Efficient Pathways to Precursors of Pyrrolidine Azasugar Structures

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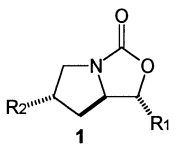
Hydroxy-substituted pyrrolidines are important structural elements in azasugars. Effective precursors for such compounds are pyrrolo-oxazolidinones of type **1**. Short asymmetric syntheses starting from easily available low-priced precursors are desirable. Two efficient pathways to these structures starting from the 4-methoxylated oxazolidinones **2** and **3**, easily accessible from the chiral pool, have been successfully developed. These oxazolidinones can be used as amidoalkylation reagents. Via Sakurai reactions and subsequent intramolecular cyclization, the synthesis of bicyclic pyrrolidines is possible in a stereocontrolled way.

Introduction

Chiral hydroxy- and hydroxymethyl-substituted pyrrolidine derivatives display interesting biological activity as they are able to inhibit glycosidases in a reversible and competitive manner.[1] Since glycosidases are key enzymes in the biosynthesis and processing of glycoproteins, their inhibitors are widely investigated as potential antibacterial, antiviral (including HIV)[2], antiinflammatory, antitumoral[3] and antidiabetic[4] agents. Pyrrolidine sugar analogues have been shown[5] to be very good mimics of the transition state for glycoside hydrolysis, with respect to both the flattened half-chair conformation and the charge distribution, while the position of the hydroxyl groups is less important. Thus, they can bind tightly to the enzyme and inhibit it competitively.

Because of their pharmacological importance, a large number of synthetic routes to such compounds have recently been developed.[6] Most of the enantioselective methods described to date are based on manipulations of natural carbohydrates as starting materials and involve sophisticated protective group strategies.[7] More efficient precursors for such compounds are pyrrolo[1,2-*c*]oxazolidinones **1**, which can be easily converted to 2-hydroxymethylpyrrolidines.[8] We present here two economical pathways to differently substituted chiral pyrrolo-oxazolidinones derived from low-priced chiral precursors via stereocontrolled routes.



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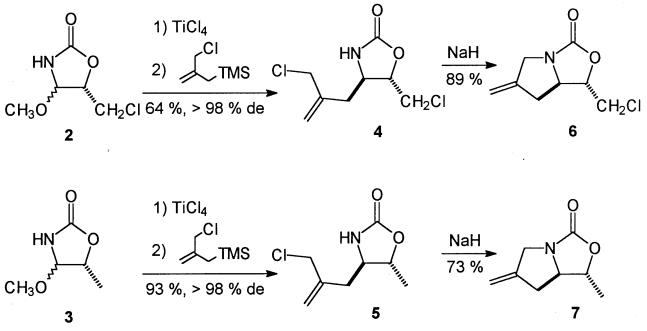
Results and Discussion

As starting materials, we selected (4*RS*,5*S*)-5-chloromethyl-4-methoxy-2-oxazolidinone (**2**) and (4*RS*,5*R*)-4-methoxy-5-methyl-2-oxazolidinone (**3**). Compound **2** is readily available from (*S*)-malic acid,[9] while **3** can be obtained from threonine[10] using an electrochemical carbamate oxidation as the key step, as we have described previously.

The oxazolidinones **2** and **3** are stable storage forms of chiral amidoalkylation reagents, which can be used as key building blocks for the synthesis of β-amino alcohols.[9][11] By treating them with $TiCl_4$ at −78 °C, *N*-acyliminium cations are generated in situ, which are then allowed to react with 2-chloromethyl-3-trimethylsilyl-1-propene in a Sakurai reaction[12] to give the products **4** and **5** in good yields and with excellent diastereoselectivities. Cyclization to enantiomerically pure bicyclic methylene pyrrolidines **6** and **7** is achieved by using NaH as a base (Scheme 1).[13]

Scheme 1. Syntheses of bicyclic methylene pyrrolidines **6** and **7**



Semiempirical calculations (AM1/RHF) show that compounds **6** and **7** have an angular structure. Thus, further transformations at the *exo*-methylene function should proceed diastereoselectively, preferentially from the convex face of the molecule. Accordingly, catalytic hydrogenation using palladium-on-charcoal as catalyst proceeds with good

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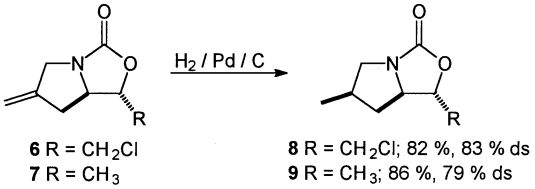
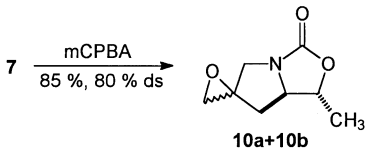
yields and high diastereoselectivities to give the compounds **8** (82%, *ds* 83%) and **9** (86%, *ds* 79%) (Scheme 2).

Scheme 2. Hydrogenation of compounds **6** and **7**



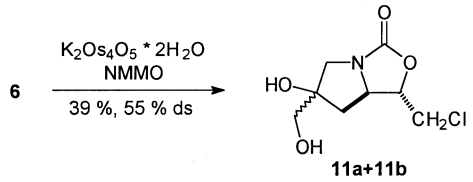
Epoxidation of **7** with *m*CPBA generates the spiro-oxiranes **10a** and **10b** in 85% yield and 80% *ds*. Diastereoselective opening of the epoxide as described in the literature[14] should give the diol.

Scheme 3. Epoxidation of the methylene group of **7**



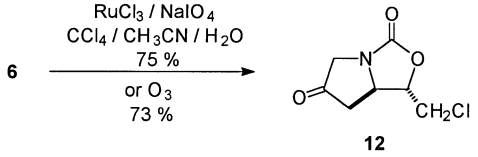
Bishydroxylation of the double bond can be performed in a single step using *N*-methylmorpholine *N*-oxide and catalytic amounts of $K_2Os_4O_5 \cdot 2\ H_2O$. Applying this procedure to compound **7**, the desired products **11a** and **11b** are obtained in 39% yield. Unfortunately, in this case the diastereoselectivity is low (55% *ds*) (Scheme 4).

