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Studies in Marine Macrolide Synthesis: Construction of a 24-Membered Macrocyclic Intermediate for Aplyronine A

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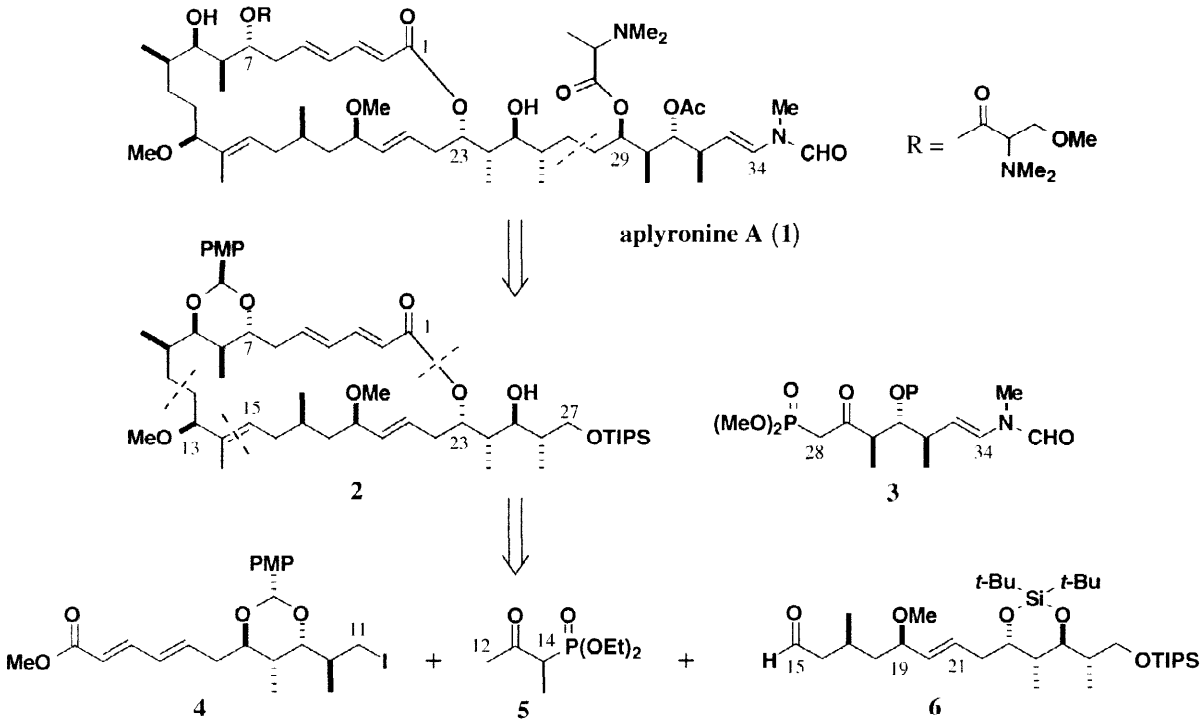
Abstract: The C_1–C_{27} macrolide **2**, which contains 11 stereocentres and 4 double bonds, was constructed by an efficient 3-component coupling followed by a macrolactonisation/isomerisation sequence. Key steps were the alkylation of the dianion of phosphonate **5** with iodide **7** and a $Ba(OH)_2$-mediated HWE reaction with **6** to install the trisubstituted double bond.

Aplyronine A (**1**) is an unusual 24-membered marine macrolide, which displays potent antitumour activity against a range of cancers including P388 leukaemia, Lewis lung carcinoma and B16 melanoma.[1] This activity may be related to its ability to inhibit the polymerisation of globular actin to fibrous actin and to depolymerise fibrous actin to globular actin.[2] Due to its scarcity from the natural source and promising anti-cancer activity, a total synthesis was undertaken by the Yamada group.[3] We have devised a different strategy for the stereocontrolled synthesis of the aplyronines,[4] which is potentially shorter and features some novel aldol chemistry developed in our laboratory.



Scheme 1

As outlined in **Scheme 1**, our strategy for the synthesis of aplyronine A (**1**) is based on the elaboration of the pivotal intermediate **2**, which corresponds to a truncated, 24-membered, macrolide having 11 of the 15 stereocentres of the full carbon chain. The subsequent introduction of the highly functionalised side-chain of the aplyronines would then be performed using a suitable HWE coupling, such as with the C_{28}–C_{34} subunit **3** containing an *N*-methyl vinylformamide terminus.[5] In this paper, we report the synthesis of macrocycle **2** by the controlled coupling of three subunits **4**–**6**, followed by a macrolactonisation step.

