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TOTAL SYNTHESIS OF (±)-GALANOLACTONE

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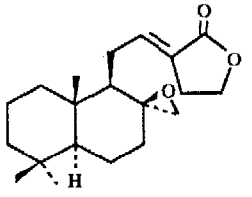
(±) - Galanolactone, 1,has been synthetised from the cyanoketone 2 prepared from geraniol .

Galanolactone, **1**, a labdanoid diterpenic lactone which possesses some antitumoral and antifungal activities, was isolated from the seeds of *Alpinia galanga* and its structure very recently described[1].

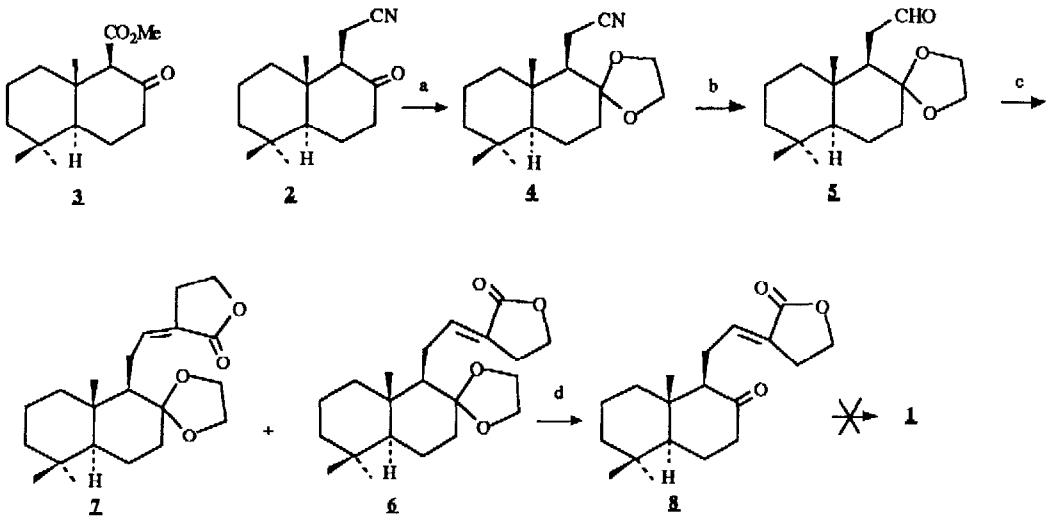
We report the synthesis of (±)-galanolactone, starting from the known cyanoketone 2[2], which we have obtained for another purpose[3] from the keto ester **3**, itself obtained from geraniol according to White' s procedure[4].



1

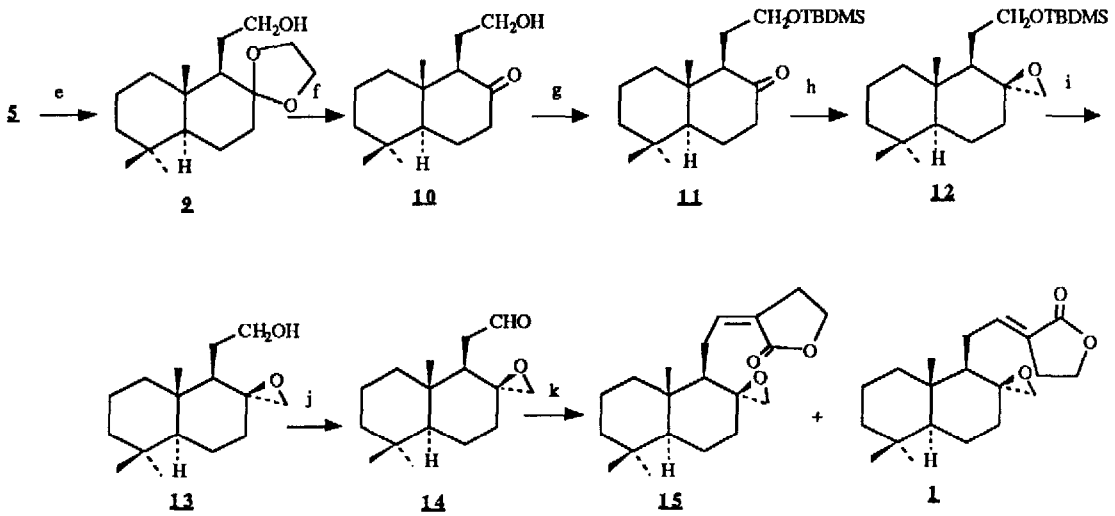
After protection of the keto group of **3** by dioxolanation, reduction of the nitrile of **4** by diisobutylaluminium hydride furnished the aldehyde **5**. A Wittig-Horner reaction between **5** and the anion of diethylphosphono-2-butyrolactone led to the isomeric lactones E, **6**[5], and Z,**7**[6], in a ratio 3/1.

