The Nonchiral Bislactim Diethoxy Ether as a Highly Stereo-Inducing Synthon for Sterically Hindered, γ-Branched α-Amino Acids: A Practical, Large-Scale Route to an Intermediate of the Novel Renin Inhibitor Aliskiren

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The diastereoselective synthesis of the sterically hindered, γ-branched α-amino acid derivative (2*S*,4*S*)-**24a** and its *N*-[(*tert*-butoxy)carbonyl](Boc)-protected alcohol (2*S*,4*S*)-**19**, both key intermediates of a novel class of nonpeptide renin inhibitors such as aliskiren (**1**), is described. Initially, the analogous methyl ester (2*S*,4*S*)-**17** was obtained by alkylation of the chiral *Schöllkopf* dihydropyrazine (*R*)-**12a** with the dialkoxy-substituted alkyl bromide (*R*)-**11a**, which proceeded with explicitly high diastereofacial selectivity (*ds* ≥98%) to give (2*S*,5*R*,2′*S*)-**13a** (*Scheme 4*), followed by mild acid hydrolysis and *N*-Boc protection (*Scheme 5*). Conversely, the complete lack of stereocontrol and poor yields for the reaction of (*R*)-**11a** with the enantiomeric (*S*)-**12b** suggested, in addition to the anticipated shielding effect by the ^{i}Pr group at C(2) of the auxiliary, steric repulsion between the MeO–C(6) and the bulky residues of (*R*)-**11a** in the proposed transition state, which would strongly disfavor both the *Si* and *Re* attack of the electrophile (see *Fig.*). Based on this rationale, alkylation of the readily accessible achiral diethoxy-dihydropyrazine **21** with (*R*)-**11a** was found to provide a 95:5 mixture of diastereoisomers (2*S*,2′*S*)-**22a** and (2*R*,2′*S*)-**23a** in high yield (*Scheme 6*), which afforded in two steps and after recrystallization enantiomerically pure (2*S*,4*S*)-**24a**. Similarly, the stereochemical course for the alkylation reactions of the related alkyl bromides (*S*)-**28a** and (*R*)-**28b** with both (*R*)-**12a** and (*S*)-**12b** as well as with the achiral **21** was investigated (*Schemes 7–9*). The precursor bromides (*R*)-**11a**, (*S*)-**11b**, (*R*)-**28a**, and (*S*)-**28b** were efficiently synthesized *via* the diastereoselective alkylation of the *Evans* 3-isovaleroyloxazolidin-2-ones (*R*)-**7a** and (*S*)-**7b** either with bromide **6** or with benzyl chloromethyl ether, and subsequent standard transformations (*Schemes 3* and *7*). A practical and economical protocol of the preparation of (2*S*,4*S*)-**24a** on a multi-100-g scale is given. This is the first report of the application of an achiral dihydropyrazine, *i.e.*, in form of **21**, as a highly stereo-inducing synthon providing rapid access to a *N*-protected γ-branched α-amino acid with (2*S*) absolute configuration.

1. Introduction. – Several classes of structurally novel hydroxyethylene dipeptide isostere inhibitors of the aspartyl protease renin, including aliskiren (=(αS,γS,δS,ζS)-δ-amino-*N*-(3-amino-2,2-dimethyl-3-oxopropyl-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)benzeneoctanamide; **1**; *Scheme 1*), have emerged recently from a target-structure-based-design approach [1]. *In vitro*, these nonpeptide, small-molecule inhibitors are highly potent and selective for human renin and are unique with respect to their specific binding interactions with a nonsubstrate pocket of the enzyme. Aliskiren (**1**) induced pronounced and long-lasting reduction in blood pressure after oral administration in monkeys [2] and is currently under clinical investigation as a new antihypertensive agent [3].

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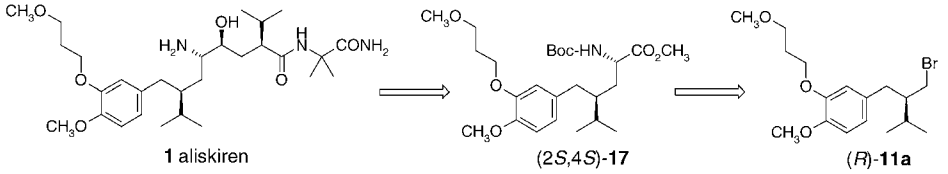
Scheme 1. retro-*Synthesis of the Novel Renin Inhibitor Aliskiren* (**1**)



The synthesis of **1** and related analogues initially relied on efficient stereoselective access to the *N*-[(*tert*-butoxy)carbonyl](Boc)-protected α-amino ester (2*S*,4*S*)-**17** as the key intermediate bearing two highly substituted and bulky residues at the branched γ-position (*Scheme 1*) [2][4][4]). Enantiomerically pure (2*S*,4*S*)-**17** was envisaged to be readily accessible from the chiral precursor electrophile (*R*)-**11a** by the bis-lactim ether approach developed by *Schöllkopf* and co-workers for the synthesis of unnatural α-amino acids [5][6]. This methodology has been applied by us previously to generate a variety of analogues of **1** for structure–activity-relationship studies [4].

We report herein a highly stereoselective route to (2*S*,4*S*)-**17** by the preparation of the fully substituted alkyl bromide (*R*)-**11a** from the *Evans* (4*R*)-benzyloxazolidinone (*R*)-**7a**, followed by an efficient diastereofacial alkylation step using the chiral *Schöllkopf* auxiliary (*R*)-**12a**.

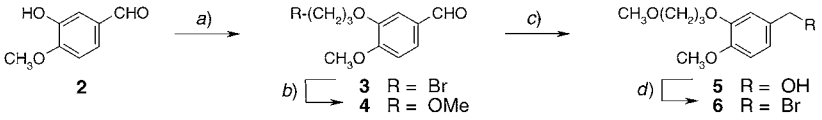
In the course of this work, we discovered an alternative and very practical protocol for the preparation of crystalline *N*-Boc-protected (2*S*,4*S*)-**24a**, the ethyl ester analogue of (2*S*,4*S*)-**17**. This procedure is based on the diastereoselective alkylation reaction of bromide (*R*)-**11a** with the nonchiral 2,5-diethoxy-3,6-dihydropyrazine (**21**), a crystalline synthon readily accessible from cheap starting materials. The rationale for this previously unprecedented stereo-induction by an achiral dihydropyrazine scaffold was derived from the unexpected ratios of doubly 'matched' and 'mis-matched' alkylation products formed between the sterically demanding electrophile and the chiral *Schöllkopf* auxiliaries (*R*)-**12a** and (*S*)-**12b**, repectively. The new route turned out to be highly advantageous as compared to the classical bis-lactim ether approach for the preparation of (2*S*,4*S*)-**24a** or (2*R*,4*R*)-**24b** and was amenable to up-scaling. The application of this method to the synthesis of the related γ-branched amino acid (2*S*,4*S*)-**31** is also described.

2. Results and Discussion. – 2.1. *Stereoselective Syntheses of Enantiomerically Pure Alkyl Bromides (*R*)-***11a*** and (*S*)-***11b***.* The (*R*)-configured bromide (*R*)-**11a** required for the synthesis of the targeted *N*-protected α-amino acid ester, as derived from the *retro*-synthetic analysis (*Scheme 1*), was efficiently accessed by diastereoselective alkylation of (4*R*)-3-isovaleroyl-4-benzyl-oxazolidin-2-one ((*R*)-**7a**) with the conveniently substituted 3,4-dialkoxybenzyl bromide **6** following the method by *Evans* and co-workers [7] as the key reaction step (see below, *Scheme 3*). The intermediate benzyl bromide **6** was obtained in a straightforward manner on a >1M reaction scale from 3-hydroxy-4-methoxybenzaldehyde (**2**) according to *Scheme 2*. The 3-methoxypropoxy side chain was introduced in a two-step procedure, first by alkylation of the phenolic

[4]) For alternative synthesis approaches to aliskiren (**1**), see the review article by *Mealy et al.* [3].

OH group with a large excess of dibromopropane[5]) in the presence of K_2CO_3 to give bromo derivative **3** in high yield (93%). Subsequent replacement of the Br-atom with NaOMe/MeOH was accompanied by elimination of HBr to give the corresponding 3-(allyloxy) derivative as a major by-product. Under optimized reaction conditions (dropwise addition of 30% NaOMe in MeOH at 61–64°, followed by brief reflux), a 4:1 ratio of the desired substitution *vs.* dehydrohalogenation products were obtained, providing aldehyde **4** in 72% isolated yield after flash-chromatography (FC) purification[6]). Subsequent reduction with $NaBH_4$ to **5** followed by bromination with Me_3SiBr gave crystalline **6**[7]) in almost quantitative yield over two steps.

Scheme 2



a) $Br(CH_2)_3Br$, K_2CO_3, MeCN, 19 h reflux; 93%. *b*) 30% NaOMe soln., MeOH, heat; 72%. *c*) $NaBH_4$, MeOH, 0–5° to r.t.; 96%. *d*) Me_3SiBr, $CHCl_3$, 20–25°; quant.

The reaction of the lithium enolate, generated by deprotonation of the auxiliary (*R*)-**7a** (1.2 equiv.) with LiHMDS (lithium salt of hexamethyldisilazane) at −75° in THF, with benzyl bromide **6** according to the method of *Evans* and co-workers [7] gave a unique alkylation product (single spot on TLC (silica gel)) (*Scheme 3*). The ^{1}H-NMR spectrum, after FC purification, clearly indicated the presence of one major diastereoisomer (2′*R*,4*R*)-**8a**, besides only trace signals within the detection limit, which were tentatively assigned to the corresponding (2′*S*,4*R*)-isomer. Recrystallization from Et_2O/hexane eventually afforded the desired (2′*R*,4*R*)-**8a** in 86% yield[8]). Removal of the chiral auxiliary was achieved by alkaline hydrolysis of (2′*R*,4*R*)-**8a** under standard conditions with $LiOH/H_2O_2$ [7] to give the carboxylic acid (*R*)-**9a** (95%) as a colorless oil, which could be crystallized from Et_2O/hexane at −20°[9]). (*R*)-**9a** was then smoothly reduced to alcohol (*R*)-**10a** with $NaBH_4$ in presence of I_2 in THF [8], followed by bromination with *N*-bromosuccinimide (NBS) in CH_2Cl_2 to give solid (*R*)-**11a** (87%, two steps). In a similar fashion, the stereoselective alkylation of (*S*)-**7b** with **6** (→ (2′*S*,4*S*)-**8b**), followed by straightforward transformation to the acid (*S*)-**9b** and alcohol (*S*)-**10b**, without purification of any intermediates, and final NBS bromination afforded the enantiomeric bromide (*S*)-**11b** (*Scheme 3*).

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5) Excess (10 equiv.) dibromopropane was recovered by evaporation of the reaction mixture.

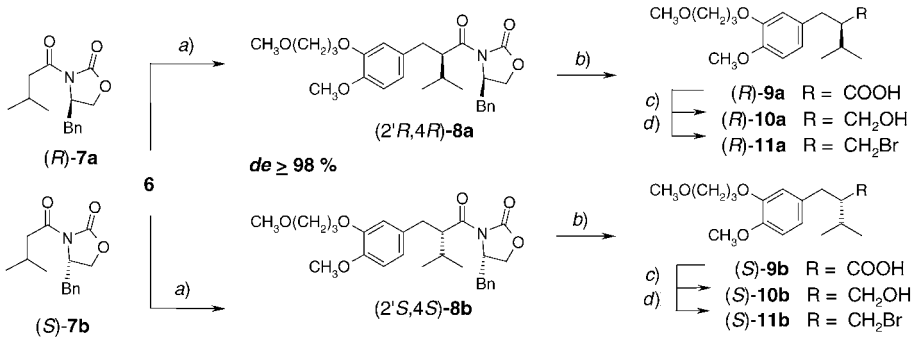
6) Alternatively, **4** was obtained from **2** by alkylation with $MeO(CH_2)_3Br$ (commercially available from *Matrix Scientific* (Columbia, SC, USA) and *Karl Industries Inc.* (Aurora, OH, USA) in presence of K_2CO_3.

7) Solid bromide **6** was found to rapidly decompose at the surface of metallic materials. Even short contact with any metal equipment such as a spatula or metal stirrer should be avoided!

8) This highly stereoselective alkylation reaction was successfully scaled up to produce several 100-g quantities of (2′*R*,4*R*)-**8a** without compromising the diastereoisomer purity.

9) On a larger reaction scale, the chiral *Evans* oxazolidinones were recovered almost quantitatively and in optically pure form by extractive separation of (*R*)-**9a** or (*S*)-**9b** and subsequent recrystallization from AcOEt/hexane.

Scheme 3



a) 1M LiHMDS, THF, $-70°$ to r.t.; 86% (for (2′*R*,4*R*)-**8a**). *b*) LiOH, 30% H_2O_2 soln., THF/H_2O 3:1, 0° to r.t.; 95% ((*R*)-**9a**) and 91% ((*S*)-**9b**). *c*) $NaBH_4$, I_2, THF, 4 d at r.t.; 90% (for (*R*)-**10a**). *d*) NBS, CH_2Cl_2, 18 h at r.t.; 97% (for (*R*)-**11a**).

The enantiomer excess (ee) of alcohols (*R*)-**10a** and (*S*)-**10b** was determined to be 98.8 and 98.2%, respectively, by HPLC resolution on a *Chiralpak AD* ® chiral stationary phase. Full separation of both enantiomers (*R*)-**11a** and (*S*)-**11b** was also achieved on *Chiralpak AD* ® under similar elution conditions; however, analysis of the ee for the first eluting (*R*)-**11a**[10]) was less accurate due to peak tailing (ee $>97\%$). These results confirm the very high diastereoisomer ratios of $>99:1$ obtained for the alkylation of the *Evans* auxiliary leading to (2′*R*,4*R*)-**8a** and (2′*S*,4*R*)-**8b**, and a negligible racemization during the alkaline hydrolysis step.

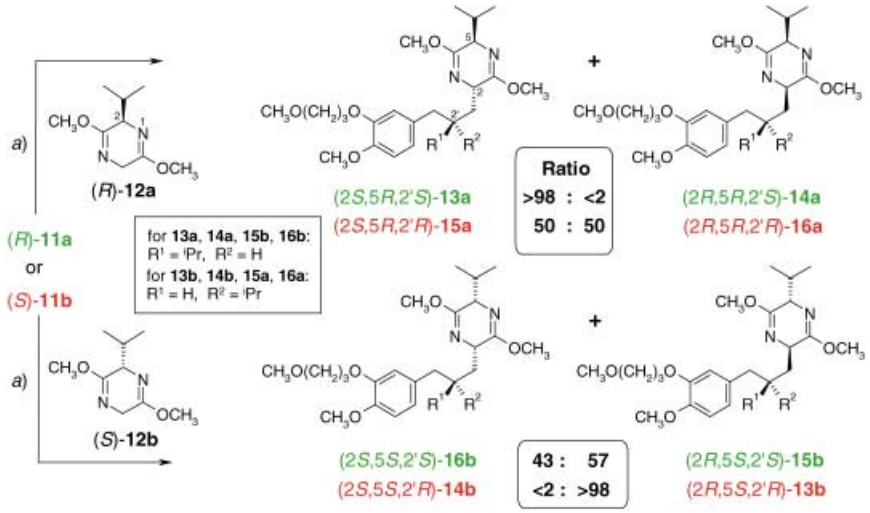
2.2. *Stereoselective Alkylation Reactions with* Schöllkopf's *(2*R*)- and (2*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine as Chiral Auxiliary Reagents.* Following the standard protocol of *Schöllkopf* and co-workers [5][6], the enantiomerically pure alkyl bromide (*R*)-**11a** (see *Scheme 3*) was treated with the lithium enolate of the chiral dihydropyrazine auxiliary (*R*)-**12a** (generated by deprotonation with BuLi at $-75°$ in THF) at $-20°$ for 18 h to give the desired (2*S*,5*R*,2′*S*)-**13a** besides a small amount of (2*R*,5*R*,2′*S*)-**14a** (*Scheme 4*). Analysis of the crude product after aqueous workup by TLC (silica gel) and reversed-phase HPLC indicated that (2*S*,5*R*,2′*S*)-**13a** was formed with remarkably high diastereoselectivity[11]). Transformation of the crude material to the mixture of diastereoisomers (2*S*,4*S*)-**17** and (2*R*,4*S*)-**18** (*Scheme 5*, *vide infra*) eventually allowed to determine the exact ratio of (2*S*,5*R*,2′*S*)-**13a** and its minor C(2) epimer (2*R*,5*R*,2′*S*)-**14a** to be $>98:2$ by reversed-phase HPLC. Hence, alkylation of the *Schöllkopf* chiral auxiliary (*R*)-**12** with the β-branched and bulky bromide (*R*)-**11a** proceeded with exeptionally high diastereoselectivity. Purification by FC (silica gel)

[10]) Note the reverse elution sequence of the (*S*)- und (*R*)-enantiomers of alcohols **10** as compared to those of bromides **11** (*cf. Exper. Part*).

