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MODELS OF FOLATE COFACTORS - 24[1a]
A ROUTE TO OPTICALLY ACTIVE OCTAHYDROINDOLO[2,3-a]QUINOLIZINES

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Abstract: L-(-)-Tryptophane derivatives react with 2-(3,3-dimethyl-3-ethoxycarbonyl-2-oxo-propyl)hexahydropyrimidine [N(5),N(10)-methylenetetrahydrofolate model] to form optically active enamino esters. The latter cyclize under basic conditions to give indolylethylpyridinediones, which, upon treatment with acids give the title compounds.

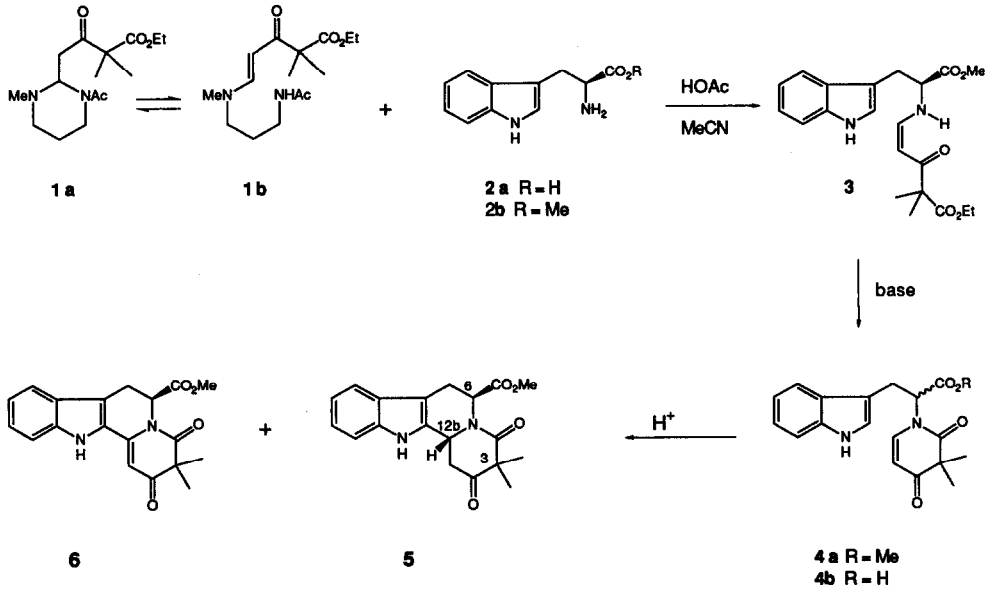
In recent years we have reported the application of 2-substituted imidazolidines, as N(5),N(10)-methylene-tetrahydrofolate models, in the synthesis of several classes of indole alkaloids[1b]. As a part of our interest in extending the scope of the group-transfer strategy based on the function of folate coenzymes, to chiral synthesis, we had earlier described the synthesis of enantiomerically pure pyrrolo[2,3-d]carbazole[3]. In this communication we present a route to the expedient stereoselective synthesis of the optically active indoloquinolizine skeleton.

It has been previously shown in our laboratory that, in analogy with the corresponding imidazolidines, the 2-substituted perhydropyrimidine derivatives can also function as folate models in group-transfer reactions[1c]. A typical example of such a model is represented by the pyrimidine derivative **1a**. It should be noted that under acidic or basic conditions, **1a** is in equilibrium with the enamino ketone form **1b**[1d]. As a consequence of this, it is implicit that under the commonly employed acidic conditions for the group-transfer process, the reaction would proceed via **1b**.

It was envisioned that a group-transfer reaction from **1b** to the L-tryptophane system would lead to an intermediate which would contain the complete carbon fragment and the required functionalization for its facile conversion to the target indoloquinolizine. A preliminary study of the reaction of optically active L-(-)-tryptophane (**2a**) with *in situ* generated **1b**, under the standard conditions for the group-transfer reaction (AcOH/MeCN, Δ), did not, however, result in any of the expected product. This may be attributed to an extremely slow reaction, due to the insolubility of the amino acid under the employed conditions. That this was indeed the reason for the lack of reactivity became obvious when the corresponding ester **2b** was employed in the reaction, whereupon, the transfer-product (**3**) was formed in 69% yield (Scheme 1). Compound **3** was optically active, exhibiting a specific rotation of -177°. Although the enantiomeric purity of **3** has not been established at present, the results clearly show that the chirality of the optically active amino acid substrate is retained during the reaction. The **Z**-configuration of the olefinic bond in **3** follows from the coupling constant (7.7 Hz) between the two vinylic protons and is presumably related to the favourable hydrogen-bonding in the (**Z**) molecule.

