Total Synthesis

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Total Synthesis of Anti-Cancer Meroterpenoids Dysideanone B and Dysiherbol A and Structural Reassignment of Dysiherbol A

*Chuanke Chong, Qunlong Zhang, Jia Ke, Haiming Zhang, Xudong Yang, Bingjian Wang, Wei Ding, and Zhaoyong Lu**

Dedicated to Professor K. C. Nicolaou on the occasion of his 75th birthday

Abstract: *The first total synthesis of marine anti-cancer meroterpenoids dysideanone B and dysiherbol A have been accomplished in a divergent way. The synthetic route features: 1) a site and stereoselective α-position alkylation of a Wieland–Miescher ketone derivative with a bulky benzyl bromide to join the terpene and aromatic moieties together and set the stage for subsequent cyclization reactions; 2) an intramolecular radical cyclization to construct the 6/6/6/6-tetracycle of dysideanone B and an intramolecular Heck reaction to forge the 6/6/5/6-fused core structure of dysiherbol A. A late-stage introduction of the ethoxy group in dysideanone B reveals that this group might come from the solvent ethanol. The structure of dysiherbol A has been revised based on our chemical total synthesis.*

Sesquiterpene quinones/hydroquinones, one of the most important class of meroterpenoid natural products,[1] feature a sesquiterpene core attached to a biosynthetically different quinone or hydroquinone moiety.[2] This class of naturally occurring substances exhibit a remarkable range of biological activities, such as antibacterial,[3] antifungal,[4] anti-HIV,[5] anti-inflammatory,[6] antioxidative,[7] antitumor,[8] as well as protein tyrosine phosphatase 1B (PTP1B) inhibitory activities.[9]

Dysideanone B (**1**, Figure 1), isolated from the South China Sea sponge *Dysidea avara* by Lin and co-workers in 2014,[10] possesses an unprecedented 6/6/6/6-fused tetracyclic carbon skeleton and showed cytotoxicity against two human cancer cell lines, HeLa and HepG2, with IC_{50} values of 7.1 and 9.4 μM, respectively. In 2016, the same group also isolated dysiherbols A–C (**2**–**4**, Figure 1),[11] which share an intriguing

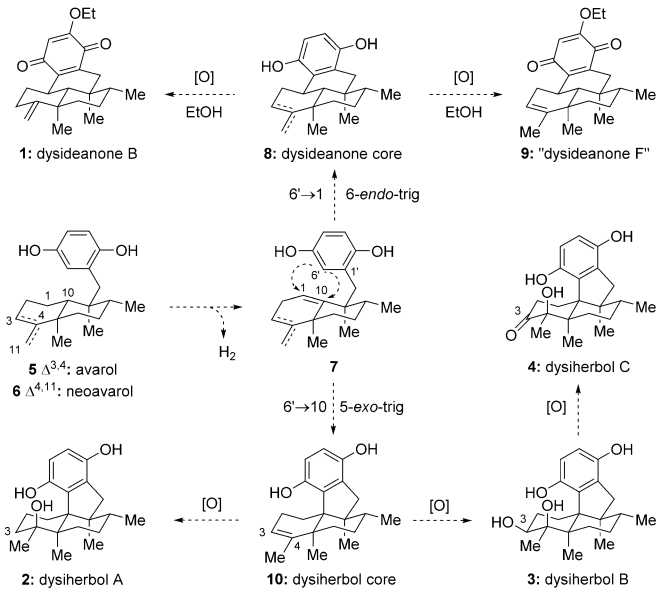

Figure 1. Biosynthetic network of dysideanones B and "F" and dysiherbols A–C.

