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Studies in Marine Macrolide Synthesis: Stereocontrolled Synthesis of the C_1–C_{11} and C_{15}–C_{27} Subunits of Aplyronine A

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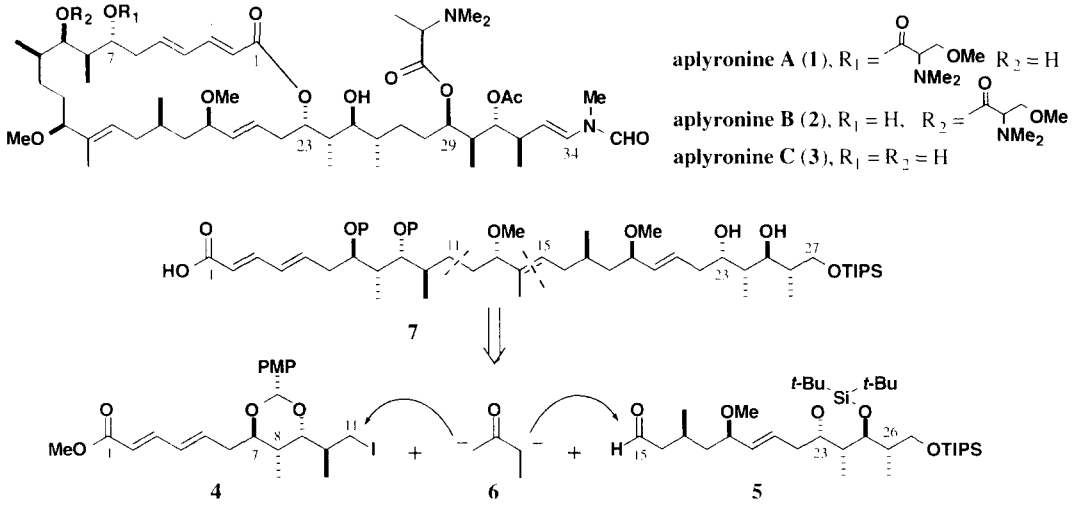
Abstract: The aplyronine C_1–C_{11} subunit **4**, containing 4 stereocentres and the (*E*,*E*)-diene system, was prepared in 7 steps from ethyl ketone (*R*)-**8** using a boron-mediated *anti* aldol reaction. The corresponding C_{15}–C_{27} subunit **5**, containing 6 stereogenic centres and an (*E*)-alkene, was obtained in 10 steps from ketone (*S*)-**14** using a tin(II)-mediated *syn* aldol reaction and CBS enone reduction.

In 1993, Yamada and co-workers reported the isolation and characterisation of aplyronines A (**1**), B (**2**) and C (**3**) from the Japanese sea hare *Aplysia kurodai*.[1] Aplyronine A, which showed potent cytotoxicity against HeLa-S_3 cells (IC_{50} 0.039 ng/mL) and pronounced activity *in vivo* against a range of tumours,[1] is a complex 24-membered macrolide with distinctive amino acid residues at C_7 and C_{29} along with an elaborate C_{23} side-chain, terminating in a vinyl *N*-methyl formamide group. More recently, the Yamada group confirmed the absolute stereochemistry of the aplyronines by total synthesis.[2]



Scheme 1

As part of our studies towards the total synthesis of this novel class of bioactive marine macrolides,[3] we now report a stereocontrolled synthesis of the aplyronine C_1–C_{11} and C_{15}–C_{27} subunits, **4** and **5** in **Scheme 1**, using aldol chemistry developed in our laboratory. A key feature of the synthesis of the iodide **4** was the temporary masking of the C_1–C_5 (*E*,*E*)-diene ester as an alkyne ester, facilitating the use of a boron-mediated *anti* aldol coupling for the installation of the C_7 and C_8 stereocentres. In the case of the aldehyde **5**, the construction of the C_{23}–C_{26} stereotetrad was based on the use of a tin(II)-mediated *syn* aldol reaction. In the accompanying paper,[4] we describe the efficient coupling of these subunits through an appropriate C_{12}–C_{14} linker **6** to generate the truncated seco acid **7**, followed by its transformation into the desired 24-membered macrolide framework of the aplyronines.