[11]) A very faint TLC spot detected at R_f 0.23 (hexane/AcOEt 2:1; UV_{254}) slightly below that of (2*S*,5*R*,2′*S*)-**13a**, may have corresponded to the diastereoisomer (2*R*,5*R*,2′*S*)-**14a**. Reversed-phase HPLC (*Nucleosil 5 C18*) showed several very minor peaks (each with AUC $\leq 2\%$) in addition to the major product peak. The ^{1}H-NMR spectrum of the crude product did not provide clear evidence for the formation of the C(2) epimer (2*R*,5*R*,2′*S*)-**14a** due to overlapping signals with (*R*)-**12** (used in excess) and unreacted bromide (*R*)-**11a**.

eventually provided the diastereomerically pure (2*S*,5*R*,2′*S*)-**13a**, as demonstrated by ^{1}H-NMR, in excellent 85% yield.

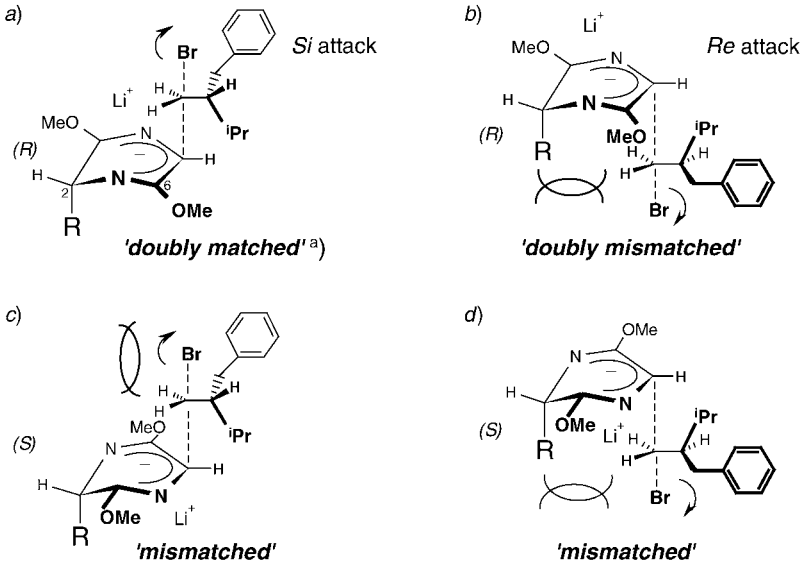
Scheme 4



a) Reagent (*R*)-**12a** or (*S*)-**12b**, 1 equiv. of BuLi, THF, −75°, 75 min; then bromide (*R*)-**11a** or (*S*)-**11b** (0.67 equiv.) in THF, −75° to −20°, 18 h.

Surprisingly, when bromide (*R*)-**11a** was treated under identical conditions with the lithium enolate of (*S*)-**12b** of opposite absolute configuration, complete loss of diastereoselectivity was observed, *i.e.*, the two stereoisomers (2*S*,5*S*,2′*S*)-**16b** and (2*R*,5*S*,2′*S*)-**15b** were formed as a 43:57 mixture (separable on silica gel) and in only moderate 54% isolated yield (*Scheme 4*). Variation of the reaction time and temperature or addition of alkyl bromide (*R*)-**11a** in large excess did not improve the diastereoselectivity or the overall conversion of reactants. The ^{1}H-NMR spectra of both FC-purified epimers provided evidence that both products (2*S*,5*S*,2′*S*)-**16b** and (2*R*,5*S*,2′*S*)-**15b** differed in their relative configuration at the dihydropyrazine moiety (2,5-*cis vs.* 2,5-*trans*, resp.) [9]. Conversely, the 'doubly matched' diastereoisomeric product (2*R*,5*S*,2′*R*)-**13b** (enantiomeric to (2*S*,5*R*,2′*S*)-**13a**) was obtained in high diastereomer excess (de ≥99%) from (*S*)-bromide (*S*)-**11b** and auxiliary (*S*)-**12b**, whereas alkylation of (*R*)-**12a** with (*S*)-**11b** remained incomplete (overall 42% isolated yield) even after prolonged reaction times, leading to a *ca.* 1:1 mixture of separable diastereoisomers (2*S*,5*R*,2′*R*)-**15a** and (2*R*,5*R*,2′*R*)-**16a** in a 'doubly mismatched' fashion (*Scheme 4*; see also the *Figure* below and *Sect. 2.6*).

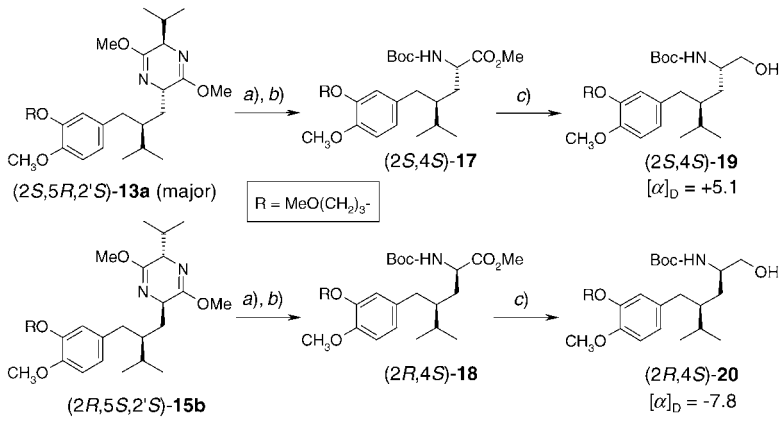
2.3. *Transformation to the Diastereoisomeric* N*-Boc-Protected Amino Esters and Their Amino Alcohols. Determination of the Absolute Configuration.* Mild acidic hydrolysis of the dihydropyrazine derivative (2*S*,5*R*,2′*S*)-**13a** and subsequent reaction with dicarbonic acid di(*tert* butyl) ester (Boc_2O) gave the crystalline *N*-Boc-protected methyl ester (2*S*,4*S*)-**17** (*Scheme 5*). Reduction of (2*S*,4*S*)-**17** with $LiBH_4$ in THF



a) Numbering of (*R*)-**12a** (R = ^{i}Pr) and (*S*)-**12b** (R = ^{i}Pr).

Figure. *Proposed mechanism for the diastereoselective alkylation of* (R)-**12a** (R = ^{i}Pr), (S)-**12b** (R = ^{i}Pr), *and* **21** (R = H; both MeO replaced by EtO) *with bromide* (R)-**11a** (the two alkoxy groups of the benzyl moiety are omitted)

Scheme 5



a) 1N HCl, MeCN, 30 min., r.t.; *b*) Boc_2O, Et_3N, CH_2Cl_2, 18 h at r.t.; 74% (2 steps, for (2*S*,4*S*)-**17**). *c*) $LiBH_4$, THF, 16 h, r.t. (95% for (2*S*,4*S*)-**19**).

provided the crystalline amino alcohol (2*S*,4*S*)-**19** as a white solid in good yield (82%) on a multi-g scale.

Similarly, epimer (2*R*,5*S*,2′*S*)-**15b** was transformed by the two-step sequence to the corresponding diastereoisomer (2*R*,4*S*)-**18** (oil) and then to the amino alcohol (2*R*,4*S*)-**20**, which, in contrast to its epimer (2*S*,4*S*)-**19**, could not be crystallized (*Scheme 5*). The ^{1}H-NMR spectra ($CDCl_3$) allowed us to clearly distinguish between the pairs of diastereoisomers (2*S*,4*S*)-**17** *vs.* (2*R*,4*S*)-**18** and (2*S*,4*S*)-**19** *vs.* (2*R*,4*S*)-**20**; for example, (2*S*,4*S*)-**19** showed a narrow *m* for both enantiotopic benzylic protons (δ 2.48), whereas (2*R*,4*S*)-**20** revealed 2 *dd* (δ 2.61 ($J = 5$, 13 Hz) and 2.21 ($J = 8$, 13 Hz)). The diastereoisomer excess of (2*S*,4*S*)-**19** was determined to be $\geq$99.9% by reversed-phase HPLC (*Nucleosil C18*)[12]).

The alcohol (2*S*,4*S*)-**19** served as a starting material for the synthesis of renin inhibitor **1** and related analogues as part of our structure-activity relationship studies [2]. In the course of this work, the X-ray crystal structure of a derivative of **1** unambiguously confirmed that alcohol (2*S*,4*S*)-**19** and the stereogenic centers of its precursor intermediates had the desired absolute configuration [10].

2.4. *Nonchiral Dialkoxy-Dihydropyrazine as a Stereo-Inducing Template for Enantioselective Alkylation Reactions.* The remarkably high diastereoselectivity of $>98:1$ observed for the alkylation of the chiral bis-lactim ether (*R*)-**12a** with bromide (*R*)-**11a** (*vice versa* that of (*S*)-**12b** with (*S*)-**11b**) and, more intriguingly, the complete lack of stereo-induction observed for the 'doubly mismatched' reaction of (*R*)-**12a** with the enantiomeric bromide (*S*)-**11b** (*Scheme 4*) could be rationalized by adapting the simplified transition-state mechanism proposed previously (*Fig.*) [5][6][13]). Accordingly, the anticipated 'matched' situation would involve the lithiated dihydropyrazine anion, generated from (*R*)-**12a**, in a 'folded' conformation with one diastereotopic side being strongly shielded by the relatively large isopropyl group on the C(2) position (*Fig.*, *a*; R = ^{i}Pr)[14]). The steric congestion on the bottom side favors the *Si* attack of the electrophile (*R*)-**11a** from above the plane of the heterocyclic species leading to the (*S*)-configuration at the newly formed stereocenter (C(2) in (2*S*,5*R*,2′*S*)-**13a**, see *Scheme 4*). This transition-state model would also suggest that (*R*)-**11a** adopts a preferred low-energy conformation, in which the bulky isopropyl residue at the stereogenic center is *anti*-periplanar to the leaving Br-atom when approaching the center of induction[15]). This conformation of the electrophile avoids also a steric clash

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[12]) Compound (2*R*,4*S*)-**20** showed a de of 70% due to incomplete separation of precursor (2*S*,5*S*,2′*S*)-**16b** from (2*R*,5*S*,2′*S*)-**15b**.

[13]) The reacting species of nucleophilic lithium enolates derived from bis-lactim ethers is currently unknown. The X-ray structure of a lithiated bis-lactim ether derived from *cyclo*-[Ala-Ala] has been resolved as a dimeric aggregate in which the two Li-atoms are σ-bonded to the negatively charged N-atoms and coordinated to a total of three THF solvent molecules [11]. On the other hand, cryoscopic experiments have demonstrated that this dimeric aggregate is in equilibrium with a monomeric species in solution at very low temperatures [12].

[14]) A violation of the '*Schöllkopf* rule' has been observed for the reaction of the lithiated bis-lactim ether derived from (*R*)-2-methyl-3-phenylalanine and glycine with 2-haloethyl triflates, as well as for the subsequent intramolecular ring closure, to give predominantly the *cis* addition products [13].

[15]) We assume an S_N2-type mechanism for the displacement reaction. Force-field calculations revealed only small energy differences of 1-2 kJ/mol for the *anti*-periplanar *vs.* both synclinal conformations, suggesting that electrophile (*R*)-**11a** does not adopt a single predominant conformation in solution [14].

between the substituted benzyl group (*syn*-clinal to the Br-atom) and the MeO group within the folded plane of the nucleophile, thereby minimizing the overall steric constraints with the lithium enolate nucleophile ('doubly matched')[16]). In contrast, attack of (*R*)-**11a** from the diastereotopic *Re* side would be even more disfavored ('doubly mismatched')[16]) due to the steric interference of the substituted benzyl group with the MeO substituent at C(6) of the heterocycle, in addition to the diastereofacial shielding effect by the ^{i}Pr group at C(2) of the auxiliary (*R*)-**12a** (*Fig.*, *b*).

In line with the postulated mechanism, the reaction of auxiliary (*S*)-**12b** of opposite chirality with (*R*)-**11a** would result in a 'mismatched' situation for both putative transition states, either due to the diastereofacial blockade by the ^{i}Pr group at C(2) (*Fig.*, *d*), or by considerable steric repulsion between the MeO group at C(6) of the *Schöllkopf* reagent and the bulky substituted benzyl residue of the electrophile (*R*)-**11a** (*Fig.*, *c*). The lack of diastereoselectivity observed experimentally for the alkylation of (*S*)-**12b** with (*R*)-**11a** giving a 43 : 57 product mixture (*Scheme 4*), as well as the poor chemical reactivity resulting in only low isolated yields, indicated that both diastereotopic sides of the heterocyclic anion are markedly congested by steric constraints. Thus, the alkoxy group at C(6) of the dihydropyrazine could, in principle, have a major directing effect to a similar extent as the stereocontrol exerted by the 'shielding' ^{i}Pr group at C(2)[17]). Most importantly, our hypothetical model suggested that, for the reaction with sterically hindered chiral electrophiles, such as bromides (*R*)-**11a** and (*S*)-**11b**, stereodifferentiation could be achieved essentially in the absence of the alkyl group at C(2) of the chiral *Schöllkopf* reagent, leading in the case of (*R*)-**11a** to the desired absolute (*S*)-configuration at the newly formed stereocenter.

Intrigued by these considerations, we initiated some work to study the stereochemical course of the alkylation reaction between the bromides (*R*)-**11a** and (*S*)-**11b** and the nonchiral diethoxy-dihydropyrazine **21** lacking the ^{i}Pr group at C(2) of the reagents (*R*)-**12a** and (*S*)-**12b**. To the best of our knowledge, a detailed investigation of the directing effect of the alkoxy residue neighboring the nucleophilic center of the bis-lactim ether relative to the directing effect of the C(2) alkyl residue of the classical *Schöllkopf* reagent has not been reported previously.

2.5. *Large-Scale Preparation of Bis-Lactim Diethyl Ether* **21**. A few general considerations prompted us to select the known bis-lactim diethyl ether **21** (*Scheme 6*) for our studies[18]). The compound is readily accessible from inexpensive starting materials, in contrast to the corresponding dimethyl ether analogue [15][19]). Furthermore, we anticipated a more-pronounced stereo-inducing effect due to the slightly increased bulkiness of the EtO *vs.* the MeO group and, hence, an increased

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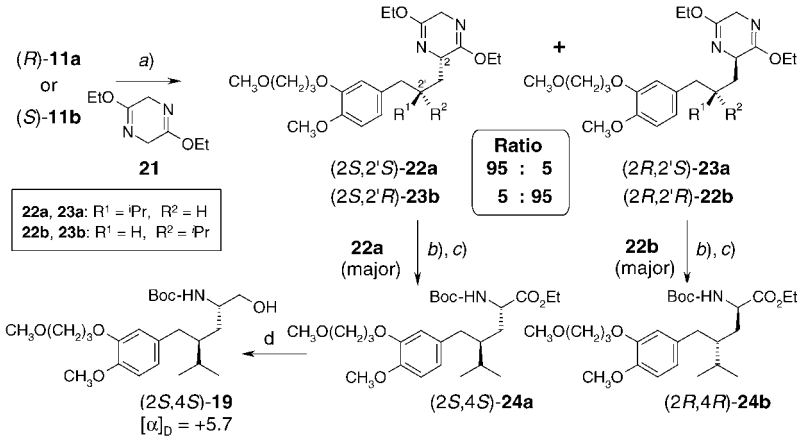
16) Referred to as a 'doubly matched' or 'doubly mismatched' situation, both with respect to the nucleophile as well as the electrophile, in contrast to the 'mismatched' situation evolving either from steric hindrance induced predominantly by the electrophile, as depicted in the *Fig.*, *c*, or by the nucleophile (*Fig.*, *d*).

17) The only moderate isolated yield for the alkylation products (2*S*,5*S*,2′S)-**16b**/(2*R*,5*S*,2′*S*)-**15b** also reflects the overall steric constraints exerted by both reaction partners.

18) For alkylation of **21** with simple alkyl and allyl bromides, see [15] and [16].

19) Preparation of the dimethyl analogue by *O*-alkylation of the diketopiperazine with trimethyloxonium tetrafluoroboate has been reported to proceed with only low yields (see [6], ref. 4 therein). Furthermore, the commercially available 'ethyl' *Meerwein* salt is less expensive than $(Me_3O)BF_4$, allowing economical production of **21** on a multi-kg scale. For the preparation of the 2,5-bis-(benzyloxy)-3,6-dihydropyrazine, see [17].