Scheme 4. Bishydroxylation of **6**



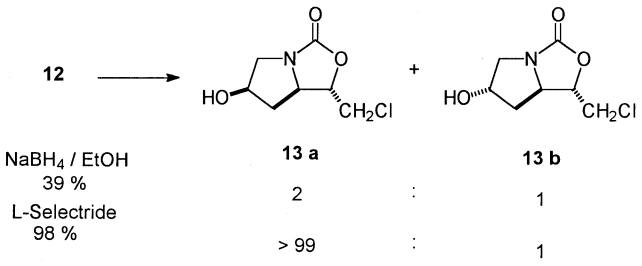
In order to introduce a hydroxy function at the 3-position of the pyrrolidine, oxidative cleavage of the double bond of **6** is first necessary to give the corresponding ketone. This can be smoothly achieved by applying one of two standard procedures, namely ozonolysis or reaction with sodium metaperiodate and catalytic amounts of ruthenium trichloride hydrate in carbon tetrachloride/acetonitrile/water (2:2:3, v/v/v). Both methods furnish the desired product **12** in enantiomerically pure form in good yields (Scheme 5).

Scheme 5. Oxidative cleavage of the double bond of compound **6**



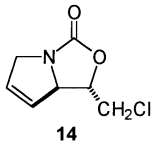
To achieve diastereoselective reduction of the carbonyl group of **12** to the corresponding alcohol, we first used sodium borohydride in ethanol, which gave a 2:1 mixture of the diastereomers **13a** and **13b** in 39% yield. To increase the diastereoselectivity, we turned to the sterically more demanding L-selectride, which was expected to favour the attack from the convex side of **12** more effectively. Indeed, the reduction with L-selectride in THF gave only **13a** in enantiomerically and diastereomerically pure form in excellent yield. The relative configuration of **13a** was proved by NOE experiments (Scheme 6).

Scheme 6. Diastereoselective reduction of the keto function of **13**



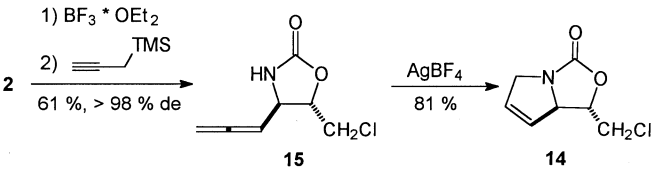
In summary, we have been able to synthesize diastereomerically and enantiomerically pure compound **13a**, a precursor of pyrrolidine sugar analogues, starting from readily available 5-chloromethyl-4-methoxy-1,3-oxazolidin-2-one in five steps in 48% overall yield.

Another very suitable precursor for hydroxy-substituted pyrrolidines is compound **14**. Here, the double bond may be further functionalized by using, for example, bishydroxylation or hydroboration to give differently substituted hydroxy- and polyhydroxypyrrolidines.



Again, starting from (4*RS*,5*S*)-5-chloromethyl-4-methoxy-2-oxazolidinone (**2**), the methoxy group of the oxazolidinone was substituted by an allene function through the use of propargyltrimethylsilane as a nucleophile and $BF_3 \cdot OEt_2$ as a Lewis acid, via the intermediate *N*-acyliminium ion. The reaction proceeded in 61% yield with excellent diastereoselectivity (> 98% *de*) to furnish compound **15**. Cyclization with 0.5 equiv. silver tetrafluoroborate led to enantiomerically pure compound **14** in 81% yield (Scheme 7).

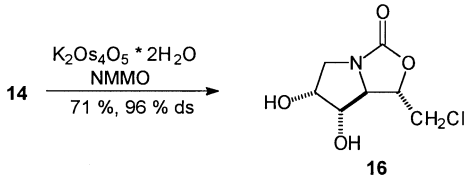
Scheme 7. Synthesis of pyrrolidine sugar precursor **14**



Compound **14** again possesses an angular structure, as shown by semiempirical calculations (AM1/RHF). In this case, the double bond is part of the pyrrolidine ring and so it is effectively shielded by the bicyclic structure. Consequently, further transformations at the double bond should proceed with higher diastereoselectivity in favour of attack from the convex face of the molecule, as compared with the cases of compounds **6** and **7**.

In fact, bishydroxylation of the double bond using *N*-methylmorpholine *N*-oxide and catalytic amounts of $K_2Os_4O_5 \cdot 2\ H_2O$ proceeded in 71% yield with 96% *ds* to give compound **16**. Its relative conformation was proved by NOE experiments. Thus, we have shown that compound **14** is a very efficient precursor for hydroxy-substituted pyrrolidines.

Scheme 8. Bishydroxylation of **14**



In conclusion, we have succeeded in synthesizing differently substituted enantiomerically pure pyrrolo[1,2-*c*]oxazolidinones along two different pathways starting from readily available chiral compounds with moderate to excellent diastereoselectivities. The products represent valuable precursors for flexible syntheses of pyrrolidine sugar analogues. Further transformations of compound **14** to products of pharmacological interest are currently under investigation.

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Experimental Section

General Methods: Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in the solvents indicated using Bruker AC 200 (200 MHz), Bruker WM 250 (250 MHz) or Bruker AC 400 (400 MHz) spectrometers. The same instruments were also used for the recording of ^{13}C spectra (22.6 MHz, 50.3 MHz; 62.9 MHz; 100.6 MHz). Chemical shifts are given in ppm downfield from tetramethylsilane. − R_f values were determined using thin-layer chromatography (TLC) on silica gel coated plastic sheets (Merck silica gel F_{254}). − Optical rotations were measured with a Perkin-Elmer P241 polarimeter at the sodium D-line (589.3 nm). − Melting points are uncorrected. − All solvents were distilled prior to use. The relative configurations were determined by comparison of ^{1}H-NMR coupling constants with those of known compounds and by measurement of NOE difference spectra.

Nucleophilic Exchange with 2-Chloromethyl-3-trimethylsilyl-1-propene. − General Procedure: In a dry Schlenk tube, a solution of **2** or **3** in dry CH_2Cl_2 was cooled to −78°C under argon atmosphere and a 1 M $TiCl_4$ solution was added dropwise. The mixture was stirred for 20 min. and then 2-chloromethyl-3-trimethylsilyl-1-propene was slowly added. After stirring for 15 h, the reaction mixture was quenched by addition of conc. aq. $NaHCO_3$ solution and the solids were filtered off. The phases were separated, the aqueous phase was extracted three times with CH_2Cl_2, and the combined organic layers were dried with Na_2SO_4. The crude material obtained after evaporation of the solvent was purified by flash chromatography on silica gel.

