Tetrahedron 64 (2008) 9384–9387

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A chemoenzymatic approach to (+)-pilocarpine

René Csuk*, Barbara Woeste

Bereich Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-.St. 2, D-06120 Halle (Saale), Germany

ARTICLE INFO

Article history:
Received 11 June 2008
Received in revised form 21 July 2008
Accepted 23 July 2008
Available online 29 July 2008

Keywords:
Pilocarpine
Total synthesis
Chemoenzymatic
Resolution
Lipases

ABSTRACT

A short synthesis for the alkaloid (+)-pilocarpine has been developed. Key step of this synthesis is a chemoenzymatic resolution utilizing the lipase AP.

1. Introduction

Investigation of the leaves of the plant *Pilocarpus jaborandi* led to the identification and subsequent isolation of several alkaloids (cf. Fig. 1) among them (+)-pilocarpine (**1**),[1–3] (+)-isopilocarpine (**2a**),[4,5] (+)-pilocarpidine (**2b**), (+)-pilosine, and (+)-isopilosine. Pilocarpine (**1**) has been isolated from the leaves of Pilocarpus plants; thus from *P. jaborandi* 0.5–0.8%,[6] *Pilocarpus pennatifolius* 0.2–0.4%,[7] *Pilocarpus microphyllus* 0.45%,[8] and from *Pilocarpus racemosous* 0.12–0.6%[9] of (+)-**1** can be isolated using an extraction process.[7] As an alternative a biochemical route has been suggested[10] but this approach has been found to be rather uneconomic.

Pilocarpine seems to be an emerging compound since the number of publications and patents dealing with it (almost 10.000 as per 06/2008) has increased tremendously during the last few years. Thus, compound **1** has been used quite successfully for the treatment of post-radiation xerostomia,[11] Sjoegren's syndrome[12] as well as glaucoma.[13] As a consequence over the past decades a number of syntheses has been devised, most of them leading to racemic pilocarpine. The very first synthesis of (+)-**1** started from diethyl 2-ethyl-succinate leading to a mixture of racemic (±)-isopilopic acid and (±)-pilopic acid (cf. Fig. 2); the latter compound was subjected to a resolution using brucine followed by a multistep sequence[14–20] that finally gave (+)-**1**.

Dey's approach[21] utilized malonic acid as a starting material that was condensed with phenoxyacetaldehyde leading finally to a mixture of racemic homopilopic acid and homoisopilopic acid in a rather low yield. Chain elongation followed by ozonolysis, construction of the imidazole ring system, its methylation and finally a resolution step utilizing tartaric acid finally gave (+)-**1**. Chumachenko et al.[22] used furfural as a starting material and obtained racemic homopilopic acid that was transformed in a rather lengthy synthesis into racemic **1**. De Graw's synthesis[23] used intermediates

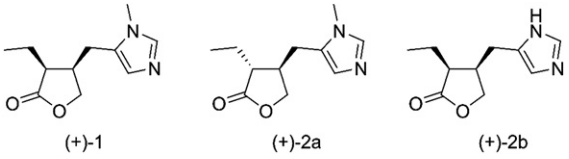


Figure 1. Main alkaloids of *Pilocarpus* sp.

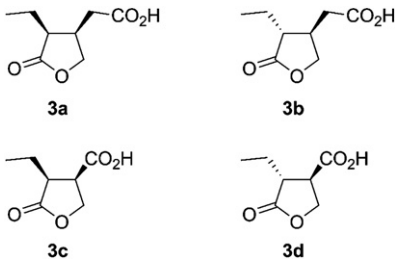


Figure 2. Depiction of homopilopic acid (**3a**), homoisopilopic acid (**3b**), pilopic acid (**3c**), and isopilopic acid (**3d**).

* Corresponding author. Tel.: +49 345 5525660; fax: +49 345 5527030.
E-mail address: rene.csuk@chemie.uni-halle.de (R. Csuk).

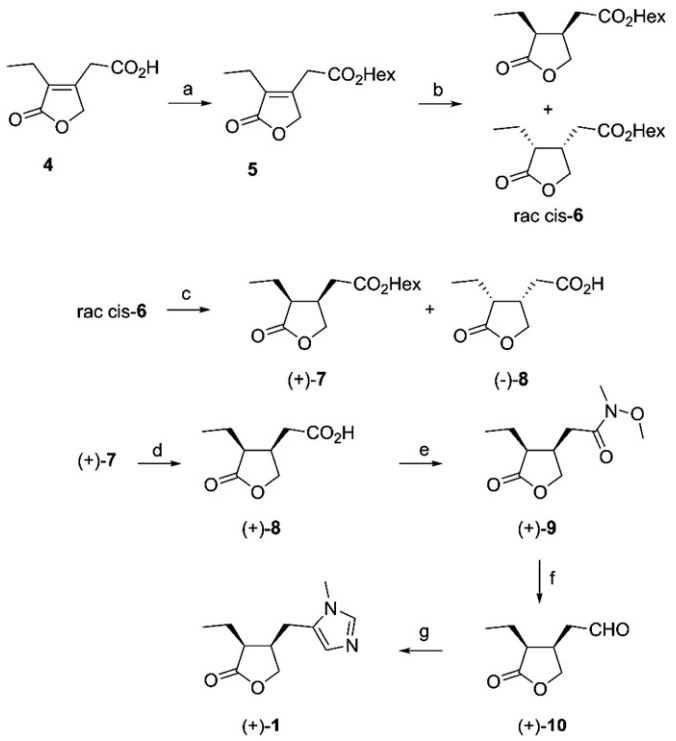
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.07.100

