Enantioselective Total Synthesis of Shahamin K

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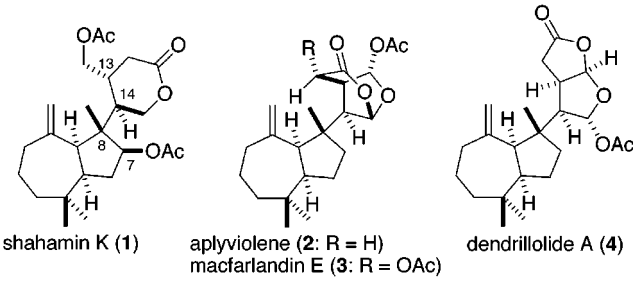
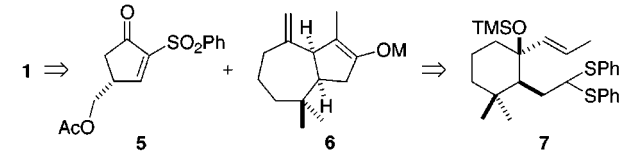
Several highly oxidized diterpenes having a rearranged spongian skeleton have been isolated from marine sponges and nudibranches.[1] Dorid nudibranches are shell-less marine mollusks, which are believed to have acquired the spongian-related compounds from sponges on which they feed.[1] An example of one such diterpene is macfarlandin E (**3**, also called aplyviolacene), which is found in both nudibranches and sponges.[2] In 1991 Andersen and co-workers reported the isolation of shahamin K (**1**) from the skin extracts of a dorid nudibranch *Chromodoris gleniei* found in coastal waters of Sri Lanka.[3] The gross structure and relative stereochemistry of **1** were secured by NMR studies, whereas the absolute configuration was not determined.[3] The common structural features of rearranged spongian diterpenes, exemplified by **1**−**4**, are a *cis*-hydroazulene unit and an attached highly oxidized six-carbon fragment, the latter of which occurs in a variety of cyclic and bicyclic motifs. Biological properties of rearranged spongian diterpenes have been little investigated, although antimicrobial and fish anti-feedant activities have been documented.[2a,4,5] We report herein the first total synthesis of a rearranged spongian diterpene; this synthesis confirms the relative and absolute stereochemistry of (+)-shahamin K and introduces a useful extension of our Prins-pinacol approach for constructing carbocyclic skeleta.[6]

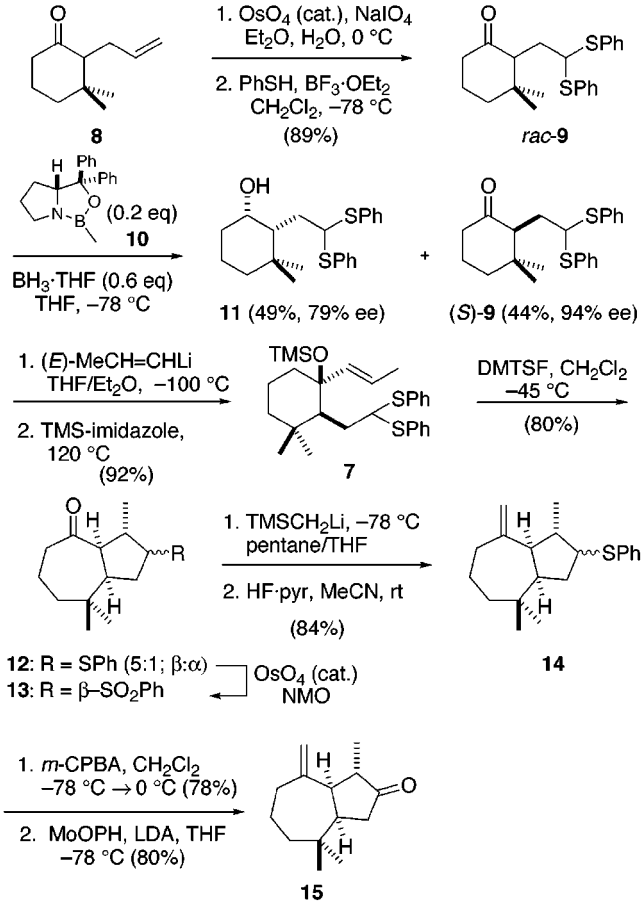


Our synthesis plan is outlined in retrosynthetic format in Scheme 1. Michael addition of cyclopentenone electrophile **5** and *cis*-hydroazulene enolate **6** was envisaged to construct the challenging C8−C14 σ-bond and relate the stereochemistry of the two attached rings. Stereocontrol in this pivotal event would derive from the facial bias of each coupling partner: preferential reaction of **6** from the convex α face and **5** from the face opposite the acetoxymethyl substituent.[7] The *cis*-fused ketone precursor of **6** was seen to derive from ring-enlarging cyclopentane annulation of cyclohexyl precursor **7**.[6]

Scheme 1



Scheme 2



The synthesis began with cyclohexanone **8**,[8] which was transformed to *rac*-**9** using an improved version of a procedure developed earlier (Scheme 2).[9] Kinetic resolution of *rac*-**9** by reaction with 0.2 equiv of (*R*)-oxazaborolidine **10** and 0.6 equiv of BH_3·THF at −78 °C provided the easily separable cyclohexanone (*S*)-**9** (44% yield, 94% ee) and alcohol **11** (49% yield, 79% ee).[10,11] Addition of (*E*)-1-propenyllithium to (*S*)-**9** at −100 °C,

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49. Also earlier reviews in this series.

