Synthetic Confirmation of the Absolute Stereochemistry at C(10), C(11), and C(13) of Palytoxin

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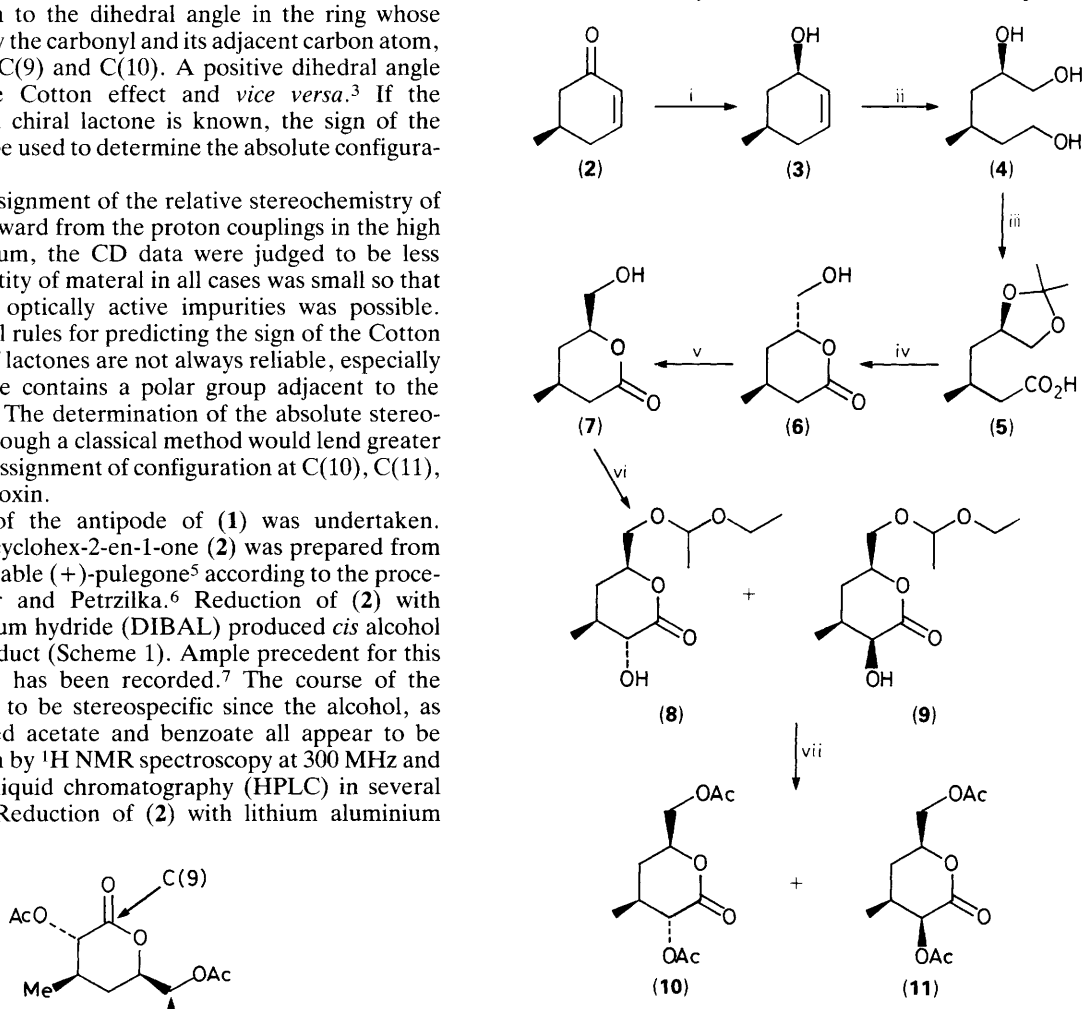
The absolute stereochemistry at C(10), C(11), and C(13) of palytoxin has been determined by NMR spectroscopy and circular dichroism.