The subsequent step in the sequence required an (base-mediated) intramolecular aminolysis of the ester function in **3**. Use of NaH/THF at 0° did result in the formation of the expected product **4a**; however, this was

accompanied by large amounts of the corresponding acid (**4b**). More significantly, both products were optically inactive, indicating that the chiral centre is racemized during the reaction, owing to the lability of the α-ester [C(6)]-proton, under the basic reaction conditions. When the cyclization was carried out under milder conditions (potassium carbonate/DMF), the hydrolysis of the ester function was, as anticipated, suppressed; although, once again, the ester (**4a**) formed was devoid of optical activity.



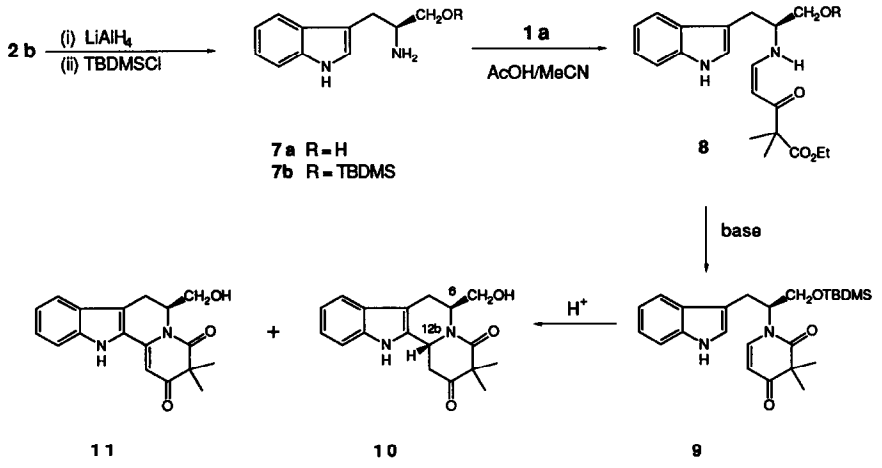
Scheme 1

The stereochemistry of cyclization of the pyridinedione system - to the target indoloquinolizine -was examined using a sample of racemic **4a**. When **4a** was subjected to an acid catalyzed cyclization, employing HCl (g), under conditions where oxygen was (attemptedly) excluded, the products of the reaction were: (i) a racemate of diastereomer **5** (5%) and (ii) the corresponding oxidized derivative **6** (76%). The latter is clearly derived via the oxidation of the initially formed product **5**, by the oxygen present as a contaminant in the HCl (g). The sensitivity of systems of type **5** to air oxidation is well known[4]. The observed oxidation could be prevented by carrying out the reaction in the presence of a catalytic amount of concentrated sulphuric acid, instead of HCl. Under these conditions, the reaction led to the formation of the same racemic diastereomer (**5**) in 52% yield. The stereochemical assignment in **5** is based on NOE difference experiments. Irradiation of of the C(6)-H (δ 5.98, d) did not shown any enhancement of the signal for the C(12b)-H, implying a trans relationship between the two hydrogens. The isolation of a single diastereomer suggests a high stereoselecivity for the cyclization process.

The racemization of the chiral center during the conversion of **3** to **4a** is, as has been pointed out earlier, a consequence of the high acidity of the C(6)-proton. In order to prevent the deprotonation process, the electron-withdrawing ester function was reduced ($LiAlH_4$)[5] to the corresponding alcohol (**7a**), which was subsequently

protected as its crystalline TBDMS derivative **7b**.

The group-transfer from **1b** to **7b** was achieved in good yield (63%), under the standard reaction conditions (AcOH/MeCN, Δ). The resulting product **8** was subsequently cyclized (K_2CO_3/DMF, 60° C; quantitatively) to give optically active **9**. This product was found to be enantiomerically pure within limits of its NMR analysis, employing a chiral shift reagent[6]. The ^{1}H-NMR spectrum of **9** did not exhibit the splitting of signals - upon addition of the chiral shift reagent [Eu(hfc)$_3$] - as would have been the case had **9** been a racemate. The formation of **9** vindicates the idea that the conversion of the ester group into the (protected) hydroxyl function prevents the loss of configurational integrity at C(6), during the basic ring-closure step.



