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Letter

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Total Synthesis of (+)-Panacene

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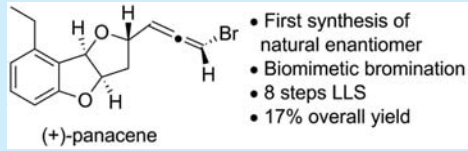
Supporting Information

ABSTRACT: The first total synthesis of the naturally occurring enantiomer of the marine bromoallene (+)-panacene is described. Central to this concise enantioselective synthesis was the use of a Noyori transfer hydrogenation for a Dynamic Kinetic Resolution (DKR) that set the desired absolute stereochemistry. A highly stereoselective Julia coupling was then used to install a Z-configured enyne, which enabled the biomimetic construction of the axially chiral bromoallene.



Although allenic natural products have been known since the late 19th century,[1] it was not until 1977 that a stereochemically defined bromoallene was isolated from natural sources.[2] Meinwald and co-workers reported the isolation of (+)-panacene (**1**) from the Florida sea-hare *Aplysia brasiliana* and originally assigned the structure as the C1-epimer (**2**) (Figure 1).[3] The molecule displayed shark antifeedant activity,

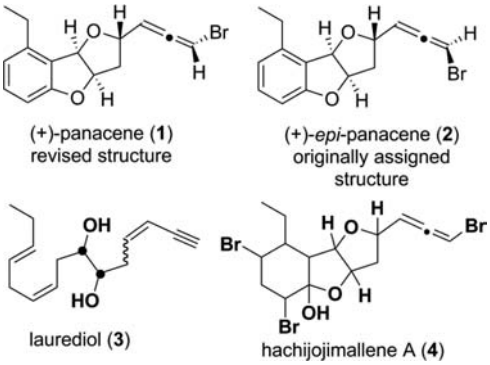
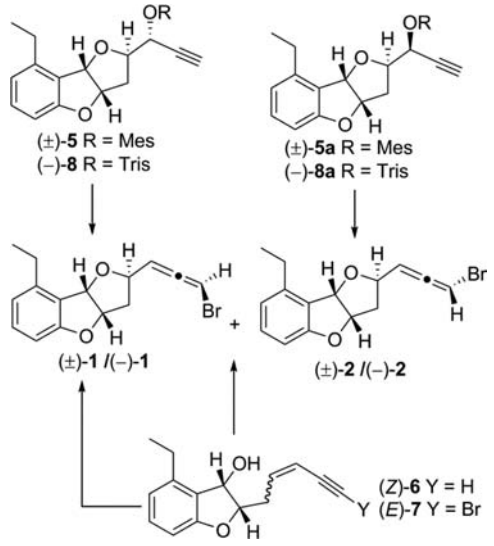


Figure 1. Revised structure of (+)-panacene (**1**) and originally assigned structure (**2**).

and the isolationists hypothesized that panacene was produced by a series of brominative cyclizations of laurediol (**3**) (a fatty acid derived enyne produced in both the *E*- and *Z*-configurations in the red algae upon which the sea hare feeds).[4] More than 30 years later, the proposed biosynthetic intermediate, hachijojimallene A (**4**), was indeed isolated from a *Laurencia* species.[5]

A racemic total synthesis of panacene (±)-**1** was completed as early as 1982 by Feldman and co-workers (Scheme 1).[6] The isomeric bromoallenes (±)-**1** and (±)-**2** were synthesized in 13 steps, with the bromoallene being constructed by the S_N2' displacement of epimeric propargylic mesylates (±)-**5** and (±)-**5a**. The same year, Feldman[7] reported a biomimetically inspired synthesis in which the bromoallene was installed via the brominative etherification of the *Z*-configured enyne (±)-**6**.[8] Disappointingly, that reaction gave a 1:1 mixture of

Scheme 1. Previous Strategies to Panacene (1)



inseparable bromoallene isomers (±)-**1** and (±)-**2**. A recent racemic synthesis by Canesi and co-workers drastically shortened the synthetic sequence and installed the bromoallene moiety by way of an oxymercuration on the *E*-configured bromoenyne (±)-**7**.[9]

