Asymmetric Synthesis with 6-*tert*-Butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one as a New Chiral Glycine Equivalent: Preparation of Enantiomerically Pure α-Tertiary and α-Quaternary α-Amino Acids

Claus-Jürgen Koch,[a] Soňa Šimonyiová,[a] Jörg Pabel,[a] Annerose Kärtner,[a] Kurt Polborn,[a] and Klaus Theodor Wanner*[a]

Dedicated to Prof. M.-H. Zenk on the occasion of his 70th birthday

Keywords: Amino acids / Asymmetric synthesis / Carboxylic acids / Glycine equivalent / α-Hydroxy acids

The chiral oxazinone **2** has been developed as a new chiral glycine equivalent for the asymmetric synthesis of mono- and disubstituted α-amino acids. It is derived from the α-hydroxycarboxylic acid **1**, which serves as a chiral auxiliary, and is easily accessible in enantiomerically pure form by optical resolution of the racemic compound **(*RS*)-1**. For alkylation reactions, **2** was deprotonated with *s*BuLi or phosphazenic base. Subsequent treatment with alkyl halides yielded the monosubstituted compounds **13/14a–c, e, f, (*ent*)-13d, (*ent*)-14d**, while a second alkylation step, via the corresponding enolates, provided the disubstituted compounds **17/18a–d**. Both alkylation steps proceeded with good yields and excellent diastereoselectivities (up to 99% *de*) and even less reactive electrophiles such as isopropyl iodide could be used. The results obtained in this reaction supported the assumption that the enolate of **2**, as well as those of the monosubstituted derivatives of **2**, have less tendency to form the aggregates that hamper alkylation reactions with other systems with higher oxygen content. From the major diastereomers of both the mono- and the disubstituted derivatives of **2** the corresponding α-amino acids **33a–c** and **34a–d** were obtained in high enantiomeric purity by hydrolytic cleavage of the oxazinone ring, accomplished either in two steps with aqueous TFA and aqueous NaOH or in one with either aqueous NaOH or 3 N HBr. Alkylation of the enolate ions of **(*S*)-2** or **(*R*)-2** with epichlorohydrins as bifunctional electrophiles provided the hydroxymethylenecyclopropyl derivatives **21** and **22**. Hydrolysis of **21** and **22** afforded the free amino acids **35** and **(*ent*)-35**. Reductive amination with aniline after oxidation of **21** and **22** to the corresponding aldehydes **24** and **26** provided the compounds **25** and **27**, whereas Mitsunobu treatment of **21** and **22** with 1-phenyl-3-(trifluoroacetyl)urea (**28**) afforded the urea derivatives **29** and **31**. Hydrolysis of these compounds yielded the corresponding 1-aminocyclopropanecarboxylic acid derivatives **36/(*ent*)-36** and **(*ent*)-37**.

Introduction

In recent years, optically active, nonproteinogenic, unnatural α-amino acids have come to play an important role in the field of peptide chemistry. α-Quaternary α-amino acids especially are of major interest, as the introduction of conformational constraints into peptides may result in improved properties or beneficial physiological effects.[1] Moreover, α-quaternary α-amino acids appear to be powerful enzyme inhibitors, and thus promising drug candidates in the field of medicinal chemistry.[2] In addition, enantiomerically pure α-quaternary α-amino acids may serve as valuable chiral building blocks for the construction of more complex molecules.[1]

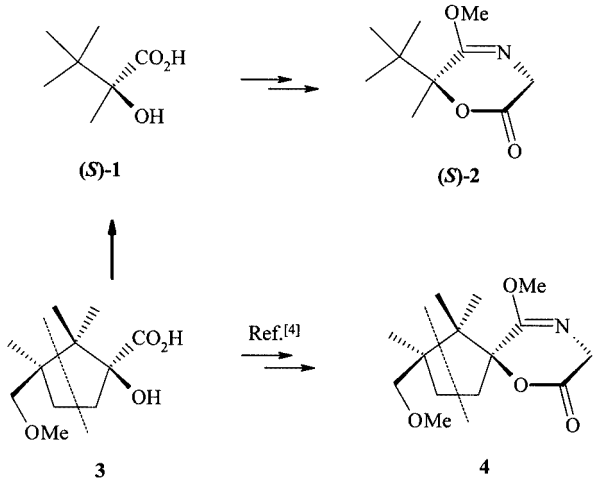
Though there exists a broad variety of methods for the asymmetric construction of α-amino acids, the number of processes for the asymmetric synthesis of α-quaternary α-amino acids was formerly quite limited, but this field is meanwhile also expanding very rapidly.[3]

We have previously reported the stereoselective preparation of α-monoalkylated and α,α-dialkylated α-amino acids by making use of the chiral glycine equivalent **4**, developed by us.[4] Both mono- and dialkylation reactions of the enolate of **4** proceeded with high diastereoselectivities. However, the reaction conditions, especially for the first alkylation, had to be carefully optimized in order to avoid undesired double alkylation reactions, resulting in a decrease in the yield of the desired product. Large-scale syntheses with **4** are furthermore restricted by the fact that the preparation of the enantiomerically pure α-hydroxycarboxylic acid **3**, which represents the chiral auxiliary in **4**, is rather costly. For the synthesis of the enantiomer of **3** this is even more true, as the more expensive (1*S*,3*R*)-(−)-camphoric acid is needed.[5]

[a] Department Pharmazie − Zentrum für Pharmaforschung − LMU München,
Butenandtstr. 7, Haus C, 81377 München, Germany
Fax: (internat.) + 49-(0)89/2180-7247
E-mail: klaus.wanner@cup.uni-muenchen.de

In this paper we report the results of our efforts to develop the chiral glycine equivalent **2** as a new building block for the asymmetric construction of α-monosubstituted α-amino acids,[1a,6] and, which seems even more important, for the synthesis of disubstituted derivatives.[3,7]

In **(*S*)-2**, in comparison with **4**, the α-hydroxycarboxylic acid **3** is replaced by the chiral auxiliary **1** (Scheme 1). This was considered to be advantageous for different reasons: the synthesis of **1** might be carried out in an easy and economic manner, and in the case of a racemic synthesis of **1** an optical resolution might give direct access to both enantiomers. In addition, the low molecular mass of **1** would result in a favorable mass balance for the overall sequence of the amino acid synthesis. A further advantage may be seen in the fact that the chiral auxiliary **1** contributes only singlets to the ^{1}H NMR spectra of **2** and the subsequent alkylation products, thus enabling simple characterization of the products. The most important fact behind our decision to evaluate **1** as a chiral auxiliary, however, was that there are no extra functionalities in **1** besides the amino and the carboxy group. Williams et al. had observed side reactions during the alkylation of their chiral glycine equivalent,[7c] which they put down to the formation of aggregates of the enolate generated for the alkylation reaction,[8] and we had had to deal with similar problems when we performed alkylation reactions with the enolate derived from **4**. Both glycine equivalents display additional functional groups that might favor the formation of such aggregates. This gave rise to the assumption that the oxazine **2** might be better suited than **4** as a chiral glycine equivalent, as it is devoid of any additional functionalities that might promote the formation of aggregates of the enolate.



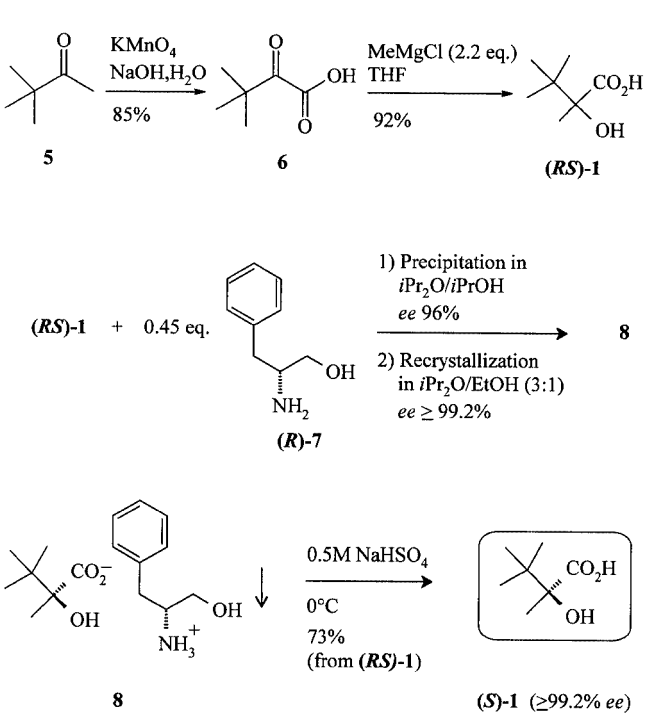
Scheme 1. Delineation of the chiral glycine equivalent **(*S*)-2** from **4**

Results and Discussion

First an efficient route to the pure enantiomers of the α-hydroxycarboxylic acid **1** was needed. As known methods seemed to be hardly suitable,[9] an alternative route, expected to allow an easy large-scale preparation of the α-hydroxycarboxylic acid **1** in enantiomerically pure form, was investigated.

As a very promising approach, the resolution of racemic α-hydroxycarboxylic acid **(*RS*)-1** was attempted. As known methods for the synthesis of **(*RS*)-1** or an ester thereof[9b,9c] did not prove satisfactory, the synthesis of **(*RS*)-1** was accomplished as follows. Upon oxidation of pinacolone **(5)** with $KMnO_4$ in aqueous NaOH[9b] and distillation, the butyric acid derivative **6** was obtained in a yield of 85%. The butyric acid derivative **6** was then treated with 2.2 equiv. of MeMgCl to give, after recrystallization from *n*-heptane, the desired **(*RS*)-1** in 92% yield. After extensive experimentation, phenylalaninol **(7)**, which is commercially available in both enantiomeric forms at a reasonable price,[10] proved to be a well suited resolving agent for the resolution of the racemic acid **(*RS*)-1**.

When a solution of **(*RS*)-1** in iPr$_2$O was treated with 0.45 equiv. of **(*R*)**-phenylalaninol [**(*R*)-7**] in iPrOH, a precipitate of a salt containing **(*S*)-1** was immediately formed (Scheme 2). The highest resolution was observed (96% *ee*) when the resolving agent was added slowly at an elevated temperature (+ 60 °C) and the reaction product was allowed to equilibrate (36 h at +60 °C, 36 h at room temp.). A further increase in the enantiomeric excess was achieved when the salt resulting from the above procedure was suspended in a solvent mixture of iPr$_2$O and EtOH for several days (36 h at +60 °C, 36 h at room temp.). Subsequent release of **(*S*)-1** from the resulting precipitate by use of $NaHSO_4$ gave a 73% yield [based on the 0.45 equiv. of **(*R*)-7**] of the carboxylic acid **(*S*)-1** with ≥ 99.2% *ee*. Of course, in full analogy to this procedure, **(*R*)-1** could be obtained



Scheme 2. Preparation of **(*S*)-1** by optical resolution of racemic **(*RS*)-1**

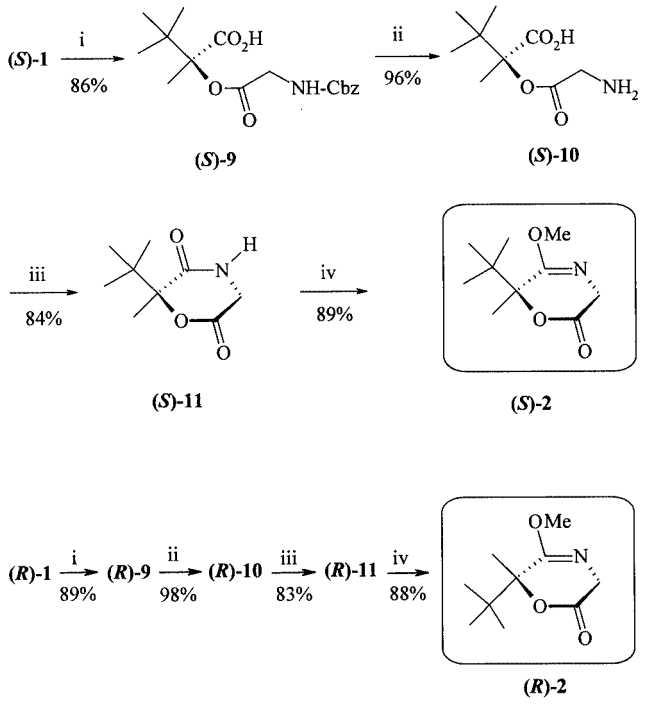
simply by switching to **(*S*)**-phenylalaninol [**(*S*)-7**] as resolving agent.

The absolute configuration of **(*S*)-1** [as well as of **(*R*)-1**] was evident from the optical rotation found for this compound in comparison to the data reported in the literature.[9d,9f]

The enantiomeric purities of samples of the α-hydroxycarboxylic acid **1** were determined by chiral HPLC. A stationary phase with hydroxyproline for ligand-exchange chromatography (with a 0.5 mM $CuSO_4$ solution as eluent[11]) was used, and separated the enantiomers of **1** very nicely.

Synthesis of the Chiral Glycine Equivalents (*S*)-2 and (*R*)-2

The chiral glycine equivalent **(*S*)-2** was synthesized analogously to the construction of the previously reported spirocyclic oxazinone derivative **4**.[4] In the first step, the carboxylic acid **(*S*)-1** was treated with CDI-activated Cbz-glycine, yielding the *N*-protected ester **(*S*)-9** (86%). Removal of the Cbz group by catalytic hydrogenolysis (Pd/C, H_2) gave the free amino acid **(*S*)-10** (96%), which underwent a clean cyclization to give **(*S*)-11** in a yield of 84% upon treatment with Mukaiyama's reagent (2-chloro-1-methyl-pyridinium iodide)[12] in the presence of diisopropylethylamine. Finally, by treatment of **(*S*)-11** with an excess of Meerwein's salt (trimethyloxonium tetrafluoroborate),[13] **(*S*)-2** was obtained in a yield of 89% (see Scheme 3). The synthesis of **(*R*)-2** was accomplished by the otherwise identical, but enantiomorphic, synthetic sequence (see Scheme 3).



Scheme 3. Synthesis of the chiral glycine equivalents **(*S*)-2** and **(*R*)-2**: i) Cbz-glycine, CDI, THF; ii) H_2, Pd/C, EtOH; iii) 2-chloro-1-methylpyridinium iodide, iPr_2EtN, CH_2Cl_2; iv) $Me_3O^+BF_4^-$, CH_2Cl_2

Enolate Alkylations with Alkyl Halides

Monoalkylation Reactions

Because of the absence of additional functional groups in **(*S*)-2**, we expected that alkylation reactions of the enolate of **(*S*)-2** should be far less problematic than those of the enolate of **4**,[4] with respect to the influence of reaction conditions on the outcome of the alkylation reactions.

When the reactions were performed under standard conditions (THF, −78 °C, *s*BuLi) the results were indeed satisfying. In contrast to the results obtained with **4**, the formation of the dialkylation products **15** while starting material was still present was almost negligible in the case of **(*S*)-2**. At low temperatures (−78 °C) only minute amounts, if any at all, of the dialkylation products **15** were observed, slightly increasing if the reaction temperature was raised to 0 °C (see Table 1). There was therefore no need for tedious optimization of the reaction conditions, especially of the solvent system (use of a co-solvent such as DMPU, or of DME in place of THF) to avoid these undesired side reactions. These results also indirectly support the assumption put forward by Williams[7c] that these undesired dialkylation reactions arise from aggregates that form from the lithiated compounds.[8]

Table 1. Alkylation reactions between **(*S*)-2** and alkyl halides

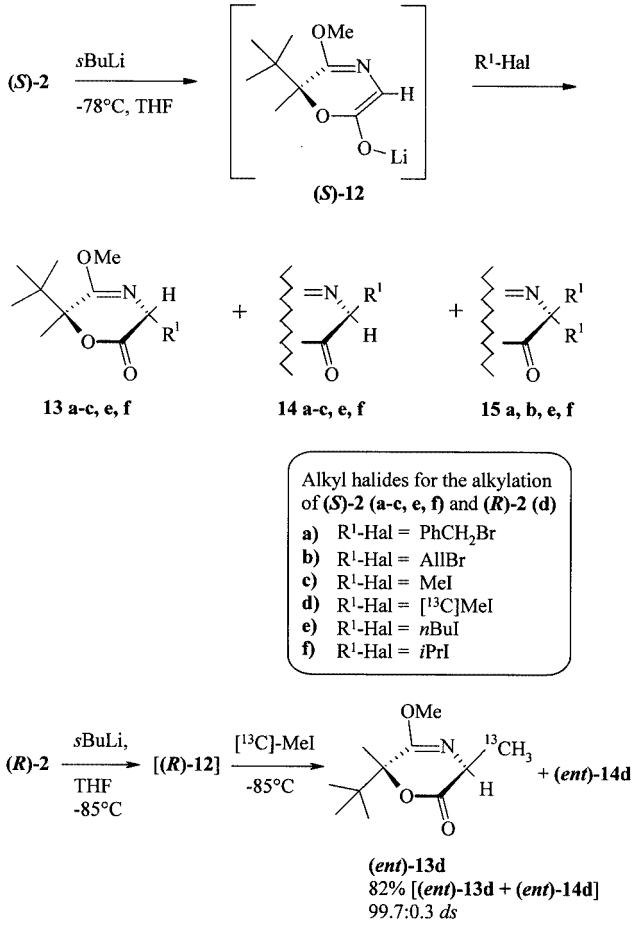
Entry[a]	R¹−Hal	Reaction temp.	*ds*[b]	Yield (%)	
			13/14	**13 + 14**	**15**
1	$PhCH_2Br$	−78 °C	99.7:0.3	90	2
2	$PhCH_2Br$	−78 °C → 0 °C	95.2:4.8	66	3
3	AllBr	−78 °C	99.2:0.8	76	1
4	AllBr	−90 °C	99.7:0.3	94	
5	AllBr	−78 °C → 0 °C	95.8:4.2	76	4
6	MeI	−78 °C	96.8:3.2	72	
7	MeI	−93 °C	98.7:1.3	62	
8	*n*BuI	−50 °C	97.0:3.0	72	5
9	*i*PrI	−78 °C	92.7:7.3	63	5

[a] All experiments were carried out in THF with 1.1 equiv. of *s*BuLi, except for entry 8, in which DME was used, and for entry 9, in which 1.1 equiv. of *t*Bu−P_4 were used. [b] All diastereoselectivities were determined by analytical HPLC.

The experiments could therefore be simply carried out in THF, mostly at a temperature of −78 °C. For the deprotonation, 1.1 equiv. *s*BuLi were used and for the alkylation 3 equiv. of the respective alkyl halide. When isopropyl iodide was employed, however, the reactivity of the lithium enolate **(*S*)-12** appeared to be too low, so phosphazenic base *t*Bu−P_4 {*t*BuN=P[N=P(NMe$_2$)$_3$]$_3$} had to be used for the deprotonation of **(*S*)-2** in this case.

Treatment of **(*S*)-12** at −78 °C with benzyl bromide, allyl bromide, and methyl iodide provided the corresponding alkylation products **13/14a−c** with good to excellent yields (from 72 to 90%) and diastereoselectivities (from 96.8:3.2 to 99.7:0.3 *ds*; Table 1, entries 1, 3, 6). Only in the case of **13/14a−b** was the product contaminated with some dialkylation product, but the amount was very small (**15a**: 2%, **15b**: 1%). Additional reactions with allyl bromide and

methyl iodide at still lower temperatures (−90 °C and below) gave even higher diastereoselectivities (99.7:0.3 and 98.7:1.3) without any significant drop in yields (see Table 1, entries 4 and 7). Furthermore, a marked effect was seen when a precooled (−78 °C) solution of [^{13}C]MeI in THF was used for the alkylation reaction (performed in this case with **(*R*)-2** rather than **(*S*)-2**). Under these conditions we obtained the highest diastereoselectivity (99.7:0.3 *ds*, see Scheme 4) as well as the highest yield for the methylation reactions. As the material **(*ent*)-13/(*ent*)-14d** had been needed for the synthesis of radiolabeled alanine for a biological assay, the reaction had been run on a relatively large scale. Probably because of this the loss of material during workup was reduced, which might explain the higher yield observed in this case.