Scheme 6



a) Reagent **21** (1.5 equiv.), 1.4 equiv. of BuLi, THF, $-75°$; then bromide (*R*)-**11a** or (*S*)-**11b** (1.0 equiv.) in THF, $-40°$ to $-20°$, 18 h. *b*) 1N HCl, MeCN, 30 min at r.t. *c*) Boc_2O, Et_3N, CH_2Cl_2, 18 h, r.t. (3 steps, 82% for (2*S*,4*S*)-**24a**). *d*) $LiBH_4$, THF, 16 h, r.t.; 95% (for (2*S*,4*S*)-**19**).

diastereoselectivity for the alkylation reaction with the enantiomeric bromides (*R*)-**11a** and (*S*)-**11b**[20]).

The diethoxy-dihydropyrazine **21** was efficiently prepared by *O*-alkylation of commercially available pyrazine-2,5-dione with 2.5 equiv. of triethyloxonium tetrafluoroborate in CH_2Cl_2 for 18 h at room temperature, according to the protocol described previously [15][16]. The product precipitated from CH_2Cl_2/hexane to furnish white crystals in 76% yield on a 2.5-mol reaction scale.

2.6. *Diastereoselective Alkylation of Nonchiral 2,5-Diethoxy-3,6-dihydropyrazine* **21**. The lithium enolate of **21** was smoothly generated by deprotonation with BuLi in THF at $-75°$ for 20 min, and then treated in slight excess (1.5 equiv.) with (*R*)-**11a** for 18 h at $-20°$. After standard aqueous workup, the ^{1}H-NMR spectra indicated the formation of two inseparable diastereoisomeric products, (2*S*,2′*S*)-**22a** and (2*R*,2′*S*)-**23a** in a *ca.* 95:5 ratio, which were isolated in excellent yield (*Scheme 6*). Conversely, reaction of enantiomeric (*S*)-**11b** with **21** gave a 5:95 ratio of diastereoisomers (2*S*,2′*R*)-**23b** and (2*R*,2′*R*)-**22b** with almost quantitative conversion of the starting alkyl bromide[21]).

The absolute configuration of the major diastereoisomer (2*S*,4*S*)-**22a** was confirmed by transformation to its *N*-Boc-protected amino alcohol derivative (*Scheme 6*) and by comparing the resulting product with the two diastereoisomeric amino alcohols (2*S*,4*S*)-**19** and (2*R*,4*S*)-**20**, which were obtained from the corresponding methyl carboxylates (2*S*,4*S*)-**17** and (2*R*,4*S*)-**18**, respectively (*Scheme 5*). Thus, crude (2*S*,2′*S*)-**22a**/(2*R*,2′*S*)-**23a** was hydrolyzed with 1N HCl in MeCN followed by *N*-Boc protection

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[20]) For the preference for chiral bis-lactim dimethyl ethers over their diethyl analogues as commercial reagents, see [6], footnote 4 therein.

[21]) Condensation of achiral dihydropyrazine **21** (*Scheme 6*) with achiral aldehydes and ketones has been reported to give a single (or a major) diastereoisomeric product of unknown configuration [16].

to provide the amino ester (2*S*,4*S*)-**24a** in a 94.9 : 5.1 mixture (by reversed-phase HPLC on *Nucleosil 5 C18*) with its minor (2*R*,4*S*) epimer (*Scheme 6*). A single recrystallization from hexane afforded diastereoisomerically pure (2*S*,4*S*)-**24a** with a de > 99%. $LiBH_4$ reduction then gave in 95% yield the *N*-Boc-protected amino alcohol (2*S*,4*S*)-**19** as a crystalline solid, which was identical by ^{1}H-NMR to the product obtained from the methyl ester (2*S*,4*S*)-**17** (*vide supra*). In a similar fashion, the 5 : 95 mixture (2*S*,2′*R*)-**23b**/(2*R*,2′*R*)-**22b** was hydrolyzed and *N*-Boc-protected to the enantiomeric (2*R*,4*R*)-**24b**.

The high enantioface preference leading from (*R*)-**11a** and **21** to (2*S*,2′*S*)-**22a** as the predominant isomer (and from (*S*)-**11b** to (2*R*,2′*R*)-**22b**, resp.) can be explained by a transition state analogous to the one depicted in the *Figure*, *a* and *b* (for R = H; MeO replaced by EtO). In this model, a preferred conformation of the electrophile (*R*)-**11a** would be involved in which the bulkiest group at the β-position, *i.e.*, the ^{i}Pr residue, is *anti*-periplanar to the Br-atom and in which the substituted benzyl group is directed towards the less-hindered side of the reactant in its folded conformation (*Fig.*, *a*). On the other hand, the *Re*-facial attack of the electrophile (*Fig.*, *b*) would be much less favored due to steric interference of the substituted benzyl residue with the EtO group of the heterocyclic anion.

It should be emphasised that the remarkably high diastereoselectivity of 95 : 5 obtained for the reaction of **21** with bromides (*R*)-**11a** and (*S*)-**11b** is at least equally good as the stereoselectivity that is often achieved for the alkylation of chiral bis-lactim ethers such as (*R*)-**12a** and (*S*)-**12b** with different electrophiles [6][18–20]. No additional attempts were made at this point to further improve the diastereoselectivity of the alkylation reaction of (*R*)-**11a** or (*S*)-**11b** with dihydropyrazine **21** as an achiral α-amino acid synthon.

2.7. *Upscaled Synthesis of* N-*Boc-Protected Amino Ester (2*S*,4*S*)-***24a*** *with Diethoxydihydropyrazine* **21** *as a Nonchiral Auxiliary.* The stereoselective alkylation of the lithium enolate of **21** with (*R*)-**11a** (*vide supra*, *Sect. 2.6*) was readily amenable to a 1M reaction scale with only minor modifications of the original reaction conditions. Thus, deprotonation of **21** with BuLi and subsequent addition of bromide (*R*)-**11a** was performed at a slightly higher temperature (−40° instead of −75°) without compromising the *ca.* 95 : 5 diastereoisomer product ratio of (2*S*,2′*S*)-**22a** *vs.* (2*R*,2′*S*)-**23a** and the high overall isolated yield[22]). Mild acidic hydrolysis (1N HCl in MeCN) of the crude product mixture afforded the α-amino ethyl ester derivative as an oily residue. The glycine ethyl ester formed from an excess of synthon **21** was readily removed by extractive workup due to the high water solubility of this by-product, thereby avoiding any additional purification step[23]). Single recrystallization of the crude *N*-Boc-protected amino ester (2*S*,4*S*)-**24a** from hexane completely removed the minor (2*R*,4*S*)-diastereoisomer and provided (2*S*,4*S*)-**24a** with high diastereomer excess (de > 99%) and in 82% overall yield from (*R*)-**11a**.

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[22]) Notable amounts of the dialkylation by-products could not be detected in the crude product, indicating that (2*S*,2′*S*)-**22a** and (2*R*,2′*S*)-**23a** are not susceptible to further alkylation *via* lithium enolate formation in the reaction mixture.

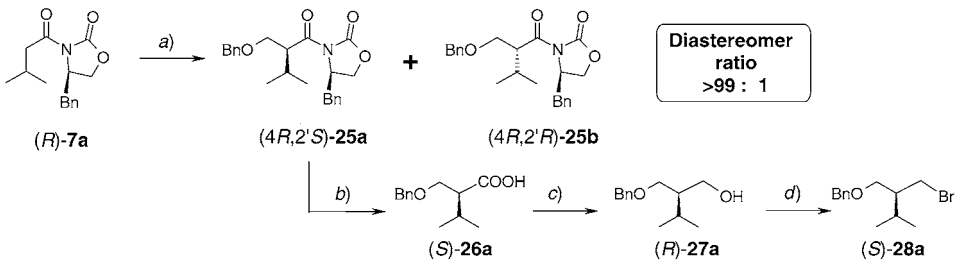
[23]) This is in contrast to the hydrolysis of **13**–**16**, requiring bulb-to-bulb distillation under high vacuum or a tedious FC step to purify the α-amino ester products from the valine methyl ester.

In summary, the new route for the preparation of the enantiomerically pure amino acid derivative (2*S*,4*S*)-**24a** *via* the stereoselective alkylation of the achiral dihydropyrazine **21** proved to be readily amenable to a larger scale. Moreover, it turned out to be superior to the classical chiral *Schöllkopf* approach in terms of practical and economical considerations.

2.8. *Stereoselective Synthesis of Related γ-Branched α-Amino Acids from Achiral Bis-lactim Diethyl Ether* **21**. To further explore the potential scope of application for the achiral synthon **21**, we envisaged the synthesis of the γ-branched *N*-Boc-protected α-amino ester (2*S*,4*S*)-**37a** *via* enantioselective alkylation of the auxiliary with the enantiomerically pure bromide (*S*)-**28a** (see below, *Scheme 9*). The *O*-benzyl-protected (2*S*,4*S*)-**37a**, and its methyl ester analogue (2*S*,4*S*)-**31** (see below, *Scheme 8*), were of major interest to us as intermediates for the synthesis of a novel series of nonpeptide, orally active renin inhibitors [21].

The precursor bromide (*S*)-**28a** was obtained with high enantiomer purity in four steps as shown in *Scheme 7*. Thus, generation of the titanium enolate from (*R*)-**7a** by treatment with $TiCl_4$ in the presence of *Hünig*'s base according to the protocol of *Evans* and co-workers [22], and subsequent reaction with chloromethyl benzyl ether afforded in a $>99:1$ diastereoisomer ratio the desired (4*R*,2′*S*)-**25a** and its more polar (TLC) epimer (4*R*,2′*R*)-**25b**. Purification by silica-gel chromatography and recrystallization from Et_2O/hexane afforded (4*R*,2′*S*)-**25a** with a de $>99\%$ (by reversed-phase HPLC) and in 50% isolated yield. LiOH/H_2O_2-Mediated hydrolysis to the carboxylic acid (*S*)-**26a** proceeded smoothly, which then was reduced by $NaBH_4/I_2$ to the alcohol (*R*)-**27a** in 83% yield (2 steps). Bromination with NBS gave (*S*)-**28a** as a colorless oil in 70% yield (*Scheme 7*), which was found to be unstable on silica gel (as detected by *TLC*). Similarly, the corresponding enantiomer (*R*)-**28b** was obtained in 43% overall yield starting from the chiral auxiliary (*S*)-**7b** (not shown). The enantiomer excess of both alcohol intermediates (*R*)-**27a** and (*S*)-**27b** was determined by HPLC on a *Chiralcel OJ*® chiral stationary phase to be $>99.5\%$ within the detection limits.

Scheme 7

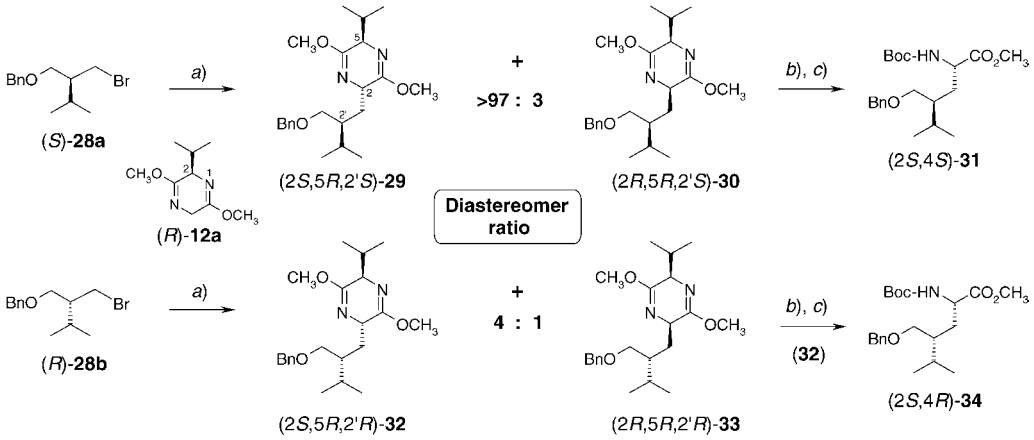


a) $TiCl_4$ (1.05 equiv.), *Hünig*'s base (1.05 equiv.), CH_2Cl_2, 0°; then $BnOCH_2Cl$ (2 equiv.), 0°, 20 h; 50%. *b*) LiOH, 30% aq. H_2O_2 soln., THF, 0° to r.t., 18 h; 92%. *c*) $NaBH_4$, I_2, THF, 0° to r.t., 72 h; 90%. *d*) NBS, Ph_3P, CH_2Cl_2, 0° to r.t., 21 h; 70%.

Alkylation of the chiral *Schöllkopf* reagent (*R*)-**12a** with bromide (*S*)-**28a** proceeded with very high diastereoselectivity of $>97:3$ to give (2*S*,5*R*,2′*S*)-**29** as the major product (*Scheme 8*). Only traces of the minor isomer (2*R*,5*R*,2′*S*)-**30** were detectable by TLC (more polar on silica gel) and were removed easily by FC to afford

diastereoisomerically pure (2*S*,5*R*,2′*S*)-**29** in 90% isolated yield. Standard hydrolysis of the latter and subsequent *N*-Boc protection provided the α-amino acid derivative (2*S*,4*S*)-**31**, which was demonstrated by high-resolution ^{1}H-NMR to be a single diastereoisomer (de > 99%).

Scheme 8

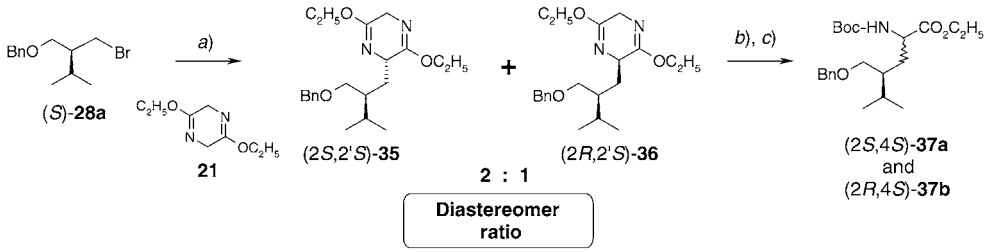


a) (2*R*)-**12a** (1.5 equiv.), BuLi (1.5 equiv.), THF, −75°; then (*S*)-**28a** or (*R*)-**28b** (1.0 equiv.) in THF, −75° to −18°, 64 h; 90% ((2*S*,5*R*,2′*S*)-**29**/(2*R*,5*R*,2′*S*)-**30** and 93% (2*S*,5*R*,2′*R*)-**32**/(2*R*,5*R*,2′*R*)-**33**). *b*) 1N HCl, MeCN, r.t. *c*) Boc_2O, Et_3N, CH_2Cl_2, r.t., 16 h, 72% ((2*S*,4*S*)-**31**; 2 steps) and 86% (2*S*,4*R*)-**34**).

Interestingly, poor 4:1 diastereoselectivity was observed for the reaction of (*R*)-**12a** with the bromide (*R*)-**28b** of opposite absolute configuration (*Scheme 8*). Separation by silica-gel chromatography furnished the major (2*S*,5*R*,2′*R*)-**32** and its epimer (2*R*,5*R*,2′*R*)-**33** in 93% overall yield. Transformation of (2*S*,5*R*,2′*R*)-**32** to the protected amino ester (2*S*,4*R*)-**34**, as described above for (2*S*,4*S*)-**31**, eventually afforded a single diastereoisomeric product (by comparison of its ^{1}H-NMR spectra with that of (2*S*,4*S*)-**31**). The substantial formation of the 'mismatched' alkylation product (2*R*,5*R*,2′*R*)-**33** on reaction of the bis-lactim ether (*R*)-**12a** and bromide (*R*)-**28b** suggested again that the MeO group at C(6) of the bis-lactim ether plays a role in the diastereofacial control additionally to the 'shielding' effect of the ^{i}Pr group at C(2) (*Fig.*).

Reaction of bromide (*S*)-**28a** with the lithium enolate of the diethoxy-dihydropyrazine **21** under standard conditions afforded a *ca.* 2:1 mixture (by ^{1}H-NMR) of the inseparable diastereoisomers (2*S*,2′*S*)-**35** and (2*R*,2′*S*)-**36** in 89% isolated yield (*Scheme 9*). The absolute configuration of the predominant alkylation product (2*S*,2′*S*)-**35** was unambiguously assigned after transformation of (2*S*,2′*S*)-**35**/(2*R*,2′*S*)-**36** to the inseparable *N*-Boc-protected ethyl esters (2*S*,4*S*)-**37a** and (2*R*,4*S*)-**37b** and comparison of the ^{1}H-NMR spectrum with that of the corresponding methyl ester analogues (2*S*,4*S*)-**31** and (2*S*,4*R*)-**34**. In particular, the chemical shifts of the signals for the NH and $C_6H_5CH_2O$ group of the major isomer (2*S*,4*S*)-**37a** were identical with that

Scheme 9



a) **21** (1.5 equiv.), BuLi (1.4 equiv.), THF, −40°; then (*S*)-**28a** (1.0 equiv.) in THF, −40° to −18°, 16 h; 89% ((2*S*,2′*S*)-**35**/(2*R*,2′*S*)-**36**). *b*) 1N HCl, MeCN, r.t. *c*) Boc_2O, Et_3N, CH_2Cl_2, r.t., 16 h; 94% for (2*S*,4*S*)-**37a**/(2*R*,4*S*)-**37b** (2 steps).

of (2*S*,4*S*)-**31**, and clearly differed from that of the isomer (2*S*,4*R*)-**34**[24]). Unfortunately, compounds (2*S*,2′*S*)-**35**/(2*R*,2′*S*)-**36** and (2*S*,4*S*)-**37a**/(2*R*,4*S*)-**37b** were obtained only as oily products, which prohibited further purification by recrystallization.