The absolute stereochemistry of palytoxin, an extraordinarily toxic compound derived from marine coelenterates of the genus *Palythoa*, has been described in recent communications.[1] Work in this Department has shown that ozonolysis of *N*-(*p*-bromobenzoyl)palytoxin in aqueous ethanol at 0 °C followed by treatment with excess sodium borohydride and acetylation produces a mixture of acetates.[2] One of the products of this degradation was lactone diacetate (**1**), which incorporates carbon atoms 9 to 14 of palytoxin (the structure of palytoxin is given in Figure 1). The relative and absolute stereochemistry of (**1**) (10*S*, 11*R*, 13*R*) was first determined through high field ^{1}H NMR spectroscopy and circular dichroism (CD) data. The Cotton effect in the CD of lactones is opposite in sign to the dihedral angle in the ring whose vertex is defined by the carbonyl and its adjacent carbon atom, in the case of (**1**) C(9) and C(10). A positive dihedral angle causes a negative Cotton effect and *vice versa*.[3] If the conformation of a chiral lactone is known, the sign of the Cotton effect can be used to determine the absolute configuration.

Although the assignment of the relative stereochemistry of (**1**) was straightforward from the proton couplings in the high field NMR spectrum, the CD data were judged to be less reliable. The quantity of materal in all cases was small so that contamination by optically active impurities was possible. Also, the empirical rules for predicting the sign of the Cotton effect in the CD of lactones are not always reliable, especially when the molecule contains a polar group adjacent to the lactone carbonyl.[4] The determination of the absolute stereochemstry of (**1**) through a classical method would lend greater confidence to the assignment of configuration at C(10), C(11), and C(13) of palytoxin.

The synthesis of the antipode of (**1**) was undertaken. (+)-(*R*)-5-Methylcyclohex-2-en-1-one (**2**) was prepared from commercially available (+)-pulegone[5] according to the procedure of Oppolzer and Petrzilka.[6] Reduction of (**2**) with di-isobutylaluminium hydride (DIBAL) produced *cis* alcohol (**3**) as the sole product (Scheme 1). Ample precedent for this type of selectivity has been recorded.[7] The course of the reduction appears to be stereospecific since the alcohol, as well as the derived acetate and benzoate all appear to be homogeneous both by ^{1}H NMR spectroscopy at 300 MHz and by high pressure liquid chromatography (HPLC) in several solvent systems. Reduction of (**2**) with lithium aluminium hydride or with 9-borabicyclo[3.3.1]nonane was less selective and produced mixtures containing small amounts of the *trans* alcohol (85/15 and 98/2, respectively). Ozonolysis of (**3**) in methanol at −78 °C followed by immediate treatment with an excess of sodium borohydride furnished triol (**4**). Conversion to the acetonide and oxidation to the carboxylic acid (**5**) with pyridinium dichromate[8] in *N*,*N*-dimethylformamide took place uneventfully. Acid catalysed hydrolysis of the protecting group produced an acid-diol which lactonized spontaneously to (**6**) during workup. The stereochemistry at C(13) (palytoxin numbering) was inverted by conversion of the primary alcohol function in (**6**) to the tosylate followed by treatment with the sodium salt of benzyl alcohol.[9] The intermediate epoxyester



Scheme 1. *Reagents and conditions*: i, (a) DIBAL; (b) NaF, H_2O; 72%; ii, (a) O_3; (b) $NaBH_4$; 68%; iii, (a) MeCOMe, *p*-TsOH (Ts = $MeC_6H_4SO_2$); (b) pyridinium dichromate (PDC); 85%; iv, (a), 1.0 M HCl, tetrahydrofuran (THF) (1/1); 93%; v, (a) *p*-TsCl, Et_3N; (b) $PhCH_2ONa$; (c) $BF_3{\cdot}Et_2O$; 74%; vi, (a) $MeCH_2OCH{-}CH_2$, *p*-TsOH; (b) lithium diisopropylamide (LDA), THF; MoOPh; vii, (a) H^+; (b) Ac_2O, pyridine (pyr); 58%.

