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Stereoselective synthesis of the C33–C44 fragment of palau'amide

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Abstract

An efficient stereoselective synthesis of the C33–C44 fragment of palau'amide is described using a Sharpless asymmetric epoxidation, a regioselective nucleophilic ring opening of the epoxide, a Grignard reaction and a Luche stereoselective reduction of a keto compound as the key steps.

Keywords: Palau'amide; Cytotoxic; Stereoselective; Sharpless asymmetric epoxidation; Luche's stereoselective reduction

In 2003, Moore and co-workers reported the isolation, structure elucidation, and biological activity (cytotoxicity to KB cells, $IC_{50} = 13$ nM) of palau'amide (**1**), an architecturally novel cyclic depsipeptide from the bioassay-guided fractionation of the extract species of *Lyngbya* from Palau.[1] Key structural elements include a five amino acid backbone fused together in a macrocycle and a novel polyketide chain incorporated into the molecule. The molecular architecture of the polyketide comprises three contiguous chiral centres, a 1,3-*syn* diol flanking an *anti* methyl group, a terminal alkyne and an α,β-unsaturated acid (Fig. 1). Potent biological activity coupled with unique structural features and limited availability prompted us to explore the synthesis of palau'amide (**1**). The first synthesis of palau'amide was reported by Ma et al.[2] The polyketide chain was synthesized following Oppolzer's protocol and utilized a vinylogous Mukaiyama aldol reaction as a key reaction. The '*anti*' aldolization strategy to build the C38 and C39 stereocentres was not successful. '*syn*' Aldolization and Mitsunobu inversion were required to obtain the required stereochemistry. However, the data for the synthetic palau'amide (**1**) did not match the reported values. A highly stereoselective and practical approach to construct the three contiguous chiral centres present in the

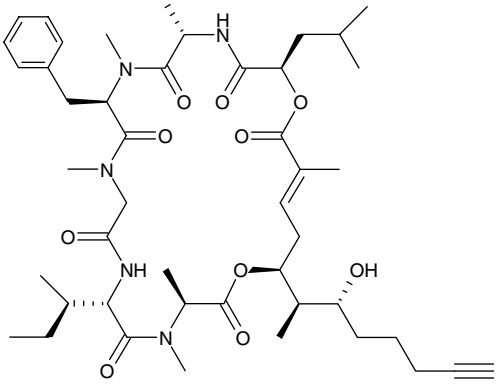

Fig. 1. Structure of palau'amide **1**.

C33–C44 fragment was therefore required to establish conclusively the structure of the natural product and to furnish additional analogues for testing.

Our retrosynthetic analysis of fragment **2** (Scheme 1) revealed that it could be synthesized from intermediate **3** which, in turn, could be prepared from fragment **4** following oxidation and a Grignard reaction with pentynylmagnesium bromide. Intermediate **4** was envisaged to be obtained by regioselective opening of epoxide **5**, which in turn could be prepared from commercially available 1,3-propane diol following a known protocol.

