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Enantioselective Synthesis of Euonyminol

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ABSTRACT: We describe an enantioselective total synthesis of the nonahydroxylated sesquiterpenoid euonyminol, the dihydro-β-agarofuran nucleus of the macrocyclic terpenoid alkaloids known as the cathedulins. Key features of the synthetic sequence include a highly diastereoselective intramolecular alkene oxyalkylation to establish the C10 quaternary center, an intramolecular aldol–dehydration to access the tricyclic scaffold of the target, a tandem lactonization–epoxide opening to form the *trans*-C2–C3 vicinal diol residue, and a late-stage diastereoselective α-ketol rearrangement. The synthesis provides the first synthetic access to enantioenriched euonyminol and establishes a platform to synthesize the cathedulins.

The "Flower of Paradise", also known as Khat (*Catha edulis*), is an erect shrub indigenous to Ethiopia, Kenya, and Yemen that when ingested produces feelings of euphoria, alertness, and satiation.[1] Pharmacological studies of Khat, dating to at least 1887, have established that its stimulatory properties derive from norpseudoephedrine (cathine).[2] Khat extracts also possess antiproliferative, antimicrobial, and antioxidant properties, but the metabolites responsible for these effects are not known.[3] Among Khat isolates, the cathedulins, as exemplified by cathedulins E-4 (**1**)[4] and K-19 (**2**),[5] are the most complex (Figure 1).[6] Both metabolites contain diester macrocycles derived from cathic acid (green in **1** and **2**) and evoninic (blue in **1**) or eudolinic acid (blue in **2**)[7] appended to a highly oxygenated *trans*-decalin core. The core itself constitutes the sesquiterpenoid metabolite euonyminol (**3**). Because of its polarity, **3** has been frequently characterized as its octaacetate.[8] White and co-workers reported a synthetic route to (±)-**3**,[9] and synthetic approaches have been recorded by the Spivey laboratory.[10] Several syntheses of less densely oxygenated dihydroagarofuran sesquiterpenoids have also been disclosed.[11] Here we describe an enantioselective synthetic route to **3** that may provide access to **1** and **2**.

The key elements of our successful route to euonyminol (**3**) are presented in retrosynthetic form in Scheme 1. We planned to access the target by C–H oxidation at C8 of lactone **4**, which was derived from the epoxide **5** via cleavage of the methyl ester and epoxide opening by the resulting carboxylic acid. The epoxide **5** was prepared from the keto aldehyde **6** via an aldol–dehydration, methyllithium addition, and oxidation sequence. The keto aldehyde **6** in turn was accessible from the vinylogous carbonate **7** via an oxidative cleavage–Baeyer–Villiger oxidation sequence. The vinylogous carbonate **7** was ultimately derived from the known carvone derivative **8** by formal intramolecular oxyalkylation of the C9–C10 alkene, addition of lithium trimethylsilylacetylide, and ring opening of the C11–C12 epoxide by the resulting C5 alcohol, a transformation that finds precedent in White's earlier studies.[9a,b]

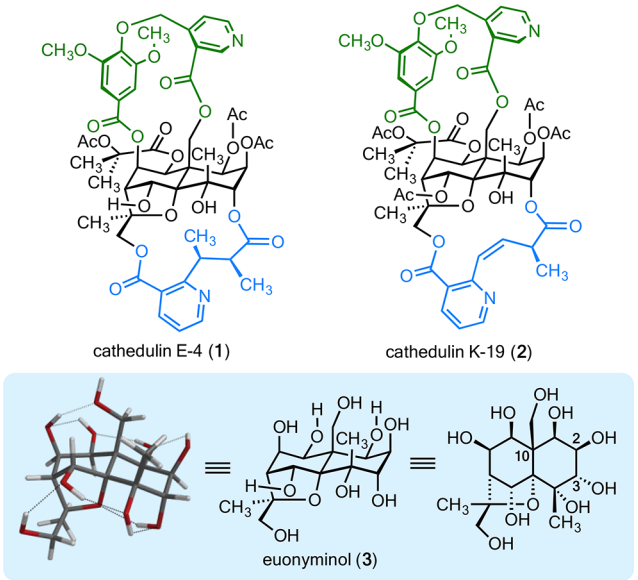

Figure 1. Structures of cathedulin E-4 (**1**), cathedulin K-19 (**2**), and euonyminol (**3**). The cathic acid residues in **1** and **2** are shown in green. The evoninic and eudolinic acid residues found in **1** and **2**, respectively, are shown in blue. The tube representation corresponds to the DFT-optimized structure of **3**. Intramolecular hydrogen bonds are shown with dashed lines.

