Diastereoselective Coupling of *N*-(*tert*-Butyl)sulfinyl Imines and Dimethyl Malonate. Synthesis of Enantiomerically Enriched β-Amino Esters and β-Lactams

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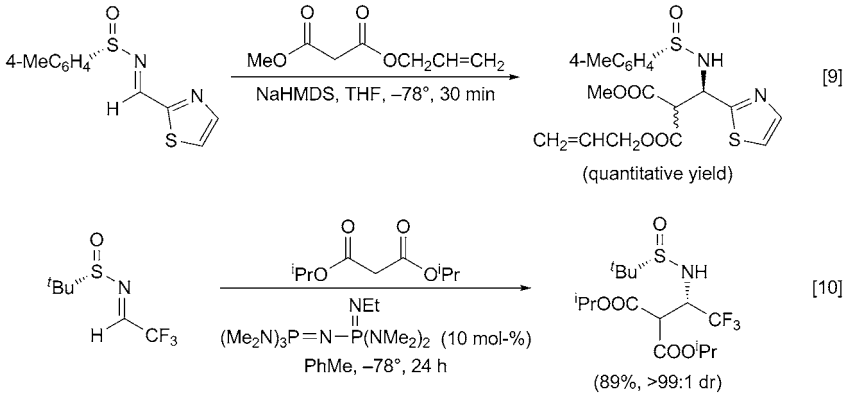
Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

A diastereoselective coupling of dimethyl malonate with *N*-(*tert*-butyl)sulfinyl imines under solvent-free conditions was developed, using $NaHCO_3$ or NaI as base promoters. The resulting dimethyl 2-(1-aminoalkyl)malonates could be easily transformed successively to β-amino esters and the corresponding β-lactams with high optical purity.

1. Introduction. – Chiral amines are important targets for synthetic organic chemists because of their importance in agrochemicals, fine chemicals, and pharmaceuticals. In addition, they have also found high applicability as chiral ligands as well as organocatalysts in asymmetric syntheses. One of the most direct and reliable methods for the synthesis of enantiomerically enriched amine derivatives is the stereoselective addition of an organometallic reagent to the C=N bond of an imine [1]. Significant achievements have been reached in the condensation of enolyzable carbonyl compounds and imines catalyzed by chiral organic and organometallic reagents [2]. The resulting β-aminocarbonyl compounds, the so-called *Mannich* adducts, are versatile intermediates that could be easily transformed into a wide range of interesting multifunctionalized molecules, as for instance, β-amino esters which are direct precursors of β-lactams [3]. A different strategy, leading to the *Mannich* adducts in a stereoselective fashion, consists in the use of chiral imines as electrophiles, and, among them, *N*-(*tert*-butyl)sulfinyl imines [4] have lately emerged as the first choice for several reasons. They are easily prepared [5] by condensation of a carbonyl compound and the corresponding *tert*-butanesulfinamide (=2-methylpropane-2-sulfinamide), which are commercially available in enantiomerically pure form on a large scale at reasonable prices. Nucleophilic additions of organometallic reagents used to take place in high diastereoselectivities, because the *tert*-butylsulfinyl group is capable of metal coordination. Importantly, practical processes for recycling the *tert*-butylsulfinyl group upon deprotection of *N*-(*tert*-butyl)sulfinyl amines have also been reported [6]. Thus, the reaction of ester enolates with *N*-(*tert*-butyl)sulfinyl imines produced β-amino esters. The highest yields and diastereoselectivities were achieved by using ester titanium enolates at $-78°$ in THF [7]. The *Reformatsky* addition of unsubstituted acetate

enolates allowed also access to these compounds under milder reaction conditions (0° or room temperature) [8]. Considering enolates derived from malonates, as far as we know, there are only two examples of nucleophilic addition to chiral *N*-sulfinyl imines: the reaction of allyl methyl malonate with *para*-toluenesulfinyl imine derived from 2-formylthiazole, which *Sunazuka* and *Ōmura* and co-workers used in one step of the synthesis of antibiotic bottromycin A_2 [9], and the organic base-catalyzed reaction of (*S*)-*N*-[(*tert*-butyl)sulfinyl]1,1,1-trifluoroacetaldimine with dialkyl malonates [10] (*Scheme*).

Scheme

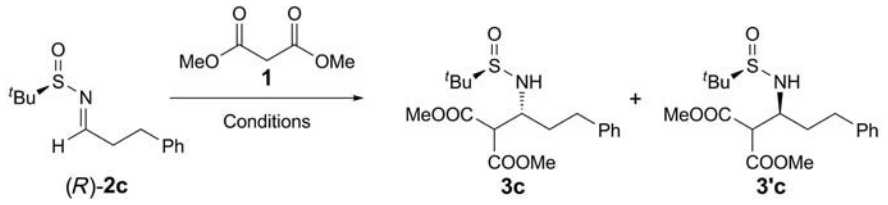


Because of our interest in enolate addition to chiral *N*-(*tert*-butyl)sulfinyl imines [11], we report here the base-mediated condensation of these imines with dimethyl malonate under mild reaction conditions and further synthetic applications of the resulting reaction products.

