Convergent Diastereoselective Synthesis of Isopilocarpine by One-Pot Michael-Addition-Alkylation Reaction

Manfred Braun,*[a] Corinna Bühne,[a] Dimitrula Cougali,[a] Klaus Schaper,[a] Walter Frank[b]

[a] Institut für Organische Chemie und Makromolekulare Chemie, Universität Düsseldorf, 40225 Düsseldorf, Germany
Fax +49(211)8115079; E-mail: braunm@uni-duesseldorf.de

[b] Institut für Anorganische Chemie und Strukturchemie, Universität Düsseldorf, 40225 Düsseldorf, Germany

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Abstract: The metalated dithiane **7b** available from imidazole aldehyde **6** is reacted with furanone **4** and ethyl iodide to give the lactone **8**, which forms diastereoselectively. Its configuration is determined to be *trans* by means of a crystal structure analysis. The desulfurization of **8** leads to the alkaloid isopilocarpine **2** in three steps and 25% overall yield. The relative energies of the diastereomeric alkaloids **1** and **2** have been calculated.

Key words: alkaloids, diastereoselectivity, drugs, lactones, metalations

The leaves of *Pilocarpus jaborandi*, a plant growing in South American tropical rainforests and extracts prepared from them served as drugs for multiple medicinal applications since they had been brought to Europe during the 19th century.[1] The main alkaloid[2] pilocarpine (**1**), which was contaminated by the isomer isopilocarpine (**2**) (Figure 1), was isolated by Hardy[3a] and Gerrard[3b] in 1875. After the structure of pilocarpine had been assigned at the beginning of the 20th century,[4] its absolute configuration [(*3S*,*4R*)-**1**] was elucidated in 1966 only.[5] Until today, pilocarpine (**1**) is the leading compound for the treatment of glaucoma.[6] Various synthetic routes have been elaborated during the past seven decades.[7] None of those, however, is able to compete from a commercial point of view with the isolation from the natural source. As a consequence, pilocarpine (**1**), used in ophthalmiatry today, is mostly obtained from *Pilocarpus microphyllus*, a member of the jaborandi family. In the course of the isolation of the drug, the diastereomer (*3R*,*4R*)-**2** inevitably forms due to an epimerization, so that it has to be removed by fractional crystallization of the alkaloid **1**.[2,8]

Pilocarpine (**1**) is a parasympathomimeticum and acts as an agonist at the muscarinic acetylcholine receptor.[9] It has been shown more recently that isopilocarpine (**2**) binds to this receptor as well, although with distinctly lower binding constant.[10] In view of the importance of muscarinic agonists as potential agents for the treatment of Alzheimer's disease,[11] short and efficient syntheses of the stereoisomeric alkaloids **1** and **2** are desirable. In this article, we describe a highly convergent – and so far the shortest – route to racemic isopilocarpine **2** taking advantage of a one-pot Michael-addition-alkylation protocol. As the conversion of the *trans*-diastereomer **2** into *cis*-**1** has been reported,[7g] the route described here is also a formal synthesis of pilocarpine.

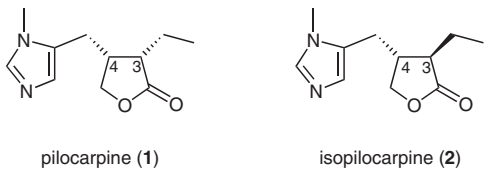
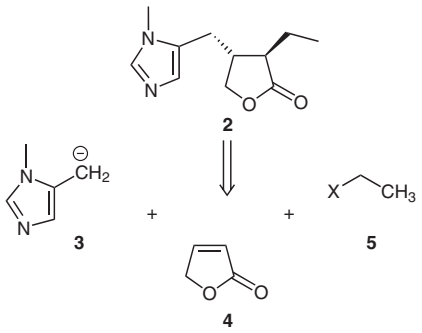


