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The chemistry of khat. An approach to the synthesis of euonyminol

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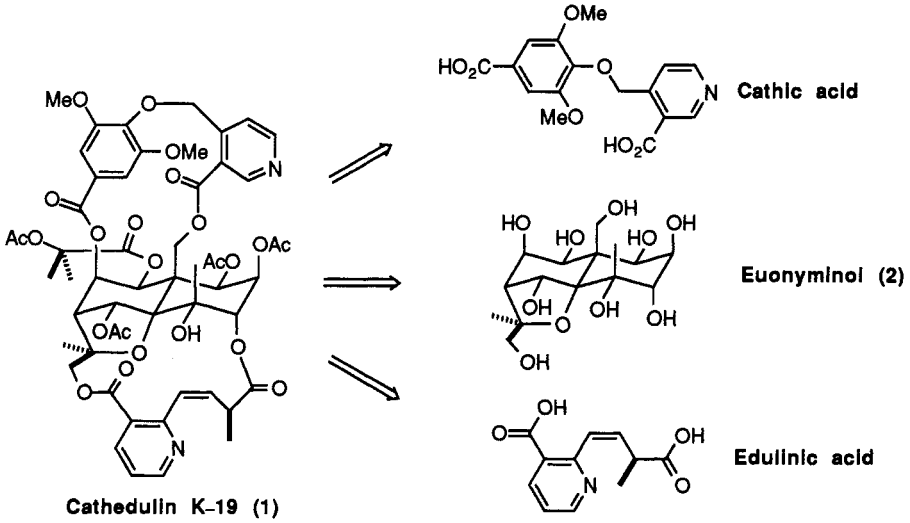
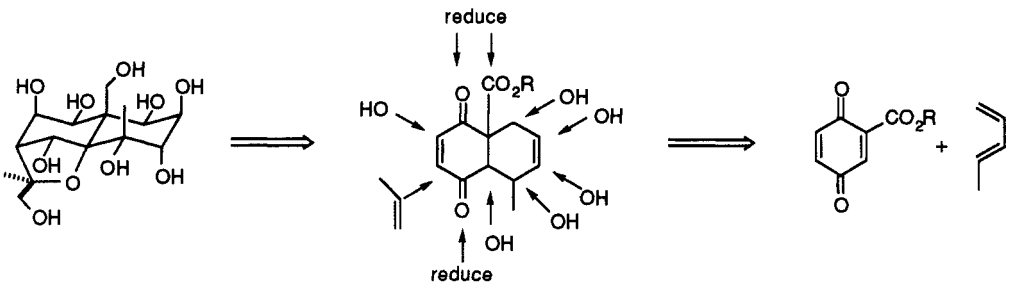
ABSTRACT
An approach to the synthesis of euonyminol, the terpenoid nucleus of the cathedulins, is described. A key step in the construction of the tricyclic core is an "epoxide cascade" which creates the tetrahydrofuran of euonyminol by a sequence of acid-catalyzed epoxide openings terminated by nucleophilic attack in the A ring. A complete regime of oxygen functionality has been installed around the perimeter of the terpenoid frame with the correct configuration at ten of the eleven stereogenic carbons. However, the final reduction of a keto group gave 9-epieuonyminol rather than the natural product. In addition, syntheses of dimethyl cathate and edulindiol were completed in anticipation of their eventual coupling to euonyminol to produce cathedulin K-19, a constituent of the drug "khat". The asymmetric synthesis of edulindiol established its absolute configuration as (*S*).



The tree *Catha edulis* (Forsk) (Celastraceae) is native to East Africa and is the source of the widely used stimulant and appetite suppressant known as "khat".[1] The latter contains, in addition to certain phenylalkylamines such as cathinone,[2] a series of structurally complex terpenoid alkaloids which have been named cathedulins.[3] K-19 (**1**)[4] is one of the most highly elaborated members of the cathedulin family and contains as its core structure the polyhydroxylated sesquiterpenoid euonyminol (**2**).[5] Herein, we describe a synthetic route to enonyminol which has led to the tricyclic framework containing all of the oxygen functionality present in **2**. The key construction which established the skeleton of **2** was an "epoxide cascade" involving closure of the tetrahydrofuran by acid-mediated cyclization of a diepoxide.

