Total Synthesis of (±)-Euonyminol, the Sesquiterpenoid Nucleus of Cathedulin K-19, via an Epoxide Cascade Cyclization

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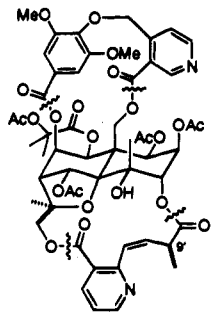
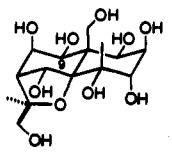
"Khat", a narcotic extract from leaves of the tree *Catha edulis* (Forsk) (Celastraceae), is in widespread use as an appetite suppressant and stimulant in impoverished areas of east Africa.[1] The extract contains in addition to cathinone[2] a family of complex terpenoid alkaloids known as cathedulins,[3] of which K-19 (**1**) is representative.[4] At the core of **1** and several related alkaloids[5,6] is a tricyclic structure, euonyminol (**2**), which to our knowledge represents the most highly oxygenated sesquiterpene known. As a first step toward the synthesis of **1**, we recently described a route to the lower portion (edulinic acid) which defined the configuration at C9′ as *S*.[7] We now report the first synthesis of racemic **2** using an "epoxide cascade" to elaborate the tetrahydrofuran ring and a remarkable α-hydroxy ketone transposition to install the correct stereochemistry at C9.[8]

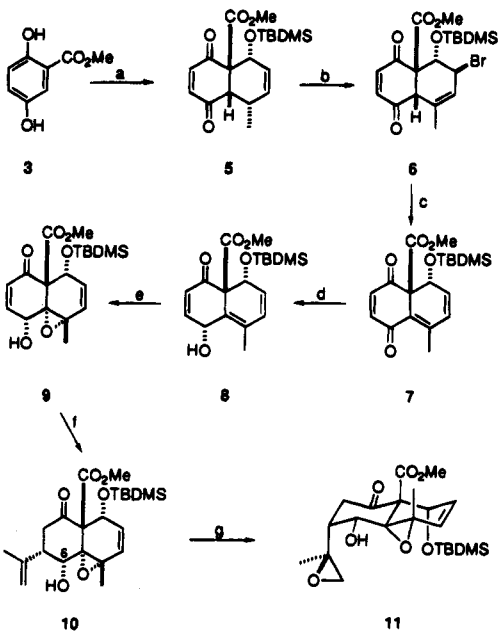


1



2

Diels−Alder adduct **5**, prepared from diene **4** and the benzoquinone derivative obtained by in situ oxidation of methyl 2,5-dihydroxybenzoate (**3**),[9] was converted to **7** via the allylic bromide **6**. Luche reduction[10] of **7** afforded **8** as the sole product, and a directed epoxidation of this alcohol with *m*-chloroperbenzoic acid yielded **9**. Treatment of enone **9** with isopropenylmagnesium bromide under conditions which generated the ate complex[11] resulted in stereoselective, conjugate addition and produced **10**.[12] Epoxidation of this homoallylic alcohol with *tert*-butyl hydroperoxide in the presence of vanadyl oxyacetylacetonate was directed by the C6 hydroxyl group to afford **11**.[13]



Reagents: (a)  (4, 3 eq), Ag_2O (2 eq), C_6H_6, 94%; (b) NBS, CCl_4, Bz_2O_2 (cat), Δ; (c) Et_3N, Δ, 98% from **5**; (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 90%; (e) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, pH 8, 0° → 25°C, 88%; (f) LDA, 15-crown-5, , THF, 63%; (g) *t*-BuOOH, 2,6-lutidine, $VO(acac)_2$, 74%.

Exposure of **11** to trifluoroacetic acid led to its clean cyclization to **12** via a sequence that is probably initiated by acid-catalyzed opening of the allylic epoxide.[14] The β orientation of the entering trifluoroacetate substituent permitted facile conversion of **12** to γ-lactone **13**, which was protected as its benzylidene acetal **14**. Cleavage of the silyl group from **14** with fluoride ion was accompanied by fortuitous epimerization to the 1β configuration of **15**,[15] presumably via retroaldol fission followed by realdolization.[16] After protection of **15** as its silyl ether **16**, the axial C8 hydroxyl group was introduced by oxidation of the ketone enolate with Davis' reagent.[17]

Attempts to reduce the keto group of **17** under a variety of conditions gave only the undesired 9α alcohol, a result that can be ascribed to the endo methyl substituent which obstructs approach to the α face of the ketone. However, contact of **17** with trimethylaluminum resulted in its quantitative rearrangement to the transposed α-hydroxy ketone **18**. This variant of the classical Lobry de Bruyn−Alberda van Eckenstein trans-

(1) Getahun, A.; Krikorian, A. D. *Econ. Bot.* **1973**, *27*, 353−377.
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(8) For an earlier study, see: White, J. D. *Pure Appl. Chem.* **1994**, *66*, 2183−2188.
(9) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1174−1175.
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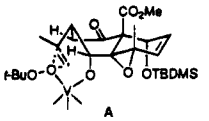
(11) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393−9394.
(12) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127−131. The complete α stereoselectivity observed in the hydroxyl-directed Grignard addition to **9** stands in contrast to cuprate addition, which led exclusively to the isopropenyl substituent with the β configuration.

(13) The vanadium complex responsible for this stereoselectivity is believed to be **A**, in which the cyclohexanone adopts a boat conformation (J_{H-H} = 1.7 Hz). The reaction of **10** with *m*-chloroperbenzoic acid gave predominantly the epoxide of opposite configuration.



