]	58
5[f]		53[f]			
6	**9**	66 (**13**)	23 (**12**)	70 (**14**)	53 (**14**)
7	**9**	81 (**13**)[e]	4 (**12**)[e]		65 (**14**)
8	**9**	84 (**13**)[i]	4 (**12**)[i]		68 (**14**)
9	**9**	0[j]	56[j]		
10		75			
11	**34**	71 (**36**)			
12	**35**	77			
13		91		38 (**37**)	
14		85		62 (**38**)	
15	**39**			65	
16	**40**	63[k]		61 (**41**)[k]	
17		47		57	
18				42 (10% **42**)	
19		66		80	60
20		62			47
21				73	

[a] In situ reduction of hydroperoxide with $[(Ph)_3P]$. [b] The polar sulfoxides have often not been isolated. [c] In situ treatment of hydroperoxide with Ac_2O/Et_3N. [d] Overall yield after Swern oxidation of hemiacetal **i**. [e] In toluene. [f] Racemic. [g] Probably of low optical purity: $[\alpha]_D = -18.0$ ($c = 0.3$, $CHCl_3$). [h] Optically pure: $[\alpha]_D = -145$ ($c = 0.58$, $CHCl_3$). [i] In *t*BuOMe. [j] In CH_2Cl_2. [k] After Me_3Si ether cleavage.

Aldehyde **4** was converted with ethyl 2-(triphenylphosphoranylidene)propionate[30] into ester **39** (73%), which was reduced with diisobutylaluminum hydride (DIBAL-H) to allyl alcohol **45** (96%). For the following oxidation, the alcohol function was protected as the trimethylsilyl ether **40**. The key sequence with $^1O_2$ addition, in situ treatment of the intermediate thiazolidine-5-hydroperoxide (general structure **h**, cf. Scheme 3) with Ac_2O/Et_3N, and acidic cleavage of the silyl ether, afforded the 5-thiazolidinone **41** in 61% yield together with acetate **46** (6%). To simplify deprotection, the thiol-lactone **46** was converted into lactone **47** (69%) with $LiOH/H_2O_2$. *O*-Phosphorylation with di-*tert*-butyl-*N*,*N*-diethylphosphoramidite/tetrazole[31] gave phos-



Scheme 7. Synthesis of phosphonoylpentenoic acid **44** from cysteine. Reagents and conditions: (a) $Ph_3P{=}C(CH_3)CO_2Et/CH_2Cl_2$, room temp. 3 d, 73%; (b) DIBAL-H/ Et_2O, 4 °C, 35 min, 96%; (c) $(CH_3)_3SiCl$/imidazole/DMF, room temp., 3 d, 51%; (d) (1) O_2/*meso*-tetraphenylporphyrin (cat.)/light, THF, –78 °C, 18 h; (2) Ac_2O/Et_3N, –78 °C, 3 h; (3) 1 N HCl (61%, 6% of **46**); (e) LiOH/H_2O_2, THF/H_2O, 0 °C, 3 h, 69%; (f) $Et_2NP(OtBu)_2$/tetrazole, room temp., 20 min., 82%; (g) MCPBA/THF, 0 °C, 38 min. (73%, 2.5% of **48**); (h) *p*TsOH/CH_2Cl_2/THF, room temp., 60 min, ion exchange chromatography, 87%.

phite **48** (82%), which was oxidized with 3-chloroperbenzoic acid (MCPBA) to phosphate **49** (73%). As a side-product arising from acidic mono-cleavage of phosphite **48**, 2–3% of the H-phosphonate **50** was formed. Removal of all protecting groups was effected with *p*-toluenesulfonic acid monohydrate (*p*TsOH) in dichloromethane/THF, which is a method originally developed for *tert*-butyl carbamate cleavage.[32] By ion exchange chromatography, *p*TsOH was separated and the target α-amino acid **44** was isolated in 87% yield as the acidic zwitterion. In a ligand binding assay, measuring displacement of radio-labeled glutamate,[28b] the affinity of phosphate **44** (IC_{50} = 449 nM) was found to be substantially lower than phosphonate **43** (IC_{50} = 8 nM).

Conclusions

(*R*)-Cysteine of natural L-configuration can readily be transformed into 4-substituted *N*-(*tert*-butoxycarbonyl)-2,2-dimethylthiazolidines of high optical purity. A key intermediate is aldehyde **4**, which is the sulfur analogue of Garner's serine aldehyde **2**. The oxidation to 5-thiazolidinones **j** relies on $^1O_2$ addition and either reduction to a hemiacetal **i**, or acetic anhydride mediated water elimination from the primary 5-hydroperoxide **h**. Compared with other conversions with $^1O_2$, this is a rather fast process that tolerates up to 12% substrate concentration; competing $^1O_2$-mediated oxidations have not been observed so far, not even for very reactive allylsilanes. In general, the optical purity is retained, but aldehyde **4** and 5-thiazolidinones **j** are prone to base-catalyzed racemization. In some extreme cases, in situ treatment of hydroperoxides **h** with Ac_2O/Et_3N at –78 °C leads to either full or partial double bond isomerization. However, reduction of such hydroperoxides **h** with triphenylphosphane leads to the formation of hemiacetals **i** with unchanged double-bond position. From such intermediates, the target 5-thiazolidinones **j** might still be obtainable with mild oxidation methods. For the deprotection to (*R*)-configured α-amino acids, selective methods allow cleavage of either the *N*-Boc group or the acetonide. Rather sensitive and complex D-amino acids, such as **44** (β,γ-unsaturated, and with an allylic phosphate) can be prepared. 3-Nitro-2-pyridinesulfenyl chloride in ethanol/$NaHCO_3$ selectively cleaves the thiazolidine ring of the parent compounds **g**, and of hemiacetals **i** after *O*-derivatization with electron-donating protecting groups.

Experimental Section

General: All reagents and solvents were purchased from commercial suppliers and used without further purification. Oxidations with $^1O_2$ were performed in a cylindrical glass vessel with a double-jacketed cylindrical insert holding the halogen lamp (100 W), with the outer jacket evacuated for insulation, the inner set-up was used for water cooling of the light bulb. Two side arms served for bubbling O_2 through the reactant solution through a Teflon® tube. For cooling, the apparatus was immersed in a Dewar vessel filled with dry-ice/acetone. Stirring was performed magnetically. Precoated silica gel 60 F-254 plates (Merck) were used for TLC, with detection by UV, I_2-vapor, $KMnO_4$, or phosphomolybdenic acid/$Ce(SO_4)_2$. Chromatography was performed with Merck 60 (40–63 μm) silica gel. A Carlo–Erba Strumentazione HRGC 5300 chromatograph was used for Capillary GLC with Chirasil-Val-III columns (50 m, 0.32 mm diameter, Alltech Applied Science Labs, Deerfield, IL 60015, Serial No 986L). Considerable variation in retention time (t_R) and separation was observed for different columns. Optical Rotations ($[a]_D$) were recorded with a Perkin–Elmer Polarimeter 241 at ambient temperatures in a 1 mL cuvette (10 cm). NMR spectra were recorded with a Bruker AC-250 or a Bruker-AM-300 spectrometer. In general, the integration corresponds to the number of protons of the signal assignment.

(4*R*)-2,2-Dimethylthiazolidine-4-carboxylic Acid Hydrochloride (5): A suspension of L-cysteine hydrochloride monohydrate (**3**, Fluka, 100 g, 0.569 mol, 99.7% *ee*) in acetone (2.3 L) and 2,2-dimethoxypropane (500 mL, 4.076 mol) was boiled under reflux for 20 h. The resulting suspension was filtered hot, and the collected solid was washed with acetone and dried under reduced pressure at 30 °C, affording **5** (92.2 g, 82%) as a white solid. Evaporation of the filtrate to 60 mL gave a second crop of **5** (13.3 g, 11%). This material was used without further purification; m.p. 153–156 °C. $[a]_D$ = –85 (*c* = 0.5, MeOH). NMR (250 MHz, D_2O): δ = 1.78 and 1.79 [2× s, $(CH_3)_2C(2)$], 3.50 (dd, *J* = 18, 10 Hz) and 3.65 (dd, *J* = 18, 11 Hz) [2 H-C(5)], 4.82 [dd, *J* = 10, 11 Hz, H-C(4)] ppm.

(4*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethylthiazolidine-4-carboxylic Acid (6): To a mixture of **5** (105 g, 0.532 mol) and pyridine (500 mL), di-*tert*-butyl dicarbonate (Fluka; 127.5 g, 0.584 mol,

1.1 equiv.) was added within 5 min under argon and with cooling to –23 °C. After stirring at room temp. for 2.5 d, toluene (1.2 L) was added and the solution was extracted with ice-cold 2 N NaOH (3 × 600 mL). The alkaline extracts were washed with toluene (3 × 700 mL) and hexane (500 mL) before being acidified at 8 to 15 °C with citric acid to pH 3. Extraction with CH_2Cl_2 (500 mL, then 2 × 400 mL), and washing of the organic phases with 10% brine (2 × 300 mL), drying with Na_2SO_4, and evaporation, gave the crude material (136.2 g). Crystallization from hexanes (550 mL) afforded carbamate **6** (109.2 g, 78%); m.p. 111–112 °C. $[\alpha]^D$ = –82.7 (*c* = 0.75, $CHCl_3$). The optical purity was determined for methyl ester **7** below. ^1H NMR (300 MHz, $CDCl_3$, 2 rotamers, 1:1 ratio): δ = 1.40 and 1.45 [2 × br. s, $(CH_3)_3CO$], 1.60 [br, $(CH_3)_2C(2)$], 3.0–3.4 [m, 2H-C(5)], 4.85 and 4.95 [2 × m, H-C(4)], 8.9–10.6 (br, CO_2H) ppm.