Scheme 4. Alkylation of the oxazinone **(*S*)-2** and **(*R*)-2** via the corresponding enolates

On the other hand, and consistently with the above results, the diastereoselectivities became significantly lower when the mixtures were allowed to warm up to 0 °C during the alkylation experiments (with benzyl bromide and allyl bromide; see Table 1, entries 2 and 5). In addition, the yields of **13/14a** and **13/14b** also dropped, whereas the amounts of the dialkylated oxazines rose slightly (**15a** 3%, **15b** 4%; see Table 1, entries 2 and 5).

After minor modifications of the reaction conditions, reasonable results were also obtained for alkylation reactions with the only moderately reactive electrophiles *n*-butyl iodide and isopropyl iodide. Treatment with *n*-butyl iodide was best performed at −50 °C in DME as solvent, whereas with isopropyl iodide the enolate of **(*S*)-2** had to be generated with the phosphazenic base *t*Bu−P$_4$. Both yields and diastereoselectivities were good (**13/14e** 72%, 97.0:3.0 *ds*; **13/14f** 63%, 92.7:7.3 *ds*; see Table 1, entries 8 and 9), though in addition small amounts of the dialkylated products occurred (**15e** 5%; **15f** 5%, see Table 1, entries 8 and 9).

The ^{1}H NMR spectra of the monobenzyl derivatives of **(*S*)-2** showed a significant effect with respect to the chemical shifts of the methyl group and the *tert*-butyl group at C-6 of the chiral auxiliary, similar to that observed for the glycine equivalent **4**.[4] In the case of **13a**, in which the benzyl group at C-3 is located on the same side of the oxazinone ring as the methyl group at C-6, the latter was detected at δ = 0.92 ppm. This represents a significant upfield shift, because the C-6 methyl group in the absence of a benzyl group is usually found around δ = 1.50 ppm. In the case of compound **14a**, in which the benzyl group is now positioned *trans* to the methyl but *cis* to the *tert*-butyl group (at C-6 of the oxazinone ring), the *tert*-butyl group is now shifted (from δ = 1.00 ppm) to higher field, becoming located at δ = 0.82 ppm. This phenomenon may be useful for the determination of the stereochemistry at C-3 for related derivatives of **2**. It should be mentioned that the above determination of the stereochemistry was verified by the optical rotation found for D-phenylalanine (**33a**) obtained by hydrolysis of **13a** (see below).

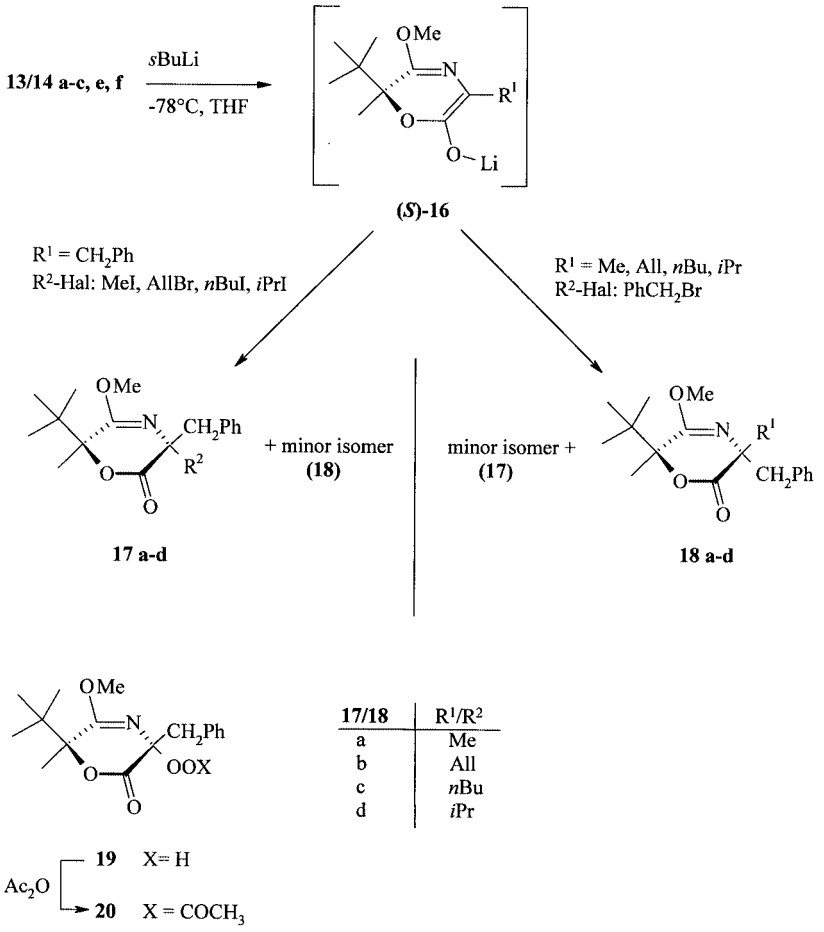
Dialkylation Reactions

All the second alkylation reactions were performed with the mixtures of diastereomers **13/14** obtained during the first alkylation step, and they were carried out in THF at −78 °C with 1.1 equiv. of *s*BuLi, except for alkylations with *n*-butyl and isopropyl iodide (see below).

As already observed for **4**,[4] it was also found for **2** that the sense of the asymmetric induction for the alkylation reactions remains unchanged. Both enantiomers of the final products are therefore easily accessible simply by changing the sequence of the introduction of the substituents at C-3 (of **2**). In order to demonstrate this useful feature clearly, the derivatives **13/14b−c** and **13/14e−f**, with allyl, methyl, *n*-butyl, or isopropyl substituents, were alkylated with benzyl bromide, whereas the monobenzyl derivatives **13/14a** were subjected to alkylation reactions with methyl iodide, *n*-butyl iodide, allyl bromide, and isopropyl iodide (see Scheme 5).

The results may be seen in Table 2. The reactions generally proceeded smoothly and gave reasonable to good yields (60−85%) and high diastereoselectivities (94.1:5.9−99.6:0.4 *ds*).

n-Butyl iodide was also sufficiently reactive for a smooth alkylation reaction, but only when the reaction was performed in DME at −50 °C (see Table 2, entry 3). For the



Scheme 5. Second alkylation of the monoalkylation products **13/14 a−c**, **e**, **f**.

Table 2. Alkylation of the monoalkylated oxazines **13a−c, e, f/14a−c, e, f**

Entry[a]	Starting material/R^1		R^2−Hal	Product major + minor diast.	Yield (%) **17** + **18**	*ds*[b] **17/18**
1	**13/14a**	$PhCH_2$	MeI	**17a** + **18a**	79	95.3:4.7
2	**13/14a**	$PhCH_2$	AllBr	**17b** + **18b**	60	96.6:3.4
3	**13/14a**	$PhCH_2$	*n*BuI	**17c** + **18c**	66	94.1:5.9
4	**13/14a**	$PhCH_2$	*i*PrI	**19**[c]	−	−
5	**13/14a**	$PhCH_2$	*i*PrI	**17d** + **18d**	86	95.1:4.9
6	**13/14c**	Me	$PhCH_2Br$	**18a** + **17a**	82	1.5:98.5
7	**13/14b**	All	$PhCH_2Br$	**18b** + **17b**	85	1.0:99.0
8	**13/14e**	*n*Bu	$PhCH_2Br$	**18c** + **17c**	85	0.8:99.2
9	**13/14f**	*i*Pr	$PhCH_2Br$	**18d** + **17d**	79	0.4:99.6

[a] All experiments were carried out in THF at −78 °C with 1.1 equiv. of *s*BuLi, except for entry 3, in which the reaction was run in DME at −50 °C and for entry 5, in which 1.1 equiv. of phosphazenic base *t*Bu−P_4 were employed. [b] All diastereoselectivities were determined by analytical HPLC. [c] Instead of **17/18d**, compound **19** was obtained in a yield of 83% when *s*BuLi was employed.

reaction with isopropyl iodide, phosphazenic base *t*Bu−P_4 again had to be used for the deprotonation of **13/14a** to generate an enolate more reactive than the lithium enolate **16**, which did not react properly.

Interestingly, in the treatment of the lithium enolate **16** with isopropyl iodide, which failed to give the alkylation product **17/18**, the hydroperoxy derivative **19** was found in a remarkable yield of 83% (see Table 2, entry 4). The formation of **19** had to be a result of oxygen that had entered the flask and which was finally trapped to give **19**. That oxygen was able to penetrate the rubber septum used to seal the reaction flask may be blamed on the long period the reaction was allowed to run. The structure of **19** was further verified by an independent synthesis in which a definite vol-

ume of dry air was bubbled through a solution of the lithium enolate **16**, which produced **19** in a yield of 81%. Upon treatment of **19** with Ac_2O the ester **20** was formed, which also supports the constitution assigned to **19**. As remarkable upfield shifts were observed for the *tert*-butyl groups of **19** and **20** in the ^1H NMR spectra (0.64 and δ = 0.60 ppm respectively), it is also reasonable to assume that **19** and **20** have the stereochemistry at C-3 as shown (*R*).

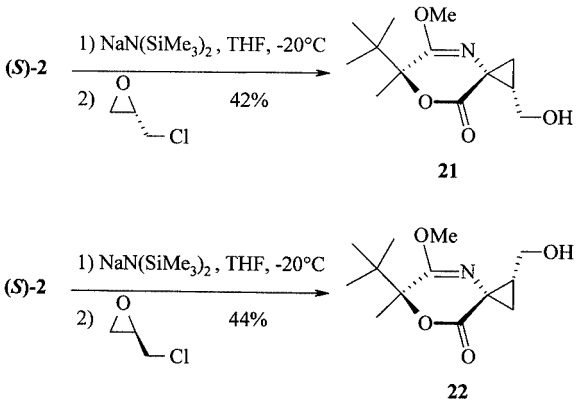
The ^1H NMR spectra of the dialkylated derivatives **17/18** with benzylic side chains in the C-3 position in their oxazine rings showed very similar behavior with respect to the chemical shift of the methyl group and the *tert*-butyl group at C-6 of the chiral auxiliary, as already described for the monoalkylated derivatives **13/14a** (see above). Hence, the *tert*-butyl group at C-6 of the chiral auxiliary undergoes a shift from a δ value of about 1.00 ppm to δ = 0.55 ppm ± 0.05 ppm for compounds **17a−d**, while the methyl group at C-6 is significantly shifted from δ ≈ 1.52 ppm towards higher field in compounds **18a−d** (**18a** δ = 0.52 ppm, **18b** δ = 0.38 ppm, **18c** δ = 0.32 ppm, **18d** δ = 0.18 ppm). The degree of chemical shifting of the 6-methyl group in **18a−d** also very closely reflects the steric demand of the alkyl group introduced into the 3-position of the oxazine ring subsequently to the benzyl substituent. Thus, in the case of the isopropyl-substituted compound **18d** the benzyl group (at C-3) is pushed to the greatest extent towards the methyl group at C-6 (far more strongly than observed for **18a−c** with sterically less demanding groups at C-3), resulting in the most pronounced upfield shift for this substituent.

Cyclopropanation Reactions

In connection with our studies aimed towards the development of new ligands acting at the glycine binding site of the NMDA-receptor complex, we were interested in various 1-aminocyclopropanecarboxylic acids,[4] especially in derivatives with a substituent in the 2-position of the cyclopropane skeleton, such as **35−36** and (***ent*)-35-(*ent*)-37**. The synthesis of these compounds was ideally to be accomplished with the chiral glycine equivalents **(*S*)-2** and **(*R*)-2**, in order to evaluate the utility of these new building blocks further, while known strategies should be used for the construction of the cyclopropane skeleton.

Alkylation reactions of **(*S*)-2** and **(*R*)-2** with **(*S*)**-epichlorohydrin and **(*R*)**-epichlorohydrin appeared most promising, as these should give access to all four stereoisomers of the desired amino acids.[4,14] When **(*S*)-2** was deprotonated with $NaN(SiMe_3)_2$ (2.2 equiv.) in THF at −20 °C in the presence of **(*S*)**- or **(*R*)**-epichlorohydrin, identified as the optimum reaction conditions, the cyclopropane derivatives **21** and **22** were obtained in 42% and 44% yields, respectively (Scheme 6).

According to X-ray analyses performed for **21** and **22** (see Figure 1),[15] these compounds did not posses the expected stereochemistry. Clearly the reaction sequence had commenced with the addition of the enolate to the terminal carbon of the epoxide ring of the respective epichlorohydrin and not, as observed in many related syntheses, by a substitution reaction of the halogen-bearing carbon atom. In addition, the subsequent ring-closure through C-2 (of the epichlorohydrin) had proceeded inconsistently, from the bottom face of the oxazine ring for **21** and from the top face for **22**.



Scheme 6. Direct conversion of **(*S*)-2** and **(*R*)-2** into **21** and **22** by use of epichlorohydrine

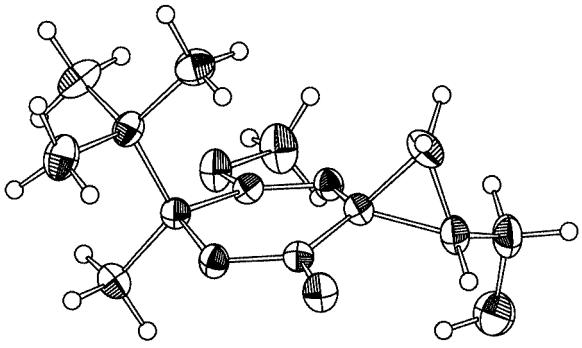
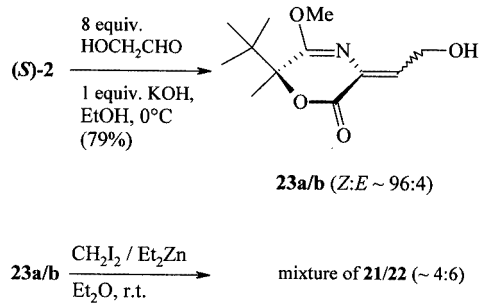


Figure 1. X-ray diffraction analysis of **21**

At present, the reasons for this phenomenon are unclear. Thus, because of the unforeseen stereochemical course of these reactions, the hydrolysis of **21** and **22** afforded the enantiomeric amino acids **35** and **(*ent*)-35** (see below, Scheme 11) and not a pair of diastereomers. The spectroscopic data found for the amino acids **35** and **(*ent*)-35** were, of course, in good accord with those reported in the literature.[16] As is evident from these results the original strategy designed for the synthesis of all four stereoisomers of the above amino acids was no longer applicable. The enantiomorphic sequence starting from **(*R*)-2** would just give the same stereoisomers of the desired amino acids[17] as had been obtained with **(*S*)-2**.

In addition, a Furukawa-style cyclopropanation reaction (Et_2Zn, 2 equiv. CH_2I_2, Et_2O, room temperature) was also performed with **23a/b**[18] and also provided the known stereoisomers **21** and **22**. As observed in the alkylation reactions, the reagent had approached the oxazine ring preferentially from the "bottom face", although with the ratio amounting to about 4:6 (= **21/22**, according to the ^1H

NMR spectrum of the crude product) the reaction was almost devoid of any stereoselectivity (Scheme 7).



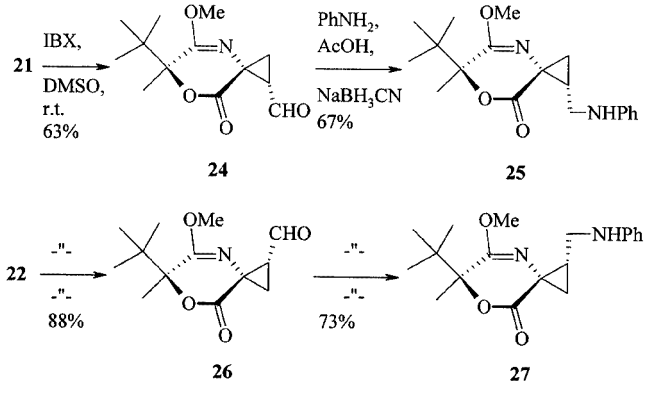
Scheme 7. Cyclopropanation of **23a/b** by use of CH_2I_2/Et_2Zn according to Furukawa

The starting material **23a/b** had been obtained by means of an aldol condensation between **(*S*)-2** and glycolaldehyde (8 equiv.) in the presence of 1.0 equiv. of KOH, carried out at 0 °C in EtOH and yielding **23a** and **23b** in 79% yield and as a 96:4 mixture. The stereochemistries of the double bonds of **23a** and **23b** were assigned on the basis of the stereochemical outcome of the cyclopropanation reactions of these compounds (see above).

Transformations of the Hydroxymethylene Cyclopropane Derivatives 21 and 22 into the Corresponding Aminomethylene Cyclopropane Derivatives

With regard to the development of bioactive compounds, various derivatives of **21** and **22** in which the hydroxy group had been replaced by suitable nitrogen-derived functionalities were of interest.

In order to replace the hydroxy group by an anilino substituent, the stereoisomers **21** and **22** were first oxidized with *ortho*-iodoxybenzoic acid to give the corresponding aldehydes **24** and **26** (63% and 88%, respectively). Subsequent reductive amination with aniline, acetic acid, and sodium cyanoborohydride provided the desired compounds **25** and **27**, both in good yields (67% and 73%), as can be seen in Scheme 8. The same sequence had been utilized previously for the chiral glycine equivalent **4**.[4]



Scheme 8. Oxidation and subsequent reductive amination of **21**, and **22** to the corresponding aniline derivatives. IBX = *ortho*-iodoxybenzoic acid

Further attempts to synthesize the amino derivatives of **21** and **22** remained unsuccessful. The aldehydes **24** and **26** could not be directly converted into the corresponding primary amines by any of the reductive amination procedures investigated (e.g., reductive amination with ammonia, ammonium acetate or ammonium chloride in the presence of sodium cyanoborohydride, or the use of hexamethyldisilazane to generate an imine for subsequent reduction). Either no conversion occurred, or else the secondary and tertiary amines were formed even though starting material was still present. Substitution of the tosylates derived from **21** and **22** with $NaN(SiMe_3)_2$ was also unsuccessful.

Finally it was discovered that the hydroxy functions in **21** and **22** could successfully be replaced by 1-phenyl-3-(trifluoroacetyl)urea (**28**) under Mitsunobu conditions,[19] providing **29** and **31** in good yields (63% and 65%). To the best of our knowledge, this is the first time that **28** has been employed in this type of reaction, in which the trifluoroacetyl moiety in **28** serves as an activating group for the urea moiety. This gives rise to a reasonable acidity, necessary if the Mitsunobu reaction is to be performed successfully,[19e] and is easily removable after the reaction as well.

