

A NEW SYNTHETIC ROUTE TO THE TETRACYCLIC FRAMEWORK OF
STRYCHNOS ALKALOIDS VIA INTRAMOLECULAR ALDOL REACTION

Süleyman Patir^{*a}, Peter Rosenmund^b, and Peter H. Götz^c

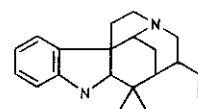
^aDepartment of Science, Faculty of Education, Hacettepe
University, TR-06525 Beytepe-Ankara, Turkey

^bInstitut für Organische Chemie, J.-W.-Goethe-
Universität Frankfurt, Theodor-Stern-Kai 7, D-60596
Frankfurt/Main, Germany

^cFachbereich MND, Fachhochschule Gießen-Friedberg,
Wilhelm-Leuschner-Straße 13, D-61169 Friedberg, Germany

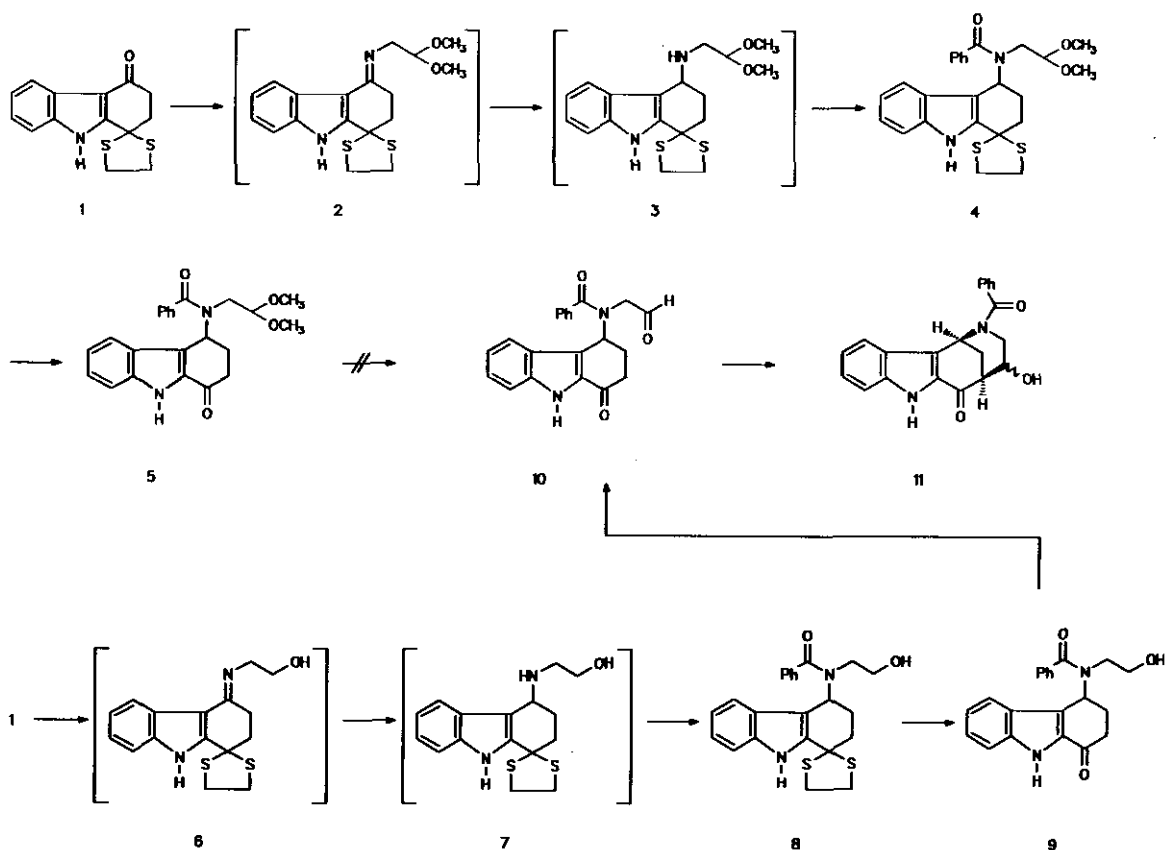
Abstract - By treatment of 2,3,4,9-tetrahydrospiro[1*H*-
carbazole-1,2'-[1,3]dithiolan]-4(9*H*)-one (**1**) with
ethanolamine, followed by reduction of the
corresponding imine (**6**) with NaBH₄ to the amine (**7**) and
benzylation, *N*-benzoyl-*N*-(2-hydroxyethyl)-{2,3,4,9-
tetrahydrospiro-[1*H*-carbazole-1,2'-(1,3)dithiolan]-4-
yl}amine (**8**) is formed, which can be deprotected to 4-
[Benzoyl-(2-hydroxyethyl)amino]-2,3,4,9-tetrahydro-1*H*-
carbazol-1-one (**9**). Oxidation of the primary hydroxyl
group yields [benzoyl-(1-oxo-2,3,4,9-tetrahydrocarb-
azol-1-one-4-yl)amino]acetaldehyde (**10**), a key-
intermediate for the cyclization to 2-benzoyl-4-
hydroxy-1,2,3,4,5,7-hexahydro-1,5*c*-methanoazocino[4,3-
b]indol-6-one (**11**), which represents the tetracyclic
skeleton of Strychnos-type alkaloids.

