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Efficient Pathways to (*R*)- and (*S*)-5-Hydroxymethyl-2-oxazolidinone and some Derivatives

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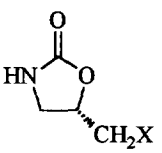
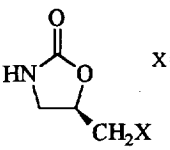
Abstract: 2-Oxazolidinones are a very interesting class of compounds due to their various pharmacological effects. Two new syntheses of enantiomerically pure (*R*)- and (*S*)-5-hydroxymethyl-2-oxazolidinone have been developed starting with *D*- mannitol, *L*-ascorbic acid and (*R*)- or (*S*)-malic acid. (*R*)- and (*S*)-5-hydroxymethyl-2-oxazolidinone have been used to synthesize some new homochiral 2-oxazolidinone derivatives.

2-Oxazolidinones are a very interesting class of compounds due to their various pharmacological effects. They are described as potential neuroleptics with high affinity to sigma receptors[1], as phychotropics[2], as antiallergy agents[3], as antibacterials and antibiotics[4], as intermediates in the syntheses of renin inhibitors[5], of β-lactam and macrolide antibiotics[6], of immunosupressants[7] and in many other applications[8].

We are mainly interested in a short synthesis of enantiomerically pure 5-substituted 2-oxazolidinones starting from low-priced homochiral precursors such as amino acids, carbohydrates, or hydroxy acids and their application in further stereoselective transformations[9]. Here we present two different economical pathways to 5-hydroxymethyl-2-oxazolidinone **7** starting from *D*-mannitol **1**, *L*-ascorbic acid **8** or (*R*)- and (*S*)-malic acid **15** and the formation of the derivatives **21, 22, 23**. Among these derivatives, 5-chloromethyl-2-oxazolidinone **21** is particulary interesting as a building block for biologically active compounds which is demonstrated by the fact that the racemic form has already been mentioned in several publications and patents[10].



X = Cl **(S)-21**
Br **(S)-22**
I **(S)-23**



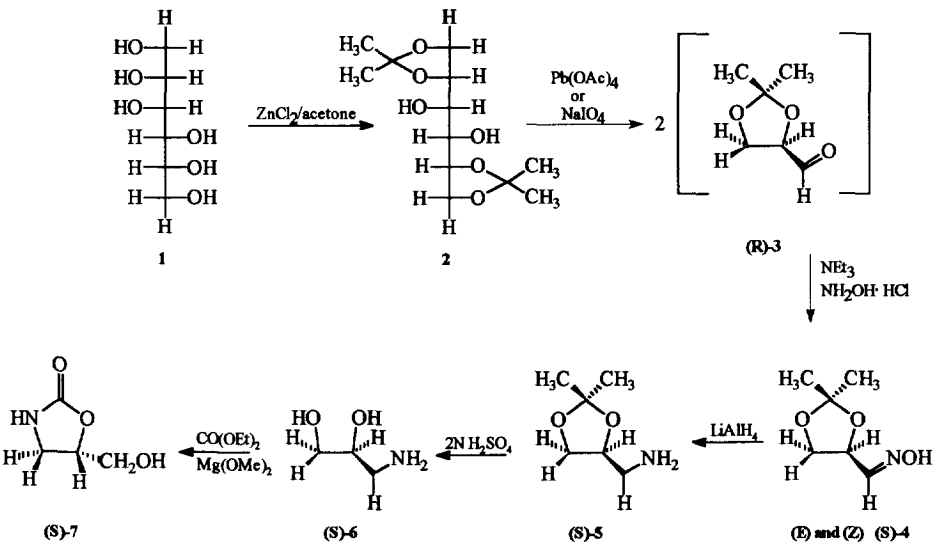
X = Cl **(R)-21**
Br **(R)-22**
I **(R)-23**

D-Mannitol **1** as starting material allows (*S*)-5-hydroxymethyl-2-oxazolidinone (***S***)-**7** to be synthesised in 6 steps with an overall yield of 19% (Scheme 1).

At first, **1** is protected as 1,2;5,6-di-*O*-isopropylidene-*D*-mannitol **2** with $ZnCl_2$ and acetone (52%) using the method of *Tipson* and *Cohen*[11]. Cleavage of the diol with $Pb(OAc)_4$ yields the protected glyceraldehyde ***(R)*-3** which is transformed *in situ* to the oxime **(*S*)-4**[12] (84%). Reduction of **(*S*)-4** with $LiAlH_4$ and subsequent removal of the protecting group (80%) gives **(*S*)-6** as the key intermediate. Cyclisation with diethylcarbonate and $Mg(OMe)_2$ leads to (*S*)-5-hydroxymethyl-2-oxazolidinone (***S***)-**7** in 60% yield.

The synthesis of the (*R*)-enantiomer (***R***)-**7** is possible following the same route but it is uneconomical because of the high price of the starting material. As a better source for the protected (*S*)-glyceraldehyde **(*S*)-3** the easy to handle and cheap *L*-ascorbic acid **8**[13] was introduced by *Jung* and *Shaw*.

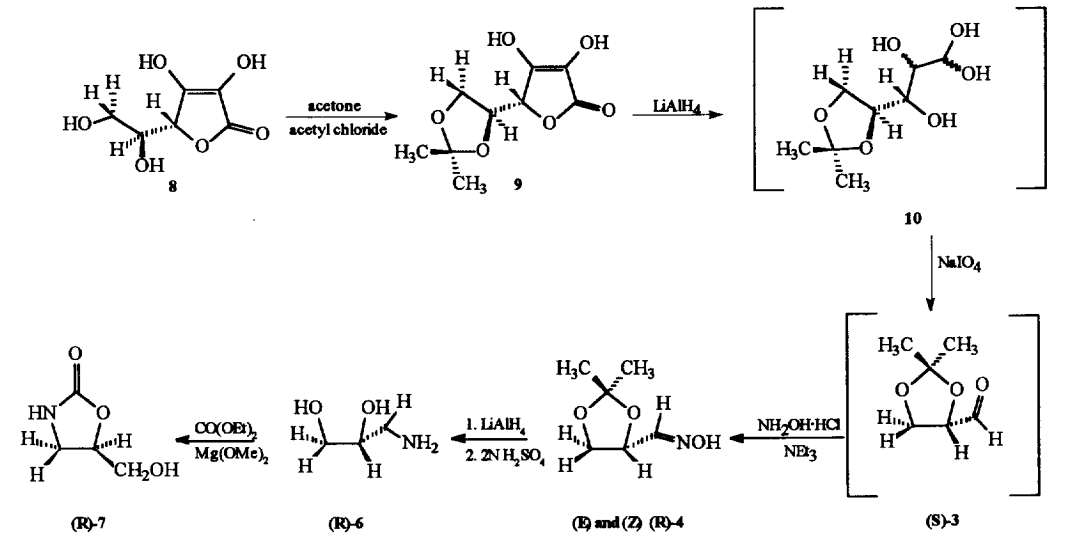
Its protected form 5,6-isopropylidene-*L*-ascorbic acid **9** (62.6% after purification; lit.[13]; 81% without purification) is transformed to the protected (*S*)-glyceraldehyde **(*S*)-3** by $LiAlH_4$-reduction and diol cleavage using the method of *Takano et al.*[14] and *in situ* derivatised to the oxime **(*R*)-4** (22% over 3 steps). The further steps (reduction, deprotection and cyclisation) are performed as described for the (*S*)-enantiomer. The overall yield is 6% over 7 steps.



