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Divergent total synthesis of the revised structures of marine anti-cancer meroterpenoids (+)-dysiherbols A–E†

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We report here a concise and divergent enantioselective total synthesis of the revised structures of marine anti-cancer sesquiterpene hydroquinone meroterpenoids (+)-dysiherbols A–E (**6–10**) using dimethyl predysiherbol **14** as a key common intermediate. Two different improved syntheses of dimethyl predysiherbol **14** were elaborated, one starting from Wieland–Miescher ketone derivative **21**, which is regio- and diastereoselectively α-benzylated prior to establishing the 6/6/5/6-fused tetracyclic core structure through intramolecular Heck reaction. The second approach exploits an enantioselective 1,4-addition and a Au-catalyzed double cyclization to build-up the core ring system. (+)-Dysiherbol A (**6**) was prepared from dimethyl predysiherbol **14** *via* direct cyclization, while (+)-dysiherbol E (**10**) was synthesized through allylic oxidation and subsequent cyclization of **14**. Epoxidation of **14** afforded allylic alcohol **45** or unexpectedly rearranged homoallylic alcohol **44**. By inverting the configuration of the hydroxy groups, exploiting a reversible 1,2-methyl shift and selectively trapping one of the intermediate carbenium ions through oxy-cyclization, we succeeded to complete the total synthesis of (+)-dysiherbols B–D (**7–9**). The total synthesis of (+)-dysiherbols A–E (**6–10**) was accomplished in a divergent manner starting from dimethyl predysiherbol **14**, which led to the revision of their originally proposed structures.

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Introduction

Sesquiterpene quinone/hydroquinone meroterpenoids are a class of mixed biosynthetic origin natural products mainly isolated from marine sources.[1] In the past decade, a variety of sesquiterpene quinone/hydroquinone marine natural products with novel skeletons and anti-cancer activities were isolated and elucidated. Dysiherbols A–C (**1–3**, Fig. 1) are sesquiterpene hydroquinones isolated by Lin and colleagues from a *Dysidea* sp. marine sponge collected from the South China Sea in 2016.[2] These three sesquiterpene hydroquinone natural products were reported to possess an intriguing 6/6/5/6-fused tetracyclic carbon skeleton.[2] Preliminary bioactivity evaluation showed that dysiherbol A (**1**, Fig. 1) exhibited potent NF-κB inhibitory activity and cytotoxicity against human myeloma cancer cell line NCI H-929 with respective IC_{50} values of 0.49 and 0.58 μM, while dysiherbols B and C (**2** and **3**, Fig. 1) were about 10-fold and 20-fold less potent.[2] In 2022, dysiherbols D and E (**4** and **5**, Fig. 1) were isolated by the same group from the marine sponge *Dysidea avara* collected from the South China Sea and were proposed to have the same carbon backbone but opposite absolute configuration than dysiherbols A–C (**1–3**).[3] TNF-α-induced NF-κB activation evaluation in human HEK-293T cells showed that dysiherbols D and E (**4** and **5**) exhibited inhibitory activity with IC_{50} values of 10.2 and 8.6 μM, respectively.[3]

With their interesting structures, impressive bioactivities, and sparse availability from natural resources, dysiherbols A–E have attracted much attention from the synthetic community. In 2021, the Lu group disclosed the first total synthesis of (±)-dysiherbol A and revised the structure of dysiherbol A, which possesses an additional ether ring between C4 and C5′ instead of an alcohol group at C4 and a phenol group at C5′, as shown in Fig. 1.[4] Only a few weeks later, the Schmalz group reported an enantioselective total synthesis of (−)-dysiherbol A, which not only confirmed the constitutional reassignment of dysiherbol A but also led to a revision of the absolute configuration of this natural product based on CD spectroscopic data.[5] Last year, Liu *et al.* constructed the tetracyclic core structure of the dysiherbols through an intramolecular [2 + 2] cycloaddition,

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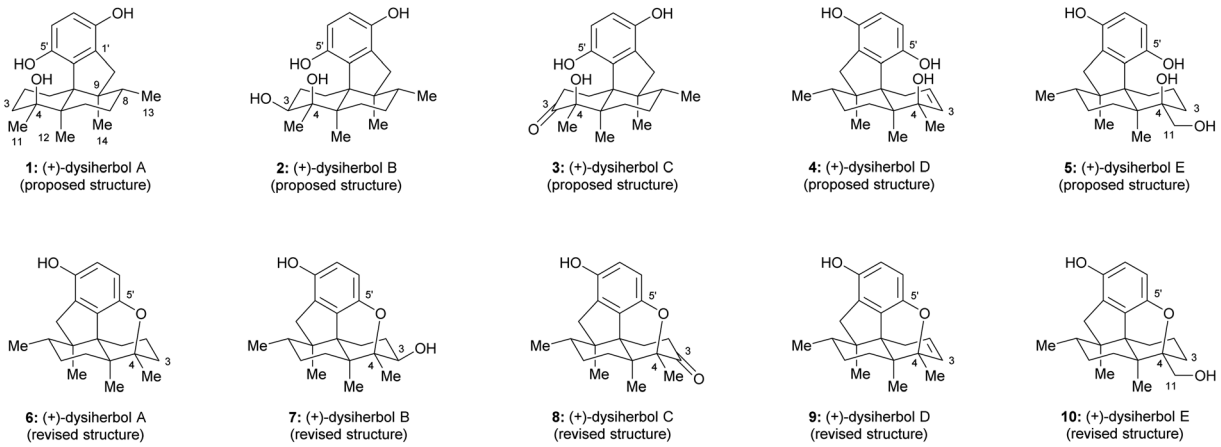


Fig. 1 Proposed and revised structures of (+)-dysiherbols A–E.

a Pd-catalyzed semipinacol rearrangement/C_{sp^2}–H arylation cascade and a visible-light-mediated ring-opening of a cyclopropyl silyl ether.[6] Very recently, Tang and co-workers disclosed an elegant divergent total synthesis of dysiherbols A, C, and D by using a photo-induced quinone–alkene [2 + 2] cycloaddition and a tandem [1,2]-anionic rearrangement/cyclopropane fragmentation strategy.[7]

Due to the close relationship with dysiherbol A, it was proposed that the structures of dysiherbols B–E (**2–5**) also need to be revised as **7–10**,[4,5,7,8] as shown in Fig. 1. Here, we report a concise and divergent enantioselective total synthesis of the revised structures of (+)-dysiherbols A–E (**6–10**) in their natural absolute configuration.

