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First Total Synthesis of the Novel Cytotoxic Benzocycloheptenes (±)-Deoxofaveline and (±)-Faveline methyl ether

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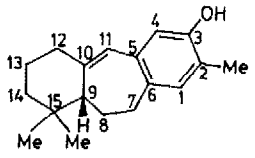
Key Words : (±)-Deoxofaveline, (±)-Faveline methyl ether, Cytotoxic benzocycloheptenes.

Abstract: Simple and efficient syntheses of the cytotoxic benzocycloheptenes (±)-deoxofaveline **(1)** and (±)-faveline methyl ether **(2)** have been developed by a convergent route from the ketone **7** via the tricyclic ketone **12**.

Very recently, Endo et al reported[1] the isolation and structural determination of three novel tricyclic benzocycloheptene derivatives, deoxofaveline **(1)**, faveline methyl ether **(2)** and faveline **(3)** from the bark of Cnidoscolus phyllacanthus (MART.) PAX et K. HOFFM (Euphorbiaceae). The significant activity of these compounds against P-388 murine leukemia cells has prompted us to undertake the total synthesis of these compounds. We report in this communication the first and efficient total synthesis of (±)-deoxofaveline **(1)** and (±)-faveline methyl ether **(2)** following our earlier reported[2] method for the synthesis of (±)-isopisiferin **(4)**, a rearranged 9(10→20) abeo-abieta-8,11,13-triene diterpenoid.



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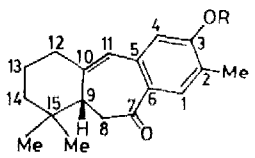
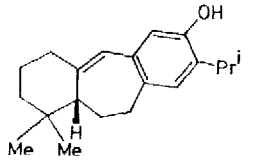


2; R = Me
3; R = H

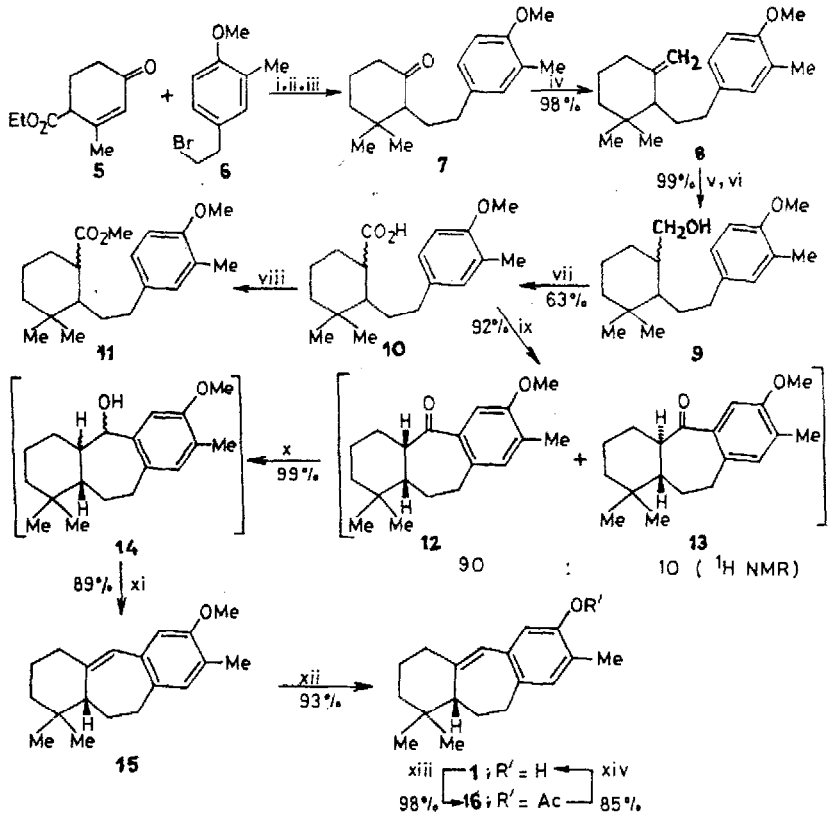


4

The gem-dimethyl cyclohexanone **7**[3] (Scheme-1), obtained in excellent yield from Hagemann's ester **(5)**, was smoothly converted to the alkene **8**[4] by Wittig reaction[2]. Hydroboration of the alkene **8** followed by oxidation with alkaline hydrogen peroxide gave an inseparable stereoisomeric mixture of the alcohols **9** which, on oxidation with Jones reagent[5], gave the epimeric mixture of the acids **10**[4]. The cyclization of the epimeric mixture of this acid **10** gave a solid stereoisomeric mixture of the cis and the trans-ketones **12** and **13** in a ratio of ca. 90:10 (^{1}H NMR). Recrystallization of

this mixture of **12** and **13** afforded the major epimer **12**[4], m.p. 116-117°C, assigned cis by analogy[2,6]. Reduction of the epimeric ketone mixtures **12** and **13** followed by dehydration of the crude alcohols **14** gave the styrene **15**[4], m.p. 85-86°C. Deprotection

