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Studies in marine macrolide synthesis: stereocontrolled synthesis of a C21–C34 subunit of the aplyronines

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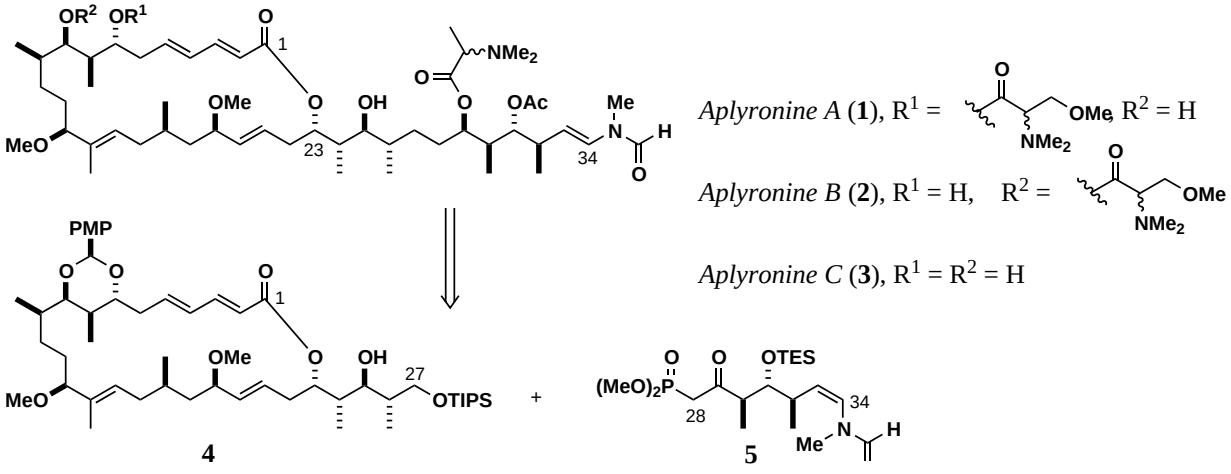
Abstract—The C21–C34 subunit **27** of the aplyronines, containing eight stereocentres and a terminal *N*-methyl-*N*-vinylformamide moiety, was prepared using the Horner–Wadsworth–Emmons coupling of β-ketophosphonate **5** with aldehyde **19**. The two stereotetrad sequences were constructed by chiral ketone aldol reactions, while the *N*-methyl-*N*-vinylformamide was introduced using a novel Wittig olefination. © 2002 Elsevier Science Ltd. All rights reserved.

Aplyronine A (**1**, Scheme 1) is an unusual 24-membered marine macrolide which was first isolated in 1993, along with two congeners, aplyronines B (**2**) and C (**3**), from the Japanese sea hare *Aplysia kurodai* by Yamada and co-workers.[1] The aplyronines displayed potent cytotoxicity in vitro against a range of cancer cell lines including P388 leukaemia, Lewis lung carcinoma and B16 melanoma. Furthermore, aplyronine A exhibited pronounced in vivo activity against a range of tumour cells in xenograft experiments.[1,2] Aplyronine A has been shown to function as a novel actin depolymerising agent,[3] by accelerating fibrous actin depolymerisation and sequestering globular actin. Recently, an actin-dependent cell cycle checkpoint that ensures the proper orientation of microtubule spindles during metaphase has been uncovered by Gachet and Hyams and co-workers,[4] and although the biochemical pathway responsible for this checkpoint is still undefined, this may be linked to the antimitotic activity of the aplyronines.

The potent antitumour activity and novel actin-binding properties of the aplyronines has led to interest in evaluating their chemotherapeutic potential,[3] as well as attracting synthetic attention towards this unique group of marine macrolides.[2,5–7] Notably, the Yamada group established the absolute configuration by completing the first total synthesis of aplyronines A–C.[2] We have



Scheme 1.

