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AN APPROACH TO ERYTHROPHLEUM ALKALOIDS. SYNTHESIS OF METHYL(-)-4-EPI-CASSAMATE

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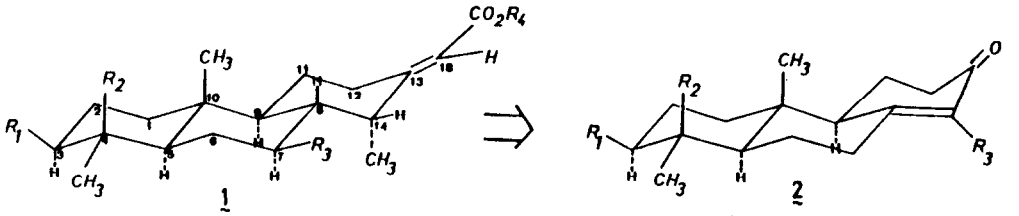
Abstract: A synthetic approach to Erythrophleum alkaloids, involving as a key-step the regiospecific deprotonation of the ketone 5a, is described.

A large number of alkaloids have been isolated from several Erythrophleum species[1] some of which, possessing the general structure 1 (see Scheme I), showed interesting cardiotonic[2a,b,c] or cytotoxic[2d] properties.

However their synthesis has attracted little attention to date, only formal total syntheses[3a] of cassaine 1 (R_1=OH, R_2=CH_3, R_3=O, R_4=CH_3) and cassaidine 1 (R_1=OH, R_2=CH_3, R_3=OH, R_4=CH_3) as well as the synthesis of several cassaic and cassamic acid analogues[3b,c,d] having been reported. All these syntheses have as common intermediates the α,β-unsaturated tricyclic ketones 2 in which the A ring is already functionalised (Scheme I), but a good route for their transformation into Erythrophleum alkaloids has not yet been developed. This has mainly been due to problems associated with the oxidation of C-7 and the introduction of the axial C-14 methyl group.

SCHEME I



1 2

R_1 = H, OH, OAc ; R_2 = CH_3, CO_2CH_3, CHO

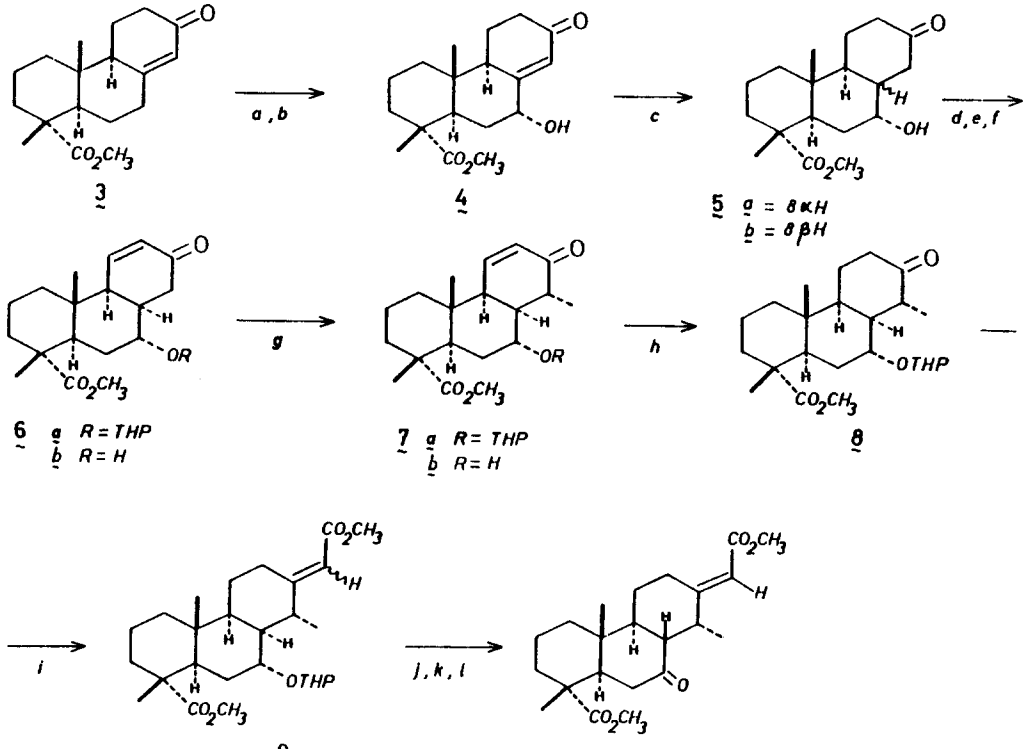
R_3 = OH, =O ; R_4 = $(CH_2)_2N(CH_3)_2$, $(CH_2)_2NHCH_3$

