Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5701-5704, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01215-4

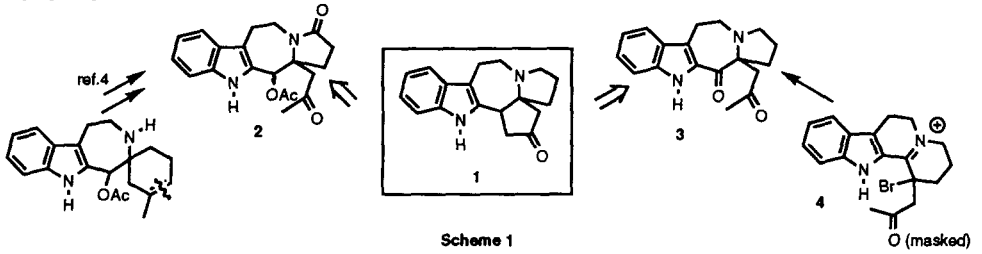
Synthesis of the New (Cyclopenta [b]pyrrolo[1,2-d])azepino[4,5-b]indole Ring System

Eric Noé[1], Denis Séraphin[2], Qiang Zhang[3], Frédéric Djaté, Jacques Hénin, Jean-Yves Laronze* and Jean Lévy.

Laboratoire de Transformation et Synthèse de Produits Naturels, associé au CNRS, Université de Reims Champagne Ardenne, Faculté de Pharmacie, 51 rue Cognacq-Jay, F-51096 Reims Cedex, France
Fax (33) 26.05.35.52; E mail jean.levy@univ-reims.fr

Abstract : *The 2-oxo functionalized title compound 1 was synthesised in 7 steps from tryptamine via rearrangement of the bromoiminium ion 13 in alkaline medium to azepinone 14 with concomitant formation of ketone 15. The ratio 14:15 was shown to depend on the nature of the hydroxide counter-ion.* Copyright © 1996 Published by Elsevier Science Ltd

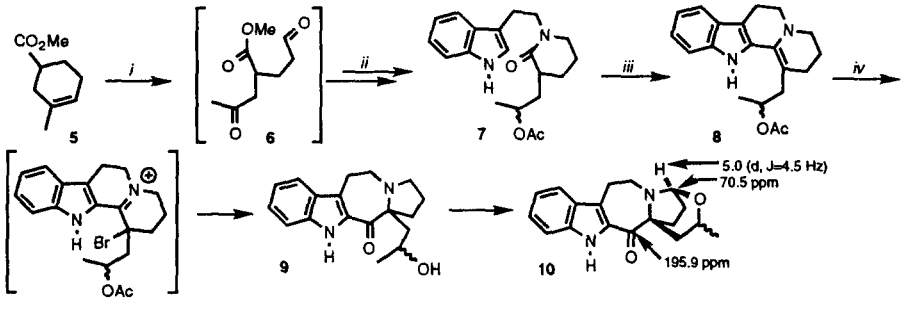
As part of our work on indole analogues of the derivatives of cephalotaxine, we recently reported[4] the synthesis of **2**, as a possible intermediate towards the hitherto unknown indole pentacycle **1** (Scheme 1). Unfortunately we were unable to improve the yield of the last stage of our synthesis and so we decided to follow a more conventional route to the pyrroloazepinoindole ring system of the target compound **3**, *i.e.* Duhamel's[5] oxidative rearrangement of α-bromoiminium ion **4** that was also used by Buzas[6] and Husson[7] to transform indoloquinolizidines into pyrroloazepinoindoles. This route requires protection of the side chain carbonyl group.



Scheme 1

The non-tryptamine carbons of the molecules were first derived from ester **5**,[8] (Scheme 2) which was transformed in 3 steps into enamine **8**, *via* oxidation to the tricarbonyl derivative **6**, regioselective reductive cyclisation to **7**, and finally Bischler-Napieralski ring closure. Under Buzas' conditions, (Br_2, then KOH-H_2O), **8** smoothly gave the rearranged hydroxyketones **9**,[9] which, unfortunately, could not be oxidised to the target ketone **3**. It appears that the position α to nitrogen in the pyrrolidine ring is extremely prone to oxidation and we observed formation of the amino-ether **10** in 81% yield (catalytic tetra-*n*-propylammonium tetraoxoruthenate, 4-methylmorpholine-N-oxide, 1 eq., CH_2Cl_2, 20°C, 16 h).