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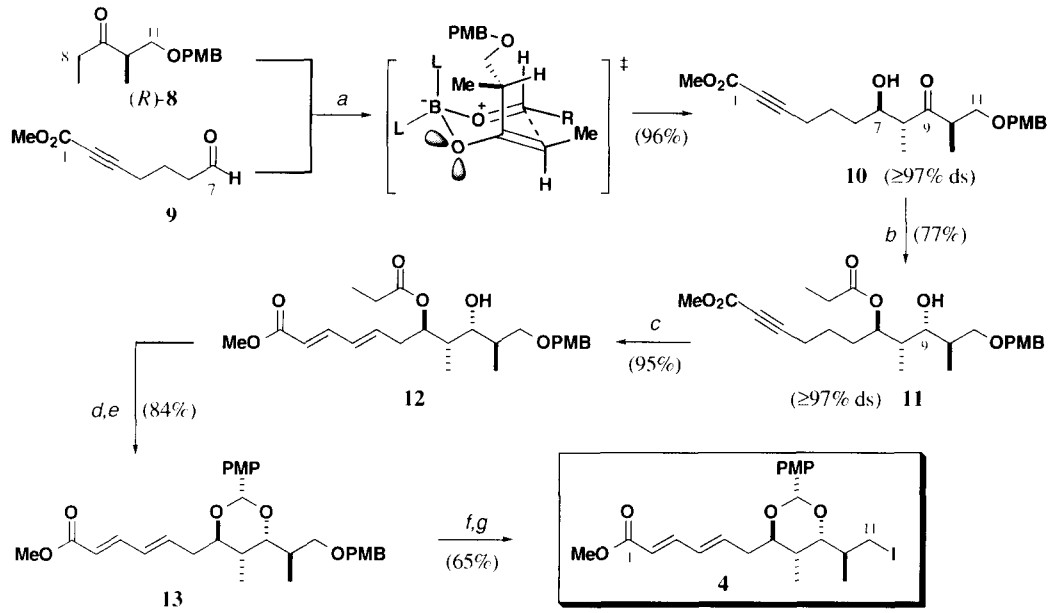
The synthesis of the C_1–C_{11} subunit **4** is outlined in **Scheme 2**. Using our standard conditions for the generation of the (*E*)-enol borinate,[5] enolisation of ethyl ketone (*R*)-**8**[6] was followed by addition of aldehyde **9**,[7] leading to formation of the *anti-anti* aldol adduct **10** in 96% yield with ≥97% ds.[8] Notably, the acetylenic ester was carried through this reaction without difficulty. Stereoselective reduction of the C_9 carbonyl of **10** was achieved using a modified, samarium-catalysed, Evans-Tishchenko reaction.[9] Hence, treatment of **10** with a premixed solution of SmI_2 (15 mol%) and EtCHO gave the 1,3-*anti* reduction product **11** in 77% yield with ≥97% ds.[10] After some experimentation, it was found that the isomerisation[11] of the alkyne ester to the desired (*E*,*E*)-diene was best achieved at this stage. Use of Ph_3P in conjunction with PhOH smoothly equilibrated the alkyne in **11** to diene **12** (95%), isolated as a single geometric isomer. Next, ester cleavage (K_2CO_3 / MeOH) in **12** gave a diol which was protected as its *p*-methoxyphenyl (PMP) acetal **13**.[12] Selective deprotection[13] of the PMB ether of **13** with DDQ was followed by conversion of the primary alcohol into the corresponding iodide **4**.