A

(14) The allylic hydroxy trifluoroacetate from **11** was isolated and was shown to undergo cyclization to **12**.
(15) The structure of **15** was established by an X-ray crystallographic determination.
(16) The bridging γ lactone is a prerequisite for this epimerization; the opened hydroxy ester does *not* behave analogously.
(17) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742.

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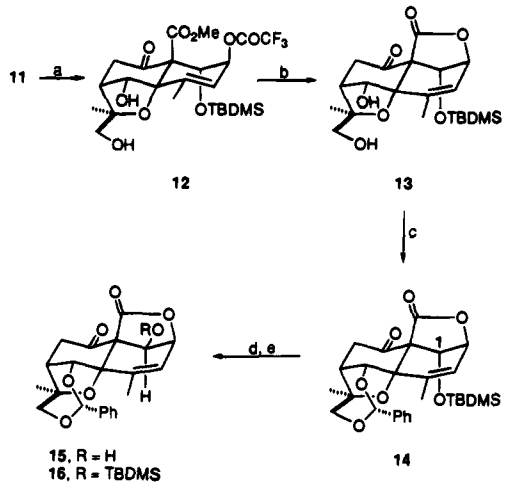
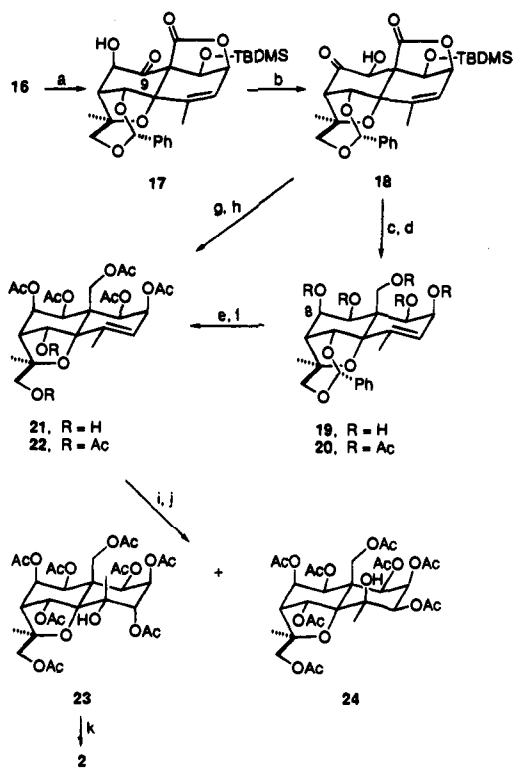


Reagents: (a) TFA, $CHCl_3$; (b) Pyr-THF-H_2O, then imidazole, MeCN, 75% from 11; (c) $PhCH(OMe)_2$, PPTS, toluene, Δ, 83%; (d) *n*-Bu_4NF, THF, 96%; (e) TBDMSOTf, Et_3N, CH_2Cl_2, 100%.

formation[18] conveniently solved our stereochemical problem by placing the C9 hydroxyl group in an equatorial orientation. Exhaustive reduction of **18** with lithium aluminum hydride, with an acidic workup that removed the silyl protecting group at C1, gave pentaol **19** and its 8α epimer (4:1 respectively). The pentaacetate **20** derived from **19** underwent clean acidic hydrolysis of its benzylidene acetal to give **21**, which was conveniently purified as its heptaacetate **22**. Alternatively, **22** could be obtained directly from **18** by reduction, treatment with Amberlite resin, and finally acetylation. Hydroxylation of the trisubstituted olefin **22** with excess osmium tetraoxide, followed by acetylation, afforded the known euonyminol octaacetate **23**[5] accompanied by its stereoisomer **24**. The disappointing ratio of **23**:**24** (1:8) may reflect an unfavorably directed osmylation in the heavily oxygenated milieu of **22**, in which case functionalization of the $\Delta^{3,4}$ bond could be effected earlier in the sequence. Nevertheless, methanolysis of **23** following Yamada's protocol[6] gave (±)-euonyminol (**2**), identical by comparison of chromatographic behavior and spectroscopic properties (IR, ^{1}H NMR, MS) with the naturally derived material.

In summary, a sequence of 19 steps leads from easily accessible **3** and **4** to (±)-euonyminol (**2**) in which every ring carbon is stereogenic and 11 of the 15 carbons carry an oxygen substituent. The route is potentially applicable to less functionalized variants of **2** such as maytoline and maytine,[19] and efforts to this end as well as toward completion of a synthesis of **1** are in progress.

(18) Speck, J. C. *Adv. Carbohydr. Chem.* **1958**, *13*, 63–103. Driving force for rearrangement in this case arises from replacement of an axial, non-hydrogen-bonded hydroxyl substituent at C8 by an equatorial alcohol at C9 (which hydrogen bonds to the lactone carbonyl group).



Reagents: (a) KHMDS, $Ph\overset{O}{\underset{}{}}N{\cdot}SO_2Ph$, THF, 86%; (b) Me_3Al, THF, 2 h, 0 °→ 25 °C, quant.; (c) $LiAlH_4$, THF, then 0.5N HCl; (d) Ac_2O, Et_3N, DMAP (cat), 31% from **18**; (e) 5% HF, MeCN; (f) Ac_2O, Et_3N, DMAP (cat), 43% from **20**; (g) $LiAlH_4$, THF, then Amberlite IR-120, HOAc-H_2O (1:1); (h) Ac_2O, Et_3N, DMAP (cat), 33% from **18**; (i) OsO_4, Pyr; (j) Ac_2O, Pyr, 76% from **22**; (k) NaOMe, MeOH, quant. (ref 6).

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Supporting Information Available: Physical and spectral data for **5**, **7**–**18**, **20**, **22**, and **24** and X-ray crystallographic data for **15** including tables of atomic coordinates, anisotropic thermal parameters for all atoms, and bond distances and angles (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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