Figure 1 Diastereomers pilocarpine and isopilocarpine

The retrosynthesis outlined in Scheme 1 underlines the highly convergent character of the anticipated concept. The imidazole synthon **3** that acts as nucleophile was expected to add to the Michael acceptor **4** in a 1,4 manner. The enolate arising from this reaction should be alkylated in situ by alkyl halide **5**. Two of the building blocks arising from the retrosynthetic disconnection of the target **2**, the furanone **4** and ethyl halide **5**, are commercially available compounds. However, the imidazole synthon **3** with a donor methylene functionality in the side chain is not directly available, as the most acidic proton of 1,5-dimethylimidazole is the ring proton in 2-position.[12] As a consequence, lithiated dithane **7b** was chosen as a synthetic equivalent of the donor synthon **3**.



Scheme 1 Retrosynthesis of isopilocarpine (**2**)

The synthesis of isopilocarpine (**2**) following the retrosynthetic concept outlined above turned out to be straightforward, as shown in Scheme 2. Dithiane **7a** was prepared by protection of the aldehyde **6**, which itself is available in two steps[13] from *N*-methylimidazole. In a one-pot protocol, treatment of the imidazole building block **7a** with *n*-BuLi led to the generation of lithiated dithiane **7b**, the

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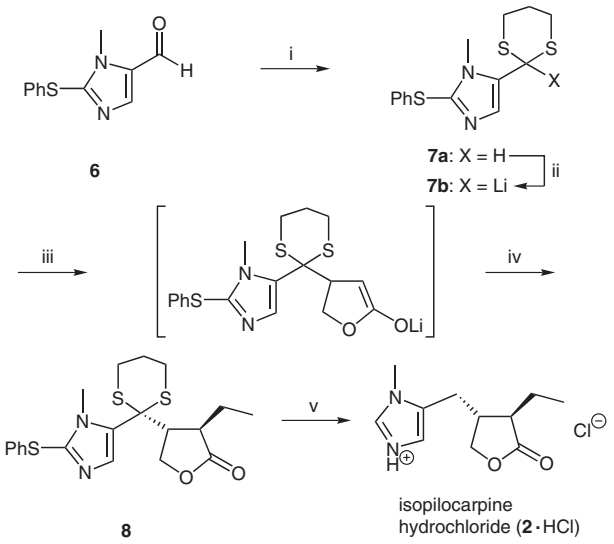
synthetic equivalent of the donor synthon **3**. Then, furanone **4** was added and, finally, ethyl iodide. Thus, the product **8** was obtained in 76% isolated yield, as a result of the anticipated Michael-addition-alkylation reaction. According to the NMR spectra, a single product was formed. Vinylogous additions to the furanone **4** followed by alkylations give *trans*-disubstituted γ-lactones as a rule.[14] Thus, the *rac-trans*-configuration was assigned to the product **8**. This assumption was unambiguously confirmed by a crystal structure analysis, whose result is shown in Figure 2. Aside from the fact that the *trans*-3,4-configuration of the furanone moiety is clearly shown, it becomes also evident that the lactone moiety occupies the equatorial position in the dithiacyclohexane **8**, whereas the imidazole residue is axially oriented. The synthesis of isopilocarpine was completed by a Raney nickel desulfurization, which removed both the thiophenyl and the dithiane group and delivered the hydrochloride of the alkaloid **2** in 43% yield.



Scheme 2 Synthesis of isopilocarpine (**2**) by one-pot Michael-addition-alkylation route. *Reagents and conditions*: i) $HS(CH_2)_3SH$, *p*-TsOH, $CHCl_3$, reflux, 78%; ii) *n*-BuLi, THF, –78 °C; iii) **4**, –78 °C; iv) EtI, –78 °C to 25 °C, 76%; v) Raney nickel, MeOH, reflux, HCl, 43%.