The diene **8** is accessible in four steps and 68% yield from (−)-carvone by a scalable and robust procedure developed by Lee and Floreancig.[12] Oxidation of **8** using the levorotatory enantiomer of the Shi ketone proceeded with 2.4:1 selectivity in favor of the desired diastereomer **9** (70%, Scheme 2).[13]

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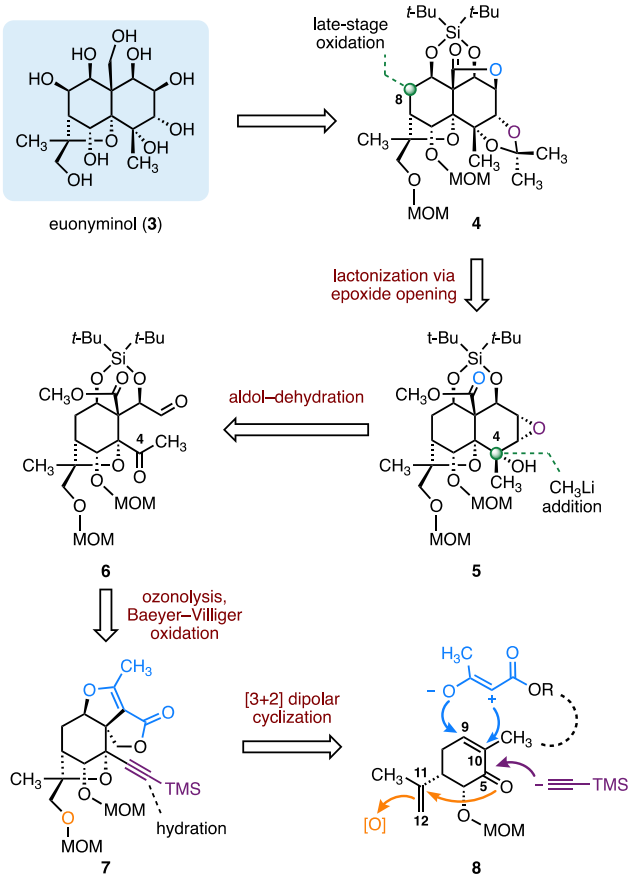
Scheme 1. Retrosynthetic Analysis of Euonyminol (3)

