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Synthetic studies on a phenyl-laulimalide analogue

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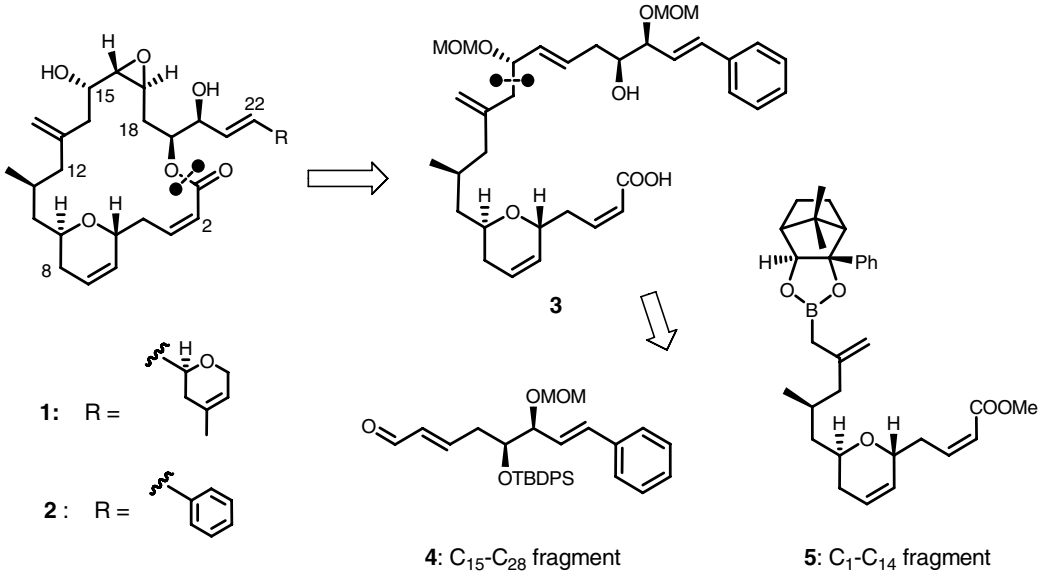
Abstract—An analogue of the paclitaxel-like antimicrotubule agent laulimalide with a phenyl in place of the dihydropyran has been synthesized. The fragments C_1–C_{14} and C_{15}–C_{28} were coupled via a stereoselective intermolecular allylboration. Ring closure was achieved using Yamaguchi's protocol.

The marine macrolide (−)-laulimalide **1** (Scheme 1) exhibits a strong cytotoxicity against several human cancer cell lines.[1] Its microtubule-stabilizing mode of action is related to Taxol® (paclitaxel).[2] Laulimalide is superior in that it retains activity against cancer cells that are resistant to Taxol.[3] As a result of this biological profile, a number of total syntheses of laulimalide[4] and laulimalide analogues[5,6] has been reported. Here, we present our efforts towards laulimalide analogues, where the dihydropyran is replaced by an aromatic moiety. As a



Scheme 1. Retrosynthetic analysis.

Keywords: Synthesis; Natural product analogues; Laulimalide; Stereoselective synthesis; Allylboration.
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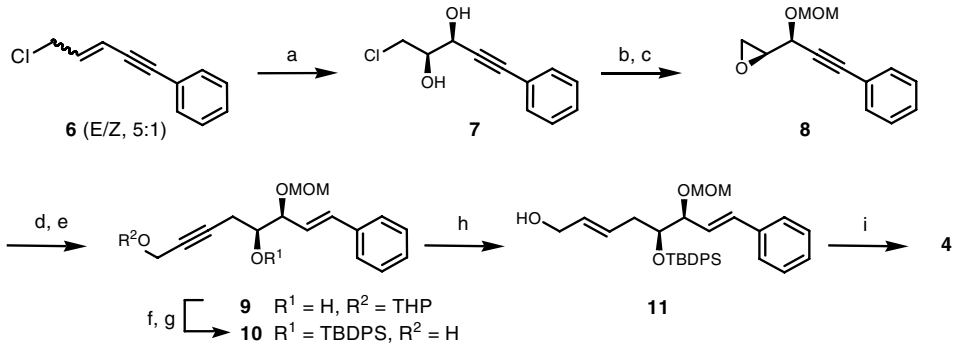
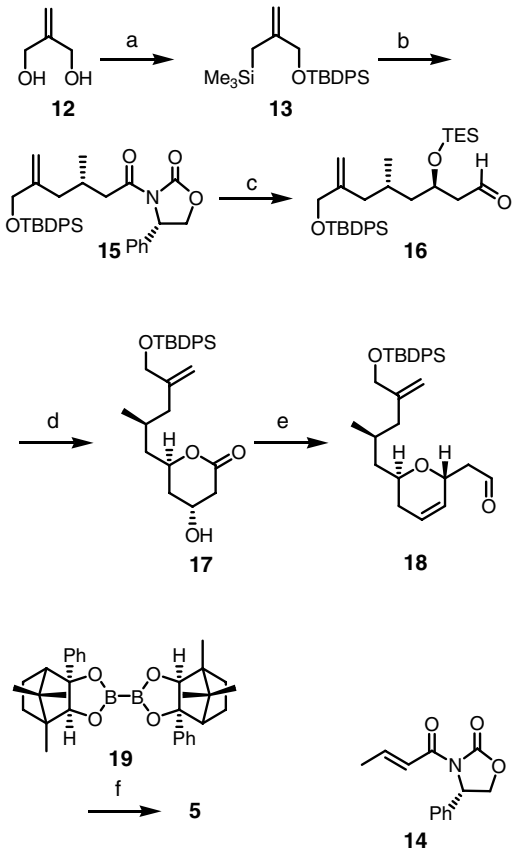


