Asymmetric Synthesis Employing a Chiral 5-Methoxy-1,4-oxazin-2-one Derivative: Preparation of Enantiomerically Pure α-Quaternary α-Amino Acids

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Dedicated to Prof. Dr. Dr. h.c. mult. H. Nöth on the occasion of his 70th birthday

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A new asymmetric synthesis of disubstituted α-amino acids is presented. This synthesis is based on the chiral 5-methoxy-1,4-oxazin-2-one derivative **5** relying on the α-hydroxy acid **1** as a chiral auxiliary. Alkylation reactions of the glycine equivalent **5** are performed by deprotonation with *sec*-butyllithium and subsequent reaction with alkyl halides, yielding the monoalkylated compounds **13** and **14**. A second alkylation step of the lithium enolates of **13** and **14** leads to the α,α-disubstituted compounds **17**. Both steps proceed with good yields and excellent stereoselectivities (up to 99% de). From the major diastereomers **17c–d** the corresponding α-amino acids **19c–d** are obtained enantiomerically pure upon hydrolytic cleavage with aqueous sodium hydroxide. Alkylation of the enolate ion of **5** with epichlorohydrines as bifunctional electrophiles provides the cyclopropyl derivatives **20a–b**. Direct hydrolysis or oxidation of **20a–b**, followed by reductive amination and hydrolysis leads to the substituted 1-aminocyclopropanecarboxylic acids **21a–b** and **24a–b**.

Introduction

Nonproteinogenic unnatural α-amino acids play an important role in the field of peptide chemistry and for the design of enzyme inhibitors. In this context α-quaternary α-amino acids are of special interest because of their rigidity resulting from the quaternary center at the α-carbon atom. Furthermore, such compounds are valuable chiral building blocks in the asymmetric synthesis of more complex molecules. Although there are numerous methods for the asymmetric synthesis of monosubstituted α-amino acids in the literature,[1] there are only a few for the preparation of α,α-disubstituted compounds.[2]

In a recent paper[3] we described the synthesis of chiral α-substituted pipecolic acid derivatives **3** employing 1,4-oxazine-2,5-dione **2** as a building block with the chiral information derived from the enantiomerically pure α-hydroxy carboxylic acid **1**. In this report we describe our efforts to develop the imidate **5** derived from the 1,4-oxazine-2,5-dione **4** as a versatile substrate for the asymmetric construction of α,α-disubstituted α-amino acids **6**. The imidate **5** was selected for this purpose as it appeared to be more suitable for alkylation reactions than the amide precursor **4**.

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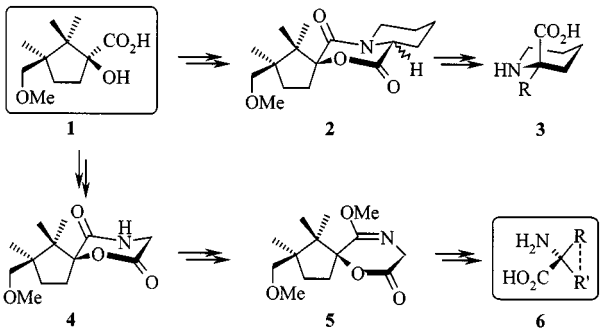


Scheme 1. Synthesis of α-quaterny α-amino acids employing oxazinedione **2** and oxazinone **5**

Results and Discussion

Synthesis of the Glycine Equivalent 5

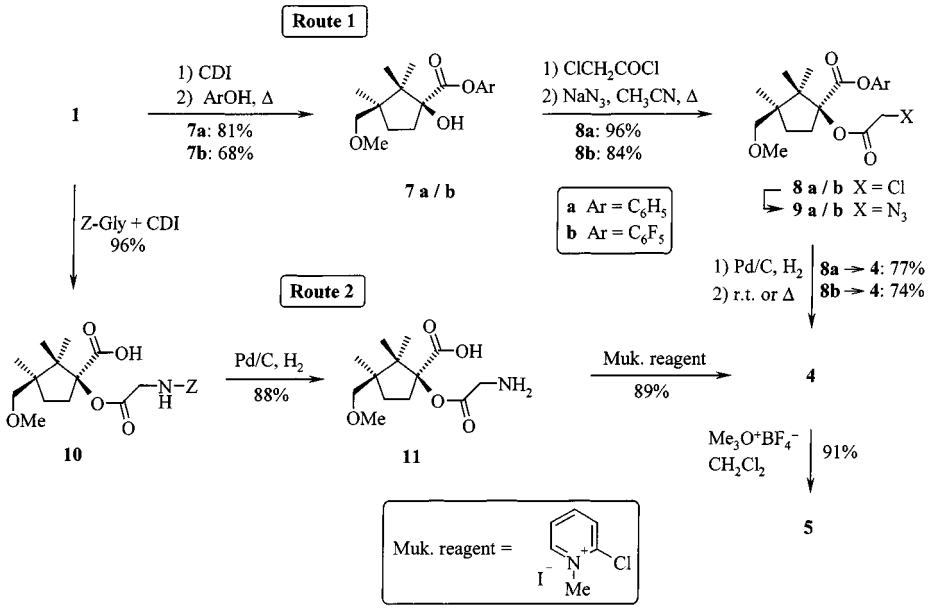
We developed two alternative routes (Scheme 2) for the preparation of **5**, both starting from **1** as the chiral auxiliary, which is easily accessible by two synthetic steps.[4]

In the case of route 1, in the first step compound **1** was transformed into the corresponding phenyl ester **7a** in order to modestly activate the carboxylic acid function. This transformation could be effected in a yield of 81% by treating **1** with *N*,*N*-carbonyldiimidazole (CDI) and phenol. In order to set up the glycine moiety, **7a** was treated with an excess of chloroacetyl chloride to give the diester **8a** (96%), which upon heating with 2 equiv. of sodium azide in acetonitrile provided the azide **9a** (93%). In a one-pot reaction

  1434−193X/99/0808−1967v $ 17.50+.50/0

by hydrogenation in the presence of Pd/C and subsequent heating of the crude reaction mixture to reflux, azide **9a** was then transformed into **4** (83%). Though a clean cyclization occurred, it took seven days to obtain a complete reaction. Therefore, the more reactive pentafluorophenyl ester **9b**, prepared in analogy to **9a**, was also tested as an alternative precursor to **4**. In this case the ring closure of the amine, generated from **9b** (by hydrogenation in the presence of Pd/C), occurred already at room temperature and was complete after stirring the reaction mixture for about 12 h (85%).

Finally, a more direct and efficient strategy for the preparation of **4** was found. Treatment of the carboxylic acid **1** with cbz-protected glycine that had been activated with CDI (in THF, room temperature, 30 min.) yielded the ester **10** (91%). Upon removal of the cbz group by catalytic hydrogenation (Pd/C, H_2) the amino acid **11** (88%) was obtained. This acid underwent a clean cyclization upon heating when treated with Mukaiyama's reagent[6] (2-chloro-1-methylpyridinium iodide) in the presence of ethyldiisopropylamine (8 h) to give **4** in a yield of 89%.



Scheme 2. Syntheses of the chiral glycine equivalent **5**

The appearance of the ^{1}H-NMR spectrum of the oxazinedione **4** was strongly dependent on the amount of water present in the solvent used ($CDCl_3$). In the absence of water (in anhydrous $CDCl_3$) the two signals for the diastereotopic methylene protons at C-8 appeared as doublets at $\delta = 4.14$ and $\delta = 4.24$ ($J = 18.8$ Hz), which were accompanied by two further, but very weak signals that overlapped with the former [$\delta = 4.15$ (dd, $J = 18.8/4.1$ Hz), 4.25 (d, $J = 18.8$ Hz)]. The two major signals, however, disappeared completely after a small amount of water (one drop) had been added to the NMR sample, whereas the two minor signals increased to the expected size. This phenomenon may be the result of hydrogen bonds involving the lactam function which lead to dimers or even oligomers of **4**.[5] Such aggregates could dominate in the absence of water and be diminished in favor of a monomeric species when water is added. But it may also be a simple hydration of **4** (present as a monomer) that changes the nature and thus the NMR spectrum of this compound.

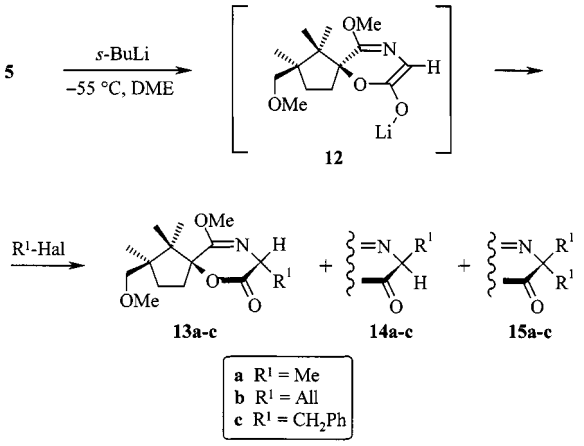
From the two methods for the preparation of **4** presented above the one that was based on a phenyl ester gave a total yield of 60% (**1b** → **4**) but was less convenient because of the duration of this cyclization reaction (7 d). In contrast, the time required for the cyclization of the pentafluorophenyl ester was markedly less, but in this case the overall yield was somewhat lower (**1b** → **4**; 44%).

The reaction of **4** with 2 equiv. of trimethyloxonium tetrafluoroborate[7] afforded finally the oxazinone **5** in a yield of 91%.

Enolate Alkylations with Alkyl Halides

The results of the alkylation reactions obtained for the enolate of **5** were strongly dependent on the reaction conditions employed. The first experiments were performed with THF as solvent generating the enolate **12** by treating **5** with strong bases like *sec*-butyllithium or potassium hexamethyldisilylamide at low temperatures (−50 and −78 °C, 15−20 min). Though the addition of alkyl halides ($PhCH_2Br$, allyl bromide) led to the diastereomeric alkylation products **13** and **14** with good to excellent diastereoselectivities (> 90% *de*), the yields of these reactions were, however, generally very low. Surprisingly, the crude reaction products contained large amounts of the starting material besides significant amounts of dialkylation products **15**. This indicated that the poor yields obtained for the monoalkylation products **13/14** were not simply due to an insufficient deprotonation of **5** for whatever reason. Extensive studies performed for the benzylation revealed that the solvent was crucial for the product distribution (**13**+**14** versus **15** and **5**) of these alkylations. In Table 1 some representa-

tive results obtained for alkylations of enolate **12**, formed by deprotonation of **5** with *sec*-butyllithium [except for entry 5 in Table 1 where $KN(SiMe_3)_2$ was used] are shown.



Scheme 3. Alkylation of the oxazinone **5** via the enolate **12**

Table 1. Enolate alkylation reactions of **5** with alkyl halides

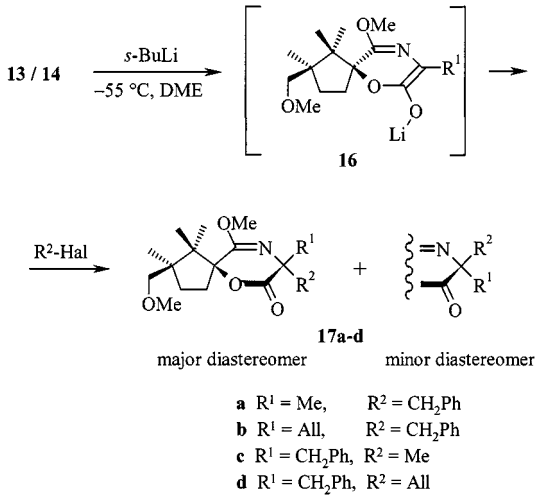
Entry	R^1−Hal	Reaction conditions[a]	Product **13,14**	Yield (%) **13+14**	**5**[d]	d.s.[b] **13/14**	Conversion rate[c] **13 + 14**	**15**	**5**[d]
1	MeI	−55°C, DME	**a**	67		> 99:1[e]	93	3	4
2	AllBr	−55°C, DME	**b**	61		99.2:0.8	94	6	0
3	AllBr	−55°C → room temp., DME	**b**	74		92.4:7.6	−	−	−
4	$PhCH_2Br$	−80°C, THF	**c**	57	35	−	60	3	37
5	$PhCH_2Br$	−78°C, THF, inverse[f]	**c**	25	40	−	25	20	55
6	$PhCH_2Br$	−80°C → room temp., THF	**c**	51	8	96:4	73	8.5	18.5
7	$PhCH_2Br$	−80°C, THF/DMPU 2:1	**c**	55		94:6	94	4.5	1.5
8	$PhCH_2Br$	−55°C → room temp., DME	**c**	82		95:5	92.5	3.5	4
9	$PhCH_2Br$	−55°C, DME	**c**	76		98.4:1.6	95	1	4

[a] Deprotonation with 1 equiv. of *s*BuLi, except entry 5. − [b] For entries 2, 3 and 9 determined by analytical HPLC, in all other cases from the integrals of the ^{1}H-NMR spectra of the crude products. − [c] Calculated from the integrals of the ^{1}H-NMR spectra of the crude products. − [d] Recovered starting material. − [e] For entry 1 in the ^{1}H-NMR spectrum only a trace amount of **14a** was detectable (ca. 0.2%). − [f] Addition of 1.1 equiv. of $KN(SiMe_3)_2$ to a mixture of 1 equiv. of **5** and 1.2 equiv. of $PhCH_2Br$.

