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Synthetic studies toward the microtubule-stabilizing agent laulimalide: synthesis of the C_{15}–C_{28} fragment

B. Travis Messenger and Bradley S. Davidson*

Department of Chemistry and Biochemistry, Utah State University, Logan, UT 84322-0300, USA

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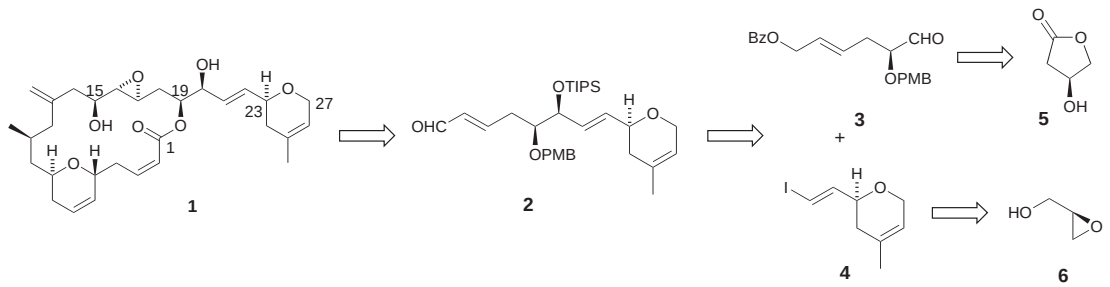
Abstract—The C_{15}–C_{28} fragment of the paclitaxel-like antimicrotubule agent laulimalide has been synthesized in 12 linear steps with an overall yield of 14%. The methyldihydropyran ring of the side chain was efficiently prepared using ring-closing olefin metathesis chemistry and the 19,20-*syn*-diol was generated through the addition of a mixed vinyl zincate to a protected α-hydroxyaldehyde. © 2001 Published by Elsevier Science Ltd.

As part of a program aimed at the discovery of new antimicrotubule agents, we recently identified the marine macrolide laulimalide (**1**)[1] as a new paclitaxel (Taxol™)-like microtubule-stabilizing agent.[2] Like paclitaxel, laulimalide induces the dose-dependent reorganization of cellular microtubules, as well as the formation of abnormal mitotic spindles. It stimulates the polymerization of tubulin in the absence of polymerization promoters such as glycerol and GTP. Laulimalide is a potent inhibitor of cellular proliferation with IC_{50} values in the low nanomolar range against drug sensitive cell lines and, in contrast to paclitaxel, it retains activity against SKVLB-1 cells, a P-glycoprotein overexpressing multidrug resistant ovarian cancer cell line, suggesting that it is a poor substrate for transport by P-glycoprotein. Furthermore, laulimalide triggers apoptotic cell death. Laulimalide, therefore, represents a new class of microtubule-stabilizing agent, with activities that may prove therapeutically useful, placing it within an exclusive group of compounds that, in addition to the taxanes, includes only the marine metabolites discodermolide[3] and eleutherobin[4] and the microbial metabolites the epothilones.[5]

Considering its potent biological activity and interesting structure, laulimalide has attracted surprisingly little interest from synthetic organic chemists. Three groups have published a total of seven papers describing their synthetic efforts related to laulimalide,[6,7] including five reports of syntheses of the C_1–C_{16} portion of the macrocyclic ring and two reports of a preparation of the C_{12}–C_{29} fragment of the molecule.[6a–c] In addition, we recently completed a hetero Diels–Alder approach to the preparation of the C_{20}–C_{26} side chain of laulimalide,[8] and in the adjoining paper we describe a synthesis of the C_1–C_{14} segment of laulimalide.[9] In this communication, we would like to describe our approach to the synthesis of the C_{15}–C_{28} portion of laulimalide.



Scheme 1. Retrosynthetic analysis.

* Corresponding author.

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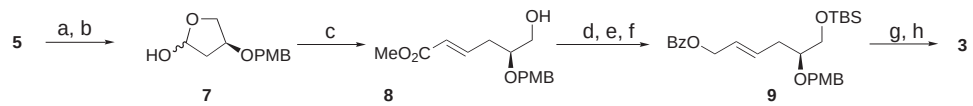
Our retrosynthetic analysis is shown in Scheme 1. Considering the lability of the epoxide group, we envisioned its incorporation late in the synthesis. Our strategy involves dividing the C_{15}–C_{28} fragment (**2**) into two pieces, **3** (C_{15}–C_{20}) and **4** (C_{21}–C_{28}), which we proposed to couple via the chelation-controlled addition of a vinyl anion generated from **4** to the aldehyde of **3**.[10] Fragment **3** was to be prepared in a straightforward manner from commercially available (*S*)-(−)-β-hydroxy-γ-butyrolactone **5**,[11] while fragment **4** was to be constructed from (*R*)-glycidol **6**, using ring-closing olefin metathesis chemistry.[12]

