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Asymmetric Total Synthesis of (−)-Panacene and Correction of Its Relative Configuration

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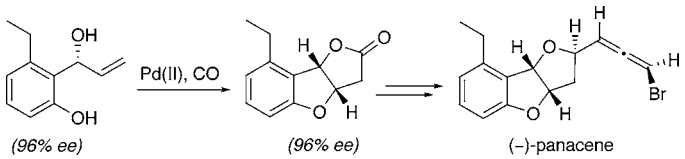
ABSTRACT



The first synthesis of (−)-panacene has been accomplished in concise, highly stereoselective fashion from commercially available 2-methoxy-6-methylbenzoic acid (15 steps, 8.3% overall yield). The synthesis unambiguously establishes the correct relative and absolute configuration of panacene, and demonstrates the serviceability of Pd(II)-mediated tandem intramolecular alkoxycarbonylation−lactonization for the expedient assembly of its tricyclic core, and the dual role of asymmetric alkynylation as an initial source of chirality and as a powerful tool for manipulating diastereoselectivity.

Isolated in 1977 from *Aplysia brasiliana*,[1] a sea hare indigenous to the gulf coast of Florida, panacene (**1** or **2**) holds the prominent position of being the archetypical member of a family of marine bromoallenes that includes over 30 additional members to date.[2,3] Besides a bromoallene moiety, panacene displays an unusual tetrahydrofurobenzofuran core and is believed to serve as a feeding deterrent to sharks and other predatory fish.[1] The combination of novel structural features and intriguing biological activity has generated considerable interest among synthetic chemists.[4] However, only the pioneering work of Feldman led to the total synthesis of (±)-**1** and (±)-**2** along with the assignment of the relative stereochemistry of panacene as **1**.[5] Since the absolute stereochemistry of the bromoallene moiety had previously been assigned as *S* on the basis of Lowe's rule,[1,6] panacene is depicted as **1** throughout the chemical literature.[2,4c,7] We report here the first enantioselective synthesis of **1** and its 1-epimer (*ent*-**2**) by a concise, stereodivergent pathway that unequivocally establishes the relative and absolute configuration of panacene as **2**.

The key elements of our retrosynthetic analysis are outlined in Figure 1. Either of the two bromoallene epimers (**1** or *ent*-**2**) was envisioned to arise at will from the same aldehyde **3** by Carreira's reagent-controlled asymmetric

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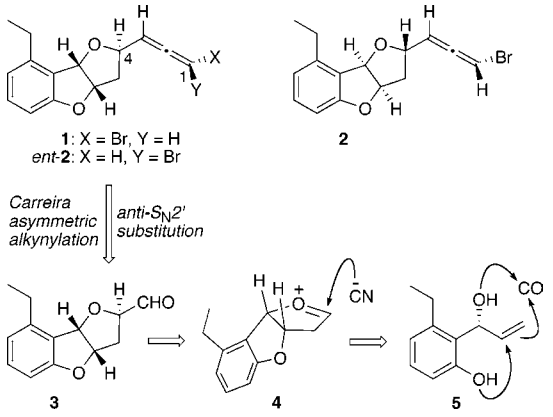
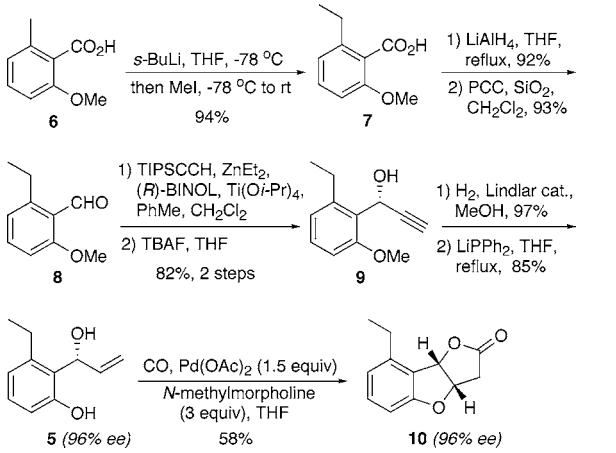


Figure 1. Retrosynthetic analysis of bromoallenes **1** and *ent*-**2**.

alkynylation,[8] followed by sulfonylation and center-to-axis chirality transfer by *anti*-S_N2' displacement with bromide.[9] The desired C4-stereochemistry would be installed by taking advantage of the steric bias provided by oxonium ion **4** for cyanation from the less hindered convex face. Stereocontrolled assemblage of the tricyclic core would rely on Pd(II)-mediated intramolecular alkoxycarbonylation−lactonization[10−12] of alcohol **5**. In light of the anticipated acid sensitivity of **5**, lack of examples involving phenols, and well-documented problems with even less labile substrates,[12] we viewed this tandem process as a central issue to be explored en route to panacene.