R_1 = OAc ; R_2 = CH_3, CO_2CH_3

R_3 = H, CH_3

Here we report a synthetic approach towards Erythrophleum alkaloids from methyl podocarp-8-(14)-en-13-one-18-oate 3, easily prepared from abietic acid[4]. This approach is bases (Scheme II) on the oxidation of C-7, methylation of C-14 and stereoselective formation of the methoxycarbonylmethylene moiety at C-13.

SCHEME II



a)AcCl,Ac_2O,H^+; b)m-CPBA; c)H_2,Rh/Al_2O_3; d)DHP,PPTS; e)Ph_3CLi,PhSeBr; f)H_2O_2, py; g)LDA,CH_3I-HMPT; h)H_2,Pd/C; i)$Me_3SiCHLiCO_2Me$; j)EtOH,PPTS; k)PCC;l)MeONa.

Oxidation of C-7 involves firstly the transformation of the enone 3 into the corresponding 7,13-dienyl acetate in essentially quantitative yield following the literature procedure[5]. Its oxidation[6] with m-chloroperbenzoic acid (1.5 eq, 95% EtOH, 0°C to r.t., 2h) gave the hydroxyenone 4[7] (75% yield from 3). Catalytic chemoselective hydrogenation (5% Rh/Al_2O_3) of hydroxyenone 4, in ethyl acetate[8] afforded a nearly equimolar mixture of the two diastereoisomeric hydroxyketones 5a[9] and 5b (98% yield), readily separated by column chromatography on silica gel. Structure assignation of both isomers followed from spectroscopic data and the (9α,8α)cis-ring junction of B/C rings in 5a was later confirmed when this compounds was oxidised to the corresponding diketone which was smoothly epimerized with sodium methoxide in methanol to the thermodynamically more stable diketone obtained from 5b.

In order to alkylate C-14 in 5a the secondary hydroxyl group was quantitatively protected by forming the tetrahydropyranyl ether in the usual manner (3,4-dihydro-2H-pyran, 1.5 eq, PPTS, CH_2Cl_2, r.t., 2h). Regiospecific methylation at C-14 involved firstly kinetically-controlled regiospecific deprotonation at C-12 (triphenylmethyllithium, 1.0 eq, THF, -78°C)[10] to

afford the corresponding enolate, which on treatment with phenylselenenyl bromide (1.2 eq, THF, -78°C) and subsequent oxidation[11] to the selenoxide at 0°C using 30% hydrogen peroxide in aqueous dichloromethane followed by syn-elimination in the presence of pyridine at r.t. gave the enone 6a[12] (77% yield from 5a). Treatment of this with lithium diisopropylamide (1.0 eq, THF, -30°C, 15 min) resulted in regiospecific formation of the 13,14-enolate which after quenching with an excess of methyl iodide (hexamethylphosphoramide, 3 eq, -30°C to r.t., 30 min) gave the 14α-methylketone 7a[13] (75% yield). Once the double bond had served its purpose as a blocking group for the C-12 methylene function during the methylation of C-14 it was removed by hydrogenation (5% Pd/C, EtOAc).

The methoxycarbonylmethylene moiety was then introduced at C-13 using the Peterson olefination procedure. Thus, reaction of 8 with methyl 2-lithio-2-(trimethylsilyl)acetate[14] (4 eq, THF, -78°C to r.t., 4h) gave the α,β-unsaturated ester 9 as an 8:2 mixture of E and Z-isomers (87% yield from 7a). Wadsworth-Emmons olefination using the corresponding phosphonate ester resulted in only 30% conversion to the α,β-unsaturated ester, probably due to ketone enolization competing with nucleophilic attack at the carbonyl group[15]. The mixture of E- and Z-isomers proved difficult to separate at this stage. However, removal of the tetrahydropyran group of 9 (PPTS, 0.3 eq, 95% EtOH, 55°C, 24 h), followed by oxidation of the free hydroxyl group (pyridinium chlorochromate, 5 eq, CH_2Cl_2, r.t., 1 h), epimerization (sodium methoxide, CH_3OH, r.t., 1h) of the (9α,8α) cis-ring junction of B/C rings to the more stable (9α,8β) trans-isomer and subsequent chromatography on silica gel afforded methyl (-)-4-epi-cassamate 10[16] (74% yield from 9) and its Z-isomer (16% from 9).

