Diastereo- and Enantioselective Synthesis of α-Substituted β-Amino Acid Esters by Tandem Michael-addition / α-Alkylation with TMS-SAMP as Chiral Equivalent of Ammonia

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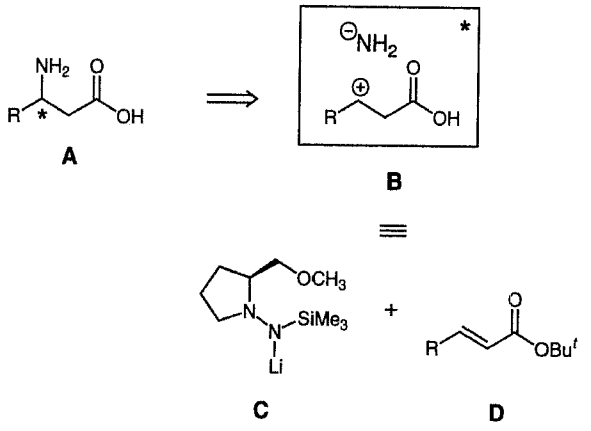
Abstract: The hetero Michael-addition of (*S*)-(−)2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) to α,β-unsaturated esters 1, followed by α-alkylation of the intermediate esterenolates with various electrophiles yields α-substituted β-hydrazino esters **3** of anti-configuration in good to excellent diastereomeric excesses (de = 63 - ≥96 %). Subsequent reductive N-N bond cleavage leads to β-amino acid esters **4** ($R^1 = C_6H_{11}$) in good yields and high diastereo- and enantiomeric purity (de,ee ≥96 %). The stereochemistry was confirmed by NMR-spectrocopy and X-ray structure analysis.

β-Amino acids **A**, although of less importance than the parent α-amino acids, are crucial structural features of many biologically active and natural products[1]. In addition, they are key building blocks of β-lactam antibiotics[2,3]. Consequently, the asymmetric synthesis of β-amino acids[4] is a rapidly growing field, as shown by a flood of publications in recent years[5-9]. Besides syntheses starting from enantiopure natural building blocks, such as aspartic acid[5], and enatioselective syntheses under C-C bond formation[6], stereoselective C-N bond forming reactions according to the retrosynthetic analysis **A** ⇒ **B** have been studied recently. Both variants in these hetero Michael-additions, employing either achiral N-nucleophiles and chirally modified acceptors[7] or *vice versa* chiral amine donors and achiral acceptors[8], have been reported. To avoid regioselectivity problems (1,2- *vs* 1,4-addition) N-silylated amines proved to be especially useful as weak nucleophiles[9].

In a separate paper[10] we disclosed our independent results[11,12] in this field based on lithiated (*S*)-(−)-2-methoxymethyl-1-trimethylsilylamino-pyrrolidine (TMS-SAMP) **C** as chiral Michael donor and its conjugate addition to enoates **D** affording β-amino acids of high enantiomeric purity.

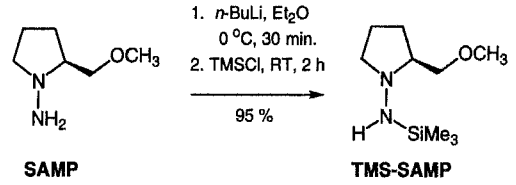


Formula **A** - **D**

The new hydrazine TMS-SAMP is easily prepared from the well established auxiliary (*S*)-(−)1-amino-2-methoxymethylpyrrolidine (SAMP) by metalation with *n*-butyllithium and N-silylation with chlorotrimethylsilane in 95 % yield (scheme 1).

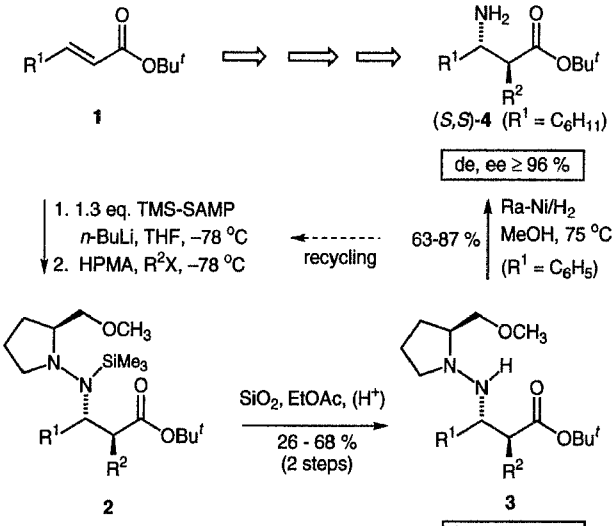
We now wish to report on a useful extension of this approach towards α-substituted β-amino acids based on a tandem hetero Michael-addition / α-esterenolate alkylation protocol and taking advantage of the weak N-N hydrazine bond to recycle the chiral auxiliary.