The moderate diastereoselectivity obtained for the reaction of the benzyloxy derivative (*S*)-**28a** with **21**, forming the alkylation products (2*S*,2′*S*)-**35** and (2*R*,2′*S*)-**36** in only a 2:1 ratio, could be simply explained by the lower steric demand of the electrophile (*S*)-**28a** (*cf. Fig.*), as compared to (*R*)-**11a**, although other reasons, such as electronic effects induced by the side-chain-ether O-atom in (*S*)-**28a**, cannot be excluded.

3. Conclusions and Outlook. – The explicitly high diastereoselectivity (ds > 98%) observed for the 'matched' alkylation reaction between the chiral *Schöllkopf* dihydropyrazine (*R*)-**12a** and the sterically hindered, enantiomerically pure bromide (*R*)-**11a**, and, conversely, the complete lack of stereo-induction for the same reaction between (*S*)-**12b** and (*R*)-**11a** ('mismatched') strongly suggested that the MeO residue at C(6) of the reagent exerted a strong diastereofacial control in addition to the chirality of the auxiliary (*Scheme 4*, *Fig.*). These considerations provided the rationale that led us to investigate the stereochemical course for the alkylation of the achiral auxiliary **21** with alkyl bromides (*R*)-**11a** and (*S*)-**11b** (*Scheme 6*), and in addition with the related sterically less-demanding (*S*)-**28a** (*Scheme 9*). As demonstrated by the high diastereoisomer ratio of 95:5 for products (2*S*,2′*S*)-**22a**/(2*R*,2′*S*)-**23a** (*vice versa*, 5:95 for the enantiomeric (2*S*,2′*R*)-**23b**/(2*R*,2′*R*)-**22b**), this previously unrecognized directing effect by the EtO group of **21** may become predominant even over the shielding effect of the C(2) alkyl residue of the classical *Schöllkopf* auxiliary (*R*)-**12a**.

No further efforts towards improvement of the alkylation diastereoselectivity by optimizing the reaction parameters (*e.g.*, variation of the base, solvent, temperature, *etc.*) or by changing the leaving group of the electrophile were made at this stage of our work. The effect of the leaving group on the diastereoselectivity for the alkylation of the chiral *Schöllkopf* auxiliary has been investigated recently by employing various

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[24]) The absence of rotamer signals was established by temperature-dependent ^{1}H-NMR measurements in various solvents such as (D_6)DMSO and (D_6)benzene [9].

achiral bromide, tosylate, and diphenyl phosphate electrophiles [18], demonstrating the tosylate to be superior over the bromide with respect to diastereoselectivity and isolated yield in almost all studied cases. On the other hand, the proper choice of the dialkoxy substituents of modified dihydropyrazines may be beneficial to improve the alkylation diastereoselectivity, *e.g.*, by incorporating bulkier branched alkyl groups, without compromising the overall reactivity of the synthon enolate with a sterically demanding electrophile.

Furthermore, the achiral synthon **21** may find successful application for the stereoselective synthesis of optically active unnatural amino acid derivatives by other transformations, including the aldol reaction with chiral aldehydes, ketones, and epoxides for the preparation of enantiomerically pure β-hydroxy amino acids [20][23][25]), asymmetric acylation of lithiated bis-lactim ethers [5], and conjugate addition reactions [24]. In general, a more-detailed study of the structural requirements which are essential to control the stereoselectivity of reactions with the achiral dihydropyrazine synthon should confirm this methodology as a potentially versatile principle in future work.

The highly stereoselective and efficient alkylation of the achiral bis-lactim ether **21** with the highly substituted, enantiomerically pure alkyl bromide (*R*)-**11a**, and subsequent hydrolysis followed by *N*-Boc protection provided an economic and practical protocol for the preparation on a multi-100-g scale of the α-amino acid derivative (2*S*,4*S*)-**24a**, a synthetic intermediate of a novel class of orally active renin inhibitors such as aliskiren (**1**), which is currently under clinical investigation.

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Experimental Part

General. All commercial chemicals were reagent grade and used without further purification, if not otherwise stated. Low-temp. reactions were carried out under Ar. THF was distilled over potassium/benzophenone. TLC: precoated silica gel *60* F_{254} glass plates (*E. Merck*); visualization: UV (254 nm), I_2 chamber, or CPS staining (reagent: soln. of phosphomolybdic acid hydrate (25 g), cerium(IV) sulfate (10 g), and conc. H_2SO_4 soln. (60 ml) in H_2O (1 l). Flash chromatography (FC): silica gel *60* (0.04–0.063 mm; *E. Merck*). Reversed-phase HPLC: *Kontron-Instruments 322* system with autosampler *465*; *C18-Nucleosil®* (5 μm) column (l = 25 cm; d = 0.46 cm); gradient MeCN/H_2O/CF_3COOH 20:80:0.1 → 100:0:0.1 within 20 min; if not stated otherwise; t_R in min. M.p.: uncorrected; *Büchi 510*. $[\alpha]_D$: *Perkin-Elmer 291* polarimeter; l = 10 cm, c in g/100 ml; at 22° or 25°. IR Spectra: *Perkin-Elmer-983* spectrometer. ^{1}H-NMR Spectra: *Varian Gemini-200* (200 MHz) or *Gemini-300* (300 MHz) spectrometer; if not otherwise stated, all spectra in $CDCl_3$; δ in ppm rel. to nondeuterated solvent $CHCl_3$ (= 7.27 ppm), J in Hz. ^{13}C-NMR Spectra: *Bruker AM-360* spectrometer (90 MHz); δ in ppm rel. to $CHCl_3$ (= 77.0 ppm); ^{13}C multiplicities from DEPT spectra. Fast atom bombardment (FAB) MS: *ZAB-HF* mass spectrometer with thioglycerol as matrix; only selected peaks are indicated, in m/z (%). Elemental analysis: *Perkin-Elmer PE-240*; measured values are within ±0.4% of the calculated values for C, H, and N.

4-Methoxy-3-(3-methoxypropoxy)benzaldehyde (**4**). To a mixture of 3-hydroxy-4-methoxybenzaldehyde (**2**; 200 g, 1.32 mol) and MeCN were added K_2CO_3 (272.3 g, 1.973 mol) and 1,3-dibromopropane (1.34 l, 13.2 mol). The resulting mixture was refluxed for 19 h. After cooling, the solid was filtered followed by evaporation of the solvent and excess 1,3-dibromopropane. The residue was purified by FC (silica gel, AcOEt/hexane 1:3): 334 g (93%) of *3-(3-bromopropoxy)-4-methoxybenzaldehyde* (**3**). Solid. M.p. 61–62°. TLC

[25]) For aldol-type reactions with zinc or tin(II) aza-enolates of chiral dihydropyrazines, see [23b].

(hexane/AcOEt 3:1): R_f 0.50. IR (CH_2Cl_2): 3051*w*, 2842*w*, 1687*s*, 1596*m*, 1586m, 1510*s*, 1435*m*, 1395*m*, 1135*s*, 1022*m*. ^{1}H-NMR ((D$_6$)DMSO): 9.85 (*s*, 1 H); 7.60 (*dd*, *J* = 2, 8, 1 H); 7.44 (*d*, *J* = 2, 1 H); 7.21 (*d*, *J* = 8, 1 H); 4.15 (*t*, *J* = 7, 2 H); 3.90 (*s*, 3 H); 3.70 (*t*, *J* = 7, 2 H); 2.30 (*m*, 2 H). Anal. calc. for $C_{11}H_{13}BrO_3$ (273.13): C 48.37, H 4.80, Br 29.26; found: C 48.61, H 4.84, Br 29.19.

To a soln. of **3** (844 g, 3.09 mol) in MeOH (4.15 l) was added dropwise 30% NaOMe soln. in MeOH (0.86 l, 4.64 mol) at 61–64°. After stirring an additional 1.5 h at reflux temp., the mixture was cooled to r.t., and H_2O (180 ml) was added. Subsequently, MeOH (*ca.* 3 l) was partially removed *in vacuo* (at 35°), and the residue was partitioned between Et_2O (3 × 3 l) and ice-cooled 4N HCl. The org. phases were washed with H_2O and sat. aq. $NaHCO_3$ soln., combined, dried ($MgSO_4$), and evaporated. The residue was purified by FC (silica gel, hexane/AcOEt 3:1): 498 g (72%) of pure **4**. Oil. TLC (hexane/AcOEt 2:1): R_f 0.18. IR (CH_2Cl_2): 3020–2840*w*, 1686*s*, 1596*m*, 1586*m*, 1510*s*, 1441*m*, 1135*s*, 1021*m*. ^{1}H-NMR ((D$_6$)DMSO): 9.85 (*s*, 1 H); 7.57 (*dd*, *J* = 8, 2, 1 H); 7.40 (*d*, *J* = 2, 1 H); 7.18 (*d*, *J* = 8, 1 H); 4.08 (*t*, *J* = 7, 2 H); 3.88 (*s*, 3 H); 3.49 (*t*, *J* = 7, 2 H); 3.26 (*s*, 3 H); 1.95 (*m*, 2 H).

4-Methoxy-3-(3-methoxypropoxy)benzenemethanol (**5**). To a soln. of **4** (336 g, 1.50 mol) in MeOH (3.36 l) at 0° was added in portions $NaBH_4$ (39.7 g, 1.05 mol) while the temp. was maintained at 0–5°. The mixture was stirred for 60 min at r.t. and then evaporated. The residue was partitioned between ice-cooled 2N HCl and AcOEt (3 × 2 l). The org. layers were washed with H_2O and sat. aq. $NaHCO_3$ soln., combined, dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 96:4) afforded pure **5** (326 g, 96%). Oil. TLC (AcOEt/hexane 2:1): R_f 0.31. IR (CH_2Cl_2): 3602*w*, 3046*w*, 2935–2880*m*, 1605*w*, 1592*w*, 1515*s*, 1464*m*, 1442*m*, 1426*m*, 1235*m*, 1138*s*, 1026*m*. ^{1}H-NMR: 6.8–6.95 (*m*, 3 H); 4.58 (*d*, *J* = 5.4, 2 H); 4.11 (*t*, *J* = 6.5, 2 H); 3.84 (*s*, 3 H); 3.56 (*t*, *J* = 6.5, 2 H); 2.33 (*s*, 3 H); 2.11 (*m*, 2 H); 1.95 (*t*, *J* = 5.4, 1 H). Anal. calc. for $C_{12}H_{18}O_4$ (226.27): C 63.70, H 8.02; found: C 63.70, H 8.24.

4-Methoxy-3-(3-methoxypropoxy)benzyl Bromide (=*4-(Bromomethyl)-1-methoxy-3-(3-methoxypropoxy)-benzene*; **6**). To a soln. of **5** (111 g, 0.50 mol) in $CHCl_3$ (1.3 l) was added dropwise (5 min) Me_3SiBr (97 ml, 0.75 mol) at 20–25° (ice-bath cooling). After stirring for additional 10 min at r.t., the mixture was evaporated and the residue immediately purified by FC (hexane/AcOEt 3:1): 144.5 g (quant.) of pure **6**[26]). White solid. M.p. 50–51° (from hexane). TLC (hexane/AcOEt 2:1): R_f 0.34. IR (CH_2Cl_2): 2935–2835*w*, 1604*w*, 1590*w*, 1517*s*, 1464*m*, 1442*m*, 1426*m*, 1240*m*, 1211*s*, 1141*s*, 1025*m*. ^{1}H-NMR: 6.93 (*m*, 2 H); 6.80 (*d*, *J* = 8, 1 H); 4.48 (*s*, 2 H); 4.12 (*t*, *J* = 7, 2 H); 3.85 (*s*, 3 H); 3.56 (*t*, *J* = 7, 2 H); 3.35 (*s*, 3 H); 2.10 (*m*, 2 H). Anal. calc. for $C_{12}H_{17}BrO_3$ (289.17): C 49.84, H 5.93, Br 27.63; found: C 50.27, H 6.11, Br 27.04.

*(2*R*)-2-[4-Methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutanoic Acid* (=*(α*R*)-4-Methoxy-3-(3-methoxypropoxy)-α-(1-methylethyl)benzenepropanoic Acid*; (*R*)-**9a**). To a stirred soln. of 1M LiHMDS in anh. THF (600 ml, 0.60 mol) at −70° was added dropwise a soln. of (*R*)-**7a** [7] (156.6 g, 0.60 mol) in THF (500 ml). The mixture was stirred for an additional 75 min at −70°. Then, a soln. of **6** (145 g, 0.50 mol) in THF (500 ml) was added, and the temp. was raised from −70° to 0° during 2 h. After stirring for 18 h at 0°, the reaction was quenched by addition of 10% aq. NH_4Cl soln. (250 ml). Volatiles were removed *in vacuo*, and the product was extracted with AcOEt (3 × 1.2 l). The org. layers were washed with brine (1.2 l), dried ($MgSO_4$), and evaporated. FC (hexane/AcOEt 1:1) and recrystallization gave *(4*R*)-3-{(2*R*)-2-{[4-methoxy-3-(methoxypropoxy)phenyl]methyl}-3-methyl-1-oxobutyl}-4-(phenylmethyl)oxazolidin-2-one* ((2′*R*,4*R*)-**8a**; 202 g, 86%). Solid. M.p. 55–56° (from Et_2O/hexane). TLC (hexane/AcOEt 2:1): R_f 0.29. IR (CH_2Cl_2): 2960–2840*w*, 1777*s*, 1694*m*, 1605w, 1590*w*, 1515*m*, 1442*w*, 1387*m*, 1349*w*, 1234*m*. ^{1}H-NMR: 7.21 (*m*, 3 H); 6.75–6.95 (*m*, 5 H); 4.58 (*m*, 1 H); 4.27 (*m*, 1 H); 4.07 (*t*, *J* = 7, 2 H); 3.9–4.05 (*m*, 2 H); 3.78 (*s*, 3 H); 3.51 (*t*, *J* = 7, 2 H); 3.30 (*s*, 3 H); 2.75–3.0 (*m*, 3 H); 2.15–2.25 (*dd*, *J* = 14, 11, 1 H); 2.07 (*t*, *J* = 6.5, 2 H); 1.95–2.05 (*m*, 1 H); 1.05 (*m*, 6 H). Anal. calc. for $C_{27}H_{35}NO_6$ (469.58): C 69.06, H 7.51, N 2.98; found: C 68.64, H 7.66, N 3.04.

To a soln. of (2′*R*,4*R*)-**8a** (300 g, 0.639 mol) in THF/H_2O 3:1 (4.8 l), cooled in an ice bath, were added 30% aq. H_2O_2 soln. (434 ml, 3.83 mol) and LiOH (31.2 g, 1.28 mol). The mixture was stirred at 20° for 3 h, followed by cooling to 0°. Then, 1.5M aq. Na_2SO_3 (2.55 l, 3.83 mol) was added dropwise within 30 min (*CAUTION: check for complete removal of residual peroxides before concentrating the mixture!*). After addition of sat. aq. $NaHCO_3$ soln. (1 l), volatiles were evaporated, and the aq. phase was washed with CH_2Cl_2 (3 × 3 l). The aq. layer was adjusted to pH 3 by adding 2N HCl, followed by CH_2Cl_2 extraction (3 × 3 l). The org. phase was dried ($MgSO_4$) and evaporated: (*R*)-**9a** (187 g, 94%). Oil; a fraction of this material crystallized from Et_2O/hexane at −20°. M.p. 43.5–44°. TLC (AcOEt/hexane 2:1): R_f 0.30. $[\alpha]_D^{25}$ + 42.1 (*c* = 1, CH_2Cl_2). IR (CH_2Cl_2): 3300–3000 (br.), 2962*m*, 2935*m*, 2880*m*, 1740*m*, 1705*s*, 1608*w*, 1590*w*, 1515*s*, 1235*s*, 1140*s*, 1027*m*. ^{1}H-NMR: 6.65–6.80 (*m*, 3 H);

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[26]) For the instability of compound **6** on metal surfaces, see *Footnote 7*.

