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Synthetic studies toward the microtubule-stabilizing agent laulimalide: synthesis of the C_1–C_{14} fragment

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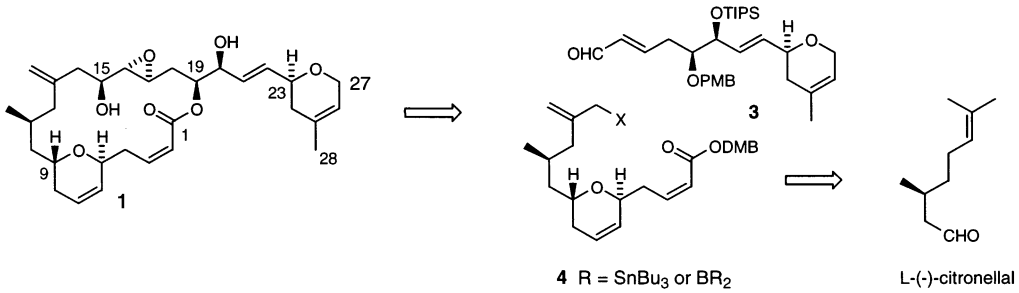
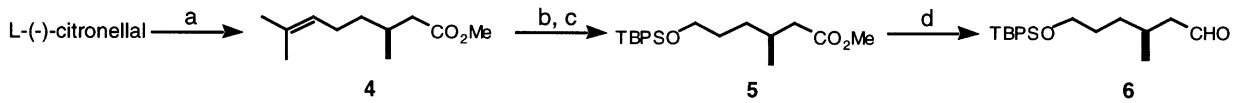
Abstract—The C_1–C_{14} fragment of the paclitaxel-like antimicrotubule agent laulimalide has been synthesized in 15 steps from L-(−)-citronellal. The C_9 chiral center was established using an asymmetric allylation, the dihydropyran ring was prepared through ring-closing metathesis, and the *exo*-methylene was incorporated using Eschenmoser's salt. © 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] Laulimalide is a potent inhibitor of cellular proliferation with IC_{50} values in the low nanomolar range against drug sensitive cell lines and it retains activity against a P-glycoprotein overexpressing multidrug resistant ovarian cancer cell line, suggesting that it is a poor substrate for transport by P-glycoprotein. Laulimalide, therefore, joins the marine metabolites discodermolide[3] and eleutherobin[4] and the microbial metabolites the epothilones[5] as a new class of microtubule-stabilizing agent, with activities that may prove therapeutically useful.

To date, three groups have published a total of seven papers describing synthetic efforts targeting laulimalide.[6,7] Among these, are five reports of syntheses of the C_1–C_{16} portion of the macrocyclic ring. 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_{15}–C_{28} segment of laulimalide.[9] In this letter, we describe our synthesis of the C_1–C_{14} portion of laulimalide.



Scheme 1. Retrosynthetic analysis.



Scheme 2. (a) PDC, MeOH, DMF, rt (80%); (b) O_3, MeOH, −78°C; then $NaBH_4$ (82%); (c) TBPSCl, DMAP, imidazole, DMF, rt, 10 h (89%); (d) DIBAL, CH_2Cl_2, −78°C, 1.5 h (85%).

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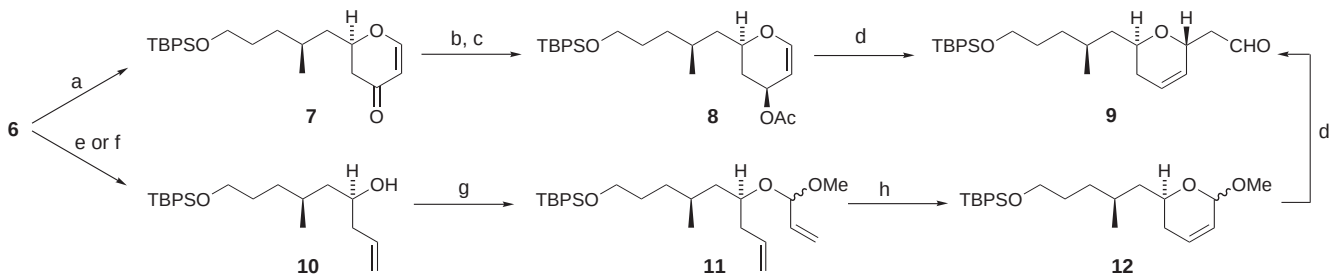
Our retrosynthetic strategy (Scheme 1) involves dividing the molecule into two primary fragments; the C_1–C_{14} fragment (**2**) and the C_{15}–C_{28} fragment (**3**).[9] Fragments **2** and **3** are to be coupled using asymmetric allylstannane or allylborane chemistry, either before or after epoxidation. Because of the sensitivity of the (*Z*)-α,β-unsaturated ester in **2** to basic conditions, we have utilized a 2,4-dimethoxybenzyl (DMB) ester protecting group,[10] envisioning simultaneous cleavage of the C_{19} PMB ether (fragment **3**) and the DMB ester immediately prior to macrolactonization. We felt that the dihydropyran ring in compound **2** could be prepared either through an asymmetric hetero Diels–Alder approach or through the use of an asymmetric allylation/ring-closing olefin metathesis sequence.

