Pergamon

Tetrahedron, Vol. 53, No. 27, pp. 9213-9218, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00619-4

Syntheses of (3*S*)-3-Hydroxy-2-pyrrolidinone from (*S*)-Malic Acid

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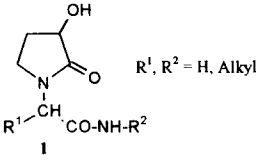
Abstract: *(S)-Malic acid* **2** *is transformed into (3S)-3-hydroxy-2-pyrrolidinone* ***(8)*** *using hexafluoroacetone as protecting and activating agent. Two alternative routes were developed; key step of both routes is the intramolecular aminolytic cleavage of the lactone ring of the intermediate, 5-(2-aminoethyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one* ***(7)***. © 1997 Elsevier Science Ltd.

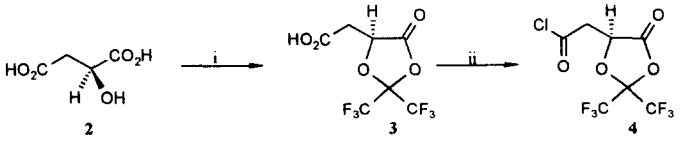
Certain compounds of general formula **1** exhibit valuable pharmacological properties. They are of interest for treatment of brain insufficiences and as cognition activators. Because of their low toxicity they are of current pharmaceutical interest.[1]



1

Several syntheses of the racemic core of **1**, namely of 3-hydroxy-2-pyrrolidinone **(8)**, a valuable building block for drug synthesis, are described starting from γ-butyrolactone,[2] from 2-hydroxy-4-phthalimidobutyric acid,[3] from 2-bromo-γ-butyrolactone[4] and from 1-(trimethylsilyl)-2-pyrrolidinone.[5] Recently, an enzymatic synthesis starting from 4-benzyloxycarbonylamino-2-oxobutanoic acid was described.[6] In the course of our investigations concerning the synthesis of rare and non-natural amino acids,[7] we developed stereoconservative syntheses of (3*S*)-3-hydroxy-2-pyrrolidinone **(8)**, starting from commercially available (*S*)-malic acid **(2)**.

Dioxolan-4-one **3** is obtained in high yield on reaction of (*S*)-malic acid **(2)** with hexafluoroacetone (Scheme 1).[8] Reaction of **3** with thionyl chloride affords the acid chloride **4**. The position of highest electrophilicity of the molecule is now shifted from the α- to the β-carboxylic group.



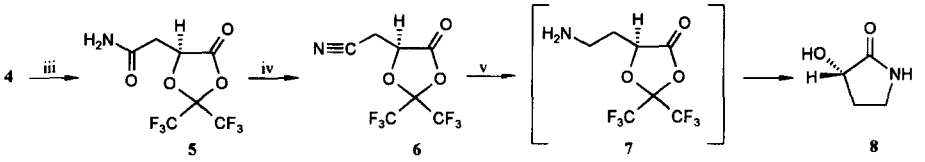
2 **3** **4**

Scheme 1: i) $(CF_3)_2CO$, DMSO, 87%; ii) $SOCl_2$, reflux, 89%.

Starting from **4** two different routes to (3*S*)-3-hydroxy-2-pyrrolidinone **(8)** have been developed.

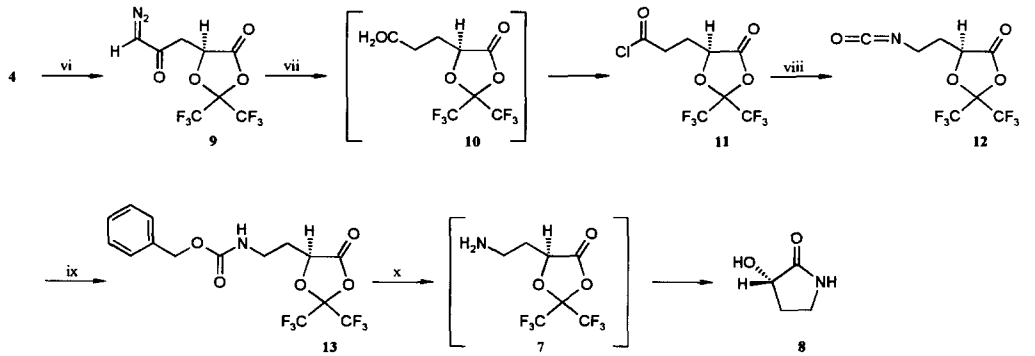
In route 1 (Scheme 2), acid chloride **4** reacts with neat ammonia at -78°C to yield the amide **5**. In contrary, treatment with aqueous ammonia results in a complete decomposition of the dioxolanone ring. Dehydratisation of the amide **5** to form nitrile **6** is achieved on treatment with thionyl chloride. Catalytic reduction of the nitrile

function to give the aminomethylene group produces compound **7**, which cyclises spontaneously to provide the desired (3*S*)-3-hydroxy-2-pyrrolidinone **(8)**.