Scheme 2. Reagents and conditions: (a) AD-mix α, *tert*-BuOH/H_2O, $MeSO_2NH_2$, 20 °C, 80%; (b) NaOH, THF, 20 °C, 85%; (c) $(i\text{-Pr})_2NEt$, $MeOCH_2Cl$, 76%; (d) *n*-BuLi, $HCCCH_2OTHP$, BF_3–OEt_2, THF, −78 °C, 83%; (e) Red-Al, THF, −20 °C 84%; (f) imidazole, TBDPSCl, DMF, 20 °C, 90%; (g) HCl/MeOH, 20 °C, 82%; (h) see (e), 55%; (i) MnO_2, CH_2Cl_2, 40 °C, 95%.

prototype of these compounds we focused on phenyllaulimalide **2**. Our synthetic strategy (Scheme 1) was based on a final macrolactonization (**3**→**2**) and a stereoselective allylboration to connect C_{15-28} aldehyde **4** with the C_{1-14} allyl boronate **5**.

As outlined in Scheme 2, the synthesis of **4** relies on the Sharpless asymmetric dihydroxylation reaction[7] of the 1,3-enyne **6**,[8] to introduce the two stereocentres C_{19} and C_{20}. Using AD-mix-α,[9] (2*R*,3*S*)-diol **7** (ee 98%, determined by Chiracel OD-H HPLC) was obtained. Compound **7** contained traces of the (2*S*,3*S*) isomer derived from traces of the *Z*-isomer in **6**. These diastereoisomers were difficult to separate, however *E*-**6** allylic chloride was more reactive than *Z*-**6**, which allowed to obtain (2*R*,3*S*)-**7** diastereoisomer in a 16:1 ratio. Treatment of the chlorodiol (2*R*,3*S*)-**7** with sodium hydroxide led after purification by flash chromatography to the corresponding pure (*S*,*S*)-(−)-epoxy alcohol in an 85% yield. MOM protection of the hydroxyl group furnished epoxide **8** in 76% yield. Subsequent chain extension (C_{15}–C_{17}) by the opening of epoxide **8** with the lithium salt of THP propargylic ether[10] in the presence of BF_3–Et_2O[11] furnished the di-protected triol in an 83% yield. Reduction using Red-Al®[12] led to *E*-alkene **9**. No reduction of the other triple bond was observed. Alcohol **9** was subsequently protected as the TBDPS ether and after removal of the THP ether with HCl in methanol, compound **10** was obtained. The propargylic alcohol in **10** was reduced with Red-Al® using the same conditions as previously, to furnish the *E*-allylic alcohol **11**. The MnO_2-oxidation of **11** completed the synthesis of C_{15}–C_{28} fragment **4**.[13]

The synthesis of allyl boronate **5** is summarized in Scheme 3. The stereogenic centre C_{11} was built up via a stereocontrolled Sakurai reaction.[14] Starting point was the mono-protection of diol **12** with TBDPSCl. Conversion of the alcohol into an allyl chloride followed by treatment with TMSMgCl afforded the allylsilane **13**.[15] The reaction of **13** and **14**[16] with $TiCl_4$ gave **15** in a 91% yield and 98% ds. After conversion of the oxazolidinone into an aldehyde, the reaction with lithiated (*R*)-(+)-2-acetoxy-1,1,2-triphenylethanol ((*R*)-(+)-HYTRA)[17] introduced the C_9 stereocentre (ds 89:11). A subsequent TES protection followed by a DIBAH



