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Enantioselective Total Synthesis and Structural Revision of Dysiherbol A

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Dedicated to Professor K. Barry Sharpless on the occasion of his 80th birthday

Abstract: *A 12-step total synthesis of the natural product dysiherbol A, a strongly anti-inflammatory and anti-tumor avarane meroterpene isolated from the marine sponge Dysidea sp., was elaborated. As key steps, the synthesis features an enantioselective Cu-catalyzed 1,4-addition/enolate-trapping opening move, an Au-catalyzed double cyclization to build up the tetracyclic core-carbon skeleton, and a late installation of the C5-bridgehead methyl group via proton-induced cyclopropane opening associated with spontaneous cyclic ether formation. The obtained pentacyclic compound (corresponding to an anhydride of the originally suggested structure for dysiherbol A) showed identical spectroscopic data as the natural product, but an opposite molecular rotation. CD-spectroscopic measurements finally confirmed that both the constitution and the absolute configuration of the originally proposed structure of (+)-dysiherbol A need to be revised.*

In 2016 Jiao et al. reported the isolation and structural elucidation of dysiherbols A–C (**1**–**3**) and dysideanone E (**4**) as metabolites of the sponge *Dysidea* sp. collected in the South China Sea (Figure 1).[1] Initial biological testing revealed dysiherbol A (as the most active of these compounds) to exhibit cytotoxic activity towards the cancer cell line NCI H-929 at sub-micromolar concentrations. Furthermore, **1** showed strong inhibition of NF-κB, a protein involved in the regulation of inflammatory, immunological and carcinogenic processes.[1,2] From a structural point of view, dysiherbol A (**1**) and its congeners **2** and **3** belong to the hydroquinone sesquiterpenes, a large family of meroterpenes of mixed biosynthetic origin.[3] More specifically, the dysiherbols are members of the avarane sub-family, according to the substitution pattern of the decalin AB ring system. Since the discovery of avarol (**5**) in 1974[4] as a multi-bioactive compound,[5] a variety of avarane meroterpenoids have been described, among them aureol B (**6**)[6] and the cycloaurenones (such as **7** and **8**),[7] the latter featuring the same carbon skeleton as the dysiherbols, however, with a *cis*-configuration of the decalin system.

Due to their interesting structural and biological properties, meroterpenoids of the avarane family have attracted much attention of synthetic chemists.[8–10] In 2017, Echavarren and co-workers succeeded in synthesizing simplified compounds displaying the tetracyclic carbon ring system of dysiherbols and cycloaurenones.[11] However, the total synthesis of these natural products remained an unsolved challenge.

Considering the promising biological activities of dysiherbol A and the challenge of stereoselectively constructing the tetracyclic 6/6/5/6-fused carbon skeleton with five adjacent (mostly quaternary) stereocenters, we decided to tackle its synthesis. We report here the first enantioselective total synthesis of dysiherbol A, which also led to a revision of both the constitution and the absolute configuration of the natural product.

As outlined in Scheme 1, our strategic plan was to synthesize dysiherbol A (**1**) from the simplified tetracyclic

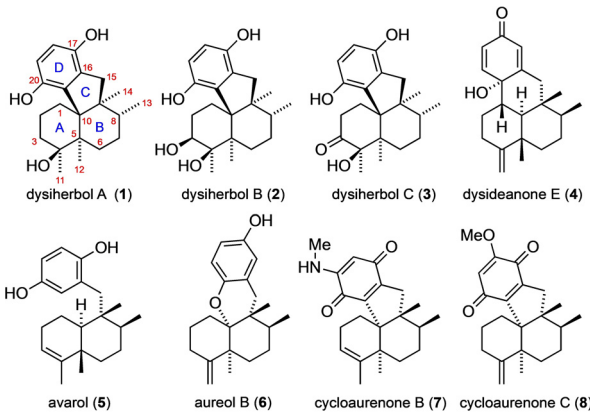
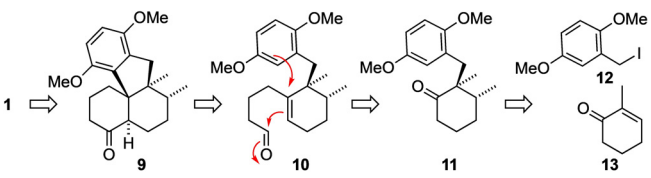


Figure 1. Proposed structure of dysiherbols A–C, dysideanone E and selected related meroterpenoids with an avarane skeleton.



Scheme 1. Retrosynthetic analysis of dysiherbol A.

