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Synthetic Studies Towards Faveline Methyl Ether

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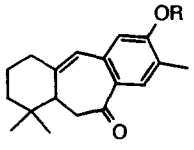
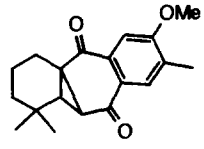
Abstract. A convergent approach to faveline methyl ether based on Claisen rearrangement is delineated. Thus the benzylic and allylic alcohol substrate was assembled by a Grignard reaction, and the rearrangement product was oxidized and cyclized. Double bond isomers of faveline methyl ether were obtained.

Introduction

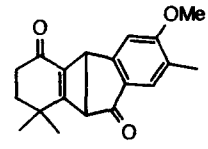
Recent investigations of the organic constituents of *Cnidoscolus phyllacanthus* (MART.) Pax et K. HOFFM. which is indigenous to the semiarid region of northwestern Brazil led to the isolation and structural elucidation of several interesting bisnorditerpenes. The plant is known to local inhabitants as Favela, and it has been used as folk medicine for treatment of a number of ailments. Methanolic extracts which contain these diterpenes are shown to possess in vitro antileukemic activities against P-388 cell line. Three types of novel molecular frameworks are represented by faveline (**1**) and its methyl ether (**1m**)[1], favelanone (**2**)[2], and neofavelanone (**3**)[3].



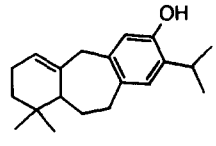
(**1**) R=H Faveline
(**1m**) R= Me Faveline methyl ether



(**2**) Favelanone



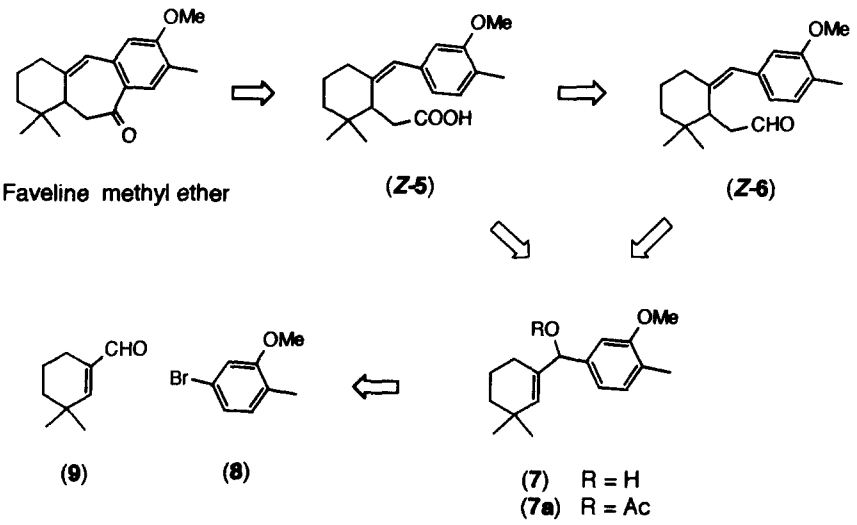
(**3**) Neofavelanone



(**4**) Pisiferin

Faveline has a tricyclic skeleton reminiscent of pisiferin (**4**)[4], and it is reasonable to assume they share the same biosynthetic pathway until a divergence point probably before aromatization of the C-ring at which methyl group migration or loss of a two-carbon fragment takes place.

Both the structural features and biological properties of the Favela substances attracted our attention with respect to their synthesis. During our study a short paper appeared[5] that described the work leading to faveline methyl ether (**1m**) and deoxofaveline. The method is quite different from our approaches which were designed to be concise and convergent. Thus retrosynthetic analysis of faveline methyl ether by dissection at the Ar-C=O single bond gives a γ,δ-unsaturated acid (**5**), which is amenable to Claisen rearrangement transform. A benzylic allylic alcohol (**7**) is readily identified as a potential intermediate.This alcohol should be accessible from two building blocks to be united by an organometallic reaction.