Most of the routes to the tetracyclic substructures of the Strychnos-type alkaloids which have been reported in the literature¹ start with the aromatic A- and a heterocyclic D-ring and build up the complete system by closing the other rings later.



Strychnan-type skeleton

In this paper we describe a synthetic strategy utilising a *N*-substituted 1-oxo-4-aminotetrahydrocarbazole (carbazole numbering) as a key-intermediate.



This tricyclic compound containing the rings A, B and C allows an intramolecular closure of the D-ring by aldol reaction in the last synthetic step, yielding the tetracyclic skeleton of many indole alkaloids. For the preparation of the open chain precursor (10) we developed a simple route using mild reaction conditions and easily

available starting materials.

To get the aldehyde (10) we studied two different routes: the first is proceeding from 1² to form the instable imine (2)³ by reaction with aminoacetaldehyde dimethylacetal/SnCl₂ in benzene, which can be reduced to amine (3) with NaBH₄ without isolation and trapped by acylation with benzoyl chloride to form 4. Cleavage of the thioketal⁴ of 4 with benzeneseleninic anhydride gives 5 in good yield.

Unfortunately all attempts to cleave the acetal group of 5 to get the desired aldehyde (10) failed and yielded only decomposition products. So we tried a second way. We converted 1 into 6 using ethanolamine and FeCl₃ as catalyst. Without isolation of the instable imine (6) we reduced it with NaBH₄ and trapped the resulting amine with benzoyl chloride to form the amide (8). Cleavage of the ketal group of 8 with benzeneseleninic anhydride gives 9, which can be oxidized to 10 using oxalyl chloride/DMSO at -60°C.⁵ 10 can be cyclized under mild conditions by intramolecular aldol reaction using NaH as base. The tetracyclic compound (11) is formed as a mixture of the epimeric alcohols.

ACKNOWLEDGEMENT

This investigation was supported by the "DAAD" (Deutscher Akademischer Austauschdienst).

EXPERIMENTAL

Melting points (uncorrected): Copper block. ¹H-Nmr: Bruker WH-270 and WH-300, internal standard TMS. - Ms: IMS-HX 110. - Ir: Hitachi 270-30. - Chromatography: Thin-layer: 0.25 mm Silica gel plates 60 F 254, Merck. - Column chromatography: Silica gel 70-230 mesh (0.063-0.2 mm), Merck.

