Tetrahedron Vol. 44, No. 11, pp. 3203 to 3208, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

STEREOCONTROLLED SYNTHESIS OF 19-EPIAJMALICINE FROM LOGANIN AGLUCONE.**

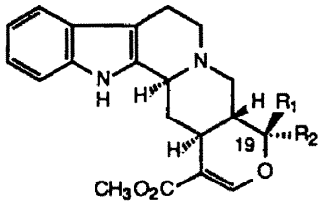
Enrico G. Baggiolini,* Giacomo Pizzolato and Milan R. Uskokovic

Chemistry Research Department, Hoffmann-La Roche Inc., Nutley, N. J. 07110, USA

(*Received in USA* 2 *November* 1987)

Abstract: The rare naturally occurring heteroyohimbine alkaloid 19-epiajmalicine (1) was prepared from loganin aglucone **6** via a sequence which involves as the central step the conversion of the δ-lactone **7**, easily derived from **6**, to the 6-epielenolic acid acetal **8**. After transformation of the latter to the aldehyde ester **12**, reductive condensation with tryptamine to give the lactam **13** and Bischler-Napieralski reaction resulted in the formation of the desired alkaloid **1**.

In the past decade, a great deal of attention has been focussed on the classification, localization and subdivision of α-adrenoceptors. Due to the far reaching pharmacological implications of these receptors, several studies have been directed toward the development of α-adrenergic agonists and antagonists[1]. Pentacyclic yohimbine and heteroyohimbine alkaloids have been found to display unsuspected activity and selectivity as α-adrenoceptor blocking agents and this prompted us to take a closer look at the biological consequences which are brought about by subtle stereochemical changes in the molecules of these compounds. One of the members of this family that was needed for our evaluation was 19-epiajmalicine (δ-yohimbine, raubasine) **1**. This alkaloid was originally isolated in 1951 from the bark and leaves of *Pseudocinchona mayumbensis (Corynanthe mayumbensis)* and named mayumbine[2]. More recently, the structure of the latter was revised and shown to be that of 19-epiajmalicine[3]. Its biogenetic pathway was later established in detail using cell free extracts from *Catharanthus roseus*[4,5]. This rare naturally occurring alkaloid has been prepared in racemic form by total synthesis[6] and in optically active form by partial synthesis[7].

