Stereoselective Synthesis of the C13–C28 Subunit of (–)-Laulimalide Utilizing an α-Chlorosulfide Intermediate

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Abstract: A stereoselective route to the C13–C28 subunit of (–)-laulimalide is described. L-Tartaric acid is the source of the hydroxy groups at C19 and C20. An α-chlorosulfide is employed as the key intermediate for the creation of the C17–C18 bond and the C16–C17 double bond was introduced using the Mislow–Braverman rearrangement and Hutchin's dexoxygenation with concomitant double bond transposition reaction. The C15 and C23 stereogenic centers were created using catalytic asymmetric reactions. The trisubstituted and *trans*-disubstituted alkenes were created stereoselectively by taking advantage of ring-closing metathesis and the Julia–Kocienski olefination reaction, respectively.

Key words: laulimalide, α-chloro sulfide, Julia–Kocienski olefination, Mislow–Braverman rearrangement, ring-closing metathesis

Laulimalide (**1**; Figure **1**) and isolaulimalide (**2**) were isolated in 1988 by Crews et al. from *Cacospongia mycofijiensis*,[1a] and at almost the same time by Moore and co-workers from the marine sponge *Hyatella sp*.[1b] Both the groups also isolated them from the nudibranch predator, *Chromodoris lochi* that was feeding on the sponges.[1a,b] In 1996, Higa and co-workers isolated **1** and **2** along with neolaulimalide from the sponge *Fasciospongia rimosa*[1c,d] and recently Riccio isolated them from a sponge belonging to the genus *Dactylospongia*.[1e] Laulimalide (**1**) inhibits the proliferation of several tumor cell lines with IC_{50} values in the nanomolar range (KB IC_{50} = 15 nM, MDA-MB-435 IC_{50} = 6–7 nM, P388, A549, HT29, MEL28, IC_{50} = 10–50 nM). It also exhibits potent activity against cell lines showing multidrug resistance. Laulimalide binds to tubulin in a fashion similar to paclitaxel though the binding site is different.[2,3] The structure of **1** was initially assigned by NMR analysis[1a,b] and later confirmed by X-ray diffraction studies.[1c] Laulimalide is a 20-membered macrolide wherein its C16–C17-epoxide is susceptible to nucleophilic attack from the C20-hydroxyl group to form isolaulimalide (**2**) and the 2,3-*cis*-enoate readily undergoes *Z/E*-isomerization. Owing to its potential as an anticancer lead, its restricted natural supply, and unique structure, the total synthesis of **1** and the preparation of analogues has attracted interest.[4,5]

Herein, we describe the synthesis of the C13–C28 subunit **3** of laulimalide utilizing catalytic asymmetric reactions and an α-chlorosulfide as key intermediate for C–C bond formation. The retrosynthetic analysis is depicted in Scheme 1. The subunits **3** (C3–C12 fragment) and **4** (C13–C28 subunit) were proposed to be united by addition of the anion from sulfone **3** to the aldehyde derived from silyl ether **4**. Dihydropyran **4** constituting the C13–C28 subunit of laulimalide was envisaged to be obtained from sulfone **5** and aldehyde **6** taking advantage of Julia–Kocienski reaction.[6] Aldehyde **6** can be traced to sulfide **7** and alkyne **8** by utilizing a methodology developed recently exploiting α-chlorosulfides as reactive intermediates.[7] Substrates **7** and **8** can be traced back to L-(+)-tartaric acid and 1,3-propane diol, respectively. Sulfone **5** was envisaged to be obtained from aldehyde **28** utilizing Keck methallylation and ring-closing-metathesis reactions as key steps.

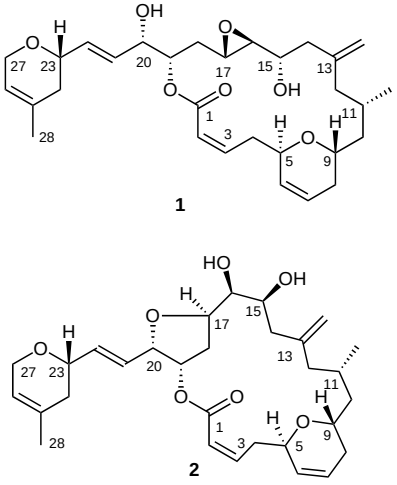

Figure 1 Tumor growth inhibitors laulimalide (**1**) and isolaulimalide (**2**)

The synthesis of acetonide **7** began from L-(+)-tartaric acid (**9**) that, upon reaction with 2,2-dimethoxypropane in the presence of PTSA following literature precedent,[8] furnished acetonide **10**. Reduction of the diester in **10** with $LiAlH_4$ yielded diol **11**. Selective monoprotection of **11** using NaH and benzyl bromide yielded benzyl ether **12**. The sulfide **7** was obtained cleanly from **12** following Hata's protocol,[9] using tri-*n*-butyl phosphine and diphenyl disulfide (Scheme 2).

