Kurzmitteilungen:

Synthesis of Tricyclic Azaergoline Analogues

Synthese tricyclischer Azaergolin-Analoga

Peter Gmeiner*, #) and Josef Sommer

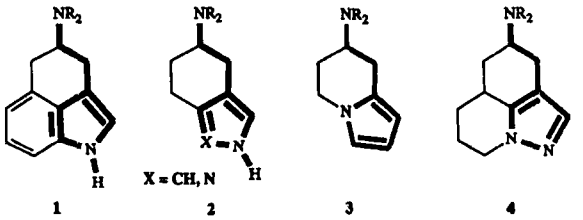
Institut für Pharmazie und Lebensmittelchemie der Ludwig-Maximilians-Universität München, Sophienstraße 10, 8000 München 2, BRD

Received June 5, 1990

The synthesis of ergoline congeners continues to be an active field of investigation in medicinal chemistry[1]. Along with the tetracycles, there have been investigated tricyclic and bicyclic analogues (**1**, **2**), which were found to be strong dopamine agonists[2]. It was suggested that the dopaminergic activity of ergoline analogues is due to a pyrrole- (or pyrazole-) ethylamine moiety including an aromatic N-H feature to represent one of the dopamine hydroxyl groups[3].

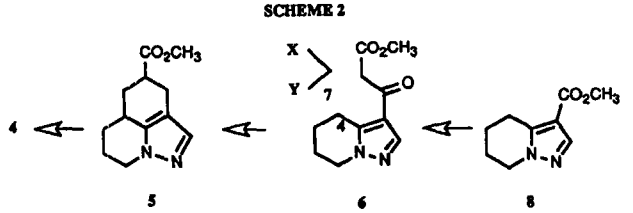
In order to examine whether the latter demand is really essential for dopaminergic activity, we recently disclosed an EPC synthesis for the aminoindolizidine derivatives **3**, which are devoid of the N-H subunit[4]. In fact our preliminary studies revealed **3** to be highly CNS active *in vivo*[5]. Another interesting model compound to verify this hypothesis is the pyrazolo[2,3,4-*j*,*i*]quinoline derivative **4**.

SCHEME 1

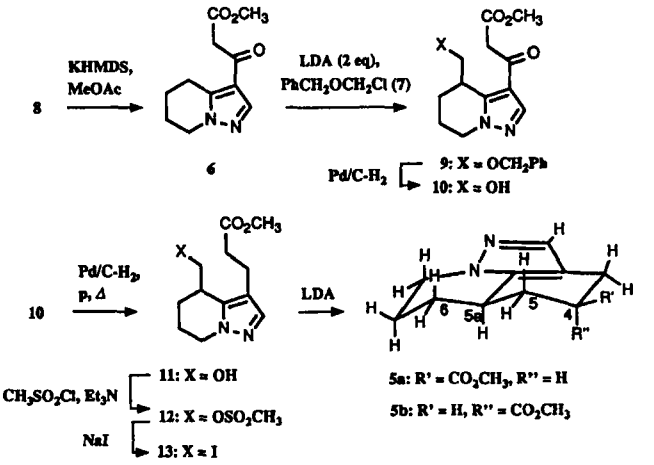


In this communication we describe the preparation of its synthetic precursor **5**, which is a strong candidate to afford **4** *via Curtius* rearrangement. It was envisioned to approach to **5** *via* the β-ketoester **6**, which should be obtained from the pyrazolo[1,5-*a*]pyridine derivative **8** by ester condensation. When treated with an excess of strong base the dianion of the key intermediate **6** should react selectively at C-4 with a dielectrophilic C-1 equivalent (**7**). After reduction of the ketone function and deprotonation, the ester enolate was expected to afford the target compound **5**. This cyclization was predicted to be favored as a 6-(enolexo)-exo-tet case according to the *Baldwin* Rules[6].