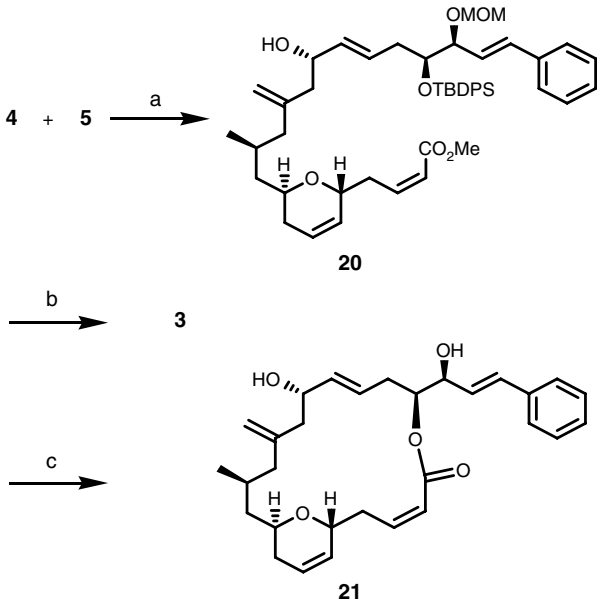
Scheme 3. Reagents and conditions: (a) (i) NaH, TBDPSCl, THF, 0 °C, 96%, (ii) MsCl, NEt_3, CH_2Cl_2, −5 °C, (iii) LiCl, acetone, 45 °C, 87% (two steps), (iv) Mg, TMSCl, THF, reflux, 87%; (b) **14**, $TiCl_4$, CH_2Cl_2, −78 °C, 91%; (c) (i) DIBAH, toluene, −78 °C, 83%, (ii) LDA, (*R*)-(+)-HYTRA, THF, −100 °C, 99%, (iii) TESCl, imidazole, CH_2Cl_2, 20 °C, 98%, (iv) DIBAH, THF, −78 °C, 92%, (v) Dess–Martin, 0 °C, 99%; (d) (i) LDA, (*R*)-(+)-HYTRA, THF, −100 °C, 4 h, 97%, de 88:12, (ii) TFA, H_2O 20 °C, 50 min, 99%, (iii) NaOH, MeOH, 20 °C, 80 min, (iv) *p*-TsOH, CH_2Cl_2, 20 °C, 85 min, 93% (two steps); (e) (i) MsCl, NEt_3, CH_2Cl_2, 0 °C, 97%, (ii) DIBAH, toluene, −78 °C, (iii) CSA, EtOH 20 °C, 91% (two steps), (iv) $LiClO_4$, $H_2C{=}CH$–OTBS, EtOAc, 20 °C, 75%; (f) (i) Still–Gennari, −78 °C, *Z*:*E* = 10:1, 89%, (ii) HF/pyridine, 20 °C, CH_3CN, 97%, (iii) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 0 °C, 97%, (iv) **19**, $Pd(dba)_2$, DMSO, 50 °C, 74%.

reduction/Dess–Martin oxidation afforded aldehyde **16**. A second (*R*)-(+)-HYTRA addition (ds 88:12) and

an acid-mediated lactonization led to the β-hydroxy lactone **17**.

Mesylation/elimination of **17** introduced the $C_{6,7}$ double bond. Subsequent DIBAH-reduction led to the lactol and the corresponding ethyl acetal. The installation of the C_5 stereocentre was achieved using Mulzer's enol ether method.[4f] Compound **18** was the only stereoisomer obtained. The *trans* configuration of the dihydropyran was proven by NOESY-NMR experiments. A Still–Gennari-reaction of **18** led to the corresponding *Z* α,β-unsaturated ester. After deprotection of the TBDPS ether, the resulting alcohol was converted into the corresponding allylic acetate. A Pd(0) mediated reaction of the allylic acetate with the chiral diborane reagent **19**[18] in DMSO,[19] furnished the desired allyl boronate **5**[20] (74% based on recovered starting material).

