The Directed Cleavage of Substituted 1-Phenylethylamines: A Novel Route to Enantiomerically Pure β-Amino Acid Esters and β-Lactams[1]

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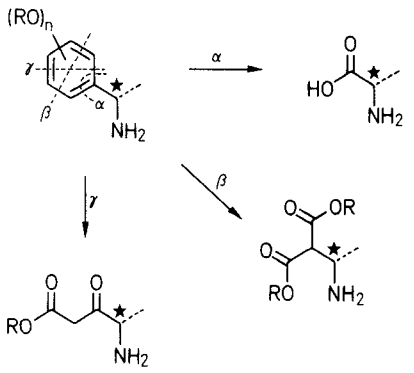
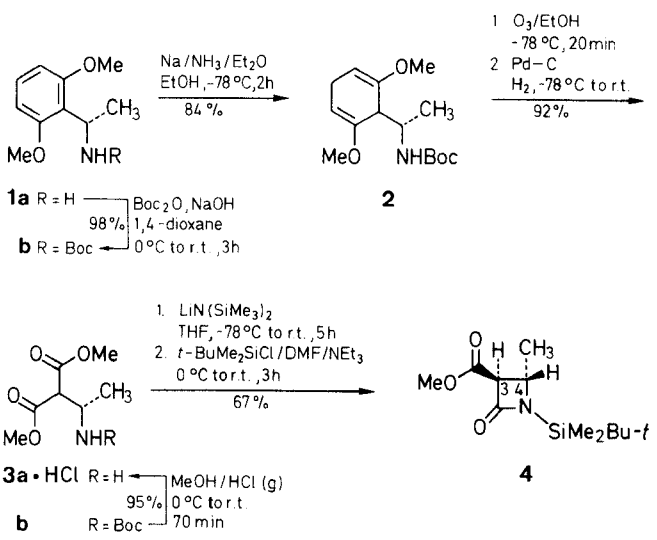
An efficient novel access to enantiomerically pure β-amino acid esters and β-lactams (e.g., methyl (3*S*,4*S*)-1-(*tert*-butyldimethylsilyl-4-methyl-2-oxoazetidine-3-carboxylate) from optically active 1-arylethylamines is described. Regiospecific cleavage is performed by Birch reduction and subsequent ozonolysis.

Optically pure 1-arylethylamines, especially when bearing oxygen function on the aromatic nucleus, have proved to be most useful nitrogen-containing chiral building blocks for the synthesis of nonracemic natural products.[2] They not only constitute partial structures of naturally occurring substances with chiral arylethylamine elements (such as 1-alkyl substituted tetrahydroisoquinolines[3,4]), but are also well-suited precursors to optically active target molecules that are devoid of aromatic units, since the benzene ring can specifically be cleaved, leading to α-amino acids[5] (path α) or, optionally, to γ-amino acids (path γ) as utilized in the synthesis of statine.[6]



We have recently reported a short and efficient synthetic pathway to such nucleus-oxygenated optically active 1-arylethylamines, optionally with (*R*)- or (*S*)-configuration at the stereogenic centre, by stereoselective reductive amination of the corresponding acetophenones.[2] In this paper, we wish to describe an alternative directed cleavage of the aromatic ring (way β), this time specifically leading to synthetically valuable β-amino acid esters, thus providing a practicable novel access to enantiomerically pure mono- or disubstituted β-lactams.

As starting material for our synthesis we chose the 1-arylethylamine **1a**,[2] whose oxygenation pattern was supposed to unambiguously guarantee the required regiospecificity of the ring cleavage site. The second task of the methoxy group should consist in the direct formation of ester functionalities in the cleavage step. Thus, **1a** was converted into its *N*-*tert*-butoxycarbonyl derivative and submitted to Birch reduction, regiospecifically leading to the substituted 1,4-cyclohexadiene **2**. Ozonolysis of this diene, followed by reductive work up, gives rise to the desired 1-aminoethyl substituted malonate **3b**, in excellent yield. Compound **3b** constitutes an interesting novel *N*-containing chiral building block.