of Chumacheno's approach; the resolution was performed using (+)-α-methyl-benzylamine to afford enantiomerically pure homopilopic acid that was transformed into (+)-**1** following Chumachenko's approach (vide supra). Büchi's synthesis[24] of 1992 utilized 2-acetyl-butyrolactone as a starting material; key steps of this synthesis were a selenylation, a cycloaddition, and a vacuum pyrolysis followed by a stereoselective borane reduction and a Claisen rearrangement. Isopilocarpine as well as (+)-homoisopilopic acid has been accessed by rather tedious[25–28] procedures; the latter of these compounds can be transformed[26] into (+)-**1**.

In addition, a chiral pool approach[29–32] has been performed using L-histidine as a starting material; by this synthetic sequence a mixture of (+)-**1** and (+)-isopilocarpine was obtained. As an alternative, (*R*)-2-aminobutanoic acid was suggested[33,34] as a starting point to obtain (+)-isopilocarpin that was partially epimerized[35–37] (+)-**1**. However, for the separation of (+)-**1** from (+)-isopilocarpine preparative HPLC had to be used. A similar sequence started from L-asparginic acid[38,39] whereas several other attempts[40–42] failed to give pilocarpine at all. The synthesis patented[43] by Merck & Co resulted in the formation of racemic pilocarpine. In addition, two formal syntheses[44] of (+)-**1** have been reported: Zhang's approach utilizes an Rh(I) catalyzed intramolecular Alder ene reaction as a key step whereas Lu's Pd-catalyzed synthesis resulted in the formation of homopilopic aldehyde.

2. Results and discussion

In summary, all of these sequences are either long thus resulting in lowered yields or they afford mixtures of (stereo)isomers that have to be separated by preparative HPLC or racemic pilocarpine is obtained. We developed a short synthetic scheme (Scheme 1) that allows the synthesis of (+)-**1** in an enantiomerically pure form.



Scheme 1. (a) Hex-OH, $SOCl_2$, Δ, 98%; (b) $Rh/Al_2O_3/H_2$, quant.; (c) lipase PS, pH=7, 48%; (d) PLE, pH=7, 96%; (e) NMM, $ClCO_2$-*i*-Bu, $H_3CNHOCH_3$, 85%; (f) $LiAlH_4$, −45 °C, 95%; (g) $H_3CNH_2/K_2CO_3/H_3CC_6H_4SO_2CH_2NC$, NEt_3, 60%.

Known **4** [23b,45] was transformed into its corresponding *n*-hexylester **5** in almost quantitative yield. Hydrogenation of **5** with rhodium on aluminum oxide at room temperature for 5 days furnished cis-configurated racemic **6** whereas hydrogenation using Pd/C under a variety of different conditions invariably led to the formation of a mixture of cis/trans configurated products that could not be separated even by exhaustive chromatography. Treatment of (±)-**6** with the lipase PS (Amano) at pH=7 using pH-stat conditions gave 48% of (+)-**7** of ee>99% as determined by HPLC and 42% of (−)-**8** (ee >99%). Low ee values were obtained, however, using the lipases from *Candida lipolytica*, *Penicillium roqueforti*, lipase AY, Amano 10, lipolase 100, lipozyme, protease (type XXIII) from *Aspergillus oryzae*, PLE or subtilisin.

In order to avoid cis/trans isomerization of (+)-**7** the ester was hydrolyzed under very mild conditions using the esterase from porcine liver (PLE) under pH-stat conditions at pH=7 to afford 96% of the corresponding (+)-homopilopic acid [(+)-**8**]. Formation of the *Weinreb* amide[46] was accomplished by reaction of (+)-**8** with isobutyl chloroformate in the presence of *N*-methyl-morpholine to afford 85% of (+)-**9** that was reduced to the corresponding aldehyde (+)-**10** with lithium aluminum hydride in dry ether at −45 °C; reduction of (+)-**9** at higher temperatures invariably led to an inseparable mixture of products. Following a known procedure[24] treatment of (+)-**10** with methylamine/K_2CO_3 led to the formation of the corresponding *Schiff's* base that was allowed to react in a [3+2] cycloaddition[47] with *p*-tosylmethylisocyanide for 7 days to afford (+)-**1** in 60% isolated yield possessing an ee >99% as determined by HPLC.

