Enantioselective Total Synthesis of the Kinesin Motor Protein Inhibitor Adociasulfate 1

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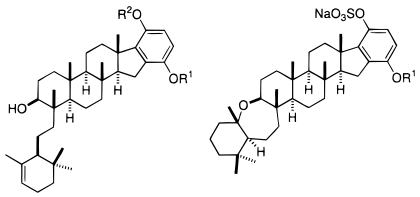
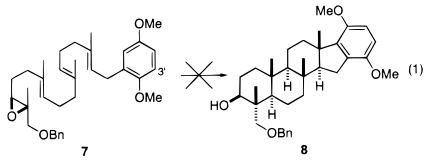
Utilizing the energy of ATP hydrolysis, the kinesin super family of motor proteins is responsible for movement of cellular cargo along microtubule tracks from the center of eukaryotic cells to their periphery (anterograde transport).[1] These proteins are important targets for inhibition since they play a necessary role in cell division[2] and in vesicle and organelle transport.[3] A family of hexaprenoid hydroquinone sulfates, the adociasulfates (e.g., **1**−**5**), was isolated recently from extracts of the sea sponge *Haliclona* (a.k.a. *Adocia*) sp. collected off Palau,[4,5] and Queensland, Australia.[6] Adociasulfates 1 (**1**) and 2 (**2**) and congeners **3** and **4** inhibit members of the kinesin motor protein super family in the low micromolar range and are the first kinesin inhibitors identified that are not nucleotide analogues.[4,5] Kinesin inhibition by the most extensively investigated of these, **2**, has been shown to result from interfering with microtubule binding.[4] Adociasulfates 1 (**1**) and 7 (**5**) have also been reported to be proton pump inhibitors.[6] Motivated by the opportunity to exploit the tools of synthesis to enhance understanding of kinesin inhibition by the adociasulfates, we undertook as our initial objective the total synthesis of these novel hydroquinone bis-sulfates.



1: $R^1 = R^2 = SO_3Na$ (AS-1)
3: R^1 = H, $R^2 = SO_3Na$ (AS-5)
5: $R^1 = SO_3Na$, R^2 = H (AS-7)
6: $R^1 = R^2$ = H

2: $R^1 = SO_3Na$ (AS-2)
4: R^1 = H (AS-6)

Hexacyclic hydroquinone **6** is a potential precursor of adociasulfates **1**−**5**. This intermediate contains nine stereogenic carbon centers, of which eight are contiguous and four are quaternary. Inspired by the pioneering investigations of Eschenmoser, Stork, van Tamelen, Johnson, and Corey, we envisaged construction of the bulk of this challenging stereochemical array in one step by a cationic polyene cyclization.[7] Recent notable success by the Corey group in nonenzymatic epoxide-initiated polyene tetracyclizations[8] suggested that **6** might be obtained by the cyclization cascade shown in eq 1. From the outset we were mindful that the two known epoxide-initiated polyene tetracyclizations featured termination of the cationic cyclization by an enoxysilane,[8] while the proposed tetracyclization of **7** would require termination by a significantly less-nucleophilic arene.[9,10] Our concerns about the



nucleophilicity of the arene were borne out in early scouting studies when treatment of **7** with a variety of Lewis acids under a range of reaction conditions delivered only bi-, tri-, and tetracyclic products and not the desired pentacycle **8**. This failure led us to examine the pivotal tetracyclization with a polyene substrate containing an additional activating substituent at the 3′-position of the arene, an approach that culminated in the total synthesis of **1**.

Geranylgeraniol cyclization substrate **19** was assembled from the union of two geraniol-derived fragments, **14** and **13** (Scheme 1). The sulfone piece **14** was prepared according to literature procedures,[11] while allylic bromide **13** was accessed by initially alkylating the lithium reagent derived from aryl bromide **9** with silyl-protected allylic bromide **10**.[12] Discharge of the silyl-protecting group of **11** and standard conversion to the allylic bromide provided **13** in 56% overall yield from **9**. Coupling of the potassium salt of **14** with **13** furnished isomerically pure **15** in nearly quantitative yield.[13] Desulfonylation of this intermediate was initially problematic; for example, reduction of **15** with Na (EtOH−THF) or Li ($EtNH_2$) gave mixtures of tetraene stereo- and regioisomers. Selectivity in the reduction of the allylic sulfone was finally achieved by the method of Inomata[14] by treating the crude coupled product with $LiEt_3BH$ and Pd(dppp) at 0 °C to furnish isomerically pure tetraene **16** on multigram scales in 64% yield for the coupling and desulfonylation steps. It is notable in this transformation, and not presaged in earlier publications, that competing reduction of the allylic silyl ether functionality is minimal when the reduction is conducted at 0 °C.[15] The phenol was reprotected and the silyl ether-protecting group was removed with acidic methanol to provide **17**. Sharpless asymmetric epoxidation[16] of **17** using the catalyst derived from (+)-diethyl tartrate generated **18** (in 95% yield and 95% ee), which was *O*-benzylated to give **19**.