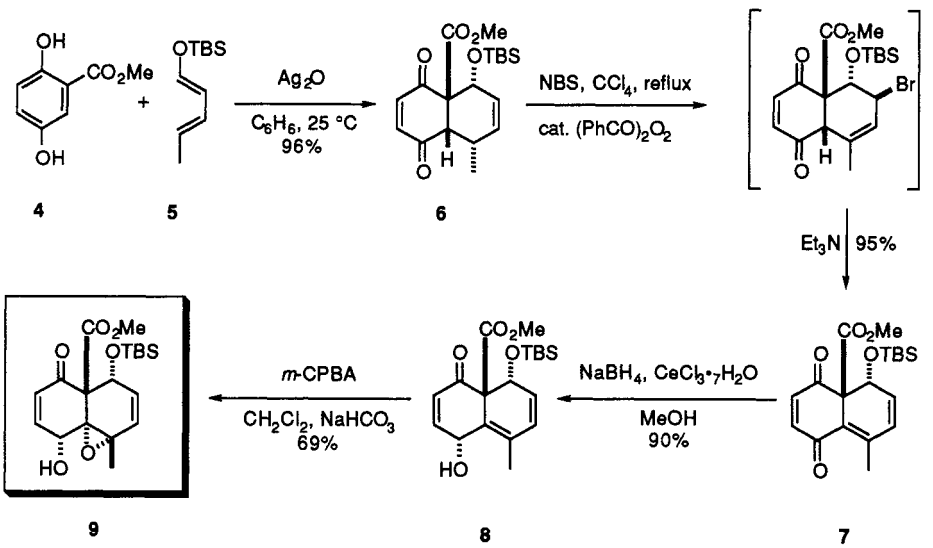
Scheme 1



Euonyminol (2) **3**

Our strategy for the synthesis of **2** is outlined in scheme 1 and is based upon successive elevation of the oxidation level of Diels-Alder adduct **3** along with incorporation of the requisite three-carbon unit at C7. The initial stages of this route are exemplified in scheme 2 where the pivotal intermediate **9** is acquired in four steps from **6**, assembled by means of a cycloaddition of diene **5** to the hydroquinone **4**.[6] A noteworthy feature of this sequence is the Luche reduction[7] of **7** with complete regio and stereoselectivity. The α configuration of the C6 hydroxyl substituent directs a syn epoxidation of **8** and thus inverts the ring fusion from cis in **6** to trans in **9**. Although the 1α configuration of **9** is incorrect for euonyminol, this center is inverted at a later step in the pathway.

