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A de Novo Enantioselective Total Synthesis of (−)-Laulimalide

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Laulimalide (**1**) is a naturally occurring microtubule-stabilizing agent first isolated from the marine sponges *Hyattella* sp. and *Spongia mycofijiensis*.[1,2] This pharmacological profile undoubtedly contributed toward inspiring the recent total syntheses of laulimalide.[3] We were attracted to laulimalide as a platform for evaluating the utility of catalytic asymmetric acyl halide−aldehyde cyclocondensation (AAC) reactions in complex molecule synthesis (Figure 1).[4] The synthesis of laulimalide would proceed from the indicated "lower (**2**)" and "upper (**3**)" fragments in which AAC-based bond constructions would play a central role in defining the requisite sterechemical relationships. The utility of AAC-based reaction methodology in an enantioselective total synthesis of (−)-laulimalide is described herein.

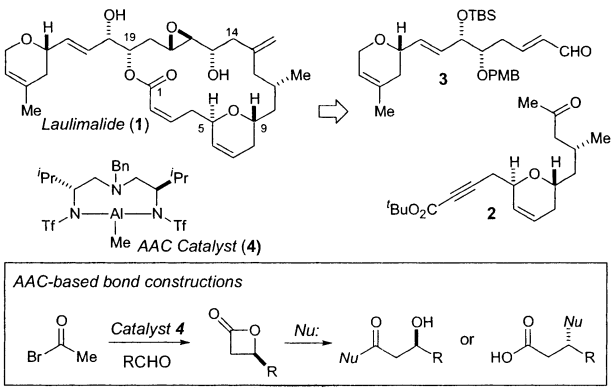
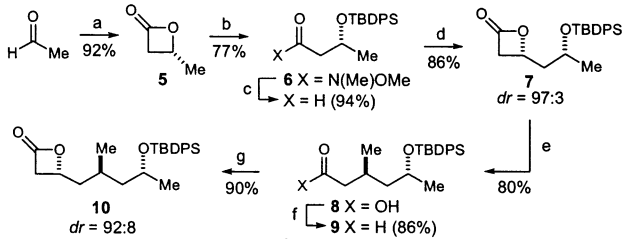


Figure 1. AAC methodology applied to laulimalide synthesis.

Construction of the lower subunit **2** commenced with the AAC-derived (*R*)-propiolactone (**5**, >98% ee) (Scheme 1). Aluminum *N*,*O*-dimethylhydroxylamide-mediated lactone ring opening and hydroxyl protection afforded the *β*-silyloxy amide **6**.[5] Amide-to-aldehyde interconversion and ensuing AAC homologation afforded the 1,3-*syn*-*β*-lactone **7** (dr = 97:3). Cuprate-mediated S_N2 *β*-lactone ring opening next installed the C_{11} methyl-bearing stereocenter in providing carboxylic acid **8**.[6] Acid-to-aldehyde interconversion then afforded aldehyde **9** required for iterative AAC homologation.[7] In the event, subjecting **9** to the AAC reaction conditions established the C_9 stereocenter in delivering the *anti*,*anti*-*β*-lactone **10** (dr = 92:8).

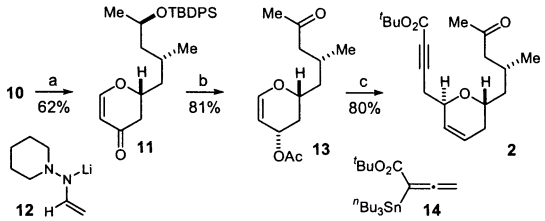
Completing the lower synthon next required the interconversion of *β*-lactone **10** to the dihydropyrone **11** (Scheme 2). The *β*-lactone-to-dihydropyrone relationship was established by reacting **10** with hydrazone anion **12** followed by acid treatment to afford dihydropyrone **11**.[8] Diastereoselective carbonyl reduction of **11** to give the diequatorial glycal proceeded according to Danishefsky's precedent with routine functional group manipulations delivering glycal acetate **13**.[9] Glycal **13** provided the conduit for installing the C_1-C_4 enone side chain via nucleophilic addition to the glycal acetate electrophile. Glycal alkylation with carboalkoxy allenylstannane **14** (5 equiv)[10]

Scheme 1 [a]



