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Synthesis of the C1–C12 fragment of amphidinolide T1☆

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Abstract—A synthesis of the C1–C12 fragment of amphidinolide T1 utilising Evans' aldol, oxy-Michael and cross metathesis reactions as the key steps is described.
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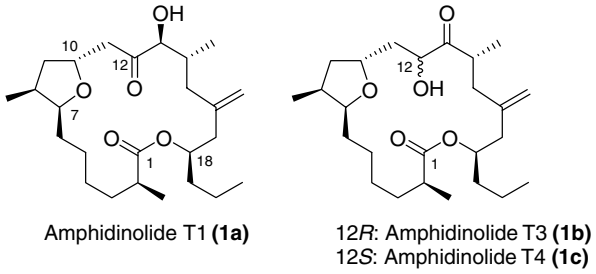
Amphidinolides are a rapidly growing class of cytotoxic macrolides isolated from the marine dinoflagellates *Amphidinium* sp.,[1] and have shown significant antitumour properties against a variety of NCI tumour cell lines. Amphidinolides **1** are extremely scarce, and as a result, biological studies have been limited. Amphidinolide T1 (**1a**) (Fig. 1) is a 19-membered macrolide possessing a trisubstituted tetrahydrofuran moiety, an α-hydroxy ketone, an exocyclic methylene group and a homoallylic ester linkage and has shown potent activity against murine lymphoma L1210 as well as human epidermoid carcinoma KB cell lines.[2] The structure of **1a** was initially established by NMR studies followed by X-ray analysis by Kobayashi and co-workers.[3] The significant clinical potential and unique structural architecture of amphidinolides have stimulated considerable interest in this synthesis to provide SARs of this class of molecules.

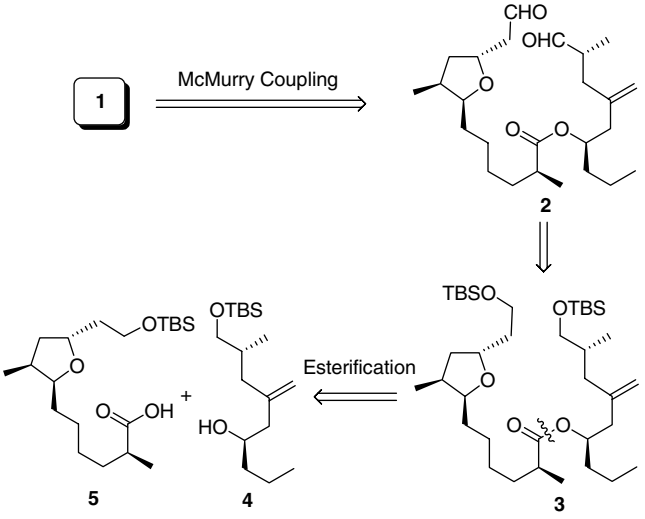


Amphidinolide T1 **(1a)**

12*R*: Amphidinolide T3 **(1b)**
12*S*: Amphidinolide T4 **(1c)**

Figure 1.

For the total synthesis[4] of **1a**, we envisioned retrosynthetically an intramolecular McMurry coupling on intermediate **2** (Scheme 1) to construct the C12–C13 bond keeping in mind that suitable manipulation of the McMurry product might also give amphidinolide T3 (**1b**) and amphidinolide T4 (**1c**) as they are the constitutional isomers of **1a**, displaying a reversal of the hydroxyl ketone pattern (ketone at C13 and hydroxyl group at C12). Intermediate **2**, in turn, could be obtained from **3**. Compound **3** could be obtained by coupling fragments **4** and **5**. Herein, we report a



Scheme 1.

Keywords: Amphidinolide; Evans' aldol; Oxy-Michael; Cross metathesis.

