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Establishment of the absolute configuration of the bioactive marine alkaloid eudistomin X by stereospecific synthesis

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ABSTRACT

A stereospecific synthesis of both enantiomers of the marine alkaloid eudistomin X using the amino acid chiral pool is achieved. Comparison of ^{1}H and ^{13}C NMR chemical shifts of the synthetic product as either the free base, mono-salt or disalt with those reported for the natural product established that the ascidian metabolite was originally characterised as a mono-salt and that the absolute configuration was (10*R*).

Marine organisms of the class Ascidiacea (ascidians) are noted for their abilities to biosynthesise secondary metabolites derived from amino acids.[1,2] After cyclic peptides, one of largest subclasses of metabolites reported are the β-carboline alkaloids, exemplified by eudistomins C (**1**),[3] G (**2**), H (**3**) and I (**4**),[4] woodinine (**5**),[5] eudistalbin A (**6**)[6] and eudistomidin B (**7**)[7] (Fig. 1). Biosynthetically, these alkaloids are derived from tryptophan/tryptamine condensation with a second amino acid, as evidenced by ^{3}H-labelled L-proline incorporation into eudistomins G and H.[8] The eudistomin alkaloids appear to serve ecological roles related to inhibition of larval settlement[9] though much of the discovery and synthetic chemistry attention paid to this class of alkaloid derives from their potent pharmacological activities.[10] Of the 65 β-carboline-containing alkaloids reported from ascidians to date,[11] only 13 contain an asymmetric centre at C-10 with defined configuration, potentially suggestive of the configuration of the second amino acid utilised in the biosynthetic pathway. The oxathiazepine ring containing examples, eudistomins C (**1**), E, F, K, K-sulfoxide, debromo K and L have (10*S*) configuration consistent with biosynthetic incorporation of D-cysteine,[3] as do the structurally-simpler analogues, eudistomidin C[7a] and an *N*-methyl analogue.[12]

The (10*S*) absolute configuration of woodinine (**5**),[5] eudistalbin A (**6**)[6] and eudistomidins B (**7**)[7] and G[7c] is consistent with the

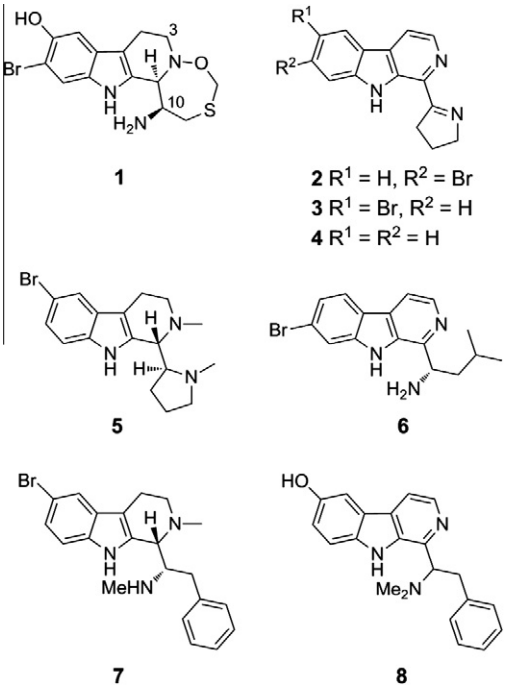

Figure 1. Structures of eudistomins C (**1**), G (**2**), H (**3**) and I (**4**), woodinine (**5**), eudistalbin A (**6**), eudistomidin B (**7**) and eudistomin X (**8**).