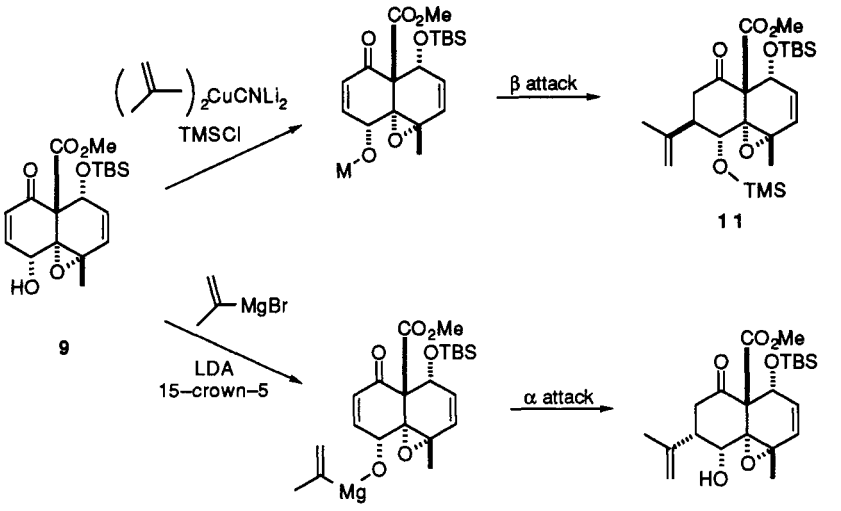
Scheme 2



4 **5** **6** **7** **8** **9**

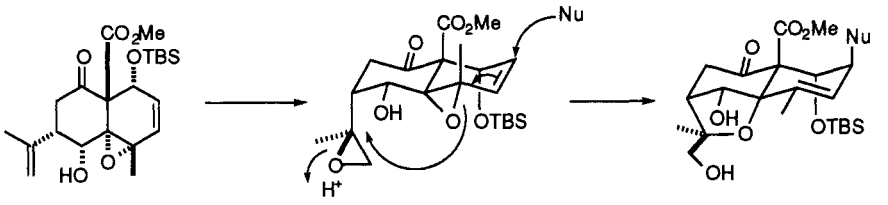
Introduction of an isopropenyl substituent into the 7α position of **9** initially proved to be troublesome, the higher and lower order cuprates yielding exclusively the product **10** resulting from β face atttack in the presence of a silylating agent.[8] However, the Grignard reaction of isopropenylmagnesium bromide with **9** under conditions which promoted coordination of the reagent to the 6α hydroxyl substituent[9] led to clean conjugate addition and resulted in the formation of **11** with high stereoselectivity. A rationale for the opposite stereochemical outcome in the reaction of **9** with cuprate and with Grignard reagent is shown in scheme 3 and conforms to the model of directed Grignard conjugate addition proposed by Liotta and Maryanoff.[10]

Scheme 3



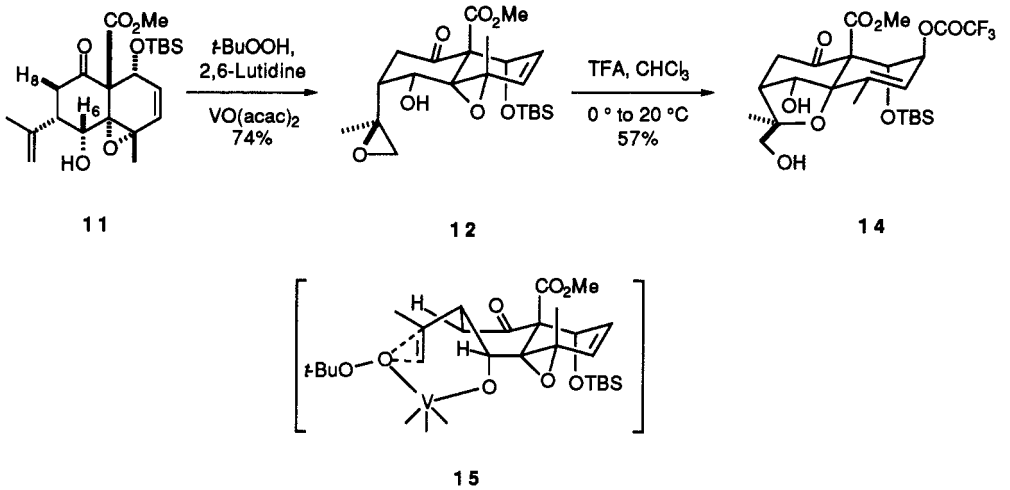
With **11** in hand the objective became its conversion to diepoxide **12** as the precursor for the "epoxide cascade" which would lead to **13**. The pathway envisioned for this process is shown in scheme 4 and is initiated by electrophilic opening of the terminal epoxide of **12**. This triggers attack by the internal epoxide, which is followed by a double bond shift and final entry of the nucleophile at C2, all presumed to occur in concerted fashion. Two important stereochemical requirements which must be met for this transformation to be successful are (a) the terminal epoxide must possess the correct configuration and (b) the nucleophile must enter **12** from the axial direction.

Scheme 4



Epoxidation of **11** with *m*-chloroperbenzoic acid, although selective for the isopropenyl group, gave a 1:1 mixture of stereoisomers which could not be separated. On the other hand, the use of *t*-butyl hydroperoxide in the presence of vanadium oxybis(acetonylacetate)[11] afforded a 4:1 ratio of stereoisomeric epoxides in which the desired stereoisomer **12** predominated. A probable explanation for this result is shown in scheme 5 in the form of complex **15**, where the substrate in a boat conformation undergoes epoxidation directed by the homoallylic alcohol at the si face of the isopropenyl substituent. Support for a stable boat conformer of **11** is found in its proton NMR spectrum, which reveals a W coupling of 1.7 Hz between H_6 and H_8.