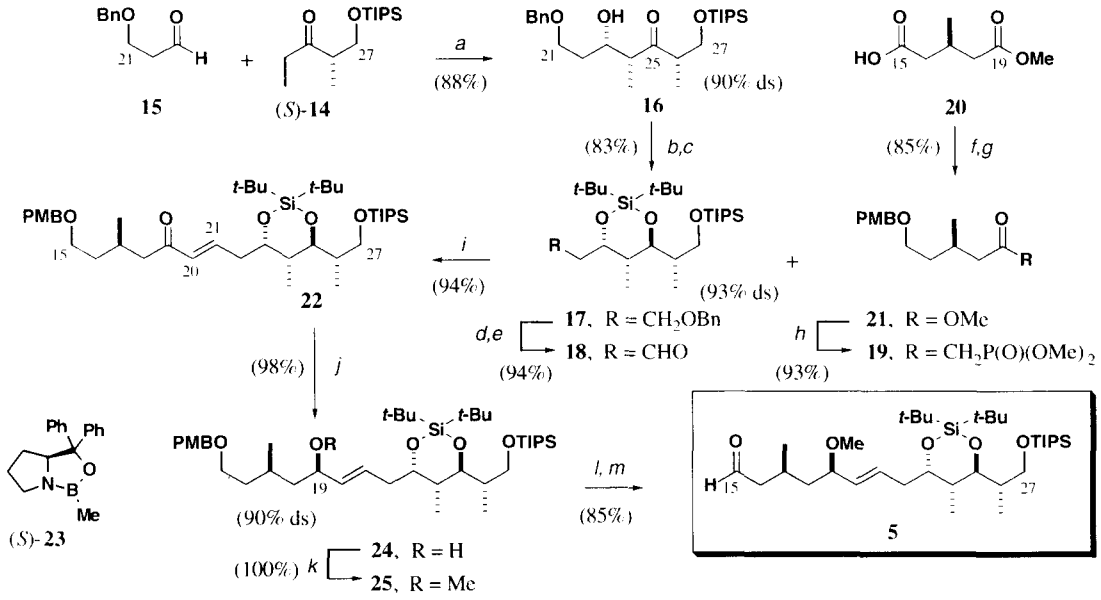


Scheme 2: (a) (c-Hex)$_2$BCl, Et_3N, Et_2O, 0 °C, 1 h; **9**, -78 → -20 °C, 12 h; H_2O_2, MeOH, pH7 buffer; (b) SmI_2 (15 mol%), EtCHO, THF, 0 °C, 15 min; **10**, 0 °C, 2 h; (c) Ph_3P, PhOH, benzene, 20 °C, 14 h; (d) K_2CO_3, MeOH, 20 °C, 2 h; (e) *p*-MeO(C_6H_4)CH(OMe)$_2$, PPTS, CH_2Cl_2, 20 °C, 14 h; (f) DDQ, CH_2Cl_2, pH7 buffer, 20 °C, 1 h; (g) I_2, PPh_3, imid, MeCN, Et_2O, 0 → 20 °C, 3 h.

As shown in **Scheme 3**, the C_{23}–C_{26} stereotetrad was generated by a $Sn(OTf)_2$ mediated *syn*-aldol coupling[14] of TIPS ether protected ketone (*S*)-**14**[15] with aldehyde **15**, which gave the adduct **16** in 88% yield with 90% ds. This was followed by a $Me_4NBH(OAc)_3$ reduction[16] of the C_{25} ketone to generate the 1,3-*anti* diol which was subsequently protected as the di-*tert*-butyl silylene **17** (83%). Benzyl ether hydrogenolysis and Dess-Martin periodinane oxidation[17] gave the aldehyde **18** (94%) in preparation for a HWE chain extension. The synthesis of the required ketophosphonate **19** started with commercially available (*R*)-methyl-3-methyl glutarate (**20**). Chemoselective reduction of the carboxylic acid (BH_3•Me_2S, THF)[18] was immediately followed by hydroxyl protection (PMBOC(=NH)CCl_3, 0.3 mol% TfOH)[19] to give the PMB ether **21**. Under these conditions, lactonisation of the hydroxy ester was not observed. Chain extension by condensation with lithiated dimethyl methylphosphonate[20] gave the C_{15}–C_{20} segment **19** in 79% yield (3 steps).

The HWE coupling of phosphonate **19** with aldehyde **18** was best performed using $Ba(OH)_2$ as a mild base.[21] This gave the (*E*)-enone **22** selectively in 94% yield. 1,2-Reduction of the enone was now required

and, not surprisingly, achiral reagents gave an *ca* 1:1 mixture of epimeric alcohols. However, a good level of reagent control was achieved using Corey's proline-derived oxazaborolidine.[22] Treatment of **22** with (*S*)-**23** (10 mol%) in THF solution with BH_3•Me_2S (0.6 equiv.) gave a 98% yield of C_{19} alcohols with 9:1 diastereoselectivity. Assignment of the configuration of the epimeric alcohols was made by Mosher ester analysis[24] and was in agreement with the anticipated sense of stereoinduction.[25] Methylation of the chromatographically separable (19*R*)-alcohol **24** gave the ether **25** and oxidative PMB removal (DDQ),[26] followed by oxidation, gave the aldehyde **5** (85%, 3 steps) representing the complete C_{15}–C_{27} subunit.



Scheme 3: (a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2; **15**, -78 °C, 2 h; (b) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, 20 °C, 48 h; (c) (*t*-Bu)$_2$Si(OTf)$_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 12 h; (d) H_2, Pd/C, EtOAc, 20 °C, 11 h; (e) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 70 min; (f) BH_3•Me_2S, THF, 0 → 20 °C, 90 min; (g) PMBOC(NH)CCl_3, TfOH (0.3 mol%), Et_2O, 20 °C, 14 h; (h) MeP(O)(OMe)$_2$, *n*-BuLi, THF, -78 °C, 10 min; **21**, -78 °C, 1.5 h; (i) **19**, Ba(OH)$_2$, THF:H_2O (40:1), 20 °C, 30 min; **18**, 20 °C, 2 h; (j) (*S*)-**23**, BH_3•Me_2S, THF, 0 °C, 40 min; (k) NaH, MeI, THF, 0 → 20 °C, 15 h; (l) DDQ, pH7 buffer, CH_2Cl_2, H_2O, 20 °C, 1 h; (m) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 2 h.