The synthesis of propargyl ether **8** commenced with the selective monoprotection of 1,3-propanediol (**13**) into silyl ether **14**. Oxidation using Swern conditions[10] furnished aldehyde **15** that, on reaction with trimethylsilylacetylene

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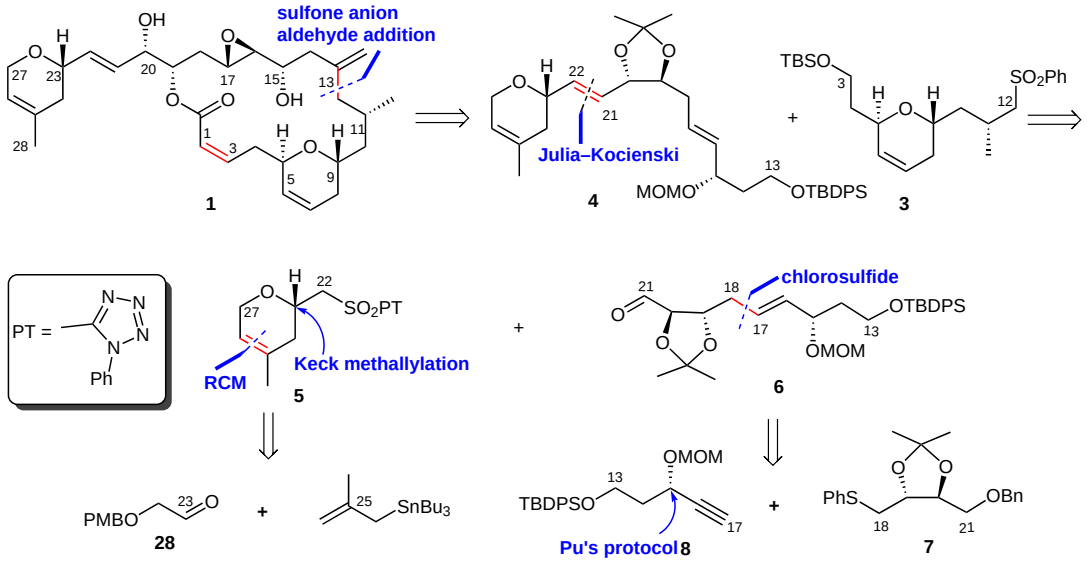
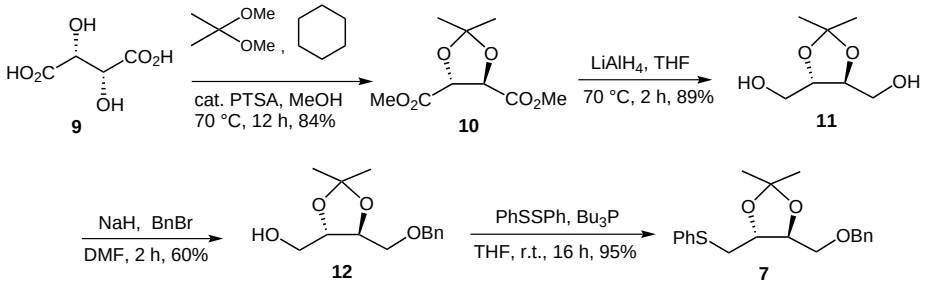


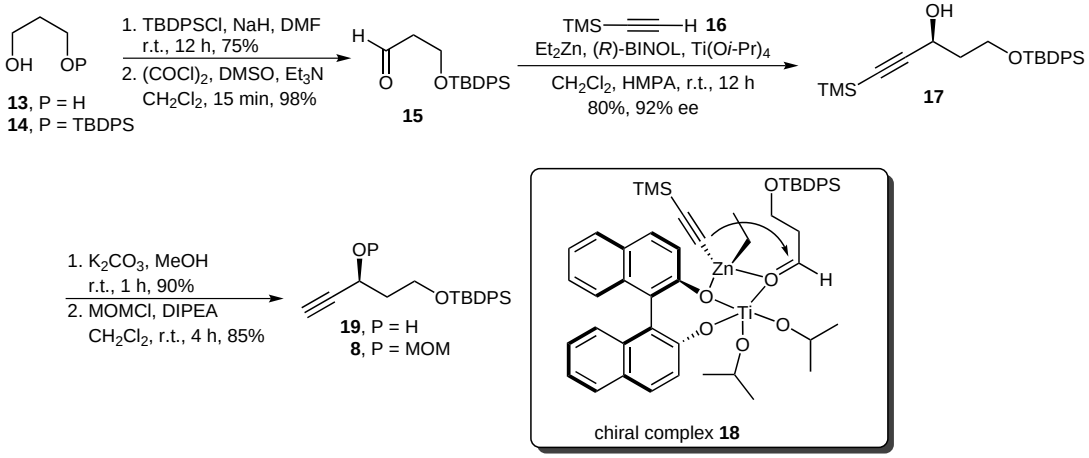
Scheme 1 Retrosynthetic disconnection of (–)-laulimalide



