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An improved synthesis of the C15–C28 fragment of laulimalide

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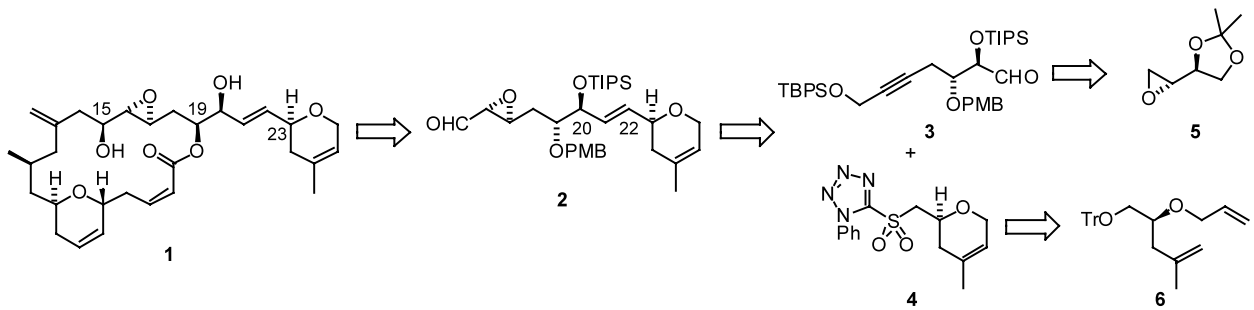
Abstract—The C_{15}–C_{28} fragment of the paclitaxel-like antimicrotubule agent laulimalide has been synthesized in 12 linear steps from known epoxide **5**, with an overall yield of 16%. The methyldihydropyran ring of the side chain was efficiently prepared using ring-closing olefin metathesis chemistry. The 19,20-diol stereochemistry originates in starting material **7** and the side chain was appended using a Kocienski-modified Julia coupling. © 2002 Elsevier Science Ltd. All rights reserved.

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 discodermalide[3] and eleutherobin[4] and the microbial metabolites the epothilones.[5]

Laulimalide has attracted significant recent attention from synthetic organic chemists, with five groups having published a total of 16 papers describing their synthetic efforts related to laulimalide.[6] The first total synthesis of laulimalide was reported,[6h] along with a follow-up paper describing an improved macrocyclization approach,[6l] by the Ghosh group. Additional completed syntheses have now been published by the Mulzer[6o] and Paterson groups.[6p] In this communication, we would like to describe our second generation synthesis of the C15–C28 portion of laulimalide.

Our revised retrosynthetic analysis is shown in Scheme 1. It involves dividing the C15–C28 fragment (**2**) into two pieces, aldehyde **3** (C15–C21) and sulfone **4** (C22–C28), which we proposed to connect via a Julia/Kocienski coupling reaction.[7] Fragment **3** was to be prepared in a straightforward manner from known epoxide **5**,[8]



Scheme 1. Retrosynthetic analysis.

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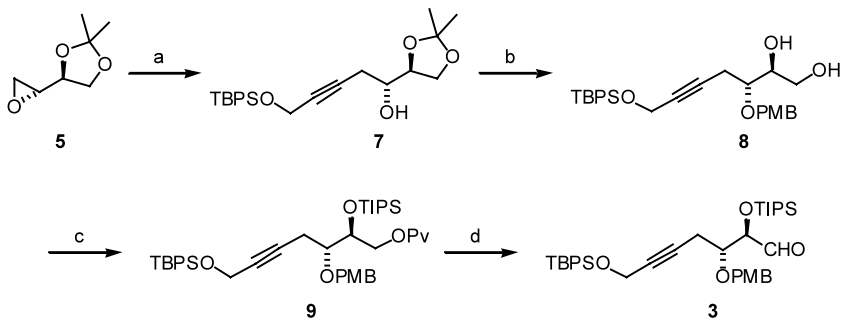
available in seven steps from L-ascorbic acid.[9] Sulfone **4** is available from diene **6**, an intermediate in our previous synthesis,[6k] using ring-closing olefin metathesis chemistry.[10] This approach differs from our previous synthesis in several important ways: (1) it targets the 19*R*-epimer necessary for application of a Mitsunobu macrocyclization reaction, as reported by Paterson;[6h] (2) the starting material (**5** or L-ascorbic acid) contains the stereochemical information necessary for both the C19 and C20 chirality centers; and (3) the epoxide is incorporated early in order to direct the asymmetric allylation reaction to be used for coupling the two major fragments of the molecule.

