Synthesis of Isoquinoline Alkaloids through a 10-Membered Lactam Obtained by Radical Macrocyclisation

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Key words: Radical macrocyclisation; transannular cyclisation; isoindolobenzazepine; protoberberine,

Abstract: A new versatile method for the synthesis of isoquinoline alkaloids 3 and 5 is based on transannular cyclisation of a key macrocycle 2b obtained by an intramolecular addition of an aryl radical to a trimethylsilylacetylene.

In connection with our interest in the development of new methodologies for the synthesis of isoquinoline alkaloids¹ we envisioned a new approach which is based on regiochemically controlled transannular cyclisations of azamacrocyclic precursors. We now report the preliminary results of the application of this idea by using the 10-membered lactam 2b from which the isoindolobenzazepine and the protoberberine basic nuclei of two representative families of isoquinoline alkaloids, have been prepared.²

The macrolactam skeleton 2 was synthesized starting from amide $1a^3$ which was chemoselectively condensed with trimethylsilylacetylene (1.1 eq.) in Et3N at reflux under argon in the presence of CuI (0.05 eq.) and (Ph3P)2PdCl2 (0.05 eq.)⁴ to give 1b (mp 90-91° C) in a 90% yield.⁵ Desilylation of 1b with KOH (1.05 eq.) in MeOH at r.t. afforded an 84% yield of 1c (mp 113-115° C).⁵ Initial attempts to cyclise the bromoacetylene 1c by the palladium-catalyzed intramolecular coupling failed to provide the desired acetylenic macrolactam.



We then investigated the macrocyclisation under radical conditions.⁶ While the synthesis of five or six membered rings is a very common procedure, the generation of macrocycles is not so extended being pioneered by Porter.⁷ Furthermore, the small macrocycles (10-12 membered rings) are very difficult or even not possible to produce in contrast with the larger ones (14-16 membered rings).⁸ Interestingly we found that the more

conformationally rigid bromoacetylene 1c leads efficiently to an *endo*-selective intramolecular attack of the aryl radical to the triple bond giving the corresponding 10-membered ring lactam. Thus, dropwise addition of tributyltin hydride (2.1 eq.) to a refluxing benzene solution (1 mM) of the bromoacetylene 1c and AIBN (20% by weight) under argon produced, after 4.5 h., a mixture of Z and E-olefins 2a in a 45% combined yield.⁵ Better results were obtained when the reaction was carried out with the more radicophilic silylated acetylene 1b (5 mM) with 1.2 eq. of the hydride giving a 60% yield of a single vinylsilane 2b (mp 170-171° C).^{5,9}

Having prepared the macrocycle 2b, we next addressed the study of its transannular cyclisation by nucleophilic attack of the nitrogen atom. We found that under basic conditions (0.2 eq. of potassium *t*-butoxide in THF under argon at r.t.) the cyclisation takes place by addition to the β -position of the vinylsilane to give a 70% yield of 3a (mp 169-172° C) as a single syn-diastereoisomer.^{5,10} Desilylation of 3a using tetrabutylammonium fluoride (1.1 eq.) in THF at r.t.¹¹ led quantitatively to the isoindolobenzazepine 3b.¹² On the other hand, cyclisation via the alternative α -position of 2b to the azabicyclic[4,4,0] system 5¹³ was achieved in a 70% overall yield by epoxidation of 3a with *m*-CPBA (3 eq.) in refluxing CH₂Cl₂ followed, after work-up, by acid treatment (MeOH/SOCl₂ at r.t.) of the crude reaction mixture. This takes place most probably by acid catalyzed rearrangement of the α -epoxysilane¹⁴ to the ketone 4, followed by nitrogen attack and dehydration.

We are currently exploring the scope and the synthetic potential of macrocyclic systems as key precursors of different alkaloids including also those derived by cyclisation through carbon-carbon bond formation.

Acknowledgements: We are grateful to the DGICYT (project No PB90-0764) for financial support and to the Ministerio de Educación y Ciencia for a fellowship to C. Lamas.

References and notes

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- 9. Spectroscopic data for 2b: ¹<u>H-NMR</u> (250 MHz, CDCl₃) δ: 7.70 (dd, 1H, J= 7.4 and 1.5, Ar-H), 7.47-7.10 (m, 7H, Ar-H), 7.06 (s, 1H, CH=C), 5.59 (d, broad, 1H, J= 6, NH), 4.27 (m, 1H, CH-N), 3.23-3.01 (m, 2H), 2.54 (dd, 1H, J= 13.4 and 4.3), -0.17 (s, 9H, -SiMe₃). ¹³<u>C-NMR</u> (62.83 MHz, CDCl₃) δ: 171.06 (CO), 152.25 (C), 146.53 (C), 144.83 (CH), 139.34 (C), 138.52 (C), 138.03 (C), 130.97 (CH), 130.05 (CH), 128.51 (CH), 127.78 (CH), 127.22 (CH), 126.59 (CH), 126.55 (CH), 126.33 (CH), 43.90 (CH₂), 33.31 (CH₂), -0.61 (SiMe₃). <u>IR</u> (KBr) v_{max}: 3280 (N-H), 1640 (C=O). <u>MS</u> m/z (%): 321 (M⁺, 17), 320 (M⁺-H, 22), 278 (15), 248 (93), 202 (34), 73 (100).
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(Received in UK 16 June 1992)