In conclusion, the C_1–C_{11} subunit **4**, containing 4 stereocentres and the (*E*,*E*)-diene system, was prepared in 7 steps from ethyl ketone (*R*)-**8** in 38% yield with ≥94% ds. The corresponding C_{15}–C_{27} subunit **5**, containing 6 stereogenic centres and an (*E*)-alkene, was obtained in 10 linear steps from ethyl ketone (*S*)-**14**, with an overall yield of 53% and 75% ds. The elaboration of these two subunits into an advanced macrolide intermediate for the aplyronines is discussed in the accompanying paper.[4]

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6. Ketone (*R*)-**8** was prepared in 3 steps from methyl (*R*)-3-hydroxy-2-methylpropionate with the PMB protecting group introduced using PMBC(=NH)CCl_3/TfOH (ref. 5, 19).

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8. All new compounds gave spectroscopic data in agreement with the assigned structures. Aldehyde **5** had: ^{1}H NMR δ (500 MHz, $CDCl_3$) 9.83 (1H, s, CHO), 5.81 (1H, dt, *J* = 15.5, 6.6 Hz, H_{21}), 5.32 (1H, dd, *J* = 15.5, 8.3 Hz, H_{20}), 4.05 (1H, m, H_{23}), 3.90 (1H, dd, *J* = 9.6, 5.8 Hz, H_{27A}), 3.80 (1H, dd, *J* = 9.1, 2.2 Hz, H_{25}), 3.59-3.53 (2H, m, H_{19} and H_{27B}), 3.23 (3H, s, OMe), 2.44 (1H, qd, *J* = 7.2, 1.9 Hz, H_{16}), 2.37-2.29 (2H, m, H_{24} and H_{22A}), 2.26-2.17 (3H, m, H_{22B}, H_{16B} and H_{17}), 1.89 (1H, m, H_{26}), 1.62-1.56 (1H, m, H_{18A}), 1.43 (1H, dt, *J* = 13.8, 6.3 Hz, H_{18B}), 1.10 (3H, septet, *J* = 5.0 Hz, OSi(CHMe$_2$)$_3$), 1.06 (18H, d, *J* = 5.0 Hz, OSi(CHMe$_2$)$_3$), 1.03 (3H, d, *J* = 6.8 Hz, C_{26}Me), 1.03 (3H, d, *J* = 7.0 Hz, C_{17}Me), 0.99 (18H, s, Si(CMe$_3$)$_2$), 0.85 (3H, d, *J* = 7.2 Hz, C_{24}Me); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 202.8, 132.6, 131.6, 80.3, 76.7, 76.6, 63.6, 55.6, 50.9, 42.7, 39.0, 38.8, 34.1, 27.5, 27.3, 24.8, 21.6, 20.9, 20.4, 18.1, 15.2, 13.8, 11.9.

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10. While the $Me_4NBH(OAc)_3$ reduction (ref. 16) of **10** was successful, the subsequent isomerisation of the alkyne ester proved problematic in the presence of a free hydroxyl group at C_7.

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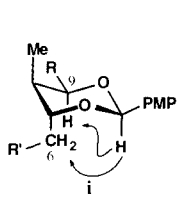
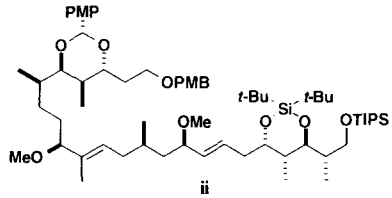
12. The PMP acetal configuration in **4** and **13** was assigned based upon the nOe's indicated for **i**.



i



ii

13. Selective removal of a PMB ether in the presence of a PMP acetal has been reported previously. For example, see: Smith, A. B. III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. In contrast, our initial route to the aplyronines was revised because of the inability to deprotect the PMB ether in **ii** without reaction at the PMP acetal.

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23. Use of the butyl oxazaborolidine and/or catecholborane as stoichiometric reductant did not improve the selectivity and lower yields resulted (see Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611). Other asymmetric reducing agents such as those derived from $LiAlH_4$ also proved unsatisfactory.

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