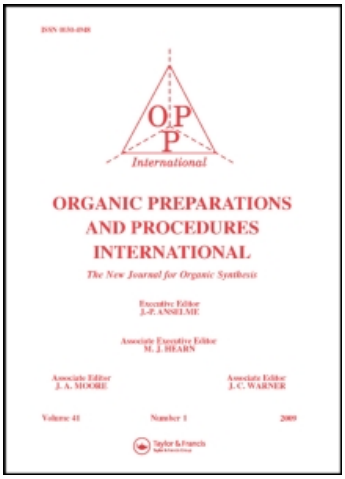


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# SYNTHESIS OF THE DASYCARPIDONE SKELETON

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# SYNTHESIS OF THE DASYCARPIDONE SKELETON

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(06/25/02)

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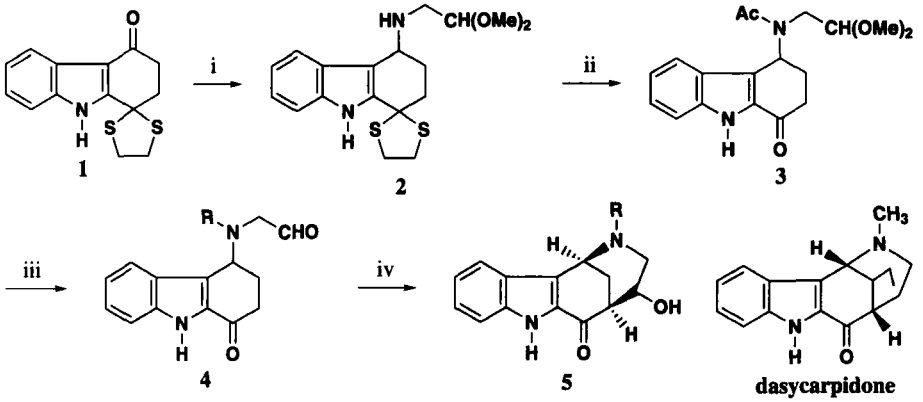
The tetracyclic ring skeleton of indole alkaloids (*e.g.* **5**) often serves as a key intermediate for the synthesis of pentacyclic strychnos alkaloids such as dasycarpidone.[1] The recent conversion *N*-benzoyl-(2,3,4,9-tetrahydrocarbazole-1-one-4-yl)amino]acetaldehyde (**4b**) to the azocino-[4,3-b] indole (**5b**) (*Scheme 1*)[2] suggests that this compound might provide a facile entry




a) R = $CH_3CO$ b) R = PhCO

i) $H_2NCH_2CH(OMe)_2$, then $NaBH_4$ ii) $Ac_2O$, then $(PhSeO)_2$) iii) $BBr_3$, –70°C iv) NaH

**Scheme 1**

into these types of core structures. Since the preparation of **4b** involves five steps starting from **1** and proceeds in only 12% overall yield,[2] we sought a shorter and more efficient route to the *N*-acetyl analogue (**4a**). *In situ* reduction of imine **2**, generated from **1**[3] by reaction with aminoacetaldehyde dimethyl acetal and tin(II) chloride in benzene,[3] gave **2** which was acetylated[4] prior to removal of the thioketal group to afford **3**.[5] Cleavage of the acetal group[6] gave **4a** in 20% overall yield (from **1**); upon treatment of **4a** with sodium hydride, compound **5a** was obtained in 65% yield as an epimeric mixture.

## EXPERIMENTAL SECTION

Melting points determined on Gallenkamp capillary melting point apparatus and are uncorrected. The $^1$H-NMR spectra were obtained on a Bruker WH- 400 NMR spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on Hitachi 270-30 IR spectrometer. Mass spectra were determined on the electron impact mode by direct insertion at 70eV with a LC-MS spectrometer. Analytical and preparative thin-layer chromatographies were carried out by using 70-230 mesh silica gel (0.063-0.2 mm, Merck).