4.10 (t, J = 7, 2 H); 3.82 (s, 3 H); 3.56 (t, J = 7, 2 H); 3.35 (s, 3 H); 2.78 (m, 2 H); 2.40–2.50 (m, 1 H); 2.07 (m, 2 H); 1.85–2.0 (m, 1 H); 1.03 (m, 6 H). Anal. calc. for $C_{17}H_{26}O_5$ (310.39): C 65.78, H 8.44; found: C 65.96, H 8.70.

(2S)-2-[4-Methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutanoic Acid ((*S*)-**9b**). As described for (*R*)-**9a**, with 1M LiHMDS in THF (72 ml, 72.0 mmol), (*S*)-**7b** (18.8 g, 72.0 mmol), and **6** (17.3 g, 60.0 mmol). Quenching with sat. aq. NH_4Cl soln. and extractive workup gave pure (2′*S*,4*S*)-**8b** as a yellow oil (33 g, crude), which was used in the next step without further purification. TLC (hexane/AcOEt 2:1): R_f 0.28. ^{1}H-NMR: 7.1–7.2 (m, 3 H); 6.65–6.90 (m, 5 H); 4.65 (m, 1 H); 4.26 (m, 1 H); 3.95 (t, J = 7, 2 H); 3.95–4.15 (m, 2 H); 3.68 (s, 3 H); 3.41 (t, J = 7, 2 H); 3.19 (s, 3 H); 2.45–2.85 (m, 4 H); 1.8–2.0 (m, 3 H); 0.98 (m, 6 H).

Crude (2′*S*,4*S*)-**8b** (33.0 g) was hydrolyzed as described for (*R*)-**9a**: crude (*S*)-**9b** (17.0 g, 91%). Pale yellow oil. ^{1}H-NMR: identical to that of (*R*)-**9a**.

(2R)-2-[4-Methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl Bromide (=*4-[(2R)-2-(Bromomethyl)-3-methylbutyl]-1-methoxy-2-(3-methoxypropoxy)benzene*; (*R*)-**11a**). A soln. of (*R*)-**9a** (186 g, 0.60 mol) in THF (0.50 l) was added to a suspension of $NaBH_4$ (27.2 g, 0.72 mol) in THF (1.50 l) at r.t. over 10 min. The mixture was stirred until gas evolution ceased (45 min). A soln. of I_2 (76.2 g, 0.30 mol) in THF (1.0 l) was added slowly, and the mixture was then stirred for 4 days at r.t. MeOH (1.0 l) was added carefully over 20 min, followed by stirring for 30 min and evaporation of volatiles. The residue was extracted with AcOEt (3 × 2 l). The org. layers were washed with 2N HCl (2 l), H_2O (2 l), sat. aq. $Na_2S_2O_3$ soln. (2 l), H_2O (2 l), 0.1N NaOH (1 l), and brine and evaporated. The crude product was purified by FC (silica gel, AcOEt/hexane 1:1): 160 g (90%) of *(αR)-4-methoxy-3-(3-methoxypropoxy)-α-(1-methylethyl)benzenepropanol* (*R*)-**10a**. Oil. TLC (AcOEt/hexane 1:1): R_f 0.27; IR (CH_2Cl_2): 3618*w*, 2959*m*, 2930*m*, 2870*m*, 1589*w*, 1514*s*, 1465*m*, 1442*m*, 1422*m*, 1234*m*, 1140*m*, 1030*m*. ^{1}H NMR: 6.70–6.8 (m, 3 H); 4.10 (t, J = 7, 2 H); 3.85 (s, 3 H); 3.70 (m, 4 H); 3.35 (s, 3 H); 2.65 (dd, J = 13, 4, 1 H); 2.45 (dd, J = 13, 8, 1 H); 2.10 (m, 2 H); 1.86 (m, 1 H); 1.62 (m, 1 H); 1.15 (t, J = 7, 1 H); 0.96 (m, 6 H). Anal. calc. for $C_{17}H_{28}O_4$ (296.41): C 68.89, H 9.52; found: C 68.34, H 9.49.

To a soln. of (*R*)-**10a** (102.2 g, 0.345 mol) in CH_2Cl_2 (2 l) at 0°, Ph_3P (108.6 g, 0.414 mol) and NBS (73.7 g, 0.414 mol) were added in portions. After stirring for 18 h at r.t., the mixture was evaporated and the residue purified by FC (silica gel, hexane/AcOEt 4:1): 120.2 g (97%) of **11a**. White solid. M.p. 52–53° (from Et_2O/hexane). TLC (AcOEt/hexane 1:1): R_f 0.56. IR (CH_2Cl_2): 2960*m*, 2935*m*, 2878*m*, 1589*w*, 1514*s*, 1465*m*, 1442*m*, 1236*m*, 1140*m*, 1119*m*, 1028*m*. ^{1}H NMR ($CDCl_3$): 6.7–6.85 (m, 3 H); 4.10 (t, J = 7, 2 H); 3.84 (s, 3 H); 3.58 (t, J = 7, 2 H); 3.26–3.45 (m, 2 H); 3.35 (s, 3 H); 2.77 (dd, J = 15, 3, 1 H); 2.48 (dd, J = 15, 8, 1 H); 2.10 (m, 2 H); 1.86 (m, 1 H); 1.60 (m, 1 H); 1.00 (m, 6 H). Anal. calc. for $C_{17}H_{27}BrO_3$ (359.30): C 56.83, H 7.57, Br 22.24; found: C 56.81, H 7.34, Br 22.06.

(2S)-2-[4-Methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl Bromide ((*S*)-**11b**). As described for (*R*)-**11a**, with crude (*S*)-**9b** (16.5 g, 53.2 mmol), THF (220 ml), $NaBH_4$ (2.41 g, 63.8 mmol), and I_2 (6.75 g, 26.6 mmol): (*S*)-**10b** (15.5 g, 100%). Pale yellow oil. TLC (AcOEt/hexane 1:1): R_f 0.27.

Crude (*S*)-**10b** (14.8 g, 50.0 mmol) was treated without further purification with NBS (10.7 g, 60 mmol), CH_2Cl_2 (290 ml), and Ph_3P (15.7 g, 60.0 mmol): (*S*)-**11b** (16.6 g, 100%). Colorless oil, which solidified on storage. ^{1}H-NMR ((D_6)DMSO): 6.87 (d, J = 11, 1 H); 6.78 (d, J = 1.5, 1 H); 6.70 (q, J = 11, 1.5, 1 H); 3.98 (t, J = 7.5, 2 H); 3.73 (s, 3 H); 3.44–3.48 (m, 3 H; t at 3.46, J = 7.5); 3.34 (dd, J = 13, 7, 1 H); 3.23 (s, 3 H); 2.71 (dd, J = 17, 7.5, 1 H); 2.38 (dd, J = 17, 9.5, 1 H); 1.93 (m, 2 H); 1.76 (m, 1 H); 1.71 (m, 1 H); 0.94 (t, J = 7.5, 6 H).

Enantiomer-Excess (ee) *Determination by Chiral HPLC*. Complete enantiomer separation of the alcohol intermediates (*R*)-**10a** and (*S*)-**10b**, as well as of the bromides (*R*)-**11a** and (*S*)-**11b**, was achieved by HPLC (*Chiralpak AD*® column (25 cm × 4.6 mm), flow rate 1.0 ml/min, 30 bar pressure, UV detection at 230 nm). Eluent hexane/^{i}PrOH 95:5: t_R 17.8 for (*S*)-**10b** and t_R 19.4 for (*R*)-**10a**. Eluent hexane/^{i}PrOH 98:2: t_R 7.6 for (*R*)-**11a** and t_R 8.4 for (*S*)-**11b**. The ee of (*R*)-**10a** and (*S*)-**10b**, prepared as described above, was determined by HPLC analyses to be 98.8 and 98.2%, resp. A similar ee (>97%) was determined for (*R*)-**11a**.

(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-{(2S)-2-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-3-methylbutyl}-5-(1-methylethyl)pyrazine ((2*S*,5*R*,2′*S*)-**13a**). To a soln. of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazine ((*R*)-**12a**; 51.3 g, 0.279 mol) in THF (0.5 l) at −75° was added dropwise 1.6M BuLi in hexane (174 ml, 0.279 mol) during 45 min. After additional stirring for 30 min at −75°, a soln. of (*R*)-**11a** (66.8 g, 0.186 mol) in THF (0.3 l) was added dropwise over 30 min. The mixture was stirred for 2 h at −75° and then for 18 h at −20°. After evaporation, the residue was partitioned between AcOEt (3 × 1 l) and H_2O (3 × 1 l). The org. layers were washed with brine (1 l), combined, dried ($MgSO_4$), and evaporated. The residue was dried under high vacuum (50°/0.02 bar) to remove excess (*R*)-**12** and purified by FC (AcOEt/hexane 1:5): crude (2*S*,5*R*,2′*S*)-**13a** (78.0 g, 91%). Reversed-phase HPLC: only traces of (2*R*,5*R*,2′*S*)-**14a** present in the crude product. Oil. TLC (hexane/AcOEt 2:1): R_f 0.34. ^{1}H-NMR: 6.65–6.80 (m, 3 H); 4.10 (t, J = 7, 2 H); 3.90–4.0

(*m*, 2 H); 3.83 (*s*, 3 H); 3.69 (*s*, 6 H); 3.57 (*t*, *J* = 7, 2 H); 3.35 (*s*, 3 H); 2.70 (*dd*, *J* = 4, 13.5, 1 H); 2.42 (*dd*, *J* = 7.5, 13.5, 1 H); 2.28 (*m*, 1 H); 2.10 (*m*, 2 H); 1.85 (*m*, 1 H); 1.45–1.70 (*m*, 3 H); 1.04 (*d*, *J* = 7, 3 H); 0.80 (*m*, 6 H); 0.65 (*d*, *J* = 7, 3 H). FAB-MS: 463 (100, $[M+H]^+$), 419 (60), 209 (35), 183 (60), 141 (85).

*(2*S*,5*S*)- and (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-{(2*S*)-2-{[4-methoxy-3-(3-methoxypropoxy)phenyl]-methyl}-3-methylbutyl}-5-(1-methylethyl)pyrazine* ((2*S*,5*S*,2′*S*)-**16b** and (2*R*,5*S*,2′*S*)-**15b**, resp.). As described for (2*S*,5*R*,2′*S*)-**13a**, with (*S*)-**12b** (2.4 g, 13.3 mmol), THF (20 ml), 1.6M BuLi in hexane (8.2 ml, 13.3 mmol), (*R*)-**11a** (3.2 g, 9.9 mmol), and THF (20 ml); at −75° for 2 h and at −20° for 48 h: (2*S*,5*S*,2′*S*)-**16b**/(2*R*,5*S*,2′*S*)-**15b** 43:57 as a yellow oil (5.9 g) containing unreacted starting materials. Separation of both diastereoisomers was achieved by FC (hexane/AcOEt 5:1) of the crude product and repeated chromatography of enriched fractions.

*Data of (2*S*,5*S*,2′*S*)*-**16b**: Pale yellow oil (1.05 g, 26%). TLC (hexane/AcOEt 4:1): R_f 0.18. ^{1}H-NMR: 6.7–6.8 (*m*, 3 H); 4.09 (*t*, *J* = 6.5, 2 H); 3.9–4.0 (*m*, 2 H); 3.83 (*s*, 3 H); 3.66 (*s*, 3 H); 3.65 (*s*, 3 H); 3.56 (*t*, *J* = 6.5, 2 H); 3.48 (*s*, 3 H); 2.69 (*dd*, *J* = 4.5, 14, 1 H); 2.46 (*dd*, *J* = 7.5, 14, 1 H); 2.0–2.15 (*m*, 4 H); 1.65–1.75 (*m*, 2 H); 1.36 (*m*, 1 H); 1.03 (*d*, *J* = 7, 3 H); 0.81 (*d*, *J* = 7, 3 H); 0.80 (*d*, *J* = 7, 3 H); 0.73 (*d*, *J* = 7, 3 H). ^{13}C-NMR ($CDCl_3$): 164.4; 162.5; 148.0; 147.3; 134.4; 121.1; 114.4; 111.6; 69.2 (CH_2); 65.8 (CH_2); 60.8; 58;3; 55.8; 53.5; 51.9; 51.8; 41.3; 36.6 (CH_2); 35.8 (CH_2); 31.3; 29.4 (CH_2); 28.1; 19.9 (Me); 19.2 (Me); 17.4 (Me); 16.9 (Me). FAB-MS: 463 (100, $[M+H]^+$), 419 (70), 209 (45), 183 (50), 141 (85).

*Data of (2*R*,5*S*,2′*S*)*-**15b**: Pale yellow oil (1.13 g, 28%; containing 10–15% of (2*S*,5*S*,2′*S*)-**16b** by ^{1}H-NMR). TLC (hexane/AcOEt 4:1): R_f 0.13. ^{1}H-NMR: 6.65–6.8 (*m*, 3 H); 4.06 (*t*, *J* = 6.5, 2 H); 4.02 (*m*, 1 H); 3.69 (*m*, 1 H); 3.84 (*s*, 3 H); 3.65 (*s*, 3 H); 3.62 (*s*, 3 H); 3.58 (*t*, *J* = 6.5, 2 H); 3.35 (*s*, 3 H); 2.51 (*dd*, *J* = 4, 14, 1 H); 2.36 (*dd*, *J* = 7.5, 14, 1 H); 2.27 (*m*, 1 H); 2.10 (*m*, 2 H); 1.75–1.9 (*m*, 3 H); 1.35 (*m*, 1 H); 1.03 (*d*, *J* = 7, 3 H); 0.91 (*d*, *J* = 7, 3 H); 0.86 (*d*, *J* = 7, 3 H); 0.68 (*d*, *J* = 7, 3 H). ^{13}C-NMR ($CDCl_3$): 164.4; 163.0; 148.2; 147.5; 134.8; 121.3; 114.4; 111.9; 69.4 (CH_2); 66.1 (CH_2); 60.5; 58.6; 56.2; 54.3; 52.2 (2C); 41.6; 36.6 (CH_2); 34.8 (CH_2); 31.5; 29.7 (CH_2); 27.8; 19.1 (Me); 16.6 (2 Me); 16.2 (Me). FAB-MS: 463 (90, $[M+H]^+$), 419 (100), 209 (45), 183 (35), 141 (95).

*(2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-{(2*R*)-2-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-3-methylbutyl}-5-(1-methylethyl)pyrazine* ((2*R*,5*S*,2′*R*)-**13b**). As described for (2*S*,5*R*,2′*S*)-**13a**, with (*S*)-**12b** (553 mg, 3.0 mmol), THF (10 ml), 1.6M BuLi in hexane (1.88 ml, 3.0 mmol), (*S*)-**11b** (719 mg, 2.0 mmol), and THF (6 ml); at −75° for 2 h and at −20° for 16 h. FC (silica gel (20 g), hexane/AcOEt 2:1) afforded pure (2*R*,5*S*,2′*R*)-**13b** (630 mg, 68%). Pale yellow oil. TLC (hexane/AcOEt 2:1): R_f 0.71. ^{1}H-NMR ((D$_6$)DMSO): 6.6–6.9 (*m*, 3 H); 3.9–4.0 (*m*, 4 H); 3.71 (*s*, 3 H); 3.64 (*s*, 3 H); 3.60 (*s*, 3 H); 3.46 (*t*, *J* = 7, 2 H); 3.24 (*s*, 3 H); 2.60 (*dd*, *J* = 4.5, 15, 1 H); 2.38 (*dd*, *J* = 8, 15, 1 H); 2.20 (*m*, 1 H); 3.92 (*m*, 2 H); 1.55–1.8 (*m*, 3 H); 1.46 (*m*, 1 H); 1.00 (*d*, *J* = 7, 3 H); 0.78 (*d*, *J* = 7, 3 H); 0.74 (*d*, *J* = 7, 3 H); 0.60 (*d*, *J* = 7, 3 H).

*(2*S*,5*R*)- and (2*R*,5*R*)-2,5-Dihydro-3,6-dimethyl-2-{(2*R*)-2-[[4-methoxy-3-(3-methoxypropoxy)phenyl]-methyl}-3-methylbutyl}-5-(1-methylethyl)pyrazine* ((2*S*,5*R*,2′*R*)-**15a** and (2*R*,5*R*,2′*R*)-**16a**, resp.). As described for (2*S*,5*R*,2′*S*)-**13a**; with (*R*)-**12a** (8.29 g, 45 mmol), THF (70 ml), 1.6M BuLi in hexane (28.1 ml, 45 mmol), (*S*)-**11b** (10.8 g, 30 mmol), and THF (70 ml); at −75° for 2 h and at −20° for 16 h. FC (0.5 kg, CH_2Cl_2/Et_2O 20:1) afforded (2*S*,5*R*,2′*R*)-**15a** (2.72 g, 20%) and (2*R*,5*R*,2′*R*)-**16a** (3.07 g, 22%). Pale yellow oils. ^{1}H-NMR: identical to those of the corresponding enantiomers (2*R*,5*S*,2′*S*)-**15b** and (2*S*,5*S*,2′*S*)-**16b**, resp.