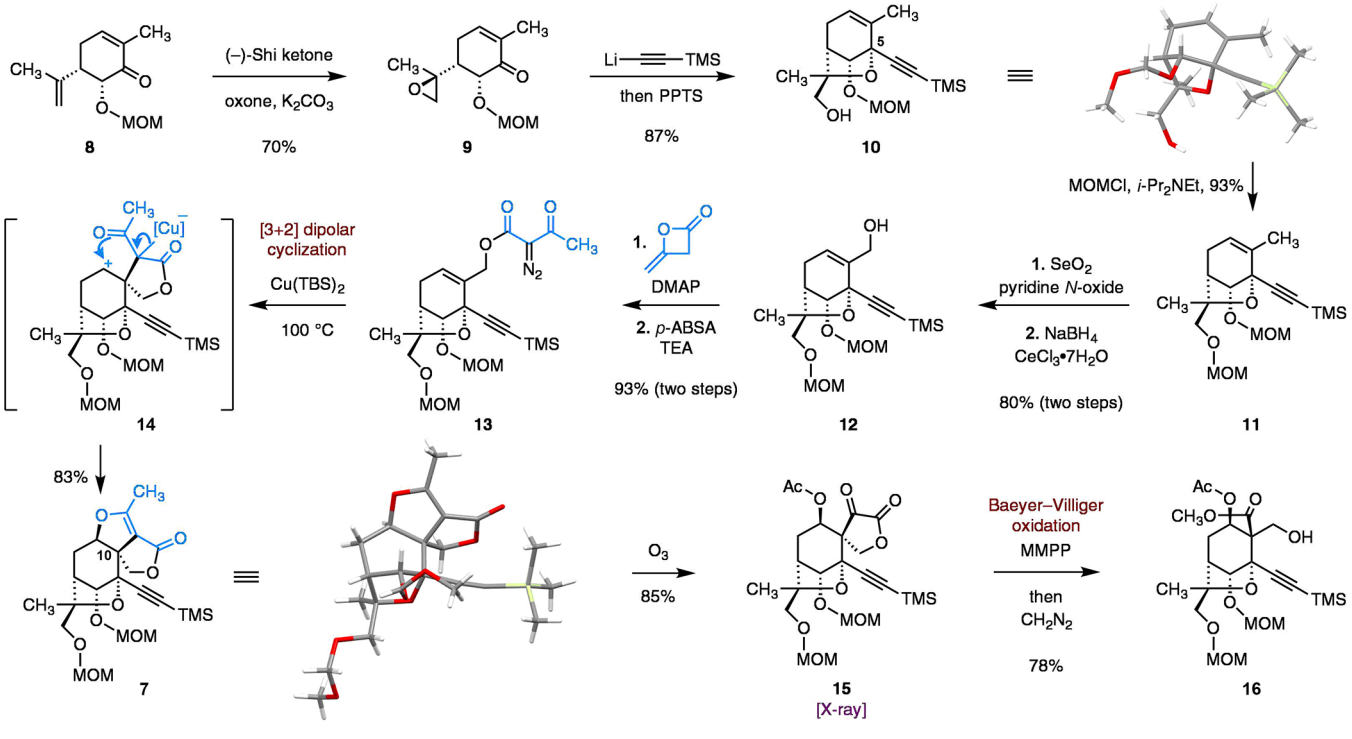


Extensive efforts to improve the diastereoselectivity in this step using other dioxiranes or substrate-directed processes were unsuccessful. Addition of lithium trimethylsilylacetylide provided the expected tertiary alcohol (not shown) with 13:1 diastereoselectivity at C5.[13] Because the product was found to undergo intramolecular epoxide opening upon purification, the unpurified product mixture was directly treated with pyridinium *p*-toluenesulfonate (PPTS) to provide the crystalline ether **10** (87% from **9**). Alternative nucleophiles, such as (1-ethoxyvinyl)lithium, were less efficient (8:1 dr, 67%). Protection of the primary alcohol (methoxymethyl chloride, Hünig's base, 93%) followed by allylic oxidation (selenium dioxide) and reduction of the aldehyde product (sodium borohydride, cerium chloride) generated the primary alcohol **12** (80% over two steps). (4-Dimethylamino)pyridine (DMAP)-catalyzed addition of **12** to diketene followed by diazo transfer ((4-acetamido)benzensulfonyl azide, ABSA, triethylamine)[14] provided the α-diazo-β-keto ester **13** (93% over two steps).

In a key step, thermolysis of the α-diazo-β-keto ester **13** in the presence of bis(*N*-(*tert*-butyl)salicylaldiminato)copper(II) (30 mol %) generated the vinylogous carbonate **7** (83%) as a single detectable diastereomer (^{1}H NMR analysis; see Table S1 for optimization studies). It seems plausible that the mechanism of this transformation involves an asynchronous dipolar addition pathway, as depicted in structure **14**. The closest precedent for this transformation of which we are aware, by Davies and co-workers, involves the formal rhodium-catalyzed [3 + 2] addition of furans to ketocarbenoids.[15] The transformation of **13** to **7** constitutes a formal oxyalkylation of an allylic alcohol and may find applications beyond that described here. The relative stereochemistry of **7** was determined by X-ray analysis. This transformation serves to simultaneously establish the C9 oxidation state and C10 quaternary center of the target.

Oxidative cleavage of the vinylogous carbonate (ozone, 85%) provided the α-keto lactone **15**, the structure of which