6/6/5/6-fused tetracyclic ring system but differ in their functionalities at the C3 position (with **2**, **3**, and **4** containing a C3-methylene, alcohol, and ketone group, respectively). Dysiherbol A exhibited potent NF-κB inhibitory activity and cytotoxicity against the human myeloma cancer cell line NCI H-929 with IC_{50} values of 0.49 and 0.58 μM, respectively. On the other hand, the reported NF-κB inhibitory activity and cytotoxicity of the two more oxidized members, dysiherbols B and C (**3** and **4**), against NCI H-929 were about 10-fold and 20-fold less potent than those of dysiherbol A (**2**),[11] showing that the removal of the oxygen functionality at the C3 position remarkably increased their NF-κB inhibitory and cytotoxic activities, thus suggesting the possible structural optimization for structure–activity relationship (SAR) study.

This collection of meroterpenoids has attracted much attention from the synthetic community due to their diverse structures and varied biological activities.[12] Recently, Jana and co-workers reported the construction of dysideanone carbotetracycles[13] and the biological evaluation of synthetic dysideanone analogues.[14] In 2017, Echavarren et al. disclosed the assembly of the tetracyclic carbon skeleton of dysiherbol by using a gold(I)-catalyzed formal [3+2] cycloaddition reaction.[15] To date, however, the total synthesis of dysideanone B and dysiherbol A have not been accomplished

[*] C. Chong, Q. Zhang, J. Ke, H. Zhang, X. Yang, B. Wang, Prof. Dr. Z. Lu
State Key Laboratory of Medicinal Chemical Biology,
College of Pharmacy, Nankai University
38 Tongyan Rd, Tianjin 300350 (China)
E-mail: zlu@nankai.edu.cn
Dr. W. Ding
Tianjin Key Laboratory of Human Development and Reproductive Regulation, Tianjin Central Hospital of Gynecology Obstetrics, Nankai University
156 Third Rd, Tianjin 300052 (China)
Prof. Dr. Z. Lu
State Key Laboratory of Natural Medicines,
China Pharmaceutical University
24 Tongjiaxiang, Nanjing 210009 (China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
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successfully. Herein, we report the first total synthesis of dysideanone B and dysiherbol A and the revision of the structure of dysiherbol A.

From the viewpoint of biogenesis, it was postulated that dysideanone B and dysiherbols A–C might be derived from two common sesquiterpene hydroquinone meroterpenoids, avarol **5**[16] or neoavarol **6**,[17] also known from *Dysidea* sponges, as depicted in Figure 1. Thus, dehydrogenation of the C1–C10 single bond in avarol **5** or neoavarol **6** gives rise to unconjugated diene **7** as a key branching point, from which a putative 6-*endo*-trig cyclization connecting C6′ of the hydroquinone moiety with C1 of the neighboring double bond would give the 6/6/6/6-fused tetracyclic framework as found in intermediate **8**. Oxidation of the hydroquinone moiety within the latter intermediate to a quinone followed by the introduction of an ethoxy group could then furnish dysideanone B (**1**). It should be noted that the ethoxy group might come from the solvent EtOH in the extraction process.[10] According to the structural types of isolated sesquiterpene quinone/hydroquinone meroterpenoids,[2] the internal alkene congener of dysideanone B might also be a natural product, which we tentatively named as "dysideanone F" (**9**). On the other hand, intermediate **7** could undergo a 5-*exo*-trig cyclization, which joins C6′ with C10 to give the dysiherbol core structure **10**. Hydration of its C3=C4 bond would provide dysiherbol A (**2**), whereas a formal dihydroxylation of the same double bond would afford dysiherbol B (**3**). Further oxidation of the secondary alcohol at C3 in dysiherbol B (**3**) could furnish dysiherbol C (**4**).

Inspired by the above biosynthetic hypothesis, we undertook a retrosynthetic analysis of both dysideanone B (**1**) and dysiherbol A (**2**), as depicted in Figure 2. We envisioned that the ethoxy group within dysideanone B (**1**) could be introduced at a late stage and the quinone moiety could be obtained via oxidation of the protected and more stable hydroquinone **11**. Disconnection of the C6′ and C1 single bond revealed alkene bromide **12** as a potential precursor. On the other hand, dysiherbol A could be synthesized from alkene **13** through oxidation state adjustment and deprotection of the methyl groups. Disassembly of the C6′ and C10 single bond would give the aforementioned alkene bromide **12**. The methyl group at C8 position of **12** was envisioned to derive from ketone functionality of **14** through methylenation and diastereoselective reduction. Finally, ketone **14** could be traced back to Wieland-Miescher ketone derivative **15** and benzyl bromide **16**.

