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Metal halide-mediated opening of three membered rings: enantioselective synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid and (3*R*)-3-aminodecanoic acid

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Abstract: Regio and stereoselective opening of three membered rings by metal halides was utilized for the enantioselective synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid and (3*R*)-3-aminodecanoic acid. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Chiral aziridines[1] and epoxides[2] are attractive classes of compounds for their ring strain, which is the driving force of their reactivity. In fact the chemo- and regio- and stereocontrolled opening of the ring with a wide variety of nucleophiles can allow easy access to a large variety of compounds in optically active form. In the last years we have focused our attention on the use of metal halides[3] to open strained rings such as epoxides and aziridines; subsequently the introduced halogen can be easily removed by a radical reduction or by a nucleophile in stereospecific fashion.

Our more recent studies on the regio and stereoselective opening of α,β-epoxy esters[4,5] and 3-substituted *N*-ethoxycarbonyl aziridine-2-carboxylate[6] have shown that: 1) the selection of the proper metal halide allows to attack smoothly the C-2 or C-3 position of the ring and 2) the behaviour of both oxirane or aziridine is very similar toward the metal-halide opening of the rings.

Scheme 1 shows a summary of the proper conditions to effect the ring opening. The use of $MgBr_2$ in ether at room temperature provides diastereomerically pure β-bromo derivatives in almost quantitative yield, mild conditions and with short reaction time (about 2–3 h) (equations 1 and 3). NaX/Amberlyst 15 in acetone at −30°C was found to be the best reagent to obtain stereocontrolled α-halo derivatives (C-2 attack) (equations 2 and 4). Under these conditions the ratio C-2/C-3 is quite good; it becomes excellent when a bulky group is present on C-3 position (i-Pr, cyHex). It should be emphasized that, in the case of substitution of the halogen by a nucleophile, a syn relationship between the stereocenter is obtained, which is not an easy goal to obtain with other approaches.

The usefulness of these methodologies can be demonstrated in the synthesis of two optically active compounds: the (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA) **1** and the (3*R*)-3-amino decanoic acid **2** (Figure 1).

AHDA is the N-terminal moiety of Microgenin, a linear pentapeptide recently isolated from the freshwater blue–green alga *Microcystis aeruginosa* and only recently synthesized.[7] It has medical interest as antihypertensive agent for its angiotensin-converting enzyme (ACE) inhibitory properties.[8] It was also established unambiguously[9] that the naturally occurring AHDA possessed the (2*S*,3*R*) stereochemistry; therefore we have thought that **1** could be easily accessible with our $MgBr_2$-mediated opening of α,β-epoxy ester and the reaction sequence is shown in Scheme 2.

The chiral *trans*-methyl α,β-epoxy decanoate **4** was easily obtained from the known corresponding chiral epoxy alcohol **3**,[10] which, following our methodology, was treated with $MgBr_2$ to give quantitatively the methyl-3-bromo-2-hydroxy-decanoate **5**. The opening of the epoxy ring and the

