Pergamon

Tetrahedron Letters 41 (2000) 6323–6326

TETRAHEDRON LETTERS

# Synthesis of the C15–C27 fragment of the antitumor agent laulimalide

E. Kate Dorling, Elisabeth Öhler and Johann Mulzer*

*Institut für Organische Chemie der Universität Wien, Währinger Str. 38, A-1090 Wien, Austria*

Received 6 June 2000; accepted 15 June 2000

**Abstract**

A stereocontrolled synthesis of the C15–C27 fragment of laulimalide is described. Key features are a divergent–convergent synthesis from (*R*)-glycidol, an interesting formation of a trisubstituted double bond via ring closing metathesis with Grubbs' ruthenium catalyst and a site selective protection of a *syn*-1,2-diol.


Since the discovery of paclitaxel (Taxol™) and the elucidation of its mode of action,[1] a great deal of effort has been focused on the discovery of new classes of compounds with similar activity. Among recent advances have been the epothilones,[2] discodermolide[3] and eleutherobin.[4] However, laulimalide (**1**) has been distinguished by an unusually high activity against multidrug resistant cell lines.[5] Laulimalide and isolaulimalide (**2**) have been isolated from the marine sponges *Cacospongia mycofijiensis*,[6] *Hyatella* sp.[7] and *Fasciospongia rimosa*[8] (Fig. 1). Laulimalide shows strong cytotoxicity ($IC_{50} = 15$ ng/mL) against the KB cell line and a high level of activity against the multidrug resistant cell line SKVLB-1 ($IC_{50} = 1210$ nM).[5] In contrast, isolaulimalide (**2**), which is easily obtained from **1** by treatment with acid,[7] shows lower activity against both the KB cell line ($IC_{50} > 200$ ng/mL) and the SKVLB-1 line ($IC_{50} = 2650$ nM).

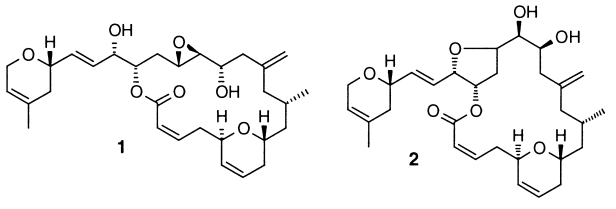
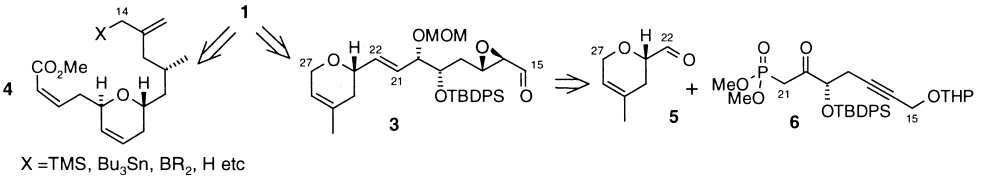



Figure 1. Laulimalide and its isomer

* Corresponding author. Fax: +43-1-4277-9521; e-mail: johann.mulzer@univie.ac.at

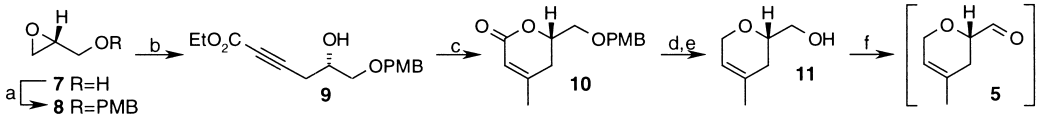
0040-4039/00/$ - see front matter 
PII: S0040-4039(00)00961-8

To date, there have been no reported total syntheses of **1**, although major fragments have been prepared by the groups of Ghosh[9,10] and Nishiyama[11] and we have recently published a synthesis of the C1–C12 segment.[12] Our current retrosynthetic concept is shown in Scheme 1 and features CC connections between C14 and C15 (allylic transfer type reaction) and between C21 and C22 (HWE reaction). In this letter, we report a novel approach to the C15–C27 fragment, including two methods of formation of the C22–C27 dihydropyran moiety **5** and a totally stereoselective Luche reduction.[13]



