

SYNTHESIS OF 3- $\omega$ -EPOXIDO FARNESYL INDOLES, INTERMEDIATES IN THE  
BIOGENESIS OF SESQUITERPENIC INDOLE ALKALOIDS

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Summary : Epoxides 1a,b, the probable bioprecursors of a serie of indoloterpene alkaloids, were synthesized from indole and farnesyl bromides through application of the Van Tamelen regiospecific epoxidation process to the derived N-acylindolines 14a,b.

The cationic species 2 (Chart 1) resulting from cyclization of a 3- $\omega$ -epoxido farnesyl indole 1 and related to drimanol simply accounts for the biogenesis of polyalthenol 3<sup>1</sup> and of polyveoline 5<sup>2</sup> along largely precedented rearrangements. Polyveoline 5 could also result from a 2-farnesylindole, as it is probably the case with neopolyalthenol 6<sup>3</sup> and with polyavolensine 4<sup>4</sup>. It then seemed interesting to prepare such indoles bearing an  $\omega$ -epoxidofarnesyl substituent from the corresponding farnesyl indoles. This paper deals with the 3-substituted series<sup>5</sup>.

The main difficulty stays in the regioselective epoxidation, a problem solved more than 20 years ago by Van Tamelen in the non nitrogenous terpene series<sup>6</sup>. However, with unprotected indoles primary oxidation at the 3-position was predictable. Nevertheless, a 3-oxidated indolenine could act as a relay in a regioselective remote oxidation of the terpenoid chain. Therefore, 3-geranylindole 7 (35% from geranyl bromide and indolymagnesium iodide, Chart 2) was treated with ClOtBu (Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 5min) in a model experiment. This attempt failed and afforded only compound 8, which was identified with a sample prepared by alkylation of oxindole.

3-E,E-farnesyloxindole 9 was similarly obtained from E,E-farnesyl bromide<sup>7,8</sup> and oxindole (5 eq ; MeONa, 5 eq ; MeOH, 0°C, 2h, 40%). In strong difference with the indole series<sup>3</sup>, 9 could be oxidized (NBS, 1.2 eq, DME-H<sub>2</sub>O 9:1, satd soln, rt 3h) to bromohydrin 10 (50%), which gave epoxide 11 (80%, interconvertible mixture of C(3)-epimers) upon treatment with K<sub>2</sub>CO<sub>3</sub>.

By analogy with oxindole 9, N-acylindolines were next thought to be suitable for oxidation to bromohydrins. Indolymagnesium iodide (8 eq) was alkylated with E,E-farnesylbromide to give 12a (35%)<sup>3,13</sup>. NaBH<sub>3</sub>CN reduction<sup>9,10</sup> (HClO<sub>4</sub>, rt, 20 min) yielded 13a (77%), which was quantitatively N-acylated to 14a. Van Tamelen's conditions actually allowed oxidation to 15a (53%), which generated epoxide(s) 16a upon K<sub>2</sub>CO<sub>3</sub> treatment. The free indole nucleus was then