The synthesis of fragment **3** is outlined in Scheme 2. Opening of the epoxide with the anion generated from TBPS propargyl ether gave **7**, which was converted into aldehyde **3** via a series of protection and deprotection steps. Protection of the secondary alcohol as its PMB ether is followed by acetonide deprotection[11] to give diol **8**. Selective pivaloylation of the primary alcohol, silylation of the secondary alcohol, pivaloate ester reduction, and Swern oxidation gave compound **3**.

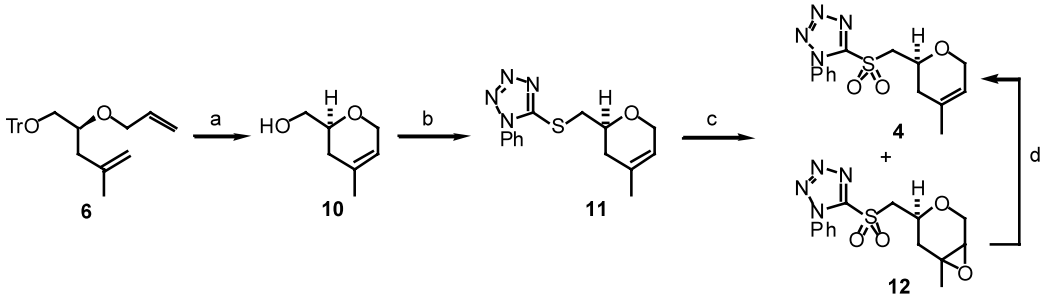
The synthesis of sulfone **4** (Scheme 3) started with diene **6**, available in three steps from (*R*)-glycidol, as previously described.[6k] Ring closing olefin metathesis and deprotection gives alcohol **10**, which can be coupled with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions to give sulfide **11**. The oxidation of the sulfide to the desired sulfone, however, proved troublesome. A survey of the usual oxidizing agents, showed ammonium molybdate/H_2O_2[12] to give the best results. Still, although the initial oxidation of the sulfide to a sulfoxide was extremely facile, further oxidation to give sulfone **4** proved quite difficult. In fact, over oxidation of the alkene in **4** to the epoxide (**12**) was competitive with sulfoxide oxidation, typically yielding a mixture of sulfoxide, sulfone (**4**), and epoxysulfone (**13**) products. Fortunately, treatment of **12** with PPh_3/I_2 cleanly converted the epoxide back to the desired alkene.[13] Thus, the ammonium molybdate catalyzed oxidation was allowed to run until the sulfoxide was completely consumption, giving a 1.1:1 ratio of **4**:**12**, the later of which could be recycled back to sulfone **4**, ultimately giving an 80% yield of sulfone, from **11**.

The coupling of fragments **3** and **4** (Scheme 4) was accomplished using the Kocienski-modified Julia coupling procedure.[7] Our initial attempt involved deprotonation of sulfone **4** with KHMDS in DME followed by addition of aldehyde **3**, giving the crude product in a respectable 80% yield, but with a disappointing 1:1.3 *trans*:*cis* isomeric ratio. Fortunately, substituting DMF for DME provided the product in an equivalent 81% yield, but with an improved 5:1 *trans*:*cis* ratio. Selective removal of the TBPS group with NaOH in refluxing MeOH[14] yielded a propargylic alcohol that was reduced with Red-Al[14] to give allylic alcohol **14**. A Sharpless asymmetric epoxidation reaction[15] provided the epoxy-alcohol, which could be oxidized to give the C15–C28 fragment of laulimalide (**2**).[16]

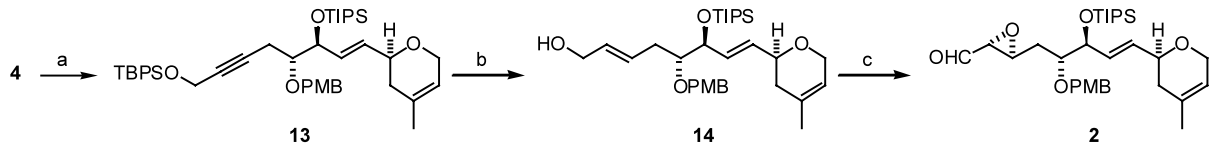
In summary, we have reported an improved synthesis of the C_{15}–C_{28} fragment of the microtubule-stabilizing agent laulimalide. Salient features include: (1) the use