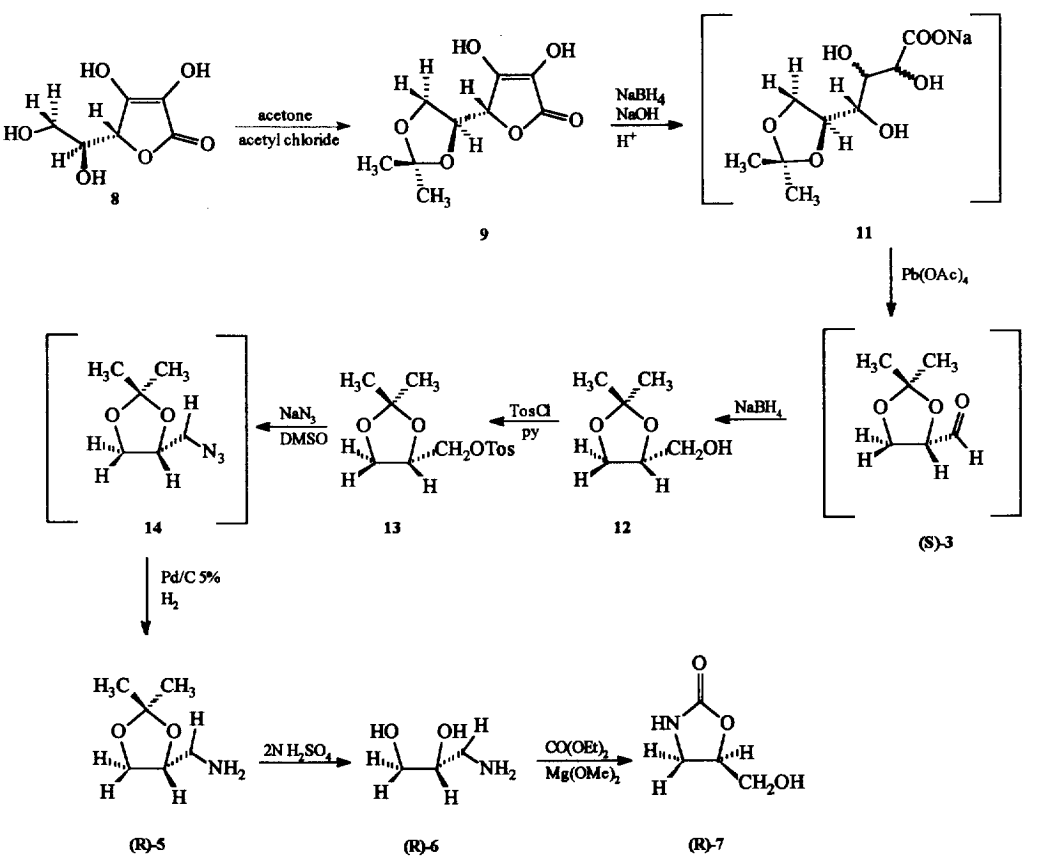
Scheme 1

This method is unsatisfactory because of the moderate yield which is due to the difficult transformation to **(*R*)-4**. An alternative proposed by *Knight* and *Cleveland*[15] is the reduction of the protected glyceraldehyde **(*R*)-4** *in situ* with $NaBH_4$ to form the protected glycerol **12** (43%)[13] followed by its transformation to the tosylate **13** (80%). Substitution by the azide ion yields **14** (78%, crude) which is *in situ* hydrogenated with Pd/C and H_2 to the amine **(*R*)-5** (86%) (Scheme 3). We were able to optimize the transformation of **12** to **(*R*)-6** by improving the reduction of the azide.

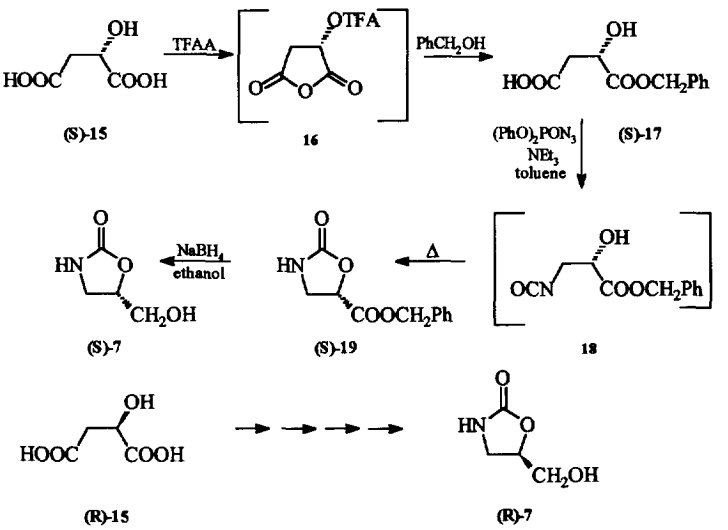
As compared with the synthesis according to scheme 2 this pathway to the oxazolidinone **(*R*)-7** has two more steps but is easier to handle and leads to a higher overall yield (7% over 9 steps). These two new syntheses are more straight forward than former syntheses[16] which either have more steps (*Cardillo et al.*[16a]), allow only to form one isomer of 7 (*Sato et al.*[16c]) or require a lipoproteine lipase (*Hamaguchi, Hasegawa et al.*[16b]). However, both strategies still have some drawbacks as the number of steps is high and the overall yield for **(*R*)-7** is too low. Therefore we developed a different and more efficient strategy starting with (*R*)- or (*S*)-malic acid **15** both enantiomers of which can be obtained at a reasonably low price. Malic acid is quantitatively transformed to the malic acid 1-monobenzylester **17** using the strategy of *Suzuki et al.*[17] and *Miller et al.*[18] in which the formation of the anhydride **16** is followed by nucleophilic regioselective ring opening with benzylic alcohol (100%). *Curtius*-rearrangement with the diphenylphosphoryl azide followed by intramolecular cyclisation gives (*S*)-2-oxazolidinone-5-carboxylic acid benzylester **19** (49%). Reduction of the ester with either $NaBH_4$ in ethanol (85%) or with $LiBH_4$ in diethylether and methanol (46%)[19] yields (*R*)- or (*S*)-5-hydroxymethyl-2-oxazolidinone **7** in 42% over 5 steps (Scheme 4).