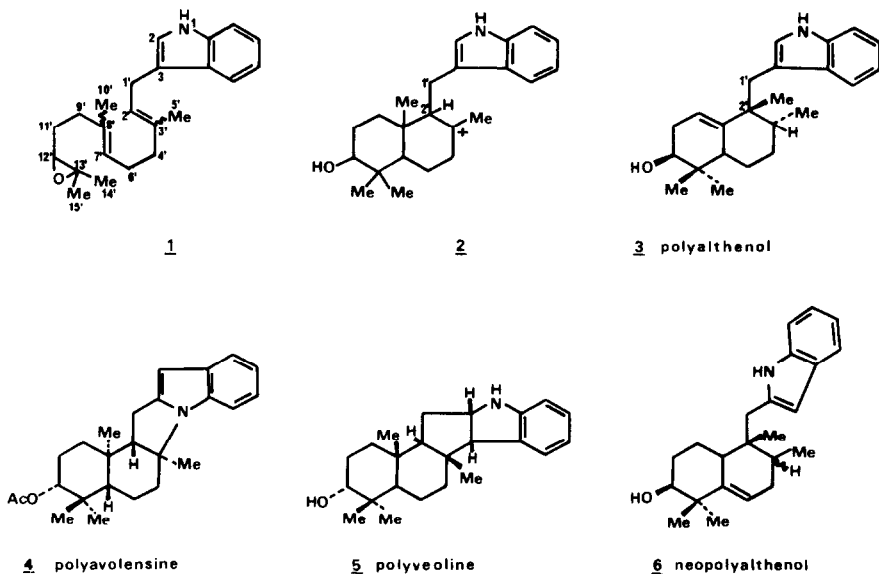


Chart 1

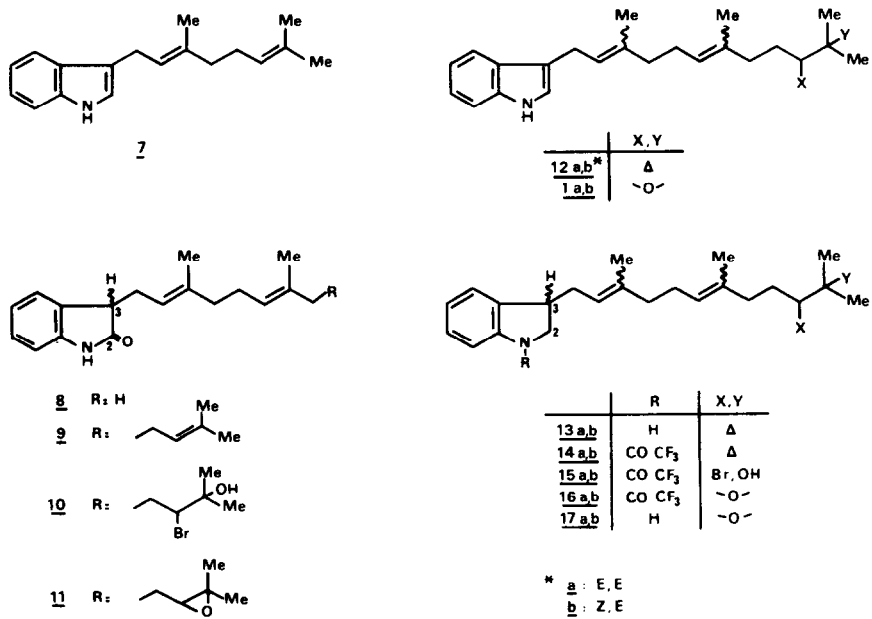



Chart 2

regenerated through careful reduction ( $\text{NaBH}_4$ , MeOH, rt, 5min) : 17a (85%) and further oxidation:  $\text{MnO}_2$ ,  $\text{CuCl}_2$ /py,  $\text{PhSe}_2\text{O}^{11}$ , or a modified Ruschig procedure gave only poor yields (10-20%). However, the last method showed formation of some 1a in the chlorination step, due to the basicity of the unreacted indoline. This observation dictated the experimental "one pot" conditions ( i) NCS, 1eq ;  $\text{Et}_3\text{N}$ , 2eq ;  $\text{CH}_2\text{Cl}_2$ ,  $-10^\circ\text{C}$ , 5min ii) DBU, instantaneous), which allowed isolation of 1a in 60% yield from 17a.

Similarly, 3-Z,E-farnesylindole 12b gave successively 13b (69%), 14b (100%), 15b (48%), 16b (94%), 17b (85%) and finally 1b (52%).

Epoxide 1a was submitted to a preliminary attempt of cyclisation ( $\text{BF}_3$ / $\text{Et}_2\text{O}$ , 1.2eq, PhH,  $5^\circ\text{C}$ , 15min). A complex mixture of at least 13 isomers ( $\text{M}^+$  337) was produced. GC/MS<sup>12</sup> examination selected two compounds, which exhibited significant peaks  $m/z$  130 ( i : , ), 207 ( $\text{M}^+ - \underline{i}$  ), 206 ( $\text{M}^+ - \underline{i} - 1$ ) and 189 ( $\text{M}^+ - \underline{i} - \text{H}_2\text{O}$ ). Peak i was significantly present in the spectra of all 13 compounds, of epoxides 1a, of farnesylindoles 12a and of polyalthenol 3<sup>1</sup>. The three other fragments were only present in the spectrum of polyalthenol 3<sup>1</sup>, but not in that of 1a, nor was peak  $m/z$  189 present in the spectrum of 12a. The specific occurrence of charged species  $m/z$  207, 206 and 189 in the MS of only 2 over 13 isomeric oxygenated products might indicate that they are tetracyclic : retention of the charge on the oxygen moiety could be due to the breakage of an allylic C-C bond, like C(1')-C(2') in polyalthenol.