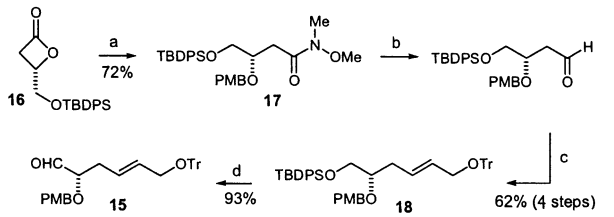
[a] a) 10 mol % **4**, MeCOBr, ^{i}Pr$_2$NEt, ^{n}Bu$_4$NBr, −78 °C. b) i. Me$_2$AlCl, (MeO)MeNH$_2$Cl; ii. ^{t}BuPh$_2$SiCl, imidazole. c) ^{i}Bu$_2$AlH. d) 10 mol % **4**, MeCOBr, ^{i}Pr$_2$NEt, −50 °C. e) MeMgBr, CuBr·DMS. f) i. BH$_3$·SMe$_2$; ii. PCC. g) 15 mol % **4**, MeCOBr, ^{i}Pr$_2$NEt, −50 °C.

Scheme 2 [a]



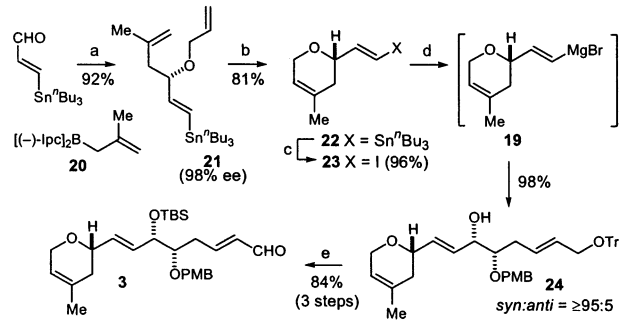
[a] a) Reference 8. b) i. NaBH$_4$, CeCl$_3$·7H$_2$O,; ii. Ac$_2$O, Et$_3$N, DMAP; iii. ^{n}Bu$_4$NF; iv. PDC. c) ^{n}Bu$_3$SnOTf, 5 equiv **14**, CH$_2$Cl$_2$.

Scheme 3 [a]



[a] a) i. (MeO)MeNH$_2$Cl, Me$_2$AlCl; ii. PMBO(C=NH)CCl$_3$, triflic acid. b) ^{i}Bu$_2$AlH. c) Ph$_3$P=CHCO$_2$Et; ii. ^{i}Bu$_2$AlH; iii. TrCl, 2,6-lutidine. d) i. ^{n}Bu$_4$NF; ii. Dess−Martin periodinane.

Scheme 4 [a]



[a] a) i. **20**, CH$_2$Cl$_2$.; ii. KHMDS, CH$_2$CHCH$_2$Br. b) Schrock catalyst (ref 14). c) NIS. d) i. ^{t}BuLi, Et$_2$O; ii. MgBr$_2$; iii. **15**, CH$_2$Cl$_2$. e) i. TBSCl, imid.; ii. HCOOH, MeNO$_2$; iii. Dess−Martin periodinane.

was best achieved using ^{n}Bu$_3$SnOTf (1 equiv) as the Lewis acid activator and afforded stereoselective anti S_N2' addition in delivering the completed lower synthon **2**.[11]

Preparing the upper synthon **3** was initiated by synthesizing the

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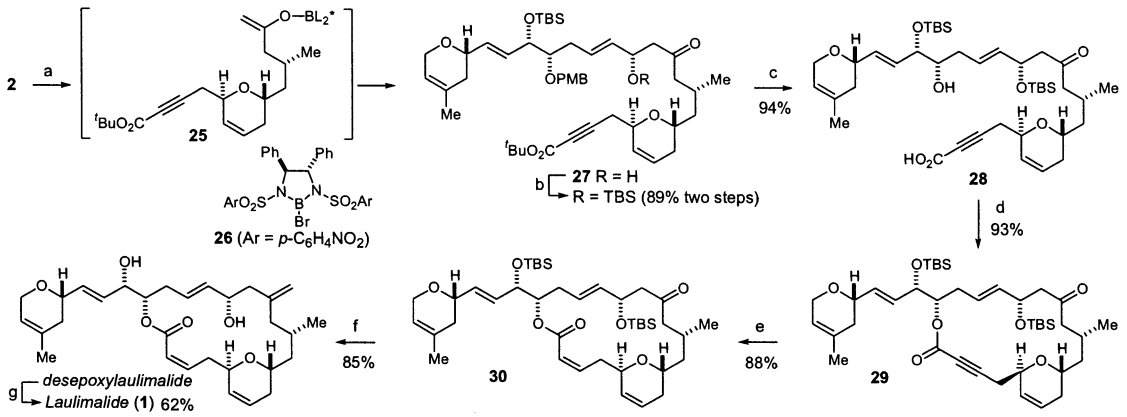
Scheme 5 [a]