The only enantioselective approach reported to date has been Snieckus, Boukouvalas, and co-workers' 15-step synthesis of the non-natural enantiomer, (−)-panacene (−)-(**1**).[10] Those authors subjected an enantioenriched allylic alcohol to Semmelhack-type alkoxypalladation−cyclization−lactonization conditions to build the tricyclic core of (−)-panacene.[11] Chirality transfer by S_N2' displacement of the stereochemically defined propargylic sulfonates (−)-**8** and (−)-**8a** with $LiCuBr_2$ gave the individual epimeric bromoallenes (−)-**1** and (−)-**2**. Careful comparison of the ^1H NMR spectra and the magnitudes of optical rotation of the natural and the synthetic

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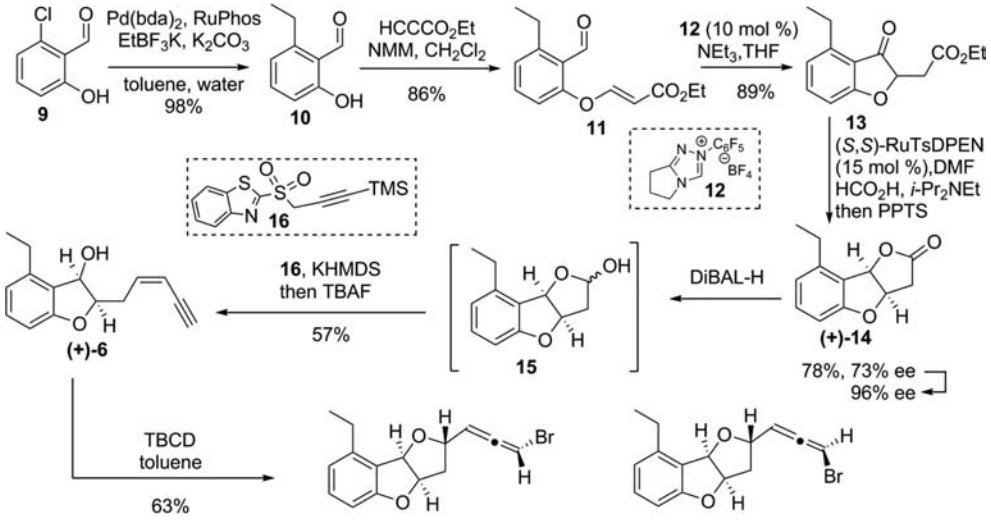
Scheme 2. Synthesis of Panacene (+)-1

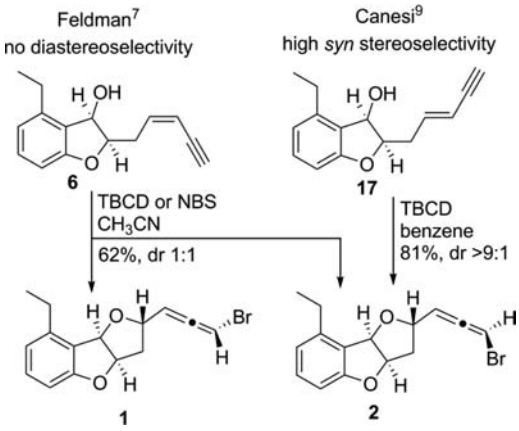


material showed discrepancies, and as such, the structure of (+)-panacene was revised to be **1** shown in Figure 1. The total synthesis of the naturally occurring enantiomer, (+)-panacene (**1**), has not yet been reported. Our continuing interest in both the development of synthetic methods for the construction 2,5-disubsituted-3-oxygenated tetrahydrofurans[12] and brominative cyclizations[13] impelled us to undertake the total synthesis of (+)-panacene (**1**), which is described in this *Letter*.

As depicted in Scheme 2, 6-chlorosalicylaldehyde (**9**) underwent smooth sp^2–sp^3 Suzuki cross-coupling with ethyltrifluoroborate to give **10** in excellent yield.[14] Nucleophilic-catalyzed conjugate addition of **10** onto ethyl propiolate gave the acrylate ester **11** as a single geometric isomer.[15] An intramolecular Stetter reaction was accomplished by the catalytic action of the pentafluorophenyltriazolium salt **12**[16] and diisopropylethylamine. This combination of carbene precursor and base was crucial for obtaining a reproducible yield for this transformation. The racemic benzofuranone **13** was subjected to a Noyori[17] asymmetric transfer hydrogenation with the (*S*,*S*)-RuTsDPEN catalyst which resulted in a Dynamic Kinetic Resolution (DKR) with spontaneous lactonization to give the enantioenriched tricyclic lactone (+)-**14** in 72% yield and 73% *ee*, which increased to 96% after recrystallization.[10] Having rapidly generated the tricyclic core of (+)-panacene, we turned our attention to the biomimetic construction of the bromoallene.

