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Studies Towards the Synthesis of the Marine Metabolite, Octalactin A

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Abstract: Studies towards the synthesis of the marine metabolite octalactin A **1**, are described. Key steps in this strategy include an *anti* aldol reaction to set the C_7-C_8 stereochemistry, Horner Wadsworth Emmons coupling to give the trisubstituted *E*-double bond and a novel samarium-mediated cyclisation reaction. © 1997 Elsevier Science Ltd.

The metabolites octalactin A and B were isolated in 1991 from a marine actinomycete of the genus *Streptomyces*, found on the surface of a gorgonian octacoral.[1] Octalactin A **1** has been shown to have significant *in vitro* cytotoxicity towards both murine melanoma and human colon tumour cell lines (IC_{50} = 7.2 x 10^{-3} μg/mL and 0.5 μg/mL respectively).[1] Its novel fully saturated eight-membered ring lactone structure has made it the target of a number of recent synthetic studies.[2,3]

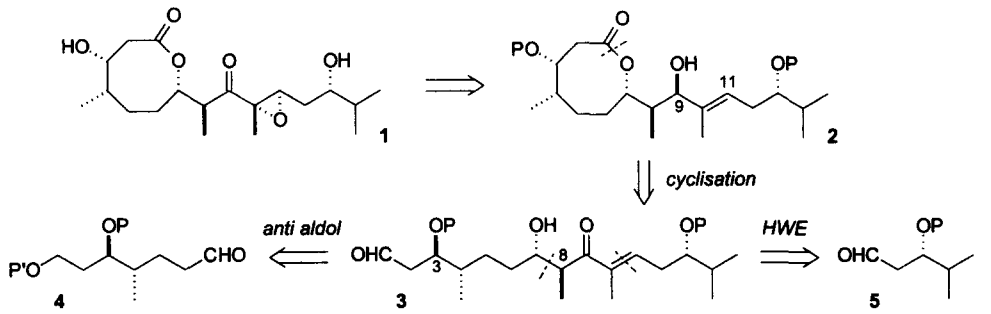
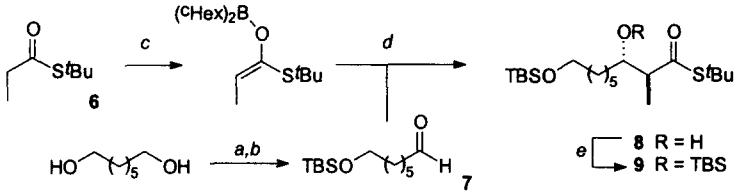


Figure 1

A retrosynthetic analysis of octalactin A is shown in **Figure 1**. Allylic alcohol **2**, a key intermediate, has previously been used to direct introduction of the C_{10}-C_{11} epoxide,[2] which is essential for the cytotoxic activity of this metabolite. In contrast to previous syntheses, the novel samarium-mediated cyclisation utilised in our strategy allows the *stereoselective* generation of the alcohol functionality at C_9. Synthesis of linear precursor **3** was planned from fragments **4** and **5** coupled *via anti* aldol and Horner Wadsworth Emmons reactions to a central five carbon unit. In order to study the cyclisation reaction we used a simple 1,7-difunctional aldehyde in place of the left hand fragment **4**, isovaleraldehyde as a model for aldehyde **5**, and we chose to work on racemic material.

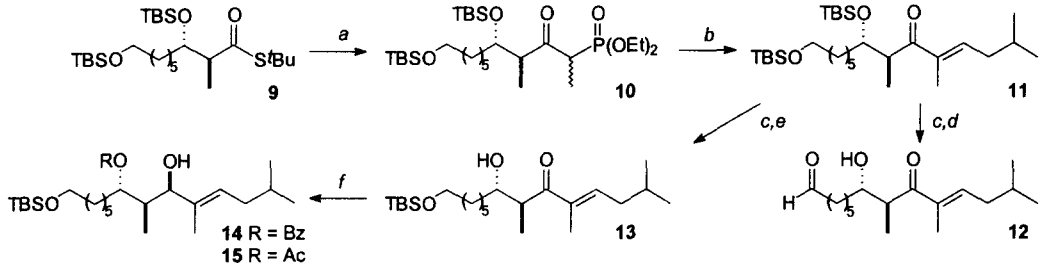
Recent advances in the boron mediated *anti* aldol reaction with thioesters have shown that high levels of both diastereo- and enantioselectivity may be achieved with the appropriate choice of ligand on boron and as a result it has been used successfully in the synthesis of many natural products containing such *anti*

stereochemistry.[4] Enolisation of *t*-butyl thioester **6**[5] (Et_3N, $^cHex_2BBr$) and reaction of the *E*(O)-enol borinate with 1,7-difunctionalised aldehyde **7** resulted in a 79% yield of the aldol adduct **8** with excellent diastereocontrol (>20:1 *anti:syn* as determined by ^1H nmr).[6] Silyl protection of the β-hydroxy ketone proceeded to give **9** in high yield (93%).