3-*tert*-Butyl 4-Methyl (4*R*)-2,2-Dimethylthiazolidine-3,4-dicarboxylate (7): To a solution of 3-methyl-1-(*p*-tolyl)triazene[11] (CA Reg. No. 21124-13-0; 4.44 g, 29.77 mmol) in dichloromethane (200 mL), a solution of acid **6** (7.77 g, 29.77 mmol) in dichloromethane (100 mL) was added from a dropping funnel in 20 min at 15 to 20 °C. The mixture was stirred at room temperature for 3 h. Ice was added, and the mixture was washed with 2 N HCl (2 × 80 mL), 10% $NaHCO_3$ (2 × 80 mL), and with 10% brine (2 × 80 mL). The organic phase was dried (Na_2SO_4) and evaporated, and the residue (7.34 g) was distilled (micro distillation apparatus, 125 °C, 0.3 mbar) to afford ester **7** (5.65 g, 69%). $[\alpha]_D$ = –59 (*c* = 1, $CHCl_3$). GC-Analysis (Chirasil-Val; 50 m; 120 °C; carrier: 50 kPa): 37.0 min (100%, optically pure). ^1H NMR (300 MHz, $CDCl_3$; 2 rotamers, ratio 1:1): δ = 1.41 and 1.50 [2 × s, $(CH_3)_3CO$], 1.77, 1.79, 1.81, 1.86 [4 × s, $(CH_3)_2C(2)$], 3.10 (br d, *J* = 10.5 Hz) and 3.28 (dd, *J* = 10.5, 6.5 Hz) [2 H-C(5)], 3.77 (s, OCH_3), 4.80 and 4.97 [2 × m, H-C(4)].

***tert*-Butyl (4*R*)-4-(Methoxymethylcarbamoyl)-2,2-dimethylthiazolidine-3-carboxylate (8):** To an ice-cooled solution of acid **6** (40 g, 0.152 mol) and *N*-methoxy-*N*-methylamine (10 g, 0.164 mol) in ethyl acetate (500 mL) a solution of dicyclohexylcarbodiimide (33.3 g, 0.162 mol) in ethyl acetate (200 mL) was added from a dropping funnel within 50 min. The mixture was stirred at room temperature for 4 d, while at day 1 and day 2 further *N*-methoxy-*N*-methylamine (1 g, 16.4 mmol) and dicyclohexylcarbodiimide (3.4 g, 16.5 mmol) were added. The mixture was filtered, the filtrate evaporated, and the residue was dissolved in hexanes (300 mL), and filtered hot. Crystallization of the residue of the evaporated filtrate from a mixture of methanol (100 mL) and water (90 mL) gave amide **8** (27.45 g, 59%); m.p. 99–99.5 °C. $[\alpha]_D$ = –64.1 (*c* = 1.25, $CHCl_3$). Chromatography (330 g of silica gel; hexanes/EtOAc, 2:1) and crystallization from methanol/water gave a further 6.98 g (15%) of product **8**; m.p. 99.5–100 °C. $[\alpha]_D$ = –63.6 (*c* = 1.48, $CHCl_3$). $C_{13}H_{24}N_2O_4S$ (304.40) calcd. C 51.30, H 7.95, N 9.20, S 10.53; found C 51.29, H 8.02, N 9.40, S 10.58. GC-Analysis (Chirasil-Val; 50 m; 130 to 200 °C; 2 °C/min; carrier 50 kPa): 29.1 min (100%, optically pure). ^1H NMR (300 MHz, $CDCl_3$; 2 rotamers, ratio 1:1): δ = 1.41 and 1.50 [2 × s, $(CH_3)_3CO$], 1.80, 1.83, 1.90, and 1.91 [4 × s, $(CH_3)_2$-C(2)], 2.98 (dd, *J* = 12.5, 4 Hz) and 3.35 (dd, *J* = 12.5, 7.5 Hz) [2 H-C(5)], 3.22 (2 × s, NCH_3), 3.38 and 3.42 (2 × s, OCH_3), 5.05 and 5.20 [2 × m, H-C(4)] ppm.

***tert*-Butyl (4*R*)-4-Formyl-2,2-dimethylthiazolidine-3-carboxylate (4):** To an ice-cooled solution of amide **8** (15.2 g, 50 mmol) in dry diethyl ether (175 mL), $LiAlH_4$ (1.27 g, 33.5 mmol) was added under argon. After stirring at 0 to 5 °C for 20 min, the mixture was diluted with diethyl ether (200 mL) before dropwise addition (15 min.) of a solution of $KHSO_4$ (3 g) in water (10 mL) under ice-cooling. Stirring at 0 °C was continued for 20 min, then solids were removed by filtration and washing with diethyl ether. The filtrate was washed with 0.1 N HCl (130 mL), 10% $NaHCO_3$ (130 mL), and twice with saturated brine. Drying with Na_2SO_4, evaporation of solvent, and distillation of the residue (kugelrohr; 150–170 °C, 0.4 Torr) gave **4** (11.7 g, 95%). $[\alpha]_D$ = –99.1 (*c* = 0.94, $CHCl_3$). GC-Analysis (Chirasil-Val; 50 m; 125 °C; carrier 50 kPa): 22.3 min (100%, optically pure). ^1H NMR (250 MHz, $CDCl_3$; 2 rotamers, ratio 1:1): δ = 1.43 and 1.52 [2 × s, $(CH_3)_3CO$], 1.80 and 1.86 [2 × s, $(CH_3)_2$-C(2)], 3.04–3.80 [m, 2H-C(5)], 4.55 and 4.71 [2 × m, H-C(4)], 9.60 [s, HCO-C(4)] ppm.

Racemization: A sample (0.49g) was dissolved in CH_2Cl_2 and, after the addition of Et_3N (1 mL), the mixture was heated under reflux for 18 h. Washing with 1 N HCl (2 × 25 mL), drying (Na_2SO_4), and evaporation gave the crude oil (0.51 g). $[\alpha]_D$ = –3.9 (*c* = 0.77, $CHCl_3$). GC-Analysis (Chirasil-Val; 50 m; 125 °C; carrier 50 kPa): 21.4 (47.4%) and 21.7 min (49.1%, 2% *ee*).

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (9):** To a stirred suspension of ethyltriphenylphosphonium bromide (47.81 g, 129 mmol) in anhydrous THF (500 mL), butyllithium (1.6 M in hexanes, 78 mL, 124.8 mmol) was added with cooling (5–9 °C), under argon, within 10 min. Stirring at 5 °C was continued for 10 min before a solution of aldehyde **4** (24.27 g, 9.9 mmol) in THF (100 mL) was added from a dropping funnel within 20 min at 5–9 °C to the orange reaction solution. After stirring at low temperature for 40 min, the reaction was quenched by the addition of 1 M phosphate buffer (pH 7, 400 mL). After 18 h at room temp. the white precipitate was removed by filtration and washed with ethyl acetate (3 × 100 mL). The aqueous phase was separated, extracted with ethyl acetate (2 × 150 mL), the organic phases were dried with Na_2SO_4, and solvents were removed by evaporation at reduced pressure. The residue was treated with hexanes/ethyl acetate (19:1), and the insoluble material was removed by filtration. After washing with hexanes/ethyl acetate (19:1), the filtrate was evaporated and the residue was purified by chromatography on silica gel (1 kg; hexanes/ethyl acetate, 29:1) to afford a mixture of isomeric olefins **9** and **10** (20.48 g, 80%) containing approximately 90% of the major (*Z*)-isomer **9**. Solids that separated spontaneously and upon addition of pentane to the liquid fraction were recrystallized twice from methanol/water to give the (*Z*)-isomer **9** (6.98 g, 27%), containing 0.3% (*E*)-isomer **10**; m.p. 34.0–34.5 °C. $[\alpha]^D$ = 48.9 (*c* = 0.45, $CHCl_3$). $C_{13}H_{23}NO_2S$ (257.39): calcd. C 60.66, H 9.01, N 5.44, S 12.46; found C 61.04, H 9.13, N 5.15, S 11.64. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 [s, $(CH_3)_3CO$], 1.71 (dd, *J* = 7, 1.7 Hz, CH_3CH=), 1.78 and 1.80 [2 × s, $(CH_3)_2$-C(2)], 2.58 (dd, *J* = 11.5, 2 Hz) and 3.26 (dd, *J* = 11.5, 6 Hz) [2 H-C(5)], 5.11 [m, 3 main peaks, H-C(4)], 5.5 (dqd, *J* = 11, 7, 1 Hz, CH_3CH=), 5.68 (ddq, *J* = 11, 8.5, 1.7 Hz, CH_3CH=C*H*) ppm; addition of the chiral shift agent TFAE[14] showed no signals for the L-enantiomer, for example, in contrast to the racemic reference, only one signal was observed for the *tert*-butyl ester. Kugelrohr distillation of the mother liquors under high vacuum afforded further product **9** (8.14 g, 32%) containing 12.3% (*E*)-isomer **10**. Capillary GC (Chirasil-Val; 50 m; 120 °C; carrier 50 kPa): t_R = 30.7 (12.3%, **10**), 34.4 min (86.9%, **9**); racemic reference: t_R = 30.2 [1.6%, (*S*)-**10**], 30.5 [2.0%, (*R*)-**10**], 33.8 [48.2%, (*S*)-**9**], 34.1 min [48.1%, (*R*)-**10**].