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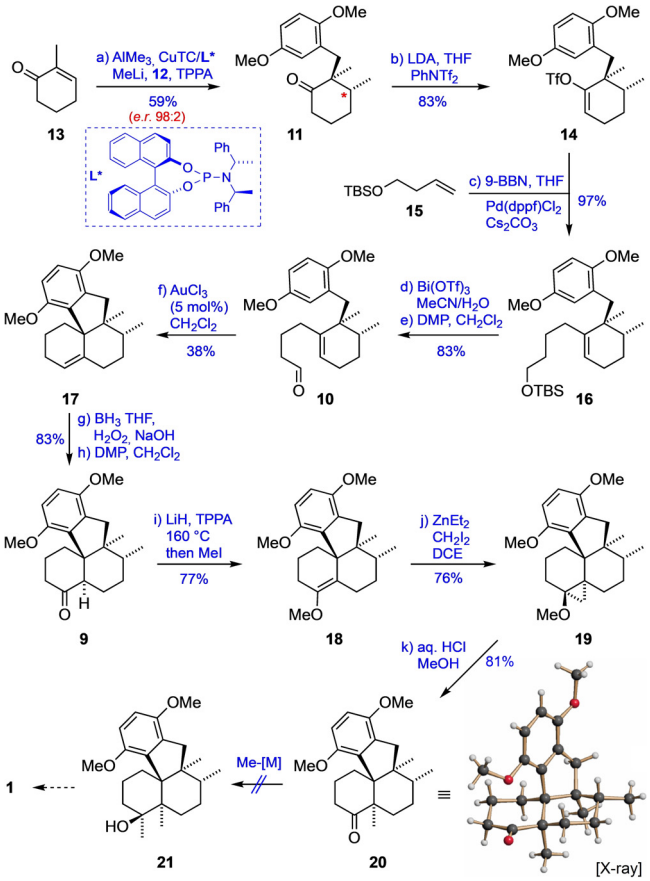
precursor **9** by late-stage (diastereoselective) introduction of the methyl groups in ring A. We envisioned that ketone **9** could possibly be obtained from aldehyde **10** through Lewis acid-mediated twofold (cationic) cyclization and subsequent oxidation. In this key step, the tetracyclic ring skeleton would be diastereoselectively built up under concomitant formation of two strategic C–C bonds.

We further reasoned that the synthesis of the required cyclization precursor **10** could be achieved from the cyclohexanone derivative **11** which in turn could be prepared through enantioselective Cu-catalyzed conjugate addition of a methyl anion equivalent to 2-methyl-2-cyclohexenone (**13**)[12] followed by diastereoselective alkylation of the resulting enolate with the benzylic iodide **12**, in analogy to a report by Cramer and co-workers.[13]

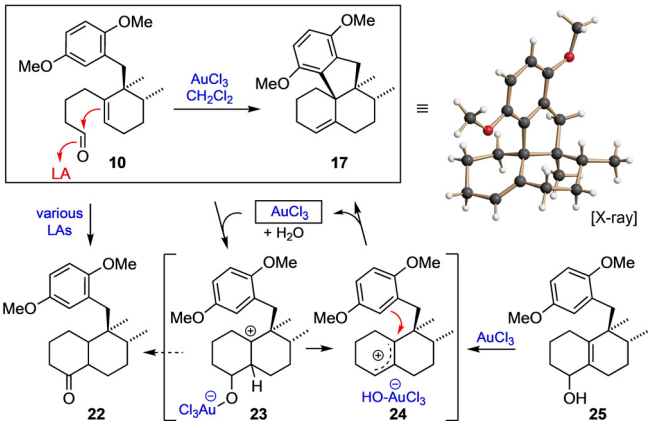
According to this plan, we started our investigation by reacting **13**[14] with $AlMe_3$ in the presence of a catalyst generated in situ from copper(I) thiophene-2-carboxylate (CuTC) and the (*R*)-BINOL-derived chiral phosphoramidite ligand **L***.[15] After activating the resulting aluminum enolate as an ate-complex by addition of methyllithium, the subsequent C-alkylation with iodide **12**[16] proceeded smoothly in the presence of tripyrrolidinophosphoric acid triamide (TPPA) as a cosolvent[17] to afford ketone **11** (96% *ee*, HPLC) in 59% yield as a single diastereomer after chromatographic purification (Scheme 2).