Scheme 2. (a) $TBPSOCH_2C{\equiv}CH/n$-BuLi, THF, BF_3–OEt_2, −78°C (82%); (b) (i) PMB–Br, KHMDS, DMF, 0°C, (ii) 1,3-propanedithiol (6 equiv.), BF_3–OEt_2, −78°C (71% over two steps); (c) (i) $(CH_3)_3COCl$, Et_3N, CH_2Cl_2 (93%), (ii) TIPS–OTf, 2,6-lutidine, DMF (95%); (d) (i) DIBALH, CH_2Cl_2, −78°C (98%), (ii) $(COCl)_2$, DMSO, −78°C, then Et_3N, −78°C to rt (88%).



Scheme 3. (a) (i) Grubbs' catalyst, CH_2Cl_2, (95%), (ii) TFA, MeOH (81%); (b) DIAD, PPh_3, 1-phenyl-1*H*-tetrazole-5-thiol (85%); (c) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH (**4**, 45%; **13**, 40%); (d) PPh_3, I_2, CH_3CN (87%).



Scheme 4. (a) KHMDS, DMF, then **3** (81%; 5:1, *trans*:*cis*); (b) (i) 10% NaOH in MeOH, reflux (87%), (ii) Red-Al, ether (85%); (c) (i) (+)-DIPT, TBHP (84%; 85% d.e.), (ii) $(COCl)_2$, DMSO, −78°C, Et_3N, −78°C to rt (85%).

RCM chemistry for the preparation of the terminal dihydropyran ring; (2) the incorporation of both the C19 and C20 stereochemistries in the starting material; and (3) the application of a Julia/Kocienski coupling for the successful addition of the dihydropyran side chain. Further work toward the synthesis of laulimalide is underway.

Acknowledgements

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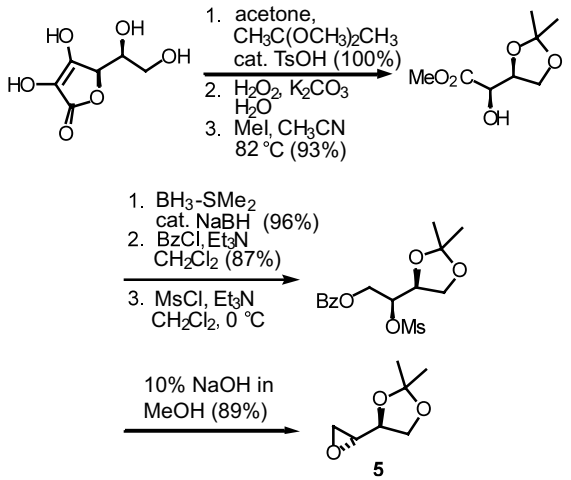
9. Although based upon the methods reported in Ref. 8, the following modified procedure was used:



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16. Selected data for compound **2**: ^{1}H NMR δ 8.87 (1H, d, $J=6.3$ Hz), 7.24 (2H, d, $J=8.6$ Hz), 6.84 (2H, d, $J=8.6$ Hz), 5.73 (2H, m), 5.41 (1H, brs), 4.71 (1H, d, $J=11.4$ Hz), 4.43 (1H, d, $J=11.4$ Hz), 4.38 (1H, m), 4.16 (2H, m), 4.02 (1H, dt, $J=9.9$, 3.3 Hz), 3.54 (1H, dt, $J=8.4$, 3.3), 3.26 (1H, ddd, $J=6.2$, 5.2, 1.9 Hz), 3.06 (1H, dd, $J=6.2$, 1.9 Hz), 2.07 (1H, ddd, $J=14.6$, 8.7, 5.1 Hz), 2.03 (1H, m), 1.89 (1H, brd, 16.7 Hz), 1.70 (3H, s), 1.66 (1H, ddd, $J=14.6$, 6.3, 3.8 Hz); ^{13}C NMR δ 198.1, 159.3, 133.0, 131.2, 130.6, 130.3, 129.6, 119.79, 113.8, 80.2, 75.6, 73.3, 72.3, 65.5, 59.0, 55.0, 55.0, 35.5, 32.4, 22.9, 18.1, 12.4; HRFABMS (MNBA+NaI) calcd for $C_{31}H_{48}NaO_6Si$: 567.3118; found: 567.3105.