(4R,5S)-4-[2-(Chloromethyl)allyl]-5-chloromethyl-2-oxazolidinone (**4**): Following the general procedure, (4*RS*,5*S*)-5-chloromethyl-4-methoxy-2-oxazolidinone (**2**) (0.2 g, 1.2 mmol) was treated with 1 M $TiCl_4$ solution (1.5 ml, 1.5 mmol) and 2-chloromethyl-3-trimethylsilyl-1-propene (0.298 g, 1.8 mmol) in CH_2Cl_2 (20 ml). Purification of the crude product by flash chromatography on silica gel (cyclohexane/EtOAc, 1:1) afforded 0.199 g (74%) of **4** as a colourless oil. The (4*R*,5*S*) product was obtained in > 98% *ds*. − R_f = 0.37 (cyclohexane/EtOAc, 1:1). − $[\alpha]_D^{25}$ = +91 (*c* = 1 in methanol). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.19 (br, NH, 1 H), 5.28 (s, *H*HC=CRH, 1 H), 5.06 (s, H*H*C=CRH, 1 H), 4.38 (ddd, ^3J = 6.2 Hz, ^3J = 4.7 Hz, ^3J = 4.4 Hz, OCH), 4.0 (d, ^4J = 0.7 Hz, ClH_2CC=C, 2 H), 3.93 (m, NCH, 1 H), 3.64 (dd, ^2J = 11.8 Hz, ^3J = 4.8 Hz, OCHCH*H*Cl, 1 H), 3.60 (dd, ^2J = 11.8 Hz, ^3J = 6.2 Hz, OCHC*H*HCl, 1 H), 2.48 (dd, ^2J = 14.5 Hz, ^3J = 5.7 Hz, NHCCH*H*), 2.41 (ddd, ^2J = 14.5 Hz, ^3J = 8.3 Hz, ^4J = 0.7 Hz, NHCC*H*H, 1 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 157.9, 139.7, 119.2, 79.7, 53.7, 47.8, 44.0, 39.7. − MS (70 eV, EI); *m/z* (%): 224 (1) [M^+ + H], 188 (27) [M^+ − Cl], 174 (19) [M^+ − CH_2Cl], 134 (100) [M^+ − C_4H_6Cl], 90 (26) [M^+ − C_4H_6Cl − CO_2], 63 (28). − HRMS: calcd. for $C_8H_{12}Cl_2NO_2$ [M^+ + H] 224.0245; found 224.0245. − $C_8H_{11}Cl_2NO_2$ (224.09): calcd. C 42.88, H 4.95, N 6.25; found C 43.14, H 5.04, N 6.23.

(4R,5R)-4-[2-(Chloromethyl)allyl]-5-methyl-2-oxazolidinone (**5**): Following the general procedure, (4*RS*,5*R*)-4-methoxy-5-methyl-2-oxazolidinone (**3**) (0.131 g, 1 mmol) was treated with 1 M $TiCl_4$ solution (1.3 ml, 1.3 mmol) and 2-chloromethyl-3-trimethylsilyl-1-propene (0.248 g, 1.5 mmol) in CH_2Cl_2 (15 ml). Purification of the crude product by flash chromatography on silica gel (cyclohexane/EtOAc, 1:1) afforded 0.175 g (93%) of **5** as a colourless oil. The (4*R*,5*S*) product was obtained in > 98% *ds*. − R_f = 0.39 (cyclohexane/EtOAc, 1:2). − $[\alpha]_D^{25}$ = +55 (*c* = 0.2 in $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (br, NH, 1 H), 5.24 (s, *H*HC=CRH, 1 H), 5.01 (s, H*H*C=CRH, 1 H), 4.28 (dq, ^3J = 6.2 Hz, ^3J = 6.2 Hz, OCH), 4.0 (s, ClH_2CC=C, 2 H), 3.58 (ddd, ^3J = 8.3 Hz, ^3J = 6.2 Hz, ^3J = 5.0 Hz, NCH, 1 H), 2.42 (dd, ^2J = 14.7 Hz, ^3J = 8.3 Hz, NHCCH*H*), 2.32 (dd, ^2J = 14.7 Hz, ^3J = 8.3 Hz, NHCC*H*H, 1 H), 1.45 (d, ^3J = 6.2 Hz, CH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.4, 140.1, 118.4, 78.5, 57.6, 48.0, 38.6, 20.1. − MS (70 eV, EI); *m/z* (%): 190 (1) [M^+ + H], 154 (1) [M^+ − Cl], 100 (100) [M^+ − C_4H_6Cl].

Cyclization to Methylenepyrrolidines. − General Procedure: To a solution of **4** or **5** in THF, sodium hydride was added at 0°C. The reaction mixture was stirred at this temp. for 3 h and then at 25°C for 12 h. It was subsequently poured into a saturated NH_4Cl solution. The resulting mixture was repeatedly extracted with Et_2O, the combined extracts were dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography.

(7R,8S)-8-Chloromethyl-5-methylene-4,6,7,8-tetrahydropyrrolo-[1,2-c]oxazol-2-one (**6**): According to the general procedure, **4** (0.09 g, 0.4 mmol) was dissolved in THF (5 ml) and 5 equiv. of sodium hydride (0.097 g, 2.4 mmol) were added. Purification of the crude product on silica gel (cyclohexane/EtOAc, 2:1) afforded 0.079 g (89%) of **6** as a colourless solid, m.p. 54°C. − R_f = 0.34 (cyclohexane/EtOAc, 2:1). − $[\alpha]_D^{25}$ = +69 (*c* = 1 in methanol). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.07 (dtt, ^2J = 4.0 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, C=CH*H*, 1 H), 5.01 (dtt, ^2J = 4.0 Hz, ^4J = 1.2 Hz, ^4J = 1.0 Hz, C=C*H*H, 1 H), 4.45 (ddd, ^3J = 8.0 Hz, ^3J = 4.4 Hz, ^3J = 3.2 Hz, OCH, 1 H), 4.18 (ddd, ^2J = 15.5 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, NCH*H*, 1 H), 3.88 (ddd, ^3J = 9.6 Hz, ^3J = 6.4 Hz, ^3J = 3.2 Hz, NCH, 1 H), 3.71 (dd, ^2J = 11.3 Hz, ^3J = 4.4 Hz, ClCH*H*, 1 H), 3.66 (ddd, ^2J = 15.5 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, NC*H*H, 1 H), 3.59 (dd, ^2J = 11.3 Hz, ^3J = 8.1 Hz, ClC*H*H, 1 H), 2.70 (dddd, ^2J = 15.1 Hz, ^3J = 6.4 Hz, ^4J = 1.2 Hz, ^4J = 1.0 Hz, CCH*H*C, 1 H), 2.33 (m, CC*H*HC, 1 H). − ^{13}C NMR (100.6 MHz,

$CDCl_3$): δ = 159.8, 144.7, 109.0, 78.4, 62.2, 50.1, 44.2, 38.3. − MS (70 eV, EI); *m/z* (%):188 (0.44) [M^+ + H], 187 (41) [M^+], 152 (100) [M^+ − Cl], 108 (79) [M^+ − C_4H_6 − CO + H], 82 (33) [M^+ − C_4H_6 − CH_2Cl], 67 (19) [$C_4H_6N^+$], 54 (51) [$C_4H_6^+$]. − HRMS: calcd. for $C_8H_{10}ClNO_2$ [M^+] 187.0400; found 187.0404.