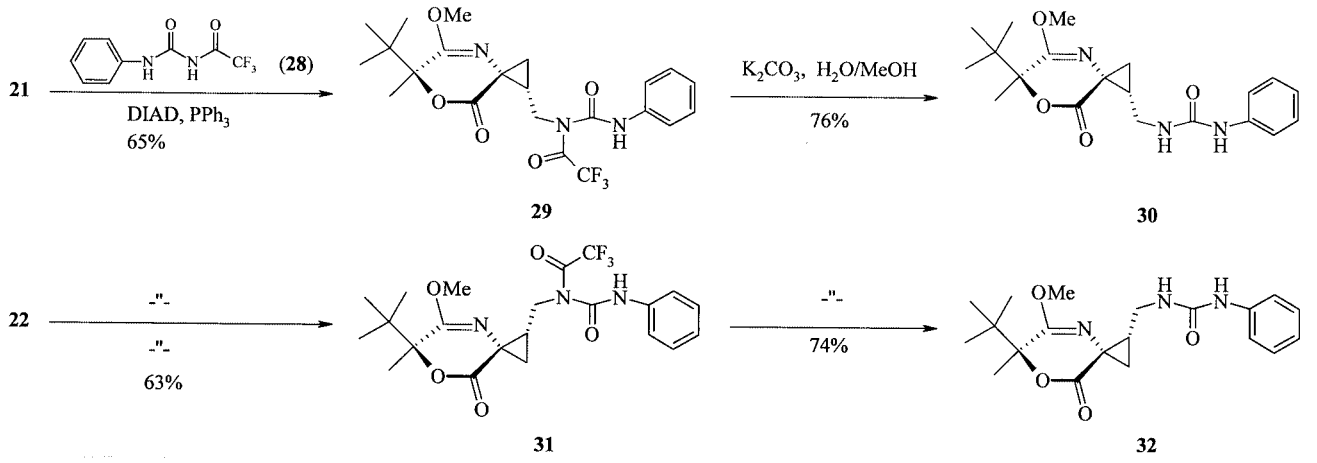
Thus, when **29** and **31** were stirred in aqueous K_2CO_3 to remove the trifluoroacetyl group the desired compounds **30** and **32** were obtained in good yields (74 and 76%, see Scheme 9).

In addition it should be mentioned that the required urea **28**[20] may be efficiently prepared in a new procedure by stirring phenylurea with trifluoroacetic acid anhydride at room temperature (yield 86%).

Although 1-aminocyclopropanecarboxylic acids with an aminomethylene side chain were of interest for biological studies, as were those with the original phenylurea group still present, it was questionable whether the amino acids latent in **30** and **32** could be released without destruction of the urea side chain. Unsurprisingly, despite extensive experimentation with **30** and **32**, all attempts to obtain the corresponding amino acid with the urea side chain still present failed and the free diamino acid **(*ent*)-37**, for example, was obtained instead (see Scheme 11).[21]

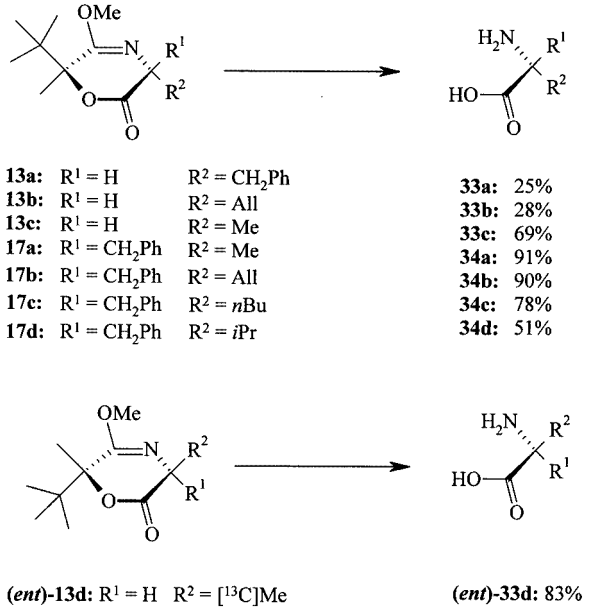
Liberation of the Amino Acids

A two-step sequence was employed for the hydrolysis of the monosubstituted and the cyclopropyl derivatives of **(*S*)-2** and **(*R*)-2** to give the free amino acids. In the first step the compounds were treated with TFA at 60 °C for 20 h. This resulted in complete cleavage of the imidate function.[22] Finally, the cleavage products thus obtained were treated with NaOH in various solvents at either room temp. (**13a**−**c**, 20 h), 60 °C (**21** and **22**, 20 h), or 90 °C (**25** and **27**, 5d) to hydrolyze the remaining ester function. After workup with 6 N HCl and subsequent purification by ion-exchange chromatography (Dowex 50 W X 8) the free monoalkylated amino acids **33a**−**c** and the cyclopropyl derivatives **35**, **(*ent*)-35**, **36**, and **(*ent*)-36** were obtained. The yields for the monosubstituted amino acids **33a**−**c** were low to moderate (25%−69%, see Scheme 10), whereas the yields for the cyclopropyl derivatives **35**, **(*ent*)-35**, **36**, and **(*ent*)-36**



Scheme 9. Preparation of the urea derivatives **30** and **32** by Mitsunobu reaction of **21** and **22** with 1-phenyl-3-(2,2,2-trifluoroacetyl)urea (**28**) and subsequent removal of the trifluoroacetyl group by basic hydrolysis

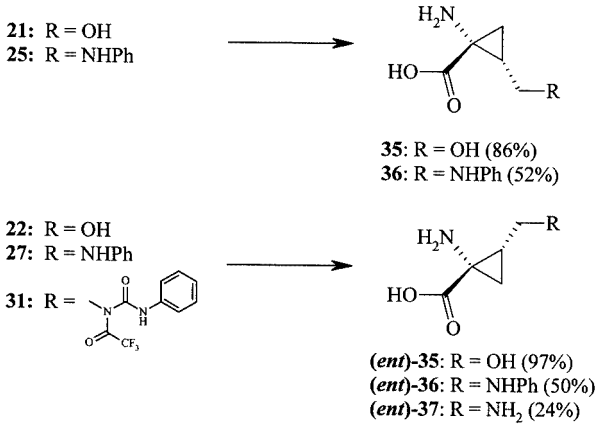
were reasonable to very good (50−97%, see Scheme 11). In the case of the disubstituted amino acids an enantiomeric purity of > 99% *ee* may be assumed, as racemization cannot occur because of the structure of these compounds and as the precursors had been employed in diastereomerically (>99.5% *de*) and enantiomerically pure form (>99.5% *ee*).



Scheme 10. Hydrolysis of mono- and dialkylated derivatives of **2**

The monosubstituted amino acids **33a−c** were subjected to chiral HPLC analysis, which revealed enantiomeric purities of 87% *ee* (**33a**), 90% *ee* (**33b**), and 94% *ee* (**33c**), where a value of at least 99% *ee* had been expected. Accordingly, some significant racemization had occurred during the hydrolysis in this case.

In order to find a method in which the extent of racemization would be reduced, additional hydrolysis experiments



Scheme 11. Hydrolysis of cyclopropyl derivatives to the corresponding free amino acids

were performed, different reaction conditions being tested with regard to their suitability. Thus, in one case, 5 equiv. of LiOH in a mixture of dioxane/H_2O (1:1) was employed in place of an excess of 40% aqueous NaOH for the hydrolysis of the ester function of **13c** after the compound had been treated with 0.2 M TFA. This was accompanied by severe drops in both the chemical and the optical yields (26%, 77% *ee* determined by chiral HPLC[11]), however, and so this kind of hydrolysis was not pursued any further.

Finally, in further hydrolysis experiments, **13c** and **(*ent*)-13d** were treated with 25 equiv. of 3 N aqueous HBr in a pressure tube at 130 °C for one day.[23] When the resulting hydrobromides of the amino acids were purified by ion-exchange chromatography (Dowex 50 W X 8 resin) 85% of D-alanine (**33c**) and 83% of the [^{13}C]-labeled L-alanine [**(*ent*)-33d**] were obtained. Gratifyingly, a loss of enantiomeric purity of only 1%−2% *ee* had occurred in this case [determined by HPLC,[11] **33c** and **(*ent*)-33d** 97−98% *ee*].

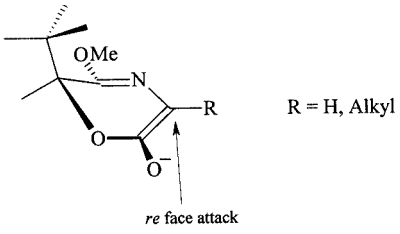
As mentioned above, all attempts at selective hydrolysis of **30** and **32** with the urea side chain remaining untouched failed.[24] Complete hydrolysis also appeared to be difficult,

though. It turned out that a two-step procedure based on treatment with 0.1 M TFA (60 °C overnight) followed by aqueous NaOH at 90 °C (in DME) for the cleavage of the lactim ether and the ester function provided the best results, though these were still not fully satisfactory. Thus, when applied as an example to **31**, chosen for purposes of convenience, only a 24% yield of the diamino acid **(*ent*)-37** was obtained after ion-change chromatography (DOWEX 50Wx8). Though the yield was already low, the material was still contaminated by some inseparable by-product.

As there was no risk of racemization, the hydrolysis of the doubly alkylated compounds **17a−d** was effected in a single step by use of 40% aqueous NaOH in methanol (4:1 mixture), although 3 days at 60 °C were required for **17a−c** to make the reaction go to completion and 2 days at reflux for the bulkier **17d**. After the usual workup the free doubly alkylated amino acids **34a−d** were obtained in reasonable to good yields (51%−91%, see Scheme 10).

Model for the Asymmetric Induction

From the stereochemistry found for the alkylation products, the alkylation reactions of the enolates **(*S*)-12** and **(*R*)-16** had proceeded consistently with *re* selectivity, and those for the enantiomers of the former compounds [**(*R*)-12** and **(*R*)-16**] with, of course, *si* selectivity. To explain the observed sense of the asymmetric induction, the model in Scheme 12, representing the putative structure of the enolates **(*S*)-12** and **(*R*)-16**, is put forward. As previously proposed for **4**,[4] it is reasonable to assume that the ring atoms O-1, C-2, C-3, N-4, and C-5 are all essentially located in one plane, whereas C-6 adopts a position above this plane in order to reduce allylic strain.[7a]



Scheme 12. Hypothetical model for the asymmetric induction in the alkylation reactions of the enolates (*S*)-**12** and (*S*)-**16**

Because of the steric encumbrance of the top face arising from the pseudoaxial disposition of the *tert*-butyl group, electrophiles should approach the enolate from the "bottom face" of the oxazine ring. This would give rise to *re* stereoselectivity for **(*S*)-12** and **(*R*)-16** and to *si* stereoselectivity for the enantiomeric enolates, as was indeed the case for all alkylation reaction. Only the formation of the cyclopropane derivative **22** by treatment of **(*S*)-2** with **(*R*)**-epichlorohydrin did not obey this rule.

Conclusion

From the results presented in this paper, the chiral glycine equivalent **2** compares well with other literature methods used for the asymmetric construction of α-amino acids. The syntheses of both enantiomers of **2** − **(*S*)-2** and **(*R*)-2** − are easily and efficiently accomplishable starting from the pure enantiomers of the chiral auxiliary **1**. These are accessible in a short and high-yielding process, starting from cheap and readily available compounds. The optical resolution of racemic **(*RS*)-1** appears to be highly efficient and may be performed even on large scale.

The chiral glycine equivalents **(*R*)-2** and **(*S*)-2** appear to be especially useful for the construction of α,α-disubstituted amino acids, but may also be used for the synthesis of α-monosubstituted amino acids. In contrast, other systems (Schöllkopf's bislactim ether method, for example) are often limited to a greater or lesser extent to the synthesis of α-monosubstituted amino acids. Most alkylation reactions of **2** proceeded smoothly in pure THF in the absence of additives such as HMPA or DMPU. Only for the alkylation with butyl iodide was a different solvent (DME) used. In general, as long as reactive alkyl halides were used, there was also no need to employ particular bases for the deprotonation of **2** in order to perform alkylation reactions, as only very small amounts − if any at all − of double alkylation products were formed under these conditions (in the first alkylation step). This result nicely supports the assumption that the presence of fewer oxygen functions in an intermediate such as **12** (or **16**) reduces the tendency to the formation of aggregates, which would otherwise hamper alkylation reactions. Furthermore, alkylation reactions almost always proceeded in good yields and with excellent stereoselectivities, even when less reactive alkyl halides were used, this being true both for the first and for the second alkylation step, whereas other systems are often limited if less reactive electrophiles are employed. Hydrolysis of compounds **13** was carried out in a two-step procedure (first by using TFA for cleaving the lactim ether function, then by using NaOH for cleaving the ester function), providing the monosubstituted amino acids **33a−c**. Racemization occurred to some extent. From the hydrolysis of the dialkylated compounds **17a−d**, performed in a single step with aqueous NaOH, the disubstituted amino acids **34a−d** were obtained. This method also proved useful for the preparation of the substituted cyclopropanecarboxyclic acids **35−36** and **(*ent*)-35-(*ent*)-37**. The nature of the chiral auxiliary **1** also had additional benefits: the mass balance of the synthetic sequence may be deemed to be quite favorable as the molecular mass of **1** is relatively low, and the ^{1}H NMR spectra of **2** and of subsequent products show only a few signals − all singlets − resulting from the chiral auxiliary, which is very helpful for the interpretation of these spectra. In addition, the stereochemistry of the alkylation products may be predicted with high reliability, as the same sense of asymmetric induction was observed in all cases [except for the reaction with **(*R*)**-epichlorohydrin], with the electrophile

preferentially approaching the enolates from the face opposite to the one defined by the *tert*-butyl group.

Experimental Section

General Remarks: All experiments were carried out in oven-dried glassware under a dry N_2 atmosphere. Standard vacuum techniques were used for the handling of air-sensitive materials. Solvents were dried and kept under N_2 and freshly distilled before use. Reagents were used as commercially available. Solvents used for HPLC were degassed prior to use. M.p. (uncorrected values): Melting point apparatus according to Dr. Tottoli (Büchi no. 510). Optical rotation: 241 MC polarimeter (Perkin−Elmer). ^{1}H NMR spectra: J NMR-GX 400 (Jeol), 400 MHz, ^{13}C NMR spectra: J NMR-GX 400 (Jeol), 100 MHz, chemical shifts (δ) are reported in ppm, TMS as internal standard. IR: FT-IR spectrometer 1600 and FT-IR spectrometer Paragon 1000 (Perkin−Elmer), liquids were run as films, solids as KBr pellets. MS: 5989 mass spectrometer with 59980 B particle beam LC/MS interface (Hewlett Packard); API 2000 LC/MS/MS System (Applied Biosystems). HRMS: MStation 700 (Jeol). Combustion analysis: CHN Rapid (Heraeus). Column chromatography (CC): Flash chromatography[25] on silica gel (Merck 60 0.040−0.063 mm). TLC: TLC plates 60 F-254, detection with UV (λ = 254 nm) or with ammonium cerium(IV) heptamolybdate. Analytical HPLC: L-6000 pump and L-6200 intelligent pump, L-4000 and L-7400 UV/Vis detectors, D-2500, D-7500, and D-7000 (PC, cartridge supported) Chromato integrators (Merck−Hitachi), columns: LiChroCart® with LiChrospher® Si 60 cartridge (5 μm, 250 × 4 mm with precolumn 4 × 4 mm) (Merck), ET250/4 Nucleosil® Chiral-1 (5 μm, 250 × 4 mm) (Macherey−Nagel), column oven: High temperature oven (Knauer). Preparative HPLC: L-6000 pump, L-4000 UV/Vis, D-2000 Chromato Integrator (Merck−Hitachi), column: Hibar RT LiChrosorb® Si 60 (7 μm, 250 × 25 mm) (Merck).

Preparation of the Chiral Glycine Equivalent 2 from Pinacolone (5):

3,3-Dimethyl-2-oxobutanoic Acid (6)[9b,26] (Procedure Modified from the Literature Method[9b]): $KMnO_4$ (61.60 g, 390.0 mmol) was added at 0 °C, in portions and with vigorous stirring, to a solution of NaOH (16.20 g, 405.0 mmol) and **5** (20.25 g, 202.0 mmol, 25.00 mL) in H_2O (750 mL). The mixture was stirred for 5 h at 0 °C and for another 12 h at room temp. The resulting suspension was filtered and the MnO_2 was washed several times with H_2O. The filtrate was then treated, with cooling, with $HCl_{conc.}$ (50 mL) and extracted with Et_2O (4 × 250 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a pale yellow liquid, which upon distillation (20 Torr/85 °C) yielded **6** (21.55 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 9 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6 (CH_3), 42.5 [$C(CH_3)_3$], 163.7 (CO_2 H), 201.9 (CO) ppm. $C_6H_{10}O_3$ (130.1): calcd. C 55.37, H 7.74; found C 54.89, H 7.74.

(*R*,*S*)-2-Hydroxy-2,3,3-trimethylbutanoic Acid [(*RS*)-1]: Compound **6** (21.40 g, 164.5 mmol) was dissolved in THF (160 mL) and the mixture was cooled to 0 °C. With vigorous stirring, a solution of MeMgCl in THF (3.0 M, 120 mL, 362.0 mmol, 2.2 equiv.) were slowly added in such a way as to maintain the temperature below 20 °C. The reaction mixture was stirred for another 24 h at room temp. and finally carefully hydrolyzed (with cooling!) with HCl (6 M, 100 mL). After removal of the organic solvent, the aqueous solution was extracted with Et_2O (4 × 200 mL). Washing of the combined organic layers with brine, drying over $CaCl_2$, filtration, and removal of the solvent produced a white precipitate. Recrystallization from hot *n*-heptane (50 mL) and subsequent washing of the precipitate with cold *n*-heptane (3 ×) yielded **(*RS*)-1** (22.07 g, 92%) as colorless crystals, m.p. 139−140 °C {ref.[27] 141−142 °C}. ^{1}H NMR ($CDCl_3$): δ = 1.03 [s, 9 H, $C(CH_3)_3$], 1.43 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.4 (CH_3), 25.1 [$C(CH_3)_3$], 36.6 [$C(CH_3)_3$], 78.3 (COH), 178.6 (CO_2 H) ppm. IR: $\tilde{\nu}$ = 3453 cm^{-1}, 2964, 1725, 1376, 1265. MS (CH_4; CI): *m*/*z* (%) = 147 (18) [M + H$^+$], 129 (89), 101 (100), 71(56). $C_7H_{14}O_3$ (146.2): calcd. C 57.51, H 9.65; found C 57.33, H 9.84.

(*S*)-(−)-2-Hydroxy-2,3,3-trimethylbutanoic Acid [(*S*)-1]. By Optical Resolution: A solution of enantiomerically pure (*R*)-phenylalaninol [**(*R*)-7,** 6.81 g, 45.0 mmol] in *i*PrOH (75 mL) was added at 60 °C over a period of 2.5 h to **(*RS*)-1** (14.62 g, 100.0 mmol) in 370 mL of iPr_2O. The resulting suspension was stirred for 36 h at 60 °C and then allowed to cool to room temp., at which it was kept whilst stirring for another 36 h. After filtration and washing with iPr_2O, the salt obtained was dried. The diastereomeric salt was then suspended in a mixture of iPr_2O/EtOH (3:1, 800 mL), and stirred for 36 h at 60 °C and then for 36 h at room temp. After filtration and washing with iPr_2O, the diastereomeric salt was dried and then treated with ice-cooled $NaHSO_4$ (0.5 M, 260 mL). The solution was extracted with cold Et_2O (4 ×) and the combined organic layers were washed with water and dried over $CaCl_2$. Filtration and removal of the solvent in vacuo gave **(*S*)-1** (5.31 g, 73%) as colorless crystals, m.p. 99 °C. Chiral HPLC with a Nucleosil® Chiral-1 column[11] (H_2O, 0.5 mmol $CuSO_4 \cdot 5\,H_2O$/L; 1.0 mL/min), kept at 55−60 °C, revealed 99.6:0.4 *es*; **(*S*)-1:** t_R = 5.25 min; **(*R*)-1:** t_R = 11.87 min. $[\alpha]_D^{20}$ = −1.1 (*c* = 2.50, C_2H_5OH); {ref.[9d,9e,9f]: $[\alpha]_D^{20}$ = −1.4 (*c* = 8.63, C_2H_5OH)}. $[\alpha]_D^{20}$ = −11.7 (*c* = 1.80, $CHCl_3$). $C_7H_{14}O_3$ (146.2): calcd. C 57.51, H 9.65; found C 57.21, H 9.95.