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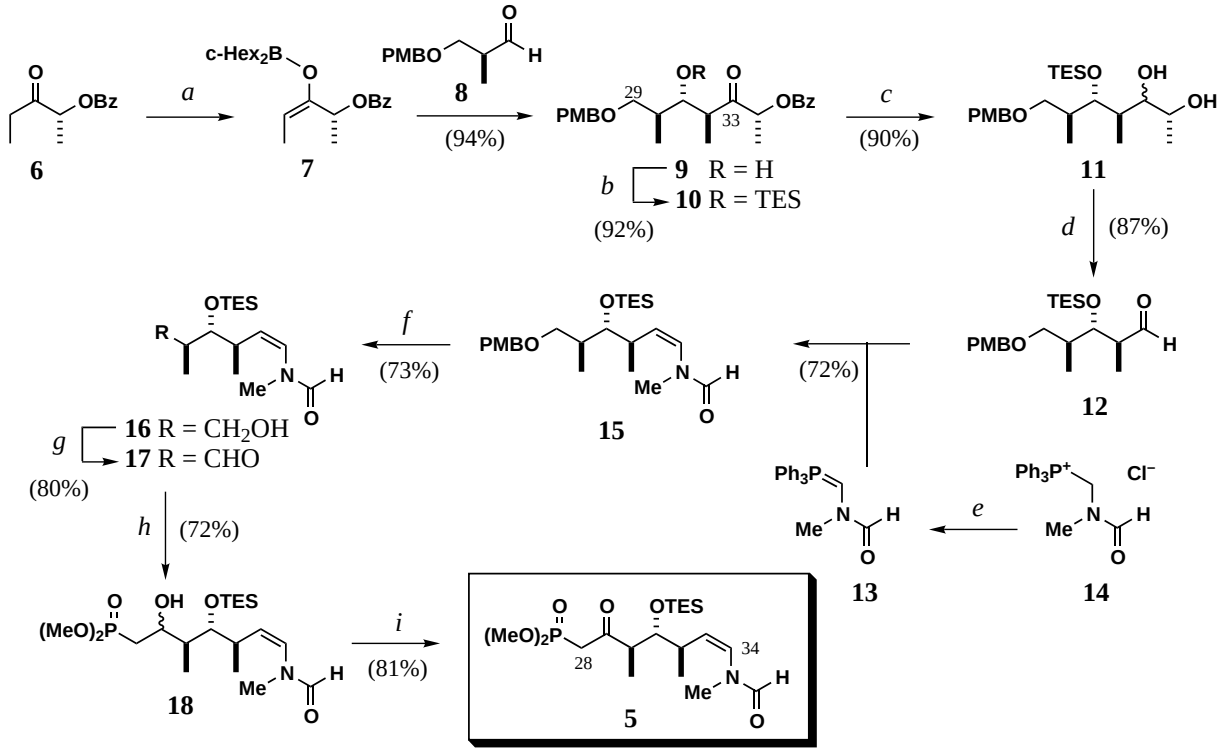
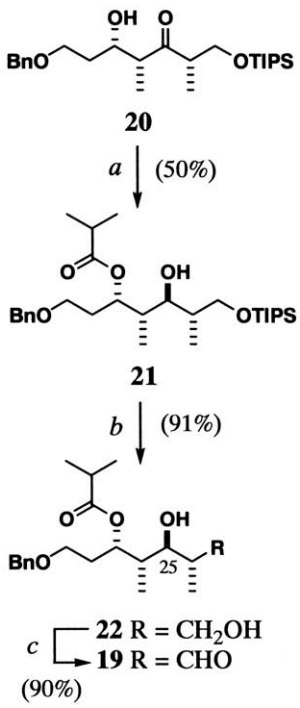
adopted an alternative strategy for the stereocontrolled synthesis of the aplyronines, which is potentially shorter and relies upon a key Horner–Wadsworth–Emmons (HWE) coupling of a suitable C27 aldehyde, derived from the previously described macrolide **4**,[5] with the β-ketophosphonate **5** for elaboration of the side chain. We now report a synthesis of the C28–C34 phosphonate **5** and demonstrate its use in the HWE-based construction of an advanced C21–C34 fragment of the aplyronines. The strategic decision to incorporate the terminal *N*-methyl-*N*-vinyl formamide in subunit **5** with *cis*-geometry and to carry this potentially sensitive moiety through to the closing stages of the synthesis before isomerisation, contrasts with established approaches in which the required *trans*-alkenyl formamide is generally introduced by a testing, late-stage, condensation reaction with a highly functionalised aldehyde.[2,7]