SCHEME 2



SCHEME 3



Application of our newly developed synthesis of tetrahydropyrazolo[1,5-*a*]pyridine derivatives[7] afforded **8** by catalytic hydrogenation and transesterification of ethyl pyrazolo[1,5-*a*]pyridine-3-yl-carboxylate, which is efficiently available by 1,3-dipolar cycloaddition[8]. Subsequent ester condensation was best accomplished by treating **8** with the ester enolate, derived from methyl acetate and potassium hexamethyldisilazide (KHMDS). It is worthy to note that LDA is a less effective base for this reaction. In contrast, LDA did a perfect job by converting **6** into its dianion which can be reacted selectively at the more reactive 4-position with benzyloxymethylchloride (BOM-Cl) as a convenient formaldehyde equivalent to provide a 71% yield of **9**. Then the benzyloxy group was removed by hydrogenolysis with Pd/C in acetic acid. Also deserving comment is the fact that the hydrogenolytic ether cleavage required equimolar amounts of Pd to work regioselectively; otherwise the primary alcohol **10** was contaminated with the corresponding methyl side product. It was possible to reduce selectively the aromatic ketone function with Pd/C-H_2 in methanol to give **11** in 39% yield. Subsequently **11** was activated for ring closure by conversion to the sulfonic ester **12**, which was heated with NaI in acetone to accomplish **13** (77% overall yield from **11**). Finally cyclization was achieved by deprotonation of **13** with LDA in THF (-78 to 0°) yielding a 1:1 diastereomeric mixture of **5a** and **5b** which can be separated by HPLC.

#) Dedicated to Prof. *F. Eiden* on the occasion of his 65th birthday.

  0365-6233/90/1212-0991 $ 3.50+.25/0

The structures of **5a** and **5b** were elucidated by appropriate ^{1}H-NMR experiments. After determination of the various peaks with H,H-COSY the conformation could be determined by observation of diagnostic coupling constants and NOE difference spectroscopy. 5a-H and 5-H_{ax} as well as 5a-H and 6-H_{ax} were found to be positioned anti in both diastereomers (^{3}J = 11.4 - 12.7 Hz, no significant NOE). This means that in **5a** and **5b** both six membered rings must exist in a half chair conformation. The relative configuration was determined *via* the coupling constants between 4-H and 5-H_{axial}. ^{3}J = 3.8 Hz indicates the carboxylic ester to be positioned axially in **5b**, whereas the corresponding value for **5a** assures 4*RS*, 5a*SR* configuration (^{3}J = 12.3 Hz).

We wish to thank Prof. *F. Eiden* for stimulating discussions and generous support. This work is supported by the Deutsche Forschungsgemeinschaft and the Fond der Chemischen Industrie.

Experimental Part

General

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately before use. CH_2Cl_2, acetone and Et_3N were distilled from CaH_2. All liquid reagents were purified by distillation. Unless otherwise noted reactions were conducted under dry N_2. Flash chromatography: 230-400 mesh silica gel. Preparative HPLC: 20 x 250 mm, 7 µm LiChrosorb SI 60 normal phase silica gel column, flow rate of 12 ml/min.- Melting points: Büchi melting point apparatus, uncorrected.- IR spectra: Perkin Elmer 881 spectrometer.- Mass spectra: Varian CH7.- NMR spectra: Jeol 400 JNM-GX spectrometer at 400 MHz, tetramethylsilane as internal standard.- Elemental analyses: Heraeus CHN Rapid instrument.

Methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl-carboxylate (**8**)

To a solution of 2.70 g (50 mmol) sodium methoxide in 150 ml MeOH were added 9.7 g (50 mmol) ethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl-carboxylate[7] at 0°C. After 1 h the temp. was raised to room temp. and the mixture was stirred for 12 h, when 100 ml saturated aqueous $NaHCO_3$ were added. It was then adjusted to pH 7 and 2 N aqueous HCl, extracted with Et_2O and the org. layer dried ($MgSO_4$) and evaporated to give 8.46 g (94%) of pure **8** as a colorless solid; mp. 64°C.- $C_9H_{12}N_2O_2$ (180.2) Calcd. C 60.0 H 6.71 N 15.6 Found C 60.1 H 6.67 N 15.7; mol.-mass 180 (ms).- IR (NaCl): 2920; 2860; 1690 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85-1.92 (m, 2H, H_2C-5), 2.01-2.07 (m, 2H, H_2C-6), 3.06 (t, J = 6.5 Hz, 2H, H_2C-4), 3.8 (s, 3H, OCH_3), 4.15 (t, J = 6.5 Hz, 2H, H_2C-7), 7.85 (s, 1H, HC-2).

