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SYNTHETIC STUDIES ON RABDOSIA DITERPENE LACTONES II : THE SYNTHESIS OF 15-DESOXYEFFUSIN

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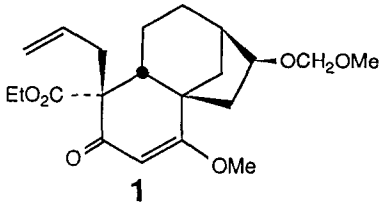
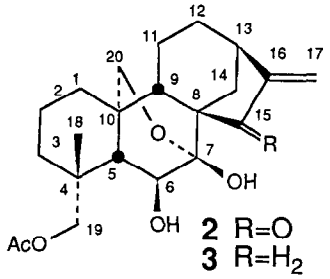
Summary: The tricyclic ester **1** was transformed by a sequence of intramolecular Michael and alkylation reactions into the pentacyclic lactone **10** from which the (±)-15-desoxy derivatives of longikaurin C **2** and effusin **4** were then prepared.

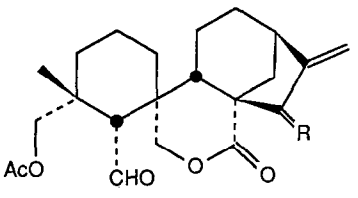
In the preceding Letter[1] we outlined a strategy for the total synthesis of the Rabdosia diterpenes[2] longikaurin C **2**[3] and effusin **4**[4], and described the preparation of the ester **1**, which was envisaged as a key intermediate in the synthesis plan. We now report the transformation of **1** into the 15-desoxy derivatives **3** and **5** corresponding to the natural products **2** and **4**, respectively.



