Enantioselective Synthesis of β-Amino Acids

Part 13

Diastereoselective Alkylation of Dianions Derived from Chiral Analogs of β-Aminopropanoic Acid Containing the α-Phenylethyl Group

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Dedicated to Professor *Dieter Seebach*, in appreciation for his example as a person and as a scientist.

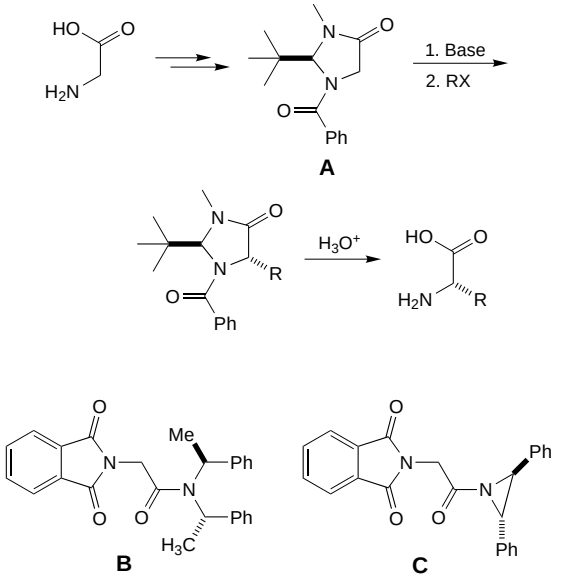
Inexpensive acryloyl chloride was converted in 91% overall yield to two derivatives of β-alanine, (*R*,*R*,*R*)-**6** and (*R*,*R*,*S*)-**6**, containing two chiral auxiliaries. *C*-Alkylation of (*R*,*R*,*R*)- and (*R*,*R*,*S*)-**6** *via* a dianion derivative, was performed by direct metallation with 2.2 equiv. of lithium hexamethyldisilazane (LHMDS) in THF at −78°. *C*-Alkylation of (*R*,*R*,*S*)-**6**-Li_2 ('matched' pair of chiral auxiliaries) afforded the mono-alkylated products **8**–**11** in 29–96% yield and 54–95% stereoselectivity. Employment of LiCl as an additive generally increased stereoselectivities, whereas the effect of HMPA as a cosolvent was erratic. Chemical correlation of the major diastereoisomer from the alkylation reactions with (*S*)-α-alkyl-β-alanine (**12**–**15**) showed that addition of the electrophile preferentially takes place on the enolate's *Si*-face. This conclusion is also supported by molecular-modeling studies (*ab initio* HF/3-21G), which indicate that the lowest-energy conformation for (*R*,*R*,*S*)-**6**-Li_2 presents the more sterically hindered *Re*-face of the enolate. The theoretical studies also predict a determining role for N–Li–O chelation in (*R*,*R*,*S*)-**6**-Li_2, giving rise to an interesting 'ion-triplet' configuration for the dilithium dianion.

Introduction. – Because of the enormous importance of amino acids and peptides in stereospecific biological interactions [1], a truly remarkable amount of research has been dedicated to the asymmetric synthesis of chiral amino acids [2]. Among the methods available for the preparation of enantiomerically enriched α-amino acids, those making use of chiral derivatives of glycine [3] have been particularly successful. Among these, *Seebach*'s chiral imidazolidinone **A** represents a prominent substrate and pioneering concept (*Scheme 1*) [4].

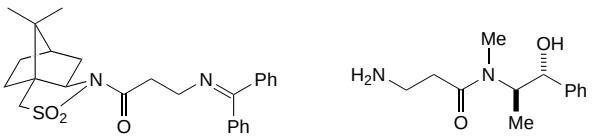
More recently, motivated by the efficiency of the α-phenylethylamino moiety as a chiral auxiliary [5] and by the advantageous effect of C_2-symmetric substrates in asymmetric synthesis [6], we successfully explored 'open-chain' glycinamides of type **B** and **C** as substrates in the preparation of enantiomerically pure α-amino acids [7].

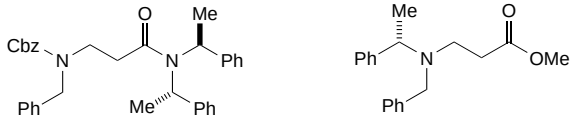
During the last few years, the preparation of β-amino acids has emerged as an important and challenging synthetic endeavor, partly because they are components of a variety of natural products, such as taxol [8], the dolastatins [9], and many others [10]. Furthermore, a number of open-chain [11] or cyclized [12] β-amino acids display interesting pharmacological properties and give rise to stabilized helical peptides with enhanced resistance to enzymatic degradation [13].