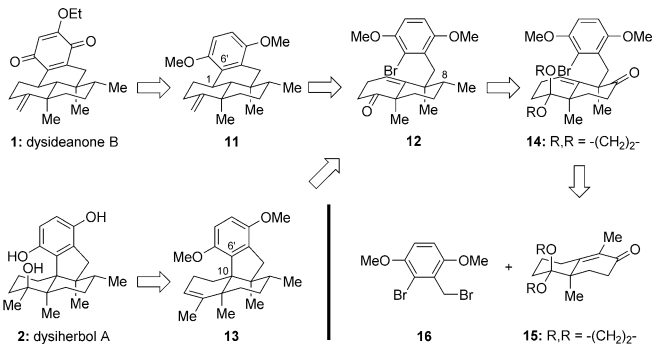
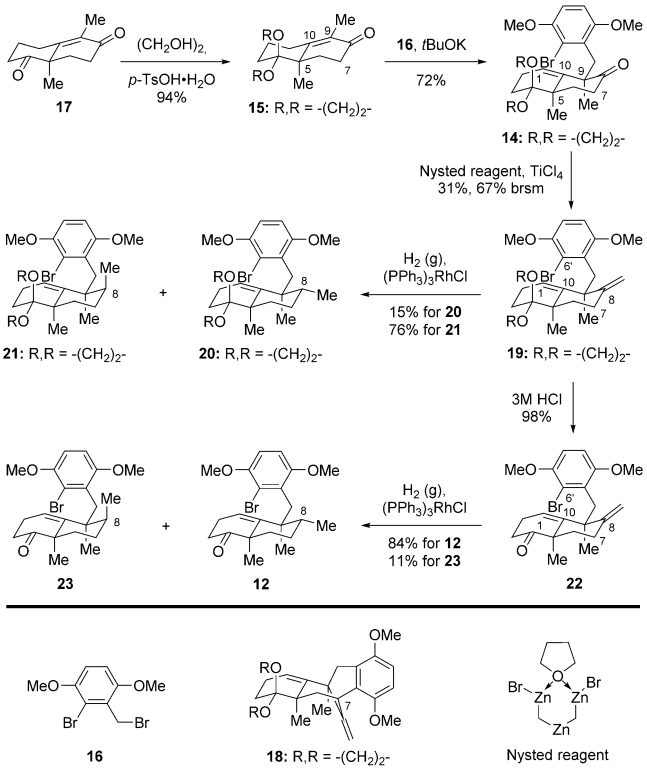


Figure 2. Retrosynthetic analysis for dysideanone B and dysiherbol A.

With the retrosynthetic analysis in mind, we started the adventure from the synthesis of common precursors for the cyclization reactions, as shown in Scheme 1. To this end, the more reactive unconjugated ketone functionality of Wieland-Miescher ketone derivative **17**, which could be efficiently