1

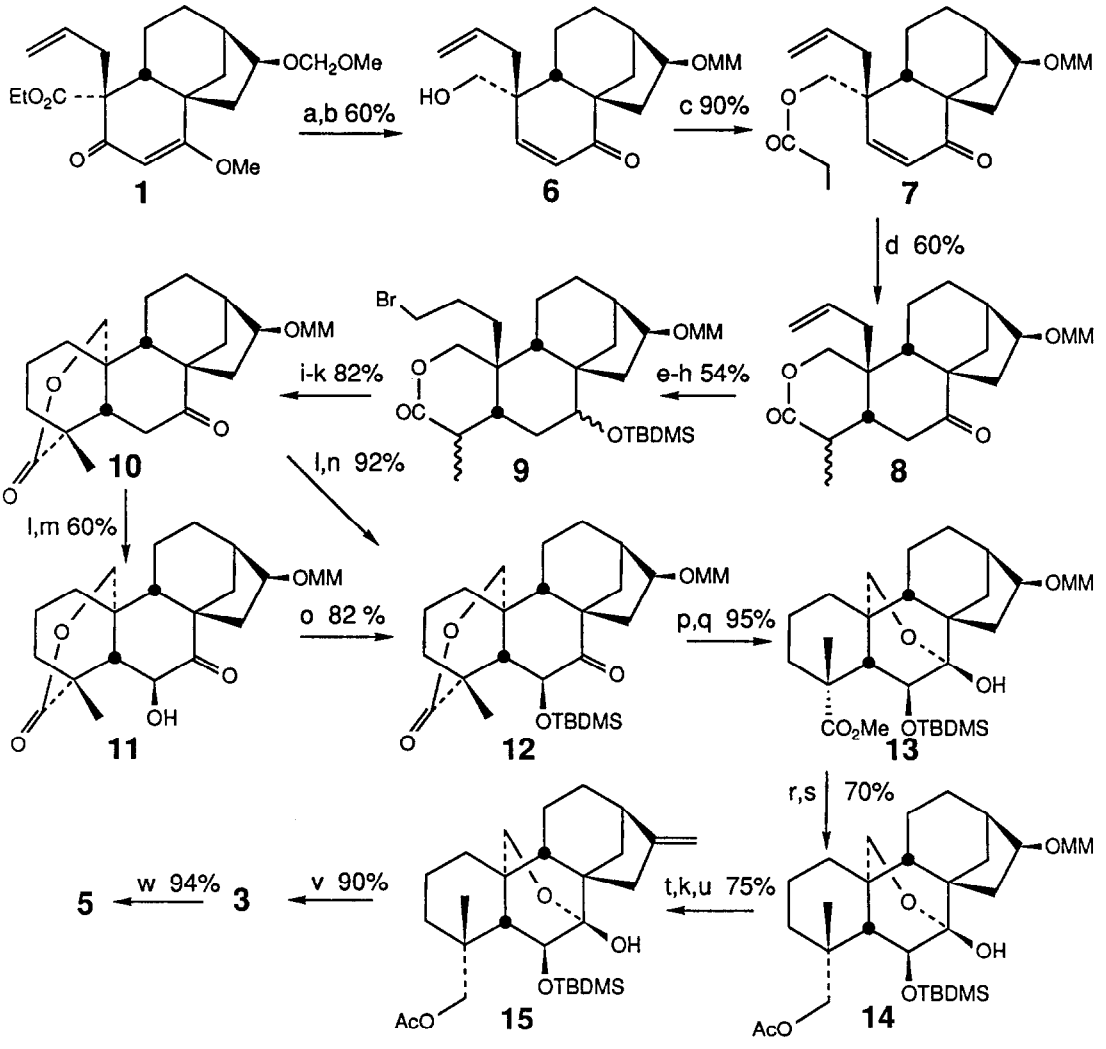


2 R=O
3 R=H_2



4 R=O
5 R=H_2

The kaurane skeleton (apart from the C(17) methylene group) was completed as indicated in the first part of the Scheme. Thus, **1** was reduced by "Red-Al" and the crude product subjected to an acid-catalysed β-elimination process, affording enone **6**.[5,6] In a variation of the intramolecular Michael reaction which had proven to be so effective in the synthesis of gibberellins,[7] the derived propionate **7** was cyclised to a 3:1 mixture of lactones **8**, m.p. 92-93° and 126.5-127.5°C, respectively. The mixture was converted to the composite bromide **9** which was treated with LDA to effect C(3)-C(4) bond formation and then the C(7) carbonyl group reconstituted to afford the homogeneous oxo lactone **10**, m.p. 146-147.5°C. 6β-Hydroxylation was then effected by osmium tetroxide oxidation[8] of the derived t-butyldimethylsilyl (TBS) enol ether[9] to give **11**, m.p. 145-146°C, but in view of the need to mask the new hydroxyl[10] during subsequent transformations, treatment of enol ether **11** by per-acid was also examined. In the event, this procedure afforded **12** more directly and efficiently.[11]



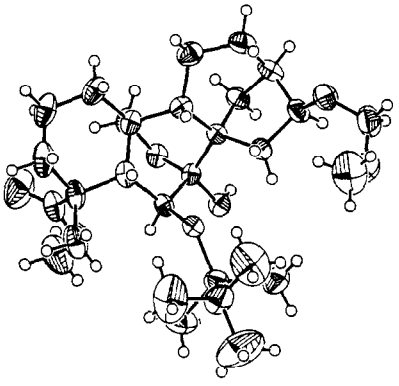
(a) Na Al(OCH$_2$CH$_2$OMe)$_2$H$_2$(3.5 equiv), PhMe, 25°C, 1h. (b) pMePhSO$_3$H, PhH, 25°C, 1h. (c) (EtCO)$_2$O, Py, DMAP, 25°C, 5h. (d) KH(1.2 equiv), DMF, -30°C, 2h. (e) NaB(CN)H$_3$, MeOH, 0.5h. (f) t-BuSiMe$_2$OSO$_2$CF$_3$(1.5 equiv), 2,6-lutidine(2 equiv), ClCH$_2$CH$_2$Cl, 25°C, 10 min. (g) Me$_2$CHCH(Me)$_2$BH$_2$(3 equiv), diglyme, 0°C, 10 min; 25°C, 1h; Me$_3$NO$^-$, 100°C, 3h. (h) Ph$_3$P(2.2 equiv), CBr(1.1 equiv), Py. (i) LDA (1.4 equiv), THF, -20°C, 0.5h. (j) Bu$_4$NF$^-$ (6 equiv), THF, 25°C, 5h. (k) (PyH)$_2$Cr$_2$O$_7$(3.0 equiv), CH$_2$Cl$_2$, 25°C, 16h. (l) t-BuSiMe$_2$OSO$_2$CF$_3$(1.5 equiv), Et$_3$N, 25°C, 12h. (m) OsO$_4$(0.05 equiv), N-methylmorpholine N-oxide (4 equiv), t-BuOH, H$_2$O, 25°C, 10h. (n) mClPhCO$_3$H(1.2 equiv), CH$_2$Cl$_2$, 25°C, 30 min. (o) t-BuSiMe$_2$OSO$_2$CF$_3$(4 equiv), iPr$_2$NEt(1.5 equiv), DMAP(catalytic), ClCH$_2$CH$_2$Cl, 25°C, 6h. (p) KOH, MeOH, 25°C, 1h. (q) CH$_2$N$_2$, Et$_2$O. (r) LiAlH$_4$(0.7 equiv), THF, (filtered solution), 25°C, 2h. (s) Ac$_2$O, Py. (t) Me$_2$BBr(2 equiv), Et$_3$N, -78°C, 5 min. (u) Ph$_3$PMeBr$^-$, iAmOK, PhMe, 25°C, 0.5h. (v) as for j, but 10 min. (w) H$_5$IO$_6$, Et$_2$O, 10 min.