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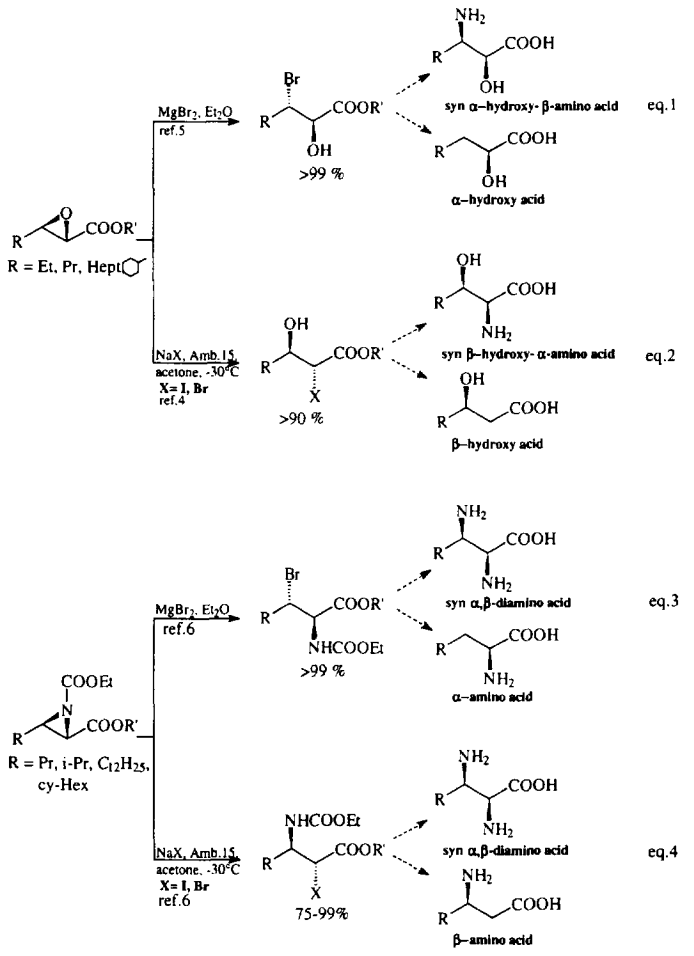


Scheme 1.

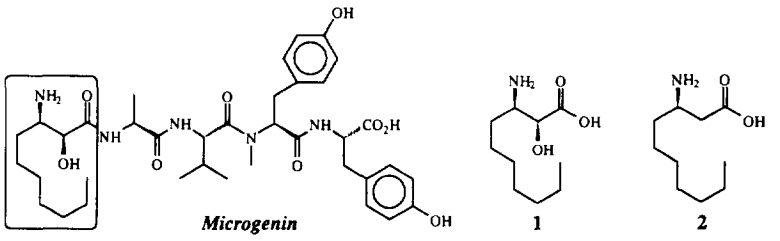
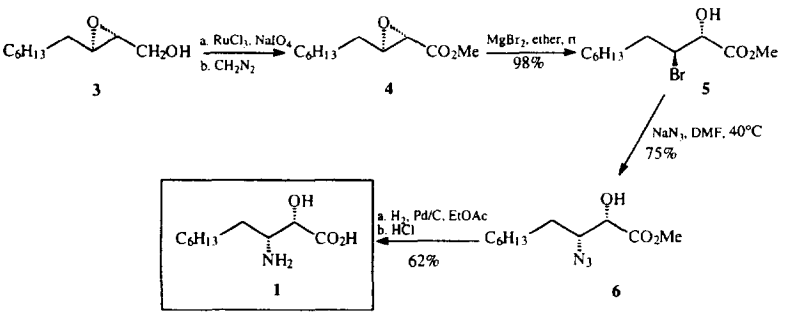


Figure 1.

subsequent azide substitution of the bromine proceed smoothly and with complete inversion of the C-3 configuration in each step, as already verified by us in the synthesis of the side chain of Taxol and of the Cyclohexil norstatin isopropilester.[5] Finally, catalytic hydrogenation of **6** and subsequent hydrolysis of methyl ester afforded the target compound **1**, in good yield and with spectroscopical data in agreement with those reported in literature.[7]

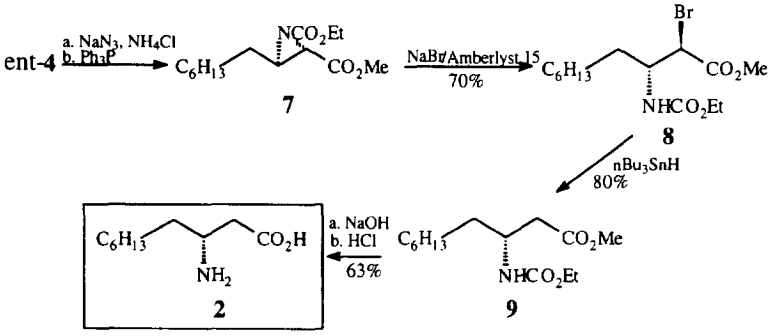
Our second target, the (3*R*)-3-amino decanoic acid **2**, is an unnatural β-amino acid which has the property of inhibiting the germination of sasanqua pollen: such compound, as well as other β-amino



