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TOTAL SYNTHESES OF *dl*-MESEMBRINE, *dl*-DIHYDROMARITIDINE AND *dl*-*epi*-DIHYDROMARITIDINE VIA REGIOSELECTIVE $NaBH_4/H^+$ REDUCTION OF IMIDES[1]

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Abstract—$NaBH_4/H^+$ reduction of α,α-disubstituted succinimides proceeds in a highly regioselective manner to afford the corresponding ω-carbinol-lactams in quantitative yield. By extension of this versatile method, the cyclic α-acylimmonium ion has been used for short and stereoselective syntheses of *dl*-mesembrine, *dl*-dihydromaritidine and *dl*-*epi*-dihydromaritidine.

The *cis*-fused octahydroindole nucleus **1** is found in a number of alkaloids from diverse sources. Among others, specific examples include mesembrine **2b**[3] and maritidine **3a**,[4] 5,10b-ethanophenanthridine alkaloids, which are produced by plants of the *Aizoaceae* and *Amaryllidaceae* respectively.

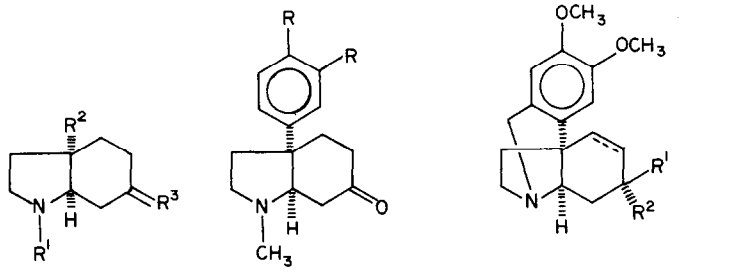
Our interest in mesembrine and other so-called mesembrine alkaloids[5] as well as the Amaryllidaceae, particularly the 5,10b-ethanophenanthridine alkaloids,[6] arose after finding that the $NaBH_4/H^+$ reduction of α,α-disubstituted succinimides proceeds in a highly regioselective manner.[7] It would seem that this principle coupled with the use of the cyclic α-acylimmonium species[8] could be applied advantageously in the design of a general synthesis of this class of alkaloids. The general scheme was tested in new syntheses of *dl*-mesembrine **2b**,[9a–g] *dl*-dihydromaritidine **3b** and *dl*-*epi*-dihydromaritidine **3c**.

The approach selected was a straightforward extension of the aforementioned principles: after $NaBH_4/H^+$ reduction of an appropriate succinimide the resulting ω-carbinol-lactam was cyclized yielding a *cis*-fused octahydroindoledione which was easily converted into **1** (R^3 = O or H, OH) (Scheme 1).

The synthesis of *dl*-desdimethoxymesembrine **2a**[9b] was selected as our initial goal.

The preparation of the requisite succinimide **7a** could not be realized in a single step since condensations of 1 - methyl - 3 - phenylsuccinimide **4a** with methyl vinyl ketone under a variety of circumstances only gave inferior results. However, 1,3 - dichloro - 2 - butene[10] as a methyl vinyl ketone equivalent in annelation reactions proved very valuable. Coupling **4a** with 1,3 - dichloro - 2 - butene gave **5a** in nearly quantitative yield. Since the $NaBH_4/H^+$ reduction of **5a** proceeded regioselectively,[7b] it appeared rather attractive to convert directly the corresponding ω-carbinol-lactam **6a** into the cyclized product **13a**. Unfortunately, attempts to realize the latter process by carrying out experiments in conc H_2SO_4 at 0°[11] or conc HCl[12] were not successful.

Therefore, an alternate route was employed. Hydrolysis of **5a** afforded **7a** in 56% yield. Protection of the CO function yielded the corresponding ketal **8a** (95%). $NaBH_4/H^+$ reduction of **8a** proceeded regioselectively.

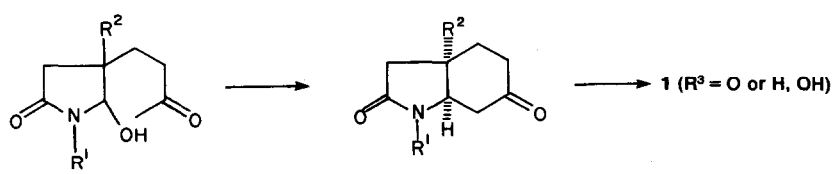


1

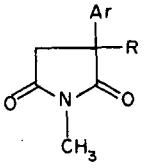
2a: R = H
b: R = OCH_3

3a: R^1 = H, R^2 = OH, dehydro
b: R^1 = H, R^2 = OH
c: R^1 = OH, R^2 = H

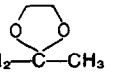
Fig. 1.



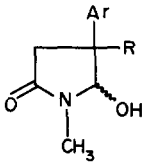
Scheme 1.



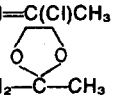
4: R = H
5: R = $CH_2CH{=}C(Cl)CH_3$
7: R = $CH_2CH_2COCH_3$



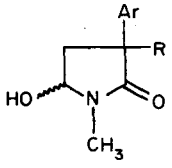
8: R = CH_2CH_2—(ketal)—CH_3
16: R = $CH_2CH_2C{\equiv}CH$

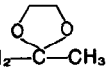


6: R = $CH_2CH{=}C(Cl)CH_3$

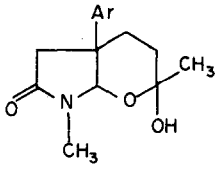


9: R = CH_2CH_2—(ketal)—CH_3
11: R = $CH_2CH_2COCH_3$
17: R = $CH_2CH_2C{\equiv}CH$





10: R = CH_2CH_2—(ketal)—CH_3
18: R = $CH_2CH_2C{\equiv}CH$



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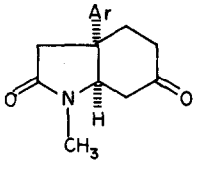

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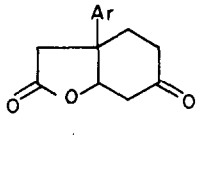

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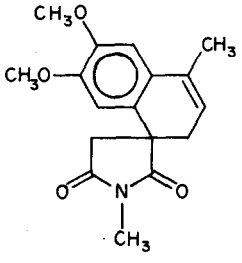

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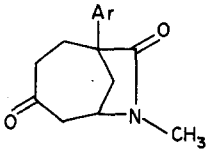

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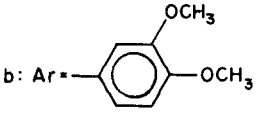
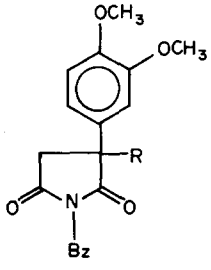
a: Ar = phenyl

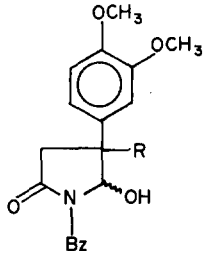


b: Ar =

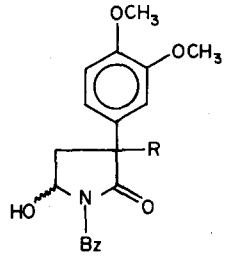
Fig. 2.



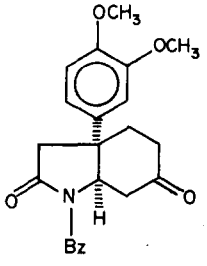
20: R = H
21: R = $CH_2CH_2C{\equiv}CH$
26: R = $CH_2CH_2CH{=}CH_2$



22: R = $CH_2CH_2C{\equiv}CH$
27: R = $CH_2CH_2CH{=}CH_2$



23: R = $CH_2CH_2C{\equiv}CH$
28: R = $CH_2CH_2CH{=}CH_2$



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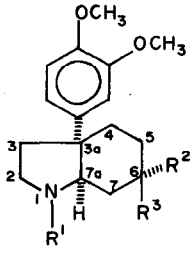


25a: R^1 = Bz, R^2R^3 = O
b: R^1 = Bz, R^2 = OH, R^3 = H
c: R^1 = Bz, R^2 = H, R^3 = OH
d: R^1 = H, R^2 = OH, R^3 = H
e: R^1 = H, R^2 = H, R^3 = OH

Fig. 3.

