Tetrahedron Letters,Vol.25,No.21,pp 2205-2208,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

# RING EXPANSION REACTIONS IN THE FORMATION OF MACROCYCLIC LACTAMS. A SYNTHESIS OF DESOXO-INANDENINE[1]

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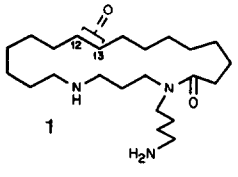
*Summary : Desoxo-inandenine, a reduction product of the macrocyclic spermidine alkaloids inandenin-12-one and -13-one has been synthesized starting from 2-nitrocyclotridecanone by ring expansion reactions including a Zip reaction step.*

The prinicples of the synthesis of amides and macrocyclic lactams starting from 2-nitro-(cyclo)alkanones were published[2]. In this paper we describe a new route for general synthesis of macrocycles containing spermidine or polyamino units[3]. The successive incorporation of an aminoalkyl and a 1,3-diaminopropane residue is possible by a combination of the ring enlargement reactions of 2-nitrocycloalkanones, followed by a Zip reaction step[4]. By application of this principle the synthesis of desoxo-inandenine (12) was performed, an important reduction product of the main alkaloids inandenin-12-one/-13-one (1)[5,6] isolated from *Onci-notis inandensis* Wood. et Evans (Apocynaceae) and of different inandeninols from *O. nigra* Pichon[7].

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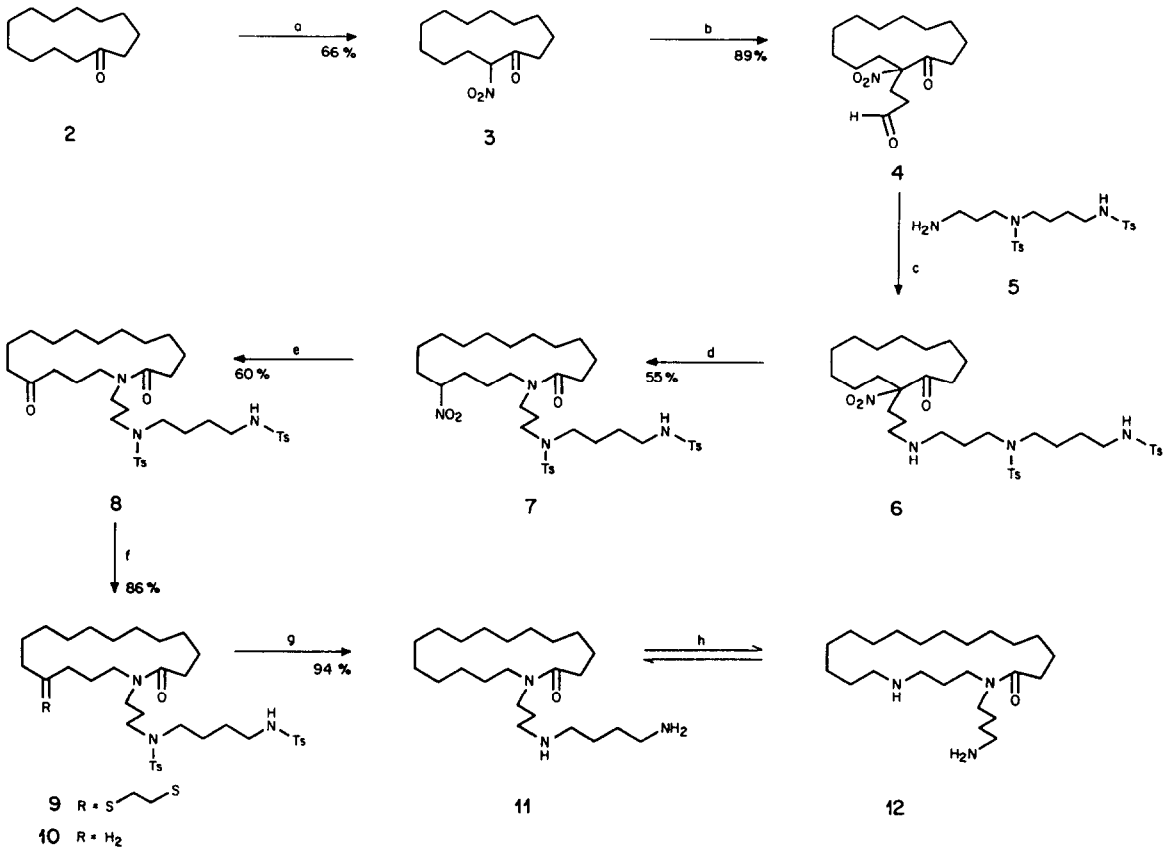
Cyclotridecanone (2) was converted via its enolacetate[8] by nitration[9] to 2-nitro-cyclotridecanone (3, mp. 68.2 - 68.5°)[10]. By Michael addition of acrylaldehyde to 3 3-(1-nitro-2-oxo-cyclotridecyl)-propanal (4, mp. 62.6 - 63.3°)[11] was formed[12]. Under the conditions of reductive amination[2] the aldehyde 4 reacted with an appropriate partially protected spermidine 5[13,14]. The amination product 6 yet containing compound 7 (tlc) was without purification[3] ring expanded to 7 (oil)[15]. The hydrolysis of the nitro group in 7 to the ketone function in 8 (mp. 114.8 - 116.0°)[16] was performed by the so-called reductive Nef reaction[17]. The reduction of 8 to the corresponding methylene lactam 10 (oil)[18] was achieved using known