Scheme 2

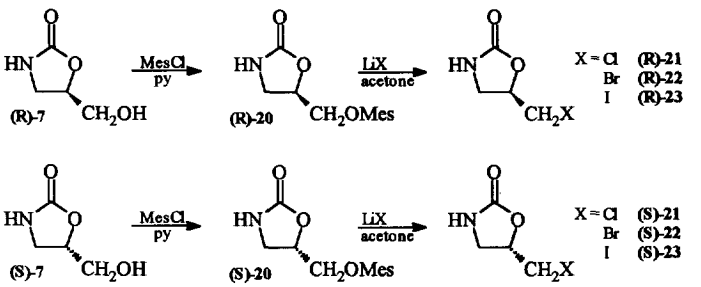


Scheme 3



Scheme 4

5-Hydroxymethyl-2-oxazolidinone **7** is also an excellent starting material for further transformations. We synthesised **21, 22** and **23** in two steps with good to excellent yields according to scheme 5. Electrochemical and other diastereoselective transformations of **21** are part of our recent work.



Scheme 5

Acknowledgement

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Experimental

General information: Infrared spectra were obtained from KBr-pellets using a Perkin-Elmer 1600 instrument and are reported in cm^{-1}. Nuclear magnetic resonance (^1H NMR) spectra were determined in the reported solvent using a Bruker WH 90 (90 MHz), Bruker AC 200 (200 MHz), Bruker WM 250 (250 MHz) and a Bruker AC 400 (400 MHz) spectrometer. The same instruments are also used for ^{13}C spectra (22.6 MHz, 50.3 MHz; 62.9 MHz; 100.6 MHz). Chemical shifts are given in ppm downfield from tetramethylsilane. Optical rotations were measured with a Perkin Elmer P241 polarimeter. All values are in relation to the Na-D-

line (589.3 nm). R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel F $_{254}$). Elemental analysis were performed by the Mikroanalytische Abteilung des Instituts fuer Organische Chemie und Biochemie der Universitaet Bonn. Melting points are uncorrected. All solvents were distilled before using.

1,2:5,6-Di-*O*-isopropylidene-*D*-mannitol 2 ($C_{12}H_{22}O_6$)

Zinc chloride (anhydrous) 140.8 g was placed in a 1000 mL flask and 704 mL acetone was added. The mixture was stirred under argon until the salt had dissolved. The suspension was filtered into a flask containing 72.8 g mannitol **1** and stirred in a bath of cool water until it had just dissolved (several hours). The solution was poured with stirring into a beaker containing a solution of 176 g of potassium carbonate in 176 mL of water. The suspension was filtered with suction and the precipitate was stirred several times with chloroform. The aqueous layer was also extracted several times with chloroform, the combined organic extracts were dried with Na_2SO_4, evaporated to dryness and recrystallised with chloroform/n-heptane(1:10 v/v). Yield: 54.4 g (52%) (lit[11].: 53%); R_f 0.72 (EtOAc); m.p.: 118-120°C (lit[11].: 117-121°C); $[\alpha]_D^{25}$ +2.1 (c=2.1, methanol) (lit[11].: +1.9 (c=2, methanol)) ^{13}C NMR (22.6 MHz, $CDCl_3$) δ=109.3 (2C), 75.8 (2C), 70.9 (2C), 66.7 (2C), 26.7 (2C), 25.2 (2C); ^{1}H NMR (90 MHz, $CDCl_3$) δ=3.88-4.33 (6H, CH_2-CH, m), 3.70 (2H, CH, dd, ^3J=7.0Hz, ^3J=7.0Hz), 2.79 (2H, OH, d, ^3J=7.0Hz), 1.34 (6H, CH_3, s), 1.29 (6H, CH_3, s); MS(35eV) *m/z*=263, 247, 229, 189, 101 (100%), 59, 43; HRMS calcd for $C_{12}H_{23}O_6$ (M^++H) 263.1494, found: 263.1483; IR ν'=3283, 2950-2992, 1372, 1267, 1210, 1160, 1126, 1068, 1009, 943, 668, 516.

(*Z*) and (*E*)-(*S*)-2,3-*O*-Isopropylidene-glyceraldoxime (*S*)-4 ($C_6H_{11}NO_3$)

To a solution of 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol **2** (12.5 g) in 130 mL THF (anhydrous) lead tetraacetate (21.1 g) was added under stirring at 15°C. The suspension was stirred (under argon) for 1.5 h. The precipitate was filtered off and a solution of NH_2OH·HCl (8.3 g), 16.7 mL triethylamine and 80 mL abs. methanol was slowly added controlling the temperature to 10°C. After 5 h the solution was filtered and the solvent was removed *in vacuo*. The precipitate was dissolved in $CHCl_3$ and extracted three times with water. The organic layer was dried and the solvent removed *in vacuo*. The resulting oil was distilled *in vacuo* to yield a colourless oil. Yield 11.7 g (84.5%) (lit[12].: 85%); b.p. 58-60°C, 0.05 Torr (lit[12].: 48-50°C, 0.04 Torr); R_f 0.30 (*E*), 0.24 (*Z*) (cyclohexane/EtOAc 7:3 v/v); ^{13}C NMR(50.3 MHz, $CDCl_3$) (*E*)-isomer δ=152.7, 109.7, 70.7, 67.8, 26.1, 25.3 ^{13}C NMR(50.3 MHz, $CDCl_3$) (*Z*)-isomer δ=149.6, 110.3, 73.2, 67.3, 26.5, 25.5;^{1}H NMR(200 MHz, $CDCl_3$) (*E*)-isomer δ=8.40-9.60 (1H, OH, bs), 6.90 (1H, CHN, d, ^3J=3.2Hz), 5.08 (1H, CHO, td, ^3J=6.4Hz, ^3J=3.2Hz), 4.33 (1H, HCHO, dd, ^2J=9.6Hz, ^3J=6.4Hz), 3.84 (1H, HCHO, dd, ^2J=9.6Hz, ^3J=6.4Hz), 1.25-1.45 (6H, CH_3, 2s) (*Z*)-isomer δ=8.40-9.60 (1H, OH, bs), 7.35 (1H, CHN, d, ^3J=6.4Hz), 4.60 (1H, CHO, ddd, ^3J=6.4Hz, ^3J=6.4Hz, ^3J=6.4Hz), 4.14 (1H, HCHO, dd, ^2J=10.2Hz, ^3J=6.4Hz), 3.75 (1H, HCHO, dd, ^2J=10.2Hz, ^3J=6.4Hz), 1.25-1.45 (6H, CH_3, 2s); MS(40eV) *m/z*=145, 130, 112, 43 (100%); HRMS calcd for $C_6H_{11}NO_3$ (M^+) 145.0739, found: 145.0730; IR ν'=3377, 2910-2988, 1456, 1374, 1216, 1155, 1063, 942, 845, 794, 513.