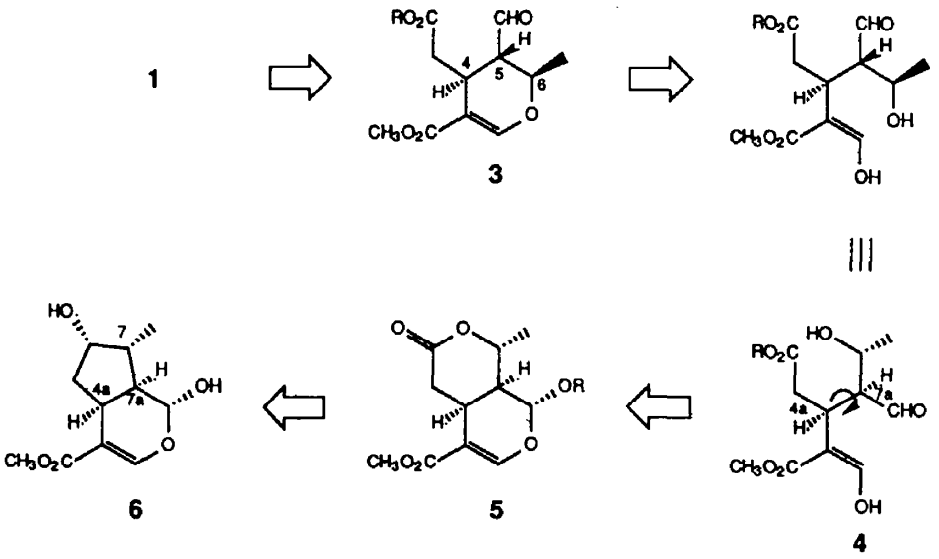


1 R_1=CH_3,R_2=H

2 R_1=H,R_2=CH_3

We were planning to synthesize 19-epiajmalicine from 6-epielenolic ester **3** and tryptamine (Scheme 1) using the methodology previously applied for the preparation of ajmalicine (**2**) from elenolic ester[8]. We envisaged to obtain **3** from the readily available iridoid loganin aglucone **6**[9], via the intermediate **5**. Our strategy was to derive the three asymmetric centers of **3** at C-4, C-5, and C-6 from the C-4a, C-7a and C-7 centers of **6**. This would involve, as depicted in Scheme 1, the opening of the lactone and vinylacetal moieties of **5**, the rotation around the C-4a and C-7a bond of the so obtained **4** and finally the ring closure to the cyclic vinylenolether **3**. This synthetic route partially mimics the biological formation of 19-epiajmalicine from loganin, which is its biogenetic precursor[4].

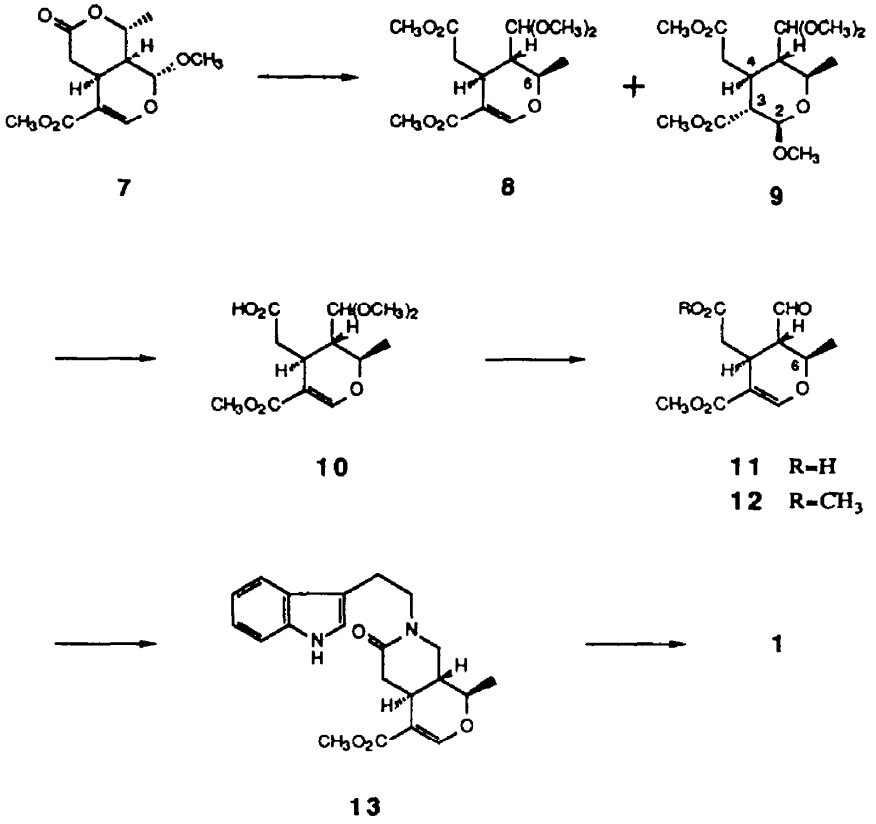
Scheme 1



Following this plan, the intermediate **7** (Scheme 2), obtained from **6** by known procedures[12], was treated with anhydrous hydrochloric acid in methanol. This gave a 3:2 equilibrium mixture of the desired, rearranged product **8** and the methoxyester **9**, together with about 20% of formally unreacted starting material. The configuration at the C-2 and C-3 centers of **9** was established via extensive proton NMR decoupling studies[14]. Since the main product **8** was contaminated with small amounts of difficult to separate epimers (at C-2 and C-3) of **9**, the entire mixture of **8** and **9** was treated with potassium *tert*-butoxide in order to effect the β-elimination of the methoxy groups of **9** and of its epimers. During this step, partial hydrolysis and transesterification of the carbomethoxy group at the C-4 side chain took place, and therefore the reaction mixture was hydrolyzed in the same reaction medium to give **10**. Treatment of the latter with aqueous trifluoroacetic acid in tetrahydrofuran gave 6-epielenolic acid **11** which was immediately converted to the corresponding methyl ester **12** by reaction with diazomethane.