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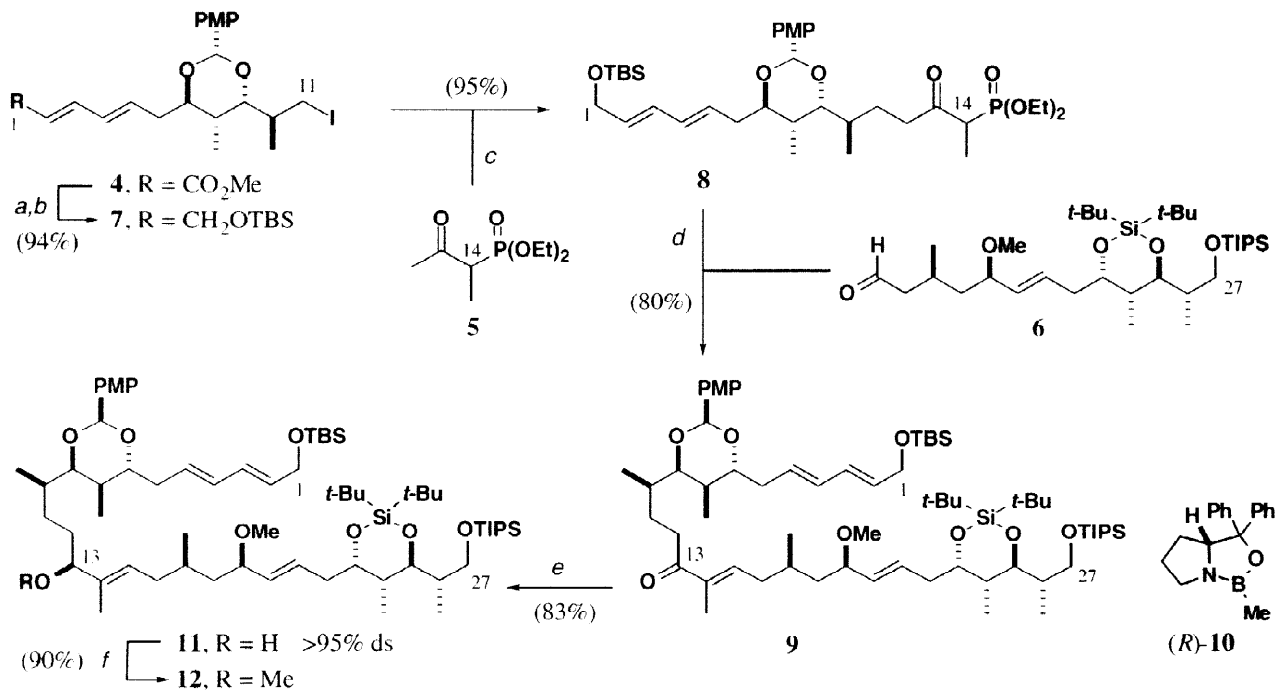
At the outset, the order of the 3-component coupling of **4**, **5** and **6** was open to change, thus allowing flexibility in our strategy. Indeed, we initially investigated the HWE addition of phosphonate **5** to aldehyde **6**, however, later difficulties were encountered with this route.[6,7] Hence, the alkylation of the dianion of β-keto phosphonate **5** with iodide **4** was pursued instead. In this case, the C_{14}–C_{15} (*E*)-trisubstituted double bond in **2** would be introduced by a HWE reaction, followed by an asymmetric reduction of the ketone to generate the C_{13} stereocentre. A similar protocol proved to be effective in the synthesis of the C_{19}–C_{21} allylic methyl ether portion of **6**.[4]