(*S*)-4-(Aminomethyl)-2,2-dimethyl-1,3-dioxolane (*S*)-5 ($C_6H_{13}NO_2$) via reduction of (*Z*) and (*E*)-(*S*)-2,3-*O*-isopropylidene-glyceraldoxime

To a suspension of $LiAlH_4$ (2.4 g) in 90 mL anhydrous THF (*Z*)- and (*E*)-(*S*)-2,3-*O*-isopropylidene-glyceraldoxime (*S*)-4 (5 g) dissolved in 70 mL anhydrous THF was slowly added (0°C, argon, vigorous stirring). The suspension was warmed to r.t. and stirred for 5 h. The reaction was quenched by adding sat. Na_2SO_4-solution at 0°C. 20 mL of a 1M NaOH-solution and 150 mL of water was added. The aqueous layer was extracted 12 times with 20 mL diethylether. The combined organic layers were dried with Na_2SO_4 and the solvent was removed *in vacuo*. The resulting oil was distilled *in vacuo* to yield a colourless oil. Yield: 4.2 g (93%); R_f 0.27 (EtOAc/methanol 5:1 v/v); b.p.: 62-65°C, 15 Torr (lit[12].: 62-65°C, 15 Torr); $[\alpha]_D^{25}$ +1.48 (neat) (lit[12].: +15 (neat))[20]; ^{13}C NMR(50.3 MHz, $CDCl_3$) δ=109.0, 77.3, 66.8, 44.7, 26.8, 25.3; ^{1}H NMR(200 MHz, $CDCl_3$) δ=3.96-4.16 (2H,OHCHCH, m), 3.63 (1H, HCHCH, dd, ^2J=7.4Hz, ^3J 5.9Hz), 2.81 (1H, HCHNH$_2$, dd, ^2J=13.2Hz, ^3J=4.8Hz), 2.73 (1H, HCHNH$_2$, dd, ^2J=13.2Hz, ^3J=6.0Hz), 1.38 (3H, CH_3, s), 1.31 (3H, CH_3, s), 1.20-1.35 (2H, NH_2, bs); MS(35eV) *m/z*=132, 131,

116, 101, 73, 56, 43 (100%); HRMS calcd for $C_6H_{13}NO_2$ (M^+) 131.0946, found: 131.0937; IR ν'=3372, 2930-2986, 1574, 1485, 1454, 1372, 1061, 827.

(*S*)-1-Amino-2,3-propanediol (*S*)-6 ($C_3H_9NO_2$)

(*S*)-4-(Aminomethyl)-2,2-dimethyl-1,3-dioxolane (2 g) (*S*)-5 was dissolved in 20 mL 2N H_2SO_4 and refluxed for 3 h. The mixture was then stirred for 12 h at r.t.. $Ba(OH)_2$ was added with vigorous stirring until pH 8 was reached. The precipitate was filtered off and washed two times with water. CO_2 was bubbled through the aqueous layer for 2 h . The precipitated $BaCO_3$ was filtered off and the solvent was removed *in vacuo*. The resulting oil was resolved in ethanol and the solvent was again removed *in vacuo*. Filtration by chromatography (ethanol/NH_3 (conc) 30:1 v/v) yielded in a slighly yellow oil which was used without further purification. Yield: 1.1 g (80%); R_f 0.1 (ethanol); ^{13}C NMR(22.6 MHz, D_2O) δ=66.6, 57.3, 36.8; ^1H NMR(200 MHz, D_2O) δ=3.44-3.58 (1H, CHO, m), 3.44-3.57 (2H, CH_2O, m), 2.72 (1H, HCHNH$_2$, dd, ^2J=13.0Hz, ^3J=4.0Hz), 2.58 (1H, HCHNH$_2$, dd, ^2J=13.0Hz, ^3J=7.5Hz); MS(35eV) *m/z*=92, 91, 73, 60 (100%), 44, 43, 42, 31; HRMS calcd for $C_3H_9NO_2$ (M^+) 91.0633, found: 91.0553.

(*S*)-5-Hydroxymethyl-2-oxazolidinone (*S*)-7 ($C_4H_7NO_3$) via cyclisation of (*S*)-1-amino-2,3-propanediol