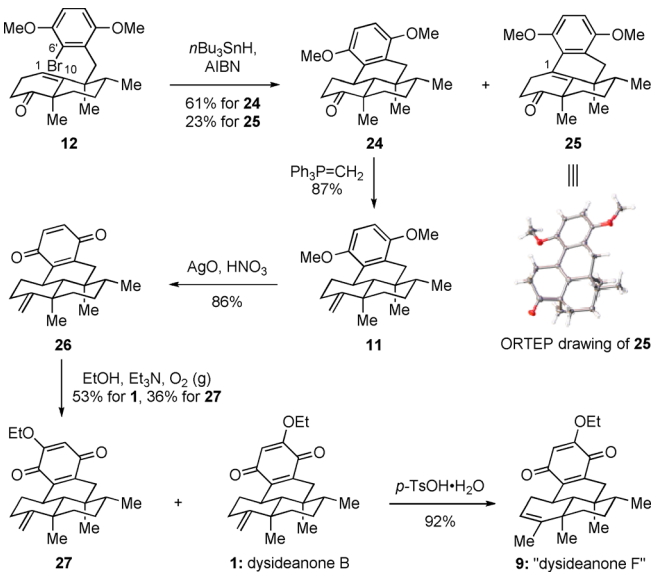
Scheme 1. Synthesis of cyclization precursors **20** and **12**. *p*-TsOH·H_2O = *p*-toluenesulfonic acid monohydrate, brsm = based on recovered starting material.

prepared from commercially available material in two steps in either racemic or enantiomeric form,[18] was chemoselectively protected as a glycol acetal to give enone **15** in 94% yield. The combination of bicyclic enone **15** with the bulky benzyl bromide **16** proved challenging with O- or C7-alkylation byproducts observed at different reaction temperatures. After optimization, the desired C9-alkylation product ketone **14** was obtained as a single diastereoisomer in satisfactory isolated yield (72%) under a thermodynamically controlled condition (*t*BuOK in THF at 40 °C). It should be noted that the C=C bond at C9 and C10 migrates to C1 and C10 position under this condition and the incoming electrophile benzyl bromide **16** approaches the generated enolate from the opposite side of the angular methyl group at the ring junction due to steric hindrance, thus affording a single diastereoisomer.

With alkylation product **14** readily available, we proceeded to the synthesis of cyclization precursors. However, the methylenation of sterically hindered carbonyl group in ketone **14** with Wittig reagent ($Ph_3P{=}CH_2$) led to an

unexpected cyclization byproduct **18** through an intramolecular arylation reaction[19] and a subsequent Wittig reaction, while the methylenation with Peterson reagent, Tebbe reagent, or Julia reagent did not give any of the desired products. Much to our delight, the methylenation problem was solved by employing Nysted reagent[20] with $TiCl_4$ as Lewis acid, rendering the desired product terminal alkene **19** in 31% yield and recovering 54% of starting material ketone **14**. Subjection of intermediate **19** to heterogenous hydrogenation conditions (10% Pd/C) resulted in the migration of the exocyclic C=C bond to the C7 and C8 position to give an endocyclic C=C bond byproduct, which could not be selectively reduced without affecting the other olefin moiety. On the other hand, homogenous hydrogenation of intermediate **19** with $(Ph_3P)_3RhCl$ only gave 15% of desired product **20** and 76% of its C8-epimer **21** (d.r. = 1:5). Delightedly, the diastereoselectivity reversed when the more advanced intermediate ketoalkene **22** was subjected to the same reaction conditions, affording the desired product **12** in 84% yield and its C8-epimer **23** in 11% yield (d.r. = 8:1). It is noteworthy that the bromide at C6′ and internal alkene between C1 and C10 survived under this condition.

With alkene bromide **12** in hand, we focused our attention on the investigation of cyclization reaction for the construction of the 6/6/6/6-tetracycle of dysideanone B, as shown in Scheme 2. We envisioned that a C6′ radical, generated from the parent aryl bromide, would attack the alkene from C1 to give the more stable tertiary radical on C10, which then reacts with a H· donor to form the 6/6/6/6-fused tetracyclic core of dysideanone B. Thus, alkene bromide **12** was subjected to radical reaction conditions (nBu$_3$SnH and AIBN, Scheme 2). The desired 6/6/6/6-fused tetracycles **24** was obtained in 61% yield and a tetrasubstituted alkene byproduct **25** was isolated in 23% yield, presumably because the tertiary radical undergoes β-H elimination from C1 to give internal alkene **25**. The