Results and Discussion

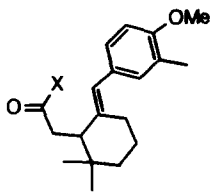
Two building blocks were required in our proposed synthetic route towards faveline methyl ether. The aromatic portion was derived from 4-bromotoluene via nitration, reduction, diazotization, hydrolysis, and methylation. The nitration products were separated by treatment with piperidine followed by acid extraction to remove 3-nitro-4-bromotoluene. The desired compound having the bromine atom meta to the nitro group was unreactive.

Bromide (**8**)[6] was converted into the Grignard reagent and reacted with 3,3-dimethyl-1-cyclohexenecarbaldehyde (**9**)[7] in THF. The benzylic alcohol (**7**) was obtained in 65% yield. The Claisen rearrangement of this alcohol using triethyl orthoacetate in the presence of propanoic acid led only to decomposition. The high sensitivity of this compound and many of its derivatives, due to the favorableness of generating a very stable carbocation, was an annoying feature. Often one could notice formation of tricyclic products, apparently arising from the Nazarov-type cyclization, if care was not taken to avoid contact of these compounds with traces of acid.

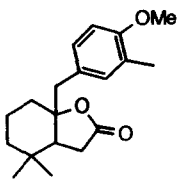
Unable to effect the Ireland version of the Claisen rearrangement on the acetate (**7a**) in reasonable yield, we were forced to employ the classical procedure for the transformation. A mixture of *(E)*- and *(Z)*-isomers of the unsaturated aldehyde (**6**) was produced which could be separated by silica gel chromatography, although this separation was totally unnecessary. Both geometrical isomers were to converge into one compound within two steps. Our reluctance to adopt the classical method was due to an extra oxidation step, which was now accomplished using the sodium chlorite-hydrogen peroxide system.[8]

The structural assignment of the major aldehyde was confirmed by nOe difference spectra. Thus, irradiation of the proton at δ 6.18 caused signal enhancement of 14.2%, 8.1%, and 2.0% at the absorption peaks at δ 2.57, 6.58 and 6.65, and 9.69 ppm, respectively. These groups of signals can be unequivocally assigned to the methylene protons adjacent to the formyl group, the two *ortho*-protons of the styrene unit, and the -CH=O proton. Accordingly, the acid (***E*-5**) derived from the major Claisen rearrangement product which has a trans relationship between the aryl group and the acid chain would not be unsuitable for direct cyclization. However, this potential problem was anticipated at the outset of our research, but it was also considered that the ring closure could be conducted under conditions which allow intervention of the γ-lactone (**10**). Thus we intended to effect the cyclization by exposing the acids to a milieu of phosphorus pentoxide and methanesulfonic acid.[9] When P_2O_5 was omitted the analogous treatment indeed produced the γ-lactone only.

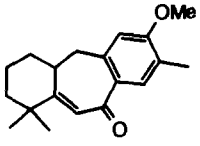
The cyclization products consisted mainly of two unsaturated ketones. From their spectral data they undoubtedly possess the structures (**11**) and (**12**), i.e., the α,β- and β,γ-unsaturated isomers of faveline methyl ether. The β,γ-unsaturated ketone (**12**) with a tetrasubstituted double bond appeared to be the most stable of the three compounds, as the reaction conditions were definitely conducive to equilibration. So far our effort in isomerizing these ketones to faveline methyl ether has ended in disconsolation.



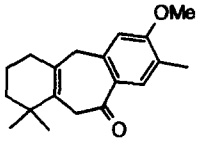
(***E*-5**) X = OH
(***E*-6**) X = H



(**10**)



(**11**)



(**12**)

Experimental Section

General: Infrared spectra were recorded neat with a Perkin-Elmer 938G spectrophotometer. NMR spectra were taken in $CDCl_3$ with TMS as internal standard at 200 or 300MHz (proton) or 75 MHz (carbon) on Bruker AC-200 or AM-300WB instrument.Mass spectra were measured in the electron impact mode at 70 eV with a Finnegan TSQ-46C spectrometer and high resolution spectra were obtained from a JEOL JMS-HX 100 Spectrometer. Silica gel (Merck) was used in all the column chromatography, and anhydrous Na_2SO_4 was used for drying of extracts during reaction workup.