Scheme 1: (*a*) NaH, THF, rt, 40 min; TBDMSCl, rt, 25 min (82%); (*b*) IBX, THF/DMSO, rt, 1.5 h (90%); (*c*) Et_3N, $^cHex_2BBr$, Et_2O, 0 °C, 2.5 h; (*d*) **7**, -78 °C, 25 min; *L*-tartaric acid, -78 °C, 2 h; NaOH, H_2O_2, 2 h (79%);[7] (*e*) TBDMSCl, imidazole, DMF, rt, 24 h (93%).

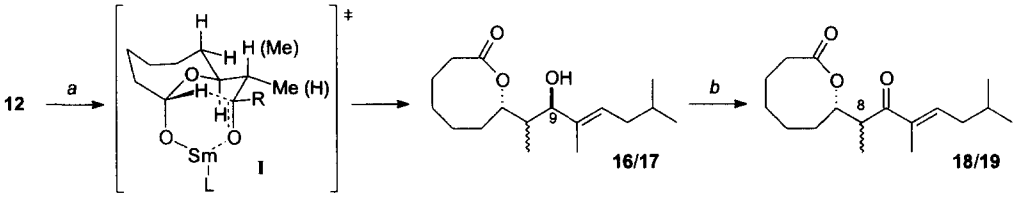
The coupling of a β-keto phosphonate and aldehyde *via* a Horner-Wadsworth-Emmons (HWE) reaction is a much utilised strategy for the formation of *E*-substituted double bonds.[8] Generation of the phosphonate substrate **10**, for the HWE reaction, was achieved by reaction of the *n*-butyl lithium derived anion of diethylethanephosphonate with protected β-hydroxy thioester **9** (**Scheme 2**).[9] Under mild HWE coupling conditions (activated $Ba(OH)_2$, THF(aq.))[10] in the presence of isovaleraldehyde, a high yield of the *E*-trisubstituted alkene **11** was obtained (85%). Subsequent deprotection (HF(aq.), MeCN/THF) and selective TEMPO oxidation[11] gave cyclisation precursor **12** (95% over two steps), which was used without further purification due to its instability.



Scheme 2: (*a*) *n*-BuLi, $EtP(O)(OEt)_2$, THF, -78 °C, 1 h; **9**, -78 °C, 1 h (94%); (*b*) $Ba(OH)_2$, THF(aq.), isovaleraldehyde, rt, 6 h (85%); (*c*) HF (40% aq.), MeCN/THF, 0 °C, 10 min; (*d*) TEMPO, $^nBu_4NCl$, NaOCl, NaBr, sat. $NaHCO_3$ (aq.), sat. NaCl (aq.), CH_2Cl_2, rt, 15 min (95% from **11**); (*e*) TBDMSCl, imidazole, DMF, rt, 4.5 h (85% from **11**); (*f*) PhCHO *or* MeCHO (4 eq.), SmI_2 (freshly prepared, 1M in THF, 60 mol%) THF, 0 °C, 10 min (70% both).

Recent reports of samarium catalysed cyclisation reactions of keto-aldehyde substrates have focused on the pinacol-based formation of 5- and 6-membered rings.[12] Of these reports, only one has examined the contrasting reactivity of Sm(II) and Sm(III) catalysts, which give rise to pinacol and Tishchenko reactions respectively.[12c] Tishchenko cyclisation reactions have also been reported using aluminium and lanthanum catalysts.[13] The Evans-Tishchenko reaction typically requires catalysis by 15-30 mol% of a SmI_2 solution in THF, and results in the directed reduction of a β-hydroxy ketone to give an *anti* diol with selective formation of a monoester (*anti:syn* >95:5).[14,15] The proposed mechanism invokes intramolecular hydride transfer from an intermediate hemiacetal *via* a transition state similar to **I** (**Scheme 3**)[14] and is thought to be catalysed by a SmI_3•$SmI(RCHO)_2$ pinacol adduct which is either preformed, or generated *in situ*. Evans-Tishchenko