According to ^{1}H NMR (DMSO-d_6) the crude reaction mixture consisted of **9a** (75%) and **10a** (25%). Purification via crystallization and chromatography gave **9a** in 66% yield as a mixture of two stereoisomers (Experimental).

Now advantage could be taken of the reactivity of the cyclic α-acylimmonium ion, although the cyclisation of **9a** required the hydrolysis of the ethylene ketal moiety. It was expected that treatment of **9a** with HCl/H_2O would give the corresponding ketone **11a**. Instead, a cyclic hemiacetal **12** was obtained predominantly. However, the latter (**12**) insoluble in most solvents, could be converted quantitatively into **11a** upon heating in DMSO. Although both **11a** as well as **12** could be cyclized to **13a** upon short heating with 65% H_2SO_4 this route proved unattractive because of the impurities formed. Therefore hydrolysis of the ethylene ketal **9a** and subsequent cyclisation in a single step seemed an alternative route.

Thus upon heating **9a** in a mixture of H_2O/dioxane 1/1 (30 ml) with 85% H_2SO_4 (1.5 ml) a mixture of **13a** (61%) and **14** (17%) was obtained. As separation proved difficult, a better result was reached upon refluxing **9a** in a mixture of MeOH and conc HCl. After chromatography **13a** was obtained in 78% yield. Structural assignment to **13a** was made upon examination of Dreiding models which showed that the rather flat 5-membered lactam-ring excluded the formation of a *trans* structure. Furthermore comparison of the spectral data of **13a** with earlier reports[9b] agreed with its *cis* structure. The conversion of **13a** into *dl*-desdimethoxymesembrine **2a** was carried out according to the procedure described by Oh-ishi and Kugita:[9e] **13a** was ketalized with ethylene glycol and *p*-TsOH. Reduction of the crude oily ketal with LAH followed by treatment with 10% HCl gave nearly pure *dl*-desdimethoxymesembrine **2a** as a pale yellow oil in 96% overall yield from **13a**. Further purification by distillation under reduced pressure afforded **2a** as a colourless oil which solidified upon standing, m.p. 73–77°. The IR and ^{1}H NMR spectra of **2a** were identical to those reported by Stevens and Wentland.[9b]

Applying the above procedure to the synthesis of *dl*-mesembrine **2b**, it was found that hydrolysis of the vinylchloride **5b** (prepared from **4b** and 1,3 - dichloro - 2 - butene) could not be achieved in a satisfactory manner. Instead of the desired transformation to **7b**, cyclisation to the spiro derivative **15** took place and was impossible to avoid by varying the conditions.

Therefore, an alternate route was employed which was indicated from parallel studies on the acetylene cyclisations of 1-alkynyl imides.[13,14]

Thus 1 - methyl - 3 - phenyl - succinimide **4a** was coupled with 4 - iodo - but - 1 - yne to give the butynyl derivative **16a** in 67.5% yield. The $NaBH_4/H^+$ reduction of **16a** again proceeded in a highly regioselective manner. According to ^{1}H NMR ($CDCl_3$) a mixture of **17a** and **18a** was formed in a ratio 4:1 respectively. Separation via chromatography yielded **17a** in pure form (67%). HCOOH cyclisation of **17a** at room temp. directly gave **13a** in 95% yield. In addition HCOOH cyclisation of **18a** afforded a 7-membered ring ketone **19**[15] illustrating the usefulness of functionally substituted ω-carbinol-lactams in the synthesis of a variety of heterocyclic derivatives.

†According to ^{1}H NMR ($CDCl_3$), the $NaBH_4/H^+$ reduction of **16b** gave a mixture of **17b** and **18b** in a ratio 4:1 (Experimental).

Having established the utility of the HCOOH cyclisation in the synthesis of **13a** a similar sequence of reactions starting with 1 - methyl - 3 - (3,4 - dimethoxyphenyl) - succinimide **4b** furnished the known ketolactam **13b**[9e] through the successive compounds **16b** and **17b**.† The actual cyclisation **17b** → **13b** again proceeded in nearly quantitative yield and the observed analytical data of **13b** fully agreed with those published before.[9e] The structure of *dl*-mesembrine **2b** was secured via the conversion **13b** → **2b** described for the synthesis of **2a**. The IR and ^{1}H NMR spectra of the naturally occurring alkaloid and those obtained from our synthetic material were identical.

dl-*Dihydromaritidine* **3b** *and* dl-epi-*dihydromaritidine* **3c**

Pfäffli and Hauth[16] recently realized the demethylation of *dl*-mesembrine **2b** to the corresponding N–H derivative and thus a synthesis of *dl*-dihydromaritidine **3b** (or *dl-epi*-dihydromaritidine **3c**) via stereoselective reduction[17] and subsequent Pictet–Spengler cyclisation.[18]

For us it was more attractive to follow the route employed in the synthesis of *dl*-mesembrine **2b** to arrive at these 5,10b-ethanophenanthridine alkaloids. Since it was found[19] that catalytic debenzylation of N-benzyl amines proceeded smoothly, only a slight variation of the scheme employed in the synthesis of *dl*-mesembrine **2b** was required to develop a general synthesis of 5,10b-ethanophenanthridine alkaloids.

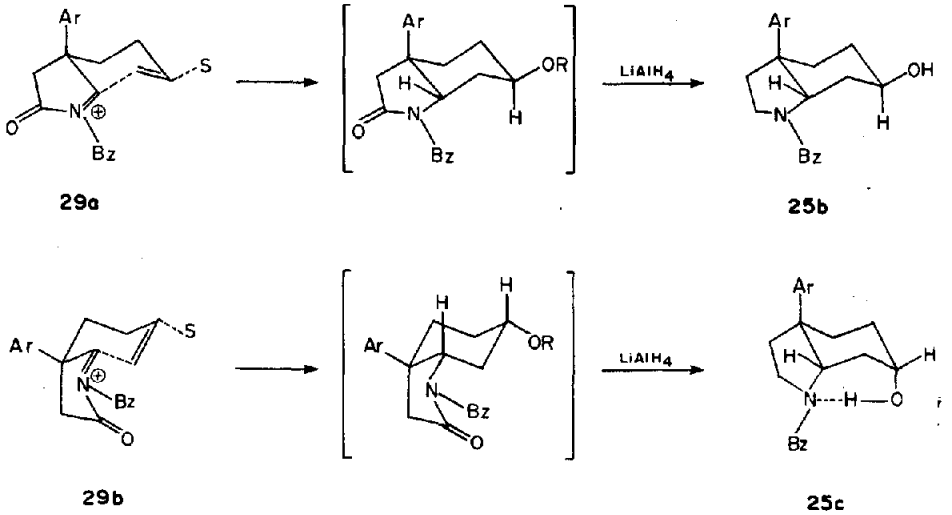
Thus coupling of 1 - benzyl - 3 - (3,4 - dimethoxyphenyl) - succinimide **20** with 4 - iodo - but - 1 - yne giving **21** was followed by $NaBH_4/H^+$ reduction and afforded the corresponding ω-carbinol-lactam **22** in 83% yield as a mixture of two stereoisomers together with **23** (9%) also formed as a mixture of two stereoisomers (Experimental). HCOOH cyclisation of **22** and subsequent conversion of **24** into **25a** proceeded in high yield. As reported by Stevens *et al.*[20] debenzylation of **25a** at this stage was accompanied by β-elimination. Therefore **25a** was reduced to the corresponding alcohol before debenzylation. LAH reduction of **25a** yielded a 1:2 mixture of two epimeric alcohols **25b** (H_6, $W_{1/2}$ = 25 Hz) and **25c** (H_6, $W_{1/2}$ = 9 Hz) which could be separated by chromatography. A more satisfactory ratio was found upon catalytic hydrogenation of **25a** in i-PrOH over PtO_2. This reaction led almost exclusively to the alcohol **25b**. On hydrogenation of **25b**, the amine **25d** was obtained in quantitative yield and in a similar reaction, its epimer **25e** was obtained from **25c** also in good yield. Transformation of **25d** and **25e** to tetracyclic compounds by Pictet–Spengler reaction yielded *dl*-dihydromaritidine **3b** and *dl-epi*-dihydromaritidine **3c** respectively.