(*S*)-1-Amino-2,3-propanediol (*S*)-6 (10.3 g) and diethylcarbonate (13.4 g) were stired for 2 h at 110°C. 150 mL diethyleneglycol dimethylether was added under vigorous stirring and followed by a very quick addition of $Mg(OMe)_2$ (10 g). The resulting suspension was heated to reflux for 24 h. The precipitate was filtered off, washed twice with methanol, and the solvent removed *in vacuo*. The resulting oil was purified by chromatography (EtOAc/methanol 5:1 v/v) to yield a colorness solid. Yield: 7.95 g (60.1%); R_f 0.49 (EtOAc/methanol 5:1 v/v); m.p.: 87-90°C (lit[16a].: 87-90°); $[\alpha]_D^{25}$ +31 (c=2.6, ethanol) (lit[16a].:+29.7 (c=2.7, ethanol)); ^{13}C NMR(50.3 MHz, d_4-methanol) δ=162.3, 78.5, 63.5, 42.8; ^1H NMR(250 MHz, d_4-methanol) δ=4.63-4.75 (1H, CHO, m), 3.75 (1H, HCHOH, dd, ^2J=12.3Hz, ^3J=3.7Hz), 3.63 (1H, NHCH (trans), dd, ^2J=12.3Hz, ^3J=5.0Hz), 3.62 (1H, HCHOH, dd, ^2J=8.7Hz, ^3J=8.7Hz), 3.44 (1H, NHCH (cis), dd, ^2J=8.7Hz, ^3J=6.2Hz); ^1H NMR(400 MHz, d_6-DMSO) additional: δ=7.4 (1H, NH, bs); 5.08 (1H, OH, dd, ^3J=3.6Hz, ^3J=3.6Hz); MS(70eV) *m/z*=118, 117, 99, 88, 86, 71, 58, 55, 44, 43, 42 (100%), 31; HRMS calcd for $C_4H_7NO_3$ (M^+) 117.0426, found: 117.0428; IR ν'=3330, 2830-2990, 1750, 1500, 1390, 1245, 1090, 1025, 970. Anal. calcd for $C_4H_7NO_3$: C 41.03 H 6.02 N 11.96. Found: C 41.16 H 6.00 N 11.63.

5,6-Isopropylidene-*L*-ascorbic acid 9 ($C_9H_{12}O_6$)

In a 250 mL flask equipped with a calcium sulfate drying tube *L*-ascorbic acid **8** (10 g) dissolved in 40 mL acetone and freshly distilled acetyl chloride (1 mL) was stirred at r.t. for 3 h. The flask was then stored for 8 h at 4°C. The solid was filtered off and washed with small amounts of cold acetone. The crude mixture was recrystallized from acetone/n-hexane. Yield: 7.7 g (62.6%) (lit[13].: 81% crude); R_f 0.66 (acetone/methanol 5:1 v/v); m.p.: 200-206°C (lit[13].: 214-218°) $[\alpha]_D^{25}$ +7.0 (c=0.56, acetone);^{13}C NMR(50.3 MHz, d_6-DMSO) δ=170.4, 152.5, 118.4, 109.2, 74.4, 73.6, 65.0, 25.9, 25.5; ^1H NMR(90 MHz, d_6-DMSO/$CDCl_3$) δ=10.30-11.50 (1H, OH, bs), 7.90-9.00 (1H, OH, bs), 4.55 (1H, =CCHO, d, ^3J=3Hz), 3.80-4.42 (3H, OCH$_2$CHO, m), 1.33 (6H,CH_3, s); MS(35eV) *m/z*=217, 216, 141, 101 (100%), 69, 59, 43; HRMS calcd for $C_9H_{12}O_6$ (M^+) 216.0634, found: 216.0630; IR ν'=3245, 2840-3000, 1754, 1664, 1432, 1375, 1333, 1222, 1140, 1105, 1068, 1044, 1011, 883, 852, 820, 768, 627.

(*Z*) and (*E*)-(*R*)-2,3-*O*-Isopropylidene-glyceraldoxime (*R*)-4 ($C_6H_{11}NO_3$)

To a stirred (KPG-stirrer) suspension of $LiAlH_4$ (1.5 g) in 50 mL abs. THF 5,6-isopropylidene-*L*-ascorbic-acid **9** (6.75 g) was added in portions under the flow of argon at 0°C. The mixture was refluxed for 2 h and after 1 h an additional amount of $LiAlH_4$ (1 g) was added until hydrogen evolution ceased. The cooled reaction mixture was quenched with a minimum of sat. NaCl-solution. $NaIO_4$ (21.5 g) was added to the brown suspension at 0°C under vigorous stirring. After 2h the mixture was diluted with ice-cold water and the aldehyde was extracted 10 times with 20 mL ice-cold diethylether. The combined organic layers were dried with Na_2SO_4 and half of the solvent was removed *in vacuo*. A solution of $NH_2OH{\cdot}HCl$ (5.4 g), 10.9 mL triethylamine and 70 mL abs. methanol was slowly added controlling the temperature to 10°C. The mixture was stirred at the same temperature for 5 h. The

solids were filtered off and the solvents were removed *in vacuo*. The solid was dissolved in $CHCl_3$, three times extrated with water, and the solvent removed *in vacuo*. Purification by flash-chromatography (cyclohexane/EtOAc 7:3 v/v) yielded a colourless oil. Yield: 995 mg (22%)

Further experimentel data see (*S*)-**4**.

(*R*)-4-(Aminomethyl)-2,2-dimethyl-1,3-dioxolane (*R*)-5 ($C_6H_{13}NO_2$) via reduction of (*Z*) and (*E*)-(*R*)-2,3-*O*-isopropylidene-glyceraldoxime

Prepared as (*S*)-**5**: $[\alpha]_D^{25}$ -1.45 (neat).

(*R*)-1-Amino-2,3-propanediol (*R*)-6 ($C_3H_9NO_2$)

Prepared as (*S*)-**6**.

(*R*)-5-Hydroxymethyl-2-oxazolidinone (*R*)-7 ($C_4H_7NO_3$) via cyclisation of (*R*)-1-amino-2,3-propanediol

Prepared as (*S*)-**7**: $[\alpha]_D^{25}$ -29.6 (c=2.7, Ethanol) (lit[16a].: -29.1 (c=1, Ethanol)); m.p.: 85-88°C.

(*R*)-1,2-*O*-isopropylidene glycerol 12 ($C_6H_{12}O_3$)