(7R,8R)-8-Methyl-5-methylene-4,6,7,8-tetrahydropyrrolo[1,2-c]-oxazol-2-one (**7**): According to the general procedure, **5** (0.228 g, 1.2 mmol) was dissolved in THF (12 ml) and 5 equiv. of sodium hydride (0.270 g, 6 mmol) were added. Purification of the crude product on silica gel (cyclohexane/EtOAc, 2:1) afforded 0.134 g (73%) of **7** as a colourless oil. − R_f = 0.40 (cyclohexane/EtOAc, 2:1). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.03 (dtt, ^2J = 3.9 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, C=CH*H*, 1 H), 4.97 (dtt, ^2J = 3.9 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, C=C*H*H, 1 H), 4.41 (qd, ^3J = 6.4 Hz, ^3J = 3.0 Hz, OCH, 1 H), 4.17 (dddd, ^2J = 15.5 Hz, ^4J = 4 Hz, ^4J = 2 Hz, ^4J = 2 Hz, NCH*H*, 1 H), 3.63 (ddd, ^2J = 15.5 Hz, ^4J = 4 Hz, ^4J = 2 Hz, NC*H*H, 1 H), 3.57 (ddd, ^3J = 10.0 Hz, ^3J = 6.4 Hz, ^3J = 3.0 Hz, NCH, 1 H), 2.63 (ddd, ^2J = 15.3 Hz, ^3J = 6.0 Hz, ^4J = 0.7 Hz, CC*H*HC, 1 H), 2.26 (dddd, ^2J = 15.3 Hz, ^3J = 10.0 Hz, ^4J = 4 Hz, ^4J = 2 Hz, CCH*H*C, 1 H), 1.43 (d, ^3J = 6.4 Hz, CH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.7, 145.4, 108.3, 76.6, 65.4, 50.0, 38.0, 21.0. − MS (70 eV, EI); *m/z* (%):153 (85) [M^+], 109 (52) [M^+ − CO_2], 94 (29) [M^+ − $C_2H_3O_2$], 80 (72) [M^+ − $C_3H_5O_2$], 68 (43) [$C_4H_7N^+$], 54 (100) [$C_4H_6^+$]. − HRMS: calcd. for $C_8H_{11}NO_2$ [M^+] 153.0790; found 153.0789.

Catalytic Hydrogenation. − General Procedure: **6** or **7** was dissolved in methanol and the catalyst Pd/C was added. The tube was filled with hydrogen at a pressure of 1 atm. After a reaction time of 12 h, the catalyst was filtered off and the solvent was removed in vacuo. The crude product was purified by flash chromatography.

(5RS,7R,8S)-8-Chloromethyl-5-methyl-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one (**8**): **6** (0.095 g, 0.53 mmol) was hydrogenated according to the general procedure and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 2:1). Compound **8** (0.079 g, 82%) was isolated as a colourless solid, m.p. 82°C. The (5*R*,7*R*,8*S*) product **8** was formed with a diastereoselectivity of 83%. − R_f = 0.35 (cyclohexane/EtOAc, 2:1).

(5*R*,7*R*,8*S*)-**8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (ddd, ^3J = 7.1 Hz, ^3J = 4.4 Hz, ^3J = 4.2 Hz, OCH, 1 H), 3.79 (ddd, ^3J = 8.1 Hz, ^3J = 5.8 Hz, ^3J = 4.2 Hz, NCH, 1 H), 3.70 (dd, ^2J = 11.4 Hz, ^3J = 4.4 Hz, CH*H*Cl, 1 H), 3.59 (dd, ^2J = 11.4 Hz, ^3J = 7.1 Hz, C*H*HCl, 1 H), 3.34 (dd, ^2J = 10.9 Hz, ^3J = 8.5 Hz, NC*H*H, 1 H), 3.03 (dd, ^2J = 10.9 Hz, ^3J = 8.1 Hz, NCH*H*, 1 H), 2.55−2.31 [m, MeC*H*$(CH_2)_2$, 1 H], 2.13 (ddd, ^2J = 11.95 Hz, ^3J = 5.9 Hz, ^3J = 5.8 Hz, CH*H*CHN, 1 H), 1.75 (m, C*H*HCHN, 1 H), 1.08 (d, ^3J = 7.0 Hz, CH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.1, 78.3, 63.4, 52.6, 44.5, 39.7, 35.6, 10.4.

(5*S*,7*R*,8*S*)-**8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.37 (m, OCH, 1 H), 3.90−3.58 (m, NCH, CH_2Cl, 3 H), 3.34 (m, NC*H*H, 1 H), 3.03 (m, NCH*H*, 1 H), 2.55−2.31 [m, MeC*H*$(CH_2)_2$, 1 H], 1.98 (m, CH*H*CHN, 1 H), 1.85 (m, C*H*HCHN, 1 H), 1.02 (d, ^3J = 7.0 Hz, CH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.1, 78.3, 63.4, 52.6, 44.5, 39.7, 35.6, 10.4. − MS (70 eV, EI); *m/z* (%): 189 (10) [M^+], 154 (100) [M^+ − Cl], 68 (83) [$C_4H_7N^+$]. − HRMS: calcd. for $C_8H_{12}ClNO_2$ [M^+] 189.0557; found 189.0560.

(5RS,7R,8R)-5,8-Dimethyl-4,6,7,8-tetrahydropyrrolo[1,2-c]-oxazol-2-one (**9**): **7** (0.153 g, 1 mmol) was hydrogenated according to the general procedure and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 1:1). Compound **9** (0.133 g, 86%) was isolated as a colourless oil. The (5*R*,7*R*,8*R*) product **9** was formed with a diastereoselectivity of 79%. − R_f = 0.48 (cyclohexane/EtOAc, 1:1).