However, after deprotection of the keto group, we failed in our attempts to introduce the epoxymethylene function on **8**[7] by treatment with dimethyl-sulfonium methylide[8] or with the lithio derivative of chloroiodomethane[9].



a) - $Me_3SiOCH_2CH_2OSiMe_3$, TMS- triflate, CH_2Cl_2, 0° C,[10]. b) - DIBAH , toluene, 0° C, 30 min., 80% yield. c) - diethylphosphono-2-butyrolactone, NaH, toluene, 0°C, then **5**, toluene, 80°C, 1h ,80%, E/Z = 3/1. d) - HCl, 0.1 N, acetone.

Therefore, the aldehyde **5** was reduced to the alcohol **9**, transformed to the keto-alcohol **10** and then to the t-butyldimethylsilyl derivative **11**. Reaction of **11** with dimethylsulfonium methylide afforded the epoxide **12** by addition on the less hindered α-side ofthe molecule. After cleavage of the silyl protective group, a Swern oxidation on **13**[11] furnished the aldehyde **14**[12] which, when reacted with the anion of diethylphosphono-2-butyrolactone, gave the isomeric lactones E **1**[13] and Z **15**[14], separable by column chromatography. The E isomer **1** has spectroscopic data (^1H NMR, ^{13}C NMR) identical with those given for galanolactone[1].



- e) - $NaBH_4$, EtOH, r.t., 1h., 100% yield. f) - HCl 0.1 N, acetone, r.t. g) - TBDMSCl, imidazole, THF, r.t., overnight. h) - (CH_3)$_3$ S $^+I^-$, t- BuOK, DMSO / THF 1/1, 0°C, 30 min., then r.t., 1h.. i) - Bu_4NF, THF, r.t., 3h..j) - DMSO,(COCl)$_2$, - 60°C, 10 min., then **13**, 15 min., then Et_3N. k) - diethylphosphono-2-butyrolactone, NaH, toluene, 0°C, then **14**, toluene, 80°C, 1h., 66% yield, E/Z = 3/1 .

References and Notes

(NMR in $CDCl_3$, at 400 MHz for ^1H, TMS as reference).

1. H. Morita and H. Itokawa, *Planta Medica* , 1988, 117.
2. T.H. Kim and S. Isoe, *J. Chem. Soc. Chem. Comm..*, 1983, 730.
3. D. Herlem, J. Kervagoret, F. Khuong-Huu and A.S. Kende, unpublished work.
4. R.W. Skeean, G.L. Trammell and J.D. White , *Tetrahedron Letters*,, 1976, 525.
5. Compound 6 : mp 120° (MeOH); IR (CCl_4) : 1760 and 1680 cm^{-1}; UV (EtOH) : 227 nm (ε 11 500); ^1H NMR δ ppm : 0.81 (3H, s, CH_3 - 18), 0.87 (3H, CH_3 - 19), O.91 (3H, s, CH_3 - 20),2.84(2H,m, CH_2 - 14), 3.73 (1H, m), 3.90 (1H,m) and 3.99(2H, m), (2 CH_2, ethylene ketal),4.35 (2H, t, J = 7.5 Hz, CH_2 - 15), 6.9 (1H, m, H-12); EIMS : M+ 348, m/z 333, 257, 208, 99.
6. Compound 7 : mp 153° (MeOH) ; IR (CCl_4) : 1765 and 1670 cm^{-1}; UV (EtOH) : 227 nm (ε 11 490);^1H NMR , δ ppm : 0,78 (3H, s, CH_3 - 18), 0.83 (3H, s, CH_3 -19), 0.88 (3H, s, CH_3 - 20), 2.67 and 2.73 (2H, m, CH_2 - 11), 2.84 (2H, m, CH_2 - 14), 3.62, 3.80, 3.89 and 4.0 (4m, 2 CH_2, ethylene ketal), 4.25 (2H, t, J = 7.5 Hz, CH_2 - 15), 6.3 (1H, m, H- 12); EIMS : M+ 348, m/z 333, 208, 99 .