A solution of recystallised 5,6-isopropylidene-*L*-ascorbic acid **9** (4 g) in abs. ethanol (350 mL) was added over 1 h to a stirring solution of 715 mg $NaBH_4$ in 50 mL of abs. ethanol. The suspension was then stirred for additional 4 h at room temperature. After 3 h it was made basic by some pellets of NaOH followed by 50 mL of 1N NaOH-solution. The basic solution was then stirred overnight at r.t. and then exactly neutralized with conc. HCl (slight change of colour). The solvent was removed *in vacuo*, the white powder mixed with 200 mL of EtOAc and cooled to 0°C. Lead tetraacetate (30 g) was added in one portion and the brown mixture was stirred for 1.5 h at the same temperature and then for 2 h at r.t.. After recooling to 0°C the mixture was filtered through a bed of Celite into a pre-cooled receiver. This cold solution was added over a period of 30 min to a cooled solution of 7.2 g $NaBH_4$ in 150 mL of abs. ethanol. The resulting mixture was stirred for 2.5 h at r.t., then made basic by adding several pellets of NaOH followed by 100 mL of 1N NaOH-solution and stirred for additional 30 min. 100 mL of diethylether were added, the layers were seperated and the aqueous layer was extracted twice with 50 mL of diethylether. The combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent evapored *in vacuo*. The aqueous phase was saturated with NaCl, and again extracted 4 times with 50 mL of diethylether. The combined organic layers were dried (Na_2SO_4) and the solvent was evapored *in vacuo*. The product was purified by Kugelrohrdistillation. Yield: 1.31 g (43%) (lit[13].: 50%); R_f 0.61 (EtOAc/cyclohexane 1:1 v/v); b.p.: 102-103°C (15Torr) (lit[13].: 180°C 760 Torr); $[\alpha]_D^{25}$ -10.3 (c=16.3, methanol) (lit[13].: -10.76 (c=16.9, methanol); ^{1}H NMR(90 MHz, $CDCl_3$) δ = 3.62-4.40 (5H, $OC\underline{H}_2C\underline{H}OC\underline{H}_2O$, m), 3.03 (1H, OH, bs), 1.42 (3H, CH_3, s), 1.38 (3H, CH_3, s); GC-MS *m/z*=117 (M^+-CH_3), 101, 83, 72, 59, 57, 43 (100%).

(*S*)-2,2-Dimethyl-(hydroxymethyl)-1,3-dioxolane p-toluene-sulfonate 13 ($C_{13}H_{18}SO_5$)

To a solution of (*R*)-1,2-*O*-isopropylidene glycerol **12** (1 g) in 3.5 mL abs. pyridine p-toluenesulfonyl chloride (1.45 g) was added at 0°C. The solution was stirred overnight at r.t., and then 100 mL diethylether was added. The precipitate was filtered off and washed with a small amount of ether. The organic phase was extracted with dil. HCl, H_2O, sat. $NaHCO_3$-solution and again with H_2O, dried with Na_2SO_4 and the solvent was removed *in vacuo*. The resulting oil was purified by flash-chromatography (CH_2Cl_2) to yield a light yellow oil.

Yield: 7.7 g (80.3%) (lit[13].: 71% including a further reaction); R_f 0.66 (CH_2Cl_2); $[\alpha]_D^{25}$ +4.30 (c=1, ethanol) (lit.: +4.48 (c=1, ethanol); ^{13}C NMR(22.6 MHz, d_6-DMSO) δ=145.0, 132.0, 129.9 (2C), 127.9 (2C), 110.0, 72.9, 69.9, 66.1, 26.5, 25.1, 21.6; ^{1}H NMR(90 MHz, $CDCl_3$) δ=7.75 (2H, $H_3CCCHC\underline{H}$, d, ^3J=8.2Hz), 7.30 (2H, $H_3CCC\underline{H}$, d, ^3J=8.2Hz), 3.50-4.31 (5H, $OC\underline{H}_2C\underline{H}OC\underline{H}_2O$, m), 2.40 (3H, CH_3(ar), s), 1.27 (3H, CH_3, s), 1.25 (3H, CH_3, s); MS(35eV) *m/z*=287, 271, 155, 101 (100%), 91, 43; HRMS calcd for $C_{13}H_{18}SO_5$ (M^++H) 287.0953, found: 287.0953; IR ν'=3045, 2986, 1598, 1495, 1455, 1372, 1175, 822, 667, 555.

(*R*)-4-(Aminomethyl)-2,2-dimethyl-1,3-dioxolane (*R*)-6 ($C_6H_{13}NO_2$) via S_N2 reaction followed by reduction of 14[15]

(*S*)-2,2-Dimethyl-(hydroxymethyl)-1,3-dioxolane p-toluene-sulfonate **13** (2.35 g) and NaN_3 (5.3 g) were dissolved in 40 mL DMSO and stirred for 70 min at 100°C. After being cooled to r.t. 40 mL of $CHCl_3$ was added and the solution was extracted several times with water. The solvent was removed and the resulting oil (1 g, crude) was dissolved in 10 mL methanol. 200 mg Pd(5%)/C was added and hydrogen was bubbled through the mixture for 8 h. The catalyst was filtered off (Celite), the solvent removed and the amine was purified by flash-chromatography (EtOAc/methanol 2:1 v/v). Yield 67%; R_f 0.31 (EtOAc/methanol 2:1 v/v). Further experimentel data see (*S*)-6.

(*S*)-Malic acid 1-monobenzylester (*S*)-17 ($C_{11}H_{12}O_5$)[18]

To (*S*)-malic acid (*S*)-**15** (10 g) pre-cooled trifluoracetic acid anhydride (25 mL) was added at 0°C with vigorous stirring. The suspension was stirred for 2 h at r.t., the volatiles were then removed by distillation at a minimum temperature, freshly distilled benzylic alcohol (50 mL) was added and the solution stirred overnight. The excess of the alcohol and of the trifluoracetic acid was removed *in vacuo* to yield a colourless oil. Yield: 100%; R_f 0.25 (EtOAc/cyclohexane 2:1 v/v); $[\alpha]_D^{25}$ +13.2 (c=0.99, DMF); ^{13}C NMR(50.3 MHz, $CDCl_3$) δ=175.8, 173.1, 134.8, 128.7 (3C), 128.5 (2C), 67.9, 67.1, 38.4; ^1H NMR(200 MHz, $CDCl_3$) δ=7.35 (5H, H(ar), m), 6.90 (1H, COOH, bs), 5.20 (2H, $OC\underline{H}_2$, s), 5.15 (1H, OH, d, ^3J=3.5Hz), 4.55 (1H, C<u>H</u>O, ddd, ^3J=5.8Hz, ^3J=5.8Hz, ^3J=3.5 Hz), 2.95 (1H, CH_2, dd, ^2J=9.2Hz, ^3J=5.8Hz), 2.85 (1H, CH_2, dd, ^2J=9.2Hz, ^3J=5.8Hz); MS(FAB; mNBA) *m/z*=225.1 (M^++H), 247.1 (M^++Na); IR ν'=3300, 3060, 3160, 2970, 2950, 1735, 1558, 1494.