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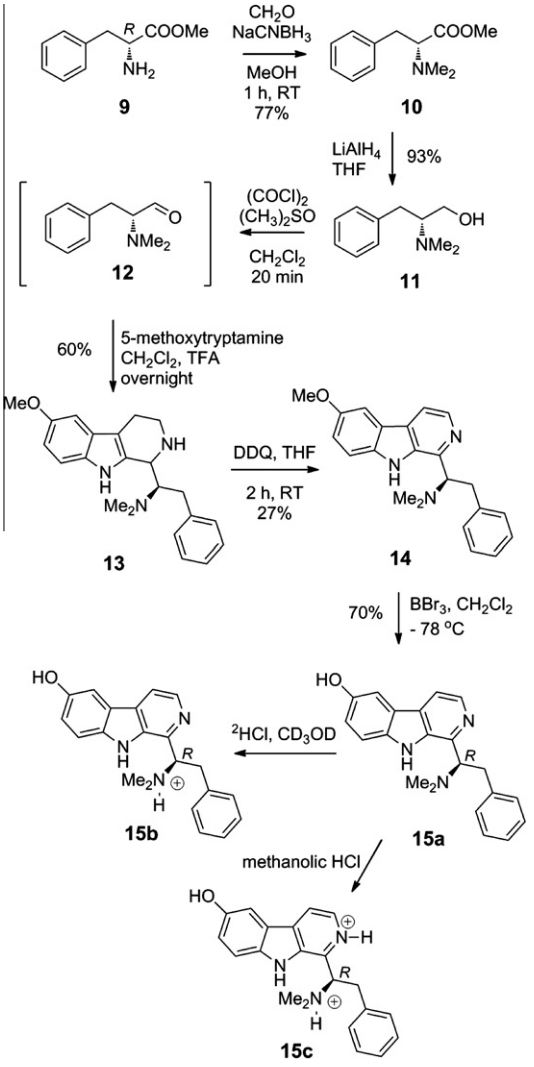
incorporation of L-proline, L-leucine and L-phenylalanine, respectively, during the biosynthesis of these natural products.

The 2003 publication of eudistomin X (**8**) from a Micronesian collection of *Eudistoma* sp. was of interest to us due to it being chiral, but with undefined configuration and that it exhibited relatively potent in vitro antimicrobial properties.[13] We undertook the stereospecific synthesis of both enantiomers of **8**, using the amino acid phenylalanine as the chiral pool source, to address two questions: what is the C-10 configuration of eudistomin X, and is there any influence of the C-10 configuration on the biological activity of the alkaloid? Our synthesis of eudistomin X made use of the classical Pictet-Spengler β-carboline ring-forming reaction between an appropriately substituted (1*H*-indol-3-yl)ethanamine and a chiral aldehyde, derived from phenylalanine.[14] (*R*)-(−)-2-(*N*,*N*-dimethylamino)-3-phenyl-propionic acid methyl ester (**10**) ($[\alpha]_D$ −5.0 (*c* 2.84, ethyl acetate), lit.[15] data for the (*S*) enantiomer $[\alpha]_D$ +4.7 (*c* 2.84, ethyl acetate)) was prepared in 77% yield by reaction of the amino acid methyl ester (**9**) with formaldehyde and sodium cyanoborohydride in methanol (Scheme 1).[16] Reduction of the ester functionality present in **10** using $LiAlH_4$ in THF afforded chiral aminoalcohol **11** ($[\alpha]_D$ +19.3 (*c* 1.00, CH_2Cl_2), lit.[17] data for the (*S*) enantiomer, also as the free base $[\alpha]_D$ −18.4 (*c* 1.00, CH_2Cl_2)) in 93% yield. Oxidation under Swern conditions yielded unstable (*R*)-2-(dimethylamino)-3-phenylpropanal (**12**) that was used in the next step without purification. Pictet-Spengler reaction of chiral aldehyde **12** with 5-methoxytryptamine yielded the expected tetrahydro-β-carboline (**13**) as a yellow foam in 60% yield. The subsequent sequence of oxidation with DDQ in THF (27% yield), de-*O*-methylation using BBr_3 in dichloromethane (70% yield), and finally silica gel column chromatography using 5% MeOH/CH_2Cl_2 with 2% NH_3 as eluent afforded (10*R*)-eudistomin X as the free base (**15a**). The optical rotation observed for **15a** ($[\alpha]_D$ −106.1 (*c* 0.49, MeOH)) was substantially different from that reported for the natural product ($[\alpha]_D$ −7.0 (*c* 0.49, MeOH)).[13] Comparison of the ^1H and ^{13}C NMR data observed for our synthetic **15a**[18] with



Scheme 1. Total synthesis of (10*R*)-eudistomin X (**15a**).

