Stereoselective Methoxylation at the 11β-Position of the Erythrinan Skeleton: Total Synthesis of (±)-Erythristemine

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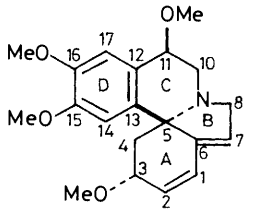
Treatment of *cis*-erythrinan-8-one or 1,7-cyclo-*cis*-erythrinan-8-one with ceric ammonium nitrate in methanol gave the appreciable yields of the corresponding 11β-methoxy compounds; these were converted into the natural 11-oxygenated erythrinan alkaloid, erythristemine, in high yield.

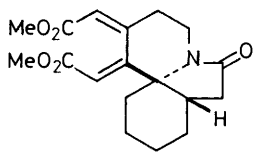
Several *Erythrina* alkaloids bear an oxygenated function at C-11, *e.g.*, erythristemine (**1**). These alkaloids occur in relatively small quantities and all those characterized so far have the 11β-configuration.[1] Previous attempts[2] at synthesizing these alkaloids from more abundant 11-non-oxygenated alkaloids have only resulted in either the 11α-isomer or produced the desired 11β-acetoxy alkaloid in very low yield. We now report that ceric ammonium nitrate (CAN) in methanol gives directly the 11-methoxy-*cis*-erythrinan with the desired β-configuration in appreciable yield.

Oxidation of 15,16-dimethoxy-*cis*-erythrinan-8-one (**2**) with CAN (2.2 mol equiv.) in methanol at room temperature for 30 min produced (**3a**) (gum, 73%), (**3b**) (gum, 3%), (**4**) (m.p. 179—181 °C, 6%), and (**5**) (m.p. 92 °C, 7%). The structure of each product was determined spectroscopically.† Compounds (**3a**) and (**3b**) were 11-methoxy derivatives (with three OMe groups each) and (**4**) was the 11-oxo derivative (ν 1 700 cm^{-1}), while (**5**) was identical with the seco compound[3] obtained by ozonolysis of (**2**). The configuration of the methoxy group in (**3a**) and (**3b**) was determined by comparison of their ^{1}H-n.m.r. spectra with that of the natural alkaloid, erythristemine (**1**), whose 11-methoxy group has been established as having the β-configuration, or *cis* to C(5)–C(13) bond.[4] The major product (**3a**) exhibited the 11-H signal at δ 4.20 with small couplings (dd, *J* 3, 2 Hz), while that of the minor product (**3b**) appeared at δ 4.44 with large couplings (dd, *J* 8.8, 6.8 Hz). The amine (**6**) derived from (**3a**) by lithium aluminium hydride reduction showed 11-H signal at δ 3.93 (d, *J* 4 Hz) indicating that the coupling with one of the 10-H protons is nearly zero. The proton at the 11-position of erythristemine (**1**) appears at δ 3.94 with small couplings (t, *J* 4 Hz).[4] We consider that the reaction sequence proceeds (**2**) ⟶ (**7**) ⟶ (**3a**), and the assigned 11β-configuration of the methoxy group in (**3a**) agrees well with the stereochemical consideration that the β-face of ring C in *cis*-erythrinan (**2**) is less hindered for the reagent approach.

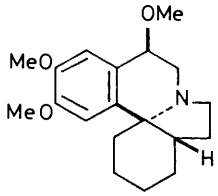
A similar oxidation of 15,16-methylenedioxy-*cis*-erythrinan-8-one (**8**) also produced the 11β-methoxy derivative (**9**) (gum),



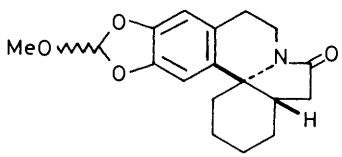
(**1**)



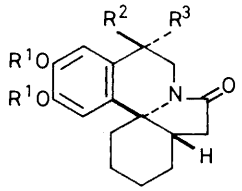
(**5**)

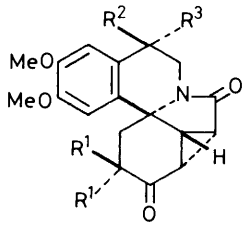


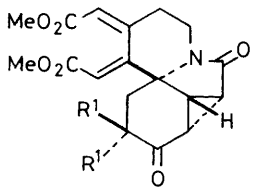
(**6**)

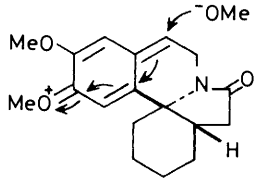


(**10**)