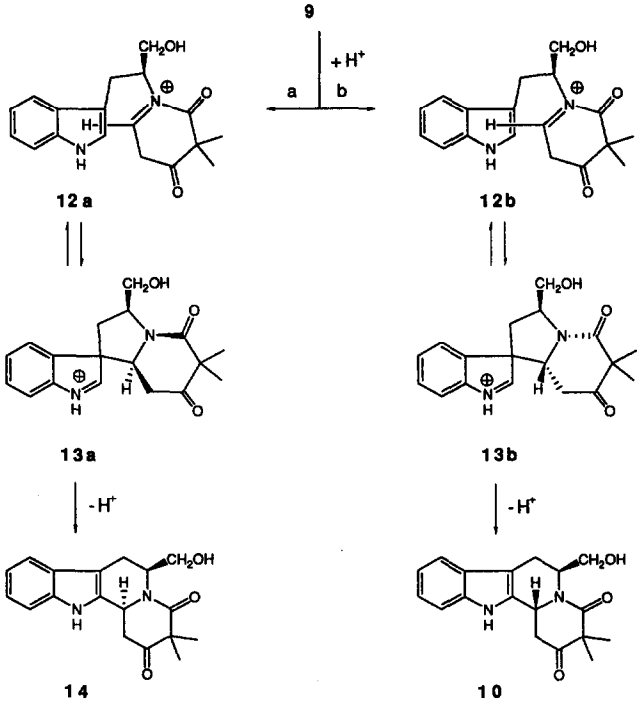
Scheme 2

The cyclization of **9**, in the presence of concentrated sulphuric acid, proceeded quantitatively to the single, optically active diastereomer **10** [$(\alpha)^{20}_D$ = +149°, c = 0.08, $CHCl_3$]. Not unexpectedly, the TBDMS group is cleaved under the acidic reaction conditions. Once again, it is noteworthy that the cyclization process is highly stereoselective. The cis relationship between C(12b)-H and the C(6)-CH_2OH group is attested by the enhancement of the signal of one of the (hydroxy)-methylene protons, upon irradiation of the C(12b)-hydrogen at δ 5.04 (br.d). It is also significant that irradiation of the C(6)-H did not affect the C(12b)-H in an nuclear Overhauser experiment.

In contrast to the formation of **10** , from **9**, in the presence of sulphuric acid; the use of HCl (g) for the same transformation (of **9**) led to **11** as the major (70%) isolable compound from the reaction mixture, in addition to **10** as a minor product.

The stereochemistry of the last step of the sequence leading to the indoloquinolizine skeleton of compounds **5** and **10** can be understood by considering the mechanism of the Pictet-Spengler cyclization (Scheme 3). The Pictet-Spengler reaction is generally assumed to proceed via a spiroindolenine inermediate[7], which is formed by a nucleophilic attack of the enamine double bond of the indole nucleus on the (generated) iminium ion intermediate. The formation of this spiro intermediate is rapid and reversible[8], and the stereochemistry of the transition state of

the cyclization reaction is favoured by a trans antiparallel relationship between the attacking nucleophile and the developing lone-pair of electrons on the nitrogen[9]. In the subsequent rearrangement step of the spiro intermediate to the β-carboline system, the stereochemistry is expected to be retained.



Scheme 3

The stereospecificity of the Pictet-Spengler condensation with tryptophane derivatives has been investigated[10] and it has been shown that the reaction of methyl N_b-benzyltryptophanate with aldehydes leads specifically to trans 1,3-disubstituted tetrahydro-β-carbolines[11]. These results have been ascribed to the unfavourable steric interactions in the all-cis spiro intermediate, which is formed by attack of the enamine moiety on the β-face of the iminium intermediate.

The stereochemical outcome of the acid catalyzed cyclization of **4a** and **9** can be explained on the basis of the aforementioned mechanistic rationalization[10a]. According to path (a) (**12a**, Scheme 3), the iminium ion approaches the α-face of the indole ring, with the nucleophile entering trans with respect to the developing lone-pair of electrons. The tri-substituted spiro intermediate thus formed involves an all-cis geometry of three contiguous substituents (**13a**), which would be sterically unfavourable to accomodate. On the other hand, in pathway (b) (**12b**), the indole nucleus is approached at its β-face by the iminium system, thereby resulting in spiroindolenine **13b** in which the hydroxymethylene group is trans to the other two substituents. Since this intermediate is sterically favoured in comparison to **13a**, rearrangement leads to β-carboline **10** (and **5**) with the observed stereochemistry.