(5*R*,7*R*,8*R*)-**9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (qd, ^3J = 6.4 Hz, ^3J = 4.05 Hz, OCH, 1 H), 3.51 (ddd, ^3J = 10.3 Hz, ^3J = 5.9 Hz, ^3J = 4.05 Hz, NCH, 1 H), 3.31 (dd, ^2J = 10.85 Hz, ^3J = 8.45 Hz, NCH*H*, 1 H), 3.05 (dd, ^2J = 10.85 Hz, ^3J = 8.1 Hz, NC*H*H, 1 H), 2.50−2.25 [m, MeC*H*$(CH_2)_2$, 1 H], 2.10 (dd, ^2J = 11.8 Hz, ^3J = 5.9 Hz, CH*H*CHN, 1 H), 1.68 (m, C*H*HCHN, 1 H), 1.41 [d, ^3J = 6.4 Hz, $(CH_2)_2CH_3$, 3 H], 1.08 (d, ^3J = 6.8 Hz, OCHCH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.4, 77.3, 66.7, 52.3, 39.2, 35.6, 20.7, 18.3.

(5*S*,7*R*,8*R*)-**9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (qd, ^3J = 6.25 Hz, ^3J = 4.8 Hz, OCH, 1 H), 3.85 (dd, ^2J = 11.6 Hz, ^3J = 7.35 Hz, NCH*H*, 1 H), 3.60 (ddd, ^3J = 7.35 Hz, ^3J = 7.35 Hz, ^3J = 4.8 Hz, NCH, 1 H), 2.60 (dd, ^2J = 11.6 Hz, ^3J = 6.4 Hz, NC*H*H, 1 H), 2.50−2.25 [m, MeC*H*$(CH_2)_2$, 1 H], 2.10 (m, C*H*HCHN, 1 H), 1.68 (m, CH*H*CHN, 1 H), 1.43 [d, ^3J = 6.25 Hz, $(CH_2)_2CH_3$, 3 H], 1.02 (d, ^3J = 7.0 Hz, CH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.5, 78.4, 64.5, 53.3, 38.1, 33.7, 20.9, 18.6.

Spiro-8-methyl-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one-5,2′-oxirane (**10**): To a solution of **7** (0.189 g, 1 mmol) in CH_2Cl_2 (10 ml), *m*CPBA (0.431 g, 2.5 mmol) was added at 0°C. After stirring for 30 h at room temp., the mixture was washed with $NaHSO_3$ and $NaHCO_3$ solutions, and dried with Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 1:1), affording **10** (0.174 g, 85%) as a colourless oil. − R_f = 0.18 (cyclohexane/EtOAc, 1:1).

10a (*Major Isomer*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (qd, ^3J = 6.4 Hz, ^3J = 2.95 Hz, OCH, 1 H), 3.93 (d, ^2J = 13.2 Hz, NCH*H*, 1 H), 3.84 (ddd, ^3J = 10.6 Hz, ^3J = 5.9 Hz, ^3J = 2.95 Hz, NCH, 1 H), 3.05 (d, ^2J = 13.4 Hz, NC*H*H, 1 H), 2.92 (s, OCH_2, 2 H), 2.05 (dd, ^2J = 13.5 Hz, ^3J = 10.6 Hz, CH*H*CHN, 1 H), 1.85 (dd, ^2J = 13.5 Hz, ^3J = 5.9 Hz, C*H*HCHN, 1 H), 1.46 (d, ^3J = 6.8 Hz, OCHCH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.9, 76.6, 64.7, 63.5, 50.4, 48.8, 37.9, 21.1.

10b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47 (qd, ^3J = 6.4 Hz, ^3J = 4.0 Hz, OCH, 1 H), 3.71 (ddd, ^3J = 9.1 Hz, ^3J = 6.9 Hz, ^3J = 4.0 Hz, NCH, 1 H), 3.64 (d, ^2J = 13.1 Hz, NCH*H*, 1 H), 3.28 (d, ^2J = 13.1 Hz, NC*H*H, 1 H), 2.90 (d, ^2J = 4.8 Hz, OCH*H*, 1 H), 2.85 (d, ^2J = 4.8 Hz, OC*H*H, 1 H), 2.17 (dd, ^2J = 13.5 Hz, ^3J = 6.9 Hz, CH*H*CHN, 1 H), 1.93 (dd, ^2J = 13.5 Hz, ^3J = 9.1 Hz, C*H*HCHN, 1 H), 1.44 (d, ^3J = 6.4 Hz, OCHCH_3, 3 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.9, 77.6, 64.3, 63.8, 51.8, 49.7, 36.5, 21.1. − MS (70 eV, EI); *m/z* (%): 169 (27) [M^+], 125 (38) [M^+ − CO_2], 97 (100) [M^+ − CO_2 − CO], 68 (49), 55 (43). − HRMS: calcd. for $C_8H_{11}NO_3$ [M^+] 169.0739; found 169.0739.

(5RS,7R,8S)-8-Chloromethyl-5-hydroxy-5-hydroxymethyl-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one (**11a/11b**): A solution of *N*-methylmorpholine *N*-oxide·2 H_2O (0.1 g, 0.75 mmol) was prepared in a mixture of water (2.5 ml) and acetone (1 ml). To this was added a solution of potassium osmate·2 H_2O (0.002 g, 0.006 mmol) in water (5 ml), followed by a solution of **6** (0.1 g, 0.52 mmol) in acetone (2 ml). The mixture was stirred for 15 h under argon atmosphere and then a slurry of conc. aq. sodium hydrogen sulfite was added. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried with Na_2SO_4 and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc) affording **11a/11b** (0.046 g, 39%) as a colourless oil. **11a** was formed with a diastereoselectivity of 55%. − R_f = 0.21 (EtOAc).

11a (*Major Isomer*): ^{1}H NMR (200 MHz, CD_3OD): δ = 4.65 (m, OCH, 1 H), 4.01 (ddd, ^3J = 8.8 Hz, ^3J = 5.1 Hz, ^3J = 4.1 Hz, NCH, 1 H), 3.83 (d, ^3J = 4.6 Hz, CH_2Cl, 2 H), 3.54 (dd, ^2J = 12.1 Hz, ^4J = 1.7 Hz, NCH*H*, 1 H), 3.50 (s, CH_2OH, 2 H), 3.12 (d, ^2J = 12.1 Hz, NC*H*H, 1 H), 2.28 (dd, ^2J = 13.9 Hz, ^3J = 8.8 Hz, NHCCH*H*, 1 H), 1.95 (m, NHCC*H*H, 1 H). − ^{13}C NMR (50.3 MHz, CD_3OD): δ = 164.4, 83.2, 83.0, 66.2, 62.2, 57.6, 46.0, 41.6.