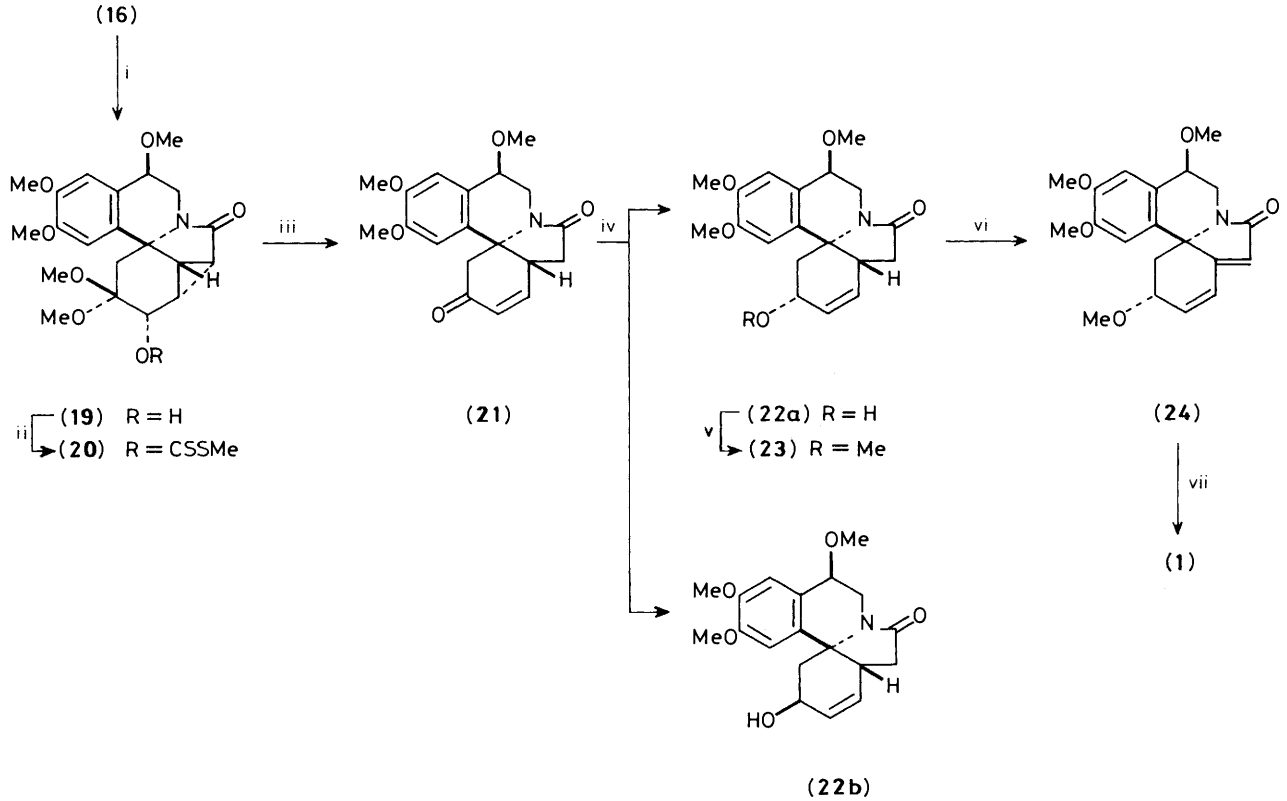
(**7**)

(**2**) R^1 = Me, R^2 = R^3 = H
(**3a**) R^1 = Me, R^2 = OMe, R^3 = H
(**3b**) R^1 = Me, R^2 = H, R^3 = OMe
(**4**) R^1 = Me, R^2, R^3 = O
(**8**) R^1, R^1 = CH_2, R^2 = R^3 = H
(**9**) R^1, R^1 = CH_2, R^2 = OMe, R^3 = H

(**11**) R^1 = R^2 = R^3 = H
(**12**) R^1 = R^3 = H, R^2 = OMe
(**13**) R^1 = H, R^2, R^3 = O
(**15**) R^1 = OMe, R^2 = R^3 = H
(**16**) R^1 = R^2 = OMe, R^3 = H
(**17**) R^1 = OMe, R^2, R^3 = O

(**14**) R^1 = H
(**18**) R^1 = OMe

† All new compounds in this paper gave satisfactory spectral data and elementary analyses (and/or molecular ions in high resolution mass spectra).