To avoid the problem of oxidation we chose to introduce the acetonyl side-chain in the protected form of a halogeno-propenyl substituent (Scheme 3). The yellow bromo-iminium ion **13a** was prepared in 3 steps



i : O_3, -70°C, then Me_2S; *ii*: tryptamine, PhH, r.t. until dissolution, then $NaBH_4$, MeOH, r.t., then Ac_2O, Et_3N (overall *i+ii* : 28%); *iii* : $POCl_3$, 60°C then 30% aqueous NH_3 (94%); *iv* : Br_2 1 eq., THF, -70°C, then KOH 2 eq. in H_2O.

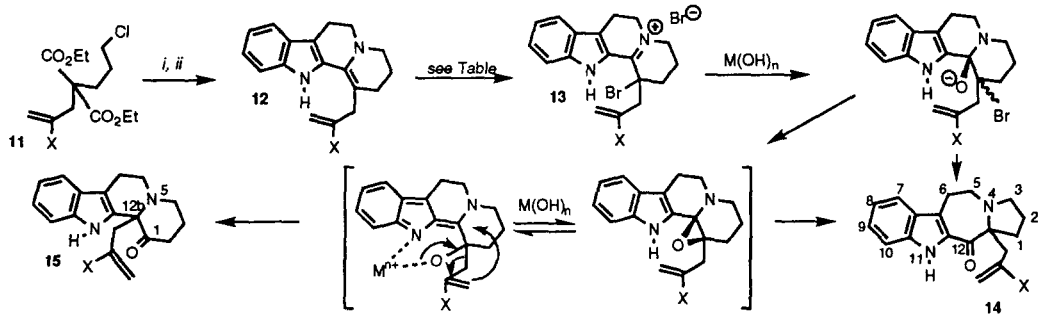
Scheme 2

from tryptamine and chloro-diester **11a**[10] in 59% overall yield, *via* enamine **12a**[11], following a similar strategy as above; the yield was slightly higher (67%) in the **b** bromo-series. Unfortunately, the rearrangement step did not proceed cleanly as before. The expected azepinone **14a**[12] (25%) was accompanied by a new rearrangement product **15a**[13] (30%). Such a rearrangement has not been previously observed by us or others (for a range of substituents : H, Et, 2-alkoxypropyl...) and we suppose that it is due to the nature of the side chain giving rise to a [2,3] allylic transposition instead of a classical [1,2] Wagner-Meerwein radical migration.

Table : Rearrangement of bromoiminium ion **13**

Entry	X	M^{n+}	**14**§	**15**§
1	Cl	K	25	30
2	Cl	K(*)	18	1
3	Cl	Cs	9	37
4	Cl	Li	62	12
5	Cl	Mg	31	1
6	Cl	Ba	37	16
7	Br	Li	46	10
8	Br	Ba	23	26

§ : isolated yield from **12**, (*) : 1 eq. 18-C-6



a : x=Cl **b** : x=Br *i* : tryptamine, K_2CO_3 1.1 eq., *iso*-amylalcohol, reflux, 72 h (75%); *ii* : $POCl_3$ 1.5 eq., toluene, reflux, 5 h (85%).

