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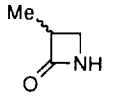
3-Methylazetidin-2-one and Its Precursors: Optical Resolution and Absolute Configurations

G. V. Shustov*[1] and A. Rauk

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

Abstract: Enantiomers of 3-methylazetidin-2-one - (3*R*)-(+)- and (3*S*)-(-)-**1** and of 3-amino-2-methylpropionic acid - (2*R*)-(-)- and (2*S*)-(+)-**2** were obtained from corresponding diastereomers of methyl (α*S*)-*N*-α-methylbenzyl-3-amino-2-methylpropionate **3A,B** which had been separated by recrystallization of their salts **4A,B** with p-toluenesulfonic acid. The absolute configurations of azetidinones (+)- and (-)-**1** and their diastereomeric precursors, i.e. amino esters **3A,B**, (α*S*)-*N*-α-methylbenzyl-3-amino-2-methylpropionic acids **5A,B**, and (α*S*)-*N*-α-methylbenzyl-3-methylazetidin-2-ones **6A,B** were established by conversion of (+)-**1** to amino acid (2*R*)-(-)-**2** and of amino acid (2*S*)-(+)-**2** to (-)-**1**. Copyright © 1996 Elsevier Science Ltd

3-Methylazetidin-2-one (**1**) attracted our attention as one of the simplest β-lactams which can exist in an optically active form. This compound like 4-methylazetidin-2-one is a convenient model for theoretical and experimental studies[2] of the optical activity (circular dichroism) of the β-lactam ring. Optically active azetidinone **1** is also of potential value as a starting material for the synthesis of more complicated pharmacological agents.[3]



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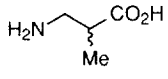

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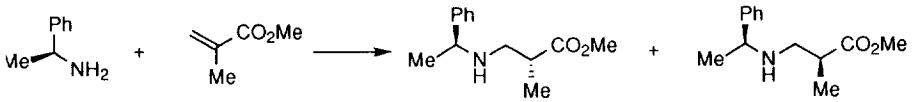
Nevertheless, we know of only one previous report[4] of an attempt to prepare azetidinone **1** in optically active form. Methylation of a lithium salt of (αS)-1-α-methylbenzylazetidin-2-one and chromatographic separation of the diastereomeric products were key steps of that work.[4] However, the absolute configuration and optical purities of the enantiomers (+)- and (-)-**1** were not determined.

We now describe the preparation of (+)- and (-)-**1** *via* separation of diastereomeric *N*-α-methylbenzyl derivatives of 3-amino-2-methylpropionic acid. It should be noted that the development of a simple and inexpensive method of optical resolution of 3-amino-2-methylpropionic acid (**2**) is of a considerable importance

in itself. This β-amino acid has been isolated from human urine[5,6] and bulbs of *Iris tingitana*,[7] and recently has attracted attention in preparations of protease inhibitors.[8]

Earlier, optical resolutions of amino acid **2** were carried out *via* salts of its *N*-acyl derivatives with brucine[9] and cinchonidine.[6] Asymmetric synthesis[10-12] of **2** and chromatographic separations of the amino acid enantiomers using chiral stationary phases[13] have also been reported.

The method of resolution *via* the *N*-α-methylbenzyl derivatives of **2** has been chosen on the base of our experience in the preparation of optically active 4-methylazetidin-2-one.[14] The ready availability of starting materials was one of the arguments on behalf of the method. However, unlike solid (α*S*)-*N*-α–methylbenzyl-3-aminobutyric acid, a key compound in the resolution of 4-methylazetidin-2-one,[14] the adduct of (*S*)-α-methylbenzylamine and methacrylic acid has been described as an oil and was obtained in a less than moderate yield (45%).[15] Addition of α–methylbenzylamine to methacrylonitrile has also been reported to proceed in a poor yield (*ca.* 14%).[10] We have found that prolonged refluxing (9 days) of a solution of (*S*)-α-methylbenzylamine and methyl methacrylate in methanol affords amino ester **3**, which was isolated as *ca.* 1:1 diastereomeric mixture, in 74% yield.