Experimental

Chromatographic separations were carried out by means of flash chromatography on freshly filled silica gel (230-400 mesh) columns, following literature procedure.[12] All m.ps are uncorrected. Infrared spectra were recorded on a Perkin Elmer 257 or 298 spectrometer. The absorbtions are given in cm^{-1}. ^{1}H-NMR measurements were performed on Varian A-60, HA-100 or XL-100 instruments or on Brucker WM-250 or AC-200 instruments. ^{13}C-NMR spectra were recorded on the Brucker WM-250 or AC-200 instruments. The chemical shifts are given in ppm downfield from tetramethylsilane. Unless stated otherwise IR and NMR spectra are taken in $CHCl_3$ and $CDCl_3$, respectively. Exact mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF. The IUPAC nomenclature is used in naming the compounds.

Ethyl 5-((1S)-2-(3-indolyl)-1-methoxycarbonyl)-ethylamino-2,2-dimethyl-3-oxo-4-pentenoate (**3**)

The HCl-salt of the methyl ester of tryptophane **2b** (35.3 mmol, 8.98 g) and 35.3 mmol (10.52 g) of **1a** were suspended in 200 ml of acetonitrile and 20 ml of acetic acid. The mixture was refluxed for 90 minutes and concentrated under vacuum. The residue was dissolved in ethyl acetate and washed with 10 % $NaHCO_3$ solution and with saturated NaCl solution. The solution was dried over $MgSO_4$. After addition of silica gel the mixture was concentrated under vacuum. The powder was brought on top of a silica gel column for chromatography with ethyl acetate/petroleum ether 60-80 as eluent. 9.5 g of the product **3** (69 %) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$, 250 MHz): 1.23 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.36 (s, 6H, 2 x C(3)CH_3), 3.13 (dd, 1H, J = 8.1 and 14.4 Hz, $CH_2CH(CO_2Me)NH$), 3.34 (dd, 1H, 4.8 and 14.5 Hz, $CH_2CH(CO_2Me)NH$), 3.71 (s, 3H, CO_2CH_3), 4.05-4.19 (mp, 3H, $CO_2CH_2CH_3$ and $CH_2CH(CO_2Me)NH$), 4.91 (d, 1H, J = 7.7 Hz, NCH=CHC(=O)), 6.40 (dd, 1H, J = 7.7 and 12.7 Hz, NCH=CHC(=O)), 7.02 (d, 1H, J = 2.3 Hz, C(2)H indole), 7.08-7.22 (mp, 2H, C(5)H and C(6)H indole), 7.35 (d, 1H, J = 7.8 Hz, C(7)H indole), 7.54 (d, 1H, J = 7.7 Hz, C(4)H indole), 8.20 (br.s, 1H, NH indole), 9.86 (br.dd, 1H, NHCH=CHC(=O)). **IR** ($CHCl_3$): 3480 (m), 1740 (s), 1720 (s), 1630 (s), 1560 (s). $[\alpha]^{20}_D = -177^o$ ($CHCl_3$, c = 0.023 g/ml).

1-(2-(3-Indolyl)-1-methoxycarbonyl)-ethyl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-dioxopyridine (**4a**)

Compound **3** (910 mg) and 1.0 eq K_2CO_3 (325 mg) were dissolved in 30 ml of dry DMF and refluxed for 5 h. The mixture was concentrated under vacuum and 595 mg of the product (74 %) was isolated after flash chromatography (ethyl acetate/petroleum ether 60-80 1:2 → 1:1).

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.08 and 1.34 (2 x s, 2 x 3H, $C(CH_3)_2$), 3.43 (dd, 1H, J = 10.6 and 15.2 Hz, 1 x $CH_2CH(CO_2Me)N$), 3.62 (dd, 1H, J = 5.0 and 15.2 Hz, 1 x $CH_2CH(CO_2Me)$, 3.79 (s, 3H, CO_2CH_3), 5.25-5.35 (mp, 1H, $CH_2CH(CO_2Me)N$), 5.32 (d, J = 8.5 Hz, NCH=CHCO), 6.93 (d, J = 8.5 Hz, NCH=CHC(=O)), 6.99 (d, 1H, J = 1.9 Hz, C(2)H indole), 7.09-7.22 (mp, 2H, C(5)H and C(6)H indole), 7.35 (d, 1H, J = 7.8 Hz, C(7)H indole), 7.54 (d, 1H, J = 7.7 Hz, C(4)H indole), 8.14 (br.s, 1H, NH indole). **IR** ($CHCl_3$): 3480(m), 1740(s), 1700(s), 1655 (s), 1620(s). **MS** exact mass: found 326.1285 (calculated for $C_{18}H_{18}N_2O_4$ 326.1266).