With both fragments **4** and **5** in hand, we focused on the $Sc(OTf)_3$ mediated[21] intermolecular allylboration (Scheme 4). The use of 10 equiv of $Sc(OTf)_3$ in CH_2Cl_2 gave the homoallylic alcohol **20** with a 7:1 stereoselectivity. The diastereoselectivity of the allylboration was determined after esterification with (*R*)-(−)-methoxyphenylacetic acid. In preparation of the following macrolactonization, **20** was converted into hydroxy acid **3**. Macrolactonization under Yamaguchi conditions[22] furnished a 1:1.3 mixture of *E*- and *Z*-enoate. The *Z*/*E* isomerization is in accordance with earlier observations.[4c] The desired *Z* isomer **21**[23] could be obtained after MOM-ether cleavage and chromatography. The first attempts to introduce the epoxide according to Mulzer[5a] led to an inseparable mixture of phenyl-laulimalide **2** and its isolaulimalide isomer.



Scheme 4. Reagents and conditions: (a) $Sc(OTf)_3$, CH_2Cl_2, −78 °C, 92%; (b) (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 20 °C, 92%, (ii) DIBAH, toluene, −78 °C, 92%, (iii) MnO_2, CH_2Cl_2, 40 °C, 88%, (iv) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}CHCH_3$, *t*BuOH, H_2O, 20 °C, 89%, (v) TBAF, THF, 20 °C, 79%; (c) (i) Yamaguchi, 20 °C, 42%, (ii) Me_2BBr, CH_2Cl_2, −78 °C, 71%.

Due to the *Z*/*E* isomerization under Yamaguchi conditions, a Mitsunobu macrolactonization strategy would be advantageous. This requires the synthesis of the C_{19} epimer of aldehyde **4**, which is under current investigation. In conclusion, the intermolecular allylboration proved to be an efficient synthetic route to the molecular framework of laulimalide analogues.