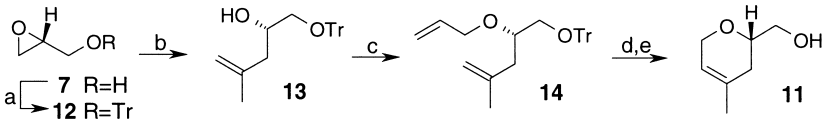

Scheme 1. Retrosynthetic analysis

In the first approach to aldehyde **5** (Scheme 2), (*R*)-glycidol was protected as the 4-methoxybenzyl ether[14] and the epoxide opened with the lithium salt of ethyl propiolate to give alcohol **9** quantitatively. Treatment with lithium dimethyl cuprate and ring closure under acidic conditions yielded the required lactone **10**.[15] DIBAL-H reduction followed by ionic hydrogenation[16] gave the dihydropyran in good yield. Removal of the PMB group with DDQ produced the highly water soluble alcohol **11** and oxidation with $SO_3$·pyr complex yielded aldehyde **5**, which was used without isolation.




Scheme 2. Reagents and conditions: (a) NaH, PMBCl (1.4 equiv.), $^n$Bu$_4$NI, DMF, 5 h, –20°C to rt, 72%; (b) ethyl propiolate, $^n$BuLi, $BF_3$·$OEt_2$ (each 3 equiv.), then **7**, THF, 30 min, –78°C, 100%; (c) (i) $Me_2CuLi$ (3 equiv.), then **9**, THF, –78°C; (ii) AcOH, PhMe, 80°C, 12 h, 91%; (d) (i) DIBAL-H (1.2 equiv.), $CH_2Cl_2$, 1 h, –78°C; (ii) $Et_3SiH$ (1.5 equiv.), $BF_3$·$OEt_2$ (1.0 equiv.), $CH_2Cl_2$, 20 min, –78°C, 77%; (e) DDQ (1.2 equiv.), $CH_2Cl_2$:$H_2O$ (20:1), 85%; (f) $SO_3$·pyr, TEA, DMSO:$CH_2Cl_2$ (1:1)

The second, more convenient approach to aldehyde **5** included formation of the double bond by RCM[17] (Scheme 3). Thus, (*R*)-glycidol was protected to give trityl ether **12**, the epoxide opened with isopropenyl Grignard under copper(I) catalysis and the resulting alcohol allylated to yield **14**. When diene **14** (0.015 M in $CH_2Cl_2$) was exposed to 2.5–3% of the ruthenium-based