Finally, conversion to 19-epiajmalicine **1** was effected[8] by first condensing **12** with tryptamine in benzene, followed by *in situ* sodium borohydride reduction of the intermediate imine and cyclization to the lactone **13**.

Scheme 2



Bischler-Napieralski cyclization of the latter gave the desired alkaloid **1**, mp. 215-216°C, $[\alpha]^{25}_D$ + 58.2° (*c* 1.4, $CHCl_3$), the spectroscopic proprieties of which were identical with those of a sample of authentic, racemic material prepared by total synthesis[6c] and with the data reported in the literature[6,7]. Since the crystalline free base is relatively unstable and turns yellow after a few days, it was converted to the corresponding stable hydrochloride salt, mp. 254-255°C, $[\alpha]_D^{25}$ + 80.1° (*c* 0.2, CH_3OH).

In conclusion, 19-epiajmalicine (**1**) was synthesized in the naturally occurring enantiomeric form from loganin aglucone **6** via a process which mimics its biogenesis. Loganin alglucone has been previously prepared in our laboratory by total asymmetric synthesis[6c].

EXPERIMENTAL

Materials and Methods

Melting points were measured on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were obtained on a Digilab Model FTS-15E spectrometer. The proton NMR spectra were recorded on a Varian XL-400 (400 MHz), Varian XL 200 (200 MHz), or Varian XL 100 (100 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in ppm downfield from internal Me_4Si. Mass spectral data were obtained on a Varian MAT CH-5 instrument. The ultraviolet absorption spectra were measured with a Cary Model 14 spectrophotometer and the optical rotations with a Perkin-Elmer 241 polarimeter. Chromatographic purifications were carried out with EM Merck silica gel (60, particle size 0.040-0.063 mm).

6-Epielenolic Acid Dimethyl Acetal (10)

A solution of 3.40 g (13.28 mmol) of [1R-(1α,4aα, 8α, 8aα)-4.4a,8,8a-tetrahydro-8-methoxy-1-methyl-3-oxo-1H,3H-pyrano[3,4-c]pyran-5-carboxylic acid methyl ester 7[12] dissolved in 220 ml of 10% anhydrous hydrogen chloride in methanol was refluxed for 2.5 h. After cooling at 0°C, the resulting mixture was made basic by careful addition of 2N potassium carbonate solution. Extraction with methylene chloride, after addition of brine, followed by washing of the combined organic extracts with brine, drying and evaporating to dryness gave a mixture of products **8** and **9** together with unreacted starting material **7**. The latter was separated from the product mixture by flash chromatography on silica, using hexane-ethyl acetate (4:1) as eluent. It was obtained 800 mg of unreacted **7** together with 2.10 g of a mixture of products **8** and **9**. Without further separation, this mixture was dissolved in 130 ml of anhydrous toluene, cooled at 0°C and treated with 2.0 g (1.78 mmol) of potassium *tert*-butoxide. After stirring at 0°C for 5 h, 0.5 ml of water was added, and the mixture allowed to come at room temperature and stirred for 30 min. It was then partitioned between toluene and 2N potassium bicarbonate and the organic phase was extracted repeatedly with potassium bicarbonate solution. The combined aqueous extracts were combined, acidified with 1N hydrochloric acid and extracted with dichloromethane. The organic extracts were washed with brine, dried and evaporated to give 1.69 g (58% yield based on recovered starting material) of 6-epielenolic acid dimethyl acetal **10** as a thick oil: $[\alpha]_D^{25}$-13.1 (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz) δ 1.38 (d, J = 7.0 Hz, 3 H), 2.08 (br d, J = 6.0 Hz, 1 H), 2.58 (dd, J = 12.4, 7.2 Hz, 1 H), 2.88 (dd, J = 12.4, 3.2, 1 H), 3.08 (br m, 1 H), 3.33 (s, 3 H), 3.38 (s, 3 H), 3.73 (s, 3 H), 4.15 (d, J = 6.0 Hz, 1 H), 4.58 (br q, J = 7.0 Hz, 1 H) 7.59 (s, 1 H) 11.1 (br s, 1 H); IR ($CHCl_3$) 3510-3400, 1740, 1710, 1630, 1440, 1290, 1190, 1100 cm^{-1} mass spectrum, m/e (rel. intensity). 256 (8), 225 (12), 210 (21), 196 (54), 178 (10), 165 (38), 85 (58), 75 (100); UV (EtOH) λ_{max} 238 (10, 280).