Having thus achieved the chirogenic opening step with high enantioselectivity on a multi-gram scale, the next task was the conversion of ketone **11** into aldehyde **10** under introduction of a C_4 chain. For this purpose, ketone **11** was first converted into the enol triflate **14** by treatment with LDA and *N*-phenyl triflimide. Suzuki–Miyaura cross-coupling of **14** with the borane prepared in situ from TBS-protected homoallylic alcohol **15** and 9-BBN then proceeded cleanly under the chosen conditions (cat. $Pd(dppf)Cl_2$, Cs_2CO_3, H_2O, DMF)[18] to deliver **16** in excellent yield. The cleavage of the TBS group was achieved with catalytic amounts of $Bi(OTf)_3$ in the presence of water,[19] and the resulting alcohol was directly subjected to oxidation with the Dess–Martin periodinane (DMP) to give **10** in high yield (68% overall from **11**).

With substantial amounts of the aldehyde **10** in our hands, we went on to investigate the planned twofold cyclization. Initial experiments revealed that treatment of **10** with common Lewis acids (such as $BF_3{\cdot}OEt_2$, $AlCl_3$ or $SnCl_4$) only resulted in the formation of complex product mixtures usually containing the ketone **22** as a major component. However, after extensive screening of various Lewis acids, we succeeded in identifying $AuCl_3$ as the only catalyst capable of achieving the desired transformation (under elimination of water) to give the olefin **17** as a sole major product according to GC–MS analysis. On a preparative scale, this unique reaction proved to be insensitive towards air and moisture and proceeded within minutes in the presence of only 5 mol% of $AuCl_3$. After chromatographic purification, **17** was obtained in 38% yield, and its structure was secured by X-ray crystallography (Scheme 3). To explain the unique performance of $AuCl_3$ in this transformation, we suppose that, in contrast to all other Lewis acids tested, $AuCl_3$ is able to convert the primary cyclization intermediate **23** rapidly



Scheme 2. Synthesis of key intermediate **9** and unsuccessful attempts at its conversion to **1**. Reagents and conditions: a) $AlMe_3$, CuTC/L[1]* (2.4 mol%), Et_2O, −30 °C, 4.5 h; then MeLi, **12**, TPPA, −30→25 °C, 17 h; b) LDA, THF, $PhNTf_2$, −78→25 °C, 3 h; c) **15**, 9-BBN, THF, 25 °C, 2 h; then **14**, $Pd(dppf)Cl_2$ (3 mol%), Cs_2CO_3, H_2O, DMF, 25 °C, 1 h; d) $Bi(OTf)_3$ (4 mol%), CH_3CN/H_2O, 25 °C, 1.5 h, 97%; e) DMP, CH_2Cl_2, 0→25 °C, 2 h, 86%; f) $AuCl_3$ (5 mol%), CH_2Cl_2, 0 °C, 11 min; g) BH_3·THF, THF, 0→30 °C, 10 h; then NaOH, H_2O_2, THF/H_2O, 0→25 °C, 14 h; h) DMP, CH_2Cl_2, 0→30 °C, 2 h; i) LiH, TPPA, 160 °C, 1.5 h; then MeI, 25 °C, 20 h; j) $ZnEt_2$, CH_2I_2, DCE, 25 °C, 35 min; k) aq. HCl, MeOH, reflux, 35 min. CuTC = copper(I) thiophene-2-carboxylate, TPPA = tripyrrolidinophosphoric acid triamide, LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, 9-BBN = 9-borabicyclo-[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DMP = Dess–Martin periodinane, DCE = dichloroethane.

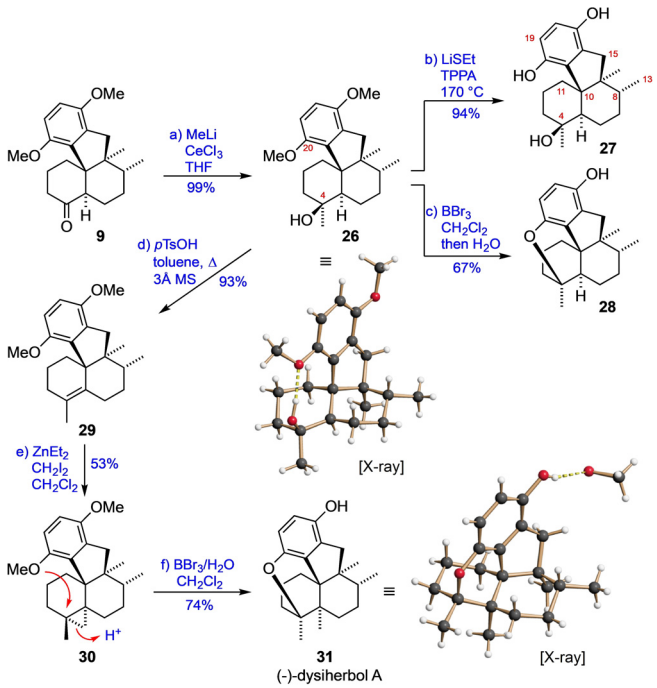


Scheme 3. A mechanistic proposal for the $AuCl_3$-catalyzed twofold cyclization of aldehyde **10** to the tetracyclic olefin **17**.