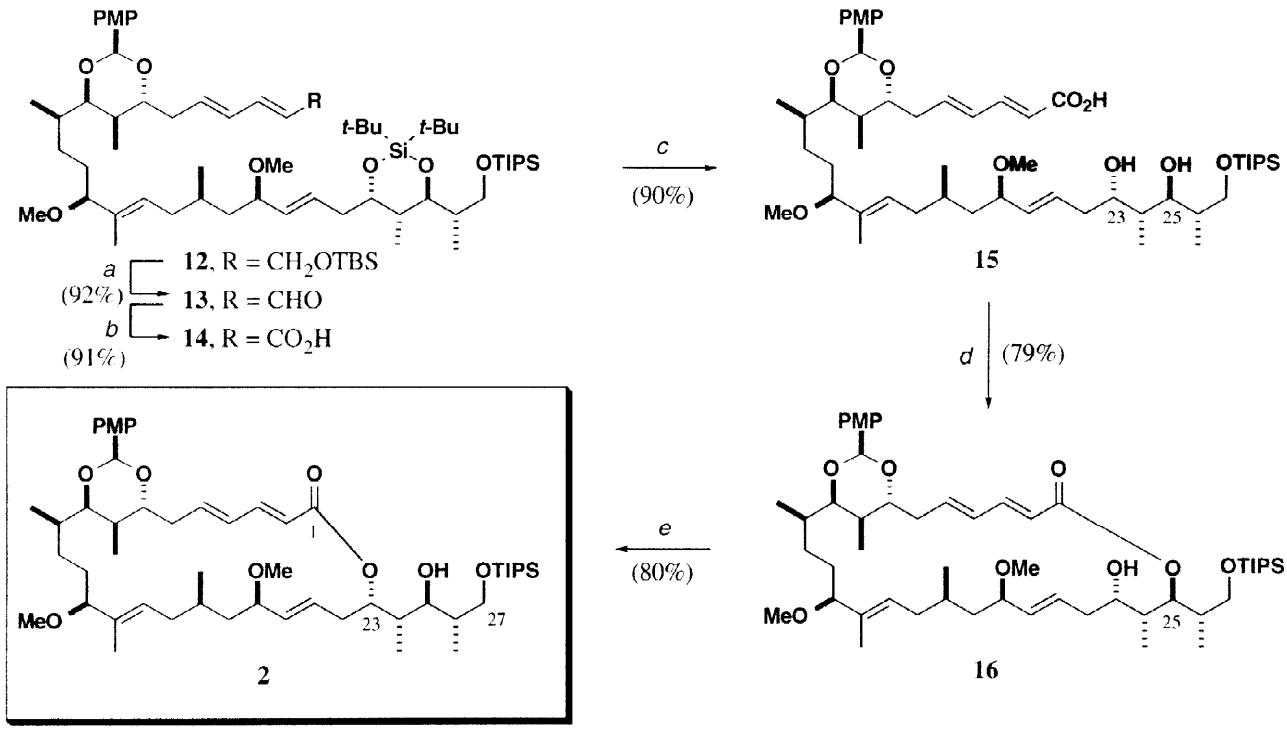
The synthesis of the C_1–C_{27} chain of the aplyronines is shown in **Scheme 2**. Attempted alkylation of iodide **4** with the dianion of phosphonate **5** according to Grieco's conditions[8] failed, presumably due to competing reaction at the diene ester. Therefore, the ester was first reduced to the corresponding alcohol and protected as its TBS ether **7**. This time, alkylation using the dianion of **5** in THF proceeded, albeit slowly, at −78 °C. When a small amount of HMPA (2 equiv.) was introduced, a 95% yield of the β-keto phosphonate **8** was obtained. The HWE olefination reaction between **6** and **8** proceeded in good yield (80%) using $Ba(OH)_2$ as a mild base.[9] Notably, complete selectivity for **9** was realised, demonstrating that this is an effective coupling method for constructing (*E*)-trisubstituted double bonds. The C_{13} stereocentre was then introduced with >95:5 selectivity by CBS reduction[10] of the enone **9**, using the (*R*)-proline derived oxazaborolidine **10** in conjunction with BH_3•SMe_2, giving the (*S*)-alcohol **11** in 83% yield. Finally, methylation of **11** (NaH/MeI) provided the methyl ether **12**, which possesses the C_1–C_{27} carbon chain of the aplyronines.



Scheme 2: (a) DIBAL, CH_2Cl_2, −78 °C, 2 h; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 3 h; (c) NaH, THF, 0 °C, 90 min; *n*-BuLi, 0 °C, 30 min; **7**, HMPA, THF, −78 °C, 1 h; (d) $Ba(OH)_2$, THF, 20 °C, 30 min; **6**, THF/H_2O (40:1), 20 °C, 2.5 h; (e) (*R*)-**10**, BH_3•Me_2S, THF, 0 °C, 20 min; (f) NaH, MeI, THF, 20 °C, 4 h.

As shown in **Scheme 3**, the TBS ether at C_1 in **12** was next removed oxidatively using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in CH_2Cl_2/pH7 buffer (0 °C, 10 min) to give aldehyde **13** in 92% yield.[11] Notably, these mild, neutral conditions selectively removed the TBS ether in the presence of the di-*tert*-butylsilylene and TIPS ether, as well as the potentially labile PMP acetal. Moreover, this reaction achieved concomitant oxidation at C_1 to generate the (*E*,*E*)-diene aldehyde. Further oxidation of **13** using buffered sodium chlorite[12] gave acid **14** in 91% yield. Removal of the di-*tert*-butyl silylene in the presence of the primary TIPS ether was then achieved (HF•pyr) to provide seco acid **15**, in preparation for macrolactonisation.