Our synthesis began with lateral lithiation−methylation[13] of commercially available 2-methoxy-6-methylbenzoic acid (**6**) to provide the ethyl homologue **7** in excellent yield (Scheme 1). Conversion of **7** to aldehyde **8**, followed by asymmetric alkynylation with Pu's protocol,[14] afforded propargyl alcohol **9** (96% ee) whose *R* configuration was firmly established by X-ray analysis of the 4-bromobenzoate ester of its antipode. Reduction of **9** with Lindlar catalyst over hydrogen and subsequent demethylation with lithium diphenylphosphide[15] furnished phenol **5** in 82% yield over two steps.

Scheme 1. Enantioselective Assembly of the Tricyclic Core



With ready access to **5**, the stage was set to investigate the crucial Pd(II)-mediated alkoxycarbonylation−lactonization. After initial attempts to carry out this reaction under classical catalytic conditions,[11,12a] which led exclusively to side products,[12] the desired tandem cyclization was achieved by using 2 equiv of $Pd(OAc)_2$ in dichloromethane to afford lactone **10** in 55% yield (Scheme 1). Moreover, running the reaction in the presence of an excess of *N*-methylmorpholine improved the yield to 81%. To our dismay, however, the ee of **10** obtained from these experiments was 71% and 60%, respectively,[16] suggesting that inadvertent racemization had occurred. To the best of our knowledge, this finding is unprecedented. While the precise mechanism is unclear, it would appear that racemization of alcohol **5** occurs before alkoxycarbonylation, possibly by a competing Pd-mediated hydrogen transfer process.[17,18] Gratifyingly, further experimentation revealed that the use of THF as a solvent completely suppresses racemization, delivering **10** in reproducibly high ee (96%)[16] and a yield of 58%.

Reductive acylation[19] of **10** provided the separable β and α anomers of **11** (2:1 ratio) in quantitative yield (Scheme 2); the stereochemistry at the anomeric center is inconsequential at this stage since both acetates would provide the same oxonium ion (**4**, Figure 1). Despite the apparent steric bias for cyanide attack from the convex face, attaining the required *exo*-selectivity proved to be a more difficult task than initially anticipated.[20] After exploring several methods,[21] we were pleased to find that the reaction of **11** with

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(16) The ee of **10** was determined by ^{1}H NMR analysis of the Mosher ester of the diol obtained by reduction with $LiAlH_4$; see the Supporting Information for details.

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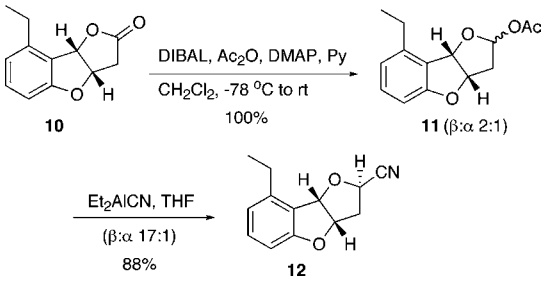
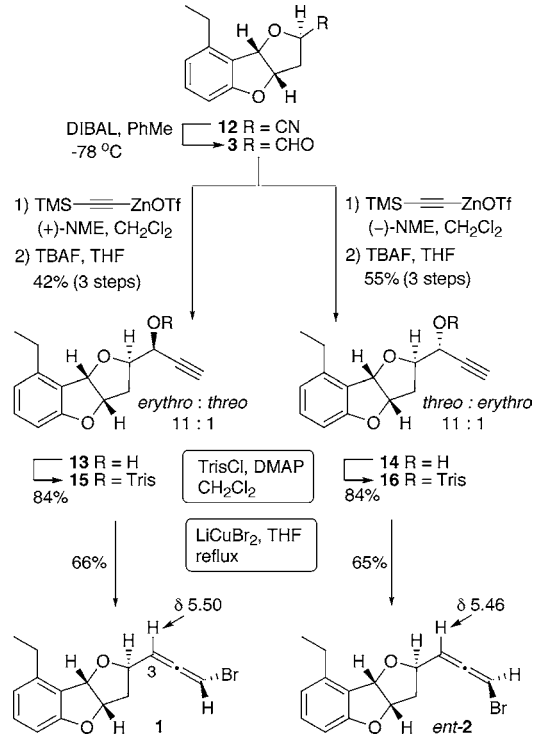
Scheme 2. Stereocontrolled Access to Cyanide **12**