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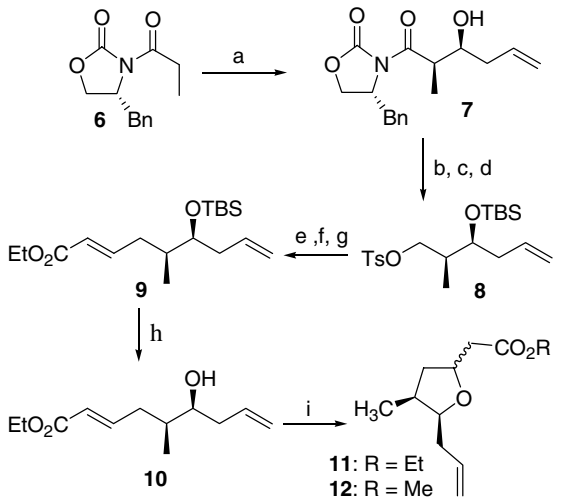
facile synthesis of the C1–C12 fragment (**5**) of amphidinolide T1.

Our synthesis commenced with the Crimmins modified Evans' strategy[5] involving condensation of 3-butenal[6] with (*R*)-4-benzyl-*N*-propionyloxazolidinone **6**, to give the *syn* aldol adduct **7** in 92% yield as a single diastereomer, as confirmed by NMR spectroscopy (Scheme 2). The hydroxyl group was protected as its TBS ether and the chiral auxiliary was reductively removed[7] with $NaBH_4$ to give the corresponding alcohol which was converted to its tosyl derivative **8** in 66% overall yield. The tosyl group was converted to a cyanide which was reduced with DIBAL-H, and the aldehyde thus obtained was homologated with carbethoxymethylene triphenylphosphorane to afford the α,β-unsaturated ester **9** in 71% overall yield. Treatment of **9** with TBAF led to the desilylated product which on in situ oxy-Michael reaction[8] gave the tri-substituted furan moiety **11** as a 1:1 diastereomeric mixture of 2,5-trans/cis isomers.



Scheme 2. Reagents and conditions: (a) $TiCl_4$, (−)-sparteine, 3-butenal, dry CH_2Cl_2, 0 °C, 30 min, 92%; (b) TBSOTf, DEIA, dry CH_2Cl_2, 0 °C, 2 h, 90%; (c) $NaBH_4$, THF/H_2O, 0 °C to rt, 40 h, 80%; (d) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 16 h, 92%; (e) NaCN, dry DMF, rt, 4 d, 88%; (f) DIBAL-H, dry CH_2Cl_2, −78 °C, 5 h, 90%; (g) $Ph_3P{=}CHCO_2Et$, C_6H_6, reflux, 16 h, 90%; (h) 3 N HCl, THF, rt, 16 h, 94%; (i) NaOMe, MeOH, −15 °C, 24 h, 95%.

At this juncture it was crucial to utilise conditions which forced higher trans selectivity in the oxy-Michael process. Towards this purpose compound **9** was desilylated with 3 N HCl in THF at room temperature to furnish alcohol **10** in 94% yield. The use of acidic conditions did not give any cyclised oxy-Michael product. Next, alcohol **10** was subjected to oxy-Michael reaction under various conditions some of which are summarised in Table 1. It was observed that in most of cases, poor selectivity was obtained irrespective of using different bases in different solvents at various temperature,[9] whereas in the case of NaOEt in EtOH at −15 °C (entry 3) compound **11** was obtained with 3.5:1 selectivity in favour of the trans isomer.[10] When alcohol **10** was treated with NaOMe in MeOH at −15 °C (entry 6), a slightly better selectivity of 4.5:1 was observed with concomitant transesterification to produce compound **12** in 95% isolated yield. Selectivity of 4:1 in favour of the trans isomer was also obtained using Triton B in MeOH (entry 7).