With the seco acid **15**, there are two possible macrolactonisation products, *i.e.* **2** and **16**. At the outset, it was anticipated that some selectivity for acylation at the less sterically encumbered C_{23} hydroxyl might be achieved.[13] In practice, however, use of the Yonemitsu variant[14] of the Yamaguchi macrolactonisation procedure[15] in $CHCl_3$ gave exclusively the undesired, 26-membered, macrocycle **16** in 79% yield. In contrast to previous studies on macrolactonisation of related 1,3-diol systems,[16] changing the solvent polarity had little effect; highlighting the uncertainty in predicting kinetic macrocyclisation selectivity in such complex cases. We decided to explore the isomerisation of **16**, which was formed in good yield, to produce the desired, 24-membered, macrocycle **2**. Treatment[3,17] with $Ti(O\textit{i}\text{-}Pr)_4$ in CH_2Cl_2 led to isomerisation of **16** with 3:1 selectivity in favour of **2** with good mass recovery (80%). The two macrolides[18] were readily separated by chromatography, allowing resubmission of **16** to the isomerisation step. In this way, we were able to obtain the key intermediate **2**,[6] having the desired 24-membered macrolide framework for the aplyronines.



Scheme 3: (a) DDQ, CH_2Cl_2, pH7 buffer, 0 °C, 10 min; (b) $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH, 2-methylbut-2-ene, 20 °C, 18 h; (c) HF•pyr, pyr, THF, 20 °C; (d) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, $CHCl_3$, 20 °C, 4 h; (e) $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2, 20 °C, 24 h.

In conclusion, the C_1–C_{27} macrolide **2** which contains 11 stereocentres and 4 double bonds was synthesised by an efficient 3-component coupling of subunits **5**, **6** and **7** followed by a macrolactonisation/ isomerisation sequence. Studies towards the synthesis of the remaining C_{28}–C_{34} subunit and its elaboration into aplyronine A by coupling with a suitable derivative of **2** are currently under investigation.

