Published in final edited form as:

Tetrahedron Lett. 1997 April 7; 38(14): 2427–2430. doi:10.1016/S0040-4039(97)00416-4.

SYNTHETIC STUDIES OF ANTITUMOR MACROLIDE LAULIMALIDE: ENANTIOSELECTIVE SYNTHESIS OF THE C₃-C₁₄ SEGMENT BY A CATALYTIC HETERO DIELS-ALDER STRATEGY

Arun K. Ghosh, Packiarajan Mathivanan, and John Cappiello

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607.

Abstract

The C₃-C₁₄ segment of the novel antitumor agent laulimalide has been constructed enantioselectively by utilizing a catalytic asymmetric hetero Diels-Alder reaction of benzyloxyacetaldehyde and Danishefsky's diene followed by Ferrier rearrangement and asymmetric conjugate reaction as the key steps.

Laulimalide **1** also known as figianolide B, is a 20-membered macrolide isolated from the Indonesian sponge *Hyattella* Sp.¹ More recently, laulimalide has also been isolated from an Okinawan sponge *Fasciospongia rimosa*.² Laulimalide represents a new and novel class of macrolide with potent cytotoxicity against the KB cell line with an IC₅₀ value of 15 ng/mL.^{1b} The cytotoxicity of laulimalide against P388, A549, HT29 and MEL28 cell lines is also in the range of 10–50 ng/mL (IC₅₀ values).^{2b} The gross structure of laulimalide was established by NMR studies and more recently its absolute configuration has been elucidated by X-ray crystallographic analysis.^{2a} In view of its limited supply and unique structural features as well as its potential utility as an anticancer agent, synthetic studies of laulimalide became of interest to us. Herein, we report on the asymmetric synthesis of the C₃-C₁₄ segment of laulimalide in which a chiral bis(oxazoline)-metal complex catalyzed hetero Diels-Alder reaction, a Ferrier type rearrangement of the derived glycal and diastereoselective conjugate addition were utilized to set the C-9, C-5 and C-11 asymmetric centers.

Chiral bis(oxazoline)-metal complex catalyzed cycloaddition reactions have received increasing attention in recent years.³ We recently reported⁴ constrained chiral bis(oxazoline)-metal complex catalyzed hetero Diels-Alder reactions of Danishefsky's diene and alkyl glyoxalates to provide dihydropyranone derivatives up to 72% ee. In an effort to further improve the enantioselectivity in this catalytic process, we have investigated the scope and utility of readily accessible bidentate aldehydes such as benzyloxyacetaldehyde **5** and 1,3-dithianecarboxaldehyde **6**. Of particular interest, dihydropyranone derivatives⁶ resulting from such cyclocondensation reactions are appropriately functionalized for the

synthesis of laulimalide segment **2**. As shown in Table 1, cyclocondensation of aldehyde **5**⁷ and Danishefsky's diene **4** in the presence of 10% Cu(II)-bis(oxazoline) complex provided good yield (62–76%) of versatile dihydropyranone **7**⁸ in high enantiomeric excess. Constrained ligands **9** and **12**^{3e} are particularly effective providing 2S and 2R-dihydropyranones in 85 and 87% ee's respectively. In comparison, phenyl and t-butyl based bis(oxazoline) ligands **10** and **11** are less effective (51 and 38% ee). Cyclocondensation of 1,3-dithianecarboxaldehyde **6**⁹ with constrained Cu(II)-bis(oxazoline) **12** complex also afforded the dihydropyranone **8** in 46% yield and 81% ee compared to Cu(II)-bis(oxazoline) ligand **10** which has shown 59% ee¹⁰ and only 20% isolated yield.

For synthesis of the C₃-C₁₄ segment of laulimalide, dihydropyranone **7** was prepared on a multigram scale.¹¹ To append the hydroxyethyl side chain and to establish the C-5 stereocenter appropriately, a Ferrier type rearrangement of the corresponding glycal acetate was sought. Thus, dihydropyranone **7** was reduced with 1.5 equiv of DIBAL in benzene at 0° to 5°C for 2 h and the resulting glycal was acetylated with 1.5 equiv of Ac₂O and 3 equiv of Et₃N in CH₂Cl₂ in the presence of a catalytic amount of DMAP at 23°C for 6 h to provide **13** in 66% yield (from **7**). Ferrier rearrangement of **13** with 2 equiv of tert-butyldimethylsilyl vinyl ether¹² and stoichiometric amount of Montmorillonite clay K-10¹³ as the Lewis acid in CH₂Cl₂ at 0°C followed by NaBH₄ reduction of the resulting mixture of aldehydes afforded good yield (65–70% from **13**) of the dihydropyran **14** (diastereomeric ratio >95:5 by ¹H and ¹³C-NMR). Protection of the alcohol with MOMCl and *i*Pr₂NEt furnished the MOM derivative **15** in 88% yield.