For the benzylation in THF severe amounts of the double alkylation product **15** and unchanged starting material **5** were found, when the reaction temperature was kept at −80°C (for conversion rates see Table 1, entry 4) or raised to room temperature (see Table 1, entry 6). With an inverse alkylation protocol the product distribution became even worse (see Table 1, entry 5). According to Williams et al.[8] such side reactions may be due to aggregates formed from the enolate ions. In a further alkylation reaction we added DMPU as a cosolvent (see Table 1, entry 7) in order to counteract this phenomenon that might apply here, too. Indeed this led to a significantly improved conversion rate with respect to the diastereomeric monoalkylation products **13** + **14**. But the yield of isolated product (**13/14**) was still moderate (55%), possibly as a result of the aqueous workup to remove the cosolvent DMPU. Finally, we found that in dimethoxyethane[9] (DME) the reactions proceeded in the desired manner, the double alkylation reactions being almost completely suppressed. Thus, as outlined in Table 1 (entry 1, 2 and 9) the monoalkylation products were isolated in good yields (61% for R^1 = allyl to 76% for R^1 = benzyl) and with excellent diastereoselectivities (d.s. > 98:2 to > 99:1).

For the second alkylation step the above-mentioned procedure developed for the monoalkylation reactions was employed. This afforded the dialkylation products **17** in good to high yields and with excellent diastereoselectivities (see Table 2). Similar results were obtained when the reactions were performed in THF (at −78°C, *s*BuLi), indicating that the second alkylation step is quite insensitive to the reaction conditions. In each case both diastereomers (**17a/c** and **17b/d**) were available as major compounds on changing the sequence for the introduction of the different substituents. The diastereoselectivities followed from the ^{1}H-NMR spectra of the crude products. Though both diastereomers (**17**) were available as reference compounds, in no case could the corresponding minor diastereomer (**17c,d** for **17a,b** and **17a,b** for **17c,d)** be detected. This indicated that the diastereoselectivities should be at least d.s. > 99:1. In the case of the benzylation of **13b/14b** (see entry 2 Table 2) minute amounts of a side product were present that partially interfered with the areas where the signals for the minor diastereomer were expected. Therefore, in this case a conservative diastereoselectivity of only d.s. > 98:2 is claimed. The results are summarized in Table 2.

The ^{1}H-NMR spectra of the mono- and disubstituted benzyl derivatives **13c**, **14c**, **15c** and **17a−d** showed a significant behavior with respect to the chemical shift for one or even both of the two methyl groups at C-1 (of the chiral auxiliary). In the case of the monosubstituted compounds the stereoisomer **13c** with the benzyl group being on the opposite side of the two methyl substituents at C-1 the signal of the most shielded methyl group was detected at δ = 0.85. This is close to the range of δ = 0.90 to δ = 1.02 where the respective signals of the methyl- and allyl-substituted compounds **13a−b**, **14a−b** and **15a−b** appear. For the products **14c** and **15c** where a benzyl group is at the same side as the methyl groups at C-1 the signal of one (**14c**: δ = 0.69) or both (**15c**: δ = 0.01 and δ = 0.28) of those methyl substituents were shifted significantly to higher field.



Scheme 4. Alkylation of the monoalkylation products **13/14** via the enolate **16**

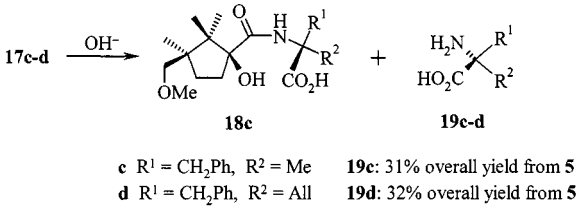
Table 2. Enolate alkyation of the monoalkylation products **13/14** with alkyl halides[a]

Entry	R^1	R^2–Hal[b]	Yield (%) **17**	d.s.[c]
1	Me	$PhCH_2Br$	55	> 99:1
2	All	$PhCH_2Br$	85	> 98:2
3	$PhCH_2$	MeI	78	> 99:1
4	$PhCH_2$	AllBr	88	> 99:1

[a] A diastereomeric mixture of **13** + **14** was used, as obtained from various alkylations. – [b] Reaction conditions: 1) 1.5–2.0 equiv. of *s*BuLi, –55°C, DME; 2) 2.0–3.0 equiv. of R^2–Hal, –55°C, DME. – [c] Determined from the ^{1}H-NMR spectra of the crude reaction products; the diastereomers were inseparable or only insufficiently separable by analytical HPLC.

For the ^{1}H-NMR spectra of the disubstituted compounds **17** a related phenomenon was found. For the compounds **17a** and **17b** with the benzyl groups on the "bottom side" the signals of the methyl groups were detected at δ = 0.83 and δ = 0.80, respectively. And again as it had been observed for **15c** in the case of **17c** and **17d** with the benzyl group up the signals of both methyl groups (at C-1) exhibited a marked upfield shift (**17c**: δ = 0.26, 0.53; **17d**: δ = 0.16, 0.46).

It is obvious that this phenomenon is indicative of the stereochemistry at C-8 and thus may be used for the assignment of the absolute configuration of the newly created stereocenter.



Scheme 5. Hydrolysis of the dialkylation products **17c–d**

In the final step the alkylation products **17** had to be hydrolyzed to give the free amino acids **19**. This could be best performed under basic conditions with 40% aqueous sodium hydroxide, whereas a two-step procedure that had successfully been applied for the cyclopropyl compounds **23a–b** described below gave only poor results. For the hydrolysis the diastereomers **17c–d** each representing one isomer of the two pairs of diastereomers **17** were selected. The reaction was performed by stirring the compounds at room temperature (with 40% aqueous sodium hydroxide) for eight (**17c**) and twelve days (**17d**), respectively. Workup including purification by ion exchange chromatography provided the amino acids **19c**[10a,10c] and **19d**[10b] in a yield of 52% and 48%, respectively. For the hydrolysis of **17c**, in addition to the amino acid **19c** the amide **18c** (35%) was isolated, indicating that the reaction time applied had been insufficient. With a prolonged reaction time (twelve days) as applied for the cleavage of **17d** no such side product was found.

From the optical rotations found for the amino acids **19c–d**, which are known in the literature,[10] it became evident that these compounds **19c–d** have (*S*) configuration. According to these results the precursors **17c–d** must have (*S*) configuration (at C-8) as well and as a consequence this stereocenter (at C-8) must have (*R*) configuration in the diastereomers **17a–b**.

The chiral center in **5** will keep its integrity even under strong basic conditions. For this reason compound **5** is a useful tool for the synthesis of α,α-dialkylated α-amino acids.

From this point of view it was only of minor interest to employ **5** also in the synthesis of α-monoalkylated α-amino acids. Therefore and as the hydrolysis of the dialkylation products **17** proceeded only under strong alkaline reaction conditions no attempts for the hydrolysis of **13/14** to give the respective α-tertiary amino acids were made.

Broad applicability and high diastereoselectivities for monoalkylation reactions are main features of the bislactim ether method developed by Schöllkopf et al. as well as the mild acidic conditions sufficient to liberate the amino acids. However, the suitability of the bislactim ethers for the synthesis of α-quaternary α-amino acids is strongly limited. The second alkylation step includes the risk of deprotonating the stereocenter of the chiral auxiliary. Therefore, usually only monoalkylations are performed with bislactim ethers, whereas the preparations of dialkylation products are limited to some more or less rare examples with special structural features.[11]

In contrast to the former reagents compounds like BOC-BMI (*N*-BOC-*tert*-butyl-methyl-imidazolidinone) developed by Seebach et al. ("self-reproduction of chirality") allow the synthesis of mono- as well as of α,α-disubstituted derivatives almost equally well. Yields and diastereoselectivities for the various steps are generally very high. For the hydrolysis of the α,α-disubstituted glycine derivatives to the free α-amino acids, however, mostly severe reaction conditions, or multistep sequences are necessary.[12]

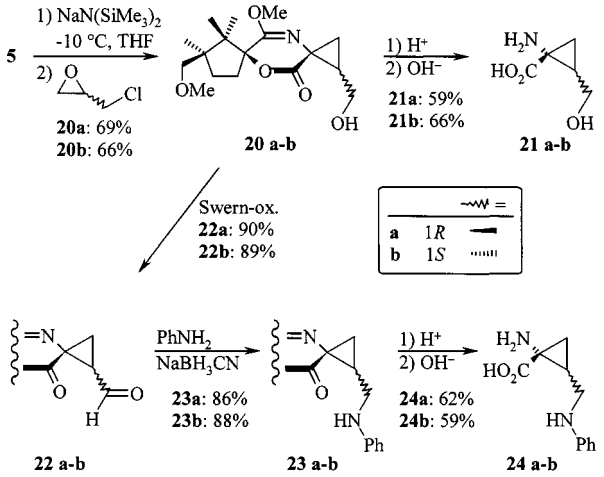
Thus, with respect to the synthesis of α-quaternary α-amino acids compound **5** may be a valuable alternative to the aforementioned methods.

Alkylation with Epichlorohydrines as Bifunctional Electrophiles for the Synthesis of Aminocyclopropanecarboxylic Acids

In the context of a project directed toward the development of new CNS-active compounds we were interested in a synthetic access to 1-aminocyclopropanecarboxylic acids like **21** and **24**. For the construction of these compounds we performed double alkylations employing enantiomerically pure epichlorohydrines. Upon treatment of **5** with 2.1 equivalents of $NaN(SiMe_3)_2$ (in THF at −10°C) followed by 4 equivalents of (*S*)-(+)-epichlorohydrine the cyclopropane derivative **20a** was formed in a yield of 69%. This procedure was also effective with (*R*)-(−)-epichlorohydrine providing the diastereomer **20b** in a yield of 66%. In both cases no other stereoisomers could be detected, neither by ^{1}H-NMR spectroscopy nor by HPLC.

The hydrolysis of **20a** and **20b** to give the free amino acids could be best performed by a two-step procedure using first hydrochloric acid (c = 0.2 mol/L) to cleave the imidate function and then 40% aqueous sodium hydroxide to finally hydrolyze the remaining ester. This gave the two diastereomeric 1-amino-2-(hydroxymethyl)-cyclopropanecarboxylic acids **21a** and **21b** in overall yields of 40% and 43%, respectively. A comparison of the spectroscopic data and the optical rotations of these compounds with those of authentic materials [(*E*)- and (*Z*)-1-amino-2-(hydroxymethyl)cyclopropanecarboxylic acids] reported in the literature[13] revealed that their structure corresponds to **21a** and **21b**.

The stereochemical outcome of these reactions is also in accord with results observed for related reactions,[14][15] indicating that the anion of **5** has attacked the halide-bearing carbon atom of the epichlorohydrins.

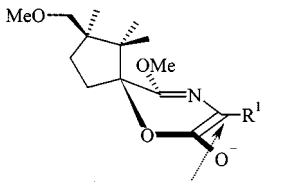


Scheme 6. Synthesis of 1-aminocyclopropanecarboxylic acids **21a−b** and **24a−b**

Further efforts were directed towards the development of a synthetic sequence for the preparation of amino derivatives like **24a** and **24b** from the alcohols **20a** and **20b**. It turned out that this could easily be accomplished by oxidation of **20a** and **20b** according to Swern to give the aldehydes **22a** and **22b**, respectively, which upon reductive amination − performed with aniline and $NaBH_3CN$ (in THF at room temperature) − provided **23a** and **23b**. The total yields for the two steps amounted to 86% (**23a**) and 90% (**23b**), and there was no loss of diastereomeric purity to be observed. Finally, the hydrolysis of **23a** and **23b**, performed by the two-step procedure described above, afforded the two diastereomeric amino acids **24a** and **24b** in reasonable yields of 62% and 59%, respectively.