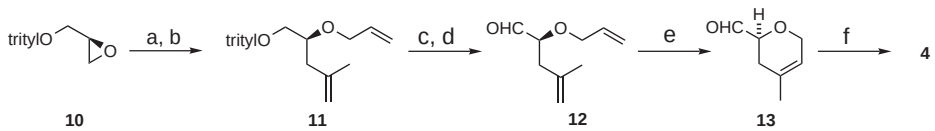
The synthesis of fragment **3** is outlined in Scheme 2. Treatment of **5** with PMB–trichloroacetimidate[13] and BF_3–OEt_2 provided the protected lactone. Reduction with one equivalent of DIBAL gave hemiacetal **7** (99%), which was treated directly with methyl (triphenylphosphoranylidene)acetate in benzene, yielding unsaturated ester **8** in 90% yield. The protection of the primary alcohol as its TBS ether (99%) was followed by reduction of the ester (97%), and protection of the resulting alcohol as its benzoate ester, giving fully protected **9** in 82% yield. Finally, treatment of **9** with TBAF provided a primary alcohol (63%) that was oxidized to give fragment **3** (88%).

The synthesis of fragment **4** (Scheme 3) started with the copper(I)-catalyzed addition of isopropenylmagnesium bromide to trityl-protected (*S*)-glycidol **10**, to give a secondary alcohol (99%) that was converted to its allyl ether **11** with allyl bromide/KH (99%). After cleavage of the trityl group with TFA in CH_2Cl_2 (71%), the primary alcohol was oxidized to aldehyde **12** (92%). The diene aldehyde was then subjected to RCM conditions using Grubbs' catalyst,[12] cleanly providing ring-closed product **13** in 66% yield. Vinyl iodide **4** was then obtained using Takai's iodoolefination reaction,[14] albeit in low yield (48%) after purification from a 6:1 mixture of *trans*:*cis* isomers.

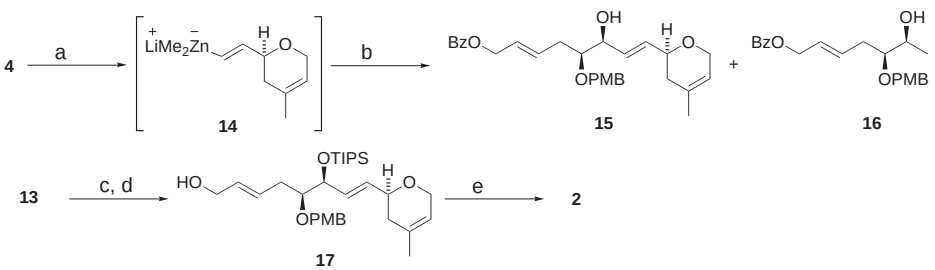
Completion of fragment **2** (Scheme 4) was accomplished using the zinc-catalyzed, chelation-controlled addition of a vinyl anion formed from **4** to the aldehyde of compound **3**.[10] The sequential transmetallation of vinyl iodide **4** with *tert*-BuLi followed by $ZnMe_2$ yielded a mixed zincate species (i.e. **14**), which was then added to a mixture of **3** and $ZnMe_2$. While the reaction yielded exclusively the *syn*-diol stereochemistry (see below), the desired product **15** was unexpectedly contaminated with approximately 25% of methyl adduct **16**, presumably resulting from the transfer of methyl from a zincate species formed from excess *tert*-BuLi and $ZnMe_2$.[15] Attempts to reduce the amount of *tert*-BuLi or to perform the initial halogen–metal exchange with *n*-BuLi led to lower yields and more complex mixtures. Because **15** and **16** were difficult to separate chromatographically, the mixture was treated with TIPS triflate, followed by DIBAL to give a mixture of primary alcohols that were chromatographically sepa-



Scheme 2. (a) PMB–trichloroacetimide, BF_3–OEt_2, CH_2Cl_2, −78°C, 1 h (76%); (b) DIBAL, toluene, −78°C, 5 min (99%); (c) Ph_3P=$CHCO_2Me$, PhH, reflux, 1 h (90%); (d) TBSCl, Et_3N, DMAP, CH_2Cl_2, 2 h (99%); (e) DIBAL, toluene, −78°C, 2 h (97%); (f) PhCOCl, pyridine, DMAP, CH_2Cl_2, rt, 16 h (82%); (g) TBAF, THF, rt, 2 h (63%); (h) $(COCl)_2$, DMSO, −78°C; then Et_3N, −78°C to rt (88%).