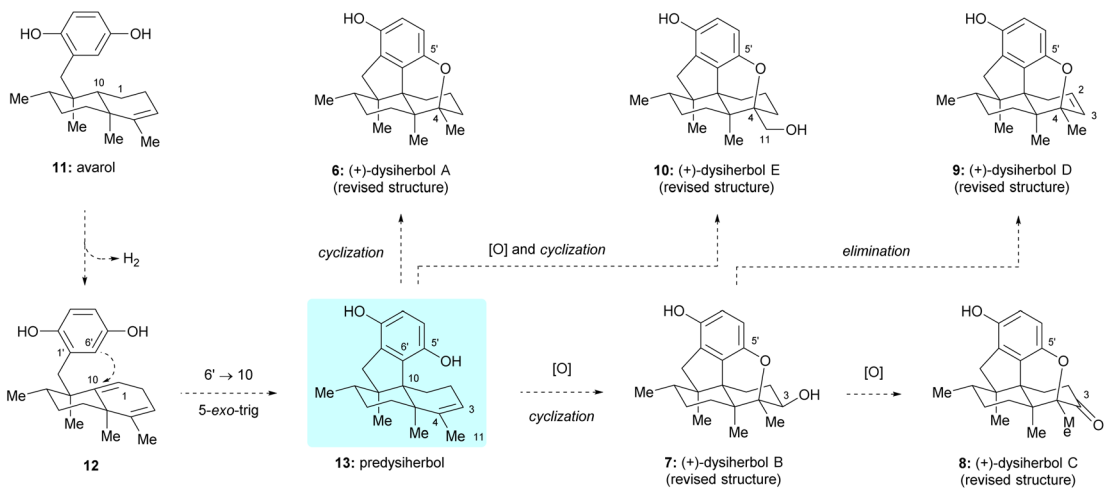
Results and discussion

Biosynthetic hypothesis of dysiherbols A–E

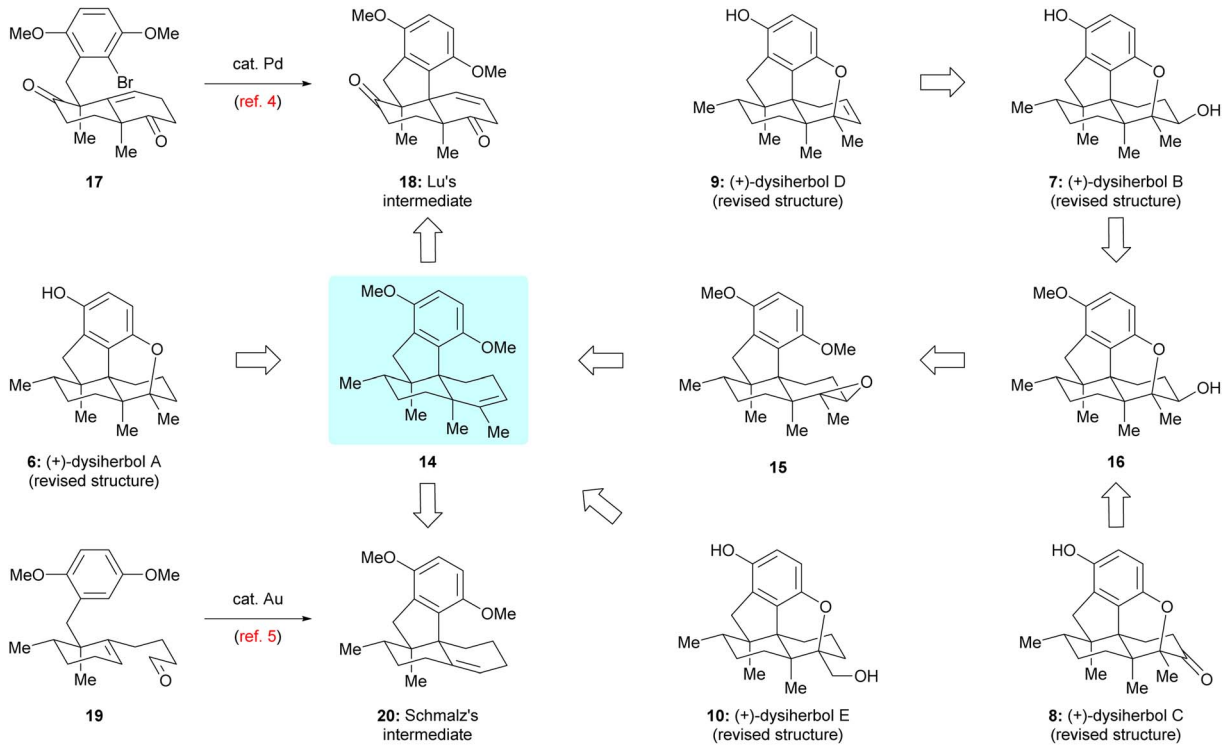
From a biosynthetic point of view, it was postulated that dysiherbols A–E (**6–10**) might be generated from a common sesquiterpene hydroquinone natural product avarol (**11**),[9] as shown in Scheme 1. Dehydrogenation of the C1–C10 single bond in avarol (**11**) gives rise to unconjugated diene **12** as a key intermediate. A 5-*exo*-trig cyclization of **12**, connecting C6′ of hydroquinone moiety with C10 of the decalin unit, would give predysiherbol **13**, which contains the core 6/6/5/6-fused tetracyclic framework of dysiherbols A–E (**6–10**). Direct cyclization of the C5′ phenol group with C4 of the double bond would give dysiherbol A (**6**). Oxidation of predysiherbol **13** and subsequent cyclization in a similar manner as in the case of dysiherbol A would afford dysiherbols B (**7**) and E (**10**). Further oxidation or elimination of the C3 hydroxy group of dysiherbol B (**7**) would render dysiherbols C (**8**) and D (**9**), respectively.