(**1**)

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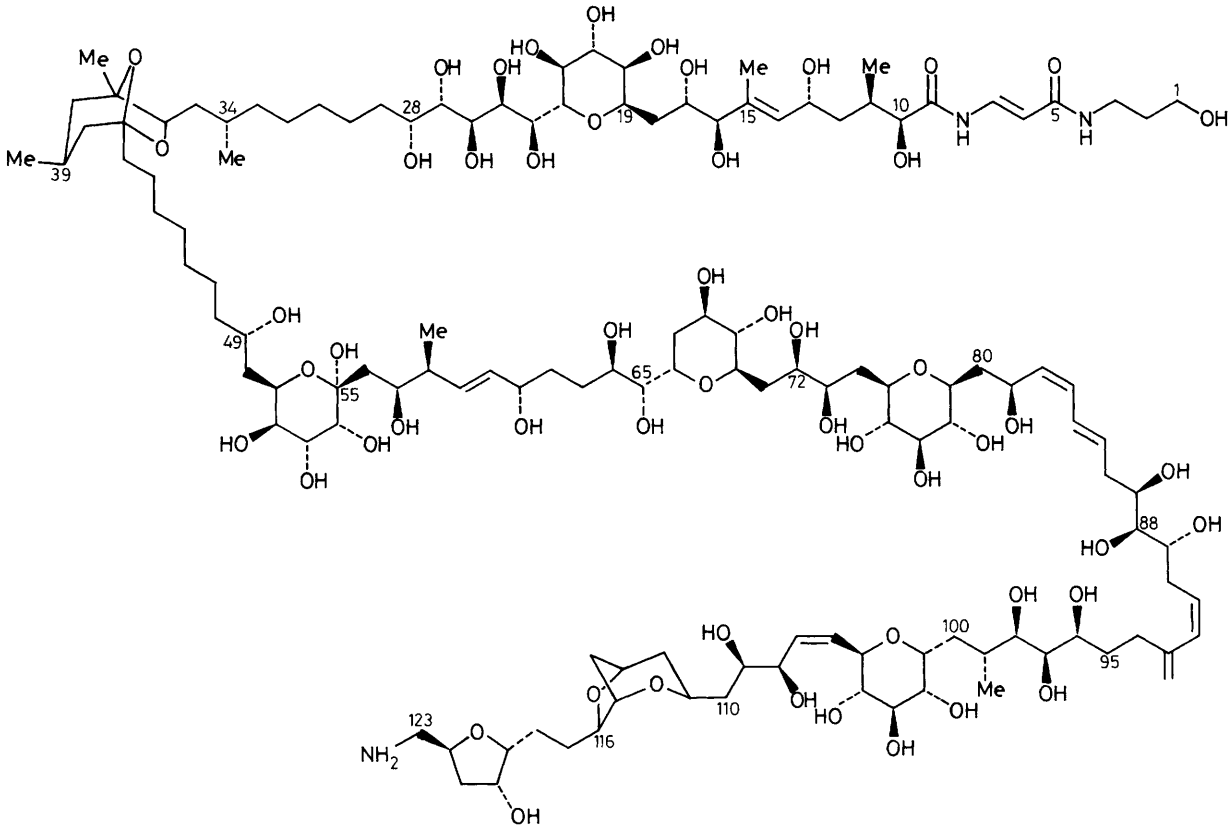

Figure 1. Palytoxin.

was unstable and slowly rearranged to (**7**) upon standing. The conversion to (**7**) was completed by treatment with a catalytic amount of boron trifluoride etherate.

The final synthetic transformation required the introduction of a hydroxy function adjacent to the carbonyl carbon. The C(11) methyl group was expected to direct the incoming oxidant to produce the *trans* alcohol. Protection of (**7**) as the 2-ethoxyethyl ether followed by deprotonation and reaction with freshly prepared Vedejs' reagent[10] furnished a 8.5 : 1 mixture of (**8**) and its C(10) epimer (**9**). Hydrolytic removal of the protecting group and acetylation produced a mixture of epimeric diacetates(**10**) and (**11**) which were readily separable by HPLC.

The ^{1}H NMR spectra of diacetates (**1**) and (**10**) were identical. The CD spectrum of (**10**) shows a simple band with a negative maximum at 222 nm. The CD spectrum of (**1**) has a positive maximum at 224 nm, so that (**1**) and (**10**) are enantiomers. Since the absolute stereochemistry of (+)-pulegone is *R* it follows that the absolute stereochemistry of (**10**) is 10*R*, 11*S*, and 13*R*, and that the assignment of (**1**) was correct.

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