**(2,2-Dimethoxyethyl)-{2,3,4,9-tetrahydrospiro[1H-carbazole-1,2'(1,3)dithiolan]-4-yl}amine (2).**- A mixture of 5.0 g (18.3 mmoles) of **1**, 5 mL (46 mmoles) of aminoacetaldehyde dimethyl acetal and 3.0 g (15.8 mmoles) of tin(II) chloride in 150 mL of benzene was heated for 6 hrs using a Dean-Stark trap to remove the water. The progress of the reaction was monitored by TLC (ethyl acetate). Evaporation of the solvent gave a solid which was dissolved in methanol-tetrahydrofuran (1:1) and cooled in an ice bath. Then with stirring, 3.0 g (79.3 mmoles) of sodium borohydride was added in several portions. The ice bath was removed and the mixture was stirred for 6 hrs under nitrogen atmosphere. Evaporation of the solvent under reduced pressure left a residue which was dissolved in ethyl acetate. After washing with 100 mL 10% sodium hydroxide, the solvent was evaporated and the residue was purified by chromatography on silica gel, and eluted with dichloromethane-ethyl acetate (3:1) to give 3.7 g (55%) of **2** as a colorless oil. TLC: $R_f$ 0,48 (ethyl acetate). IR (NaCl): 3390 (NH) cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.90-2.20 (m, 4H), 2.50 (s, 1H, NH), 2.89 (s, 3H, $OCH_3$), 3.18 (s, 3H, $OCH_3$), 3.32-3.59 (m, 4H,-$SCH_2CH_2S$-), 3.61-3.78 (m, 2H), 4.18 (t, 1H, J = 8.7Hz), 5.24 (t, 1H, J=7.9Hz), 7.25-7.46 (m, 3H, ArH), 7.59 (d, 1H, ArH), 8.61 (s, 1H, NH indole).



**N-Acetyl-N-(2,2-dimethoxyethyl-{2,3,4,9-tetrahydrospiro[1H-carbazole-1,2'-(1,3)dithiolan]-4-yl}amine (2a).**- A solution of 2 mL (21.2 mmoles) of acetic anhyride in chloroform was added dropwise into a solution of 3.7 g (10.1 mmoles) of **2** in 30 mL of chloroform and 2 mL (14.2 mmoles) of triethylamine. The mixture was stirred for 30 minutes at room temperature. After extraction with 25 mL of 10% sodium hydroxide, the organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate to afford 4.02 g (98%) of a colorless solid, mp 150°C. TLC: $R_f$ 0.39, (ethyl acetate). IR (KBr): 3240 (NH), 1620 (C=O,amide) cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 2.07-2.29 (m, 2H), 2.31 and 2.36 (2s, 3H, two rotamers, $CH_3CO$), 2.40-2.79 (m, 2H), 3.10 (s, 3H, $OCH_3$), 3.21 (s, 3H, $OCH_3$), 3.29 and 3.36 (2s, 2H, two rotamers), 3.47-3.67 (m, 4H, -$SCH_2CH_2S$-), 4.10 and 4.76 (2t, 1H, two rotamers, J = 5.36 Hz and J = 5.08 Hz), 5.18 and 6.15 (2t, 1H, two rotamers, J = 7.4 Hz and J = 7.6 Hz),7.01-7.35 (m, 4H, ArH), 8.41 (brs, 1H, NH indole).

*Anal.* Calcd for $C_{20}H_{26}N_2O_3S_2$: C, 59.08; H, 6.45; N, 6.89. Found: C, 58.90; H, 6.51; N, 7.01

**4-[Acetyl-(2,2-dimethoxyethyl)amino]-2,3,4,9-tetrahydro-1H-carbazole-1-one (3a).**- A mixture of 1.0 g (2.5 mmoles) of the thioketal **2a** and 1.9 g (5.2 mmoles) of benzeneseleninic anhydride in 50 mL of anhydrous tetrahydrofuran, and 2 mL of pyridine was stirred under

nitrogen atmosphere at room temperature for 48 hrs. After extraction with 30 mL of 10% sodium hydroxide, the organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel and eluted with chloroform. After evaporation of the solvent, 0.56 g (69%) of the pure product was isolated as a white solid and crystallized from diethyl ether, mp 117°C. TLC: $R_f$ 0.35 (chloroform). IR (KBr): 3150 (NH), 1670 (C=O ketone), 1620 (C=O, amide) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.37 (s, 3H, $CH_3CO$), 2.39-2.87 (m, 4H), 3.21 (s, 3H, $OCH_3$), 3.24 (s, 3H, $OCH_3$), 3.52 (d, 1H, J = 9.4 Hz), 3.68 (d,1H, J = 9.1 Hz), 4.22 and 4.77 (2t, 1H, two rotamers, J = 5.17 Hz and J = 5.12 Hz), 5.36 and 6.31 (2t, 1H, two rotamers), 7.1-7.53 (m, 4H, ArH), 9.78 and 9.86 (2s, 1H, two rotamers, NH indole).