The corresponding methyl ester **8** was obtained as an oil by treatment of **10** with diazomethane: $[\alpha]_D^{25}$ +78.9° (*c* 0.3, $CHCl_3$): $[\alpha]_D^{25}$ -13.1 (0.2,$CHCl_3$): ^1H NMR (400 MHz) δ 1.39 (d, J = 8.0 Hz, 3 H), 2.06 (br d, J = 9.6 Hz, 1 H), 2.56 (dd, J = 12.0, 9.6 Hz, 1 H), 2.92 (dd, J = 12.0, 4.8 Hz, 1 H), 3.14 (br m, 1 H), 3.32 (s, 3 H), 3.38 (s, 3 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 4.14 (d, J = 9.6 Hz, 1 H), 4.57 (br q, J = 9.6 Hz, 1 H), 7.58 (s, 1 H); IR ($CHCl_3$) 1730, 1698, 1625, 1435 cm^{-1}: mass spectrum, m/e (relative intensity) 270 (5), 210 (42), 178 (22), 165 (50), 75 (100); UV (EtOH) λ_{max} 236 (11,600), 350 (70). Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34. Found: C 55.49; H, 7.24.

6-Epielenolic Acid Methyl Ester (12)

A solution of 1.050 g (3.65 mmol) of 6-epielenolic acid dimethyl acetal (**10**) in 8 ml of tetrahydrofuran was cooled at 0°C and treated dropwise with 8 ml of trifluoroacetic acid, followed by 4 ml of water. The system was then brought to room temperature and stirred for 5 h. Most of the tetrahydrofuran present was then evaporated and the remaining mixture was extracted with methylene chloride. The combined organic extracts were washed with water, then brine, dried and evaporated to dryness to give 800 mg of 6-epielenolic acid (90% yield) (**11**). This was dissolved in ether and treated with an ethereal solution of diazomethane, until the yellow color persisted. Evaporation of the solvent and purification of the residue by flash chromatography, using chloroform-ethyl acetate (9:1) as eluent gave 528 mg (56% yield) of pure **12** as an oil: $[\alpha]_D^{25}$ + 78.9 (*c* 0.3, $CHCl_3$) ^1H NMR (400 MHz) δ 1.43 (d, J = 7.6, 3 H), 2.57 (dd, J = 16.2, 9.4 Hz, 1 H), 2.71 (td, J = 7.2, 1.8 H, 1 H), 2.93 (dd, J = 16.2, 3.75 Hz, 1 H), 3.42 (m, 1 H) 3.68 (s, 3 H), 3.73 s, 3 H), 4.43 (quin., J = 6.5, 1 H), 7.59 (s, 1 H), 9.64 (d, J = 1.8, 1 H); IR ($CHCl_3$) 2725, 1728, 1700, 1630 cm^{-1}: mass spectrum, m/e (rel. intensity) 256 (M^+, 15), 225 (40), 224 (24), 196 (100), 195 (42), 153 (67), 135 (42): UV (EtOH) λ_{max} 236 (9,930). Anal. Calcd for $C_{12}H_{16}0_6$: C, 56.25; H, 6.29. Found: C, 56.17; H, 6.42.