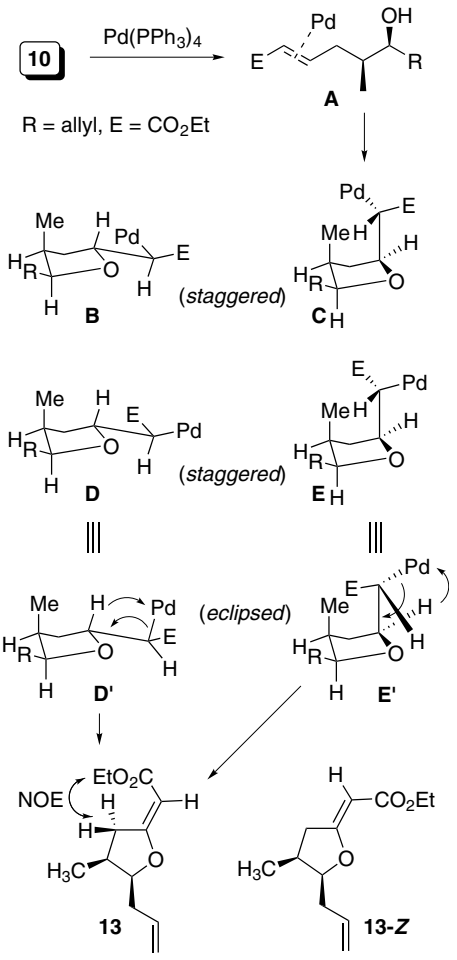
When compound **10** was treated with a palladium reagent in toluene, there was no oxy-Michael product, but instead compound **13** was obtained in 50% yield. The *E* configuration of **13** was confirmed by the fact that a NOE was observed between the ester group and the C-3 methylene group, whereas no significant NOE was detected between the latter and the exocyclic olefinic proton in **13**. Comparison of the chemical shift at δ 5.29 of the exocyclic olefinic proton within compound **13** with those of related compounds[11] also independently confirmed the *E* configuration of **13**.

Generally, this class of 2-alkylidenetetrahydrofurans are obtained from the corresponding β-keto esters.[12] Although, in the literature, palladium mediated intramolecular alkoxy-carbonylation[13] of hydroxy alkenes has been addressed, in our case, only the α,β-unsaturated olefin was engaged in the reaction leaving the

Table 1. Stereochemical outcome of oxy-Michael reactions of compound **10** under different conditions

Entry	Reaction conditions[a]	trans:cis[b]	Yield[c] (%)
1[d]	TBAF (1.1 equiv), THF, rt, 1 h	1:1	82
2	KO^{t}Bu (1.1 equiv), THF, −15 °C, 2 h	1:1	90
3	NaOEt (1.1 equiv), EtOH, −15 °C, 24 h	3.5:1	95
4	DBU (1.1 equiv), EtOH, 0 °C, 24 h	3:1	88
5	NaOEt (1.1 equiv), Ph_3P (1.1 equiv), EtOH, −15 °C, 24 h	2:1	92
6	NaOMe (1.1 equiv), MeOH, −15 °C, 24 h	4.5:1	95[e]
7	Triton B (1.1 equiv), MeOH, −15 °C, 24 h	4:1	90[e]
8	$BF_3{\cdot}OEt_2$, $CHCl_3$, rt, 12 h	—	[f]
9	NaHMDS (1.1 equiv), ether, −20 °C, 2 h	1:1	83
10	$Pd(PPh_3)_4$ (0.5 equiv), toluene, rt, 48 h	—	50 (**13**)[g]

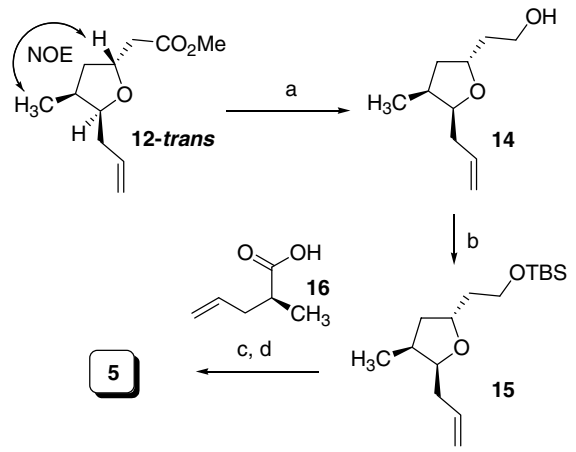
[a] 1.0 mmol of compound **10** was used.
[b] trans/cis ratio was measured by ^1H NMR spectroscopy.
[c] Isolated yield.
[d] Compound **9** was used as starting material.
[e] Compound **12** was obtained by transesterification.
[f] Complex reaction mixture was obtained.
[g] Recovered **10**, 40%.