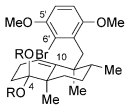
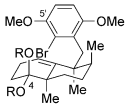
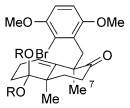
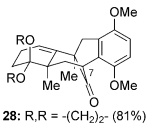
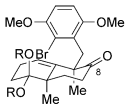
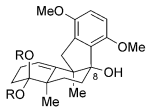
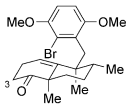
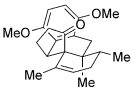
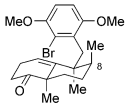
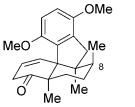
Scheme 2. Total synthesis of dysideanone B and "dysideanone F". AIBN = 2,2′-azoisobutyronitrile. Thermal ellipsoids are shown at the 50% probability level.

structure of **25** was verified by X-ray crystallographic analysis.[21]

Having successfully constructed the tetracyclic framework for dysideanone B, we proceeded to the final stage of the total synthesis of dysideanone B. Thus, as depicted in Scheme 2, methylenation of ketone **24** proceeded smoothly (87% yield) with Wittig reagent to afford terminal alkene **11**, whose methyl protected hydroquinone moiety was oxidized using AgO and HNO_3, delivering quinone **26** in 86% yield and setting the stage for the introduction of the ethoxy group. A series of ethoxy group introduction reactions were performed. Metal mediated reactions (e.g., EtOH with $Co(OAc)_2$, $Mn(OAc)_3{\cdot}2H_2O$, $Ni(OAc)_3{\cdot}4H_2O$, or AgOAc)[22] led to either low yields or decomposition of starting material. Finally, we were pleased to find that Et_3N in EtOH under O_2[23] proved effective for the introduction of ethoxy functionality, affording dysideanone B (**1**) in 53% yield and its regioisomer **27** in 36% yield. Driven by our suspicion that the ethoxy group might come from the solvent EtOH, we opted to mimic the isolation conditions. In this regard, quinone **26** was heated in 95% EtOH under air and dysideanone B (**1**) and its regioisomer **27** were also isolated but in lower combined yield (64%), revealing that the ethoxy group might come from the solvent ethanol. The spectroscopic data of synthetic dysideanone B (**1**) matched with those reported for the natural product. The transformation of dysideanone B (**1**) to its congener "dysideanone F" (**9**) was achieved in 92% yield under acidic condition. The synthesis and characterization of this hitherto unknown congener might facilitate its isolation from natural sources in the future.

Having completed the first total synthesis of dysideanone B (**1**), we turned our attention to the formation of the 6/6/5/6-fused backbone of dysiherbol A, as depicted in Table 1. However, the construction of the five-membered ring of dysiherbol A (**2**) turned out to be a difficult task. Various Heck reaction conditions[24] (different Pd catalysts such as $Pd_2(dba)_3$, $Pd(OAc)_2$, and $Pd(dppf)Cl_2$, ligands such as SPhos, P(*o*-tol)$_3$, P(2-furyl)$_3$, and BINAP, bases such as DBU, Et_3N, PMP, K_2CO_3, and $NaHCO_3$) were explored on substrate **20**, but no desired product was observed (Table 1, entry 1). The C8-epimer **21** was also investigated for the cyclization but did not give any desired cyclization product (Table 1, entry 2). We also examined the cyclization reaction on **14**, whose ketone functionality could be transformed to methyl group on C8 at a late stage. Arylation byproduct **28** was obtained in 81% yield with DBU as base (Table 1, entry 3), while addition byproduct tertiary alcohol **29** was isolated in 86% yield with Et_3N as base (Table 1, entry 4) through a Grignard-type nucleophilic addition of arylpalladium to ketone.[25] Molecular modeling showed that the methoxy group on C5′ of the benzene ring and the acetal group on C4 of the decalin ring would be very close if the C10–C6′ single bond was generated. We expected that the removal of the acetal group on C4 might reduce the hindrance between these functionalities. To this end, a range of Heck or reductive Heck reaction[26] conditions were examined on ketoalkene bromide **12**. However, the desired cyclization product was also not observed. Indeed, ring contraction byproduct **30** was obtained in 81% yield when $Pd_2(dba)_3$ was used as catalyst with SPhos as ligand and

Table 1: Attempts for the construction of the 6/6/5/6-tetracycle of dysiherbol A.