As is depicted in scheme 2, TMS-SAMP was metalated in tetrahydrofuran at -78°C and trapped with enoates **1** of (E)-configuration. After 15 h the reaction mixture was treated with



Scheme 1

hexamethylphosphoric triamide (HMPA, 3 equiv.), followed by the appropriate halide R^2X. The crude tandem products **2** were directly desilylated by stirring over a suspension of silica gel/ethyl acetate and a trace of concentrated hydrochloric acid. In this way, the α-substituted β-hydrazinoesters **3** were obtained in 26 - 68 % overall yield after purification by chromatography (scheme 2, table 1).



2 - 4	R^1	R^2	2 - 4	R^1	R^2	2 - 4	R^1	R^2
a	Et	Me	f	Et	$(CH_2)_3OH$	j	Ph	*n*-Bu
b	Et	Et	g	*n*-$C_{11}H_{23}$	*n*-Pr	k	Ph	allyl
c	Et	*n*-Pr	h	Ph	Et	l	Ph	Bn
d	Et	Bn	i	Ph	*n*-Pr	m	*p*-MeOPh	Me
e	Et	Bn						

Scheme 2

The diastereomeric excesses were determined by ^{13}C-NMR spectroscopy and ranged from de = 63 - ≥ 96 % for aliphatic groups R^1, whereas with an aromatic R^1 the asymmetric inductions were virtually complete (de ≥ 96 %). Because in simple 1,4-additions of TMS-SAMP to enoates generating one new stereogenic center through C-N bond formation excellent inductions are observed (ee ≥ 93 %)[10], the de-values measured were those for the α-epimers of **3**. Assuming a uniform relative topicity for all Michael-additions described here, the relative (*anti*) and absolute configurations [(*S,S*) or (*S,R*) in the case of R^1 = aryl] of the two new stereocenters are based on a X-ray structure analysis of (*S,S,R*)-**3l** (figure 1). This result is also in agreement with an assignment of the configuration regarding the β-center by polarimetry [10]. Needless to mention that the enantiomeric auxiliary

TMS-RAMP leads to the optical antipodes as was demonstrated in the case of (*S,S,R*)- and (*R,R,S*)-**3l** (table 1). In order to avoid the toxic HMPA, N,N'-dimethylpropyleneurea (DMPU) was tried as cosolvent, but this led to either lower yields or a decrease of the diastereoselectivity. The spectroscopic data of the α-substituted β-hydrazino esters **3** are summarized in table 2.

Table 1. α-Substituted β-Hydrazino Esters **3** Prepared

Product	R^1	R^{2a}	yield (%)	$[\alpha]_D^{RT}$ (*c*,$CHCl_3$)	de[b] (%)
(*S,S,S*)-**3a**	C_2H_5	CH_3	56	−52.0 (1.29)	77
(*S,S,S*)-**3b**	C_2H_5	C_2H_5	48	−60.9 (1.08)	66
(*S,S,S*)-**3c**	C_2H_5	*n*-C_3H_7	53	−78.4 (0.74)	68
(*S,S,S*)-**3d**	C_2H_5	*n*-C_4H_9	33	−69.9 (0.90)	65
(*S,S,S*)-**3e**	C_2H_5	$C_6H_5CH_2$	26	−71.2 (1.20)	76
(*S,S,S*)-**3f**	C_2H_5	$(CH_2)_3OH$[c]	51	−41.4 (0.80)	>96
(*S,S,S*)-**3g**	*n*-$C_{11}H_{23}$	*n*-C_3H_7	41	−68.0 (1.01)	63
(*S,S,R*)-**3h**	C_6H_5	C_2H_5	34	−35.2 (1.41)	>96
(*S,S,R*)-**3i**	C_6H_5	*n*-C_3H_7	68	−63.4 (0.95)	>96
(*S,S,R*)-**3j**	C_6H_5	*n*-C_4H_9	64	−58.8 (0.67)	>96
(*S,S,R*)-**3k**	C_6H_5	$CH_2{=}CHCH_2$	52	−48.3 (1.13)	>96
(*S,S,R*)-**3l**	C_6H_5	$C_6H_5CH_2$	67	−64.7 (1.00)	>96
(*R,R,S*)-**3l**[d]	C_6H_5	$C_6H_5CH_2$	48	+68.6 (0.90)	>96
(*S,S,R*)-**3m**	*p*-$H_3COC_6H_4$	CH_3	53	−64.8 (1.23)	>96

[a] Except for benzyl bromide and allyl bromide (X = Br), the corresponding iodides (X = I) were used as electrophiles.
[b] Determined by ^{13}C-NMR spectroscopy.
[c] Electrophile: $I(CH_2)_3OSi(CH_3)_3$.
[d] TMS-RAMP was used instead of TMS-SAMP as nitrogen nucleophile.