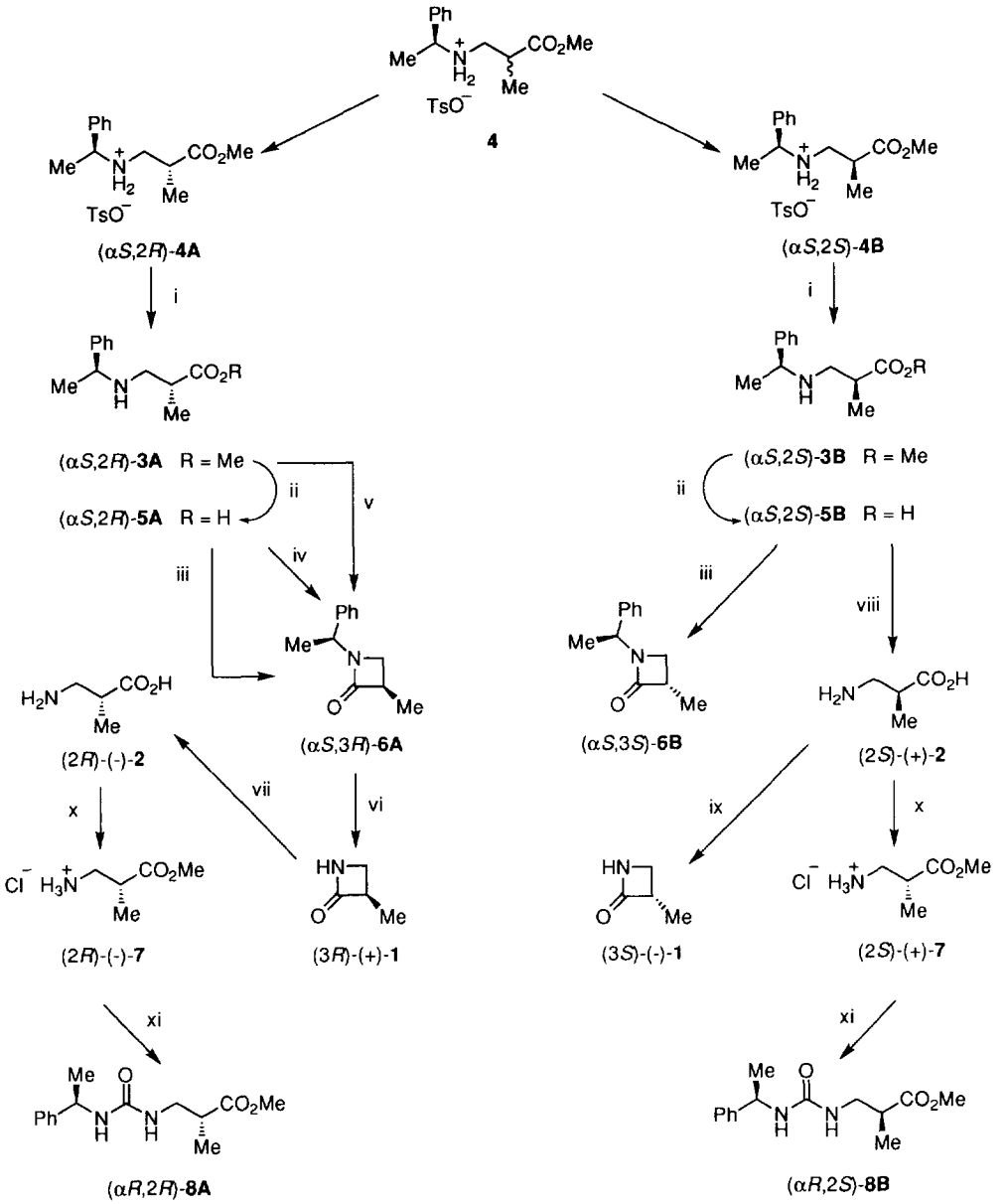
(α*S*,2*R*)-**3A** (α*S*,2*S*)-**3B**

Scheme 1

The mixture of diastereomers **3A,B** so obtained gave a crystalline salt **4** with p-toluenesulfonic acid. Two recrystallizations of the salt from benzene afforded diastereomer **4A** with *ca.* 92% diastereomeric excess, and in 79% yield (based on the pure diastereomer) (Scheme 2). A third recrystallization from benzene gave practically pure **4A** (de > 98%). Proton NMR spectra are a suitable means to follow the progress of the diastereomeric separation because diastereomers **4A,B** differ in chemical shifts of most of their groups (see Experimental Section). The quantitative determination of the diastereomeric excess was performed by integration of the peaks due to the MeO groups. A mixture enriched with diastereomer **4B** (the ratio of **4A/4B** is equal to *ca.* 23:77) was isolated from the mother liquor obtained after the first recrystallization of salt **4**. Recrystallization of this mixture from CCl_4 yields **4B** with *ca.* 80% diastereomeric excess.

Amino esters **3A,B** prepared from salts **4A,B** are quantitatively hydrolyzed in neutral conditions into amino acids **5A,B**, which unlike their mixture described earlier,[15] are crystalline substances. The crystallinity of **5A,B** gives an additional possibility for diastereomeric enrichment. For example, a single recrystallization of amino acid **5B** (de 80%) from acetone increased its diastereomeric excess to *ca.* 90%.