Recovery of (*R*)-Phenylalaninol [(*R*)-7]: The filtrates from the crystallization and the recrystallization steps and the aqueous phase of the extraction step were combined, treated with an excess of NaOH, and subsequently extracted with CH_2Cl_2 (4 ×). The combined organic extracts were dried over Na_2SO_4 (1 h), filtered, and concentrated in vacuo, and the residue was recrystallized from *n*-hexane/ethyl acetate (1:1) to give **(*R*)-7** (5.41 g, 80%).[10]

(*R*)-(+)-2-Hydroxy-2,3,3-trimethylbutanoic Acid (*R*)-1. By Optical Resolution: The same procedure as described for the preparation of **(*S*)-1** was employed, except that (*S*)-phenylalaninol [**(*S*)-7**] was used for the resolution. Colorless crystals, m.p. 98 °C. Chiral HPLC [as specified for **(*S*)-1**]: 99.5:0.5 *es*; **(*S*)-1:** t_R = 6.35 min; **(*R*)-1:** t_R = 8.75 min. $[\alpha]_D^{20}$ = +1.2 (*c* = 2.85, C_2H_5OH); {ref.[9d,9e,9f]: $[\alpha]_D^{20}$ = +1.5 (*c* = 9.83, C_2H_5OH)}. $[\alpha]_D^{20}$ = +11.8 (*c* = 2.10, $CHCl_3$). $C_7H_{14}O_3$ (146.2): calcd. C 57.51, H 9.65; found C 57.69, H 9.47.

Recovery of (*S*)-Phenylalaninol [(*S*)-7]: As described above for the recovery of **(*R*)-7**.

(*S*)-2-(*N*-Benzyloxycarbonylaminoacetoxy)-2,3,3-trimethylbutanoic Acid [(*S*)-9]: A solution of *N,N′*-carbonyldiimidazole (CDI) (256 mg, 1.57 mmol) in THF (4 mL) was added to a solution of Cbz-glycine (330 mg, 1.57 mmol) in THF (4 mL), followed after 4 h of stirring at room temp by **(*S*)-1** (115 mg, 0.790 mmol, 0.5 equiv.) in THF (4 mL). After the mixture had been stirred for another 20 h at room temp. the solvent was removed in vacuo. CC (petroleum ether/ethyl acetate/acetic acid, 10:3:1) yielded **(*S*)-9** (229 mg, 86%) as colorless crystals, m.p. 58 °C. $[\alpha]_D^{20}$ = +12.4 (*c* = 0.485, $CHCl_3$). TLC: R_f = 0.30 (petroleum ether/ethyl acetate/acetic acid, 10:3:1). ^{1}H NMR ($CDCl_3$): δ = 1.02 [s, 9 H, $(CH_3)_3C$], 1.64 (s, 3 H, CH_3), 3.95 (dd, *J* = 18.1/4.9 Hz, 1 H, NHCH_2CO), 4.05 (dd, *J* = 18.1/6.0 Hz, 1 H, NHCH_2CO), 5.11 (s, 2 H,

OCH_2Ph), 5.41 (s, broad, 1 H, NH), 7.30−7.35 ppm (m, 5 H, C_6H_5), CO_2H not located. IR: $\tilde{\nu}$ = 3348 cm^{-1}, 2977, 1720, 1528, 1377, 1277. MS (CH_4; CI): *m*/*z* (%) = 338 (76) [M + H^+], 210 (100). $C_{17}H_{23}NO_6$ (337.4): calcd. C 60.52, H 6.87, N 4.15; found C 60.55, H 7.13, N 3.86.

(*R*)-2-(*N*-Benzyloxycarbonylaminoacetoxy)-2,3,3-trimethylbutanoic Acid [(*R*)-9]: This compound was obtained by the procedure described for the synthesis of **(*S*)-9**, from **(*R*)-1** (500 mg, 3.42 mmol). Yield: 1.027 g (89%) as colorless crystals, m.p. 56 °C. $C_{17}H_{23}NO_6$ (337.4): calcd. C 60.52, H 6.87, N 4.15; found C 60.80, H 7.12, N 3.93.

(*S*)-2-Aminoacetoxy-2,3,3-trimethylbutanoic Acid [(*S*)-10]: Pd/C (10% Pd, 14 mg) was added to **(*S*)-9** (200 mg, 0.580 mmol) in ethanol (8 mL), and the resulting slurry was stirred overnight under H_2. The precipitate that had formed was redissolved by addition of H_2O (6 mL). Filtration and removal of the solvent yielded **(*S*)-10** (113 mg, 96%) as colorless crystals, which were used without further purification. ^1H NMR (D_2O): δ = 1.01 [s, 9 H, $(CH_3)_3C$], 1.58 (s, 3 H, CH_3), 3.90 (d, *J* = 17.5 Hz, 1 H, $COCH_2NH_2$), 3.96 (d, *J* = 17.5 Hz, 1 H, $COCH_2NH_2$) ppm. IR: $\tilde{\nu}$ = 3380 cm^{-1}, 2977, 1759, 1635, 1596, 1370, 1247, 1212. MS (CH_4; CI): *m*/*z* (%) = 204 (69) [M + H^+], 76 (100).

(*R*)-2-Aminoacetoxy-2,3,3-trimethylbutanoic Acid [(*R*)-10]: This compound was produced by the procedure described for the synthesis of **(*S*)-10**, from **(*R*)-9** (1.00 g, 2.96 mmol). Yield: 590 mg (98%) as colorless crystals, which were used without further purification.

(*S*)-6-*tert*-Butyl-6-methyl-1,4-oxazine-2,5-dione [(*S*)-11]: Compound **(*S*)-10** (100 mg, 0.490 mmol) was suspended in CH_2Cl_2 (10 mL) and treated with 2-chloro-1-methylpyridinium iodide (138 mg, 0.54 mmol, 1.1 equiv.). After addition of ethyldiisopropylamine (255 μL, 1.47 mmol, 3.0 equiv.), the reaction mixture was kept under reflux for 4 h. Finally the solvent was removed in vacuo and the residue was purified by CC (petroleum ether/ethyl acetate, 20:80) to yield **(*S*)-11** (75 mg, 82%) as colorless crystals, m.p. 124 °C. $[\alpha]_D^{20}$ = +37.3 (*c* = 0.57, $CHCl_3$). TLC: R_f = 0.37 (petroleum ether/ethyl acetate, 20:80). ^1H NMR ($CDCl_3$): δ = 1.12 [s, 9 H, $(CH_3)_3C$], 1.60 (s, 3 H, CH_3), 4.22 (d, *J* = 2.6 Hz, 1 H, $NHCH_2CO$), 4.23 (d, *J* = 2.6 Hz, 1 H, $NHCH_2CO$), 6.53 (s, 1 H, NH) ppm. IR: $\tilde{\nu}$ = 3321 cm^{-1}, 2967, 1751, 1682, 1374, 1342, 1283. MS (CH_4; CI): *m*/*z* (%) = 186 (100) [M + H^+]. $C_9H_{15}NO_3$ (185.2): calcd. C 58.36, H 8.16, N 7.56; found C 58.33, H 8.21, N 7.43.

(*R*)-6-*tert*-Butyl-6-methyl-1,4-oxazine-2,5-dione [(*R*)-11]: This compound was produced by the procedure described for the synthesis of **(*S*)-11**, from **(*R*)-10** (550 mg, 2.71 mmol). Yield: 416 mg (83%) as colorless crystals, m.p. 125 °C. $C_9H_{15}NO_3$ (185.2): calcd. C 58.36, H 8.16, N 7.56; found C 58.48, H 8.20, N 7.40.

(*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(*S*)-2]: A solution of **(*S*)-11** (73 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) was added to a suspension of $Me_3O^+BF_4^-$ (92 mg, 0.64 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temp. for 24 h. After hydrolysis with a phosphate buffer (pH 7, 2 mL) the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo, which after CC (petroleum ether/ethyl acetate, 90:10) afforded **(*S*)-2** (69 mg, 89%) as colorless crystals, m.p. 83 °C. $[\alpha]_D^{20}$ = +121.4 (*c* = 0.58, $CHCl_3$). TLC: R_f = 0.18 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ = 1.04 (s, 9 H, $[CH_3)_3C]$, 1.56 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.26 (d, *J* = 21.6 Hz, 1 H, NCH_2CO), 4.39 (d, *J* = 21.6 Hz, 1 H, NCH_2CO) ppm. IR: $\tilde{\nu}$ = 2975 cm^{-1}, 1744, 1689, 1472, 1374, 1336. MS (CH_4; CI): *m*/*z* (%) = 200 (1) [M + H^+], 83 (100). $C_{10}H_{17}NO_3$ (199.3): calcd. C 60.28, H 8.60, N 7.03; found C 60.29, H 8.85, N 6.77.

(*R*)-6-*tert*-Butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(*R*)-2]: This compound was obtained by the procedure described for the synthesis of **(*S*)-2**, from **(*R*)-11** (350 mg, 1.89 mmol). Yield: 331 mg (88%) as colorless crystals, m.p. 81 °C. $C_{10}H_{17}NO_3$ (199.3): calcd. C 60.28, H 8.60, N 7.03; found C 60.39, H 8.80, N 6.99.

Alkylation Reactions with Monofunctional Alkyl Halides. General Procedure (GP A) for the Monoalkylation of (*S*)-2 and (*R*)-2: Unless otherwise stated, a solution of **(*S*)-2** or **(*R*)-2** in THF (0.1 M) was treated at −78 °C with *s*BuLi (1.3 M solution in hexane, 1.1 equiv.). After 30 min, the alkyl halide (3.0 equiv.) was added and the solution was stirred overnight at −78 °C. The mixture was then either quenched at this temperature (and allowed to warm to room temp.) or it was slowly allowed to warm to room temp. (≈ 5 h). The hydrolysis was performed by addition of phosphate buffer (pH = 7, *c* = 1.0 mol/L). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5−20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by CC.

(3*R*,6*S*)-3-Benzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (13a), (3*S*,6*S*)-3-Benzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (14a), and (*S*)-3,3-Dibenzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (15a). A: The compounds were produced by GP A, from **(*S*)-2** (100 mg, 0.50 mmol), *s*BuLi (423 μL, 0.55 mmol), and benzyl bromide (257 mg, 178 μL, 1.5 mmol), with quenching at −78 °C. Purification by CC (*n*-pentane/ethyl acetate, 96:4) without separation of the diastereomers yielded **13a/14a** (130.5 mg, 90%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5, 1.75 mL/min) of the crude product: *ds* **13a/14a** = 99.7:0.3; **13a**: t_R = 14.75 min, **14a**: t_R = 16.77 min.

Compound 13a: Colorless crystals, m.p. 52 °C. $[\alpha]_D^{20}$ = +29.9 (*c* = 0.60, $CHCl_3$). TLC: R_f = 0.22 (*n*-pentane/ethyl acetate, 96:4). ^1H NMR ($CDCl_3$): δ = 0.92 (s, 3 H, CH_3), 0.94 [s, 9 H, $(CH_3)_3C$], 3.23 (dd, *J* = 13.2/ 4.7 Hz, 1 H, $CH_2C_6H_5$), 3.30 (dd, *J* = 13.2/ 5.5 Hz, 1 H, $CH_2C_6H_5$), 3.71 (s, 3 H, OCH_3), 4.47 (dd, *J* = 5.5/ 4.7 Hz, 1 H, NCHCO), 7.20−7.27 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2964 cm^{-1}, 1740, 1695, 1376, 1344, 1308. MS (CH_4; CI): *m*/*z* (%) = 290 (100) [M + H^+]. $C_{17}H_{23}NO_3$ (289.4): calcd. C 70.56, H 8.01, N 4.84; found C 70.55, H 8.08, N 4.83.

Since the amount of **14a** formed in the synthesis described above was small, **14a** was synthesized separately by epimerization of **13a**: **13a** (14 mg, 0.07 mmol) in THF (0.7 mL) was treated with *s*BuLi (60 μL, 0.078 mmol) and the reaction was quenched after 30 min at −78 °C with a solution of citric acid (29 mg, 0.15 mmol, 2.2 equiv., in 0.3 mL of H_2O). The workup was performed as in GP A. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5, 1.5 mL/min) on the crude product: *ds* **13a/14a** = 26.7:73.3; **13a:** t_r = 19.20 min, **14a:** t_r = 21.45 min. The diastereomers were separated by preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 16.5 mL/min).

Compound 14a: Colorless crystals, m.p. 48 °C. Yield: 6 mg (60%). TLC: R_f = 0.35 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ = 0.83 [s, 9 H, $(CH_3)_3C$], 1.47 (s, 3 H, CH_3), 3.16 (dd, *J* = 13.3/7.5 Hz, 1 H, $CH_2C_6H_5$), 3.35 (dd, *J* = 13.3/4.5 Hz, 1 H, $CH_2C_6H_5$), 3.68 (s, 3 H, OCH_3), 4.44 (dd, *J* = 7.5/4.5 Hz, 1 H,

NCHCO), 7.20−7.27 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2966 cm^{-1}, 1749, 1695, 1370, 1312, 1250. MS (CH_4; CI): *m*/*z* (%) = 290 (100) [M + H^+]. $C_{17}H_{23}NO_3$ (289.4): calcd. C 70.56, H 8.01, N 4.84; found C 70.85, H 8.24, N 4.64.

B: The compounds were produced by GP A, from **(*S*)-2** (46 mg, 0.23 mmol), *s*BuLi (195 μL, 0.25 mmol), and benzyl bromide (118 mg, 82 μL, 0.690 mmol); the reaction mixture was allowed to warm to 0 °C; quench after 4 h at 0 °C; workup by GP A. Preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 16.5 mL/min) gave a diastereomeric mixture of **13a** and **14a** (66%) and **15a** (2.8 mg, 3%). The diastereoselectivity **13a/14a** was determined by analytical HPLC on the crude product as described above: *ds* **13a/14a** = 95.2:4.8.

Compound 15a: Colorless oil. TLC: R_f = 0.65 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ = 0.46 [s, 9 H, $(CH_3)_3C$], 1.55 (s, 3 H, CH_3), 2.94 (d, *J* = 12.6 Hz, 1 H, $CH_2C_6H_5$), 3.12 (d, *J* = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.43 (d, *J* = 12.6 Hz, 1 H, $CH_2C_6H_5$), 3.51 (d, *J* = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.77 (s, 3 H, OCH_3), 7.13−7.26 (m, 10 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2957 cm^{-1}, 1737, 1688, 1348, 1299, 1225. MS (CH_4; CI): *m*/*z* (%) = 380 (64) [M + H^+], 83 (100). $C_{24}H_{29}NO_3$ (379.4): calcd. C 75.98, H 7.71, N 3.69; found C 75.69, H 7.54, N 3.98.

(3*R*,6*S*)-3-Allyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (13b), (3*S*,6*S*)-3-Allyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (14b), and (*S*)-3,3-Diallyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (15b). A: These compounds were produced by GP A; the reaction was conducted at −90 °C, with **(*S*)-2** (60 mg, 0.301 mmol), *s*BuLi (255 μL, 0.331 mmol), and allyl bromide (109 mg, 77 μL, 0.903 mmol); quenching at −90 °C. Purification by CC (petroleum ether/ethyl acetate, 90:10) yielded **13b/14b** (68 mg, 94%) as a diastereomeric mixture. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5, 1.5 mL/min) on the crude product: *ds* **13b/14b** = 99.7:0.3; **13b:** t_r = 19.84 min, **14b:** t_r = 23.15 min. The diastereomers were separated by preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 16.5 mL/min).

Compound 13b: Colorless crystals, m.p. 64 °C. $[\alpha]_D^{20}$ = +84.4 (*c* = 0.61, $CHCl_3$). TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ = 0.99 [s, 9 H, $(CH_3)_3C$], 1.49 (s, 3 H, CH_3), 2.64−2.78 (m, 2 H, $CH_2CH=CH_2$), 3.72 (s, 3 H, OCH_3), 4.23 (dd, *J* = 6.2/4.8 Hz, 1 H, NCHCO), 5.09−5.18 (m, 2 H, $CH_2CH=CH_2$), 5.79 (ddt, *J* = 17.2/10.2/7.2 Hz, 1 H, $CH_2CH=CH_2$) ppm. IR: $\tilde{\nu}$ = 3078 cm^{-1}, 1739, 1690, 1441, 1348, 1328, 1223. MS (CH_4; CI): *m*/*z* (%) = 240 (100) [M + H^+]. $C_{13}H_{21}NO_3$ (239.3): calcd. C 65.25, H 8.84, N 5.85; found C 65.42, H 8.94, N 5.59.

Compound 14b: Only characterized by NMR: ^1H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 1.52 (s, 3 H, CH_3), 2.66−2.80 (m, 2 H, $CH_2CH=CH_2$), 3.70 (s, 3 H, OCH_3), 4.30 (dd, *J* = 6.2/4.8 Hz, 1 H, NCHCO), 5.08−5.17 (m, 2 H, $CH_2CH=CH_2$), 5.90 (ddt, *J* = 17.2/10.2/7.2 Hz, 1 H, $CH_2CH=CH_2$).

B: The compounds were obtained by GP A, from **(*S*)-2** (60 mg, 0.301 mmol), *s*BuLi (255 μL, 0.331 mmol), and allyl bromide (109 mg, 77 μL, 0.903 mmol), with quenching at −78 °C. Purification by CC (petroleum ether/ethyl acetate, 90:10) yielded **13b/14b** (55 mg, 76%) as a diastereomeric mixture and **15b** (1 mg, 1%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5, 1.75 mL/min) on the crude product: *ds* **13b/14b** = 99.2:0.8; **13b**: t_R = 9.03 min, **14b:** t_R = 11.63 min.

C: The compounds were obtained by GP A, from **(*S*)-2** (86 mg, 0.43 mmol), *s*BuLi (365 μL, 0.475 mmol), and allyl bromide (156 mg, 109 μL, 1.29 mmol), the reaction mixture being allowed to warm to 0 °C and quenched after 4 h at 0 °C. Workup was by GP A. Preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 16.5 mL/min) gave a diastereomeric mixture of **13b** and **14b** (76%) and **15b** (5 mg, 4%). The diastereoselectivity **13b/14b** was determined as described above by analytical HPLC on the crude product: *ds* **13b/14b** = 95.8:4.2.

Compound 15b: Colorless crystals, m.p. 68 °C. $[\alpha]_D^{20}$ = −1.0 (*c* = 0.59, $CHCl_3$). TLC: R_f = 0.69 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ = 1.02 [s, 9 H, $(CH_3)_3C$], 1.50 (s, 3 H, CH_3), 2.41 (dd, *J* = 13.2/7.3 Hz, 1 H, $CH_2CH=CH_2$), 2.52−2.66 (m, 3 H $CH_2CH=CH_2$), 3.70 (s, 3 H, OCH_3), 5.08−5.16 (m, 4 H, $CH_2CH=CH_2$), 5.64 (ddt, *J* = 16.1/11.0/8.4 Hz, 1 H, $CH_2CH=CH_2$), 5.83 (ddt, *J* = 17.2/10.1/7.5 Hz, 1 H, $CH_2CH=CH_2$) ppm. IR: $\tilde{\nu}$ = 3080 cm^{-1}, 2957, 1736, 1686, 1440, 1348, 1297. MS (CH_4; CI): *m*/*z* (%) = 280 (100) [M + H^+]. $C_{16}H_{25}NO_3$ (279.4): calcd. C 68.79, H 9.02, N 5.01; found C 68.90, H 9.13, N 4.80.