Methyl-3-oxo-3-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl)-propionate (6)

To a stirred solution of 140 ml (70 mmol) KHMDS (0.5 molar in toluene) in 60 ml THF were added 3.7 g (50 mmol) methyl acetate, dissolved in 50 ml THF, dropwise, at -78°C. The solution was stirred at -78°C for 15 min, then 3.6 g (20 mmol) of **8** dissolved in 40 ml THF were added. After 2.5 h the mixture was allowed to warm to room temp. and stirred for 24 h. It was then added to a mixture of Et_2O and saturated aqueous $NaHCO_3$. The org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petrolether-EtOAc 1:1) to give 3.2 g (72%) of pure **6** as a colorless solid; mp. 55°C.- $C_{11}H_{14}N_2O_3$ (222.2) Calcd. C 59.4 H 6.35 N 12.6 Found C 59.4 H 6.44 N 12.4; mol.-mass 222 (ms).- IR (NaCl): 2940; 1740; 1650 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85-1 .91 (m, 2H, H_2C-5), 2.02-2.08 (m, 2H, H_2C-6), 3.10 (t, J = 6.5 Hz, 2H, H_2C-4), 3.75 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2CO_2R), 4.16 (t, J = 6.5 Hz, 2H, H_2C-7), 7.84 (s, 1H, HC-2).

Methyl-3-(4-benzyloxymethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl)-3-oxo-propionate (**9**)

To a solution of 6.31 ml (45.0 mmol) diisopropylamine in 90 ml THF were added 24.8 ml n-BuLi (1.6 molar in hexane) at -78°C. Subsequently the mixture was stirred at 0°C for 30 min, when it was added to 4.0 g (18.0 mmol) **6** in 340 ml THF at -78°C. Then the temp. was raised to -20°C and after 30 min the dark red solution was added dropwise (over 30 min) to a precooled solution (-50°C) of 3.0 ml (21.6 mmol) benzyloxymethylchloride (BOM-Cl) in 80 ml THF. After 10 min it was added to a mixture of Et_2O and citric acid (10% in water). The org. layer was dried ($MgSO_4$) and evaporated and the residue was separated by flash chromatography (petrolether-EtOAc 1:1) to give 4.4 g (71%) of pure **9** as a colorless oil.- $C_{19}H_{22}N_2O_4$ (342.2) Calc. C 66.6 H 6.48 N 8.2 Found C 66.6 H 6.50 N 8.2; mol.-mass 342 (ms).- IR (NaCl): 3050; 2950; 2850; 1740; 1665 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.75-1.84 (m, 1H, HC-5 or HC-6), 1.85-1.96 (m, 1H, HC-5 or HC-6), 2.13-2.22 (m, 1H, HC-5 or HC-6), 2.25-2.35 (m, 1H, HC-5 or HC-6), 3.60 (dd, J = 10.2; 9.5 Hz, 1H, C<u>H</u>$_2$OCH$_2$Ph), 3.74 (s, 3H, OCH_3), 3.75 (d, J = 14.7 Hz, 1H, CH_2CO_2R), 3.80 (d, J = 14.7 Hz, 1H, CH_2CO_2R), 3.73-3.80 (m, 2H, C<u>H</u>$_2$OCH$_2$Ph and HC-4), 4.0 (ddd, J = 13.2, 11.3, 4.9 Hz, 1H, H_{ax}C-7), 4.25 (ddd, J = 13.2, 5.9, 2.2 Hz, 1H, H_{eq}C-7), 4.45 (d, J = 11.7 Hz, 1H, OCH_2Ph), 4.64 (d, J = 11.7 Hz, 1H, OCH_2Ph), 7.18-7.39 (m, 5H, Ph), 7.85 (s, 1H, HC-2).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.89 (H_2C-5), 21.51 (H_2C-6), 33.08 (HC-4), 47.38 (H_2C-7), 48.35 (<u>C</u>H$_2$CO$_2$R), 52.43 (OCH_3), 69.99 (<u>C</u>H$_2$OCH$_2$Ph), 72.68 (OCH_2Ph), 118.42 (C-3), 127.51 (p-Ph), 127.59 (2x-Ph), 128.33 (2x-Ph), 138.40 (i-Ph), 141.19 (HC-2), 144.53 (C-3a), 167.95 (-CO_2R), 186.26 (R_2CO).