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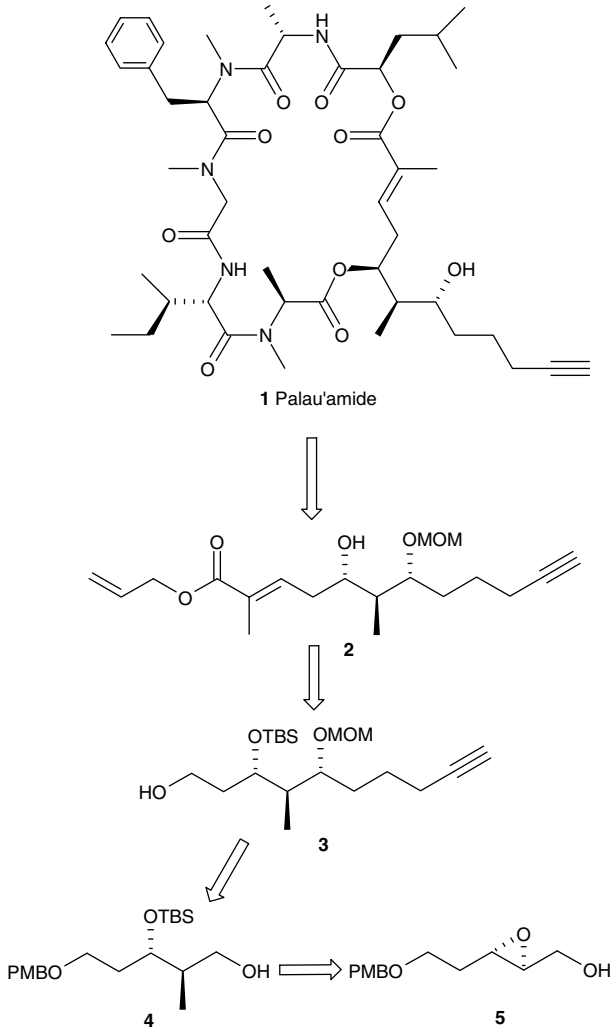
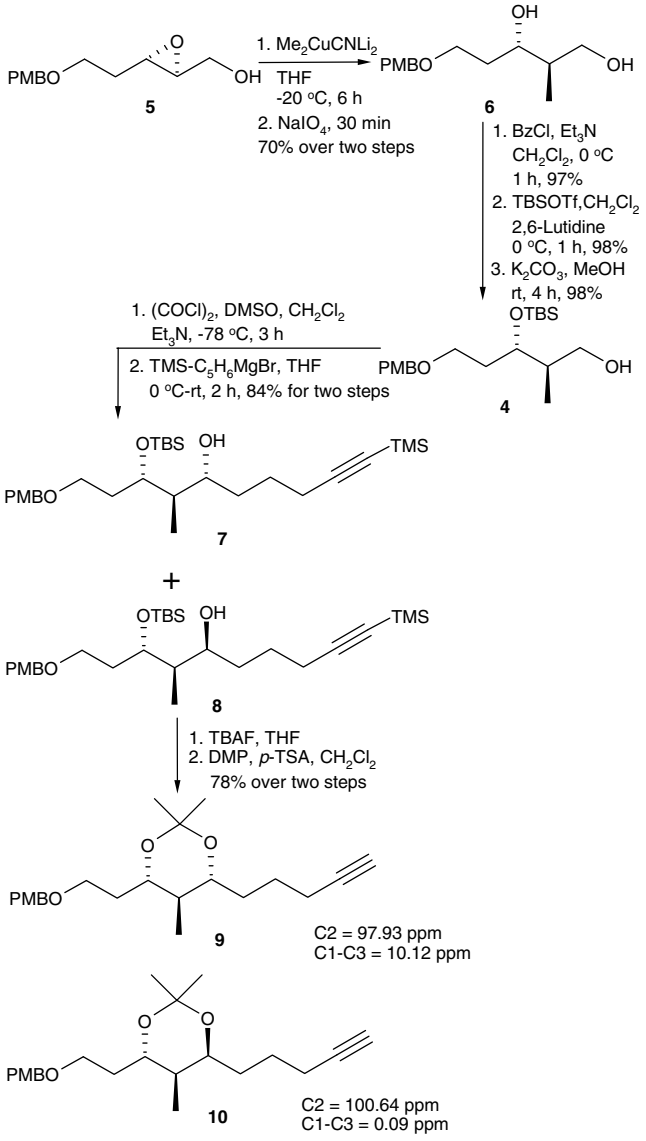


Scheme 1. Retrosynthetic analysis.