N-Benzoyl-N-(2,2-dimethoxyethyl)-(2,3,4,9-tetrahydrospiro[1H-carbazole-1,2'-(1,3)dithiolan]-4-yl)amine (4): 2.0 g (7.26 mmol) of

2,3,4,9-tetrahydrospiro[1H-carbazole-1,2'-(1,3)dithiolan]-4(9H)-one (1), 3 ml (27.5 mmol) of aminoacetaldehyde dimethylacetal and 1.1 g (8 mmol) of SnCl₂ in 70 ml of benzene are heated for 7 h using a water trap. The progress of the reaction is monitored by tlc. When the reaction is complete, the solvent is evaporated. The residue is dissolved in methanol/THF (1:1) and cooled in an ice bath. Under stirring 1.5 g (40 mmol) of NaBH₄ are added in several portions. The ice bath is removed and the mixture is stirred for 6 h under nitrogen atmosphere. After this the solvent is evaporated under reduced pressure and the residue is dissolved in ether. After washing with 20 ml of 10% NaOH the organic layer is dried with MgSO₄ and the solvent is evaporated. The residue is dissolved in 30 ml of CHCl₃ and 2 ml (14.4 mmol) of triethylamine and 2 ml (17.2 mmol) of benzoyl chloride are added. The mixture is allowed to stir for 30 min at room temperature. Then washing with 20 ml of 10% NaOH follows. The organic layer is dried with MgSO₄ and the solvent is evaporated under reduced pressure. The residue is chromatographed using silica gel and toluene/ethyl acetate (2:1). After evaporation of the solvent 1.82 g (55%) of the pure product are isolated. mp 209°C (ethyl acetate). Tlc: R_f = 0.54 (benzene/ethyl acetate 1:2). - ¹H-Nmr (CDCl₃, 300 MHz): δ = 2.16-2.33 (m; 2H), 2.46-2.60 (m; 2H), 2.82-2.91 (m; 1H), 3.30-3.62 (m; 10 H, -OCH₃, S-CH₂-CH₂-S), 3.70-3.77 (m; 1H), 4.89-4.93 (m; 1H), 5.12-5.29 (m; 1H), 7.03-7.44 (m; 7H, arom.), 7.56-7.59 (m; 2H, arom.), 8.41 (s; 1H, NH). - Ir (KBr): ν = 3330 cm⁻¹ (NH), 1630 (C=O). Anal. Calcd for C₂₅H₂₈N₂O₃S₂: C, 64.08; H, 6.02; N, 5.98. Found: C, 63.92; H, 6.17; N 6.21.

4-[Benzoyl-(2,2-dimethoxyethyl)amino]-2,3,4,9-tetrahydro-1H-carbazol-1-one (5): 1.6 g (3.53 mmol) of the thioketal (4) and 1.44 g (4 mmol)

of benzeneseleninic anhydride are dissolved in 30 ml of CHCl_3 . 1.0 ml (12.4 mmol) of pyridine is added. The mixture is stirred under nitrogen atmosphere at room temperature. After 40 h washing with 20 ml of 10% NaOH follows. The organic layer is dried with MgSO_4 and the solvent is removed under reduced pressure. The residue is purified by chromatography using silica gel and toluene/ethyl acetate (2:1).

0.965 g (69%) of the product are isolated. mp 208°C (ethyl acetate).

Tlc: $R_f = 0.32$ (toluene/ethylacetate 1:1). - $^1\text{H-Nmr}$ (CDCl_3 , 300 MHz):

$\delta = 2.35\text{-}2.56$ (m; 2H), $2.67\text{-}2.87$ (m; 3H), 3.40 (s; 3H, OCH_3), 3.50 (s; 3H, OCH_3), 3.93 (d; 1H, $J = 12.78$ Hz), 4.89 (d; 1H, $J = 5.75$ Hz), 5.43 (d; 1H, $J = 8.9$ Hz), $7.14\text{-}7.28$ (m; 1H, aromat.), $7.33\text{-}7.50$ (m; 5H, aromat.), $7.54\text{-}7.60$ (m; 3H, aromat.), 9.42 (s; 1H, NH).