In summary, this short synthesis starting from an easy accessible precursor leads to enantiomerically pure (+)-**1**.

3. Experimental

3.1. General

Melting points are uncorrected (*Leica* hot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm micro cell), NMR spectra were recorded using the Varian spectrometers Gemini 200 orGemini 2000 (δ given in ppm, *J* in Hz, internal Me_4Si), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, and MS spectra were taken on a Intectra GmbH AMD 402 (*m*/*z* and % given). TLC was performed on silica gel (Merck 5554, detection by UV absorption). The solvents were dried according to usual procedures.

3.2. Hexyl 2-(4-ethyl-5-oxo-2,5-dihydro-3-furanyl) acetate (5)

To an ice cold solution of **4** (10.0 g, 58.8 mmol) in 1-hexanol (200 ml, 160 mmol), thionyl chloride (20 ml, 100 mmol) was slowly added. After completion of addition, the reaction mixture was heated under reflux for 24 h, the solvents were removed in vacuo, and the residue subjected to chromatography (silica gel, hexanes/ethyl acetate 5:1) to afford **5** (14.5 g, 98%) as a colorless oil. R_f=0.27 (silica gel, hexanes/ethyl acetate 5:1); IR (film): ν=2959 s, 2933 s, 2860 m, 1755 s, 1675 m, 1456 m, 1379 m, 1342 m, 1266 m, 1198 s, 1177 s, 1105 m, 1090 m, 1058 m, 1036 s, 949 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.81 (s, 2H, H–C(5)), 4.13 (t, *J*=6.7 Hz, 2H, H–C(10)), 3.47 (s, 2H, H–C(8)), 2.32 (q, *J*=7.6 Hz, 1H, H–C(6)), 1.63 (q, *J*=7.0 Hz, 2H, H–C(11)), 1.30 (br s, 6H, H–C(12, 13, 14)), 1.10 (t, *J*=7.6 Hz, 3H, H–C(7)), 0.89 (t, *J*=6.7 Hz, 3H, H–C(15)); ^{13}C NMR (90 MHz, $CDCl_3$): δ=174.06 (s, C(9)), 168.37 (s, C(2)), 151.22 (s, C=*C*–CH_2), 131.44 (s, CO–*C*=C), 71.55 (t, C–*C*H_2–O), 65.92 (t, O–*C*H_2–C_5H_9), 35.52 (t, C–*C*H_2–CO_2), 31.35 (t, C(11)), 28.47 (t, C(12)), 25.52 (t, C(13)), 22.51 (t, C(14)), 17.10 (t, C(6)), 13.96 (q, C(15)), 12.56 (C7); MS (EI, 80 eV, 115 °C): *m*/*z*=254 (M, 1.7), 155 (7.3), 124 (14.7), 57 (11.8), 43 (100). Anal. Calcd for $C_{14}H_{22}O_4$ (254.33): C, 66.12; H, 8.72. Found: C, 66.06; H, 8.68.

3.3. (±)-Hexyl 2-[(3*RS*, 4*SR*)-4-ethyl-5-oxo-tetrahydro-3-furanyl]-acetate [(±)-6]

Hydrogenation (1 bar, 25 °C) of a solution of **5** (12.3 g, 48.2 mmol) in dry THF (100 ml) in the presence of Rh/Al_2O_3 (5% Rh, 1 g) for 1 week furnished **6** (12.3 g, quant.) as a colorless oil. An analytical sample was obtained after flash chromatography (silica gel, hexanes/ethyl acetate 3:1). R_f=0.52 (silica gel, hexanes/ethyl acetate 3:1); IR (film): ν=2960 s, 2933 s, 2860 m, 1773 s, 1734 s, 1467 m, 1376 m, 1323 m, 1215 m, 1174 s, 1112 m, 1059 m, 1027 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.21 (ddd, J=9.9, 5.9, 0.4 Hz, 1H, CH–CH_2–O–), 4.10 (dd, J=9.6, 3.7 Hz, 1H, CH–CH_2–O), 3.98 (t, J=6.7 Hz, 2H, H–C(10)), 3.03–2.99 (m, 1H, H–C(4)), 2.55 (dd, J=14.8, 8.0 Hz, 1H, H–C(3)), 2.48 (dd, J=16.5, 4.7 Hz, H_A–C(8)), 2.29 (dd, J=16.5, 10.5 Hz, 1H, H_B–C(8)), 1.86–1.74 (m, 1H, H_A–C(6)), 1.62 (q, J=7.0 Hz, 2H, H–C(11)), 1.52–1.43 (m, 1H, H_B–C(6)), 1.43–1.31 (m, 6H, H–C(12, 13, 14)), 1.06 (t, J=7.4 Hz, 3H, H–C(7)), 0.90 (t, J=6.7 Hz, 3H, H–C(15)); ^{13}C NMR (90 MHz, $CDCl_3$): δ=177.96 (s, C(9)), 171.73 (s, C(2)), 70.91 (t, C(5)), 65.20 (t, C(10)), 44.16 (d, C(3)), 35.17 (d, C(4)), 32.03 (t, C(8)), 31.39 (t, C(11)), 28.52 (t, C(12)), 25.58 (t, C(13)), 22.53 (t, C(14)), 18.52 (t, C(6)), 13.99 (q, C(15)), 12.07 (q, C(7)); MS (EI, 80 eV, 55 °C): m/z=257 (M+1, 0.8), 256 (M, 1.2), 228 (10.6), 169 (41.1), 155 (16.1), 144 (10.0), 127 (15.5), 126 (26.0), 114 (10.0), 113 (14.2), 85 (89.9), 69 (36.3), 43 (100). Anal. Calcd for $C_{14}H_{24}O_4$ (256.34): C, 65.60; H, 9.44. Found: C, 65.41; H, 9.37.