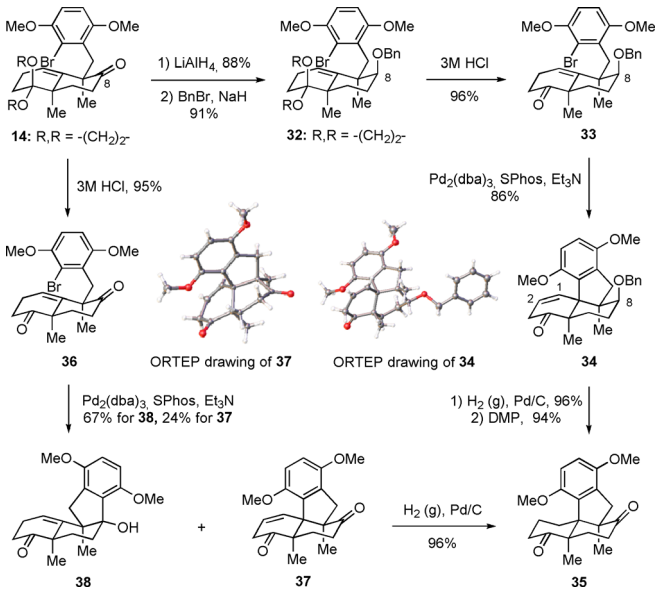
Entry	Substrate	Conditions	Result[a]
1	 **20:** R,R = -$(CH_2)_2$-	various Heck conditions	n.p.[b]
2	 **21:** R,R = -$(CH_2)_2$-	various Heck conditions	n.p.[b]
3	 **14:** R,R = -$(CH_2)_2$-	$Pd_2(dba)_3$, SPhos, DBU	 **28:** R,R = -$(CH_2)_2$- (81%)
4	 **14:** R,R = -$(CH_2)_2$-	$Pd_2(dba)_3$, SPhos, Et_3N	 **29:** R,R = -$(CH_2)_2$- (86%)
5	 **12**	$Pd_2(dba)_3$, SPhos, Et_3N	 **30** (81%)
6	 **23**	$Pd_2(dba)_3$, SPhos, Et_3N	 **31** (83%)

[a] Isolated yield after flash column chromatography. [b] n.p. = no product. dba = dibenzylideneacetone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

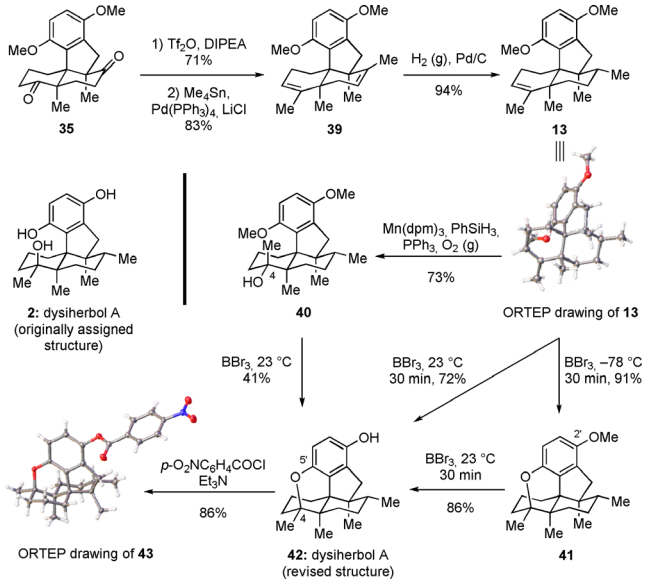
Et_3N as base (Table 1, entry 5). The structure of **30** was elucidated by extensive 2D NMR and X-ray crystallographic analysis (see SI for a possible mechanism for the formation of **30**).[21] Unexpectedly and surprisingly, the desired cyclization reaction proceeded efficiently when C8-epimer **23** was subjected to the same set of Heck reaction conditions, furnishing cyclized product **31** in 83% yield as a sole product (Table 1, entry 6).