α-(3-Methoxy-4-methylphenyl)-3,3-dimethylcyclohex-1-enylmethanol :

To a stirred suspension of magnesium turnings (635 mg, 28.6 mg-atom) in dry THF (10 mL) under nitrogen was added one small crystal of iodine and a solution of 4-bromo-2-methoxy-1-methylbenzene (**8**) (5.0 g, 23.8 mmol) in THF (5 mL) slowly. After the formation of the Grignard reagent was complete a solution of 3,3-dimethyl-1-cyclohexenecarbaldehyde (**9**) (2.73 g, 19.7 mmol) in THF (5 mL) was introduced from a dropping funnel during 10 min. Stirring continued overnight and the reaction mixture was quenched with aq. NH_4Cl, and extracted thrice with ether. The combined extracts were washed with brine, dried, evaporated, and the residue was chromatographed (eluent: hexane/ethyl acetate 9:1) to afford alcohol (**7**) (3.54 g, 65% yield).

M^+ Calcd. for $C_{17}H_{24}O_2$ m/z 260.1777; found 260.1775. ν 3424 cm^{-1}. δ_H 1.00 (3H, s), 1.01 (3H, s), 1.36-1.40 (2H, m), 2.21 (3H, s), 2.29 (1H, br), 4.98 (1H, s), 5.61-5.62 (1H, m), 6.81 (1H, d, J=4.8 Hz), 6.85 (1H, s), 7.07 (1H, d, J=4.8 Hz). δ_C 15.82, 19.55, 24.04, 29.79, 29.88, 31.47, 37.19, 55.04, 107.91, 118.17, 125.31, 130.12, 133.08, 137.24, 141.56, 157.52.

α-(3-Methoxy-4-methylphenyl)-3,3-dimethylcyclohex-1-enylmethyl Acetate :

The alcohol (**7**) (860 mg, 3.31 mmol) was dissolved in dichloromethane (10 mL) and treated with with pyridine (262 mg, 3.31 mmol) and acetic anhydride (338 mg, 3.31 mmol). The mixture was stirred overnight, decomposed with sodium bicarbonate solution, diluted with dichloromethane, and separated into layers. The organic solution was washed with 5% NaOH, brine, 5% HCl, and brine successively, dried, and evaporated. Column chromatography (eluent: hexane/ethyl acetate 19:1) gave the acetate (**7a**) (900 mg, 90% yield).

M^+ Calcd. for $C_{19}H_{26}O_3$ m/z 302.1883; found 302.1879. ν 1736 cm^{-1}. δ_H 0.98 (3H, s), 1.00 (3H, s), 1.36-1.40 (2H, m), 1.54-1.59 (2H, m), 1,75-1.78 (2H, m), 2.10 (3H, s), 2.18 (3H, s), 3.80 (3H, s), 5.53 (1H, s), 6.07 (1H, s), 6.75 (1H, s), 6.80 (1H, d, J=7.6 Hz), 7.07 (1H, d, J=7.6 Hz). δ_C 15.77, 19.35, 21.03, 24.72, 29.58, 29.70, 31.42, 36.88, 54.87, 78.46, 108.48, 118.73, 125.88, 130.14, 133.59, 134.07, 137.82, 157.39, 169.59.

***(E)*-2-(3-Methoxy-4-methylbenzylidene)-6,6-dimethylcyclohexaneacetaldehyde and *(Z)*-2-(3-Methoxy-4-methylbenzylidene)-6,6-dimethylcyclohexaneacetaldehyde :**

A mixture of the alcohol (**7**) (3.0 g, 11.5 mmol), sodium acetate (146 mg), mercuric acetate (244 mg), and *n*-butyl vinyl ether (23.03 g, 230 mmol) was heated at 140°C under nitrogen for 2 days. The cooled reaction mixture was diluted with ether, washed with brine, dried, evaporated, and chromatographed (eluent: hexane/ethyl acetate 39:1-19:1). The three compounds isolated were the unreacted alcohol (973 mg), aldehyde (***E*-6**) (1.052 g), and aldehyde (***Z*-6**) (217 mg). The yield of the Claisen rearrangement products was 57% as calculated from unrecovered alcohol.

