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Synthetic studies on amphidinolides C and F: synthesis of the C18-C29 segment of amphidinolide F

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Graphical Abstract

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These led us to require the THF fragment **1** (Scheme 1), which could be obtained by appropriate manipulation of the α -hydroxy-diester **2**. Diester **2** could in principle be accessed directly *via* a desymmetrising mono-Sharpless AD/Michael reaction on symmetrical dienolate **3**. In the forward sense, this process would raise interesting questions of regio- and stereocontrol (*vide infra*), but it would potentially provide a highly concise route to the key intermediate **2**.

We first required an efficient route for the synthesis of diene dioate **3**. Of several methods evaluated, the two proving most efficient in our hands are shown in Scheme 2. Hydrolysis of 2,5-dimethoxytetrahydrofuran **4** gave the dialdehyde **5** which underwent double Wittig reaction to give **3**⁶ in 36% overall yield (*E,E:E,Z* = 92:8) from **4**. The low yield is believed to be at least partly due to the volatility and water miscibility of **5**. A higher overall yield was obtained in a sequential oxidation/olefination process using methodology recently reported by Graham.⁷ Thus, *in*

We envisaged key bond disconnections across the diene at C9-C10 and the macrolactone, as well as at C17-C18.

situ MnO₂ monooxidation/olefination of diol **6** afforded **7**, which was isolated and purified before application of a second oxidation/olefination step, this time using PCC as oxidant, to give **3** (65% overall) with similar stereoselectivity (*E,E,E,Z* = 92:8).

With dienoate **3** in hand, we could now study the key conversion to THF **2**. Ideally, this would be effected directly *via* a novel one-pot Sharpless AD/Michael reaction. *Mono-* versus *bis*-dihydroxylation of the diene was a potential concern. While we could not find direct literature precedent for selective mono-AD on 2,6-dienoates, there was literature precedent for mono-dihydroxylation of this type of substrate under Upjohn conditions.⁸ Additionally, we hoped that *in situ* Michael reaction of the initially formed AD product would remove the potentially reactive second alkene before any second dihydroxylation could take place.

Scheme 2. Reagents and Conditions: (a) HCl (aq), THF, reflux, 2 h; (b) Ph₃P=CHCO₂Et, 3 Å MS, CH₂Cl₂, r.t., 36 h, 36%; (c) MnO₂, Ph₃P=CHCO₂Et, 48 h, 95%; (d) PCC, imidazole, Ph₃P=CHCO₂Et, 19 h, 65%.

question involved stereoselectivity in the Michael reaction, given the lack of stereocentres in the linking chain between C20 and C23. In one relevant precedent, Kobayashi observed non-diastereoselective cyclisation in a Michael reaction as part of his synthesis of the amphidinolide C17-C29 fragment.^{3d} While this was not encouraging, we hoped that use of alternative cyclisation conditions would allow improved stereocontrol. Application of standard Sharpless AD conditions¹⁰ to **3** with 1 equivalent of AD-mix-β (Table 1, entry 1) in the presence of methanesulfonamide effected complete reaction in < 2 h. The diol **8** was isolated in 85% yield together with 10% of the THF **2**, which was obtained as a 3:2 mixture of diastereoisomers according to ¹H NMR analysis. The enantiomeric excess of diol **8** was determined by chiral HPLC and found to be 73%. For comparison AD was also carried out with AD-mix-α (entry 2). Interestingly, this gave diol *ent*-**8** of lower ee (57% ee), despite the fact that the quinidine and quinine-derived ligands in the two AD-mixes usually behave as “pseudoenantiomers”, giving products of similar enantiomeric excess. We next attempted the AD reaction in the presence of additional base in an attempt to promote the cyclisation reaction (entries 3 and 4). While conversion was high and the THF **2** was now the major product, the yield was low, suggesting base-mediated decomposition. Moreover, the diastereoselectivity was consistently low (3:2). Since we had been able to isolate only low amounts of THF **2**, but good yields of diol **8**, we decided to investigate the cyclisation step separately. Treatment of **8** with 1 equiv of EtONa in EtOH/THF for 2 h gave **2** in 50% yield, again as a 3:2 mixture of diastereoisomers. Aprotic conditions (LHMDS in THF) gave very low conversion and an unchanged stereoisomeric ratio. We were able to separate small quantities of the two diastereomers, and re-submission of these to base allowed us to tentatively conclude that the minor, *cis*-diastereomer was thermodynamically preferred. We therefore decided to abandon the Michael addition and investigate alternative methods for THF formation.