3.4. (+)-Hexyl 2-[(3*S*,4*R*)-4-ethyl-5-oxo-tetrahydro-3-furanyl]-acetate [(+)-7]

A solution of (±)-**6** (12.6 g, 49.2 mmol) in distilled water (500 ml, 22 °C) was treated with lipase PS (Amano, 5.0 g) using pH-stat conditions (pH=7.0, 0.1 N aq NaOH) for 4 days (274 ml NaOH consumed). The pH was adjusted to 6 (5% aq HCl), the mixture extracted with ether (7×200 ml), the solvents were removed under diminished pressure, and the residue was subjected to chromatography (silica gel, hexanes/ethyl acetate 7:1 → 5:1 → 3:1 → 0:1) to afford (+)-**7** (6.1 g, 48%) as an oil. $[\alpha]_D$ +64.5 (c 1.26, $CHCl_3$); ee >99% by HPLC (Chiralcel OC hexanes/ethanol 95:5), 0.6 ml/min, λ=225 nm, t_R(+)=22.6 min, t_R(−)=24.6 min; Chiralpak AS (hexanes/Prop-2-OH, 98:2, 1.0 ml/min, t_R(+)=17.0 min, t_R(−)=22.4 min); IR (film): ν=3565 br m, 2970 m, 1760 s, 1699 s, 1436 m, 1405 m, 1374 m, 1327 m, 1250 m, 1178 s, 1117 s, 1055 m, 1030 m, 989 s, 912 m, 730 m, 679 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.95 (br s, 1H, CH2–CO_2H), 4.34 (dd, J=9.5, 5.1 Hz, 1H, H_A–C(5)), 4.14 (dd, J=9.5, 3.3 Hz, 1H, H_B–C(5)), 3.05–2.96 (m, 1H, H–C(4)), 2.58 (dd, J=14.8, 8.1 Hz, 1H, H–C(3)), 2.51 (dd, J=10.5, 4.6 Hz, 1H, H_A–C(8)), 2.36 (dd, J=16.7, 10.5 Hz, 1H, H_B–C(8)), 1.89–1.74 (m, 1H, H_A–C(6)), 1.55–1.37 (m, 1H, H_B–C(6)), 1.07 (t, J=7.4 Hz, 3H, H–C(7)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.93 (s, C(9)), 176.97 (s, C(2)), 70.81 (t, C(5)), 44.01 (d, C(3)), 34.97 (d, C(4)), 31.73 (t, C(8)), 18.53 (t, C(6)), 12.02 (q, C(7)); MS (EI, 80 eV, 59 °C): m/z=174 (M+2, 0.4), 173 (M+1, 0.7), 172 (M, 1.0), 143 (27.0), 126 (22.7), 114 (9.5), 113 (12.0), 85 (100). Anal. Calcd for $C_{14}H_{24}O_4$ (256.34): C, 65.60; H, 9.44. Found: C, 65.51; H, 9.49.