It was found recently[21] that olefin cyclisations of 1-alkenyl imide derivatives in HCOOH occur in a highly stereoselective manner. Therefore a comparable reaction of α,α-disubstituted succinimides in which the alkenyl moiety is one of the substituents would also give access to the indole skeleton. If, after the $NaBH_4/H^+$ reduction of the imide the cyclisation of the corresponding ω-carbinol-lactam would proceed in a stereospecific manner the employed route in the synthesis of *dl*-dihydromaritidine **3b** or *dl-epi*-dihydromaritidine **3c** could be simplified.

$NaBH_4/H^+$ reduction of **26** (prepared from **20** and 4 - bromo - 1 - butene), afforded **27** in 70% yield as a mixture of two stereoisomers (Experimental). The HCOOH cyclisation of **27** and subsequent LAH reduction gave a mixture of OH-epimers **25b** and **25c** in a ratio 1:4.

Although the cyclisation was not completely stereoselective the result proved more satisfactory for the synthesis of *dl-epi*-dihydromaritidine **3c** as compared to the procedure outlined before. In different acid medium ($HOAc/H_2SO_4$ 10/1) the stereoselectivity of the cyclisation decreased (**25b**:**25c** = 1:2).

A likely explanation of the observed selectivity of the latter cyclisation process is visualized in Scheme 2.



Scheme 2. Acid cyclisation via chairlike transition state, S = HCOOH, product ratio **25b**:**25c** = 1:4; S = $HOAc/H_2SO_4$ 10/1, product ratio **25b**:**25c** = 1:2; Ar = 3,4-dimethoxyphenyl.

The projected α-acylimmonium ion **29** (derived from **27**) is non-symmetric which implies the possibility of cyclisation via two different chair forms **29a** and **29b** possessing axial and equatorial aryl substituents. As might be expected for steric reasons cyclisation via the equatorial form is preferred. Subsequent LAH reduction gave a mixture of **25b** and **25c** in which **25c** was the major stereoisomer. The projected conformations of **25b** and **25c** show the aryl substituent in an axial position because Stevens *et al.*[20] have demonstrated that these substances, regardless of the nature of the substituent on N (i.e. H, Me, Bz) prefer the conformation in which the C_{7a} proton is equatorial and the adjacent aryl group axial.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined on Unicam SP-200 or Perkin-Elmer 257 instruments. The absorptions are located by their wave numbers (in cm^{-1}). ^1H NMR spectra were measured with a Varian A-60D, HA-100 or XL-100 spectrometer using TMS as internal reference. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Mass spectra were recorded on an AEI MS-902 or Varian Mat-711 mass spectrometer. Analyses were performed by Mr. H. Pieters of the Micro-analytical Department of our laboratory. Column chromatography was carried out on silicagel (activity grade II, Woelm). Pre-coated TLC Plates silicagel 60 F254 Merck were used for TLC, the spots being detected by exposure to iodine vapour. Pre-coated PLC Plates silicagel F254 Merck were used for preparative layer chromatography.

Preparation of imides

1 - *Methyl* - 3 - *phenyl* - *succinimide* **4a** was prepared from benzaldehyde as described.[22]

†Prepared from 3,4-dimethoxyphenylsuccinic acid[23] via standard procedure.

1 - *Methyl* - 3 - (3,4 - *dimethoxyphenyl*) - *succinimide* **4b** was prepared from 3,4-dimethoxyphenylsuccinic anhydride† (11.57 g, 49.03 mmole) according to the procedure described,[8a] yield: 79%, m.p. 80–82° (EtOH). IR ($CHCl_3$): 1770 (w) 1700 (vs) (imide-CO); ^1H NMR: δ ($CDCl_3$) 2.66–3.36 (2H, $-CH_2-CO$) 3.04 (s, 3H, $-N-CH_3$) 3.80–4.00 (1H, $-CO-CH-Ar$) 3.83 (s, 3H, $-O-CH_3$) 3.85 (s, 3H, $-O-CH_3$) 6.66–6.92 (3H, aromatic H) (Found: C, 62.6; H, 6.1; N, 5.6. Calc. for $C_{13}H_{15}NO_4$ M = 249.26: C, 62.24; H, 6.07; N, 5.62%).

1 - *Benzyl* - 3 - (3,4 - *dimethoxyphenyl*) - *succinimide* **20** was prepared from 3,4-dimethoxyphenylsuccinic anhydride† (12.35 g, 52.33 mmole) and benzylamine (5.7 ml) according to the procedure described for the synthesis of **4b**, yield: 88%, m.p. 126–129° (EtOH). IR ($CHCl_3$) 1780 (w) 1710 (vs) (imide-CO); ^1H NMR: δ ($CDCl_3$) 2.46–4.06 (3H, $-CH_2-CH-Ar$) 3.71 (s, 3H, $-O-CH_3$) 3.80 (s, 3H, $-O-CH_3$) 4.78 (s, 2H, $-N-CH_2-Ar$) 6.50–6.93 (3H, aromatic H) 7.10–7.60 (5H, aromatic H) (Found: C, 70.2; H, 6.0; N, 4.4. Calc. for $C_{19}H_{19}NO_4$ M = 325.35: C, 70.14; H, 5.89; N, 4.31%).

1 - *Methyl* - 3 - (3 - *chloro* - 2 - *butenyl*) - 3 - *phenyl* - *succinimide* **5a** was prepared from **4a** and 1,3 - dichloro - 2 - butene as described.[7b]

1 - *Methyl* - 3 - (3 - *chloro* - 2 - *butenyl*) - 3 - (3,4 - *dimethoxyphenyl*) - *succinimide* **5b** was prepared from **4b** (2.50 g, 10.04 mmole) according to the procedure described for the synthesis of **5a**, yield: 82%, m.p. 110–112° (EtOH). IR ($CHCl_3$): 1770 (w) 1700 (vs) (imide-CO); ^1H NMR: δ ($CDCl_3$) 2.02 (3H, $-C=C-CH_3$) 2.63–3.26 (4H) 3.01 (s, 3H, $-N-CH_3$) 3.85 (s, 3H, $-O-CH_3$) 3.88 (s, 3H, $-O-CH_3$) 5.16–5.54 (1H, $-C=CH-$) 6.74–7.10 (3H, aromatic H) (Found: C, 60.4; H, 5.9; N, 4.2. Calc. for $C_{17}H_{20}NO_4Cl$ M = 337.80: C, 60.44; H, 5.97; N, 4.15%).

1 - *Methyl* - 3 - (3 - *oxobutyl*) - 3 - *phenyl* - *succinimide* **7a**. To conc H_2SO_4 (50 ml) through which N_2 was vigorously bubbled, pulverized **5a** (8.83 g, 31.88 mmole) was added at once. After stirring at r.t. for 5 min the mixture was poured into ice-water (400 ml) and extracted with $CHCl_3$ (4 × 100 ml). The combined extracts were washed with 5% Na_2CO_3 aq and sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale yellow oil (6.11 g). Distillation under reduced pressure afforded 4.65 g of **7a** (170–180°/0.02 mm) as a colourless oil which crystallized upon standing, yield: 56%, m.p. 72–74°. IR ($CHCl_3$): 1770 (w) (imide-CO) 1700 (vs) 1690 (vs) (CO); ^1H NMR: δ ($CDCl_3$) 2.06 (s, 3H, $-CO-CH_3$) 2.15–2.73 (4H) 3.00 (AB system, J = 18 Hz, 2H, $-CH_2-CO$) 3.02 (s, 3H, $-N-CH_3$) 7.21–7.46 (5H, aromatic H). MS: *m/e* = 131 (66%) 189 (100) 259 (6) M^+. (Found: C, 69.4; H, 6.6; N, 5.3. Calc. for $C_{15}H_{17}NO_3$ M = 259.29: C, 69.48; H, 6.61; N, 5.40%).

1 - *Methyl* - 3 - (3 - *oxobutyl*) - 3 - *phenyl* - *succinimide ethylene ketal* **8a**. A mixture of **7a** (2.96 g, 11.42 mmole) and ethylene glycol (10 ml) in C_6H_6 (250 ml) was refluxed with *p*-TsOH

(0.025 g) during 19 hr, using a Dean and Stark apparatus, filled with molecular sieves 4A. The soln was washed with sat $NaHCO_3$ aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale yellow oil (3.50 g). Distillation under reduced pressure afforded 3.29 g of **8a** (194–195°/0.01 mm) as a viscous oil which crystallized upon standing, yield: 95%, m.p. 68–70°. IR ($CHCl_3$): 1770 (w) 1700 (vs) (imide-CO); ^{1}H NMR: δ ($CDCl_3$) 1.26 (s, 3H, –C–CH_3) 1.39–2.35 (4H) 3.00 (AB system, J = 18 Hz, 2H, –CH_2–CO) 3.01 (s, 3H, –N–CH_3) 3.88 (4H, ethylene ketal) 7.13–7.57 (5H, aromatic H). MS: *m/e* = 87 (100%) 288 (2). (Found: C, 67.3; H, 7.0; N, 4.7. Calc. for $C_{17}H_{21}NO_4$ M = 303.35: C, 67.31; H, 6.98; N, 4.62%).