2,3-Seco-19-epiajmalicine-3-one (13)

A solution of 736 mg (2.88 mmol) of 6-epielenolic acid methyl ester (**12**) in 2 ml of anhydrous benzene was treated with a solution of 550 mg (3.44 mmol) of tryptamine in 10 ml of anhydrous benzene. The resulting solution turned cloudy almost immediately, due to the separation of water. After 10 min stirring at room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in 20 ml of methanol and treated with 300 mg (7.93 mmol) of sodium borohydride, stirred first at room temperature for 10 min then at 50°C for 5 min. After evaporation of most of the solvent, the residue was diluted with 1N hydrochloric acid, and extracted with dichloromethane. The combined organic extracts were washed with 2N aqueous potassium bicarbonate, then

brine, dried and evaporated. The crude product was purified by flash chromatography on silica, using ethyl acetate-hexane (7:3) as eluent to give 923 mg (87% yield) of pure 2,3-seco-19-epiajmalicine-3-one (**13**), mp 144-145°C (after recrystallization from hexane-ethyl acetate): $[\alpha]_D^{25}$ + 294.9 (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz) δ 1.05 (d, J = 6.4, 3 H), 3.71 (s, 3 H) 7.06 (br s, 1 H), 7.16 (m, 2 H), 7.52 (br s, 1 H), 7.66 (d, J = 7.2 Hz, 1 H), 8.05 (br s, 1 H); IR (K Br) 3210, 3185, 1708, 1625 cm^{-1}: mass spectrum, m/e (relative intensity) 368 (M^+, 4), 143 (100), 130 (18): UV (EtOH) λ_{max} 221 (35,500), 240 (9,720), 272 (4,630), 281 (5,120), 289 (4,450) nm. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.74; H, 6.68; N, 7.62.

19-Epiajmalicine (**1**) and 19-Epiajmalicine Hydrochloride

A solution of 730 mg (1.98 mmol) of 2,3-seco-19-epiajmalicine-3-one (**13**) in 35 ml of anhydrous benzene was treated with dropwise and at room temperature with 2 ml (21.46 mmol) of freshly distilled phosphorous oxychloride and the mixture refluxed for 40 min. It was then evaporated *in vacuo* to remove the solvent and the excess of phosphorus oxychloride and the residue dissolved in 25 ml of methanol, cooled at 0°C and treated with 300 mg (7.93 mmol) of sodium borohydride, added in small portions. After stirring at 0°C for 5 min, the resulting mixture was evaporated and the residue partitioned between 1N sodium hydroxide solution and a mixture of 95% dichloromethane and 5% methanol. The aqueous phase was extracted repeatedly and the combined organic extracts washed with brine, dried and evaporated to dryness. The residue was purified by flash chromatography on silica, using hexane-ethyl acetate (1:2) as eluent to give 545 mg (78% yield) of 19-epiajmalicine (**1**), mp 215-216°C (dec.) (after recrystallization from methanol): $[\alpha]_D^{25}$ + 58.2° (*c* 1.4, $CHCl_3$) ^1H NMR (200 MHz) δ 1.36 (d, J = 6.2, 3 H), 3.72 (s, 3 H) 3.84 (m, 1 H), 7.08 (m, 2 H), 7.28 (d, J = 8.0 1 H), 7.44 (d, J = 7.2, 1 H), 7.54 (s, 1 H), 7.93 (br s, 1 H); IR ($CHCl_3$) 3470, 2750-2850, 1700, 1620 cm^{-1}; mass spectrum, m/e (relative intensity) 353 (M^+ + 1, 24), 352 (M^+, 100), 351 (88), 184 (29), 156 (68): UV (EtOH) λ_{max} 225 (37,350), 245 (10,390), 273 (6,310), 282 (6,480), 289 (5,490). The corresponding stable 19-epiajmalicine hydrochloride was prepared by dissolving 19-epiajmalicine in methanolic hydrochloric acid, followed by addition of ether. The salt was recrystallized from methane-ether: mp 254-255°C, $[\alpha]_D^{25}$ + 80.1 (*c* 0.2, CH_3OH). Anal. Calcd for $C_{22}H_{24}N_2O_3Cl$: C, 64.86; H, 6.48; N, 7.20; Cl, 9.12. Found: C, 64.54; H, 6.21; N, 7.20; Cl, 9.30.

Acknowledgement. We wish to thank the members of the Physical Chemistry Department of Hoffmann-La Roche Inc. for determination of spectra and analytical data.