The synthesis of the C28–C34 phosphonate subunit **5**, containing the terminal *N*-methyl-*N*-vinyl formamide, is outlined in Scheme 2. Enolisation of lactate-derived ketone **6** using $(c\text{-Hex})_2BCl/Me_2NEt$ gave the (*E*)-boron enolate **7**.[8] Addition of freshly prepared aldehyde **8** gave, on oxidative workup, *anti*-aldol adduct **9** in 94% yield with >95% diastereoselectivity. Notably, the high level of stereoinduction exerted by the enolate leads here to anti-Felkin attack on the α-chiral aldehyde. Treatment of **9** with TESOTf and 2,6-lutidine gave TES ether **10** (92%). Reduction by $LiBH_4$ then furnished 1,2-diol **11** which was oxidatively cleaved with $NaIO_4$ to give aldehyde **12** (87%). Following our standard conditions,[9] Wittig olefination of aldehyde **12** with ylide **13**, generated in situ by the addition of LiHMDS to phosphonium salt **14**, proceeded smoothly to give *cis*-alkene **15** in 72% yield. After PMB ether cleavage with DDQ to give **16**, the liberated C29 hydroxyl group was oxidised with catalytic TPAP and NMO[10] to give aldehyde **17** (80%). Addition of lithiated methyl dimethylphosphonate to aldehyde **17** gave the desired hydroxyphosphonate **18** in 72% yield. Subsequent oxidation, again using the TPAP/NMO protocol, provided β-ketophosphonate **5** in nine steps and 17% yield from ketone **6**. Notably, the vinyl formamide was carried through this sequence of reactions without complication. In contrast to *trans*-*N*-methyl-*N*-vinyl formamides, which tend to exist as mixtures of rotamers in solution at ambient temperature, the corresponding *cis*-isomers appear as a single rotamer by ^1H NMR spectroscopy. As this facilitates analysis, we decided to retain the *cis*-geometry in **5** for as long as possible through the remainder of the synthesis.

In preparation for examining the key HWE coupling step, the C21–C27 aldehyde **19** was prepared from the previously described aldol adduct **20** (Scheme 3).[5a] Subjection of β-hydroxyketone **20** to Evans–Tishchenko reduction conditions[11] gave the desired monoprotected 1,3-*anti* diol **21**. HF·pyridine mediated removal of the TIPS ether then gave diol **22** cleanly (91%). Subsequent selective oxidation of the primary alcohol using cata-



Scheme 2. (a) $(c\text{-Hex})_2BCl$, Me_2NEt, Et_2O, 0°C, 1 h; **8**, −78→−20°C, 16 h; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 2 h; (c) $LiBH_4$, THF, −78°C→rt, 24 h; (d) $NaIO_4$, MeOH/pH 7 buffer, 0°C→rt, 2 h; (e) LiHMDS, THF, −78°C→rt; **12**, −78°C, 2 h; (f) DDQ, CH_2Cl_2/pH 7 buffer, rt, 0.5 h; (g) 10 mol% TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 0.5 h; (h) $(MeO)_2POCH_3$, *n*-BuLi, 4 Å mol. sieves, THF, −78°C, 4 h; (i) 10 mol% TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 1 h.