***tert*-Butyl (4*R*,5*S*)-5-Hydroxy-2,2-dimethyl-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (13):** A solution of thiazolidine **9** (8.5 g, 33.07 mmol, 6.1% *trans*-isomer **10**) and *meso*-tetraphenylporphyrin (20 mg) in THF (85 mL) was cooled to –78 °C, and oxygen was bubbled through under irradiation with a 100 W halogen lamp for 18 h. TLC (hexanes/ethyl acetate, 4:1) showed complete conversion

into hydroperoxide **11**. Triphenylphosphane (8.68 g, 33.07 mmol) was added, and the temperature was allowed to reach room temperature. After 40 min. solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (450 g; hexanes/ethyl acetate, 4:1) to give **13** (1.58 g, 17%), which still contained some sensitizer, followed by purer **13** (4.42 g, 49%). $C_{13}H_{23}NO_3S$ (273.39): calcd. C 57.11, H 8.48, N 5.12, S 11.73; found C 57.01, H 8.58, N 4.95, S 11.75. MS: *m*/*z* = 273 [M^+], 258 [M^+ – 15], 216 [M^+ – 57]. $[a]_D$ = +152.7 (*c* = 1.91, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 [s, $(CH_3)_3CO$], 1.75 (dd, *J* = 7, 1.7 Hz, H_3CCH=), 1.81 and 1.97 [2× s, $(CH_3)_2$-C(2)], 2.25 [d, *J* = 4 Hz, *H*O-C(5)], 4.95 [d, *J* = 4 Hz, H-C(5)], 5.15–5.3 [m, 2 main peaks, H-C(4)], 5.38 (ddq, *J* = 10.5, 9, 1.7 Hz, H_3CH=C*H*), 5.59 (dq, *J* = 10.5, 7 Hz, H_3C-C*H*=) ppm. Further elution with hexanes/ethyl acetate (1:1) afforded the sulfoxide *tert*-butyl (*R*)-2,2-dimethyl-1-oxo-4-[(*Z*-propenyl)thiazolidine-3-carboxylate (**12**; 2.11 g, 23%) as a single epimer. MS: *m*/*z* = 273 [M^+], 240, 217 [M^+ – 56], 173 [M^+ – 100]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (s, $(CH_3)_3$-CO], 1.57 and 1.79 [2× s, $(CH_3)_2$-C(2)], 1.69 (dd, *J* = 7, 1.6 Hz, H_3CCH=), 2.72 (dd, *J* = 13, 8.5 Hz), and 3.10 (dd, *J* = 13, 6 Hz) [2 H-C(5)], 5.2–5.45 [m, H-C(4) and H_3C-CH=C*H*], 5.56 (dq, *J* = 11, 7 Hz, H_3C-C*H*=) ppm.

tert-Butyl (*R*)-2,2-Dimethyl-5-oxo-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (14)

Method a. From Hydroperoxide 11: A solution of thiazolidine **9** (8.36 g, 32.53 mmol, 0.5% *trans*-isomer) and *meso*-tetraphenylporphyrin (25 mg) in THF (100 mL) was cooled to –78 °C, and oxygen was bubbled through under irradiation with a 100 W halogen lamp for 18 h. TLC (hexanes/ethyl acetate, 4:1) showed complete conversion into hydroperoxide **11**. Et_3N (10 mL) and acetic anhydride (10 mL) were added at –78 °C, and stirring was continued for 3.5 h. The reaction mixture was added with stirring to 0.5 N HCl (350 mL), and extracted with ethyl acetate (2× 200 mL). The organic phase was washed with saturated brine, dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. The residue (9.2 g) was purified by chromatography on silica gel (250 g; hexanes/ethyl acetate, 10:1) to give a red product **14** (6.2 g), which was treated with Tonsil (3 g) in hexanes (200 mL). Filtration and evaporation of the solvent gave white crystalline **14** (6.176 g, 70%). Recrystallization from methanol/water gave pure **14** (5.89 g, 66%); m.p. 74–75 °C. $[a]_D$ = –242.6 (*c* = 0.452, $CHCl_3$). $C_{13}H_{21}NO_3S$ (271.37): calcd. C 57.54, H 7.80, N 5.16, S 11.82; found C 57.74, H 7.83, N 5.06, S 11.77. Capillary GC (Chirasil Val; 50 m; 130 °C; carrier 50 kPa): t_R^{et} = 34.26 (*trans*), 36.14 (*cis*) min, no separation of enantiomers. MS: *m*/*z* = 243 [M^+ – 28]. IR ($CHCl_3$): $\tilde{\nu}$ = 1695 (strong), 1655 (weak) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 [s, $(CH_3)_3CO$], 1.81 (d, *J* = 7 Hz, further high order splitting, H_3C-CH=), 1.99 and 2.05 [2×s, $(CH_3)_2C(2)$], 5.3–5.4 [m, H-C(4), H_3CH=C*H*-], 5.75–5.85 (m, H_3CCH=) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 198.0 [C(5)], 151.7 [N-C(O)-O], 129.8 (H_3C-*C*H=), 127.2 (H_3CCH=*C*H-), 81.2 [$(CH_3)_3CO$], 73.1 [C(2)], 67.9 [C(4)], 32.0 and 30.9 [$(CH_3)_2C(2)$], 28.3 [$(CH_3)_3CO$], 13.6 (H_3C-CH=) ppm.

Method b. From Hemithioacetal 13: To a solution of oxalyl chloride (0.49 mL, 5.73 mmol) in CH_2Cl_2 (25 mL), DMSO (0.81 mL, 11.5 mmol) was added by using a syringe at –60 to –70 °C within 2 min, followed by the dropwise addition of a solution of **13** (1.37 g, 5 mmol) in CH_2Cl_2 (25 mL) at the same temperature within 20 min. The mixture was stirred at –70 °C for 15 min before ethyldiidopropylamine (8.6 mL, 50 mmol) was added within 10 min, keeping the temperature below –60 °C. The mixture was allowed to reach room temperature, and was stirred for 2 h before dilution with CH_2Cl_2 (350 mL). This solution was washed with 0.5*N* HCl (2× 100 mL) and with 10% brine (100 mL). Drying with Na_2SO_4 and evaporation of solvents gave a residue (1.4 g), which was purified on silica gel (57 g; hexane/ethyl acetate, 10:1) to afford **14** {1.114 g, 81%; $[a]_D$ = –215.8 (*c* = 1.8, $CHCl_3$)}, followed by starting material **13** (146 mg, 10%).

(*R*)-2,2-Dimethyl-4-(*Z*)-propenylthiazolidin-5-one (17): To a solution of thiazolidinone **14** (2.0 g, 7.38 mmol) in anhydrous CH_2Cl_2 (8 mL), trimethylsilyl bromide (1.9 mL, 14.76 mmol) was added dropwise at 0 °C, followed by the addition of phenol (4 M in CH_2Cl_2, 10.66 mL, 42.6 mmol). After stirring at 0 °C for 5 h, volatiles were evaporated under reduced pressure from the white suspension. Diethyl ether (50 mL) was added and the suspension was stirred at room temp. for 30 min. The suspension was filtered, and the solids were washed three times with diethyl ether. Drying in a vacuum desiccator gave hydrobromide **15** (1.822 g, 98%). $[a]_D$ = –40 (*c* = 0.33, EtOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.86 (dd, *J* = 7, 1.7 Hz, H_3C-CH=), 2.03 [s, $(CH_3)_2$-C(2)], 5.45 (ddq, *J* = 11, 9, 1.7 Hz, H_3C-CH=C*H*), 5.56 [dd, *J* = 9, 1 Hz, H-C(4)], 6.25 (dqd, *J* = 11, 7, 1 Hz, H_3C-C*H*=) ppm. ^{13}C NMR (62.9 MHz, D_2O): δ = 203.6 [C(5)], 143.1 (H_3C-*C*H=), 120.4 (H_3C-CH=*C*H), 75.6 [C(2)], 66.2 [C(4)], 31.2 [(CH_3)$_2$-C(2)], 17.0 (H_3C-CH=) ppm.

Crude hydrochloride **16** (185 mg), obtained analogously from **14** with trimethylsilyl chloride/phenol in CH_2Cl_2 (see below[17]) was partitioned between ethyl acetate (20 mL) and 10% aqueous Na_2CO_3 (20 mL). The aqueous phase was separated and extracted with ethyl acetate (20 mL), the organic phases were washed with 10% brine (3 × 10 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Kugelrohr distillation (120 °C, 0.4 mbar) of the residue (117 mg) gave **17** (108 mg, 70%). MS: *m*/*z* = 171 [M^+], 143 [M^+ – 28]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.67 and 1.82 [2× s, $(CH_3)_2$-C(2)], 1.79 (dd, *J* = 7, 1.7 Hz, H_3C-CH=), 2.31 (br d, *J* = 9 Hz, NH), 4.55 [br. t, *J* = 9 Hz, H-C(4)], 5.31 (ddq, *J* = 10.5, 8, 1.7 Hz, H_3C-CH=C*H*), 5.93 (dqd, *J* = 10.5, 7, 1 Hz, 1 H, H_3C-C*H*=) ppm.