3.5. (+)-2-[(3*S*,4*R*)-4-Ethyl-5-oxo-tetrahydro-3-furanyl]-acetate [(+)-8]

A solution of the hexylester (+)-**7** (6.7 g, 26.1 mmol) in distilled water (300 ml) was hydrolyzed with PLE (Boehringer, 300 µl, 30 mg/ml) under pH-stat conditions at pH=7 using 0.1 N NaOH until 263.3 ml were consumed (approx. 8 h). The aq phase was acidified to pH=5 by the addition of 0.1 N hydrochloric acid and extracted with ether (5×150 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to yield (+)-**8** (4.32 g, 96%). $[\alpha]_D$ +87.97 (c 1.2, $CHCl_3$) (lit.: $[\alpha]_D$ 82.2 (c 1.0, Et_2O), $[\alpha]_D$ +73.2–81.5 ($CHCl_3$)[23]); ee >99% (by HPLC); R_f=0.9 (methanol/ethyl acetate 1:4); IR (film): ν=3565 br m, 2970 m, 1760 s, 1699 s, 1436 m, 1405 m, 1374 m, 1327 m, 1250 m, 1178 s, 1117 s, 1055 m, 1030 m, 989 s, 912 m, 730 m, 679 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.95 (br s, 1H, COOH), 4.34 (dd, J=9.5, 5.1 Hz, 1H, H_A–C(5)), 4.14 (dd, J=9.5, 3.3 Hz, 1H, H_B–C(5)), 3.05–2.96 (m, 1H, H–C(4)), 2.58 (dd, J=14.8, 8.1 Hz, 1H, H–C(3)), 2.51 (dd, J=10.5, 4.6 Hz, 1H, H_A–C(8)), 2.36 (dd, J=16.7, 10.5 Hz, 1H, H_B–C(8)), 1.89–1.74 (m, 1H, H_A–C(6)), 1.55–1.37 (m, 1H, H_B–C(6)), 1.07 (t, J=7.4 Hz, 1H, H–C(7)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.93 (s, COOH), 176.97 (s, CO), 70.81 (t, C(5)), 44.01 (d, C(3)), 34.97 (d, C(4)), 31.73 (t, C(8)), 18.53 (t, C(6)), 12.02 (q, CH3); MS (EI, 80 eV, 59 °C): m/z=174 (M+2, 0.4), 173 (M+1, 0.7), 172 (M, 1.0), 113 (12.0), 85 (100). Anal. Calcd for $C_8H_{12}O_4$ (172.18): C, 59.81; H, 7.02. Found: C, 59.71; H, 7.13.

3.6. (+)-(3*R*,4*S*)-2-(4-Ethyl-5-oxo-tetrahydrofuran-3-yl)-*N*-methoxy-*N*-methyl-acetamide [(+)-9]

To an ice cold solution of (+)-**8** (6.0 g, 34.8 mmol) in ethyl acetate (200 ml) a 0 °C cold solution of *N*-methyl-morpholine (NMM, 3.9 ml, 34.9 mmol) in ethyl acetate (50 ml) was slowly added followed by an addition of isobutyl chloroformate (4.55 ml, 34.8 mmol) in ethyl acetate (5 ml). Stirring was continued for another 15 min, then *N*,*O*-dimethyl-hydroxylamine hydrochloride (3.8 g, 38.3 mmol) was added in several portions followed by the addition of NMM (3.9 ml, 34.8 mmol) in ethyl acetate (30 ml). Stirring at 0 °C was continued for an additional 30 min, then the cooling bath was removed, and the mixture was stirred at 25 °C for 1 day. The reaction mixture was washed with water (10 ml), aq citric acid (10%, 10 ml), and brine (10 ml), the organic layers were dried ($MgSO_4$), the solvents evaporated under diminished pressure, and the residue was subjected to flash chromatography (silica gel, hexanes/ethyl acetate 5:1 → 3:1 → 2:1 → 0:1) to afford (+)-**9** (6.37 g, 85%) as a colorless oil. R_f=0.31 (silica gel, hexane/ethyl acetate 1:1), $[\alpha]_D$ +114.09 (c 1.05, $CHCl_3$); IR (film): ν=2968 m, 2940 m, 2881 m, 1771 s, 1661 s, 1652 s, 1434 m, 1422 m, 1386 m, 1353 m, 1260 w, 1174 s, 1118 m, 1056 m, 1007 m, 984 m, 948 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.32 (dd, J=9.3, 5.7 Hz, 1H, H_A–C(5)), 4.11 (dd, J=9.3, 2.7 Hz, 1H, H_B–C(5)), 3.70 (s, 3H, $NOCH_3$), 3.20 (s, 3H, N–CH_3), 3.16–3.03 (m, 1H, H–C(4)), 2.58 (dd, J=7.3, 7.3 Hz, 1H, H–C(3)), 2.53 (dd, J=10.6, 6.2 Hz, 1H, H_A–C(8)), 2.42 (dd, J=16.7, 10.6 Hz, 1H, H_B–C(8)), 1.87–1.75 (m, 1H, H_A–C(6)), 1.53–1.42 (m, 1H, H_B–C(6)), 1.07 (t, J=7.4 Hz, 3H, H–C(7)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=178.16 (s, CO–N), 171.84 (s, CO), 71.26 (t, C(5)), 61.29 (q, N–OCH_3), 44.19 (d, C(3)), 34.63 (d, C(4)), 34.62 (q, N–CH_3), 29.32 (t, C(8)), 18.56 (t, C(6)), 12.05 (q, C(7)); MS (EI, 80 eV, 75 °C): m/z=217 (M+2, 0.02), 216 (M+1, 0.5), 215 (M, 4.2), 214 (M−1, 0.1), 184 (0.9), 156 (0.9), 155 (6.5), 128 (1.6), 127 (10.4), 126 (0.6), 109 (1.7), 103 (7.8), 99 (0.6), 98 (0.6), 97 (4.0), 81 (18.2), 69 (31.4), 61 (100). Anal. Calcd for $C_{10}H_{17}NO_4$ (215.25): C, 55, 80; H, 7.96; N, 6.51. Found: C, 55.72; H, 8.03; N, 6.42.