Scheme 2: iii) NH_3(l), -78°C, 76%; iv) $SOCl_2$, reflux, 35%; v) H_2/Pd-C, propan-2-ol, 35%.

In route 2 (Scheme 3), acid chloride **4** is transformed into diazoketone **9** on reaction with diazomethane. Photolytic Wolff rearrangement of **9** in the presence of water results in formation of the homologue acid **10**. The crude product **10** is treated with thionyl chloride to give acid chloride **11**. Heating of **11** with trimethylsilylazide results in the formation of isocyanate **12,** which represents a double activated 4-amino-2-hydroxybutyric acid („homoisoserine") derivative. Routes to homoisoserine and its derivatives, which also are of pharmacological interest are currently under investigation in our group and will be published elsewhere. Addition of equimolar amounts of benzyl alcohol to isocyanate **12** furnishes urethane **13**. Hydrogenolytic removal of the Z-group of **13** in the presence of Pd/C yields (3*S*)-3-hydroxy-2-pyrrolidinone **(8)** via 5-(2-aminoethyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one **(7)**.



Scheme 3: vi) CH_2N_2, diethyl ether, 92%; vii) a) hν, dioxane/water; b) $SOCl_2$, reflux, 52%; viii) a) TMS-N_3, toluene; b) heating, 88%; ix) benzyl alcohol, $CHCl_3$, 51%; x) H_2/Pd-C, propan-2-ol, 40%.

Considering that route 2 also opens a new entry towards pharmaceutical relevant α-functionalized γ-amino butanoic acid derivatives, this route appears to be the more attractive one of the two synthetic alternatives. (*S*)-4-Amino-2-hydroxybutanoic acid is one of the most potent inhibitors of 4-amino-butanoic acid (*GABA*)-uptake.[9] Furthermore, it exhibits anticancer activity.[10]

EXPERIMENTAL PART

Melting points were determined with a Totolli apparatus and are uncorrected. Optical rotations were measured at 589 nm (Na D line). NMR-spectra were recorded on a Varian GEMINI 300. ^{1}H NMR spectra were recorded at 300.075 MHz, ^{13}C NMR spectroscopy was performed at 75.462 MHz, ^{19}F NMR spectra were recorded at 282.330 MHz with trifluoroacetic acid (TFA) as external standard. Splitting multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept.), broad (br.) and multiplet (m). The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) in $CDCl_3$, or DMSO-d_6; J values are given in Hertz (Hz). The IR spectra were produced on a Specord (Carl-Zeiss-Jena) spectrometer as liquid films or KBr pellets. Mass spectra (EI) were obtained at 70 eV with a Masslab spectrometer. Elemental analyses were performed with a Heraeus RAPID analyzer. Organic solvents were dried and distilled prior to use.

The preparation of (5*S*)-2,2-bis(trifluoromethyl)-4-oxo-1,3-dioxolan-5-ylacetic acid (**3**) and (5*S*)-2,2-bis(trifluoromethyl)-4-oxo-1,3-dioxolan-5-ylacetyl chloride (**4**) was described previously.[8]