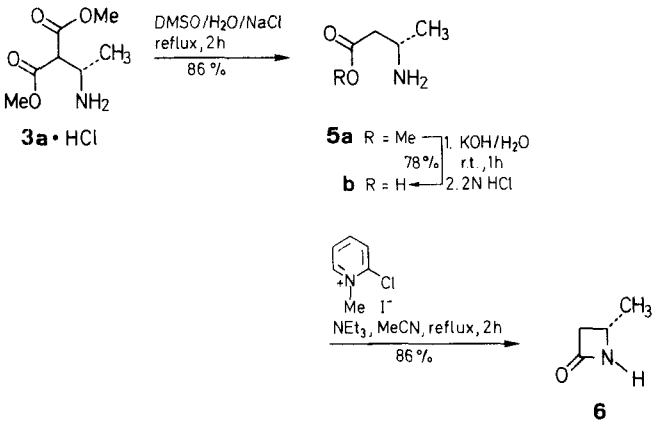


Scheme 1

Direct β-lactam ring closure of **3b** under basic conditions proved to be most difficult, due to a largely competing E_1cB-type elimination of the nitrogen substituent. In contrast, cyclization of the primary amine **3a**, obtained by acid-catalyzed *N*-deprotection of **3b**, using lithium hexamethyldisilazane[7] for the *N*-deprotonation, smoothly leads to the desired β-lactam **4**, obtained as a single diastereomer. The relative configuration at the stereogenic centres in **4** is deduced to be *trans* from ^{1}H-NMR: the H-3/H-4 coupling constant (J = 2.8 Hz) is in the typical range (J = 1.5–2.9 Hz) for known *trans*-configurated monolactams,[8,9] significantly different from the constants for β-lactams with *cis*-configuration (J = 5–6 Hz).[8,9] The corresponding *cis*-diastereomer could not be detected.

This step completes the first preparation of a nonracemic β-lactam from readily available 1-arylethylamines. The short and efficient synthesis of **4**, which may conveniently be performed on a multigram-scale, simultaneously represents the first synthetic access to chiral β-lactams bearing a alkoxycarbonyl substituent in the 3-position, which thus may serve as potential precursors to further functionalized azetidinones.

For an investigation of the optical purity of the intermediate **3a**, this malonic ester was decarboxylated under Krapcho's conditions,[10,11] giving rise to methyl (*S*)-3-aminobutyrate (**5a**),[12] the enantiomeric purity of which was determined as 95 %, using a procedure established by us earlier.[13] Furthermore, this preparation of **5a** opens up the possibility for the analogous synthesis of 3-unsubstituted 4-alkylazetidin-2-ones. Thus, the known[14] acid **5b**, which is obtained by saponification of **5a**, is ring closed to **6**, using procedures established in the literature.[15] This very simple chiral β-lactam **6** (ee = 95 %) had hitherto been prepared only as a racemate.[15]



Scheme 2

Work to extend the strategy presented herein to the preparation of more complex β-lactams, as well as the biological evaluation of these compounds, is in progress.

All reagents were of commercial quality: *tert*-butylchlorodimethylsilane was purchased from Aldrich Chemical Co.; 2-chloro-1-methylpyridinium iodide and di-*tert*-butyl dicarbonate were purchased from Merck. Melting points were measured with a Kofler hot-stage apparatus and are corrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed by the microanalytical laboratory of the Inorganic Institute of the University of Würzburg. IR spectra were taken on a Perkin-Elmer 298 Infrared spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker AC 200 spectrometer using TMS as internal reference. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer. GC analyses were performed with a Carlo Erba HRGC 5160 Mega Series instrument, equipped with a FID and a fused silica capillary column 0.33 mm (I.D.) × 30 m, coated with OV-225.