2. Results and Discussion. – Compound (*R*)-**2c**, derived from 3-phenylpropanal and (*R*)-*tert*-butanesulfinamide, was taken as the imine model for the optimization of the reaction conditions in the base-promoted coupling reaction of dimethyl malonate (**1**) and (*tert*-butyl)sulfinyl imines **2**. Many assays were undertaken, and the most significant ones are compiled in *Table 1*. A good conversion (68%) but a relativety poor diastereoselectivity (32:68) were obtained in the reaction of imine (*R*)-**2c** (1M) with 2 equiv. of dimethyl malonate (**1**) in the presence of 1.5 equiv. of MeONa in MeOH (1M) in THF as solvent at 0° for 12 h (*Table 1*, *Entry 1*). A similar result was obtained with 1.5 equiv. of NaOH as a base, but in this case, performing the reaction at room temperature for 72 h (*Table 1*, *Entry 2*). However, conversion and diastereoselectivity were slightly improved, when a stronger base, such as ^{t}BuOK, was used under the same reaction conditions (*Table 1*, *Entry 3*). The reaction with 2 equiv. of $NaHCO_3$ in THF at room temperature led to a lower conversion (39%) but, surprisingly, to a significantly higher and opposite diastereoselectivity (91:9; *Table 1*, *Entry 4*). It seems that the nucleophilic addition of **1** to chiral (*tert*-butyl)sulfinyl imines follows different stereochemical pathways, depending on the base. A better result (90% conversion) was obtained, when the reaction was performed in the absence of any solvent but using

4 equiv. of dimethyl malonate (**1**). Importantly, a single diastereoisomer **3c** was isolated as reaction product (*Table 1*, *Entry 5*). Switching from $NaHCO_3$ to $KHCO_3$ as a base did not lead to a better result (slightly higher conversion, but poorer diastereoselectivity, *Table 1*, *Entry 6*), as in the case of using Et_3N (*Table 1*, *Entry 7*). NaI has recently been used successfully as a base in the condensation of compounds with acidic H-atoms, such as $BrCH_2NO_2$, with imines [12], and identical results were obtained, when 1 equiv. of NaI was used instead of $NaHCO_3$ (*Table 1*, compare *Entries 5* and *8*). In these heterogeneous reactions, the conversion was not improved using 3 equiv. of NaI (*Table 1*, *Entry 9*). Finally, KI was not as effective as a base as the Na salt to perform this coupling reaction (*Table 1*, *Entry 10*).

Table 1. *Reaction of Aldimine (*R*)-***2c*** with Dimethyl Malonate* (**1**)



(*R*)-**2c** **3c** **3'c**

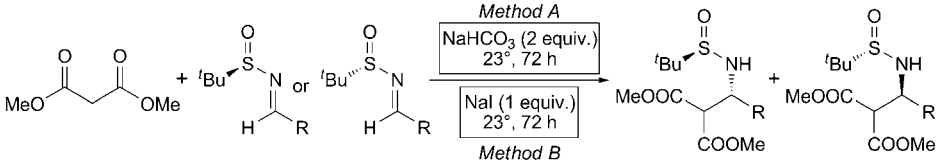
Entry	Conditions[a])	Conversion [%][b])	**3c**/**3′c** ratio[c])
1	**1** (2 equiv.), 1M MeONa/MeOH (1.5 equiv.), THF (2 ml), 0°, 12 h	68	32 : 68
2	**1** (2 equiv.), NaOH (1.5 equiv.), THF (2 ml), 23°, 72 h	69	28 : 72
3	**1** (2 equiv.), *t*BuOK (1.5 equiv.), THF (2 ml), 23°, 72 h	77	17 : 83
4	**1** (2 equiv.), $NaHCO_3$ (2 equiv.), THF (2 ml), 23°, 72 h	39	91 : 9
5	**1** (4 equiv.), $NaHCO_3$ (2 equiv.), 23°, 72 h	90	99 : 1
6	**1** (4 equiv.), $KHCO_3$ (2 equiv.), 23°, 72 h	93	75 : 25
7	**1** (2 equiv.), Et_3N (2 equiv.), 23°, 72 h	15	–
8	**1** (2 equiv.), NaI (1 equiv.), 23°, 72 h	90	99 : 1
9	**1** (2 equiv.), NaI (3 equiv.), 23°, 72 h	88	99 : 1
10	**1** (2 equiv.), KI (1 equiv.), 23°, 72 h	5	–

[a]) All the reactions were carried out with 0.2 mmol of aldimine (*R*)-**2c**. [b]) Conversion is given based on the disappearance of the starting (*R*)-**2c** by ^{1}H-NMR. [c]) Diastereoisomer ratio was determined by ^{1}H-NMR.

We studied next the coupling reaction of different *N*-(*tert*-butyl)sulfinyl imines **2** with dimethyl malonate (**1**) by applying the optimized conditions depicted in *Table 1*, *Entries 5* (*Method A*) and *8* (*Method B*). The expected 2-(1-aminoalkyl)malonates **3** were obtained in moderate-to-good yields as single diastereoisomers in all cases (*Table 2*) except for aldimine **2d** derived from PhCHO. Compound **3d** was isolated in only 7% yield with $NaHCO_3$ as a base (*Table 2*, *Entry 7*) and was not detected when the reaction was conducted in the presence of NaI (*Table 2*, *Entry 8*). In these two cases, the starting aldimine (*R*)-**2d** was the major component of the reaction mixture. *Mannich* coupling reaction also did not occur with aromatic aldimines derived from 4-nitro- and 4-hydroxybenzaldehyde. It has been previously reported that *N*-sulfonyl imines derived from PhCHO react with dialkyl malonates al low temperature, but

easily undergo a *retro-Mannich* process when standing at room temperature under basic conditions [13] as in *Methods A* and *B*. In general, *Method B* led to slightly higher yields than *Method A* (*Table 2*, *Entries 1–6*).