(*Z*)-(*R*)-2-Aminopent-3-enoic Acid (18): Crude hydrobromide **15** (200 mg, 0.794 mmol) was dissolved in 1 N HCl (6 mL). After 13 d at room temperature, lyophilization gave the hydrobromide of **18** (127 mg). Part of this material (114 mg) was subjected to a column of ion exchange resin (Dowex 50W × 8 H^+; 200–400 mesh; 4.5 g). After elution with water, the product was eluted with 1% aqueous ammonia. Lyophilization gave **18** (53 mg, 64%). $[a]_D$ = –283 (*c* = 0.27, AcOH). $C_5H_9NO_2$ (115.13): calcd. C 52.16, H 7.88, N 12.17; found C 52.20, H 7.93, N 12.14. MS (FAB): *m*/*z* = 116 [M + H^+]. ^{1}H NMR (300 MHz, D_2O): δ = 1.79 [dd, *J* = 7.0, 1.7 Hz, 3H-C(5)], 4.61 [dd, *J* = 10.0, 0.8 Hz, H-C(2)], 5.46 [ddq, *J* = 11.5, 10.0, 1.7 Hz, H-C(3)], 6.02 [dqd, *J* = 11.5, 7.0, 0.8 Hz, H-C(4)] ppm.

Methyl (*Z*)-(*R*)-2-(*tert*-Butoxycarbonylamino)pent-3-enoate (20): For analytical purposes, part of the above material was dissolved in 10% aqueous $NaHCO_3$ (10 mL/mmol) and an equal amount of dioxane. Di-*tert*-butyl dicarbonate (Boc_2O, 2 equiv.) was added and the mixture was stirred vigorously for 30 min. Addition to 2 N HCl was followed by extraction with ethyl acetate (3×). The organic phase was washed with 10% brine, dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. The crude residue was dissolved in diethyl ether and treated with an excess of ethereal diazomethane. Evaporation of solvent after quenching of excess diazomethane with acetic acid, and chromatography on silica gel (hexanes/ethyl acetate, 4:1) gave **20**. $[a]_D$ = –140.2 (*c* = 0.51, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 [s, $(CH_3)_3CO$], 1.83 [dd, *J* = 7.0, 1.7 Hz, 3H-C(5)], 3.74 (s, OCH_3), 4.95–5.20 [m, H-C(2), NH], 5.26 [ddq, *J* = 11.5, 10.0, 1.7 Hz, H-C(3)], 5.80 [dqd, *J* =

11.5, 7.0, 0.8 Hz, H-C(4)] ppm. Capillary GC (Chirasil-L-Val; 50 m; 100 °C; carrier 80 kPa) racemic reference: t_R = 42.48 [*cis*(*R*)], 43.38 [*cis*(*S*)], 46.97 [*trans*(*R*)], 48.57 [*trans*(*S*)] min; 94% *ee*.

Methyl (*Z*)-(*R*)-2-Aminopent-3-enoate Hydrochloride (19): To a solution of thiazolidinone **14** (2.0 g, 7.38 mmol) in CH_2Cl_2 (8 mL), trimethyl chlorosilane (1.87 mL, 14.76 mmol) was added at 0 °C, followed by a solution of phenol (4 M in CH_2Cl_2, 10.66 mL, 42.64 mmol).[17] After stirring for 5 h at 0 °C, trimethyl chlorosilane (1.9 mL) was added and stirring was continued overnight. Another portion of trimethyl chlorosilane (1.9 mL) and phenol solution (4 M in CH_2Cl_2, 5.33 mL) were added, and stirring at 0 °C was continued for 5 h. Addition of reagents was repeated and, after stirring for 30 min, volatiles were removed at 25 °C under reduced pressure. Diethyl ether (100 mL) was added, and the resulting suspension was stirred for 30 min. Filtration, washing with diethyl ether (3×), and drying under high vacuum gave hydrochloride **16** (1.48 g, 96%) as a white powder. Part of this material (50 mg) was taken up in anhydrous methanol (1 mL) and trimethyl chlorosilane (0.1 mL). After stirring at room temp. for 6 d, solvents were evaporated under reduced temperature to give ester **19** (35 mg, 87%). $[\alpha]_D$ = –174 (*c* = 0.44, MeOH). ^{1}H NMR (250 MHz, D_2O): δ = 1.87 [dd, *J* = 7, 1.7 Hz, 3H-C(5)], 3.90 (s, OCH_3), 5.10 [d, *J* = 10 Hz, H-C(2)], 5.51 [ddq, *J* = 11, 10, 1.7 Hz, H-C(3)], 6.20 [dq, *J* = 11, 7 Hz, H-C(4)] ppm. For analysis by capillary GC, an analytical probe of the above material was derivatized with Boc_2O/$NaHCO_3$ in dioxane/water as described above, affording the *tert*-butyl carbamate **20** in 98.8% *ee*.

***tert*-Butyl (*R*)-2,2-Dimethyl-5-oxo-4-[(*Z*)-propenyl]oxazolidine-3-carboxylate (21):** To a solution of thiazolidinone **14** (1.003 g, 3.7 mmol) in THF (56 mL) and water (20 mL), 30% H_2O_2 (2.2 mL) was added dropwise under cooling (6–7 °C), followed by LiOH monohydrate (3.7 mmol). The mixture was stirred for 30 min at 0 °C, then the reaction was quenched by adding 0.1 N $Na_2S_2O_3$ (20 mL), immediately followed by partition between ethyl acetate (100 mL) and water (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL), and the organic phase was washed with water (60 mL) and brine, to separate the phases. After additional washing with saturated brine (2× 60 mL) the organic phase was dried (Na_2SO_4), and volatiles were evaporated under reduced pressure. Chromatography of the residue (773 mg) on silica gel (35 g; hexanes/ethyl acetate, 10:1) afforded starting material **14** (131 mg, 13%). $[\alpha]_D$ = –229 (*c* = 0.675, $CHCl_3$), corresponding to 94% optical purity (no signal from the other enantiomer was detected by ^{1}H NMR analysis by addition of TFAE, see above). Further elution gave lactone **21** (528 mg, 56%); m.p. 101.5–102.5°. $[\alpha]_D$ = –75.6 (*c* = 0.71, $CHCl_3$). $C_{13}H_{21}NO_4$ (255.31): calcd. C 61.16, H 8.29, N 5.49; found C 61.15, H 8.52, N 5.41. MS: *m*/*z* = 255 [M^+], 240 [M^+ – 15], 199 [M^+ – 56]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 [s, $(CH_3)_3CO$], 1.76 [s, $(CH_3)_2$-C(2)], 1.83 (d, *J* = 7 Hz, H_3C-CH=), 4.9–5.2 [m, H-C(4)], 5.32 (tq, *J* = 11, 1.7 Hz, H_3C-CH=C*H*), 5.86 (dq, *J* = 11, 7 Hz, H_3C-C*H*=) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 169.6 [C(5)], 151.2 [NC(O)O], 130.3 (H_3C-*C*H=), 125.5 (H_3C-CH=*C*H), 96.5 [$(CH_3)_3CO$], 81.3 [C(2)], 54.8 [C(4)], 28.3 [$(CH_3)_3CO$], 27.7 and 26.0 [$(CH_3)_2$-C(2)], 13.4 (H_3*C*-CH=) ppm.

The aqueous phase was carefully acidified under cooling with 2 N HCl (20 mL) and extracted with ethyl acetate (3 × 100 mL). The organic phases were washed with 10% brine (3× 60 mL), dried (Na_2SO_4), and solvents were evaporated under reduced pressure. The residue (117 mg) was redissolved in ethyl acetate and treated with an excess of ethereal diazomethane. Chromatography (silica gel; hexanes/ethyl acetate, 6:1) of the residue after evaporation of solvents gave an additional 20 mg (2%) of lactone **21**, followed by 34 mg (4%) of methyl ester **20** in better than 99% *ee* according to capillary GC analysis (see above).

(*Z*)-(*R*)-2-(*tert*-Butoxycarbonylamino)pent-3-enoic Acid (22): To a solution of lactone **21** (186 mg, 0.729 mmol) in THF (11 mL) and water (4 mL), 30% H_2O_2 (0.44 mL) was added at 0 °C, followed by LiOH·H_2O (33.6 mg, 0.802 mmol). After stirring at 0 °C for 2 h, the mixture was diluted with ethyl acetate (150 mL), washed with 0.1 N NaS_2O_3 (150 mL), and water. From the organic phase, starting material **21** (28 mg, 15%) was recovered. The aqueous phase was acidified to pH 1 with 2 N HCl and extracted with ethyl acetate (3 × 50 mL). The residue of the organic phase (220 mg) contained elemental sulfur, which was separated from the product by filtration and by several chromatographic columns on silica gel. A final column with 9 g of silica gel (hexanes/ethyl acetate, 1:1, 1% AcOH) gave acid **22** (102 mg, 65%). $[\alpha]_D$ = –123 (*c* = 1.29, $CHCl_3$). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.38 [s, $(CH_3)_3CO$], 1.69 [dd, *J* = 7, 1.7 Hz, 3H-C(5)], 4.69 [t, *J* = 9 Hz, H-C(2)], 5.35 [dd, *J* = 11, 9 Hz, H-C(3)], 5.63 [dq, *J* = 11, 7 Hz, H-C(4)], 7.24 (d, *J* = 9 Hz, NH), 12.43 (br., CO_2H) ppm. ^{13}C NMR (75.4 MHz, [D_6]-DMSO): δ = 172.8 [C(1)], 155.2 [HNC(O)O], 128.3 [C(4)], 125.4 [C(3)], 78.1 [$(CH_3)_3CO$], 51.3 [C(2)], 28.2 [$(CH_3)_3CO$], 13.3 [C(5)] ppm. Part of this material was esterified as above with ethereal diazomethane, giving methyl ester **20** in 98% *ee*.