3.7. (+)-2-[(3*S*,4*R*)-4-Ethyl-5-oxo-tetrahydro-3-furanyl]-acetaldehyde [(+)-10]

To a well stirred suspension of lithium aluminium hydride (0.42 g, 11.1 mmol) in dry ether (200 ml) at −45 °C, a solution of (+)-**9** (1.96 g, 9.1 mmol) in dry ether (50 ml) was slowly added. After the completion of addition, the mixture was allowed to warm to +5 °C and was stirred until the reaction became complete (as checked by TLC; approx. 30–60 min). The reaction mixture was cooled to −35 °C and an aq solution of $KHCO_3$ (2.0 g in 10 ml) was slowly added to destroy the excess of the hydride. The mixture was diluted with ether (200 ml), the layers were separated, and the aq phase was extracted with ether (3×100 ml). The combined organic phases were washed with cold hydrochloric acid (3 N, 3×10 ml), satd aq sodium carbonate (3×10 ml), and brine (3×10 ml). After drying ($MgSO_4$), the solvents were evaporated

under diminished pressure to result in oily **10** (1.35 g, 95%). An analytical sample was obtained after flash chromatography (silica gel, hexane/ethyl acetate 5:1→2:1→1:1); R_f=0.45 (hexane/ethyl acetate 1:2); IR (film): ν=3418 br s, 2962 s, 2878 s, 1771 m, 1732 s, 1463 m, 1382 m, 1180 m, 1156 m, 1120 s, 1071 s, 1036 s, 938 s, 900 m, 860 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.84 (s, 1H, H–C(9)), 4.34 (ddd, J=9.4, 5.8, 0.9 Hz, 1H, H_A–C(5)), 4.01 (dd, J=9.4, 3.2 Hz, 1H, H_B–C(5)), 3.12–3.07 (m, 1H, H–C(4)), 2.67 (dd, J=18.7, 4.5 Hz, 1H, H–C(3)), 2.55 (dd, J=10.3, 3.7 Hz, 1H, H_A–C(8)), 2.50 (dd, J=10.3, 1.6 Hz, 1H, H_B–C(8)), 1.86–1.78 (m, 1H, H_A–C(6)), 1.50–1.35 (m, 1H, H_B–C(6)), 1.05 (t, J=7.4 Hz, 3H, H–C(7)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.19 (d, CHO), 177.65 (s, CO), 70.51 (t, C(5)), 44.24 (d, C(3)), 34.60 (d, C(4)), 26.46 (t, C(8)), 18.55 (t, C(6)), 12.02 (q, C(7)); MS (EI, 80 eV, 76 °C): m/z=158 (M+2, 8.5), 157 (M+1, 8.5), 156 (M, 0.7), 155 (M−1, 1.1), 112 (14.5), 97 (24.6), 85 (39), 69 (76.1), 68 (40.4), 57 (61.6), 55 (99.6), 43 (42.1), 41 (100). Anal. Calcd for $C_8H_{12}O_3$ (156.18): C, 61.52; H, 7.74. Found: 61.63; H, 7.83.

3.8. (+)-(3*S*,4*R*)-3-Ethyl dihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]furan-2(3*H*)-on, (+)-pilocarpine [(+)-1]