The results inspired us to adjust the substrates for the five-membered ring formation reaction, which is shown in Scheme 3. Towards this end, ketone **14** was reduced with lithium aluminium hydride ($LiAlH_4$) in 88% yield (d.r. > 20:1) to give a secondary alcohol, which was then protected with benzyl ether, affording **32** in 91% yield with the BnO group of C8 at the axial position. Removal of glycol acetal within **32** rendered ketone **33** in almost quantitative yield, which was then investigated for the cyclization reaction. Gratifyingly, treatment of **33** with $Pd_2(dba)_3$, SPhos and Et_3N afforded the desired cyclization product **34** in high yield (86%). The connectivity of the newly established ring system was confirmed by single crystal X-ray diffraction analysis of **34**.[21] The removal of Bn group and the reduction of newly formed alkene at C1 and C2 were accomplished with Pd/C under H_2 in one pot in 96% yield. Dess–Martin periodinane (DMP) oxidation of the released secondary alcohol gave diketone **35** efficiently (94% yield). Diketone **36**, prepared from **14** with the deprotection of glycol acetal in 95% yield, was also tested for the cyclization reaction. Much to our delight, Heck reaction of diketone **36** with Et_3N as base afforded the desired product **37** in 24% yield and addition byproduct tertiary alcohol **38** in 67% yield. The chemoselectivity and the connection of **37** was unambiguously confirmed by single crystal X-ray diffraction analysis.[21] The hydrogenation of diketoalkene **37** with 10% Pd/C under H_2 resulted in the aforementioned diketone **35** in 96% yield.

Having forged the 6/6/5/6-tetracycle of dysiherbol A, we switched to our next goal of pursuing the total synthesis of dysiherbol A (Scheme 4). Direct methylenation of diketone **35** with Wittig reagent, Peterson reagent or Petasis reagent was met with failure, presumably due to the severe steric hindrance of the ketone functionalities. Consequently, a two-step sequence was adopted to achieve this transformation. Diketone **35** was first transformed through the action of trifluoromethanesulfonic anhydride (Tf_2O) and *N*,*N*-diisopropylethylamine (DIPEA) to bis(enol-triflate),[27] which was then coupled with Me_4Sn, giving diene **39** in 59% overall yield for the two steps. The chemo- and diastereoselective reduction of diene **39** was achieved via heterogeneous hydrogenation with 10% Pd/C under H_2, and the desired monoalkene **13** was obtained as a sole diastereoisomer in excellent



Scheme 3. Synthesis of diketone **35**. DMP = Dess–Martin periodinane. Thermal ellipsoids are shown at the 50% probability level.



Scheme 4. Total synthesis and structural reassignment of dysiherbol A. DIPEA = *N*,*N*-diisopropylethylamine, dpm = dipivaloylmethanato, Tf_2O = trifluoromethanesulfonic anhydride. Thermal ellipsoids are shown at the 50% probability level.

yield (94%). The chemo- and diastereoselectivity of reduction was unambiguously verified by single crystal X-ray diffraction analysis.[21]