Scheme 2. Synthesis of the Methyl Ester 16 from the Carvone Derivative 8



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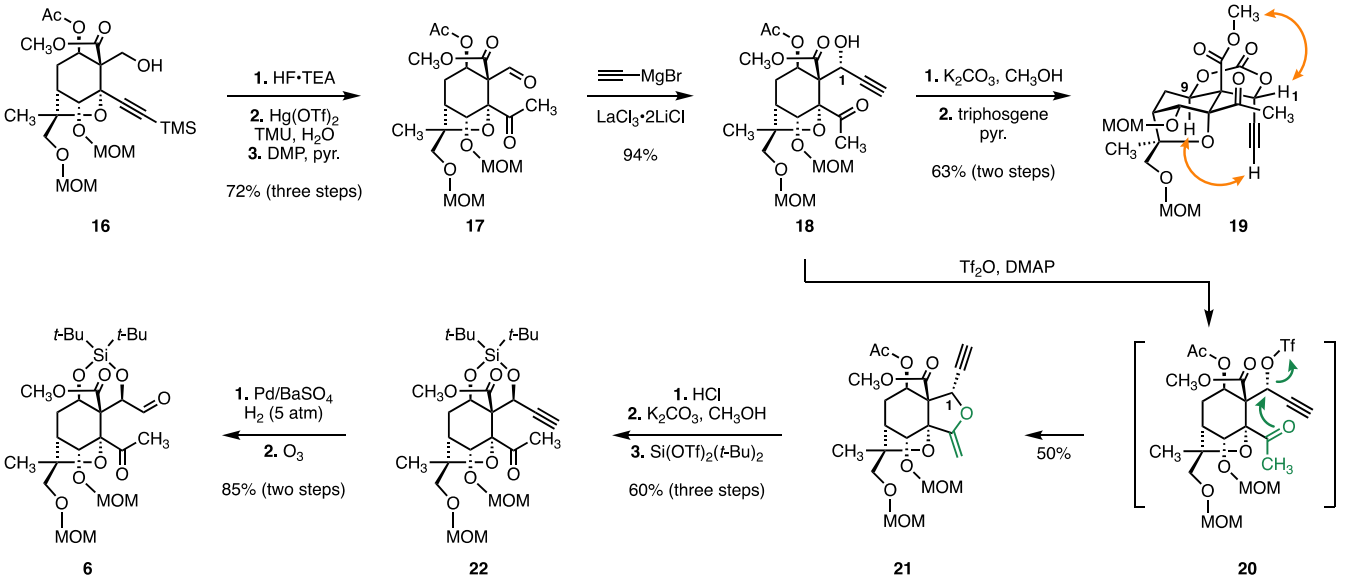
Scheme 3. Synthesis of the Keto Aldehyde 6; NOE Enhancements Supporting the Relative Stereochemistry of 19 Are Indicated by Orange Arrows



was also confirmed by X-ray analysis. Baeyer–Villiger oxidation of **15** using magnesium monoperoxyphthalate (MMPP) proceeded smoothly to provide, after treatment with diazomethane, the methyl ester **16** (78%). Oxidation of **15** with *m*-chloroperoxybenzoic acid or hydrogen peroxide proceeded in low yield (<50%).

The ester **16** was elaborated to the keto aldehyde **6** by the pathway shown in Scheme 3. A three-step sequence comprising cleavage of the silylalkyne (hydrogen fluoride–triethylamine complex) followed by Markovnikov-selective alkyne hydration (mercury triflate, tetramethylurea, TMU)[16] and oxidation of the primary alcohol (Dess–Martin periodinane, DMP)[17] provided the neopentyl aldehyde **17** (72% over three steps). Addition of ethynylmagnesium bromide to **17** in the presence of lanthanum chloride[18] formed the propargylic alcohol **18** (94%) as a single detectable diastereomer (^{1}H NMR and LC/MS analysis). The configuration of the C1 stereocenter was established by the conversion of **18** to the cyclic carbonate **19** (potassium carbonate, methanol, followed by triphosgene, pyridine; 63% overall). NOE enhancements between the C1 hydrogen and the methyl ester as well as the alkynyl and C9 hydrogens supported the structure assignment shown.

A stereochemical model that rationalizes the selectivity in the conversion of **17** to **18** is shown in Figure 2. We postulate that the substrate preferentially forms a tridentate chelate between the aldehyde, the methyl ketone, the methyl ester, and the lanthanum additive, as shown in structure **23**. Approach of the acetylide nucleophile to the less hindered α face of the aldehyde would then provide the observed product **18**. The alternative tridentate chelate **24**, which would provide the C1 configuration of the target, may be disfavored because of the presence of *syn*-pentane interactions between the methyl ester and ketone substituents (highlighted in blue). We found that, presumably due to the steric hindrance of the aldehyde, the addition proceeded only in the presence of lanthanum chloride, and extensive efforts to overturn the selectivity were unsuccessful.