To a mixture of (+)-**10** (1.2 g, 7.7 mmol) and dry K_2CO_3 (3.2 g, 38.5 mmol) in abs dichloromethane/benzene (1:1, 150 ml) a 2.3 M solution of methylamine in benzene (3.9 ml, 9 mmol) was added. After stirring for 3 h the solvent was removed under diminished pressure, dichloromethane (20 ml) was added and removed. Then *p*-toluenesulfonylmethylisocyanide (3.31 g, 38.5 mmol) and triethylamine (5.4 ml, 38.5 mmol) were added and the mixture was stirred at 25 °C for 7 days. The solvents were removed and the residue was subjected to chromatography (silica gel, methanol/dichloromethane (1.25%→2.5%→5%)) to afford (+)-**1** (0.96 g, 60%) as a colorless oil. R_f=0.58 (CH_2Cl_2/MeOH/aq NH_4OH(25%) 95:4:1), $[\alpha]_D$ +115.58 (*c* 1.2, $CHCl_3$) (lit.: $[\alpha]_D$ +91 (0.01, EtOH),[48] $[\alpha]_D$ +106 ($CHCl_3$)[49]), ee >99% (by HPLC: Chiralcel OC, hexanes/ethanol 3:7, 0.3 ml/min, UV–vis λ=215 nm, t_R (+)-**1**=47.1 min, t_R (−)-**1**=52.32 min; in hexanes/ethanol (1:1), t_R (+)-**1**=62.06 min, t_R (−)-**1**=70.8 min); IR (film): ν=3374 w, 3116 w, 2965 m, 2879 m, 1770 s, 1654 w, 1559 w, 1505 m, 1458 m, 1424 w, 1374 m, 1315 w, 1290 w, 1271 w, 1224 m, 1176 s, 1109 m, 1052 m, 1023 m, 981 m, 948 w, 924 w, 813 w, 733 w, 703 w, 664 m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.42 (s, 1H, N=C*H*–N–CH_3), 6.80 (s, 1H, C=C*H*–N), 4.21 (dd, J=9.2, 5.6 Hz, 1H, CH–CH_2–O), 4.09 (dd, J=9.2, 2.7 Hz, 1H, CH–CH_2–O), 3.58 (s, 3H, N–CH_3), 2.86–2.74 (m, 1H, CH–C*H*–CH_2), 2.70 (dd, J=15.3, 3.9 Hz, 1H, CH–CH_2–CHO), 2.63 (dd, J=8.4, 6.8 Hz, 1H, CO–C*H*–CH), 2.42 (dd, J=15.3, 12.0, 1H, CH–CH_2–CHO), 1.96–1.81 (m, 1H, CH–CH_2–CH_3), 1.68–1.50 (m, 1H, CH–CH_2–CH_3), 1.12 (t, J=7.5, 3H, CH–CH_2–CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ=177.92 (s, CO), 138.32 (d, N=C*H*–N–CH_3), 128.64 (s, CH_2–*C*=CH), 127.07 (d, C=C*H*–N), 69.91 (t, CH–CH_2–O), 44.86 (d, CO–C*H*–CH), 37.86 (d, CH–C*H*–CH_3), 31.32 (q, N–CH_3), 21.40 (t, CH–CH_2–CHO), 18.34 (t, CH–CH_2–CH_3), 12.22 (q, CH_2–CH_3); MS (EI, 80 eV, 90 °C): m/z=209 (M+1, 1.7), 208 (M, 10.9), 151 (0.5), 149 (0.7), 135 (0.6), 133 (0.7), 124 (0.7), 123 (1.8), 122 (1.1), 121 (2.9), 110 (1.0), 109 (10.2), 108 (0.7), 107 (0.5), 97 (1.5), 96 (27.5), 95 (100). Anal. Calcd for $C_{11}H_{16}N_2O_2$ (208.26): C, 63.44; H, 7.74; N, 13.45. Found: C, 63.37; H, 7.83; N, 13.36.

Acknowledgements

We like to thank Dr. Hanns Wurziger (Merck KGaA, Darmstadt) for the donation of natural pilocarpine and for many helpful discussions. Financial support by the 'Fonds der Chemischen Industrie' is gratefully acknowledged.