Compounds (2*R*,5*R*,2′*R*)-**16a** and (2*S*,5*R*,2′*R*)-**15a** were derivatized to the *N*-Boc-protected amino alcohols (2*R*,4*R*)-**19** (white crystals; $[\alpha]_D^{25} = -5.1$ (*c* = 1, $CHCl_3$)) and (2*S*,4*R*)-**20** (colorless oil), as described below for (2*S*,4*S*)-**19** and (2*R*,4*S*)-**20**.

*Methyl (2*S*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexanoate* (= *Methyl (α*S*,γ*S*)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-4-methoxy-3-(3-methoxypropoxy)-γ-(1-methylethyl)benzenepentanoate*; (2*S*,4*S*)-**17**). To a stirred soln. of (2*S*,5*R*,2′*S*)-**13a** (77.5 g, 0.167 mol) in MeCN (0.67 l) at r.t. was added 1N HCl (0.67 l, 0.670 mol), and stirring was continued for 1.5 h. The mixture was poured into ice-cooled sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2 (3 × 1 l). Evaporation of the org. phase gave 82 g of a pale yellow oil. The valine methyl ester by-product was removed by evaporation under high vacuum (50°/0.02 bar). FC (CH_2Cl_2/MeOH/conc. NH_3 soln. 950:50:1) of the oily residue gave *methyl (2*S*,4*S*)-2-amino-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexanoate* (55.5 g, 90%). Oil. TLC (CH_2Cl_2/MeOH/conc. NH_3 soln. 700:50:1): R_f 0.41. ^{1}H-NMR: 6.65–6.80 (*m*, 3 H); 4.10 (*t*, *J* = 7, 2 H); 3.83 (*s*, 3 H); 3.67 (*s*, 3 H); 3.57 (*t*, *J* = 7, 2 H); 3.34 (*s*, 3 H); 3.32 (*m*, 1 H); 2.50 (*m*, 2 H); 2.10 (*m*, 2 H); 1.75 (*m*, 2 H); 1.2–1.65 (*m*, 4 H); 0.86 (*m*, 6 H).

To a stirred soln. of this material (55.0 g, 0.149 mol) in CH_2Cl_2 (450 ml) at 0° were added Et_3N (35.6 ml, 0.208 mol) and Boc_2O (42.3 g, 0.194 mol) in CH_2Cl_2 (100 ml). The mixture was stirred for 20 h at r.t. Evaporation and FC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/$Et_2O$ 8:2) afforded, after recrystallization, pure (2*S*,4*S*)-**17** (57.0 g,

82%). White solid. TLC (AcOEt/hexane 1:1): R_f 0.45. M.p. 70–71° (from Et_2O/hexane). $[\alpha]_D^{22} = +8.3$ ($c = 1$, $CHCl_3$). IR (CH_2Cl_2): 3433*w*, 2957*m*, 2940*m*, 2880*m*, 1741*s*, 1712*s*, 1589*w*, 1514*s*, 1367*m*, 1235*m*, 1162*s*, 1140*m*, 1027*m*. ^{1}H-NMR: 6.66–6.79 (*m*, 3 H); 4.87 (*d*, 1 H); 4.36 (*m*, 1 H); 4.10 (*t*, $J = 7$, 2 H); 3.83 (*s*, 3 H); 3.67 (*s*, 3 H); 3.57 (*t*, $J = 7$, 2 H); 3.34 (*s*, 3 H); 2.64 (*m*, 1 H); 2.44 (*m*, 1 H); 2.10 (*m*, 2 H); 1.50–1.78 (*m*, 4 H); 1.45 (*s*, 9 H); 0.83 (*m*, 6 H). Anal. calc. for $C_{25}H_{41}NO_7$ (467.61): C 64.25, H 8.84, N 3.00; found: C 64.20, H 8.97, N 3.22.

*Methyl (2*R*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexanoate* ((2*R*,4*S*)-**18**). As described for (2*S*,4*S*)-**17**, with (2*R*,5*S*,2′*S*)-**15b** (1.1 g, 2.37 mmol), 1N HCl (9.5 ml), and MeCN (9.5 ml); for 90 min at r.t. FC (silica gel (100 g), CH_2Cl_2/MeOH/conc. NH_3 soln. 800:50:1) gave 610 mg (70%) of a yellow oil. TLC (CH_2Cl_2/MeOH/conc. NH_3 soln. 700:50:1): R_f 0.50. ^{1}H-NMR: 6.65–6.8 (*m*, 3 H); 4.09 (*t*, $J = 7$, 2 H); 3.84 (*s*, 3 H); 3.69 (*s*, 3 H); 3.58 (*t*, $J = 7$, 2 H); 3.35 (*s*, 3 H); 3.3–3.4 (*m*, 1 H); 2.60 (*dd*, $J = 4$, 15, 1 H); 2.31 (*dd*, $J = 7.5$, 15, 1 H); 2.11 (*m*, 2 H); 1.25–1.85 (*m*, 6 H); 0.95 (*d*, $J = 7$, 3 H); 0.85 (*d*, $J = 7$, 3 H).

This material (605 mg, 1.64 mmol) was treated in CH_2Cl_2 (20 ml) with Boc_2O (465 mg, 2.13 mmol) in the presence of *Hünig*'s base (392 µl, 2.29 mmol) for 16 h at r.t. FC (silica gel (100 g), CH_2Cl_2 and CH_2Cl_2/Et_2O 9:1) gave (2*R*,4*S*)-**18** (700 mg, 91%; containing 10–15% of isomer (2*S*,4*S*)-**17** by ^{1}H-NMR). Oil. TLC (CH_2Cl_2/Et_2O 9:1): R_f 0.28. ^{1}H-NMR: 6.6–6.8 (*m*, 3 H); 4.61 (br. *d*, $J = 9$, 1 H); 4.28 (*m*, 1 H); 4.10 (*t*, $J = 7$, 2 H); 3.74 (*s*, 3 H); 3.70 (*s*, 3 H); 3.58 (*t*, $J = 7$, 2 H); 3.35 (*s*, 3 H); 2.61 (*dd*, $J = 5.5$, 13, 1 H); 2.24 (*dd*, $J = 9$, 13, 1 H); 2.11 (*m*, 2 H); 1.5–1.9 (*m*, 4 H); 1.42 (*s*, 9 H); 0.95 (*d*, $J = 7$, 3 H); 0.86 (*d*, $J = 7$, 3 H).

*(2*S*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexan-1-ol* (=*(α*S*,γ*S*)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-4-methoxy-3-(3-methoxypropoxy)-γ-(1-methylethyl)-benzenepentanol*; (2S,4S)-**19**). To a mixture of (2*S*,4*S*)-**17** (53.8 g, 0.115 mol) in THF (800 ml) at r.t. was added $LiBH_4$ (5.6 g, 0.258 mol) in portions. The mixture was stirred for 16 h, followed by dropwise addition of MeOH (800 ml). Solvents were evaporated at 40°, followed by addition of MeOH (800 ml). The mixture was again evaporated, and ice-cooled 1N HCl (800 ml) was added carefully. After extraction with CH_2Cl_2 (3 × 800 ml), the org. phase was dried ($MgSO_4$) and evaporated: diastereoisomerically pure (2*S*,4*S*)-**19** (48.0 g, 95%). A sample of this material was recrystallized from Et_2O/hexane. White crystals. TLC (CH_2Cl_2/AcOEt 7:3): R_f 0.30. M.p. 64–66°[27]). $[\alpha]_D^{25} + 5.1$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 6.65–6.8 (*m*, 3 H); 4.53 (br. *d*, 1 H); 4.10 (*t*, $J = 7$, 2 H); 3.82 (*s*, 3 H); 3.4–3.75 (*m*, 3 H); 3.56 (*t*, $J = 7$, 2 H); 3.35 (*s*, 3 H); 2.48 (*m*, 2 H); 2.09 (*m*, 2 H); 1.43 (*s*, 9 H); 1.15–1.8 (*m*, 4 H); 0.88 (*d*, $J = 7$, 3 H); 0.87 (*d*, $J = 7$, 3 H).

*(2*S*,4*S*)-***19*** from (2*S*,4*S*)-***24a***: Reduction of (2*S*,4*S*)-**24a** (28.9 g, 61.8 mmol) with $LiBH_4$ (3.0 g, 138 mmol) in THF (430 ml) afforded, after recrystallization from Et_2O/hexane, (2*S*,4*S*)-**19** (25.2 g, 93%), identical to (2*S*,4*S*)-**19** from (2*S*,4*S*)-**17** by ^{1}H-NMR and TLC (CH_2Cl_2/AcOEt 7:3). White solid. M.p. 66–67°. TLC (AcOEt/hexane 1:1): R_f 0.19. $[\alpha]_D^{22} + 5.7$ ($c = 1$, $CHCl_3$). IR (CH_2Cl_2): 3434*w*, 2959*m*, 2938*m*, 2880*m*, 1708*s*, 1589*w*, 1513*s*, 1465*m*, 1367*m*, 1235*m*, 1163*m*, 1028*m*. ^{1}H-NMR ((D$_6$)DMSO, 80°): 6.82 (*d*, $J = 8$, 1 H); 6.80 (*d*, $J = 2$, 1 H); 6.70 (*dd*, $J = 8$, 2, 1 H); 5.98 (br. *d*, 1 H); 4.19 (*t*, $J = 6$, 1 H); 4.01 (*t*, $J = 6.4$, 2 H); 3.74 (*s*, 3 H); 3.35–3.55 (*m*, 1 H); 3.49 (*t*, $J = 6.4$, 2 H); 3.25–3.35 (*m*, 2 H); 3.26 (*s*, 3 H); 2.57–2.6 (*m*, 1 H); 2.30–2.35 (*m*, 1 H); 1.93 (*m*, 2 H); 1.58–1.65 (*m*, 2 H); 1.41 (*s*, 9 H); 1.23–1.42 (*m*, 2 H); 0.80 (*m*, 6 H). Anal. calc. for $C_{24}H_{41}NO_6$ (439.59): C 65.58, H 9.40, N 3.19; found: C 65.39, H 9.68, N 3.11.

*(2*R*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexan-1-ol* ((2*R*,4*S*)-**20**). As described for (2*S*,4*S*)-**19**, with (2*R*,4*S*)-**18** (18.9 mg, 0.04 mmol), $LiBH_4$ (14.0 mg, 0.6 mmol), and THF (5 ml); at r.t. overnight. Colorless oil. TLC (CH_2Cl_2/AcOEt 7:3): R_f 0.28. $[\alpha]_D^{25} - 7.8$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 6.6–6.8 (*m*, 3 H); 4.16 (br. *m*, 1 H); 4.10 (*t*, $J = 7$ H, 2 H); 3.79 (*s*, 3 H); 3.33 (*s*, 3 H); 3.75–3.4 (*m*, 3 H); 3.54 (*t*, $J = 7$, 2 H); 2.61 (*dd*, $J = 5$, 13, 1 H); 2.21 (*dd*, $J = 8$, 13, 1 H); 2.10 (*m*, 2 H); 1.9–1.2 (*m*, 4 H); 1.39 (*s*, 9 H); 0.96 (*d*, $J = 7$, 3 H); 0.84 (*d*, $J = 7$, 3 H).

The diastereomer purity of alcohols (2*S*,4*S*)-**19** and (2*R*,4*S*)-**20** was determined by reversed-phase HPLC (*Nucleosil-5-C18* anal. column, 30 → 90% MeCN/H_2O + 0.1% CF_3COOH over 60 min): t_R 36.1 for (2*S*,4*S*)-**19** and 37.2 for (2*R*,4*S*)-**20**. (2*S*,4*S*)-**19** obtained from (2*S*,4*S*)-**17**, as well as from (2*S*,4*S*)-**24a** after recrystallization, was diastereoisomerically pure (single HPLC peak); (2*R*,4*S*)-**20** contained 14.5% of the (2*S*,4*S*)-isomer.

2,5-Diethoxy-3,6-dihydropyrazine (**21**). To the soln. of glycine anhydride (256.7 g, 2.25 mol) in CH_2Cl_2 (2.5 l) in a 20-l reaction vessel was added at r.t. and under N_2 a soln. of triethyloxonium tetrafluoroborate (*Fluka*; 1.07 kg, 5.53 mol) in CH_2Cl_2 (5.0 l) in one portion with stirring. The turbid mixture was stirred for 64 h at r.t., followed by cooling to 0° with a CO_2/EtOH bath. An aq. phosphate buffer soln. of pH 7.36 (prepared from

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[27]) Material obtained from a 0.7M-scale reaction showed a slightly higher melting point of 70–71°.

K_2HPO_4 (3.29 kg, 4.19 mol) and KH_2PO_4 (0.945, 1.54 mol) dissolved in 11.2 l of distilled H_2O) was then added over 5 min by keeping the temp. of the mixture $< 10°$. Stirring was continued for 30 min, followed by filtration of the suspension/emulsion through *Hyflo*®. After washing the precipitate with CH_2Cl_2 (3.0 l), the org. phase of the combined filtrates was separated and the aq. phase extracted twice with CH_2Cl_2 (2 l). The combined org. phase was washed with brine (2 l), filtered through a cotton pad, and evaporated. The residue was dissolved in CH_2Cl_2 (400 ml), and hexane (4 l) was added with stirring. The precipitate was filtered off and washed with hexane and the combined filtrate evaporated (bath. temp. 40°) until the product began to crystallize. The suspension was cooled in an ice bath with stirring and then filtered and the solid washed with small amounts of cold hexane and finally dried at 30° under high vacuum. **21** (291 g, 76%). White crystalline solid. M.p. 82–83° ([25]: m.p. 84°). ^{1}H-NMR: 4.08 (q, $J = 7$, 4 H); 3.98 (s, 4 H); 1.23 (t, $J = 7$, 6 H). Anal. calc. for $C_8H_{14}N_2O_2$ (170.2): C 56.45, H 8.29, N 16.45; found: C 56.42, H 8.47, N 16.50.

*(2*S*)- and (2*R*)-3,6-Diethoxy-2,5-dihydro-2-{(2*S*)-2-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-3-methylbutyl}pyrazine* ((2*S*,2′*S*)-**22a** and (2*R*,2′*S*)-**23a**). To a soln. of **21** (229.8 g, 1.35 mol) in THF (3.0 l) at $-40°$ was added dropwise 1.6M BuLi in hexane (0.788 l, 1.26 mol) during 20 min. After stirring for 15 min at $-40°$, a soln. of (*R*)-**11a** (323.4 g, 0.90 mol) in THF (1.0 l) was added dropwise over 20 min, and stirring was continued at $-20°$ for 18 h. The mixture was evaporated, the residue partitioned between AcOEt (3×3 l) and H_2O (3×3 l), and the org. layers were washed with brine (1 l), combined, dried ($MgSO_4$), and evaporated. The residue was dried for 1 h at 35° under high vacuum: crude (2*S*,2′*S*)-**22a**/(2*R*,2′*S*)-**23a** (472 g; containing excess **21**) in the ratio 94.9:5.1 (determined by reversed-phase HPLC after transformation to (2*S*,4*S*)-**24**). Oil. TLC (hexane/AcOEt 2:1): R_f 0.20. ^{1}H-NMR[28]): 6.65–6.80 (m, 3 H); 3.93–4.18 (m, 9 H); 3.83 (s, 3 H); 3.57 (t, $J = 6.4$, 2 H); 3.35 (s, 3 H); 2.34–2.70 (m, 2 H); 2.03–2.18 (m, 2 H); 1.52–1.88 (m, 4 H); 1.3–1.25 (m, 6 H); 0.74–0.94 (m, 6 H).

*(2*S*)- and (2*R*)-3,6-Diethoxy-2,5-dihydro-2-{(2*R*)-2-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-3-methylbutyl]pyrazine* ((2*S*,2′*R*)-**23b** and (2*R*,2′*R*)-**22b**). As described for (2*S*,2′*S*)-**22a**/(2*R*,2′*S*)-**23a**, with **21** (511 mg, 3.00 mmol), THF (6 ml), 1.6M BuLi in hexane (1.75 ml, 2.80 mmol), (*S*)-**11b** (719 mg, 2.00 mmol), and THF (10 ml) at $-20°$ for 18 h: (2*S*,2′*R*)-**23b**/(2*R*,2′*R*)-**22b** (1.0 g; containing excess **21**), in the ratio 5:95 (determined by reversed-phase HPLC after transformation to crude (2*R*,4*R*)-**24b**). Oil. TLC (hexane/AcOEt 2:1): R_f 0.20. ^{1}H-NMR: identical to that of the enantiomers (2*S*,2′*S*)-**22a**/(2*R*,2′*S*)-**23a**.

