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SYNTHETIC STUDIES ON RABDOSIA DITERPENE LACTONES I: THE PREPARATION OF A KEY TRICYCLIC INTERMEDIATE

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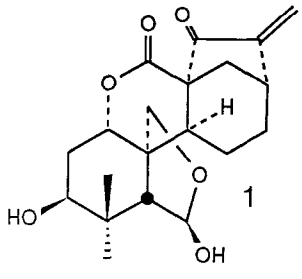
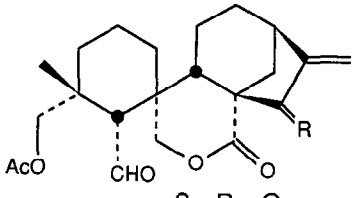
Summary: A strategy is proposed for the synthesis of Rabdosia diterpene lactones, eg. effusin **2** and the preparation of a suitable tricyclic intermediate **6** described.

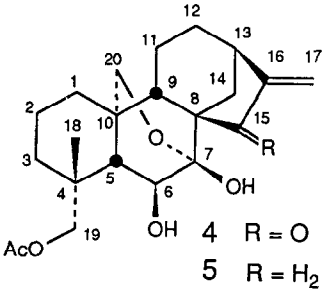
More than 100 highly oxygenated kaurane derivatives have been isolated from the Rabdosia genus.[1] A significant number of these compounds have undergone oxidative fission at C(6)-C(7) in the B-ring to form one of two new skeletal arrangements typified by enmein **1**[2] and effusin **2**[3], respectively A relay synthesis of **1**, encompassing 40 or so steps, has been completed by E. Fujita et al.,[4] but otherwise these structurally complex molecules, many with promising antineoplastic properties, have received little synthetic attention. In this and the following Letter[5] we describe the first total synthesis of a derivative of these diterpene lactones, that of (±)-15-desoxy-effusin **3**.



1



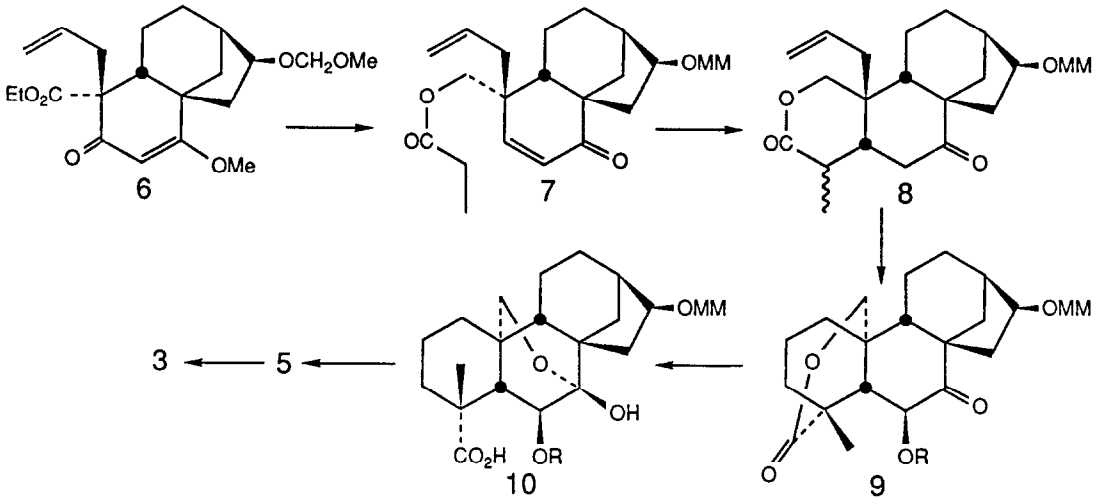
2 R = O
3 R = H_2



4 R = O
5 R = H_2

A summary of the synthetic plan is given in Scheme 1. The key features are (a) the synthetic equivalence between the methoxyenone **6** and enone **7**[6], (b) the construction of the A-ring and associated lactone moieties by sequential intramolecular Michael (**7**→**8**) and alkylation reactions (**8**→**9**) modelled on our earlier syntheses of gibberellins A_1, A_4 and A_{38})[7], (c) the utilization of the B-ring hemi-acetal function in **10** as a thermodynamic sink following hydrolytic fission of the lactone ring in **9**, (d) the periodate induced fission of the B-ring (c.f.(**5**→**3**)[3]. The preparation of **6** is outlined in Scheme 2 and described below, while the details of its elaboration into (±)-15-desoxy-effusin **3** are disclosed in the following Letter.