Retrosynthetic analysis of dysiherbols A–E

Guided by the above biosynthetic hypothesis, a retrosynthetic analysis of dysiherbols A–E (**6–10**) was conceived. To meet the challenge of synthesizing all dysiherbols in the natural absolute configuration, we envisioned using dimethyl predysiherbol **14** as a common late key precursor. As illustrated in Scheme 2, while this advanced key intermediate can be readily converted



Scheme 1 Possible biosynthetic pathway of dysiherbols A–E.



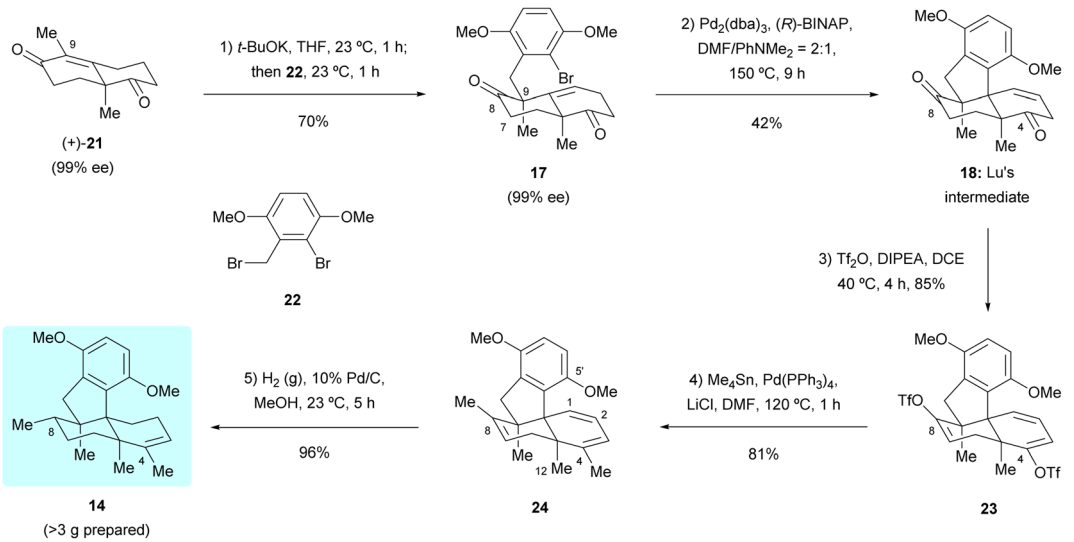
Scheme 2 Retrosynthetic analysis of dysiherbols A–E by two different routes.

to dysiherbol A (**6**) by treatment with BBr_3 as described previously,[4,5] dysiherbol E (**10**) could be synthesized through allylic oxidation and subsequent cyclization of dimethyl predysiherbol **14**.

We also reasoned that the synthesis of dysiherbols B–D (**7**–**9**) could be achieved by epoxidation of the double bond within **14** to give **15** followed by cyclization to an advanced intermediate such as pentacyclic alcohol **16**. We report here the implementation of this concept, which proved to be surprisingly challenging due to the high tendency of the systems to undergo Wagner–Meerwein rearrangements. In addition, we elaborated two different efficient routes to dimethyl predysiherbol **14** by adapting, shortening, and optimizing our previously developed synthetic sequences.[4,5] Noteworthy, both strategies exploit a metal-catalyzed cyclization step to set up the tetracyclic carbon skeleton. While the Lu's synthesis uses an intramolecular Heck reaction for the conversion of bromoalkene **17** into tetracyclic diketone **18**, the Schmalz's synthesis features a gold-catalyzed double cyclization of aldehyde **19** to give tetracyclic olefin **20**. Thus, besides confirming the proposed structures of the dysiherbols by total synthesis, the present work also demonstrates the power of modern synthetic methodology for the construction of complex polycyclic molecules displaying a high density of quaternary carbon centers.[10]

Synthesis of dimethyl predysiherbol 14

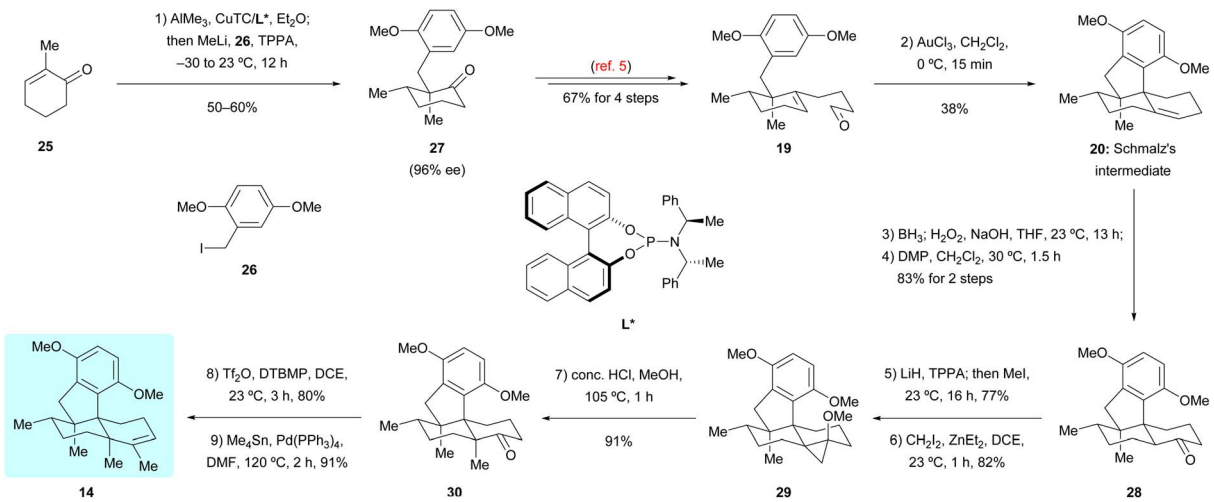
Our first synthetic route towards dimethyl predysiherbol **14** started from the union of Wieland–Miescher ketone derivative **21** and benzyl bromide **22**. As shown in Scheme 3, treatment of enantioenriched Wieland–Miescher ketone derivative **21** (99% ee)[11] with benzyl bromide **22** in the presence of *t*-BuOK proceeded smoothly on a gram scale to give bromoalkene **17** in high isolated yield (70%). The enantiomeric purity of bromoalkene **17** retained well (99% ee). However, the following intramolecular Heck reaction of **17** to construct tetracyclic diketone **18** proved to be unexpectedly challenging due to a competing arylation reaction[12] at C7 and Grignard-type nucleophilic addition[13] of the arylpalladium intermediate to the keto group at C8. After extensive exploration of catalysts, ligands, bases, and solvents,[14] we were pleased to find that the intramolecular Heck reaction of **17** with $Pd_2(dba)_3$ as catalyst, (*R*)-BINAP as ligand and $PhNMe_2$ as base rendered the cyclized product **18** in acceptable isolated yield (42%). All our attempts to perform a reductive Heck reaction[15] of **17** under various conditions only led to trace amounts of the desired product. The tetracyclic diketone **18** was then converted to the bistriflate **23**, the Stille coupling of which with Me_4Sn afforded the triene **24** in 69% overall yield over both steps.[16] The chemo- and diastereoselective reduction of triene **24** was perfectly achieved by heterogeneous hydrogenation, giving dimethyl predysiherbol **14** in almost quantitative yield (96%). The excellent chemo- and diastereoselective hydrogenation occurs at C8 is attributed to steric hindrances. We found that the disubstituted olefin at C1 and C2 was first reduced. For the hydrogenation of these two trisubstituted olefins, the C12 methyl group blocks the approach of H–Pd species to C3=C4 and C7=C8 double bonds from the bottom face and the methoxyl group on C5′ blocks the approach of H–Pd species to C3=C4 double bond from the top face, which also explains the easy formation of the bridged ether