The *N*-bromosuccinimide (NBS) mediated bromoetherification of stereochemically defined enynes has been extensively studied by Braddock and co-workers.[18] For linear enynes, the process in deuterochloroform was found to be highly *syn* selective. Braddock proposed that formation of a cyclic bromonium ion was followed by etherification under stereoelectronic control, with orbital overlap dictating the relative stereochemical relationship between the newly formed stereogenic elements. The logical corollary is that the alkene geometry of the starting enyne dictates the relative stereochemical outcome of the reaction. However, the situation becomes confused when there are pre-existing stereocenters, in which case the correlation between enyne configuration and product stereochemistry appears absent.[7,19] As shown in Scheme 3, Canesi and co-workers were able to transform the *E*-configured enyne **17** into *epi*-panacene **2** with a high degree of selectivity.[9] In contrast, Feldman reported that the reaction of the *Z*-configured enyne **6** with either NBS or tetrabromocyclohexadienone (TBCD) produced **1** and **2** as a 1:1 mixture.[7] The stereoselecivity of the process appeared to correlate with the polarity of the solvent employed. In the former instance, a nonpolar solvent resulted in high *syn* stereocontrol, and in the latter case, a polar solvent resulted in no stereocontrol. We therefore planned to generate the *Z*-configured enyne (+)-**6** and subject it to brominative conditions in a nonpolar solvent.

Scheme 3. Stereochemical Outcomes of Bromoetherifications of 6 and 7



Reduction of (+)-**14** produced the lactol intermediate **15** (Scheme 2), which was treated with KHMDS in the presence of a stoichiometric amount of sulfone **16**.[20] Removal of the silyl protecting group gave the desired *Z*-configured enyne (+)-**6** as a single geometric isomer.

A series of bromoetherifications were performed on a small scale. As expected, TBCD-mediated brominative cyclization of (+)-**6** in the relatively polar solvent, acetonitrile, gave a 1:1 mixture of panacene (+)-**1** and the epimeric bromoallene (−)-**2** (Table 1, entry 1).[21] When the reaction was performed in the nonpolar solvent, cyclohexane, we obtained a 3:1 mixture favoring the naturally occurring epimer (+)-**1**. Pleasingly, when the reaction was performed in toluene the level of selectivity increased and we obtained a 9:1 mixture favoring (+)-**1** (entry 3). On a preparative scale, however, the level of selectivity

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Table 1. Biomimetic Brominative Cyclization of (+)-6

entry	reagent	solvent	temp (°C)	yield (%)	ratio **1:2**
1	TBCD	CH_3CN	rt	64	1:1
2	TBCD	cyclohexane	rt	65	3:1
3	TBCD	toluene	rt	63	9:1[a]
4	TBCD	toluene	rt	63	4:1[b]

[a]Reaction performed on <5 mg scale. [b]Reaction performed on a 14 mg scale.

diminished and a 4:1 mixture in favor of (+)-**1** was obtained. A comparison of ^{1}H and ^{13}C NMR shifts showed that synthetic panacene (+)-**1** was spectroscopically identical to the data reported for the natural product.[22]

In summary, we report the first total synthesis of the naturally occurring enantiomer of the marine natural product (+)-panacene (+)-**1**, in 17% overall yield, in a longest linear sequence of just eight steps. Noyori transfer hydrogenation enabled the absolute stereochemistry of the molecule to be set via a DKR, and Julia-type olefination allowed easy access to the desired *Z*-configured enyne (+)-**6**. Biomimetically inspired brominative cycloetherification installed the axially chiral bromoallene unit in a diastereoselective manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03219.

Experimental procedures, ^{1}H and ^{13}CNMR spectra for all synthesized compounds, HPLC traces (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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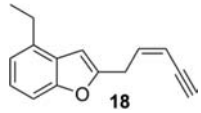
(21) It was important that the TBCD was predried, as even trace amounts of water liberated HOBr. This resulted in a fast elimination reaction to give the benzofuranone **18**.



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(22) The diagnostic signals in the ^{1}H NMR spectra are C3-H, which appears at 5.46 ppm for (+)-**1** and 5.50 ppm for (+)-**2**.

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