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Enantioselective Total Synthesis of Dysidavarone A, a Novel Sesquiterpenoid Quinone from the Marine Sponge *Dysidea avara*

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Dedicated to Professor Philip D. Magnus FRS on the occasion of his 70th birthday

Abstract: Dysidavarone A, a structurally unprecedented sesquiterpenoid quinone, was synthesized in 30% overall yield in a longest liner sequence of 13 steps from commercially available *o*-vanillin. A highly strained and bridged eight-membered carbocyclic core was established by the C7–C21 carbon bond formation through a copper enolate mediated Michael addition to the internal quinone ring.

In 2012, Lin et al. reported the isolation and structural elucidation of four novel sesquiterpenoid quinones, dysidavarones A–D (**1**–**4**, Figure 1), from the marine sponge, *Dysidea avara*, collected along the coast of Yongxing Island in the South China Sea.[1] These marine natural products were found to have an unprecedented tetracyclic dysidavarane carbon skeleton (see structure **5**) with a highly strained and bridged eight-membered carbocycle.[1] Lin et al. proposed that this unusual tetracyclic carbon skeleton might be produced biogenetically from well-known drimane-type sesquiterpenoid quinones, avarone (**6**) and neoavarone (**7**), by the C7–C21 bond formation through an intramolecular Prins-type reaction.[1] Compounds **1** and **4** have shown inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 9.98 and 21.6 μM, respectively.[1] PTP1B is a major negative regulator in both insulin and leptin signalling pathways, and it acts as a positive regulator in the tumorigenesis and progression of cancers.[2] It has also been shown that **1** and **4** exhibit antiproliferative activities against several human cancer cell lines in the micromolar range (IC_{50} = 11.6–28.8 μM).[1] More recently, **1** has been demonstrated to show potent inhibitory effects against Gram-positive bacteria, in particular against various *Staphylococci* (MIC_{50} = 0.2–9.9 μg mL^{-1}).[3] Therefore, we anticipated that dysidavarones may be promising candidates or provide new leads for the treatment of pathogenic states such as diabetes, obesity, cancer and infections. However, further biological studies of these natural products are severely restricted by the scarcity of samples from marine sponge *Dysidea* species (0.0002–0.0004% yields upon isolation). Consequently, developing methods for synthesis of **1**–**4** is desirable and worthwhile from the viewpoint of medicinal chemistry and pharmaceuticals.

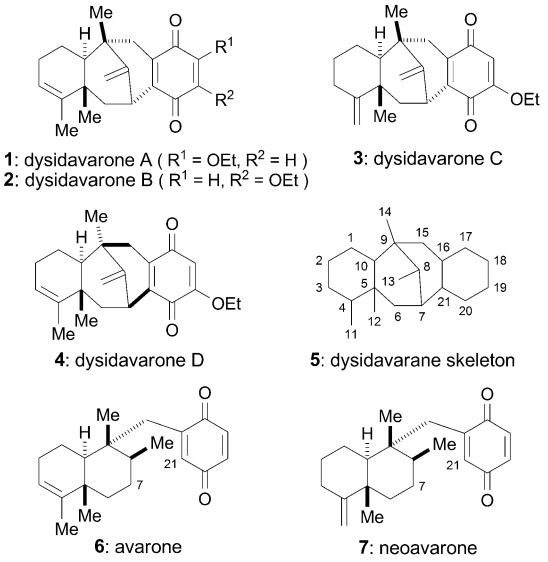

Figure 1. Structures of dysidavarones A–D (**1**–**4**), dysidavarane skeleton (**5**), avarone (**6**) and neoavarone (**7**).

Their unique structural features, attractive biological activities and limited availability from natural resources have made **1**–**4** exceptionally intriguing and timely targets for total synthesis. Recently, while our synthetic studies of **1**–**4** were in progress, Menche et al. reported the first and elegant total synthesis of **1**, which was rendered in a longest liner sequence of 10 steps with 11% overall yield.[3] Their synthetic route is outlined in Scheme 1, where the strategic Pd-catalyzed intramolecular α-arylation[4] of appropriately elaborated ketone **10**, which was prepared from known (+)-enone **8**[5] and aryl bromide **9**, to construct the requisite tetracyclic structure **11** was the key step (**10**→**11**, 66% yield).[3] Herein, we describe our total synthesis of **1** using an alternative strategy that involves an advantageous intramolecular Michael addition to construct the requisite tetracyclic core structure.