The vicinity of the C2 chiral center and the carbonyl group in amino esters **3A,B** and amino acids **5A,B** poses some possibility of epimerization during of β-lactamization of these compounds. We have checked three ring closure methods: (a) *via* the chlorides of amino acids **5A** and **5B** by their reaction with Et_3N;[14] (b) dehydration of amino acid **5A** using methanesulfonyl chloride under conditions of phase transfer catalysis;[16] (c) cyclization of amino ester **3A** under the action of methylmagnesium bromide.[17] It was found that the products,



Reagents: (i) K_2CO_3; (ii) H_2O; (iii) $SOCl_2$, Et_3N; (iv) MsCl / $KHCO_3$; (v) MeMgBr; (vi) Na-NH_3; (vii) HCl; (viii) HCO_2H / Pd-C; (ix) MsCl / $NaHCO_3$; (x) $SOCl_2$-MeOH; (xi) (R)-Ph(Me)CHN=C=O

Scheme 2

azetidinones **6A,B**, had the same diastereomeric excess as starting materials **3A,5A,B** in all of these cases. Romanova *et al.*[4,15] have described diastereomers (αS)-**6A,B** (without assignment of the absolute configuration of the C3 atom). However in their earlier paper,[15] $[\alpha]_D$ values of these diastereomers -19.9 (*c* 0.6, CCl_4) and -32.3 (*c* 1.0, CCl_4) were given, whereas later[4] the authors gave other values, i.e. 68.7 (*c* 2.5, CCl_4) and 120 (*c* 2.5, CCl_4) and do not comment on the discrepancy with their previous data. The $[\alpha]_D$ values -61.6 (*c* 2.1, CCl_4) and -123.9° (*c* 1.8, CCl_4) measured for **6A** (de 92%) and **6B** (de 90%), respectively, in the present work, are in closer agreement with the data of the later paper[4] (the absence of the "-" signs is apparently a typographical error).

The removal of the α-methylbenzyl group of diastereomer **6A** under the action of sodium metal in liquid ammonia gave 3-methylazetidin-2-one (+)-**1** which was hydrolyzed with concentrated hydrochloric acid[18] to afford amino acid (2*R*)-(-)-**2**. Hence, the (3*R*) absolute configuration for (+)-**1** as well as the corresponding absolute configurations for other compounds on Schemes 1,2 was established.

It was found that the reaction of the methyl ester of the racemic amino acid **2** with *R*-(+)-α-methylbenzyl isocyanate was not accompanied by kinetic enrichment and the products, diastereomers **8A,B** (Scheme 2), differ in their ^1H NMR spectra. Therefore this reaction was used for the determination of the enantiomeric excess of (+)-**1**, (-)-**2** and, subsequently, of (-)-**1**, (+)-**2**. The diastereomeric purity of urea **8A** *ca.* 86% was determined by integration of the MeO peaks. Hence, the enantiomeric excess of amino acid (-)-**2** and, correspondingly, of azetidinone (+)-**1** is equal to *ca.* 86%. Thus partial epimerization of **6A** or/and racemization of (+)-**1** takes place under the conditions of debenzylation with sodium metal in liquid ammonia. Undesirable epimerization can be avoided if the α-methylbenzyl group is removed by catalytic hydrogenolysis of *N*-α-methylbenzylamino acid **5**. Indeed, the enantiomeric excess *ca.* 90% of amino acid (2*S*)-(+)-**2** obtained by catalytic transfer hydrogenation[19] of **5B** corresponded to the diastereomeric excess (90%) of **5B**.

Cyclodehydration of amino acid (2*S*)-(+)-**2** with methanesulfonyl chloride[20] gave 3-methylazetidin-2-one (3*S*)-(-)-**1**. The ratio of the optical rotation angles of enantiomers (+)- and (-)-**1** is approximately in agreement with the ratio of their optical purities, i.e. 86% and 90%, respectively.

It should be noted, that in the papers[6,7,9] describing the isolation of the natural amino acid (-)-**2** and resolution of synthetic **2**, different $[\alpha]_D$ values of aqueous solutions of this amino acid are given. In particular, the value for the sample of **2**, isolated from iris bulbs was equal to -21 (*c* 0.43, H_2O).[7] In spite of the authors[7] pointing out a possibility of an error, this value has been included in the Dictionary of Organic Compounds.[21] The samples, one isolated from human urine[6] and two others prepared by resolution of synthetic **2**[6] were respectively characterized by specific rotations of -15.3 and ±15.4 (*c* 1, H_2O). Independent determination of enantiomeric excess of (-)- and (+)-**2** was not provided in all of these cases, but such a determination was carried out in the present work, and shows that the data of Kakimoto and Armstrong[6] are correct.

The proposed method of preparation of optically active azetidinone **1** can be also considered as an alternative to the optical resolution of amino acid **2**. The availability of the source of chirality, i.e. α-methylbenzylamine in both enantiomeric forms provides the possibility of the preparation of either enantiomer of **1** or **2** as required. All procedures can be easily realized on a multigram scale and quite small efforts would be needed for the optimization of the procedures in order to obtain the optically pure compounds.

