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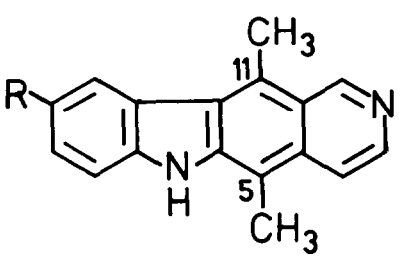
SYNTHESIS OF 17-OXOELLIPTICINE

Mark G Saulnier and Gordon W Gribble*

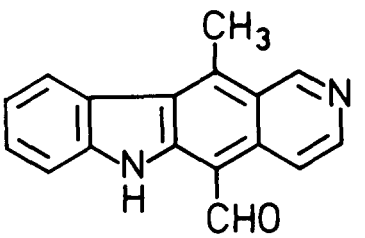
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Summary A synthesis of the Strychnos dinklagei alkaloid 17-oxoellipticine (2) is described that illustrates the versatility of ketolactam 3 in the construction of dissimilar dialkyl-substituted pyridocarbazoles

The 6H-pyrido[4,3-b]carbazole alkaloids ellipticine (1a) and 9-methoxyellipticine (1b) have been isolated from plants of the Ochrosia, Aspidosperma, Bleekeria, and Tabernaemontana genera of the family Apocynaceae.[1] These alkaloids possess considerable anticancer activity[2] and a derivative of 1b has recently been commercialized for human use in Europe [2d] Therefore, it is not surprising that synthetic activity in this area has been intense for nearly 25 years [3] Our own work in this area recently culminated in a highly efficient synthesis of 1a (55% yield from indole)[4a] as well as in a synthesis of the isomeric "isoellipticine" (5,11-dimethyl-10H-pyrido[3,4-b]carbazole) [4b]



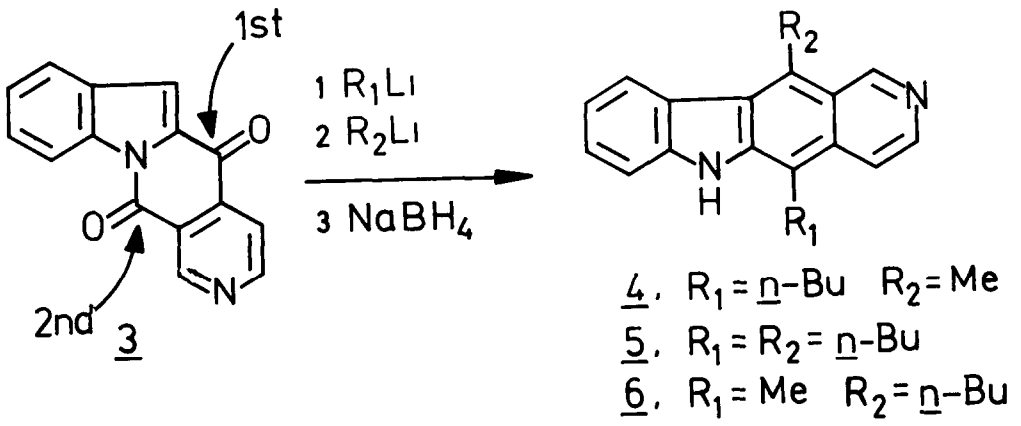
1a, R = H
1b, R = OCH3



2

The recent isolation and identification of 17-oxellipticine (2) (alkaloid numbering) by Koch[5] from the African tree Strychnos dinklagei is of chemotaxonomic and biogenetic interest, and

the structure advanced for this alkaloid is in concordance with the hypothesis of Potier and Janot[6] for the biogenesis of ellipticine and related alkaloids We describe herein the first synthesis of 17-oxoellipticine (2) that confirms the proposed structure and illustrates the versatility of our general approach[4] to the synthesis of pyridocarbazoles using the sequential addition of alkyllithium reagents to ketolactam 3 followed by reduction (i e , ⟶ 4)