into a more stable allylic cation (**24**) under formation of the $AuCl_3(OH)^-$ anion. The cation **24** is then attacked by the electron-rich aromatic ring to yield the observed product **17** in a S_EAr cyclization under regeneration of the catalyst ($AuCl_3$). To support this mechanistic proposal, we separately treated a sample of compound **25**[20] with 4 mol% of $AuCl_3$, which is known to catalyze substitution reactions of allylic alcohols.[21,22] And indeed, in this case the tetracyclic olefin **17** was again formed, even in an improved yield of 50%.

Having developed a reliable protocol for constructing the tetracyclic core structure of the dysiherbols by double cyclization of aldehyde **10**, the remaining challenge was the installation of the two missing methyl groups as well as the hydroxy function at ring A. To prepare for this, we first converted **17** into the originally devised ketone **9** through hydroboration/oxidation and subsequent DMP oxidation (Scheme 2). As the introduction of the bridgehead methyl group (C12) could not be achieved by direct α-methylation of the ketone (due to the steric hindrance), we had to take a deviation via opening of an enolether-derived cyclopropane intermediate.[23] Remarkably, the regioselective, thermodynamically controlled ketone deprotonation was achieved only by treatment of **9** with LiH in TPPA at 160°C, and the resulting lithium enolate was O-alkylated with MeI to give the enolether **18**. The subsequent Simmons–Smith cyclopropanation[24] proceeded diastereoselectively to give **19**, from which the desired α-methyl ketone **20** was obtained under acidic conditions (47% overall yield from **9**). To our disappointment, all attempts to convert **20** into the tertiary alcohol **21**, that is, "dysiherbol A dimethyl ether", by nucleophilic introduction of a methyl anion equivalent (MeMgBr, MeLi, $MeLi/CeCl_3$,[25] $AlMe_3$ or $ZrMe_4$[26]) failed. This result, however, was not completely unexpected, as the crystal structure of **20** not only confirmed the steric shielding of both faces of the carbonyl group but also indicated an electronic deactivation, as reflected by a distance of only 2.51 Å between the carbonyl C-atom and the adjacent methoxy oxygen ($n\rightarrow\pi^*$ interaction).[27]

In contrast to **20**, the non-methylated ketone **9** reacted smoothly with $MeLi/CeCl_3$ to give alcohol **26** as a single diastereomer in virtually quantitative yield without the need of chromatographic purification (Scheme 4). Notably, the crystal structure of **26** displays an intramolecular hydrogen bond between the OH and the methoxy group, once again pinpointing the spatial proximity and the interaction of the functionalities at C4 and C20. The close structural relationship of **26** with the target molecule **1** prompted us to investigate its deprotection. The triol **27**, that is, putative 12-nor-dysiherbol A, was obtained in high yield by heating **26** with an excess of LiSEt in TPPA to 170°C.[28] In contrast, reaction of **26** with BBr_3 in CH_2Cl_2 followed by hydrolytic workup resulted in the formation of **28** under spontaneous dehydrative cyclization. Besides characteristic changes in the NMR spectrum, the structure of **28** was supported by its mass spectrum which indicated the loss of one water molecule. It is noteworthy that comparison of the NMR data for compounds **27** and **28** with those reported for dysiherbol A showed a much closer relationship of the natural product to **28** compared to **27** (Table 1).



Scheme 4. Completion of the synthesis of (−)-dysiherbol A. Reagents and conditions: a) $CeCl_3$, MeLi, THF, −78°C→25°C, 18 h; b) LiSEt (10 equiv), TPPA, 170°C, 4 h; c) BBr_3, CH_2Cl_2, 25°C, 25 h, then H_2O, 25°C, 1 h; d) *p*TsOH·H_2O, 3 Å MS, toluene, reflux, 4 h; e) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 25°C, 2 h, 2 cycles; f) BBr_3, H_2O, CH_2Cl_2, 27°C, 40 min. *p*TsOH = *p*-toluenesulfonic acid, 3 Å MS = molecular sieves (pore size: 3 Å).