Scheme 1



Reduction of 3,5-dimethoxybenzoic acid **11** by lithium metal in liquid ammonia, followed by *in situ* alkylation with ethyl 4-bromobutanoate afforded the dihydroaromatic acid **12**, m.p 129-130°C,[8] which readily underwent oxidative decarboxylation to ester **13**,[9]. Vilsmeier formylation followed by potassium ethoxide condensation gave a mixture of acid **15** with its ethyl ester which was not separated but hydrolysed directly, furnishing acid **15** as a pale yellow solid, m.p. 310-314°C (methyl ester, m.p. 88-89°C). Acid **15** was resistant to catalytic hydrogenation so it was reduced by sodium metal in liquid ammonia to saturated acid, m.p. 131.5-133°C, which was converted into diazoketone **16**, m.p. 94-95°C and cyclized in trifluoroacetic acid at -20°C[10,11] to give methoxydienone **17**, m.p. 184.5-185.5°C.[12]

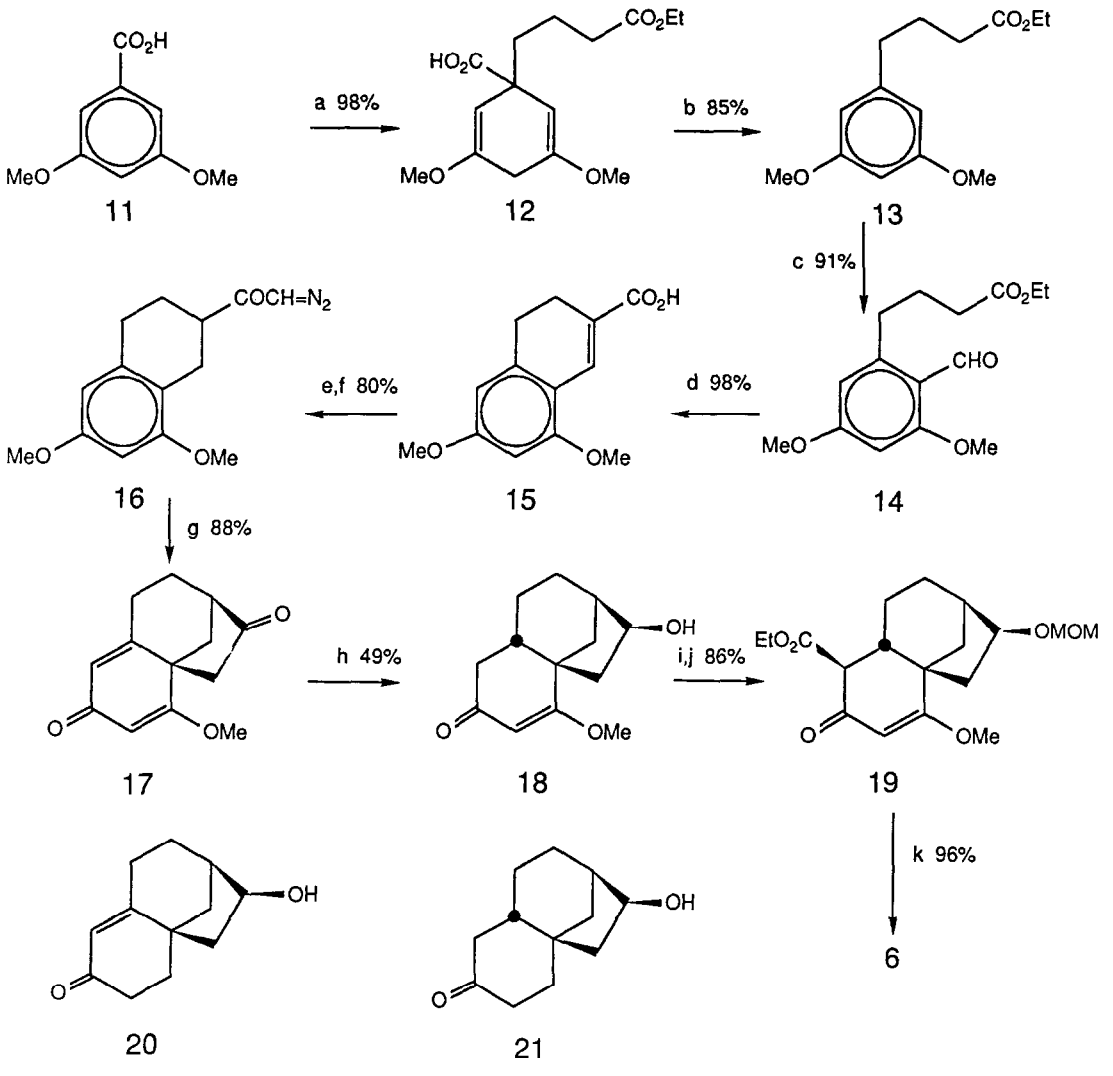
The methoxy group in **17** deactivates the Δ(6) olefinic bond towards most reagents, thereby allowing selective reduction of the Δ(9) double bond by lithium aluminum hydride, which afforded methoxyenone **18** m.p. 162-163°C as a 5:2:2 mixture (88% yield) with its B,C-*trans* isomer, m.p. 95.5-96.5°C and enone **20**.[13] The stereochemical assignment of a B,C *cis*-fusion to **18** was based initially on its ^{13}C-NMR spectrum which showed, *inter alia*, that the clearly identifiable resonances from C(11) and C(12) (δ 24.2 and 22.6, respectively) were upfield relative to the B,C-*trans* isomer (δ 25.7 and 26.5) as a consequence of additional γ-gauche interactions in the former isomer.[14] Confirmation was obtained, however, by reduction to **21**, m.p. 92-93°C, (hydrogenation, β-elimination, and further hydrogenation) which was identical with an authentic sample.[15]