1 - *Methyl* - 3 - (3 - *butynyl*) - 3 - *phenyl* - *succinimide* **16a**. To an ice-cooled suspension of NaH (0.58 g, 24 mmole) in dry THF (25 ml) under N_2 a soln of **4a** (1.89 g, 10.0 mmole) in dry THF (25 ml) was added. To the stirred mixture DMSO (25 ml) was quickly added dropwise and stirring was continued for an additional 15 min at 0°. A soln of 4 - iodo - but - 1 - yne[24] (3.97 g, 22 mmole) in dry THF (10 ml) was added dropwise in 5 min and after addition was complete the mixture was stirred at 0° for 1 hr, poured into H_2O (300 ml) and extracted with ether (3 × 75 ml). The combined extracts were washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a yellow oil (2.07 g) which showed 2 spots on TLC (silicagel, $CHCl_3$) with R_f 0.49 and 0.0. Column chromatography on silicagel with $CHCl_3$ as an eluent afforded the fraction R_f 0.49 as a yellow oil (1.84 g) which according to ^{1}H NMR (CCl_4) was pure **16a**. Further purification by distillation under reduced pressure afforded 1.63 g of **16a** (134–136°/0.03 mm) as a colourless oil, yield: 67.5%. IR ($CHCl_3$): 3330 (w) (C≡C–H) 1770 (w) 1700 (vs) (imide-CO); ^{1}H NMR: δ (CCl_4) 1.85 (1H, –C≡C–H) 2.00–2.50 (4H) 2.92 (s, 3H, –N–CH_3) 3.01 (s, 2H, –CH_2–CO) 7.10–7.55 (5H, aromatic H) (Found: C, 74.8; H, 6.4; N, 5.7. Calc. for $C_{15}H_{15}NO_2$ M = 241.28: C, 74.66; H, 6.27; N, 5.81%).

1 - *Methyl* - 3 - (3 - *butynyl*) - 3 - (3,4 - *dimethoxyphenyl*) - *succinimide* **16b** was prepared from **4b** (2.49 g, 10 mmole) according to the procedure described for the synthesis of **16a**, yield: 56.5%, m.p. 90–92° (diisopropylether). IR ($CHCl_3$): 3350 (w) (C≡C–H) 1770 (w) 1700 (vs) (imide-CO); ^{1}H NMR: δ ($CDCl_3$) 1.93 (1H, –C≡C–H) 2.00–2.40 (4H) 2.98 (s, 3H, –N–CH_3) 3.10 (AB system, J = 18 Hz, 2H, –CH_2–CO) 3.83 (s, 3H, –O–CH_3) 3.86 (s, 3H, –O–CH_3) 6.71–7.09 (3H, aromatic H) (Found: C, 67.6; H, 6.3; N, 4.6. Calc. for $C_{17}H_{19}NO_4$ M = 301.33: C, 67.76; H, 6.36; N, 4.65%).

1 - *Benzyl* - 3 - (3 - *butynyl*) - 3 - (3,4 - *dimethoxyphenyl*) - *succinimide* **21** was prepared from **20** (5.42 g, 16.67 mmole) according to the procedure described for the synthesis of **16a**. Purification by column chromatography on silicagel with ether as an eluent afforded **21** in 68% yield, m.p. 89–91° (EtOH). IR ($CHCl_3$): 3400 (w) (C≡C–H) 1780 (w) 1710 (vs) (imide-CO): ^{1}H NMR: δ ($CDCl_3$) 1.93 (1H, –C≡C–H) 2.05–2.40 (4H) 3.14 (s, 2H, –CH_2–CO) 3.81 (s, 3H, –O–CH_3) 3.88 (s, 3H, –O–CH_3) 4.70 (s, 2H, –N–CH_2–Ar) 6.75–6.98 (3H, aromatic H) 7.20–7.46 (5H, aromatic H) (Found: C, 73.2; H, 6.1; N, 3.7. Calc. for $C_{23}H_{23}NO_4$ M = 377.42: C, 73.19; H, 6.14; N, 3.71%).

1 - *Benzyl* - 3 - (3 - *butenyl*) - 3 - (3,4 - *dimethoxyphenyl*) - *succinimide* **26** was prepared from **20** (1.62 g, 5.0 mmole) and 4 - bromo - but - 1 - ene (1.51 g, 11.22 mmole) according to the procedure described for the synthesis of **16a**. Purification by column chromatography on silicagel with ether as an eluent afforded **26** as an oil in 80% yield. IR ($CHCl_3$): 1770 (w) 1700 (vs) (imide-CO); ^{1}H NMR: δ ($CDCl_3$) 1.70–2.20 (4H) 2.98 (AB system, J = 18 Hz, 2H, –CH_2–CO) 3.75 (s, 3H, –O–CH_3) 3.82 (s, 3H, –O–CH_3) 4.68 (s, 2H, –N–CH_2–Ar) 4.76–5.06 (2H, –C=CH_2) 5.47–5.90 (m, 1H, –CH=C–) 6.68–6.96 (3H, aromatic H) 7.19–7.44 (5H, aromatic H) (Found: C, 72.6; H, 6.6; N, 3.8. Calc. for $C_{23}H_{25}NO_4$ M = 379.44: C, 72.80; H, 6.64; N, 3.69%).

Spiro derivative **15**. To conc H_2SO_4 (10 ml) through which N_2 was vigorously bubbled, pulverized **5b** (0.24 g, 0.71 mmole) was added at once. After stirring at 8–9° for 3 min the mixture was poured into ice-water (100 ml). Work-up as described for **7a** afforded an oil (0.21 g) which showed 2 spots on TLC (silicagel, $CHCl_3$) with R_f 0.30 and 0.08. Column chromatography on silicagel with $CHCl_3$ as an eluent gave the fraction R_f 0.30 (0.11 g) as a solid which consisted of pure **15**, m.p. 150–154° (EtOH).

IR ($CHCl_3$): 1770 (w) 1700 (vs) (imide-CO); ^{1}H NMR: δ ($CDCl_3$) 2.08 (3H, –C=C–CH_3) 2.12–3.06 (4H) 3.12 (s, 3H, –N–CH_3) 3.81 (s, 3H, –O–CH_3) 3.87 (s, 3H, –O–CH_3) 5.67 (m, 1H, –C=CH–) 6.39 (s, 1H, aromatic H) 6.84 (s, 1H, aromatic H) (Found: C, 67.8; H, 6.9; N, 4.5. Calc. for $C_{17}H_{19}NO_4$ M = 301.33: C, 67.76; H, 6.36; N, 4.65%). Further elution afforded the fraction R_f 0.08 (MS: *m/e* = 302 (100%) 602 (3) M^+) which could not be identified via IR and ^{1}H NMR.

General procedure for the $NaBH_4/H^+$ *reduction*. This was carried out with a stirred soln of the imide in EtOH at 0° with an excess of $NaBH_4$. At regular intervals (mostly 15 min) 3–4 drops 2 N HCl in EtOH were added. The reaction time was 4–6 hr. After reduction the soln was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded the crude reduction product.