(1*S*)-*N*-*tert*-Butoxycarbonyl-1-(2,6-dimethoxyphenyl)ethylamine (1b):

To a mixture of **1a** (1.71 g, 9.44 mmol) in 1,4-dioxane (30 mL) and 0.5 N NaOH (20 mL), Boc_2O (2.27 g, 10.4 mmol) is added over a period of 2 min at 0 °C. The resulting mixture is then stirred for 3 h at r.t. After addition of Et_2O (20 mL), the organic layer is separated, washed with H_2O (10 mL), and dried ($MgSO_4$). The solvent is evaporated *in vacuo* and the yellow oily residue is recrystallized from a mixture of petroleum ether (40–60 °C) and Et_2O to afford **1b** as white needles; yield: 2.60 g (98%); mp 113–114.5 °C; $[\alpha]_D$ + 1.1° (*c* = 0.89, MeOH).

$C_{15}H_{23}NO_4$	calc.	C 64.03	H 8.24	N 4.98
(281.4)	found	64.10	8.24	5.19

IR (KBr): *v* = 3430, 3080, 2970, 1700, 1585, 1490, 1465, 1360, 1340, 1245, 1160, 1110, 775, 725 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.34 (d, 3H, *J* = 6.9 Hz), 1.41 s, 9H), 3.82 (s, 6H), 5.52 (dq, 1H, *J* = 10.1, 6.8 Hz), 5.93 (d, 1H, *J* = 10 Hz), 6.52 (d, 2H, *J* = 8.4 Hz), 7.13 (t, 1H, *J* = 8.5 Hz).

MS: *m/z* (%) = 281 (M^+, 3), 266, 210.

(1*S*)-*N*-*tert*-Butoxycarbonyl-1-(2,6-dimethoxy-2,5-cyclohexadienyl)ethylamine (2):

To a solution of **1b** (1.84 g, 6.54 mmol) in a solvent mixture of NH_3 (30 mL), dry Et_2O (60 mL), and dry EtOH (10 mL), Na (1.52 g, 66.1 mmol) is added in small portions over a period of 20 min at −78 °C. The resulting blue solution becomes colorless during stirring at the same temperature. After 2 h a white solid precipitates and the suspension is quenched with sat. aq NH_4Cl (5 mL). Subsequent evaporation under reduced pressure affords a light gray solid, which is suspended in dry Et_2O (40 mL). The insoluble residue is filtered off, the colorless filtrate is dried ($MgSO_4$) and after addition of petroleum ether (40–60 °C) to the filtrate colorless crystals of **2** precipitate; yield: 1.56 g (84%); mp 55.5–57 °C; $[\alpha]_D$ + 5.5° (*c* = 1.03, MeOH).

$C_{15}H_{25}NO_4$	calc.	C 63.58	H 8.89	N 4.94
(283.4)	found	63.48	8.72	5.14

IR (KBr): *v* = 3470, 2980, 2960, 1580, 1490, 1380, 1360, 1340, 1220, 1190, 1160, 1130 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.92 (d, 3H, *J* = 6.8 Hz), 1.41 (s, 9H), 2.76 (m, 2H), 2.98 (dt, 1H, *J* = 2.5, 5.6 Hz), 3.50 (s, 3H), 3.54 (s, 3H), 4.18 (m, 1H), 4.75 (td, 2H, *J* = 3.6, 13.3 Hz), 5.30 (d, 1H, *J* = 9.5 Hz).

MS: *m/z* (%) = 283 (M^+, 4), 210, 166.

Dimethyl 2-[(1*S*)-1-(*tert*-Butoxycarbonylamino)ethyl]malonate (3b):

Through a solution of **2** (530 mg, 1.24 mmol) in dry EtOH (15 mL) a dry O_3/O_2 mixture is bubbled gently over a period of 20 min at −78 °C. The resulting blue solution is then treated with 10% Pd-C (10 mg) and allowed to raise to r.t. under H_2 atmosphere by vigorous stirring. The catalyst is filtered off and the filtrate is evaporated to dryness in vacuo. Subsequent recrystallization of the colorless oily residue from a mixture of petroleum ether (30–75 °C) and Et_2O affords **3b** as white crystals; yield: 314 mg (92%); mp 44–46 °C; $[\alpha]_D$ + 2.6° (*c* = 0.97, MeOH).