Scheme 3 Synthesis of dimethyl predysiherbol **14** by Lu's intermediate **18**. (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-dinaphthalene, DCE = 1,2-dichloroethane, DIPEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium (0), Tf_2O = trifluoromethanesulfonic anhydride.

ring between C5′ and C4 (*vide infra*). Thus, the hydrogenation of **24** occurs at C8 from the top face, giving **14** in excellent yield and diastereoselectivity. Noteworthy, a total of more than 3 grams of **14** were prepared, which ensured the material supply for the synthesis of (+)-dysiherbols A–E (**6–10**) and their designed analogs for further bioactivity evaluation.

The second route towards dimethyl predysiherbol **14** was developed based on the previously reported synthesis of Schmalz's intermediate **20**,[5] as shown in Scheme 4. Now, we employed the enantiomeric phosphoramidate ligand **L*** in the chirogenic opening step (Cu-catalyzed 1,4-addition/enolate trapping) to ensure the required absolute configuration. Starting from 2-methylcyclohexenone **25** and benzyl iodide **26**, the triple substituted cyclohexanone **27** was obtained with high enantioselectivity (96% ee). While the conversion of **27** into tetracyclic ketone **28** *via* intermediate **19** and its Au-catalyzed tandem cyclization to Schmalz's intermediate **20** succeeded smoothly under reported conditions,[5] we spend some effort to optimize the remaining steps of the synthesis of dimethyl predysiherbol **14**. The challenging α-methylation of ketone **28** at the bridgehead carbon to give **30** was achieved by (1) regioselective deprotonation/O-methylation (LiH, TPPA, 160 °C; then MeI), (2) Simmons–Smith cyclopropanation of the resulting enol ether, and (3) proteolytic cleavage of the cyclopropane **29**. This way, ketone **30** was obtained in an improved overall yield of 57% (3 steps) on a 120 mg scale. The final conversion of ketone **30** into dimethyl predysiherbol **14** was then achieved in 73% overall yield through enol triflate formation and subsequent Stille coupling.



Scheme 4 Synthesis of dimethyl predysiherbol **14** by Schmalz's intermediate **20**. CuTC = copper(I) 2-thiophenecarboxylate, DTBMP = 2,6-bis(1,1-dimethylethyl)-4-methylpyridine, TPPA = tripyrrolidinophosphoric acid triamide.

Total synthesis of (+)-dysiherbols A and E

With sufficient quantities of dimethyl predysiherbol **14** in hand, we entered the final stage of its transformation to target natural products (+)-dysiherbols A and E (**6** and **10**). As shown in Scheme 5, exposure of dimethyl predysiherbol **14** with BBr_3 at −78 °C gave cyclized compound **31** in 91% yield under the previously developed reaction conditions.[4] Deprotection of the remaining *O*-methyl group of **31** with BBr_3 at 23 °C afforded (+)-dysiherbol A in 86% yield, which also could be prepared from dimethyl predysiherbol **14** directly in 72% overall yield. The spectroscopic and optical rotation data of synthetic (+)-dysiherbol A (**6**) matched well with those for natural (+)-dysiherbol A.