Model for the Asymmetric Induction

As is evident from the data reported above the alkylation reactions of the enolates **12** and **16** proceeded consistently with *re* selectivity. As a rationale for this stereoselection the model in Scheme 7 representing the putative structure of the enolates **12** and **16** is proposed. It is reasonable to assume that in the enolate ions of **12** and **16** O-6, C-7, C-8, N-9 and C-10 are substantially coplanar, while C-5 lies above this plane defined by the aforementioned atoms.[16]



re face attack

12, R^1 = H
16, R^1 = Me, All, CH_2Ph

Scheme 7. Preferential attack in the alkylation of oxazinone **5** and of monoalkylation products **13/14**

In this conformation the geminal dimethyl group at C-1 is placed in a favorable pseudoaxial orientation in which the allylic strain of that group with the methoxy group at C-10 in the neighborhood is avoided. As a result of the differences in steric hindrance of the top versus the bottom face of the enolates **12** and **16**, caused by the disposition of this group in an axial orientation, the approach of the electrophile should proceed preferentially from below. This approach would give rise to a *re* stereoselectivity and it is this stereoselectivity (*re*) that has been, indeed, observed for all alkylation reactions.

Conclusion

In summary, we have prepared compound **5** as a new chiral glycine equivalent. For the alkylation reactions DME appeared to be advantageous over THF as a solvent. In the former solvent (DME) good yields and diastereoselectivities for the monoalkylation products were obtained, whereas (in contrast to THF) only insignificant amounts of double al-

kylation products were formed. The second alkylation step proceeded in comparison to the first with improved yields (55−88%) and with almost complete asymmetric induction as never any minor isomer could be detected. Hydrolysis led to the corresponding α-quaternary amino acids **19**. In addition the alkylation method could be successfully extended to the stereoselective synthesis of the substituted aminocyclopropanecarboxylic acids **21a−b** and **24a−b**. The absolute configuration of the alkylation products could be delineated by comparing the optical rotation of the amino acids (**19c−d**, **21a−b**) with literature data.

Experimental Section

General Remarks: Standard vacuum techniques were used in the handling of air-sensitive materials. Solvents were dried and kept under N_2 and freshly distilled before use. All reagents were used as commercially available. Phenol was distilled in vacuo and stored under nitrogen. − M.p. (uncorrected values): Melting point apparatus according to Dr. Tottoli (Büchi no. 510). − Optical rotations: Polarimeter 241 MC (Perkin−Elmer). − ^{1}H NMR: JNMR-GX 400 (Jeol), 400 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). − Combustion analysis: CHN Rapid (Heraeus). − Column chromatograhy (CC): Flash chromatography[17] on silica gel (Merck 60 F-254, 0.040−0.063 mm). − TLC: TLC plates 60 F-254 (Merck), detection with UV (λ = 254 nm) or with ammonium cerium(IV) heptamolybdate. − Analytical HPLC: L-6000 pump, L-4000 UV/Vis detector (λ = 254 nm), D-7500 and D-2500 Chromato Integrator (Merck-Hitachi), column: LiChroCart® with LiChrospher® Si 60 cartridge (5 μm, 250 × 4 mm with precolumn 4 × 4 mm), (Merck). − Preparative HPLC: L-6000 pump, L-4000 UV/Vis (λ = 254 nm), D-2000 Chromato Integrator(Merck-Hitachi), column: Hibar RT LiChrosorb® Si 60 (7 μm, 250 × 25 mm) (Merck).

Preparation of the Chiral Glycine Equivalent 5 from 1

(2*R*,5*S*)-2-Methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro-[4.5]decane-7,10-dione (4): A) To a solution of 1.75 g (4.66 mmol) of **9a** in 470 mL of dioxane 150 mg of Pd/C (10% Pd) was added and the resulting mixture was stirred at room temp. under H_2 for 5 h. After H_2 had been substituted by N_2 the mixture was heated to reflux for 7 d. Finally, the solvent was evaporated in vacuo and the crude product, still contaminated with the catalyst, was purified by CC (*n*-heptane/ethyl acetate, 25:75; R_f = 0.25) to give 0.987 g (83%) of **4** as colorless oil, which crystallized upon standing at room temp., affording colorless crystals. − B) To a solution of 1.50 g (3.23 mmol) of **9b** in 500 mL of THF 170 mg of Pd/C (10% Pd) was added and the resulting mixture was stirred at room temp. under H_2 for 15 h. After the solvent was evaporated in vacuo, the crude product, still contaminated with the catalyst, was purified by CC (petroleum ether/ethyl acetate, 2:8; R_f = 0.39) to give 0.326 g (85%) of **4** as colorless crystals. − C) A suspension of 0.252 g (0.92 mmol) of **11** in 20 mL of CH_2Cl_2 was treated with 0.280 g (1.1 mmol, 1.2 equiv.) of 2-chloro-1-methylpyridinium iodide. After addition of 0.5 mL of diisopropylethylamine, the suspension turned into a clear solution, which was refluxed for 8 h before CH_2Cl_2 was removed in vacuo. Purification by CC (petroleum ether/ethyl acetate, 2:8, R_f = 0.39) gave 0.209 g of **4** (89%) as colorless crystals. − M.p. 92−95°C. − $[\alpha]_D^{20}$ = +122.0 (*c* = 0.10, $CHCl_3$). − TLC: R_f = 0.25 (*n*-heptane/ethyl acetate, 25:75; detected with cerium molybdate solution). − ^{1}H NMR ($CDCl_3$): δ = 1.02 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.47−1.58 (m, 1 H, CH_2CH_2), 1.94−2.04 (m, 2 H, CH_2CH_2), 2.77−2.86 (m, 1 H, CH_2CH_2), 3.25 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.33 (s, 3 H, CH_2OCH_3), 3.40 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 4.14 (d, *J* = 18.8 Hz, 1 H, $COCH_2NH$), 4.24 (d, *J* = 18.8 Hz, 1 H, $COCH_2NH$), 6.32 (s, br., 1 H, $CONHCH_2$). − ^{1}H NMR ($CDCl_3/H_2O$); after addition of a small amount of H_2O to the ^{1}H-NMR sample, we observed different chemical shifts and a different coupling pattern for the two protons of the $COCH_2N$ group: δ = 4.15 (dd, *J* = 18.8/4.1 Hz, 1 H, $COCH_2NH$), 4.25 (d, *J* = 18.8 Hz, 1 H, $COCH_2NH$). − IR: ṽ = 3433 cm^{-1}, 1757, 1686. − 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 61.20, H 8.33, N 5.40.

(2*R*,5*S*)-10-Methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-aza-spiro[4.5]dec-9-en-7-one (5): To a solution of 3.78 g (14.8 mmol) of **4** in 150 mL of CH_2Cl_2 4.52 g (30.7 mmol, 2.1 equiv.) of $Me_3O^+BF_4^-$ was added and the resulting mixture was stirred for 16 h at room temp. Then the mixture was cooled with ice, and treated under stirring with 30 mL of phosphate buffer (pH 7, *c* = 1.0 mol/L). After saturation with solid NaCl, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by CC (*n*-heptane/ethyl acetate, 70:30) afforded 3.62 g (91%) of **5** as colorless crystals, m.p. 45−47°C. − $[\alpha]_D^{20}$ = +160.0 (*c* = 1.45, $CHCl_3$). − TLC: R_f = 0.20 (*n*-heptane/ethyl acetate, 70:30; detected with cerium molybdate solution). − HPLC: t_R = 11.0 min (*n*-heptane/ethyl acetate, 70:30; 1.0 mL/min). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.47−1.53 (m, 1 H, CH_2CH_2), 1.90−2.05 (m, 2 H, CH_2CH_2), 2.60−2.67 (m, 1 H, CH_2CH_2), 3.17 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.33 (s, 3 H, CH_2OCH_3), 3.45 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.70 (s, 3 H, $N{=}COCH_3$), 4.18 (d, *J* = 21.6 Hz, 1 H, $COCH_2N$), 4.32 (d, *J* = 21.6 Hz, 1 H, $COCH_2N$). − IR: ṽ = 1755 cm^{-1}, 1687. − MS (70 eV); *m/z* (%): 269 (28) [M$^+$], 113 (100). − $C_{14}H_{23}NO_4$ (269.3): calcd. C 62.43, H 8.61, N 5.20; found C 62.26, H 8.59, N 5.40.

Phenyl (1*S*,3*R*)-1-Hydroxy-3-methoxymethyl-2,2,3-trimethylcyclo-pentane-1-carboxylate (7a): To a solution of 3.63 g (16.8 mmol) of **1** in 150 mL of THF 2.99 g (18.5 mmol, 1.1 equiv.) of CDI, dissolved in 25 mL of THF, was added. After stirring for 16 h at room temp., the solution was treated with 1.67 g (17.7 mmol, 1.05 equiv.) of phenol, dissolved in 10 mL of THF, and heated to reflux for 7 h. The residue obtained after concentration in vacuo was dissolved in 50 mL of Et_2O and washed with 0.5 N NaOH (4 × 15 mL). The aqueous layers were reextracted with Et_2O (2 × 10 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. CC (cyclohexane/ethyl acetate/AcOH, 85:13:2) yielded 4.00 g (81%) of **7a** as colorless oil. − $[\alpha]_D^{20}$ = −8.4 (*c* = 0.27, $CHCl_3$). − TLC: R_f = 0.47 (cyclohexane/ethyl acetate/AcOH, 64:34:2; detected with cerium molybdate solution) − ^{1}H NMR ($CDCl_3$): δ = 0.94 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.64 (ddd, *J* = 13.3/11.1/4.9 Hz, 1 H, CH_2CH_2), 1.89 (ddd, *J* = 14.3/9.4/4.9 Hz, 1 H, CH_2CH_2), 2.04 (ddd, *J* = 13.3/9.4/7.3 Hz, 1 H, CH_2CH_2), 2.79 (ddd, *J* = 14.3/11.1/7.3 Hz, 1 H, CH_2CH_2), 3.12 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.40 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.41 (s, 3 H, CH_2OCH_3), 5.36 (s, br., 1 H, OH), 7.12 (dd, *J* = 8.8/1.1 Hz, 2 H, aromatic H), 7.21−7.25 (m, 1 H, aromatic H), 7.36−7.41 (m, 2 H, aromatic H). − IR: ṽ = 3354 cm^{-1}, 1753. − MS (CH_4; CI); *m/z* (%): 293 (16) [M+H$^+$], 171 (100). − $C_{17}H_{24}O_4$ (292.4): calcd. C 69.84, H 8.27; found C 69.79, H 8.32.

Pentafluorophenyl (1*S*,3*R*)-1-Hydroxy-3-methoxymethyl-2,2,3-trimethyl-cyclopentane-1-carboxylate (7b): To a solution of 0.395 g (1.83 mmol) of **1** in 15 mL of THF 0.334 g (2.0 mmol, 1.1 equiv.) of CDI, dissolved in 8 mL of THF, was added. After stirring the mixture for 22 h at room temp., a solution of 0.336 g (1.83 mmol) of pentafluorophenol in 5 mL of THF was added. After refluxing the mixture for 15 h, THF was removed in vacuo, and the remaining oil was dissolved in 5 mL of Et_2O. The ethereal solution was washed with 0.5 N NaOH (5 × 2 mL) and brine (1 × 2 mL). The aqueous phases obtained were reextracted with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (petroleum ether/ethyl acetate, 7:3; R_f = 0.35) gave 0.475 g of **7b** (68%) as colorless crystals, m.p. 59°C. − $[\alpha]_D^{20}$ = +34.8 (*c* = 0.48, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.93 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.69 (ddd, *J* = 13.6/11.3/4.1 Hz, 1 H, CH_2CH_2), 1.93 (ddd, *J* = 14.2/9.6/4.1 Hz, 1 H, CH_2CH_2), 2.06 (ddd, *J* = 13.6/9.6/7.7 Hz, 1 H, CH_2CH_2), 2.74 (ddd, *J* = 14.2/11.3/7.7 Hz, 1 H, CH_2CH_2), 3.10 (d, *J* = 9.4 Hz, 1 H, C*H*$_2$OCH$_3$), 3.36 (d, *J* = 9.4 Hz, 1 H, C*H*$_2$OCH$_3$), 3.43 (s, 3 H, OCH_3), 6.08 (s, br., 1 H, OH). − IR: ṽ = 3324 cm^{-1}, 1779, 1520. − MS (CH_4; CI); *m*/*z* (%): 383 (3) [M + H^+], 355 (100). − $C_{17}H_{19}F_5O_4$ (382.3): calcd. C 53.41, H 5.01; found C 53.44, H 4.96.