Our retrosynthetic analysis of dysidavarone A (**1**) is illustrated in Scheme 2. We envisioned that the requisite tetracyclic structure **13** could be established from appropriately functionalized

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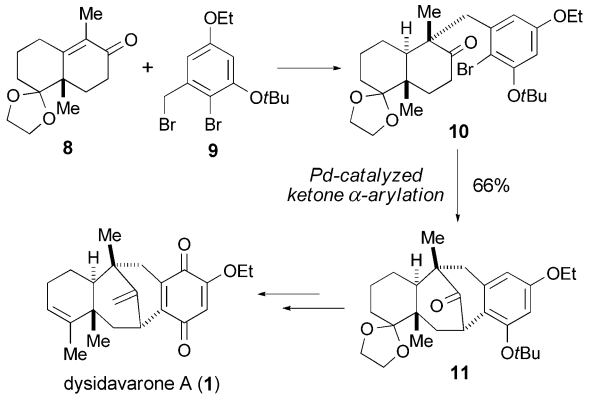
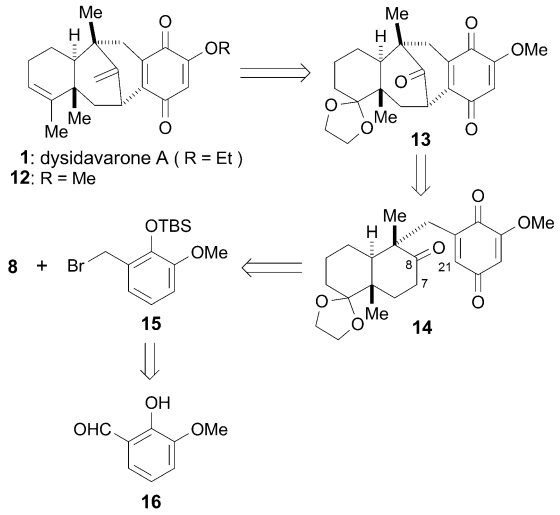


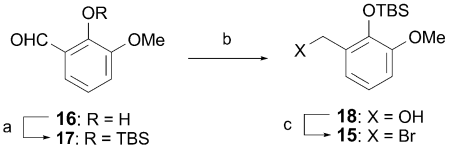
Scheme 1. Outline of the total synthesis of dysidavarone A (**1**) by Menche et al.



Scheme 2. Retrosynthetic analysis of dysidavarone A (**1**).

decalone **14** by the C7–C21 bond formation through a Michael addition of the C8 carbonyl derived enolate to the internal quinone ring,[6] followed by in situ air oxidation of the resulting hydroquinone. To the best of our knowledge, this type of cyclization to construct a highly strained and bridged eight-membered carbocycle fused with a quinone ring has not been previously reported; thus, this approach posed a considerable challenge from a synthetic viewpoint.[7] The cyclization product **13** could be converted into the target molecule **1** via the advanced intermediate **12** by deprotection and functional-group manipulation or vice versa. The cyclization precursor **14**, in turn, was to be prepared by the stereocontrolled reductive alkylation of known optically active enone **8**[5] and benzyl bromide **15**, which is accessible from commercially available inexpensive *o*-vanillin (**16**), under Birch conditions. This devised scheme involves the substitution reaction of the alkoxy group in the final stage of the synthesis (see **12**→**1**); therefore, this method is applicable to the synthesis of structural analogues of **1** possessing various alkoxy groups on the quinone ring.