(*S*)-2-Oxazolidinone-5-carboxylic acid benzylester (*S*)-19 ($C_{11}H_{11}NO_4$)[17]

(*S*)-Malic acid 1-monobenzylester (*S*)-**17** (30 g), 21 mL triethylamine and diphenoxyphosphorylazide (40 g) were refluxed for 2 h in 450 mL toluene. The mixture was cooled to 70°C, stirred for another 2 h and than stirred for 70h at r.t.. The solvent was removed *in vacuo*, the slurry dissolved in water, and this solution was extracted several times with EtOAc. The organic layer was washed twice with sat. $NaHCO_3$, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by chromatography (EtOAc/cyclohexane 2:1 v/v) yielded in a colourless solid. Yield: 14.5 g (49%) (lit[17].: 74%); R_f 0.26 (EtOAc/cyclohexane 2:1 v/v); m.p.: 130°C (lit[17].: 130°C); $[\alpha]_D^{25}$ +4.5 (c=1, DMF) (lit[17].: +3.6 (c=1, DMF)); ^{13}C NMR(50.2 MHz,$CDCl_3$) δ = 168.8, 159.1, 134.6, 128.7 (3C), 128.5 (2C), 72.6, 67.7, 43.6; ^1H NMR(200 MHz, $CDCl_3$) δ =7.30 (5H, H_{ar}, bs), 6.65 (1H, NH, bs), 6.65 (2H, $COOC\underline{H}_2$, s), 5.00 (1H, C<u>H</u>O, dd, ^3J=9Hz, ^3J=7.2Hz), 3.83 (1H, HN<u>H</u>CH (cis), ddd, ^2J=9Hz, ^3J=9Hz, ^3J=1.8Hz), 3.63 (1H, HNHC<u>H</u> (trans), ddd, ^2J=9Hz, ^3J=7.2Hz, ^3J=0.9Hz); MS(35eV) *m/z*=221, 177, 139, 115, 107, 92, 91 (100%), 86, 65, 42; IR ν'=3257, 3160, 2924, 1752, 1651, 1558, 1490, 1278, 1217, 1091. Anal. calcd for $C_{11}H_{11}NO_4$: C 59.73 H 5.01 N 6.33. Found: C 59.50 H 5.00 N 6.30.

(*S*)-Hydroxymethyl-2-oxazolidinone (*S*)-7 ($C_4H_7NO_3$) via reduction of (*S*)-2-oxazolidinone-5-carboxylic acid benzylester

(*S*)-2-Oxazolidinone-5-carboxylic acid benzylester (*S*)-**19** (8.5 g) was suspended in 155 mL abs. ethanol. $NaBH_4$ (1.45 g) was added slowly at 0°C. The mixture was stirred 3 h at this temperature, then warmed up to r.t. and 5 mL NH_4Cl was added before stirring for additional 30 min. The solids were filtered off, and the solvent was removed *in vacuo*. Purification by flash-chromatography (EtOAc/methanol 5:1 v/v) yielded a colourless solid. Yield: 3.4 g (76%); R_f 0.49 (EtOAc/methanol 5:1 v/v); m.p.: 92°C (lit[16a].: 87-90°); $[\alpha]_D^{25}$ +39 (c=2.7, ethanol) (lit[16a].:+29.7 (c=2.7 ethanol)). Anal. calcd for: calc C 41.03 H 6.02 N 11.96. Found: N 11.91 C 41.18 H 6.10. For further experimentel data see (*S*)-7 via cyclisation of (*R*)-1-amino-2,3-propanediol.

(*S*)-5-(Methanesulfonyloxymethyl)-2-oxazolidinone (*S*)-20 ($C_5H_9NO_5S$)

To a solution of (*S*)-5-hydroxymethyl-2-oxazolidinone (*S*)-**7** (1 g) in 20 mL abs. pyridine freshly distilled methanesulfonyl chloride (1.24 g) dissolved in abs. CH_2Cl_2 was added at -10°C. After 3 h 3 mL 1M $AgNO_3$-solution was added and volatiles were removed *in vacuo* at a minimum temperature. The residue was chromatographed on silica gel (CH_2Cl_2/methanol 95:5 v/v) yielding a colourless solid. Yield: 1.58 g (95%) (lit.: 95%); R_f 0.35 (CH_2Cl_2/methanol 95:5 v/v); m.p.: 118-120°C (lit.: 113°C); $[\alpha]_D^{25}$ +34.4 (c=0.25, ethanol) (lit[101].: +30.9 (c=0.7, ethanol); ^{13}C NMR(22.6 MHz,d_6-DMSO) δ = 158.3, 72.6, 70.1, 41.1, 36.8; ^1H NMR(250

MHz, d_6-DMSO/D_2O) δ=4.77-4.89 (1H, CHO, m), 4.38 (1H, HCHO, dd, ^2J=12Hz, ^3J=3.2Hz), 4.28 (1H, HCHO, dd, ^2J=12Hz, ^3J=5.3Hz), 3.56 (1H, HNHCH (cis), dd, ^2J=9.7Hz, ^3J=9.7Hz), 3.23 (1H, HNHCH (trans), dd, ^2J=9.7Hz, ^3J=6.5Hz), 3.18 (3H, CH_3, s); MS(40eV) *m/z*=196, 116, 87, 86 (100%), 80, 79, 55, 43, 42; HRMS calcd for $C_5H_9NO_5S$ (M^++H) 196.0279; found: 196.0287; IR ν'=3292, 2920-3020, 1751, 1500, 1353, 1244, 1181, 1095, 967, 879, 826, 767, 730, 528. Anal. calcd for $C_5H_9NO_5S$: C 30.77 H 4.65 N 7.18. Found: C 30.73 H 4.55 N 7.10.

(*S*)-5-(Chloromethyl)-2-oxazolidinone (*S*)-21 ($C_4H_6ClNO_2$)

(*S*)-5-(Methanesulfonyloxymethyl)-2-oxazolidinone (*S*)-**20** (3.84 g) and LiCl (15.1 g) were refluxed in 200 mL acetone for 100 h. The solvent was removed, the solid dissolved in H_2O and extracted several times with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The resulting white powder was almost pure and could be purified by flash-chromatography (EtOAc/cyclohexane 2:1 v/v). Yield: 2.53 g (95%); R_f 0.20 (EtOAc/cyclohexane 1:1 v/v); m.p.: 86°C (racemic compound 108°C); $[\alpha]_D^{25}$ +19.1 (c=3.3, CH_2Cl_2); ^{13}C NMR(50.2 MHz, $CDCl_3$) δ = 159.2, 74.7, 44.5, 43.6; ^1H NMR(200 MHz, $CDCl_3$) δ =6.13 (1H, NH, bs), 4.76-4.92 (1H, CHO, m), 3.75 (1H, HCHN (cis), dd, ^2J=9.1Hz, ^3J=9.1Hz), 3.68 (2H, H_2CCl, d, ^3J=6.4Hz), 3.52 (1H, HNHCH (trans), ddd, ^2J=9.1Hz, ^3J=5.5Hz, ^3J=1.25Hz); MS(40eV) *m/z*=135, 86 (100%), 42, 36; HRMS calcd for $C_4H_6ClNO_2$ (M^+) 135.0087; found: 135.0088; IR ν'=3252, 3018, 2961, 2910, 1751, 1250, 1075, 1016, 958, 762. Anal. calcd for $C_4H_6ClNO_2$: C 35.44 H 4.46 N 10.33. Found: C 35.56 H 4.37 N 10.36.