$\text{BF}_3$  treatment of oxindole epoxide(s) 11 gave rise to a mixture of 8 isomeric compounds,  $\text{M}^+$  353 (GC/MS), one of which exhibited peaks at  $m/z$  189, 206, 207.

Further work is undertaken to answer the question of indole acting as terminator in such biomimetic polyene cyclizations.

#### References and Notes

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- 12) We thank Prof. H.Choisy and Dr D.Lamiabile for these measurements.
- 13) Spectral data of the principal compounds (UV(MeOH)  $\lambda_{max}$  nm ; IR(films)  $\nu_{cm^{-1}}$  ; MS:m/z ;  $^1H$  NMR, 60MHz,  $CDCl_3$ :  $\delta$ ppm).
- 9: 220, 250, 278 ; 1620, 1710, 3200 ; 133, 145, 146, 172, 192, 268, 294, 337( $M^{+}$ ) ; 1.68(s,  $H_3-5'$ ,  $H_3-10'$ ,  $H_3-14'$ ,  $H_3-15'$ ), 3.4(m, H-3), 4.7-5.3(m, H-2', H-7', H-12'), 6.8-7.3(m, H-5, H-6, H-7, H-8), 9.2(s, H-1).
- 10: 222, 251, 278 ; 1620, 1710, 3240 ; 133, 167, 203, 268, 353, 415, 417, 433, 435( $M^{+}$ ) ; 1.34(s,  $H_3-14'$ ,  $H_3-15'$ ), 1.55(s,  $H_3-5'$ ,  $H_3-10'$ ), 2.65(s, OH-13'), 3.48(m, H-3), 3.95(m, H-12'), 4.9-5.3(m, H-2', H-7'), 6.7-7.4(m, H-5, H-6, H-7, H-8), 9.1(s, H-1).
- 11: 220, 250, 277 ; 1620, 1700, 3240 ; 133, 145, 146, 172, 200, 226, 282, 335, 353( $M^{+}$ ) ; 1.28(s,  $H_3-14'$ ,  $H_3-15'$ ), 1.55(s,  $H_3-5'$ ,  $H_3-10'$ ), 3.48(m, H-3), 4.8-5.3(m, H-2', H-7'), 6.7-7.5(m, H-5, H-6, H-7, H-8), 9.35(s, H-1).
- 12a: 220, 278, 290 ; 3400 ; 117, 130, 168, 170, 184, 185, 321( $M^{+}$ ) ; 1.60(s), 1.65(s), 1.75(s) ( $H_3-5'$ ,  $H_3-10'$ ,  $H_3-14'$ ,  $H_3-15'$ ), 3.45(d,  $J=7$ Hz,  $H_2-1'$ ), 5.1(m), 5.4(t,  $J=7$ Hz) (H-2', H-7', H-12'), 6.85(s, H-2), 7.0-7.6(m, H-5, H-6, H-7, H-8), 7.8(s, H-1).
- 12b: 220, 278, 290 ; 3420 ; 117, 130, 168, 170, 184, 185, 321( $M^{+}$ ) ; 1.60(s), 1.65(s), 1.75(s) ( $H_3-5'$ ,  $H_3-10'$ ,  $H_3-14'$ ,  $H_3-15'$ ), 3.45(d,  $J=7$ Hz,  $H_2-1'$ ), 5.10(m), 5.45(t,  $J=7$ Hz) (H-2', H-7', H-12'), 6.9(s, H-2), 7.0-7.6(m, H-5, H-6, H-7, H-8), 7.8(s, H-1).