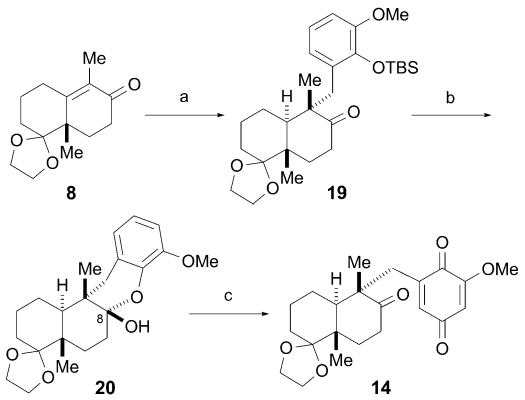
We first pursued the synthesis of intermediate **15**, the coupling partner of the decalin portion (see structure **8**), starting



Scheme 3. Synthesis of intermediate **15**. Reaction conditions: a) TBSCl, imidazole, CH_2Cl_2, RT, 12 h, 97%; b) $NaBH_4$, THF/H_2O, 0 °C, 30 min, 99%; c) PBr_3, CH_2Cl_2, 0 °C to RT, 5 min, 98%. TBS = *tert*-butyldimethylsilyl.

from *o*-vanillin (**16**) (Scheme 3). After protection of the hydroxy group in **16** (97% yield), the formyl group in the resulting *tert*-butyldimethylsilyl (TBS) ether **17** was reduced with $NaBH_4$ to provide benzylic alcohol **18** in quantitative yield. Subsequent bromination of **18** (PBr_3, CH_2Cl_2, 0 °C to RT) afforded the desired intermediate **15** in 98% yield.

Having synthesized intermediate **15**, we approached the synthesis of intermediate **14**, a precursor of the key cyclization reaction, as shown in Scheme 4. The critical reductive alkyla-

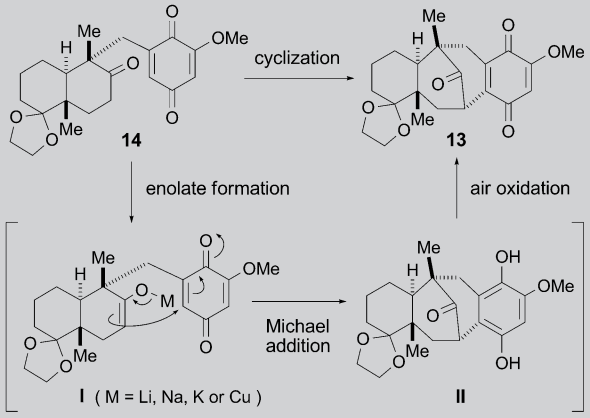


Scheme 4. Synthesis of intermediate **14**. Reaction conditions: a) Li, NH_3/THF, −78 to −30 °C, 45 min; isoprene, **15**, −78 to −30 °C, 2 h, 81%; b) TBAF, THF, RT, 30 min, 98%; c) O_2 (1 atm), salcomine, MeCN, RT, 15 h, 86%. TBAF = tetra-*n*-butylammonium fluoride, salcomine = *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II).

tion of enone **8**[5] (>99% *ee*) with **15** under Birch conditions[8] proceeded smoothly and cleanly to give the expected coupling product **19** in 81% yield as the single diastereomer. Deprotection of the TBS group in **19** resulted in the formation of hemiacetal **20** in 98% yield. The stereochemistry at the C8 position in **20** was confirmed by NOESY experiment (see the Supporting Information). To construct the quinone system directly, **20** was allowed to react with molecular oxygen (O_2 balloon) in the presence of salcomine, that is, *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II),[9] in acetonitrile at ambient temperature for 15 h, thus producing the desired quinone **14** in high yield (86%).

