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A chirally catalysed ene reaction in a novel formal total synthesis of the antitumor agent laulimalide

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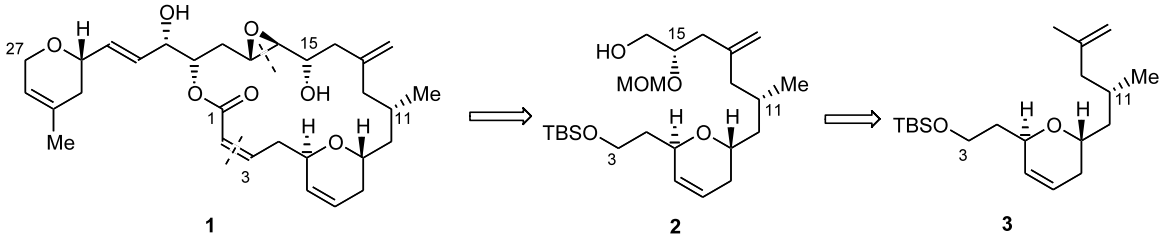
Abstract—A short highly efficient synthesis of the C3–C16 fragment **2** of laulimalide **1** is described. Fragment **2** was a key intermediate in a previous approach and thus constitutes a formal total synthesis with improved efficiency. The key steps are an Evans' alkylation, a Brown allylation and a chirally catalysed stereocontrolled ene-reaction.

The marine natural product laulimalide **1**, a metabolite of various sponges[1] has received attention as a potential anti-tumour agent due to its ability to stabilise microtubuli.[2] As part of a wider study of such 'Taxol™-like' compounds,[3] including the epothilones,[4] discodermolide[5] and eleutherobin,[6] we required multiple, flexible approaches to the synthesis of laulimalide and suitable analogues.[7] To this end we wished to improve the efficiency of our earlier syntheses,[7] in particular the preparation of the 'right-hand' C3–C16 fragment (**2**). Previous synthetic efforts[8–11] generally started with derivatives from the chiral carbon pool as a commercial source for the stereogenic centre at C11. Our intention was to install this stereogenic unit via asymmetric synthesis. Another key part of the strategy lay in the use of a chirally catalysed ene reaction[12] between olefin **3** and ethyl glyoxylate for the creation of the C15 stereocentre (Scheme 1). This enabled us to have no reactive functionality at one end of the molecule, and eliminated the need for protecting groups. This route also avoided the harsh conditions and low yields associated with methods for installing exo-methylene units late in the synthesis.[8,10a,c,d]

The synthesis (Scheme 2) began with the alkylation of Evans' *N*-propionyl-oxazolidinone **4** with 3-bromo-2-methylpropene, which proceeded in excellent yield and d.e. to provide **5** having the required laulimalide stereochemistry for the C11 methyl. Following cleavage of the auxiliary (which was recovered in >80% yield and recycled) the resulting alcohol was homologated to nitrile **6**. These steps could be carried out without purification and were achieved in good overall yield. The aldehyde **7** generated from the nitrile was immediately treated with (−)-Ipc-allylborane[13] to provide the compound with the required stereocentre for C9 in excellent d.e. (**8**). The dihydropyran **10** was constructed by formation of the mixed allylic acetal and ring closure by metathesis with Grubbs' catalyst **9**.[14] No side-reaction with the exo-methylene was observed, presumably due to the unfavoured ring-size (7 versus 6) and the lower reactivity of the di-substituted double



1 2 3

Scheme 1.

Keywords: antitumor compounds; microtubule stabilisation; stereoselective synthesis; natural products; ene reaction.