Phenyl (1*S*,3*R*)-1-Chloracetoxy-3-methoxymethyl-2,2,3-trimethyl-cyclopentane-1-carboxylate (8a): A solution of 2.91 g (9.95 mmol) of **7a** in 8.0 mL (100 mmol, 10 equiv.) of chloroacetyl chloride was stirred for 24 h at room temp. The chloroacetyl chloride was removed in vacuo. The oily residue was dissolved in 50 mL of Et_2O, washed with sat. Na_2CO_3 solution (3 × 5 mL) and with brine (2 × 10 mL). The aqueous layers were reextracted with Et_2O (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 3.52 g (96%) of **8a** as colorless crystals, m.p. 84−88°C. − $[\alpha]_D^{20}$ = +46.3 (*c* = 0.40, $CHCl_3$). − TLC: R_f = 0.38 (cyclohexane/ethyl acetate, 80:20; determined by UV). − ^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.57−1.63 (m, 1 H, CH_2CH_2), 1.97−2.05 (m, 2 H, CH_2CH_2), 3.04−3.10 (m, 1 H, CH_2CH_2), 3.24 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.36 (s, 3 H, CH$_2$OC*H*$_3$), 3.53 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 4.10 (d, *J* = 14.5 Hz, 1 H, $COCH_2Cl$), 4.14 (d, *J* = 14.5 Hz, 1 H, $COCH_2Cl$), 7.07 (d, *J* = 7.7 Hz, 2 H, aromatic H), 7.24 (t, *J* = 7.7 Hz, 1 H, aromatic H), 7.38 (t, *J* = 7.7 Hz, 2 H, aromatic H). − IR: ṽ = 1755 cm^{-1}, 1756. − MS (CH_4; CI); *m*/*z* (%): 369 (7) [M + H^+], 275 (100). − $C_{19}H_{25}ClO_5$ (368.9): calcd. C 61.87, H 6.83; found C 61.85, H 6.85.

Pentafluorophenyl (1*S*,3*R*)-1-Chloroacetoxy-3-methoxymethyl-2,2,3-trimethylcyclopentane-1-carboxylate (8b): A solution of 0.217 g (0.57 mmol) of **7b** in 0.5 mL of chloroacetyl chloride was stirred for 24 h at room temp. Chloroacetyl chloride was removed in vacuo. The remaining oil was taken up in 10 mL of Et_2O and washed with a 5% $NaHCO_3$ solution (5 × 5 mL). The ethereal phase was dried ($MgSO_4$) and concentrated in vacuo to give 0.218 g of **8b** (84%) as colorless oil. − $[\alpha]_D^{20}$ = +41.7 (*c* = 0.41, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.60 (ddd, *J* = 10.6/5.6/5.3 Hz, 1 H, CH_2CH_2), 1.99−2.12 (m, 2 H, CH_2CH_2), 3.02 (ddd, *J* = 14.8/6.0/5.3 Hz, 1 H, CH_2CH_2), 3.24 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.36 (s, 3 H, OCH_3), 3.54 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 4.12 (d, *J* = 14.5 Hz, 1 H, $COCH_2Cl$), 4.16 (d, *J* = 14.5 Hz, 1 H, $COCH_2Cl$). − IR: ṽ = 1787 cm^{-1}, 1743, 1523. − MS (CH_4; CI); *m*/*z* (%): 460 (8) [M + H^+], 153 (100). − $C_{19}H_{20}ClF_5O_5$ (458.8): calcd. C 49.74, H 4.39; found C 49.66, H 4.47.

Phenyl (1*S*,3*R*)-1-Azidoacetoxy-3-methoxymethyl-2,2,3-trimethyl-cyclopentane-1-carboxylate (9a): To a solution of 0.837 g (2.27 mmol) of **8a** in 25 mL of MeCN 0.298 g (4.59 mmol) of NaN_3 was added. The resulting mixture was heated for 7 h (70−75°C) and then concentrated in vacuo. The resulting oil was dissolved in 20 mL of Et_2O, washed with a 20% $NaHCO_3$ solution (3 × 3 mL) and with brine (2 × 5 mL). The aqueous layers were reextracted with Et_2O (2 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (cyclohexane/ethyl acetate, 80:20) yielded 0.791 g (93%) of **9a** as a pale yellow oil. − $[\alpha]_D^{20}$ = +31.6 (*c* = 0.36, $CHCl_3$). − TLC: R_f = 0.45 (cyclohexane/ethyl acetate, 80:20; detetermined by UV). − ^{1}H NMR ($CDCl_3$): δ = 0.95 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.45−1.54 (m, 1 H, CH_2CH_2), 1.92−2.02 (m, 2 H, CH_2CH_2), 2.98−3.06 (m, 1 H, CH_2CH_2), 3.16 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.29 (s, 3 H, CH$_2$OC*H*$_3$), 3.40 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.86 (d, *J* = 16.9 Hz, 1 H, $COCH_2N_3$), 3.92 (d, *J* = 16.9 Hz, 1 H, $COCH_2N_3$), 6.99−7.01 (t, *J* = 7.7 Hz, 2 H, aromatic H), 7.15−7.18 (t, *J* = 7.7 Hz, 1 H, aromatic *p*-H), 7.29−7.34 (t, *J* = 7.7 Hz, 2 H, aromatic H). − IR: ṽ = 2108 cm^{-1}, 1760, 1748. − MS (CH_4; CI); *m*/*z* (%): 376 (7) [M + H^+], 275 (100). − $C_{19}H_{25}N_3O_5$ (375.4): calcd. C 60.79, H 6.71, N 11.19; found C 60.72, H 6.79, N 11.17.

Pentafluorophenyl (1*S*,3*R*)-1-Azidoacetoxy-3-methoxymethyl-2,2,3-trimethylcyclopentane-1-carboxylate (9b): A solution of 0.138 g (0.30 mmol) of **8b** in 5 mL of MeCN was treated with 0.042 g (0.63 mmol) of NaN_3 and stirred for 7 h at 70°C. MeCN was removed in vacuo. The residue was taken up in 10 mL of Et_2O and washed with 5% $NaHCO_3$ solution (3 × 5 mL) and brine (2 × 5 mL). The aqueous layers were reextracted with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 0.122 g (87%) of **9b** as colorless oil. − $[\alpha]_D^{20}$ = +30.8 (*c* = 0.45, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.93 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.51 (ddd, *J* = 16.4/5.6/5.2 Hz, 1 H, CH_2CH_2), 1.92−2.06 (m, 2 H, CH_2CH_2), 2.96 (ddd, *J* = 20.4/5.5/5.2 Hz, 1 H, CH_2CH_2), 3.17 (d, *J* = 9.2 Hz, 1 H, C*H*$_2$OCH$_3$), 3.29 (s, 3 H, OCH_3), 3.46 (d, *J* = 9.2 Hz, 1 H, C*H*$_2$OCH$_3$), 4.04 (d, *J* = 14.5 Hz, 1 H, $COCH_2N_3$), 4.09 (d, *J* = 14.5 Hz, 1 H, $COCH_2N_3$). − IR: ṽ = 2109 cm^{-1}, 1789, 1753, 1522. − MS (CH_4; CI); *m*/*z* (%): 466 (2) [M + H^+], 181 (100). − $C_{19}H_{20}F_5N_3O_5$ (465.4): calcd. C 49.04, H 4.33, N 9.03; found C 49.32, H 4.24, N 8.76.

(1*S*,3*R*)-1-(*N*-Benzyloxycarbonylaminoacetoxy)-3-methoxymethyl-2,2,3-trimethylcyclopentane-1-carboxylic Acid (10): To a solution of 0.548 g (2.62 mmol) of cbz-glycine in 5 mL of THF 0.424 g (2.62 mmol) of CDI, dissolved in 5 mL of THF, was added. The resulting mixture was stirred for 30 min at room temp. Then a solution of 0.283 g (1.31 mmol) of **1** in 5 mL of THF was added. After stirring the mixture for 15 h at room temp., THF was removed in vacuo. Purification by CC (petroleum ether/ethyl acetate/AcOH, 10:3:1; R_f = 0.22) gave 0.51 g (96%) of **10** as colorless oil. − $[\alpha]_D^{20}$ = +89.4 (*c* = 0.85, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.45−1.50 (m, 1 H, CH_2CH_2), 1.87−1.95 (m, 2 H, CH_2CH_2), 2.86−2.91 (m, 1 H, CH_2CH_2), 3.12 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.32 (s, 3 H, OCH_3), 3.41 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.97 (dd, *J* = 18.4/5.6 Hz, 1 H, COC*H*$_2$NH), 4.03 (dd, *J* = 18.4/5.6 Hz, 1 H, COC*H*$_2$NH), 5.11 (s, 2 H, OC*H*$_2$C$_6$H$_5$), 5.45 (t, *J* = 5.6 Hz, 1 H, NH), 7.28−7.35 (m, 5 H, C_6H_5). − IR: ṽ = 3342 cm^{-1}, 2970, 1723, 1530. − MS (CH_4; CI); *m*/*z* (%): 408 (72) [M + H^+], 280 (100). − $C_{21}H_{29}NO_7$ (407.5): calcd. C 61.90, H 7.17, N 3.44; found C 61.79, H 7.27, N 3.45.

(1*S*,3*R*)-1-Aminoacetoxy-3-methoxymethyl-2,2,3-trimethyl-cyclopentanecarboxylic Acid (11): To a solution of 0.490 g

(1.20 mmol) of **10** in 20 mL of ethanol 0.024 g of Pd/C (10% Pd) was added and the resulting heterogenous mixture was stirred for 15 h under H_2 at room temp. The solid formed was dissolved by addition of 5 mL of H_2O and the solution was filtered to remove Pd/C. The filtrate was concentrated in vacuo to give 0.287 g (88%) of **11** as colorless crystals, m.p. 129°C. − $[\alpha]_D^{20}$ = +81.8 (*c* = 0.50, H_2O). − ^{1}H NMR (D_2O): δ = 0.92 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.46−1.48 (m, 1 H, CH_2-CH_2), 1.83−1.94 (m, 2 H, CH_2-CH_2), 2.87−2.94 (m, 1 H, CH_2CH_2), 3.16 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.38 (s, 3 H, OCH$_3$), 3.45 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.68 (d, *J* = 17.0 Hz, 1 H, COC*H*$_2$NH$_2$), 3.82 (d, *J* = 17.0 Hz, 1 H, COC*H*$_2$NH$_2$). − IR: ṽ = 3423 cm^{-1}, 2968, 1731, 1650. − MS (CH_4; CI); *m*/*z* (%): 274 (2) [M + H$^+$], 256 (100). − $C_{13}H_{23}NO_5$ (273.3): calcd. C 57.14, H 8.48, N 5.14; found C 57.28, H 8.69, N 5.18.

Alkylation Reactions with Monofunctional Alkyl Halides

General Procedure 1 (GP 1). − Alkylation Reactions of 5: A solution of 1.0 equiv. of **5** in DME was cooled to −55°C and treated with 1.0 equiv. of *s*BuLi (*c* = 1.3 mol/l, *n*-heptane/cyclohexane, 90:10). After stirring for 15 min at −55°C, a solution of 2.0−3.0 equiv. of alkyl halide in DME was added. The mixture was stirred for 16 h at −55°C and then either quenched at this temperature (and warmed to room temp.) or after it had been slowly warmed to room temp. The quenching was performed by addition of 1.0 mL of phospate buffer (pH = 7, *c* = 1.0 mol/L). Then the reaction mixture was concentrated in vacuo and the residue was dissolved in Et_2O (10−20 mL). The organic layer was washed with brine. The aqueous layers were extracted with Et_2O (2 × 5−10 mL), and the combined organic layers were washed with brine (2 × 3−5 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by CC.

