Tetrahedron Letters,Vol.27,No.30,pp 3539-3542,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

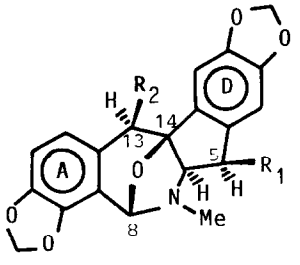
AN APPROACH TO THE TOTAL SYNTHESIS OF RIBASINE ALKALOIDS

Ricardo Alonso, Luis Castedo and Domingo Domínguez

Departamento de Química Orgánica de la Facultad de Química y
Sección de Alcaloides del CSIC. Santiago de Compostela, Spain

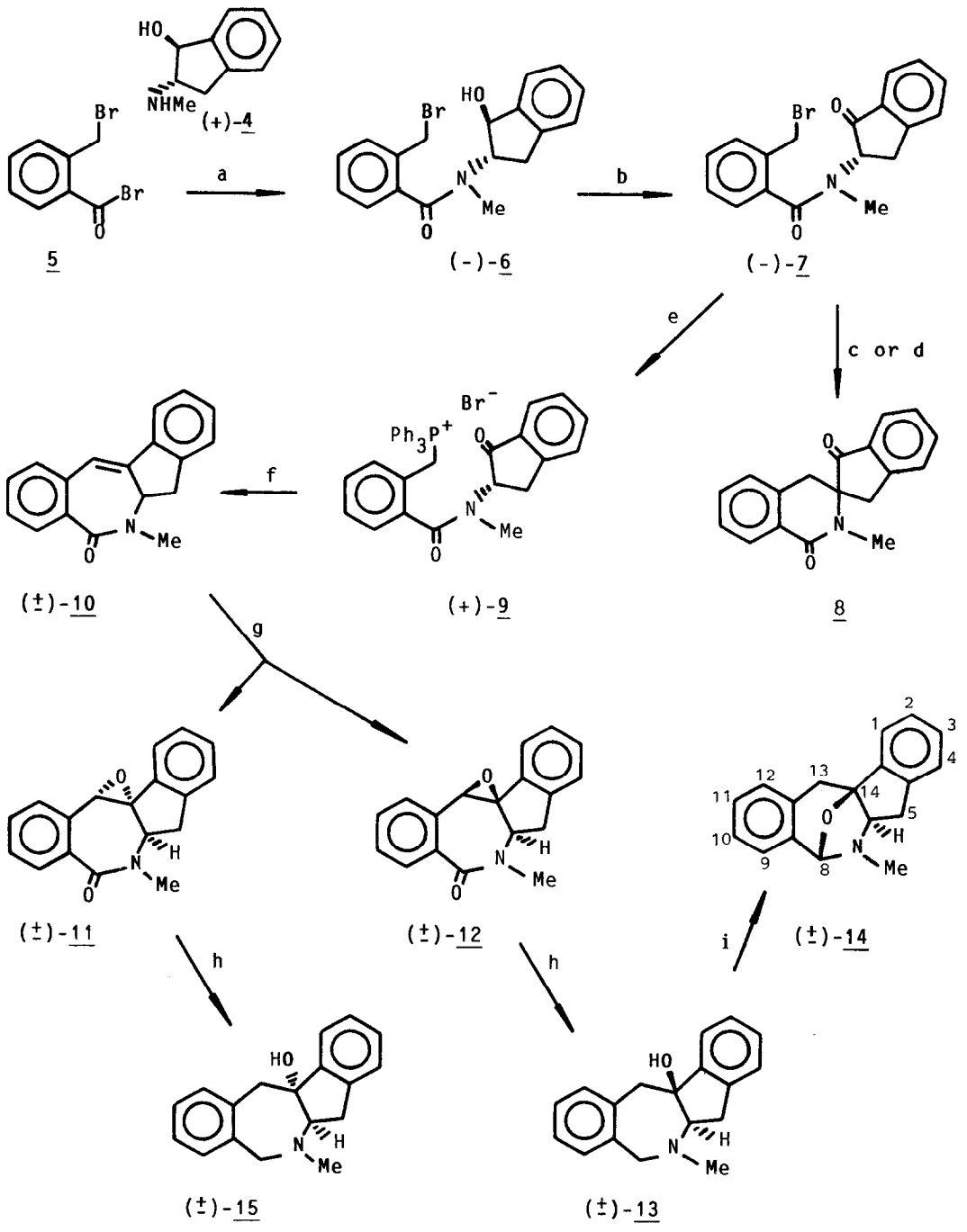
Abstract: The first total synthesis of A- and D-ring unsubstituted ribasine compound (14) is reported, the key step being the formation of the azepine ring by an intramolecular Wittig reaction.