The C1 configuration could be inverted by treatment of the propargylic alcohol **18** with trifluoromethanesulfonic anhydride and DMAP. Under these conditions, the cyclic enol ether **21** was obtained in 50% yield (63% based on recovered **18**) as a single detectable diastereomer (^{1}H NMR analysis, Scheme 3). In spite of the modest yield (see Table S3 for optimization), this strategy was singularly successful among a range of inversion strategies surveyed (see Figure S3). All attempts to directly establish the desired C1 configuration by the addition of other nucleophiles to **17** were uniformly unsuccessful (see Table S2). The addition of more basic nucleophiles resulted in recovery of starting material, suggesting that proton transfer from the methyl ketone occurred preferentially.

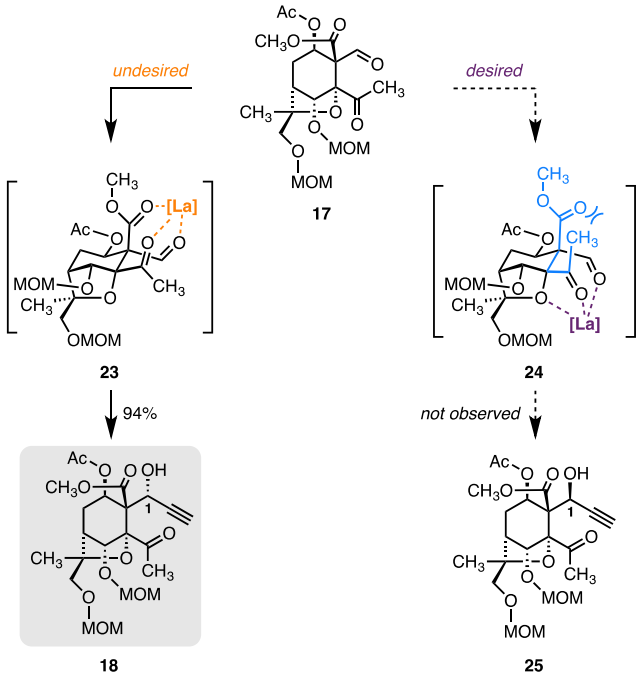


Figure 2. Stereochemical model for the addition of ethynylmagnesium bromide to the neopentyl aldehyde **17**.

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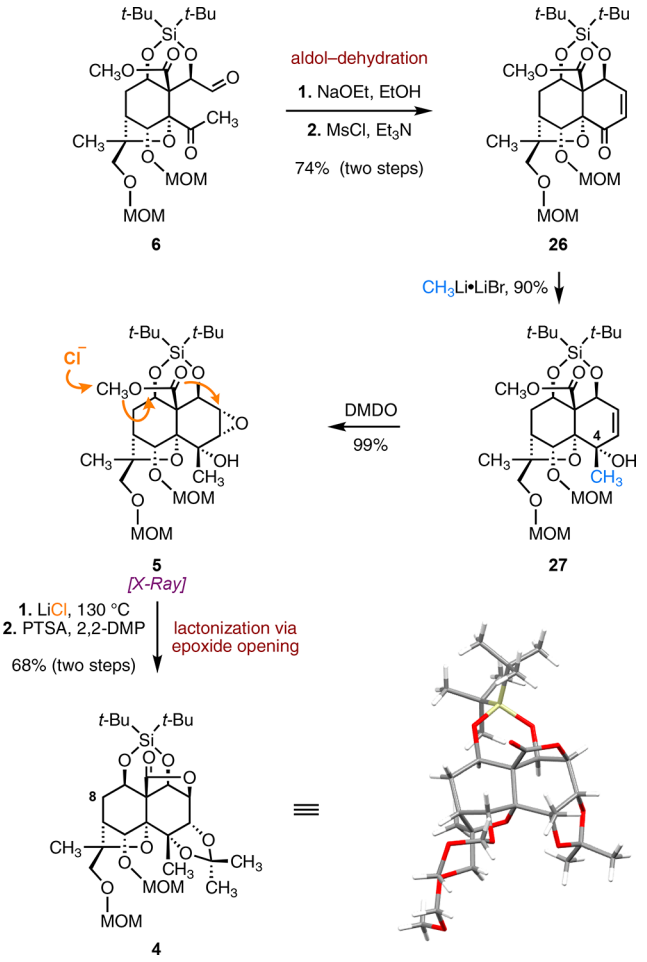
Hydrolysis of the enol ether (hydrochloric acid), removal of the acetate (potassium carbonate, methanol), and silylene ether formation (di-*tert*-butylsilyl ditrifluoromethanesulfonate)[19] provided the tricycle **22** (60% over three steps). Semihydrogenation of the alkyne (palladium−barium sulfate, dihydrogen) followed by ozonolysis of the resulting alkene formed the keto aldehyde **6** (85% over two steps).

