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A STEREOSELECTIVE SYNTHESIS OF (±)-VEADEIROIC ACID AND (±)-VEADEIROL - TWO NOVEL DITERPENES WITH CLEISTANTHANE SKELETON

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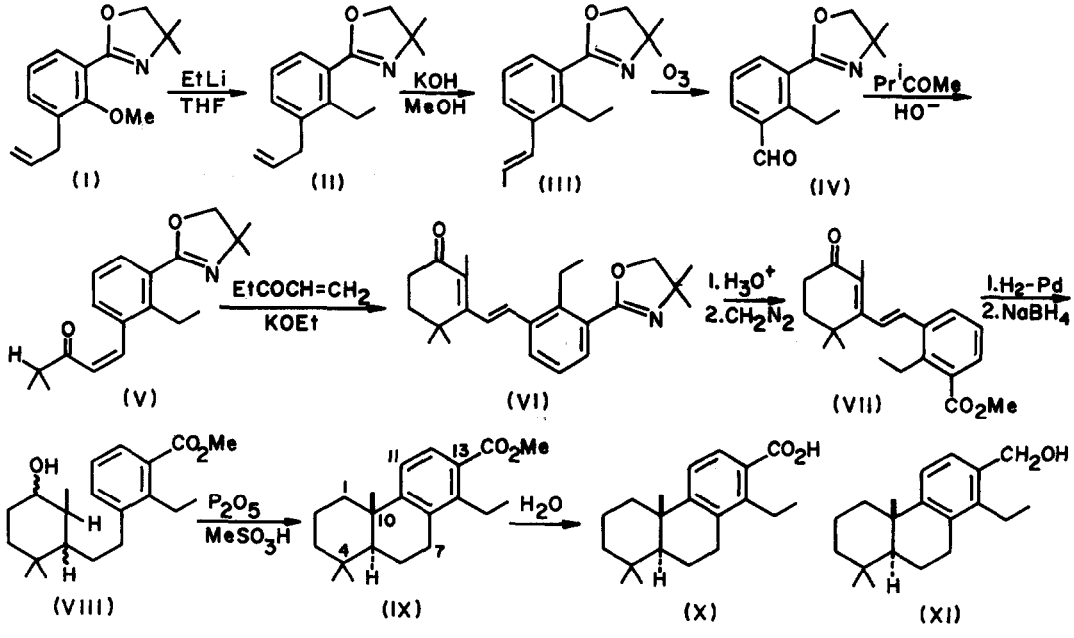
Summary: A stereoselective synthesis of (±)-veadeiroic acid (X) and (±)-veadeirol (XI), diterpenes with cleistanthane skeleton is described. The key step in the synthesis is a stereoselective ring-closure of a substituted arylethyltrimethylcyclohexanol (VIII).

Veadeiroic acid (X) and veadeirol (XI), two novel diterpenes with the rare and unusual cleistanthane skeleton have recently been isolated from Vellozia flavicans and their structures determined by spectral data (UV, IR, NMR, and mass).[1] We report here a totally stereoselective and unambiguous synthesis of these two diterpenes confirming the structures. To our knowledge, this is the first ever synthesis of this rare group of diterpenes with cleistanthane framework (one C at C-13 and a C-C unit at C-14).

3-Allyl-2-methoxybenzoic acid on reaction with $SOCl_2$ and subsequent condensation[2] with 2-amino-2-methylpropanol furnished the oxazoline (I). The OMe group in the latter was smoothly replaced[3] by an Et on treatment with EtLi in THF at -45°C to provide II in 90% yield. The double bond in the allyl chain was brought into conjugation with the aromatic ring by heating with alkali and the product (III) on ozonolysis and reductive work-up with thiourea furnished the aldehyde (IV), ^{1}H-NMR:δ1.26 (3H, t, J = 7Hz), 1.40 (6H, s), 3.32 (2H, q, J = 7 Hz), 4.12 (2H, s), 7.40 (1H, t, J = 8 Hz), 7.90 (2H, m), and 10.42 (1H, s), in



near quantitative yield. This is essentially a synthesis of 3-carboxy-2-ethylbenzaldehyde with CO_2H masked in an oxazoline ring. Although a number of steps are involved, the overall yield is very good (70%).[4]

The aldehyde (IV) was next condensed with 3-methylbutan-2-one and the resultant styryl ketone (V) subjected to Robinson's annelation reaction using ethyl vinyl ketone according to an earlier procedure[5,6] to furnish the cyclohexenone (VI). The masked CO_2H group was then set free and esterified with CH_2N_2 to yield VII (50% based on V), ^{1}H-NMR:δ1.20 (3H, t, J = 7 Hz), 1.24 (6H, s), 1.84-2.10 (2H, m), 1.94 (3H, s), 2.56 (2H, t, J = 8 Hz), 2.96 (2H, q, J = 7 Hz), 3.90 (3H, s), 6.60 (1H, d, J = 16 Hz), 6.90 (1H, d, J = 16 Hz), and 7.20-7.80 (3H, m). Catalytic hydrogenation and reduction with $NaBH_4$ furnished the cyclohexanol (VIII) as a mixture of stereoisomers. This was cyclodehydrated with P_2O_5-$MeSO_3H$[7] to yield 13-methoxycarbonyl-14-ethylpodocarpa-8,11,13-triene (IX) exclusively in the trans form. There was no trace of any high field methyl peak at δ 0.37-0.45 in ^{1}H-NMR which is diagnostic of the cis isomer. It has recently been suggested[8] that an arylethyltrimethyl-cyclohexanol (as VIII with OH at the tertiary C atom) or the corresponding cyclohexene[7] with the aryl group unactivated at the reaction site undergoes only trans ring-closure through a tertiary cyclohexyl cation (steric reason) while the same with an activated aryl group (OMe or Me *para* to the reaction site) leads to an appreciable extent (≃40%) of cis ring-closure through a concerted 1,2-anti addition of the aryl group and a proton at the two ends of the cyclohexene double bond.[9] In VIII, the CO_2Me group strongly deactivates the aromatic nucleus and thus leads to the exclusive formation of the trans isomer. The methyl ester (IX), m.p. 78-80°C, ^{1}H-NMR:δ0.96 (3H, s), 0.98 (3H, s), 1.20 (3H, t, J = 7 Hz), 1.21 (3H, s), 1.38-2.04 (9H, m), 2.80-3.04 (4H, m), 3.88 (3H, s), 7.21 (1H, d, J = 8 Hz), and 7.60 (1H, d, J = 8 Hz), on hydrolysis afforded (±)-veadeiroic acid (X), m.p. 204-205°C and on reduction with $LiAlH_4$ afforded (±)-veadeirol (XI), m.p. 105-106°C. The spectral data (UV, IR, NMR, and mass) of the synthetic compounds (X) and (XI) were found to be identical with those reported for the natural veadeiroic acid, m.p. 226-227°C and veadeirol, m.p. 128-129°C.

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References and notes

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