Scheme 1. Seebach*'s Imidazolidinone* **A** *as a Convenient Precursor in the Stereoselective Synthesis of α-Amino Acids*

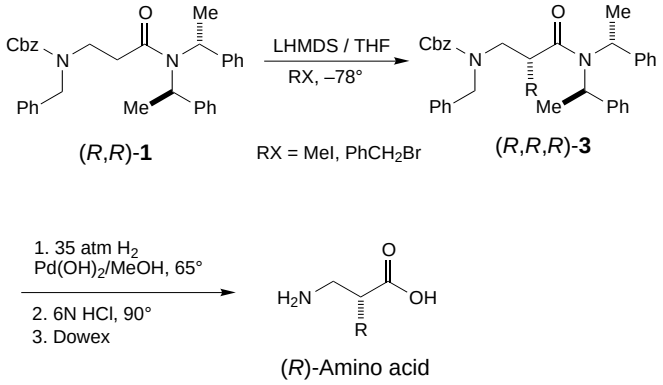


Much of the work regarding the stereoselective preparation of β-amino acids has been reviewed [14]. Recently, the potential of chiral derivatives of β-aminopropanoic acid, such as **D**, **E**, **1**, and **2** was explored [15][16]. In particular, the alkylation of (*R*,*R*)-**1** at $-78°$ in THF with lithium hexamethyldisilazane (LHMDS) afforded diastereoselectivities of 56–80% in 28–65% yield. The addition of LiCl or hexamethylphosphortriamide (HMPA) had no significant effect on yield or stereoselectivity. The major diastereoisomer in this reaction was (*R*,*R*,*R*)-**3** after deprotection (*Scheme 2*) [16].



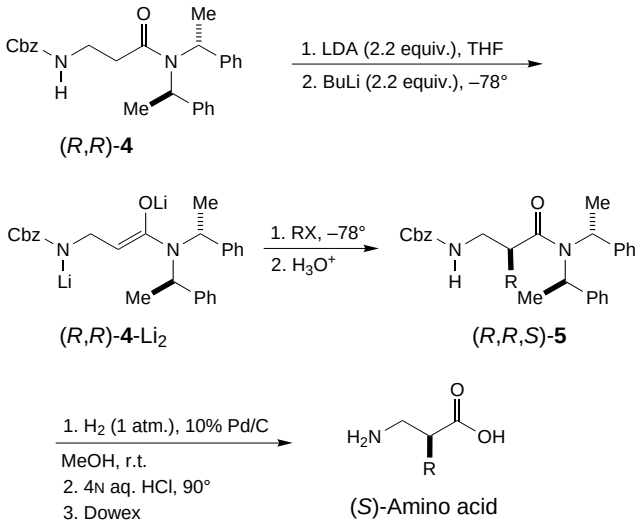


Scheme 2. *Stereoselectivity of Enolate (*R,R*)-***1***-Li Alkylations and Chemical Correlation of Major Product with α-Substituted β-Amino Acids of Known Configuration* [16]

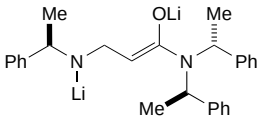


Motivated by the elegant work of *Myers* [17], *Berkowitz* [18], *McIntosh* [19], *Seebach* [20], and others [21], who have demonstrated the highly stereoselective alkylation of chiral dianions, we examined the stereoselectivity of alkylation of the chiral, β-alanine-derived dianion (*R*,*R*)-**4**-Li_2 (*Scheme 3*) [22].

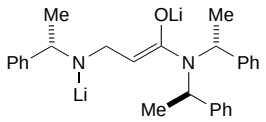
Scheme 3. *Stereoselectivity of Dianion (*R,R*)-***4***-Li_2 Alkylations and Chemical Correlation of the Major Diastereoisomer to α-Substituted β-Amino Acids of Known Configuration* [22]



In general, both higher yields and stereoselectivities were observed in the *C*-alkylation of the dianion (*R*,*R*)-**4**-Li_2 relative to the enolate (*R*,*R*)-**2**-Li_2. Also, the major diastereoisomeric products (*R*,*R*,*R*)-**3** and (*R*,*R*,*S*)-**5** were found with opposite configurations at the newly created stereogenic center. Considering that stereoinduction in (*R*,*R*)-**4**-Li_2 (*Scheme 3*) is of *unlike* topicity (*i.e.*, (*R*)-configured auxiliary



(*R*,*R*,*R*)-**6**-Li_2

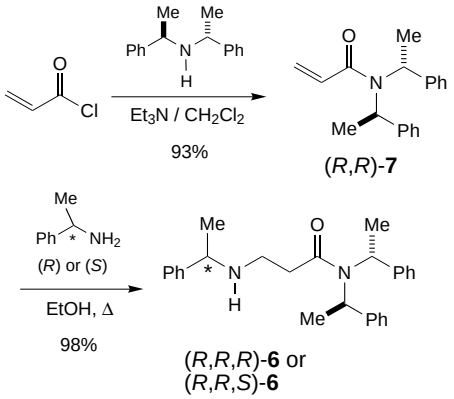


(*R*,*R*,*S*)-**6**-Li_2

favors reaction on the *Si*-face [23]), and that the same applies to (*S*)-**2**-Li (*i.e.*, (*S*)-configured auxiliary favors addition to the *Re*-face [23]), we deemed it of interest to determine the stereoselective alkylation of (*R*,*R*,*R*)-**6**-Li_2 and (*R*,*R*,*S*)-**6**-Li_2. According to *Masamune*'s theory [24], one might expect the all-(*R*)-configured dianion to correspond to a 'matched' pair of auxiliaries, whereas the (*R*,*R*,*S*) diastereoisomeric dianion could be anticipated as a 'mismatched' combination of auxiliaries[1]).