Table 1. Dihydroxylation/Cyclisation of Dienoate **3**

Entry	AD-mix	Additive	Time (h)	Yield 8 (%)	Yield 2 (%)	2 <i>trans</i> : <i>cis</i> ^a
1	β	-	2	85	10	3:2
2 ^b	α	-	2	82	12	3:2
3	β	DBU (2 eq)	18	-	35	3:2
4	β	NaOH (2 eq)	8	-	40	3:2

^aDetermined by ¹H NMR analysis. Major isomer is the *trans*-THF by correlation with products from the iodocyclization route. ^b*Ent*-**8** and *ent*-**2** obtained in this experiment.

For the cyclisation step, we envisaged that the desired 5-*exo*-trig cyclisation mode would be kinetically preferred over the alternative possible 6-*exo*-trig.⁹ A further key

Iodocyclisation has been widely employed for THF synthesis¹¹ and was an attractive option. This was first attempted with the “unnatural” diol, *ent*-**8** (Scheme 3), affording a 3:1 mixture of *trans* and *cis* furans *ent*-**9b** and

ent-**9a**. Separation of the two diastereoisomers using flash chromatography gave the *trans*-diastereoisomer *ent*-**9b** as a pale yellow semi-crystalline solid, recrystallisation of which resulted in enhanced ee (93%) according to chiral HPLC analysis. X-ray crystallography¹² verified both the relative and the absolute configuration of *ent*-**9b**.

Scheme 3

We repeated the iodocyclisation with **8** itself (Scheme 3) to obtain **9b**. Resolution during recrystallisation again resulted in enrichment from 73% to over 93% ee.¹³ The improved cyclisation diastereoselectivity (albeit in a still-moderate 3:1 ratio), the significantly increased overall yield and the opportunity to improve the enantiomeric excess *via* resolution during the recrystallisation meant that the iodocyclisation approach towards the synthesis of this fragment was preferable to the earlier, base-mediated cyclisation.

Having desymmetrised the diene dioate **3**, we were now in a position to install the required functionality at either side of the THF unit (Scheme 4). Deiodination of **9b** could be effected efficiently using either tributyltin/cat. AIBN in toluene at 50 °C or with indium hydride,¹⁴ generated from NaBH₄/cat. InCl₃. Differentiation of the two ethyl esters was now accomplished by selective reduction of the α-hydroxy ester¹⁵ using BH₃·SMe₂/cat. NaBH₄. Hydroxy group differentiation was achieved by *bis*-TBS ether formation and selective primary deprotection, affording **11**. Dess-Martin oxidation in the presence of 1 equiv of H₂O¹⁶ afforded an unstable aldehyde in 80% yield which was then subjected to an *E*-selective olefination¹⁷ with a tributylphosphonium ylide to provide **12**¹⁸ (43% from alcohol **11**; 87:13, *E:Z*). The *E*-isomer was distinguished from the minor *Z*-isomer by coupling constant analysis (*J* H25-H26 = 15.1 vs 11.3 Hz). Reduction of the ethyl ester with DIBAL-H gave the corresponding aldehyde which was then converted to the 1,3-dithiane **1**.¹⁹ Use of BF₃·OEt₂ as Lewis acid in this step afforded **1** in only moderate yields due to competitive cleavage of the TBS ether. However, use of the milder Lewis acid MgBr₂·OEt₂ solved this problem, leading to formation of **1** (87:13, *E:Z*) in 75% yield (over two steps).