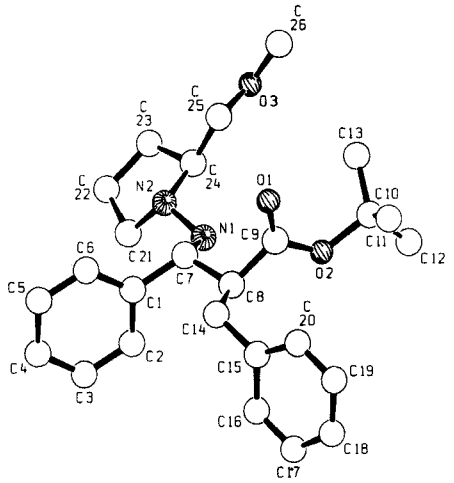


Figure 1. Molecular structure of one of the two independent molecules (A) (*S,S,R*)-**3l** in the solid state (Schakal[13] plot).

Finally, reductive N-N bond cleavage of the hydrazino esters **3** by neutral Raney-nickel [14] in methanol at 80°C and a hydrogen pressure of 8.5 bar afforded the β-amino acid esters (*S,S*)-**4h-j,l** in good yields (63-87%). When the Raney-nickel was washed with aqueous formic

Table 2. Spectroscopic Data of α-Substituted β-Hydrazino Esters **3** Prepared[a]

3[b]	IR (neat) ν (cm^{-1})	MS (70 eV) m/z (%)	^1H-NMR ($CDCl_3$/TMS) δ (ppm) *J* (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ (ppm)
a	3420, 2960, 2920, 1720, 1455, 1390, 1365, 1155, 1120	300 ($M^{+\cdot}$,12), 255 (13), 199 (100), 171 (35), 129 (23), 70 (22), 57 (7)	0.91 (t, *J* = 7.5, 3H, CH_2CH_3), 1.04 (d, *J* = 7.5, 3H, CH_2CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 1.5-2.0 (m, 6H, CH_2CH_2, CH_2CH_3), 2.08 (m, 1H, NCHH), 2.25 (s(br), 1H, NH), 2.56 (m, 1H, NCH), 2.75 (qd, *J* = 4.6, 7.5, 1H, CHCHCO), 3.10 (dt, *J* = 7.8, 4.0, 1H, CHCHCO), 3.28-3.37 (m, 1H, $CHHOCH_3$), 3.35 (s, 3H, OCH_3), 3.40-3.50 (m,1H, NCHH), 3.54 (dd, 1H, $CHHOCH_3$)	10.60, 10.66, 20.89, 23.44, 26.25, 28.12, 41.48, 56.93, 59.02, 60.63, 65.72, 75.02, 79.52, 175.49
b	3420, 2960, 2920, 2870, 1720, 1455, 1390, 1365, 1155, 1125	314 ($M^{+\cdot}$,19), 269 (17), 258 (12), 213 (100), 171 (30), 129 (9), 70 (7)	0.88, 0.93 (2x t, *J* = 7.4, 6H, 2x CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.5-2.0 (m, 6H, CH_2CH_2, 2x CH_2CH_3), 2.12 (m, 1H, NCHH), 2.28 (s(br), 1H, NH), 2.46 (ddd, *J* = 4.0, 5.5, 10.0, 1H, CHCHCO), 2.57 (m, 1H, NCH), 2.97 (dt, *J* = 4.7, 7.2, 1H, $CH_2CHCHCO$), 3.29-3.36 (m, 1H, $CHHOCH_3$), 3.35 (s, 3H, OCH_3), 3.40-3.47 (m, 1H, NCHH), 3.55 (dd, *J* = 3.7, 9.0, 1H, $CHHOCH_3$)	10.14, 12.64, 19.62, 21.02, 22.44, 26.41, 28.19, 49.74, 57.36, 59.07, 61.48, 66.14, 75.23, 79.69, 174.80
c	3420, 2980, 2920, 2860, 1720, 1455, 1390, 1365, 1245, 1155, 1030	328 ($M^{+\cdot}$,17), 283 (17), 272 (10), 228 (100), 171 (65), 129 (31), 114 (12), 85 (12), 70 (29), 57 (12)	0.87 (t, *J* = 7.5, 3H, CH_2CH_3), 0.93 (t, *J* = 7.0, 3H, CH_2CH_3), 1.17-1.98 (m, 10H, CH_2CH_2, CH_2CH_3, $(CH_2)_2CH_3$), 1.45 (s, 9H, $C(CH_3)_3$), 2.13 (m, 1H, NCHH), 2.49 (s(br), 1H, NH), 2.49-2.64 (m, 2H, NCH, CHCHCO), 2.96 (dt, 1H, *J* = 5.0, 7.5, $CH_2CHCHCO$), 3.31 (dd, *J* = 7.0, 10.0, 1H, $CHHOCH_3$), 3.35 (s, 3H, OCH_3), 3.37-3.47 (m, 1H, NCHH), 3.56 (dd, 1H, $CHHOCH_3$)	10.13, 14.38, 21.02, 21.48, 22.48, 26.45, 28.18, 28.72, 47.87, 57.34, 59.06, 61.59, 66.12, 75.34, 79.73, 174.97
d	3420, 2950, 2910, 2860, 1720, 1475, 1455, 1390, 1360, 1150	342 ($M^{+\cdot}$,18), 297 (18), 286 (10), 241 (100), 171 (74), 129 (34), 114 (14), 70 (37), 57 (17)	0.88 (t, *J* = 7.5, 3H, CH_2CH_3), 0.90 (t, *J* = 7.5, 3H, CH_2CH_3), 1.20-1.98 (m, 12H, CH_2CH_2, CH_2CH_3, $(CH_2)_3CH_3$), 1.45 (s, 9H, $C(CH_3)_3$), 2.13 (m, 1H, NCHH), 2.40-2.57 (m, 2H, NH, CHCHCO), 2.59 (m, 1H, NCH), 2.97 (dt, *J* = 7.0, 9.5, 1H, $CH_2CHCHCO$), 3.31 (dd, *J* = 7.0, 9.5, 1H, $CHHOCH_3$), 3.35 (s, 3H, OCH_3), 3.40-3.47 (m, 1H, NCHH), 3.36 (dd, *J* = 3.8, 9.5, 1H, $CHHOCH_3$)	10.16, 14.10, 21.02, 22.42, 23.04, 26.19, 26.47, 28.18, 30.58, 48.07, 57.32, 59.06, 61.61, 66.10, 75.36, 79.73, 174.96
e	3420, 3030, 2970, 2930, 2870, 1720, 1455, 1395, 1370, 1150	376 ($M^{+\cdot}$,29), 331 (20), 275 (100), 171 (72), 129 (30), 125 (14), 114 (13), 70 (36), 57 (12)	0.96 (t, *J* = 7.5, 3H, CH_2CH_3), 1.31 (s, 9H, $C(CH_3)_3$), 1.35-1.98 (m, 6H, CH_2CH_2, CH_2CH_3), 2.12 (m, 1H, NCHH), 2.33 (s(br), 1H, NH), 2.61 (m, 1H, NCH), 2.80-2.98 (m, 4H, $CH_2C_6H_5$, NCHH, CHCO), 3.36 (s, 3H, OCH_3), 3.40 (dd, *J* = 7.0, 10.0, 1H, $CHHOCH_3$), 3.68 (dd, *J* = 3.8, 9.0, 1H, $CHHOCH_3$), 7.17-7.27 (m, 5H, CH_{arom})	10.90, 20.99, 23.56, 26.62, 28.02, 34.42, 50.65, 57.30, 59.06, 62.24, 65.99, 75.17, 79.88, 125.81, 128.06, 129.03, 140.77, 173.56