Results and Discussion. – *Synthesis of Diastereoisomeric Derivatives of β-Alanine Containing Two Chiral Auxiliaries.* Diastereoisomers (*R*,*R*,*R*)-**6** and (*R*,*R*,*S*)-**6** were prepared from acryloyl chloride *via* a sequential reaction with bis[(*R*)-1-phenylethyl]-amine [26] to furnish (*R*,*R*)-**7** in 93% yield, followed by conjugate addition of (*R*)- or (*S*)-1-phenylethylamine (*Scheme 4*). The desired products were purified by flash chromatography (FC) and isolated in excellent yield.

Scheme 4. *Preparation of Diastereoisomeric β-Alanine Derivatives (*R,R,R*)- and (*R,R,S*)-***6***

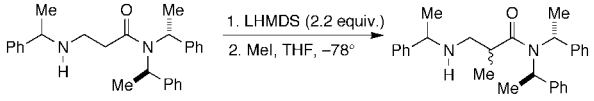


Stereoselectivity of C*-Alkylation of (*R,R,R*)-***6*** *and (*R,R,S*)-***6***. *C*-Alkylation of (*R*,*R*,*R*)- and (*R*,*R*-*S*)-**6** proceeded best with 2.2 equiv. of LHMDS as the base. The resulting dianion was treated with the electrophile at $-78°$. Results of the methylation reaction, in the absence of additives, are summarized in *Table 1*.

For comparison, the methylation of (*R*,*R*)-**4**-Li_2 (*Scheme 3*) under similar conditions afforded a diastereoisomer ratio (dr) of 73:27 [22]. Thus, the comparable

[1]) For an example of double stereo-induction in chiral derivatives of glycine, see [25].

Table 1. *Stereoselectivity of the Methylation of Dianions (*R,R,R*)- and (*R,R,S*)-***6***-Li_2 in the Absence of Additives*



(*R*,*R*,*R*)- or (*R*,*R*,*S*)-**6** **8**

Substrate	dr[a])	Yield [%]
(*R*,*R*,*R*)-**6**	83 : 17	67
(*R*,*R*,*S*)-**6**	62 : 38	60

[a]) Diastereoisomer ratio determined by NMR integration of appropriate signals of **8**.

selectivities reported in *Table 1* indicate that the β-alanine derivative (*R*,*R*,*S*)-**6** corresponds to the 'matched' pair of chiral auxiliaries (dr 83 : 17), whereas (*R*,*R*,*R*)-**6** could be seen as the corresponding 'mismatched' combination. This result was not anticipated in the light of the stereo-induction found previously for the chiral enolate **2**-Li [16] and suggests that the influence of the phenylethyl group is not the same in (*R*,*R*,*R*)-**6**-Li_2 and (*R*,*R*,*S*)-**6**-Li_2 relative to **2**-Li. Probably, the reactive intermediates are present in different conformations upon approach of the electrophile (*vide infra*). Further alkylation studies were then carried out with the better substrate (*R*,*R*,*S*)-**6** in the absence or presence of additives (*Table 2*).

In the absence of additives, methylation proceeded with the highest stereoselectivity (dr 83 : 17; *Entry 1*, *Table 2*). For comparison, alkylation with EtI afforded a moderate stereoselectivity (dr 74 : 26, *Entry 15*), and BnBr and PrI gave the poorest results (dr 68 : 32 and 62 : 38, *Entries 8* and *20*, respectively).

The addition of 'inert' salts to reaction media has been found to affect the stereoselectivity of alkylation reactions [27 – 29]. As can be seen from *Entries 5 – 7*, *12 – 14*, *18*, *19*, and *23 – 25*, stereoselectivities increased with LiCl as an additive. Concomitantly, both methylation and benzylation proceeded in higher yields in the presence of LiCl. Nevertheless, the opposite was true with EtI and PrI as electrophiles (*Entries 18*, *19*, and *23 – 25*). Addition of polar HMPA as a cosolvent led to erratic trends in the alkylation reactions. For example, stereoselectivities decreased in the methylation reaction, although the observed yields went up[2]) (*Entries 2 – 4* in *Table 2*). In contrast, stereoselectivities for the benzylation reaction (*Entries 10* and *11*) increased in the presence of three or 6 equiv. of HMPA, but yields remained low. Finally, both selectivity and yield tended to decrease in the presence of HMPA in the reaction with EtI and PrI (*Entries 16*, *17*, *21*, and *22*)[3]).

Configuration of the Diastereoisomeric Products **8** – **10**. The absolute configuration at the new stereogenic center of (*R*,*R*,*S*)-**6**-Li_2 (*Table 2*) was ascertained by chemical correlation with α-substituted β-amino acids of known configuration, (*S*)-**12** – (*S*)-**14** (*Scheme 5*). In the case of **11**, debenzylation and hydrolysis afforded the β-amino acid

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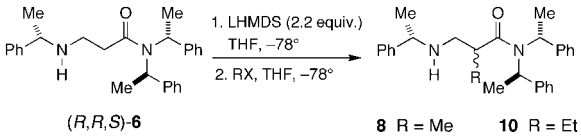
[2]) The idea behind HMPA is that it solvates Li^+, thus generating free anions instead of ion pairs or aggregates [30].