Scheme 5

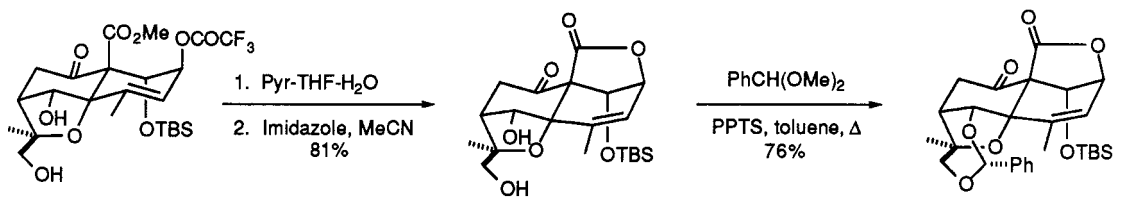


11 12 14

15

The cyclization of **12** proceeded smoothly in the presence of trifluoroacetic acid to yield **14** possessing the euonyminol skeleton. The syn relationship of the newly formed hydroxymethyl substituent and the C6 alcohol was confirmed by formation of a cyclic acetal with benzaldehyde. The axial disposition of the trifluoroacetate in **14** became apparent when this group was hydrolyzed and the resultant hydroxy ester underwent facile lactonization to the bridged γ-lactone **16** (scheme 6). This substance appeared to be a good candidate for attaching the syn hydroxyl groups at C3 and C4 by stereoselective osmylation from the α face of the trisubstituted double bond, but this olefin proved to be completely unreactive towards osmium tetroxide. Steric hindrance by the endo *t*-butyldimethylsilyl ether was judged to be a likely reason for this failure, and epimerization to the natural 1β configuration was therefore undertaken as a means for removing this obstruction. Before this was accomplished, however, diol **16** was protected as its benzylidene acetal **17**.