1 - *Methyl* - 4 - (3 - *chloro* - 2 - *butenyl*) - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **6a** was prepared from **5a** as described.[7b]

1 - *Methyl* - 4 - (3 - *oxobutyl*) - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone ethylene ketal* **9a**. Compound **8a** (2.01 g, 6.63 mmole) was reduced in EtOH (200 ml) with 3.0 g $NaBH_4$ at 0° for 5 hr. Work-up afforded an oil (2.10 g) which showed 2 spots on TLC (silicagel, EtOAc) with R_f 0.30 and 0.20. After trituration with EtOAc/di-isopropylether white crystals were obtained. Crystallization from EtOAc yielded 0.96 g of **9a** (R_f 0.20), m.p. 171–173° (EtOAc). IR ($CHCl_3$): 3400 (w) (OH) 1690 (lactam-CO); ^{1}H NMR: δ (DMSO-d_6) 1.05–1.45 (2H) 1.15 (s, 3H, –C–CH_3) 1.74–2.10 (2H) 2.33–2.81 (AB system, J = 17 Hz, 2H, –CH_2–CO) 2.66 (s, 3H, –N–CH_3) 3.74 (4H, ethylene ketal) 4.93 (d, J = 7 Hz, 1H, –N–CH–OH; becomes an s with D_2O added) 6.37 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 7.10–7.42 (5H, aromatic H). MS: *m/e* = 28 (95%) 43 (25) 59 (40) 87 (100) (Found: C, 66.8; H, 7.6; N, 4.5. Calc. for $C_{17}H_{23}NO_4$ M = 305.36: C, 66.86; H, 7.59; N, 4.59%). Column chromatography of the mother liquor on silicagel with EtOAc as an eluent firstly gave the fraction R_f 0.30 (0.27 g), as a thin oil, which according to ^{1}H NMR ($CDCl_3$) probably was a mixture of 2 stereoisomers **10a**. The N–Me signals were found at δ 2.65 (s) and δ 2.69 (s). Further elution with EtOAc afforded a fraction R_f 0.30 and 0.20 (0.18 g) and finally a pure fraction R_f 0.20 (0.48 g). The latter fraction was crystallized from EtOAc and afforded another sample of **9a** (R_f 0.20; 0.37 g) which appeared to be the stereoisomer of the former isolated **9a**, m.p. 143–146° (EtOAc). IR ($CHCl_3$): 3400 (w) (OH) 1690 (vs) (lactam-CO); ^{1}H NMR: δ (DMSO-d_6) 0.72–1.95 (4H) 1.07 (s, 3H, –C–CH_3) 2.33 (A part AB system, J = 16 Hz, 1H, –CH–CO) 2.79 (s, 3H, –N–CH_3) 2.83 (B part AB system, J = 16 Hz, 1H, –CH–CO) 3.73 (4H, ethylene ketal) 5.02 (d, J = 8 Hz, 1H, –N–CH–OH; becomes an s with D_2O added) 5.60 (d, J = 8 Hz, 1H, –OH; disappears with D_2O added) 7.05–7.44 (5H, aromatic H) (Found: C, 67.0; H, 7.5; N, 4.5. Calc. for $C_{17}H_{23}NO_4$ M = 305.36. C, 66.86; H, 7.59; N, 4.59%). The total yield of **9a** (as a mixture of two stereoisomers) amounts to 1.33 g (66%).

1 - *Methyl* - 4 - (3 - *butynyl*) - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **17a**. Compound **16a** (1.55 g, 6.43 mmole) was reduced in EtOH (110 ml) with 1.75 g $NaBH_4$ at 0° for 4 hr. Work-up afforded an oil (1.60 g) which showed 2 spots on TLC (silicagel, EtOAc) with R_f 0.46 and 0.36. After trituration with EtOAc/di-isopropylether white crystals were obtained. Crystallization from EtOAc afforded 0.65 g of **17a** (R_f 0.36). Column chromatography of the mother liquor on silicagel with EtOAc as an eluent gave 2 essentially pure fractions: 0.32 g (R_f 0.46) and 0.58 g (R_f 0.36). The fractions R_f 0.46, a colourless oil, mainly consisted of **18a** as a mixture of 2 stereoisomers. IR ($CHCl_3$): 3500 (w) (OH) 3400 (w) (C≡C–H) 1700 (vs) (lactam-CO); the N–Me signals in $CDCl_3$ were found at δ 2.83 (s) and δ 2.89 (s). The fraction R_f 0.36, a white solid,[25] was crystallized from EtOAc to give 0.40 g of an additional crop of **17a**. The total yield of **17a** amounted to 1.05 g (67%), m.p. 145–148° (EtOAc). IR (KBr): 3320 (w) (C≡C–H) 3250 (w) (OH) 1660 (vs) (lactam-CO); ^{1}H NMR: δ (DMSO-d_6) 1.60–2.25 (5H, –CH_2–CH_2– and –C≡C–H) 2.50–2.75 (2H, –CH_2–CO) 2.63 (s, 3H, –N–CH_3) 4.95 (d, J = 7 Hz, 1H, –N–CH–OH; becomes an s with D_2O added) 6.39 (d, J =

7 Hz, 1H, –OH; disappears with D_2O added) 7.14–7.41 (5H, aromatic H) (Found: C, 74.0; H, 7.0; N, 5.7. Calc. for $C_{15}H_{17}NO_2$ M = 243.29: C, 74.05; H, 7.04; N, 5.76%).

1 - *Methyl* - 4 - (3 - *butynyl*) - 4 - (3,4 - *dimethoxyphenyl*) - 5 - *hydroxy* - 2 - *pyrrolidinone* **17b**. Compound **16b** (1.52 g, 5.05 mmole) was reduced in a mixture of EtOH (100 ml) and THF (15 ml) with 1.77 g $NaBH_4$ at 0° for 5 hr. Work-up afforded a residue (1.58 g) which showed 3 spots on TLC (silicagel, EtOAc) with R_f 0.34, 0.29 and 0.19. Crystallization from EtOAc yielded 0.65 g of **17b** (R_f 0.19). The mother liquor was chromatographed on silicagel with EtOAc as an eluent and firstly gave an oily fraction with R_f 0.34 and 0.29 which according to ^1H NMR ($CDCl_3$) probably consisted of **18b** as a mixture of 2 stereoisomers (0.32 g). The N-Me signals were found at δ 2.83 (s) and δ 2.89 (s). Further elution with EtOAc afforded another sample of **17b** which was purified[25] by crystallization from EtOAc (0.40 g) (R_f 0.19). The total yield of **17b** amounted to 1.05 g (69%), m.p. 117–119° (EtOAc). IR ($CHCl_3$): 3400 (m) (OH) 3360 (w) (C≡CH) 1690 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.74–2.40 (5H, $-CH_2-CH_2-$ and $-C\equiv C-H$) 2.60–3.00 (2H, $-CH_2-$CO) 2.79 (s, 3H, $-N-CH_3$) 3.85 (s, 6H, 2×$-O-CH_3$) 4.57 (d, J = 7.5 Hz, 1H, –OH; disappears with D_2O added) 5.07 (d, J = 7.5 Hz, 1H, –N–CH–OH; becomes an s with D_2O added) 6.64–6.97 (3H, aromatic H) (Found: C, 67.3; H, 7.0; N, 4.6. Calc. for $C_{17}H_{21}NO_4$ M = 303.35: C, 67.31, H, 6.98; N, 4.62%).