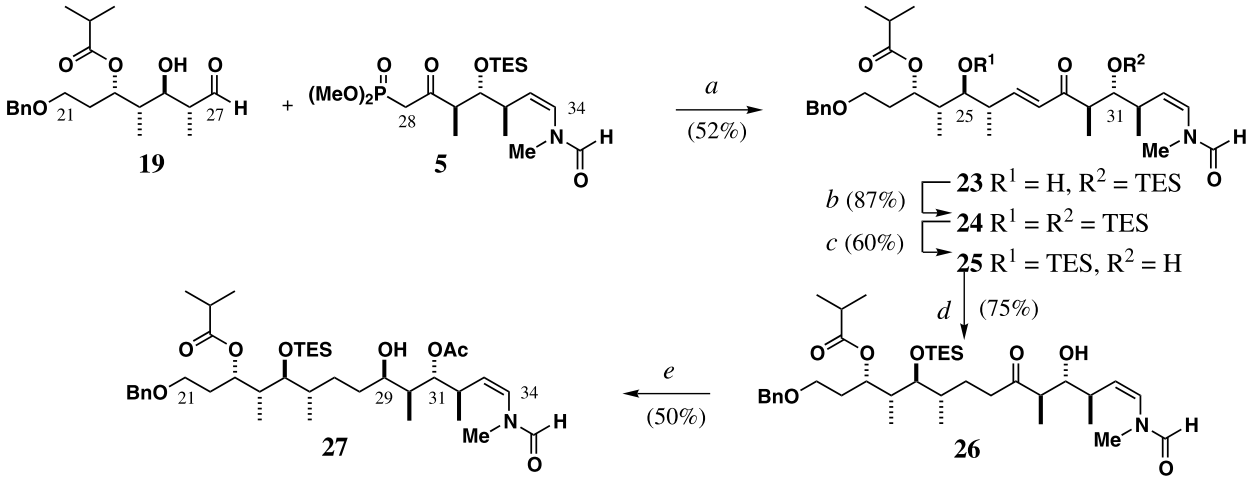
Scheme 3. (a) *iso*-butyraldehyde, SmI_2 (20 mol%), THF, 0°C, 2.5 h; (b) HF·pyridine, THF, rt, 7 h; (c) cat. TEMPO, $PhI(OAc)_2$, rt, 2 h.

lytic TEMPO, with iodobenzene diacetate (BAIB) as a co-oxidant, as developed by Piancatelli and co-workers,[12] provided the desired aldehyde **19** (90%) without any oxidation at C25.

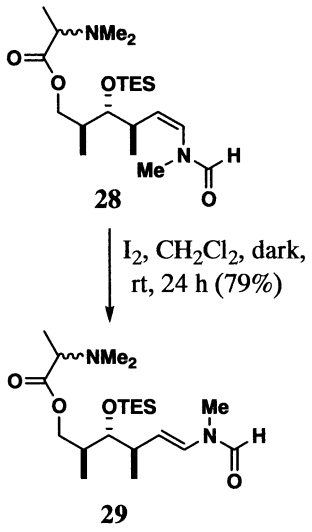
In order to form the C27–C28 bond of the aplyronines, the crucial HWE reaction between aldehyde **19** and β-ketophosphonate **5** was carried out using the LiCl/DBU conditions of Masamune and Roush,[13] producing the (*E*)-enone **23** in 52% yield (Scheme 4). Subsequent attempts to protect the C25 alcohol as either a PMB or TBS ether proved unsuccessful, presumably due to the particularly hindered nature of this hydroxyl group. However, treatment of **23** with TESCl and imidazole in DMF gave the bis-TES ether **24** in high yield (87%). By using mild hydrolysis conditions ($AcOH/THF/H_2O$), selective deprotection of the C31 TES ether was achieved to give alcohol **25**. Stryker's reagent ($[Ph_3P{\cdot}CuH]_6$) was then employed to reduce selectively the enone functionality in a 1,4-sense, providing ketone **26** (75%).[14] Our synthesis of fragment **27**,[15] corresponding to an advanced C21–C34 subunit of the aplyronines, was then concluded by performing an Evans–Tishchenko reduction on **26** using acetaldehyde. This served to set simultaneously the configuration of the C29 hydroxyl-bearing stereocentre and introduce the required C31 acetate.

Whilst retaining the *cis*-geometry of the terminal vinyl formamide through the above reaction sequence proved useful in simplifying the ^1H NMR spectra, ultimately it needs to be isomerised to the *trans*-geometry in the presence of the full aplyronine functionality. To date, this transformation has been demonstrated in a series of model substrates using iodine under light-free conditions.[9] For example, the *cis*-vinylformamide **28** (prepared in 94% yield by acylation of **16** with (*R*,*S*)-*N*,*N*-dimethylalanine using DCC, DMAP, CH_2Cl_2) was isomerised cleanly to the corresponding *trans*-*N*-methyl-*N*-vinylformamide **29** in 79% yield (Scheme 5).