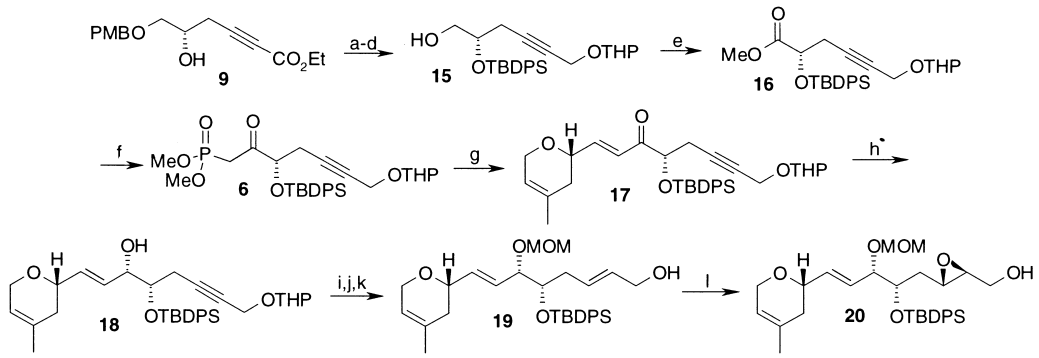



Scheme 3. Reagents and conditions: (a) TrCl, TEA, $CH_2Cl_2$, 0°C to rt, 24 h, 88%; (b) isopropenyl magnesium bromide (2 equiv.), copper(I) iodide (0.2 equiv.), THF, –30°C, 1 h, 99%; (c) (i) KO$^t$Bu, THF, rt to 45°C; (ii) allyl bromide, rt, 1 h, 95%; (d) $Cl_2(Cy_3P)_2Ru$=CHPh (3 mol%), $CH_2Cl_2$, 0.015 M, rt, 1–2 h, 99%; (e) HCl (*g*) in $CH_2Cl_2$ (5 equiv.), 0 to 5°C, 30 min, 84%

Grubbs' catalyst for only 1–2 h at room temperature, the corresponding dihydropyran was obtained in nearly quantitative yield.

This result is particularly remarkable as literature precedent indicates that RCM of dienes bearing one *gem*-disubstituted double bond, when performed with Grubbs' catalyst, is not possible[18] or requires careful optimization of the reaction conditions.[19,20] Acidic removal of the trityl group in the absence of water yielded alcohol **11**.

The synthesis of the C15–C21 segment **6** was perceived as being derived from the epoxide-opened alkyne **9** (Scheme 4). Alcohol **15**, formed by standard transformations, was converted to the ester and treated with the lithium salt of dimethyl methylphosphonate, yielding phosphonate **6** in good yield.




Scheme 4. Reagents and conditions: (a) TBDPSCl (1.3 equiv.), imidazole, DMF, 5 h, 100%: (b) DIBAL-H (2.2 equiv.), $CH_2Cl_2$, 1 h, –78°C, 91%; (c) dihydropyran, TsOH, 20 min, 96%; (d) DDQ (1.2 equiv.), $CH_2Cl_2$:$H_2O$ (20:1), 30 min, 97%; (e) (i) $SO_3$·pyr, TEA, $CH_2Cl_2$:DCM (1:1), 30 min; (ii) $NaClO_2$, (3 equiv.), $KH_2PO_4$, 2,3-dimethylbut-2-ene:$^t$BuOH (1:1), 1 h; (iii) $CH_2N_2$, $Et_2O$, 80%; (f) dimethyl methylphosphonate (2.5 equiv.), $^n$BuLi, then **17**, THF, 3 h, –78°C, 91%; (g) $^n$BuLi then $H_2O$, **6** then **5**, THF:$Et_2O$ (1:1), 0°C to rt, 2 h, 80%; (h) $NaBH_4$ (1.0 equiv.), $CeCl_3$, MeOH, 5 min, 67% (plus 20% mixed regioisomers); (i) MOMCl (20 equiv.), DIPEA, DMF, 3 h, 90%; (j) 2.5% HCl (aq.), MeOH, 0°C to rt, 30 min, 100%; (k) Red-Al® (1.2 equiv.), $Et_2O$, rt, 24 h, 84%; (l) (+)-DET, Ti($O^i$Pr)$_4$, TBHP, 4 Å MS, $CH_2Cl_2$, –20°C, 9 h, 55%, dr 94:6.

The Horner–Wadsworth–Emmons coupling was achieved with lithium hydroxide, which was prepared in situ from *n*-butyllithium and water[21] and gave better results than commercial lithium hydroxide. Reduction of the C20 ketone with L-Selectride® yielded a single diastereomer, which was assigned as *syn* by analogy.[22] However, a significant proportion of migration of the silyl group from C19 to C20 was observed. It was believed that a cerium(III) counterion would result in lower nucleophilicity of the alkoxide, limiting the migration to a great extent and hence a Luche reduction[14] was performed. Under these conditions, less than 10% migration was observed and to our surprise, only a single diastereomer was isolated, which was identical in all respects to the single product of the L-Selectride reduction. Protection of the newly formed alcohol as the MOM ether proceeded well and the THP group could be selectively cleaved with 2.5% HCl in MeOH. Reduction of the triple bond with Red-Al® gave a single double bond isomer, assigned as *E* by the vicinal coupling constant of 15.3 Hz. We envisage that aldehydes derived from **18** and **19** are both possible coupling partners with fragment **4**. Finally, Sharpless epoxidation with (+)-DET gave epoxide **20**[23] in 55% yield and diastereomeric ratio of 94:6 (by $^1$H NMR). Current work focuses both on methodology for the removal of the C20 protecting group in the presence of the sensitive γ,δ-epoxide functionality and on coupling of the two fragments.