Scheme. *Reagents and conditions:* i, $NaBH_4$; ii, NaH, imidazole/MeI/CS_2; iii, (*a*) Bu_3SnH, heat, (*b*) H^+; iv, $NaBH_4$–$CeCl_3$; v, NaH, imidazole/MeI, Bu_4NHSO_4; vi, (*a*) LDA/$(PhSe)_2$, (*b*) $NaIO_4$; vii, $LiAlH_4$–$AlCl_3$

though in low yield (30%). The major product in this oxidation was an ortho ester (**10**) [(46%) gum; δ_H 3.33, OMe; 6.55, OCH(–O)O (16%)].

1,7-Cyclo-erythrinans were also smoothly methoxylated at C-11 by a similar oxidation. Thus oxidation of 15,16-dimethoxy-1,7-cyclo-*cis*-erythrinan-2,8-dione (**11**)[5] gave (**12**) (m.p. 199—201 °C, 68%), (**13**) (m.p. 287—290 °C, 13%), and (**14**) (m.p. 178—184 °C, 8%). Again a methoxy group was introduced at the 11β-position (δ 4.20, br s) stereoselectively. Similarly, oxidation of (**15**)[6] with CAN in methanol produced the 11β-methoxylated product (**16**) (63%), m.p. 212—214 °C, together with the 11-oxo derivative (**17**) (m.p. 206—207 °C, 29%) and the seco compound (**18**) (m.p. 117—119 °C, 8%).

Compound (**16**) was converted into the natural alkaloid, erythristemine (**1**), as follows. Reduction of (**16**) with sodium borohydride followed by dithiocarbonylation of the resulting alcohol (**19**), m.p. 173—175 °C, gave the dithiocarbonate (**20**) which on reduction with tributyltin hydride followed by acid treatment gave an enone (**21**), m.p. 165—167 °C [100% from (**16**)]. This was reduced with cerium(III) chloride and sodium borohydride in methanol to give the 3α-alcohol (**22a**), m.p. 147—149 °C (ArH, δ 6.75 and 6.58) and 3β-alcohol (**22b**), m.p. 161—162 °C, (ArH, δ 6.76 and 6.70) in a ratio of 2:1. The 3α-alcohol (**22a**) was *O*-methylated to yield (**23**) (91%), m.p. 134—136 °C. Treatment of (**23**) with lithium di-isopropylamide followed by phenylselenenylation and oxidation of the resulting phenylselenenyl derivative gave the dienoid lactam (**24**) as a gum (83%) [$\delta_H(C_6D_6)$ 6.29 (1 H, dd, *J* 10, 2.5 Hz, 2-H), 5.94 (1 H, br d, *J* 10 Hz, 1-H), 5.86 (1 H, br s, 7-H), and 4.17 (1 H, t, *J* 4 Hz, 11-H)]. Reduction of (**24**) with $LiAlH_4$–$AlCl_3$[7] gave the amine (73%) whose ^1H n.m.r. spectrum was found to be identical with the reported spectrum of erythristemine (**1**),[4] thus achieving the total synthesis of the 11β-methoxy natural erythrinan alkaloid in a racemic form.

Experimental

(±)-3,3,11β,15,16-*Pentamethoxy*-1,7-*cyclo*-cis-*erythrinan*-2,8-*dione* (**16**).—CAN (485 mg) was added to 3,3,15,16-tetramethoxy-*cis*-erythrinan-2,8-dione (**15**) (150 mg) in methanol (15 ml) and stirred (10 min) at room temperature. After dilution with dichloromethane, the mixture was washed with water and brine, dried, and concentrated. Chromatography of the residue over silica gel gave (**16**) (111 mg, 63%), (**17**) (49 mg, 29%), and (**18**) (14 mg, 8%): (**16**), m.p. 207—209 °C (Found: C, 62.45; H, 6.35; N, 3.5. $C_{21}H_{25}NO_7$ requires C, 62.52; H, 6.25; N, 3.47%); $\nu_{max.}$(Nujol) 1 720 and 1 695 cm^{-1}; $\delta_H(CDCl_3)$ 2.25 (1 H, dd, *J* 9.6, 6.8 Hz), 2.24 and 2.51 (2 H, ABq, *J* 14.6 Hz, 4-H), 2.45 (1 H, dd, *J* 9.6, 6.8 Hz), 2.92 (1 H, dd, *J* 15.1, 2.7 Hz, 10α-H), 2.93 (1 H, t, *J* 6.8 Hz), 3.22, 3.23, 3.49, 3.91, and 3.94 (each 3 H, s, OMe), 4.15 (1 H, br s, 11α-H), 4.47 (1 H, d, *J* 15.1 Hz, 10β-H), 6.77 (1 H, s, ArH), and 6.81 (1 H, s, ArH).

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