[3]) It is to be expected that our seemingly contrasting observations will be better understood when the knowledge of salt and solvent effects on Li enolates is more advanced [30].

Table 2. *Stereoselectivity for the Alkylation of (*R,R,S*)-***6***-Li_2*. Effect of LiCl and HMPA additives.*



(*R,R,S*)-**6**

8 R = Me **10** R = Et
9 R = CH_2Ph **11** R = Pr

Entry	RX	Additive (equiv.)	dr[a])	Yield [%]
1	MeI	–	83 : 17	67
2	MeI	HMPA (1)	79 : 21	87
3	MeI	HMPA (3)	74 : 26	94
4	MeI	HMPA (6)	60 : 40	68
5	MeI	LiCl (1)	92 : 8	86
6	MeI	LiCl (3)	91 : 9	71
7	MeI	LiCl (6)	89 : 11	89
8	$PhCH_2Br$	–	68 : 32	42
9	$PhCH_2Br$	HMPA (1)	68 : 32	29
10	$PhCH_2Br$	HMPA (3)	85 : 15	44
11	$PhCH_2Br$	HMPA (6)	89 : 11	34
12	$PhCH_2Br$	LiCl (1)	92 : 8	84
13	$PhCH_2Br$	LiCl (3)	95 : 5	81
14	$PhCH_2Br$	LiCl (6)	92 : 8	96
15	EtI	–	74 : 26	74
16	EtI	HMPA (1)	65 : 35	76
17	EtI	HMPA (3)	58 : 42	54
18	EtI	LiCl (1)	87 : 13	39
19	EtI	LiCl (3)	87 : 13	60
20	PrI	–	62 : 38	62
21	PrI	HMPA (1)	60 : 40	58
22	PrI	HMPA (3)	54 : 46	27
23	PrI	LiCl (1)	67 : 33	54
24	PrI	LiCl (3)	80 : 20	29
25	PrI	LiCl (6)	69 : 31	63

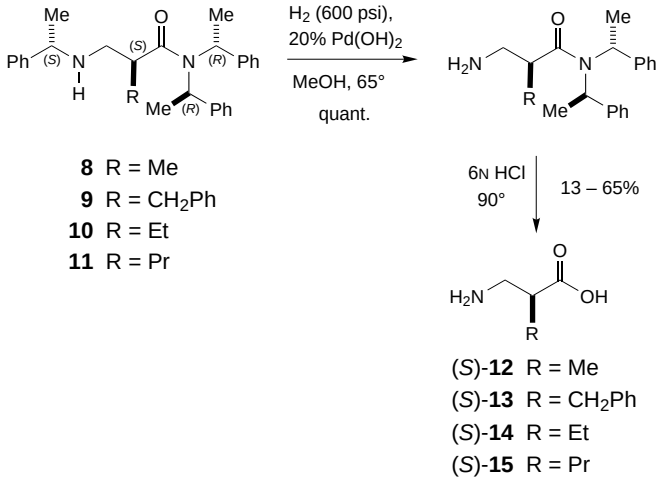
[a]) Diastereoisomer ratio.

15, previously unknown in enantiomerically pure form. Given the similar spectroscopic behaviors of **8**, **10**, and **11**, we tentatively also assigned the (*S*)-configuration to **15**.

The major diastereomers **8**–**11** were purified by FC and subjected to hydrogenolytic debenzylation with 20% $Pd(OH)_2$ in MeOH under 600 psi H_2 pressure at 65° for 12 h. Given the poor stability of the debenzylated products, the crude mixtures were filtered over *Celite*, concentrated, and hydrolyzed immediately with 6N HCl in a sealed ampoule at 90°. Final purification was achieved with *Dowex* ionic resin or by silica-gel column chromatography to give the free amino acids **12**–**15** (*Table 3*).

Molecular-Modeling Studies. In order to rationalize the observed stereoinduction by the chiral bis(1-phenylethyl)amino auxiliary in (*R,R,S*)-**6**-Li_2, we resorted to semi-empirical PM3 [31] as well as *ab initio* HF/3-21G [32] calculations. First of all, a search for low-energy conformations of the starting chiral amide (*R,R*)-**4** (*Scheme 3*) was undertaken at the PM3 level by means of the *PC Spartan-Pro* program [31], which makes use of Monte Carlo stochastic methods [33]. This conformational search

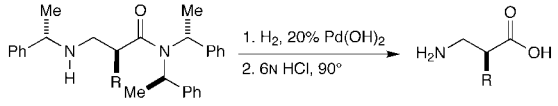
Scheme 5. *Chemical Correlation of Alkylated Products* **8**–**11** (major diastereoisomers) with *α-Substituted β-Amino Acids* **12**–**15**