Experimental Section

The NMR spectra were recorded on Bruker ACE-200 (^{1}H at 200 MHz and ^{13}C at 50 MHz) and Bruker AM-400 (^{1}H at 400 MHz) spectrometers. Chemical shifts are denoted in δ units (ppm) relative to the solvent and converted to the TMS scale using δ($CHCl_3$) = 7.27 ppm, δ(H_2O) = 4.80 ppm for the ^{1}H spectra and δ($CDCl_3$) = 77.23 ppm for the ^{13}C spectra. In the cases of N-α–methylbenzyl derivatives **3-6,8** with a diastereomeric excess ≥90%, the NMR data of the more abundant diastereomer **A** or **B** are given. The optical rotation angles were measured on a Rudolph Autopol III polarimeter.

Methyl *N*-α-Methylbenzyl-3-amino-2-methylpropionate (3). A solution of (*S*)-(-)-α-methylbenzylamine[22] (19.39 g, 0.16 mol) and methyl methacrylate[22] (16.02 g, 0.16 mol) in MeOH (80 mL) was refluxed for 9 days. The solvent was evaporated in vacuo and the residue was distilled, providing **3** (26.20 g, 74%) as a *ca.* 1:1 mixture of diastereomers (according to the ^{1}H NMR spectrum in $CDCl_3$; the spectra of separated diastereomers **3A,B** see below), bp 102-104°C (0.25 mm), $[\alpha]^{20}_D$ -40.5 (*c* 3.0, $CHCl_3$).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.31; H, 8.68; N, 6.34.

Separation of diastereomers 3A,B *via* p-toluenesulfonates 4A,B. p-Toluenesulfonic acid monohydrate (21.47 g, 0.113 mol) was added to a solution of **3** (25.09 g, 0.113 mol) in MeOH (100 mL) with cooling (15°C) and stirring. Evaporation of the solvent in vacuo and trituration of the residue with absolute ether (100 mL) gave crude salt **4** as a white solid (44.62 g, mp 117-150°C) which was twice recrystallized from benzene (250, 250 mL) to afford diastereomer (α*S*,2*R*)-**4A** (17.71 g, 79% based on the pure diastereomer), mp 164-166°C, $[\alpha]^{20}_D$ -21.3 (*c* 2.8, MeOH), de *ca.* 92%.[23]

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.17 (d, 3H, 2-Me, ^{3}J = 7.1), 1.83 (d, 3H, α-Me, ^{3}J = 6.8), 2.39 (3H, Me-Ar), 2.90-3.20 (br.m, 3H, 2-H+3-H_A,H_B), 3.56 (3H, MeO), 4.28 (br.m, 1H, α-H), 7.23 and 7.82 (dd, 2H and 2H, Ar, ^{2}J = 8.1), 7.38-7.47 (m, 5H, Ph), 8.16 (br.s, 1H, NH), 9.50 (br.s, 1H, NH).

Anal. Calcd for $C_{20}H_{27}NO_5S$: C, 61.04; H, 6.92; N, 3.56. Found: C, 60.82; H, 6.83; N, 3.56.

p-Toluenesulfonate **4A** (15.74 g, 40 mmol, de 92%) was added to a stirred mixture of ether (250 mL) and an aqueous solution of K_2CO_3 (11.06 g, 80 mmol in 25 mL of water) and the stirring was continued for 20 min. After separation of the organic layer, the aqueous solution was extracted with ether (3 x 50 mL). The combined extract was dried over K_2CO_3 and evaporated in vacuo. The residue was distilled, providing amino ester (αS,2R)-**3A** (8.68 g, 98%), bp 104-105°C (0.25 mm), $[\alpha]^{20}_D$ -56.1 (*c* 2, $CHCl_3$), de *ca.* 92%.[24]

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.12 (d, 3H, 2-Me, ^{3}J = 6.6), 1.33 (d, 3H, α-Me, ^{3}J = 6.6), 1.58 (br.s, 1H, NH), 2.72-2.51 (m, 3H, 2-H+3-H_A,H_B), 3.69 (3H, MeO), 3.75 (q, 1H, α-H, ^{3}J = 6.6), 7.20-7.38 (m, 5H, Ph).

The mother liquor obtained after the first recrystallization of **4** was evaporated to dryness in vacuo and the white solid residue (17.11 g, mp 121-129°C, **4A/4B** ratio ≈ 23:77) was recrystallized from CCl_4 (300 mL) yielding diastereomer (α*S*,2*S*)-**4B** (12.47 g, 56%), mp 130-132°C, $[\alpha]^{20}_D$ -1.35 (*c* 3.0, MeOH), de *ca.* 80%.