We recently described the isolation and X-ray structure determination of ribasine (1), the first member of a new class of minor plant alkaloids bearing an 8,14-epoxy-indano(2,1-c)(2)benzazepine skeleton[1]. Himalayamine (2)[2] and ribasidine (3)[3], two new members reported soon afterwards, are both hydroxy derivatives of ribasine and the novelty of treir structure has prompted us to initiate work on their synthesis. In order to obtain the basic skeleton we started by condensing (1S,2S)-2-(Methylamino)-1-indanol (+)-(4)[4] with o-bromomethylbenzoyl bromide (5)[5]. This gave the bromoalcohol (-)-6 in 71% yield[6], which we next tried to cyclize in order to establish the azepine ring. We reasoned that this might be achieved by intramolecular addition to the carbonyl group of the indanone (-)-7 by means of a suitable derivative of its brominated carbon. PCC oxidation of (-)-6 led to (-)-7 in 70% yield, but when we tried to generate a benzyl anion by metal-halogen exchange with t-butyllithium at very low temperature, kinetically favoured enolization took place followed by an intramolecular displacement of the bromide ion to give the spiroderivative 8 as the sole isolated product (57% yield)[7]. Other cyclization attempts using an intramolecular Barbier reaction[8] (treatment of the bromoindanone (-)-7 with magnesium under a variety of conditions or with samarium di-iodide[9]) also failed.



1, Ribasine, R_1=R_2=H
2, Himalayamine, R_1=OH, R_2=H
3, Ribasidine, R_1=H, R_2=OH

A Wittig intramolecular reaction was then tried. The required phosphonium salt (+)-9 was easily prepared in nearly quantitative yield[10] from the bromoindanone (-)-7 by reaction with triphenylphosphine in refluxing benzene. Subsequent treatment with sodium hydride in THF at room temperature for several hours gave the desired cyclized product (±)-10 in at least 80% yield[11].



a) Et_3N/THF/rt, 71%; b) PCC/CH_2Cl_2/rt, 70%; c) t-BuLi/THF/-90ºC, 57%; d) 10% aq.NaOH:THF,(1:1)/rt, 98%; e)Ph_3P/C_6H_6/reflux, quant.; f) NaH/THF/rt, 80%; g) m-CPBA/CH_2Cl_2/-7ºC; h) LAH/THF/reflux; i) Fremy's salt-5% aq.Na_2CO_3/Py/rt.

In this step the stereochemical integrity of the chiral centre was completely lost due to racemization under the basic conditions, thus ruling out the possibility of achieving an enantiospecific synthesis.

The next step was to functionalize azepine 10 to obtain the aminoalcohol 13, which degradation studies of the natural product have shown to be the immediate precursor needed for the construction of the ether bridge present in the ribasine alkaloids.[3]

Compound 13 was obtained from the indanobenzazepine 10 by epoxidation followed by reduction with lithium aluminium hydride. Thus reaction of 10 with m-chloroperbenzoic acid at 0ºC gave the diastereomeric epoxides 11 and 12 in 31% and 35% isolated yield[12] respectively, along with compounds derived from the opening of the epoxides by m-chlorobenzoic acid. Due to the difficulty in separating 12, it was found preferable to carry out epoxidation at -7ºC with slow addition of excess mCPBA and then reduce the crude mixture obtained after work-up with LAH. This gave a 37% overall yield of the 14-hydroxyindanobenzazepine 13[13] which was easily separated from its epimer 15(21% overall yield)[14].

Attempts to improve the stereoselectivity in the introduction of the oxygen function by using t-butylhydroperoxide and catalysis by titanium or vanadium in the epoxidation step, were unsuccessful. We also tried the epimerization of the alcohol 15 to its epimer 13 by acid catalysis, which at room temperature did not take place to any synthetically useful extent. Upon heating at 65ºC decomposition was observed.

Finally, the (±)-aminoindanol 13 was oxidatively cyclized by Fremy's salt to yield the (±)-unsubstituted ribasine 14, which had similar spectral properties to those of the natural compound[15].

We have thus achieved the first total synthesis of the basic skeleton of the ribasine alkaloids. We are now trying to extend this procedure to the preparation of the naturally occurring products.

Acknowledgement: We thank the Comision Asesora (Spain) for financial support and the Ministry of Education and Science for a grant to R. Alonso.

References and Notes:

1. J.M.Boente, L.Castedo, R.Cuadros, J.M.Saá, R.Suau, A.Perales, M.Martínez-Ripoll and J.Fayos, Tetrahedron Lett., 24, 2029, 1983.

2. D.P.Allais, H.Guineaudeau, A.J.Freyer, M.Shamma, N.C.Ganguli, B.Talapatra and S.K.Talapatra, Tetrahedron Lett., 24, 2445, 1983.

3. J.M.Boente, M.J.Campello, L.Castedo, D.Domínguez, J.M.Saá, R.Suau and M.C.Vidal, Tetrahedron Lett., 24, 4481, 1983.

4. D.E.McClure, P.K.Lumma, B.H.Arison, J.H.Jones and J.J.Baldwin, J.Org.Chem., 48, 2675, 1983.

5. W.Davies and W.H.Perkin,Jr., J.Chem.Soc., 121, 2202, 1922. Compound 5 was prepared from phthalide and Ph_3PBr_2 following the procedure of D. J. Burton

and W.M.Koppes, J.Org.Chem., 40, 3026, 1975.