8 R = Me
9 R = CH_2Ph
10 R = Et
11 R = Pr

(*S*)-**12** R = Me
(*S*)-**13** R = CH_2Ph
(*S*)-**14** R = Et
(*S*)-**15** R = Pr

Table 3. *Chemical Correlation of Alkylated Derivatives* **8**–**11** *with α-Substituted β-Amino Acids* **12**–**15**



8 – **11** (*S*)-**12** – (*S*)-**15**

Substrate	Reaction time [h]	Yield [%]	$[\alpha]_D^{28}$	Product
8 R=Me	8[a])	63	+14.2	(*S*)-**12**
9 R=$PhCH_2$	14	13	−15.5	(*S*)-**13**
10 R=Et	48	55	+5.6	(*S*)-**14**
11 R=Pr	12	60	−3.2	(*S*)-**15**

[a]) 4N HCl was used in the hydrolysis reaction.

afforded nine structures corresponding to local minima within a 10 kcal/mol energy threshold. These nine low-energy conformers were used as starting geometries for optimizing (*R*,*R*,*S*)-**6**-Li_2 by means of HF/3-21G. All studies converged into a global energy minimum **F**, which is shown in the *Figure*.

The most-salient feature of **F** is the 'ion-triplet' configuration [34] of the dilithium salt. From the calculated lowest-energy conformation of (*R*,*R*,*S*)-**6**-Li_2, it can be assumed that the enolate's *Si*-face is less-hindered towards an electrophilic approach relative to the *Re*-face, which is *syn* to the phenyl rings. Such a predicted mode of addition of the electrophile (on the *Re*-face) should, thus, lead to the preferential formation of the (*S*)-configured stereogenic center, as experimentally observed (*Table 2*).

Conclusions. – *C*-Alkylation of (*R*,*R*,*S*)-**6**, a chiral *β*-alanine derivative containing the bis(1-phenylethyl)amine and *N*-(1-phenylethyl)amine chiral auxiliaries, was

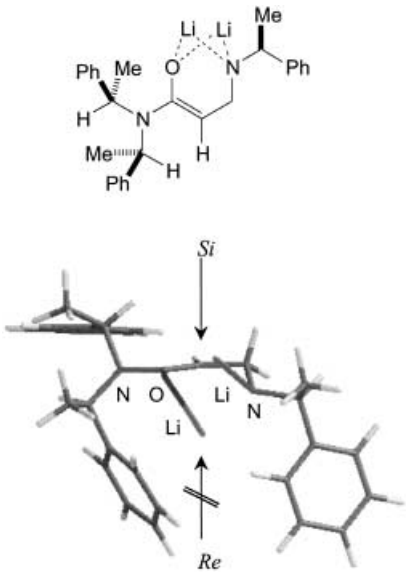


Figure. Ab initio *HF/3-21G Conformation of Minimum Energy for (*R,R,S*)-***6***-Li$_2$ (***F***) representing an 'ion-triplet' configuration* [34]

accomplished in moderate to good yields *via* the dianion (*R*,*R*,*S*)-**6**-Li$_2$. Stereoselectivities in the alkylation with various alkyl halides in the presence of one to three equivalents of LiCl as an additive varied from 67:33 to 95:5. Assignment of the (*S*)-configuration at the newly created stereogenic center was achieved by chemical correlation with known (*S*)-α-substituted β-amino acids. This configuration for the main alkylation product can be rationalized by *ab initio* calculations of the conformation of (*R*,*R*,*S*)-**6**-Li$_2$, which exhibits a relatively unhindered *Si*-face with respect to the enolate.

Experimental Part

General. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for *ca*. 12 h at 120° and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anh. solvents were obtained by distillation from benzophenone/ketyl radical [35]. BuLi was titrated according to [36]. TLC: *Merck DC-F$_{254}$* plates, detection by UV light. Flash (FC) [37] and column chromatography (CC): *Merck* silica gel (0.040–0.063 mm). Melting points: *Mel Temp* apparatus, not corrected. ^{1}H-NMR spectra: *Jeol Eclipse-400* (400 MHz), *Bruker Ultra Shield* (300 MHz), and *Jeol GSX-270* (270 MHz) spectrometers; ^{13}C-NMR spectra: *Jeol Eclipse-400* (100 MHz), *Bruker Ultra Shield* (75 MHz), and *Jeol GSX-270* (67.5 MHz); chemical shifts δ in ppm relative to Me_4Si as internal reference, coupling constants *J* in Hz. High-resolution mass spectra (HR-MS) were obtained at the *Instituto de Química*, UNAM, México. Elemental analyses were obtained from *Galbraith Laboratories, Inc.*, Knoxville, TN.