After obtaining intermediate **14**, we next investigated the key cyclization reaction to construct the requisite dysidavarane skeleton (**14**→**I**→**II**→**13**; see scheme above Table 1). The sequence involved Michael addition of the metallic enolate **I**[10,11] to the internal quinone ring and subsequent air oxidation of

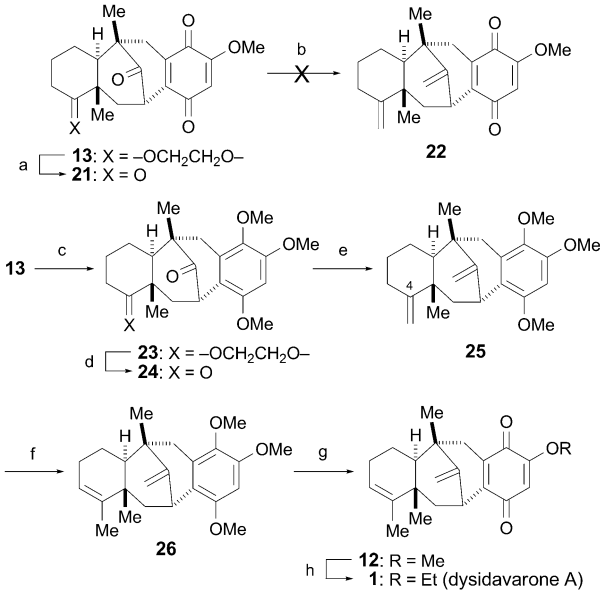
Table 1. Cyclization of **14** leading to dysidavarane skeleton **13**.



Entry	Conditions[a]	Yield[b] [%]
1	LiN*i*Pr$_2$ (3 equiv), THF (1 mM), −78 to −40 °C	dec.[c]
2	LiN(SiMe$_3$)$_2$ (5 equiv), THF (1 mM), −40 °C to RT, 48 h	28
3	NaN(SiMe$_3$)$_2$ (5 equiv), THF (1 mM), −40 °C to RT, 24 h	~5
4	KN(SiMe$_3$)$_2$ (3 equiv), THF (1 mM), −78 to −40 °C	dec.[c]
5	LiN(SiMe$_3$)$_2$ (5 equiv), CuBr·SMe$_2$ (2 equiv), THF (1 mM), −40 °C to RT, 48 h	84

[a] All reactions were carried out in the presence of air. [b] Yield upon isolation. [c] dec. = Decomposition.

the resulting intermediate **II**[12] during the cyclization reaction. To achieve cyclization, initial screening was carried out using several metal amide reagents, such as LiN*i*Pr$_2$, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$ and KN(SiMe$_3$)$_2$ in a THF solvent (entries 1–4, Table 1).[10,11] Among these reagents, LiN(SiMe$_3$)$_2$ proved to be superior from the viewpoint of reaction cleanliness (entry 2, Table 1); however, the yield of the desired cyclized product **13** was not satisfactory (28%). In the cases of LiN*i*Pr$_2$ and KN(SiMe$_3$)$_2$, the reaction was not clean, and the complete decomposition of material was observed (entries 1 and 4, Table 1). When NaN(SiMe$_3$)$_2$ was used, only a trace amount of **13** (~5% yield) was produced and a large amount of the starting material **14** (90–95% yield) was recovered (entry 3, Table 1). After repeated attempts, we found that the addition of CuBr·SMe$_2$ was extremely effective and reliable for this cyclization event (entry 5, Table 1). Thus, reaction of **14** with LiN(SiMe$_3$)$_2$ (5 equiv) in the presence of CuBr·SMe$_2$ (2 equiv) in a dilute THF solution (1 mM) from −40 °C to RT over the course of 48 h, resulted in the formation of **13** in high yield (84%). In this reaction, we believed that copper enolate **I** (M = Cu) was generated in situ[10] and that this intermediate species promoted the intramolecular Michael addition reaction. Thus, the expected cyclization reaction proceeded in a clean and efficient way. To the best of our knowledge, this is the first successful example of



Scheme 5. Completion of the total synthesis of dysidavarone A (**1**). Reaction conditions: a) 3 M HCl, THF, RT, 62%; b) Ph$_3$P$^+$CH$_3$Br$^-$, *t*BuOK, benzene, RT to reflux, decomposition; c) 30% Na$_2$S$_2$O$_4$, Me$_2$SO$_4$, 30% KOH, *n*Bu$_4$NBr, THF, RT, 80%; d) 3 M HCl, THF, 40 °C, 98%; e) Ph$_3$P$^+$CH$_3$Br$^-$, *t*BuOK, benzene, reflux, 95%; f) 3 M HCl, THF, reflux, 87%; g) CAN, MeCN/H$_2$O, −7 °C, 97%; h) DBU, EtOH, RT, 90%. CAN = ceric ammonium nitrate, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

Michael addition reaction of a copper enolate with a quinone to construct a highly strained medium-sized carbocycle.