Table 2. *Reactions of Different* N-*(*tert-*Butyl)sulfonyl Imines* ***2*** *with Dimethyl Malonate* (**1**)



1 (*R*)-**2** (*S*)-**2** **3** *ent*-**3**

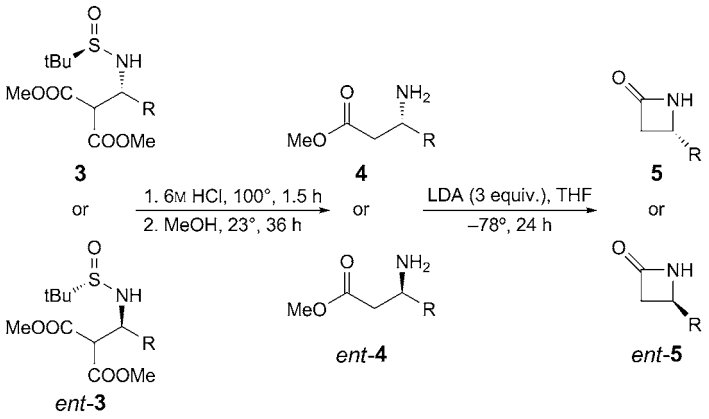
Entry	R	Imine **2**	*Method*[a])	2-(1-Aminoalkyl)malonates **3**[b])	Yield [%][c])
1	$Me(CH_2)_7$	(*R*)-**2a**	*A*	**3a**	74
2	$Me(CH_2)_7$	(*R*)-**2a**	*B*	**3a**	86
3	^{i}Pr	(*R*)-**2b**	*A*	**3b**	43
4	^{i}Pr	(*R*)-**2b**	*B*	**3b**	60
5	$Ph(CH_2)_2$	(*R*)-**2c**	*A*	**3c**	77
6	$Ph(CH_2)_2$	(*R*)-**2c**	*B*	**3c**	86
7	Ph	(*R*)-**2d**	*A*	**3d**	7
8	Ph	(*R*)-**2d**	*B*	**3d**	–
9	$Me(CH_2)_7$	(*S*)-**2a**	*A*	*ent*-**3a**	78
10	^{i}Pr	(*S*)-**2b**	*A*	*ent*-**3b**	47
11	$Ph(CH_2)_2$	(*S*)-**2c**	*A*	*ent*-**3c**	82
12	$PhCH_2$	(*R*)-**2e**	*B*	**3e**	78
13	^{i}Bu	(*R*)-**2f**	*B*	**3f**	77

[a]) *Method A:* 4 equiv. of **1** were used; *Method B:* 2 equiv. of **1** were used. [b]) All products were >95% pure (GLC and/or 300-MHz ^{1}H-NMR). [c]) Yield of isolated product after CC (SiO_2; hexane/AcOEt) based on the starting aldimine **2**.

To establish the utility of the obtained 2-(1-aminoalkyl)malonates **3**, some of them were transformed first to the corresponding β-amino ester **4** and then to the β-lactams **5** in high optical purity, this being the same as the starting *Mannich* products **3**. Acidic hydrolysis was performed with 6M HCl under reflux, and crude reaction products **4** were obtained in high purity with very good yields (*Table 3*), without further purification for the next step being needed. Intramolecular cyclization of β-amino esters **4** was achieved upon treatment with an excess of lithium diisopropylamide (LDA) at $-78°$, leading to the expected β-lactam **5**, but in moderate yields in all cases (*Table 3*).

The configuration of the newly created stereogenic center in 2-(1-aminoalkyl)malonates **3** was determined by comparing the specific rotation of **5c** ($[\alpha]_D^{23} = +10.3$ (c = 1.35, $CHCl_3$)), derived from **3c**, with that provided in the literature for (*R*)-4-(2-phenylethyl)azetidin-2-one ($[\alpha]_D^{25} = +19$ ($c = 0.21$, $CHCl_3$)) [14]. This experimental result could be explained considering that a six-membered ring model **TSI** (*Fig.*), with a four-membered metallacycle, in which the metal is chelated both by the O- and the N-atoms of the imine moiety, would be involved. Thus, we assume that the nucleophilic attack occurs to the *Si*-face of the imine unit for (R_S)-isomers (*Table 2*, *Entries 1–8*, *12*,

Table 3. *Transformations of Dimethyl 2-(1-Aminoaltyl)malonates* **3** *to β-Amino Esters* **4** *and β-Lactams* **5**



Entry	R	Starting imine **3**	*β*-Amino ester **4**	Yield [%][a])	*β*-Lactam **5**	Yield [%][b])
1	$Me(CH_2)_7$	**3a**	**4a**	91	**5a**	45
2	$Ph(CH_2)_2$	**3c**	**4c**	82	**5c**	58
3	$Ph(CH_2)_2$	*ent*-**3c**	*ent*-**4c**	83	*ent*-**5c**	53
4	$PhCH_2$	**3e**	**4e**	81	**5e**	43

[a]) Yield of isolated product based on the starting dimethyl 2-(1-aminoalkyl)malonates **3**. [b]) Yield of isolated product after CC (SiO_2; hexane/AcOEt) based on the starting amino ester **4**.

and *13*) and to the *Re*-face in the case of (S_S)-derivatives (*Table 2*, *Entries 9–11*). As previously commented, the stereochemical pathway under the solvent-free reaction conditions in *Methods A* and *B* is the opposite to that obtained when the reaction is performed in THF (*Table 1*, *Entries 1–3*). This result is consistent with an approach of the malonate to the less-hindered *Re* face of C=N in a s-*cis*-like conformation (the most stable conformation according to theoretical calculations [15]) through a non-chelated transition state model **TSII** (*Fig.*).