Methyl-3-(4-hydroxymethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl)-3-oxo-propionate (**10**)

A mixture of 4.4 g (12.9 mmol) **9** and 10 g Pd/C (10%) in 150 ml acetic acid was stirred under a balloon of H_2 for 6 h at room temp.. The mixture was filtered through celite, the filtrate was evaporated, and the residue was purified by flash chromatography (CH_2Cl_2-MeOH 98:2) to give 2.76 g (85%) of **10** as a colorless oil.- $C_{12}H_{16}N_2O_4$ (252.3); mol.-mass 252 (ms).- IR (NaCl): 3380; 2950; 2850; 1740; 1665 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.77-1.86 (m, 1H, HC-5), 1.90-2.07 (m, 1H, HC-5), 2.12-2.24 (m, 2H, H_2C-6), 3.56-3.62 (m, 1H, HC-4), 3.69 (dd, J = 10.5, 4.6 Hz, 1H, <u>C</u>H$_2$OH), 3.74 (s, 3H, OCH_3), 3.81 (d, J = 1.5 Hz, 2H, CH_2CO_2R), 3.89 (dd, J = 10.5, 7.5 Hz, 1H, C<u>H</u>$_2$OH), 4.03 (ddd, J = 13.2, 11.0, 5.1 Hz, 1H, H_{ax}C- 7), 4.28 (ddd, J = 13.2, 5.1, 2.2 Hz, 1H, H_{eq}C-7), 7.89 (s, 1H, HC-2).

Methyl-3-(4-hydroxymethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl)-propionate (**11**)

A mixture of 900 mg (3.57 mmol) **10** and 500 mg Pd/C (10%) in 40 ml MeOH was stirred under H_2 pressure (50 bar) for 5 h at 130°C. The mixture was filtered through celite, the filtrate was evaporated, and the residue was purified by flash chromatography (CH_2Cl_2-MeOH 97:3) to give 330 mg (39%) of pure **11** as a colorless oil.- $C_{12}H_{18}N_2O_3$ (238.3) Calcd. C 60.4 H 7.61 N 11.7 Found C 60.0 H 8.05 N 11.2; mol.-mass 238 (ms).- IR (NaCl): 3350; 2960; 1740 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.80-1.90 (m, 2H, H_2C-5), 2.06-2.16 (m, 2H, H_2C-6), 2.53-2.69 (m, 2H, CH_2CO_2R), 2.70-2.83 (m, 2H, $ArCH_2R$), 3.11-3.16 (m, 1H, HC-4), 3.65 (s, 3H, OCH_3), 3.74-3.79 (m, 2H, C<u>H</u>$_2$OH), 3.95-4.01 (m, 1H, H_{ax}C-7), 4.15-4.20 (m, 1H, H_{eq}C-7), 7.29 (s, 1H, HC-2).