6. All new compounds gave satisfactory analytical data or high resolution mass spectra.

7. Compound 8 was also obtained in very good yield by sodium hydroxide treatment of an aqueous tetrahydrofuran solution of (-)-7.

8. Review: C.Blomberg and F.A.Hartog, Synthesis, 18, 1977.

9. P.Girard, J.L.Namy, H.B.Kagan, J.Am.Chem.Soc., 102, 2693, 1980.

10. (+)-Phosphonium salt 9 was obtained as a white solid, MS m/e (%) 359(6), 357(6), 278(47), 277(94), 262(100), 261(66), 260(38), 183(69), 160(44) and 108(38); H-NMR(250 MHz, $CDCl_3$, δ) 2.77 and 2.80(s,3H,N-Me of two rotamers), 3.24(dd,1H,J=16.8 and 5.3), 3.53(dd,1H,J=16.8 and 8.3), 4.53 and 4.68(broad m,1H), 5.30 and 5.67(m,2H) and 7.2-7.8(m,23H).

11. (±)-Indanobenzazepine 10 crystallized from EtOH as colorless needles, mp 178-180º; MS 261(M^+,100), 260(63), 232(26) and 230(37); H-NMR 3.03(s,3H, N-Me), 3.35(dd,1H,J=18.3 and 8.4,H-5), 3.50(dd,1H,J=18.3 and 1.9,H-5), 4.50(dt,1H,J=8.4 and 1.9,H-6), 7.08(d,1H,J=1.5,H-13), 7.3-7.5(m,6H), 7.61(m,1H) and 8.02(dd,1H,J=7.7 and 1.4,H-9).

12. Both epoxides were purified after repeated PTLC in neutral alumina using CH_2Cl_2-hexane(1:1) as eluant. (±)-Epoxide 12; mp 187-189ºC(EtOH); MS 277(M^+,1), 259(9), 248(2), 232(4), 220(7), 189(9) and 146(100); H-NMR 3.15(s,3H,N-Me), 3.40(dd,1H,J=17.4 and 10.1,H-5), 3.69(dd,1H,J=17.4 and 6.9,H-5), 4.30(dd,1H,J=10.1 and 6.9,H-6), 4.49(s,1H,H-13), 7.2-7.6(m,7H) and 7.95(m,1H,H-9). (±)-Epoxide 11: mp 237-239ºC(EtOH), MS 277(M^+,5), 259(40), 248(14), 232(17), 220(62), 189(31), 146(100) and 116(79); H-NMR 2.96(s,3H,N-Me), 3.39(d,1H,J=17.2,H-5), 3.52(dd,1H,J=17.2 and 5.5,H-5), 4.09(d,1H,J=5.5,H-6), 4.80(s,1H,H-13) and 7.2-7.8(m,8H).

13. (±)-14-Hydroxy-indanobenzazepine 13: mp 123º (EtOH-hexane); MS 265(M^+,41), 248(20), 247(12), 246(14), 232(12), 217(29), 216(76), 215(20), 160(100), 134(55) and 132(78); H-NMR 2.63(s,3H,N-Me), 2.87-3.15(m,3H,CH-CH_2), 3.20(d,1H,J=14.7,H-13), 3.63(d,1H,J=14.7,H-13), 3.68(d,1H,J=12,H-8), 3.84(d,1H,J=12, H-8) , 7.2-7.4(m,7H) and 7.45(m,1H).

14. (±)-14-Hydroxy-indanobenzazepine 15: MS 265(M^+,40), 264(38), 248(18), 247(8), 246(15), 232(13), 217(25), 216(63), 215(15), 160(88), 134(65), 132(98) and 104(100); H-NMR 2.54(s,3H,N-Me), 2.80(d,1H,J=15.1,H-13), 3.08(m,2H,H-5), 3.38(m,1H,H-6), 3.54(d,1H,J=15.1,H-13), 3.78(d,1H,J=15.3, H-8), 4.25(d,1H,J=15.3,H-8) and 7.1-7.4(m,8H).

15. (±)-8,14-Epoxy-indano(2,1-c)(2)benzazepine 14; was obtained in 55% yield MS 263(M^+,58), 262(34), 248(4), 235(10), 234(20), 220(6), 205(8), 204(34), 203(14), 202(8), 178(10), 158(10) and 144(100); H-NMR 2.29(s,3H,N-Me), 2.80(d,1H,J=16.5,H-13), 2.99-3.31(m,3H,CH-CH_2), 3.77(d,1H,J=16.5,H-13), 5.41(s,1H,H-8) and 7.0-7.6(m,8H).

(Received in UK 5 June 1986)