In conclusion, we have described a novel and efficient approach to the C15–C27 fragment of laulimalide. Further investigations towards the total synthesis of **1** are currently underway in our laboratories.

## Acknowledgements

We thank the Austrian Science Fund (FWF) for financial support.

## References

1. For a review, see: Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem.* **1994**, *106*, 38–69; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.
2. For a review, see: Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem.* **1998**, *110*, 2120–2153; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2014–2045.
3. (a) Gunasekara, S. P.; Gunasekara, M.; Longley, R. E. *J. Org. Chem.* **1990**, *55*, 4912–4915.
4. Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745.
5. Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653–660.
6. Quiñoà, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642–3644.
7. Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J. *J. Org. Chem.* **1988**, *53*, 3644–3646.
8. Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159–162.
9. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427–2430.
10. Ghosh, A. K.; Wong, Y. *Tetrahedron Lett.* **2000**, *41*, 2319–2322.
11. (a) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011–6014. (b) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209–1210.
12. Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33–36.
13. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
14. Smith, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667–8670.
15. Takano, S.; Shimazaki, Y.; Iwabuki, Y.; Ogaswara, K. *Tetrahedron Lett.* **1990**, *31*, 3619–3622.
16. Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651.
17. For recent reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (b) Fürstner, A. *Top. Catal.* **1997**, *4*, 285–299. (c) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2055.
18. (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020–1022. (b) Callam, C. S.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 167–169. (c) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123–126. (d) Miller, J. F.; Termin, A.; Koch, K.; Piscpio, A. D. *J. Org Chem.* **1998**, *63*, 3158–3159.
19. de Rosa, M.; Solladié-Cavallo, A.; Scettri, A. *Tetrahedron Lett.* **2000**, *41*, 1593–1596.
20. For an in-depth study of olefin substitution effects, see Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318.
21. Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem.* **2000**, *112*, 591–593; *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 581–583.
22. Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291–3303.
23. Data for compound **20**. $^1$H NMR (400 MHz, $C_6D_6$) 1.22 (9H, s), 1.41 (1H, bm), 1.52 (3H, bs), 1.69 (1H, bd, $J=16.7$), 1.86 (1H, dt, $J=13.6$, 6.7), 2.02 (2H, m), 2.56 (2H, m), 3.04 (3H, s), 3.13 (1H, m), 3.30 (1H, m), 3.46 (1H, m), 3.97 (1H, dt, $J=9.8$, 4.7), 4.03 (1H, bd, $J=15.4$), 4.15 (1H, bd, $J=15.9$), 4.24 (1H, t, $J=5.4$), 4.30 (1H, m), 4.35 (1H, m), 4.50 (1H, m), 5.16 (0.96H, bs), 5.22 (0.04H, bs), 5.94 (1H, dd, $J=4.7$, 15.7), 6.07 (1H, dd, $J=6.3$, 15.7), 7.24 (6H, m) and 7.86 (4H, m); $^{13}$C NMR (100 MHz, $C_6D_6$) 19.8, 23.0, 27.4, 35.8, 36.6, 53.2, 55.3, 59.4, 51.8, 65.8, 73.5 (two signals) 78.8, 81.4, 94.8, 120.5, 126.4, 128.1, 128.6, 130.1, 131.3, 134.3, 134.4, 135.4 and 136.5 (two signals); HRMS (EI, 160°C, 70 eV) found: 495.2223. $C_{18}H_{35}O_6Si$ requires: 495.2203.