1-(1-Carboxy-2-(3-indolyl))-ethyl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-dioxopyridine (**4b**)

Sodium hydride (52 mg of a 60 % suspension in oil, 1.3 mmol) was added to a solution of 1.3 mmol **3** (506 mg) in THF. The mixture was stirred overnight at room temperature and after 20 h a 10 % $NaHCO_3$ solution was added to the clear reddish brown reaction mixture. Extraction with ethyl acetate gave the basic organic layer. The water layer was acidified with 3 M HCl to pH = 1 and extracted with ethyl acetate, this gave the acid organic layer. Both fractions were dried over $MgSO_4$ and concentrated under vacuum. The basic fraction gave 156 mg of the ester **4a** as a white foam (35 %). The acid fraction gave 199 mg of the acid **4b** (46 %) as a reddish brown foam.

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.08 and 1.34 (2 x s, 2 x 3H, $C(CH_3)_2$), 3.42 (dd, 1H, J = 10.6 and 15.2 Hz, 1 x $CH_2CH(CO_2Me)N$), 3.66 (dd, 1H, J = 5.0 and 15.2 Hz, 1 x $CH_2CH(CO_2Me)N$), 4.80-5.20 (br.s, 1H, COOH), 5.25-5.35 (mp, 1H, $CH_2CH(CO_2Me)N$), 5.32 (d, J = 8.3 Hz, NCH=CHC(=O)), 6.93 (d, J = 8.3 Hz, NCH=CHC(=O)), 6.99 (d, 1H, J = 2.1 Hz, C(2)H indole), 7.09-7.22 (mp, 2H, C(5)H and C(6)H indole), 7.35 (d, 1H, J = 7.4 Hz, C(7)H indole), 7.54 (d, 1H, J = 7.3 Hz, C(4)H

indole), 8.14 (br.s, 1H, NH indole). **IR** ($CHCl_3$): 3480 (m), 3500-3200 (br.w), 1730(s), 1700(s), 1650 (s), 1620(s).

3,3-Dimethyl-2,4-dioxo-6-methoxycarbonyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizine (**5**)

Acid **4b** (0.51 mmol, 168 mg) was dissolved in 20 ml of dry MeOH. After addition of a few drops of 95 % H_2SO_4 the reaction mixture was refluxed overnight and after concentrating under vacuum the residue was taken up in ether and washed with sat. $NaHCO_3$ to remove the acid. The organic layer was dried over $MgSO_4$ and concentrated under vacuum and chromatographed over silica gel (ethyl acetate/petroleum ether 60-80 1:2). The product was obtained (92 mg, 52 %) as a brown oil.

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.47 and 1.50 (2 x s, 2 x 3H, C(3)$(CH_3)_2$), 2.77 (dd, 1H, J = 12.4 and 16.1 Hz, C(1)H_{ax}), 3.10-3.22 (mp, 2H, C(1)H_{eq}, C(7)H), 3.54 (d, 1H, J = 16.0 Hz, C(7)H), 3.62 (s, 3H, OCH_3), 5.38 (br.d, 1H, J = 12.4 Hz, C(12b)H), 5.98 (d, 1H, J = 5.1 Hz, C(6)Heq), 7.12-7.20 (mp, 2H, C(9)H, C(10)H), 7.35 (d, 1H, J = 7.3 Hz, C(11)H), 7.56 (d, 1H, J = 7.1 Hz, C(8)H), 8.15 (br.s, 1H, NH). **IR** ($CHCl_3$): 3460 (m), 1730 (s), 1650 (s), 1600 (m), 1410 (s). **MS** (FD 10 mA): 340.

3,3-Dimethyl-2,4-dioxo-2,3,4,6,7,12-hexahydro-6-methoxycarbonyl-indolo-[2,3-a]quinolizine (**6**).