N,N-*Bis[(1*R*)-1-phenylethyl]prop-2-enamide* ((*R*,*R*)-**7**). To a soln. of 1.5 g (16.6 mmol) of acryloyl chloride in 25 ml of anh. CH_2Cl_2 at 0° under N_2 was added dropwise *via* cannula 3.73 g (16.6 mmol) of *N*,*N*-bis[(1*R*)-1-phenylethyl]amine. The resulting mixture was stirred at 0° for 1 h. At this point, 2.33 ml (1.68 g, 16.6 mmol) of Et_3N was added *via* syringe, the mixture was allowed to come to r.t., and stirred overnight. The resulting suspension was treated with 25 ml of H_2O, extracted with CH_2Cl_2 (3×20 ml), the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by FC (hexane/AcOEt 8,5:1,5) to afford

4.32 g (93%) of (*R*,*R*)-**7** as a clear oil. $[\alpha]_D^{28} = +215.0$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.75 (br., 6 H); 4.72–5.03 (br., 1 H); 5.42 (*dd*, *J* = 10.3, 2.2, 1 H); 5.83–6.08 (br., 1 H); 6.12 (*dd*, *J* = 16.8, 10.3, 1 H); 6.29 (*dd*, *J* = 16.5, 2.2, 1 H); 6.80–7.50 (*m*, 10 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6; 20.7; 52.5; 126.9; 127.3; 128.3; 130.6; 141.1; 166.8. MS (70 eV): 279 (M^+), 174, 120, 106, 77. Anal. calc. for $C_{19}H_{21}NO$ (279.38): C 81.68, H 7.58; found: C 81.81, H 7.81.

N,N-*Bis[(1*R*)-1-phenylethyl]-3-{[(1*R*)-1-phenylethyl]amino}propanamide* ((*R*,*R*,*R*)-**6**). A mixture of 2.52 g (9.0 mmol) of (*R*,*R*)-**7** and 1.64 g (13.5 mmol) of (*R*)-1-phenylethylamine were dissolved in 130 ml EtOH, and the resulting mixture was heated to reflux for 36 h. Solvent removal at reduced pressure and FC (hexane/AcOEt 7:3) afforded 3.6 g (98%) of (*R*,*R*,*R*)-**6** as a clear oil. $[\alpha]_D^{28} = +135.2$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 100°, 300 MHz): 1.27 (*d*, *J* = 6.5, 3 H); 1.69 (*d*, *J* = 7.0, 6 H); 2.35 (*ddd*, *J* = 15.1, 6.8, 6.8, 1 H); 2.51 (*ddd*, *J* = 15.1, 6.7, 6.7, 1 H); 2.59 (br., 1 H); 2.67 (*dd*, *J* = 6.6, 6.6, 2 H); 3.71 (*q*, *J* = 6.6, 1 H); 5.13 (*q*, *J* = 7.0, 2 H); 7.10–7.34 (*m*, 15 H). ^{13}C-NMR ((D_6)DMSO, 100°, 75 MHz): 19.5; 24.8; 36.6; 44.5; 53.9; 58.2; 127.2; 127.3; 127.4; 128.2; 128.3; 128.6; 128.9; 142.5; 147.1; 172.4. MS (20 eV): 401 ($[M+1]^+$), 295, 191, 120, 105. HR-MS: 401.2583 ($[M+1]^+$, $C_{27}H_{33}N_2O^+$; calc. 401.2593).

N,N-*Bis[(1*R*)-1-phenylethyl]-3-{[(1*S*)-1-phenylethyl]amino}propanamide* ((*R*,*R*,*S*)-**6**). The procedure described for (*R*,*R*,*R*)-**6** was followed, with 5.7 g (20.0 mmol) of (*R*,*R*)-**7** and 3.7 g (30.6 mmol) of (*S*)-1-phenylethylamine. Yield: 7.8 g (98%), clear oil. $[\alpha]_D^{28} = +98.5$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 100°, 400 MHz): 1.24 (*d*, *J* = 6.7, 3 H); 1.68 (*d*, *J* = 7.0, 6 H); 2.31 (*ddd*, *J* = 15.1, 6.7, 6.7, 1 H); 2.50 (*ddd*, *J* = 15.0, 6.6, 6.6, 1 H); 2.60 (*ddd*, *J* = 11.7, 6.6, 6.6, 1 H); 2.70 (*ddd*, *J* = 11.7, 6.6, 6.6, 1 H); 3.66 (*q*, *J* = 6.5, 1 H); 5.13 (*q*, *J* = 7.1, 2 H); 7.11–7.32 (*m*, 15 H). ^{13}C-NMR ((D_6)DMSO, 100°, 100 MHz): 19.2; 24.6; 36.2; 44.1; 53.4; 57.7; 126.8; 126.9; 127.1; 127.8; 128.2; 128.5; 142.1; 146.8; 172.0. MS (15 eV): 401 ($[M+1]^+$), 295, 191, 120, 105. HR-MS: 401.2602 ($[M+1]^+$, $C_{27}H_{33}N_2O$; calc. 401.2593).

*General Procedure for the Reaction of the β-Alanine-Derived Dianion (*R,R,S*)-***6***-*Li_2 *with Electrophiles.* To a soln. of 0.2 g (0.5 mmol) (*R*,*R*,*S*)-**6** in 10 ml of anh. THF under N_2 and at −78° was added dropwise 2.2 equiv. of LHMDS. The resulting soln. was stirred for 1 h at −78°. The alkylating agent (1.1 equiv.) was added with continuous stirring, and the mixture was stirred at −78° for 3–4 h and quenched with aq. NH_4Cl soln. The product was extracted with AcOEt (3 × 10 ml), the combined org. extracts were dried (Na_2SO_4), filtered, and concentrated. Diastereoisomer separation was accomplished by FC [37] (hexane/AcOEt 80:20) and CC (CH_2Cl_2/MeOH/NH_4OH 9:0.5:0.05).