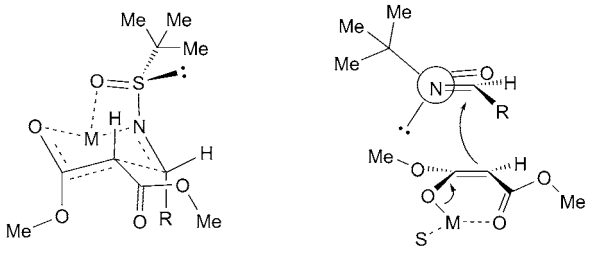


Figure. *The six-membered-ring model* **TSI** *and non-chelated transition-state model* **TSII** *for 2-(1-aminoalkyl)malonates* **3**

3. Conclusions. – We have reported that a direct *Mannich*-type reaction of dimethyl malonate and *N*-(*tert*-butyl)sulfinyl imines could be performed under solvent-free conditions in the presence of $NaHCO_3$ or NaI. The process is highly diastereoselective, giving rise to a single stereoisomer. The configuration of the newly created stereogenic center is determined by the configuration of the starting chiral imine. Enantiomerically pure β-amino esters and β-lactams can be easily obtained from the *Mannich* products.

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Experimental Part

1. *General*. TLC: Silica gel *60* F_{254} using aluminum plates; visualization with phosphomolybdic acid (PMA) stain. Flash chromatography (FC): handpacked columns of silica gel *60* (SiO_2; 230–400 mesh). M.p.: *Reichert Thermovar* hostage microscope; uncorrected. Optical rotations: *Perkin-Elmer Model 341* polarimeter with a thermally jacketted 5-cm cell at *ca.* 20°; concentrations (*c*) in g/100 ml. IR Spectra: *Nicolet Impact 400D* spectrophotometer equipped with an ATR component; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Bruker AV300* and *Bruker AV400* spectrometers; at 300 or 400 MHz, with $CDCl_3$ as the solvent and TMS as internal standard (0.00 ppm). ^{13}C-NMR Spectra: *Bruker AV300* or *Bruker AV400* spectrometers; ^{1}H-decoupling at 75 or 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3 (δ in ppm, *J* in Hz). EI-MS: *Agilent 5973N* gas chromatographer/mass spectrometer instrument; at 70 eV; and fragment ions in *m*/*z* with relative intensities [%] in parentheses. HR-EI-MS: *Finnigan MAT955* instrument; at 70 eV.

2. *Starting Materials.* (R_S)-*tert*-Butanesulfinamide and its enantiomer were a gift of *Medalchemy* (> 99% ee by chiral HPLC on a *Chiracel AS* column; hexane/^{i}PrOH (90:10) 1.2 ml/min, λ 222 nm). Other used reagents and solvents such as dimethyl malonate, MeOH, THF, MeONa, NaOH, ^{t}BuOK, $NaHCO_3$, $KHCO_3$, Et_3N, NaI, KI, HCl, $^i Pr_2NH$, BuLi, and AcOEt are commercially available. *N*-(*tert*-Butyl)sulfinyl imines **2** were prepared according to known protocols [5].

3. *Reaction of Dimethyl Malonate* **1** *with* N-*(*tert-*Butyl)sulfinyl Imines* **2**. *Synthesis of Methyl 2-(1-Aminoalkyl)malonates* **3** *(Method A)*. A heterogeneous mixture of *dimethyl malonate* (**1**; 1.056 g, 0.94 ml, 8.0 mmol), $NaHCO_3$ (236 mg, 4.0 mmol), and the corresponding *N*-(*tert*-butyl)sulfinyl imine **2** (2.0 mmol) was stirred at r.t. for 72 h. The resulting mixture was hydrolyzed with H_2O (10 ml), acidified with 2M HCl (3 ml), and extracted with AcOEt (3 × 15 ml). The combined org. layer was dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by CC (SiO_2; hexane/AcOEt) to give pure compounds **3**.

*Dimethyl [(1*R*)-1-{[(*R*)-(*tert-*Butyl)sulfinyl]amino}nonyl]propanedioate* (**3a**). Yield: 558 mg (74%). Colorless oil. $[\alpha]_D^{23} = -38$ ($c = 1.23$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.37. IR (neat): 2953, 2925, 2856, 1735, 1434, 1240, 1159, 1075. ^{1}H-NMR: 0.88 (*t*, *J* = 6.8, *Me*CH_2); 1.22 (*s*, ^{t}Bu); 1.24–1.46 (*m*, 6 CH_2); 1.54–1.59 (*m*, CH_2); 3.77 (*s*, Me); 3.80 (*s*, Me); 3.78–3.84 (*m*, CHCHN); 4.53 (*d*, *J* = 9.3, NH). ^{13}C-NMR: 14.1 (Me); 22.6 (CH_2); 22.7 (Me); 26.2, 29.0, 29.2, 29.4, 31.8, 34.1 (CH_2); 52.5, 52.8 (Me); 56.0 (CH); 56.2 (C); 56.9 (CH); 168.3, 168.8 (C). EI-MS: 270 (7, [*M* – ^{t}BuSOH$_2$]$^+$), 255 (11), 225 (23), 200 (24), 187 (100), 175 (68), 143 (30), 133 (81), 101 (21), 69 (38), 55 (43). HR-EI-MS: 320.1520 ([*M* – ^{t}Bu]$^+$, $C_{14}H_{26}NO_5S^+$; calc. 320.1532).