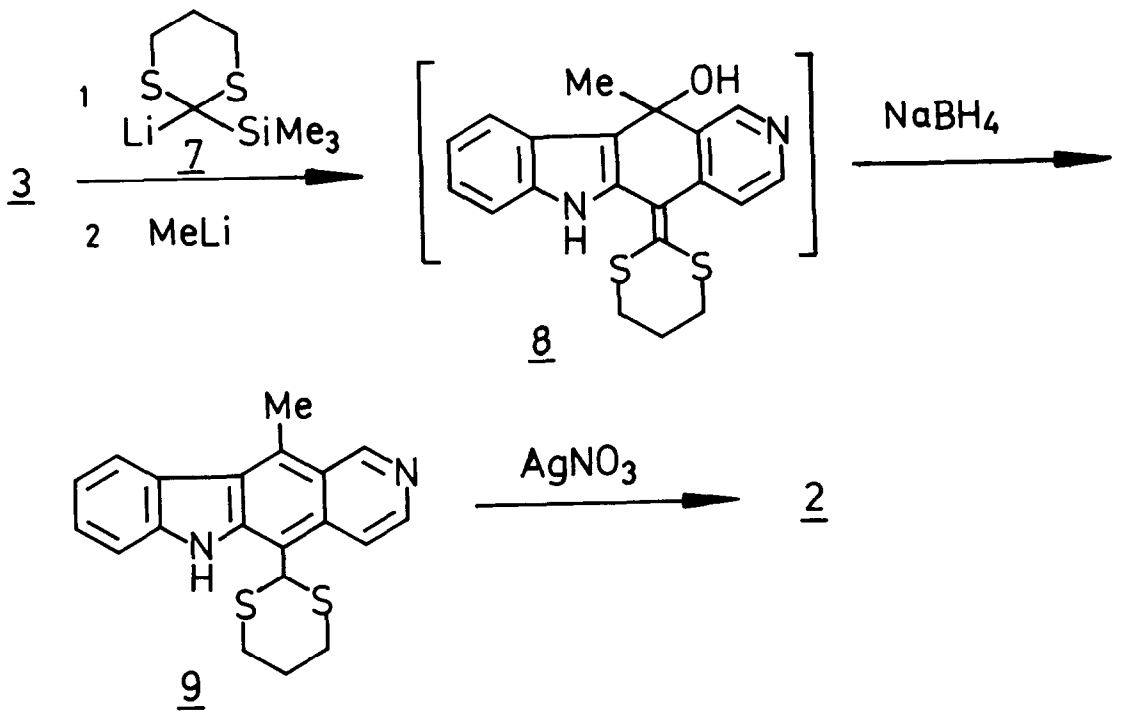


4. R_1 = n-Bu R_2 = Me
5. R_1 = R_2 = n-Bu
6. R_1 = Me R_2 = n-Bu

In order to be certain of our predicted sequence of alkyllithium addition to 3 (C-5 ketone C=O more reactive than C-12 amide C=O), we had to distinguish the methyl group signals in the ^1H NMR spectrum of ellipticine (1a) These peaks are well-separated at 2 8 and 3 3 ppm and it seemed likely that the lower-field singlet was due to the C-11 methyl group being in the deshielding region of the A-ring This assignment was confirmed by the following nuclear Overhauser effect (NOE)[7] experiment Irradiation of the 3 3 ppm signal caused a 16% increase in the intensity of the C-1 proton singlet at 9 7 ppm, while irradiation of the 2 8 ppm signal caused a 10% enhancement of the C-4 proton doublet at 7 9 ppm [8] Thus, in 1a the C-5 and C-11 methyl group protons are unambiguously assigned 2 8 and 3 3 ppm, respectively [9] Having this information we could examine the sequential addition of two different alkyllithium reagents to 3

In the event, treatment of ketolactam 3[4a] with 1 equiv of n-butyllithium (-100°C, THF) followed after 5 min by 1 equiv of methyllithium gave, after reduction of the intermediate diol mixture ($NaBH_4$, EtOH, reflux) and flash chromatography, 5-n-butyl-11-methyl-6H-pyrido[4,3b]carbazole (4)[10, 11] (70% yield) along with a lesser amount of 5[10, 12] (18% yield) The structure of 4 is secured as such, rather than as the alternative regioisomer 6, by virtue of a single deshielded methyl singlet at 3 28 ppm in the ^1H NMR spectrum

Having established the regiochemistry for the sequential addition of alkyllithium reagents to 3, we pursued the synthesis of 17-oxoellipticine (2). Treatment of 3 with 1 equiv of 2-lithio-2-trimethylsilyl-1,3-dithiane (7)[13, 14] (-100°C, THF) followed after 20 min by 1 equiv of methyllithium afforded thioketene alcohol 8. This material was reduced with sodium borohydride (EtOH, reflux) to give dithioacetal 9[15] in 25% overall yield after flash chromatography. Hydrolysis of 9 with silver nitrate (2 equiv, aq. acetone, 25°C, 48 h)[16] gave 17-oxoellipticine (2)[17] in essentially quantitative yield, mp 266-268°C, identical (IR, UV, TLC, ^{1}H NMR, mass spec) with a sample of the alkaloid kindly furnished by Dr. Koch.[5]



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11 4 Mp 303°C dec (soft at 285°C), IR (KBr) 3470, 2960, 2935, 2875, 1615, 1598, 1468 cm^{-1}, partıal 360 MHz ^1H NMR (d_6-DMSO) δ 11 38 (s, 1H), 9 71 (s, 1H), 8 4 (m, 2H), 7 93 (d, 1H, J=6.OHz), 7 55 (m, 2H), 7 25 (m, 1H), 3 28 (s, 3H), 0 94 (t, 3H, J=7 3Hz), UV (95% EtOH) λ max 286 5, 295, 333 nm, (95% EtOH + HCl) λ max 307, 354 nm, mass spectrum, m/e 288(M+), 245(100%), m/e 288 1656(M+, calcd 288 1627)

12 5 Mp 201-206°C dec, IR (KBr) 3430, 2865, 1602, 1462, 1410 cm^{-1}, UV (95% EtOH) λ max 286, 294, 333 nm, mass spectrum, m/e 330(M+), 287(100%), m/e 330 2103(M+, calcd 330 2096)

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14 2-Lıthıo-1,3-dıthıane gave a much lower yıeld ın thıs transformatıon

15 9 Mp 236-240°C dec, partıal 360 MHz ^1H NMR ($CDCl_3$) δ 9 73 (s, 1H), 9 47 (bs, 1H), 8 57 (d, 1H, J=6 OHz), 8 37 (d, 1H, J=8 1Hz), 7 97 (d, 1H, J=6 OHz), 7 47-7 62 (m, 2H), 7 36-7 28 (m, 1H), 6 38 (s, 1H), 3 33 (s, 3H), UV (95% EtOH) λ max 287, 333, mass spectrum, m/e 350 (M+), 276, 275, 245, m/e 350 0900(M+, calcd 350 0912)

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17 2 360 MHz ^1H NMR ($CDCl_3$) δ 11 24 (bs, 1H), 11 06 (s, 1H), 9 75 (s, 1H), 8 69 (d, 1H, J=6.1Hz), 8.45 (d, 1H, J=6.1Hz), 8.37 (d, 1H, J=8 1Hz), 7 65-7 55 (m, 2H), 7 45-7 38 (m, 1H), 3 38 (s, 3H), mass spectrum, m/e 260 0929(M+, calcd 260 0950)

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