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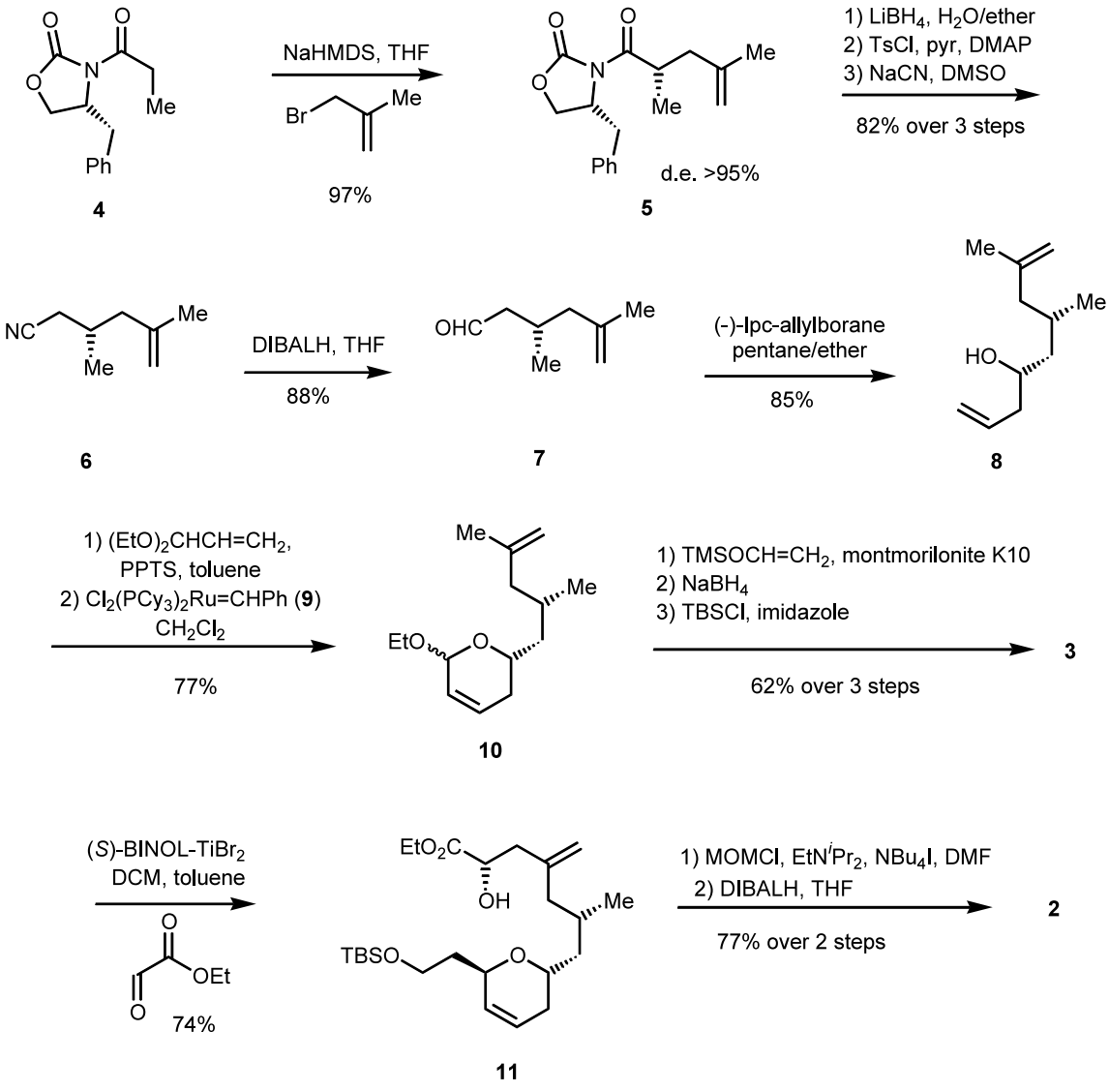

Scheme 2.

bond compared with the terminal double bonds. The C3/4 side chain was then easily installed by acid-catalysed formation of the oxonium ion and reaction with trimethyl-vinyloxysilane; the stereochemistry at C5 being completely controlled by the existing C9 centre. The crude product was then reduced to the alcohol and protected as the TBS ether (**3**). The C15 centre was then formed by an ene reaction. Treatment of the terminal allyl with ethyl glyoxylate in the presence of catalytic (*S*)-BINOL–$TiBr_2$ provided[15] the required alcohol **11** with excellent stereocontrol (>95% ds) which was subsequently protected as the MOM-ether and reduced to the intermediate alcohol **2**[16] from our first laulimalide synthesis.[8]

The described route improves our previous preparation of **2** to 14 steps (10 purification steps) and a 16% overall yield and, within 10 more steps,[8] constitutes a formal total synthesis of laulimalide itself. All four chiral centres in **2** were created via stereocontrolled synthesis, without recourse to chiral carbon pool fragments as with the majority of earlier syntheses. The route also compares very favourably with previous preparations of similar C3–C16 fragments.[8–11]