Table 1: Comparison of selected ^1H and ^{13}C NMR signals[a] of compounds **27** and **28** with those of dysiherbol A (taken from ref. [1])

δ [ppm]	**27**[b]	**28**[b]	dysiherbol A[c]
C4	72.5	79.0	82.4
C10	58.0	47.7	49.1
C11	31.4	25.9	21.9
C19	116.3	111.3	111.1
H-8	1.43	1.13	1.24
H-13	0.76	0.82	0.83
H-15a	2.66	2.64	2.57
H-15b	2.42	2.59	2.54

[a] All spectra in $CDCl_3$ (77.00 ppm). [b] 500 MHz (^1H)/126 MHz (^{13}C). [c] 600 MHz (^1H)/150 MHz (^{13}C).

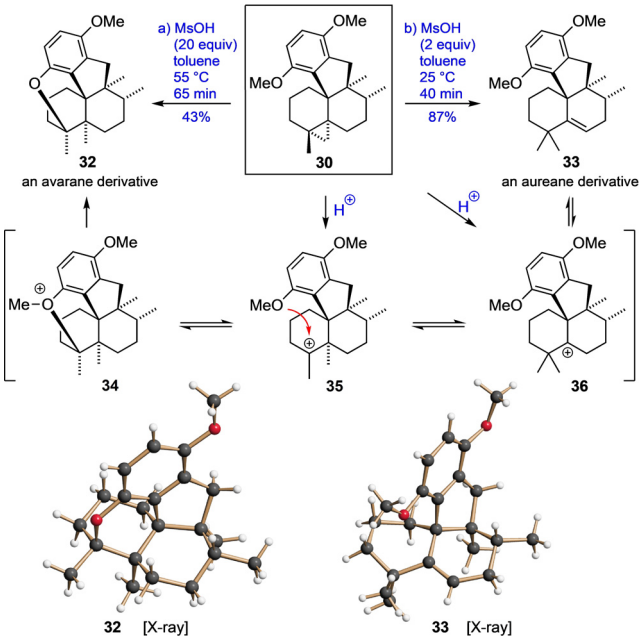
We therefore reasoned that dysiherbol A might actually have a similar pentacyclic structure as **28**, which also opened a new option for the end game of the synthesis, as the protolytic opening of a cyclopropane (**30**) could possibly be linked to the installation of the ether bridge (Scheme 4). Therefore, we proceeded with the conversion of **26** to **30**, which was achieved in two steps by acid-mediated elimination of water and subsequent cyclopropanation ($ZnEt_2$, CH_2I_2) of the olefin **29**. Much to our satisfaction, we then succeeded in realizing the final key step. Under optimized conditions, the reaction of cyclopropane **30** with an excess of BBr_3 in the presence of water afforded compound **31** in 74% yield, the structure of which (crystallized as an MeOH adduct) was secured by X-ray crystallography. The spectroscopic data of

31 agreed perfectly with those reported for natural dysiherbol A,[1] thus confirming the necessary revision of the originally proposed structure.

To gain insight into the proton-induced cyclopropane opening step, we also investigated the reaction of **30** with methanesulfonic acid (MsOH) in toluene (Scheme 5). Interestingly, the aureane derivative **33** was formed in high yield under comparably mild conditions (2 equiv MsOH, 25 °C) while the pentacyclic avarane **32** (i.e. dysiherbol A methyl ether) was formed as the only main product in the presence of a large excess of MsOH at 55 °C. This result indicates the regioselectivity of the primary cyclopropane opening step being unimportant due to a Wagner–Meerwein rearrangement equilibrium between the two cationic intermediates **35** and **36**. While at lower temperature the proton elimination of **36** (to **33**) is favored, the cyclization of **35** to **34** and the subsequent cleavage of the O–Me bond occur only under harsher conditions, under which, incidentally, **33** is converted to **32** in 40% yield, as shown in a separate experiment. Noteworthy, the carbon skeleton of the tetracyclic aureane **33**, has never been found in nature (yet).

Another surprise was that the molecular rotation of synthetic dysiherbol A (**31**) ($[\alpha]_D = -23°$; $c = 0.5$ in MeOH) did not match the one reported for the natural product ($[\alpha]_D = +23°$; $c = 0.1$ in MeOH).[1] While the absolute configuration of our sample was secured by X-ray crystal structure analysis, the original configurational assignment was based on the comparison of the experimental CD spectrum with those calculated for **1**. We therefore took a CD spectrum of **31** which clearly confirmed it being the enantiomer of natural dysiherbol A (Figure 2).

In conclusion, we have elaborated a reliable and efficient enantioselective synthesis of the unnatural enantiomer of



Scheme 5. Acid-mediated conversion of cyclopropane **30** to either the pentacyclic avarane **32** or the aureane **33**. MsOH = methanesulfonic acid.