The diastereomers **1**·HCl and **2**·HCl clearly differ in the ^{1}H NMR signals of the diastereotopic protons at carbon atom 5 of the furanone ring, each of them displaying a doublet of doublet. It has been reported that racemic isopilocarpine (**2**) can be converted into pilocarpine (**1**) by deprotonation and subsequent reprotonation of the enolate.[7g] Although this procedure does not occur under complete inversion at carbon atom 3 of the furanone ring, subsequent chromatography and recrystallization permits to obtain pilocarpine **1** from the *trans*-diastereomer **2**. Thus a novel formal route to pilocarpine is also opened.

The stereochemical lability of pilocarpine (**1**), i.e. its tendency to a facile isomerization to isopilocarpine (**2**) is well known.[15,16] According to a semiempirical calculation (AM1),[17] the *cis*-isomer **1** has been found to be less stable

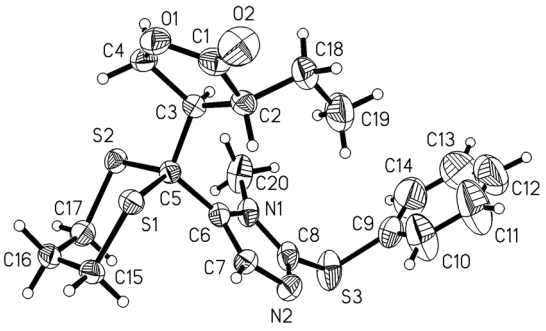


Figure 2 Diagram of **8**. Displacement ellipsoids are drawn at the 30% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. Selected torsion angles [°]: C(4)-O(1)-C(1)-O(2) 174.5, C(4)-O(1)-C(1)-C(2) –5.9, O(2)-C(1)-C(2)-C(3) 177.6, O(1)-C(1)-C(2)-C(3) –1.9, O(2)-C(1)-C(2)-C(18) –57.5, O(1)-C(1)-C(2)-C(18) 122.9, C(1)-C(2)-C(3)-C(4) 8.1, C(18)-C(2)-C(3)-C(4) –111.8, C(1)-C(2)-C(3)-C(5) –115.7, C(18)-C(2)-C(3)-C(5) 124.3, C(2)-C(3)-C(5)-C(6) –57.4, C(4)-C(3)-C(5)-C(6) –176.0.

than *trans*-**2** by 2.49 kcal/mol. We have performed an ab initio calculation of the heat of formation of pilocarpine and isopilocarpine. Thus a Gaussian STO-6-31G* geometry optimization[18] revealed a difference of 3.35 kcal/mol, again in favor of isopilocarpine (**2**). Optimized geometries of both **1** and **2** calculated by means of the ab initio method are shown in Figures 3 and 4 and confirm a conformational analysis based on NMR spectra.[19] The steric hindrance that is due to the eclipsed *cis*-oriented substitu-

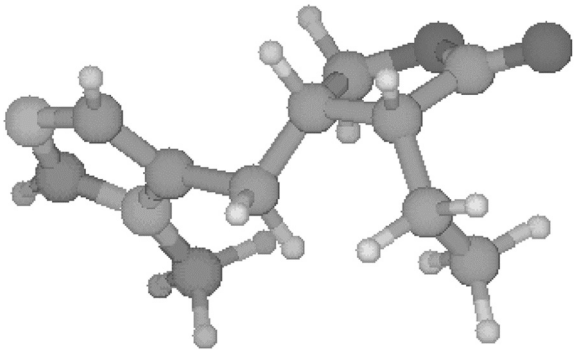


Figure 3 Optimized geometries of **1** according to STO-6-31G* calculations.

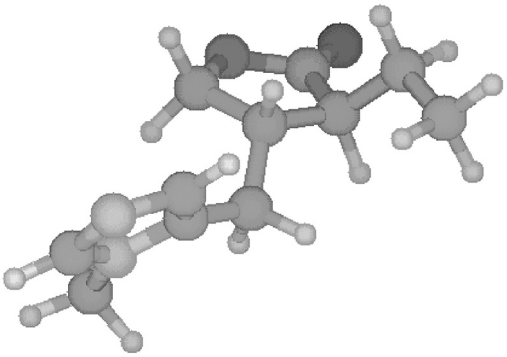


Figure 4 Optimized geometries of **2** according to STO-6-31G* calculations.

ents at the lactone moiety of pilocarpine (**1**) is in evidence therein.