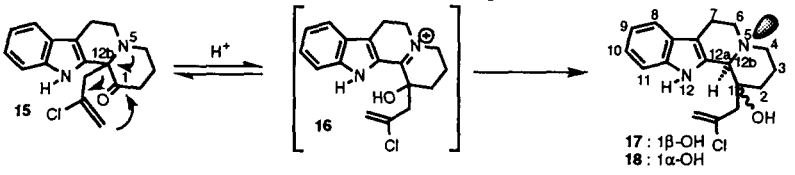
Scheme 3

It was soon apparent that the hydroxide counter-ion plays an important role in the course of the rearrangement : the addition of a selective cryptand for K^+ (entry 2) considerably reduced the formation of **15a**, in favour of the desired ketone **14a**. CsOH favored **15a** (entry 3), but LiOH finally gave quite good selectivity for **14a**.[14] The same result was obtained with the divalent cations Mg^{++} and Ba^{++}, (entries 5 and 6) but the overall yields were lower, relative to Li^+. It is noteworthy that, in contrast to **14**, **15** was never isolated in more than 50% yield. All these facts can be explained as follows : under the action of the metal hydroxide $M(OH)_n$, both *cis* and *trans* bromohydrins are formed, whose oxyanionic forms can rearrange to **14**. Only the *trans* one (C1-αBr) can give rise to an epoxyamine which either rearranges (Stevens *et al*[15]) to

ketone **14** or equilibrates with a metal-chelated form. In these intermediates, hard cations (Li^+, Mg^{++}) strongly interact with the oxygen site and increase its stability.

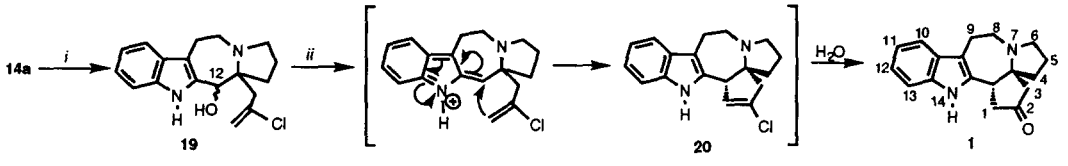
In contrast, larger cations like Cs^+ allow the alkoxide to induce the allylic rearrangement to **15**. As the Br-series (entries 7 and 8) did not give any improvement in yield or selectivity, the following work was carried out with the cheaper chloro-compounds.

Whatever the cation, we were unable to avoid completely the formation of **15**, and we speculated that it could be further rearranged to an indolopyrroloazepine system by reductive N5-C12b bond cleavage of the α-aminoketone and N5-C1 bond formation in Zn-AcOH.[16] Under these conditions (Zn powder 12 eq., AcOH, reflux 2 h), we found that **15a** gave rise only to a mixture of the alcohols **17** (less polar, 69%) and **18** (more polar, 11%).[17] Obviously, nitrogen did not directly attack C1=O. First, an allylic rearrangement of the side chain occurred to iminium ion **16**, which was further reduced to **17+18** whose structures were established by extensive COSY, HMBC and HMQC NMR measurements. Bohlman's bands[18] between 2780 and 2750 cm^{-1} in their IR spectra showed that both isomers **17**and **18** are *trans*-quinolizidines.



Scheme 4

As ketone **15a** was not useful for our purpose, we concentrated our attention on azepinone **14a**, which was cleanly converted to ketone **3** in 84% yield (mercuric acetate 1.1 eq., 88% formic acid, 0°C, 15 min then r.t., 3 h, H_2S gas). Unfortunately all attempts at ring-closure to the target pentacycle failed, probably on account of the low reactivity of the indole-deactived C12=O, and the sensitivity of β-aminoketones to acid or alkaline conditions (*retro*-Mannich). However reduction of **14a** gave a mixture of alcohols **19** which underwent rapid intramolecular cyclisation in acidic medium. The reaction was conveniently carried out in a degassed 95% solution of H_2SO_4, leading directly to the pentacyclic ketone **1**[19] (75-80%), sometimes accompanied by the intermediate chloro-olefin **20** (0-5%).



i : $NaBH_4$ 2eq., MeOH, r.t., 24h (98%); *ii* : 95% H_2SO_4, 0°C (15 min) then r.t. (4h).

Scheme 5

Work is currently in progress on the oxidation of the 1-position, and on the extension of this work to the cephalotaxane skeleton.