In conclusion, we have prepared the β-ketophosphonate **5** to be employed as a highly functionalised C28–C34 side chain coupling unit for the aplyronines. The synthesis features a boron-mediated *anti*-aldol reaction of the chiral ketone **6** to set up the stereochemistry and a novel Wittig olefination to introduce the *N*-methyl-*N*-vinylformamide moiety. An advanced C21–C34 fragment **27** for the aplyronines was then assembled by a testing HWE coupling between **5** and aldehyde **19** and elaboration of the resulting enone **23**. Studies towards completing a total synthesis of the aplyronines using this chemistry are currently under investigation.



Scheme 4. (a) LiCl, DBU, THF/MeCN, rt, 3 h; (b) TESCl, imidazole, DMF, rt, 2 h; (c) $AcOH/THF/H_2O$, 40°C, 4 h; (d) $[Ph_3P{\cdot}CuH]_6$, C_6H_6, rt, 1 h; (e) SmI_2, CH_3CHO, THF, −5°C, 2.5 h.



Scheme 5.

Acknowledgements

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15. All new compounds gave spectroscopic data in agreement with the structures indicated. Compound **27** was isolated as a colourless oil: R_f 0.19 (40% EtOAc/40–60 pet. ether); IR (film) 3406 (s br, O-H), 2963 (s, C-H), 1734 (s, C=O), 1715 (s, C=O), 1684 (s, C=O), 1647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 8.15 (1H, s, NCHO), 7.33 (3H, m, ArH), 7.26 (2H, m, ArH), 5.98 (1H, d, $J=8.7$ Hz, C_1H), 5.25 (1H, dd, $J=10.7$, 9.0 Hz, C_2H,), 5.16 (1H, m, $C_{12}H$), 4.80 (1H, dd, $J=10.2$, 3.0 Hz, C_4H), 4.47 (2H, ABq, $J=11.8$ Hz, $ArCH_2O$), 3.46 (2H, m, $BnOCH_2$), 3.40 (2H, m, C_6HOH, $C_{10}HOTES$), 3.02 (3H, s, NCH_3), 2.90 (1H, m, C_3H), 2.49 (2H, septet, $J=7.0$ Hz, $C_{2'}H(CH_3)_2$, OH), 2.15 (3H, s, $C(O)CH_3$), 1.94 (1H, m, $C_{13}H_AH_B$), 1.86 (1H, m, $C_{13}H_AH_B$), 1.77 (1H, m, $C_{11}H$), 1.68 (1H, m, C_5H), 1.55 (2H, obs, $C_8H_AH_B$, C_9H), 1.39 (3H, m, C_7H_2, $C_8H_AH_B$), 1.13 (3H, d, $J=7.0$ Hz, $(C_{3'}H_3)_A$), 1.13 (3H, d, $J=7.1$ Hz, $(C_{3'}H_3)_B$), 1.06 (3H, d, $J=6.8$ Hz, C_3HCH_3), 0.93 (15H, ap t, $J=8.0$ Hz, C_9HCH_3, $C_{11}HCH_3$, $Si(CH_2CH_3)_3$), 0.77 (3H, d, $J=6.9$ Hz, C_5HCH_3), 0.62 (6H, q, $J=8.0$ Hz, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.6, 172.2, 162.4, 138.4, 128.8, 128.3, 127.7, 127.5, 124.7, 79.1, 78.6, 77.7, 73.0, 71.8, 67.5, 41.4, 38.7, 34.3, 32.1, 31.4, 28.9, 23.7, 23.0, 20.8, 19.1, 18.9, 17.4, 14.0, 10.9, 8.3, 7.1, 5.5; HRMS (ES^+) $[M+Na]^+$ found 728.4569, $C_{39}H_{67}O_8NNaSi$ requires 728.4534.