General Procedure 2 (GP 2). − Alkylation Reactions of 13 and 14: The reactions were performed in analogy to the alkylation reactions of **5** employing a mixture of **13** and **14** instead of **5**.

(2*R*,5*S*,8*R*)-10-Methoxy-2-methoxymethyl-1,1,2,8-tetramethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (13a), (2*R*,5*S*,8*S*)-10-Methoxy-2-methoxymethyl-1,1,2,8-tetramethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (14a), and (2*R*,5*S*)-10-Methoxy-2-methoxymethyl-1,1,2,8,8-pentamethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (15a): According to GP 1 from 133 mg (0.494 mmol) of **5** in 8 mL of DME, with 0.38 mL (0.494 mmol, 1.0 equiv.) of *s*BuLi and 141 mg (62 μL, 0.992 mmol, 2.0 equiv.) of MeI; quenching at −55°C. The ^{1}H-NMR spectrum of the crude product showed that the mixture consisted of 93% of **13a** and **14a** (d.s. > 99:1), 3% of **15a** and 4% of unchanged **5**. Purification by CC (*n*-heptane/ethyl acetate, 80:20) afforded 94.0 mg (67%) of **13a** and **14a** and 1.8 mg (3%) of **15a** as colorless oils. The major diastereomer **13a** was purified by preparative HPLC (*n*-heptane/ethyl acetate, 85:15; 13.5 mL/min). Analytical HPLC gave only an incomplete resolution of the two diastereomers (*n*-heptane/ethyl acetate, 85:15; 1.0 mL/min; major diastereomer **13a**: t_R = 10.7 min; minor diastereomer **14a**: t_R = 11.0 min).

13a: $[\alpha]_D^{20}$ = +175.5 (*c* = 0.92 in $CHCl_3$). − TLC: R_f = 0.32 (*n*-heptane/ethyl acetate, 70:30; detected with cerium molybdate solution). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.42−1.50 (m, 1 H, CH_2CH_2), 1.53 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$CH), 1.88−2.04 (m, 2 H, CH_2CH_2), 2.59−2.67 (m, 1 H, CH_2CH_2), 3.16 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.32 (s, 3 H, CH$_2$OC*H*$_3$), 3.43 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.70 (s, 3 H, C*H*$_3$OC=N), 4.12 (q, *J* = 7.2 Hz, 1 H, CH$_3$C*H*). − IR: ṽ = 1746 cm^{-1}, 1683. − MS (70 eV); *m*/*z* (%): 283 (14) [M$^+$], 268 (18), 255 (60), 83 (100). − $C_{15}H_{25}NO_4$ (283.4): calcd. C 63.58, H 8.89, N 4.94; found C 63.51, H 8.98, N 4.92.

14a: A small amount (11.0 mg, 0.038 mmol) of **13a** in 1 mL of DME was treated with 30 μL (0.039 mmol, 1 equiv.) of *s*BuLi at −55°C. After stirring for 20 min, quenching at −55°C, workup and purification by CC, as described for the alkylation reaction, 10.0 mg (91%) of **13a** and **14a** were obtained as a diastereomeric mixture (d.s. = 48:52). In the ^{1}H-NMR spectrum the following signals for **14a** were observed. − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.39−1.50 (m, 1 H, CH_2CH_2), 1.56 (d, *J* = 7.6 Hz, 3 H, C*H*$_3$CH), 1.88−2.04 (m, 2 H, CH_2CH_2), 2.54−2.68 (m, 1 H, CH_2CH_2), 3.17 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.32 (s, 3 H, CH$_2$OC*H*$_3$), 3.42 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.67 (s, 3 H, CH$_3$OC=N), 4.37 (q, *J* = 7.6 Hz, 1 H, CH$_3$C*H*).

15a: TLC: R_f = 0.51 (*n*-heptane/ethyl acetate, 70:30; detected with cerium molybdate solution). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.40−1.48 (m, 1 H, CH_2CH_2), 1.48 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.89−2.02 (m, 2 H, CH_2CH_2), 2.52−2.62 (m, 1 H, CH_2CH_2), 3.17 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.33 (s, 3 H, CH$_2$OC*H*$_3$), 3.44 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.66 (s, 3 H, CH$_3$OC=N). − IR: ṽ = 1741 cm^{-1}, 1688. − MS (CH_4; CI); *m*/*z* (%): 298 (100) [M + H$^+$], 270 (80).

(2*R*,5*S*,8*R*)-8-Allyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (13b), (2*R*,5*S*,8*S*)-8-Allyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (14b) and (2*R*,5*S*)-8,8-Diallyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (15b): According to GP 1 from 69.3 mg (0.257 mmol) of **5** in 7 mL of DME with 200 μL (0.260 mmol, 1.0 equiv.) of *s*BuLi and 63 mg (45 μL, 0.52 mmol, 2.0 equiv.) of allyl bromide; quenching at −55°C. The ^{1}H-NMR spectrum of the crude product showed that the mixture consisted of 94% of **13b** and **14b** and 6% of **15b**. Purification by CC (*n*-heptane/ethyl acetate, 85:15) yielded 48.2 mg (61%) of **13b** and **14b** (d.s. = 99.2:0.8) and 5.0 mg (5%) of **15b**. The mixture of the diastereomeric compounds **13b** and **14b** was separated by prep. HPLC (*n*-heptane/ethyl acetate, 85:15; 13.5 mL/min). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 85:15; 1.0 mL/min) from the crude product: d.s. = 99.2:0.8; **13b**: t_R = 6.7 min; **14b**: t_R = 8.7 min; **15b**: t_R = 5.7 min.

13b: Colorless oil. − $[\alpha]_D^{20}$ = +150.7 (*c* = 0.76 in $CHCl_3$). − TLC: R_f = 0.13 (*n*-heptane/ethyl acetate, 85:15; detected with cerium molybdate solution). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.47 (ddd, *J* = 12.4/9.2/6.9 Hz, 1 H, CH_2CH_2), 1.92 (ddd, *J* = 14.0/8.2/6.9 Hz, 1 H, CH_2CH_2), 2.01 (ddd, *J* = 12.4/8.2/5.6 Hz, 1 H, CH_2CH_2), 2.61 (dtt, *J* = 14.0/7.0/1.2 Hz, 1 H, C*H*$_2$CH=CH$_2$), 2.63 (ddd, *J* = 14.0/9.2/5.6 Hz, 1 H, CH_2CH_2), 2.77 (dddt, *J* = 14.0/7.0/4.6/1.2 Hz, 1 H, C*H*$_2$CH=CH$_2$), 3.17 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.33 (s, 3 H, CH$_2$OC*H*$_3$), 3.45 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$), 3.72 (s, 3 H, C*H*$_3$OC=N), 4.14 (dd, *J* = 7.0/4.6 Hz, 1 H, C*H*CH$_2$CH=CH$_2$), 5.10 (ddt, *J* = 10.1/2.2/1.2 Hz, 1 H, CH$_2$CH=C*H*$_2$), 5.17 (ddt, *J* = 17.1/2.2/1.2 Hz, 1 H, CH$_2$CH=C*H*$_2$), 5.88 (ddt, *J* = 17.1/10.1/7.0 Hz, 1 H, CH$_2$C*H*=CH$_2$). − IR: ṽ = 1743 cm^{-1}, 1683. − MS (CH_4; CI); *m*/*z* (%): 310 (100) [M + H$^+$]. − $C_{17}H_{27}NO_4$ (309.4): calcd. C 65.99, H 8.80, N 4.53; found C 65.87, H 8.70, N 4.39.

14b: Colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 0.91 (s, 6 H, CH_3), 1.01 (s, 3 H, CH_3), 1.41−1.50 (m, 1 H, CH_2CH_2), 1.91−2.01 (m, 2 H, CH_2CH_2), 2.39 (dddt, *J* = 14.0/9.3/7.0/1.2 Hz, 1 H, C*H*$_2$CH=CH$_2$), 2.54−2.63 (m, 1 H, CH_2CH_2), 2.79 (dddt, *J* = 14.0/7.0/5.4/1.2 Hz, 1 H, C*H*$_2$CH=CH$_2$), 3.16 (d, *J* = 9.0 Hz, 1 H, C*H*$_2$OCH$_3$),

3.34 (s, 3 H, CH_2OCH_3), 3.42 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.70 (s, 3 H, $CH_3OC{=}N$), 4.32 (dd, J = 9.3/5.4 Hz, 1 H, $CHCH_2CH{=}CH_2$), 5.13−5.22 (m, 2 H, $CH_2CH{=}CH_2$), 6.00 (ddt, J = 17.0/10.1/7.0 Hz, 1 H, $CH_2CH{=}CH_2$). − IR: $\tilde{\nu}$ = 1745 cm^{-1}, 1686. − MS (CH_4; CI); *m/z* (%): 310 (100) [M + H^+].

15b: Colorless oil. − TLC: R_f = 0.51 (*n*-heptane/ethyl acetate, 70:30; detected with cerium molybdate solution). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.40−1.48 (m, 1 H, CH_2CH_2), 1.83−1.98 (m, 2 H, CH_2CH_2), 2.37−2.66 (m, 1 H, CH_2CH_2, 4 H, 2 × $CH_2CH{=}CH_2$), 3.16 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.32 (s, 3 H, CH_2OCH_3), 3.39 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.68 (s, 3 H, $CH_3OC{=}N$), 5.03−5.18 (m, 4 H, 2 × $CH_2CH{=}CH_2$), 5.56 (ddt, 1 H, J = 16.0/11.5/7.3 Hz, $CH_2CH{=}CH_2$), 5.85 (ddt, 1 H, J = 16.9/10.4/7.3 Hz, $CH_2CH{=}CH_2$). − IR: $\tilde{\nu}$ = 1740 cm^{-1}, 1691. − MS (CH_4; CI); *m/z* (%): 298 (100) [M^+].

(2*R*,5*S*,8*R*)-8-Benzyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (13c), (2*R*,5*S*,8*S*)-8-Benzyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (14c) and (2*R*,5*S*)-8,8-Dibenzyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (15c): According to GP 1 from 64.5 mg (0.240 mmol) of **5** in 6 mL of DME, with 180 μL (0.234 mmol, 1.0 equiv.) of *s*BuLi and 84 mg (60 μL, 0.49 mmol, 2.0 equiv.) of $PhCH_2Br$; quenching at room temp. The ^{1}H-NMR spectrum of the crude product showed that the mixture consisted of 95% of **13c** and **14c**, 1% of **15c** and 4% of unchanged **5**. Purification by CC (*n*-heptane/ethyl acetate, 75:25) afforded 59.6 mg (76%) of **13c** and **14c** (d.s. = 98.4:1.6) and 0.2 mg (2%) of **15c**. The diastereomeric mixture containing **13c** and **14c** was separated by prep. HPLC (*n*-heptane/ethyl acetate, 85:15; 13.5 mL/min). The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 90:10; 1.0 mL/min) from the crude product: d.s. = 98.4:1.6; **13c**: t_R = 13.6 min; **14c**: t_R = 20.0 min; **15c**: t_R = 8.0 min.

13c: Colorless oil. − $[\alpha]_D^{20}$ = +92.2 (c = 1.01 in $CHCl_3$). − TLC: R_f = 0.48 (cyclohexane/ethyl acetate, 70:30; detected by UV). − ^{1}H NMR ($CDCl_3$): δ = 0.85 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.43 (ddd, J = 13.1/9.2/7.2 Hz, 1 H, CH_2CH_2), 1.76 (ddd, J = 14.5/8.5/7.2 Hz, 1 H, CH_2CH_2), 1.95 (ddd, J = 13.1/8.5/6.2 Hz, 1 H, CH_2CH_2), 2.50 (ddd, J = 14.5/9.2/6.2 Hz, 1 H, CH_2CH_2), 3.11 (dd, J = 13.5/7.5 Hz, 1 H, CH_2Ph), 3.16 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.32 (s, 3 H, CH_2OCH_3), 3.37 (dd, J = 13.5/4.3 Hz, 1 H, CH_2Ph), 3.43 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.68 (s, 3 H, $CH_3OC{=}N$), 4.31 (dd, J = 7.5/4.3 Hz, 1 H, $CHCH_2Ph$), 7.18−7.32 (m, 5 H, aromatic H). − IR: $\tilde{\nu}$ = 1745 cm^{-1}, 1688, 701. − MS (CH_4; CI); *m/z* (%): 360 (100) [M + H^+]. − $C_{21}H_{29}NO_4$ (359.5): calcd. C 70.17, H 8.13, N 3.90; found C 70.20, H 8.09, N 3.91.