Scheme 4. Reagents and Conditions: (a) AIBN, *n*Bu₃SnH, toluene, reflux, 1 h, 95% or InCl₃, cat. NaBH₄, CH₃CN, 3 h, 73%; (b) (i) BH₃·SMe₂/THF, r.t.; (ii) NaBH₄; (iii) EtOH, TsOH, 60% (+ 18% starting material); (c) (i) TBSCl, imidazole DMF, r.t., overnight, 81%; (ii) HF.pyridine, pyridine, THF, r.t., 8 h, 86%; (d) Dess-Martin periodinane, CH₂Cl₂ (wet), rt, 5-15 min; (e) Me₂C=CHCH₂P⁺Bu₃Br⁻, *n*BuLi (in hexanes), DMSO, toluene, -78 °C to 0 °C, 43% (over two steps), 87:13 *E:Z*; (f) DIBAL-H, THF, -78° C, 1 h; (g) HS(CH₂)₃SH, MgBr₂·OEt₂, CH₂Cl₂, r.t., 1 h, 75% (over two steps).

Finally, we have performed preliminary studies demonstrating the feasibility of converting the amphidinolide F side-chain into that of amphidinolide C, *via* selective allylic oxidation at C29 (Scheme 5). We could find little literature precedent for SeO₂-mediated allylic oxidation²⁰ of acyclic 1,3-dienes, and this process could potentially result in a mixture of regioisomeric products. In the event, **12** underwent SeO₂ allylic oxidation to give, after chromatography, the desired allylic alcohol **13**²¹ (*ca.* 70%; *E,E*-configuration confirmed by NOE analysis), along with a 2:1 mixture assigned tentatively by ¹H NMR as aldehyde **14** and regioisomeric allylic alcohols **15**. This key transformation potentially allows access into amphidinolide C and analogues bearing unnatural side-chains at C29.

In conclusion, we have achieved a synthesis of the C18-C29 fragment **1** of amphidinolide F in twelve steps starting from commercially available butane-1,4-diol **6**. We have also demonstrated potential for further elaboration to amphidinolide C and analogues *via* oxidation at C29. Further studies towards these targets are currently underway.