*(2*S*)-*N,N*-Bis[(1*R*)-1-phenylethyl]-2-methyl-3-{[(1*S*)-1-phenylethyl]amino}propanamide* ((*R*,*R*,*S*,*S*)-**8**). Prepared and purified according to the general alkylation procedure. Yield: 67–94% (*cf. Table 2*). $[\alpha]_D^{28} = +112.2$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 100°, 300 MHz): 0.76 (*d*, *J* = 6.5, 3 H); 1.21 (*d*, *J* = 6.6, 3 H); 1.67 (*d*, *J* = 7.0, 6 H); 2.36 (*dd*, *J* = 11.4, 6.0, 1 H); 2.72 (*dd*, *J* = 11.2, 7.3, 1 H); 2.84 (*ddq*, *J* = 6.5, 6.5, 6.5, 1 H); 3.65 (*q*, *J* = 6.5, 1 H); 5.11 (*q*, *J* = 7.0, 2 H); 7.16–7.32 (*m*, 15 H). ^{13}C-NMR ((D_6)DMSO, 100°, 75 MHz): 14.7; 18.3; 23.4; 37.5; 50.9; 52.4; 56.8; 125.7; 125.8; 125.9; 126.1; 126.8; 127.0; 127.4; 127.8; 127.9; 138.6; 141.1; 145.7; 175.0. HR-MS: 415.2751 ($[M+1]^+$, $C_{28}H_{35}N_2O$; calc. 415.2749).

*(2*S*)-*N,N*-Bis[(1*R*)-1-phenylethyl]-3-{[(1*S*)-1-phenylethyl]amino}-2-(phenylmethyl)propanamide* ((*R*,*R*,*S*,*S*)-**9**). Prepared and purified according to the general alkylation procedure. Yield: 29–96% (*cf. Table 2*). $[\alpha]_D^{28} = +76.5$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 100°, 400 MHz): 1.16 (br., 3 H); 1.24 (*d*, *J* = 6.6, 3 H); 1.60 (br., 3 H); 2.57 (*dd*, *J* = 11.5, 5.3, 1 H); 2.70–2.78 (*m*, 2 H); 2.81 (*dd*, *J* = 11.4, 7.7, 1 H); 3.34 (*dddd*, *J* = 6.6, 6.6, 6.6, 6.6, 1 H); 3.67 (*q*, *J* = 6.5, 1 H); 4.56 (br., 1 H); 5.20 (br., 1 H); 6.94–7.40 (*m*, 20 H). ^{13}C-NMR ((D_6)DMSO, 100°, 100 MHz): 18.3; 19.5; 24.3; 37.7; 45.7; 51.2; 53.5; 54.9; 58.2; 126.4; 126.8; 128.5; 128.6; 129.7; 140.5; 146.7; 174.3. HR-MS: 491.3066 ($[M+1]^+$, $C_{34}H_{39}N_2O^+$; calc. 491.3062).

*(2*S*)-*N,N*-Bis[(1*R*)-1-phenylethyl]-2-ethyl-3-{[(1*S*)-1-phenylethyl]amino}propanamide* ((*R*,*R*,*S*,*S*)-**10**). Prepared and purified according to the general alkylation procedure. Yield: 39–76% (*cf. Table 2*). $[\alpha]_D^{28} = +107.9$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 100°, 300 MHz): 0.74 (*t*, *J* = 7.5, 3 H); 1.27 (*d*, *J* = 6.6, 3 H); 1.45 (*ddq*, *J* = 7.1, 7.0, 2.5, 2 H); 1.72 (*d*, *J* = 7.0, 6 H); 2.51 (*dd*, *J* = 11.4, 5.4, 1 H); 2.78 (*dd*, *J* = 11.4, 7.5, 1 H); 2.91 (*dddd*, *J* = 6.5, 6.5, 6.5, 6.5, 1 H); 3.69 (*q*, *J* = 6.6, 1 H); 4.90–5.28 (br., 2 H); 6.97–7.38 (*m*, 15 H). ^{13}C-NMR ((D_6)DMSO, 100°, 75 MHz): 10.7; 18.2; 23.1; 23.2; 44.0; 49.5; 52.9; 57.1; 125.7; 126.8; 126.9; 127.4; 142.0; 145.7; 174.1. HR-MS: 429.2894 ($[M+1]^+$, $C_{29}H_{37}N_2O^+$; calc. 429.2906).