*Dimethyl [(1*R*)-1-{[(*R*)-(*tert-*Butyl)sulfinyl]amino}-2-methylpropyl]propanedioate* (**3b**). Yield: 264 mg (43%). Colorless oil. $[\alpha]_D^{23} = -30$ ($c = 1.23$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.28. IR (neat): 2957, 2930, 1731, 1434, 1262, 1194, 1159, 1076. ^{1}H-NMR: 0.92 (*d*, *J* = 6.8, 2 Me); 1.25 (*s*, ^{t}Bu); 1.75 (*sept.*, *J* = 6.8, Me_2CH); 3.61–3.68 (*m*, CHN); 3.73–3.76 (*m*, CHCHN); 3.79 (*s*, Me); 3.82 (*s*, Me); 4.89 (*d*, *J* = 8.4, NH). ^{13}C-NMR: 18.8, 20.2, 23.0 (Me); 33.3 (CH); 52.6, 53.1 (Me); 53.9 (CH); 56.5 (C); 62.6 (CH); 168.0, 169.4 (C). EI-MS: 251 (6, [*M* – $Me_2C{=}CH_2$]$^+$), 231 (15), 207 (18), 163 (19), 140 (37), 55 (100). HR-EI-MS: 251.0833 ([*M* – $Me_2C{=}CH_2$]$^+$, $C_9H_{17}NO_5S^+$; calc. 251.0827).

*Dimethyl [(1*R*)-1-{[(*R*)-(*tert*-Butyl)sulfinyl]amino}-3-phenylpropyl]propanedioate* (**3c**). Yield: 568 mg (77%). Colorless oil. $[\alpha]_D^{23} = -32$ ($c = 1.43$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.29. IR (neat): 3060, 3024, 2953, 2924, 2855, 1734, 1434, 1240, 1071, 1045. ^{1}H-NMR: 1.26 (*s*, ^{t}Bu); 1.89–1.95 (*m*, CH_2); 2.59–2.66 (*m*, 1 H of CH_2); 2.80–2.87 (*m*, 1 H of CH_2); 3.72 (*s*, Me); 3.78 (*s*, Me); 3.80–3.86 (*m*, CHN); 3.88 (*d*, $J = 4.1$, C*H*CHN); 4.64 (*d*, $J = 9.6$, NH); 7.15–7.21 (*m*, 3 arom. H); 7.26–7.30 (*m*, 2 arom. H). ^{13}C-NMR: 22.7 (Me); 32.4, 35.8 (CH_2); 52.4, 52.8 (Me); 56.0 (CH); 56.2 (C); 56.3 (CH); 126.0, 128.2, 128.3, 140.8 (arom. C); 168.0, 168.6 (C). EI-MS: 263 (4, $[M - {}^t\text{BuSOH}]^+$), 247 (11), 207 (36), 175 (100), 143 (44), 132 (23), 115 (30), 91 (82), 77 (19), 65 (16). HR-EI-MS: 207.0204 ($[M - {}^t\text{Bu} - \text{Ph}(CH_2)_2]^+$, $C_6H_9NO_5S^+$; calc. 207.0201).

*Dimethyl [(1*S*)-1-{[(*R*)-(*tert*-Butyl)sulfinyl]amino}-3-phenylpropyl]propanedioate* (**3′c**). Side product. Colorless oil. $[\alpha]_D^{23} = -96$ ($c = 1.15$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.35. IR (neat): 3183, 3062, 3028, 2955, 2931, 2860, 1727, 1258, 1239, 1152, 1039, 1021. ^{1}H-NMR: 1.19 (*s*, ^{t}Bu); 1.86–1.95 (*m*, CH_2); 2.14–2.23 (*m*, 1 H of CH_2); 2.67–2.75 (*m*, 1 H of CH_2); 2.82–2.90 (*m*, 1 H of CH_2); 3.68 (*d*, $J = 5.7$, C*H*CHN); 3.70 (*s*, Me); 3.75 (*s*, Me); 3.83–3.92 (*m*, CHN); 4.30 (*d*, $J = 9.3$, NH); 7.15–7.21 (*m*, 3 arom. H); 7.26–7.30 (*m*, 2 arom. H). ^{13}C-NMR: 22.6 (Me); 32.1, 36.1 (CH_2); 52.5, 52.6 (Me); 56.1 (CH); 56.2 (C); 57.0 (CH); 126.0, 128.4, 128.5, 140.7 (arom. C); 168.0, 168.5 (C). EI-MS: 263 (1, $[M - {}^t\text{BuSOH}]^+$), 248 (10), 216 (21), 183 (40), 156 (17), 128 (23), 117 (12), 91 (100), 65 (18). HR-EI-MS: 263.1160 ($C_{14}H_{17}NO_4^+$; $[M - {}^t\text{BuSOH}]^+$, calc. 263.1158).