A variety of Lewis acids and cyclization conditions were screened to induce polyene tetracyclization of **19** in CH_2Cl_2 (Scheme 2). Pentacycle **20** was produced in ∼10% yield using $BF_3{\cdot}Et_2O$ (−94 → −50 °C) or $FeCl_3{\cdot}6H_2O$ (23 °C),[17] whereas $MeAlCl_2$ (−90 → 0 °C), the Lewis acid reported optimal for epoxide-initiated tetracyclizations terminated by enoxysilanes,[8] gave only trace amounts (<5%) of **20**. Of the Lewis acids screened to date, $Sc(OTf)_3$ (−90 → 0 °C) is optimal and provides

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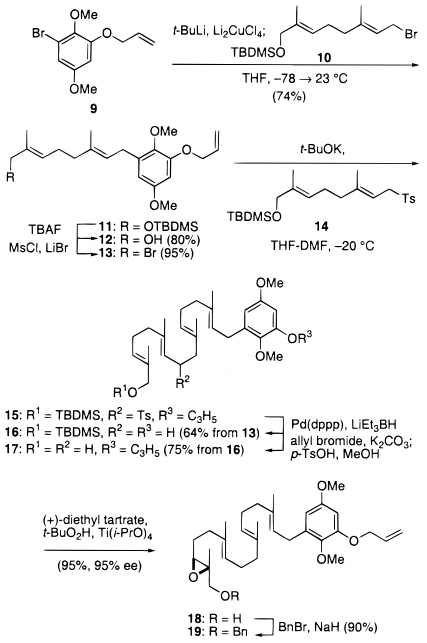
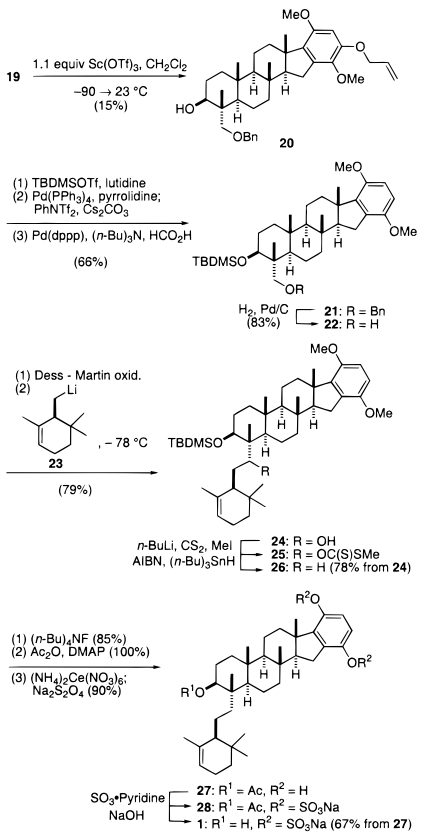
Scheme 1



Scheme 2



20 in 15% yield.[18] The secondary alcohol of **20** was protected as a *tert*-butyldimethylsilyl (TBDMS) ether and the activating allyloxy group was removed by a two-pot, three-step sequence involving deallylation, triflation, and palladium-catalyzed reduction of the aryl triflate intermediate.[19] The product, pentacycle **21**, was obtained in 66% yield for the three steps. Hydrogenolysis of the benzyl group then yielded crystalline alcohol **22**.[20]

Next, the union of a cyclogeranyl fragment with **22** was explored and found to be quite demanding due to the high degree of steric congestion surrounding the two carbons to be joined.[21,22] We eventually found that this junction was best accomplished by addition of (*S*)-cyclogeranyllithium **23**[23,24] to the aldehyde formed from **22** by Dess−Martin oxidation.[25] Adduct **24** was produced as a single isomer, whose stereochemistry was inconsequential and not determined, in 79% yield for the two steps. The congested steric environment surrounding C8 also complicated removal of the hydroxyl group of **24**, and many common procedures for deoxygenation failed. The desired reduction was finally achieved when a neat solution of xanthate derivative **25**,[26] *n*-Bu_3SnH (100 equiv) and 2,2′-azobisisobutyronitrile (AIBN, 0.1 equiv) was warmed to 80 °C giving **26** in 78% yield from alcohol **24**.

Preliminary survey experiments suggested that cleavage of an acetate, rather than a silyl ether, from a hydrophilic hydroquinone bis-sulfate precursor would simplify purification of the natural product. Thus, the protecting group of the C10 alcohol was changed to acetate.[27] Next the phenolic methyl groups were removed by oxidation to the quinone followed by reductive workup to give hydroquinone **27** in 76% overall yield from **26**. Sulfation of **27** with excess SO_3·pyridine and pyridine for 14 h at 23 °C provided bis-sulfate **28**. The synthesis of adociasulfate 1 (**1**) was then completed by hydrolysis of **28** with a solution of aqueous NaOH and MeOH (60 °C, 10 h), giving **1** in 67% yield from **27**. Synthetic adociasulfate 1 (**1**) was indistinguishable by ^{1}H NMR, ^{13}C NMR, HRMS, and reverse phase C-18 TLC comparisons with an authentic sample. The optical rotation of synthetic adociasulfate 1, $[\alpha]^{25}_D$ −30° (c = 0.10), was the same sign as that reported for natural **1**, $[\alpha]^{26}_D$ −34° (c = 0.1)[6] and −15.0° (c = 0.1).[5]

In conclusion, the first total synthesis of (−)-adociasulfate **1** was completed from commercially available geraniol and 2-hydroxy-5-methoxybenzaldehyde.[28] In addition to establishing the absolute configuration of the natural product, the synthesis provides the first example of using an arene to terminate an epoxide-initiated polyene tetracyclization. Tetracyclization to form **20** proceeded with a yield per ring of 62% (15% overall). However, for this route to meet the challenge of providing a practical synthetic entry to the adociasulfates, substantial improvement in the yield of the critical polyene cyclization will be needed.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for new compounds described in Schemes 1 and 2, and ^{1}H and ^{13}C NMR spectra of synthetic and natural adociasulfate 1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The authors have deposited coordinates for this compound with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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(23) Made by conversion of (*S*)-α-cyclogeraniol[24] (98% ee) to the corresponding iodide (PPh_3, I_2, imidazole, benzene) followed by lithium−iodide exchange using *tert*-butyllithium.

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(27) (*R*)- and (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl derivatives of the alcohol formed on desilylation were analyzed by ^{19}F NMR.

(28) The synthetic sequence is 28 steps from either starting material.