Ester **4a** (1.70 mmol, 580 mg)was dissolved in 25 ml of dry MeOH. Nitrogen gas was led through the solution during one hour to remove oxygen. Then HCl gas (from a cylinder) was led through the solution during one half hour, upon which the reaction mixture turned red. The reaction mixture was stirred overnight under a nitrogen atmosphere at room temperature. Work up was done as above. This furnished 442 mg (76 %) of the product as yellow crystals (mpt 124-125 °C). Beside the main product 54 mg of the non-oxidized compound **5** could be isolated (9 %).

^{1}H-NMR ($CDCl_3$, 250 MHz): 1.58 and 1.60 (2 x s, 2 x 3H, C(3)$(CH_3)_2$), 3.35 (dd, 1H, J = 6.7 and 17.0 Hz, C(7)H_{ax}), 3.62 (s, 3H, OCH_3), 3.90 (dd, 1H, J = 1.3 and 17.0 Hz, C(7)H_{eq}), 5.79 (d, 1H, J = 5.4 Hz, C(6)Heq), 6.38 (s, 1H, C(1)H), 7.16 (t, 1H, J = 7.4 Hz, C(10)H), 7.36 (t, 1H, J = 7.0 Hz, C(9)H), 7.53 (d, 1H, J = 7.4 Hz, C(11)H), 7.60 (d, 1H, J = 7.0 Hz, C(8)H), 10.60 (br.s, 1H, NH). **IR** ($CHCl_3$): 3460 (w), 3370 (br.s), 1740 (s), 1690 (s), 1620 (m), 1595 (s). **MS** (FD 10 mA): 338.

(2S)-3-(3-Indolyl)-2-aminopropanol (**7a**)

(L)-(-)-Tryptophane·HCl (4.0 g) was added to a suspension of 3.0 g $LiAlH_4$ in 250 ml of THF at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed overnight. The mixture was cooled in an ice-bath and a saturated $NaSO_4$ solution was added carefully. The salts were filtered off and after concentration under vacuum the residue was dissolved in chloroform, washed with brine and the organic layer was dried over $MgSO_4$. After concentration under vacuum the alcohol was obtained as a colourless foam (2.68 g, 72 %).

^{1}H-NMR (D_6-DMSO, 250 MHz): 2.05-2.37 (mp, 3H, C(2)H and 2 x C(3)H), 2.77 (dd, 1H, J = 6.6 and 10.2 Hz, 1 x C(1)H), 2.90 (dd, 1H, J = 4.8 and 10.2 Hz, 1 x C(1)H), 6.48-6.63 (mp, 2H, C(5)H and C(6)H indole) 6.88 (d, 1H, J = 8.0 Hz, C(7)H indole), 7.09 (d, 1H, J = 7.7 Hz, C(4)H indole), 10.37 (s, 1H, NH indole). **IR** ($CHCl_3$): 3480 (s), 3350 (br.m).

Ethyl 5-[(1S)-1-tert-butyl-dimethylsilyloxymethyl-2-(3-indolyl)-ethyl]amino-2,2-dimethyl-3-oxo-4-pentenoate (**8**)

Compound **7b** derived from **7a** (3.25 mmol) and model **2** (1 eq) were refluxed in a mixture of acetonitrile and acetic acid (25 and 2.5 ml, respectively) under a nitrogen atmosphere. According to TLC the starting compounds disappeared in 3 h. The reaction mixture was concentrated under vacuum dissolved in ethyl acetate and washed with a sat. sodium bicarbonate solution and with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The mixture was chromatographed with ethyl acetate/petroleum ether 60-80 1:1 whereupon compound **8** was obtained as a colourless oil (784 mg, 51%).

^{1}H-NMR ($CDCl_3$, 250 MHz): 0.01 (s, 6H, Si$(CH_3)_2$), 0.88 (s, 9H, SiC$(CH_3)_3$), 1.21 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.34 (s, 6H, C$(CH_3)_2$), 2.85 (dd, 1H, J = 7.6 and 14.5 Hz, 1 x (indole-CH_2), 3.08 (dd, 1H, J = 5.6 and 14.5 Hz, 1 x indole-CH_2), 3.37-3.46 (mp, 1H, CH_2CHCRNHR), 3.55 (dd, 1H, J = 6.2 and 10.1 Hz, 1 x CH_2OSi), 3.67 (dd, 1H, J = 5.0 and 10.1 Hz, 1 x CH_2OSi), 4.12 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.86 (d, 1H, J = 7.5 Hz, NCH=CHC(=O)), 6.60 (dd, 1H, J = 7.5 and 12.9 Hz, NCH=CHC(=O)), 7.00 (d, 1H, J = 2.2 Hz, C(2)H indole), 7.06-7.19 (mp, 2H, C(5)H and C(6)H indole), 7.33 (d, 1H, J = 7.8 Hz, C(7)H indole), 7.53 (d, 1H, J = 7.7 Hz, C(4)H indole), 8.13 (s, 1H, NH indole), 9.75 (br.mp, 1H, NHCH=CHCO). **IR** ($CHCl_3$): 3480 (s), 1720(s), 1630(s), 1560(s), 835(s).