Methyl-3-(4-mesyloxymethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl)-propionate (**12**)

To a mixture of 750 mg (3 mmol) of **11** and 0.500 ml (3.6 mmol) of triethylamine in 20 ml THF were added 0.280 ml (3.6 mmol) of methanesulfonic chloride at room temp.. After 5 h the mixture was filtered and the filtrate evaporated and purified by flash chromatography (CH_2Cl_2-MeOH 97:3) to give 900 mg (95%) of pure **12** as a colorless oil.- $C_{13}H_{20}N_2O_5S$ (316.4) Calcd. C 49.3 H 6.37 N 8.8 Found C 49.3 H 6.55 N 8.7 mol.-mass 316 (ms).- IR (NaCl): 2955; 1730; 1350; 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.89-1.96 (m, 1H, HC-5), 1.99-2.08 (m, 1H, HC-5), 2.12-2.17 (m, 2H, H_2C-6), 2.61 (t, J = 7.2 Hz, 1H, CH_2CO_2R), 2.62 (t, J = 7.2 Hz, 1H, CH_2CO_2R), 2.78 (t, J = 7.2 Hz, 2H, $ArCH_2R$), 3.03 (s, 3H, OSO_2CH_3), 3.45-3.50 (m, 1H, HC-4), 3.6 7 (s, 3H, OCH_3), 4.01-4.04 (m, 1H, H_{ax}C-7), 4.24 (dd, J = 10.3, 9.4 Hz, 1H, $C\underline{H}_2SO_3CH_3$), 4.27-4.33 (m, 1H, H_{eq}C-7), 4.39 (dd, J = 10.3, 4.7 Hz, 1H, -$C\underline{H}_2SO_3CH_3$), 7.38 (s, 1H, HC-2).

Methyl-3-(4-iodomethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-yl)-propionate (**13**)

A mixture of 632 mg (2 mmol) **12** and 6 g (40 mmol) NaI was stirred in 30 ml of boiling acetone for 10 h. After being cooled to room temp. the solvent was removed and the residue was extracted with Et_2O. The extract was evaporated and purified by flash chromatography (petrolether-EtOAc 1:1) to give 565 mg (81%) of pure **13** as a colorless oil.- $C_{12}H_{17}IN_2O_2$ (348.2) Calcd. C 41.4 H 4.92 N 8.0 Found C 41.5 H 5.16 N 7.9; mol.-mass 348 (ms).- IR (NaCl): 2950; 1730 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.93-2.07 (m, 3H, HC-6, H_2C-5), 2.10-2.18 (m, 1H, HC-6), 2.60-2.63 (m, 2H, CH_2CO_2R), 2.74 (t, J = 7.2 Hz, 2H, $ArCH_2R$), 3.23-3.28 (m, 2H, CH_2I, HC-4), 3.43-3.48 (m, 1H, CH_2I), 3.69 (s, 3H, OCH_3), 3.96-4.03 (m, 1H, H_{ax}C-7), 4.13-4.18 (m, 1H, H_{eq}C-7), 7.30 (s, 1H, HC-2).

Methyl(4RS,5aSR)-4,5,5a,6,7,8-hexahydro-3H-pyrazolo[2,3,4-j,i]quinolin-4-yl-carboxylate (**5a**) *and Methyl(4RS,5aRS-4,5,5a,6,7,8-hexahydro-3H-pyrazolo[2,3,4-j,i]quinolin-4-yl-carboxylate* (**5b**)

To a solution of 79 mg (0.23 mmol) **13** in 8 ml THF were added 0.7 ml (0.23 mmol) of LDA (0.33 molar in THF). The temp. was raised to 0°C and stirring was continued for 1 h. It was then added to a mixture of Et_2O and saturated aqueous $NaHCO_3$. The org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petrolether-EtOAc 1:1) to yield 23 mg (47%) of **5a** and **5b** as a 1:1 mixture of diastereomers, which were separated by preparative HPLC (silica gel, petrolether - isopropanol 85:15).