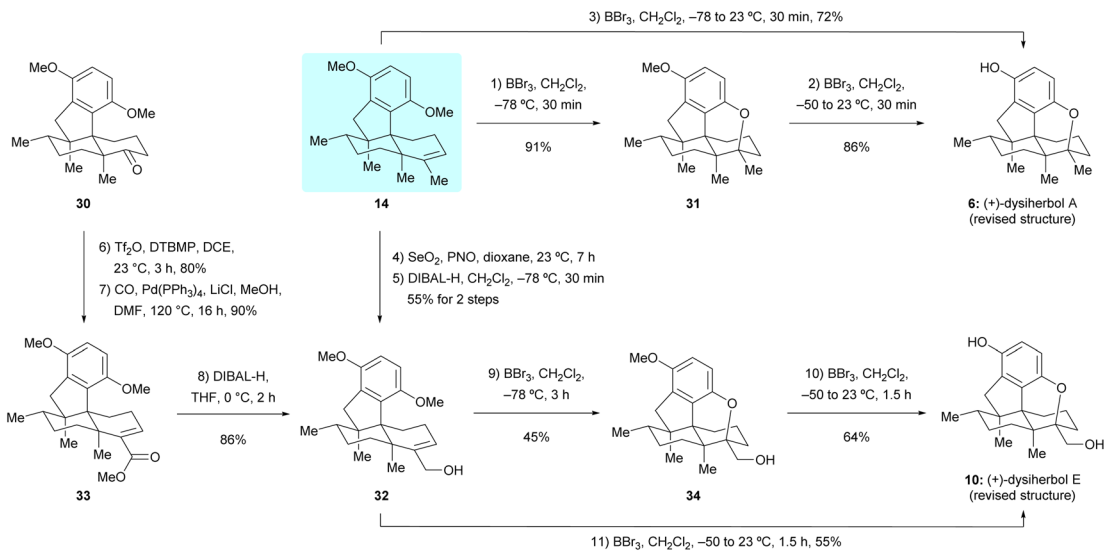
We then turned our attention to the synthesis of (+)-dysiherbol E. Allylic oxidation of dimethyl predysiherbol **14** to alcohol **32** proved to be challenging due to the existence of different oxidizable positions. SeO_2 and other tested oxidation reagents only led to poor yields of **32**.[17] After extensive screening of oxidating reagents and reaction conditions, we were pleased to find that the combination of SeO_2 and pyridine *N*-oxide (PNO)[18] gave the best combined yield of allylic alcohol **32** and the corresponding aldehyde resulting from overoxidation. Treatment of the crude product mixture with diisobutylaluminium hydride (DIBAL-H) afforded allylic alcohol **32** in 55% yield for the two steps. As an alternative access to the alcohol **32**, we found that the enol triflate derived from ketone **30** can be efficiently methoxycarbonylated by reaction with CO and MeOH in the presence of $Pd(PPh_3)_4$ as a catalyst and LiCl as an additive. Reduction of the resulting ester **33** using DIBAL-H then afforded **32** in 77% yield over two steps. Under similar cyclization conditions as used in the synthesis of (+)-dysiherbol A (**6**), exposure of allylic alcohol **32** to BBr_3 at −78 °C for 3 h gave the cyclized intermediate **34** in 45% yield besides a small amount of unreacted starting material **32** and the *O*-demethylated product, namely (+)-dysiherbol E (**10**). Deprotection of the methyl group of **34** with BBr_3 at 23 °C gave (+)-dysiherbol E (**10**) in 64% yield. Direct treatment of allylic alcohol **34** with BBr_3 at 23 °C for 1.5 h also gave (+)-dysiherbol E (**10**) in 55% yield. The spectroscopic and optical rotation data of synthetic (+)-dysiherbol E (**10**) matched well with those reported for natural (+)-dysiherbol E. The calculated electronic circular dichroisms (ECDs) of (+)-dysiherbols A (**6**) and E (**10**) matched well with experimental ECDs (see Fig. 2b).

1,2-Methyl shift processes in dysiherbol-related compounds

In studying the cyclization reaction of dimethyl predysiherbol **14**, we found that treatment of this compound with 1.0 equivalent of methanesulfonic acid (MsOH) at 0 °C gave the rearranged product **35** in 95% yield, while treatment of **14** with 20 equivalents of MsOH at 23 °C afforded the cyclized ether **31** in 61% yield, as shown in Scheme 6.[5] Further experiments showed that the rearranged product **35** could also be converted to the cyclized ether **31** in 65% yield by treatment with 20 equivalents of MsOH at 23 °C. We rationalized that the carbenium ion **36** is first generated from dimethyl predysiherbol **14** under acidic conditions. Then reversible methyl migration (Wagner–Meerwein rearrangement) gives the cation **37**, from which the rearranged product **35** is formed by proton elimination (pathway c). Under more drastic conditions, however, the carbenium ion **36** is trapped by the adjacent methoxy group to irreversibly yield the cyclized product **31** *via* the oxonium intermediate **38** (pathway a). This proves the reversibility of such 1,2-methyl shift processes in dysiherbol-related compounds.[5]

Oxidation and cyclization investigation of dimethyl predysiherbol 14

Having successfully accomplished the total synthesis of (+)-dysiherbols A (**6**) and E (**10**), we switched our attention to the synthesis of (+)-dysiherbols B–D (**7–9**). However, the transformation of dimethyl predysiherbol **14** to (+)-dysiherbols B–D (**7–9**) proved to be surprisingly challenging and could not be achieved in the envisioned straightforward manner. Aiming at



Scheme 5 Total synthesis of the revised structures of (+)-dysiherbols A and E. DIBAL-H = diisobutylaluminium hydride, PNO = pyridine *N*-oxide.