*(2*S*)-*N,N*-Bis[(1*R*)-1-phenylethyl]-3-{[(1*S*)-1-phenylethyl]amino}-2-propylpropanamide* ((*R*,*R*,*S*,*S*)-**11**). Prepared and purified according to the general alkylation procedure. Yield: 27–63% (*cf. Table 2*). $[\alpha]_D^{28} = +107.5$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 100°, 300 MHz): 0.75 (*t*, *J* = 7.3, 3 H); 1.0–1.19 (*m*, 2 H); 1.22 (*d*, *J* = 6.5, 3 H); 1.35 (*ddt*, *J* = 8.9, 6.2, 3.6, 2 H); 1.67 (*d*, *J* = 7.0, 6 H); 2.45 (*dd*, *J* = 11.5, 5.4, 1 H); 2.72 (*dd*, *J* = 11.5, 7.6, 1 H); 2.92 (*dddd*, *J* = 6.5, 6.5, 6.5, 6.5, 1 H); 3.64 (*q*, *J* = 6.6, 1 H); 4.70–5.44 (br., 2 H); 6.90–7.37

(*m*, 15 H). ^{13}C-NMR ((D$_6$)DMSO, 100°, 75 MHz): 13.4; 18.2; 19.3; 19.9; 23.3; 32.6; 42.5; 49.8; 52.2; 57.1; 125.8; 126.9; 127.5; 141.0; 145.7; 174.2. HR-MS: 443.3058 ([$M+1$]$^+$, $C_{30}H_{39}N_2O^+$; calc. 443.3062).

*(*S*)-3-Amino-2-methylpropanoic Acid* ((*S*)-**12**). A hydrogenation flask was loaded with 0.46 g (0.86 mmol) of (*R*,*R*,*S*,*S*)-**8**, 0.05 g 20% Pd(OH)$_2$, and 25 ml EtOH containing 5 drops of AcOH. The flask was pressurized to 33 atm of H_2, heated to 65°, and shaken for 12 h. The mixture was filtered over *Celite* and concentrated *in vacuo* to afford 0.27 g (quant.) of the deprotected amine, which was transferred to a glass ampoule, dissolved in 7.0 ml 6N HCl soln., and heated to 90° for 12 h. The crude product was washed with CH_2Cl_2 (3 × 20 ml), the aq. phase was concentrated, and the residue was adsorbed to acidic *Dowex 50W-X4*. The resin was washed with distilled H_2O until neutral, then with 0.1N aq. NH_4OH soln. Evaporation of the basic filtrate afforded 0.06 g (63%) of (*S*)-**12**. $[\alpha]_D^{28} = +14.2$ ($c = 1.3$, 1N aq. HCl); lit. $[\alpha]_D^{28} = -14.2$ ($c = 0.42$, H_2O) for (*R*)-**12** [38].

*(*S*)-3-Amino-2-(phenylmethyl)propanoic Acid* ((*S*)-**13**). According to the procedure described for the preparation of (*S*)-**12**, 0.58 g (1.1 mmol) of (*R*,*R*,*S*,*S*)-**9** was hydrogenolyzed (0.06 g 20% Pd(OH)$_2$) and then hydrolyzed (12 ml 6N aq. HCl, 12 h) to give (*S*)-**13** in 13% yield. $[\alpha]_D^{28} = -15.5$ ($c = 1.0$, 1N aq. HCl); lit. $[\alpha]_D^{28} = -11.0$ ($c = 1.0$, 1N aq. HCl) [39].

*(*S*)-3-Amino-2-ethylpropanoic Acid* ((*S*)-**14**). According to the procedure described for the preparation of (*S*)-**12**, 0.45 g (1.0 mmol) of (*R*,*R*,*S*,*S*)-**10** was hydrogenolyzed (0.09 g 20% Pd(OH)$_2$) and then hydrolyzed (12 ml 6N aq. HCl, 48 h) to give (*S*)-**14** in 55% yield. $[\alpha]_D^{28} = +5.6$ ($c = 1.0$, H_2O); lit. $[\alpha]_D^{28} = +4.6$ ($c = 1.0$, H_2O) wrong sign in [40]!).

*(*S*)-3-Amino-2-propylpropanoic Acid* ((*S*)-**15**). According to the procedure described for the preparation of (*S*)-**12**, 0.58 g (1.3 mmol) of (*R*,*R*,*S*,*S*)-**11** was hydrogenolyzed (0.1 g 20% Pd(OH$_2$) and then hydrolyzed (12 ml 6N aq. HCl, 12 h) to give (*S*)-**15** in 60% yield. $[\alpha]_D^{28} = -3.2$ ($c = 1.0$, 1N aq. HCl). ^{1}H-NMR (D_2O, 400 MHz): 0.83 (*t*, $J = 7.3$, 3 H); 1.25 (*tq*, $J = 7.3$, 7.3, 2 H); 1.44 (*ddt*, $J = 13.2$, 6.7, 6.6, 1 H); 1.50 (*ddt*, $J = 13.6$, 9.2, 6.9, 1 H); 2.51 (*dddd*, $J = 6.9$, 6.7, 6.5, 6.5, 1 H); 2.97 (*dd*, $J = 12.8$, 5.1, 1 H); 3.05 (*dd*, $J = 12.8$, 8.4, 1 H). ^{13}C-NMR (D_2O, 100 MHz): 13.3; 19.6; 32.1; 41.0; 45.1; 181.0.

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