11b: ^{1}H NMR (200 MHz, CD_3OD): δ = 4.65 (m, OCH, 1 H), 4.19 (ddd, ^3J = 10.3 Hz, ^3J = 6.1 Hz, ^3J = 4.0 Hz, NCH, 1 H), 3.84 (d, ^3J = 4.8 Hz, CH_2Cl, 2 H), 3.68 (d, ^2J = 12.1 Hz, NCH*H*, 1 H), 3.56 (s, CH_2OH, 2 H), 3.05 (d, ^2J = 12.1 Hz, NC*H*H), 2.01 (m, NHCCH*H*, 1 H), 1.80 (m, NHCC*H*H, 1 H). − ^{13}C NMR (50.3 MHz, CD_3OD): δ = 162.4, 83.9, 80.5, 66.9, 63.1, 56.7, 46.1, 42.3. − MS (70 eV, EI); *m/z* (%): 222 (1) [M^+ + H], 221 (1) [M^+], 203 (16) [$M^+ - H_2O$], 190 (10) [$M^+ - CH_2OH$], 168 (14) [$M^+ - Cl - H_2O$], 147 (21) [$M^+ - C_3H_6O_2$], 68 (100) [$C_4H_6N^+$]. − HRMS: calcd. for $C_8H_{12}ClNO_4$ [M^+] 221.0454; found 221.0459.

(7R,8S)-8-Chloromethyldihydropyrrolo[1,2-c]oxazol-2,5-dione (**12**). − *Method I:* **6** (0.065 g, 0.35 mmol) and sodium metaperiodate (0.304 g, 1.4 mmmol) were dissolved in carbon tetrachloride (2 ml), acetonitrile (2 ml) and water (3 ml). To this two-phase solution, ruthenium trichloride hydrate (0.002 g, 0.01 mmol) was added and the entire mixture was stirred vigorously for 12 h at room temp. Then, CH_2Cl_2 (10 ml) was added and the phases were separated. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and concentrated. The resulting residue was diluted with diethyl ether (20 ml), filtered through a Celite pad, and concentrated. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 2:1) and product **12** (0.048 g, 75%) was obtained as a colourless solid.

Method II: **6** (0.05 g, 0.26 mmol) was dissolved in abs. CH_2Cl_2 (7 ml) and ozone was bubbled through the solution at −78°C until a blue colour persisted. The excess ozone was then expelled with a stream of argon and dimethyl sulfide (0.1 ml) was added. The mixture was allowed to warm to room temp. and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 2:1) and **12** (0.036 g, 73%) was obtained as a colourless solid, m.p. 92°C. − R_f = 0.19 (cyclohexane/EtOAc, 2:1). − $[\alpha]_D^{25}$ = +16 (*c* = 1 in methanol). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.62 (ddd, ^3J = 7.6 Hz, ^3J = 4.1 Hz, ^3J = 3.7 Hz, OCH, 1 H), 4.22 (ddd, ^3J = 9.9 Hz, ^3J = 6.6 Hz, ^3J = 3.7 Hz, NCH, 1 H), 3.97 (d, ^2J = 8.3 Hz, NCH*H*, 1 H), 3.77 (dd, ^2J = 11.6 Hz, ^3J = 4.1 Hz, CH*H*Cl), 3.68 (dd, ^2J = 11.6 Hz to 2-H, ^3J = 7.6 Hz, C*H*HCl, 1 H), 3.42 (d, ^2J = 8.3 Hz, NC*H*H, 1 H), 2.69 (dd, ^2J = 17.9 Hz, ^3J = 6.6 Hz, COC*H*HCHN, 1 H), 2.46 (dd, ^2J = 17.9 Hz, ^3J = 9.9 Hz, COCH*H*CHN, 1 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.3, 158.9, 79.3, 58.9, 52.4, 43.8, 42.8. − MS (70 eV, EI); *m/z* (%): 189 (39) [M^+], 161 (92) [M^+ − CO], 126 (21) [M^+ − Cl − CO], 82 (96) [$C_4H_6NO^+$], 68 (39) [$C_4H_6N^+$], 55 (100) [$C_4H_6^+$]. − HRMS: calcd. for $C_7H_8ClNO_3$ [M^+] 189.0193; found 189.0194.

(5RS,7R,8S)-8-Chloromethyl-5-hydroxy-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one (**13a/13b**): **12** (0.08 g, 0.42 mmol) was suspended in abs. ethanol (3ml) and $NaBH_4$ (0.016 g, 0.42 mmol) was added slowly at 0°C. The mixture was stirred for 3 h, and was then allowed to warm to room temp. A satured solution of NH_4Cl (0.5 ml) was then added and stirring was continued for an additional 30 min. The solids were filtered off and the solvent was removed in vacuo. Purification by flash chromatography on silica gel (cyclohexane/EtOAc, 1:2) yielded **13** (0.3 g, 39%) as a colourless solid, m.p. 53°C. The (5*R*,7*R*,8*S*) product was obtained with a diastereoselectivity of 67%. − R_f = 0.15 (cyclohexane/EtOAc, 1:2).

(5R,7R,8S)-8-Chloromethyl-5-hydroxy-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one (**13a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58 (ddd, ^3J = 7.4 Hz, ^3J = 6.6 Hz, ^3J = 5.4 Hz, OCH, 1 H), 4.43 (m, HOC*H*, 1 H), 3.86 (ddd, ^3J = 9.0 Hz, ^3J = 5.4 Hz, ^3J = 3.7 Hz, NCH, 1 H), 3.74−3.62 (m, CH_2Cl, NC*H*H, 3 H), 2.99 (dd, ^2J = 12.5 Hz, ^3J = 7.1 Hz, NCH*H*, 1 H), 2.17 (ddd, ^2J = 14.1 Hz to 5-H, ^3J = 9.0 Hz to 4-H, ^3J = 4.7 Hz, NCHC*H*H, 1 H), 1.82 (ddd, ^2J = 14.1 Hz, ^3J = 3.7 Hz, ^3J = 1.7 Hz, ^3J = 1.7 Hz, NCHCH*H*, 1 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.6, 81.2, 72.1, 60.9, 56.6, 44.6, 39.6.