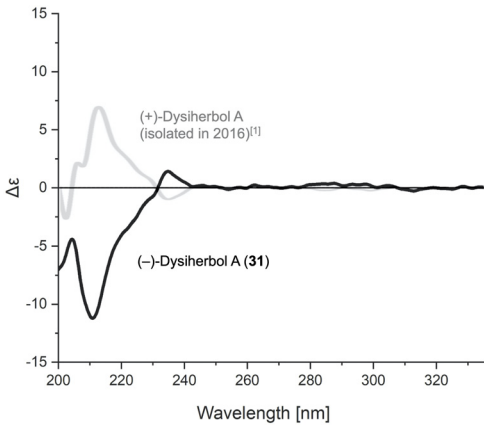


Figure 2. Experimental CD spectra of natural (+)-dysiherbol A (gray)[1] and synthetic (−)-dysiherbol A (black).

dysiherbol A (**31**). Structural assignments were confirmed by X-ray crystal structure analyses.[29] The elaborated sequence (12 steps, 5% overall yield from **13**) features some remarkable steps, such as the Au-catalyzed two-fold cyclization of **10** to build up the carbocyclic core, and the single-step conversion of cyclopropane **30** to the target.[30] As the enantiomer of the chiral ligand used in the chirogenic opening step is readily available, we are now going to use the developed protocol to also prepare substantial amounts of the natural enantiomer of dysiherbol A in order to further explore its biological properties.

The work presented here furthermore demonstrates the importance of total synthesis in the context of structure elucidation. Specifically, we have proven that the structures of the dysiherbols have to be revised, both with respect to their constitution (as cyclic ethers) and their absolute configuration. Noteworthy, the revised structures (Figure 3) now display the same absolute configuration at the stereocenters C8 and C9 as virtually all other avarane meroterpenes from *Dysidea* sp. including the dysideanones.[3]

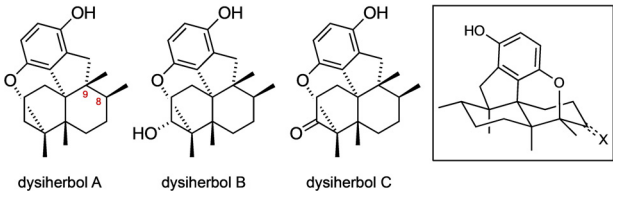


Figure 3. Revised structures of dysiherbols A–C and a general 3D representation idealizing the chair conformation of the *trans*-decalin ring system.

Last but not least we would like to mention that while we were in the process of finalizing this manuscript, a publication by Lu and co-workers appeared describing a total synthesis of (racemic) (±)-dysiherbol A following a different strategy.[31]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclization · enantioselectivity · gold catalysis · natural products · rearrangement

[1] W. H. Jiao, G. H. Shi, T. T. Xu, G. D. Chen, B. B. Gu, Z. Wang, S. Peng, S. P. Wang, J. Li, B. N. Han, W. Zhang, H. W. Lin, *J. Nat. Prod.* **2016**, *79*, 406 – 411.

[2] D. Faustman, M. Davis, *Nat. Rev. Drug Discovery* **2010**, *9*, 482 – 493.

[3] a) P. A. García, Á. P. Hernández, A. San Feliciano, M. Á. Castro, *Mar. Drugs* **2018**, *16*, 292; b) M. Menna, C. Imperatore, F. D'Aniello, A. Aiello, *Mar. Drugs* **2013**, *11*, 1602 – 1643; c) I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, J. G. Urones, *Mini-Rev. Org. Chem.* **2010**, *7*, 230 – 254.

[4] L. Minale, R. Riccio, G. Sodano, *Tetrahedron Lett.* **1974**, *15*, 3401 – 3404.

[5] a) G. Tommonaro, N. García-Font, R. M. Vitale, B. Pejin, C. Iodice, S. Cañadas, J. Marco-Contelles, M. J. Oset-Gasque, *Eur. J. Med. Chem.* **2016**, *122*, 326 – 338; b) T. Namba, R. Kodama, *Mar. Drugs* **2015**, *13*, 2376 – 2389.

[6] P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. V. Arnold, J. Clardy, *J. Org. Chem.* **1980**, *45*, 1435 – 1441.

[7] C.-K. Kim, J.-K. Woo, S.-H. Kim, E. Cho, Y.-J. Lee, H. S. Lee, C. J. Sim, D.-C. Oh, K.-B. Oh, J. Shin, *J. Nat. Prod.* **2015**, *78*, 2814 – 2821.