Table 2. (continued)

3[b]	IR (neat) ν (cm^{-1})	MS (70 eV) m/z (%)	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ (ppm)
f	3660-3100, 2960, 2920, 2860, 1715, 1455, 1365, 1150, 1055	344 ($M^{+\cdot}$,15), 298 (17), 243 (100), 171 (68), 129 (33), 114 (15), 70 (36), 57 (17)	0.90 (t, J = 7.5, 3H, CH_2CH_3), 1.20-1.98 (m, 10H, CH_2CH_2, CH_2CH_3, $(CH_2)_2CH_2OH$), 1.56 (s, 9H, $C(CH_3)_3$), 2.11 (m, 1H, NCHH), 2.45 (s(br), 2H, NH, OH), 2.60 (m, 1H, NCH), 2.62-2.70 (m, 1H, CHCO), 3.02 (dt, J = 4.5, 7.5, 1H, $CH_2CHCHCO$), 3.28-3.38 (m, 1H, $CHHOCH_3$), 3.35 (s, 3H, OCH_3), 3.41-3.48 (m, 1H, NCHH), 3.55 (dd, J = 4.0, 9.5, 1H, CHHOCH3), 3.59-3.69 (m, 2H, CH_2OH)	10.64, 20.95, 21.59, 22.46, 26.34, 28.17, 31.45, 47.58, 59.09, 61.43, 62.56, 65.82, 75.25, 80.09, 175.05
g	3420, 2950, 2860, 2840, 1720, 1460, 1390, 1365, 1150, 1125	454 ($M^{+\cdot}$,35), 409 (33), 398 (16), 353 (71), 297 (100), 129 (34), 114 (19), 70 (32), 57 (18)	0.90 (2x t, J = 7.0, 6H, 2x CH_2CH_3), 1.26 (m, 24H, CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.48-1.98 (m, 4H, CH_2CH_2), 2.09 (m, 1H, NCHH), 2.27 (s(br), 1H, NH), 2.46-2.64 (m, 2H, NCH, $CHCHCO$), 3.00-3.07 (m, 1H, CHCHCO), 3.31 (dd, J = 7.0, 9.0, 1H, $CHHOCH_3$), 3.35 (s, 3H, OCH_3), 3.40-3.50 (m, 1H, NCHH), 3.55 (dd, J = 3.8, 9.0, 1H, $CHHOCH_3$)	14.13, 14.44, 22.72, 26.08, 26.49, 28.19, 29.39, 29.61, 29.64, 29.67, 29.93, 30.44, 30.89, 31.96, 48.16, 57.19, 59.05, 60.02, 65.93, 75.42, 79.65, 174.92
h	3430, 3020, 2960, 2920, 2860, 1720, 1450, 1385, 1360, 1145	362 ($M^{+\cdot}$,14), 317 (5), 261 (10), 219 (9), 129 (100), 70 (10), 57 (7)	0.78 (t, J = 7.2, 3H, CH_2CH_3), 1.11 (ddq, J = 14.0, 7.2, 4.0, 1H, $CHCHHCH_3$), 1.30 (m, 1H, $CHCHHCH_3$), 1.51 (s, 9H, $C(CH_3)_3$), 1.78-1.92 (m, 4H, CH_2CH_2), 1.89 (m, 1H, NCHH), 2.49 (s(br), 1H, NH), 2.59 (m, 1H, NCH), 2.86 (m, 1H, NCHH), 3.31 (dd, J = 7.2, 10.0, 1H, $CHHOCH_3$), 3.38 (s, 3H, OCH_3), 3.72 (dd, J = 3.5, 9.0, 1H, $CHHOCH_3$), 4.02 (d, J = 9.5, 1H, CHCHCO), 7.21-7.31 (m, 5H, CH_{arom})	11.64, 21.21, 23.23, 26.54, 28.24, 53.30, 57.54, 59.11, 66.55, 66.64, 76.84, 79.98, 127.36, 128.26, 142.38, 174.46
i	3420, 3030, 2960, 2920, 2870, 1725, 1455, 1390, 1365, 1150	376 ($M^{+\cdot}$,9), 331 (4), 275 (7), 129 (100), 70 (10), 57 (6)	0.75 (t, J = 6.5, 3H, CH_2CH_3), 0.92-1.94 (m, 9H, NCHH, CH_2CH_2, $(CH_2)_2CH_3$), 1.50 (s, 9H, $C(CH_3)_3$), 2.44-2.54 (m, 2H, CHCHCO, NH), 2.58 (m, 1H, NCH), 2.79-2.85 (m, 1H, NCHH) 3.31 (dd, J = 8.0, 10.0, 1H, $CHHOCH_3$), 3.38 (s, 3H, OCH_3), 3.72 (dd, J = 3.5, 9.0, 1H, $CHHOCH_3$), 4.02 (d, J = 9.5, 1H, CHCHCO), 7.22-7.32 (m, 5H, CH_{arom})	13.92, 20.37, 21.21, 26.48, 28.21, 32.14, 51.36, 57.54, 59.07, 66.65, 66.79, 75.71, 79.93, 127.29, 127.97, 128.23, 142.39, 174,54