[a] a) i. **26**, $^{i}Pr_2NEt$, CH_2Cl_2, −78 °C; ii. **3**. b) TBSCl, imidazole. c) i. DDQ, CH_2Cl_2/pH 7 buffer; ii. TMSOTf, 2,6-di-^{t}butylpyridine; iii. pH 5 buffer. d) 2,4,6-$Cl_3C_6H_2COCl$, $^{i}Pr_2NEt$, 4-pyrrolidinopyridine. e) H_2, Pd-$CaCO_3$. f) i. CH_2I_2, Zn, $PbCl_2$, $TiCl_4$; ii. HF·pyr. g) 20 mol% $Ti(O^{i}Pr)_4$, 20 mol% (+)-DIPT, ^{t}BuOOH.

α-alkoxy aldehyde **15** (Scheme 3). The synthesis began with *β*-lactone **16** (92% ee) derived from the corresponding AAC reaction. Amine-mediated ring opening and hydroxyl group protection delivered Weinreb amide **17**. Following amide-to-aldehyde interconversion, Wittig olefination, ester reduction, and alcohol protection afforded the orthogonally protected triol **18**. Silyl ether deprotection and alcohol oxidation completed the targeted α-alkoxy aldehyde synthon **15**.

Completing the upper synthon was predicated on achieving the diastereoselective coupling of vinyl anion **19** and α-alkoxy aldehyde electrophile **15** (Scheme 4). The synthesis of the requisite precursor to **19** commenced with Brown allylation[12] of *β*-tributylstannyl acrolein using allyl borane **20** to provide the desired secondary alcohol (98% ee); subsequent alcohol etherification provided triene **21**. Olefin metathesis within **21** was expected to exhibit a kinetic preference for engaging the mono- and 1,1-disubstituted olefins in six-membered ring formation in preference to the sterically more encumbered 1,2-disubstituted stannyl alkene.[13] Schrock's Mo(VI)-based metathesis catalyst proved especially efficient in mediating the desired pyran ring formation to give pyran **22**;[14] subjecting **22** to tin−halogen exchange completed the vinyl anion precursor **23**. Coupling of **15** and **23** was achieved with complete chelate-controlled diastereoselection by reacting the vinyl Grignard reagent **19**[15] derived from **23** with aldehyde **15** in dichloromethane solvent to afford the desired $C_{19}-C_{20}$ *syn*-diol relationship present in **24**.[16] A routine protection−deprotection−oxidation sequence then completed the upper synthon **3**.

Coupling the intact major synthons was predicated on establishing the $C_{14}-C_{15}$ bond with concomitant control of the C_{15} carbinol stereocenter (Scheme 5). Diastereoselective fragment coupling was achieved by first converting methyl ketone **2** to the chiral boron enolate **25** derived from the optically active bromo-borane reagent **26**.[17,18] Reacting boron enolate **25** with the top-half aldehyde **3** delivered aldol adduct **27** as a 9:1 (*S*:*R*) mixture of C_{15} diastereomers.[19] Successive deprotection of the PMB ether and *tert*-butyl ester present in **27** delivered the lactonization precursor **28**. Subjecting propargylic acid **28** to modified Yamaguchi macrolactonization conditions efficiently provided the desired macrolactone **29**.[20] Catalyzed alkyne dihydrogenation under Lindlar conditions successfully transformed propargylic ester **29** to the requisite C_2-C_3 *Z*-alkene **30**. Paterson had previously transformed **30** to synthetic (−)-laulimalide;[3b] this same sequence of C_{13} ketone methylenation, silyl ether deprotection, and diastereoselective Sharpless epoxidation[21] of the $C_{16}-C_{17}$ olefin completed the present total synthesis.

A de novo enantioselective total synthesis of (−)-laulimalide has been achieved. The synthesis is characterized by extensive use of new reaction methodology derived from asymmetric AAC reactions and ensuing transformations of the derived enantioenriched *β*-lactones.

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Supporting Information Available: Experimental procedures and representative ^{1}H and ^{13}C spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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