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Study on the absolute configuration of (−)-palau'amine

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ABSTRACT

The absolute stereochemistry of the immunosuppressive pyrrole–imidazole alkaloid (−)-palau'amine from the marine sponge *Stylotella aurantium* is analyzed by CD spectroscopy. With the help of a series of model compounds it is shown that the CD spectrum of (−)-palau'amine can be explained based on the assumption that the pyrrolopyrazinone partial structure is planar in 2,2,2-trifluoroethanol (TFE). Surprisingly, the natural product (−)-dibromophakellin shows the opposite Cotton effect, despite exhibiting the same absolute configuration.

1. Introduction

Pyrrole–imidazole alkaloids constitute a prominent, biogenetically related group of marine natural products.[1] In 1993, Scheuer and co-workers published the structure of the hexacyclic alkaloid (−)-palau'amine (**1**, Fig. 1) from the marine sponge *Stylotella aurantium*.[2]

(−)-Palau'amine (**1**) exhibits a challenging architecture, in addition to immunosuppressive and cytotoxic properties. The relative stereochemistry of (−)-palau'amine (**1**) was revised in 2007 independently by the Köck[3] and Quinn[4] groups who discovered that the five-membered rings C and E are *trans*-fused. In 2010, Baran and co-workers published the first total synthesis of racemic palau'amine.[5] However, the absolute stereochemistry of **1** has remained unknown until today.

2. Results

In the absence of an X-ray crystal structure and with research on the enantioselective total synthesis still ongoing, we investigated the absolute stereochemistry of (−)-palau'amine (**1**) by CD spectroscopy. Comparative analysis of a series of model compounds of known geometry and absolute configuration results in our proposal that (−)-palau'amine (**1**) and (−)-dibromophakellin (**2**)[6] share the same absolute configuration at C10.[7]

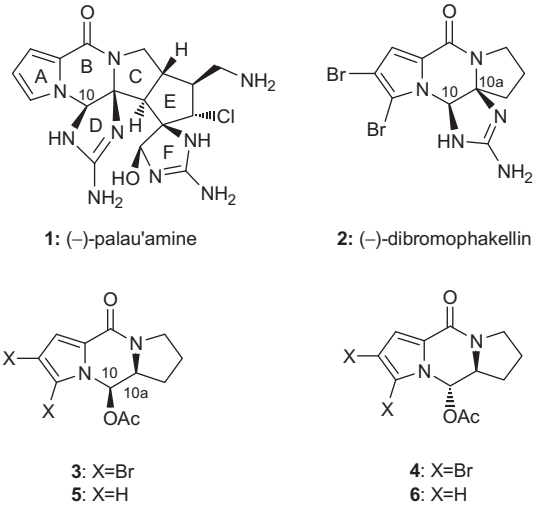

Figure 1. Marine natural products (−)-palau'amine (**1**), (−)-dibromophakellin (**2**), and the tricyclic model compounds **3**–**6**.[9]

We used 2,2,2-trifluoroethanol (TFE) as solvent, because CD spectra of our compounds experience a red-shift and are more dispersed at wavelengths above 240 nm when compared to CD spectra taken in MeCN or MeOH. While we were able to calculate the CD spectra of the less complex tetracycles (−)-dibromophakellin (**2**) and (−)-dibromophakellstatin in MeOH following the quantum

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chemical time dependent density functional theory,[8] the CD spectrum of (−)-palau'amine (**1**) in TFE resisted any such approach. Therefore, our study presented here is experimental.

Originally, we expected the CD spectra of the natural products (−)-palau'amine (**1**) and (−)-dibromophakellin (**2**) to be very similar. But this was not the case (Fig. 2). Compound **1** solely shows a positive Cotton effect at 280 nm ($\Delta\varepsilon$ = +3.5 L mol^{-1} cm^{-1}) as a single broad peak, whereas for (−)-dibromophakellin (**2**) a trough at 251 nm ($\Delta\varepsilon$ = −4.6) and a shoulder at 286 nm ($\Delta\varepsilon$ = −1.9) are found. As the key difference, the band at about 250 nm is absent in the CD spectrum of (−)-palau'amine (**1**). Instead the CD curve of **1** crosses the zero line at 249 nm.