Acknowledgements : We are grateful to MESR, Servier Laboratories, and ARC for grants to D.S., E.N. and Q.Z., respectively. We thank J. Chuche (Université de Reims) for helpful discussions, J.D. Connolly (University of Glasgow) for language criticism, ADIR and CNRS for financial support.

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2. Present adress : Université d'Angers (France).
3. Present adress : Medical University of Shanghaï (People's Republic of China).
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8. Obtained by chromic oxidation of 3-methyl-1-formylcyclohex-3-ene (ref.4) and esterification by MeOH-HCl.
9. All new compounds were characterized by UV, IR, ^{1}H and ^{13}C NMR, HRMS or elemental analysis.
10. Prepared in two steps as follows : *i* : Na 1 eq., EtOH, diethyl malonate 1 eq., r.t. 30 min then 2,3-dichloropropene 1.1 eq., r.t., 96 h; *ii* : NaH 1 eq., 1-bromo-3-chloropropane 1 eq., THF, reflux, 48 h; overall yield 64 %.
11. **12a**: mp 77°C; UV (MeOH) 229, 308, 318 nm
12. **14a**: mp 142°C; UV (MeOH) 208, 238, 314 nm; IR (KBr) 3325, 1610 cm^{-1};^{1}H NMR ($CDCl_3$) δ 9.25 (br s, NH), 7.65 (d, J = 7, C7-H), 7.45-7.30 (m, C9-H, C10-H), 7.12 (m, C8-H), 5.32 and 5.25 (s, CH_2=), 3.60-3.40 (m, C5-H_2, C6-H), 3.15-2.95 (m, C3-H_2, C6-H', CH_2CCl), 2.30-2.20 (m, C1-H'), 2.15-2.00 (m, C1-H), 2.00-1.80 (m, C2-H), 1.70-1.60 (m, C2-H'); ^{13}C NMR ($CDCl_3$) δ 201.0 (C12), 138.9 (CCl), 136.9 (C10a), 132.0 (C11a), 127.7 (C6b), 126.7 (C9), 123.6 (C6a), 121.7 (C8), 120.1 (C7), 116.5 (CH_2=), 111.9 (C10), 75.0 (C12b), 48.9 (C3), 45.8 ($\underline{C}H_2$-CCl), 44.7 (C5), 37.5 (C1), 25.0 (C2), 22.4 (C6).
13. **15a**: mp 153°C; UV (MeOH) 224, 284, 293 nm; IR (KBr) 3370, 1700 cm^{-1};^{1}H NMR ($CDCl_3$) δ 8.22 (br s, NH), 7.50 (d, J=7, C8-H), 7.30 (d, J=7, C11-H), 7.15 (t, J=7, C10-H), 7.10 (t, J=7, C9-H), 5.30 and 5.20 (s, CH_2=), 3.65 (d, J=14, C2-H), 3.45 -3.30 (ddd, J=14, J=12, J=4.5, C2-H'), 3.30 -3.15 (dd, J=14, J=5, C3-H), 3.15 -2.90 (m, C4-H_2, C6-H_2), 2.80 - 2.65 (m, C7-H), 2.65 - 2.50 (dd, J=14, J=4.5, C3-H'), 2.45 - 2.15 (m, CH_2-CCl), 2.00 -1.80 (m, C7-H'); ^{13}C NMR ($CDCl_3$) δ 210.3 (C1), 138.2 (CCl), 135.8 (C11a), 130.4 (C12a), 127.3 (C7b), 122.2 (C10), 119.5 (C9), 118.3 (C8), 115.6 (CH_2=), 111.1 (C11), 107.9 (C7a), 69.7 (C12b), 47.8 (C4), 47.0 (C6), 46.5 (C2), 37.9 ($\underline{C}H_2$-CCl), 21.8 (C7), 16.5 (C3).
14 Reaction performed in 2 steps : *i* : Br_2 1 eq., THF, -70°, 1 h; *ii* : LiOH 2eq., H_2O, r.t., 2 h then reflux 4 h .