1 - *Benzyl* - 4 - (3 - *butynyl*) - 4 - (3,4 - *dimethoxyphenyl*) - 5 - *hydroxy* - 2 - *pyrrolidinone* **22**. Compound **21** (3.11 g, 8.25 mmole) was reduced in EtOH (200 ml) with 4.5 g $NaBH_4$ at 0° for 4 hr. Work-up afforded an oil (3.20 g) which showed 4 spots on TLC (silicagel, EtOAc/C_6H_{12} 1/1) with R_f 0.37, 0.32, 0.21 and 0.14. Column chromatography on silicagel with EtOAc/C_6H_{12} 1/1 as an eluent afforded a fraction with R_f 0.37 and 0.32 (0.28 g) which according to ^1H NMR ($CDCl_3$) was a mixture of 2 stereoisomers **23** and *epi*-**23** in a ratio 1:1.8. A sample of this mixture was separated by preparative layer chromatography (silicagel, EtOAc/C_6H_{12} 1/1). **23** was removed from the plate and crystallized upon removal of the solvent. Crystallization from EtOAc/di-isopropylether provided pure **23**, m.p. 138–140° (EtOAc/di-isopropylether). ^1H NMR ($CDCl_3$) 1.90 (1H, –C≡C–H) 1.95–2.44 (5H) 2.70 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 2.71–2.95 (m, 1H) 3.80 (s, 3H, $-O-CH_3$) 3.83 (s, 3H, $-O-CH_3$) 4.18 (A part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.86 (B part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.86–5.15 (m, 1H, –N–CH–OH; sharpens with D_2O added) 6.70–7.30 (8H, aromatic H). MS: *m/e* = 91 (100%) 163 (71) 327 (71) 379 (50) M^+. *epi*-**23** was removed from the plate and crystallized upon removal of the solvent. Crystallization from EtOAc/di-isopropylether provided pure *epi*-**23**, m.p. 135–137° (EtOAc/di-isopropylether). ^1H NMR: δ ($CDCl_3$) 1.86 (1H, –C≡C–H) 1.92–2.70 (6H) 2.23 (d, J = 9.5 Hz, 1H, –OH; disappears with D_2O added) 3.83 (s, 6H, 2×$-O-CH_3$) 4.13 (A part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.82 (B part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.83–5.07 (m, 1H, –N–CH–OH; sharpens with D_2O added) 6.70–7.40 (8H, aromatic H). MS: *m/e* = 91 (100%) 163 (73) 327 (70) 379 (52) M^+. Further elution gave a fraction with R_f 0.21 and 0.14 (2.59 g) which according to ^1H NMR ($CDCl_3$) was a mixture of 2 stereoisomers **22** and *epi*-**22** in a ratio 1:1. A sample of the latter mixture was separated by preparative layer chromatography (silicagel, EtOAc, C_6H_{12} 1/1) giving **22** as well as *epi*-**23** in pure form. Compound **22**: m.p. 147–149° (EtOAc/di-isopropylether; R_f 0.21). IR (KBr): 3260 (m) (C≡C–H) 3140 (w) (OH) 1650 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.86–2.50 (5H) 2.97 (AB system, J = 16.5 Hz, 2H, $-CH_2-$CO) 3.85 (s, 3H, $-O-CH_3$) 3.97 (s, 3H, $-O-CH_3$) 4.06 (d, J = 7.5 Hz, 1H, –OH; disappears with D_2O added) 4.21 (A part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.96 (B part AB system, J = 15 Hz, 1H, –N–CH–Ar) 5.11 (d, J = 7.5 Hz, 1H, –N–CH–OH; becomes an s with D_2O added) 6.74–7.35 (8H, aromatic H). MS: *m/e* = 91 (75%) 185 (83) 216 (41) 379 (100) M^+. (Found: C, 72.8; H, 6.7; N, 3.7. Calc. for $C_{23}H_{25}NO_4$ M = 379.44: C, 72.80; H, 6.64; N, 3.69%). *epi*-**22**: m.p. 162–168° (EtOAc/di-isopropylether; R_f 0.14). IR (KBr): 3310 (w) (OH) 3280 (m) (C≡C–H) 1675 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.70–2.20 (5H) 2.50 (d, J = 6.5 Hz, 1H, –OH; disappears with D_2O added) 2.75 (A part AB system, J = 16.5 Hz, 1H, –CH–CO) 3.14 (B part AB system, J = 16.5 Hz, 1H, –CH–CO) 3.96 (s, 6H, 2×$-O-CH_3$) 4.26 (A part AB system, J = 14.5 Hz, 1H, –N–CH–Ar) 5.03 (d, J = 6.5 Hz, 1H, –N–CH–OH; becomes an s with D_2O added) 5.05 (B part AB system, J = 14.5 Hz, 1H, –N–CH–Ar) 6.73–7.10 (3H, aromatic H) 7.44 (s, 5H, aromatic H). MS: *m/e* = 91 (95%) 185 (96) 216 (46) 379 (100) M^+. (Found: C, 72.3; H, 6.7; N, 3.5. Calc. for $C_{23}H_{25}NO_4$ M = 379.44: C, 72.80; H, 6.64; N, 3.69%).

1 - *Benzyl* - 4 - (3 - *butenyl*) - 4 - (3,4 - *dimethoxyphenyl*) - 5 - *hydroxy* - 2 - *pyrrolidinone* **27**. Compound **26** (1.18 g, 3.12 mmole) was reduced in EtOH (100 ml) with 1.50 g $NaBH_4$ at 0° for 4 hr. Work-up afforded an oil (1.20 g) which showed 4 spots on TLC (silicagel, EtOAc/n-C_6H_{14} 1/1) with R_f 0.30, 0.25, 0.17 and 0.11. Column chromatography on silicagel with EtOAc/n-C_6H_{14} 1/1 as an eluent afforded a fraction with R_f 0.30 and 0.25 (0.14 g) which probably was a mixture of 2 stereoisomers **28** and *epi*-**28**. Attempts to separate this fraction were not successful. Further elution gave a fraction with R_f 0.17 and 0.11 (0.87 g) which according to ^1H NMR ($CDCl_3$) was a mixture of 2 stereoisomers **27** and *epi*-**27** in a ratio 1.75:1. A sample of the latter mixture was separated by preparative layer chromatography (silicagel, EtOAc/n-C_6H_{14} 1/1) giving both stereoisomers **27** and *epi*-**27** in pure form. Compound **27**: m.p. 100–102° (di-isopropylether; R_f 0.17). IR ($CHCl_3$): 3650 (w) 3400 (m) (OH) 1680 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.57–2.14 (4H) 2.80 (AB system, J = 17 Hz, 2H, $-CH_2-$CO) 3.74 (s, 3H, $-O-CH_3$) 3.85 (s, 3H, $-O-CH_3$) 3.93 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 4.10 (A part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.67–5.04 (4H, –C=CH_2, –N–CH–Ar and –N–CH–OH; sharpens with D_2O added) 5.47–5.95 (m, 1H, –CH=C–) 6.67–7.30 (8H, aromatic H). MS: *m/e* = 91 (100%) 187 (51) 203 (45) 218 (100) 381 (42) M^+. (Found: C, 72.4; H, 7.1; N, 3.7. Calc. for $C_{23}H_{27}NO_4$ M = 381.46: C, 72.41; H, 7.13; N, 3.67%). *epi*-**27**: m.p. 145–147° (di-isopropylether; R_f 0.11). IR ($CHCl_3$): 3620 (w) 3400 (w) (OH) 1680 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.40–1.96 (4H) 2.44 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 2.52 (A part AB system, J = 16.5 Hz, 1H, –CH–CO) 3.00 (B part AB system, J = 16.5 Hz, 1H, –CH–CO) 3.84 (s, 6H, 2×$-O-CH_3$) 4.12 (A part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.65–5.03 (4H, –C=CH_2, –N–CH–Ar and –N–CH–OH; sharpens with D_2O added) 5.30–5.80 (m, 1H, –CH=C–) 6.60–6.89 (3H, aromatic H) 7.31 (s, 5H, aromatic H). MS: *m/e* = 91 (91%) 187 (42) 203 (46) 218 (100) 381 (88) M^+. (Found: C, 72.5; H, 7.1; N, 3.6. Calc. for $C_{23}H_{27}NO_4$ M = 381.46: C, 72.41; H, 7.13; N, 3.67%).

2 - *Hydroxy* - 2,7 - *dimethyl* - 4a - *phenyl* - 6 - *oxo* - *octahydropyrano*[2,3-b]*pyrrole* **12**

A soln of **9a** (0.29 g, 0.94 mmole) in a mixture of EtOH (25 ml) and 4.5 N HCl (10 ml) was stirred at r.t. for 22 hr. The mixture was poured into H_2O (100 ml) and extracted with $CHCl_3$ (5× 30 ml). The combined extracts were washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded an oil (0.27 g) which after trituration with a small amount of EtOAc crystallized. The crystals were filtered off and washed with ether yielding 0.17 g of pure **12**, m.p. 143–146° (MeOH). IR (KBr): 3400 (m) (OH) 1670 (vs) (lactam-CO); ^1H NMR: δ (DMSO-d_6) 1.37 (s, 3H, $-C-CH_3$) 1.40–2.90 (6H) 2.76 (s, 3H, $-N-CH_3$) 5.28 (s, 1H, –N–CH–O–) 5.95 (s, 1H, –OH; disappears with D_2O added) 7.20–7.45 (5H, aromatic H). MS: *m/e* = 131 (100%) 144 (92) 145 (61) 173 (90) 261 (9) M^+. (Found: C, 68.9; H, 7.4; N, 5.2. Calc. for $C_{15}H_{19}NO_3$ M = 261.31: C, 68.94; H, 7.33; N, 5.36%). Column chromatography of the mother liquor on silicagel with $CHCl_3$/acetone 4/1 as an eluent afforded another sample of **12** (0.01 g).