Methoxyenone **18** was protected[16] as its methoxymethyl ether, m.p. 66-67°C, C-acylated at C(10) to give ester **19**, m.p. 101-102°C and then alkylated with allyl bromide to give the key intermediate **6**, m.p. 102-103°C. The assignment of stereochemistry at C(10) in ester **10** was based on the expectation that the convexity imposed by the B,C-*cis* fusion on the top face of the molecule would ensure alkylation on this same side.[17] This was ultimately confirmed by a single crystal X-ray structure determination carried out at a later stage in the synthesis.[5]

The elaboration of **6** into (±)-15-desoxyeffusin **3** is described in the following Letter.

Acknowledgement: We are indebted to Bruce Twitchin for technical support.

Scheme 2



(a) Li(2.3 equiv), NH_3, -33°C; $Br(CH_2)_3CO_2Et$, 1h. (b) $Pb(OAc)_4$(1.2 equiv), $Cu(OAc)_2$, PhH, 25°C, 10 min; $(CH_2OH)_2$. (c) $POCl_3$(2 equiv), DMF, 25°C, 4h; 40°C, 1h; aq. NaOAc, ice. (d) NaOEt, THF, 24°C, 1h; NaOH, EtOH-H_2O, 20°C, 1h. (e) Na(3 equiv), NH_3, t-BuOH, -33°C, 45 min, 97% yield. (f) $(COCl)_2$(3.0 equiv), CH_2Cl_2, 20°C, 45 min; Δ 1h; CH_2N_2(3 equiv), Et_2O, -30°C. (f) CF_3CO_2H, CH_2Cl_2(1:1), -25°C, 5 min. (h) substrate/THF→filtered solution of $LiAlH_4$ in Et_2O, 0°C, 1h. (i) $ClCH_2OMe$, iPr_2NEt, CH_2Cl_2, 25°C, 12h. (j) LDA(2.5 equiv), THF, 25°C, 30 min; $ClCO_2Et$(3 equiv), -78°C, 5 min. (k) NaH(2.5 equiv), DMF, 25°C, 15 min; CH_2=$CHCH_2Br$(3 equiv), 25°C, 3h.

References and Footnotes

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6. Cf. G. Stork and R.L. Danheiser, J. Org. Chem., 1973, **38**, 1775.
7. L. Lombardo, L.N. Mander, and J.V. Turner, J. Am. Chem. Soc., 1980, **102**, 6626; A.L. Cossey, L. Lombardo, and L.N. Mander, Tetrahedron Lett., 1980, 4383; L. Lombardo and L.N. Mander, J. Org. Chem., 1983, **48**, 2298.
8. Structures **10** and **14-19** represent racemic compounds and are fully consistent with their ^{1}H-NMR, IR and mass spectra. All crystalline compounds gave satisfactory microanalytical data (±<0.3%). Atoms are numbered throughout on the basis of the full kaurane structure.
9. Cf. A.J. Birch and J. Slobbe, Tetrahedron Lett., 1976, 2079.
10. Cf. D.J. Beames, T.R. Klose, and L.N. Mander, Aust. J. Chem., 1974, **27**, 1269.
11. Cf. D.W. Johnson, L.N. Mander, and T.J. Masters, Aust. J. Chem., 1981, **34**, 1243.
12. This intermediate had been prepared earlier by D.W. Johnson (Ph.D Thesis, University of Adelaide, 1975). In this case, however, 6,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid was prepared (47% yield) from 6,7,8-trimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid[10] by Birch reduction (Na, liq.NH_3) followed by Clemmensen reduction (Zn-Hg, HCl, PhMe).
13. Catalytic hydrogenation under a variety of conditions or lithium-liquid ammonia reduction also allowed selective reduction of the Δ(9) olefinic bond, but strongly favoured formation of the trans isomer.
14. J.B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, pp.52-69.
15. A.L. Cossey, L.N. Mander, and S.G. Pyne, Aust. J. Chem., 1979, **32**, 817.
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17. Steric factors are often outweighed by stereoelectronic ones in the alkylation of conformationally restricted β-keto esters, but the incorporation of the α',β' olefinic bond allows the substrate to adopt a quasi-boat conformation for a minimal energy penalty and maintain good orbital overlap with an incoming reagent on the β-face. Cf. A. Afonso, J. Org. Chem., 1970, **35**, 1949.

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