Scheme 2.

acids with C>9, have been found to show biological activity similar to those exibit to some ants' pheromones.[11] Compound **2** ha• been already synthesized by a diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to the appropriate α,β-unsaturated ester.[7]

In this case we thought that the NaX/Amberlyst 15-mediated opening of an appropriate aziridine-2-carboxylate could be a straightforward entry to the synthesis of (3*R*)-3-aminodecanoic acid. Scheme 3 shows the overall reaction sequence starting from methyl *N*-ethoxycarbonyl aziridine-2-decanoate **7**, prepared in homochiral form from ent-**4** by means of the Zwanenburg procedure.[12]



Scheme 3.

The use of NaBr/Amberlyst 15 in acetone at −30°C gave preferentially C-2 attack (70%); the subsequent radical reduction of the bromo derivatives **8** to the protected amino acid **9** was followed by alkaline and acid hydrolyses to afford the final compound **2**. ^{1}H- and ^{13}C-NMR spectra were found identical to those reported by other authors.[7]

In conclusion we believe that the described regioselectively controlled openings by metal halides of the strained rings (as of the aziridines and epoxides) represents a useful approach for many stereocontrolled syntheses.

Experimental section

General

Flash chromatography was carried out on silica gel Merck (70–230 mesh). TLC analyses were carried out on Merck Kieselgel 60 F-254 plates. All solvents used, except CH_3CN, were distilled and dried before use. ^{1}H-NMR spectra were recorded on a Varian Gemini (200 MHz) instrument in a $CDCl_3$ solution. ^{13}C-NMR spectra were determined on the same instrument (50.3 MHz) in a $CDCl_3$ solution.

(2S,3R)-Methyl-2,3-epoxy-decanoate **4**

To a vigorously stirred mixture of (2*R*,3*R*)-2,3-epoxydecan-1-ol **3** [10] (0.172 g, 1 mmol), $NaIO_4$ (0.67 g, 3 mmol) in CCl_4 (2 mL), CH_3CN (2 mL) and H_2O (3 mL), $RuCl_3 \cdot H_2O$ (5 mg, 0.003 mmol) were added. The mixture was stirred at 20°C for 2 h, after which the acidic material was carefully extracted at 0°C with ether, which was dried briefly over Na_2SO_4. The residue obtained after evaporation of the solvents was diluted in Et_2O and treated with CH_2N_2. After evaporation in vacuo, the residue was purified by flash chromatography (hexane/ether 8:2) to afford **4** (0.160 g, 78%). $[\alpha]_D=-13.4$ (c 2.02, $CHCl_3$). ^{1}H-NMR: 3.71 (s, 3H), 3.16 (d, 1H, J=2.4 Hz), 3.12–3.05 (m, 1H), 1.65–1.12 (m, 12H), 0.8 ppm (t, 3H, J=6.5 Hz). ^{13}C-NMR: 169.9, 58.3, 52.7, 52.1, 31.4, 31.1, 28.9, 28.8, 25.4, 22.3, 19.7 ppm.

(2R,3S)-Methyl-2-hydroxy-3-bromodecanoate **5**

To a solution of compound **4** (200 mg, 1 mmol) in Et_2O (7 mL), $MgBr_2 \cdot Et_2O$ (193 mg, 1.5 meq) was added. The solution was stirred at room temperature for 2 h (TLC monitoring), washed with brine and the organic layers were dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) affording **5** (276 mg, 98%). $[\alpha]_D=+5.6$ (c 1.98, $CHCl_3$). ^{1}H-NMR: 4.38 (d, 1H, J=3.1 Hz), 4.22–4.12 (m, 1H), 3.78 (s, 3H), 3.28 (bd, 1H, OH, J=6,7 Hz), 2.0–1.12 (m, 12H), 0.83 ppm (t, 3H, J=6.6 Hz). ^{13}C-NMR: 171.9, 74.4, 56.9, 52.7, 33,6, 31.5, 28.8, 28.5, 27.5, 22.4, 13.9 ppm.