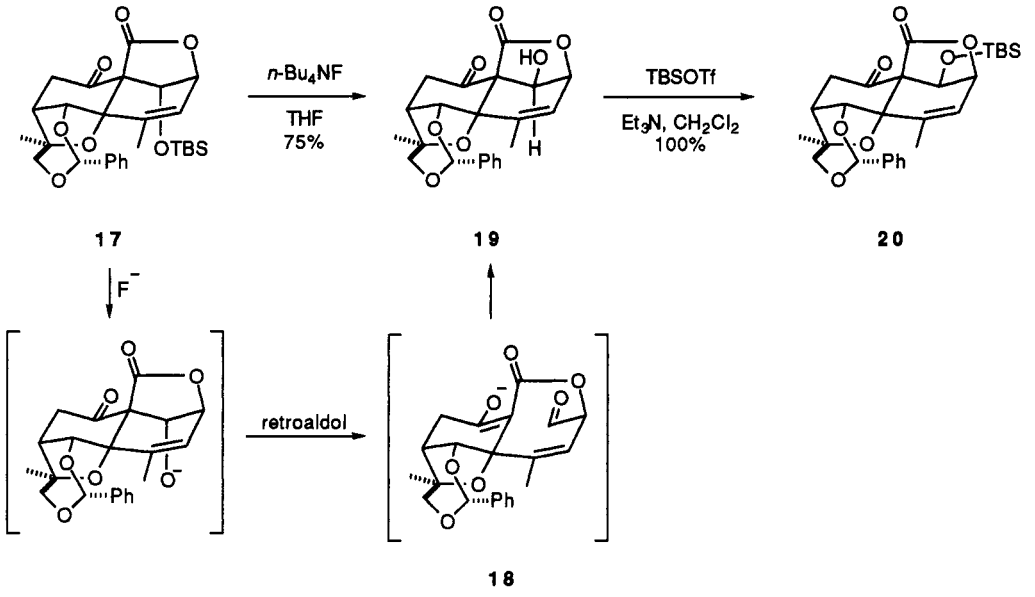
Scheme 6



14 16 17

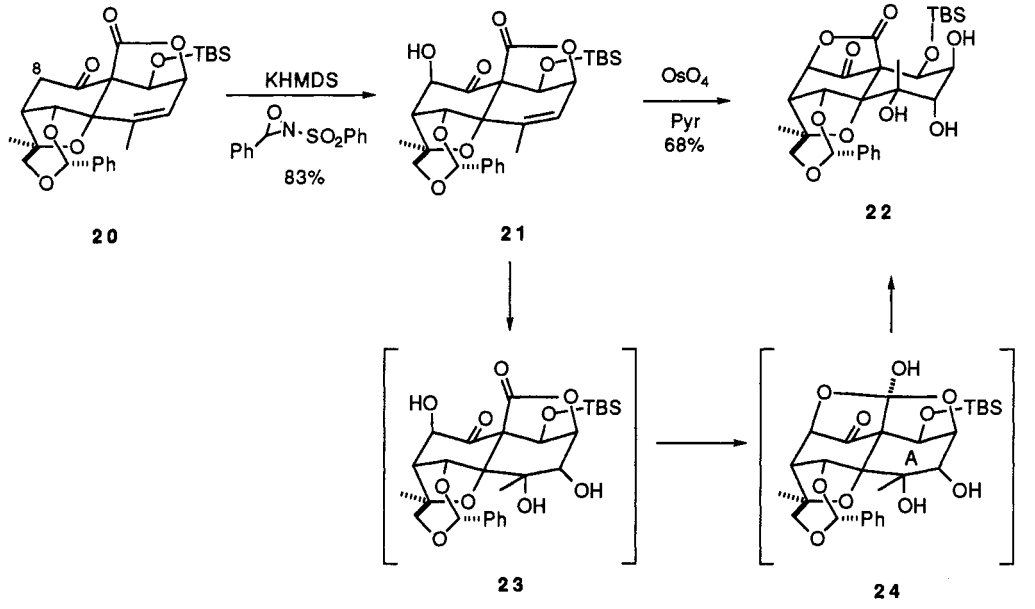
Removal of the silyl ether from **17** with fluoride brought the unexpected bonus of a clean and virtually instantaneous epimerization at C1 to the crystalline alcohol **19**. This is clearly the result of retroaldol fission, as shown in scheme 7, followed by thermodynamically driven reclosure of the derived enolate **18**. The steric constraint imposed by the bridging lactone of **17** is apparently a prerequisite for this inversion since the corresponding open γ-hydroxy ester does not follow a similar path. Firm verification of the structural and stereochemical features present in **19** was obtained by X-ray crystallographic analysis.

Scheme 7



The final stages of our route to **2** require introduction of a hydroxyl substituent at C8, hydroxylation at the $\Delta^{3,4}$ olefin, and reduction of the ketone and lactone functions. For the first of these transformations, **19** was protected as silyl ether **20** before its potassium enolate was subjected to hydroxylation with the Davis oxaziridine reagent.[12] Stereoselective β-hydroxylation was observed in this reaction based on the infrared spectrum of **21** which shows an intramolecular hydrogen bond with the lactone carbonyl. It is clear from a molecular model of **20** that the endo methyl substituent of the tetrahydrofuran moiety shields the α face of the enolate, a property which is used to advantage in the conversion to **21** but which obviously bodes ill for the stereochemical outcome in the reduction of the C9 keto group.

Scheme 8



As expected, osmylation of **21** now proceeded easily and with complete stereoselectivity to yield the product **22** of dihydroxylation from the α face of the $\Delta^{3,4}$ bond. Removal of the endo silyl ether permits ready access to the underside of the olefin and this selectivity is reinforced by shielding of the top face of the alkene by the bridging lactone. Unexpectedly, the hydroxylation was accompanied by a γ-lactone interchange involving the axial C8 hydroxyl group. The translactonization is presumed to pass through **23** and ortho ester **24**, and is probably driven by a change in conformation of ring B from boat to chair.

In principle, **22** requires only reduction of the two carbonyl functions followed by deprotection to reach euonyminol. However, as presaged in the hydroxylation of **20**, reduction of the keto group of **22** with hydride reagents occurred exclusively from the top face leading to the undesired α alcohol. Reversal of the stereochemical course of this reduction can be envisioned through the use of alternative reagents, and studies along these lines are in progress. In the meantime, variants of the synthetic pathway are being examined to determine whether reduction of the C9 ketone at an earlier stage in the sequence will furnish the desired configuration of **2**. After synthesis of euonyminol is completed, research directed towards synthesis of cathedulin K-19 (**1**) can begin. This will require accurate knowledge of the reactivity of the nine hydroxyl groups of **2** in order to effect their selective esterification with cathic and edulinic acids. Our studies of the final stages of the assault on cathedulin K-19 will be disclosed in subsequent publications.

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