To obtain the lactone **4**, the keto aldehyde **6** was first exposed to freshly prepared sodium ethoxide in ethanol, which generated the expected intramolecular aldol addition product (not shown) as an uncharacterized mixture of diastereomers (Scheme 4). Activation of the alcohol with methanesulfonyl chloride followed by elimination of the resulting mesylate afforded the α,β-unsaturated ketone **26** (74% over two steps).

Scheme 4. Synthesis of the Fully Protected Lactone 4



1,2-Addition of methyllithium proceeded with 9:1 diastereoselectivity (^{1}H NMR analysis) to provide the alcohol **27** in 90% yield.[13] Oxidation with dimethyldioxirane proceeded smoothly to afford the epoxide **5** as a single detectable diastereomer (^{1}H NMR analysis). Nucleophilic cleavage of the methyl ester (lithium chloride, 130 °C) proceeded with opening of the epoxide in situ. Protection of the resulting vicinal diol (*p*-toluenesulfonic acid, 2,2-dimethoxypropane) generated the lactone **4** (68% over two steps). X-ray crystallographic analysis of **4** served to confirm its structure as well as the stereoselectivity in the epoxidation step (**27** → **5**).

Unfortunately, all attempts to achieve an intermolecular or directed oxidation of C8 of **4** (and various derivatives) were ultimately unsuccessful. Many of these attempted oxidations[20] returned unreacted starting material **4** or proceeded to selectively oxidize the methoxymethyl ether protecting groups (see Table S4). We envisioned employing the primary alcohol derived from the lactone in a directed oxidation; however, we were unable to successfully reduce **4**. We also attempted an intramolecular dioxirane insertion using the C9 alcohol as a directing group.[21]

In light of these difficulties, an alternative sequence was devised (Scheme 5). Removal of the silylene protecting group (tetra-*n*-butylammonium fluoride, TBAF) followed by site-selective oxidation of the resulting 1,3-diol (DMP) and silyl ether formation (*tert*-butyldimethylsilyl trifluoromethanesulfonate, triethylamine) provided the ketone **28** (67% from **4**). Oxidation of **28** (lead tetraacetate, 88%) generated an α-acetoxy ketone (not shown) as a single detectable diastereomer (^{1}H NMR analysis). Cleavage of the resulting acetate protecting group (potassium carbonate, methanol) formed the α-hydroxy ketone **29** (88% over two steps). Attempts to reduce the C9 ketone of **29** using sodium borohydride, diisobutylaluminum hydride, or Superhydride provided the undesired *trans*-vicinal diol predominantly. Consequently, we employed an α-ketol rearrangement mediated by trimethylaluminum (as first reported by White and co-workers[9a,b] for a similar substrate) to access the isomeric α-hydroxy ketone **30** (90%, single diastereomer, ^{1}H NMR analysis). Reduction of the ketone (sodium borohydride, cerium chloride) proceeded with 4:1 diastereoselectivity at C8. We found that the major diastereomer in the reduction step underwent partial trans-lactonization upon purification. Consequently, the unpurified reduction product was protected (*p*-toluenesulfonic acid, 2,2-dimethoxypropane) to provide the stable bis(acetonide) **31** (61% over two steps).[13] Removal of the silyl ether (TBAF) followed by exhaustive reduction of the lactone (lithium aluminum hydride, LAH) afforded the triol **32** (66% over two steps). All attempts to reduce the lactone within the silyl ether **31** resulted in recovery of starting material, presumably because of the steric encumbrance introduced by the silicon substituents.

Finally, removal of the protecting groups (aqueous acetic acid, 85 °C) afforded euonyminol (**3**). Because of the polarity of **3** and the lack of a chromophore to guide purification, the unpurified sample was subjected to exhaustive acetylation (acetic anhydride),[22] to provide, following normal-phase chromatographic purification, euonyminol octaacetate (**33**) in analytically pure form (60% over two steps). Spectroscopic data for synthetic **33** obtained in this way were identical in all respects to those reported in the literature for the natural and synthetic material (see Tables S5 and S6). Removal of the acetate residues (sodium methoxide, methanol, >99%) then provided **3**. To the best of our knowledge, spectroscopic data for natural euonyminol (**3**) have not been published. White and co-workers reported proton chemical shifts for synthetic **3** in deuterium oxide,[9a,b] but our spectroscopic data were not in agreement (see the Supporting Information). The basis for the discrepancy is not known but the polar nature of **3** may render its chemical shifts sensitive to concentration and impurities. We eluted our sample over an ion-exchange resin as in White's report,[9a,b] but the NMR spectroscopic data were unchanged. Unfortunately, White and co-workers did not disclose ^{13}C NMR data or graphical reproductions of their proton NMR