1 - *Methyl* - 4 - (3 - *oxobutyl*) - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **11a**. Compound **12** was converted quantitatively into **11a** upon heating in DMSO at 145–150° for 15 min. Compound **11a**: m.p. 138–141° (EtOAc). IR (KBr): 3260 (w) (OH) 1700 (vs) 1655 (vs) (CO); ^1H NMR: δ ($CDCl_3$) 1.75–2.34 (4H) 1.95 (s, 3H, $-CO-CH_3$) 2.43 (A part AB system, J = 17 Hz, 1H, –CH–CO) 2.85 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 2.87 (s, 3H, $-N-CH_3$) 2.94 (B part AB system, J = 17 Hz, 1H, –CH–CO) 5.04 (d, J = 7 Hz, 1H, –N–CH–OH; becomes an s with D_2O

added) 7.05–7.50 (5H, aromatic H). MS: *m/e* = 118 (40%) 131 (100) 144 (34) 145 (42) 173 (17) 189 (56) 261 (10) M^+. (Found: C, 68.9; H, 7.3. Calc. for $C_{15}H_{19}NO_3$ M = 261.31: C, 68.94; H, 7.33%).

1 - *Methyl* - 3a - *phenyl* - cis - *octahydroindol* - 2,6 - *dione* **13a**. A soln of **9a** (0.32 g, 1.05 mmole) in MeOH (25 ml) was refluxed during 21 hr with conc HCl (6.5 ml). The mixture was poured into H_2O (100 ml), extracted with $CHCl_3$ (3 × 50 ml), washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded an oil (0.28 g) which was chromatographed on silicagel with $CHCl_3$/acetone 4/1 as an eluent giving **13a** as a white solid (0.20 g), yield: 78%, m.p. 126–128° (di-isopropylether). IR ($CHCl_3$): 1710 (vs) 1680 (vs) (CO); ^{1}H NMR: δ ($CDCl_3$) 1.95–2.92 (8H) 2.86 (s, 3H, –N–CH$_3$) 4.39 (t, J = 4.5 Hz, 1H, –N–CH–) 7.25–7.48 (5H, aromatic H). MS: *m/e* = 185 (41%) 186 (37) 243 (100) M^+. (Found: C, 73.9; H, 7.0; N. 5.7. Calc. for $C_{15}H_{17}NO_2$ M = 243.29: C, 74.05; H, 7.04; N, 5.76%).

A soln of **17a** (0.25 g, 1.03 mmole) in HCOOH (5 ml) was stirred at r.t. for 72 hr. The mixture was evaporated to dryness under reduced pressure, dissolved in $CHCl_3$ (50 ml), washed with sat $NaHCO_3$ aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale yellow solid (0.24 g) (95%) which according to ^{1}H NMR ($CDCl_3$) was pure **13a**.

1 - *Methyl* - 3a - (3,4 - *dimethoxyphenyl*) - cis - *octahydroindol* - 2,6 - *dione* **13b**

A soln of **17b** (0.79 g, 2.61 mmole) in HCOOH (10 ml) was stirred at r.t. for 120 hr. Work-up as described for **13a** afforded a pale yellow oil which was chromatographed on silicagel eluting with EtOAc to give pure **13b** as a colourless oil (0.67 g), yield: 85%. IR ($CHCl_3$): 1720 (vs) 1680 (vs) (CO); ^{1}H NMR: δ ($CDCl_3$) 2.00–3.04 (8H) 2.87 (s, 3H, –N–CH$_3$) 3.90 (s, 6H, 2 × –O–CH$_3$) 4.32 (t, J = 4.5 Hz, 1H, –CH–N–) 6.72–6.95 (3H, aromatic H). (Found: C, 67.1; H, 6.8; N, 4.5. Calc. for $C_{17}H_{21}NO_4$ M = 303.35: C, 67.31; H, 6.98; N, 4.62%).

1 - *Phenyl* - 7 - *aza* - 7 - *methyl* - 4,8 - *dioxobicyclo*-[4,2,1]*nonane* **19**. A soln of **18a** (0.09 g, 0.37 mmole) in HCOOH (5 ml) was stirred at r.t. for 45 hr. Work-up as described for **13a** afforded a solid (0.09 g) which showed one main spot (R_f 0.38) and weak spots of by-products on TLC (silicagel, $CHCl_3$/acetone 4/1). Crystallization from EtOH gave pure **19** (0.033 g), yield: 37%, m.p. 168–171° (EtOH). IR (KBr): 1700 (vs) 1665 (vs) (CO); ^{1}H NMR: δ ($CDCl_3$) 1.80–3.00 (8H) 3.01 (s, 3H, –N–CH$_3$) 3.70–3.98 (m, 1H, –N–CH–) 7.15–7.62 (5H, aromatic H). MS: *m/e* = 144 (43%) 172 (48) 173 (100) 185 (41) 243 (87) M^+. (Found: C, 74.1; H, 7.0; N, 5.8. Calc. for $C_{15}H_{17}NO_2$ M = 243.29: C, 74.05; H, 7.04; N, 5.76%).

1 - *Benzyl* - 3a - (3,4 - *dimethoxyphenyl*) - cis - *octahydroindol* - 2,6 - *dione* **24**

A soln of **22** (2.27 g, 5.99 mmole) in HCOOH (20 ml) was stirred at r.t. for 65 hr. Work-up as described for **13a** afforded a yellow oil (2.30 g). Column chromatography on silicagel with EtOAc as an eluent gave a colourless oil (1.98 g) which according to ^{1}H NMR ($CDCl_3$) was pure **24**, yield: 87%. IR ($CHCl_3$): 1730 (vs) (CO) 1690 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 2.02–3.06 (8H) 3.75 (s, 3H, –O–CH$_3$) 3.83 (s, 3H, –O–CH$_3$) 3.85 (A part AB system, J = 15 Hz, 1H, –N–CH–Ar) 4.16 (t, J = 4.5 Hz, 1H, –N–CH–) 5.17 (B part AB system, J = 15 Hz, 1H, –N–CH–Ar) 6.55–6.90 (3H, aromatic H) 7.21–7.55 (5H, aromatic H). (Found: C, 72.7; H, 6.8; N, 3.6. Calc. for $C_{23}H_{25}NO_4$ M = 379.44: C, 72.80; H, 6.64; N, 3.69%).

dl-*Desdimethoxymesembrine* **2a** was prepared from **13a** (0.89 g, 3.66 mmole) according to the procedure described.[9e] The crude product (0.80 g) was distilled under reduced pressure giving pure *dl*-**2a** (0.40 g; 126–128°/0.03 mm) as a colourless oil which solidified slowly, yield: 47%, m.p. 73–77°. IR ($CHCl_3$) and ^{1}H NMR ($CDCl_3$) were identical with those of *dl*-desdimethoxymesembrine reported.[9b] (Found: C, 78.4; H, 8.4; N, 6.0. Calc. for $C_{15}H_{19}NO$ M = 229.31: C, 78.56; H, 8.35; N, 6.11%).

dl-*Mesembrine* **2b** was prepared from **13b** (0.47 g, 1.56 mmole) according to the procedure described for the synthesis of **2a**, yield: 68%. Its IR (CCl_4) and ^{1}H NMR ($CDCl_3$) were identical with those of natural mesembrine. A *dl*-mesembrine hydrochloride of m.p. 185–187° (i-PrOH; lit. 185–187°[9e]) was analyzed. (Found: C, 62.8; H, 7.5; N, 4.2; Cl, 10.9. Calc. for $C_{17}H_{24}NO_3Cl$ M = 325.82: C, 62.66; H, 7.42; N, 4.30; Cl, 10.88%). Alternatively in a similar experiment starting from **17b** (1.08 g, 3.55 mmole) the HCOOH-cyclisation and following reactions were carried out without purification giving a pale yellow oil (0.89 g) which was nearly pure *dl*-**2b**. Distillation under reduced pressure gave pure *dl*-**2b** (0.64 g; 176–180°/0.01 mm; lit. 178°/0.07 mm[9e]) in 62% overall yield from **17b**.