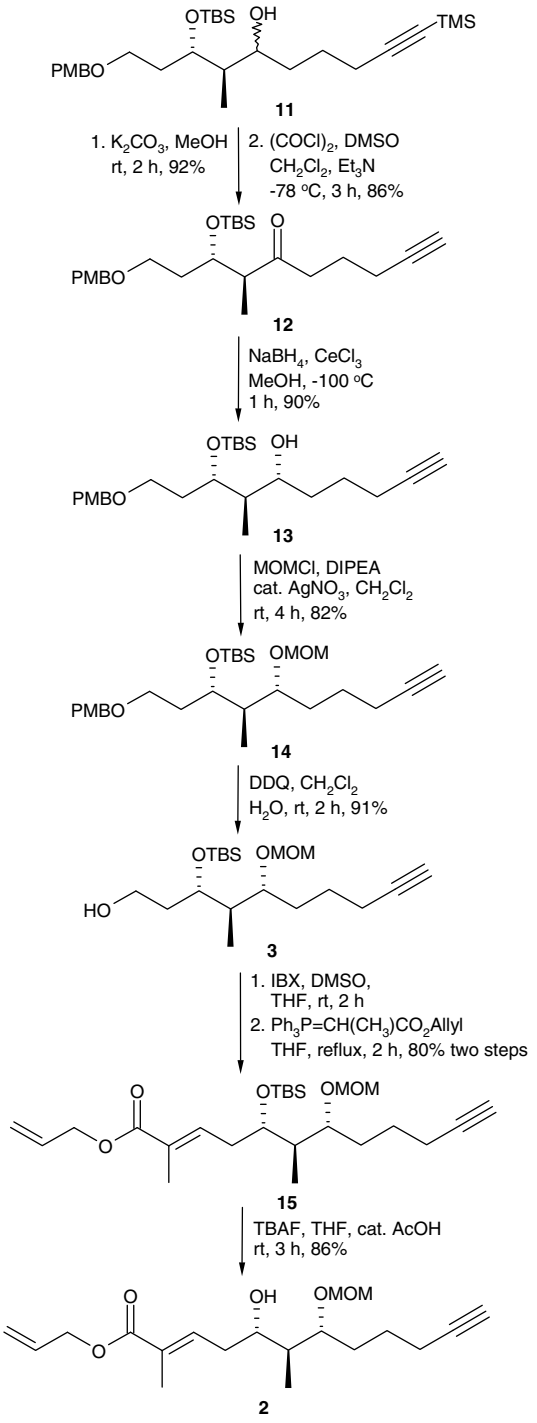
Scheme 2. Synthesis of **7** and **8**.

Chiral epoxide **5** was elaborated from 1,3-propane diol via a five-step sequence following the literature methods.[3] A key reaction was the Sharpless asymmetric epoxidation with titanium tetraisopropoxide and *t*-butylhydroperoxide in the presence of (−)-DIPT. The enantiomeric excess of epoxide **5**[4] was determined by HPLC analysis[5] and was found to be greater than 97%. Regioselective nucleophilic opening of **5** with $Me_2CuCNLi_2$[6] afforded a mixture of the desired 1,3-diol **6** and the corresponding 1,2-diol in a ratio of 8:1. The minor product was easily removed by treatment with $NaIO_4$ (Scheme 2). Chemoselective benzoylation of the primary hydroxyl group of **6**, followed by silylation of the secondary hydroxyl group using TBSOTf[7] and 2,6-lutidine in dichloromethane and subsequent hydrolysis of the benzoyl ester, afforded alcohol **4**[8] in excellent yield.