(3*R*,6*S*)-6-*tert*-Butyl-5-methoxy-3,6-dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (13c) and (3*S*,6*S*)-6-*tert*-Butyl-5-methoxy-3,6-dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (14c): The compounds were obtained by GP A, from **(*S*)-2** (60 mg, 0.301 mmol), *s*BuLi (331 μL, 0.255 mmol), and methyl iodide (128 mg, 56 μL, 0.903 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **13c/14c** (46 mg, 72%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5; 1.5 mL/min) on the crude product: *ds* **13c/14c** = 96.8:3.2; **13c**: t_R = 20.05 min, **14c**: t_R = 23.95 min. **13c** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 15 mL/min).

Compound 13c: Colorless crystals, m.p. 50 °C. $[\alpha]_D^{20}$ = +109.6 (*c* = 0.45, $CHCl_3$). TLC: R_f = 0.32 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ = 1.01 [s, 9 H, $(CH_3)_3C$], 1.51 (s, 3 H, CH_3), 1.54 (d, *J* = 7.5 Hz, 3 H, CH_3CH), 3.71 (s, 3 H, OCH_3), 4.17 (q, *J* = 7.5 Hz, 1 H, CH_3CH) ppm. IR: $\tilde{\nu}$ = 2974 cm^{-1}, 1746, 1690, 1475, 1370, 1310. MS (CH_4; CI): *m*/*z* (%) = 214 (100) [M + H^+]. $C_{11}H_{19}NO_3$ (213.3): calcd. C 61.95, H 8.98, N 6.57; found C 62.13, H 9.07, N 6.31.

Compound 14c: Only characterized by NMR: ^1H NMR ($CDCl_3$): δ = 1.03 [s, 9 H, $(CH_3)_3C$], 1.54 (s, 3 H, CH_3), 1.58 (d, *J* = 7.5 Hz, 3 H, CH_3CH), 3.83 (s, 3 H, OCH_3), 4.16 (q, *J* = 7.5 Hz, 1 H, CH_3CH) ppm.

(3*S*,6*R*)-6-*tert*-Butyl-5-methoxy-[3-^{13}C]methyl-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(*ent*)-13d] and (3*R*,6*R*)-6-*tert*-Butyl-5-methoxy-[3-^{13}C]methyl-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(*ent*)-14d]: *s*BuLi (3.91 mL, 5.08 mmol, 1.1 equiv.) was added at −85 °C with stirring to **(*R*)-2** (920 mg, 4.62 mmol) in THF (10 mL). After 45 min, a precooled solution (−78 °C) of [^{13}C]methyl iodide (0.992 g, 438 μL, 6.94 mmol, 1.5 equiv.) in THF (3 mL) was added. The reaction mixture was stirred for 24 h at −85 °C and subsequently quenched at −85 °C with phosphate buffer (pH = 7, 5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. CC (petroleum ether/ethyl acetate, 90:10) afforded **(*ent*)-13d** and **(*ent*)-14d** as a colorless oil (815 mg, 82%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5, 1.5 mL/min) on the crude product: *ds* **(*ent*)-13d/(*ent*)-14d** = 99.7:0.3; **(*ent*)-13d**: t_R = 16.63 min, **(*ent*)-14d**: t_R = 21.27 min.

Compound (*ent*)-13d: $[\alpha]_D^{20}$ = −103.6 (*c* = 2.20, $CHCl_3$). TLC: R_f = 0.32 (petroleum ether/ethyl acetate, 90:10). ^1H NMR ($CDCl_3$): δ =

1.02 [s, 9 H, $(CH_3)_3C$], 1.51 (s, 3 H, CH_3), 1.55 (dd, J = 129.8/7.3 Hz, 3 H, $^{13}CH_3CH$), 3.71 (s, 3 H, OCH_3), 4.17 (dq, J = 7.3/7.3 Hz, 1 H, CH_3CH) ppm. IR: $\tilde{\nu}$ = 2972 cm^{-1}, 1747, 1692, 1447, 1376, 1325, 1122. MS (CH_4; CI): m/z (%) = 215 (100) [M + H^+]. $C_{10}{}^{13}CH_{19}NO_3$ (214.3): calcd. C 61.95, H 8.94, N 6.54; found C 61.64, H 9.09, N 6.55.

Compound (*ent*)-14d: Only characterized by NMR: ^{1}H NMR ($CDCl_3$): δ = 1.03 [s, 9 H, $(CH_3)_3C$], 1.52 (s, 3 H, CH_3), 1.54 (dd, J = 129.8/7.3 Hz, 3 H, $^{13}CH_3CH$), 3.68 (s, 3 H, OCH_3), 4.17 (dq, J = 7.3/7.3 Hz, 1 H, CH_3CH) ppm.

(3*R*,6*S*)-3-*n*-Butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (13e), (3*S*,6*S*)-3-*n*-Butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (14e), and (6*S*)-3,3-Di-*n*-Butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (15e): The compounds were obtained by GP A, from **(*S*)-2** (50 mg, 0.25 mmol) in DME (2.5 mL) at −50 °C with *s*BuLi (212 µL, 0.275 mmol) and *n*-butyl iodide (138 mg, 86 µL, 0.75 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **13e/14e** (46 mg, 72%), together with **15e** (4.2 mg, 5%) and **(*S*)-2** (8.4 mg, 17%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5, 1.75 mL/min) on the crude product: *ds* **13e/14e** = 97.0:3.0; **13e:** t_R = 6.32 min, **14e:** t_R = 8.10 min. Compound **13e** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 17 mL/min).

Compound 13e: Colorless crystals, m.p. 71 °C. $[\alpha]_D^{20}$ = +90.9 (c = 0.45, $CHCl_3$). TLC: R_f = 0.38 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.88−0.95 [m, 3 H, $CH_3(CH_2)_3$], 1.01 [s, 9 H, $(CH_3)_3C$], 1.31−1.39 [m, 4 H, $CH_3(CH_2)_2CH_2$], 1.50 (s, 3 H, CH_3), 1.81−1.89 (m, 1 H, $CH_2C_3H_7$), 1.93−2.05 (m, 1 H, $CH_2C_3H_7$), 3.72 (s, 3 H, OCH_3), 4.13 (dd, J = 6.6/4.8 Hz, 1 H, NCHCO) ppm. IR: $\tilde{\nu}$ = 2960 cm^{-1}, 1743, 1692, 1458, 1344, 1313. MS (CH_4; CI): m/z (%) = 256 (100) [M + H^+]. $C_{14}H_{25}NO_3$ (255.4): calcd. C 65.85, H 9.87, N 5.49; found C 65.92, H 9.80, N 5.50.

Compound 14e: Only characterized by NMR: ^{1}H NMR ($CDCl_3$): δ = 0.84−0.91 (m, 3 H, $CH_3(CH_2)_3$], 1.01 [s, 9 H, $(CH_3)_3C$], 1.35−1.45 (m, 4 H, $CH_3(CH_2)_2CH_2$), 1.51 (s, 3 H, CH_3), 1.83−1.88 (m, 1 H, $CH_2C_3H_7$), 1.96−2.01 (m, 1 H, $CH_2C_3H_7$), 3.70 (s, 3 H, OCH_3), 4.13 (dd, J = 6.6/4.8 Hz, 1 H, NCHCO) ppm.

Compound 15e: Colorless crystals, m.p. 30 °C. $[\alpha]_D^{20}$ = +6.2 (c = 1.035, $CHCl_3$). TLC: R_f = 0.51 (petroleum ether/diethyl ether, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.83−0.92 (m, 6 H, CH_3), 1.04 [s, 9 H, $(CH_3)_3C$], 1.11−1.20 (m, 2 H, CH_2), 1.24−1.35 (m, 6 H, CH_2), 1.52 (s, 3 H, CH_3), 1.63−1.70 (m, 1 H, CH_2), 1.72−1.88 (m, 3 H, CH_2), 3.69 (s, 3 H, OCH_3) ppm. IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2873, 1740, 1686, 1458, 1303, 1100. MS (CH_4; CI): m/z (%) = 312 (100) [M + H^+]. $C_{18}H_{33}NO_3$ (311.5): calcd. C 69.41, H 10.68, N 4.50; found C 69.91, H 10.86, N 4.41.

(3*R*,6*S*)-6-*tert*-Butyl-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (13f), (3*S*,6*S*)-6-*tert*-Butyl-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (14f), and (6*S*)-6-*tert*-Butyl-3,3-diisopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (15f): The compounds were obtained by GP A, from **(*S*)-2** (25 mg, 0.125 mmol), phosphazenic base *t*Bu−P_4 (c = 1 M in *n*-hexane, 138 µL, 0.138 mmol, 1.1 equiv.), and isopropyl iodide (64 mg, 38 µL, 0.38 mmol, 3.0 equiv.). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **13f/14f** (19.2 mg, 63%), together with **15f** (1.9 mg, 5%) and **(*S*)-2** (4.1 mg, 16%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 95:5; 1.75 mL/min) on the crude product: *ds* **13f/14f** = 92.7:7.3; **13f**: t_R = 4.89 min, **14f**: t = 6.05 min. Compound **13f** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 95:5; 17 mL/min).

Compound 13f: Colorless crystals, m.p. 52 °C. $[\alpha]_D^{20}$ = +90.2 (c = 0.65, $CHCl_3$). TLC: R_f = 0.42 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.78 [d, J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.01 [s, 9 H, $(CH_3)_3C$], 1.12 [d, J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.49 (s, 3 H, CH_3), 2.52 [septd, J = 6.9/3.1 Hz, 1 H, $CH(CH_3)_2$], 3.73 (s, 3 H, OCH_3), 4.00 (d, J = 3.1 Hz, 1 H, NCHCO) ppm. IR: $\tilde{\nu}$ = 2963 cm^{-1}, 2874, 1745, 1698, 1462, 1312, 1104. MS (CH_4; CI): m/z (%) = 242 (26) [M + H^+], 149 (100). $C_{13}H_{23}NO_3$ (241.3): calcd. C 64.70, H 9.61, N 5.80; found C 64.66, H 9.75, N 5.65.

Compound 14f: Only characterized by NMR: ^{1}H NMR ($CDCl_3$): δ = 0.82 (d, J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.06 [s, 9 H, $(CH_3)_3C$], 1.14 (d, J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.49 (s, 3 H, CH_3), 2.52 (septd, J = 6.9/3.1 Hz, 1 H, $CH(CH_3)_2$], 3.72 (s, 3 H, OCH_3), 3.97 (d, J = 3.1 Hz, 1 H, NCHCO).

Compound 15f: Colorless crystals, m.p. 74−77 °C. $[\alpha]_D^{20}$ = +0.5 (c = 0.39, $CHCl_3$). TLC: R_f = 0.49 (*n*-pentane/ethyl acetate, 97:3). ^{1}H NMR ($CDCl_3$): δ = 0.90 [d, J = 7.0 Hz, 3 H, $CH(CH_3)_2$], 0.93 [d, J = 7.0 Hz, 3 H, $CH(CH_3)_2$], 0.95 [d, J = 7.0 Hz, 3 H, $CH(CH_3)_2$], 0.99 [d, J = 7.0 Hz, 3 H, $CH(CH_3)_2$], 1.06 [s, 9 H, $(CH_3)_3C$], 1.55 (s, 3 H, CH_3), 2.19 [sept, J = 7.0 Hz, 1 H, $CH(CH_3)_2$], 2.33 [sept, J = 7.0 Hz, 1 H, $CH(CH_3)_2$], 3.71 (s, 3 H, OCH_3) ppm. IR: $\tilde{\nu}$ = 2973cm^{-1}, 2879, 1728, 1690, 1476, 1296, 1094, 831. MS (CH_4; CI): m/z (%) = 284 (24) [M + H^+], 225 (68), 105 (100). $C_{16}H_{29}NO_3$ (283.4): calcd. C 67.81, H 10.31, N 4.94; found C 67.36, H 10.40, N 4.76.

General Procedure B (GP B) for the Alkylation of 13/14a-c, e, f: Unless otherwise stated, a solution of the monoalkylation product (0.1 M, either pure or as diastereomeric mixture) in THF was treated at −78 °C with *s*BuLi (1.3 M solution in hexane, 1.1 equiv.). After 30 min, alkyl halide (3.0 equiv.) was added and the solution was stirred at −78 °C overnight. The mixture was quenched at this temperature and allowed to warm to room temp. The hydrolysis was performed by addition of phosphate buffer (pH = 7, c = 1.0 mol/L). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5−10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by CC.

(3*S*,6*S*)-3-Benzyl-6-*tert*-butyl-5-methoxy-3,6-dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17a) and (3*R*,6*S*)-3-Benzyl-6-*tert*-butyl-5-methoxy-3,6-dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18a): The compounds were obtained by GP B, from **13a/14a** (30 mg, 0.104 mmol), *s*BuLi (88 µL, 0.114 mmol), and methyl iodide (44 mg, 20 µL, 0.312 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **17a/18a** (25 mg, 79%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2; 1.5 mL/min) on the crude product: *ds* **17a/18a** = 95.3:4.7; **17a:** t_r = 30.25 min, **18a:** t_r = 26.29 min. Compound **17a** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 15 mL/min).

Compound 17a: Colorless crystals, m.p. 72 °C. $[\alpha]_D^{20}$ = +49.9 (c = 0.225, $CHCl_3$). TLC: R_f = 0.49 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.54 [s, 9 H, $(CH_3)_3C$], 1.37 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.84 (d, J = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.33 (d, J = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.65 (s, 3 H, OCH_3), 7.05−7.15 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2972 cm^{-1}, 1738, 1694, 1454, 1369, 1308, 1220. MS (CH_4; CI): m/z (%) = 304 (100) [M +

H^+]. $C_{18}H_{25}NO_3$ (303.4): calcd. C 71.26, H 8.31, N 4.62; found C 71.41, H 8.45, N 4.50.

Compound 18a: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see below).

(3*S*,6*S*)-3-Allyl-3-benzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17b) and (3*R*,6*S*)-3-Allyl-3-benzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18b): The compounds were obtained by GP B, from **13a/14a** (30 mg, 0.104 mmol), *s*BuLi (88 μL, 0.114 mmol), and allyl bromide (38 mg, 27 μL, 0.312 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **17b/18b** (20.4 mg, 60%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2, 1.75 mL/min) on the crude product: *ds* **17b/18b** = 96.6:3.4; **17b:** t_R = 15.32 min, **18b:** t_R = 14.34 min. Compound **17b** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 16.5 mL/min).

Compound 17b: Colorless crystals, m.p. 64 °C. $[\alpha]_D^{20}$ = +27.1 (*c* = 0.47, $CHCl_3$). TLC: R_f = 0.46 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.60 [s, 9 H, $(CH_3)_3C$], 1.44 (s, 3 H, CH_3), 2.46 (dd, *J* = 13.2/7.5 Hz, 1 H, CH_2−CH=CH_2), 2.74 (dd, *J* = 13.2/7.5 Hz, 1 H, CH_2−CH=CH_2), 3.00 (d, *J* = 13.0 Hz, 1 H, $CH_2C_6H_5$), 3.35 (d, *J* = 13.0 Hz, 1 H, $CH_2C_6H_5$), 3.72 (s, 3 H, OCH_3), 5.11−5.18 (m, 2 H, CH_2−CH=CH_2), 5.71 (ddt, *J* = 17.6/9.5/7.5 Hz, 1 H, CH_2−CH=CH_2), 7.14−7.21 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 3086 cm^{-1}, 2987, 1730, 1685, 1482, 1372, 1299. MS (CH_4; CI): *m*/*z* (%) = 330 (100) [M + H^+]. $C_{20}H_{27}NO_3$ (329.4): calcd. C 72.92, H 8.26, N 4.25; found C 72.77, H 8.30, N 3.96.

Compound 18b: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see below).

(3*S*,6*S*)-3-Benzyl-3-*n*-butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17c) and (3*R*,6*S*)-3-Benzyl-3-*n*-butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18c): The compounds were obtained by GP B, from **13a/14a** (29 mg, 0.10 mmol) in DME at −50 °C, with *s*BuLi (1.19 M in *n*-hexane, 92 μL, 0.11 mmol), and *n*-butyl iodide (55 mg, 35 μL, 0.30 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **17c/18c** (22.6 mg, 66%), together with **13a/14a** (6.1 mg, 21%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2, 1.75 mL/min) on the crude product: *ds* **17c/18c** = 94.1:5.9; **17c:** t_R = 8.13 min, **18c**: t_R = 9.16 min. Compound **17c** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 16.5 mL/min).

Compound 17c: Colorless oil. $[\alpha]_D^{20}$ = +29.3 (*c* = 1.15, $CHCl_3$). TLC: R_f = 0.63 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.63 [s, 9 H, $(CH_3)_3C$], 0.89 [t, *J* = 7.1 Hz, 3 H, $(CH_2)_3CH_3$), 1.19−1.34 [m, 4 H, $CH_2(CH_2)_2CH_3$], 1.46 (s, 3 H, CH_3), 1.67−1.75 (m, 1 H, $CH_2C_3H_7$), 1.95−2.03 (m, 1 H, $CH_2C_3H_7$), 2.99 (d, *J* = 12.9 Hz, 1 H, $CH_2C_6H_5$), 3.32 (d, *J* = 12.9 Hz, 1 H, $CH_2C_6H_5$), 3.72 (s, 3 H, OCH_3), 7.10−7.22 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2959 cm^{-1}, 2872, 1736, 1693, 1456, 1302, 1221. MS (CH_4; CI): *m*/*z* (%) = 346 (100) [M + H^+]. $C_{21}H_{31}NO_3$ (345.5): calcd. C 73.01, H 9.04, N 4.05; found C 73.07, H 9.08, N 3.96.

Compound 18c: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see below).

(3*R*,6*S*)-3-Benzyl-6-*tert*-butyl-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17d) and (3*S*,6*S*)-3-Benzyl-6-*tert*-butyl-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18d): The compounds were obtained by GP B, from **13a/14a** (29 mg, 0.10 mmol), phosphazenic base *t*Bu−P_4 (*c* = 1.0 M in *n*-hexane, 110 μL, 0.11 mmol, 1.1 equiv.), and isopropyl iodide (53 mg, 30 μL, 0.30 mmol) immediately added, with quenching after 1 h. Purification by CC (*n*-pentane/ethyl acetate, 98:2) without separation of the diastereomers yielded **17d/18d** (28.3 mg, 86%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2, 1.75 mL/min) on the crude product: *ds* **17d/18d** = 95.1:4.9; **17d:** t_R = 8.83 min, **18d:** t_R = 8.11 min. Compound **17d** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 16.5 mL/min).

Compound 17d: Colorless crystals, m.p. 74 °C. $[\alpha]_D^{20}$ = +34.7 (*c* = 2.73, $CHCl_3$). TLC: R_f = 0.45 (*n*-pentane/ethyl acetate, 96:4). ^{1}H NMR ($CDCl_3$): δ = 0.51 [s, 9 H, $(CH_3)_3C$], 0.98 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.08 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.45 (s, 3 H, CH_3), 2.21 [sept, *J* = 6.8 Hz, 1 H, $CH(CH_3)_2$], 3.06 (d, *J* = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.30 (d, *J* = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.74 (s, 3 H, OCH_3), 7.12−7.18 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2966 cm^{-1}, 1743, 1689, 1456, 1368, 1311. MS (CH_4; CI): *m*/*z* (%) = 332 (100) [M + H^+]. $C_{20}H_{29}NO_3$ (331.5): calcd. C 72.47, H 8.82, N 4.23; found C 72.48, H 8.79, N 4.25.