We hoped that hydrolysis of the lactone function in **12** would lead to formation of a 20→7 hemiacetal, and spectroscopic examination of the product, m.p. 145-146°C, (following diazomethane treatment) indicated that this had indeed occurred: ^{13}C-NMR spectra were compatible with the loss of the C(7) carbonyl function (δ 209.9) and its replacement by an acetal carbon (δ 97.6). The ^{1}H-methine resonance from H(6) which had been observed as a doublet (J=8.6Hz) in **11** and **12** (ie trans-diaxial coupling and therefore commensurate with a 6β-oxygen substituent) now gave rise to a doublet with J=4Hz, ie. consistent with a boat conformation for ring B. Although the value of 4Hz was rather smaller than that reported for longikaurin C [3] and its congeners[2] (6-7Hz), it seemed reasonable that the discrepancy was due to torsional differences arising from hydrogen bonding with the C(15) carbonyl function in the latter compounds; 4Hz coupling constants have been reported for derivatives more closely analogous to our synthetic intermediate.[12] Formation of the hemi-acetal **13** was finally confirmed by single crystal X-ray analysis (Figure 1), which also established that the earlier stereochemical assignments at C(5), C(9), C(10) had been made correctly.[13]

Figure 1

Ortep plot of ester **13**

(50% probability)



Reduction of the methoxycarbonyl group by lithium aluminum hydride and acetylation gave acetate **14**, m.p. 152.5-153.5°C. The recently reported procedure for the removal of methoxymethyl groups with dimethylbromoborane[14] then enabled us to unmask the C(17) hydroxyl in the presence of the C(6) TBDMS ether. Oxidation of the product to the C(17) ketone [15], m.p. 207-209°C, followed by Wittig methylenation gave **15** which was desilylated to afford a product, m.p. 200-201°C whose spectroscopic constants (MS, HRMS, IR, and NMR) were fully consistent with structure **3**.[16] Further evidence for the structural assignment was obtained by periodate induced cleavage to an aldehyde, m.p. 118-119.5°C, (δ 9.89, d, J=4Hz), the spectra of which were in agreement with structure **5**.[17] The introduction of a C(15) carbonyl group into **3** or **5** by procedures[18] which we have been able to apply satisfactorily to gibberellins and kaurenoic acid, has not yet been realised, however. We expect to report on the successful resolution of this remaining problem in the full paper describing this synthetic endeavour.

Acknowledgements:

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References and Footnotes

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13. X-ray Analysis: crystallized from ether-hexane in the triclinic, space group $P\bar{1}$, a = 13.116(2)Å, b = 11.995(2)Å, c = 10.636(2)Å, α = 107.36(1)°, β = 104.36(1)°, γ = 102.55 (1)°, V = 1468.4 Å^3, D_{calc} (Z=2) = 1.187g cm^{-3}. Intensity data collected on Philips PW1100 diffractometer, Mo Kα radiation ($\lambda(K\alpha_1)$=0.70930Å: 3851 unique reflections with 2θ<45°, 2656 observed ($I>3\sigma(I)$). Solved by MULTAN and refined to final R=0.042. The thermal ellipsoid diagram shows 50% probability levels except for the hydrogen atoms which are drawn as spheres of arbitrary radius.
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16. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11,s,3H,Me(18); 2.08,s,3H,OAc; 3.87,d,J=5Hz,1H,H(6); 3.89,s,2H,CH_2(19); 4.21,4.44,ABq,J=12Hz,2H,CH_2(20); 4.75,4.93,bs,2x1H,CH_2(17). ^{13}C-NMR(6-TBDMS ether): δ -2.6,(TBDMS); 15.8,C(2); 18.4,C(11); 21.0(OAc); 26.0,(TBDMS); 26.5,C(18); 30.2,C(12); 30.6,C(1); 31.6,C(14); 35.8,C(3); 35.9,C(4); 37.1,C(10); 37.4,C(13); 44.8,C(15); 48.8,C(8); 53.3,C(5); 57.8,C(9); 66.5,C(19); 66.6,C(20); 74.2,C(6); 99.0,C(7); 104.6,C(17); 160.0,C(16); 171.1,(OAc): ν_{max} 3580,3300,1730,1655 cm^{-1}. HRMS 376.2236. Calcd. for $C_{22}H_{32}O_5$: 376.2250.
17. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18,s,3H,Me(18); 2.11,s,3H,OAc; 2.38,d,1H,J=4Hz,H(5); 4.03,4.21,ABq,J=12Hz,2H,CH_2(19); 4.52,4.62,ABq,J=12Hz,2H,CH_2(20); 4.89,4.99,6s,2x1H,CH_2(17); 9.89,d,J=4Hz,1H,H(6). ν_{max} 2710,1730,1710,1655 cm^{-1}. HRMS 374.2092. Calcd. for $C_{22}H_{30}O_5$: 374.2093.
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