Acknowledgement

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13. Compound **4**: $R_f = 0{,}16$ (*n*hexane/MTBE = 5:1); IR (cm^{-1}): 3070 w, 2932 m, 2890 m, 2858 m, 1693 s, 1427 m, 1152 m, 1106 s, 1030 s, 974 m, 741 m, 704 s, 508 m; ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 1.09$ (s, 9H, SiC(CH_3)$_3$), 2.42–2.65 (m, 2H, 4-H_2), 3.23 (s, 3H, O–CH_3), 4.06–4.11 (m, 1H, 5-H), 4.20–4.24 (m, 1H, 6-H), 5.94 (dd, $J = 15.6$ Hz, 8.1 Hz, 1H, 2-H), 6.22 (dd, $J = 16.1$ Hz, 6.8 Hz, 1H, 7-H), 6.59 (d, $J = 16.1$ Hz, 1H, 8-H), 6.63–6.74 (m, 1H, 3-H), 7.18–7.39 (m, 11H, TBDPS-Ph, Ph), 7.55–7.61 (m, 4H, TBDPS-Ph), 9.27 (d, $J = 8.1$ Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$ 75 MHz) $\delta = 19.4$ (Si*C*(CH_3)$_3$), 27.0 (SiC(*C*H_3)$_3$), 36.1 (C-4), 55.6 (O–*C*H_3), 74.2 (C-5), 78.9 (C-6), 94.6 (O–*C*H_2–O), 125.5 (C-7), 126.5, 127.7, 127.8, 128.6, 129.9, 130.0, 133.3, 133.4, 135.9 Ph, TBDPS-Ph, 134.4 (C-8), 136.0 (C-2), 155.7 (C-3), 193.8 (C-1); HRMS (ESI) calcd for $C_{32}H_{38}NaO_4Si$ $[M+Na]^+$: 537.2437, found: 537.2426.
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20. Compound **5**: $R_f = 0.14$ (*n*hexane/MTBE = 10:1); $[\alpha]_D^{20}$ +38.8 (*c* 0.98 in $CHCl_3$); IR (cm^{-1}): 2950 (m), 2927 (m), 1722 (s), 1643 (w), 1438 (m), 1372 (m), 1324 (m), 1216 (m), 1168 (s), 1017 m, 699 (m); ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 0.75$ (d, $J = 6.0$ Hz, 3H, CH_3–C-2′), 0.83–1.05 (m, 3H, 1′-H_2, 6‴-H_2), 0.93 (s, 3H, 10‴-H_3), 1.08 (s, 3H, 8‴-H_3), 1.22 (s, 3H, 9‴-H_3), 1.47–1.61 (m, 3H, 1′-H_2, 5‴-H_2), 1.67 (s, 2H, 1⁗-H_2), 1.83–2.00 (m, 5H, 5-H_2, 2′-H, 3′-H_2), 2.34 (pd, $J = 3.6$ Hz, 1H, 4‴-H), 2.86–3.04 (m, 2H, 4″-H_2), 3.70 (s, 3H, O–CH_3), 3.71–3.78 (m, 1H, 6-H), 4.23–4.25 (m, 1H, 2-H), 4.54 (s, 2H, 2‴-H), 4.61 (s, 1H, 5′-H_2), 4.66 (s, 1H, 5′-H_2), 5.67–5.70 (m, 1H, 3-H), 5.81–5.83 (m, 1H, 4-H), 5.86 (pd, $J = 11.6$ Hz, 1H, 2″-H), 6.39 (dt, $J = 11.6$ Hz, 7.0 Hz, 1H, 3″-H), 7.29–7.43 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 11.2$ (C-10‴), 19.3 (*C*H_3–C-2′), 21.1 (C-8‴), 22.8 (C-9‴), 24.2 (C-6‴), 26.4 (C-2′), 31.1 (C-5), 31.8 (C-5‴), 33.5 (C-4″), 42.2 (C-3′), 46.0 (C-1′), 48.5 (C-1⁗), 49.0 (C-7‴), 51.0 (O–CH_3), 52.9 (C-4‴), 65.1 (C-6), 71.8 (C-2), 90.9 (C-1‴), 93.5 (C-2‴), 93.7 (C-3‴), 111.0 (C-5′), 120.3 (C-2″), 124.9 (C-4), 126.1, 127.4, 128.3, 142.7 Ph, 128.9 (C-3), 144.5 (C-4′), 147.4 (C-3″), 166.8 (C-1″); ^{11}B NMR (160 MHz, $CDCl_3$) $\delta = 10.6$; HRMS (ESI) calcd for $C_{33}H_{45}BNaO_5$ $[M+Na]^+$: 555.3258, found: 555.3263.
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23. Compound **21**: $R_f = 0.34$ (*n*hexane/MTBE = 1:2); ^1H NMR: (600 MHz, $CDCl_3$) $\delta = 0.74$ (ddd, $J = 14.2$ Hz, 10.9 Hz, 3.1 Hz, 1H, 10-H_2), 0.87 (d, $J = 6.4$ Hz, 3H, CH_3–C-11), 1.60–1.72 (m, 2H, 8-H_2, 11-H), 1.81–2.03 (m, 5H, 10-H_2, 12-H_2, 14-H_2, O*H*–C-15, O*H*–C-20), 2.07–2.13 (m, 1H, 12-H_2), 2.16–2.23 (m, 2H, 4-H_2, 14-H_2), 2.32–2.49 (m, 3H, 8-H_2, 18-H_2), 3.38–3.42 (m, 1H, 4-H_2), 4.00–4.10 (m, 1H, 9-H), 4.12–4.15 (m, 1H, 5-H), 4.17–4.22 (m, 1H, 15-H), 4.32–4.36 (m, 1H, 20-H), 4.88, 4.92 (je s, 2H, 23-H_2), 5.13–5.18 (m, 1H, 19-H), 5.60–5.72 (m, 3H, 6-H, 16-H, 17-H), 5.75–5.77 (m, 1H, 7-H), 5.90 (d, $J = 11.6$ Hz, 1H, 2-H), 6.19 (dd, $J = 16.0$ Hz, 6.4 Hz, 1H, 21-H), 6.52–6.57 (m, 1H, 3-H), 6.70 (d, $J = 16.0$ Hz, 1H, 22-H), 7.25–7.31 (m, 5H, Ph); ^{13}C NMR: (125 MHz, $CDCl_3$) $\delta = 18.3$, 19.8 (*C*H_3–C-11), 25.8 (C-11), 29.1 (C-8), 33.8 (C-18), 38.0 (C-10), 42.5 (C-14), 45.9 (C-12), 67.5 (C-9), 68.5 (C-15), 69.1 (C-5), 74.4 (C-20), 74.9 (C-19), 114.5 (C-23), 120.2 (C-2), 123.7 (C-7), 124.9 (C-17), 126.6, 128.0, 129.0, 129.2, 135.8 Ph, 127.5 (C-21), 128.0 (C-6), 132.8 (C-22), 136.6 (C-16), 144.6 (C-13), 149.3 (C-3), 165.5 (C-1); IR (cm^{-1}): 3435 (br), 3029 (m), 2924 (s), 1717 (s), 1641 (m), 1433 (w), 1410 (w), 1327 (w), 1216 (m), 1167 (s), 1076 (m), 969 (m), 894 (w), 818 (w), 751 (w), 694 (w); $[\alpha]_D$ −108.1 (*c* 1.27, $CHCl_3$); HR-MS (ESI) calcd for $C_{30}H_{38}NaO_5$ $[M+Na]^+$: 501.2611, found: 501.2616.