(*R*)-2,2-Dimethyl-5-oxo-4-[(*Z*)-propenyl]oxazolidinium Bromide (23): To a solution of lactone **21** (306 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (4 mL), trimethylbromosilane (0.31 mL, 2.4 mmol) was added at 5 °C, followed by a solution of phenol (452 mg, 4.8 mmol) in CH_2Cl_2 (1.2 mL). After stirring for 3.5 h at 0–5 °C, volatiles were evaporated from the suspension and the residue was taken up in diethyl ether (40 mL). Filtration, washing with diethyl ether and drying at room temp. in a desiccator afforded hydrobromide **23** (226 mg, 80%). ^{1}H NMR (250 MHz, CD_3OD, immediate measurement): δ = 1.74 (dd, *J* = 7, 1.7 Hz, H_3C-CH=), 2.40 and 2.50 [2× br. s, 1.8 H, $(CH_3)_2$C(2)], 5.43 (dd, *J* = 11, 9 Hz, H_3CH=C*H*), 5.56 [d, *J* = 9 Hz, H-C(4)], 5.97 (dq, *J* = 11, 7 Hz, H_3C-C*H*=) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 170.2 [C(5)], 135.9 (H_3C-*C*H=), 122.3 (H_3CH=*C*H), 101.8 [C(2)], 60.0 [C(4)], 26.7 and 22.6 [2× m, $(CD_3)_2$-C(2)], 14.5 (H_3*C*-CH=) ppm.

(*Z*)-(*R*)-2-Aminopent-3-enoic Acid Hydrobromide (18)

(a) NMR Experiment: The above NMR solution was measured after 3 d. ^{1}H NMR (250 MHz, CD_3OD): δ = 1.27 [m, $(CD_3)_2$C-$(OCD_3)_2$], 1.83 (dd, *J* = 7, 1.7 Hz, H_3C-CH=), 4.83 [d, *J* = 9 Hz, H-C(2)], 5.42 (ddq, *J* = 11, 9, 1.7 Hz, H_3C-CH=C*H*), 6.04 (dq, *J* = 11, 7 Hz, H_3C-C*H*=) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 171.5 [C(1)], 136.4 (H_3C-*C*H=), 122.5 (H_3C-CH=*C*H), 51.9 [C(2)], 14.7 [C(5)] ppm. ^{1}H NMR (250 MHz, D_2O, immediate measurement): δ = 1.67 (dd, *J* = 7, 1.7 Hz, H_3C-CH=), 2.09 (s, 5 H, acetone), 4.75 [d, *J* = 9 Hz, H-C(2)], 5.32 (ddq, *J* = 11, 9, 1.7 Hz, H_3CH=C*H*), 5.97 (dq, *J* = 11, 7 Hz, H_3C-C*H*=) ppm.

(b) Preparative Experiment: Deprotected lactone **23** (109 mg, 0.462 mmol) was dissolved in CD_3OD (0.7 mL). After 3 d at room temperature, NMR analyses indicated complete cleavage of the acetonide. Evaporation of solvent gave hydrobromide **18** (90.0 mg, 99%). The two NMR samples were transformed into *N*-Boc methyl ester **20** and subjected to capillary GC analysis as described above: 99% *ee*, ca. 2% *trans*-isomer.

(*Z*)-(*R*)-2-(*tert*-Butoxycarbonylamino)pent-3-enoic Acid Benzyl Amide (24)

(a) From Aminobutenoate 18: To a solution/suspension of the hydrobromide of **18** (90 mg, 0.459 mmol) in dioxane (9 mL) and 10%

aqueous $NaHCO_3$ (9 mL), di-*tert*-butyl dicarbonate (Boc_2O) (200 mg, 0.918 mmol) was added at room temp. After 18 h stirring, the mixture was taken up in water (20 mL), 10% $NaHCO_3$, and ethyl acetate (20 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 25 mL) then the organic phases were washed with 10% $NaHCO_3$ (2 × 20 mL). The aqueous phases were cooled with ice before careful acidification to pH 1 with 2 N HCl. Extraction with ethyl acetate (3 × 50 mL), washing with 10% brine (3 × 30 mL), drying (Na_2SO_4), and evaporation of solvents gave the crude material (95 mg). Chromatography on silica gel (10 g; hexanes/ethyl acetate, 1:1 with 1% AcOH) gave carbamate **22** (73 mg, 74%) (see above) with 97.6% *ee* according to capillary GC analysis of its methyl ester derivative **20** (1.8% *trans*-isomer, see above). Part of this material (35 mg, 0.163 mmol) was dissolved in DMF (2 mL) and treated with HOBT (30 mg, 13% water, 0.195 mmol) and DCC (50.5 mg, 0.2445 mmol) for 1 h at room temperature. After the addition of further amount of reagents (15 mg of HOBT, 25 mg of DCC) stirring was continued for 30 min before the addition of benzylamine (53 μL, 0.489 mmol) to the suspension. After 3 h at room temp, the mixture was taken up in diethyl ether (35 mL) and 0.1 N HCl (50 mL) and the separated aqueous phase was extracted with diethyl ether (40 mL). The organic phases were washed with 10% brine (2 × 30 mL), the organic phase was dried (Na_2SO_4) and the solvent was evaporated to afford the crude material (131 mg). Chromatography (9 g of silica gel; hexanes/ethyl acetate, 2:1) gave amide **24** (33 mg, 71%). $[\alpha]_D$ = –54.6 (c = 0.39, $CHCl_3$). MS: m/z = 304 [M^+], 248 [M^+ – 56], 231 [M^+ – 73]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 [s, $(CH_3)_3CO$], 1.80 [dd, J = 7, 1.7 Hz, 3H-C(5)], 4.46 (m, 2 peaks, 2 H, PhCH_2NH), 4.92 [t, J = 9 Hz, H-C(2)], 5.15–5.35 (m, NH), 5.48 [ddq, J = 11, 9, 1.7 Hz, H-C(3)], 5.83 [dq, J = 11, 7 Hz, H-C(4)], 6.2–6.4 (m, NH), 7.1–7.4 (m, PhH) ppm.

(b) From Thiolactone 14: To a solution of thiolactone **14** (100 mg, 0.369 mmol) in toluene (2 mL, freshly distilled from Na) a solution of *N*-benzyl-dimethylaluminum amide (1.7 M in CH_2Cl_2, 0.33 mL) [22] was added by syringe. The mixture was stirred for 18 h at room temperature before additional aluminum amide (0.33 mL) was added. After 2 h, the mixture was diluted with ethyl acetate and washed with 10% aqueous tartaric acid (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL and 2 × 20 mL), and the organic phases were washed with 10% tartaric acid solution (25 mL) and with 10% brine (3 × 30 mL). The organic phase was dried (Na_2SO_4) to give a residue (104 mg), which was purified by chromatography (10 g silica gel; hexanes/ethyl acetate, 2:1) to give amide **24** (64 mg, 57%). $[\alpha]_D$ = –57 (c = 0.54, $CHCl_3$).

***tert*-Butyl [(*Z*)-(*R*)-1-(3-Nitropyridin-2-yl-disulfanylmethyl)but-2-enyl]carbamate (26):** To a solution of thiazolidine **9** (257 mg, 1.0 mmol) in ethanol (4 mL), $NaHCO_3$ (252 mg, 3.0 mmol) was added, followed by 3-nitro-2-pyridinesulfenyl chloride (**25**; 286 mg, 1.5 mmol[24a]) at 0 °C. After stirring for 5.5 h at 0 °C (during which time generation of some CO_2 was observed), the mixture was filtered and the insoluble (mostly inorganic) material was washed with ethyl acetate. Chromatography of the residue (456 mg) of the filtrate (18 g silica gel; hexanes/ether, 1:1) afforded 2-ethoxysulfanyl-3-nitropyridine (40 mg), mixed fractions (145 mg), and **26** (217 mg, 58%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 [s, $(CH_3)_3$-CO], 1.73 [dd, J = 7, 1.6 Hz, 3H-C(4)], 3.03 (dd, J = 13, 5 Hz) and 3.19 (dd, J = 13, 6 Hz) (CH_2-SS), 4.65 [m, 5 peaks, H-C(1)], 5.42 [ddq, J = 11, 8, 1.6 Hz, H-C(2)], 5.64 [dqd, J = 11, 7, 1 Hz, H-C(3)], 5.97 (br. d, J = 6 Hz, 0.9 H) and 6.17 (br. d, J = 6 Hz, 0.1 H) (NH), 7.40 [dd, J = 8, 4.5 Hz, H-C(5′)], 8.55 [dd, J = 8, 1.5 Hz, H-C(4′)], 8.97 [br. d, J = 4.5 Hz, H-C(6′)]. MS: m/z = 315 [M^+ – 56], 298 [M^+ – 73], 254, 216 [M^+ – 155].

***tert*-Butyl [(*Z*)-(*R*)-1-(Mercaptomethyl)but-2-enyl]carbamate (27):** To a solution of disulfide **26** (100 mg, 0.27 mmol) in dioxane (2.7 mL) and water (0.3 mL), tri-*n*-octyl phosphane (156 μL, 0.35 mmol) was added by using a syringe. After stirring at room temperature for 30 min, dichloromethane (60 mL) was added and, after drying with Na_2SO_4, volatiles were removed under reduced pressure. Chromatography of the residue (250 mg) on silica gel (10 g; hexanes/ethyl acetate, 10:1) afforded mercaptan **27** (46 mg, 78%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 (t, J = 8.5 Hz, SH), 1.46 [s, $(CH_3)_3CO$], 1.73 [dd, J = 7, 1.7 Hz, 3H-C(4)], 2.65 (ddd, J = 13, 8.5, 6 Hz) and 2.74 (ddd, J = 13, 8.5, 5 Hz) (HS-CH_2-), 4.45–4.65 [m, H-C(1)], 4.6–4.8 (m, NH), 5.29 [ddq, J = 11, 8.5, 1.7 Hz, H-C(2)], 5.69 [dqd, J = 11, 7, 1 Hz, H-C(3)] ppm. MS: m/z = 170 (M^+ – 47, $HSCH_2$), 161 [M^+ – 56], 114, 70.