14c: Colorless oil. − $[\alpha]_D^{20}$ = +55.1 (c = 0.16 in $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.69 (s, 3 H, CH_3), 0.80 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.40−1.48 (m, 1 H, CH_2CH_2), 1.89−2.00 (m, 2 H, CH_2CH_2), 2.50−2.59 (m, 1 H, CH_2CH_2), 2.98 (dd, J = 13.5/8.8 Hz, 1 H, CH_2Ph), 3.12 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.32 (s, 3 H, CH_2OCH_3), 3.39 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.40 (dd, J = 13.5/4.3 Hz, 1 H, CH_2Ph), 3.66 (s, 3 H, $CH_3OC{=}N$), 4.52 (dd, J = 8.8/4.3 Hz, 1 H, $CHCH_2Ph$), 7.20−7.33 (m, 5 H, aromatic H). − IR: $\tilde{\nu}$ = 1740 cm^{-1}, 1685, 702. − MS (CH_4; CI); *m/z* (%): 360 (100) [M + H^+].

15c: A sufficient quantity for characterization was obtained by combining the samples of several experiments: Colorless oil. − $[\alpha]_D^{20}$ = +37.0 (c = 0.57 in $CHCl_3$). − TLC: R_f = 0.55 (cyclohexane/ethyl acetate, 70:30; detected by UV). − ^{1}H NMR ($CDCl_3$): δ = 0.01 (s, 3 H, CH_3), 0.28 (s, 3 H, CH_3), 0.44−0.51 (m, 1 H, CH_2CH_2), 0.77 (s, 3 H, CH_3), 1.01−1.08 (m, 1 H, CH_2CH_2), 1.40−1.55 (m, 2 H, CH_2CH_2), 2.87 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 2.96 (d, J = 12.5 Hz, 1 H, CH_2Ph), 3.07 (d, J = 12.9 Hz, 1 H, CH_2Ph), 3.08 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.20 (s, 3 H, CH_2OCH_3), 3.36 (d, J = 12.9 Hz, 1 H, CH_2Ph), 3.58 (d, J = 12.5 Hz, 1 H, CH_2Ph), 3.77 (s, 3 H, $CH_3OC{=}N$), 7.08−7.26 (m, 10 H, aromatic H). − IR: $\tilde{\nu}$ = 1734 cm^{-1}, 1691. − MS (70 eV); *m/z* (%): 449 (15) [M^+], 358 (100). − $C_{28}H_{35}NO_4$ (449.6): calcd. C 74.80, H 7.85, N 3.12; found C 74.74, H 7.90, N 3.13.

(2*R*,5*S*,8*R*)-8-Benzyl-10-methoxy-2-methoxymethyl-1,1,2,8-tetramethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (17a): According to GP 2 from 46.4 mg (0.164 mmol) of **13a** and **14a** in 5 mL of DME, with 190 μL (0.247 mmol, 1.5 equiv.) of *s*BuLi and 56 mg (40 μL, 0.33 mmol, 2.0 equiv.) of $PhCH_2Br$; quench at −55°C. Purification by CC (*n*-heptane/ethyl acetate, 85:15) yielded 33.5 mg (55%) of **17a** (d.s. > 99:1, **17a/17c**). In the ^{1}H-NMR spectrum of the crude product no signals of the minor diastereomer **17c** could be detected.

17a: Colorless oil. − $[\alpha]_D^{20}$ = +63.0 (c = 0.135 in $CHCl_3$). − TLC: R_f = 0.35 (*n*-heptane/ethyl acetate, 85:15; detected by UV, 254 nm, and with cerium molybdate solution). − HPLC: t_R = 13.4 min (*n*-heptane/ethyl acetate, 90:10; 0.75 mL/min). − ^{1}H NMR ($CDCl_3$): δ = 0.83 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 1.04 (ddd, J = 14.3/8.1/7.0 Hz, 1 H, CH_2CH_2), 1.27 (ddd, J = 13.0/8.6/7.0 Hz, 1 H, CH_2CH_2), 1.62 (s, 3 H, CH_3CCH_2Ph), 1.75 (ddd, J = 13.0/8.1/7.0 Hz, 1 H, CH_2CH_2), 1.96 (ddd, J = 14.3/8.6/7.0 Hz, 1 H, CH_2CH_2), 2.89 (d, J = 12.7 Hz, 1 H, CH_2Ph), 3.11 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.26 (d, J = 12.7 Hz, 1 H, CH_2Ph), 3.28 (s, 3 H, CH_2OCH_3), 3.31 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.70 (s, 3 H, $CH_3OC{=}N$), 7.08−7.13 (m, 2 H, aromatic H), 7.15−7.25 (m, 3 H, aromatic H). − IR: $\tilde{\nu}$ = 1738 cm^{-1}, 1693, 701. − MS (CH_4; CI); *m/z* (%) = 374 (100) [M + H^+], 346 (72). − $C_{22}H_{31}NO_4$ (373.5): calcd. C 70.75, H 8.37, N 3.75; found C 70.70, H 8.58, N 3.59.

(2*R*,5*S*,8*R*)-8-Allyl-8-benzyl-10-methoxy-2-methoxymethyl-1,1,2-trmethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (17b): According to GP 2 from 39.3 mg (0.127 mmol) of **13b** and **14b** in 2 mL of DME, with 150 μL (0.195, 1.5 equiv.) of *s*BuLi and 70 mg (50 μL, 0.40 mmol, 3.0 equiv.) of $PhCH_2Br$; quenching at −55°C. Purification by CC (*n*-heptane/ethyl acetate, 90:10) yielded 42.9 mg (85%) of **17b** (d.s. > 98:2, **17b/17d**). In the ^{1}H-NMR spectrum of the crude product no signals of the minor diastereomer **17d** could be detected.

17b: Colorless oil. − $[\alpha]_D^{20}$ = +30.0 (c = 1.0 in $CHCl_3$). − TLC: R_f = 0.39 (*n*-heptane/ethyl acetate, 70:30; deteced by UV, 254 nm, and with cerium molybdate solution). − HPLC: t_R = 6.90 min (*n*-heptane/ethyl acetate, 90:10; 1.0 mL/min). − ^{1}H NMR ($CDCl_3$): δ = 0.63−0.74 (m, 1 H, CH_2CH_2), 0.80 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 1.12−1.21 (m, 1 H, CH_2CH_2), 1.58−1.71 (m, 2 H, CH_2CH_2), 2.62 (dd, J = 13.4/7.4 Hz, 1 H, $CH_2CH{=}CH_2$), 2.82 (dd, J = 13.4/7.3 Hz, 1 H, $CH_2CH{=}CH_2$), 2.88 (d, J = 12.6 Hz, 1 H, CH_2Ph), 3.05 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.19 (d, J = 12.6 Hz, 1 H, CH_2Ph), 3.21 (d, J = 9.0 Hz, 1 H, CH_2OCH_3), 3.26 (s, 3 H, CH_2OCH_3), 3.71 (s, 3 H, $CH_3OC{=}N$), 5.12−5.22 (m, 2 H, $CH_2CH{=}CH_2$), 5.83 (ddt, J = 17.3/10.0/7.3 Hz, 1 H, $CH_2CH{=}CH_2$), 7.04−7.08 (m, 2 H, aromatic H), 7.14−7.24 (m, 3 H, aromatic H). − IR: $\tilde{\nu}$ = 1733 cm^{-1}, 1689, 702. − MS (CH_4; CI); *m/z* (%) = 400 (100) [M + H^+], 372 (53). − $C_{24}H_{33}NO_4$ (399.5): calcd. C 72.15, H 8.33, N 3.51; found C 72.10, H 8.40, N 3.48.

(2*R*,5*S*,8*S*)-8-Benzyl-10-methoxy-2-methoxymethyl-1,1,2,8-tetramethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (17c): According to GP

2 from a solution of 59.0 mg (0.164 mmol) of **13c** and **14c** in 6 mL of DME, with 250 µL (0.325 mmol, 2.0 equiv.) of *s*BuLi and 48 mg (21 µL, 0.34 mmol, 2.0 equiv.) of MeI; quenching at −55°C. Purification by CC (*n*-heptane/ethyl acetate, 85:15) yielded 47.6 mg (78%) of **17c** (d.s. > 99:1, **17c/17a**). In the ^{1}H-NMR spectrum of the crude product no signals of the minor diastereomer **17a** could be detected.

17c: Colorless oil. − $[\alpha]_D^{20}$ = +73.5 (*c* = 1.51 in $CHCl_3$). − TLC: R_f = 0.33 (*n*-heptane/ethyl acetate, 85:15; detected by UV, 254 nm, and with cerium molybdate solution). − HPLC: t_R = 9.5 min (*n*-heptane/ethyl acetate, 90:10; 1.0 mL/min). − ^{1}H NMR ($CDCl_3$): δ = 0.26 (s, 3 H, CH_3), 0.53 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 1.35−1.42 (m, 1 H, CH_2CH_2), 1.49 (s, 3 H, CH_3CCH_2Ph), 1.83−1.94 (m, 2 H, CH_2CH_2), 2.83−2.47 (m, 1 H, CH_2CH_2), 2.97 (d, *J* = 13.1 Hz, 1 H, CH_2Ph), 3.03 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.28 (s, 3 H, CH_2OCH_3), 3.29 (d, *J* = 13.1 Hz, 1 H, CH_2Ph), 3.33 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.70 (s, 3 H, $CH_3OC{=}N$), 7.16−7.24 (m, 5 H, aromatic H). − IR: ṽ = 1741 cm^{-1}, 1689. − MS (CH_4; CI); *m*/*z* (%) = 374 (87) [M + H^+], 346 (100). − $C_{22}H_{31}NO_4$ (373.5): calcd. C 70.75, H 8.37, N 3.75; found C 70.75, H 8.31, N 3.80.

(2*R*,5*S*,8*S*)-8-Allyl-8-benzyl-10-methoxy-2-methoxymethyl-1,1,2-trimethyl-6-oxa-9-azaspiro[4.5]dec-9-en-7-one (17d): According to GP 2 from 56.6 mg (0.158 mmol) of **13c** and **14c** in 6 mL of DME, with 180 µL (0.234 mmol, 1.5 equiv.) of *s*BuLi and 39 mg (27 µL, 0.32 mmol, 2.0 equiv.) of allyl bromide. Purification by CC (*n*-heptane/ethyl acetate, 80:20) yielded 55.4 mg (88%) of **17d** (d.s. > 99:1, **17d/17b**). In the ^{1}H-NMR spectrum of the crude product no signals of the minor diastereomer **17b** could be detected.

17d: Colorless crystals, m.p. 66−67°C. − $[\alpha]_D^{20}$ = +59.8 (*c* = 0.47 in $CHCl_3$). − TLC: R_f = 0.48 (*n*-heptane/ethyl acetate, 70:30; detected by UV, 254 nm, and with cerium molybdate solution). − HPLC: t_R = 7.04 min (*n*-heptane/ethyl acetate, 90:10; 1.0 mL/min). − ^{1}H NMR ($CDCl_3$): δ = 0.16 (s, 3 H, CH_3), 0.46 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 1.31−1.39 (m, 1 H, CH_2CH_2), 1.77−1.90 (m, 2 H, CH_2CH_2), 2.32−2.40 (m, 1 H, CH_2CH_2), 2.43 (dd, *J* = 13.0/7.5 Hz, 1 H, $CH_2CH{=}CH_2$), 2.73 (dd, *J* = 13.0/7.5 Hz, 1 H, $CH_2CH{=}CH_2$), 2.99 (d, *J* = 13.0 Hz, 1 H, CH_2Ph), 3.01 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.27 (s, 3 H, CH_2OCH_3), 3.31 (d, *J* = 9.0 Hz, 1 H, CH_2OCH_3), 3.37 (d, *J* = 13.0 Hz, 1 H, CH_2Ph), 3.78 (s, 3 H, $CH_3OC{=}N$), 5.06−5.13 (m, 2 H, $CH_2CH{=}CH_2$), 5.59 (ddt, *J* = 16.2/11.0/7.5 Hz, 1 H, $CH_2CH{=}CH_2$), 7.16−7.26 (m, 5 H, aromatic H). − IR: ṽ = 1726 cm^{-1}, 1686, 700. − MS (CH_4; CI); *m*/*z* (%) = 400 (99) [M + H^+], 372 (100). − $C_{24}H_{33}NO_4$ (399.5): calcd. C 72.15, H 8.33, N 3.51; found C 72.01, H 8.51, N 3.54.