Interestingly, the CD spectra of the tetracyclic (−)-dibromophakellin (**2**, $\Delta\varepsilon$ = −4.6 L mol^{-1} cm^{-1} at 251 nm, −1.9 at 285 nm) and of the tricyclic dipyrrolopyrazinone **4** (+4.9 at 252, +1.0 at 280 nm) behave almost mirror-like above 240 nm, despite different structures (Fig. 2). The CD spectra of (−)-dibromophakellin (**2**) and of our tricyclic model compounds are governed by the twist of the pyrrole carboxamide moiety (dihedral angle $\varphi_{C6-C5a-C5-O}$) and by the configuration of the acetal center C10 (dihedral angle $\varphi_{C8-N9-C10-X}$).[9] Pyrrole carboxamide twist is a consequence of the sp^3 bridge-head carbon C10a. (−)-Dibromophakellin (**2**) exhibits the negative dihedral angles −8° and −52° for the bonds $\varphi_{C6-C5a-C5-O}$ and $\varphi_{C8-N9-C10-N}$, respectively (X-ray analysis[10]). The corresponding dihedral angles of dipyrrolopyrazinone **4** are both positive and estimated as +12° and +35° (MM2 molecular modeling). The diastereomeric dipyrrolopyrazinone **3** with an axial instead of an equatorial 10-OAc group (dihedral angle $\varphi_{C8-N9-C10-OAc}$ −87° by MM2 estimation) exhibits a stronger CD absorption at 285 nm ($\Delta\varepsilon_{285}$ = +7.4), whereas the 'twist band' ($\Delta\varepsilon_{253}$ = +3.2) remains almost unchanged (Fig. 3). Recent CD spectra of bicyclic pyrrolopyrazinones with an axial alkyl substituent such as the natural products (−)-cyclooroidin and (−)-longamide B methyl ester are also in accordance with this observation.[11]

It is possible to estimate the effect of $\varphi_{C8-N9-C10-OAc}$ on $\Delta\varepsilon_{285}$ in the case of the diastereomeric dipyrrolopyrazinones **3** and **4**. We synthesized reference compound **8** from precursor **7**[12] under Mitsunobu conditions (Scheme 1).[13] We found that the contribution of a hydrogen substituent to the CD absorption at 285 nm (+2.4) is smaller than that of an axial OAc substituent, but greater than that of an equatorial OAc group (Fig. 3). At about 255 nm, the intensity of the twist-induced Cotton effects of compounds **3**, **4**, and **8** is comparable.

The absence of the twist band (≈255 nm) in the CD spectrum of (−)-palau'amine (**1**) led us to the hypothesis that the pyrrole carboxamide moiety of **1** is nearly planar in TFE. Molecular modeling (MM2) studies do not contradict this, because the energy difference between planar and twisted arrangements of the pyrrole and carboxamide moieties in the gas phase is below the accuracy of the method. To support this hypothesis, we could have tried to construct a molecule with a planar pyrrole carboxamide moiety and a stereogenic acetal carbon. However, this would require the conversion of C10a to an sp^2-hybridized carbon which would then

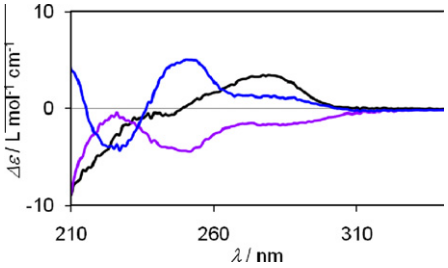


Figure 2. CD spectra of (−)-palau'amine (**1**, black), (−)-dibromophakellin (**2**, violet), and ABC tricycle **4** (blue) in TFE.

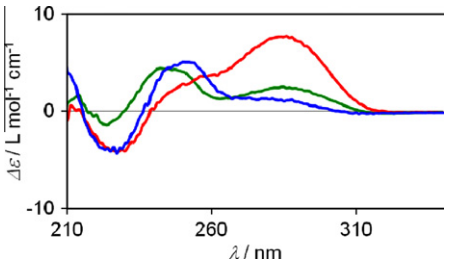
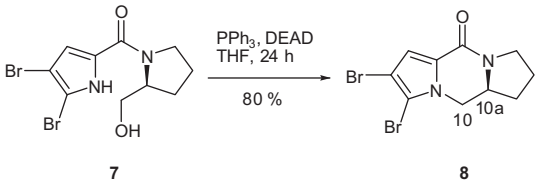


Figure 3. CD spectrum of the 10-unsubstituted model compound **8** (green), compared to the CD spectra of the dibrominated model compounds **3** (red), and **4** (blue) in TFE.



Scheme 1. Mitsunobu cyclization to the C10-unsubstituted model tricycle **8**.

be in conjugation with the pyrrole carboxamide π-system, altering its CD absorption properties.

Fortunately, there is another approach to the problem. For the prediction of the CD spectrum of a non-brominated compound with a planar pyrrole carboxamide moiety, the CD spectra of the non-brominated model compounds **5** and **6** with identical helicities can be subtracted from each other, eliminating absorptions caused by the twist component.[14] The remaining curve reflects the difference of the dihedral angle components of the acetals. Since the dihedral angle $\varphi_{C8-N9-C10-(10-OAc)}$ of **6** is positive, that difference corresponds to the addition of CD absorptions of planarized ABC tricycles with averaged acetal dihedral angles of −90° and −30° (Fig. 4). Therefore, the arithmetic average of the CD curve of **5** and the CD curve of *ent*-**6** should be a good approximation to the CD spectrum of (−)-palau'amine (**1**), the acetal dihedral angle of which is to be expected around −60°. As shown above with (−)-dibromophakellin (Fig. 2), the effect of acetoxy and guanidine groups on the CD spectra is comparable.