coupling with either excess benzaldehyde, or acetaldehyde, on protected β-hydroxy enone **13** afforded the *anti* diol monoesters **14** and **15** each in 70% yield as single diastereomers (**Scheme 2**). To our knowledge, these are the first examples of an Evans-Tishchenko reaction using a β-hydroxy enone, thus considerably extending this methodology. However, when the intramolecular reaction was attempted on **12** using the preformed Sm(III) catalyst (**Scheme 3**), the formation of a 1:1 ratio of two inseparable diastereomers **16** and **17** was observed (30% combined yield). We believe that an Evans-Tishchenko coupling has occurred to give the lactone, since Tishchenko, or pinacol coupling onto the C_9 carbonyl itself can be excluded on the basis of the ^{1}H nmr data for the C_7H (δ=4.86-4.81, m) and C_9H (δ=3.88-3.85, 0.5H, m, & δ=3.84-3.91, 0.5H, m), which correlates extremely well with the data for acetate **15**.[6] A significant change in the chemical shift of the C_{11} vinylic proton (δ=6.62 ppm (**12**) → δ=5.47 ppm (**16/17**)) also confirmed reduction of the enone functionality.



Scheme 3: (*a*) PhCHO/SmI_2 (premixed, 0.4M in THF, 30 mol%) THF, 0 °C, 10 min (30%); (*b*) IBX, THF/DMSO, rt, 2.5 h (82%).

Oxidation of the diastereomeric mixture **16/17** with *o*-iodoxybenzoic acid (IBX) cleanly afforded two diastereomers **18** and **19**, which were now readily separable by chromatography.[16] This indicated that stereoselective hydride transfer had occurred during cyclisation (the *anti* stereochemical assignment at C_9 has been made on the basis of precedent[14]) and that loss of stereochemical integrity was perhaps due to epimerisation at C_8 prior to cyclisation.[17] Further evidence for this was found when the ^{1}H nmr spectrum of the reaction mixture prior to chromatography was examined and it was observed that the unreacted aldehyde **12** was now also a mixture of two diastereomers. Unfortunately, isolation of this unreacted aldehyde was not possible, due to its instability.

With hindsight, our approach to the initial investigation of the construction of the octalactin framework using an unfunctionalised eight membered ring precursor may have required the most demanding mode of cyclisation. In his approach to the octalactins, Andrus has shown that an unfunctionalised C_1-C_9 precursor gives only a 24% yield of the lactone under modified Keck-Boden macrolactonisation conditions, whereas the TBDMS protected, functionalised C_1-C_9 precursor cyclises in 81% yield under the same conditions.[2a] This has been ascribed to a predisposition of the functionalised substrate to adopt a chair-boat conformation favourable to cyclisation. We are hopeful that fully functionalised precursor **3** will give a similar increase in yield in our cyclisation reaction, and enhance the rate of cyclisation relative to that of competing epimerisation at C_8, (as seen with the reduction of β-hydroxy enone **13**).

We have demonstrated a convergent approach to the carbon framework of octalactin A **1**, which should allow a highly stereocontrolled synthesis of the key intermediate, allylic alcohol **2**. This approach has relied upon a novel samarium-mediated cyclisation strategy. Furthermore, we believe that this synthetic strategy offers an extremely flexible approach towards the synthesis of analogues of the octalactins that may be used to further investigate the structure-activity relationship of this cytotoxic marine metabolite.