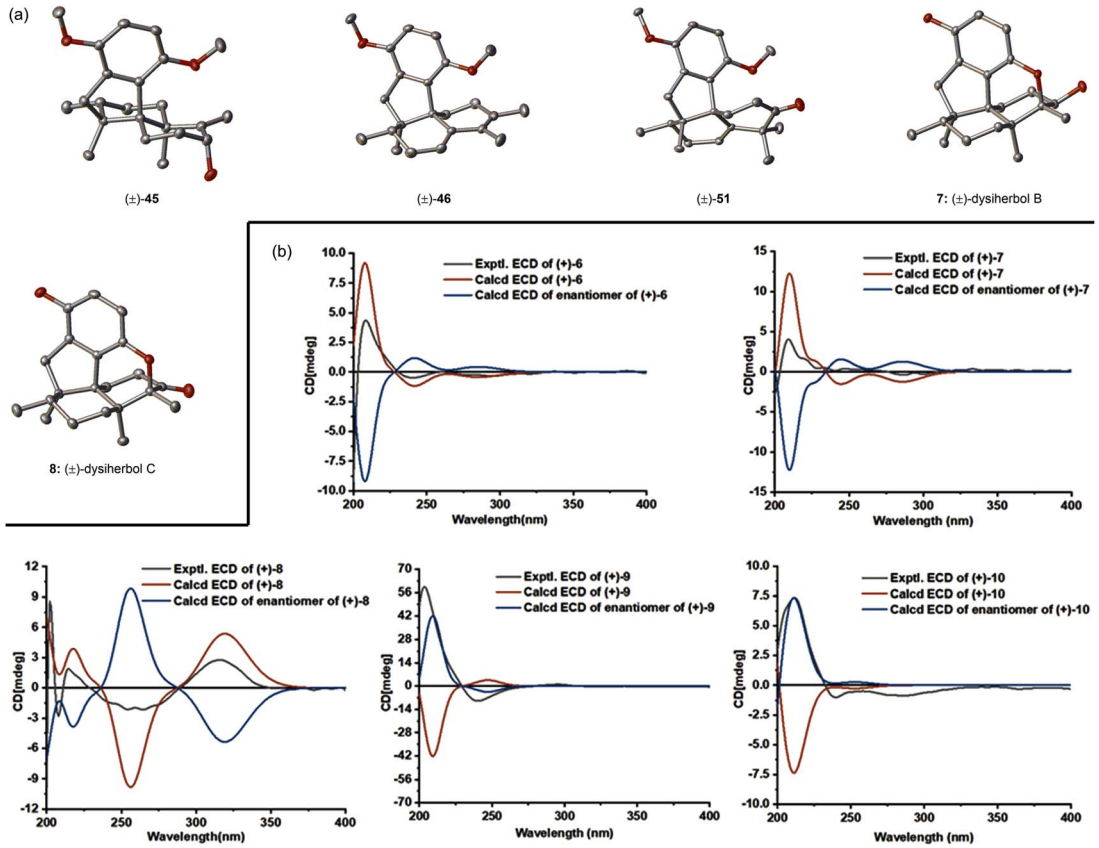
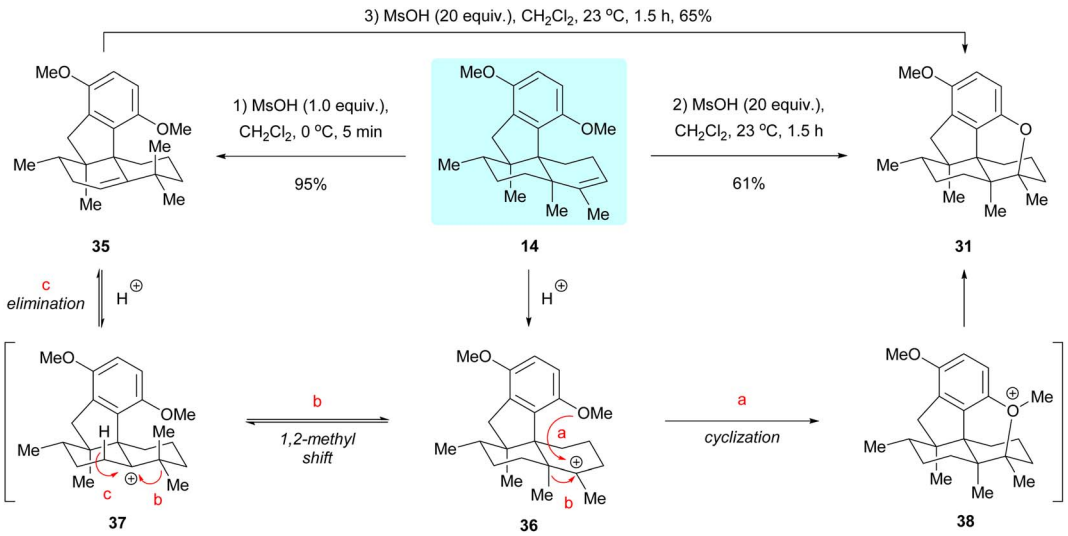
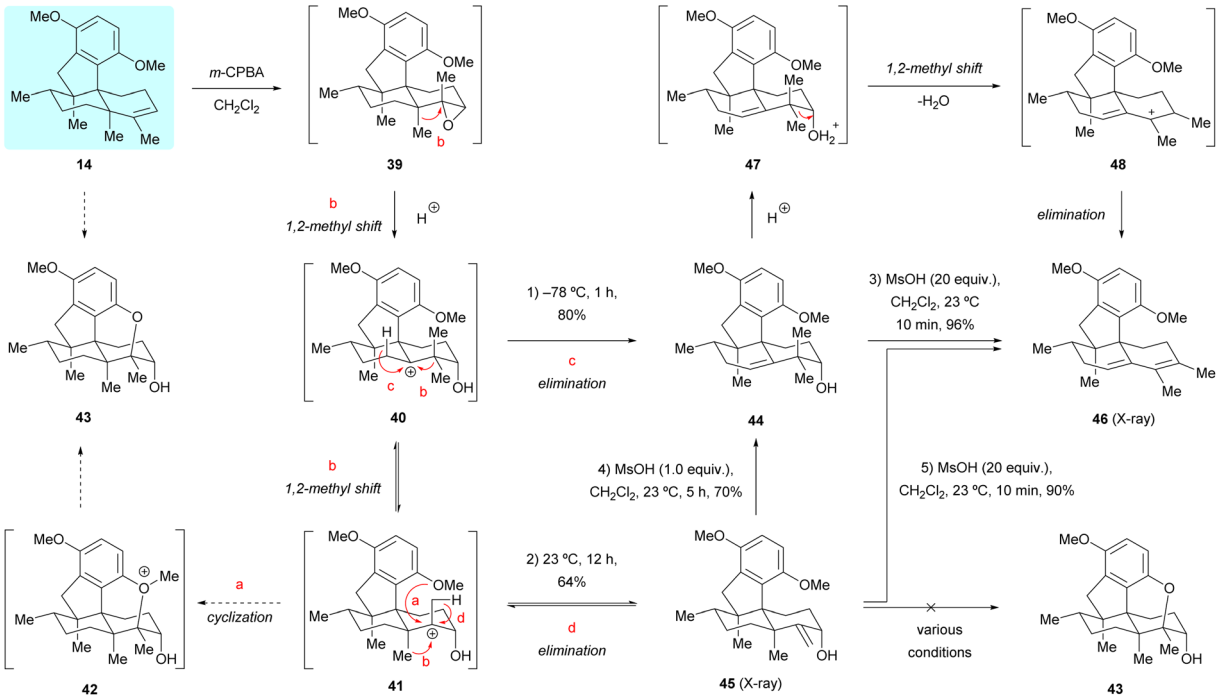