Transformation of the α,β-unsaturated methyl ester to the corresponding α,β-unsaturated 2-(dimethylamino)ethyl ester has been accomplished in related systems[3a].

The synthetic sequence developed here may be adapted to the synthesis of several naturally occurring Erythrophleum alkaloids starting from the appropriate α β-unsaturated ketone 2.

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7. 4: M.p. 154-155°C (hexane-ether); lit. 153-154°C, See: S.W. Pelletier, K.N. Iyer and C.W.J. Chang, J.Org.Chem., 35, 3535 (1970).

8. If a protic solvent, e.g. EtOH, is used some hydrogenolysis of the C_7-O bond is observed.

9. 5a: M.p.95-97°C (hexane-ether); $[\alpha]_D^{31}$ -95°(c 2.0,$CHCl_3$); IR (KBr) 3560, 1710 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$)δ3.80 (m, 1H, H-7β), 3.67 (s, 3H, CO_2CH_3), 1.20 (s, 3H, C_4-CH_3), 1.01 ppm (s, 3H, C_{10}-CH_3); high resolution MS m/e 308.1988 (M^+), $C_{18}H_{28}O_4$) requires 308.1988.

10. Higher temperatures or use of less bulky bases results in a mixture of the two possible enolates.

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12. All the compounds containing a tetrahydropyranyl group exist as diastereoisomeric mixtures, and are best characterized as the free alcohol. 6b: M.p. 165-167°C (hexane-ether); $[\alpha]_D^{27}$+69°C(c 0.54, $CHCl_3$); IR (KBr) 3410, 1720, 1660, 1605 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) δ 6.97 (dd, J=10 and 5 Hz, 1H, H-11), 6.15 (d, J=10 Hz, 1H, H-12), 3.78 (m, 1H, H-7β), 3.63 (s, 3H, CO_2CH_3), 1.17 (s, 3H, C_4-CH_3), 0.93 ppm (s, 3H, C_{10}-CH_3); high resolution MS m/e 306.1838 (M^+), $C_{18}H_{26}O_4$ requires 306.1831.

13. 7b: M.p. 115-116°C (hexane-ether); $[\alpha]_D^{27}$+73°(c 0.63, $CHCl_3$); IR (KBr) 3470, 1725, 1670 cm^{-1}; 1H-NMR (200 MHz, $CDCl_3$) δ 6.94 (dd, J=10 and 6 Hz, 1H, H-11), 6.18 (d, J=10 Hz, 1H, H-12), 4.13 (m, 1H, H-7β), 3.73 (s, 3H, CO_2CH_3), 2.64(t, J=6 Hz, 1H, H-9β), 2.35 (m, 1H, H-14β), 1.19 (d, J=7 Hz, 3H, C_{14}-CH_3), 1.19(s, 3H, C_4-CH_3), 0.90 ppm (s, 3H, C_{10}-CH_3). The signal at 2.35 (H-14β) collapses to a doublet (J=14 Hz) when C_{14}-CH_3 is irradiated; high resolution MS m/e 320.1978 (M^+), $C_{19}H_{28}O_4$ requires 320.1988.

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16. 10: M.p. 127-128°C (hexane-ether); $[\alpha]_D^{27}$-118°(c 4.5, $CHCl_3$); IR (KBr) 1720, 1700, 1645 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.71 (d, J=1Hz, 1H, H-18), 3.78 (dt,J=15 and 4 Hz, 1H, H-12β), 3.68 (s, 3H, CO_2CH_3), 3.65(s, 3H, CO_2CH_3), 3.03 (dq, J=8 and 4 Hz, 1H, H-14β), 1.21 (s, 3H, C_4-CH_3), 1.06 (d, J=8 Hz, 3H, C_{14}-CH_3), 0.99 ppm (s, 3H, C_{10}-CH_3). The signal at 3.03 (H-14β) collapses to a doublet (J=4 Hz) upon irradiation of C_{14}-CH_3 at 1.06 ppm. A 20% n.O.e. between protons H-14β and H-18 is observed. High resolution MS m/e 376.2239 (M^+), $C_{22}H_{32}O_5$ requires 376.2249.

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