a) $CH_2=C(CH_3)OAc$/cat. p-TsOH; $HNO_3/AcOH/Ac_2O$/cat. $H_2SO_4$ - b) $CH_2=CH-CHO$/$P(C_6H_5)_3$ - c) $NaCNBH_3$ - d) $H_2O$/MeOH/$NaHCO_3$ - e) NaOMe/MeOH; $TiCl_3/AcONH_4/H_2O$ - f) 10% $BF_3$ in MeOH/$HSCH_2CH_2SH$; Raney Ni/$H_2O$/MeOH - g) electrolysis - h) 0.8 equiv. p-TsOH/xylene/reflux/12 hr

procedures [19] via 9 (mp. 117.6 - 118.0°)[20]. For detosylation of 10 potential controlled electrolytic reduction (Hg-cathode, -2.3 V versus SCE, 0.3 mol $Me_4NCl$, EtOH)[21] was used to yield 11 (as dihydrochloride, mp. with decomp. 170 - 171°)[22]. The transformation of 11 to desoxo-inandenine (12) was accomplished by a Zip reaction step. The equilibration mixture 11 $\rightleftharpoons$ 12[23] (ratio approx. 1 : 1) was separated by prep. tlc yielding 12 · 2 HCl as crystals, identical in all respects (mp., IR, tlc, MS, $^1$H-NMR) with the dihydrochloride of desoxo-inandenine obtained from natural source[5,24].

Acknowledgement. We wish to thank the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung for a generous grant support.

## References and Notes

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10. 3 : IR ($CHCl_3$) 1730, 1550, 1360 $cm^{-1}$; NMR ($CDCl_3$) δ 5.15 (t, J = 7.0 Hz, OC-C<u>H</u>-$NO_2$).
11. 4 : IR (KBr) 2745, 1725, 1540, 1345 $cm^{-1}$; NMR ($CDCl_3$) δ 9.80 (1 H, s).
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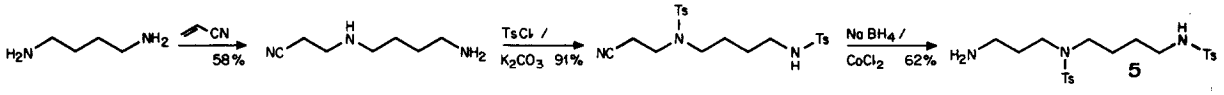
14. Synthesis of the partially protected spermidine 5 :




15. 7 : IR ($CHCl_3$) 1625, 1545, 1330, 1155, 1090 $cm^{-1}$; NMR ($CDCl_3$) δ 7.80 - 7.60 (4 H, m), 7.30 (4 H, m), 5.90 (0.3 H, t, J = 7.0 Hz, exchangeable with $D_2O$), 4.90 (0.7 H, t, J = 7.0 Hz, exchangeable with $D_2O$), 4.70 - 4.50 (1 H, m), 3.80 - 2.90 (10 H, m), 2.70 - 1.10 (38 H, m); vgl. Y. Nakashita and M. Hesse, *Helv.Chim.Acta 66*, 845 (1983).

16. 8 : IR ($CHCl_3$) 1705, 1620, 1330, 1155, 1090 $cm^{-1}$; mass m/z 548 ($M^+$-Ts).

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18. 10 : IR ($CHCl_3$) 1620, 1330, 1155, 1080 $cm^{-1}$; mass m/z 534 ($M^+$-Ts).

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20. 9 : IR ($CHCl_3$) 1625, 1330, 1160, 1090 $cm^{-1}$; mass m/z 779 ($M^{+\cdot}$).

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22. 11 : IR (KBr) 1610 $cm^{-1}$; NMR ($CD_3OD$) δ 3.70 - 2.90 (10 H, m), 2.50 (2 H, t, J = 7 Hz), 2.20 - 1.10 (32 H, m); mass m/z 381 ($M^{+\cdot}$).

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24. Concerning elemental analysis, mass, $^{13}C$-NMR and detailed $^1H$-NMR spectra see ref. 3.

(Received in Germany 21 February 1984)