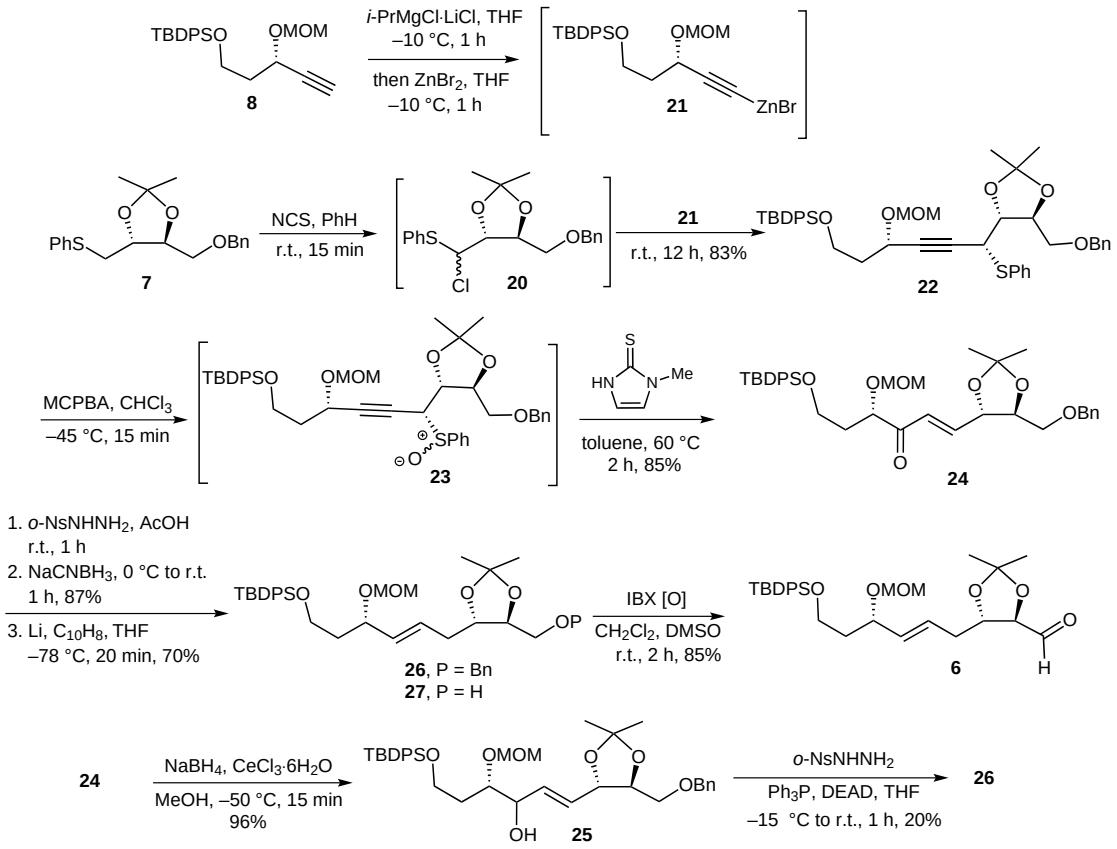
Scheme 2 Preparation of sulfide **7**

(**16**) following the protocol of Lin Pu,[11] yielded propargylic alcohol **17** (92% ee)[12] probably via chiral complex **18**. Removal of TMS moiety in **17** proceeded cleanly on treatment with K_2CO_3 in methanol to furnish propargyl alcohol **19**. Protection of the hydroxy group in **19** using MOMCl under standard conditions yielded compound **8** (Scheme 3).