Compound 18d: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see below).

(3*R*,6*S*)-3-Benzyl-6-*tert*-butyl-5-methoxy-3,6-dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18a) and (3*S*,6*S*)-3-Benzyl-6-*tert*-butyl-5-methoxy-3,6-dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17a): The compounds were obtained by GP B, from **13c/14c** (48 mg, 0.225 mmol), *s*BuLi (191 μL, 0.248 mmol), and benzyl bromide (116 mg, 81 μL, 0.68 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **17a/18a** (56 mg, 82%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2, 1.5 mL/min) on the crude product: *ds* **18a/17a** = 98.5:1.5; **18a:** t_R = 25.12 min, **17a:** t_R = 33.33 min. Compound **18a** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 15 mL/min).

Compound 18a: Colorless crystals, m.p. 69 °C. $[\alpha]_D^{20}$ = −35.2 (*c* = 0.305, $CHCl_3$). TLC: R_f = 0.49 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.52 (s, 3 H, CH_3), 0.91 [s, 9 H, $(CH_3)_3C$], 1.63 (s, 3 H, CH_3), 2.85 (d, *J* = 12.6 Hz, 1 H, $CH_2C_6H_5$), 3.32 (d, *J* = 12.6 Hz, 1 H, $CH_2C_6H_5$), 3.72 (s, 3 H, OCH_3), 7.09−7.23 (m, 5 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 2970 cm^{-1}, 1741, 1692, 1450, 1373, 1311, 1221. MS (CH_4; CI): *m*/*z* (%) = 304 (100) [M + H^+]. $C_{18}H_{25}NO_3$ (303.4): calcd. C 71.26, H 8.31, N 4.62; found C 71.28, H 8.40, N 4.55.

Compound 17a: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see above).

(3*R*,6*S*)-3-Allyl-3-benzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18b) and (3*S*,6*S*)-3-Allyl-3-benzyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17b): The compounds were obtained by GP B, from **13b/14b** (32 mg, 0.135 mmol), *s*BuLi (114 μL, 0.149 mmol), and benzyl bromide (69 mg, 48 μL, 0.41 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **17b/18b** (37.6 mg, 85%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2; 1.5 mL/

min) on the crude product: *ds* **18b/17b** = 99.0:1.0; **18b:** t_R = 13.97 min, **17b**: t_R = 15.55 min. Compound **18b** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 16.5 mL/min).

Compound 18b: Colorless crystals, m.p. 70 °C. $[\alpha]_D^{20} = -36.7$ (c = 0.51, $CHCl_3$). TLC: R_f = 0.46 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.38 (s, 3 H, CH_3), 0.89 [s, 9 H, $(CH_3)_3C$], 2.64−2.82 (m, 2 H, CH_2−CH=CH_2), 2.92 (d, J = 12.7 Hz, 1 H, $CH_2C_6H_5$), 3.26 (d, J = 12.7 Hz, 1 H, $CH_2C_6H_5$), 3.76 (s, 3 H, OCH_3), 5.12−5.22 (m, 2 H, CH_2−CH=CH_2), 5.90 (ddt, J = 16.8/10.3/7.7 Hz, 1 H, CH_2−CH=CH_2), 7.14−7.21 (m, 5 H, C_6H_5) ppm. IR: ṽ = 3089 cm^{-1}, 2985, 1735, 1686, 1477, 1369, 1220. MS (CH_4; CI): *m*/*z* (%) = 330 (100) [M + H$^+$]. $C_{20}H_{27}NO_3$ (329.4): calcd. C 72.92, H 8.26, N 4.25; found C 73.09, H 8.42, N 4.50.

Compound 17b: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see above).

(3*R*,6*S*)-3-Benzyl-3-*n*-butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18c) and (3*S*,6*S*)-3-Benzyl-3-*n*-butyl-6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17c): The compounds were obtained by GP B, from **13e/14e** (38 mg, 0.15 mmol), *s*BuLi (1.19 M in *n*-hexane, 139 μL, 0.165 mmol), and benzyl bromide (77 mg, 54 μL, 0.45 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) without separation of the diastereomers yielded **17c/18c** (44.1 mg, 85%), together with **13e/14e** (4.1 mg, 11%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2; 1.5 mL/min) on the crude product: *ds* **18c/17c =** 99.2:0.8; **18c:** t_R = 9.29 min, **17c:** t_r = 8.55 min. Compound **18c** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 16.5 mL/min).

Compound 18c: Colorless oil. $[\alpha]_D^{20} = -33.6$ (c = 0.955, $CHCl_3$). TLC: R_f = 0.60 (petroleum ether/ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): δ = 0.32 (s, 3 H, CH_3), 0.85−0.99 (m, 3 H, $(CH_2)_3CH_3$), 0.91 [s, 9 H, $(CH_3)_3C$], 1.30−1.40 [m, 4 H, $CH_2(CH_2)_2CH_3$], 1.86−1.95 (m, 1 H, $CH_2C_3H_7$), 2.02−2.10 (m, 1 H, $CH_2C_3H_7$), 2.90 (d, J = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.26 (d, J = 12.8 Hz, 1 H, $CH_2C_6H_5$), 3.74 (s, 3 H, OCH_3), 7.10−7.25 (m, 5 H, C_6H_5) ppm. IR: ṽ = 2948 cm^{-1}, 2665, 1731, 1689, 1452, 1296, 1121, 1101. MS (CH_4; CI): *m*/*z* (%) = 346 (100) [M + H$^+$], 290 (18). $C_{21}H_{31}NO_3$ (345.5): calcd. C 73.01, H 9.04, N 4.05; found C 72.59, H 9.05, N 3.99.

Compound 17c: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see above).

(3*S*,6*S*)-3-Benzyl-6-*tert*-butyl-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (18d) and (3*R*,6*S*)-3-Benzyl-6-*tert*-butyl-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (17d): The compounds were obtained by GP B, from **13f/14f** (31 mg, 0.128 mmol), *s*BuLi (c = 1.24 M in cyclohexane, 114 μL, 0.141 mmol), and benzyl bromide (66 mg, 46 μL, 0.38 mmol). Purification by CC (*n*-pentane/ethyl acetate, 98:2) without separation of the diastereomers yielded **17d/18d** (33.6 mg, 79%). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 98:2; 1.75 mL/min) on the crude product: *ds* **18d/17d =** 99.6:0.4; **18d:** t_r = 7.87 min, **17d:** t_r = 8.79 min. Compound **18d** was isolated by preparative HPLC (*n*-heptane/ethyl acetate, 98:2; 16.5 mL/min).

Compound 18d: Colorless crystals, m.p. 70 °C. $[\alpha]_D^{20} = -58.2$ (c = 0.52, $CHCl_3$). TLC: R_f = 0.38 (isohexane/ethyl acetate, 98:2). ^{1}H NMR ($CDCl_3$): δ = 0.18 (s, 3 H, CH_3), 0.91 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 0.92 [s, 9 H, $(CH_3)_3C$], 1.15 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 2.41 [sept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 3.02 (d, J = 12.7 Hz, 1 H, $CH_2C_6H_5$), 3.18 (d, J = 12.7 Hz, 1 H, $CH_2C_6H_5$), 3.76 (s, 3 H, OCH_3), 7.10−7.25 (m, 5 H, C_6H_5) ppm. IR: ṽ = 2964 cm^{-1}, 2876, 1727, 1692, 1439, 1298, 1097, 1039, 702. MS (CH_4; CI): *m*/*z* (%) = 332 (100) [M + H$^+$], 184 (12). $C_{20}H_{29}NO_3$ (331.5): calcd. C 72.47, H 8.82, N 4.23; found C 72.32, H 8.97, N 4.04.

Compound 17d: A selective synthesis of this compound, not isolated from the above experiment, was accomplished by an inverse alkylation sequence (see above).

(3*R*,6*S*)-3-Benzyl-6-*tert*-butyl-3-hydroperoxy-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (19). A: Mixture **13a/14a** (189 mg, 0.632 mmol) in THF (7 mL) was treated at −80 °C with *s*BuLi (c = 1.15 M in cyclohexane, 0.60 mL, 0.717 mmol, 1.1 equiv.) and stirred for 30 min. Dry air (700 mL) was then slowly bubbled at −78 °C through the solution over 2 h. Finally, after the reaction mixture had been quenched with phosphate buffer (pH = 7, 10 mL), it was extracted with Et_2O (4 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by CC (petroleum ether/ethyl acetate, 90:10) yielded **19** (170 mg, 81%) as colorless crystals, m.p. 85 °C. $[\alpha]_D^{20} = +25.2$ (c = 0.72, $CHCl_3$). TLC: R_f = 0.34 (isohexane/ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$): δ = 0.64 [s, 9 H, $(CH_3)_3C$], 1.55 (s, 3 H, CH_3), 1.62 (s, broad, 1 H, OH), 3.08 (d, J = 12.9 Hz, 1 H, $CH_2C_6H_5$), 3.40 (d, J = 12.9 Hz, 1 H, $CH_2C_6H_5$), 3.85 (s, 3 H, OCH_3), 7.16−7.24 (m, 5 H, C_6H_5) ppm. IR: ṽ = 3347 cm^{-1}, 2965, 1746, 1716, 1685, 1663, 1460, 1348, 1226. MS (CH_4; CI): *m*/*z* (%) = 322 (2) [M + H$^+$], 288 (32), 232 (49), 214 (100). $C_{17}H_{23}NO_5$ (321.4): calcd. C 63.50, H 7.21, N 4.36; found C 63.50, H 7.15, N 4.36.

B: The compound was obtained by GP B, from **13a/14a** (53 mg, 0.18 mmol), *s*BuLi (154 μL, 0.20 mmol), and isopropyl iodide (92 mg, 51 μL, 0.54 mmol). Purification by CC (petroleum ether/ethyl acetate, 90:10) afforded **19** (46 mg, 83%) as colorless crystals, m.p. 85 °C.

(3*R*,6*S*)-(3-Benzyl-6-*tert*-butyl-5-methoxy-6-methyl-2-oxo-3,6-dihydro-2*H*-1,4-oxazin-3-yl) Peracetate (20): Compound **19** (59 mg, 0.18 mmol) was dissolved in acetic anhydride (18 mL) and stirred for 2 h at room temp. After addition of H_2O (46 mL) and extraction with Et_2O (4 × 10 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to yield **20** (54 mg, 81%) as colorless crystals, m.p. 56−57 °C. $[\alpha]_D^{20} = +64.5$ (c = 0.75, $CHCl_3$). TLC: R_f = 0.23 (isohexane/ethyl acetate, 80:20). ^{1}H NMR ($CDCl_3$): δ = 0.60 [s, 9 H, $(CH_3)_3C$], 1.53 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3CO), 3.23 (d, J = 12.6 Hz, 1 H, $CH_2C_6H_5$), 3.52 (d, J = 12.6 Hz, 1 H, $CH_2C_6H_5$), 3.80 (s, 3 H, OCH_3), 7.19−7.26 (m, 5 H, C_6H_5) ppm. IR: ṽ = 2969 cm^{-1}, 1796, 1750, 1676, 1456, 1342, 1187, 1102. MS (CH_4; CI): *m*/*z* (%) = 364 (26) [M + H$^+$], 214 (100). $C_{19}H_{25}NO_6$ (363.4): calcd. C 62.80, H 6.93, N 3.85; found C 62.84, H 6.74, N 3.87.

(1*S*,3*R*,6*S*)-6-*tert*-Butyl-1-hydroxymethyl-5-methoxy-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one (21): $NaN(SiMe_3)_2$ (c = 1.0 M in THF, 4.42 mL, 4.42 mmol, 2.2 equiv.) was slowly (30 h) added at −20 °C to **(*S*)-2** (400 mg, 2.01 mmol) and (*S*)-(+)-epichlorohydrin (1.12 g, 946 μL, 12.06 mmol, 6.0 equiv.) in THF (20 mL). After another 16 h stirring at −20 °C the reaction mixture was hydrolyzed with phosphate buffer (pH = 7, 20 mL) and the organic solvent was removed in vacuo. The aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. CC (petroleum ether/ethyl acetate, 70:30) yielded 215 mg (42%) of

21 as colorless crystals, m.p. 90 °C. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 85:15; 2.0 mL/min) on the crude product: no other diastereomer being detected, *ds* > 99.9:0.1; **21:** t_r= 25.74 min. $[\alpha]_D^{20}$ = +61.5 (*c* = 0.183, $CHCl_3$). TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 70:30). ^{1}H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 1.47 (dd, *J* = 7.7/4.6 Hz, 1 H, C*H*$_2$CH), 1.56 (s, 3 H, CH_3), 1.78 (dd, *J* = 9.7/4.6 Hz, 1 H, C*H*$_2$CH), 2.20−2.27 (m, 1 H, CH_2CH), 3.67 (s, 3 H, OCH_3), 3.90 (dd, *J* = 12.1/5.6 Hz, 1 H, C*H*$_2$OH), 4.10 (dd, *J* = 12.1/2.8 Hz, 1 H, C*H*$_2$OH), OH ppm, not located. IR (KBr): ṽ = 3448 cm^{-1}, 1739, 1685, 1370, 1211. MS (CH_4; CI): *m*/*z* (%) = 256 (100) [M + H$^+$]. $C_{13}H_{21}NO_4$ (255.3): calcd. C 61.16, H 8.29, N 5.49; found C 61.23, H 8.26, N 5.44.

(1*R*,3*S*,6*S*)-6-*tert*-Butyl-1-hydroxymethyl-5-methoxy-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one (22). A: The preparation was performed in analogy to the procedure described for **21**, from **(*S*)-2** (669 mg, 3.36 mmol), (*R*)-(−)-epichlorohydrin (1.87 g, 1.58 mL, 20.16 mmol, 6.0 equiv.) in THF (30 mL), and $NaN(SiMe_3)_2$ (*c* = 1.0 M in THF, 7.4 mL, 7.4 mmol, 2.2 equiv.). CC (petroleum ether/ethyl acetate, 70:30) yielded **22** (373 mg, 44%) as colorless crystals, m.p. 95 °C. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 85:15; 2.0 mL/min) on the crude product, no other diastereomer being detected: *ds* > 99.9:0.1; **22:** t_r= 29.51 min.− $[\alpha]_D^{20}$ = −4.0 (*c* = 0.56, $CHCl_3$). TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 70:30). ^{1}H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 1.55 (dd, *J* = 7.5/4.5 Hz, 1 H, C*H*$_2$CH), 1.56 (s, 3 H, CH_3), 1.90 (dd, *J* = 9.8/4.5 Hz, 1 H, C*H*$_2$CH), 2.08−2.14 (m, 1 H, CH_2CH), 3.67 (s, 3 H, OCH_3), 3.89 (dd, *J* = 12.2/4.8 Hz, 1 H, C*H*$_2$OH), 3.98 (dd, *J* = 12.2/2.6 Hz, 1 H, C*H*$_2$OH), OH ppm, not located. IR: ṽ = 3432 cm^{-1}, 1736, 1684, 1376, 1219. MS (CH_4; CI): *m*/*z* (%) = 256 (100) [M + H$^+$]. $C_{13}H_{21}NO_4$ (255.3): calcd. C 61.16, H 8.29, N 5.49; found C 61.13, H 8.32, N 5.49.

B: A Et_2Zn solution (1.0 M in *n*-hexane, 110 μL, 0.11 mmol, 1.5 equiv.) was added at room temp. to **23a/b** (as a 96:4 mixture of *Z*/*E* isomers, 18 mg, 0.074 mmol) in Et_2O (0.5 mL), followed after 15 min by diiodomethane (40 mg, 12 μL, 0.149 mmol, 2.0 equiv.). The mixture was stirred for 18 h at room temp. and then quenched with phosphate buffer (pH 7, 1 mL). The aqueous layer was extracted with Et_2O (3 × 3 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. By the ^{1}H NMR spectrum the crude product (≈ 20 mg) was composed of a 4:6 mixture of **21/22** (65%), together with some starting material (35%).

(*Z*)-(*S*)-6-*tert*-Butyl-3-(2-hydroxyethylidene)-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (23a) and (*E*)-(*S*)-6-*tert*-Butyl-3-(2-hydroxyethylidene)-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (23b): Powdered KOH (30 mg, 0.544 mmol) was added at 0 °C to **(*S*)-2** (102 mg, 0.512 mmol) in EtOH (5 mL), followed over 2 h by glycolaldehyde dimer (4 portions each of 61 mg, 1.02 mmol, 2 equiv.). After additional stirring for 30 min the reaction mixture was hydrolyzed with phosphate buffer (pH = 7, 3 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 70:30) yielded a 96:4 mixture of **23a/23b** (98 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$ = −86.7 (*c* = 1.787, $CHCl_3$). TLC: R_f = 0.24 (petroleum ether/ethyl acetate, 70:30). ^{1}H NMR ($CDCl_3$): δ = 0.99 [s, 0.04 × 9 H, $(CH_3)_3C$], 1.02 [s, 0.96 × 9 H, $(CH_3)_3C$], 1.53 (s, 0.04 × 3 H, CH_3), 1.56 (s, 0.96 × 3 H, CH_3), 3.82 (s, 0.04 × 3 H, OCH_3), 3.84 (s, 0.96 × 3 H, OCH_3), 4.61−4.66 (m, 3 H, $CHCH_2OH$), 6.33 (t, *J* = 6.0 Hz, 0.04 × 1 H, C*H*CH_2OH), 6.64 (t, *J* = 4.0 Hz, 0.96 × 1 H, C*H*CH_2OH) ppm. IR: ṽ = 3422 cm^{-1}, 2961, 1711, 1656, 1332, 1264, 1212. MS (CH_4; CI): *m*/*z* (%) = 242 (100) [M + H$^+$]. $C_{12}H_{19}NO_4$ (241.3): calcd. C 59.73, H 7.94, N 5.81; found C 59.79, H 8.04, N 5.75.

(1*S*,3*R*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-azaspiro[2.5]oct-4-ene-1-carbaldehyde (24): Compound **21** (50 mg, 0.196 mmol) in DMSO (2.5 mL) was added to *ortho*-iodoxybenzoic acid (67.4 mg, 0.235 mmol, 1.2 equiv.) in DMSO (3 mL). The reaction mixture was stirred for 3 h at room temp. and Et_2O (5 mL) and H_2O (5 mL) were then added. The organic layer was separated and the aqueous layer was saturated with NaCl and extracted with Et_2O (4 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 70:30) yielded **24** (31 mg, 63%) as a colorless oil. $[\alpha]_D^{20}$ = −19.1 (*c* = 0.23, $CHCl_3$). TLC: R_f = 0.58 (petroleum ether/ethyl acetate, 70:30). ^{1}H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 1.55 (s, 3 H, CH_3), 2.03 (dd, *J* = 7.1/4.9 Hz, 1 H, C*H*$_2$CH), 2.13 (dd, *J* = 9.2/4.9 Hz, 1 H, C*H*$_2$CH), 2.73−2.79 (m, 1 H, CH_2CH), 3.64 (s, 3 H, OCH_3), 9.40 (d, *J* = 4.6 Hz, 1 H, CHO) ppm. IR: ṽ = 2959 cm^{-1}, 1739, 1716, 1684, 1354, 1253. MS (CH_4; CI): *m*/*z* (%) = 254 (100) [M + H$^+$]. $C_{13}H_{19}NO_4$ (253.3): calcd. C 61.64, H 7.56, N 5.53; found C 61.84, H 7.65, N 5.32.