[(5*S*)-2,2-Bis(trifluoromethyl)-4-oxo-1,3-dioxolan-5-yl]acetamide 5

To a stirred solution of acid chloride **4** (6.01 g, 20.0 mmol) in 100 ml of diethyl ether liquid ammonia (40.0 mmol, 0.68 g) was added at -78°C, which led to the formation of a white precipitate. The reaction mixture was warmed up to -10°C and excess of ammonia removed in vacuo. The residue was taken up in dichloromethane and the organic layer was washed with ice-water, dried over anhydrous $MgSO_4$ and concentrated. Yield: 4.23 g (76%). M.p.: 75°C. $[\alpha]_D^{20}$: -19 (*c* = 1, CH_2Cl_2). IR (KBr): ν = 3540-3480, 1830, 1670 cm^{-1}. ^{1}H NMR (d_6-DMSO): δ = 2.77 (dd, J = 5 Hz / 17 Hz, 1H, C***H***$_2$); 2.92 (dd, J = 4.5 Hz / 17 Hz, 1H, C***H***$_2$); 5.34 (m, 1H, C***H***); 7.21 (s, br., 1H, N***H***); 7.58 (s, br., 1H, N***H***). ^{13}C NMR (d_6-DMSO): δ = 35.1 (***C***H$_2$); 71.9 (***C***H); 96.8 (sept, J = 35 Hz, ***C***(CF$_3$)$_2$); 118.2 (q, J = 288 Hz, ***C***F$_3$); 119.3 (q, J = 290 Hz, ***C***F$_3$); 167.5, 167.8 (C=O, lactone, amide). ^{19}F NMR ($CDCl_3$): δ = -3.03 (q, J = 8 Hz, 3F, C***F***$_3$); -2.76 (q, J = 8 Hz, 3F, C***F***$_3$). MS m/z (%): 281 [M]$^+$ (4.1); 263 [M-H_2O]$^+$ (0.7); 115 [M-HFA]$^+$ (24.5); 69 [CF_3]$^+$ (78.6); 44 [O=C=NH_2]$^+$ (100). Anal. Calcd for $C_7H_5F_6NO_4$: C, 29.91%; H, 1.80%; N, 5.00%. Found C, 29.93%; H, 1.87%; N, 4.70%.

(5*S*)-5-Cyanomethyl-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one 6

Amide **5** (8.0 mmol, 2.25 g) and thionyl chloride (27.4 mmol, 2 ml) were kept under reflux for 12 h. The excess of thionyl chloride was removed under reduced pressure and the remaining residue was purified by Kugelrohr distillation. Yield: 0.74 g (35%). B.p.: 90°C/0.8 Torr. $[\alpha]_D^{25}$: -11.3 (*c* = 1.5, CH_2Cl_2). IR (film): ν = 2250, 1845 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.94 (dd, J = 7 Hz / 17.5 Hz, 1H, C***H***$_2$-CH-O); 3.08 (dd, J = 5 Hz / 17.5 Hz, 1H, C***H***$_2$-CH-O); 4.92 (m, 1H, C***H***-O). ^{13}C NMR ($CDCl_3$): δ = 20.6 (***C***H$_2$-CH-O); 70.6 (***C***H-O); 97.9 (sept., J = 37 Hz, ***C***(CF$_3$)$_2$); 113.2 (***C***≡N); 118.4 (q, J = 288 Hz, ***C***F$_3$); 119.3 (q, J = 289 Hz, ***C***F$_3$); 164.8 (***C***=O, lactone). ^{19}F NMR ($CDCl_3$): δ = -3.19 (q, J = 8 Hz, 3F, C***F***$_3$); -2.90 (q, J = 8 Hz, 3F, C***F***$_3$). MS m/z (%): 263 [M]$^+$ (5.5); 166

$[C_3F_6O]^+$ (23.5); 69 $[CF_3]^+$ (46.2); 44 $[C_2H_6N]^+$ (100). Anal. Calcd for $C_7H_3F_6NO_3$: C, 31.95%; H, 1.15%; N, 5.32%. Found C, 31.76%; H, 1.47%; N, 5.25%.

(3*S*)-3-Hydroxy-2-pyrrolidinone (8) via route 1

A mixture of **6** (2.0 mmol, 0.526 g), 100 mg of 10% palladium on charcoal and 10 ml of propan-2-ol were stirred under a hydrogen atmosphere for 12 h. The catalyst was filtered off and the reaction mixture was concentrated *in vacuo*. The solid residue was dried by lyophilisation and recrystallised from ethanol/diethyl ether. Yield 0.07 g (35%). For analytical data see below.