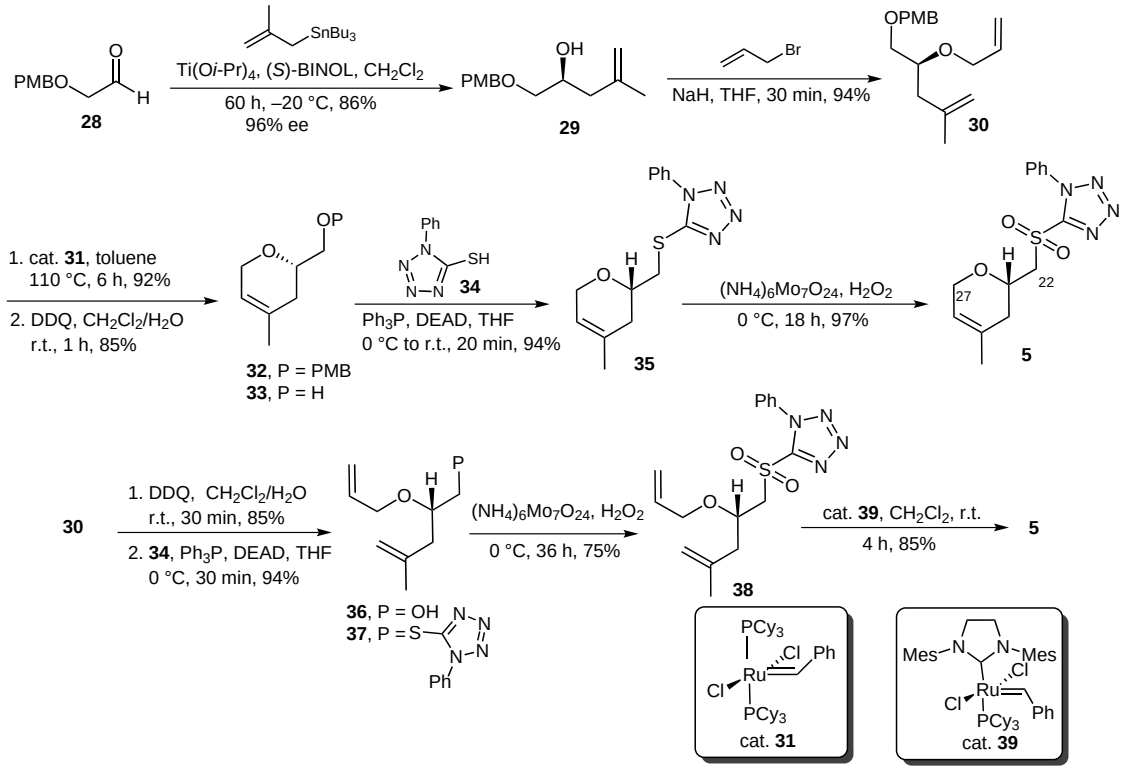
The reaction of sulfide **7** with NCS in benzene[7] furnished chlorosulfide **20** which, without isolation, was reacted with an excess of alkynylzinc bromide **21**, obtained by sequential treatment of **8** with *i*-PrMgCl·LiCl and $ZnBr_2$, to afford propargyl sulfide **22** diastereoselectively**.** Sulfide **22** was proposed to be transformed into alkene **26** by taking advantage of the Mislow–Braverman rearrangement[13] and reductive deoxygenation (Scheme 4). Thus selective oxidation of **22** using *m*CPBA yielded an epimeric mixture of sulfoxides **23** which was directly heated in toluene in the presence of 2-mercapto-1-methylimidazole[14] to fur-



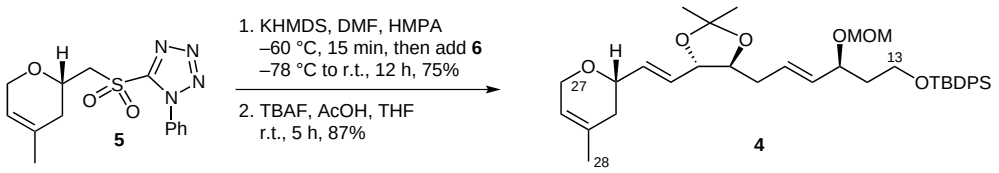
Scheme 3 Preparation of alkyne **8**



Scheme 4 Synthesis of alcohol **6**



Scheme 5 Preparation of sulfone **5**



Scheme 6 Synthesis of C13–C28 fragment **4**

nish α,β-unsaturated ketone **24**. In the first approach, the α,β-unsaturated ketone **24** was reduced diastereoselectively utilizing the Luche protocol[15] to furnish allyl alcohol **25** as the sole isomer. Since the newly created carbinol centre was to be destroyed, the configuration was not established. Attempted reductive deoxygenation with double bond transposition using Myer's protocol[16] afforded alkene **26**, although in poor yield (20%). Therefore, in the second approach, ketone **24** was deoxygenated using Hutchins's protocol.[17] The *o*-nitrobenzenesulfonyl hydrazone obtained from **24** was subjected to reduction with sodium cyanoborohydride in the presence of acetic acid to yield alkene **26** in excellent yield.[18] Debenzylation of **26** using lithium naphthalinide[19] yielded alcohol **27** that, when subjected to IBX oxidation, afforded aldehyde **6**.