(2S,3R)-Methyl-2-hydroxy-3-azido-decanoate **6**

A mixture of **5** (282 mg, 1 mmol), NaN_3 (270 mg, 4.4 mmol) in DMF (1.3 mL) was stirred at 65°C for 6 h. The mixture was then diluted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/ether 8:2) afforded pure **6** (170 mg, 70%). $[\alpha]_D=+19.7$ (c 2.08, $CHCl_3$). ^{1}H-NMR: 4.2 (d, 1H, J=2.1 Hz), 3.82 (s, 3H), 3.52–3.41 (m, 1H), 3.12 (bs, 1H, OH), 2.35–2.21 (m, 1H), 1.90–1.7 (m, 2H), 1.68–1.15 (m, 9H), 0.85 ppm (t, 3H, J=6.5 Hz). ^{13}C-NMR: 173.5, 72.5, 69.0, 52.9, 31.5, 29.6, 29.5, 28.9, 25.9, 22.4, 13.8 ppm.

(2S,3R)-2-Hydroxy-3-aminodecanoic acid **1**

A mixture of **6** (243 mg, 1 mmol) was hydrogenated with 10% Pd/C (85.6 mg) in EtOAc (8.6 mL) under H_2 for 4 h. Then the solution was filtered and concentrated in vacuo. The crude material was treated with HCl 2 N (2 mL), at 40°C for 4 h. After concentration in vacuo, the amino acid **1** was crystallized by CH_3OH/EtOH (126 mg, 40%). $[\alpha]_D=+4.9$ (c 0.71, 1 N HCl) (lit.[7] $[\alpha]_D=5.4$ (c 0.59, 1 N HCl). ^{1}H-NMR (D_2O): 4.3 (d, 1H, J=3.7 Hz), 3.51 (m, 1H), 1.78–1.12 (m, 12H), 0.78 ppm (t, 3H, J=7.2 Hz). ^{13}C-NMR (D_2O): 178.0, 72.1, 56.1, 33.6, 31.5, 30.8, 30.7, 27.1, 24.6, 15.9 ppm.

(2S,3R)-Methyl (N-ethoxycarbonyl)-3-heptylaziridine-2-carboxylate **7**

A solution of compound ent-**4** (200 mg, 1 mmol), NaN_3 (202 mg, 3.1 mmol) and NH_4Cl (166 mg, 3.1 mmol) in MeOH (3.5 mL) was refluxed for 5 h (TLC monitoring). After evaporation of the solvent, the residue was diluted with Et_2O and washed with brine; the organic layer were dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture, without purification, was treated with Ph_3P (390 mg, 1.5 mmol) in CH_3CN (5 mL). The reaction mixture was stirred at room temperature for 1 h (until N_2 evolution was ceased) and then heated at reflux for 5 h (TLC monitoring). After the evaporation of the solvent the crude reaction mixture, containing the aziridine and $POPh_3$, was stirred with ClCOOEt (136 mg, 1.25 mmol) and Et_3N (0.18 mL, 1.25 mmol) in Et_2O (2 mL) at 0°C for 1 h. After 3 h at room temperature (TLC monitoring), the mixture was filtered over a Celite pad and the solvent was evaporated. The corresponding *N*-ethoxycarbonyl derivative **7**, easily separable from $POPh_3$ by flash-chromatography (hexanes/EtOAc, 9:1) was obtained with an overall yield of 62% (168 mg). $[\alpha]_D=+3.3$ (c 2.4, $CHCl_3$). ^{1}H-NMR: 4.14 (q, 2H, J=7.2 Hz), 3.73 (s, 3H), 2.84 (d, 1H, J=2.7 Hz), 2.82–2.72 (m, 1H), 1.68–1.24 (m, 15H), 0.85 ppm (t, 3H, J=6.1 Hz). ^{13}C-NMR: 168.5, 160.5, 62.5, 52.5, 44.1, 40.4, 31.6, 30.9, 28.9, 28.8, 26.4, 22.4, 14.1, 13.98 ppm.