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.20 (d, 3H, 2-Me, ^3J = 7.1), 1.82 (d, 3H, α-Me, ^3J = 6.9), 2.39 (3H, Me-Ar), 2.70-3.12 (br.m, 3H, 2-H+3-H_A,H_B), 3.61 (3H, MeO), 4.34 (br.m, 1H, α-H), 7.23 and 7.82 (dd, 2H and 2H, Ar, ^2J = 8.1), 7.34-7.53 (m, 5H, Ph), 8.92 (br.s, 1H, NH), 9.13 (br.s, 1H, NH).

Anal. Calcd for $C_{20}H_{27}NO_5S$: C, 61.04; H, 6.92; N, 3.56. Found: C, 60.80; H, 6.71; N, 3.41.

The treatment of p-toluenesulfonate **4B** (11.81 g, 30 mmol, de 80%) with aqueous K_2CO_3 as described above gave amino ester (α*S*,2*S*)-**3B** (6.37 g, 96%), bp 104-105°C (0.25 mm), $[\alpha]^{20}_D$ -24.7 (*c* 2.3, $CHCl_3$), de *ca.* 80%.

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.13 (d, 3H, 2-Me, ^3J = 6.8), 1.33 (d, 3H, α-Me, ^3J = 6.6), 1.58 (br.s, 1H, NH), 2.45 (dd, 1H, 3-H_A, ^2J = 11.1, ^3J = 5.2), 2.59 (m, 1H, 2-H, ^3J = 7.6, 6.8, 5.2), 2.77 (dd, 1H, 3-H_B, ^2J = 11.1, ^3J = 7.6), 3.68 (3H, MeO), 3.74 (q, 1H, α-H, ^3J = 6.6), 7.21-7.35 (m, 5H, Ph).

***N*-α-Methylbenzyl-3-amino-2-methylpropionic acid (5).** A stirred mixture of amino ester **3** (6.20 g, 28 mmol) and distilled water (80 mL) was refluxed for 24 h. Concentration of the clear solution at reduced pressure and prolonged drying of the white crystalline residue at 50°C in vacuo (0.25 mm) gave amino acid **5**.

(α*S*,2*R*)-**5A**: 5.75 g, yield 99%, mp 177-179°C, $[\alpha]^{20}_D$ -55.3 (*c* 3.7, MeOH), de *ca.* 92%.

^{1}H NMR (200 MHz) in D_2O (J, Hz): δ 1.07 (d, 3H, 2-Me, ^3J = 7.3), 1.66 (d, 3H, α-Me, ^3J = 6.9),2.57 (m, 1H, 2-H), 2.80-2.99 (m, 2H, 3-H_A,H_B), 4.41 (q, 1H, α-H, ^3J = 6.9), 7.49 (5H, Ph).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.18; H, 8.41; N, 6.74.

(α*S*,2*S*)-**5B**: 5.80 g, yield 100%, mp 175-179°C, $[\alpha]^{20}_D$ +7.0 (*c* 3.5, MeOH), de *ca.* 80%. Recrystallization of this material from acetone (150 mL) yielded **5B** (5.12 g) with de *ca.* 90%, mp 180-182°C, $[\alpha]^{20}_D$ +10.6 (c 3.7, MeOH).

^{1}H NMR (200 MHz) in D_2O (J, Hz): δ 1.08 (d, 3H, 2-Me, ^3J = 7.3), 1.68 (d, 3H, α-Me, ^3J = 6.9), 2.50 (m, 1H, 2-H, ^3J = 9.1, 7.3, 4.8), 2.82 (dd, 1H, 3-H_A, ^2J = 12.5, ^3J = 4.8), 3.05 (dd, 1H, 3-H_B, ^2J = 12.5, ^3J = 9.1), 4.42 (q, 1H, α-H, ^3J = 6.9), 7.48 (5H, Ph).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.44; H, 8.09; N, 6.76.

1-α-Methylbenzyl-3-methylazetidin-2-one (6).

Method a. Thionyl chloride (5.95 g, 50 mmol) was added dropwise to a stirred mixture of amino acid **5** (2.073 g, 10 mmol), DMF (5 drops), and absolute CH_2Cl_2 (80 mL). The stirring was continued at rt for 24 h and the solvent and excess of $SOCl_2$ were evaporated in vacuo. The solid residue was dissolved in absolute CH_2Cl_2 (80 mL), and the obtained solution was added dropwise to a boiling solution of Et_3N (5.06 g, 50 mmol) in absolute CH_2Cl_2 (90mL). The refluxing was continued for 0.5 h, and the cooled reaction mixture was washed with water (2 x 20 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the product was extracted from the residue with hexane. After the removal of hexane in vacuo, the oily residue was distilled, providing azetidinone **6**.