Acknowledgements

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6. All new compounds gave spectroscopic data in agreement with the assigned structures: aldehyde **12**: Clear oil; IR (neat) υ_{max} 3456, 1722, 1655 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 9.69 (1H , t, J = 0.7 Hz), 6.62 (1H, t, J = 7.2 Hz), 3.74-3.52 (1H, m), 3.29-3.15 (1H, m), 3.07 (1H, br s), 2.36 (2H, td, J = 7.3 & 0.7 Hz), 2.10 (2H, dd≡t, J = 7.2 Hz), 1.82-1.20 (9H, m), 1.70 (3H, s), 1.09 (3H, d, J = 7.3 Hz), 0.88 (6H, d, J = 6.6 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 206.4, 201.7, 141.9, 136.4, 72.9, 42.6 (2C), 37.0, 33.6, 27.8, 27.1, 24.4, 21.2 (2C), 20.7, 14.8, 10.2; acetate **15**: Clear oil; IR (neat) υ_{max} 3456, 1717, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 5.44 (1H, t, J = 7.4 Hz), 4.79 (1H, dt≡q, J = 6.4 Hz), 3.90-3.82 (1H, m), 3.55 (2H, t, J = 6.2 Hz), 2.03 (3H, s), 1.90 (2H, dd≡t, J = 7.0 Hz), 1.88-1.72 (1H, m), 1.68-1.18 (11H, m), 1.54 (3H, s), 0.90-0.79 (18H, m), 0.0 (6H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) 171.3, 135.3, 125.0, 76.0, 75.9, 63.0, 39.0, 36.6, 32.6, 30.6, 29.1, 28.6, 25.8 (3C), 25.5, 25.4 , 22.3 (2C), 21.0, 18.2, 12.8, 9.3, -5.5 (2C); m/z (FAB) 443 ($[M+H]^+$, 1), 425 (10), 364 (31), 73 (100%); HRMS (FAB) Calculated for $C_{25}H_{51}O_4Si$ $[M+H]^+$: 443.3557, found: 443.3556; lactones **16/17**: Clear oil; IR (neat) υ_{max} 3420, 1726 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 5.47 (1H, tq, J = 7.4 & 1.3 Hz), 4.86-4.81 (1H, m), 3.88-3.85 (0.5H, m), 3.84-3.81 (0.5H, m), 2.42-2.27 (2H, m), 2.09 (0.5H, d, J = 3.7 Hz), 2.05 (0.5H, d, J = 3.7 Hz), 1.93 (2H, dd≡t, J = 7.4 Hz), 1.88-1.82 (1H, m), 1.81-1.50 (8H, m), 1.40-1.20 (4H, m), 0.90-0.87 (6H, m), 0.82 (1.5H, d, J = 7.0 Hz), 0.81 (1.5H, d, J = 7.0Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 174.1, 173.8, 135.3, 135.2, 125.0, 124.8, 75.7, 75.6*, 74.7, 38.8*, 36.6*, 33.6, 33.4, 30.5*, 28.6*, 28.5, 28.2, 24.4*, 24.0*, 22.4*, 22.2*, 13.0*, 9.1, 9.0 (*=peaks common to **16** and **17**); m/z (FAB) 283 ($[M+H]^+$, 2), 265 (20), 55 (100%); HRMS (FAB) Calculated for $C_{17}H_{31}O_3$ $[M+H]^+$: 283.2273, found: 283.2267; enone **18**: Clear oil; IR (neat) υ_{max} 1726, 1658 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 6.89 (1H, t, J = 7.3 Hz), 5.06-5.00 (1H, m), 3.67 (1H, dq≡qn, J = 6.8 Hz), 2.32-2.22 (2H, m), 2.18 (2H, dd≡t, J = 7.0 Hz), 1.90-1.75 (1H, m), 1.75 (3H, s), 1.65-1.20 (8H, m), 1.00 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.6 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 202.5, 172.8, 142.8, 137.1, 74.5, 41.6, 38.2, 33.8, 28.8, 28.3 (2C), 24.6, 23.8, 22.4 (2C), 11.6, 11.2; m/z (FAB) 281 ($[M+H]^+$, 7), 263 (4), 125 (44), 92 (100%); enone **19**: Clear oil; IR (neat) υ_{max} 1731, 1665 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 6.78 (1H, td, J = 7.3 & 1.2 Hz), 5.07-5.01 (1H, m), 3.58 (1H, dq≡qn, J = 7.0 Hz), 2.23 (2H, t, J = 6.0 Hz), 2.15 (2H, dd, J = 7.3 & 6.6 Hz), 1.84 (1H, spt, J = 6.6 Hz), 1.72 (3H, d, J = 1.2 Hz), 1.71-1.20 (8H, m), 1.02 (3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) 202.7, 172.9, 142.3, 137.2, 75.4, 42.0, 38.2, 33.6, 29.6, 28.6, 28.3, 24.4, 24.2, 22.4 (2C), 12.5, 11.7; m/z (FAB) 281 ($[M+H]^+$, 4), 263 (3), 92 (82), 74 (100%).
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