Oxidation of the primary hydroxyl group of **4** under Swern oxidation conditions[9] gave an aldehyde, which on treatment with trimethylsilyl protected pentynylmagnesium bromide in THF at 0 °C furnished diastereomeric alcohols **7** and **8** in a ratio of 1:1.5. The stereochemistry at the newly created stereogenic centers in **7**[10] and **8**[11] was assumed to be *R* and *S* resulting from 1,3-asymmetric induction based on a model proposed by Evans and co-workers.[12] This assumption was further confirmed using the method reported by Rychnovsky and co-workers.[13] Accordingly, cleavage of the silyl ether in **7** and **8** produced diols, which were protected as 1,3-diol acetonides **9** and **10** by treatment with dimethoxypropane in the presence of a catalytic amount of *p*-TSA. Since the C(2)-acetals in **9** and **10** showed ^{13}C chemical shifts at δ 97.94 and 100.62 ppm and the differences between the two ^{13}C methyl signals in **9** and **10** were 10.12 and 0.09 ppm, respectively, the *syn* and *anti* juxtaposition of the acetonide moieties was confirmed (Scheme 2).

To obtain the desired alcohol **13** exclusively, the mixture of alcohols **7** and **8** was treated with K_2CO_3 and MeOH to effect TMS deprotection. The resulting secondary hydroxyl group was oxidized by the Swern oxidation protocol to give keto compound **12**, which was reduced by Luche's[14] procedure using $NaBH_4$ and $CeCl_3$ in MeOH at −100 °C to

afford **13** as a single isomer (Scheme 3). The secondary alcohol moiety of **13** was protected as its methoxymethyl ether using MOMCl and DIPEA to afford **14** in 82% yield. The *p*-methoxybenzylether of **14** was cleaved using DDQ in CH_2Cl_2 to furnish alcohol **3** in 91% yield. Alcohol **3** was oxidized to the aldehyde with IBX; further treatment with the Wittig reagent allyloxycarbonylethylenetriphenylphosphorane in refluxing THF gave only *E*-isomer **15** as a single product in an 80% yield over two steps. Finally, deprotection of the *tert*-butyldimethylsilyl group with tetrabutylammonium fluoride afforded the C33–C44 core fragment **2** with the required stereocenters in 86% yield. The ^{1}H, ^{13}C NMR and elemental analysis of fragment **2**[15] were in good agreement with the assigned structure. For example, the ^{1}H NMR spectrum revealed signals due to the olefinic protons at δ 6.94 (m, 1H), 5.97 (m, 1H) and 5.39–5.20 (m, 2H), which were characteristic of an α,β-unsaturated ester and a terminal olefin group. A signal due to the alkyne proton appeared at δ 1.97 (t, $J = 2.6$ Hz), the methyl group attached to the double bond carbon appeared as a singlet at δ 1.89 and the methyl group present between the two hydroxyl groups appeared as a doublet at δ 0.88 (d, $J = 6.9$ Hz). In the ^{13}C NMR spectrum, the corresponding olefinic carbons appeared at 138.9, 132.4, 129.5 and 117.7 ppm, respectively. The carbonyl carbon of the ester group resonated at δ 167.5 ppm.



Scheme 3. Synthesis of **2**.

In conclusion, a practical and stereoselective synthesis of the C33–C44 fragment of palau'amide has been achieved using a Sharpless asymmetric epoxidation, a regioselective nucleophilic epoxide opening, a Grignard reaction, a Luche stereoselective reduction and an *E*-selective Wittig reaction. Further investigations towards the total synthesis of palau'amide are in progress.

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4. *Analytical and spectral data of* **5**: $[\alpha]_D^{25}$ −20.34 (*c* 1.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 4.44 (s, 2H), 3.87 (dd, $J = 2.6$, 12.6 Hz, 1H), 3.80 (s, 3H), 3.64–3.53 (m, 3H), 3.08 (m, 1H), 2.95 (m, 1H), 2.00–1.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.9, 129.9, 128.9, 113.5, 72.3, 66.2, 61.5, 58.3, 54.8, 53.4, 31.7. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.50; H, 7.56. Found: C, 65.35; H, 7.48.
5. Enantiomeric purity of the product formed was verified by HPLC analysis. HPLC conditions: column, CHIRALCEL [OJ-H (5 μm spherical) 250 × 4.6 mm]; mobile phase, IPA–petroleum ether (1:9); flow rate, 0.5 mL/min; UV detection at 220 nm.
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8. *Analytical and spectral data of* **4**: $[\alpha]_D^{25}$ −1.32 (*c* 1.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.41 (ABq, $J = 11.6$, 13.1 Hz, 2H), 3.89 (q, $J = 5.9$ Hz, 1H), 3.81 (s, 3H), 3.69 (dd, $J = 3.9$, 10.9 Hz, 1H), 3.50 (t, $J = 6.5$ Hz, 3H), 2.69 (br s, 1H), 1.88–1.74 (m, 3H), 0.97 (d, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 130.3,