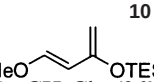
To prepare for the dihydropyran ring synthesis, L-(−)-citronellal was converted to aldehyde **6** in four steps (see Scheme 2). Oxidation of the aldehyde with PDC in MeOH gave ester **4**, which was treated with ozone followed by $NaBH_4$, yielding a primary alcohol that was protected as its TBPS ether **5**. Finally, conversion of the ester back to an aldehyde yielded compound **6**, bearing an aldehyde in the position that is to become C_9 of laulimalide.

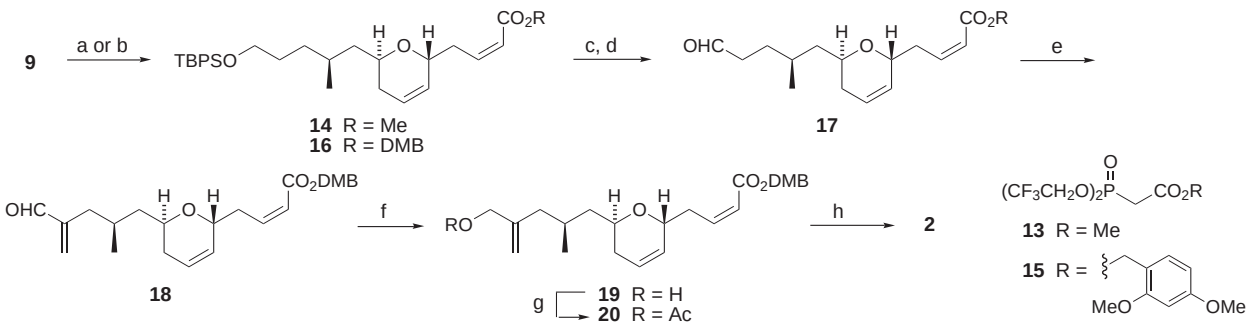
Our initial approach to the dihydropyran ring (Scheme 3) involved the use of Keck's asymmetric hetero Diels–Alder conditions.[11] Reaction of **6** with a Danishefsky-type diene yielded dihydropyranone **7** in 53% yield, but with a disappointing 67% *de*. Compound **7** was then converted to aldehyde **9** using methodology similar to that developed by Paterson and Grieco in their syntheses of swinholide.[12,13] Specifically, **7** was reduced under Luche conditions[14] to give exclusively the equatorial alcohol, which was acetylated to give **8**. A Ferrier rearrangement with CH_2=CHOTBS in the presence of $LiOCl_4$–EtOAc yielded **9**, exclusively with the *trans* disposition of dihydropyran ring substituents.

A second approach utilized a strategy analogous to the one we used for the preparation of compound **2**.[9] Using Keck's asymmetric allylation conditions,[15] aldehyde **6** was treated with allyltributyltin in the presence of the chiral Lewis acid formed from (*S*)-BINOL and $Ti(O^iPr)_4$, giving homoallylic alcohol **10** in 80% yield and 71% *de*. An MPA ester analysis[16] of the alcohol confirmed that the new chiral center had the desired *S*-chirality. The use of chiral allyl borane *B*-allyldiisopinocampheylborane (Ipc_2BAll)[17] resulted in a comparable yield, but provided an improved diastereomeric excess (92%). The reaction of **10** with methoxyallene in the presence of $Pd(OAc)_2$[18] provided allylic acetal **11**, which was poised for a ring closing olefin metathesis reaction.[18,19] Indeed, treatment of **11** with Grubbs' catalyst in CH_2Cl_2 cleanly yielded compound **12**, which could then be converted to **9** using the same conditions as were used for the conversion of **8** to **9**, presumably via the identical oxonium ion intermediate.

From aldehyde **9**, three tasks remained: (1) preparation of the (*Z*)-α,β-unsaturated ester; (2) incorporation of the *exo*-methylene at C_{13}; and (3) installation of the



Scheme 3. (a)  , (*S*)-BINOL, $Ti(O^iPr)_4$; then TFA (53%); (b) $NaBH_4$, $CeCl_3$–$7H_2O$, MeOH (97%); (c) Ac_2O, $^iPrNEt_2$, DMAP, CH_2Cl_2 (96%); (d) CH_2=CHOTBS, 3.0 M $LiClO_4$–EtOAc (86% from **8**; 78% from **12**); (e) allyltributyltin, (*S*)-BINOL, $Ti(O^iPr)_4$ (80%); (f) Ipc_2BAll, THF, −78°C, 1 h; NaOH, H_2O_2, 3 h (80%); (g) methoxyallene, $Pd(OAc)_2$, CH_3CN, reflux, 20 h (83%); (h) 0.1 M $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, rt, 36 h (85%).