From the reaction mixture, the corresponding hydroxy compound was also isolated (yield 5%).

Ethyl 5-[(1S)-1-hydroxymethyl-2-(3-indolyl)-ethyl]amino-2,2-dimethyl-3-oxo-4-pentenoate **(8; R=H)**

^{1}H-NMR (250 MHz, $CDCl_3$): 1.21 (t, 3H, J = 7.1 Hz, $OCH_2\underline{CH_3}$), 1.35 (s, 6H, $C(\underline{CH_3})_2$), 2.89 (dd, 1H, J = 7.2 and 14.5 Hz) and 3.02 (dd, 1H, J= 5.3 and 14.5 Hz) both indole-$\underline{CH_2}$, 3.44-3.59 (mp, 2H, 1 x CH_2OSi and $CH_2\underline{CH}RNH$), 3.71 (dd, 1H, J = 3.9 and 10.8 Hz, 1 x CH_2OSi), 4.13 (q, 2H, J = 7.1 Hz, $O\underline{CH_2}CH_3$), 4.90 (d, 1H, J = 7.5 Hz, NCH=C$\underline{H}$CO), 6.63 (dd, 1H, J = 7.5 and 12.8 Hz, NC$\underline{H}$=CHCO), 6.97 (d, 1H, J = 2.3 Hz, C(2)H indole), 7.08-7.19 (mp, 2H, C(5)H and C(6)H indole), 7.33 (d, 1H, J = 7.8 Hz, C(7)H indole), 7.51 (d, 1H, J = 7.7 Hz, C(4)H indole), 8.30 (s, 1H, NH indole), 9.75-9.81 (br.mp, 1H, N$\underline{H}$CH=CHCO). **IR** ($CHCl_3$): 3480 (s), 3420 (br.m), 1720 (s), 1630 (s), 1560 (s).

1-[(1S)-1-(t-Butyl-dimethylsilyloxymethyl)-2-(3-indolyl)]ethyl-1,2,3,4-tetra-hydro-3,3-dimethyl-2,4-dioxopyridine **(9)**

Enaminone **8** (1.158 g) was stirred with 1.1 eq K_2CO_3 (363 mg) in 40 ml of DMF for 4 h under reflux. The reaction mixture was concentrated under vacuum and the residue dissolved in ethyl acetate. The organic layer was washed once with water and twice with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in some ether and left overnight at -20 °C. The product could be isolated as white crystals (400 mg, 39 %, mpt 138-139 °C) after filtration. Concentration of the mother liquor yielded yellow crystals (561 mg, 53 %, mpt. 138-139 °C).

^{1}H-NMR ($CDCl_3$, 250 MHz): 0.01 and 0.03 (2 x s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.10 and 1.33 (2 x s, 2 x 3H, $C(3)(CH_3)_2$), 3.15-3.20 (mp, 2H, $C\underline{H_2}CH(CO_2Me)N$), 3.70-3.85 (mp, 2H, CH_2OSi), 4.90-5.05 (br.mp, 1H, $CH_2\underline{C}H(COSi)N$), 5.38 (d, 1H, J = 8.5 Hz, NCH=C$\underline{H}$CO), 6.97 (d, 1H, J = 2.2 Hz, C(2)H indole), 7.07-7.20 (mp, 2H, C(5)H and C(6)H indole), 7.32 (d, 1H, J = 7.5 Hz, C(7)H indole), 7.42 (d, 1H, J = 8.5 Hz, NC$\underline{H}$=CHCO), 7.59 (d, 1H, J = 7.5 Hz, C(4)H indole), 8.14 (br.s, 1H, NH indole). **IR** ($CHCl_3$): 3480 (s), 1680 (s), 1645 (s), 1620 (s), 835 (s). **MS** (FD 10 mA): 426. $[\alpha]^{20}_D$ = -26.5° ($CHCl_3$, c = 0.0095 g/ml).