129.2, 113.7, 73.6, 72.7, 66.4, 65.1, 55.1, 39.1, 34.2, 25.8, 18.0, 13.7, −4.4, −4.6. Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.21; H, 9.78. Found: C, 65.24; H, 9.69.

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10. *Analytical and spectral data of* **7**: $[\alpha]_D^{25}$ +3.05 (*c* 1.3, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 4.40 (s, 2H), 4.02 (m, 1H), 3.78 (s, 3H), 3.53–3.44 (m, 3H), 2.33 (dt, $J = 2.02$, 7.07 Hz, 2H), 2.20 (m, 1H), 1.94–1.44 (m, 7H), 0.86 (s, 9H), 0.82 (d, $J = 6.9$ Hz, 3H), 0.12 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 130.2, 129.3, 113.7, 107.5, 84.7, 72.8, 72.7, 71.5 67.0, 55.1, 44.2, 33.6, 33.3, 25.8, 18.0, 16.2, 11.6, 0.18, −4.4, −4.5. Anal. Calcd for $C_{28}H_{50}Si_2O_4$: C, 66.40; H, 9.88. Found: C, 66.32; H, 10.14.
11. *Analytical and spectral data of* **8**: $[\alpha]_D^{25}$ −2.85 (*c* 0.7, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 4.39 (ABq, $J = 11.6$, 19.4 Hz, 2H), 4.12 (m, 1H), 3.95 (dt, $J = 2.4$, 6.8 Hz, 1H), 3.80 (s, 3H), 3.54 (m, 1H), 3.46–3.38 (m, 2H), 2.26 (t, $J = 6.9$ Hz, 2H), 1.94 (q, $J = 6.7$ Hz, 2H), 1.81–1.63 (m, 2H), 1.55–1.25 (m, 3H), 0.99 (d, $J = 7.1$ Hz, 3H), 0.88 (s, 9H), 0.13 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 130.2, 129.2, 113.7, 107.1, 84.5, 76.0, 72.6, 69.1, 66.2, 55.1, 38.6, 35.0, 33.5, 25.8, 17.9, 16.6, 11.3, 0.2, −4.4, −4.7. Anal. Calcd for $C_{28}H_{50}Si_2O_4$: C, 66.40; H, 9.88. Found: C, 66.51; H, 10.02.
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15. *Analytical and spectral data of* **2**: $[\alpha]_D^{25}$ −16.71 (*c* 1.0, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): δ 6.94 (m, 1H), 5.97 (m, 1H), 5.39–5.20 (m, 2H), 4.68–4.66 (m, 3H), 4.64 (t, $J = 1.3$ Hz, 1H), 3.81–3.63 (m, 2H), 3.40 (s, 3H), 2.78 (br s, 1H), 2.48–2.16 (m, 4H), 1.97 (t, $J = 2.6$ Hz, 1H), 1.89 (s, 3H), 1.76–1.55 (m, 5H), 0.88 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 167.5, 138.9, 132.4, 129.5, 117.7, 95.7, 84.1, 79.7, 73.2, 68.5, 65.1, 55.9, 41.5, 34.1, 29.3, 23.6, 18.3, 12.6, 12.0. Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.40; H, 8.87. Found: C, 67.54; H, 8.69.