- Ir (KBr):

$\nu = 3320$ cm^{-1} (NH), 1670 (C=O, ketone), 1617 (C=O, amide). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.56; H, 6.29; N, 6.98.

N-Benzoyl-*N*-(2-hydroxyethyl)-{2,3,4,9-tetrahydrospiro[1*H*-carbazole-

1,2'-(1,3)dithiolan]-4-yl}amine (8): 3.0 g (10.89 mmol) of 2,3,4,9-tetrahydrospiro-[1*H*-carbazole-1,2'-[1,3]dithiolan]-4(9*H*)-one (**1**), 10 ml (162 mmol) of aminoethanol and 2.1 g (13 mmol) of FeCl_3 in 100 ml of benzene are heated for 24 h using a water trap. Then the solvent is evaporated, the residue is dissolved in 50 ml methanol/THF (1:1) and cooled in an ice bath. Under stirring 2.5 g (65 mmol) of NaBH_4 are added in several portions. The ice bath is removed and the mixture is stirred for 6 h under nitrogen atmosphere. After this 50 ml of 10% NaOH are added and the mixture is extracted three times with 50 ml of ethyl acetate. The combined organic layers are dried with MgSO_4 and the solvent is evaporated. The residue is dissolved in 50 ml of CHCl_3 and 3 ml (21.6 mmol) of triethylamine and 3 ml (25.8 mmol) of benzoyl chloride are added. The mixture is allowed to stir for 10 min at room temperature. Washing with 20 ml of 10% NaOH follows. The

organic layer is dried with MgSO_4 and evaporated under reduced pressure. The residue is chromatographed using silica gel and toluene/ethyl acetate (1:1). After evaporation of the solvent 2.20 g (47%) of the pure product are isolated. mp 221°C (ethyl acetate). Tlc: $R_f = 0.24$ (toluene/ethyl acetate 1:1). - $^1\text{H-Nmr}$ ($\text{CDCl}_3/\text{DMSO-d}_6$ 1:1, 300 MHz): $\delta = 2.14\text{--}2.58$ (m; 4H), $3.04\text{--}3.59$ (m; 4H), $3.65\text{--}3.51$ (m; 4H), 4.44 (t; 1H, $J = 5.22$, OH), $5.12\text{--}5.18$ (m; 1H), $7.02\text{--}7.59$ (m; 9H), 10.21 (s; 1H, NH). - Ir (KBr): $\nu = 3400\text{ cm}^{-1}$ (OH), 3200 (NH), 1619 (C=O). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2$: C, 65.07; H, 5.70; N, 6.60. Found C, 65.23; H, 5.90; N, 6.47.

4-[Benzoyl-(2-hydroxyethyl)amino]-2,3,4,9-tetrahydro-1H-carbazol-1-one (9): 2.50 g (5.88 mmol) of the thioketal (8) and 2.34 g (6.5 mmol) of benzeneseleninic anhydride are dissolved in 50 ml of CHCl_3 . 2.0 ml (24.8 mmol) of pyridine are added. The mixture is stirred under nitrogen atmosphere at room temperature. After 48 h washing with 20 ml of 10% NaOH follows. The organic layer is dried with MgSO_4 and the solvent is removed under reduced pressure. After crystallization from ether 1.26 g (62%) of the product are isolated. mp 207°C (ether). Tlc: $R_f = 0.54$ (ethyl acetate). - $^1\text{H-Nmr}$ (DMSO- d_6 , 300 MHz): $\delta = 2.21\text{--}2.23$ (m; 2H), $2.14\text{--}2.45$ (m; 1H), $2.70\text{--}2.75$ (m; 1H), $3.34\text{--}3.74$ (m; 4H), 4.72 (t; $J = 5.5$ Hz, OH), 5.00 (t; $J = 7.0$ Hz, 1H), $7.00\text{--}7.55$ (m; 9H, arom.), 11.10 (s; 1H, NH). - Ir (KBr): $\nu = 3440\text{ cm}^{-1}$ (OH), 3200 (NH), 1650 (C=O ketone) 1620 (C=O amide). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.13; H, 5.80; N, 7.86.