***tert*-Butyl (4*R*,5*S*)-5-Acetoxy-2,2-dimethyl-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (28):** To a solution of thiazolidine **13** (546 mg, 2 mmol) in pyridine (4 mL), acetic anhydride (4 mL) was added at 0 °C. The solution was stirred for 18 h at room temperature, then solvents and reagents were removed by evaporation at 50 °C under reduced pressure. Traces of pyridine were removed by co-evaporation with hexanes (2 × 150 mL). Chromatography of the residue on silica gel (25 g; hexanes/ethyl acetate, 10:1) gave acetate **28** (529 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 [s, $(CH_3)_3CO$], 1.73 (br. d, J = 7 Hz, H_3C-CH=), 1.81 and 1.89 [2 × br. s, $(CH_3)_2$-C(2)], 2.13 [s, CH_3C(O)O-C(5)], 5.05–5.35 [m, H-C(4)], 5.41 (ddq, J = 11, 9, 1.7 Hz, H_3C-CH=CH), 5.53–5.70 (m, H_3C-CH=), 5.70 [s, H-C(5)] ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.9 [CH_3-C(O)O], 152.4 [NC(O)O], 129.0 (H_3C-CH=), 127.2 (br., H_3C-CH=CH), 81.3 and 80.4 [C(2), C(5)], 67.2 [C(4)], 32.8 and 30.0 [br., (CH_3)$_2$-C(2)], 28.5 [(CH_3)$_3$CO], 21.4 [CH$_3$-C(O)O], 13.3 (H_3C-CH=) ppm. MS: m/z = 315 [M^+], 300 [M^+ – 15], 259 [M^+ – 56].

***tert*-Butyl (4*R*,5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethyl-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (29):** To a solution of 5-hydroxythiazolidine **13** (546 mg, 2 mmol) in anhydrous DMF (3 mL), imidazole (204 mg, 3 mmol) and *tert*-butylchlorodimethylsilane (362 mg, 2.4 mmol) were added at room temperature. After stirring for 18 h, water (150 mL) was added, and the mixture was extracted with hexanes (3 × 100 mL). The combined organic phases were washed with saturated brine (2 × 80 mL), dried (Na_2SO_4), and volatiles were evaporated under reduced pressure. Chromatography on silica gel (50 g; hexanes/ethyl acetate, 10:1) of the residue (700 mg) gave silyl ether **29** (659 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 and 0.13 [2 × s, $(CH_3)_2$Si], 0.91 [s, $(CH_3)_3$C-Si], 1.45 [s, $(CH_3)_3CO$], 1.72 (dd, J = 7, 1.7 Hz, H_3C-CH=), 1.77 and 1.92 [2 × br. s, $(CH_3)_2$-C(2)], 4.87 [s, H-C(5)], 5.0–5.2 [br., 2 peaks, H-C(4)], 5.37 (ddq, J = 11, 10.5, 1.7 Hz, H_3C-CH=CH), 5.54 (dq, J = 11, 7 Hz, H_3C-CH=) ppm. MS: m/z = 372 [M^+ – 15], 330 [M^+ – 57], 316 [M^+ – 15 – 56], 272 [M^+ – 15 – Boc].

***tert*-Butyl (4*R*,5*R*)-5-Chloro-2,2-dimethyl-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (30):** To a solution of 5-hydroxythiazolidine **13** (1.4 g, 5.128 mmol, 13% *trans* isomer) in anhydrous CH_2Cl_2 (14 mL), 1-chloro-1-dimethylamino-2-methylpropene (2.17 mL, 15.4 mmol[12]) were added at 0 °C within 3 min (syringe). The mixture was stirred at 0 °C for 18 h then added to pH 7 phosphate buffer (1 M, 100 mL), cooled to 0 °C. Extraction with ethyl acetate (200 mL), drying (Na_2SO_4), and evaporation of volatiles under reduced pressure gave crude **30** (1.16 g, 78%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 [s, $(CH_3)_3CO$], 1.76 (d, J = 7 Hz, H_3C-CH=), 1.80 and 2.06 [2 × s, $(CH_3)_2$-C(2)], 5.20 [s, H-C(5)], 5.35–5.55 [m, H-C(4), H_3CH=CH], 5.55–5.7 (m, H_3C-CH=) ppm. MS: m/z = 255 [M^+ – Cl], 199 [M^+ – 56 – Cl].

***tert*-Butyl (4*R*,5*S*)-5-Methoxy-2,2-dimethyl-4-[(*Z*)-propenyl]thiazolidine-3-carboxylate (31):** Chloride **30** (1.16 g, 3.98 mmol) was dis-

solved in CH_3OH (5 mL). After stirring at room temperature for 2 h, this solution was added to pH 7 phosphate buffer (1 M, 50 mL). Extraction with ethyl acetate (100 mL and 50 mL), drying of the organic phase (Na_2SO_4), evaporation of solvent, and chromatography on silica gel (50 g; hexanes/ethyl acetate, 10:1) afforded **31** (615 mg, 54%). MS: *m*/*z* = 255 [M^+ – OCH_3], 216, 211, 199 [M^+ – OCH_3 – 56], 172 [M^+ – OCH_3 – 73], 155 [M^+ – OCH_3 – Boc]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 [s, $(CH_3)_3CO$], 1.72 (d, *J* = 7 Hz, H_3C-CH=), 1.80 and 1.82 [2× s, $(CH_3)_2$-C(2)], 3.33 [s, H_3CO-C(5)], 4.46 [s, H-C(5)], 5.41 (ddq, *J* = 11, 9, 1.7 Hz, H_3CH=C*H*), 5.45–5.65 (m, H_3C-C*H*=) ppm. Further elution gave (4*R*,5*S*)-5-methoxy-2,2-dimethyl-4-[(*Z*)-propenyl]thiazolidine (114 mg, 15%). MS: *m*/*z* = 187 [M^+], 172 [M^+ – 15], 155 [M^+ – 32]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.63 and 1.66 [2× s, $(CH_3)_2$-C-(2)], 1.79 (dd, *J* = 7, 1.7 Hz, H_3C-CH=), 1.95–2.2 (br., NH), 3.33 [s, H_3CO-C(5)], 4.41 [dd, *J* = 10, 4 Hz, H-C(4)], 5.08 [d, *J* = 4 Hz, H-C(5)], 5.40 (ddq, *J* = 11, 10, 1.7 Hz, H_3C-CH=C*H*), 5.70 (dq, *J* = 11, 7 Hz, H_3C-C*H*=) ppm.

***tert*-Butyl {(*Z*)-(*R*)-1-[(*S*)-(*tert*-Butyldimethylsilanyloxy)-(3-nitropyridin-2-yl-disulfanyl)methyl]but-2-enyl}carbamate (32):** To a solution of 5-(silyloxy)thiazolidine **29** (212 mg, 0.548 mmol) in ethanol (4 mL), $NaHCO_3$ (138 mg, 1.64 mmol) and sulfenyl chloride **25** (157 mg, 0.822 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 3 h before more reagents (138 mg of $NaHCO_3$, 157 mg of **25**) were added. After 2 h, further portions of $NaHCO_3$ (138 mg) and sulfenyl chloride **25** (157 mg) were added. The mixture was left at 0–8 °C before filtration and washing with ethyl acetate. Chromatography of the residue of the filtrate (520 mg) on silica gel (hexanes/ethyl acetate, 4:1) gave **32** (228 mg, 88%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.0 and 0.09 [2× s, $(CH_3)_2$-Si], 0.73 [s, $(CH_3)_3$C-Si], 1.24 [s, $(CH_3)_3CO$], 1.68 [dd, *J* = 7, 1.7 Hz, 3H-C(4)], 4.6–4.9 [m, H-C(1)], 4.95 (d, *J* = 3 Hz, -SC*H*O-), 5.26 (d, *J* = 8 Hz, NH), 5.37 [ddq, *J* = 11, 9, 1.7 Hz, H-C(2)], 5.66 [dq, *J* = 11, 7 Hz, H-C(3)], 7.21 [dd, *J* = 8, 4.5 Hz, H-C(5′)], 8.36 [dd, *J* = 8, 1.5 Hz, H-C(4′)], 8.80 [dd, *J* = 4.5, 1.5 Hz, C(6′-H)] ppm.

