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The Absolute Configuration of Edulinic Acid, a Constituent of the "Khat" Alkaloid Cathedulin K-19

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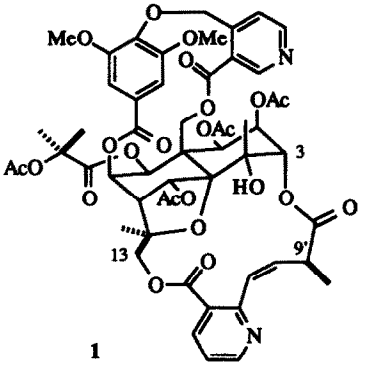
Abstract: The absolute configuration of edulinic acid, and hence of the C-9' centre of cathedulin K-19, was found to be (*S*) by synthesis of edulindiol, which was also obtained by degradation.

The expanding traffic in "khat",[1] a narcotic drug pervasive in East African countries, has become a serious concern, particularly with the increasing use of the drug as an article of commerce in Somalia and Kenya. The principal physiological effects of khat are appetite suppression and stimulant action, with dependence being psychological rather than physical. These effects have been attributed to the presence of cathine (norpseudoephedrine) in khat;[2] however, certain complex terpenoid-alkaloids known as cathedulins may also be implicated.



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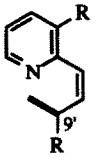
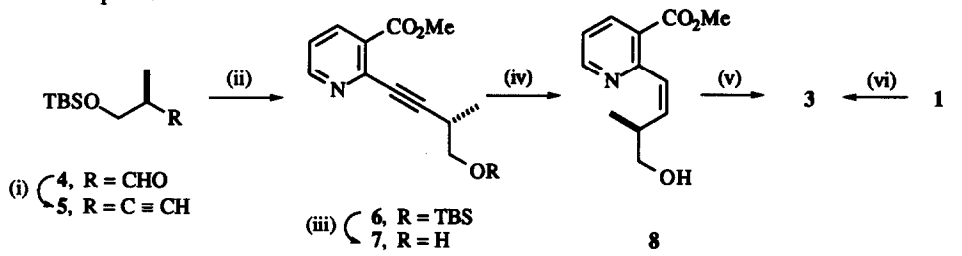


2, R = CO_2H
3, R = CH_2OH

Extraction of the leaves of *Catha edulis* (Forsk) (Celastraceae), a tree clutivated as the source of khat, has yielded over 20 cathedulins,[3] of which K-19 **1**[4] is among the most structurally complex. K-19 is unique among this family of macrolactones in containing a new pyridinedicarboxylic ("edulinic") acid **2**, which bridges C3–C13 of the highly functionalized sesquiterpenoid core of euonyminol. Although the stereochemical designation made to cathedulin K-19 by the Crombie group is complete in all other respects,[4] the stereogenicity at C-9' was left undefined. In anticipation of a synthetic assault on cathedulin K-19, it was necessary to remove this last ambiguity, and we now report a synthesis of (*S*)-edulindiol **3** which proves that the corresponding centre in edulinic acid **2**, and hence at C9' of cathedulin K-19, possesses (*S*) configuration.

Methyl (*R*)-3-hydroxy-2-methylpropionate was converted to aldehyde **4**,[5] which was condensed with dimethyl diazomethylphosphonate[6] to give the terminal acetylene **5**. The latter was coupled to methyl 2-chloronicotinate in the presence of a palladium(II) catalyst and cuprous iodide,[7] and the resulting alkyne **6** ($[\alpha]_D^{22}$ -3.5°) was unmasked to yield the alcohol **7** ($[\alpha]_D^{22}$ -4.9°). Semi-hydrogenation of the alkyne **7** over

Lindlar catalyst afforded the cis olefin **8** ($[\alpha]_D^{23}$ +109°), accompanied by *ca* 10% of its trans isomer. These isomers were separated and the ester **8** was reduced with lithium aluminum hydride to edulindiol **3** ($[\alpha]_D^{22}$ +126°). The same substance ($[\alpha]_D^{22}$ +210°) was obtained upon reduction of cathedulin K-19 with lithium aluminum hydride, and was shown to be identical with synthesized edulindiol by comparison of IR, and ^1H and ^{13}C NMR spectra.



Scheme I *Reagents and conditions*: (i) $(MeO)_2POCHN_2$, *t*-BuOK, THF, (90%); (ii) Methyl 2-chloronicotinate, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, (61%); (iii) 5% HF/MeCN (100%); (iv) H_2, Lindlar cat., MeOH, (76%); (v) $LiAlH_4$, THF, 0 °C, (72%); (vi) $LiAlH_4$, THF-Et_2O, 0° → 25 °C (28%).

The discrepancy between the magnitude of optical rotations of edulindiol acquired by synthesis and that obtained by degradation of cathedulin K-19 was traced to partial racemization of **7** during its hydrogenation to cis olefin **8**. Whereas the Mosher ester[8] derived from **7** was a single diastereomer, as judged by its ^1H and ^{19}F NMR spectra as well as by the observation of a single peak upon GLC and HPLC, the corresponding α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA), prepared from **8**, showed the presence of two diastereomers. A ^{19}F NMR measurement indicated that the ratio of stereoisomers was 2.56:1, corresponding to 44% enantiomeric excess. This stipulates a specific rotation of $[\alpha]_D$ +286° for optically pure edulindiol, a value which implies that partial racemization also must have occurred during the reduction of cathedulin K-19 to edulindiol. Nevertheless, the results clearly demonstrate that edulindiol **3**, and hence edulinic acid **2**, possess the (*S*) configuration. The absolute configuration of cathedulin K-19 **1** is therefore completely defined.

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