In summary, the imidazole alkaloid isopilocarpine (**2**) has been made accessible in a diastereoselective manner by a straightforward synthesis taking advantage of a Michael-addition-alkylation procedure. The hitherto shortest synthesis of **2** involves three steps from known compounds or 5 steps from commercially available starting materials. Enantioselective variants of this method are investigated and are aimed at a short and convergent synthesis of non-racemic isopilocarpine.

Melting points (uncorrected) were determined with a Büchi melting point apparatus. NMR spectra were recorded in $CDCl_3$ or D_2O solution (internal standard) with a Bruker DRX 500 spectrometer. IR spectra were recorded with a Bruker Vector 22. Mass spectra were measured with a Varian MAT 311 spectrometer. TLC plates silica gel F_{254} (Merck) were used for the identification of products. Column chromatography was performed using Macherey–Nagel Kieselgel 60 and Merck Kieselgel 60, mesh size 0.04–0.063. Elemental analyses were carried out with a Perkin-Elmer CHN-Analysator 263 at the Institut für Pharmazeutische Chemie (Universität Düsseldorf).

All reactions involving organolithium compounds were carried out under an atmosphere of anhyd N_2. THF was pre-dried with KOH and distilled under N_2 from Na/benzophenone. It was taken from the distillation flask, which was closed by a septum with syringes or cannulas. *n*-BuLi was purchased as solution in hexane, Raney nickel as a suspension in water. Reactions at temperatures below 0 °C were monitored by a thermocouple connected to a resistance thermometer (Ebro). 1-Methyl-2-phenylsulfanylimidazole (**6**) was prepared from *N*-methylimidazole according to ref.[13a] 3-Methyl-2-phenylsulfanylimidazole-4-carbaldehyde (**7**) was synthesized according to ref.[13b]

5-(1,3-Dithian-2-yl)-1-methyl-2-phenylsulfanyl-imidazole (7a)

A 250-mL two-necked flask was charged with **6** (2.00 g, 9.16 mmol), *p*-toluenesulfonic acid monohydrate (1.90 g, 10 mmol) and anhyd $CHCl_3$ (150 mL). The flask was closed with a septum and equipped with a magnetic stirrer and a Soxhlet extractor filled with molecular sieves 4 Å with a reflux condenser that was closed with a drying tube ($CaCl_2$). 1,3-Propanedithiol (1.48 g, 13.74 mmol) was injected by syringe, and the solution was refluxed for 4 h. After cooling to r.t., a 3 N solution of NaOH (50 mL) was added. The layers were separated, the organic phase was dried with $MgSO_4$ and concentrated in a rotary evaporator. The crude product thus obtained was purified by column chromatography or recrystallization to yield colorless crystalline **7a** (2.21 g, 78%); mp 124 °C; R_f 0.57 (Et_2O–*n*-hexane, 15:2).

IR (KBr): 2933, 2903, 2825, 1579, 1479, 1450, 1275, 1024, 772, 739, 698, 687 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.90–1.98 (m, 1 H, SCH_2CHHCH_2S), 2.13–2.29 (m, 1 H, SCH_2CHHCH_2S), 2.93 (ddd, *J* = 14.5 Hz, *J* = 5.0 Hz, *J* = 3.2 Hz, 2 H, $SCHHCH_2CHHS$), 3.02 (ddd, *J* = 14.5 Hz, *J* = 11.7 Hz, *J* = 2.7 Hz, 2 H, $SCHHCH_2CHHS$), 3.69 (s, 3 H, NCH_3), 5.18 (s, 1 H, SCHS), 7.13–7.27 (m, 5 H, phenyl-H), 7.29 (s, 1 H, imidazyl-H).