(α*S*,3*R*)-**6A**: 1.59 g, yield 84%, bp 108-109°C (0.25 mm), $[\alpha]^{20}_D$ -81.1 (*c* 2.1, $CHCl_3$), $[\alpha]^{20}_D$ -61.6 (*c* 2.1, CCl_4), de *ca.* 92% {lit.[15] $[\alpha]^{20}_D$ -19.9 (*c* 0.6, CCl_4); lit.[4] $[\alpha]^{20}_D$ 68.7 (*c* 2.5, CCl_4)}.

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.31 (d, 3H, 3-Me, ^3J = 7.2), 1.59 (d, 3H, α-Me, ^3J = 7.1), 2.83 (dd, 1H, 4-H_a, ^2J = 5.1, $^3J_{aa}$ = 2.1), 3.10 (m, 1H, 3-H_a, ^3J = 7.2, $^3J_{aa}$ = 2.1, $^3J_{ae}$ = 5.1), 3.19 (t, 1H, 4-H_e, $^2J = {}^3J_{ea}$ = 5.1), 4.92 (q, 1H, α-H, ^3J = 7.1), 7.23-7.41 (m, 5H, Ph).

^{13}C NMR (50 MHz) in $CDCl_3$: δ 13.62 (3-Me), 18.54 (α-Me), 43.19 (C4), 44.65 (C3), 51.16 (α-C), 126.64, 127.31, 128.66, and 140.73 (Ph), 170.55 (CO).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.98; H, 7.85; N, 7.32.

(α*S*,3*S*)-**6B**: 1.55 g, yield 82%, bp 108-109°C (0.25 mm), $[\alpha]^{20}_D$ -125.0 (*c*, 2.3, $CHCl_3$), $[\alpha]^{20}_D$ -123.9 (*c* 1.8, CCl_4), de *ca.* 90% {lit.[15] $[\alpha]^{20}_D$ -32.3 (*c* 1.0, CCl_4); lit.[4] $[\alpha]^{20}_D$ 120 (*c* 2.5, CCl_4)}.

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.25 (d, 3H, 3-Me, ^3J = 7.3), 1.58 (d, 3H, α-Me, ^3J = 7.1), 2.64 (dd, 1H, 4-H_a, ^2J = 5.2, $^3J_{aa}$ = 2.3), 3.13 (m, 1H, 3-H_a, ^3J = 7.3, $^3J_{aa}$ = 2.3, $^3J_{ae}$ = 5.2), 3.36 (t, 1H, 4-H_e, $^2J = {}^3J_{ea}$ = 5.2), 4.94 (q, 1H, α-H, ^3J = 7.1), 7.24-7.42 (m, 5H, Ph).

^{13}C NMR (50 MHz) in $CDCl_3$: δ 13.51 (3-Me), 18.32 (α-Me), 43.19 (C4), 44.54 (C3), 50.97 (α-C), 126.64, 127.31, 128.66, and 140.73 (Ph), 170.55 (CO).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.00; H, 8.05; N, 7.15.

Method b. The procedure of Watanabe and Mukaiyama[16] was followed. To a stirred mixture of amino acid **5A** (2.073 g, 10 mmol, de 92%), $KHCO_3$ (4.01 g, 40 mmol), $Bu_4N(HSO_4)$ (0.51 g, 1.5 mmol), and water (10 mL) was added dropwise a solution of MsCl (2.29 g, 20 mmol) in $CHCl_3$ (50 mL). The reaction mixture was stirred for 24 h and partitioned by addition of water (10 mL). After separation, the organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo. Distillation of the residue afforded azetidinone **6A** (1.14 g, 60%, de *ca.* 92%) identical to that described above.

Method c. A 3.0M ether solution of MeMgBr (4 mL, 12 mmol) was added dropwise to a stirred solution of amino ester **3A** (1.107 g, 5 mmol, de 92%) in absolute ether (50 mL). The mixture was stirred at rt for 3 h in an inert atmosphere, cooled to 0°C and decomposed with 10% aqueous solution of NH_4Cl (20 mL). The organic layer was separated, washed with cooled 5% aqueous HCl (5 mL), water, and saturated aqueous solution of $NaHCO_3$ and dried over K_2CO_3. The removal of the solvent in vacuo and distillation of the residue gave azetidinone **6A** (0.549 g, 58%, de *ca.* 92%) identical to that described above.