j	3430, 3030, 2970, 2930, 2870, 1725, 1455, 1390, 1365, 1150	390 ($M^{+\cdot}$,10), 345 (4), 289 (8), 129 (100), 70 (13), 57 (10)	0.76 (t, J = 6.5, 3H, CH_2CH_3), 1.00-1.94 (m, 11H, NCHH, CH_2CH_2, $(CH_2)_3CH_3$), 1.50 (s, 9H, $C(CH_3)_3$), 2.40-2.53 (m, 2H, NH, CHCHCO), 2.58 (m, 1H, NCH), 2.79-2.89 (m, 1H, NCHH), 3.26-3.34 (m, 1H, $CHHOCH_3$), 3.38 (s, 3H, OCH_3), 3.72 (dd, J = 3.5, 9.0, 1H, $CHHOCH_3$), 4.01 (d, J = 9.5, 1H, CHCHCO), 7.19-7.32 (m, 5H, CH_{arom})	13.65, 21.25, 22.44, 26.57, 28.24, 29.36, 29.64, 51.52, 57.56, 59.09, 66.68, 66.79, 76.62, 79.93, 127.32, 128.02, 128.24, 142.43, 174.58
k	[c] 3225, 3030, 2975, 2930, 2870, 1705, 1455, 1355, 1155	374 ($M^{+\cdot}$,29), 329 (2), 273 (19; 129 (100), 114 (3), 70 (11), 57 (9)	1.47 (s, 9H, $C(CH_3)_3$), 1.50-1.65 (m, 2H, $CH_2CH=CH_2$), 1.80-2.08 (m, 5H, NCHH, CH_2CH_2), 2.50 (s(br), 1H, NH), 2.55-2.66 (m, 2H, NCH, CHCHCO), 2.90-3.00 (m, 1H, NCHH), 3.31 (dd, J = 8.3, 10.0, 1H, $CHHOCH_3$), 3.38 (s, 3H, OCH_3), 3.74 (dd, J = 3.8, 9.0, 1H, $CHHOCH_3$), 4.09 (d, J = 9.0, 1H, CHCHCO), 4.86-4.95 (m, 2H), 5.56-5.71 (m, 1H, $CH_2CH=CH_2$), 7.23-7.30 (m, 5H, CH_{arom})	21.21, 26.61, 28.24, 34.19, 51.11, 57.39, 59.10, 66.04, 66.48, 75.79, 80.20, 116.18, 127.51, 128.06, 128.28, 135.58, 141.73,173.61
l	[d] 3030, 2980, 2970, 2930, 1705, 1460, 1390, 1370, 1150	424 ($M^{+\cdot}$,28), 379 (7), 219 (11), 129 (100), 114 (2), 70 (10), 57 (8)	1.21 (s, 9H, $C(CH_3)_3$), 1.42-1.89 (m, 4H, CH_2CH_2), 1.92 (m, 1H, NCHH), 2.45 (dd, J = 4.5, 14.0, 1H, $CHHC_6H_5$), 2.53 (dd, J = 11.2, 13.0, 1H, $CHHC_6H_5$), 2.60-2.70 (m, 2H, NCH, NH), 2.84-2.95 (m, 2H, NCHH, CHCHCO), 3.32 (dd, J = 8.0, 10.0, 1H, $CHHOCH_3$), 3.37 (s, 3H, OCH_3), 3.74 (dd, J = 3.5, 9.0, 1H, $CHHOCH_3$), 4.15 (d, J = 9.0, 1H, CHCHCO), 7.03-7.32 (m, 10H, CH_{arom})	21.16, 26.56, 27.84, 36.15, 53.09, 57.41, 59.11, 66.56, 66.67, 75.77, 79.99, 125.94, 127.57, 127.93, 128.01, 128.41, 129.06, 139.34, 141.94, 173.59
m	3420, 3060, 2960, 2920, 2865, 1720, 1460, 1390, 1360, 1150		0.80 (d, 3H, $CHCH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.50-1.98 (m, 5H, NCHH, CH_2CH_2), 2.52 (s(br), 1H, NH), 2.54 (m, 2H, NCH, CHCHCO), 3.14-3.24 (m, 1H, NCHH), 3.34 (dd, J = 8.5, 9.0, 1H, $CHHOCH_3$), 3.39 (s, 3H, OCH_3), 3.75 (dd, J = 3.5, 10.0, 1H, $CHHOCH_3$)), 3.78 (s, 3H, OCH_3), 4.12 (d, J = 8.0, 1H, CHCHCO), 6.8-6.87 (m, 2H, CH_{arom}), 7.17-7.27 (m, 2H, CH_{arom})	14.60, 21.13, 26.72, 28.13, 54.59, 55.12, 57.02, 60.32, 64.98, 66.14, 75.82, 79.57, 113.55, 129.16, 133.44, 158.97, 175.29 .