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- We thank Dr. A.J.P. White, Dept. of Chemistry, Imperial College London, for determination of this crystal structure.
- Data for **9b**: pale yellow crystalline solid, m.p.= 58-60 °C, ee = 93% (chiral HPLC, chiralcel OD, 10% ⁱPrOH/hexane, 0.05 mL/min, 254 nm **9b** (153.8 min), *ent*-**9b** (164.0 min); **9b**; R_f 0.75, (50% EtOAc/petrol); [α]_D²⁰ -22.7 (c. 1.06, EtOH); IR (CHCl₃): ν_{max} 3436, 2982, 1736, 1281, 469 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.43 (td, *J* 7.6, 2.0 Hz, 1H), 4.38-4.31 (m, 1H), 4.30-4.12 (m, 4H), 4.02 (d, *J* 2.0 Hz, 1H), 2.93 (d, *J* 8.4 Hz, 1H), 2.44-2.36 (m, 1H), 2.17-2.01 (m, 2H), 1.87-1.78 (m, 1H), 1.68 (bs, 1H), 1.27 (t, *J* 7.2 Hz, 3H), 1.25 (t, *J* 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 172.5, 169.6, 80.84, 80.75, 72.4, 61.77, 61.75, 32.2, 27.5, 25.7, 14.1, 13.7; HRMS (CI) *m/z* calcd for C₁₂H₂₃NO₆I (MNH₄⁺), 404.0570, found: 404.0574.
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- Data for **12** (87:13, *E:Z*) R_f 0.82 (20% EtOAc/petrol); [α]_D²⁵ -32.0 (c. 1.04, EtOH); IR (CHCl₃): ν_{max} 1739, 1659, 1463, 1430, 1379, 1254 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.49 (dd, *J* 15.1, 11.1 Hz, 1H_{major}), 6.23 (app t, *J* 11.3 Hz, 1H_{minor}), 6.10 (d, *J* 11.3 Hz, 1H_{minor}), 5.85 (d, *J* 10.8 Hz, 1H_{major}), 5.56 (dd, *J* 15.1, 5.5 Hz, 1H_{major}), 5.30 (app t, *J* 10.6 Hz, 1H_{minor}), 4.38-4.28 (m, 1H), 4.23 (t, *J* 5.5 Hz, 1H), 4.15 (q, *J* 7.1 Hz, 2H), 4.00 (dt, *J* 7.1, 5.5 Hz, 1H), 2.61 (dd, *J* 15.0, 7.1 Hz, 1H), 2.43 (dd, *J* 15.0, 6.3 Hz, 1H), 2.15-2.03 (m, 1H), 1.95-1.85 (m, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.65-1.38 (m, 2H), 1.28 (t, *J* 7.1 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C (101 MHz, CDCl₃): δ 171.3, 137.0 (*Z*), 135.0 (*E*), 129.6 (*E*), 128.5 (*Z*), 127.5 (*E*), 125.7 (*Z*), 124.7 (*E*), 120.3 (*Z*), 82.3, 75.7, 75.1, 60.4, 40.9, 31.9, 26.9, 26.0, 25.9 (3 x C), 18.2 (2 x C), 14.2, -4.7 (2 x C); HRMS (CI) *m/z* calcd for C₂₁H₄₂NO₄Si (MNH₄⁺), 400.2883, found: 400.2883.
- Data for **1**: R_f 0.52 (10% EtOAc/Petrol); [α]_D²⁵ -25.3 (c. 1.02, EtOH); IR (CHCl₃): ν_{max} 1654, 1462, 1378, 1264, 1063 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.29 (app t, *J* 14.3 Hz, 1H), 5.87 (bd, *J* 11.1 Hz, 1H), 5.50-5.37 (m, 1H), 4.34-4.26 (m, 1H), 4.24-4.19 (m, 1H), 4.18-4.11 (m, 1H), 4.10-4.00 (m, 1H), 2.95-2.73 (m, 4H), 2.70-2.55 (m, 2H), 2.14-1.77 (m, 4H), 1.80 (s, 3H), 1.78 (s, 3H), 1.62-1.34 (m, 2H), 0.94 (s, 9H), 0.12 (s, (6H)); ¹³C NMR (101 MHz, CDCl₃): δ 137.6 (C_Z), 135.5 (C_E), 129.9 (CH_Z), 129.2 (CH_E), 128.0 (CH_E), 125.3 (CH_Z), 124.4 (CH_E), 122.9 (CH_Z), 81.3, 80.5, 76.1, 44.4, 41.8, 37.4, 33.5, 31.3, 30.4, 26.0, 25.6, 23.9, 20.8, 18.5, -3.6; HRMS (ESI) *m/z* calcd for C₁₆H₂₅OS₂ (M-OTBS⁺), 297.1347, found: 297.1374.
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- Data for **13**: R_f 0.76 (50% EtOAc/Petrol); ¹H NMR (400 MHz, CDCl₃): δ 6.56 (ddd, *J* 15.1, 11.1, 1.4 Hz, 1H), 6.11 (d, *J* 11.1 Hz, 1H), 5.73 (dd, *J* 15.1, 5.1 Hz, 1H), 4.37-4.27 (m, 2H), 4.17 (q, *J* 7.1 Hz, 2H), 4.11 (d, *J* 4.1 Hz, 2H), 4.06-4.00 (m, 1H), 2.61 (dd, *J* 15.0, 7.1 Hz, 1H), 2.45 (dd, *J* 15.0, 6.2 Hz, 1H), 2.12-1.84 (m, 2H), 1.82 (s, 3H), 1.83-1.72 (m, 1H), 1.58-1.36 (m, 2H), 1.29 (t, *J* 7.1 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).