Fig. 2 (a) ORTEP drawing of the structures of key intermediates and the revised structures of dysiherbols B and C. (b) Experimental and calculated ECDs for (+)-dysiherbols A–E. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms have been omitted for clarity.

the synthesis of (+)-dysiherbols B–D (**7**–**9**), we envisioned that epoxidation of the double bond of dimethyl predysiherbol **14** and subsequent cyclization would give pentacyclic alcohol **43** *via* intermediates **39**, **40**, **41** and **42** (pathway a), as depicted in Scheme 7. For this purpose, dimethyl predysiherbol **14** was treated with *m*-chloroperbenzoic acid (*m*-CPBA). Surprisingly, only the rearranged homoallylic alcohol **44** was obtained in 80% yield when the reaction was quenched at −78 °C, presumably by direct proton elimination of carbenium **40** (pathway c). The desired cyclization did not occur when the reaction mixture was



Scheme 6 1,2-Methyl shift processes in dysiherbol-related compounds. MsOH = methanesulfonic acid.



Scheme 7 Oxidation and cyclization investigation of dimethyl predysiherbol **14**.

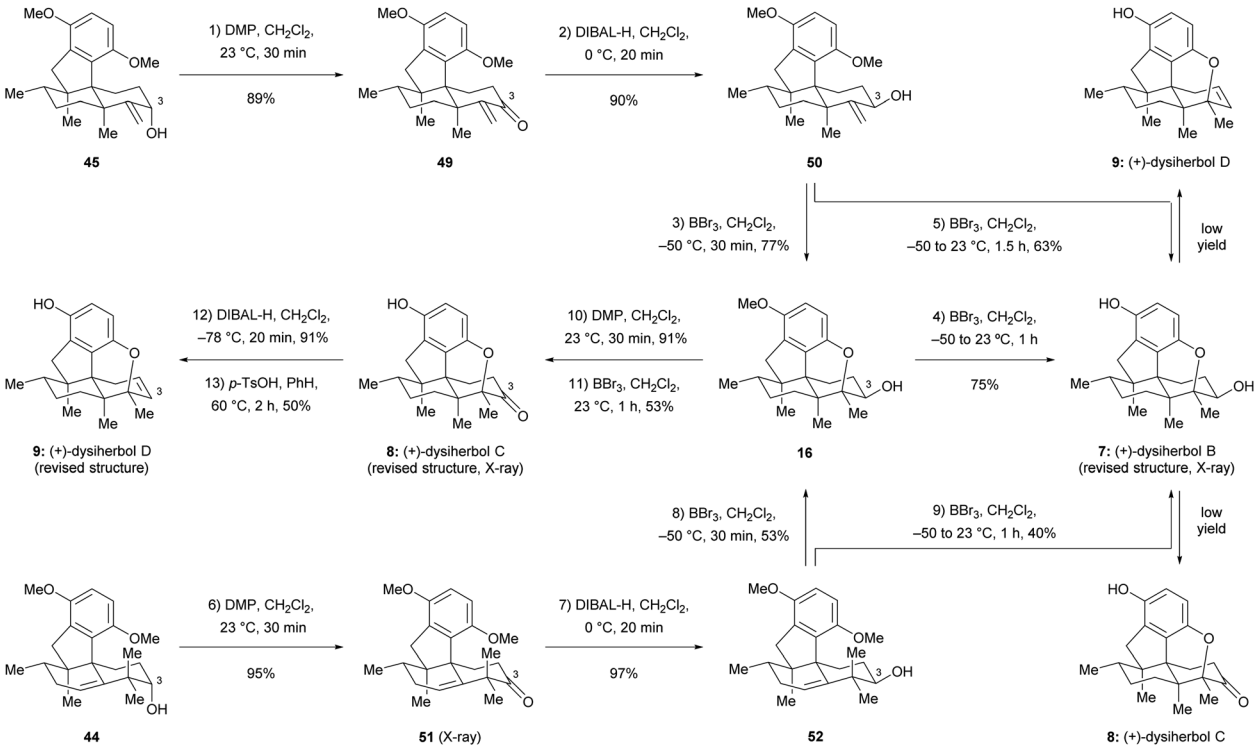
warmed to 23 °C. Instead, the allylic alcohol **45** was isolated in 64% yield presumably through a similar rearrangement (1,2-methyl migration) of the carbenium ion **40** to **41** and proton elimination of the latter (pathway d). The structure of allylic alcohol **45** and the orientation of the newly generated hydroxy group were verified by X-ray crystallographic analysis (see Fig. 2a).

We assumed that the homoallylic alcohol **44** could be transformed to cyclized ether **43** through the 1,2-methyl shift of **40** to the cation **41** and subsequent cyclization. However, when homoallylic alcohol **44** was treated with various Brønsted acids (*e.g.*, TsOH and MsOH) or Lewis acids (*e.g.*, BBr_3 and $BF_3{\cdot}OEt_2$) the expected cyclized product was not observed. In addition, upon treatment of **44** with excess MsOH, the tetracyclic diene **46** was isolated in near quantitative yield (96%), presumably *via* the cationic intermediates **47** and **48**. The transformation of **45** to pentacyclic alcohol **43** also met with failure under various tested conditions. Indeed, treatment of allylic alcohol **45** with various Brønsted acids or Lewis acids also led to the elimination product **46** in high yield probably *via* the homoallylic alcohol **44**.[19] The structure of **46** was secured by X-ray crystallographic analysis (see Fig. 2a). We would like to note that homoallylic alcohol **44** could be prepared in high yield (67–80%) from dimethyl predysiherbol **14** either using magnesium monoperoxyphthalate (MMPP)[20] or trifluoroacetone-oxone-Na_2EDTA[21] and the isomeric, non-rearranged allylic alcohol **45** could also be prepared from dimethyl predysiherbol **14** through $^1O_2$ ene reaction[22] under photochemical conditions in 62% yield (see ESI† for details).