*Dimethyl [(*S*)-{[(*R*)-(*tert*-Butyl)sulfinyl]amino}(phenyl)methyl]propanedioate* (**3d**). Yield: 47 mg (7%). Colorless oil. $[\alpha]_D^{23} = -21$ ($c = 0.98$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.26. IR (neat): 3281, 3060, 2985, 2955, 1755, 1715, 1312, 1263, 1067, 1057. ^{1}H-NMR: 1.19 (*s*, ^{t}Bu); 3.67 (*s*, Me); 3.69 (*s*, Me); 4.01 (*d*, $J = 6.7$, C*H*CHN); 4.81 (*d*, $J = 9.4$, NH); 5.09 (*dd*, $J = 9.3$, 6.7, CHN); 7.30–7.41 (*m*, 5 arom. H). ^{13}C-NMR: 22.5 (Me); 52.6, 52.7 (Me); 56.4 (C); 58.1, 60.1 (CH); 127.0, 128.1, 128.6, 138.8 (arom. C); 167.2, 168.2 (C). EI-MS: 235 (14, $[M - {}^t\text{BuSOH}]^+$), 219 (77), 164 (12), 152 (100), 132 (29), 103 (51), 77 (48), 69 (17), 59 (21), 51 (20). HR-EI-MS: 235.0849 ($[M - {}^t\text{BuSOH}]^+$, $C_{12}H_{13}NO_4^+$; calc. 235.0845).

*Dimethyl [(1*S*)-1-{[(*S*)-(*tert*-Butyl)sulfinyl]amino}nonyl]propanedioate* (*ent*-**3a**). Yield: 588 mg (78%). Physical and spectroscopic data were found to be same as for **3a**. $[\alpha]_D^{23} = +36$ ($c = 1.46$, CH_2Cl_2).

*Dimethyl [(1*S*)-1-{[(*S*)-(*tert*-Butyl)sulfinyl]amino}-2-methylpropyl]propanedioate* (*ent*-**3b**). Yield: 288 mg (47%). Physical and spectroscopic data were found to be same as for **3b**. $[\alpha]_D^{23} = +42$ ($c = 1.40$, CH_2Cl_2).

*Dimethyl [(1*S*)-1-{[(*S*)-(*tert*-Butyl)sulfinyl]amino}-3-phenylpropyl]propanedioate* (*ent*-**3c**). Yield: 738 mg (82%). Physical and spectroscopic data were found to be same as for **3c**. $[\alpha]_D^{23} = +29$ ($c = 0.94$, CH_2Cl_2).

4. *Reaction of Dimethyl Malonate* (**1**) *with* N-(tert-*Butyl)sulfinyl Imines* **2**. *Synthesis of Dimethyl 2-(1-Aminoalkyl)malonates* **3** (*Method B*). A heterogeneous mixture of **1** (0.528 g, 0.47 ml, 4.0 mmol), NaI (0.300 g, 2.0 mmol), and the corresponding *N*-(*tert*-butyl)sulfinyl imine **2** (2.0 mmol) was stirred at r.t. for 72 h. The resulting mixture was hydrolyzed with H_2O (10 ml), acidified with 2M HCl, and extracted with AcOEt (3×15 ml). The combined org. layer was dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by CC (SiO_2; hexane/AcOEt) to give pure compounds **3**.

Compound **3a**. Yield: 649 mg (86%). Physical and spectroscopic data are given above.

Compound **3b**. Yield: 368 mg (60%). Physical and spectroscopic data are given above.

Compound **3c**. Yield: 635 mg (86%). Physical and spectroscopic data are given above.

*Dimethyl [(1*R*)-1-{[(*R*)-(*tert*-Butyl)sulfinyl]amino}-2-phenylethyl]propanedioate* (**3e**). Yield: 554 mg (78%). Colorless oil. $[\alpha]_D^{23} = -35$ ($c = 1.62$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.39. IR (neat): 3050, 3023, 2978, 2954, 2924, 2854, 1734, 1240, 1073, 1046. ^{1}H-NMR: 1.07 (*s*, ^{t}Bu); 2.92 (*d*, $J = 7.0$, CH_2); 3.76–3.78 (*m*, C*H*CHN); 3.80 (*s*, Me); 3.81 (*s*, Me); 4.11–4.14 (*m*, CHN); 4.62 (*d*, $J = 9.3$, NH); 7.17–7.31 (*m*, 5 arom. H). ^{13}C-NMR: 22.4 (Me); 40.6 (CH_2); 52.6, 53.0 (Me); 55.0 (CH); 56.1 (C); 58.5 (CH); 126.7, 128.5, 129.4, 137.5 (arom. C); 168.2, 168.8 (C). EI-MS: 249 (15, $[M - {}^t\text{BuSOH}]^+$), 234 (29), 132 (12), 117 (22), 91 (100), 65 (13). HR-EI-MS: 249.0999 ($[M - {}^t\text{BuSOH}]^+$, $C_{13}H_{15}NO_4^+$; calc. 249.1001).