[8] For previous total syntheses of avarane meroterpenoids, see: a) A. S. Sarma, P. Chattopadhyay, *J. Org. Chem.* **1982**, *47*, 1727 – 1731; b) S. D. Bruner, H. S. Radeke, J. A. Tallarico, M. L. Snapper, *J. Org. Chem.* **1995**, *60*, 1114 – 1115; c) E. P. Locke, S. M. Hecht, *Chem. Commun.* **1996**, 2717 – 2718; d) J. An, D. F. Wiemer, *J. Org. Chem.* **1996**, *61*, 8775 – 8779; e) T. Ling, A. X. Xiang, E. A. Theodorakis, *Angew. Chem. Int. Ed.* **1999**, *38*, 3089 – 3091; *Angew. Chem.* **1999**, *111*, 3277 – 3279; f) M. Nakatani, M. Nakamura, A. Suzuki, M. Inoue, T. Katoh, *Org. Lett.* **2002**, *4*, 4483 – 4486; g) M. Nakamura, A. Suzuki, M. Nakatani, T. Fuchikami, M. Inoue, T. Katoh, *Tetrahedron Lett.* **2002**, *43*, 6929 – 6932; h) J. Sakurai, T. Oguchi, K. Watanabe, H. Abe, S.-i. Kanno, M. Ishikawa, T. Katoh, *Chem. Eur. J.* **2008**, *14*, 829 – 837; i) K. Watanabe, J. Sakurai, H. Abe, T. Katoh, *Chem. Commun.* **2010**, *46*, 4055 – 4057; j) J. Sakurai, T. Kikuchi, O. Takahashi, K. Watanabe, T. Katoh, *Eur. J. Org. Chem.* **2011**, 2948 – 2957; k) T. Katoh, *Heterocycles* **2013**, *87*, 2199 – 2224; l) Y. Sumii, N. Kotoku, A. Fukuda, T. Kawachi, Y. Sumii, M. Arai, M. Kobayashi, *Bioorg. Med. Chem.* **2015**, *23*, 966 – 975; m) T. Katoh, S. Atsumi, R. Saito, K. Narita, T. Katoh, *Eur. J. Org. Chem.* **2017**, 3837 – 3849; n) Y. Takeda, K. Nakai, K. Narita, T. Katoh, *Org. Biomol. Chem.* **2018**, *16*, 3639 – 3647; for a general review on meroterpene total synthesis, see: o) M. Gordaliza, *Mar. Drugs* **2012**, *10*, 358 – 402.

[9] For recent syntheses of polycyclic aureane meroterpenes, see: a) A. Rosales, J. Muñoz-Bascón, E. Roldan-Molina, N. Rivas-Bascón, N. M. Padial, R. Rodríguez-Maecker, I. Rodríguez-García, J. E. Oltra, *J. Org. Chem.* **2015**, *80*, 1866 – 1870; b) K. Speck, R. Wildermuth, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 14131 – 14135; *Angew. Chem.* **2016**, *128*, 14337 – 14341; c) R. Wildermuth, K. Speck, F. L. Haut, P. Mayer, B. Karge, M. Bronstrup, T. Magauer, *Nat. Commun.* **2017**, *8*, 2083; d) K. Speck, T. Magauer, *Chem. Eur. J.* **2017**, *23*, 1157 – 1165; e) F.-L. Haut, K. Speck, R. Wildermuth, K. Möller, P. Mayer, T. Magauer, *Tetrahedron* **2018**, *74*, 3348 – 3357.

[10] Synthesis of carbotetracycles related to dysideanone: M. A. Haque, C. K. Jana, *Chem. Eur. J.* **2017**, *23*, 13300 – 13304.

[11] Synthesis of carbotetracycles related to dysiherbol and cycloaurenone: X. Yin, M. Mato, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2017**, *56*, 14591 – 14595; *Angew. Chem.* **2017**, *129*, 14783 – 14787.

[12] a) M. Vuagnoux-d'Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647 – 9662; b) A. Alexakis, V. Albrow, K. Biswas, M. Augustin, O. Prieto, S. Woodward, *Chem. Commun.* **2005**, 2843.

[13] D. T. Ngoc, M. Albicker, L. Schneider, N. Cramer, *Org. Biomol. Chem.* **2010**, *8*, 1781 – 1784.

[14] 2-Methyl-2-cyclohexenone (**13**) was prepared from 2-methylcyclohexanone by α-bromination and elimination as described by: D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet, P. K. Chiang, *J. Org. Chem.* **1997**, *62*, 6888 – 6896.