Total synthesis of (+)-dysiherbols B–D

Since the direct cyclization of homoallylic alcohol **44** or allylic alcohol **45** to the cyclized ether **43** failed, we anticipated that the configuration of the C3 hydroxy group of these two compounds might affect the formation of the additional ether bridge by changing the conformational bias of the carbenium ion intermediates. To this end, we inverted the configuration of the C3 hydroxy group prior to the cyclization. As shown in Scheme 8, Dess–Martin periodinane (DMP) oxidation of allylic alcohol **45** (89% yield) and subsequent DIBAL-H reduction of the resulting ketone **49** (90% yield) afforded allylic alcohol **50**, which possesses the correct configuration of the C3 hydroxy group, as found in (+)-dysiherbol B. Much to our delight, the ether ring formation reaction now proceeded smoothly when allylic alcohol **50** was treated with BBr_3 at −50 °C for 30 min, affording cyclized ether **16** in 77% yield. Removal of the remaining methyl group by the same reagent but at 23 °C for 1 h resulted in (+)-dysiherbol B (**7**) in 75% yield. In addition, (+)-dysiherbol B (**7**) could be directly prepared from **50** through a one-pot procedure in 63% yield. The synthetic (+)-dysiherbol B (**7**) exhibited identical spectroscopic and optical rotation data as those reported for the natural product. X-ray crystallographic analysis of synthetic dysiherbol B (**7**) clearly showed the additional ether bridge between C4 and C5′, thus confirming the revised structure of this natural product (see Fig. 2a).

Prompted by the above results, we anticipated that homoallylic alcohol **44** also could be transformed to (+)-dysiherbol B (**7**) after inversion of the configuration at C3 and subsequent cyclization. Thus, homoallylic alcohol **44** was converted to its epimer **52** through DMP oxidation and subsequent DIBAL-H reduction in 92% yield over two steps. The structure of ketone **51** was also confirmed by X-ray crystallographic analysis (see Fig. 2a). As we expected, the subjection of homoallylic alcohol



Scheme 8 Total synthesis of the revised structures of (+)-dysiherbols B–D. DMP = Dess–Martin periodinane, *p*-TsOH = *p*-toluenesulfonic acid.

52 to BBr_3 also gave the cyclized ether **16** in 53% yield, probably *via* above-mentioned methyl migration and subsequent ether ring formation, along with a significant amount of elimination byproduct **46** (43%). Homoallylic alcohol **52** was also converted to (+)-dysiherbol B in a one-pot procedure in 40% yield, besides 40% of **46**.

With (+)-dysiherbol B (**7**) readily available, we anticipated that oxidation and elimination of the C3 hydroxy group could afford (+)-dysiherbols C (**8**) and D (**9**), respectively. However, under various tested oxidation and elimination reagents and conditions, very low yields of (+)-dysiherbols C (**8**) or D (**9**) were obtained presumably due to the instability of the free phenol functionality. (+)-Dysiherbols C (**8**) and D (**9**) could be alternatively synthesized from **16** avoiding exposure of the sensitive free phenol to oxidation and elimination conditions. To this end, DMP oxidation of the C3 hydroxy group (91%) and deprotection of the remaining methyl group of **16** resulted in (+)-dysiherbol C (**8**) in 53% yield. Attempts to directly eliminate the equatorial OH group in **16** proved to be fruitless. After inversion of the configuration of the hydroxy group by DIBAL-H reduction (91% yield) of (+)-dysiherbol C (**8**), acid-mediated elimination afforded (+)-dysiherbol D (**9**) in acceptable yield (50%). The spectroscopic and optical rotation data of synthetic (+)-dysiherbols C (**8**) and D (**9**) matched with those reported for natural products. The revised structure of dysiherbol C (**8**) was also confirmed by X-ray crystallographic analysis (see Fig. 2a). The calculated ECDs of (+)-dysiherbols B–D (**7–9**) matched well with experimental ECDs (see Fig. 2b).

Conclusions

In summary, we have elaborated a concise and divergent total synthesis of the revised structures of marine anti-cancer sesquiterpene hydroquinone meroterpenoids (+)-dysiherbols A–E (**6–10**) in their natural absolute configuration *via* the common intermediate dimethyl predysiherbol **14**. The key common intermediate dimethyl predysiherbol **14** was efficiently synthesized in non-racemic form by two different routes, both exploiting a transition metal-catalyzed cyclization reaction to construct the tetracyclic carbon skeleton. The synthesis of (+)-dysiherbols A (**6**) and E (**10**) was accomplished through direct cyclization and allylic oxidation and subsequent cyclization of dimethyl predysiherbol **14**, respectively. The synthesis of (+)-dysiherbols B–D (**7–9**) was achieved by epoxidation of dimethyl predysiherbol **14** and cationic cyclization, overcoming unexpected difficulties resulting from the tendency of the systems to undergo reversible 1,2-methyl migration ("methyl shuttle"). Importantly, the synthesis of (+)-dysiherbols A–E (**6–10**) confirmed their revised structures. The work described here also paves the way for the synthesis and evaluation of the anti-cancer activity of a wide variety of analogs of (+)-dysiherbols A–E (**6–10**), which is currently underway in our laboratories and will be reported in due course.

Data availability

All experimental and characterization data in this manuscript are available in the ESI.† Crystallographic data for compounds

45, **46**, **51**, **7**, and **8** have been deposited at the Cambridge Crystallographic Data Center and assigned numbers 2124205, 2192301, 2192302, 2141304, and 2141326.

Author contributions

Z. L. and H.-G. S. conceived and supervised the project. C. C., L. C., I. G., Q. Z., Y. K., B. W., J. K., and J. B. carried out the experimental work, collected the data, and analyzed the results. W. L. and Y. G. conducted the DFT calculations of ECDs. Z. L. and H.-G. S. wrote the paper.

Conflicts of interest

There are no conflicts to declare.

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