(*S*)-2-Amino-2-methyl-3-phenylpropanoic Acid (19c) and (2*S*)-2-*N*-[(1*S*,3*R*)-1-Hydroxy-3-methoxymethyl-2,2,3-trimethylcyclopentyl-1-carbonyl]amino-2-methyl-3-phenylpropanoic Acid (18c): To a solution of 42.8 mg of **17c** in 0.1 mL of THF 0.3 mL of NaOH (40%) was added. After stirring for 8 d, the mixture was diluted with 2 mL of H_2O and washed with CH_2Cl_2 (2 × 1 mL). The organic layers were reextracted with H_2O (2 × 2 mL). The combined aqueous phases were acidified with 2 N HCl and after washing with CH_2Cl_2 (2 × 1 mL) concentrated in vacuo. The residue was dissolved in a minimum amount of H_2O and subjected to ion exchange chromatography (Dowex 50 W X 8 cation exchange resin, H^+ form, elution with H_2O until the eluent was neutral and chloride-free, then 10% NH_3) to give 10.7 mg (52%) of **19c** as colorless crystals, m.p. > 300°C. − $[\alpha]_D^{20}$ = −20 (*c* = 0.17, H_2O) {ref.[10a], $[\alpha]_D^{20}$ = −21.5 (*c* = 1, H_2O)}. − ^{1}H NMR (D_2O): δ = 1.40 (s, 3 H, CH_3), 2.83 (d, *J* = 14.2 Hz, 1 H, CH_2), 3.15 (d, *J* = 14.2 Hz, 1 H, CH_2), 7.12−7.16 (m, 2 H, aromatic H), 7.22−7.30 (m, 3 H, aromatic H) (the ^{1}H-NMR-spectroscopic data are in good accordance with the data given in ref.[10a,10c]; the chemical shifts, given in ref.[10b], however, showed a difference from the former for each signal of 0.16 ppm). − IR: ṽ = 1651 cm^{-1}. − MS (CH_4; CI); *m*/*z* (%) = 180 (100) [M + H^+]. − The above-mentioned CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and concentrated. The resulting residue was purified by CC (*n*-heptane/ethyl acetate/AcOH, 65:25:10). This gave 15.0 mg (35%) of **18c** as a colorless oil. − TLC: R_f = 0.55 (2-propanol/H_2O, 95:5; detected by UV, 254 nm, and with cerium molybdate solution). − ^{1}H NMR ($CDCl_3$): δ = 0.74 (s, 3 H, CH_3), 0.85 (s, 6 H, CH_3), 1.46 (s, 3 H, CH_3CCH_2Ph), 1.59−1.69 (m, 2 H, CH_2CH_2), 1.91−2.03 (m, 1 H, CH_2CH_2), 2.65−2.77 (m, 1 H, CH_2CH_2), 3.03 (d, *J* = 9.5 Hz, 1 H, CH_2OCH_3), 3.14 (d, *J* = 13.8 Hz, 1 H, CH_2Ph), 3.24 (d, *J* = 9.5 Hz, 1 H, CH_2OCH_3), 3.39 (s, 3 H, CH_2OCH_3), 3.47 (d, *J* = 13.8 Hz, 1 H, CH_2Ph), 6.05 (s, 1 H, NH), 7.16−7.19 (m, 2 H, aromatic H), 7.23−7.33 (m, 3 H, aromatic H). − IR: ṽ = 1737 cm^{-1}, 1648, 1517. − MS (CH_4; CI); *m*/*z* (%) = 378 (100) [M + H^+]. − $C_{21}H_{31}NO_5$ (377.5): calcd. C 66.82 H 8.28 N 3.71; found C 67.01 H 8.36 N 3.49.

(*S*)-2-Amino-2-benzyl-4-pentenoic Acid (19d): The preparation was performed in analogy to the procedure described for **19c** the reaction time being increased to 12 d. From 33.7 mg of **17d** 8.3 mg (48%) of **19d** was obtained as colorless crystals, m.p. 220°C (dec.). − $[\alpha]_D^{20}$ = +26 (*c* = 0.11, H_2O) {ref.[10b] $[\alpha]_D^{20}$ = +27.3 (*c* = 1, H_2O)}. − ^{1}H NMR (D_2O): δ = 2.38 (dd, *J* = 14.6/8.8 Hz, 1 H, CH_2CH), 2.70 (dd, *J* = 14.6/6.3 Hz, 1 H, CH_2CH), 2.89 (d, *J* = 14.4 Hz, 1 H, CH_2Ph), 3.22 (d, *J* = 14.4 Hz, 1 H, CH_2Ph), 5.12−5.18 (m, 2 H, $CH_2{=}CH$), 5.65 (dddd, *J* = 15.9/11.0/8.8/6.3 Hz, 1 H, $CH_2CH{=}CH_2$), 7.14−7.18 (m, 2 H, aromatic H), 7.22−7.31 (m, 3 H, aromatic H) (as described for **19c** the ^{1}H-NMR signals given in ref.[10b] showed a difference in chemical shifts of 0.16 ppm from those reported above). − IR: ṽ = 1627 cm^{-1}. − MS (CH_4; CI); *m*/*z* (%) = 206 (100) [M + H^+].

Synthesis of Aminocyclopropanecarboxylic Acids

(1*R*,3*R*,6*S*,8*R*)-1-Hydroxymethyl-11-methoxy-8-methoxymethyl-7,7,8-trimethyl-5-oxa-12-azadispiro[2.2.4.2]dodec-11-en-4-one (20a): To a solution of 0.21 g (0.78 mmol) of **5** in 8 mL of THF, 1.64 mL (1.64 mmol, 2.1 equiv.) of a solution of $NaN(SiMe_3)_2$ (*c* = 1.0 mol/L in THF) and 0.29 g (3.12 mmol, 4 equiv.) of (*S*)-(+)-epichlorohydrin was added at −10°C. The mixture was stirred at −10°C for 24 h. After addition of 5 mL of phosphate buffer (pH = 7, *c* = 1 mol/L), THF was removed in vacuo, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 7:3, R_f = 0.20) gave 0.17 g (69%) of **20a** as colorless crystals, m.p. 68°C. − $[\alpha]_D^{20}$ = −35.8 (*c* = 0.65, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.89 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.46−1.53 (m, 1 H, CH_2CH_2), 1.56 (dd, *J* = 7.7/4.3 Hz, 1 H, CH_2CH), 1.95 (dd, *J* = 9.8/4.3 Hz, 1 H, CH_2CH), 1.99−2.08 (m, 3 H, CH_2CH_2 and CH_2CH), 2.49 (s, 1 H, OH), 2.61−2.68 (m, 1 H, CH_2CH_2), 3.16 (d, *J* = 9.1 Hz, 1 H, CH_2OCH_3), 3.34 (s, 3 H, CH_2OCH_3), 3.51 (d, *J* = 9.1 Hz, 1 H, CH_2OCH_3), 3.66 (s, 3 H, OCH_3), 3.88 (dd, *J* = 12.2/5.1 Hz, 1 H, CH_2OH), 4.00 (dd, *J* = 12.2/2.6 Hz, 1 H, CH_2OH). − IR: ṽ = 3450 cm^{-1}, 1732, 1682. − MS (CH_4; CI); *m*/*z* (%): 326 (100) [M + H^+]. − $C_{17}H_{27}NO_5$ (325.4): calcd. C 62.75, H 8.36, N 4.30; found C 62.73, H 8.42, N 4.35.

(1*S*,3*R*,6*S*,8*R*)-1-Hydroxymethyl-11-methoxy-8-methoxymethyl-7,7,8-trimethyl-5-oxa-12-azadispiro[2.2.4.2]dodec-11-en-4-one (20b): To a solution of 0.13 g (0.48 mmol) of **5** in 5 mL of THF 1.01 mL

(1.01 mmol, 2.1 equiv.) of a solution of $NaN(SiMe_3)_2$ (c = 1.0 mol/L in THF) and 0.18 g (1.92 mmol, 4 equiv.) of (*R*)-(−)-epichlorohydrine was added at −10°C. The mixture was stirred at −10°C for 24 h. After addition of 3 mL of phosphate buffer (pH = 7, c = 1 mol/L), THF was removed in vacuo, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by CC (petroleum ether/ethyl acetate, 7:3, R_f = 0.20) gave 0.10 g (66%) of **20b** as colorless crystals, m.p. 66°C. − $[\alpha]_D^{20}$ = +88.2 (c = 0.70, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.44−1.52 (m, 1 H, CH_2CH_2), 1.50 (dd, J = 7.3/4.7 Hz, 1 H, CH_2CH), 1.71 (dd, J = 9.6/4.7 Hz, 1 H, CH_2CH), 1.95−2.06 (m, 2 H, CH_2CH_2), 2.25−2.30 (m, 1 H, CH_2CH), 2.63−2.70 (m, 1 H, CH_2CH_2), 2.97 (s, 1 H, OH), 3.18 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.33 (s, 3 H, CH_2OCH_3), 3.48 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.66 (s, 3 H, OCH_3), 3.88 (dd, J = 12.2/5.8 Hz, 1 H, CH_2OH), 4.11 (dd, J = 12.2/2.8 Hz, 1 H, CH_2OH). − IR: ṽ = 3440 cm^{-1}, 1734, 1682. − MS (CH_4; CI); *m*/*z* (%): 326 (100) [M + H$^+$]. − $C_{17}H_{27}NO_5$ (325.4): calcd. C 62.75, H 8.36, N 4.30; found C 62.67, H 8.58, N 4.16.

(1*R*,3*R*,6*S*,8*R*)-11-Methoxy-8-methoxymethyl-7,7,8-trimethyl-4-oxo-5-oxa-12-azadispiro[2.2.4.2]dodec-11-en-1-carbaldehyde (22a): To a solution of 0.037 g, (26 μL, 0.29 mmol) of oxalyl chloride in 1 mL of CH_2Cl_2, a solution of 0.050 g (46 μL, 0.64 mmol) of DMSO in 1 mL of CH_2Cl_2 was added slowly at −60°C. After stirring for 15 min at −60°C, a solution of 0.074 g (0.226 mmol) of **20a** in 4 mL of CH_2Cl_2, after another 15 min at −60°C, 0.127 g (0.18 mL, 1.26 mmol) of NEt_3 was added. The reaction was still kept for 10 min at −60°C and then for 5 min at room temp., before it was quenched by addition of 4 mL of H_2O. Then, after 10 min, the organic layer was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 9:1, R_f = 0.18) gave 0.066 g (90%) of **22a** as colorless crystals, m.p. 44°C. − $[\alpha]_D^{20}$ = −41.9 (c = 0.40, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.81 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.46−1.52 (m, 1 H, CH_2CH_2), 1.95−2.08 (m, 2 H, CH_2CH_2), 2.16 (dd, J = 7.1/4.9 Hz, 1 H, CH_2CH), 2.37 (dd, J = 9.2/4.9 Hz, 1 H, CH_2CH), 2.51 (ddd, J = 9.2/7.1/6.8 Hz, 1 H, C*H*CHO), 2.61−2.68 (m, 1 H, CH_2CH_2), 3.14 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.33 (s, 3 H, CH_2OCH_3), 3.47 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.67 (s, 3 H, OCH_3), 9.26 (d, J = 6.8 Hz, 1 H, CHO). − IR: ṽ = 1744 cm^{-1}, 1719, 1676. − MS (CH_4; CI); *m*/*z* (%): 324 (100) [M + H$^+$]. − $C_{17}H_{25}NO_5$ (323.4): calcd. C 63.14, H 7.79, N 4.33; found C 62.97, H 8.00, N 4.34 .