$C_{12}H_{21}NO_6$	calc.	C 52.35	H 7.69	N 5.09
(275.3)	found	52.03	7.47	5.21

IR (KBr): *v* = 3350, 2970, 2940, 2840, 1720, 1530, 1490, 1450, 1430, 1240, 1160 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (d, 3H, *J* = 6.9 Hz), 1.36 (s, 9H), 3.55 (d, 1H, *J* = 4.5 Hz), 3.67 (s, 3H), 3.70 (s, 3H), 4.29 (m, 1H), 5.28 (d, 1H, *J* = 9.2 Hz).

MS: *m/z* (%) = 275 (M^+, 1), 219, 188.

Dimethyl 2-[(1*S*)-1-Aminomethyl]malonate Hydrochloride (3a · HCl):

A solution of **3b** (360 mg, 1.31 mmol) in dry MeOH (20 mL) is saturated with dry HCl gas over a period of 10 min at 0 °C and then stirred at r.t. for 1 h. Evaporation in vacuo and subsequent recrystallization of the resulting yellow oil from a mixture of MeOH and petroleum ether (40–60 °C) gives the hydrochloride **3a** · HCl as colorless needles; yield: 263 mg (95%); mp 116 °C; $[\alpha]_D$ − 0.6° (*c* = 0.90, MeOH).

$C_7H_{14}ClNO_4$	calc.	C 39.73	H 6.67	N 6.62
(211.6)	found	40.09	6.87	6.63

IR (KBr): *v* = 3440, 2950, 2900, 2840, 2800, 1745, 1500, 1430, 1380, 1305, 1230, 1150 cm^{-1}.

^{1}H-NMR (CD_3OD/TMS): δ = 1.63 (d, 3H, *J* = 6.7 Hz), 4.04 (s, 3H), 4.06 (s, 3H), 4.13 (m, 2H).

MS: *m/z* (%) = 175 (M^+ − HCl, 1), 116, 101.

Methyl (3*S*,4*S*)-1-*tert*-Butyldimethylsilyl-4-methyl-2-oxoazetidine-3-carboxylate (4):

A solution of freshly prepared $LiN(SiMe_3)_2$[7] (1.57 g, 9.43 mmol) in dry THF (10 mL) is added dropwise to **3a** · HCl (285 mg, 1.35 mmol) in dry THF (10 mL) at −78 °C under Ar. After 5 h the yellow suspension is quenched with sat. aq NH_4Cl (2 mL). The organic layer is separated, dried (Na_2SO_4) and the solvent is evaporated *in vacuo*. The yellow oily residue is dissolved in dry DMF (5 mL) and *t*-$BuMe_2SiCl$ (234 mg, 1.55 mmol) is added. Subsequent addition of NEt_3 (157 mg, 1.55 mmol) at 0 °C immediately affords a white suspension, which is then stirred at r.t. for 3 h and subsequently diluted with dry Et_2O (5 mL). The organic layer is washed with H_2O (2 × 20 mL) and with sat. aq NaCl (10 mL), then dried ($MgSO_4$) and finally evaporated *in vacuo*. The yellow oily residue is chromatographed on a silica gel column (20 cm * 2 cm, 0.032–0.063 mesh). Elution with petroleum ether (40–60 °C)/Et_2O (3:1) gives the *trans* configurated β-lactam **4** as a yellow oil; yield: 233 mg (67%).