(6S,12bR)-3,3-Dimethyl-2,4-dioxo-6-hydroxymethyl-1,2,3,4,6,7,12,12b-octa-hydro-indolo[2,3-a]quinolizine **(10)**

A mixture of 15 ml of methanol and 0.2 ml of conc. H_2SO_4 was dried via the following procedure: the mixture was refluxed overnight and the condensed liquid was passed over 3 Å mol sieves, which were placed in a soxhlet apparatus. To this mixture 561 mg of **9** in MeOH was added and it was stirred for 75 min. at room temperature. Sat. $NaHCO_3$ was added to neutralize the acid and the mixture was concentrated under vacuum. The residue was taken up in ether and the organic layer was washed with brine and dried over $MgSO_4$, concentrated under vacuum and chromatographed over silica gel (ethyl acetate/petroleum ether 60-80 1:1 → 9:1). The product was isolated as a yellow foam 398 mg (99 %).

^{1}H-NMR ($CDCl_3$, 250 MHz): 1.43 and 1.46 (2 x s, 2 x 3H, $C(3)(CH_3)_2$), 2.77-2.89 (mp, 2H, $C(1)H_{ax}$ and C(7)H), 2.97 (br.s, 1H, $CH_2O\underline{H}$), 3.06 (ddd, 1H, J = 2.0, 6.2 and 16.2 Hz, C(7)H), 3.24 (dd, 1H, J = 3.2 and 15.3 Hz, $C(1)H_{eq}$), 3.47-3.61 (mp, 1H, 1 x $C\underline{H_2}OH$), 3.69-3.78 (mp, 1H, 1 x $C\underline{H_2}OH$), 5.04 (br.d, 1H, J = 12.1 Hz, $C(12b)H_{ax}$), 5.45-5.54 (mp, 1H, $C(6)H_{eq}$), 7.09-7.20 (mp, 2H, C(9)H and C(10)H), 7.35 (d, 1H, J = 7.7 Hz, C(11)H), 7.49 (d, 1H, J = 7.5 Hz, C(8)H), 8.65 (s, 1H, NH indole). **IR** ($CHCl_3$): 3460 (s), 3300 (br.m), 1720 (s), 1630 (s), 1410 (s), 1060 (s). **MS** (FD 10 mA): 312; (EI 150 °C): 312 (49 %), 281 (29 %), 183 (21 %), 169 (74 %), 156 (28 %), 128 (13 %), 115 (17 %). Exact mass: found 312.1489 (calculated for $C_{18}H_{20}N_2O_5$ 312.1475). $[\alpha]^{20}_D$ = +149.8° ($CHCl_3$, c = 0.08 g/ml).

3,3-Dimethyl-2,3,4,6,7,12-hexahydro-6-hydroxymethyl-2,4-dioxo-indolo[2,3-a]–quinolizine **(11)**

A solution of 50 mg of compound **8** in 3 ml of MeOH was added to a HCl/MeOH mixture. The reaction mixture was stirred for one hour at room temperature during which HCl was passed through the solvent. After addition of sat. $NaHCO_3$ solution the mixture was concentrated under vacuum and the residue was taken up in ether. The organic layer was washed with brine and dried over Na_2SO_4. Flash chromatography over silica gel with ethyl acetate gave 25 mg of the oxidized product **11** (70 %) and 11 mg (30 %) of the product **10**.

^{1}H-NMR ($CDCl_3$, 250 MHz): 1.53 (s, 6H, $C(3)(CH_3)_2$), 2.35 (br.s, 1H, $CH_2O\underline{H}$), 3.13-3.22 (mp, 1H, $C(7)H_{eq}$), 3.32-3.38 (mp, 1H, $C(7)H_{ax}$), 3.50-3.58 (mp, 2H, $C\underline{H_2}OH$), 5.27-5.32 (mp, 1H, $C(6)H_{eq}$), 7.09-7.35 (mp, 2H, C(9)H and C(10)H), 7.47 (d, 1H, J = 8.2 Hz, C(11)H), 7.58 (d, 1H, J = 7.9 Hz, C(8)H), 10.44 (s, 1H, NH indole). **IR** ($CHCl_3$): 3460 (w), 3270 (br.s), 1680 (s), 1615 (s), 1595 (s).

References and notes

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