5(*S*)-5-(3-Diazo-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one 9

To a stirred solution of 10.0 mmol of diazomethane in diethyl ether (50 ml) at 0°C the acid chloride **4** (5.0 mmol, 1.50 g) in 10 ml of diethyl ether was added dropwise. The solution was allowed to warm up to room temperature and then the solvent was removed giving a yellow solid. For further reactions, diazoketone **8** was not purified. Yield 1.40 g (92%). M.p. 45°C. IR (KBr): ν = 2120, 1850, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.85 (dd, J = 7 Hz / J = 17 Hz, 1H, C***H***$_2$); 2.98 (dd, J = 3 Hz / J = 17 Hz, 1H, C***H***$_2$); 5.17 (dd, J = 3 Hz / J = 7 Hz, 1H, C***H***-O); 5.41 (s, 1H, C***H***=N_2). ^{13}C NMR ($CDCl_3$): δ = 41.2 (***C***H_2); 56.2 (***C***H=N_2); 71.6 (***C***H-O); 97.9 (sept, J = 36 Hz, ***C***$(CF_3)_2$); 119.0 (q, J = 287 Hz, ***C***F_3); 119.8 (q, J = 289 Hz, ***C***F_3); 167.8 (***C***=O, lactone); 187.0 (***C***=O, ketone). ^{19}F NMR ($CDCl_3$): δ = -2.22 (q, J = 6 Hz, 3F, C***F***$_3$); -2.06 (q, J = 6 Hz, 3F, C***F***$_3$). MS m/z (%): 306 $[M]^+$ (8.4); 278 $[M\text{-}N_2]^+$ (7.8); 265 $[M\text{-}CHN_2]^+$ (10.1); 237 $[M\text{-}CF_3]^+$ (1.9); 69 $[CF_3]^+$ (97.6); 55 $[C_3H_3O]^+$ (100); 28 $[CO]^+$ (40.0).

3-[2,2-Bis(trifluoromethyl)-5-oxo-1,3-dioxolan-4-yl]-propionyl chloride 11

A solution of unpurified diazoketone **9** in diethyl ether (20 mmol, 6.12 g) was dissolved in a mixture of 225 ml dioxane/25 ml water and irradiated for 3h. After removal of the solvent, the residue was taken up in a diethyl ether/ice-water mixture and the layers were separated. The aqueous portion was extracted thoroughly with diethyl ether (3x). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product **10** was not purified and further heated with 30 ml of thionyl chloride under reflux for 12 h. Finally the excess of thionyl chloride was removed under reduced pressure and the remaining residue was purified by Kugelrohr distillation. Yield 3.24 g (52%). B.p. 47-48°C/0.6 Torr. IR (film): ν = 1850, 1790 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.20 (m, 1H, C***H***$_2$-CH-O); 2.41 (m, 1H, C***H***$_2$-CH-O); 3.19 (m, 2H, C***H***$_2$-CO); 4.68 (dd, J = 5 Hz / 8 Hz, 1H, C***H***-O). ^{13}C NMR ($CDCl_3$): δ = 26.9 (***C***H_2-CH-O); 41.5 (***C***H_2-CO); 73.3 (***C***H-O); 97.8 (sept, J = 36 Hz, ***C***$(CF_3)_2$); 118.9 (q, J = 287 Hz, ***C***F_3); 119.6 (q, J = 289 Hz, ***C***F_3); 166.9 (***C***=O, lactone); 172.6 (***C***=O, acid chloride). ^{19}F NMR ($CDCl_3$): δ = -2.18 (m, 6F, C***F***$_3$). MS m/z (%): 279 $[M\text{-}Cl]^+$; 245/247 $[M\text{-}CF_3]^+$; 69 $[CF_3]^+$; 42 $[C_2H_2N]^+$.

(5*S*)-5-[2-(Isocyanato)ethyl]-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one 12

To a solution of the acid chloride **10** (16.0 mmol, 5.05 g) in 25 ml of toluene trimethylsilyl azide (16.5 mmol, 1.92 g) in 25 ml of toluene was added dropwise and stirred at 80°C for several hours until N_2 evolution ceased. After removal of the solvent, the residue was distilled *in vacuo*. Yield 4.14 g (88%). B.p. 65°C/0.4 Torr. $[\alpha]_D^{20}$: -15.3 (*c* = 1.1, $CHCl_3$). IR (Film): ν = 2470, 1850 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.07 (m, 1H, C*H*$_2$-CH-O); 2.23 (m, 1H, C*H*$_2$-CH-O); 3.54-3.77 (m, 2H, C*H*$_2$-N); 4.82 (dd, J = 4 Hz / 9 Hz, 1H, C*H*-O). ^{13}C NMR ($CDCl_3$): δ = 32.7 (*C*H_2-CH-O); 38.3 (*C*H_2-N); 72.2 (*C*H-O); 97.7 (sept, J = 36 Hz, *C*$(CF_3)_2$); 118.8 (q, J = 287 Hz, *C*F_3); 119.5 (q, J = 288 Hz, *C*F_3); 122.9 (N=*C*=O); 167.3 (*C*=O, lactone). ^{19}F NMR ($CDCl_3$): δ = -3.32 (s, br., 6F, C*F*$_3$). MS m/z (%): 293 $[M]^+$ (2.4); 224 $[M\text{-}CF_3]^+$ (10); 69 $[CF_3]^+$(49.7); 56 $[CH_2NO]^+$ (100). Anal. Calcd for $C_8H_5F_6NO_4$ C, 32.78%; H, 1.72%; N, 4.78%. Found C, 33.29%; H, 2.07%; N, 4.33%.