The final route that led to the completion of the total synthesis of **1** is shown in Scheme 5. Initial attempts to realize the direct conversion of diketone **21**, which was prepared from **13** by deprotection of the ethylene acetal moiety, into bis-*exo*-olefin **22** under Wittig methylenation conditions[13] (Ph$_3$P$^+$CH$_3$Br$^-$, *t*BuOK, benzene, RT to reflux) were unsuccessful and resulted in decomposition of material. This result is likely due to the presence of the sensitive quinone function in **21**. Therefore, we decided to mask the reactive quinone system in the form of a *p*-dimethoxybenzene derivative.[14] Thus, methoxyquinone **13** was converted into the corresponding trimethoxybenzene **23** (80% yield) by reductive methylation (30% Na$_2$S$_2$O$_4$, Me$_2$SO$_4$, 30% KOH, *n*Bu$_4$NBr, THF, RT). After deprotection of the ethylene acetal moiety in **23** (98% yield), the resulting diketone **24** was subjected to two-fold Wittig methylenation to produce bis-*exo*-olefin **25** in high yield (95%). The subsequent site-selective isomerization of the C4 *exo* olefinic double bond in **25** (3 M HCl, THF, reflux)[3] furnished the corresponding *endo* olefin **26** in 87% yield. The quinone system was then regenerated efficiently by treating **26** with ceric ammonium nitrate (CAN) in acetonitrile/water at low temperature (−7 °C), giving rise to the desired methoxyquinone **12** in 97% yield. Finally, exposure of **12** to ethanol in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) at ambient temperature resulted in the formation of the targeted dysidavarone A (**1**) in 90% yield.[15] The spectroscopic properties (IR, ^{1}H, and ^{13}C NMR spectroscopy, and high-resolution mass spectrometry) of synthetic **1** were identical to those of natural **1**.[1] The optical rotation of

synthetic **1** , $[\alpha]_D^{25} = +105.6$ ($c = 1.00$, MeOH), matched that reported previously, natural **1**: $[\alpha]_D^{25} = +30$ ($c = 1.00$, MeOH),[1, 16] synthetic **1**: $[\alpha]_D^{25} = +125$ ($c = 1.00$, MeOH).[3]

In summary, we have accomplished the enantioselective total synthesis of dysidavarone A (**1**) in 30% overall yield in 13 steps from the starting material *o*-vanillin (**16**). The most crucial step of the synthesis involved the formation of the eight-membered carbocyclic core by the strategic intramolecular Michael addition/in situ air oxidation to establish the tetracyclic dysidavarane skeleton (**14**→**13**, Table 1). On the basis of this study, we are currently synthesizing additional analogues of **1** (for example, analogues possessing a variety of alkoxy groups on the quinone ring) with the aim of exploring its structure–activity relationships. In addition, further investigations to identify additional action mechanisms of **1** using the synthetic sample are in progress in our laboratories.

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Keywords: copper enolate · dysidavarone A · Michael addition · sesquiterpenoids · total synthesis

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[12] The highly electron-rich hydroquinone moiety present in intermediate **II** was found to be fairly unstable, and the autoxidation was observed during the cyclization reaction.

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[15] We initially suspected that dysidavarone A (**1**) was the artefact derived from **12** during the extraction operation by use of ethanol, because the ethoxy substituent on the quinone ring in **1** is unusual in the naturally occurring sesquiterpenoid quinones. In order to clear this suspicion, **12** was exposed to ethanol under neutral conditions (without basic and acidic reagents) at ambient temperature over 24 h, resulting in no production of **1**. This result verified that **1** is not the artefact but the natural product itself.

[16] It has been pointed out that the optical rotation of +30 may be caused by a lower purity of the natural sample (see Ref. [3]).

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