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15. Experimental procedure for the ene reaction of **3** to **11**: 4 Å molecular sieves (110 mg) with 6–8 weight% of water under an atmosphere of argon was added to a solution of (*S*)-(−)-1,1′-binaphthol (9 mg, 30.2 μmol) in dichloromethane (2 mL) and stirred at room temperature for 20 min. A solution of di(isopropoxy)dibromotitane (1.0 M in toluene, 27 μL) was added and the resulting deep red solution stirred for 1 h. To this mixture was added (2*S*,6*R*,2′*R*)-6-[2″-(*tert*-butyldimethylsilyloxy)-ethyl]-2-(2′,4′-dimethylpent-4-enyl)-5,6-dihydro-2*H*-pyran (**3**) (60 mg, 178 μmol) in dichloromethane (5 mL) followed by ethyl glyoxylate solution (50% in toluene w/w, 40 μL, 178 μmol). The reaction mixture was stirred at room temperature for 20 h, then quenched by addition of saturated sodium bicarbonate solution (8 mL) then diluted with water (10 mL) and extracted with ethyl acetate. Combined organic layers were dried ($MgSO_4$) and filtered through a pad of Celite. The filtrate was concentrated in vacuo then passed down a flash chromatography column (silica, 4:1 hexanes/ethyl acetate) to give **11** as a colourless oil (58 mg, 74%, >95% pure by NMR); δ_H (400 MHz; $CDCl_3$) 5.79 (1H, m, ring =CH), 5.70 (1H, m, ring =CH), 4.92 (2H, s, $=CH_2$), 4.25 (1H, m, OCH), 4.18 (3H, m and q, *J* 6.8, $OC\underline{H}_2Me$, C<u>H</u>OH), 3.68 (3H, m, $TBSOC\underline{H}_2$ and OCH), 2.58 (2H, m, $CHOHC\underline{H}_2$), 2.31–1.83 (4H, m, $2\times C\underline{H}_2C$=), 1.75 (1H, m, C<u>H</u>Me), 1.59 (2H, m, $TBSOCH_2C\underline{H}_2$), 1.24 (3H, t, *J* 6.8, $CH_2\underline{Me}$), 1.19 (2H, m, $CHMeC\underline{H}_2$), 0.84 (9H, s, ^{t}BuSi) and 0.82 (3H, d, *J* 6.6, CH<u>Me</u>); δ_C (100.6 MHz; $CDCl_3$) 175.1 (C=O), 143.6 (=C), 130.3 (=CH), 124.5 (=CH), 115.0 ($=CH_2$), 69.8 (CHO), 65.6 (CHO), 65.2 (CHO), 62.0 ($SiOCH_2$), 60.3 (OCH_2), 44.9 (CH_2), 43.2 (CH_2), 41.0 (CH_2), 37.3 (CH_2), 32.0 (CH_2), 26.3 ($C\underline{Me}_3$), 20.9 (CH), 19.5 (Me), 18.7 ($\underline{C}Me_3$), 14.6 ($CH_2\underline{Me}$) and −4.9 ($SiMe_2$).
16. Data of **2** was identical to that previously published for this compound (Ref. 8): $[\alpha]_D^{20}$ −18.0 (*c* 0.45 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 5.80 (1H, m, =CH), 5.70 (1H, m, =CH), 4.85 (2H, 2br s, $=CH_2$), 4.71 (2H, 2d (ABX), *J* 7.1, $OC\underline{H}_2OMe$), 4.35 (1H, m, OCH), 3.80–3.59 (4H, m, $TBSOC\underline{H}_2$ and $HOC\underline{H}_2$), 3.62 (1H, m, C<u>H</u>H), 3.54 (1H, m, CH<u>H</u>), 3.43 (3H, s, $OCH_2O\underline{Me}$), 2.96 (1H, m, OCH), 2.22 (2H, 2dd (ABX), *J* 14.4 and 6.8, $C\underline{H}_2C=CH_2$), 2.04–1.79 (6H, m, various), 1.66 (2H, m, CH_2), 1.13 (1H, m, C<u>H</u>Me), 0.91 (9H, s, ^{t}Bu), 0.89 (3H, d, *J* 6.4, CH<u>Me</u>) and 0.07 (6H, s, $SiMe_2$).