The synthesis of sulfone **5** began with the methallylation of the aldehyde[20] **28** using Keck's protocol[21] to furnish homoallyl alcohol **29** (ee = 96%).[22] Allyl ether formation using standard conditions yielded compound **30** that was subjected to ring-closing metathesis reaction using Grubbs' catalyst[23] **31** to furnish pyran derivative **32**. Deprotection of PMB ether using DDQ[24] followed by reaction of the resulting alcohol **33** with thiol **34** under Mitsunobu conditions[25] yielded sulfide **35**. Oxidation using ammonium molybdate and H_2O_2 yielded sulfone **5**. Alternatively, the ether **30** was deprotected with DDQ to furnish alcohol **36** that, on reaction with thiol **34**, yielded sulfide **37**. Oxidation to sulfone **38** using ammonium molybdate and H_2O_2 proceeded more readily in this instance in comparison to sulfide **35** where oxidation to sulfoxide was rapid but further oxidation to sulfone **5** proved to be slow. RCM using Grubbs' catalyst[23] **39** yielded **5** (Scheme 5).

The coupling of fragments **5** and **6** was accomplished using the Kocienski-modified Julia-olefination procedure.[6] Deprotonation of sulfone **5** with KHMDS in DMF followed by addition of aldehyde **6** furnished stereoselectively diene derivative **4**[26] constituting the C13–C28 subunit of laulimalide (Scheme 6).

In summary, we have described a new route to the C13–C28 fragment (14.49% overall yield in 12 steps by the longest linear sequence) from 1,3-propanediol (**13**). The key steps include substrate-controlled asymmetric transformations, enantioselective propargylation using Pu's protocol, C–C bond formation using α-chlorosulfide intermediate, Mislow–Braverman rearrangement, reductive deoxygenation with alkene transposition and Julia–Kocienski olefination.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(26) **Compound 4**: To a solution of sulfone **5** (54 mg, 0.17 mmol, 1.5 equiv) in anhyd DMF (0.2 mL) and HMPA (64 μL) cooled at –60 °C was added KHMDS (192 μL, 15% in toluene, 1.2 equiv) via syringe. The reaction was stirred for 15 min and cooled to –78 °C. A solution of aldehyde **6** (80 mg, 0.12 mmol, 1 equiv) in anhyd DMF (0.2 mL) and HMPA (64 μL) was added dropwise. The reaction was stirred at the same temperature for 1 h and allowed to warm to ambient temperature for over a period of 12 h. The reaction mixture was quenched by adding sat. aq NH_4Cl solution (2 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash chromatography on silica gel using 12% EtOAc–hexane as the eluent afforded **4** as a colorless oil (56 mg, 0.09 mmol) in 75% yield. TLC (SiO_2): R_f 0.6 (EtOAc–hexane, 3:7); $[\alpha]^{25}_D$ –21° (*c* = 0.98 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.70 (m, 4 H), 7.24–7.34 (m, 6 H), 5.74 (dt, *J* = 14.8, 5.0 Hz, 1 H), 5.52–5.64 (m, 2 H), 5.23–5.38 (m, 2 H), 4.56 (d, *J* = 7.0 Hz, 1 H), 4.37 (d, *J* = 7.0 Hz, 1 H), 4.08–4.16 (m, 1 H), 4.00–4.09 (m, 2 H), 3.87–3.96 (m, 1 H), 3.67–3.74 (m, 1 H), 3.62–3.66 (m, 1 H), 3.56–3.61 (m, 1 H), 3.20 (s, 3 H), 2.13–2.31 (m, 2 H), 1.91–2.04 (m, 1 H), 1.69–1.87 (m, 2 H), 1.60–1.68 (m, 4 H), 1.30 (s, 6 H), 0.98 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.6, 134.8, 133.9, 133.1, 131.2, 129.6, 128.9, 127.7, 127.0, 119.9, 108.6, 93.5, 81.1, 80.1, 73.4, 72.7, 65.6, 60.4, 55.3, 38.7, 35.8, 34.3, 27.3, 27.0, 23.1, 19.3. IR (neat): 2930, 2858, 1155, 1106, 1033, 704 cm^{-1}. MS (ESI): *m*/*z* = 643 $[M + Na]^+$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{37}H_{52}SiO_6Na$: 643.3430; found: 643.3444.