(5S,7R,8S)-8-Chloromethyl-5-hydroxy-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one (**13b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.62 (m, OCH, 1 H), 4.49 (m, HOCH, 1 H), 4.13 (ddd, ^3J = 10.6 Hz, ^3J = 5.4 Hz, ^3J = 3.3 Hz, NCH, 1 H), 3.85−3.62 (m, CH_2Cl, NCH*H*, 3 H), 3.13 (dd, ^2J = 12.7 Hz, ^3J = 0.7 Hz, NC*H*H, 1 H), 2.15 (dd, ^2J = 13.1 Hz, ^3J = 5.4 Hz, NCHC*H*H, 1 H), 1.67 (ddd, ^2J = 13.1 Hz, ^3J = 10.6 Hz, ^3J = 10.6 Hz, ^3J = 5.2 Hz, NCHCH*H*, 1 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.3, 78.2, 72.5, 61.3, 55.4, 44.4, 40.6. − MS (70 eV, EI); *m/z* (%): 191 (8) [M^+], 156 (33) [M^+ − Cl], 147 (50) [$M^+ - CO_2$], 68 (100) [$C_4H_7N^+$]. − HRMS: calcd. for $C_7H_{10}ClNO_3$ [M^+] 191.0349; found 191.0349.

(5R,7R,8S)-8-Chloromethyl-5-hydroxy-4,6,7,8-tetrahydropyrrolo[1,2-c]oxazol-2-one (**13a**): A stirred solution of **12** (0.04 g, 0.21 mmol) in THF (1ml) was cooled to −78°C and treated with a 1 M solution of L-Selectride in THF (0.25 ml, 0.25 mmol). After 15 h, 1.6 M aqueous sodium hydroxide solution (0.32 ml, 0.5 mmol) was added, followed by 30% hydrogen peroxide solution (0.15 ml, 0.15 mmol). The reaction mixture was treated with dilute aqueous hydrochloric acid, the phases were separated, and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried with Na_2SO_4 and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 1:2) yielding **13a** (0.04 g, 98%). − $[\alpha]_D^{25}$ = +55 (*c* = 1 in methanol). − HRMS: calcd. for $C_7H_{10}ClNO_3$ [M^+] 191.0349; found 191.0349. − $C_7H_{10}ClNO_3$ (191.61): calcd. C 43.88, H 5.26, N 7.30; found C 44.20, H 5.55, N 6.88.

(4R,5S)-4-Allenyl-5-chloromethyl-1,3-oxazolidin-2-one (**15**): In a dry Schlenk tube under argon, a solution of **2** (0.1 g, 0.6 mmol) in dry CH_2Cl_2 was cooled to −78°C and $BF_3{\cdot}OEt_2$ (0.1 ml, 0.75 mmol) was added dropwise. The mixture was stirred for 20 min. and then propargyltrimethylsilane (0.135 g, 1.2 mmol) was slowly added. After stirring for 15 h during warming up, the reaction mixture was quenched by the addition of conc. $NaHCO_3$ solution and the solids were filtered off. The phases were separated, the aqueous phase was extracted three times with CH_2Cl_2, and the combined organic layers were dried with Na_2SO_4. The crude product obtained after evaporation of the solvent was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 3:1). **15** (0.063 g, 61%) was obtained as a colourless oil. The (4*R*,5*S*) product was formed with a diastereoselectivity > 98%. − R_f = 0.15 (cyclohexane/EtOAc, 3:1). − $[\alpha]_D^{20}$ = +54 (*c* = 2.5 in dichloromethane). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (br, NH, 1 H), 5.17 (ddd, ^3J = 6.7 Hz, ^3J = 6.7 Hz, ^3J = 6.7 Hz, OCH, 1 H), 4.93 (m, H_2C=C), 4.49 (dt, ^3J = 5.0 Hz, ^3J = 5.0 Hz, OCH, 1 H), 4.23 (dd, ^2J = 6.7 Hz, ^3J = 5.0 Hz, NCH, 1 H), 3.62 (d, ^3J = 5.0 Hz, CH_2Cl, 2 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.2, 157.6, 90.6, 80.5, 79.4, 54.6, 43.6. − HRMS: calcd. for $C_7H_8ClNO_2$ [M^+] 173.0243; found: 173.0243.

(7R,8S)-8-Chloromethyl-4,7-dihydropyrrolo[1,2-c]oxazol-2-one (**14**): Silver tetrafluoroborate (0.057 g, 0.29 mmol) was added to a solution of **15** (0.1 g, 0.58 mmol) in CH_2Cl_2 (3 ml). The mixture was stirred in the dark at room temp. for 12 h. Saturated sodium chloride solution (0.3 ml) was then added so as to precipitate the silver ions as AgCl. The phases were separated, the aqueous phase was extracted three times with CH_2Cl_2, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 5:1). **14** (0.081 g, 81%) was obtained as a colourless oil. – R_f = 0.14 (cyclohexane/EtOAc, 5:1). – $[\alpha]_D^{20}$ = +33 (*c* = 1 in dichloromethane). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (ddd, ^3J = 6.1 Hz, ^3J = 4.0 Hz, ^3J = 2.2 Hz, HC=C*H*CH$_2$, 1 H), 5.87 (m, *H*C=CHCH$_2$, 1 H), 4.53 (ddd, ^3J = 7.6 Hz, ^3J = 6.9 Hz, ^3J = 4.1 Hz, OCH, 1 H), 4.49 (m, NCH, 1 H), 4.32 (dddd, ^2J = 15.6 Hz, ^4J = 3.0 Hz, ^3J = 2.2 Hz, ^4J = 2.2 Hz, NC*H*H, 1 H), 3.78 (dddd, ^2J = 15.6 Hz, ^3J = 4.0 Hz, ^4J = 2.7 Hz, ^4J = 1.7 Hz, NCH*H*, 1 H), 3.77 (dd, ^2J = 11.3 Hz, ^3J = 4.1 Hz, C*H*HCl, 1 H), 3.68 (dd, ^2J = 11.3 Hz, ^3J = 7.6 Hz, CH*H*Cl, 1 H). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.9, 131.2, 128.3, 79.4, 68.7, 54.8, 44.6. – MS (70 eV, EI); *m/z* (%): 173 (22) [M^+], 138 (100) [M^+ – Cl], 94 (21) [M^+ – Cl – CO_2], 67 (79) [$C_4H_5N^+$]. – HRMS: calcd. for $C_7H_8ClNO_2$ [M^+] 173.0243; found 173.0241.