[Benzoyl-(1-oxo-2,3,4,9-tetrahydrocarbazol-1-one-4-yl)amino]acetaldehyde (10): 20 ml of CH_2Cl_2 and 0.36 ml (2 mmol) of oxalyl chloride are cooled to -60°C and 0.30 ml (4 mmol) of dimethyl sulfoxide are added. After stirring for 10 min 0.50 g (1.43 mmol) of alcohol (9), dissolved in 10 ml of CH_2Cl_2 and 5 ml of DMSO, is added slowly and the

mixture is stirred for 45 min. Finally 1.96 g (14 mmol) of triethylamine are added and the mixture is allowed to warm up to room temperature. 10 ml of CHCl_3 are added and extraction with three portions of CHCl_3 (30 ml each) follows. The combined organic layers are dried with MgSO_4 and the solvent is evaporated. After crystallization of the residue 0.36 g (72%) of the product are isolated. mp 211°C (THF/ethyl acetate). Tlc: $R_f = 0.42$ (toluene/ethyl acetate 1:1). - $^1\text{H-Nmr}$ (DMSO- d_6 , 270 MHz): $\delta = 2.32\text{--}2.38$ (m; 2H), 2.45-2.73 (m; 2H), 3.78 (d; $J = 17.9$ Hz, 1H), 4.15 (d; $J = 17.6$ Hz, 1H), 5.46 (t; $J = 7.6$ Hz, 1H), 7.17-7.71 (m; 9H, aromat.), 9.50 (s; 1H, CHO), 11.96 (s; 1H, NH). - Ir (KBr): $\nu = 3260\text{ cm}^{-1}$ (NH), 1732 (C=O, aldehyde), 1660 (C=O, ketone), 1619 (C=O, amide). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.66; H, 5.34; N 7.86.

2-Benzoyl-4-hydroxy-1,2,3,4,5,7-hexahydro-1,5c-methanoazocino[4,3-b]-indol-6-one (11): 0.35 g (0.86 mmol) of NaH (60% dispersion in oil) and 0.15 g (0.43 mmol) of the aldehyde (10) are dissolved in 30 ml of tetrahydrofuran and the mixture was stirred under nitrogen atmosphere for 3 h at 50°C . Then the mixture is cooled in an ice bath and 5 ml of 5% HCl are added. After extraction with 30 ml of CHCl_3 the organic layer is washed with 10 ml of 5% NaHCO_3 solution, dried with MgSO_4 and the solvent is evaporated. After purification of the residue by chromatography using silica gel and ethyl acetate/ CHCl_3 (3:1) 0.087 g (58%) of 11 (mixture of epimeric alcohols) are isolated. mp 285°C (decomp.) (acetone). Tlc: $R_f = 0.24$ (ethyl acetate/ CHCl_3 3:1). - $^1\text{H-Nmr}$ (CDCl_3 , 270 MHz): $\delta = 2.26$ (d; $J = 13.06$ Hz, 1H), 2.64-2.74 (t; 2H, $J = 11.9$ Hz), 2.79 (s; 1H, OH), 3.11 (s; 1H), 3.77 (t; $J = 6.4$ Hz, 1H), 4.12 (d; $J = 5.15$ Hz, 1H), 6.44 (m; 1H), 7.08-7.67 (m; 8H, aromat.), 7.97 (d; $J = 7.6$ Hz, 1H), 9.34 (s; 1H, NH). - Ir (KBr): $\nu = 3570\text{ cm}^{-1}$ (OH), 3170 (NH), 1670 (C=O, ketone), 1616 (C=O, amide). -

Ms: 346 (57) [M^+], 225 (5), 213 (32), 184 (100), 166 (10), 154 (7), 105 (29), 77 (16). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.54; H, 5.28; N 8.16.

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Received, 6th February, 1995