diethylaluminum cyanide[22] proceeded with 17:1 diastereoselectivity in favor of the desired β-anomer **12**, obtained in 88% yield after separation from its α-anomer (5%). The stereochemistry of **12** was deduced from NOE experiments and ultimately confirmed by reduction to the highly labile aldehyde **3** (Scheme 3).[1,5a]

Scheme 3. Stereodivergent Synthesis of **1** and *ent*-**2**



Well aware of the modest diastereoselectivity of alkynylation of (±)-**3** and related tetrahydrofurfurals,[5a,9] we opted for a reagent-controlled, asymmetric variant. Application of Carreira's method[8] enabled stereocontrolled access to either of the two alcohols (**13** or **14**) with equally high selectivity (11:1) overriding completely the innate chirality of the starting aldehyde (Scheme 3). Unlike the alcohols, their 2,4,6-triisopropylphenylsulfonates (trisylates) could be conveniently separated by flash chromatography. Heating **15** with $LiCuBr_2$ in THF[9] provided **1** in 66% yield after HPLC purification from its epimer (*ent*-**2**, ca. 3%) and the propargyl bromides arising from S_N2 substitution (ca. 7%). Likewise, trisylate **16** was transformed to *ent*-**2** in 65% yield.

In accord with Feldman's observations on the racemates,[5a] bromoallenes **1** and *ent*-**2** were virtually indistinguishable by ^1H and ^{13}C NMR with a notable exception being the C3-H appearing at δ 5.50 for **1** and 5.46 for *ent*-**2**. Importantly, the latter value is in perfect agreement with that reported for panacene (δ 5.46).[23] Furthermore, the specific rotation of **1** ($[\alpha]^{22}_D$ +166, *c* 0.16, MeOH), although the same in sign, is substantially lower in magnitude to that of panacene ($[\alpha]^{21}_D$ +382),[1] while that of *ent*-**2** ($[\alpha]^{22}_D$ −340, *c* 0.20, MeOH) is reasonably close in magnitude and opposite in sign.[24] It is therefore beyond doubt that *ent*-**2** is the antipode of natural panacene.

In conclusion, the first synthesis of (−)-panacene has been achieved by a concise, highly stereocontrolled pathway from 2-methoxy-6-methylbenzoic acid (15 steps, 8.3% overall yield). The synthesis establishes the correct stereostructure of panacene as **2**,[25] and demonstrates (i) the dual role of asymmetric alkynylation as an initial source of chirality and as a powerful tool for manipulating diastereoselectivity and (ii) the serviceability of Pd(II)-mediated tandem alkoxycarbonylation−lactonization for the rapid assembly of novel ring systems from labile precursors.

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Supporting Information Available: Experimental procedures and characterization data including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Feldman's assignment of the relative stereochemistry of panacene as **1** is based primarily on the appearance of the C3-H (triplet rather than dd), although it is mentioned (ref 5a) that the chemical shift of C3-H in (±)-**2** (δ 5.46), but not (±)-**1** (δ 5.50), is identical with that of panacene (δ 5.46). The appearance of this peak can indeed be misleading since it depends on shimming. We found that this proton often appears like a triplet in both isomers at 300 and 400 MHz. In addition, we have observed that the two isomers can also be distinguished by the $\Delta\delta$ of C5-α-H. Once again, it is *ent*-**2** (δ 2.48), and not **1** (δ 2.46), that is a perfect match for panacene (δ 2.48, ref 1).

(24) The reported specific rotation of panacene (ref 1) was measured in MeOH (*c* 1.2). We thank Professor Robin Kinnel (Hamilton College, NY) for kindly providing to us these data.

(25) For a timely review on misassigned natural products see: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012.