^{13}C NMR ($CDCl_3$): δ = 24.90 ($SCH_2CH_2CH_2S$), 31.33 ($SCH_2CH_2CH_2S$), 31.92 (NCH_3), 40.57 (SCS), 126.71, 128.18, 129.29, 139.44 (phenyl-C), 129,64 (5-imidazyl-C), 132.26 (2-imidazyl-C), 134.41 (4-imidazyl-C).

MS (70 eV): *m*/*z* (%) = 308 (100) [M^+], 233 (90), 203 (12), 201 (24), 125 (13), 121 (13), 99 (14), 98 (14), 93 (27), 91 (34), 77 (12), 71 (13).

Anal. Calcd for $C_{14}H_{16}N_2S_3$: C, 54.51; H, 5.23; N, 9.08. Found: C, 54.26; H, 5.36; N, 9.05.

***trans*-3-Ethyl-4-[2-(1-methyl-2-phenylsulfanyl-imidazol-5-yl)-1,3-dithian-2-yl]-dihydrofuran-2-one (8)**

A 100-mL flask was charged with **7a** (1.234 g, 4.2 mmol), equipped with a magnetic stirrer, connected to the combined N_2/vacuum line, and closed with a septum. The air in the flask was replaced by N_2 and THF (20 mL) was added through a cannula. The mixture was cooled to –78 °C, *n*-BuLi (2.5 mL of a 1.6 M solution in *n*-hexane) was added dropwise by syringe, and stirring was continued for 2.5 h at –78 °C. Furanone **4** (0.336 g, 4.0 mmol) dissolved in 2 mL of THF was injected, and the mixture was stirred for another 2.5 h at –78 °C. After ethyl iodide (0.625 g, 4.0 mmol) had been added by syringe, the solution was allowed to reach r.t. overnight. Water (50 mL) was added, the solution was extracted three times with a total amount of 120 mL of EtOAc, and the combined organic layers were dried with $MgSO_4$. The solvent was removed in a rotary evaporator and the residue was purified by column chromatography to give a colorless solid **8** (1.275 g; 76%); mp 135 °C (after recrystallization from Et_2O); R_f 0.2 (Et_2O–*n*-hexane, 10:1).

IR (KBr): 2964, 2908, 1759, 1582, 1477, 1439, 1383, 1265, 1183, 1037, 991, 741, 706, 688 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.78 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.31–1.51 (m, 2 H, CH_2CH_3), 1.84–2.08 (m, 2 H, $SCH_2CH_2CH_2S$), 2.70–3.00 (m, 6 H, $SCH_2CH_2CH_2S$, 3-H, 4-H), 3.85 (s, 3 H, NCH_3), 4.22 (dd, *J* = 8.5 Hz, *J* = 10.0, 1 H, 5-H), 4.64 (dd, *J* = 5.0 Hz, *J* = 10.0 Hz, 1 H, 5-H), 7.19–7.30 (m, 5 H, phenyl-H), 7.54 (s, 1 H, imidazyl-H).

^{13}C NMR ($CDCl_3$): δ = 10.72 (CH_3), 24.18 (CH_2CH_3), 24.73 ($SCH_2CH_2CH_2S$), 27.77 ($SCH_2CH_2CH_2S$), 28.01 ($SCH_2CH_2CH_2S$), 34.72 (NCH_3), 42.5 (SCS), 47.76 (C-4), 54.75 (C-3), 67.35 (C-5), 127.58, 129.78, 143.04 (phenyl-C), 132.02 (5-imidazyl-C), 134.06 (2-imidazyl-C), 135.94 (4-imidazyl-C), 178.25 (CO).

MS (70 eV): *m*/*z* (%) = 420 (34) [M^+], 307 (100), 233 (17), 109 (6), 91 (8), 77 (6).