(3*R*)-(+)-Methylazetidin-2-one (1). Small pieces of sodium metal (1.38 g, 60 mmol) were added to a stirred mixture of **6A** (2.84 g, 15 mmol, de 92%) and liquid ammonia (150 mL) at -40÷-50°C and the stirring was continued for 2h at the same temperature. After addition of solid NH_4Cl (4 g) and the removal of ammonia, the product was extracted from the residue with CH_2Cl_2 (150 mL) and the extract was evaporated in vacuo. The residue was purified by flash chromatography (silica gel 60, 230-400 mesh, 27.5% acetone in CH_2Cl_2) and further crystallization with hexane-ether (1:1 v/v) at -30°C to afford azetidinone (3*R*)-(+)-**1** as a white needles (0.766 g, 60%), mp 43-45°C, $[\alpha]^{20}_D$ +7.6 (*c* 2.4, $CHCl_3$) {optically active[4] and racemic **1**[3,25] were described as an oil, bp 98-99°C (15 mm),[25] $[\alpha]_{300}$ +54.1 (*c* 0.17, CCl_4)[4]}.

^{1}H NMR (200 MHz) in $CDCl_3$ (J, Hz): δ 1.33 (d, 3H, 3-Me, ^3J = 7.4), 2.94 (dd, 1H, 4-H_a, ^2J = 5.3, $^3J_{aa}$ = 2.5), 3.27 (m, 1H, 3-H_a, ^3J = 7.4, $^3J_{ae}$ = 5.3, $^3J_{aa}$ = 2.5, $^4J_{HNH}$ = 1.5), 3.46 (t, 1H, 4-H_e, $^2J = {}^3J_{ea}$ = 5.3), 5.99 (br.d, 1H, NH).

These ^{1}H NMR data were similar to those reported in the literature[3] for the racemic compound.

(2*R*)-(-)-3-Amino-2-methylpropionic acid (2). Concentrated hydrochloric acid (0.5 mL) was added to azetidinone (+)-**1** (0.068 g, 0.8 mmol) and stirred for 1h. After concentration of the solution in vacuo, the residue was dissolved in distilled water (5 mL) and passed through a column containing Dowex 50WX8-100 resin[22] (4 g) followed by distilled water (150 mL). The column was eluted with 3% aqueous ammonia (60 mL) and the ammonical eluant was evaporated to dryness in vacuo to provide amino acid (2*R*)-(-)-**2** as a white solid (0.078 g, 94%), mp 184-186°C, $[\alpha]^{20}_D$ -13.2 (*c* 0.6, H_2O) {lit.[5] mp 183-184°C; lit.[7] mp 183°C, $[\alpha]_D$ -21 (*c* 0.43, H_2O); lit.[9] mp 173-175°C, $[\alpha]_D$ -14.2 (*c* 0.42, H_2O); lit.[6] mp 191-194°C, $[\alpha]_D$ -15.4 (*c* 1, H_2O)}.

^{1}H NMR (200 MHz) in D_2O (J, Hz): δ 1.01 (d, 3H, 2-Me, ^{3}J = 7.3), 2.43 (m, 1H, 2-H, ^{3}J = 5.5, 7.3, 8.3), 2.84 (dd, 1H, 3-H_A, ^{2}J = 12.7, ^{3}J = 5.5), 2.93 (dd, 1H, 3-H_B, ^{2}J = 12.7, ^{3}J = 8.3).

(2*S*)-(+)-3-Amino-2-methylpropionic acid (2). The procedure of Means *et al.*[19] was followed. A solution of **5B** (2.073 g, 10 mmol, de 95%) in 4.4% formic acid-methanol (100 mL) was added to a stirred suspension of wet 10% palladium on charcoal[22] (4.0 g) in the same solvent (100 mL). The reaction mixture was stirred for 24 h, the catalyst was filtered off and washed with MeOH (100 mL). The filtrate was concentrated in vacuo, the residue was dissolved in distilled water (100 mL) and worked up with Dowex 50WX8-100 resin (100 g) in the same method as described above to give amino acid (2*S*)-(+)-**2** as a white solid (0.908 g, 88%), mp 183-186°C, $[\alpha]^{20}_D$ +13.7 (*c* 1.0, H_2O) {lit.[6] mp 192-194°C, $[\alpha]_D$ +15.4 (*c* 1, H_2O)}.

The ^{1}H NMR spectrum of (+)-**2** in D_2O was identical to that of the (-)-enantiomer.

(3*S*)-(-)-3-Methylazetidin-2-one (1). The procedure of Loewe *et al.*[20] was followed. A solution of MsCl (0.882 g, 7.7 mmol) in absolute MeCN (20 mL) was added dropwise to a rapidly stirred boiling suspension of amino acid (2*S*)-(+)-**2** (0.722 g, 7 mmol) and $NaHCO_3$ (3.53 g, 42 mmol) in absolute MeCN (50 mL). The reaction mixture was stirred and refluxed for 4 h and cooled to 0°C. The precipitate was filtered off, the filtrate was concentrated in vacuo and the product was extracted from the residue with absolute ether (100 mL). After removal of ether, the residue was purified in the same method described for the (+)-enantiomer (see above) to give azetidinone (3*S*)-(-)-**1** as white needles (0.310 g, 52%), mp 44-46°C, $[\alpha]^{20}_D$ -7.8 (*c* 2.3, $CHCl_3$) {lit.[4] an oil, $[\alpha]_{300}$ -45.4 (*c* 0.15, CCl_4)}.