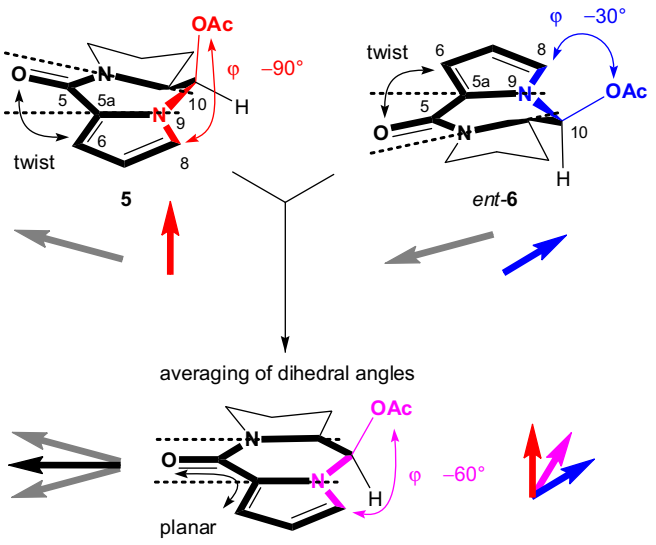


Figure 4. Approximation of the dihedral angles of a planar (−)-palau'amine (**1**) by averaging the dihedral angles of the model tricycles **5** and *ent*-**6**. Pyrrole rings are always in front of the drawing plane, pyrrolidine rings behind.

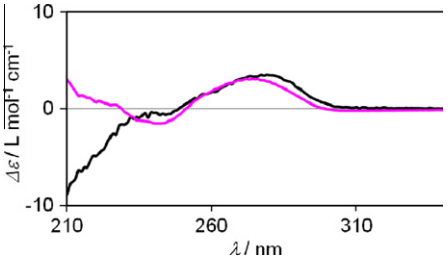


Figure 5. CD spectrum of (−)-palau'amine (**1**, black), compared to the averaged CD spectra of the model compounds **5** and *ent*-**6** (pink) in TFE.

We were surprised how well the CD spectrum of (−)-palau'amine (**1**) above 240 nm is in agreement with the arithmetic average (CD(**5**) + CD(*ent*-**6**))/2 (Fig. 5), resulting in an almost exact overlap. Therefore, we propose that (−)-palau'amine (**1**) possesses the same absolute stereochemistry as (−)-dibromophakellin (**2**), despite opposite signs of $\Delta\varepsilon_{280}$ in TFE. Scheuer already assumed that (−)-palau'amine (**1**) should have the same absolute configuration as (−)-monobromophakellin hydrochloride because of positive CDs at 280 nm in both cases.[2] That assignment is in agreement with the conclusions from our experimental study.

Acknowledgment

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11. The band at 280 nm of (−)-cyclooroidin and (−)-longamide B methyl ester is less pronounced, apparently because the electron-withdrawing OAc group is replaced by an alkyl group. (a) Patel, J.; Pelloux-Léon, N.; Minassian, F.; Vallée, Y. *Tetrahedron Lett.* **2006**, *47*, 5561–5563; See also (b) Fattorusso, E.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **2000**, *41*, 9917–9922.
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13. A solution of diethylazodicarboxylate (0.59 mL, 40% in toluene) was added to a solution of alcohol **7** (352 mg, 1.00 mmol) and PPh_3 (340 mg, 1.30 mmol) in THF (17 mL) at rt. After 24 h, the solvent was removed in vacuo and the crude material was purified by column chromatography (silica gel, ethyl acetate/hexane, 9:1) yielding **8** as colorless crystals (80%). Mp 170 °C (decomp.). $[\alpha]_{365}^{25} = 23.2°$ (c = 10.0 mg/mL, TFE). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.72–1.82 (m, 1H, 1-H_a), 1.88–2.07 (m, 1H, 2-H_a), 2.10–2.16 (m, 1H, 2-H_b), 2.26–2.32 (m, 1H, 1-H_b), 3.57 (ddd, J = 11.7, 9.5, 7.7 Hz, 1H, 3-H_a), 3.77 (ddd, J = 11.7, 9.2, 2.6 Hz, 1H, 3-H_b), 4.02 (m, 1H, 10a-H), 3.59 (dd, ^2J = 12.1 Hz, ^3J = 12.1 Hz, 1H, 10-H_a), 4.39 (dd, 1H, ^2J = 12.1 Hz, ^3J = 4.0 Hz, 1H, 10-H_b), 6.95 (s, 1H, 6-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0 (C2), 30.4 (C1), 44.1 (C3), 49.2 (C10), 56.4 (C10a), 100.3 (C7), 106.3 (C8), 114.7 (C6), 126.8 (C5a), 156.3 (CO). UV (TFE): λ_{max} (log ε) = 290 (0.60). HREIMS calcd ($C_{10}H_{10}{}^{79}Br_2N_2O$) 331.9160, found 331.9162.
14. On replacement of the pyrrole bromine substituents by hydrogen, the long wave CD maxima of our ABC model compounds **3** and **4** experience a blue-field shift of about 12 nm (compounds **5**, **6**). See Ref. 9.