Anal. Calcd for $C_{20}H_{24}N_2O_2S_3$: C, 57.11; H, 5.75; N, 6.66. Found: C, 56.90; H, 5.81; N, 6.60.

Crystal Structure Determination of Compound 8[20]

Crystals of **8** suitable for X-ray study were selected by means of a polarization microscope. They were investigated on a Stoe Imaging Plate Diffraction System using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 8000 strong reflections, distributed equally in reciprocal space. An anorthic lattice was found compatible with space groups *P*1 and *P*–1. The latter was confirmed in the course of the structure refinement. Crystal data: $M_r(C_{20}H_{24}N_2O_2S_3)$ = 420.59, *a* = 6.4707 (13) Å, *b* = 8.0160 (14) Å, *c* = 20.466 (4) Å, α = 85.61 (3)°, β = 81.69 (3)°, γ = 78.23(3), *V* = 1027.1(4) $Å^3$, Z = 2, D_x = 1.360 g cm^{-3}, μ = 0.379 mm^{-1}, *T* = 291 K, colorless crystal of dimensions 0.5 mm × 0.3 mm × 0.1 mm. 14608 intensity data (Θ_{min} = 2.60°, Θ_{max} = 25.91°) were collected and Lp corrections were applied. The structure was solved by direct methods[21] and approximate positions of all the hydrogen atoms were found via difference Fourier-synthesis. Refinement (285 parameters, all of 3714 unique reflections used) by full-matrix least-squares calculations on F^2,[22] converged to the following final indicators: $R_1[F_o^2 > 2\sigma(F_o^2)]$ = 0.047, wR_2 = 0.105 (all data), $w = 1/[\sigma^2(F_o^2) + (0.025\,P)^2 + 1.0P]$ where $P = (F_o^2 + 2F_c^2)/3$, *S* = 1.003,[22] largest peak and hole in the final difference map are 0.292 e/$Å^2$ and –0.340 e/$Å^3$, respectively. Anisotropic displacement parameters were used for all non-hydrogen atoms. Together with their parent

carbon atoms all H atoms were treated as rigid groups with fixed idealised C-H distances. The H atoms of methyl groups were allowed to move collectively around the neighboring C-C axis. The isotropic displacement parameters of the H atoms were kept equal to 120% of the equivalent isotropic displacement parameters of the parent 'aromatic', tertiary or secondary carbon atom and equal to 150% of the parent primary carbon atom, respectively. Scattering factors, dispersion corrections and absorption coefficients were taken from International Tables for Crystallography (1992, Vol. C, Tables 6.114, 4.268 and 4.2.4.2).

***trans*-3-Ethyl-4-[(1-methylimidazol-5-yl)methyl]dihydrofuran-2-one (Isopilocarpine) (2)**

A 100-mL flask was equipped with a magnetic stirrer and charged with a 10% aq suspension of Raney nickel (30 mL). The supernatant water was removed by decantation and MeOH was added to the residue. Again, the liquid phase was removed by decantation, and this procedure was repeated three times. Finally, the residue was suspended in anhyd MeOH and a solution of **8** (1.54 g, 3.66 mmol) in anhyd MeOH (50 mL) was added. After refluxing the mixture for 4 h under vigorous stirring, it was cooled to r.t. and the solid was allowed to sediment. The supernatant solution was filtered through celite in a microfilter. The solid residue and the celite were washed twice with MeOH. The combined filtrates were evaporated and dissolved in 1 N HCl acid. The acidic solution was basified by addition of solid Na_2CO_3 and extracted three times with a total volume of 100 mL of EtOAc. The combined organic layers were extracted with 10% HCl acid (25 mL). Finally, the acidic aqueous layer was concentrated in a rotary evaporator and exposed to oil pump vacuum for several hours to give isopilocarpine hydrochloride (**1**·HCl) in 43% yield (0.385 g). The product was identical with isopilocarpine according to its NMR spectra in D_2O when compared with those described in the literature.[19] No traces of pilocarpine (**1**) were detected.

Acknowledgment

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