[15] B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346 – 353.

[16] Compound **12** was prepared according to: a) U. Sudhir, B. James, S. Joly, M. S. Nair, *Res. Chem. Intermed.* **2003**, *29*, 523 – 532; b) H. Z. Kaplan, V. L. Rendina, J. S. Kingsbury, *J. Org. Chem.* **2013**, *78*, 4620 – 4626.

[17] For the use of TPPA as a substitute for carcinogenic HMPA, see: a) Y. Ozari, J. Jagur-Grodzinski, *J. Chem. Soc. Chem. Commun.* **1974**, 295 – 296; b) C. E. McDonald, J. D. Ramsey, D. G. Sampsell, J. A. Butler, M. R. Cecchini, *Org. Lett.* **2010**, *12*, 5178 – 5181; c) M. Berndt, A. Hölemann, A. Niermann, C. Bentz, R. Zimmer, H.-U. Reissig, *Eur. J. Org. Chem.* **2012**, 1299 – 1302.

[18] D. E. Kim, Y. Zhu, T. R. Newhouse, *Org. Biomol. Chem.* **2019**, *17*, 1796 – 1799.

[19] B. Barnych, J.-M. Vatèle, *Synlett* **2011**, *22*, 2048 – 2052.

[20] Compound **25** was obtained as a mixture of diastereomers by reduction of the corresponding enone with $NaBH_4/CeCl_3$ (see the Supporting Information).

[21] Selected reviews on Au catalysis: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; *Angew. Chem.* **2007**, *119*, 3478 – 3519; c) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028 – 9072; d) W. Zi, F. D. Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567 – 4589; e) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331 – 1367.

[22] For examples of Au-catalyzed allylic substitution reactions, see: a) S. Guo, F. Song, Y. Liu, *Synlett* **2007**, 964 – 968; b) W. Rao, P. W. H. Chan, *Org. Biomol. Chem.* **2008**, *6*, 2426 – 2433; c) P. Kothandaraman, W. Rao, X. Zhang, P. W. H. Chan, *Tetrahedron* **2009**, *65*, 1833 – 1838; d) B. Biannic, T. Ghebreghiorgis, A. Aponick, *Beilstein J. Org. Chem.* **2011**, *7*, 802 – 807; e) P. Mukherjee, R. A. Widenhoefer, *Org. Lett.* **2011**, *13*, 1334 – 1337; f) U. Uria, C. Vila, M. Y. Lin, M. Rueping, *Chem. Eur. J.* **2014**, *20*, 13913 – 13917; for a review, see: g) A. Quintavalla, M. Bandini, *ChemCatChem* **2016**, *8*, 1437 – 1453.

[23] a) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, G. Tosi, *J. Am. Chem. Soc.* **1970**, *92*, 7428 – 7435; b) E. J. Corey, J. Lee, D. R. Liu, *Tetrahedron Lett.* **1994**, *35*, 9149 – 9152.

[24] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53 – 58.

[25] T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233 – 4423.

[26] M. T. Reetz, R. Steinbach, J. Westermann, R. Urz, B. Wenderoth, R. Peter, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 135; *Angew. Chem.* **1982**, *94*, 133.
[27] a) R. W. Newberry, R. T. Raines, *Acc. Chem. Res.* **2017**, *50*, 1838 – 1846; a distance of 2.51 Å is clearly below the sum of the van der Waals radii, see: b) S. S. Batsanov, *Inorg. Mater.* **2001**, *37*, 871 – 885.
[28] J. Cvengros, S. Neufeind, A. Becker, H. Schmalz, *Synlett* **2008**, *2008*, 1993 – 1998.
[29] Deposition numbers 2077903 (for **17**), 2077904 (for **29**), 2077905 (for **11**), 2077906 (**32**), 2077907 (for **18**), 2077908 (for **20**), 2077909 (for **33**), 2077910 (for **26**), 2077911 (for **19**), 2077912 (for *epi*-**11**), 2077913 (for **31**), 2077914 (for **9**), and 2082956 (for **27**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
[30] For an unsuccessful attempt to apply an Au-catalyzed domino process in the synthesis of polycyclic auranes, see: R. Wildermuth, K. Speck, T. Magauer, *Synthesis* **2016**, *48*, 1814 – 1824.
[31] C. Chong, Q. Zhang, J. Ke, H. Zhang, X. Yang, B. Wang, W. Ding, Z. Lu, *Angew. Chem. Int. Ed.* **2021**, https://doi.org/10.1002/anie.202100541; *Angew. Chem.* **2021**, https://doi.org/10.1002/ange.202100541.

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