Spectral data of (***E*-6**): M^+ Calcd. for $C_{19}H_{26}O_2$ m/z 286.1934; found 286.1947. ν 1716 cm^{-1}. δ_H 0.86 (3H, s), 1.01 (3H, s), 1.34-1.55 (4H, m), 2.36 (3H, s), 2.36-2.59 (5H, m), 3.79 (3H, s), 6.18 (1H, s), 6.58 (1H, s), 6.65 (1H, d, J=7.5 Hz), 7.03 (1H, d, J=7.5 Hz), 9.69 (1H, t, J=2 Hz). δ_C 15.81, 22.92, 25.59, 26.10, 28.09, 35.10, 36.80, 41.97, 49.76, 55.07, 110.55, 120.68, 124.47, 124.74, 130.00, 136.42, 141.37, 157.26, 202.85.

Spectral data of (***Z*-6**): M^+ Calcd. for $C_{19}H_{26}O_2$ m/z 286.1934; found 286.1947. ν 1716 cm^{-1}. δ_H 0.84 (3H, s), 1.02 (3H, s), 1.20-1.35 (1H, m), 1.45-1.69 (3H, m), 2.05-2.35 (2H, m), 2.18 (3H, s), 2.35-2.60 (2H, m), 3.11 (1H, dd, J=8.7, 6.5 Hz), 3.79 (3H, s), 6.37 (1H, s), 6.60 (1H, s), 6.64 (1H, d, J=8 Hz), 7.04 (1H, d, J=8 Hz), 9.38-9.41 (1H, m). δ_C 15.87, 23.33, 27.10, 28.89, 32.06, 34.20, 34.49, 41.19, 43.63, 55.16, 110.44, 120.47, 124.47, 125.66, 130.26, 136.33, 141.63, 157.36, 202.91.

(*E*)-2-(3-Methoxy-4-methylbenzylidene)-6,6-dimethylcyclohexaneacetic Acid:

To the flask containing a solution of aldehyde (***E*-6**) (300 mg, 1.05 mmol) in acetonitrile (3.5 mL) was added 30% hydrogen peroxide (141 mg), disodium hydrogen phosphate (113 mg) and water (1.32 mL). After stirring for 10 min. the flask was cooled to 10°C, and a solution of sodium chlorite (597 mg in 5 mL water) was slowly injected during 2 hrs. At the end of 3hrs the excess oxidizing agents were destroyed by sodium sulfite, and the reaction mixture was extracted thrice with ether. The extracts were dried, evaporated, and chromatographed (eluent: hexane/ethyl acetate 9:1) to give the acid (***E*-5**) (m.p. 158°-160°C. 208 mg, 66% yield).

M^+ Calcd. for $C_{19}H_{26}O_3$ m/z 302.1883; found 302.1885. ν (KBr) 1698 cm^{-1}. δ_H 0.86 (3H, s), 0.98 (3H, s), 1.25-1.55 (5H, m), 2.17 (3H, s), 2.18-2.3 (1H, m), 2.35-2.60 (4H, m), 3.78 (3H, s), 6.19 (1H, s), 6.59 (1H, s), 6.64 (1H, d, J=7.6 Hz), 7.00 (1H, d, J=7.6 Hz). δ_C 15.89, 22.98, 25.95, 26.21, 28.15, 34.04, 35.08, 36.53, 51.65, 55.20, 110.82, 120.87, 124.39, 124.75, 130.06, 136.91, 141.18, 157.31, 179.25.

(*Z*)-2-(3-Methoxy-4-methylbenzylidene)-6,6-dimethylcyclohexaneacetic Acid :

A similar oxidation of the aldehyde (***Z*-6**) (200 mg, 0.70mmol) gave the acid (***Z*-5**) (135 mg, 64% yield).