***tert*-Butyl {(*Z*)-(*R*)-1-[(*S*)-Methoxy-(3-nitropyridin-2-yl-disulfanyl)-methyl]but-2-enyl}carbamate (33):** To a solution of 5-methoxythiazolidine (**31**; 0.348 mmol) in ethanol (2 mL), $NaHCO_3$ (88 mg, 1.044 mmol) and sulfenyl chloride **25** (99.4 mg, 0.522 mmol) were added at 0 °C. After stirring at 0 °C for 2 h, additional freshly prepared **25** (99 mg) was added, and stirring was continued for 15 min. Ethyl acetate (30 mL) was added, and the suspension was filtered. The filtrate was evaporated, and the residue (281 mg) was purified by chromatography on silica gel (hexane/ether, 1:1), followed by two chromatographic columns of the mixed fractions. A total of 33 mg (23%) of disulfide **33** was isolated. MS: *m*/*z* = 345 [M^+ – 56], 328 [M^+ – 73], 214. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.43 [s, $(CH_3)_3CO$], 1.88 [dd, *J* = 7, 1.7 Hz, 3H-C(4)], 3.57 (s, CH_3O), 4.59 (d, *J* = 4 Hz, -SC*H*OCH_3), 5.0–5.5 [m, NH, H-C(1), H-C(2)], 5.78 [dq, *J* = 11, 7 Hz, H-C(3)], 7.38 [dd, *J* = 8, 4.5 Hz, H-C(5′)], 8.52 [dd, *J* = 8, 1.5 Hz, H-C(4′)], 8.93 [dd, *J* = 4.5, 1.5 Hz, H-C(6′)] ppm.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[(*Z*)-3-(trimethylsilanyl)propenyl]thiazolidine-3-carboxylate (34):** To a suspension of methyltriphenylphosphonium bromide (8.2 g, 22.96 mmol) in absolute THF (40 mL), *n*-butyllithium (1.6 M in hexane, 16 mL, 25.5 mmol) was added within 20 min at 4–7 °C under argon. After stirring for 1 h at room temperature, (iodomethyl)trimethylsilane (3.4 mL, 4.9 g, 23 mmol) was added within 10 min at 0 °C. Stirring at room temperature for 1.5 h resulted in the formation of two liquid phases. Butyllithium (1.6 M in hexane, 16 mL) was added by using a syringe at –35 to –55 °C and the inhomogeneous mixture was warmed to room temperature and stirred for 1.5 h at this temperature. Aldehyde **4** (5.0 g, 20.41 mmol) dissolved in THF (10 mL) was then added within 10 min at –30 to –50 °C. After stirring for 30 min at –15 to –30 °C, the mixture was left overnight at room temperature, then added to saturated NH_4Cl (100 mL), and extracted three times with ethyl acetate. The combined organic phases were washed with 10% brine, dried (Na_2SO_4), and volatiles were evaporated. The residue (14.1 g) was co-evaporated with CH_2Cl_2 at normal pressure until a clear solution resulted. Addition of diethyl ether under ice-cooling led to the formation of a resinous precipitate. The mother liquor was decanted and filtered (paper filter), solvents were evaporated, and the residue (7.5 g) was subjected to column chromatography (3120 g silica gel; hexanes/toluene, 7:3 followed by toluene) to afford fractions of pure *cis*-isomer **34** (793 mg), followed by a mixture of **34** and its *trans*-isomer **35** (8%). Kugelrohr distillation of **34** (0.01 mbar, 120–150 °C) gave pure **34** (770 mg, 11%). $[\alpha]_D$ = +149.2 (*c* = 1.35, $CHCl_3$). $C_{16}H_{31}NO_2SSi$ (329.57): calcd. C 58.31, H 9.48, N 4.25, S 9.73, Si 8.52; found C 58.62, H 9.49, N 4.18, S 9.78, Si 8.50. MS: *m*/*z* = 329 [M^+], 273 [M^+ – 56]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 [s, $(CH_3)_3Si$], 1.45 [s, $(CH_3)_3CO$], 1.39 (dd, *J* = 13, 6 Hz) and 1.86 (dd, *J* = 13, 10 Hz) [$(CH_3)_3Si$-CH_2-], 1.77 and 1.79 [2× s, $(CH_3)_2$-C(2)], 2.55 (dd, *J* = 11.5, 2 Hz) and 3.25 (dd, *J* = 11.5, 6 Hz) [2 H-C(5)], 5.06 [br. dd, *J* = 8.5, 6 Hz, H-C(4)], 5.56 [dddd, *J* = 11, 10, 6, 1 Hz, $(CH_3)_3Si$-CH_2-C*H*=], 5.60 [dd, *J* = 11, 8.5 Hz, further split by small couplings, $(CH_3)_3Si$-CH_2-CH=C*H*-] ppm.

***tert*-Butyl (4*R*,5*S*)-5-Hydroxy-2,2-dimethyl-[(*Z*)-3-(trimethylsilanyl)-propenyl]thiazolidine-3-carboxylate (36):** A solution of allylsilane **34** (197 mg, 0.598 mmol) and *meso*-tetraphenylporphyrin (1 mg) in THF (5 mL) was cooled to –78 °C, and oxygen was bubbled through, while being irradiated with a 100 W halogen lamp for 2 h. TLC (hexanes/ethyl acetate, 4:1) showed almost complete conversion into the hydroperoxide. Triphenylphosphane (157 mg, 0.598 mmol) was added and the temperature was allowed to reach room temperature. After 20 min at room temperature, additional triphenylphosphane (50 mg) was added, and the mixture was left overnight. Solvent was evaporated under reduced pressure and the residue (458 mg) was subjected to column chromatography on silica gel (12 g; hexanes/ethyl acetate, 4:1) to give **36** (146 mg, 70%). MS: *m*/*z* = 327 [M^+ – 18], 271 [M^+ – 18 – 56]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.0 [s, $(CH_3)_3Si$-], 1.42 [s, $(CH_3)_3CO$], 1.75 and 1.92 [2× s, $(CH_3)_2$-C(2)], 1.8–1.9 [m, $(CH_3)_3Si$-CH_2-], 2.10 (br, OH), 4.92 [br. s, H-C(5)], 5.18 [br. d, H-C(4)], 5.29 [dd, *J* = 10.5, 9 Hz, split by further small couplings, $(CH_3)_3Si$-CH_2-CH=C*H*-], 5.54 [td, *J* = 10.5, 7 Hz, $(CH_3)_3Si$-CH_2-C*H*=] ppm.

***tert*-Butyl (*R*)-4-[(*E*)-2-(Ethoxycarbonyl)propenyl]-2,2-dimethylthiazolidine-3-carboxylate (39):** To a solution of ethyl (2-triphenylphosphoranylidene)propionate[30] (6.96 g, 19.2 mmol) in CH_2Cl_2 (155 mL), a solution of aldehyde **4** (4.65 g, 19 mmol) in CH_2Cl_2 was added at room temperature within 15 min. After stirring for 18 h, additional ethyl (2-triphenylphosphoranylidene)propionate (3.48 g, 9.6 mmol) was added, and stirring was continued until TLC analysis indicated total consumption of **4** (3 d). The mixture was cooled to 0 °C then 10% NaH_2PO_3 (154 mL) was added. After stirring at 0 °C for 20 min, the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2, the organic phases were dried (Na_2SO_4), and the solvent was evaporated. Chromatography of the residue (9.4 g) on silica gel (335 g; hexanes/ethyl acetate, 7:1) gave 1.37 g of material contaminated with some (*Z*)-isomer, followed by **39** (4.53 g, 73%). $[\alpha]_D$ = –34 (*c* = 1.18, $CHCl_3$). NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7 Hz, CH_3CH_2O), 1.42 [s, $(CH_3)_3CO$], 1.80 and 1.92 [2× s, $(CH_3)_2C(2)$], 1.92 (br. s, CH_3-C=), 2.66 (dd, *J* = 12.5, 1.5 Hz) and 3.27 (dd, *J* = 12.5, 6 Hz) [2 H-C(5)],

4.12–4.25 (m, CH_3CH_2O), 4.96–5.12 [m, H-C(4)], 6.83 (d, J = 7 Hz, *H*-C=) ppm. GC-Analysis (Chirasil-Val 50 m; 130–160 °C; carrier 100 kPa): 33.9 min (100%); racemic reference: 33.4 (46%), 33.6 min (54%).

***tert*-Butyl (*R*)-4-[(*E*)-3-Hydroxy-2-methylpropenyl]-2,2-dimethylthiazolidine-3-carboxylate (45):** To a solution of **39** (32.91 g, 100 mmol) in anhydrous diethyl ether (950 mL), a solution of diisobutylaluminum hydride (1 M in hexane, 250 mL, 250 mmol) was added from a dropping funnel within 25 min under cooling (3–10 °C). Stirring at 4 °C was continued for 10 min before the addition of ethyl acetate (315 mL), followed by the careful addition of 2 N NaOH (63 mL) at 3–9 °C within 20 min. After stirring for 2 h at room temperature, anhydrous Na_2SO_4 was added to the suspension. Filtration, evaporation of solvents from the filtrate, and chromatography of the residue (silica gel; hexanes/ethyl acetate, 3:1) afforded **45** (27.6 g, 96%), an analytical sample of which was obtained by crystallization from MeOH/H_2O and kugelrohr distillation (0.2 mbar, 200 °C). $[\alpha]_D$ = +4.78 (c = 2, $CHCl_3$). MS (FAB): m/z = 287 [M^+], 269 [M^+ – 18], 213 [M^+ – 18 – 56]. Analysis calcd. for C 58.50, H 8.77, N 4.87, S: 11.16; found C 58.52, H 8.80, N 4.79, S 10.96. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, $J \approx 6$ Hz, $HOCH_2$, exchangeable with D_2O), 1.45 [s, $(CH_3)_3CO$], 1.75 (d, J = 1 Hz, CH_3-C=), 1.78 and 1.81 [2× s, $(CH_3)_2$-C(2)], 2.56 (dd, J = 11.5, 2 Hz) and 3.24 (dd, J = 11.5, 6.5 Hz) [2 H-C(5)], 4.02 (d, $J \approx 6$ Hz, $HOCH_2$), 5.0–5.1 [m, 3 peaks, H-C(4)], 5.71 (dq, J = 8.5, 1 Hz, *H*-C=) ppm.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[(*E*)-2-methyl-3-(trimethylsilanyloxy)-propenyl]thiazolidine-3-carboxylate (40):** To a solution of **45** (2.573 g, 8.97 mmol) in DMF (8 mL), imidazole (916 mg, 13.45 mmol) and trimethylchlorosilane (1.36 mL, 10.76 mmol) were added at ambient temperature. After stirring at room temp. for 3 d, the mixture was diluted with diethyl ether (420 mL) and extracted with 10% citric acid/ice. The organic layer was washed three times with 10% brine, dried with Na_2SO_4, and solvents were removed by evaporation under reduced pressure. The residue (2.615 g) was purified by chromatography on Florisil (150 g; hexanes/ethyl acetate, 4:1) to afford silyl ether **40** (1.668 g, 51%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.0 [s, $(CH_3)_3SiO$], 1.31 [s, $(CH_3)_3CO$], 1.58 (d, J = 1 Hz, CH_3-C=), 1.65 and 1.68 [2× s, $(CH_3)_2C(2)$], 2.45 (dd, J = 11.5, 2 Hz) and 3.12 (dd, J = 11.5, 6 Hz) [2 H-C(5)], 3.87 [br. s, CH_2-OSi(Me)$_3$], 4.83–5.03 [m, 3 peaks, H-C(4)], 5.56 (dq, J = 9, 1 Hz, *H*-C=) ppm.