1 - *Benzyl* - 3a - (3,4 - *dimethoxyphenyl*) - cis - *octahydroindol* - 6 - *one* **25a** was prepared from **24** (1.88 g, 4.96 mmole) according to the procedure described for the synthesis of *dl*-**2a**. Purification by column chromatography on silicagel with $CHCl_3$/acetone 5/1 as an eluent afforded a pale yellow oil (1.57 g) which according to ^{1}H NMR ($CDCl_3$) was pure **25a**, yield: 86%. IR ($CHCl_3$): 1720 (vs) (CO); ^{1}H NMR: δ ($CDCl_3$) 1.90–2.83 (9H) 2.85–3.06 (m, 1H) 3.16 (A part AB system, J = 13 Hz, 1H, –N–CH–Ar) 3.31 (t, J = 4.5 Hz, 1H, –N–CH–) 3.90 (s, 6H, 2 × –O–CH$_3$) 4.13 (B part AB system, J = 13 Hz, 1H, –N–CH–Ar) 6.78–7.07 (3H, aromatic H) 7.18–7.42 (5H, aromatic H). (Found: C, 75.4; H, 7.5; N, 3.8. Calc. for $C_{23}H_{27}NO_3$ M = 365.45: C, 75.59; H, 7.45; N, 3.83%). Alternatively in a similar experiment starting from **21** (4.10 g, 10.87 mmole) the $NaBH_4/H^+$ reduction and following reactions were carried out without purification giving a yellow oil (3.55 g). The oil was dissolved in 2 N HCl/EtOH (10 ml), evaporated to dryness and crystallized from i-PrOH. The resulting hydrochloride salt of **25a** was converted into free amine which according to ^{1}H NMR ($CDCl_3$) was pure **25a** in 48% overall yield from imide **21**.

LAH *reduction of* **25a**. To a soln of **25a** (0.95 g, 2.60 mmole) in ether (30 ml) a suspension of LAH (0.26 g) in ether (10 ml) was slowly added dropwise with stirring. After stirring at r.t. for 45 min the mixture was refluxed for 30 min, allowed to come to r.t. and decomposed with H_2O (1 ml). The ppt was filtered off and washed with ether. The filtrate was dried over K_2CO_3 and evaporated affording a yellow oil (0.86 g) which showed 2 spots on TLC (silicagel, EtOAc) with R_f 0.24 and 0.10. According to ^{1}H NMR ($CDCl_3$) the oil was a mixture of **25b** and **25c** in a ratio 1:2. Column chromatography on silicagel with $CHCl_3$/acetone 10/1 as an eluent afforded a fraction with R_f 0.24 (0.34 g) as a colourless oil which according to ^{1}H NMR ($CDCl_3$) was pure **25c**, yield: 35%. IR (CCl_4): 3300 (m) (OH); ^{1}H NMR: δ ($CDCl_3$) 1.40–2.55 (9H) 2.96–3.30 (2H) 3.20 (A part AB system, J = 12.5 Hz, 1H, –N–CH–Ar) 3.88 (s, 3H, –O–CH$_3$) 3.90 (s, 3H, –O–CH$_3$) 4.00 (m, W1/2 = 9 Hz, 1H, –CH–OH) 4.45 (B part AB system, J = 12.5 Hz, 1H, –N–CH–Ar) 6.75–7.00 (3H, aromatic H) 7.20–7.45 (5H, aromatic H). A hydrochloride salt of **25c**, m.p. 215–230° (i-PrOH) was analyzed. (Found: C, 68.3; H, 7.4; H, 3.6; Cl, 8.6. Calc. for $C_{23}H_{30}NO_3Cl$ M = 403.93: C, 68.39; H, 7.49; N, 3.47; Cl, 8.78%). A following fraction (0.18 g) according to TLC (silicagel, EtOAc) was a mixture of **25c** (R_f 0.24) and **25b** (R_f 0.10). Further elution gave pure **25b** (0.18 g) (R_f 0.10) as a colourless oil, yield: 18%. IR (CCl_4): 3610 (m) 3400 (w) (OH); ^{1}H NMR: δ ($CDCl_3$) 1.05–2.32 (9H) 2.82–3.12 (2H) 3.12 (A part AB system, J = 13 Hz, 1H, –N–CH–Ar) 3.77 (s, 3H, –O–CH$_3$) 3.79 (s, 3H, –O–CH$_3$) 4.08 (m, W1/2 = 25 Hz, 1H, –CH–OH) 4.13 (B part AB system, J = 13 Hz, 1H, –N–CH–Ar) 6.65–6.93 (3H, aromatic H) 7.10–7.35 (5H, aromatic H). Because of decomposition (dark red colouring), even in the refrigerator, the latter compound, or its hydrochloride salt, did not crystallize and was used immediately for the next reaction.

Catalytic reduction of **25a**. A soln of **25a** (1.14 g, 3.12 mmole) in i-PrOH (100 ml) was hydrogenated over PtO_2 (0.11 g) in a Parr apparatus and an initial pressure of 52 psi. After 48 hr the catalyst was removed by filtration and the filtrate was evaporated. The residue, a pink foam, (1.12 g) showed 2 spots on TLC (silicagel, EtOAc) with R_f 0.24 (weak) and 0.10 and according to ^{1}H NMR ($CDCl_3$) was a mixture of **25b** and **25c** in a ratio 15:1. Column chromatography on silicagel with $CHCl_3$/acetone 10/1 as an eluent afforded **25b** as a colourless oil (0.64 g), yield: 56%.

Acid cyclisation of **27**. A soln of **27** (0.15 g, 0.40 mmole) in HCOOH (10 ml) was stirred at r.t. for 20 hr. Work-up as described for **13a** afforded an oil (0.17 g) which was dissolved in

THF (25 ml). After addition of LAH (0.12 g) the mixture was refluxed for 3 hr, allowed to come to r.t. and decomposed with H_2O (1 ml). The ppt was filtered off and washed with THF. The filtrate was dried over K_2CO_3 and evaporated affording an oil (0.14 g) which according to ^1H NMR ($CDCl_3$) was a mixture of **25b** and **25c** in a ratio 1:4. In a similar experiment $HOAc/H_2SO_4$ 10/1 was used instead of HCOOH giving after LAH reduction according to ^1H NMR ($CDCl_3$) a mixture of **25b** and **25c** in a ratio 1:2.

dl-*Dihydromaritidine* **3b**. Debenzylation of **25b** and the following Pictet–Spengler reaction were carried out according to the procedure described.[20] Pure *dl*-**3b** was isolated in 50% yield, m.p. 230–233° (EtOAc/MeOH). IR (KBr): 3180 (w) (OH); ^1H NMR: δ ($CDCl_3$) 1.10–2.30 (8H) 2.43 (broad s, 1H, –OH; disappears with D_2O added) 2.58–2.94 (m, 1H) 3.10–3.43 (2H) 3.70 (A part AB system, J = 17 Hz, 1H, –N–CH–Ar) 3.75 (s, 3H, –O–CH_3) 3.79 (s, 3H, –O–CH_3) 4.05–4.30 (1H) 4.30 (B part AB system, J = 17 Hz, 1H, –N–CH–Ar) 6.41 (s, 1H, aromatic H) 6.69 (s, 1H, aromatic H). MS: *m/e* = 217 (21%) 272 (22) 289 (100) M^+. (Found: C, 70.4; H, 8.1; N, 4.7. Calc. for $C_{17}H_{23}NO_3$ M = 289.36. C, 70.56; H, 8.01; N, 4.84%).

dl-epi-*Dihydromaritidine* **3c**. The same procedure as above starting from **25c** provided in 68% yield pure *dl-epi*-**3c**, m.p. 190–194° (EtOAc/MeOH). IR (KBr): 3100 (m) (OH); ^1H NMR: δ ($CDCl_3$) 1.13–2.60 (8H) 2.68–3.12 (2H) 2.80 (broad s, 1H, –OH; disappears with D_2O added) 3.24–3.85 (2H) 3.63 (A part AB system, J = 16.5 Hz, 1H, –N–CH–Ar) 3.86 (s, 3H, –O–CH_3) 3.90 (s, 3H, –O–CH_3) 4.41 (B part AB system, J = 16.5 Hz, 1H, –N–CH–Ar) 6.53 (s, 1H, aromatic H) 6.74 (s, 1H, aromatic H). MS: *m/e* = 217 (14%) 272 (12) 289 (100) M^+. (Found: C, 70.5; H, 8.0; N, 4.8. Calc. for $C_{17}H_{23}NO_3$ M = 289.36: C, 70.56; H, 8.01; N, 4.84%).

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