(*S*)-5-(Bromomethyl)-2-oxazolidinone (*S*)-22 ($C_4H_6BrNO_2$)

(*S*)-5-(Methanesulfonyloxymethyl)-2-oxazolidinone (*S*)-**20** (400 mg) and LiBr (3.4 g) were refluxed in 30 mL acetone for 40 h. The solvent was removed, the solid dissolved in H_2O and extracted several times with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The resulting white powder was almost pure and could be purified by flash-chromatography (EtOAc/cyclohexane 2:1 v/v). Yield: 284 mg (77%); R_f 0.20 (CH_2Cl_2/methanol 19:1 v/v); m.p.: 98°C (racemic compound 108°C); $[\alpha]_D^{25}$ +2.8 (c=3.2, CH_2Cl_2); ^{13}C NMR(50.2 MHz, $CDCl_3$) δ = 159.1, 74.5, 44.7, 32.4; ^1H NMR(200 MHz, $CDCl_3$) δ =6.10 (1H, NH, bs), 4.83 (1H, CHO, m), 3.70 (1H, HCHO, ddd, ^2J=9Hz, ^3J=9Hz, ^3J=1Hz), 3.40-3.60 (3H, HNHCHCHH_2, m); MS(40eV) *m/z*=181, 179,87, 86 (100%), 42, 36; IR ν'=3235, 3020, 2899, 1737, 1485, 1245, 1168, 872, 843. Anal. calcd for $C_4H_6BrNO_2$: C 26.69 H 3.36 N 7.78. Found: C 27.26 H 3.45 N 7.69.

(*S*)-5-(Iodomethyl)-2-oxazolidinone (*S*)-23 ($C_4H_6INO_2$)

(*S*)-5-(Methanesulfonyloxymethyl)-2-oxazolidinone (*S*)-**20** (400 mg) and LiI (5.1 g) were refluxed in 30 mL acetone for 40 h. The solvent was removed, the solid dissolved in H_2O.and extracted several times with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The resulting white powder was almost pure and could be purified by flash-chromatography (EtOAc/cyclohexane 3:2 v/v). Yield: 303 mg (65%); R_f 0.26 (EtOAc/cyclohexane 3:2 v/v); m.p.: 125°C (racemic compound 125°C); $[\alpha]_D^{25}$ +13.4 (c=2.5, CH_2Cl_2); ^{13}C NMR(50.2 MHz, $CDCl_3$) δ = 159.3, 75.2, 46.4, 5.9; ^1H NMR(200 MHz, $CDCl_3$) δ =5.73 (1H, NH, bs), 4.72 (1H, CHO, m), 3.76 (1H, HCHN (cis), ddd, ^2J=9.1Hz, ^3J=8.5Hz, ^3J=0.7Hz), 3.40 (1H, HCHI, dd, ^2J=10.2Hz, ^3J=4.2Hz), 3.38 (1H, HNHCH (trans), ddd, ^2J=9.1Hz, ^3J=6.2Hz, ^3J=1.1Hz), 3.28 (1H, HCHI, dd, ^2J=10.2Hz, ^3J=8.3Hz); MS(40eV) *m/z*=227, 142, 127, 100 (100%), 86, 56; IR ν'=3258, 2950, 2901, 1734, 1491, 14,11, 1342, 1186, 1093, 1003, 956,763, 719, 603. Anal. calcd for $C_4H_6INO_2$: C 21.16 H 2.66 N 6.17. Found: C 22.55 H 2.80 N 6.42 (due to slight decomposition).

(*R*)-Malic acid 1-monobenzylester (*R*)-17 ($C_{11}H_{12}O_5$)

Prepared as (*S*)-**17**; $[\alpha]_D^{25}$-13.5 (c=0.99, DMF).

(*R*)-2-Oxazolidinone-5-carboxylic acid benzylester (*R*)-19 ($C_{11}H_{11}NO_4$)

Prepared as (S)-**19**; $[\alpha]_D^{25}$-4.3 (c=1 DMF) (lit[17].:+3.6 (c=1, DMF) for the opposite enantiomer).

(*R*)-Hydroxymethyl-2-oxazolidinone (*R*)-7 ($C_4H_7NO_3$) via reduction of (*R*)-2-oxazolidinone-5-carboxylic acid benzylester

Prepared as (*S*)-7; $[\alpha]_D^{25}$-38.6 (c=2.7 ethanol) (lit[16a].:-29.1 (c=1, ethanol)).

(*R*)-5-(Methanesulfonyloxymethyl)-2-oxazolidinone (*R*)-20 ($C_5H_9NO_5S$)

Prepared as (*S*)-**20**; $[\alpha]_D^{25}$-34.4 (c=0.26 ethanol) (lit[16a].:-31.8 (c=0.43, ethanol)).

(*R*)-5-(Chloromethyl)-2-oxazolidinone (*R*)-21 ($C_4H_6ClNO_2$)

Prepared as (*S*)-**21**; $[\alpha]_D^{25}$-18.7 (c=3.2, CH_2Cl_2).

(*R*)-5-(Bromomethyl)-2-oxazolidinone (*R*)-22 ($C_4H_6BrNO_2$)

Prepared as (*S*)-**22**; $[\alpha]_D^{25}$-2.6 (c=3.2, CH_2Cl_2).

(*R*)-5-(Iodomethyl)-2-oxazolidinone (*R*)-23 ($C_4H_6INO_2$)

Prepared as (*S*)-**23**; $[\alpha]_D^{25}$-13.4 (c=2.5, CH_2Cl_2).

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20 Since the optical rotation obtained by our measurement in further steps are equal to those mentioned in the literature, we suppose that either the reported substance was not quite pure or there is an error of transfer in the literature.

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