(1*R*,3*R*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-1-phenylaminomethyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one (25): Compound **24** (25 mg, 0.10 mmol) in THF (2.5 mL) was treated with aniline (28 mg, 27 μL, 0.30 mmol) and AcOH (6 mg, 4 μL, 0.10 mmol, 1.0 equiv.) and the mixture was stirred for 30 min. $NaBH_3CN$ (6.3 mg, 0.10 mmol, 1.0 equiv.) was then added at room temp. After 2 h the solvent was removed in vacuo and Et_2O (5 mL) was added. The solution was then washed with a $NaHCO_3$ solution (5%, 3 × 3 mL) and the aqueous layer was re-extracted with Et_2O (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. CC (petroleum ether/ethyl acetate, 70:30) afforded **25** (22 mg, 67%) as colorless crystals, m.p. 74 °C. $[\alpha]_D^{20}$ = +23.9 (*c* = 0.51, $CHCl_3$). TLC: R_f = 0.69 (petroleum ether/ethyl acetate, 70:30). ^{1}H NMR ($CDCl_3$): δ = 1.03 [s, 9 H, $(CH_3)_3C$], 1.14 (dd, *J* = 7.5/4.4 Hz, 1 H, C*H*$_2$CH), 1.55 (s, 3 H, C*H*$_3$), 1.79 (dd, *J* = 9.3/4.4 Hz, 1 H, C*H*$_2$CH), 2.31 (dddd, *J* = 9.3/7.6/7.5/5.1 Hz, 1 H, CH_2CH), 3.41 (dd, *J* = 13.2/7.6 Hz, 1 H, C*H*$_2$NH), 3.52 (dd, *J* = 13.2/5.1 Hz, 1 H, C*H*$_2$NH), 3.65 (s, 3 H, OCH_3), 6.66 (d, *J* = 7.4 Hz, 2 H, C_6H_5), 6.72 (t, *J* = 7.4 Hz, 1 H, C_6H_5), 7.18 (t, *J* = 7.4 Hz, 2 H, C_6H_5), NH ppm, not located. IR: ṽ = 3379 cm^{-1}, 1735, 1689, 1377. MS (CH_4; CI): *m*/*z* (%) = 331 (100) [M + H$^+$]. $C_{19}H_{26}N_2O_3$ (330.4): calcd. C 69.06, H 7.93, N 8.48; found C 69.15, H 7.89, N 8.59.

(1*R*,3*S*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-azaspiro[2.5]oct-4-ene-1-carbaldehyde (26): The preparation was performed analogously to the procedure described for **24**, from *ortho*-iodoxybenzoic acid (132 mg, 0.39 mmol, 1.2 equiv.) in DMSO (6.4 mL) and **22** (100 mg, 0.39 mmol) in DMSO (4.3 mL). CC (petroleum ether/ethyl acetate, 70:30) yielded **26** (87 mg, 88%) as a colorless oil. $[\alpha]_D^{20}$ = +99.7 (*c* = 0.30, $CHCl_3$). TLC: R_f = 0.58 (petroleum ether/ethyl acetate, 70:30). ^{1}H NMR ($CDCl_3$): δ = 1.00 [s, 9 H, $(CH_3)_3C$], 1.57 (s, 3 H, CH_3), 2.13 (dd, *J* = 7.1/4.9 Hz, 1 H, C*H*$_2$CH), 2.31 (dd, *J* = 9.2/4.9 Hz, 1 H, C*H*$_2$CH), 2.58−2.63 (m, 1 H, CH_2CH), 3.67 (s, 3 H, OCH_3), 9.29 (d, *J* = 6.6 Hz, 1 H, CHO) ppm. IR: ṽ = 2958 cm^{-1}, 1740, 1715, 1683, 1354, 1252. MS (CH_4; CI): *m*/*z* (%) = 254 (100) [M + H$^+$]. $C_{13}H_{19}NO_4$ (253.3): calcd. C 61.64, H 7.56, N 5.53; found C 61.75, H 7.61, N 5.39.

(1*S*,3*S*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-1-phenylaminomethyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one (27): The preparation was performed analogously to the procedure described for **25**, from **26**

(82 mg, 0.32 mmol) in THF (8 mL), aniline (90 mg, 89 μL, 0.97 mmol), AcOH (19 mg, 19 μL, 0.32 mmol), and $NaBH_3CN$ (20 mg, 0.32 mmol, 1 equiv.). CC (petroleum ether/ethyl acetate, 70:30) afforded **27** (77 mg, 73%) as colorless crystals, m.p. 76 °C. $[\alpha]_D^{20} = -11.1$ ($c = 0.44$, $CHCl_3$). TLC: $R_f = 0.68$ (petroleum ether/ethyl acetate, 70:30). ^1H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 1.26 (dd, $J = 7.4/4.4$ Hz, 1 H, CH_2CH), 1.57 (s, 3 H, CH_3), 1.92 (dd, $J = 9.5/4.4$ Hz, 1 H, CH_2CH), 2.17−2.24 (m, 1 H, CH_2CH), 3.39 (d, $J = 6.4$ Hz, 2 H, CH_2NH), 3.67 (s, 3 H, OCH_3), 6.59 (d, $J = 7.4$ Hz, 2 H, C_6H_5), 6.71 (t, $J = 7.4$ Hz, 1 H, C_6H_5), 7.17 (t, $J = 7.4$ Hz, 2 H, C_6H_5), NH signal ppm, not located. IR: $\tilde{\nu}$ = 3365 cm^{-1}, 1730, 1687, 1370. MS (CH_4; CI): *m*/*z* (%) = 331 (100) [M + H^+]. $C_{19}H_{26}N_2O_3$ (330.4): calcd. C 69.06, H 7.93, N 8.48; found C 68.95, H 7.79, N 8.68.

1-Phenyl-3-(trifluoroacetyl)urea (28): *N*-Phenylurea (500 mg, 3.67 mmol) and trifluoroacetic anhydride (7.55 g, 5.00 mL, 36.0 mmol) were stirred at room temp. for 8 h. The reaction mixture was then concentrated in vacuo. CC (petroleum ether/ethyl acetate, 70:30) yielded **28** (734 mg, 86%) as colorless crystals, m.p. 211 °C (dec.) {ref.[33] 215−216 °C (dec.)}. TLC: $R_f = 0.49$ (petroleum ether/ethyl acetate, 70:30). ^1H NMR ($CDCl_3$): δ = 7.10−7.47 (m, 5 H, C_6H_5), 9.38 (s, 1 H, NH), 9.77 (s, 1 H, NH) ppm. IR: $\tilde{\nu}$ = 3306 cm^{-1}, 3152, 3000, 1719, 1616, 1568, 1233. MS (CH_4; CI): *m*/*z* (%) = 233 (100) [M + H^+]. $C_9H_7N_2O_2F_3$ (232.2): calcd. C 46.56, H 3.04, N 12.07; found C 46.61, H 3.03, N 12.03.

1-[(1*R*,3*R*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-aza-spiro[2.5]oct-4-en-1-ylmethyl]-3-phenyl-1-(trifluoroacetyl)urea (29): diisopropyl azodicarboxylate (DIAD) (71 mg, 69 μL, 0.35 mmol, 1.5 equiv.) was added at 0 °C to a solution of PPh_3 (93 mg, 0.35 mmol, 1.5 equiv.) in THF (2 mL), followed at 0 °C by a solution of **21** (60 mg, 0.235 mmol) and 1-phenyl-3-(trifluoroacetyl)-urea (**28**, 82 mg, 0.35 mmol, 1.5 equiv.) in THF (3.3 mL). The mixture was allowed to warm to room temp. After 24 h the solvent was removed in vacuo, and the residue was redissolved in CH_2Cl_2 and washed with a K_2CO_3 solution (5%). The organic layer was separated, the solvent was removed, and the residue was purified by CC (*n*-heptane/ethyl acetate, 70:30) to afford **29** (72 mg, 65%) as a colorless oil. $[\alpha]_D^{20} = -29.7$ ($c = 0.20$, $CHCl_3$). TLC: $R_f = 0.25$ (petroleum ether/iPr_2O, 55:45). ^1H NMR ($CDCl_3$): δ = 1.02 [s, 9 H, $(CH_3)_3C$], 1.24 (dd, $J = 7.2/4.8$ Hz, 1 H, CH_2CH), 1.46 (s, 3 H, CH_3), 1.87 (dd, $J = 9.5/4.8$ Hz, 1 H, CH_2CH), 2.44−2.47 (m, 1 H, CH_2CH), 3.62 (s, 3 H, OCH_3), 4.63 (dd, $J = 11.5/9.1$ Hz, 1 H, CH_2NCO), 4.98 (dd, $J = 11.5/5.9$ Hz, 1 H, CH_2NCO), 7.25−7.29 (m, 3 H, C_6H_5), 7.33−7.38 (m, 2 H, C_6H_5), 11.26 (s, 1 H, NH) ppm. IR: $\tilde{\nu}$ = 3296 cm^{-1}, 2955, 1735, 1689, 1650, 1612, 1582, 1470. MS (CH_4; CI): *m*/*z* (%) = 470 (8) [M + H^+], 238 (100). $C_{22}H_{26}F_3N_3O_5$ (469.5): calcd. C 56.29, H 5.58, N 8.95; found C 56.45, H 5.73, N 8.65.

1-[(1*R*,3*R*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-aza-spiro[2.5]oct-4-en-1-ylmethyl]-3-phenylurea (30): Compound **29** (60 mg, 0.128 mmol) was stirred at room temp. in a 20% K_2CO_3 solution (2.0 g K_2CO_3 in a mixture of 4 mL H_2O and 4 mL of MeOH, 10 mL). After 4 h, MeOH was removed in vacuo and the residual aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. CC (*n*-heptane/ethyl acetate, 20:80) yielded **30** (35 mg, 74%) as a colorless oil. $[\alpha]_D^{20} = +43.1$ ($c = 0.50$, $CHCl_3$). TLC: $R_f = 0.46$ (petroleum ether/ethyl acetate, 20:80). ^1H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 1.15 (dd, $J = 7.5/4.5$ Hz, 1 H, CH_2CH), 1.56 (s, 3 H, CH_3), 1.84 (dd, $J = 9.7/4.5$ Hz, 1 H, CH_2CH), 2.38−2.45 (m, 1 H, CH_2CH), 3.69 (s, 3 H, OCH_3), 4.07 (s, 2 H, NH), 4.45 (dd, $J = 11.5/8.6$ Hz, 1 H, CH_2NCO), 4.52 (dd, $J = 11.5/5.5$ Hz, 1 H, CH_2NCO), 6.91 (d, $J = 7.5$ Hz, 2 H, C_6H_5), 7.02 (t, $J = 7.5$ Hz, 1 H, C_6H_5), 7.29 (t, $J = 7.5$ Hz, 2 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 3357 cm^{-1}, 2962, 1734, 1680, 1594, 1372, 1260. MS (CH_4; CI): *m*/*z* (%) = 374 (100) [M + H^+]. $C_{20}H_{27}N_3O_4$ (373.5): calcd. C 64.32, H 7.29, N 11.25; found C 64.40, H 7.40, N 11.11.

1-[(1*S*,3*S*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-aza-spiro[2.5]oct-4-en-1-ylmethyl]-3-phenyl-1-(trifluoroacetyl)urea (31): This preparation was as described for **29**, from PPh_3 (154 mg, 0.59 mmol, 1.5 equiv.), DIAD (114 μL, 0.59 mmol, 1.5 equiv.) in THF (3.5 mL), **22** (100 mg, 0.39 mmol), and 1-phenyl-3-(trifluoroacetyl)urea (**28**, 136 mg, 0.59 mmol, 1.5 equiv.) in THF (5.5 mL). CC (*n*-heptane/ethyl acetate, 70:30) afforded **31** (116 mg, 63%) as a colorless oil. $[\alpha]_D^{20} = +30.1$ ($c = 0.59$, $CHCl_3$). TLC: $R_f = 0.33$ (petroleum ether/iPr_2O, 55:45). ^1H NMR ($CDCl_3$): δ = 0.86 [s, 9 H, $(CH_3)_3C$], 1.27 (dd, $J = 7.5/4.6$ Hz, 1 H, CH_2CH), 1.53 (s, 3 H, CH_3), 1.95 (dd, $J = 9.6/4.6$ Hz, 1 H, CH_2CH), 2.35−2.40 (m, 1 H, CH_2CH), 3.65 (s, 3 H, OCH_3), 4.69 (dd, $J = 11.4/8.4$ Hz, 1 H, CH_2NCO), 4.83 (dd, $J = 11.4/5.6$ Hz, 1 H, CH_2NCO), 7.24−7.29 (m, 3 H, C_6H_5), 7.35−7.39 (m, 2 H, C_6H_5), 11.28 (s, 1 H, NH) ppm. IR: $\tilde{\nu}$ = 3296 cm^{-1}, 2957, 1738, 1689, 1652, 1614, 1582, 1451. MS (CH_4; CI): *m*/*z* (%) = 470 (3) [M + H^+], 238 (100). $C_{22}H_{26}F_3N_3O_5$ (469.5): calcd. C 56.29, H 5.58, N 8.95; found C 56.22, H 5.65, N 8.95.

1-[(1*S*,3*S*,6*S*)-6-*tert*-Butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-aza-spiro[2.5]oct-4-en-1-ylmethyl]-3-phenylurea (32): This preparation was as described for **30**, from **31** (57 mg, 0.122 mmol) and a K_2CO_3 solution (20%, 9.5 mL). Yield: 34 mg (76%) of **32** as a colorless oil. $[\alpha]_D^{20} = -3.6$ ($c = 0.45$, $CHCl_3$). TLC: $R_f = 0.38$ (petroleum ether/ethyl acetate, 20:80). ^1H NMR ($CDCl_3$): δ = 1.05 [s, 9 H, $(CH_3)_3C$], 1.24 (dd, $J = 7.7/4.3$ Hz, 1 H, CH_2CH), 1.57 (s, 3 H, CH_3), 1.95 (dd, $J = 9.6/4.3$ Hz, 1 H, CH_2CH), 2.30−2.39 (m, 1 H, CH_2CH), 3.70 (s, 3 H, OCH_3), 3.99 (s, 2 H, NH), 4.37 (dd, $J = 11.4/9.0$ Hz, 1 H, CH_2NCO), 4.50 (dd, $J = 11.4/5.3$ Hz, 1 H, CH_2NCO), 6.89 (d, $J = 7.5$ Hz, 2 H, C_6H_5), 7.02 (t, $J = 7.5$ Hz, 1 H, C_6H_5), 7.29 (t, $J = 7.5$ Hz, 2 H, C_6H_5) ppm. IR: $\tilde{\nu}$ = 3359 cm^{-1}, 2963, 1730, 1679, 1590, 1373, 1262. MS (CH_4; CI): *m*/*z* (%) = 374 (100) [M + H^+]. $C_{20}H_{27}N_3O_4$ (373.5): calcd. C 64.32, H 7.29, N 11.25; found C 64.18, H 7.21, N 11.05.

Preparation of the Free Amino Acids

General Procedure (GP C) for the Hydrolysis of the Monoalkylated Derivatives 13a−c and for the Hydrolysis of the Cyclopropyl Derivatives of 2 (21, 22, 25, and 27): A solution of the respective monoalkylated derivative of **2** in acetonitrile (0.1 M) was added to trifluoroacetic acid (0.2 M solution in H_2O, 5.0 equiv.) and the mixture was stirred for 20 h at 60 °C, after which the solvent was removed in vacuo.

For **13a−c** the residue was dissolved in aqueous NaOH (40%, resulting conc. ≈ 0.1 M) and allowed to stir for 20 h at room temp.

For **21** and **22** the residue was added to NaOH (0.2 M solution in MeOH, 6 equiv.) and heated at 60 °C for 20 h.

For **25** and **27** the residue was dissolved in DME (**25**) or in 2-ethoxyethanol (**27**) (resulting conc. 0.1 M), added to NaOH (10 M aqueous solution, 40 equiv.) and heated at 90 °C for 5 d.

After the second of the hydrolyses had been finished, the solvent was removed and the residue was redissolved in a small amount of water. The solution was washed with Et_2O (3 ×) and CH_2Cl_2 (3 ×) and then acidified at 0 °C with HCl (≈ pH 3). The acidic solution was washed with Et_2O (3 ×), CH_2Cl_2 (3 ×), and ethyl acetate

(3 ×). The residue obtained by concentration of the acidic aqueous solution was finally (after it had been dissolved in a small amount of water) subjected to ion-exchange chromatography (Dowex 50 W X 8 cation exchange resin, elution with H_2O until the eluent was neutral and free of chloride, then elution with 10% aqueous NH_3) to afford the free amino acid.

General Procedure (GP D) for the Hydrolysis of the Dialkylated Derivatives of 2 (17a−d): A solution of dialkylated **2** in a mixture consisting of 40% aqueous NaOH and MeOH (4:1, 0.1 M) was either stirred at 60 °C for 1 to 3 days (**17a−c**) or heated at 120 °C for 2 days (**17d**). The alkaline solution was washed with Et_2O (3 ×) and then acidified at 0 °C with HCl (6 M). The acidic aqueous phase was concentrated in vacuo, and the residue was dissolved in a small amount of water and subjected to ion-exchange chromatography with a Dowex 50 W X 8 resin (see GP C) to give the free amino acid.

Procedure for the Hydrolysis of 13c under Acidic Conditions: Compound **13c** was treated with a HBr solution (3 M, 25 equiv.) and the mixture was stirred at 130 °C in a pressure tube for 24 h. After removal of solvent in vacuo, the residue was washed with Et_2O (3 ×), redissolved in a small amount of water and eluted on a Dowex 50 W X 8 resin (see GP C) to yield **33c** (85%). The enantiomeric excess was determined by analytical HPLC on a Nucleosil® CHIRAL−1 column,[11] (H_2O, 0.5 mmol $CuSO_4$·5 H_2O/L; 1.0 mL/min), kept at 55−60 °C. *es* = 98.1:1.9; **33c:** t_R = 5.51 min; **(*ent*)-33c:** t_R = 4.73 min.

(*R*)-Phenylalanine (33a): This compound was obtained by GP C, from **13a** (30 mg, 0.104 mmol). Colorless crystals, m.p. 279 °C (dec.) {ref.[28] 283−284 °C (dec.)}. Yield: 4.2 mg (25%). The enantiomeric excess was determined by analytical HPLC on a Nucleosil® CHIRAL−1 column,[11] (H_2O, 0.5 mmol $CuSO_4$·5 H_2O/L; 1.0 mL/min), kept at 55−60 °C. *ee* = 87%; **33a:** t_R = 16.9 min; **(*ent*)-33a:** t_R = 11.4 min. Analytical data (^{1}H NMR, IR, MS) were in agreement with literature data. $[\alpha]_D^{20}$ = +32.0 (*c* = 0.19, H_2O) {ref.[29] $[\alpha]_D^{25}$ = +34.8 (*c* = 2.0, H_2O)}.

(*R*)-2-Aminopent-4-enoic Acid (33b): This compound was obtained by GP C, from **13b** (18.9 mg, 0.079 mmol). Colorless crystals, m.p. 244 °C (dec.) {ref.[30] 240−241 °C (dec.)}. Yield: 3.5 mg (38%). The enantiomeric excess was determined by analytical HPLC on a Nucleosil® CHIRAL−1 column,[11] (H_2O, 0.5 mmol $CuSO_4$·5 H_2O/L; 1.0 mL/min) that was kept at 55−60 °C. *ee* = 90%; **33b:** t_R = 16.8 min; **(*ent*)-33b:** t_R = 11.3 min. Analytical data (^{1}H NMR, IR, MS) were in agreement with literature values. $[\alpha]_D^{20}$ = +39.7 (*c* = 0.175, H_2O) {ref.[31] $[\alpha]_D^{20}$ = +37.9 (*c* = 1.3, H_2O)}.