Scheme 3. (a) $CH_3C(MgBr)$=CH_2, CuI, THF, −30°C, 1 h (99%); (b) KH, allyl bromide, THF, 30 min (99%); (c) 10% TFA in MeOH, rt, 3 h (65%); (d) $(COCl)_2$, DMSO, −78°C; Et_3N, −78°C to rt (92%); (e) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, rt, 2 days (66%); (f) CHI_3 (3 equiv.), $CrCl_2$ (9 equiv.), THF, 0°C, 3.5 h (6:1, *trans*:*cis*; 48% *trans*).



Scheme 4. (a) *tert*-BuLi (1.6 equiv.), ether, −78°C, then $ZnMe_2$; (b) **3**, $ZnMe_2$, ether (60%, 3:1 ratio of **13**:**14**); (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2 (67%); (d) DIBAL, CH_2Cl_2, −78°C (82%); (e) $(COCl)_2$, DMSO, −78°C; Et_3N, −78°C to rt (99%).

rable, giving pure **17**. Compound **2**[16] was then obtained by oxidation of the alcohol to an aldehyde.

The stereochemistry of the newly introduced C_{20} chiral center was confirmed by α-methoxy-α-phenylacetic acid (MPA) ester analysis.[17] Esterification of separate aliquots of the **15**/**16** mixture with (*R*)-MPA and (*S*)-MPA using DCC as the coupling reagent led to the corresponding diastereomeric (*R*)- and (*S*)-esters, respectively, which were analyzed by ^{1}H NMR spectroscopy. Although complicated by significant signal overlap, several diagnostic NMR signals could be assigned and used for the stereochemical determination. Specifically, when ^{1}H NMR spectra recorded for the (*R*)- and (*S*)-MPA esters were compared, it could be clearly observed that the H_{16} and H_{17} olefinic protons were shifted more upfield in the spectrum recorded for the (*S*)-MPA ester and the signals assigned to the H_{21} and H_{22} olefinic protons appeared more upfield in the spectrum of the (*R*)-MPA ester. Using the model elaborated by Trost,[17] these results support the assignment of the C_{20} chiral center as *S*, confirming the formation of the desired *syn*-diol geometry.

In summary, we have reported a new synthesis of the C_{15}–C_{28} fragment of the microtubule-stabilizing agent laulimalide. Our approach utilized RCM chemistry for the preparation of the terminal dihydropyran ring and a Zn-catalyzed addition of a vinyl anion to an α-alkoxyaldehyde for the coupling of fragments **3** and **4** and the formation of the *syn*-diol. Further work toward the synthesis of laulimalide is underway.

Acknowledgements

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16. Compound **2**: $[\alpha]_D^{20}$ −55.4 (*c* 0.5, CH_2Cl_2); IR (film) ν_{max} 2942, 2865, 1692, 1513, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (mult., *J* in Hz) 9.39 (d, 7.9; 1 H), 7.2 (d, 8.5; 2 H), 6.84 (d, 8.6; 2 H), 6.76 (dt, 7.2, 14.9; 1 H), 6.07 (dd, 7.9, 15.6; 1 H), 5.82 (m; 2 H), 5.4 (s, 1 H), 4.56 (d, 7.6; 1 H), 4.51 (t, 3.8; 1 H), 4.45 (d, 11.6; 1 H), 4.15 (br.s; 2 H), 4.05 (m; 1 H), 3.78 (s; 3 H), 3.55 (m; 1 H), 2.59 (ddd, 2.1, 7.2, 13.9; 1 H), 2.34 (m; 1 H), 2.04 (m; 1 H), 1.89 (d, 16.8; 1 H), 1.68 (s; 3 H), 1.02 (s; 21 H); ^{13}C NMR ($CDCl_3$) δ 193.9, 159.5, 156.7, 134.1, 132.5, 131.3, 130.1, 129.6, 128.8, 119.8, 113.8, 80.6, 73.3, 72.2, 65.6, 55.3, 35.7, 33.1, 22.9, 18.1, 12.3; HRMS (FAB) calcd for $C_{31}H_{48}LiO_5Si$ 535.3431 $[M+Li]^+$, found 535.3396.
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