Scheme 4. (a) **13**, KHMDS, 18-crown-6, THF, −78°C (83%); (b) **15**, KHMDS, 18-crown-6, THF, −78°C (80%); (c) HF–py., THF (91%); (d) $(COCl)_2$, DMSO, −78°C; Et_3N, −78°C to rt (90%); (e) Me_2N^+=CH_2Cl^-, CH_2Cl_2, then Et_3N (84%); (f) $NaBH_4$, $CeCl_3$–$7H_2O$, EtOH (90%); (g) Ac_2O, DMAP, $^iPr_2NEt$, CH_2Cl_2 (90%); (h) $Bu_3SnAlEt_2$, $Pd(PPh_3)_4$ (60%).

allyltin necessary for coupling fragments **2** and **3**. Although application of Still's fluorinated phosphonate ester (**13**)[20] provided a good yield of *cis*-methyl ester **14**, for reasons described earlier, we were interested in preparing 2,4-dimethoxybenzyl ester analog **16** (Scheme 4), requiring 2,4-dimethoxybenzyl phosphonate ester **15** as a reagent. After extensive experimentation, we developed an inexpensive, three-step route from methylphosphonic dichloride that allows the preparation of large amounts of **15**.[21] Treatment of **9** with **15** in the presence of KHMDS and 18-crown-6 yielded compound **16** as the exclusive product in 83% yield. HF–pyridine cleanly removed the TBPS group, exposing the primary alcohol, which was oxidized to give aldehyde **17**. Treatment of enolizable aldehyde **17** with Eschenmoser's salt in CH_2Cl_2 for 2 days followed by addition of Et_3N yielded unsaturated aldehyde **18**, which was reduced to give alcohol **19**. Because of the tendency of the unsaturated ester to isomerize, our original plan of converting the alcohol to a bromide followed by displacement with tributylstannyllithium was aborted, substituting the more mild method reported by Trost and coworkers.[22] To this end, **19** was acetylated to give **20**.[23] In a single attempt, **20** was exposed to $Bu_3SnAlEt_2$ and $Pd(PPh_3)_4$, providing allyl stannane in approximately 60% yield, along with a small amount of the hydrodestannylation product.

In summary, we have reported a new synthesis of the C_1–C_{14} fragment of the microtubule-stabilizing agent laulimalide. In order to facilitate deprotection of the (*Z*)-α,β-unsaturated ester prior to macrolactonization, we have incorporated a 2,4-dimethoxybenzyl ester, which required the preparation of the new phosphonate ester **15**. We have described both hetero Diels–Alder and RCM approaches for the preparation of the dihydropyran ring and have generated the requisite allyl stannane in the presence of the base-sensitive (*Z*)-double bond. Further work toward the synthesis of laulimalide is underway.

Acknowledgements

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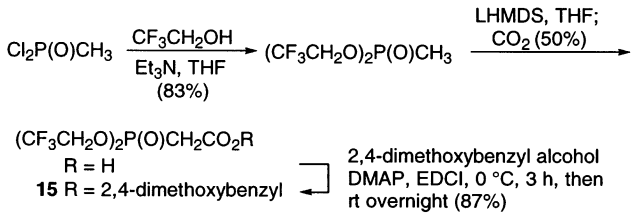
21. For the preparation of **15** see below:



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23. Compound **20** data: ^{1}H NMR ($CDCl_3$) δ (mult., J in Hz) 7.22 (d, 8.9; 1H), 6.44 (m; 2H), 6.34 (dt, 11.5, 7.1; 1H), 5.88 (dt, 11.5, 1.7; 1H), 5.80 (m; 1H), 5.66 (dq, 10.3, 2.3; 1H), 5.13 (d, 12.2; 1H), 5.09 (d, 12.2; 1H), 5.04 (s; 1H), 4.90 (s; 1H), 4.47 (s; 2H), 4.24 (m; 1H), 3.83 (s; 6H), 3.75 (m; 1H), 3.01 (dddd, 15.9, 9.5, 7.1, 1.7; 1H), 2.87 (dddd, 15.9, 7.1, 4.3, 1.9; 1H), 2.08 (s; 3H), 2.07 (m; 1H), 1.91 (m; 4H), 1.57 (ddd, 13.8, 9.7, 3.5; 1H), 1.08 (ddd, 13.8, 9.0, 3.2; 1H), 0.82 (d, 6.3; 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 166.4, 161.3, 159.0, 146.8, 142.4, 131.3, 129.1, 124.7, 121.0, 117.0, 113.7, 140.1, 98.6, 72.2, 66.8, 65.1, 61.1, 55.5, 55.4, 42.6, 41.9, 33.5, 31.3, 27.0, 20.9, 19.3; LRFAB m/z (relative intensity) 479 (M^++Li; 25), 335 (9), 151 (100); HRFAB calcd for $C_{27}H_{36}O_7$ (M^++Li) 479.2621, found 479.2613.