(*R*)-Alanine (33c): This compound was obtained by GP C, from **13c** (24 mg, 0.11 mmol). Colorless crystals, m.p. 282 °C (dec.) {ref.[32] 289−291 °C (dec.)}. Yield: 7 mg (69%). Analytical data (^{1}H NMR, IR, MS) were in agreement with literature values. $[\alpha]_D^{20}$ = −1.9 (*c* = 0.10, H_2O) {ref.[29] $[\alpha]_D^{25}$ = −2.6 (*c* = 6.0, H_2O)}.

(*S*)-[3−^{13}C]Alanine [(*ent*)-33d]: This compound was obtained by the procedure for the hydrolysis of **13c** under acidic conditions (see above), from **(*ent*)-13d** (100 mg, 0.467 mmol); *es* = 98.6:1.4; **(*ent*)-33d**: t_R = 4.51 min; **33d**: t_R = 5.28 min. Colorless crystals, m.p. 290 °C (dec.). Yield: 35 mg (83%). $[\alpha]_D^{20}$ = +1.5 (*c* = 0.80, H_2O). ^{1}H NMR (D_2O): δ = 1.49 (dd, *J* = 129.9/7.2 Hz, 3 H, CH_3), 3.78 (dq, *J* = 4.6/7.2 Hz, 1 H, CH) ppm. MS (CH_4; CI): *m*/*z* (%) = 91 (100) [M + H$^+$], 86 (12). $^{13}CC_2H_7NO_2$ (90.1): calcd. C 40.00, H 7.83, N 15.55; found C 39.01, H 7.72, N 14.88.

(*S*)-2-Amino-2-methyl-3-phenylpropanoic Acid (34a): This compound was obtained by GP D, from **17a** (6.7 mg, 0.022 mmol). Colorless crystals, m.p. >300 °C (dec.) {ref.[33] 298−299 °C (dec.)}. Yield: 3.6 mg (91%). Analytical data (^{1}H NMR, IR, MS) were in agreement with literature data.[34] $[\alpha]_D^{20}$ = −16.1 (*c* = 0.16, H_2O) {ref.[31] $[\alpha]_D^{20}$ = −21.5 (*c* = 1.0, H_2O)}.

(*S*)-2-Amino-2-benzylpent-4-enoic Acid (34b): This compound was obtained by GP D, from **17b** (17 mg, 0.052 mmol). Colorless crystals, m.p. 218 °C (dec.) {ref.[4] 220 °C (dec.)}. Yield: 9.6 mg (90%). Analytical data (^{1}H NMR, IR, MS) were in agreement with literature values.[4,35] $[\alpha]_D^{20}$ = +22.8 (*c* = 0.365, H_2O) {ref.[35] $[\alpha]_D^{20}$ = +27.3 (*c* = 1.0, H_2O)}.

(*S*)-2-Amino-2-benzylhexanoic Acid (34c):[36] This compound was obtained by GP D, from **17c** (34 mg, 0.099 mmol). Colorless crystals, m.p. 240 °C (dec.). Yield: 17 mg (78%). $[\alpha]_D^{20}$ = −19.0 (*c* = 0.31, H_2O). ^{1}H NMR (D_2O): δ = 0.76 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.05−1.16 (m, 1 H, CH_2), 1.17−1.29 (m, 3 H, CH_2), 1.58−1.66 (m, 1 H, CH_2), 1.82−1.91 (m, 1 H, CH_2), 2.87 (d, *J* = 14.4 Hz, 1 H, C$H_2C_6H_5$), 3.17 (d, *J* = 14.4 Hz, 1 H, C$H_2C_6H_5$), 7.14 (d, *J* = 6.9 Hz, 2 H, C_6H_5), 7.19−7.30 (m, 3 H, C_6H_5) ppm. IR: ṽ = 3032 cm^{-1}, 2958, 1596, 1395, 702. MS (CH_4; CI): *m*/*z* (%) = 222 (77) [M + H$^+$], 176 (90), 130 (100). $C_{13}H_{19}NO_2$·H_2O (239.3): calcd. C 65.25, H 8.84, N 5.85; found C 65.32, H 8.27, N 5.93.

(*R*)-2-Amino-2-benzyl-3-methylbutanoic Acid (34d): This compound was obtained by GP D, from **17d** (30 mg, 0.090 mmol). Colorless crystals, m.p. 189 °C (dec.). Yield: 9.6 mg (51%). Analytical data (^{1}H NMR, IR, MS) were in agreement with literature values.[34] $[\alpha]_D^{20}$ = +3.3 (*c* = 0.48, H_2O). $[\alpha]_D^{20}$ = +2.8 (*c* = 0.45, MeOH) {ref.[34] $[\alpha]_D^{20}$ = +3.3 (*c* = 1.1, MeOH)}.

(1*R*,2*S*)-1-Amino-2-(hydroxymethyl)cyclopropanecarboxylic Acid (35): This compound was obtained by GP C, from **21** (60 mg, 0.23 mmol). Colorless crystals, m.p. 198 °C (dec.). Yield: 26 mg (86%). Analytical data (^{1}H NMR, IR, MS) were in agreement with literature values.[16] $[\alpha]_D^{20}$ = +64.4 (*c* = 0.90, H_2O) {ref.[16] $[\alpha]_D^{25}$ = +73.81 (*c* = 0.48, H_2O)}.

(1*S*,2*R*)-1-Amino-2-(hydroxymethyl)cyclopropanecarboxylic Acid [(*ent*)-35]: This compound was obtained by GP C, from **22** (63 mg, 0.25 mmol). Colorless crystals, m.p. 213 °C (dec.). Yield: 32 mg (97%). Analytical data (^{1}H NMR, IR, MS) were in agreement with literature values for the (1*R*,2*S*) enantiomer.[16] $[\alpha]_D^{20}$ = −74.0 (*c* = 0.50, H_2O) {ref.[16] $[\alpha]_D^{25}$ = −74.5 (*c* = 0.184, H_2O) for the (1*R*,2*S*)-enantiomer}.

(1*R*,2*R*)-1-Amino-2-(phenylaminomethyl)cyclopropanecarboxylic Acid (36):[37] This compound was obtained by GP C, from **25** (20 mg, 0.060 mmol) in DME. Colorless crystals, m.p. 178−180 °C (dec.). Yield: 13 mg (52%). $[\alpha]_D^{20}$ = +7.1 (*c* = 0.50, H_2O). ^{1}H NMR (D_2O): δ = 1.21 (dd, *J* = 7.7/6.5 Hz, 1 H, CH_2), 1.61 (dd, *J* = 9.7/6.5 Hz, 1 H, CH_2), 1.99−2.06 (m, 1 H, C*H*), 3.36 (dd, *J* = 13.4/6.7 Hz, 1 H, NCH_2), 3.39 (dd, *J* = 13.4/6.7 Hz, 1 H, NCH_2), 6.90−6.98 (m, 3 H, Ar*H*), 7.32−7.32 (m, 2 H, Ar*H*) ppm. IR: ṽ = 3400 cm^{-1}, 1602, 1508, 1378, 1253, 750, 691. HRMS (DEI+, 70 eV): calcd. for $C_{11}H_{14}N_2O_2$ 206.10553; found *m*/*z* = 206.1056.

(1*S*,2*S*)-1-Amino-2-(phenylaminomethyl)cyclopropanecarboxylic Acid [(*ent*)-36]:[37] This compound was obtained by GP C, from **27** (34 mg, 0.10 mmol) in 2-ethoxyethanol. Colorless crystals. Yield: 10 mg (50%). $[\alpha]_D^{20}$ = −6.8 (*c* = 0.40, H_2O). The spectroscopic data (^{1}H NMR, IR, MS) were identical to those described above for **36**. HRMS (DEI+, 70 eV): calcd. for $C_{11}H_{14}N_2O_2$ 206.10553; found *m*/*z* = 206.1055.

(1*R*,2*R*)-1-Amino-2-(aminomethyl)cyclopropanecarboxylic Acid [(*ent*)-37]: Compound **31** (58 mg, 0.124 mmol) in acetonitrile

(0.62 mL) was added to trifluoroacetic acid (6 equiv. 0.1 M solution in H_2O) and the mixture was stirred for 20 h at 60 °C. The reaction mixture was concentrated in vacuo and the residue was dissolved in a mixture of aqueous NaOH (10 M, 0.5 mL, 40 equiv.) and DME (1.0 mL) and heated to 90 °C. After 7 d the alkaline solution was washed with CH_2Cl_2 (3 ×), acidified with HCl (2 M, pH 3), and again washed with CH_2Cl_2 (3 ×). The acidic aqueous solution was concentrated in vacuo and the residue was dissolved in a small amount of water and subjected to ion-exchange chromatography with a Dowex 50 W X 8 resin to give the free amino acid as colorless crystals, still contaminated with about 10% of an inseparable side product; m.p. <150 °C (dec.). Yield: 3.9 mg (24%). $[\alpha]_D^{20} = -6.9$ (c = 0.19, H_2O). ^{1}H NMR (D_2O): δ = 1.19 (dd, J = 7.4/6.4 Hz, 1 H, CH_2CH), 1.13 (dd, J = 10.0/6.4 Hz, 1 H, CH_2CH), 1.83−1.92 (m, 1 H, CH$_2$CH), 3.48 (dd, J = 12.3/6.6 Hz, 1 H, CH_2NH$_2$), 3.70 (dd, J = 12.3/4.8 Hz, 1 H, CH_2NH$_2$) ppm.

Acknowledgments

Financial support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the BMBF is gratefully acknowledged.

[1] [1a] T. Wirth, *Angew. Chem.* **1997**, *109*, 235−237; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225−227. [1b] B. M. Trost, X. Ariza, *Angew. Chem.* **1997**, *109*, 2749−2751; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2635−2637. [1c] S. Hanessian, G. McNaughton-Smith, H. G. Lombart, W. D. Lubell, *Tetrahedron* **1997**, *53*, 12789−12854.

[2] [2a] M. Goodman, H. Shao, *Pure Appl. Chem.* **1996**, *68*, 1303−1308 and references therein. [2b] W. F. Degrado, *Adv. Protein Chem.* **1988**, *39*, 51−124 and references therein.

[3] [3a] C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. [3b] C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645−732.

[4] O. Achatz, A. Grandl, K. Th. Wanner, *Eur. J. Org. Chem.* **1999**, 1967−1978.

[5] Camphanic acid, which is commercially available in both enantiomeric forms, serves as a starting material for the synthesis of the chiral auxiliary. For large-scale synthesis it is more economic to prepare it from the corresponding enantiomer of camphoric acid. However, the (−)-enantiomer of camphoric acid is far more expensive than the (+)-enantiomer.

[6] [6a] R. M. Williams, *Synthesis of Optically Active* α*-Amino Acids*, Pergamon Press, Oxford, **1989**. [6b]R. Fitzi, D. Seebach, *Tetrahedron* **1988**, *44*, 5277−5292.

[7] [7a] G. Porzi, S. Sandri, P. Verrocchio, *Tetrahedron: Asymmetry* **1998**, *9*, 119−132. [7b] G. Porzi, S. Sandri, *Tetrahedron: Asymmetry* **1998**, *9*, 3411−3420. [7c] R. M. Williams, M.-N. Im, *J. Am. Chem. Soc.* **1991**, *113*, 9276−9286. [7d] K. Hammer, K. Undheim, *Tetrahedron* **1997**, *53*, 5925−5936. [7e] K. Hammer, K. Undheim, *Tetrahedron* **1997**, *53*, 2309−2322. [7f] T. Abellán, C. Nájera, J. M. Sansano, *Tetrahedron: Asymmetry* **1998**, *9*, 2211−2214. [7g] For a review on asymmetric synthesis of α-quaternary aminocyclopropanecarboxyclic acids see: K. Burgess, K.-K. Ho, D. Moye-Sherman, *Synlett* **1994**, 575−583. [7h] A related chiral glycine equivalent based on atrolactic acid has recently been reported: S. N. Crane, E. J. Corey, *Organic Letters* **2001**, *3*, 1395−1397.

[8] For further investigations on lithio-aggregates formed in ethereal solvents see: [8a] D. Z. Wang, Y.-J. Kim, A. Streitwieser, *J. Am. Chem. Soc.* **2000**, *122*, 10754−10760. [8b] J. H. Horner, M. Vera, J. B. Grutzner, *J. Org. Chem.* **1986**, *51*, 4212−4220. [8c] L. M. Jackman, B. C. Lange, *Tetrahedron* **1977**, *33*, 2737−2769. [8d] E. M. Arnett, C. A. Palmer, *J. Am. Chem. Soc.* **1990**, *112*, 7354−7360. [8e] A. Streitwieser, S. S.-W. Leung, Y.-J. Kim, *Org. Lett.* **1999**, *1*, 145−147. [8f] A. Streitwieser, D. Z.-R. Wang, *J. Am. Chem. Soc.* **1999**, *121*, 6213−6219. [8g] D. Z.-R. Wang, A. Streitwieser, *Can. J. Chem.* **1999**, *77*, 654−658.

[9] [9a] I. A. Faworskaja, *J. Gen. Chem. (U. S. S. R.)* **1948**, *18*, 52−59; *Chem. Abstr.* **1948**, *42*, 4905d. [9b] A. Richard, *Ann. Chim. (Paris)* **1910**, *21*, 360−406. [9c] M. B. Green, W. J. Hickinbottom, *J. Org. Chem.* **1957**, *22*, 3262−3270. For an already existing asymmetric synthesis of **1** see: [9d] E. L. Eliel, J. E. Lynch, W. R. Kenan Jr., *Tetrahedron Lett.* **1987**, *28*, 4813−4816. [9e] R. J. D. Evans, S. R. Landor, *J. Chem. Soc.* **1965**, 2553−2559. [9f] S. Ahmad, S. H. Spergel, J. C. Barrish, J. DiMarco, J. Gougoutas, *Tetrahedron: Asymmetry* **1995**, *6*, 2893−2894.

[10] For the synthesis of phenylalaninol from phenylalanine by reduction with $NaBH_4/H_2SO_4$ see: A. Abiko, S. Masamune, *Tetrahedron Lett.* **1992**, *33*, 5517−5518.

[11] H. Brückner, *Chromatographia* **1987**, *24*, 725−738.

[12] E. Bald, K. Saigo, T. Mukaiyama, *Chem. Lett.* **1975**, 1163−1167.

[13] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem.* **1981**, *93*, 793−795; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798−799.

[14] [14a] J. E. Baldwin, V. Lee, C. J. Schofield, *Heterocycles* **1992**, *34*, 903−906. [14b] D. Seebach, J. D. Aebi, R. Naef, T. Weber, *Helv. Chim. Acta* **1985**, *68*, 144−154.

[15] Crystallographic data for structure **21** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 192162. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (internat.) +44 1223 336033 or E-mail: deposit@ccdc.cam.ac.uk. The X-ray diffraction analysis of **22** was performed by M. Malecka and E. Budzisz at the University of Lodz and will be published by these authors.

[16] M. C. Pirrung, S. E. Dunlap, U. P. Trinks, *Helv. Chim. Acta* **1989**, *72*, 1301−1310.

[17] The stereochemistry found for related cyclopropane derivatives derived from **4**[4] is in disagreement with the results described in the present paper and will have to be reevaluated, as the assignment then was based only on the optical rotation of the final amino acids.

[18] [18a] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53−59. [18b] J. Furukawa, N. Kawabata, *Adv. Organomet. Chem.* **1974**, *12*, 83−134.

[19] [19a] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380−2382. [19b] O. Mitsunobu, *Synthesis* **1981**, 1−28. [19c] O. Mitsunobu, M. Wada, T. Sano, *J. Am. Chem. Soc.* **1972**, *94*, 679−680. [19d] O. Mitsunobu, M. Yamada, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935−939. [19e] T. Tsunoda, Y. Yamamiya, S. Ito, *Tetrahedron Lett.* **1993**, *34*, 1639−1642.

[20] B. A. Arbuzov, N. N. Zobova, N. R. Rubinova, *Ser. Khim.* **1976**, *1*, 202−204.

[21] For a synthesis of the free racemic 1-amino-2-{(3-phenylureido)methyl}cyclopropanecarboxylic acid see: C. Balsamini, A. Bedini, G. Spadoni, G. Tarzia, A. Tontini, *Farmaco* **1998**, *53*, 181−188.

[22] TFA proved to be better than HCl, as the lactam also was formed to some extent with the latter. This phenomenon is well known and has been explained in terms of the higher nucleophilicity of the chloride ion than of the trifluoroacetate ion, see: T. Beulshausen, U. Groth, U. Schöllkopf, *Liebigs Ann. Chem.* **1991**, 1207−1209.

[23] For examples of hydrolysis of similar substrates under similar conditions see: G. Kardassis, P. Brungs, C. Nothhelfer, E. Steckhan, *Tetrahedron* **1998**, *54*, 3479−3488.

[24] For example, in the first step the imidate group was cleaved with TFA. When the subsequent hydrolysis was then attempted under basic conditions the urea side chain was destroyed, whereas under acidic conditions the cyclopropyl ring was opened. Cleavage of the cyclopropyl ring was also observed with Me_3SiI, which is known to cause this type of reaction; see: [24a] R. D. Miller, D. R. McKean, *Tetrahedron Lett.* **1979**, *20*, 2305−2308. [24b] E. W. Logusch, *Tetrahedron Lett.* **1984**,

25, 4195−4198. [24c] M. Ihara, T. Taniguchi, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.* **1994**, *59*, 8092−8100.
[25] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923−2925.
[26] C. Glücksmann, *Monatsh. Chem.* **1889**, *10*, 770−782.
[27] M. R. Heilmann, *Bull. Soc. Chim. Fr.* **1929**, *45*, 412−414.
[28] E. Fischer, A. Mouneyrat, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2384−2385.
[29] G. Porzi, S. Sandri, *Tetrahedron: Asymmetry* **1996**, *7*, 189−196.
[30] Q. B. Broxterman, B. Kaptein, J. Kamphuis, H. E. Shoemaker, *J. Org. Chem.* **1992**, *57*, 6286−6294.
[31] J. Mulzer, A. Angermann, B. Schubert, C. Seilz, *J. Org. Chem.* **1986**, *51*, 5294−5299.
[32] R. Amoroso, G. Cardillo, C. Tomasini, P. Tortoreto, *J. Org. Chem.* **1992**, *57*, 1082−1087.
[33] Y. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetkov, S. V. Vitt, N. S. Garbalinskaya, V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1* **1988**, 305−312.
[34] A. Studer, D. Seebach, *Liebigs Ann.* **1995**, 217−222.
[35] T. M. Zydowsky, E. de Lara, S. G. Spanton, *J. Org. Chem.* **1990**, *55*, 5437−5439.
[36] The configuration was the result of a comparison of the data obtained for the *N*-acetylation product of **34c** with those reported in the literature for this compound. See: U. Schöllkopf, H.-H. Hausberg, I. Hoppe, M. Segal, U. Reiter, *Angew. Chem.* **1978**, *90*, 136−138; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 117−119.
[37] Compound **36** is identical with a derivative already presented in ref.[4] (compound number **24b**). However, in that paper the stereochemical descriptors for position 2 of **24b** and for its isomer **24a** as well as for their precursors **23a** and **23b** (position 1) were assigned incorrectly.

Received September 2, 2002
[O02498]