M^+ Calcd. for $C_{19}H_{26}O_3$ m/z 302.1883; found 302.1881. ν 1698 cm^{-1}. δ_H 0.85 (3H, s), 0.91 (3H, s), 1.15-1.27 (3H, m), 2.05-2.16 (1H, m), 2.18 (3H, s), 2.18-2.35 (1H, m), 2.46 (1H, dd, J=15, 7.9 Hz), 2.59 (1H, dd, J=15, 6.8 Hz), 3.12 (1H, m) 3.77 (3H, s), 6.33 (1H, s), 6.68 (1H, d, J=7.6 Hz), 6.72 (1H, s), 7.01 (1H, d, J=7.6 Hz). δ_C 15.94, 23.75, 28.51, 32.52, 34.17, 34.86, 35.09, 43.17, 55.18, 110.49, 120.76, 124.22, 125.81, 130.11, 136.50, 141.64, 157.25, 179.66.

γ-Lactone of 2-(3-Methoxy-4-methylbenzylidene)-6,6-dimethylcyclohexaneacetic Acid :

The acid (***E*-5**) (100 mg, 0. 33 mmol) was dissolved in dichloromethane (3 mL) and stirred with methanesulfonic acid (10 drops) overnight. After dilution with dichloromethane the reaction product was washed with 5% $NaHCO_3$, brine, and dried. Evaporation and chromatography (eluent: hexane/ethyl acetate 19:1) led to the isolation of the lactone (**10**) (81 mg, 81% yield). In an analogous manner the acid (***Z*-5**) provided the same lactone in 80% yield.

M^+ Calcd. for $C_{19}H_{26}O_3$ m/z 302.1883; found 302.1875. ν 1760 cm^{-1}. δ_H 0.84 (3H, s), 1.11 (3H, s), 1.20-1.60 (4H, m), 1.85-2.05 (2H, m), 2.16 (3H, s), 2.19-2.50 (3H, m), 2.95 (1H, d, J=14.8 Hz), 3.15 (1H, d, J=14.8 Hz), 3.78 (3H, s), 6.71 (1H, d, J=7.5 Hz), 6.76 (1H, s), 7.00 (1H, d, J=7.5 Hz). δ_C 15.85, 18.82,

28.96, 30.17, 32.26, 32.99, 33.81, 34.15, 43.88, 46.74, 55.26, 87.78, 112.54, 122.68, 124.97, 130.06, 134.55, 157.20, 175.48.

1,2,3,4,4a,5-Hexahydro-7-methoxy-1,1,8-trimethyl-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one and 1,2,3,4,5,11-Hexahydro-7-methoxy-1,1,8-trimethyl-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one :

An *(E,Z)*- acid mixture (***E*-5, *Z*-5**) (670 mg, 2.21 mmol) was added to a stirred solution of phosphorus pentoxide (3.1 g) in methanesulfonic acid (25 g). At the end of a 18 hr period the contents were slowly added to water (50 mL), and extracted with dichloromethane. After brine washing the total extracts were dried, evaporated, and the residue chromatographed (eluent: hexane/ethyl acetate 39:1) to give the β,γ-enone (**12**) (283 mg) and the α,β-enone (**11**) (94 mg), in a combined yield of 60%.

Spectral data of (**11**): M^+ Calcd. for $C_{19}H_{24}O_2$ m/z 284.1777; found 284.1779. ν 1624 cm^{-1}. δ_H 1.11 ((3H, s), 1.14 (3H, s), 1.20-1.90 (6H, m), 2.16 (3H, s), 2.70-3.10 (3H, m), 3.84 (3H, s), 6.19 (1H, s), 6.51 (1H, s), 7.40 (1H, s). δ_C 15.59, 21.83, 27.47, 29.78, 34.85, 39.28, 39.35, 40.61, 41.79, 55.44, 110.03, 124.86, 125.10, 130.83, 132.97, 137.14, 160.48, 168.66, 195.32.

Spectral data of (**12**): M^+ Calcd. for $C_{19}H_{24}O_2$ m/z 284.1777; found 284.1780. ν 1644 cm^{-1}. δ_H 0.99 (6H, s), 1.36-1.40 (1H, m), 2.10 (2H, t, J=9.2 Hz), 2.17 (3H, s), 3.49 (4H, m), 3.87 (3H, s), 6.57 (1H, s), 7.92 (1H, s). δ_C 15.55, 19.70, 27.60, 31.73, 34.87, 38.86, 42.76, 45.64, 55.42, 110.43, 124.92, 127.65, 132.52, 134.09, 135.23, 143.65, 160.69, 194.18.

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