7. Compound 8 : oil ; IR (neat) : 1760, 1710 and 1680 cm $^{-1}$; UV (EtOH) : 226 nm (ε 11 400); ^{1}H NMR, δ ppm : 0.66 (3H, s, CH_3 - 18), 0.75 (3H, s, CH_3 - 19), 0.86(3H, s, CH_3-20), 4.26 (2H, t, J=7.5 Hz, CH_2 - 15), 6.41 (1H, m, H- 12); EIMS : M^+304 , m/z 289.

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10. T. Tsunoda, M. Suzuki and K. Noyori, *Tetrahedron Letters*, 1980, 1357.

11. Compound 13 : oil; ^{1}H NMR, δ ppm : 0.86 (3H, s, CH_3 - 18), 0.89 (3H, s, CH_3 -19), 0.89 (6H , s, CH_3- 19 and CH_3 - 20), 2.25 and 2. 31 (2H, 2d, J = 4 Hz, CH_2 -17), 3.45 and 3.53 (2H, 2m, CH_2 - 12); EIMS : M^+ 252, m/e 237, 221, 193.

12. Compound 14 : oil; IR (neat): 1715 cm^{-1} (ν C = O) ; ^{1}H NMR δ ppm : 0.90 (3H, s,CH_3 - 18), 0. 95 (6H, s, CH_3 - 19 and CH_3 - 20), 2.25 and 2.31 (2H, 2d, J = 4 Hz,CH_2 - 17); EIMS : M^+ 250, m/z 235 .

13. Compound 1 : mp 115° (MeOH); IR (CCl_4) : 1765 and 1680 cm^{-1}; UV (EtOH) 225 nm (ε 11 500);^{1}H NMR, δ ppm : 0.87 (3H, s, CH_3 - 18), 0.91 (3H, s, CH_3 - 19), 0.93 (3H, s, CH_3 - 20), 1.65 (1H, m, H - 9), 1.73 and 2.09 (2H, m, CH_2 - 11), 2.31 and 2,45 (2H, 2d, J = 4 Hz, CH_2 - 14), 2.84 (2H, m, CH_2 - 14), 4.4 (2H, t, J = 7.5 Hz , CH_2 - 15), 6.66 (1H, m, H - 12); ^{13}C NMR δ ppm :14.6 (CH_3 -20),1 8.7 (C - 2), 20.1 (C - 6),21.8 (CH_3 - 19), 22.8 (C - 11), 25.4 (C - 14), 33.5 (C - 4), 33.5 (CH_3 - 18), 39.4(C - 1), 39.7 (C - 10), 42.0 (C - 3), 49.0 (C - 17), 52.5 (C - 5), 55.0 (C - 9), 57.5 (C - 8), 65.3 (C - 15), 124.8 (C - 13), 142.8 (C - 12).; EIMS : M^+ 318, m/z 303

14. Compound 15 : ^{1}H NMR, δ ppm : 0.87 (3H, s, CH_3 - 18), 0.91 (3H, s, CH_3 - 19), 0.95 (3H, s,CH_3-20),2.28 and 2.51 (2H, 2d, J = 4 Hz, CH_2 - 17), 2.90 (2H,m, CH_2-14), 4.31 (2H, t, J = 7.5 Hz, CH_2 - 15), 6.13 (1H, m, H - 12); EIMS : M^+ 318, m/z 303.

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