Scheme 3.

terminal olefin untouched. The formation of compound **13** from **10** can be considered as an oxidative oxy-Michael reaction suitable for further exploration for application in synthetic organic chemistry. Mechanistically, it can be postulated that initially a palladium alkene π-complex **A** is formed (Scheme 3). Intramolecular attack by the hydroxyl group to the olefin could produce intermediates **B**–**E**; **B** and **C** are kinetically controlled intermediates whereas **D** and **E** are the thermodynamically stable intermediates with minimised dipolar and steric interactions. Intramolecular β-hydride elimination via a four-membered cyclic transition state through the *eclipsed* conformations **D**′ and **E**′ would generate compound **13**. It is also possible that intermediates **B** and **C** might initially produce compound **13-*Z*** (Scheme 3), which in the process of isolation and purification is converted into the thermodynamically more stable compound **13**.[14]

The two diastereomers of compound **12** were separated by preparative HPLC. Accordingly, the ester group within **12-*trans*** (Scheme 4) was reduced with $LiAlH_4$ in ether to give alcohol **14**. The hydroxyl group was protected as its TBS ether and the resulting olefinic compound **15** was subjected to a cross metathesis[15] reaction with **16**[16] using the second generation Grubbs' catalyst in dichloromethane under refluxing conditions.



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, dry THF, 0 °C to rt, 20 min, 70%; (b) TBSCl, imidazole, dry DMF, rt, 1 h, 90%, (c) Grubbs' 2nd generation cat, DCM, reflux, 16 h; (d) 10% Pd/C, EtOAc, 1 h, 50% (over two steps).

The crude material of this metathesis reaction was subjected to hydrogenation using 10% Pd/C in ethyl acetate and gratifyingly, we obtained desired compound **5** in 50% yield over the two steps.[17]

In conclusion, we have achieved a synthesis of the C1–C12 fragment of amphidinolide T1 utilising Evans' aldol, oxy-Michael and cross metathesis reactions as key steps. Currently, we are proceeding towards the total synthesis of this molecule. During these studies we have observed a palladium mediated oxidative oxy-Michael reaction which could be a useful protocol for the synthesis of various furan and pyran derivatives. Further studies are required to understand this process better. Optimisation of this reaction is currently underway and will be published in due course.

Acknowledgements

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17. Compound characterisation data for **12-*trans***: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.86–5.76 (m, 1H), 5.13–5.03 (m, 2H), 4.52–4.45 (m, 1H), 3.98–3.94 (m, 1H), 3.68 (s, 3H), 2.63 (dd, $J = 15.2$, 6.8 Hz, 1H), 2.43 (dd, $J = 15.2$, 6.2 Hz, 1H), 2.34–2.26 (m, 2H), 2.20–2.13 (m, 1H), 1.90–1.78 (m, 2H), 0.95 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.6, 135.2, 116.5, 80.8, 73.2, 51.6, 41.3, 39.7, 35.7, 34.9, 13.9; CIMS: *m*/*z* 199 (M+1). Compound **13**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.86–5.77 (m, 1H), 5.29 (t, $J = 1.5$ Hz, 1H), 5.19–5.11 (m, 2H), 4.37–4.32 (m, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.11 (ddd, $J = 18.0$, 7.6, 2.0 Hz, 1H), 2.99 (ddd, $J = 18.0$, 4.0, 1.6 Hz, 1H), 2.52–2.31 (m, 2H), 2.34–2.25 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 0.97 (d, $J = 7.3$, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 175.5, 168.8, 133.7, 117.7, 90.1, 85.2, 59.2, 38.8, 34.2, 33.8, 14.5, 13.6; ESMS: *m*/*z* 233 (M+23), HRMS *m*/*z* 233.1156, calcd for $C_{12}H_{18}O_3Na$ 233.1154. Compound **5**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.17–4.09 (m, 1H), 3.85–3.78 (m, 1H), 3.74–3.66 (m, 2H), 2.51–2.41 (m, 1H), 2.26–2.14 (m, 1H), 1.87–1.58 (m, 4H), 1.50–1.27 (m, 8H), 1.18 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 181.8, 80.8, 73.7, 60.7, 40.2, 39.9, 39.2, 35.9, 33.5, 30.2, 27.4, 26.7, 26.0, 18.3, 16.8, 14.1, −5.3; ESMS: *m*/*z* 395 (M+23); HRMS *m*/*z* 395.2594, calcd for $C_{20}H_{40}O_4SiNa$ 395.2589.