5a, mp. 79°C.- $C_{12}H_{16}N_2O_2$ (220.3) Calcd. C 65.4 H 7.32 N 12.7 Found C 65.3 H 7.34 N 12.6; mol.-mass 220 (ms).- IR (NaCl): 2950; 2860; 1740 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.23 (dddd, J = 12.9, 12.9, 12.7, 2.4, 1H, H_{ax}C-6), 1.44 (ddd, J = 12.5, 12.3, 11.4 Hz, 1H, H_{ax}C-5), 2.0-2.21 (m, 3H, H_{eq}C-6, H_{ax}C-7 and H_{eq}C-7), 2.26 (ddd, J = 12.5, 4.5, 2.5 Hz, 1H, H_{eq}C-5), 2.67 (br-dd, J = 12.7, 11.4 Hz, 1H, H_{ax}C-5a), 2.70-2.76 (m, 1H, H_{ax}C-3), 2.85 (dddd, J = 12.5, 12.3, 5.8, 2.6, 1H, H_{ax}C-4), 2.93 (dd, J = 14.7, 5.8 Hz, 1H, H_{eq}C-3), 3.73 (s, 3H, OCH_3), 3.87 (ddd, J = 12.5, 12.5, 5.5 Hz, 1H, H_{ax}C-8), 4.28 (dd, J = 12.5, 5.5 Hz, 1H, H_{eq}C-8), 7.31 (s, 1H, HC-2).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 23.56 (H_2C-3, H_2C-7), 26.77 (H_2C-6), 32.17 (H_2C-5), 33.14 (HC-5a), 41.24 (HC-4), 47.13 (H_2C-8), 51.88 (CH_3, OCH_3), 111.61 (C-2a), 137.23 (HC-2), 140.23 (C-2b), 175.60 (CO_2R).

5b, mp. 65°C.- $C_{12}H_{16}N_2O_2$ (220.3) Calcd. C 65.4 H 7.32 N 12.7 Found C 65.3 H 7.34 N 12.6; mol.-mass (220 ms).- IR (NaCl): 2950; 2860; 1740 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.20 (dddd, J = 12.9, 12.7, 12.7, 2.9 Hz, 1H, H_{ax}C-6), 1.43 (ddd, J = 12.7, 12.7, 3.8 Hz, 1H, H_{ax}C-5), 1.99-2.18 (m, 3H, H_{eq}C-6, H_{ax}C-7 and H_{eq}C-7), 2.40 (ddd, J = 12.7, 4.2, 3.8 Hz, 1H, H_{eq}C-5), 2.66-2.72 (m, 2H, H_{ax}C-3 and H_{ax}C-5a), 3.05 (dt, J = 7.0, 3.8, 3.8 Hz, 1H, H_{eq}C-4), 3.15 (d, J = 15.9 Hz, 1H, H_{eq}C-3), 3.68 (s, 3H, OCH_3), 3.86 (ddd, J = 12.5, 12.5, 5.8 Hz, 1H, H_{ax}C-8), 4.26 (dd, J = 12.5, 5.8 Hz, 1H, H_{eq}C-8), 7.30 (s, 1H, HC-2).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.80 (H_2C-3), 23.39 (H_2C-7), 26.75 (H_2C-6), 29.66 (HC-5a), 30.72 (H_2C-5), 38.64 (HC-4), 47.07 (H_2C-8), 51.94 (OCH3), 111.03 (C-2a), 137.23 (HC-2), 140.05 (C-2b), 175.22 (CO_2R).

References

1 For review: A.S. Horn, in Comprehensive Medicinal Chemistry, Vol. *3*, 229 (ed. C. Hansch), Pergamon Press, Oxford 1990.

2 L.A. McQuaid, F.E. Latz, J.A. Clemens, R.W. Fuller, D.T. Wong, and N.R. Mason, J. Med. Chem. *32*, 2388 (1989) and references cited therein.

3 N.J. Bach, E.C. Kornfeld, N.C. Jones, M.O. Chaney, D.E. Dorman, J.W. Paschal, J.A. Clemens, and E.B. Smalstig, J. Med. Chem. *23*, 481 (1980) and references cited therein.

4 P. Gmeiner and H. Lerche, Heterocycles *31*, 9 (1990).

5 Publication is envisioned.

6 J.E. Baldwin and M.J. Lusch, Tetrahedron *38*, 2939 (1982).

7 P. Gmeiner and J. Schünemann, Arch. Pharm. (Weinheim) *321*, 517 (1988).

8 P. Gmeiner and J. Sommer, Arch. Pharm. (Weinheim) *321*, 505 (1988) and references cited therein. [KPh539]