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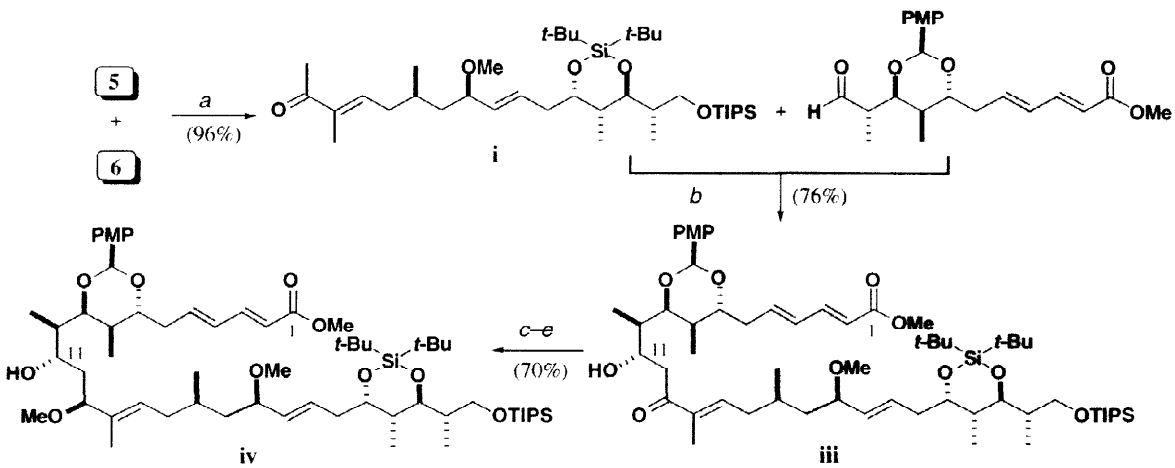
6. All new compounds gave spectroscopic data in agreement with the assigned structures. Macrolide **2** had: ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 8.7 Hz, Ar$\underline{H}$), 7.26 (2H, dd, *J* = 15.0, 11.3 Hz, $\underline{H}_3$), 6.88 (2H, d, *J* = 8.7 Hz, Ar$\underline{H}$), 6.20 (1H, dd, *J* = 14.8, 11.3 Hz, $\underline{H}_4$), 6.05 (1H, ddd, *J* = 14.8, 9.5, 4.7 Hz, $\underline{H}_5$), 5.85 (1H, d, *J* = 15.0 Hz, $\underline{H}_2$), 5.76 (1H, s, C$\underline{H}$Ar), 5.60 (1H, ddd, *J* = 15.4, 10.1, 4.0 Hz, $\underline{H}_{21}$), 5.51 (1H, bd, *J* = 10.7 Hz, $\underline{H}_{23}$), 5.23 (1H, dd, *J* = 15.4, 8.7 Hz, $\underline{H}_{20}$), 5.11 (1H, t, *J* = 6.8 Hz, $\underline{H}_{15}$), 3.95 (1H, d, *J* = 6.5 Hz, $\underline{H}_9$), 3.90 (1H, dd, *J* = 11.1, 4.0 Hz, $\underline{H}_7$), 3.80 (5H, m, ArO$\underline{Me}$ and 2 x $\underline{H}_{27}$), 3.60 (1H, d, *J* = 5.7 Hz, O$\underline{H}$), 3.55 (1H, m, $\underline{H}_{19}$), 3.42 (1H, dd, *J* = 9.0, 5.0 Hz, $\underline{H}_{13}$), 3.21 (3H, s, O$\underline{Me}$), 3.17 (1H, m, $\underline{H}_{25}$), 3.16 (3H, s, O$\underline{Me}$), 3.11 (1H, m, $\underline{H}_{6A}$), 2.58 (1H, m, $\underline{H}_{6B}$), 2.52 (1H, dd, *J* = 11.6, 6.0 Hz, $\underline{H}_{22A}$), 2.27 (1H, dm, *J* = 11.6 Hz, $\underline{H}_{22B}$), 2.05 (1H, m, $\underline{H}_{16A}$), 1.95 (3H, m, $\underline{H}_8$, $\underline{H}_{24}$ and $\underline{H}_{26}$), 1.78 (1H, m, $\underline{H}_{16B}$), 1.63 (1H, m, $\underline{H}_{12A}$), 1.53 (1H, m, $\underline{H}_{10}$), 1.48 (2H, m, $\underline{H}_{12B}$ and $\underline{H}_{18A}$), 1.47 (3H, s, $C_{14}\underline{Me}$), 1.39 (1H, m, $\underline{H}_{17}$), 1.30 (1H, m, $\underline{H}_{18B}$), 1.20 (3H, d, *J* = 6.9 Hz, $C_{10}\underline{Me}$), 1.08 (26H, Si$^i\underline{Pr}_3$, $\underline{Me}$ and 2 x $\underline{H}_{11}$), 0.96 (3H, d, *J* = 6.9 Hz, $\underline{Me}$), 0.93 (3H, d, *J* = 7.0 Hz, $\underline{Me}$), 0.74 (3H, d, *J* = 6.3 Hz, $C_{17}\underline{Me}$). ^{13}C NMR δ (100 MHz, $CDCl_3$) 167.2, 160.0, 144.5, 139.3, 134.4, 132.9, 131.7, 131.1, 130.9, 128.7, 127.5, 120.6, 113.7, 96.2, 88.2, 81.4, 79.9, 77.3, 72.5, 65.7, 55.8, 55.7, 55.3, 41.8, 41.3, 36.8, 36.2, 36.1, 35.9, 35.5, 30.4, 29.9, 29.7, 28.9, 19.7, 18.0, 17.9, 15.8, 15.5, 14.0, 11.8, 10.9, 10.0.

7. We initially examined the HWE coupling of **5** with **6** to give enone **i**. A Mukaiyama aldol coupling of the silyl enol ether from **i** with aldehyde **ii** (derived from the corresponding alcohol, see preceding paper) proceeded under Felkin-Anh control to give adduct **iii**, which was then transformed by substrate-controlled reduction (ref. 19) into the methyl ether **iv**. However, subsequent deoxygenation of the C_{11} hydroxyl proved problematic.



Conditions: (a) $Ba(OH)_2$, THF/H_2O (40:1), 20 °C, 2 h; (b) TESCl, LiHMDS, THF, –78 °C, 30 min; **ii**, BF_3•OEt_2, –60 °C, 48 h; (c) SmI_2, EtCHO, THF, 0 °C, 3 h; (d) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 20 °C, 2 h; (e) K_2CO_3, MeOH, 20 °C

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13. Intermolecular acylation of a truncated C_{21}–C_{27} diol with Bz_2O favoured reaction at the desired C_{23} hydroxyl (4:1).

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18. The 24 and 26-membered macrocycles were distinguished using 1D- and 2D-NMR techniques. In particular, compound **2** showed a diagnostic coupling between H_{22} and H_{23}.

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