The ^{1}H NMR spectrum of (-)-**1** in $CDCl_3$ was identical to that of the (+)-enantiomer.

Methyl 3-Amino-2-methylpropinate hydrochloride (7). Thionyl chloride (0.214 g, 1.2 mmol) was added dropwise to a stirred mixture of amino acid **2** (0.062 g, 0.6 mmol) and absolute MeOH (2 mL) at -70°C. The reaction mixture was stirred at rt for 10 h and evaporated to dryness in vacuo. The residue was triturated with absolute ether (3 x 5mL) and dried in vacuo (0.25 mm) to give hydrochloride **7** as white crystals.

(2*R*)-(-)-**7**: 0.089 g, yield 97%, mp 124-126°C, $[\alpha]^{20}_D$ -13.6 (*c* 1.4, MeOH).

^{1}H NMR (200 MHz) in D_2O (J, Hz): δ 1.26 (d, 3H, Me, ^{3}J = 7.2), 2.94 (m, 1H, 2-H, ^{3}J = 4.9, 7.2, 8.5), 3.13 (dd, 1H, 3-H_A, ^{2}J = 13.1, ^{3}J = 4.9), 3.27 (dd, 1H, 3-H_B, ^{2}J = 13.1, ^{3}J = 8.5), 3.76 (3H, MeO).

Anal. Calcd for $C_5H_{12}ClNO_2$: C, 39.09; H, 7.88; N, 9.12. Found: C, 38.80; H, 7.93; N, 8.90.

(2*S*)-(+)-**7**: 0.090 g, yield 98%, mp 124-126°C, $[\alpha]^{20}_D$ +14.0 (*c* 1.4, MeOH).

The ^1H NMR spectrum of (+)-**7** in D_2O was identical to that of the (-)-enantiomer.

Determination of enantiomeric excess of (+)- and (-)-7. To a stirred mixture of **7** (0.031 g, 0.2 mmol), Et_3N (0.024 g, 0.24 mmol), and absolute CH_2Cl_2 (0.5 mL) was added (*R*)-(+)-α-methylbenzyl isocyanate (0.032 g, 0.22 mmol). The reaction mixture was stirred at rt for 2h, kept for 24 h and washed with 5% aqueous HCl, water, and saturated aqueous solution of $NaHCO_3$. After being dried over $MgSO_4$, the solution was concentrated in vacuo and the residue (0.052 g) was analyzed by means of ^1H NMR(400 MHz) spectroscopy.

^1H NMR of **8A** in $CDCl_3$ (J, Hz): δ 1.07 (d, 3H, 2-Me, ^3J = 7.3), 1.44 (d, 3H, α-Me, ^3J = 6.8), 2.62 (m, 1H, 2-H, ^3J = 11.2, 7.3, 6.0), 3.24 (m, 1H, 3-H_A, ^2J = 13.8, ^3J = 6.0, $^3J_{NH}$ = 7.7), 3.36 (m, 1H, 3-H_B, ^2J = 13.8, ^3J = 11.2, $^3J_{NH}$ = 6.3, $^5J_{NH}$ = 4.6), 3.63 (3H, MeO), 4.74 (m, 1H, α-H, $^3J = {}^3J_{NH}$ = 6.8), 5.00 (br.m, 2H, NH), 7.24 - 7.33 (m, 5H, Ph);

^1H NMR of **8B** in $CDCl_3$ (J, Hz): δ 1.10 (d, 3H, 2-Me, ^3J = 7.2), 1.44 (d, 3H, α-Me, ^3J = 6.8), 2.61 (m, 1H, 2-H, ^3J = 11.6, 7.2, 4.8), 3.19(m, 1H, 3-H_A, ^2J = 13.8, ^3J = 4.8, $^3J_{NH}$ = 8.5), 3.39 (m, 1H, 3-H_B, ^2J = 13.8, ^3J = 11.6, $^3J_{NH}$ = 7.0, $^5J_{NH}$ = 4.4) 3.59 (3H, MeO), 4.74 (m, 1H, α-H, $^3J = {}^3J_{NH}$ = 6.8), 4.96 (br.m, 2H, NH), 7.25 - 7.34 (m, 5H, Ph).

The **8A/8B** ratio was found to be *ca.* 93:7 for urea **8** produced from (-)-**7** and *ca.* 5:95 for the one produced from (+)-**7** by integration of the MeO peaks. Hence enantiomeric excesses of (-)- and (+)-**7** are equal to 86% and 90%, correspondingly.

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