[a] Satisfactory microanalyses obtained: C ± 0.5, H ±0.3, N ±0.5.
[b] Data given of the major diastereomer (**3a-g**).
[c] IR (KBr) , mp.: 54-55 °C
[d] IR (KBr), mp.: 76-78 °C.

acid (5%), no α-epimerization was observed and the amino acid esters were formed with high diastereo- and enantiomeric excesses (de, ee ≥ 96%) (table 3). Due to the reductive reaction conditions the phenyl group R^1 was reduced to the cyclohexane moiety, but the benzyl group of **3l** did not react under these conditions. The spectroscopic data of the α-substituted β-amino acid esters **4** are summarized in table 4.

Table 3. α-Substituted β-Amino Acid Esters **4** Prepared

Product	R^1	R^2	yield (%)	$[a]_D^{RT}$ (c,$CHCl_3$)	de[a] (%)	ee (%)
(*S*,*S*)-**4h**	C_6H_{11}	C_2H_5	87	+7.6 (0.87)	>96	>96
(*S*,*S*)-**4i**	C_6H_{11}	*n*-C_3H_7	63	+2.4 (0.88)	>96	>96
(*S*,*S*)-**4j**	C_6H_{11}	*n*-C_4H_9	83	−1.7 (0.91)	92[b]	>96
(*S*,*S*)-**4l**	C_6H_{11}	$C_6H_5CH_2$	63	+4.6 (0.99)	>96	>96

[a] Determined by ^{13}C-NMR spectroscopy.
[b] After chromatography (silica gel; ethanol).