Scheme - 1



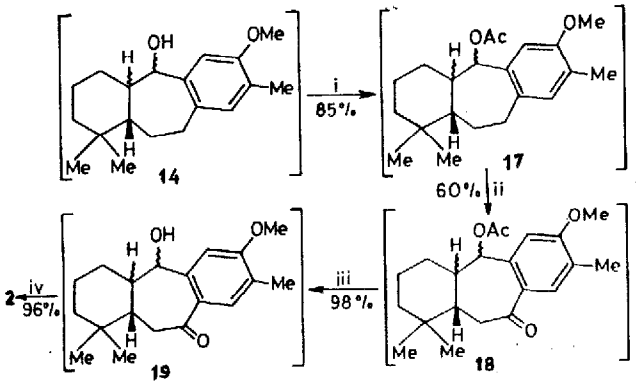
Reagents: i, Bu^tOK-Bu^tOH, H^+; ii, KOH-EtOH-H_2O, H^+; iii, $LiMe_2Cu$-$BF_3.Et_2O$-Et_2O; iv, sodium t-pentoxide-$Ph_3P^+MeI^-$-toluene; v, B_2H_6-THF; vi, NaOH-H_2O_2; vii, Jones reagent; viii, CH_2N_2-Et_2O; ix, PPA; x, $NaBH_4$-EtOH; xi, $KHSO_4$ (heat); xii, NaSEt-DMF (heat); xiii, Ac_2O-pyridine; xiv, $LiAlH_4$-Et_2O.

of the O-methyl ether **15** gave the crude phenol **1** which was purified through the corresponding acetate **16**[4], m.p. 159-160°C. Deacetylation of the acetate **16** regenerated (±)-deoxofaveline (**1**)[7].

For the synthesis of (±)-faveline methyl ether (**2**), the epimeric mixture of the acetates **17** (Scheme-2) was oxidized[8] to give **18** which was hydrolyzed and dehydrated

to give (±)-faveline methyl ether **(2)**[9] in excellent yield. Attempted demethylation of (±)-faveline methyl ether **(2)** under various conditions so far has failed to give the

Scheme - 2



Reagents : i, Ac_2O-pyridine; ii, pyridinium-chlorochromate-CH_2Cl_2; iii, 2% methanolic KOH, H^+; iv, $KHSO_4$ (heat).

desired keto-phenol **(3)** in isolable yield. An alternate synthetic route towards 3 in progress, will be reported in due course.

In conclusion, the present communication describes the first, simple, efficient and total synthesis of the novel cytotoxic compounds (±)-deoxofaveline **(1)** and (±)-faveline methyl ether **(2)** in excellent yields.

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References and Notes.

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4. Satisfactory elemental analyses and spectral data were obtained for all new compounds. The synthetic compounds described are all racemates.

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7. (±)-**1**; m.p. 148-149°C; IR ($CHCl_3$) : 3590, 3360 (br), 2930, 2860, 1615 cm^{-1}; UV (EtOH) : λ_{max} 310 (sh, log ε 3.80), 301.8 (3.52), 270 (sh, 4.27), 263.5 (4.07), 223.4 nm (4.21); ^1H NMR (300 MHz, δ $CDCl_3$) : 0.69 (s, 3H, C_{15}-Me), 0.97 (s, 3H, C_{15}-Me), 1.32-1.65 (m, 6H, 3 x $-CH_2$), 2.11-2.39 (m, 3H, -CH- and $ArCH_2CH_2$-), 2.18 (s, 3H, $ArCH_3$), 2.52 -2.68 (m, 2H, $ArCH_2$-), 4.44 (s, 1H, ArOH), 6.23 (s, 1H, >C=CH-), 6.54 (s, 1H, C_4-ArH) and 6.76 (s, 1H, C_1-ArH). The spectral data for 1 are in close accordance with those[1] of the naturally occurring optically active deoxofaveline.

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9. (±)-**2**; m.p. 139-140°C; IR ($CHCl_3$) : 2930, 2840, 1660, 1600 cm^{-1}; UV (EtOH) : λ_{max} 344 (log ε 3.80), 301 (3.95), 260.2 (4.74), 254 (sh, 4.51), 202.5 nm (4.05); ^1H NMR (300 MHz, δ $CDCl_3$) : 0.76 (s, 3H, C_{15}-Me), 1.12 (s, 3H, C_{15}-Me), 1.42-1.62 (m, 2H, $-CH_2$), 1.64-1.76 (m, 2H, $-CH_2$), 2.18 (s, 3H, $ArCH_3$), 2.28-2.37 (m, 3H, $-CH_2$ and -CH-), 3.01-3.03 (m, 2H, $ArCOCH_2$-), 3.87 (s, 3H, $ArOCH_3$), 6.29 (s, 1H, >C=CH-), 6.59 (s, 1H, C_4-ArH) and 7.62 (s, 1H, C_1-ArH). The spectral data for 2 are in close accordance with those[1] of the naturally occurring optically active faveline methyl ether.

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