(5R,6S,7R,8S)-8-Chloromethyl-5,6-dihydroxytetrahydropyrrolo-[1,2-c]oxazol-2-one ($C_7H_{10}ClNO_4$) (**16**): A solution of *N*-methylmorpholine *N*-oxide 2H_2O (0.1 g, 0.75 mmol) was prepared in a mixture of water (2.5 ml) and acetone (1 ml). To this was added a solution of potassium osmate·2 H_2O (0.002 g, 0.006 mmol) in water (5 ml), followed by a solution of **14** (0.09 g, 0.52 mmol) in acetone (2 ml). The resulting mixture was stirred for 15 h under argon atmosphere and then a slurry of conc. sodium hydrogen sulfite solution was added. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried with Na_2SO_4 and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc), affording **16** (0.076 g, 71%) as a colourless oil. **16** was formed with a diastereoselectivity of 96%. – R_f = 0.21 (EtOAc). – $[\alpha]_D^{20}$ = +58 (*c* = 0.5 in methanol). – ^{1}H NMR (400 MHz, CD_3OD): δ = 4.85 (dd, ^3J = 4.5 Hz, ^3J = 4.4 Hz CH$_2$C*H*OH, 1 H), 4.32 (ddd, ^3J = 7.6 Hz, ^3J = 7.4 Hz, ^3J = 3.5 Hz, OCH, 1 H), 3.84 (dd, ^3J = 3.5 Hz, ^3J = 3.5 Hz, NCH, 1 H), 3.79 (m, NCHC*H*OH, 1 H), 3.77 (dd, ^2J = 12.0 Hz, ^3J = 4.5 Hz, NC*H*H, 1 H), 3.71 (dd, ^2J = 12.0 Hz, ^3J = 4.4 Hz, NCH*H*, 1 H), 3.31 (dd, ^2J = 10.6 Hz, ^3J = 7.6 Hz, C*H*HCl, 1 H), 3.14 (dd, ^2J = 10.6 Hz to 1-H, ^3J = 7.4 Hz, CHHCl, 1 H). – ^{13}C NMR (100.6 MHz, CD_3OD): δ = 163.9, 75.9, 75.1, 72.1, 65.9, 51.0, 46.4. – MS (70 eV, EI); *m/z* (%): 208 (7) [M^+ + H], 207 (7) [M^+], 172 (3) [M^+ – Cl], 149 (28), 128 (100) [M^+ – Cl – CO_2], 68 (68) [$C_4H_6N^+$]. – HRMS: calcd. for $C_7H_{10}ClNO_4$ [M^+] 207.0298; found 207.0293.

[1] [1a] A. D. Elbein, *Ann. Rev. Biochem.* **1987**, *56*, 497–534. – [1b] A. D. Elbein, *FASEB J.* **1991**, *5*, 3055–3063.

[2] [2a] G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob, T. W. Rademacher, *FEBS Lett.* **1988**, *237*, 128–132. – [2b] P. S. Sunkura, T. L. Bowlin, P. S. Liu, A. Sjoerdsma, *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206–210.

[3] J. W. Dennis, K. Koch, D. Beckner, *J. Nat. Cancer. Inst.* **1989**, *81*, 1028–1033.

[4] E. Truscheit, W. Frommer, B. Junge, L. Müller, D. D. Schmidt, W. Wingender, *Angew. Chem.* **1981**, *93*, 738–755.

[5] [5a] G. C. Look, C. H. Fotsch, C.-H. Wong, *Acc. Chem. Res.* **1993**, *26*, 182–190. – [5b] M. K. Tong, G. Papandreou, B. Ganem, *J. Am. Chem. Soc.* **1990**, *112*, 6137–6139. – [5c] B. Ganem, G. Papandreou, *J. Am. Chem. Soc*. **1991**, *113*, 8984–8985.

[6] [6a] G. Casiraghi, F. Zanardi, G. Rassu, P. Spanu, *Chem. Rev.* **1995**, *95*, 1677–1716 and references therein. – [6b] J. Streith, A. Defoin, *Synlett* **1996**, 189–200. – [6c] Y. Huang, D. R. Dalton, *J. Org. Chem.* **1997**, *62*, 372–376.

[7] [7a] G. W. J. Fleet, J. C. Son, D. S. C. Green, I. C. di Bello, B. Winchester, *Tetrahedron* **1988**, *44*, 2649–2655. – [7b] J. R. Behling, A. L. Campbell, K. A. Babiak, J. S. Ng, J. Medich, P. Farid, G. W. J. Fleet, *Tetrahedron* **1993**, *49*, 3359–3366. – [7c] D. K. Thompson, C. N. Hubert, R. H. Wightman, *Tetrahedron* **1993**, *49*, 3827–3840.

[8] [8a] Y. Yuasa, J. Ando, S. Shibuya, *J. Chem. Soc., Chem. Commun.* **1994**, 1383–1384. – [8b] A. Hassner, E. Falb, A. Nudelman, A. Albeck, H. E. Gottlieb, *Tetrahedron Lett.* **1994**, *35*, 2397–2400.

[9] [9a] K. Danielmeier, E. Steckhan, *Tetrahedron: Asymmetry* **1995**, *6*, 1181–1190. – [9b] K. Danielmeier, K. Schierle, E. Steckhan, *Tetrahedron* **1996**, *52*, 9743–9754.

[10] A. Zietlow, E. Steckhan, *J. Org. Chem.* **1994**, *59*, 5658–5661.

[11] K. Danielmeier, K. Schierle, E. Steckhan, *Angew. Chem*. **1996**, *108*, 2397–2399; *Angew. Chem. Int. Ed.* **1996**, *35*, 2247–2248.

[12] H. Sakurai, *Pure Appl. Chem.* **1982**, *54*, 1–22.

[13] M. Sadakane, R. Vahle, K. Schierle, D. Kolter, *Synlett* **1997**, 95–96.

[14] [14a] J. G. Buchanan, H. Z. Sable in *Selective Organic Transformations*, (Ed.: B. S. Thyagarajan), Wiley Interscience Publ., New York, **1972**, Vol. 2, p. 1–95. – [14b] M. Schulz, R. Kluge, S. Liebsch, J. Lessig, M. Halik, F. Gadissa, *Tetrahedron* **1996**, *41*, 13151–13166.

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