*Anal.* Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.38; H, 6.78; N, 8.43

**[Acetyl-(2,3,4,9-tetrahydrocarbazole-1-one-4-yl)amino]acetaldehyde (4a).**- To a solution of 1.5 g (4.5 mmoles) of **3a** in 50 mL of dichloromethane, cooled to -70°C, was added dropwise 9.1 mL (9.1 mmoles) of boron tribromide (1.0 M solution in dichloromethane). After 45 minutes of stirring, the mixture was poured into 50 mL 10% of sodium carbonate. After extraction with 50 mL of dichloromethane, the organic layer was dried over magnesium sulfate and the solvent was evaporated. Crystallization of the residue (oil) from diethyl ether afforded 0.70 g (55%) of colorless solid, mp 188°C. TLC: $R_f$ 0.57 (chloroform). IR (KBr): 3170 (NH), 1730 (C=O, aldehyde), 1664 (C=O, ketone), 1620 (C=O, amide) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.16-2.23 (m, 1H), 2.39 (s, 3H, $CH_3CO$), 2.41-2.80 (m,3H), 3.46 and 3.93, 3.97, 4.29 (4d, 2H, two rotamers), 5.65 and 6.30 (2t, 1H, two rotamers, J = 7.54 Hz and J = 7.31 Hz), 7.02-7.07 (m, 1H, ArH), 7.23-7.45 (m, 3H, ArH), 9.34 and 9.46 (2s, 1H, two rotamers, aldehyde), 11.69 and 11.78 (2s, 1H, two rotamers, NH indole).

*Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.62; H, 5.71; N, 9.89

**2-Acetyl-4-hydroxy-1,2,3,4,5,7-hexahydro-1,5-methanoazocino[4,3b]indole-6-one (5a).**- A solution of 1.3 g (4.6 mmoles) of aldehyde **4a** in tetrahydrofuran was added into a suspension of 600 mg (15.0 mmoles) of sodium hydride (60% dispersion in oil) in 40 mL of tetrahydrofuran. The mixture was stirred under nitrogen atmosphere at room temperature for 20 hrs. Then 10 mL of methanol was added and the mixture was poured in 50 mL of 5% hydrochloric acid. After extraction with chloroform, the organic layer was dried over magnesium sulfate and solvent was evaporated. The residue was chromatographed on silica gel and eluted with ethyl acetate. After evaporation of the solvent, 0.84 g (65%) of the pure product was isolated and crystallized from isopropyl ether, mp 244°C. TLC: $R_f$ 0.48 (ethyl acetate). IR (KBr): 3344 (OH), 3174 (NH), 1666 (C=O, ketone), 1622 (C=O,amide); $^1H$ NMR (DMSO-$d_6$): δ 1.87 (s, 3H, $CH_3CO$), 2.02 (t, 1H, J = 12.49 Hz), 2.25-2.50 (m, 2H), 2.77-2.79 (m, 1H), 3.37 (br s, 1H, OH), 3.55-3.60 and 3.75-3.79 (m, 1H and m, 0.5 H, two rotamers), 3.89-3.95 and 4.06-4.23 (m, 1H and m, 0.5 H, two rotamers), 5.36 and 5.91 (2 br s, 0.5H and 1H, two rotamers), 6.99 and 7.05 (2t, 1H and 05 H, J = 7.47 Hz, J = 7.51 Hz, two rotamers, ArH), 7.19-7.25 (m, 1H, ArH), 7.35-7.40 (m, 1H, ArH), 7.49 and 7.54 (2d, 1H and 0.5 H, ArH, J = 8.08 Hz and 8.10 Hz), 10.93 (br s, 1H, NH indole). $^{13}C$

NMR (DMSO-$d_6$): δ 22.6, 34.2, 46.2, 49.9, 68.3, 113.7, 121.2, 122.2, 123.8, 124.6, 127.1, 129.2, 134.43,138.9, 169.5, 190.5. MS (70 eV): m/z (%) 284 ($M^+$,21), 213 (13), 184 (100), 166 (30), 154 (43), 128 (29), 115 (17), 102, (20) 77 (28), 55 (23), 51 (24).

*Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.69; N, 9.84

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