The next challenge became the regio- and diastereoselective introduction of a C4 hydroxyl group and the deprotection of the methyl-capped hydroquinone moiety. To this end, epoxidation of mono-alkene **13** with H_2O_2, *m*-CPBA, *t*BuOOH or $VO(acac)_2$ and *t*BuOOH[28] was explored, but only led to the skeleton rearrangement, presumably because of the severe strain of the 6/5-fused ring system. To make things worse, mono-alkene **13** was also found to be reluctant to undergo dihydroxylation (e.g., OsO_4, $K_2OsO_4{\cdot}2H_2O$, and AD-mix-α). In light of these failures, we switched to the metal-catalyzed hydrogen atom transfer (MHAT)-initiated olefin hydration[29] of the alkene within **13**. An array of catalysts (e.g., $Fe(acac)_3$, $Co(acac)_3$, and $Mn(dpm)_3$) and silanes (e.g., $PhSiH_3$ and Et_3SiH) were tested and the combination of $Mn(dpm)_3$ and $PhSiH_3$ under O_2 with PPh_3[30] as additive worked well, leading to the tertiary alcohol **40** in 73% yield. Although the stereochemistry of C4 of alcohol **40** is opposite to that of natural product dysiherbol A, the deprotection of methyl groups on hydroquinone was performed. To our disappointment, no desired product was observed under various deprotection conditions examined and an unexpected byproduct was isolated in 45% yield with BBr_3 at 23 °C. However, the byproduct displayed identical spectral properties to those reported for the natural dysiherbol A (**1**). The single crystal X-ray diffraction analysis of this byproduct derivative **43** showed an additional ether ring between C5′ of the benzene ring and C4 of the decalin moiety instead of C5′-phenol and C4-hydroxy groups.[21] Thus, the structure of dysiherbol A was revised as **42**. The structures of dysiherbols B and C may have the same issue and the effort towards the total synthesis of them is currently underway in our laboratories, hoping to elucidate the real structure of these two natural products.

Careful monitoring of the reaction showed that tertiary alcohol **40** first underwent elimination with BBr_3 to give back to alkene **13**, and subsequent etherification of C5′ oxygen with alkene and deprotection of the remaining C2′ methyl group to afford **42**. Indeed, etherification product **41** was isolated as a sole product in 91% yield with 2 equivalents of BBr_3 at −78 °C. Treatment of **41** with more BBr_3 (5 equivalents) at higher temperature (23 °C) led to the removal of C2′ methyl group, affording **42** in 86% yield. Indeed, under the latter set of conditions, dysiherbol A (**42**) was also obtained in 72% yield from alkene **13** directly.

In conclusion, we have accomplished the first total synthesis of marine anti-cancer meroterpenoids dysideanone B and dysiherbol A and revised the structure of dysiherbol A based on chemical synthesis and X-ray crystallographic analysis. The key transformations of our synthesis include an intramolecular radical cyclization to construct the 6/6/6/6-tetracycle of dysideanone B and an intramolecular Heck reaction to forge the 6/6/5/6-fused tetracyclic core structure of dysiherbol A. The developed strategy could potentially be used for the collectively total synthesis of dysiherbols B and C and structurally related sesquiterpene quinone or hydroquinone meroterpenoids. These goals are currently being pursued in our laboratories, and the results will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

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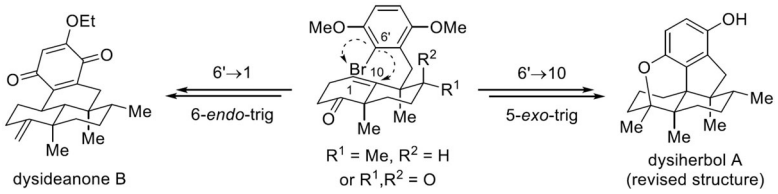
Communications

Total Synthesis

C. Chong, Q. Zhang, J. Ke, H. Zhang, X. Yang, B. Wang, W. Ding, Z. Lu* _____ ■■■■–■■■■

Total Synthesis of Anti-Cancer Meroterpenoids Dysideanone B and Dysiherbol A and Structural Reassignment of Dysiherbol A



The first total synthesis of marine anti-cancer natural products dysideanone B and dysiherbol A have been completed and the structure of dysiherbol A has been revised. A radical cyclization was employed to construct the 6/6/6/6 skeleton of dysideanone B and a Heck reaction was utilized to forge the 6/6/5/6 core structure of dysiherbol A.