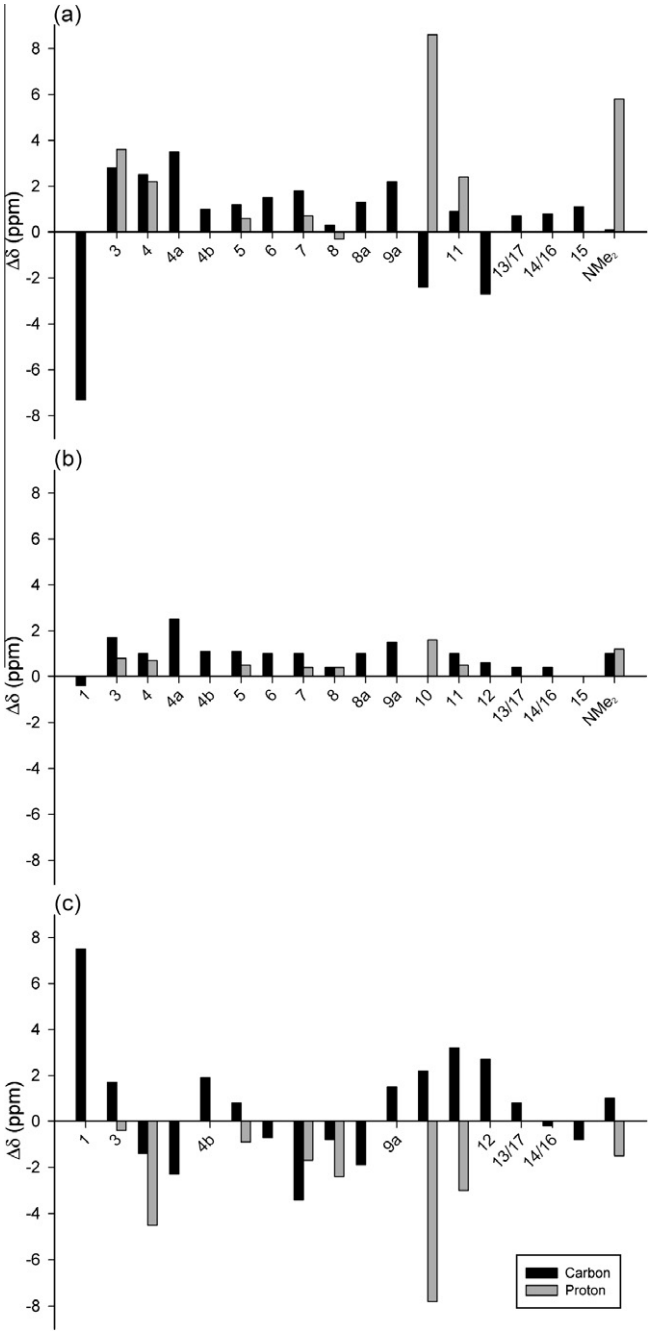


Figure 2. Plots of difference observed for ^1H and ^{13}C NMR data ($\Delta\delta = \delta_{literature} - \delta_{synthetic}$) varying by alkaloid numbered position for (a) free base **15a**, (b) mono-salt **15b**, and (c) dihydrochloride **15c** compared to published data for eudistomin X.[13] All data acquired in the same solvent (CD_3OD) at 6 mg/mL concentration. Note that $\Delta\delta$ ^1H values have been arbitrarily scaled by a factor of 10 for clarity.