$C_{12}H_{23}NO_3Si$	calc.	C 55.99	H 9.01	N 5.44
(257.4)	found	55.86	9.17	5.36

IR (NaCl): *v* = 2940, 2920, 2850, 1725, 1460, 1300, 1245, 1180, 1060, 940, 830, 820 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.20 (s, 6H), 0.93 (s, 9H), 1.37 (d, 3H, J = 6.2 Hz), 3.64 (m, 1H, J = 2.8 Hz), 3.73 (s, 3H), 3.93 (dq, 1H, J = 2.8, 6.2 Hz).

MS: m/z (%) = 257 (M^+, 1), 242, 198.

Methyl (*S*)-3-Aminobutyrate (5a):

A mixture of **3a** · HCl (340 mg, 1.60 mmol), NaCl (100 mg, 1.6 mmol) and DMSO (2 mL) in H_2O (0.4 mL, 22.2 mmol) is vigorously stirred under reflux for 2 h. The clear brown solution is then cooled to r.t. Addition of CH_2Cl_2 (50 mL) followed by filtration to remove the insoluble particles, affords a yellow solution. Evaporation in vacuo gives methyl (*S*)-3-aminobutyrate **(5a)** as a yellow oil (fully identical with an authentic sample[13] and with literature data[12]); yield: 161 mg (86%); enantiomer analysis, as recently described,[13] shows **5a** to have ee = 95%.

(*S*)-3-Aminobutyric Acid Hydrochloride (5b · HCl):

The ester **5a** (158 mg, 1.35 mmol) is hydrolyzed with aq KOH (89.8 mg, 1.60 mmol) at r.t. for 1 h and the resulting colorless product solution is acidified with 2N HCl. Freeze-drying of the aq solution followed by repeated recrystallization of the resulting white powder from a mixture of dry MeOH and Et_2O affords **5b** · HCl as white needles; yield: 150 mg (78%); mp 218°C (MeOH/Et_2O) (Lit.[14] 218–219°C); $[\alpha]_D$ + 28.2° (c = 1.48, H_2O) (Lit.[14] $[\alpha]_D$ + 28.9° (c = 1.52, H_2O).

IR (KBr): ν = 3500–2500 (br), 1650, 1550, 1400, 1280, 1210, 1140, 1120, 1020, 920, 900, 730, 610 cm^{-1}.

^{1}H-NMR (CD_3OD/TMS): δ = 1.28 (d, 3H, J = 6.7 Hz), 2.45 (d, 2H, J = 6.4 Hz), 3.57 (sext., 1H, J = 6.7 Hz).

MS: m/z (%) = 103 (M^+ – HCl, 1), 86, 70.

(*S*)-4-Methylazetidin-2-one (6):

A mixture of **5b** · HCl (438 mg, 3.14 mmol), dry NEt_3 (952 mg, 9.41 mmol) and 2-chloro-1-methylpyridinium iodide (882 mg, 3.45 mmol) in dry MeCN (10 mL) is refluxed for 2 h. The solvent is evaporated and the oily product **6** is chromatographed on a silica gel column (10 cm * 2 cm, 0.032–0.063 mesh). Elution with EtOAc/EtOH (10:1) gives the β-lactam **6** as a yellow oil; yield: 230 mg (86%); enantiomer analysis is performed by ^{1}H-NMR in the presence of the chiral solvating agent (*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol,[16] showing **5** to have ee = 95%.

C_4H_7NO	calc.	C 56.45	H 8.29	N 16.46
(85.1)	found	56.32	8.54	16.49

IR (NaCl): ν = 3500–3200 (br), 2980, 2920, 1720, 1420, 1380, 1350 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.27 (d, 3H, J = 6.1 Hz), 2.44 (dd, 1H, J = 2.4, 14.8 Hz), 2.99 (dd, 1H, J = 4.9, 14.8 Hz), 3.69 (ddq, 1H, J = 2.4, 4.9, 6.1 Hz), 6.61 (s, 1H).

MS: m/z (%) = 85 (M^+, 2), 42, 28.

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