(5*S*)-5-[2-(Benzyloxycarbonylamino)ethyl]-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one 13

To a solution of the isocyanate **11** (3.0 mmol, 0.88 g) in 10 ml of chloroform benzyl alcohol (2.8 mmol, 0.29 g) in 10 ml of chloroform was added slowly. The reaction mixture was heated under reflux for 12 h and then concentrated under reduced pressure. The excess of isocyanate was removed by Kugelrohr distillation and the solid residue recrystallised from chloroform/hexanes. Yield 0.58 g (51%). M.p. 55°C. $[\alpha]_D^{25}$: -13.4° (*c* = 1.05, CH_2Cl_2). IR (KBr): ν = 3600-3150, 1855, 1700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.92-2.20 (m, 2H, C*H*$_2$-CH-O); 3.32-3.41 (m, 2H, C*H*$_2$-N); 4.69 (dd, J = 4 Hz / 8 Hz, 1H, C*H*-O); 5.06 (s, 2H, C*H*$_2$-O); 5.23 (m, 1H, N*H*); 7.32 (s, 5H, aromatic-*H*). ^{13}C NMR ($CDCl_3$): δ = 31.2 (*C*H_2-CH-O); 36.1 (*C*H_2-NH); 66.3 (*C*H_2-O); 72.5 (*C*H-O); 97.0 (sept, J = 35 Hz, *C*$(CF_3)_2$); 118.1 (q, J = 288 Hz, *C*F_3); 118.8 (q, J = 289 Hz, *C*F_3); 127.5, 127.6, 127.9, 135.5 (aromatic-*C*); 155.8 (*C*=O, carbamate); 167.1 (*C*=O, lactone). ^{19}F NMR ($CDCl_3$): δ = -3.39 (s, 6F, C*F*$_3$). MS m/z (%): 401 $[M]^+$ (53.4); 108 $[C_6H_5CH_2OH]^+$ (100); 91 $[C_7H_7]^+$ (83). Anal. Calcd for $C_{15}H_{13}F_6NO_5$ C, 44.90%; H, 3.27%; N, 3.50%. Found C, 45.07%; H, 3.32%; N, 3.56%.

(3*S*)-3-Hydroxy-2-pyrrolidinone (8) via route 2

A mixture of **12** (2.0 mmol, 0.803 g), 100 mg of 10% palladium on charcoal and 10 ml of propan-2-ol were stirred under a hydrogen atmosphere for 12 h. The catalyst was filtered off and the reaction mixture was concentrated *in vacuo*. The solid residue was dried by lyophilisation and recrystallised from ethanol/diethyl ether. Yield 0.08 g (40%). M.p. 99°C. $[\alpha]_D$: -125.0 (*c* = 1.1, $CHCl_3$). IR (KBr): ν = 3700-3100, 1695 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.09 (m, 1H, C*H*$_2$-CH-O); 2.51 (m, 1H, C*H*$_2$-CH-O); 3.29-3.43 (m, 2H, C*H*$_2$-NH); 3.88 (s, br., 1H, O*H*); 4.34 (m, 1H, C*H*-O); 6.60 (s, br., 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ = 29.9 (*C*H_2-CH-O); 38.8 (*C*H_2-NH); 69.1 (*C*H-O); 178.9 (*C*=O, amide). MS m/z (%): 101 $[M]^+$ (72); 57 $[M\text{-}CH_2NO]^+$ (100). Anal. Calcd for $C_4H_7NO_2$ C, 47.51%; H, 6.98%; N, 13.86%. Found C, 47.75%; H, 7.04%; N, 14.12%.

ACKNOWLEDGEMENT

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support. Furthermore, we are grateful to the Hoechst AG/Frankfurt Main for generous supply of chemicals.

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(*Received in Germany* 14 *April* 1997; *accepted* 23 *May* 1997)