In summary, the asymmetric tandem Michael-addition/α-alkylation procedure described using TMS-SAMP as a chiral equivalent of ammonia and N-Michael donor offers an alternative route to α-substituted β-amino acid esters of *anti*-configurations with excellent diastereo- and enantiomeric purities. Further extensions using aldehydes as electrophiles in tandem Michael-aldol-additions or ω-halogen substituted enoates in Michael initiated ring closure (MIRC) reactions are now being studied in our laboratory.

Solvents were dried and purified according to known procedures. All reagents were distilled prior to use or were of commercial quality from freshly opened containers. Anlytical TLC plates (silica gel 60 F_{254}) and silica gel (100-200 mesh) were purchased from Merck, Darmstadt. All melting points (Büchi-apparatus, system Dr. Tottoli) are uncorrected. Optical rotation values were measured using a Perkin-Elmer P241 polarimeter. Microanalyses were obtained with a CHN-O-RAPID element analyser. IR-spectra were recorded on a Beckman Acculab 4 and a Perkin-Elmer FT/IR 1750 spectrophotometer. ^1H- and ^{13}C-NMR spectra were measured on a Varian VXR 300 (300 and 75 MHz) or Varian Unity 500 (500 and 125 MHz). MS spectra were recorded on a Varian MAT 212, EI 70 eV.

(*S*)-(−)-1-amino-2-methoxymethylpyrrolidine (SAMP)[15], (*S*)-(−)-1-trimethylsilyl-amino-2-methoxymethylpyrrolidine (TMS-SAMP)[11], the α,β-unsaturated esters and 1-iodo-3-trimethylsilyoxypropane[16] were synthesized according to literature procedures. TMS-SAMP is now commercially available from ACROS CHIMICA, Geel, Belgium.

One pot Synthesis of α-Substituted β-Hydrazino Esters 3; General Procedure:

In a dried, argon-filled round-bottom flask fitted with a septum cap was dissolved TMS-SAMP (14 mmol) in anhydrous THF (40 mL). The solution was cooled to −78 °C and *n*-butyllithium (14 mmol, 1.6 M solution in *n*-hexane) was added dropwise. After 0.5 h stirring, the appropriate α,β-unsaturated ester **1** (10 mmol) was added dropwise and the reaction mixture allowed to warm to 0 °C slowly (ca. 15 h). After cooling to −78 °C, HMPA (50 - 60 mmol) was added dropwise and the reaction mixture was allowed to warm to −30 °C. The electrophiles R^2X were added at −78 °C dropwise under stirring, whilst warming to room temperature over 15 h. The reaction mixture was then washed with saturated aqueous $NaHCO_3$ solution (20 mL), extracted with dry dichloromethane (200 mL) and dried over Na_2SO_4. After removal of CH_2Cl_2 the crude product was placed on a suspension of silica gel/ethyl acetate and a catalytic amount of concentrated hydrochloric acid (1 mL) for 15 h, then the silica was extracted with dry methanol, the solution neutralized with $NaHCO_3$ solution, extracted with CH_2Cl_2 and dried with Na_2SO_4. The α-substituted β-hydrazino esters **3** were purified by chromatography (silica gel; ethyl acetate/light petroleum 1:3).

α-Substituted β-Amino Acid Esters 4; General Procedure:

Freshly prepared Raney-nickel[14] (ca. 2 eq.) was washed twice with dilute formic acid (5 % in water, 10 mL) and methanol (3 x 20 mL). 1 eq. of **3** was diluted in methanol (20 mL) and stirred in a sealed tube with a hydrogen pressure 8.5 bar (75 °C). After 2 d the reaction mixture was filtered from the Raney-Nickel, which was washed extensively with methanol (100 mL). The product was purified by flash chromatography (silica gel;, CH_2Cl_2).