REFERENCES AND NOTES

** We dedicate this paper to Professor Edward C. Taylor on the occasion of his 65th birthday.

1. P.B.M.W.M. Timmermans and P.A. von Zwieten, *J. Med. Chem.*, **25**, 1389, (1982).
2. M. Raymond-Hamet, *C.R. Acad. Sci. Paris.* **232**, 2354 (1951).
3. J. Melchio, A. Bouquet, M. Pais and R. Goutarel, *Tetrahedron Lett.*, 315 (1977).
4. J. Stockigt in *"Indole and Biogenetic Related Alkaloids"*, eds. I.D. Phillipson and M.H. Zenk, Academic Press, London, 1980, p. 113.
5. J. Stockigt, G. Hofle and A. Pfitzner, *Tetrahedron Lett.*, **21**, 1925 (198 6.a) E. Winterfeldt, H.E. Radunz and T. Korth, *Chem. Ber*, **101**, 3172 (1968); b) E. Winterfeldt, A.Gaskell, T. Korth, H. E. Radunz and M. Walkowiak,*Chem Ber.*, **102**, 3558 (1969); c) J. Gutzwiller, G. Pizzolato and M. Uskokovic, *J. Am. Chem. Soc.*, **93**, 5907 (1971); d) E. Wenkert, G.T. Chang, H.P.S. Chawla, D. W. Cochran, E. W. Hagamar, J. C. King and K. Orito, *J. Am. Chem. Soc.*, **98**, 3645 (1976).
7. a) L. A. Djakoure, F.X. Jarreau and R. Goutarel, *Tetrahedron*, **31**, 2695 (1975); b) G. Palmisano, B. Danieli, G. Lesma and R. Riva, *J. Chem. Soc.*, Perkin Trans. I, 925 (1985).
8. a) R.B. Woodward, F.E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958); b) F. A. Mackellaar, R.C. Kelly, E.E. van Tamelen, and C. Dorschel, *J. Am. Chem.Soc.* **95**, 7155 (1973).
9. The (-)-loganin aglucone used was prepared by hydrolytic cleavage of loganin[10] which was isolated from *Strychnos nux vomica.*

10. J. J. Partridge, N.R. Chadha and M. Uskoković, *J. Am. Chem. Soc.* **95**, 532 (1973).
11. W.R. Dunstan and F. W. Short, *Pharm. J. Trans.* **14**, 1025 (1984).
12. M. Makane, C.R. Hutchinson, D. Van Engen and J. Clardy, *J. Am. Chem. Soc.*, **100**, 7079 (1978)
13. 9: mp 39-40°C; $[\alpha]_D^{25}$ + 6.1 (*c* 0.3 $CHCl_3$); ^1H NMR (400 MHz) δ 1.34 (d, J = 6.2 Hz, 3H, CH_3-C-6, 1.83 (ddd, J = 11.0, 9.8, 1.5 Hz, 1H, CH-5), 2.28 (dd, J = 17.4, 3.5 Hz, 1 H, CO-CH_2-C-4), 2.46 (dddd, J = 12.0, 11.0, 5.0, 3.5 Hz, 1 H, CH-4), 2.74 (dd, J = 12.0, 8.5 Hz, 1 H, CO-CH-3), 2.78 (dd, J = 17.4, 5.0 Hz, 1 H, CO-CH_2-C-4), 3.39 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.58 (dq, J = 9.8, 6.2 Hz, 1 H, CH-6), 3.66 (s, 3 H, $COOCH_3$), 3.70 (s, 3 H, $COOCH_3$), 4.44 (d, J = 8.5 Hz, 1 H, CH-5); IR (KBr) 1730, 1435, 1160, 1065 cm^{-1}; mass spectrum, m/e (relative intensity) 274 (5), 255 (8), 239 (22), 238 (5), 227 (6), 210 (22) 196 (7), 178 (22), 165 (24), 143 (27), 101 (45), 75 (100). Anal Calcd for $C_{15}H_{26}O_8$: C, 53.88; H, 7.84; . Found: C, 54.03; H, 7.83.
14. The coupling constant between the CH-3 and CH-4 protons was found to be 12.0 Hz, while the one between CH-3 and CH-2 was 8.5 Hz. The magnitude of these constants suggests a respective antiperiplanar conformation of the CH-2, CH-3 and CH-4 protons.