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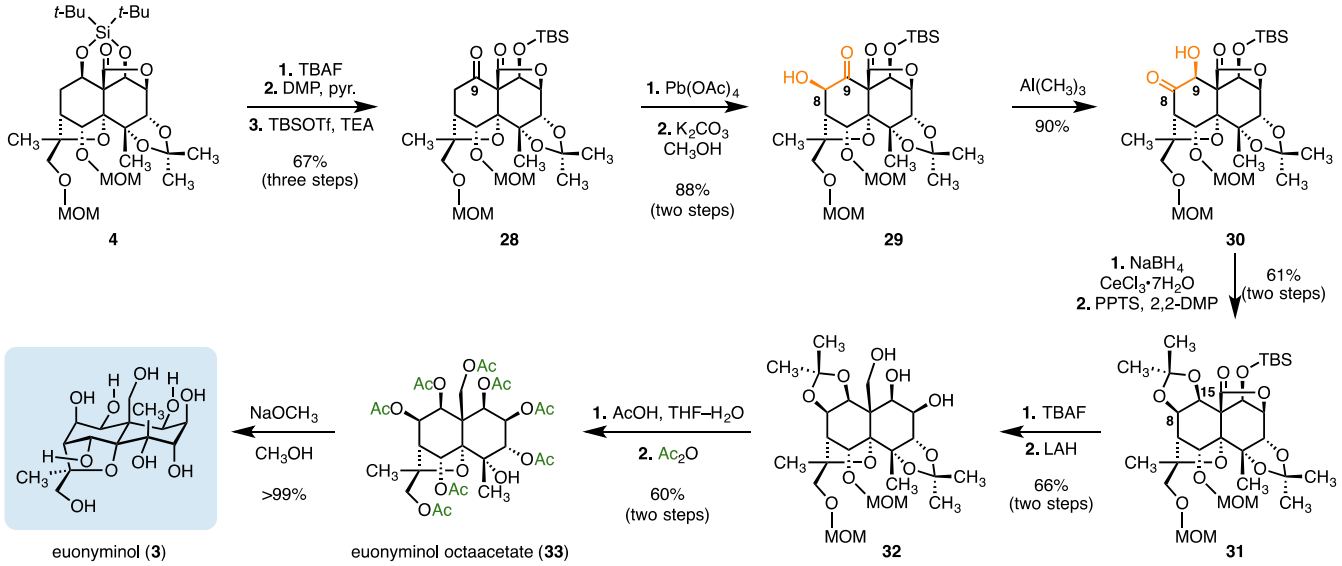
J. Am. Chem. Soc. 2021, 143, 699−704

Scheme 5. Completion of the Synthesis of Euonyminol (3)



spectrum. We calculated the ^{13}C chemical shifts for **3** using the protocol of Hehre et al.[23] and found that they were in good agreement with the experimental values (root-mean-square deviation = 2.79; see Table S8). Additionally, reacetylation of synthetic **3** provided the expected octaacetate **33**, indicating that no unexpected transformations had occurred in the original deacetylation (see the Supporting Information). Attempts to procure natural samples of **3** have to date been unsuccessful. We obtained complete characterization of **3** in deuterium oxide and methanol-d_4, which will be of use to other researchers in the area (see the Supporting Information).

In conclusion, we have described the first enantioselective synthetic route to euonyminol (**3**), the heavily oxidized sesquiterpenoid core of the cathedulins. The route features a highly diastereoselective intramolecular alkene oxyalkylation, a tandem lactonization–epoxide opening cascade, and a late-stage diastereoselective α-ketol rearrangement. The route outlined herein may be adaptable to synthesis of the cathedulins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12998.

Detailed experimental procedures and characterization data for all new compounds (PDF)

Crystallographic data for **5** (CIF)

Crystallographic data for **7** (CIF)

Crystallographic data for **4** (CIF)

Crystallographic data for **10** (CIF)

Crystallographic data for **15** (CIF)

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Notes

The authors declare no competing financial interest.

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