*Dimethyl [(1*R*)-1-{[(*R*)-(*tert*-Butyl)sulfinyl]amino}-3-methylbutyl]propanedioate* (**3f**). Yield: 495 mg (77%). Colorless oil. $[\alpha]_D^{23} = -38$ ($c = 1.59$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.51. IR (neat): 3330, 2953, 2925, 2870, 1745, 1721, 1254, 1160, 1064. ^{1}H-NMR: 0.90 (*d*, $J = 6.5$, Me); 0.92 (*d*, $J = 6.6$, Me); 1.22 (*s*, ^{t}Bu); 1.24–1.28 (*m*, 1 H of CH_2); 1.55–1.65 (*m*, 1 H of CH_2); 1.72–1.79 (*m*, Me_2CH); 3.77 (*s*,

Me); 3.80 (*s*, Me); 3.84–3.92 (*m*, CHCHN); 4.51 (*d*, *J* = 9.7, NH). ^{13}C-NMR: 20.9, 22.6 (Me); 23.1 (CH); 42.9 (CH_2); 52.3, 52.7 (Me); 55.1 (CH); 56.1 (C); 56.2 (CH); 168.1, 168.7 (C). EI-MS: 265 (4, $[M - Me_2C{=}CH_2]^+$), 133 (100), 101 (14) 69 (10), 57 (28). HR-EI-MS: 265.0981 ($[M - Me_2C{=}CH_2]^+$, $C_{10}H_{19}NO_5S^+$; calc. 265.0984).

5. *Acidic Hydrolysis of Methyl 2-(1-Aminoalkyl)malonates* **3**. *Synthesis of β-Amino Esters* **4**. A mixture of **3** (1.0 mmol) and 6M HCl (4 ml) was heated under reflux for 1.5 h. The mixture was cooled to r.t., and MeOH (16 ml) was added. The mixture was stirred for 36 h at the same temp., and the reaction was quenched with a sat. aq. $NaHCO_3$ soln. (10 ml), and the mixture was extracted with AcOEt (3 × 15 ml). The combined org. layer was dried ($MgSO_4$), and the solvent was evaporated to give compounds **4** which were pure enough for the next reaction.

*Methyl (3*R*)-3-Aminoundecanoate* (**4a**). Yield: 228 mg (91%). Colorless oil. $[\alpha]_D^{23} = -9$ ($c = 1.48$, CH_2Cl_2). R_f (AcOEt) 0.45. IR (neat): 2953, 2923, 2854, 1735, 1436, 1165, 1017. ^{1}H-NMR: 0.88 (*t*, *J* = 7.0, *Me*CH_2); 1.27–1.43 (*m*, 7 CH_2); 2.34 (*dd*, *J* = 15.9, 8.8, 1 H of CH_2); 2.52 (*dd*, *J* = 15.9, 4.1, 1 H of CH_2); 2.76 (br. *s*, NH_2); 3.20–3.26 (*m*, CHN); 3.70 (*s*, Me). ^{13}C-NMR: 14.1 (Me); 22.6, 26.0, 29.2, 29.5, 31.8, 36.9, 41.5 (CH_2); 48.4 (CH); 51.6 (Me); 172.8 (C). EI-MS: 200 (8, $[M - NH_3]^+$), 142 (79), 102 (100), 70 (31), 60 (24), 56 (15).

*Methyl (3*R*)-3-Amino-5-phenylpentanoate* (**4c**). Yield: 169 mg (82%). Colorless oil. $[\alpha]_D^{23} = +5$ ($c = 0.61$, CH_2Cl_2). R_f (AcOEt) 0.37. IR (neat): 3025, 2950, 2923, 2857, 1731, 1435, 1158, 838. ^{1}H-NMR: 1.62–1.82 (*m*, CH_2, NH_2); 2.33 (*dd*, *J* = 15.7, 6.9, 1 H of CH_2); 2.52 (*dd*, *J* = 15.7, 4.0, 1 H of CH_2); 2.62–2.81 (*m*, CH_2); 3.15–3.26 (*m*, CHN); 3.69 (*s*, Me); 7.16–7.21 (*m*, 3 arom. H); 7.24–7.31 (*m*, 2 arom. H). ^{13}C-NMR: 32.4, 39.2, 42.4 (CH_2); 48.0 (CH); 51.5 (Me); 125.9, 128.3, 128.4, 141.6 (arom. C); 172.8 (C). EI-MS: 207 (15, M^+), 190 (22), 134 (42), 130 (29), 117 (27), 102 (100), 91 (83), 70 (30), 60 (21).

*Methyl (3*S*)-3-Amino-5-phenylpentanoate* (*ent*-**4c**). Yield: 172 mg (83%). Physical and spectroscopic data were found to be same as for **4c**. $[\alpha]_D^{23} = -5$ ($c = 1.32$, CH_2Cl_2).

*Methyl (3*R*)-3-Amino-4-phenylbutanoate* (**4e**). Yield: 156 mg (81%). Colorless oil. $[\alpha]_D^{23} = +7$ ($c = 1.54$, CH_2Cl_2). R_f (MeOH/CH_2Cl_2 1:1) 0.55. IR (neat): 3060, 3026, 2950, 2922, 2853, 1731, 1454, 1436, 1258, 1195, 1160. ^{1}H-NMR: 1.69 (br. *s*, NH_2); 2.34 (*dd*, *J* = 15.9, 8.8, 1 H of CH_2); 2.52 (*dd*, *J* = 15.9, 4.1, 1 H of CH_2); 2.63 (*dd*, *J* = 13.4, 5.7, 1 H of CH_2); 3.43–3.51 (*m*, CHN); 3.68 (*s*, Me); 7.19–7.33 (*m*, 5 arom. H). ^{13}C-NMR: 41.5, 43.9 (CH_2); 49.6 (CH); 51.6 (Me); 126.5, 128.5, 129.3, 138.4 (arom. C); 172.8 (C). EI-MS: 120 (24, $[M - CH_2COOMe]^+$), 102 (100), 91 (17), 70 (22), 60 (18).