*Ethyl (2*S*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexanoate* (= *Ethyl (α*S*,γ*S*)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-4-methoxy-3-(3-methoxypropoxy)-γ-(1-methylethyl)benzenepentanoate*; (2*S*,4*S*)-**24a**). To a stirred soln. of crude (2*S*,2′*S*)-**22a**/(2*R*,2′*S*)-**23a** (472 g, 0.90 mol) in MeCN (3.6 l) at r.t. was added 1N HCl (3.6 l, 3.60 mol). After 30 min at r.t., the mixture was poured into ice-cooled sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2 (3×4 l). The org. layers were washed several times with H_2O and evaporated: 351 g of crude α-amino ester. Oil. TLC (CH_2Cl_2/MeOH/conc. NH_3 soln. 850:50:1): R_f 0.34. ^{1}H-NMR: 6.65–6.85 (m, 3 H); 4.03–4.20 (m, 4 H); 3.83 (s, 3 H); 3.57 (t, $J = 6.4$, 2 H); 3.34 (s, 3 H); 3.23–3.34 (m, 1 H); 2.38–2.60 (m, 2 H); 2.10 (m, 2 H); 1.30–1.90 (m, 6 H); 1.20–1.32 (m, 3 H); 0.80–0.98 (m, 6 H).

To a stirred soln. of the crude α-amino ester (351 g, 0.90 mol) in CH_2Cl_2 (2.7 l) at 0° were added Et_3N (200 ml, 1.17 mol) and Boc_2O (216 g, 0.99 mol) in CH_2Cl_2 (0.3 l), followed by stirring for 18 h at r.t. The mixture was evaporated and the residue dried under high vacuum for 30 min at 35° and purified by filtration through silica gel (2.5 kg) with hexane/AcOEt 4:1 (1 l) to 2:1 (1 l) to afford a pale-colored oil. Recrystallization from hexane afforded pure (2*S*,4*S*)-**24a** (353 g, 82%). White solid. M.p. 59–60°. TLC (AcOEt/hexane 1:1): R_f 0.47. $[\alpha]_D^{22} = +8.1$ ($c = 1$, $CHCl_3$). IR (CH_2Cl_2): 3434*w*, 2959*m*, 2936*m*, 2878*m*, 1738*s*, 1712*s*, 1589*w*, 1514*s*, 1368*m*, 1236*m*, 1162*s*, 1140*m*, 1027*m*. ^{1}H-NMR ((D$_6$)DMSO; 80°): 6.84 (d, $J = 8$, 1 H); 6.75 (d, $J = 2$, 1 H);); 6.68 (dd, $J = 8, 2$, 1 H); 6.66 (br. s, 1 H); 3.99–4.10 (m, 3 H); 4.00 (t, $J = 6.4$, 2 H); 3.74 (s, 3 H); 3.49 (t, $J = 6.4$, 2 H); 3.27 (s, 3 H); 2.45 (d, $J = 6$, 2 H); 1.93 (m, 2 H); 1.51–1.72 (m, 4 H); 1.39 (s, 9 H); 1.18 (t, $J = 7$, 3 H); 0.84 (m, 6 H). Anal. calc. for $C_{26}H_{43}NO_7$ (481.63): C 64.84, H 9.00, N 2.91; found: C 65.00, H 9.16, N 3.04.

*Ethyl (2*R*,4*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-methoxy-3-(3-methoxypropoxy)benzyl]-5-methylhexanoate* ((2*R*,4*R*)-**24b**). As described for (2*S*,4*S*)-**24a**, with (2*S*,2′*R*)-**23b**/(2*R*,2′*R*)-**22b** 5:95 (0.96 g, 2.00 mmol) and final FC purification (silica gel (100 g), hexane/AcOEt 3:1). The major (2*R*,4*R*)-**24b** was obtained as pale yellow oil (0.82 g, 88%), contaminated with 5.4% of its (2*S*,4*R*)-epimer (determined by reversed-phase HPLC).

*(4*R*)-3-{(2*S*)-3-Methyl-1-oxo-2-[(phenylmethoxy)methyl]butyl}-4-(phenylmethyl)oxazolidin-2-one* ((4*R*,2′*S*)-**25a**). To a stirred soln. of (*R*)-**7a** (209 g, 0.80 mol) in abs. CH_2Cl_2 (3.2 l; filtered through basic Al_2O_3),

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[28]) Only the signals for the major diastereoisomer are indicated.

cooled to 0° and under Ar, $TiCl_4$ (92.2 ml, 0.84 mol) was added dropwise over 15 min (→ orange suspension). After 5 min, *Hünig*'s base (148 ml, 0.864 mol) was added at 0° over 15 min, and stirring of the dark mixture was continued for 1 h. Then, benzyl chloro methyl ether (222 ml, 1.60 mol; *Fluka*) was slowly added over 90 min at 0°. The orange-brown soln. was stirred for 20 h at 0°, and then sat. aq. NH_4Cl soln. (0.8 l) over 5 min and H_2O (1.6 l) were added. The aq. phase was extracted with CH_2Cl_2 (2 × 2 l) and the combined org. phase washed with H_2O (4 l), dried ($MgSO_4$), and evaporated. The yellow oil was purified by FC (2 × 2.5 kg (two portions), hexane/AcOEt 4:1) and by final recrystallization from Et_2O/hexane: pure (4*R*,2′*S*)-**25a** (152 g, 50%). White solid. M.p. 74–75°. TLC (hexane/AcOEt 3:1; 2 × developed): R_f 0.32. ^{1}H-NMR: 7.15–7.35 (*m*, 10 H); 4.65–4.8 (*m*, 1 H); 4.54 (*m*, *AB*, 2 H); 4.05–4.25 (*m*, 3 H); 3.88 (*t*, *J* = 8, 1 H); 3.71 (*dd*, *J* = 4, 8, 1 H); 3.22 (*dd*, *J* = 2, 13, 1 H); 2.61 (*dd*, *J* = 9, 13, 1 H); 2.04 (*m*, 1 H); 0.96 (*t*, *J* = 7, 6 H). Anal. calc. for $C_{23}H_{27}NO_4$ (381.47): C 72.42, H 7.13, N 3.67; found: C 72.31, H 7.12, N 3.82.

Small quantities of the more-polar (TLC) isomer (4*R*,2′*R*)-**25b** were obtained from corresponding combined FC fractions. TLC (hexane/AcOEt 3:1; 2 × developed): R_f 0.21. ^{1}H-NMR: 7.15–7.4 (*m*, 10 H); 4.7–4.8 (*m*, 1 H); 4.58 (*m*, *AB*, 2 H); 4.05–4.25 (*m*, 3 H); 4.01 (*t*, *J* = 9, 1 H); 3.83 (*dd*, *J* = 3, 8, 1 H); 3.28 (*dd*, *J* = 2, 14, 1 H); 2.79 (*dd*, *J* = 9, 14, 1 H); 2.05 (*m*, 1 H); 0.95–1.0 (*m*, 6 H).

*(2*S*)-3-Methyl-2-[(phenylmethoxy)methyl]butanoic Acid* ((2*S*)-**26a**). To a stirred soln. of (4*R*,2′*S*)-**25a** (103.8 g, 0.272 mol) in THF (1.5 l) and H_2O (0.52 l), cooled to 0°, were added 30% aq. H_2O_2 soln. (186 ml, 1.63 mol), dropwise over 5 min, and LiOH (13.1 g, 0.544 mol) by keeping the temp. at 0–2°. The mixture was slowly warmed to r.t., and stirring was continued for 18 h. Then, a soln. of sodium sulfite (206 g, 1.63 mol) in H_2O (1.15 l) was added at 0–10° over 10 min (*Exothermic! CAUTION: check for complete removal of residual peroxides before concentrating the mixture!*). The suspension was filtered, the residue washed with cold H_2O, and the combined filtrate (pH 10–11) was concentrated *in vacuo* at 40° to remove excess THF. The aq. phase was washed with CH_2Cl_2 (3 × 1 l), then adjusted to pH 2 by addition of ice-cold 4N HCl and extracted with CH_2Cl_2 (3 × 800 ml). The org. phase was dried ($MgSO_4$) and evaporated and the residue dried under high vacuum at r.t.: (2*S*)-**26a** (55.5 g, 92%). Pale yellow oil. TLC (hexane/AcOEt 2:1): R_f 0.25. ^{1}H-NMR: 7.25–7.4 (*m*, 5 H); 4.54 (*s*, 2 H); 3.73 (*dd*, *J* = 9, 16, 1 H); 3.63 (*dd*, *J* = 5, 9, 1 H); 3.68 (*m*, 1 H); 2.00 (*m*, 1 H); 0.99 (*d*, *J* = 7, 3 H); 0.96 (*d*, *J* = 7, 3 H). Anal. calc. for $C_{13}H_{18}O_3$ (222.28): C 70.24, H 8.16; found: C 69.95, H 8.15.

*(2*R*)-3-Methyl-2-[(phenylmethoxy)methyl]butan-1-ol* ((*R*)-**27a**). To the mixture of $NaBH_4$ (11.3 g, 0.299 mol) in abs. THF (60 ml), cooled to 10°, a soln. of (2*S*)-**26a** (55.4 g, 0.249 mol) in abs. THF (150 ml) was added over 15 min. Stirring was continued for 40 min at 10–20°, followed by dropwise addition of I_2 (31.7 g, 0.125 mol) in abs. THF (330 ml) at 20° over 15 min. After stirring the mixture for 72 h at r.t., MeOH (220 ml) was slowly added over 10 min (gas evolution), and stirring was continued for an additional 60 min at r.t. The mixture was evaporated *in vacuo* at 40° and the residue partitioned between ice-cold 2N HCl (800 ml) and AcOEt (3 × 800 ml). The combined org. phase was subsequently washed with brine/H_2O 1:1 (800 ml), sat. aq. $Na_2S_2O_3$ soln. (800 ml), brine/H_2O 1:1 (800 ml), 0.1N NaOH (800 ml), and brine (800 ml), dried ($MgSO_4$), and evaporated. FC (silica gel (500 g), hexane/AcOEt 3:1) afforded, after drying under high vacuum (*R*)-**27a** (47.9 g, 92%). Pale yellow oil. TLC (hexane/AcOEt 2:1): R_f 0.39. ^{1}H-NMR: 7.25–7.4 (*m*, 5 H); 4.53 (*m*, 2 H); 3.55–3.8 (*m*, 4 H); 2.70 (*t*, *J* = 5, 1 H); 1.78 (*m*, 1 H); 1.65 (*m*, 1 H); 0.92 (*d*, *J* = 7, 3 H); 0.90 (*d*, *J* = 7, 3 H). Anal. calc. for $C_{13}H_{20}O_2$ (208.30): C 74.96, H 9.68; found: C 74.92, H 9.69.

Determination of the Enantiomer Excess (ee) *of (+)-(*R*)-***27a*** and (−)-(*S*)-***27b***.* By HPLC (*Chiralcel-OJ*® column (25 cm × 4.6 mm), flow rate 1.0 ml/min, 30 bar pressure, UV detection at 210 nm, hexane/^{i}PrOH 98:2): t_R 21.2 for (+)-(*R*)-**27a** (ee > 99%) and 24.4 for (−)-(*S*)-**27b** (ee > 99.5%).

*(2*S*)-2-[(Benzyloxy)methyl]-3-methylbutyl Bromide* (*=1-Bromo-3-methyl-2-[(phenylmethoxy)methyl]butane*; (*S*)-**28a**). To a soln. of (*R*)-**27a** (47.9 g, 0.229 mol) in CH_2Cl_2 (1 l), cooled to 0°, Ph_3P (72.6 g, 0.276 mol) and NBS (49.2 g, 0.276 mol) were added in portions over 15 min, keeping the temp. at 0–5°. After stirring overnight at r.t., the mixture was poured into an ice-cold sat. aq. $NaHCO_3$ soln. (800 ml) and extracted with CH_2Cl_2 (2 × 800 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue stirred at r.t. for 1 h in hexane (400 ml). The suspension was filtered, the solid washed, and the combined filtrate concentrated to 200 ml. An additional filtration gave a clear soln. of the crude product. FC (silica gel (2 kg), hexane/AcOEt 10:1) gave (*S*)-**28a** (43.2 g, 70%). Pale yellow oil. TLC (hexane/CH_2Cl_2 4:1): R_f 0.17. ^{1}H-NMR: 7.25–7.4 (*m*, 5 H); 4.53 (*s*, 2 H); 3.43–3.75 (*m*, 4 H); 1.84 (*m*, 1 H); 1.71 (*m*, 1 H); 0.96 (*d*, *J* = 7, 3 H); 0.92 (*d*, *J* = 7, 3 H). Anal. calc. for $C_{13}H_{19}BrO$ (271.20): C 57.58, H 7.06, Br 29.46; found: C 57.84, H 7.03, Br 29.22.

*(2*R*)-2-[(Benzyloxy)methyl]-3-methylbutyl Bromide* ((*R*)-**28b**). As described for (4*R*,2′*S*-**25a**, (S)-**26a**, (*R*)-**27a**, and (*S*)-**28a**, with (*S*)-**7b** (60.0 g, 0.230 mol) at 0–5°, abs. CH_2Cl_2 (960 ml; filtered through basic Al_2O_3), $TiCl_4$ (26.4 ml, 0.241 mol) (over 10 min), Et_3N (42.5 ml, 0.248 mol) (stirring at 0–5° for 60 min), and benzyl chloro methyl ether (63.8 ml, 0.460 mol) (overnight). FC (silica gel (2 kg), CH_2Cl_2/hexane 1:1) and

recrystallization gave a white solid (50.7 g, 53%). M.p. 73–74°; TLC (CH_2Cl_2/hexane 2:1; 2× developed): R_f 0.40. $[\alpha]_D^{22} = +64.8$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR: 7.15–7.4 (*m*, 10 H); 5.85 (*m*, 1 H); 5.53 (*m*, 2 H); 4.05–4.25 (*m*, 3 H); 3,88 (*dd*, *J* = 11, 9.5, 1 H); 3.73 (*dd*, *J* = 9.5, 5, 1 H); 3.23 (*dd*, *J* = 12.5, 4, 1 H); 2.65 (*dd*, *J* = 12.5, 9, 1 H); 2.04 (*m*, 1 H); 0.95 (*m*, 6 H). Anal. calc. for $C_{23}H_{27}NO_4$ (381.47): C 72.42, H 7.13, N 3.67; found: C 72.71, H 7.07, N 3.73.

Hydrolysis of the white solid (50.6 g, 0.133 mol) in THF (0.7 l) with LiOH (6.4 g, 0.266 mol) and 30% H_2O_2 soln. (90.5 ml, 0.798 mol) afforded *(2*R*)-2-[(phenylmethoxy)methyl]butanoic acid* ((*R*)-**26b**; 28.5 g, 97%). Pale yellow oil. $[\alpha]_D^{25} = -10.6$ ($c = 1$, CH_2Cl_2). Anal. calc. for $C_{13}H_{18}O_3$ (222.28): C 70.24, H 8.16; found: C 69.80, H 8.26.

Reduction of (*R*)-**26b** with $NaBH_4$ (5.81 g, 0.154 mol) in the presence of I_2 (16.3 g, 0.064 mol) in THF (550 ml) afforded, after FC purification (silica gel (700 g), hexane/AcOEt 5:1) (*S*)-**27b** (23.0 g, 86%). Pale yellow oil. $[\alpha]_D^{25} = -15.7$ ($c = 1$, CH_2Cl_2). Anal. calc. for $C_{13}H_{20}O_2$ (208.30): C 74.96, H 9.68; found: C 74.72, H 9.51.

Reaction of (*S*)-**27b** (15.0 g, 72.0 mmol) with NBS (15.4 g, 86.6 mmol) in CH_2Cl_2 (310 ml) in the presence of Ph_3P (22.8 g, 86.6 mmol) and FC purification (silica gel (310 g), hexane/AcOEt 10:1) gave (*R*)-**28b** (18.9 g, 97%). Pale yellow oil. TLC (hexane/AcOEt 9:1): R_f 0.73. $[\alpha]_D^{25} = -9.7$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR: 4.49, 4.55 (2*d*, *AB*, *J* = 13, 2 H); 3.70 (*dd*, *J* = 10, 4.5, 1 H); 3.63 (*dd*, *J* = 9.5, 4.5, 1 H); 3.57 (*dd*, *J* = 10, 6, 1 H); 3.49 (*dd*, *J* = 9.5, 7, 1 H); 1.84 (*m*, 1 H); 1.71 (*m*, 1 H); 0.96 (*d*, *J* = 7, 3 H); 0.94 (*d*, *J* = 7, 3 H); Anal. calc. for $C_{13}H_{19}BrO$ (271.20): C 57.58, H 7.06, Br 29.46; found: C 57.65, H 6.88, Br 29.01.