(2R,3R)-Methyl 2-bromo-3-(N-ethoxycarbonylamino) decanoate **8**

A solution of **7** (272 mg, 1 mmol), NaBr (104 mg, 1 mmol) and Amberlyst 15 (215 mg, 1 mmol) in acetone (8 mL) was stirred at −30°C for 6 h. After filtration the solvent was diluted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/ether 8:2) afforded pure **8** (253 mg, 70%). $[\alpha]_D$=+16 (c 1.5, $CHCl_3$). ^{1}H-NMR: 4.83 (bd, 1H (NH), J=9.8 Hz), 4.45 (d, 1H, J=2.9 Hz), 4.18–3.96 (m, 3H), 3.74 (s, 3H), 1.68–1.22 (m, 15H), 0.84 ppm (t, 3H, J=5.41 Hz). ^{13}C-NMR: 168.4, 156.2, 61.0, 52.8, 51.6, 48.8, 32.9, 31.5, 29.0, 28.9, 25.8, 22.4, 14.3, 13.8 ppm.

(3R)-Methyl 3-(N-ethoxycarbonylamino) decanoate **9**

To a solution of **8** (352 mg, 1 mmol) in benzene (8 mL), n-Bu_3SnH (290 mg, 1 mmol) and AIBN (cat.) were added. The mixture was heated at 70°C for 2 h (TLC monitoring), then the solvent was removed in vacuo; the tin residues were removed according to Curran's procedure[13] and the crude mixture, purified by silica gel chromatography (hexanes/ether 6:4), afforded pure compound **9** (218 mg, 80%). $[\alpha]_D$=−10 (c 1.2, $CHCl_3$). ^{1}H-NMR: 5.03 (bd, 1H (NH), J=8.5 Hz), 4.06 (q, 2H, J=7.0 Hz), 3.97–3.78 (m, 1H), 3.65 (s, 3H), 2.51 (d, 2H, J=5.5 Hz), 1.70–1.01 (m, 15H), 0.89 ppm (t, 3H, J=5.41 Hz). ^{13}C-NMR: 172.4, 156.3, 60.7, 51.5, 47.9, 38.8, 34.3, 31.6, 29.1, 28.9, 25.9, 22.4, 14.4, 13.9 ppm.

(3R)-3-Aminodecanoic acid **2**

A mixture of **9** (272 mg, 1 mmol), NaOH (80 mg, 2 mmol), EtOH (1.2 mL), H_2O (1.2 mL) was stirred at room temperature for 20 h. Further NaOH (80 mg, 2 mmol) was added, the mixture was stirred for an additional 8 h until homogeneous, and left overnight. With cooling (ice–water) a solution of H_2SO_4 (196 mg, 2 mmol) in H_2O (0.75 mL) was added dropwise. CO_2 was evolved. Then solid $NaHCO_3$ was added until pH=5. EtOH (1 mL) was added and the solution was filtered. Removal of the solvent under reduced pressure yielded **2** (118 mg, 63%). $[\alpha]_D$=−12.8 (c 0.6, 1 N HCl) (lit.[7] $[\alpha]_D$=−13.1 (c 0.41, 1 N HCl). ^{1}H-NMR: 3.35 (m, 1H), 2.5 (d, 2H, J=5.7 Hz), 1.70–1.01 (m, 15H), 0.81 ppm (t, 3H, J=5.41 Hz). ^{13}C-NMR: 178.2, 51.2, 38.8, 34.3, 31.6, 29.1, 28.9, 25.9, 22.4, 13.9 ppm.

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