- 15a: 210, 255, 265, 277, 285 ; 1690, 3500 ; 117, 135, 214, 418, 515, 517( $M^{+}$ ) 132(s,  $H_3-14'$ ,  $H_3-15'$ ), 1.58(s), 1.60(s) ( $H_3-5'$ ,  $H_3-10'$ ), 4.9-5.4(m, H-2', H-7'), 7.0-7.5(m, H-5, H-6, H-7) 8.3(m, H-8).
- 15b: 210, 255, 265, 277, 285 ; 1690, 3500 ; 117, 135, 214, 418, 515, 517( $M^{+}$ ) ; 1.32(s,  $H_3-14'$ ,  $H_3-15'$ ), 1.58(s), 1.72(s) ( $H_3-5'$ ,  $H_3-10'$ ), 4.9-5.3(m, H-2', H-7'), 7.1-7.4(m, H-5, H-6, H-7), 8.2(m, H-8).
- 16a: 208, 248, 260, 270, 280 ; 1690 ; 135, 214, 281, 418, 435( $M^{+}$ ) ; 1.25(s), 1.30(s) ( $H_3-14'$ ,  $H_3-15'$ ), 1.58(s,  $H_3-5'$ ,  $H_3-10'$ ), 2.65(t,  $J=6$ Hz, H-12'), 4.9-5.3(m, H-2', H-7'), 7.0-7.4(m, H-5, H-6, H-7), 8.2(m, H-8).
- 16b: 208, 255, 268, 280, 285 ; 1690, 135, 214, 281, 418, 435( $M^{+}$ ) ; 1.25(s,  $H_3-14'$ ,  $H_3-15'$ ), 1.58(s), 1.7(s) ( $H_3-5'$ ,  $H_3-10'$ ), 2.65(t,  $J=6$ Hz, H-12'), 4.9-5.3(m, H-2', H-7'), 7.0-7.4(m, H-5, H-6, H-7), 8.15(m, H-8).
- 17a: 215, 240, 290 ; 1600, 3360 ; 117, 118, 119, 170, 184, 186, 339( $M^{+}$ ) ; 1.30(s), 1.35(s), ( $H_3-14'$ ,  $H_3-15'$ ), 1.65(s,  $H_3-5'$ ,  $H_3-10'$ ), 2.7(t,  $J=6$ Hz, H-12'), 5.0-5.4(m, H-2', H-7'), 6.5-7.4(m, H-5, H-6, H-7, H-8).
- 17b: 215, 240, 290 ; 1600, 3360 ; 117, 118, 119, 130, 170, 184, 339( $M^{+}$ ) ; 1.25(s,  $H_3-14'$ ,  $H_3-15'$ ), 1.6(s), 1.7(s) ( $H_3-5'$ ,  $H_3-10'$ ), 2.65(t,  $J=6$ Hz, H-12'), 4.9-5.4(m, H-2', H-7'), 6.4-7.2(m, H-5, H-6, H-7, H-8).
- 1a: 222, 288 ; 3400 ; 117, 130, 168, 170, 182, 184, 196, 210, 238, 337( $M^{+}$ ) calc. 337.2398, meas. 337.2472 ; 1.24(s), 1.28(s) ( $H_3-14'$ ,  $H_3-15'$ ), 1.6(s), 1.7(s) ( $H_3-5'$ ,  $H_3-10'$ ), 2.65(t,  $J=6$ Hz, H-12'), 3.4(d,  $J=7.5$ Hz,  $H_2-1'$ ), 5.0-5.5(m, H-2', H-7'), 6.9(m, H-2), 7.0-7.65(m, H-5, H-6, H-7, H-8), 8.3(s, H-1).
- 1b: 220, 280 ; 3410 ; 117, 130, 168, 170, 182, 184, 196, 210, 238, 337( $M^{+}$ ) calc. 337.2398, meas. 337.2409 ; 1.20(s), 1.25(s) ( $H_3-14'$ ,  $H_3-15'$ ), 1.6(s), 1.7(s) ( $H_3-5'$ ,  $H_3-10'$ ), 2.65(t,  $J=6$ Hz, H-12'), 3.4(d,  $J=7.5$ Hz,  $H_2-1'$ ), 4.9-5.6(m, H-2', H-7'), 6.85(m, H-2), 6.9-7.1(m, H-5, H-6, H-7, H-8), 7.95(s, H-1).

(Received in France 3 May 1985)