References and notes

1. Byasson, M. *Pharm. J.* **1875**, *5*, 826.
2. (a) Gerrard, A. W. *Pharm. J.* **1875**, *5*, 865; (b) Gerrard, A. W. *Pharm. J.* **1875**, *5*, 965; (c) Gerrard, A. W. *Pharm. J.* **1875**, *6*, 227; (d) Gerrard, A. W. *Pharm. J.* **1876**, *7*, 255.
3. Hardy, E. *Bull. Soc. Chim. Fr.* **1875**, *24*, 497.
4. Harnack, E.; Meyer, H. *Liebigs Ann. Chem.* **1880**, *204*, 67.
5. (a) Petit, A.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1897**, *17*, 554; (b) Petit, A.; Polonovski, M. *Pharm. J.* **1897**, *5*, 370; (c) Petit, A.; Polonovski, M. *Pharm. J.* **1898**, *6*, 8.
6. Holmes, E. M. *Pharm. J.* **1895**, *1*, 520.
7. Chemnitius, F. *J. Prakt. Chem.* **1928**, *118*, 20.
8. Paul, B. H.; Cownley, A. J. *Pharm. J.* **1896**, *3*, 1.
9. (a) Cownley, A. J. *Pharm. J.* **1904**, *18*, 54; (b) Jowett, H. A. D.; Pyman, F. L. *Proc. Chem. Soc.* **1912**, *28*, 268; (c) Holmes, E. M. *Pharm. J.* **1903**, *17*, 713.
10. Reuter, G.; Maerkisch, U.; Hering, V.; Gizella, P.; Szoke, E.; Spasova, N. Ger. (East) DD287731A5, 1995; *Chem. Abstr.* **1991**, *115*, 7008.
11. Brosky, M. E. *J. Support. Oncol.* **2007**, *5*, 215.
12. Ramos-Casals, M.; Brito-Zeran, P. *Expert Rev. Clin. Immunol.* **2007**, *3*, 195.
13. Edwards, R. S. *Curr. Med. Res. Opin.* **1997**, *13*, 501.
14. Tschitschibabin, A. E.; Preobrashenski, N. A. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 460.
15. Preobrashenski, N. A.; Wompe, A. F.; Preobrashenski, W. A. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1187.
16. Preobrashenski, N. A.; Kabatschnik, M. J. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1541.
17. Preobrashenski, N. A.; Poljakokowa, A. M.; Preobrashenski, W. A. *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 850.
18. Preobrashenski, N. A.; Poljakokowa, A. M.; Preobrashenski, W. A. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1835.
19. Preobrashenski, N. A.; Wompe, A. F.; Preobrashenski, W. A.; Schtschukina, M. N. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1536.
20. Poljakokowa, A. M.; Preobrashenski, W. A.; Preobrashenski, N. A. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1314.
21. Dey, A. N. *J. Chem. Soc.* **1937**, *137*, 1057.
22. (a) Chumachenko, A. V.; Maurit, W. E.; Treboganov, A. D.; Smirnova, G. V.; Teplinskaya, R. B.; Vokova, L. V.; Zvankova, E. N.; Preobrashenski, N. A. *Dokl. Akad. Nauk SSSR* **1968**, *178*, 1352; (b) Chumachenko, A. V.; Zvonkova, E. N.; Preobrashenski, N. A. *J. Org. Chem. USSR (Engl. Transl.)* **1972**, *8*, 1112; (c) Chumachenko, A. V.; Zvonkova, E. N.; Preobrashenski, N. A. *J. Org. Chem. USSR (Engl. Transl.)* **1969**, *5*, 571.
23. (a) DeGraw, J. I.; Engström, J. S.; Willis, E. *J. Pharm. Sci.* **1975**, *64*, 1700; (b) DeGraw, J. I. *Tetrahedron* **1972**, *28*, 967.
24. Horne, D. A.; Fugmann, B.; Yakushijin; Büchi, G. *J. Org. Chem.* **1993**, *58*, 62.
25. Shapiro, G.; Chenzhi, C. *Tetrahedron Lett.* **1992**, *33*, 2447.
26. Link, H.; Bernauer, K. *Helv. Chim. Acta* **1972**, *55*, 1053.
27. Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849.
28. Lin, H.-J.; Bukownik, R. R.; Pednekar, P. R. *Synth. Commun.* **1981**, *11*, 599.
29. (a) Noordam, A.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 441; (b) Noordam, A.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 467.
30. Beyerman, H. C.; Maat, L.; van Zon, A. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 246.
31. Noordam, A.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 293.
32. Olofson, R. A.; Kendall, R. V. *J. Org. Chem.* **1970**, *35*, 2246.
33. Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713.
34. Dominguez, X. A.; Cavazos-Lopez, I.; Franco, R. *J. Org. Chem.* **1961**, *26*, 1625.
35. Dunn, D. L.; Scott, B. S.; Dorsey, E. D. *J. Pharm. Sci.* **1981**, *70*, 446.
36. Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1984**, 421.
37. Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733.
38. (a) Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159; (b) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164; (c) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017.
39. Gmeiner, P.; Feldmann, P. L.; Chu-Mayer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.
40. Brecker, L. Dissertation. University of Dortmund, 1996.
41. Percival, K. J. Dissertation. University of Bath, 1991.
42. Marshall, J. A.; Belletire, J. E. *Tetrahedron Lett.* **1971**, *13*, 871.
43. Reimann, E. Eur. Pat. Appl. EP 647 640, 1995; *Chem. Abstr.* **1995**, *123*, 33492.
44. (a) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198; (b) Wang, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *29*, 5213.
45. Drysdale, J. J.; Stevenson, H. B.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 4908.
46. (a) Saari, W. S.; Fischer, T. E. *Synthesis* **1990**, 453; (b) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676; (c) Goel, O. P.; Krolls, U.; Stier, M.; Kesten, S. *Org. Synth.* **1988**, *67*, 69.
47. van Leusen, A. M.; Wildemany, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.
48. Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1922**, *31*, 1314.
49. Köhling, R.; Lücke, A.; Nagao, T.; Speckmann, E.-J.; Avoli, M. *Neurosci. Lett.* **1995**, *201*, 87.