(1*S*,3*R*,6*S*,8*R*)-11-Methoxy-8-methoxymethyl-7,7,8-trimethyl-4-oxo-5-oxa-12-azadispiro[2.2.4.2]dodec-11-en-1-carbaldehyde (22b): To a solution of 0.032 g (22 μL, 0.25 mmol) of oxalyl chloride in 1 mL of CH_2Cl_2, a solution of 0.043 g (40 μL, 0.55 mmol) of DMSO in 1 mL of CH_2Cl_2 was added slowly at −60°C. After stirring for 15 min at −60°C, a solution of 0.064 g (0.196 mmol) of **20b** in 4 mL of CH_2Cl_2, after another 15 min at −60°C, 0.109 g (0.16 mL, 1.08 mmol) of NEt_3 was added. The reaction was still kept at −60°C for 10 min, then for 5 min at room temp., before it was quenched by addition of H_2O. The organic layer was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 9:1, R_f = 0.18) gave 0.057 g (89%) of **22b** as colorless crystals, m.p. 48°C. − $[\alpha]_D^{20}$ = + 80.7 (c = 0.49, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.48−1.54 (m, 1 H, CH_2CH_2), 1.95−2.07 (m, 4 H, CH_2CH_2 and CH_2CH), 2.61−2.69 (m, 1 H, CH_2CH_2), 2.83 (ddd, J = 8.1/7.8/6.0 Hz, 1 H, C*H*CHO), 3.19 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.33 (s, 3 H, CH_2OCH_3), 3.46 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.64 (s, 3 H, OCH_3), 9.42 (d, J = 6.0 Hz, 1 H, CHO). − IR: ṽ = 1743 cm^{-1}, 1712, 1675. − MS (CH_4; CI); *m*/*z* (%): 324 (100) [M + H$^+$]. − $C_{17}H_{25}NO_5$ (323.4): calcd. C 63.14, H 7.79, N 4.33; found C 62.95, H 7.99, N 4.15.

(1*R*,3*R*,6*S*,8*R*)-11-Methoxy-8-methoxymethyl-7,7,8-trimethyl-1-phenylaminomethyl-5-oxa-12-azadispiro[2.2.4.2]dodec-11-en-4-one (23a): 0.048 g (0.15 mmol) of **22a** was dissolved in 3 mL of THF and treated with 0.042 g (0.45 mmol) of aniline and 0.009 g (0.15 mmol) of $NaBH_3CN$. The mixture was stirred at room temp. for 1 h. THF was removed in vacuo, the residue was taken up in 8 mL of Et_2O and washed with 5% $NaHCO_3$ solution (3 × 5 mL) and brine (2 × 5 mL). The aqueous phases were reextracted with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 9:1, R_f = 0.26) gave 0.052 g (86%) of **23a** as colorless oil. − $[\alpha]_D^{20}$ = −89.0 (c = 0.50, $CHCl_3$) − ^{1}H NMR ($CDCl_3$): δ = 0.80 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 1.29 (dd, J = 7.7/4.3 Hz, 1 H, CH_2CH), 1.46−1.53 (m, 1 H, CH_2CH_2), 1.97 (dd, J = 9.4/4.3 Hz, 1 H, CH_2CH), 1.99−2.06 (m, 2 H, CH_2CH_2), 2.33−2.41 (m, 1 H, CH_2CH), 2.61−2.68 (m, 1 H, CH_2CH_2), 3.14 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.33 (s, 3 H, CH_2OCH_3), 3.38 (dd, J = 13.3/5.6 Hz, 1 H, CH_2NH), 3.44 (dd, J = 13.3/6.8 Hz, 1 H, CH_2NH), 3.50 (d, J = 9.0 Hz, 1 H, CH_2OCH$_3$), 3.66 (s, 3 H, OCH_3), 3.84 (s, 1 H, NH), 6.61 (d, J = 7.7 Hz, 2 H, aromatic H), 6.72 (t, J = 7.5 Hz, 1 H, aromatic H), 7.18 (t, J = 7.7 Hz, 2 H, aromatic H). − IR: ṽ = 3380 cm^{-1}, 1732, 1682, 1604. − MS (CH_4; CI); *m*/*z* (%): 401 (100) [M + H$^+$]. − $C_{23}H_{32}N_2O_4$ (400.5): calcd. C 68.97, H 8.05, N 6.99; found C 68.68, H 7.88, N 7.19.

(1*S*,3*R*,6*S*,8*R*)-11-Methoxy-8-methoxymethyl-7,7,8-trimethyl-1-phenylaminomethyl-5-oxa-12-azadispiro[2.2.4.2]dodec-11-en-4-one (23b): 0.060 g (0.18 mmol) of **22b** was dissolved in 3 mL of THF and treated with 0.050 g (0.54 mmol) of aniline and 0.011 g (0.18 mmol) of $NaBH_3CN$. The mixture was stirred at room temp. for 1 h. THF was removed in vacuo, the residue was taken up in 8 mL of Et_2O and washed with 5% $NaHCO_3$ solution (3 × 5 mL) and brine (2 × 5 mL). The aqueous phases were reextracted with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. CC (petroleum ether/ethyl acetate, 9:1, R_f = 0.26) gave 0.064 g (88%) of **23b** as colorless oil. − $[\alpha]_D^{20}$ = + 98.5 (c = 0.52, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.17 (dd, J = 7.3/4.4 Hz, 1 H, CH_2CH), 1.46−1.55 (m, 1 H, CH_2CH_2), 1.72 (dd, J = 9.4/4.4 Hz, 1 H, CH_2CH), 1.93−2.08 (m, 2 H, CH_2CH_2), 2.34−2.41 (m, 1 H, CH_2CH), 2.62−2.70 (m, 1 H, CH_2CH_2), 3.17 (d, J = 8.8 Hz, 1 H, CH_2OCH$_3$), 3.33 (s, 3 H, CH_2OCH_3), 3.38 (dd, J = 12.9/5.1 Hz, 1 H, CH_2NH), 3.49 (d, J = 8.8 Hz, 1 H, CH_2OCH$_3$), 3.54 (dd, J = 12.9/7.8 Hz, 1 H, CH_2NH), 3.64 (s, 3 H, OCH_3), 3.89 (s, 1 H, NH), 6.64 (d, J = 7.7 Hz, 2 H, aromatic H), 6.71 (t, J = 7.3 Hz, 1 H, aromatic H), 7.18 (t, J = 7.3 Hz, 2 H, aromatic H). − IR: ṽ = 3385 cm^{-1}, 1734, 1679, 1603. − MS (CH_4; CI); *m*/*z* (%): 401 (100) [M + H$^+$]. − $C_{23}H_{32}N_2O_4$ (400.5): calcd. C 68.97, H 8.05, N 6.99; found C 68.68, H 7.94, N 7.20.

Hydrolysis of 20a−b and 23a−b. − General Procedure 3 (GP 3): A solution of 0.1 mmol of the respective compound in 1 mL of 0.2 N HCl was stirred at room temp. for 24 h and then concentrated in vacuo. The residue was dissolved in 1 mL of 40% aqueous NaOH and the resulting solution was stirred for 24 h at room temp. Then it was cooled to 0°C and, after adjusting the pH to 1−2 with concd. HCl, extracted with Et_2O (3 × 2 mL). The aqueous phase

was concentrated in vacuo and the residue dissolved in a minimum amount of H_2O and subjected to ion exchange chromatography (Dowex 50 W X 8 cation exchange resin, elution with H_2O until the eluent was neutral and chloride-free, then elution with 10% aqueous NH_3) to give the free amino acid.

(1*R*,2*R*)-1-Amino-2-(hydroxymethyl)cyclopropanecarboxylic Acid (21a): According to GP 3 from 33 mg of **20a** 8 mg (59%) of **21a** was obtained as colorless crystals, m.p. 198°C (dec). − $[\alpha]_D^{20}$ = −22.5 (*c* = 0.70, H_2O) {ref.[11]; (1*S*,2*S*) enantiomer: $[\alpha]_D^{24}$ = + 23.3 (*c* = 0.95, H_2O)}. − ^{1}H NMR (D_2O): δ = 1.41 (dd, *J* = 10.2/ 6.5 Hz, 1 H, C*H*$_2$CH), 1.45 (t, *J* = 6.5 Hz, 1 H, C*H*$_2$CH), 1.75−1.85 (m, 1 H, CH$_2$C*H*), 3.81 (dd, *J* = 11.5/7.2 Hz, 1 H, C*H*$_2$OH), 3.84 (dd, *J* = 11.5/6.7 Hz, 1 H, C*H*$_2$OH). − IR: ṽ = 3250 cm^{-1}, 1630, 1570. − MS (CH_4; CI); *m/z* (%): 132 (1) [M + H^+], 101 (100). − $C_5H_9NO_3$ (131.1): calcd. C 45.80, H 6.92, N 10.68; found C 45.73, H 6.77, N 10.96.

(1*R*,2*S*)-1-Amino-2-(hydroxymethyl)cyclopropanecarboxylic Acid (21b): According to GP 3 from 33 mg of **20b** 9 mg (66%) of **21b** was obtained as colorless crystals, m.p. 230°C (dec.) − $[\alpha]_D^{20}$ = +72.8 (*c* = 0.56, H_2O) {ref.[18]; $[\alpha]_D^{25}$ = +73.81 (*c* = 0.48, H_2O)}. − ^{1}H NMR (D_2O): δ = 1.18 (t, *J* = 6.5 Hz, 1 H, C*H*$_2$CH), 1.50 (dd, *J* = 10.0/6.5 Hz, 1 H, C*H*$_2$CH), 1.83−1.95 (m, 1 H, CH$_2$C*H*), 3.77 (dd, *J* = 12.0/6.8 Hz, 1 H, C*H*$_2$OH), 3.98 (dd, *J* = 12.0/5.2 Hz, 1 H, C*H*$_2$OH). − IR: ṽ = 3235 cm^{-1}, 1639, 1568. − MS (CH_4; CI); *m/z* (%): 132 (1) [M + H^+], 101 (100) − $C_5H_9NO_3$ (131.1): calcd. C 45.80, H 6.92, N 10.68; found C 45.97, H 7.14, N 10.37.

(1*R*,2*R*)-1-Amino-2-(phenylaminomethyl)cyclopropanecarboxylic Acid (24a): According to GP 3 from 40 mg of **23a** 13 mg (62%) of **24a** was obtained as colorless crystals, m.p. 180°C (dec). − $[\alpha]_D^{20}$ = −66.4 (*c* = 0.75, H_2O). − ^{1}H NMR (D_2O): δ = 1.18 (t, *J* = 6.2 Hz, 1 H, C*H*$_2$CH), 1.32 (dd, *J* = 9.8/6.2 Hz, 1 H, C*H*$_2$CH), 1.62−1.73 (m, 1 H, CH$_2$C*H*), 3.16 (dd, *J* = 11.0/7.2 Hz, 1 H, C*H*$_2$NH), 3.32 (dd, *J* = 11.0/6.7 Hz, 1 H, C*H*$_2$NH), 6.85−6.92 (m, 3 H, aromatic H), 7.30 (t, *J* = 7.2 Hz, 2 H, aromatic H). − IR: ṽ = 3228 cm^{-1}, 1645, 1580. − MS (CH_4; CI); *m/z* (%): 207(1) [M + H^+], 106 (100). − $C_{11}H_{14}N_2O_2$ (206.3): calcd. C 64.06, H 6.84, N 13.58; found C 64.14, H 6.68, N 13.77.

(1*R*,2*S*)-1-Amino-2-(phenylaminomethyl)cyclopropanecarboxylic Acid (24b): According to GP 3 from 40 mg of **23b** 12 mg (59%) of **24b** was obtained as colorless crystals, m.p. 205°C (dec). − $[\alpha]_D^{20}$ = +90.5 (*c* = 0.60, H_2O) − ^{1}H NMR (D_2O): δ = 1.05 (t, *J* = 6.5 Hz, 1 H, C*H*$_2$CH), 1.14 (dd, *J* = 10.2/6.5 Hz, 1 H, C*H*$_2$CH), 1.48−1.56 (m, 1 H, CH$_2$C*H*), 3.02 (dd, *J* = 11.5/7.7 Hz, 1 H, C*H*$_2$NH), 3.19 (dd, *J* = 11.5/5.9 Hz, 1 H, C*H*$_2$NH), 6.70−6.80 (m, 3 H, aromatic H), 7.16 (t, *J* = 7.9 Hz, 2 H, aromatic H). − IR: ṽ = 3195 cm^{-1}, 1627, 1539. − MS (CH_4; CI); *m/z* (%): 207(1) [M + H^+], 106 (100). − $C_{11}H_{14}N_2O_2$ (206.3): calcd. C 64.06, H 6.84, N 13.58; found C 63.84, H 7.10, N 13.84.

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