6. *Synthesis of β-Lactams* **5** *from β-Amino Esters* **4**. To a THF soln. (8 ml) of ^{i}Pr$_2$NH (0.272 mg, 0.377 ml, 2.7 mmol) was added BuLi (2.5M in hexane, 1.0 ml, 2.5 mmol) at 0°. After stirring for 30 min, the mixture was cooled to −78°. To the mixture was added a soln. of the corresponding β-amino ester **4** (0.7 mmol) in THF (3 ml). After stirring at the same temp. for 24 h, the reaction was quenched with a sat. aq. $NaHCO_3$ soln. (10 ml), and the mixture was extracted with AcOEt (3 × 15 ml). The combined org. layer was dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by CC (SiO_2; hexane/AcOEt) to give pure compounds **5**.

*(4*R*)-4-Octylazetidin-2-one* (**5a**). Yield: 57 mg (45%). White solid. M.p.: 47–48° (CH_2Cl_2/hexane). $[\alpha]_D^{23} = -8$ ($c = 1.06$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.57. IR (KBr): 3190–3130, 2955, 2918, 2849, 1779, 1701, 1467, 1199. ^{1}H-NMR: 0.88 (*t*, *J* = 7.0, *Me*CH_2); 1.27–1.44 (*m*, 6 CH_2); 1.54–1.67 (*m*, CH_2); 2.52 (*ddd*, *J* = 16.9, 4.6, 3.4, 1 H of CH_2CO); 3.04 (*ddd*, *J* = 14.8, 5.0, 2.1, 1 H of CH_2CO); 3.56–3.63 (*m*, CHN); 6.61 (br. *s*, NH). ^{13}C-NMR: 13.9 (Me); 22.5, 26.1, 29.1, 29.2, 29.3, 31.7, 35.3, 43.3 (CH_2); 48.1 (CH); 168.5 (C). EI-MS: 140 (31, $[M - HN{=}C{=}O]^+$), 111 (15), 97 (32), 83 (38), 70 (100), 69 (67), 56 (96).

*(4*R*)-4-(2-Phenylethyl)azetidin-2-one* (**5c**). Yield: 71 mg (58%). Colorless oil. $[\alpha]_D^{23} = +11$ ($c = 1.35$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.40. IR (film): 3290–3220, 3060, 3025, 2925, 1736, 1495, 1454, 1373, 1182. ^{1}H-NMR: 1.97 (*t*, *J* = 7.6, CH_2); 2.57 (*ddd*, *J* = 14.9, 2.4, 1.3, 1 H of CH_2CO); 2.63–2.76 (*m*, C*H*$_2$Ph), 3.06 (*ddd*, *J* = 14.9, 5.0, 2.2, 1 H of CH_2CO); 3.60–3.67 (*m*, CHN); 5.79 (br. *s*, NH); 7.16–7.33 (*m*, 5 arom. H). ^{13}C-NMR: 32.9, 36.9, 43.5 (CH_2); 47.8 (CH); 126.3, 128.3, 128.6, 140.5 (arom. C); 167.8 (C). EI-MS: 175 (23, M^+), 158 (19), 133 (44), 132 (35), 91 (100), 65 (12). HR-EI-MS: 175.0999 (M^+, $C_{11}H_{13}NO^+$; calc. 175.0997).

*(4*S*)-4-(2-Phenylethyl)azetidin-2-one* (*ent*-**5c**). Yield: 65 mg (53%). Physical and spectroscopic data were found to be same as for **5c**. $[\alpha]_D^{23} = -10$ ($c = 1.31$, CH_2Cl_2).

(4R)-4-Benzylazetidin-2-one (**5e**). Yield: 48 mg (43%). Colorless oil. $[\alpha]_D^{23} = +18$ ($c = 1.44$, CH_2Cl_2). R_f (hexane/AcOEt 1:1) 0.36. IR (film): 3305–3210, 2951, 2923, 2852, 1738, 1454, 1364, 1179. ^{1}H-NMR: 2.69 (*ddd*, $J = 14.8, 2.3, 1.2$, 1 H of CH_2CO); 2.85 (*dd*, $J = 13.7, 7.8$, 1 H of CH_2); 2.97 (*dd*, $J = 13.7, 5.9$, 1 H of CH_2); 3.06 (*ddd*, $J = 14.8, 4.9, 2.2$, 1 H of CH_2CO); 3.80–3.87 (*m*, CHN); 6.10 (br. *s*, NH); 7.16–7.37 (*m*, 5 arom. H). ^{13}C-NMR: 41.8, 43.2 (CH_2); 48.9 (CH); 126.8, 128.7, 128.8, 137.5 (arom. C); 167.6 (C). EI-MS: 161 (9, M^+), 133 (11), 118 (100), 117 (42), 91 (64), 70 (39), 65 (16). HR-EI-MS: 161.0837 (M^+, $C_{10}H_{11}NO^+$; calc. 161.0841).

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