(2) (a) Clardy, J.; Cun-Leng, H.; Faulkner, D. J.; Molinski, T. F.; Van Duyne, G. D. *J. Org. Chem.* **1986**, *51*, 4564−4567. (b) Hambley, T. W.; Poiner, A.; Taylor, W. C. *Tetrahedron Lett.* **1986**, *27*, 3281−3282.

(3) Andersen, R. J.; Desilva, E. D.; Dumdei, E.; Miao, S. C.; Morris, S. A. *J. Nat. Prod.* **1991**, *54*, 993−997.

(4) (a) Sullivan, B.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3204−3206. (b) Bobzin, S. C.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 225−232.

(5) In recent studies, the related spongian-derived marine metabolite norrisolide was identified as the first compound to induce irreversible effects in Golgi organization: Takizawa, P. A.; Yucel, J. K.; Veit, B.; Faulkner, D. J.; Deerinck, T.; Soto, G.; Ellisman, M.; Malhotra, V. *Cell* **1993**, *73*, 1079−1090.

(6) (a) Hirst, G. C.; Howard, P. N.; Overman. L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514−1515. (b) Johnson, T. O., Jr.; Overman. L. E. *Tetrahedron Lett.* **1991**, *32*, 7361−7365. (c) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379−6387. (d) Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992−2993. (e) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940. (f) Overman, L. E.; Pennington, L. P. *Can. J. Chem.* **2000**, *78*, 732−738.

(7) Few methods exist for relating the stereochemistry of attached rings.[6f] For a recent example of the use of a similar strategy, see: Kishi, Y.; Wang, W. *Org. Lett.* **1999**, *7*, 1129−1132.

(8) Available in two steps and 70% yield from 3-methyl-2-cyclohexenone, see: Boxler, D.; Grieco, P. A.; Makaki, Y. *J. Org. Chem.* **1975**, *40*, 2261−2263.

(9) Montgomery, J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 6476−6479.

(10) (a) Kishi, Y.; Kurosu, M. *J. Org. Chem.* **1998**, *63*, 6100−6101. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

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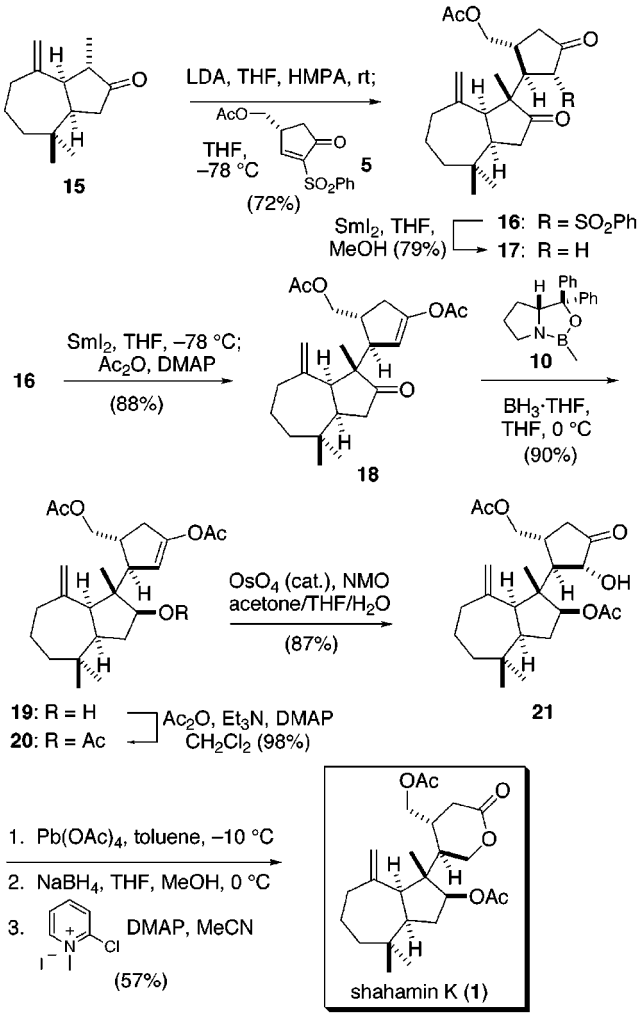
followed by silylation of the resulting alcohol with *N*-(trimethylsilyl)imidazole[12] gave a single silyl ether **7** in high yield.[13a] Exposure of **7** to 2 equiv of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[14] at −45 → 0 °C in CH_2Cl_2 initiated the Prins-pinacol reaction to produce *cis*-hydroazulene **12**, a 5:1 mixture of β and α sulfide epimers, in 80% yield.[15] The structure of **12** was confirmed by oxidation of the major β epimer to provide the crystalline sulfone **13**.[13b] The related ring-enlarging cyclopentane annulation of the dimethyl acetal analogue of **7** could not be realized, because Prins cyclization in this case took place by a 5-exo pathway.[16]

Installation of the exocyclic methylene was complicated by the propensity of **12** to epimerize under basic conditions. However, transformation of this intermediate to **14** could be accomplished in 84% yield using a modified Peterson sequence. Oxidation of **14** with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by oxidative desulfonylation[17] of the resulting mixture of epimeric sulfones provided hydroazulenone **15** in 62% overall yield.