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17 We assume that the major product **17** has the chloropropenyl chain equatorial. This is supported by the NMR shielding (approx. 0.8 ppm) of C12b-H in **17** relative to **18**, due to the influence of the allylic π system. **17**: mp 188°C; UV (MeOH) 225, 281, 290 nm; IR (KBr) 3431, 3275, 2942, 2820, 2754 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10 (br s, NH), 7.50 (d, J=7, C8-H), 7.35 (d, J=7, C11-H), 7.0 (t, J=7, C10-H), 6.95 (t, J=7, C9-H), 5.30 (m, C=CH_2), 3.25 (s, C12b-H), 3.05 -2.90 (m, C4-H, C6-H), 2.81 and 2.15 (d, J=14, CH_2-C1), 2.80-2.70 (m, C7-H), 2.65-2.45 (m, C7-H', C6-H'), 2.40-2.25 (m, C4-H'), 2.25-2.15 (m, C2-H), 1.80-1.65 (m, C3-H), 1.65-1.45 (m, C3-H', C2-H'); ^{13}C NMR (DMSO-d_6) δ 138.7 (CCl), 135.9 (C11a), 132.2 (C12a), 126.6 (C7b), 121.3 (C10), 118.9 (C9), 117.9 (C8), 116.6 ($\underline{C}H_2$=C), 110.9 (C11), 110.0 (C7a), 74.6 (C1), 68.1 (C12b), 55.7 (C4), 53.1 (C6), 41.9 (C13), 36.5 (C2), 23.3 (C3), 21.6 (C7). **18**: mp 189°C; UV (MeOH) 225, 281, 290 nm; IR (KBr) 3362, 2932, 2820, 2787 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.05 (br s, NH), 7.45 (d, J=7, C8-H), 7.30 (d, J=7, C11-H), 7.15 (t, J=7, C10-H), 7.05(t, J=7, C9-H), 5.45 and 5.35 (s, C=CH_2), 4.05 (s, C12b–H), 3.25 (d, J=14, CCl-CH), 3.25-3.15 (m, C6-H), 3.15-2.95 (m, C6-H', C7-H), 2.90 (d, J=14, CCl-CH'), 2.85-2.70 (m, C4-H), 2.65-2.50 (m, C4-H', C7-H'), 1.80-1.70 (m, C2-H, C3-H), 1.70-1.50 (m, C2-H', C3-H'); ^{13}C NMR (DMSO-d_6) δ 137.7 (CCl), 135.3 (C11a), 131.6 (C12a), 126.8 (C7b), 121.3 (C10), 119.0 (C9), 117.8 (C8), 117.5 ($\underline{C}H_2$=C), 110.9 (C11), 74.5 (C1), 66.7 (C12b), 51.8 (C6), 46.9 (C4, CCl-$\underline{C}H_2$), 31.9 (C2), 22.5 (C3), 17.9 (C7).
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19. **1**: oil; UV (MeOH) 225, 283, 291 nm; IR (film) 3400, 2930, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (br s , NH), 7.47 (d, J=7, C10-H), 7.25 (d, J=7, C13-H), 7.15 (dd, J=7, J=1.5, C12-H), 7.08 (dd, J=7, J=1.5, C11-H), 3.65 (t, J=7, C14b-H), 3.35 - 2.85 (m, C1-H_2, C6-H_2, C9-H_2), 2.70 (d, J=17, C3-H), 2.17 (d, J=17, C3-H'), 2.05 - 1.70 (m, C4-H_2, C5-H_2); ^{13}C NMR ($CDCl_3$) δ 216.1 (C2), 135.2 (C13a), 133.1 (C14a), 129.0 (C9b), 121.6 (C12), 119.2 (C11), 118.0 (C10), 111.1 (C9a), 110.4 (C13), 69.8 (C-3a), 53.2 (C6), 46.1 (C8), 45.9 (C14b), 45.8 (C3), 45.7 (C1), 40.8 (C4), 23.7 (C5), 21.7 (C9).

(*Received in France* 1 *April* 1996; *accepted* 17 *June* 1996)