***tert*-Butyl (*R*)-4-[(*E*)-3-Hydroxy-2-methylpropenyl]-2,2,dimethyl-5-oxothiazolidine-3-carboxylate (41):** A solution of **40** (1.65 g, 4.596 mmol) and *meso*-tetraphenylporphyrin (20 mg) in THF (100 mL) was irradiated for 18 h at –78 °C, while oxygen was bubbled through. TLC analysis (hexanes/ethyl acetate, 4:1) showed that all starting material had been transformed into the hydroperoxide. Triethylamine (10 mL) and acetic anhydride (10 mL) were added at –78 °C and stirring was continued for 3 h. The reaction mixture was poured into 1 N HCl (300 mL) and extracted with ethyl acetate (150 mL). Extraction with 1 N HCl (80 mL) was repeated and the aqueous phases were extracted with ethyl acetate (100 mL). The combined organic phases were washed with 10% brine (2× 100 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was dried under high vacuum at 40 °C to remove acetic anhydride. Chromatography of the residue (1.4 g) on silica gel (70 g; hexanes/ethyl acetate, 2:1), afforded thiazolidinone **41** (853 mg, 61%) and acetate **46** (90 mg, 6%). ^{1}H NMR of **41** (250 MHz, $CDCl_3$): δ = 1.43 [s, $(CH_3)_3CO$], 1.50–1.65 (br., 1 H, HO-CH_2), 1.80 (d, J = 1 Hz, CH_3-C=), 2.0 and 2.03 [2× s, $(CH_3)_2$-C(2)], 4.03 (br. s, CH_2OH), 5.38 [d, J = 9 Hz, H-C(4)], 4.41 (dq, J = 9, 1 Hz, *H*-C=) ppm.

***tert*-Butyl (*R*)-4-[(*E*)-3-Hydroxy-2-methylpropenyl]-2,2-dimethyl-5-oxo-oxazolidine-3-carboxylate (47):** To a solution of thiazolidinone **41** (851 mg, 2.83 mmol) in THF (43 mL) and water (15 mL), hydrogen peroxide (30%, 2.3 mL) was added dropwise, followed by $LiOH \cdot H_2O$ (119 mg, 2.83 mmol) under ice cooling (exothermic, 0–6 °C). The mixture was stirred for 3 h at 0 °C, before addition to 10% $NaHSO_3$ (200 mL). Extraction with ethyl acetate (3× 100 mL), washing with saturated brine, drying with Na_2SO_4, and evaporation of solvents under reduced pressure gave the crude product (800 mg), chromatography of which (silica gel; hexanes/ethyl acetate, 2:1) afforded the starting material **41** (86 mg, 10%) and lactone **47** (558 mg, 69%). MS: m/z = 267 [M^+ – 18], 167 [M^+ – 18 – 100]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 [s, $(CH_3)_3CO$], 1.77, 1.78, and 1.83 [3× s, CH_3-C=, $(CH_3)_2$-C(2)], 4.09 (br. s, HO-CH_2), 4.85–5.15 [m, H-C(4)], 5.31 (br. d, J = 9 Hz, *H*-C=) ppm.

***tert*-Butyl (*R*)-4-[(*E*)-3-(Di-*tert*-butoxyphosphoryloxy)-2-methylpropenyl]-2,2-dimethyl-5-oxo-oxazolidine-3-carboxylate (49):** To a solution of alcohol **47** (558 mg, 1.96 mmol) in anhydrous THF (30 mL, freshly distilled from Na), di-*tert*-butyl *N*,*N*-diethylphosphoramidite (1.46 g, 5.88 mmol, freshly prepared and distilled according to Perich and Johns[31]) was added, followed by tetrazole (549 mg, 7.84 mmol, crystallized from anhydrous acetonitrile). The reaction was monitored by TLC (hexanes/ethyl acetate, 1:1) on silica gel plates, which had previously been wetted with 10% Et_3N in MeOH and dried with a heat gun. After stirring at room temp. for 20 min, ethyl acetate (200 mL) was added and the solution was washed with 10% $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (2× 100 mL). Drying with Na_2SO_4, evaporation of solvents at reduced pressure, and chromatography of the residue (1.8 g) on silica gel (80 g; hexanes/ethyl acetate, 10:1, containing 1% of Et_3N), gave phosphite **48** (749 mg, 82%) {^{31}P NMR (101 MHz, $CDCl_3$, ^{1}H-decoupled): δ = 132 (s) ppm}. To a solution of **48** (748 mg) in THF (30 mL), 3-chloroperbenzoic acid (656 mg, 85%, 3.23 mmol) dissolved in THF (20 mL) was added within 5 min at 0 °C. After stirring for 30 min, further peracid (328 mg, 85%, 1.62 mmol) in THF (10 mL) was added within 3 min. TLC after 5 min showed complete conversion of phosphite **48**. At 0 °C, 10% $NaHSO_3$ (100 mL) was added and the mixture was extracted with diethyl ether (150 mL and 2× 80 mL). The organic phases were washed with 10% $NaHCO_3$ (2× 70 mL), and the aqueous phases were extracted with diethyl ether (2× 50 mL). Drying of the organic phases (Na_2SO_4), evaporation of the solvent under reduced pressure, and chromatography of the residue (844 mg) on silica gel (75 g; hexanes/ethyl acetate, 1:1, containing 1% of Et_3N) afforded phosphate **49** (689 mg, 73%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (br. s, 9 H), 1.50 (s, 18 H), 1.78 (s, 6 H) and 1.88 (s, 3 H) [3× $(CH_3)_3CO$, CH_3-C=, $(CH_3)_2C(2)$], 4.37 (d, J = 6 Hz, PO-CH_2), 4.9–5.1 [m, H-C(4)], 5.35 (dq, J = 9, 1 Hz, CH_3-C=) ppm. ^{31}P NMR (101 MHz, $CDCl_3$, ^{1}H-decoupled): δ = –10.0 ppm (s). In addition, H-phosphonate **50** (20 mg, 2.5%) was eluted afterwards. ^{1}H NMR (250 MHz, $CDCl_3$): δ (selected peaks) = 6.9 (d, J = 690 Hz, 1 H, H-PO_3) ppm. ^{31}P NMR (101 MHz, $CDCl_3$, ^{1}H-decoupled): δ = 2 ppm (s).

(*E*)-(*R*)-2-Amino-4-methyl-5-phosphonooxypent-3-enoic Acid (44): Phosphate **49** (666 mg, 1.438 mmol) was dissolved in 14 mL of a stock solution prepared by dissolving *p*-toluenesulfonic acid monohydrate (38 g) in dichloromethane (40 mL) and THF (75 mL).[32] After stirring at room temp. for 60 min, solvents were removed at room temp. by evaporation under reduced pressure. The residue (4.9 g) was dissolved in water and applied to a column of ion exchange resin (50 g of Dowex 50W × 8/H^+). Elution with water gave fractions with *p*-toluenesulfonic acid followed by fractions containing the product as the acidic zwitterion of **44** (283 mg, 87%). $[\alpha]_D$ = –114.3 (c = 0.6, H_2O). $C_6H_{12}NO_6P \cdot 0.5H_2O$: calcd. C 30.77, H

5.55, N 5.98, P 13.25; found C 30.87, H 5.60, N 5.94, P 13.06. HRMS: *m*/*z* [M – H]$^-$ calcd. 224.03295; found 224.0330. ^{1}H NMR (400 MHz, D_2O): δ = 1.77 [d, J = 1 Hz, CH_3-C(4)], 4.28 [d, J = 7 Hz, 2*H*-C(5)], ca. 4.73 [covered by solvent peak, *H*-C(2)], 5.51 [dq, J = 9.5, 1 Hz, *H*-C(3)] ppm. ^{13}C NMR (62.9 MHz, D_2O): δ = 174.3 [C(1)], 146.1 [d, J = 6 Hz, C(4)], 117.7 [C(3)], 71.3 [d, J = 5 Hz, C(5)], 53.7 [C(2)], 16.1 [CH_3-C(4)] ppm. ^{31}P NMR (101.3 MHz, ^{1}H-decoupled, D_2O): δ = 0.014 ppm. For HSQC data, see the Supporting Information.

Supporting Information (see footnote on the first page of this article): NMR spectra and capillary GC traces.

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