*(2*S*,5*R*)-2-{(2*S*)-2-[(Benzyloxy)methyl]-3-methylbutyl}-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine* (= *(2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)-5-{(2*S*)-3-methyl-2-[(phenylmethoxy)methyl]butyl}-pyrazine*; (2*S*,5*R*,2′*S*)-**29**). As described for (2*S*,5*R*,2′*S*)-**13a**; with (*R*)-**12a** (29.5 g, 160 mmol), THF (530 ml), 1.6M BuLi in hexane (100 ml, 160 mmol), (*S*)-**28a** (29.0 g, 107 mmol), and THF (130 ml); at −70° for 2 h and at −18° for 64 h. FC (silica gel (2.4 kg), hexane/AcOEt 15:1) gave pure (2*S*,5*R*,2′*S*)-**29** (36.2 g, 90%). Pale yellow oil. TLC (hexane/AcOEt 4:1): R_f 0.58. ^{1}H-NMR: 7.25–7.35 (*m*, 5 H); 4.50 (*s*, 2 H); 3.9–4.1 (*m*, 2 H); 3.69 (*s*, 3 H); 3.63 (*s*, 3 H); 3.50 (*m*, 2 H); 2.25 (*m*, 1 H); 1.2–2.0 (*m*, 4 H); 0.65–1.1 (*m*, 12 H). Anal. calc. for $C_{22}H_{34}N_2O_3$ (374.52): C 70.55, H 9.15, N 7.48; found: C 70.80, H 9.34, N 7.17.

*Methyl (2*S*,4*S*)-4-[(Benzyloxy)methyl]-2-{(*tert*-butoxy)carbonyl]amino}-5-methylhexanoate* ((2*S*,4*S*)-**31**). As described for (2*S*,4*S*)-**24a**; with (2*S*,5*R*,2′*S*)-**29** (36.2 g, 96.7 mmol), MeCN (400 ml), 1N HCl (400 ml); at r.t. for 2 h. FC (silica gel (2.4 kg), CH_2Cl_2/MeOH/conc. NH_3 soln. 950:50:1) afforded *methyl (2*S*,4*S*)-2-amino-4-[(benzyloxy)methyl)-5-methylhexanoate* (21.9 g, 80%). Colorless oil. TLC (CH_2Cl_2/MeOH/conc. NH_3 soln. 700:50:1): R_f 0.34. ^{1}H-NMR: 7.25–7.35 (*m*, 5 H); 4.49 (*m*, 2 H); 3.71 (*s*, 3 H); 1.4–1.9 (*m*, 6 H); 1.35–1.6 (*m*, 3 H); 0.85–0.9 (*m*, 6 H). Anal. calc. for $C_{16}H_{25}NO_3$ (279.23): C 68.79, H 9.02, N 5.01; found: C 68.72, H 9.10, N 5.11.

Then with this α-amino ester (21.9 g, 78.4 mmol), CH_2Cl_2 (0.5 l), Et_3N (17.4 ml, 102 mmol), Boc_2O (18.8 g, 86.2 mmol), and CH_2Cl_2 (100 ml); for 16 h at r.t. FC (silica gel (2.4 kg), hexane/AcOEt 6:1) gave (2*S*,4*S*)-**31** (27.0 g, 91%). Colorless oil. TLC (hexane/AcOEt 4:1): R_f 0.34. ^{1}H-NMR: 7.26–7.35 (*m*, 5 H); 5.45 (*d*, NH, 1 H); 4.51 (*m*, 2 H); 4.32 (*m*, 1 H); 3.71 (*s*, 3 H); 3.35–3.5 (*m*, 2 H); 1.55–1.9 (*m*, 4 H); 1.41 (*s*, 9 H); 0.8–0.9 (*m*, 6 H).

*(2*S*,5*R*)- and (2*R*,5*R*)-2-{(2*R*)-2-[(Benzyloxy)methyl]-3-methylbutyl}-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine* ((2*S*,5*R*,2′*R*)-**32** and (2*R*,5*R*,2′*R*)-**33**, resp.). As described for (2*S*,5*R*,2′*S*)-**29a**, with (2*R*)-**12a** (13.0 g, 70.6 mmol), THF (230 ml), 1.6M BuLi in hexane (44 ml, 70.4 mmol), (*R*)-**28b** (12.8 g, 47.0 mmol), and THF (60 ml). FC (silica gel (1.0 kg), hexane/AcOEt 20:1) gave the major (2*S*,5*R*,2′*R*)-**32** (12.9 g, 73%). Pale yellow oil. TLC (hexane/AcOEt 6:1): R_f 0.62. $[\alpha]_D^{25} = +26.0$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR: 7.25–7.35 (*m*, 5 H); 4.46 (*s*, 2 H); 4.01 (*m*, 1 H); 3.92 (*m*, 1 H); 3.63 (*s*, 6 H); 3.38 (*m*, 2 H); 2.26 (*m*, 1 H); 1.75–2.0 (*m*, 3 H); 1.47 (*m*, 1 H); 1.03 (*d*, *J* = 7, 3 H); 0.87 (*d*, *J* = 7, 3 H); 0.86 (*d*, *J* = 7, 3 H); 0.67 (*d*, *J* = 7, 3 H). Anal. calc. for $C_{22}H_{34}N_2O_3$ (374.52): C 70.55, H 9.15, N 7.48; found: C 70.49, H 9.26, N 7.34.

The minor (2*R*,5*R*,2′*R*)-**33** (3.49 g, 20%) was also isolated as a pale yellow oil. TLC (hexane/AcOEt 6:1): R_f 0.50. ^{1}H-NMR: 7.25-7.35 (*m*, 5 H); 4.53 (*s*, 2 H); 3.9–4.2 (*m*, 2 H); 3.67 (*s*, 3 H); 3.63 (*s*, 3 H); 3.57 (*m*, 1 H); 3.49 (*m*, 1 H); 1.75–2.25 (*m*, 4 H); 1.20 (*m*, 1 H); 1.06 (*d*, *J* = 7, 3 H); 0.87 (*d*, *J* = 7, 3 H); 0.80 (*d*, *J* = 7, 3 H); 0.76 (*d*, *J* = 7, 3).

*Methyl (2*S*,4*R*)-4-[(Benzyloxy)methyl]-2-{[(*tert*-butoxy)carbonyl]amino}-5-methylhexanoate* ((2*S*,4*R*)-**34**). As described for (2*S*,4*S*)-**17**, with diastereoisomerically pure (2*S*,5*R*,2′*R*)-**32** (15.7 g, 41.9 mmol), MeCN (180 ml), and 1N HCl (176 ml); at r.t. for 2 h. FC (silica gel (1.0 kg), CH_2Cl_2/MeOH/conc. NH_3 soln. 97:3:0.1) afforded a pale yellow oil (10.9 g, 93%). TLC (CH_2Cl_2/MeOH/conc. NH_3 soln. 9:1:0.1): R_f 0.59.

Then as described for (2*S*,4*S*)-**24a**, with this yellow oil (8.8 g, 31.5 mmol), CH_2Cl_2 (35 ml), Boc_2O (7.56 g, 34.6 mmol), and Et_3N (7.0 ml, 40.9 mmol). FC (silica gel (1.0 kg), hexane/AcOEt 6:1) gave (2*S*,4*R*)-**34** (11.1 g,

93%). Pale yellow oil. TLC (hexane/AcOEt 3:1): R_f 0.43. $[\alpha]_D^{25} = +6.24$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR: 7.3–7.4 (m, 5 H); 5.38 (br. d, $J = 8$, 1 H); 4.49 (s, 2 H); 4.21 (m, 1 H); 3.70 (s, 3 H); 3.48 (dd, $J = 9, 5$, 1 H); 3.28 (dd, $J =$ 9, 8, 1 H); 1.55–1.9 (m, 4 H); 1.43 (s, 9 H); 0.89 (d, $J = 7$, 3 H); 0.87 (d, $J = 7$, 3 H). Anal. calc. for $C_{21}H_{33}NO_5$ (379.50): C 66.46, H 8.76, N 3.69; found: C 66.49, H 8.97, N 3.69.

*(2*S*)- and (2*R*)-2-{(2*S*)-2-[(Benzyloxy)methyl]-3-methylbutyl}-3,6-diethoxy-2,5-dihydropyrazine* ((2*S*,2′*S*)-**35** and (2*R*,2′*S*)-**36**, resp.). Similarly to the method described above for (2*S*,5*R*,2′*S*)-**13a**: To a soln. of (*S*)-**28a** (1.09 g, 4.0 mmol) in THF (20 ml), cooled to $-40°$, was added 1.6M BuLi in hexane (3.5 ml, 5.6 mmol) over 15 min with stirring, followed by addition of **21** (1.02, 6.0 mmol) in THF (25 ml) over 10 min at $-40°$. The colored mixture was warmed to $-18°$, and stirring was continued for 16 h. FC (silica gel (100 g), hexane/AcOEt 4:1) gave (2*S*,2′*S*)-**35**/(2*R*,2′*S*)-**36** *ca.* 2:1 (by ^{1}H-NMR) (1.28 g, 89%). Pale yellow oil. R_f 0.32. ^{1}H-NMR: 7.25–7.4 (m, 5 H); 4.47, 4.49 (2s, *ca.* 2:1, 2 H); 3.96–4.16 (m, 7 H); 3.35–3.55 (m, 2 H); 1.4–2.06 (m, 4 H); 1.2–1.35 (m, 6 H); 0.76–0.92 (m, 6 H).

*Ethyl (2*S*,4*S*)- and (2*R*,4*S*)-4-[(Benzyloxy)methyl]-2-{[(*tert*-butoxy)carbonyl]amino}-5-methylhexanoate* ((2*S*,4*S*)-**37a** and (2*R*,4*S*)-**37b**, resp.). As described for (2*S*,4*S*)-**24a**, with (2*S*,2′*S*)-**35**/(2*R*,2′*S*)-**36** *ca.* 2:1 (1.20 g, 3.33 mmol), MeCN (12 ml), 1N HCl (12 ml); at r.t. for 20 min. Then with Et_3N (0.73 ml, 4.29 mmol), Boc_2O (0.79 g, 3.63 mmol), and CH_2Cl_2 (20 ml); at r.t. for 16 h. FC (silica gel (100 g), hexane/AcOEt 6:1) gave (2*S*,4*S*)-**37a**/(2*R*,4*S*)-**37b** *ca.* 2:1 (by ^{1}H-NMR) (1.23 g, 94%). Colorless oil. TLC (hexane/AcOEt 4:1): R_f 0.34. ^{1}H-NMR: 7.25–7.40 (m, 5 H); 5.43 (d, 0.67 H, NH); 5.35 (d, 0.33 H, NH); 4.45–4.55 (m, 2 H); 4.10–4.35 (m, 3 H); 3.25–3.52 (m, 2 H); 1.55–1.90 (m, 4 H); 1.42 (s, 9 H); 1.24–1.29 (m, 3 H); 0.83–0.90 (m, 6 H). Anal. calc. for $C_{22}H_{34}N_2O_3$ (393.52): C 67.15, H 8.96, N 3.56; found: C 66.88, H 8.67, N 3.50.

REFERENCES

[1] J. Rahuel, V. Rasetti, J. Maibaum, H. Rüeger, R. Göschke, N.-C. Cohen, S. Stutz, F. Cumin, W. Fuhrer, J. M. Wood, M. G. Grütter, *Chem. Biol.* **2000**, *7*, 493.

[2] R. Göschke, V. Rasetti, N.-C. Cohen, J. Rahuel, M. Grütter, S. Stutz, H. Rüeger, W. Fuhrer, J. M. Wood, J. Maibaum, '15th EFMC Int. Symp. Med. Chem. 1998', Sept. 6–10, Edinburgh, Abstr. P.229; J. Maibaum, S. Stutz, R. Göschke, P. Rigollier, Y. Yamaguchi, W. Schilling, J. M. Wood, '15th EFMC Int. Symp. Med. Chem., 1998, Sept. 6–10, Edinburgh, Abstr. P.230.

[3] J. Nussberger, G. Wuerzner, C. Jensen, H. R. Brunner, *Hypertension* **2002**, *39*, e1; J. Nussberger, H. Brunner, C. Jensen, J. Mann, *Eur. Heart J.* **2001**, *22*, Abstr. P2294; N. E. Mealy, J. Castañer, R. M. Castañer, J. Silvestre, *Drugs Fut.* **2001**, *26*, 1139.

[4] R. Göschke, N.-C. Cohen, J. M. Wood, J. Maibaum, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2735.

[5] U. Schöllkopf, *Pure Appl. Chem.* **1983**, *55*, 1799; U. Schöllkopf, 'Asymmetric Synthesis of Nonproteinogenic Amino Acids', in 'Peptides: Struct. Funct., Proc. 9th Am. Pept. Symp. 1985', Eds. C. M. Deber, V. Hruby, and K. D. Kopple, Pierce Chem. Co., Rockford, Ill. USA, p. 425; U. Schöllkopf, K.-O. Westphalen, J. Schröder, K. Horn, *Liebigs Ann. Chem.* **1988**, 781.

[6] U. Schöllkopf, U. Groth, Ch. Deng, *Angew. Chem., Int. Ed.* **1981**, *20*, 798.

[7] D. A. Evans, M. D. Ennis, *J. Am. Chem. Soc.* **1982**, *104*, 1737; D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141; and ref. cit. therein.

[8] M. J. McKennon, A. I. Meyers, K. Drauz, M. Schwarm, *J. Org. Chem.* **1993**, *58*, 3568.

[9] T. Winkler (*Novartis*, Analytical Department, CH-4002 Basel), personal communication.

[10] R. Göschke, S. Stutz, V. Rasetti, N. C. Cohen, J. Rahuel, M. Grütter, H. Rüeger, G. Rhis, W. Fuhrer, J. M. Wood, J. Maibaum, in preparation.

[11] D. Seebach, W. Bauer, J. Hansen, T. Laube, W. Schweizer, J. D. Dunitz, *J. Chem. Soc., Chem. Commun.* **1984**, 853.

[12] W. Bauer, D. Seebach, *Helv. Chim. Acta* **1984**, *67*, 1972.

[13] P. K. Subramanian, R. W. Woodard, 'Synthesis of (*R*)- and (*S*)-1-Amino[2,2-$^2H_2$]cyclopropane-1-carboxylic Acids: a Double Violation of *Schoellkopf*'s Rule', in 'Peptides: Struct. Funct., Proc. 9th Am. Pept. Symp. 1985', Eds. C. M. Deber, V. Hruby, and K. D. Kopple, Pierce Chem. Co., Rockford, Ill. USA, p. 437.

[14] V. Tschinke, *Speedel Experimenta AG*, CH-4123 Basel, personal communication.

[15] U. Groth, T. Huhn, B. Porsch, C. Schmeck, U. Schöllkopf, *Liebigs Ann. Chem.* **1993**, 715.

[16] J. L. Markham, P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1889.

[17] I. L. Yudin, A. B. Sheremetev, O. P. Shitov, V. A. Tartakovskii, *Mendeleev Commun.* **1995**, 196.

[18] C. Ma, X. He, X. Liu, S. Yu, S. Zhao, J. M. Cook, *Tetrahedron Lett.* **1999**, *40*, 2917.

[19] W. Hartwig, J. Mittendorf, *Synthesis* **1991**, 939.
[20] U. Schöllkopf, 'Asymmetric Synthesis via Heterocyclic Intermediates', in 'Organic Synthesis: Interdisciplinary Challenge, 5th Proc. IUPAC Symp. 1985', Blackwell Oxford, UK, p. 101; R. Gull, U. Schöllkopf, *Synthesis* **1985**, 1052.
[21] J. Maibaum, N.-C. Cohen, J. Rahuel, C. Schnell, H.-P. Baum, P. Rigollier, W. Schilling, J. M. Wood, '15th EFMC Int. Symp. Med. Chem., 1998', Sept. 6–10, Edinburgh), Abstr. P.231.
[22] D. A. Evans. R. L. Dow, T. L. Shih, J. M. Takacs, R. Zahler, *J. Am. Chem. Soc.* **1990**, *112*, 5290.
[23] a) U. Schöllkopf, J. Nozulak, M. Grauert, *Synthesis* **1985**, 55; M. Ruiz, V. Ojea, J. M. Quintela, *Synlett* **1999**, *2*, 204; b) S. Kobayashi, T. Furuta, *Tetrahedron* **1998**, *54*, 10275.
[24] G. Shapiro, D. Büchler, M. Marzi, K. Schmidt, B. Gomez-Lor, *J. Org. Chem.* **1995**, *60*, 4978; V. Ojea, M. Ruiz, G. Shapiro, E. Pombo-Villar, *J. Org. Chem.* **2000**, *65*, 1984; and ref cit. therein.
[25] K. W. Blake, A. E. A. Porter, P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1* **1972**, 2494.

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