X-Ray Structure Determination of (*S*,*S*,*R*)-3l:

Crystals of sufficient quality were obtained from Et_2O/petroleum ether (1 : 1) at 2 °C. The compound crystallizes in triclinic space group P1 (No. 1), a = 6.041(2), b = 10.187(2), c = 20.568(4) Å, α = 94.94(1), β = 96.90(1), γ = 90.14(1)°. Z = 2 (two independent molecules), V = 1251.8 Å^3 and M = 424.59 result in a calculated density of ρ_{cal} = 1.126 gcm^{-3}, while the total number of electrons per cell amounts to (F000) = 460. $\sin\Theta/\lambda_{max}$ = 0.621 for solution and refinement. The structure was solved by direct methods (SHEXS86[17]) and refined employing the XTAL3.2 package of crystallographic programs[18]. A total number of 6551 reflections were collected in the range of ±h ±k −l at 25 °C on an ENRAF-NONIUS CAD4 diffractometer. Graphite-monochromated CuK_α radiation (λ = 1.54179 Å), μ = 5.47

Table 4. Spectroscopic Data of α-Substituted β-Amino Acid Esters **4** Prepared[a]

Product	IR (neat) ν (cm^{-1})	MS (70 eV) m/z (%)	^1H-NMR ($CDCl_3$/TMS) δ (ppm) J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ (ppm)
4h	3400, 2960, 2940, 1720, 1450, 1365, 1150	255 (M^+·,1), 182 (2), 172 (22), 124 (10), 116 (100), 112 (50), 98 (18), 95 (12), 57 (18)	0.97 (t, 3H, *J* = 7.4, CH_2CH_3), 1.05-2.00 (m, 13H, CH_2CH_3, C_6H_{11}), 1.48 (s, 9H, $C(CH_3)_3$), 2.49 (dt, 1H, *J* = 9.5, 4.7, CHCHCO), 2.97-2.99 (m, 1H, CHCHCO), 5.81 (s(br), 2H, NH_2)	12.14, 23.22, 26.10, 26.26, 26.32, 28.16, 28.98, 29.92, 40.42, 48.93, 57.94, 81.29, 173.99
4i	3400, 2980, 2910, 2840, 1725, 1450, 1390, 1365, 1150	269 (M^+·,0.5), 186 (17), 130 (100), 112 (79), 95 (15), 57 (26)	0.94 (t, 3H, *J* = 7.5, CH_2CH_3), 1.05-2.95 (m, 15H, $CH_2CH_2CH_3$, C_6H_{11}), 1.47 (s, 9H, $C(CH_3)_3$), 2.57 (dt, 1H, *J* = 9.5, 4.5, CHCHCO), 2.90-2.94 (m, 1H, CHCHCO), 5.53 (s(br), 2H, NH_2)	13.91, 20.77, 26.15, 26.30, 26.35, 28.16, 28.93, 29.97, 32.14, 40.58, 46.89, 58.18, 81.20, 174.29
4j[b]	3390, 2950, 2920, 2850, 1720, 1365, 1150	283 (M^+·,0,5), 200 (23), 144 (100), 126 (17), 112 (70), 95 (12), 57 (17)	0.90 (t, 3H, *J* = 6.5, CH_2CH_3), 0.95-1.85 (m, 17H, $(CH_2)_3CH_3$, C_6H_{11}), 1.47 (s, 9H, $C(CH_3)_3$), 2.27 (s(br), 2H, NH_2), 2.43 (dt, 1H, *J* = 10.0, 5.5, CHCHCO), 2.61 (m, 1H, CHCHCO)	13.99, 22.68, 26.39, 26.59, 27.78, 28.21, 29.74, 30.09, 30.67, 41.38, 49.44, 58.40, 80.23, 174.94
4l	3400, 3030, 2970, 2915, 2850, 1715, 1450, 1365, 1145	317 (M^+·,3), 234 (43), 178 (99), 161 (20), 112 (100), 91 (42), 70 (19), 57 (20)	0.90-1.90 (m, 13H, C_6H_{11}, NH_2), 1.29 (s, 9H, $C(CH_3)_3$), 2.57 (m, 1H, CHCHCO), 2.72-3.00 (m, 3H, CHCHCO, CH_2Ph), 7.14-7.28 (m, 5H, CH_{arom})	26.36, 26.53, 27.86, 28.06, 30.57, 36.58, 41.83, 51.06, 58.31, 80.27, 126.15, 128.20, 129.03, 139.51, 173.90

[a] Satisfactory microanalyses obtained: C ± 0.5, H ±0.3, N ±0.5; **4h,i** microanalysis of the corresponding hydrochloride.
[b] Data given for the major diastereomer.

cm^{-1}, no absorption correction. 3298 reflections with $I > 2\sigma(I)$ were used in the final full-matrix least-square refinement process of 557 variables terminating at $R = 0.066$ ($R_w = 0.061$, $w = 1/\sigma^2(F)$) and a final shift/error smaller than 0.04. Residual electron density –0.3/+0.3, Zachariasen parameter $r^* = 824$[19]. The positions of the hydrogen atoms were calculated and held fixed during the refinement process, while the displacement parameters were subjected to 10 cycles of isotropic refinement.
Further details of the X-ray structure may be obtained through the Fachinformationszentrum Karsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 58479, the authors and the bibliographical data.

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