Survey experiments established that the cyclopentenone Michael acceptor had to carry an additional activating group for the C8 quaternary center to be formed efficiently. Using enantiopure α-sulfonyl ketone **5**,[18] the pivotal union with the thermodynamic lithium enolate of **15** occurred cleanly at −78 °C to deliver a single adduct **16** in 72% yield (Scheme 3). The structure of this product was confirmed by removal of the sulfone[19] to provide crystalline **17**.[13c]

To transform the cyclopentanone side chain to the required pyranone unit, β-keto sulfone **16** was reduced with SmI_2 and the resulting samarium enolate was acetylated at −78 °C with acetic anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give enol acetate **18** in 88% yield (Scheme 3). Reduction of the ketone of this intermediate with 1.5 equiv of (*R*)-oxazaborolidine **10**[10b] and 1.5 equiv of BH_3·THF gave **19** in 90% yield (ds >10:1).[20] Transformation of the secondary alcohol of **19** to an acetate followed by chemoselective dihydroxylation of the enol acetate functionality of **20** delivered α-hydroxy ketone **21** in 87% yield. Cleavage of **21** with $Pb(OAc)_4$ followed by reduction of the resulting aldehyde with $NaBH_4$ and lactonization using the Mukaiyama reagent[21] provided (+)-shahamin K (**1**) in

Scheme 3



57% yield from **21**. The optical rotation of synthetic **1**, $[\alpha]_D$ +83.4, compared well with that reported for the natural isolate, $[\alpha]_D$ +84.0, as did all other spectral and analytical properties.

In summary, this study demonstrates that the alkene participant in a Prins-pinacol construction of a cis-fused carbocycle does not need to be biased to favor endo-cyclization if the initiating electrophile is a α-thiocarbenium ion. The enantioselective total synthesis of (+)-shahamin K was accomplished in 18 linear steps and 4.2% yield from cyclohexanone **8**, constituting the first total synthesis of a rearranged spongian diterpene. Moreover, this synthesis establishes the absolute sterochemistry of (+)-shahamin K and defines a strategy that should be useful for preparing other rearranged spongian diterpenes and their analogues.

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Supporting Information Available: Experimental procedures for nonroutine transformations: preparation of **1**, **5**, **7**, (*S*)-**9**, **11**, **12**, **13**, **15**, **16**, **17**, **18,** and **19**; ^{1}H and ^{13}C NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015802O

(11) Enantiopurity was determined by HPLC analysis using a Chiracel OD-H column.

(12) Heathcock, C. H.; Jennings, R. A.; von Geldern, T. W. *J. Org. Chem.* **1983**, *48*, 3428−3431.

(13) The structure of this intermediate was determined by single-crystal X-ray analysis. 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., of the corresponding racemate, CCDC 159420 (a), CCDC 159421 (b), and CCDC 159422. (c)

(14) Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544−1550.

(15) For other examples of using DMTSF to activate dithio acetals for cationic cyclization reactions, see: Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529−6530. Also see ref 6e.

(16) In our earlier investigations of related transformations of unsaturated dimethyl acetals,[6a,d] the alkene was biased to favor endo-cyclization (terminal vinyl or 1-substituted alkenyl). In the case at hand, the termini of the alkene are equally substituted, whereas the allylic siloxy substituent should disfavor endocyclization by virtue of its inductive effect. The reason(s) why ring-enlarging cyclopentane annulation is favored by use of an α-thiocarbenium initiator is not understood and is the subject of active investigation.

(17) Little, R. D.; Myong, S. O. *Tetrahedron Lett.* **1980**, *21*, 3339−3342.

(18) Available in three steps (see Supporting Information) from a readily available enantiopure cyclopentanone: He, M.; Nakayama, M.; Tanimori, S.; Tsubota, M. *Synth. Commun.* **1997**, *27*, 2371−2378.

(19) Hahn, G.; Molander, G. A. *J. Org. Chem.* **1986**, *51*, 1135−1138.

(20) Attempted reduction of **18** with $NaBH_4$ led to partial cleavage of the enol acetate, while reduction with BH_3·THF proceeded with 4:1 diastereoselection to provide **19** in 50% yield. Competing hydroboration was not a problem when reduction of **18** was carried out using the borane complex of oxazaborolidine **10**.[8c]

(21) Mukaiyama, T.; Saigo, K.; Shimada, E.; Usui, M. *Chem. Lett.* **1975**, *10*, 1045−1048.