To elaborate the C-11 methyl group with appropriate stereochemistry, the benzyl group in **15** was deprotected by exposure to sodium in liquid ammonia (65% yield). Mesylation of the resulting alcohol followed by displacement with tetraethylammonium cyanide provided the cyanide **16** (77% yield). Reduction of **16** with DIBAL resulted in aldehyde which was immediately exposed to a Horner-Emmons olefination reaction to afford the trans α, β-unsaturated ester **17** in 45% yield. Saponification of **17** with aqueous LiOH afforded the corresponding α, β-unsaturated acid which was converted to N-enoylsultam **18** (73% yield) utilizing (1*S*)-(+)-2,10-camphorsultam. Treatment of **18** with 4 equiv of Me₂CuLi in Et₂O at –78°C for 8 h afforded the conjugate addition product **19** in 68% yield (based on 30% recovery of **18**). The ¹H-NMR (400 MHz) analysis after chromatography reveals the presence of a mixture of (90:10) diastereomers. Interestingly, reaction of Me₂CuLi with the N-enoylsultam derived from (1*R*)-(+)-2,10-camphorsultam proceeded smoothly in 3 h (no recovery of **18**), providing the corresponding diastereomers (mixture ratio 5:95 by ¹H-NMR) in 76% isolated yield. The depicted configuration is assigned based on Oppolzer's model.¹⁴ However, either C-11 methyl isomer of laulimalide can be prepared selectively by an appropriate choice of camphorsultam.

Our next synthetic strategy was to convert the sultam **19** to the methyl ketone **2** which would enable us to introduce the C-15 hydroxyl group by an aldol type reaction with an appropriately functionalized epoxyaldehyde **3**. Thus, removal of the chiral auxiliary afforded the corresponding acid which was treated with 5 equiv of MeLi at 0°C followed by workup with excess of TMSCl according to Rubottom procedure¹⁵ to furnish **2** ($\alpha_D^{23} -55.6$; c, 0.18, CHCl₃) in 63 % yield.¹⁶

In summary, the C₃-C₁₄ segment of antitumor macrolide laulimalide has been synthesized in optically active form utilizing dihydropyranone **7**, prepared enantioselectively by a chiral bis(oxazoline)-metal complex catalyzed hetero Diels-alder reaction as the key step. Further synthetic studies of laulimaide are currently under investigation.

Acknowledgments

Acknowledgment:

Financial support of this work by the University of Illinois at Chicago and by the National Institute of Health (GM 53386) is gratefully acknowledged.

References and notes:

1. (a) Quinoa E; Kskou Y; Crews P *J Org. Chem.* 1988,53,3642;(b)Corley DG; Herb R; Moore RE; Scheuer PJ; paul VJ *J. Org. Chem.* 1988,53, 3644.
2. (a) Jefford CW;Bernrdinelli G; Tanaka J-I; Higa T *Tetrahedron Lett.* 1996,37, 159;(b)Tanaka J-I; Higa T;Bernrdinell Gi.,;Jefford CW*Chemistry Lett.* 1996,255.
3. (a) Corey EJ; Imai, Zhang H-Y J. Am. Chem. soc 1991, 113, 728;(b)Corey E Isihara K *Tetrahedron Lett.* 1992, 33, 6807;(c)Evans DA; Miller SJ; Lectka T.J. *Am. Chem. soc.* 1993, 115, 6460;(d)Evans DA; Murry JA; Mat PV; Norcross RD; Miller SJ *Angew. Chem. Int. Ed. Engl* 1995, 34, 798; (e)Ghosh AK; Mathivanan P; Cappiello J *Tetrahedron Lett.* 1996, 37, 3815;(f)Davies IW; Senanayake CH; Larsen RD; Verhoeven TR; Reider PJ *Tetrahedron Lett.* 1996, 37, 1725;(g)Evans DA; Barnes DM *Tetrahedron Lett.* 1997, 38, 57;(h)Pfaltz A *Acta Chimica Scandinavia* 1996, 50, 189 and references cited therein.
4. Ghosh AK; Mathivanan P; Cappiello J; Krishnan K *Tetrahedron: Asymmetry* 1996, 7, 2615 For other recent catalytic reports, see ref. 5.
5. (a) Terada M; Mikami K; Nakai T *Tetrahedron Lett.* 1991, 32, 935;(b)Corey EJ; Cywin CL; Roper TD *Tetrahedron Lett.* 1992, 33, 6907;(c)Gao Q; Maruyama T; Mouri M; Yamamoto HJ. *org. Chem* 1992, 57, 1957;(d)Mikmli, Motoyama Y; Terada M *J. Am. Chem. soc.*, 1994, 116, 2811; (e)Motoyama Y; Mikami KJ *Chem. soc. Chem. Commun* 1994, 1563;(f)Keck G Li X-Y; Krishnamurthy D J. *org. Chem* 1995, 60, 5998.
6. For synthetic application of wide variety of dihydropyranones, see, (a) Danishefsky SJ *Aldrichim. Acta* 1986, 19, 59;(b) Bednarski MD; Lyssikatos JP *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, Trost BM Ed., 1991, 2, 661;(c)Meng D; Sorensen E Bertinato, Danishefsky SJ *J. org. Chem.* 1996, 61, 7998; [PubMed: 11667777] (c)Bertinato P; Sorensen EJ; Meng D; Danishefsky SJ *J. Org. Chem.* 1996, 61, 8000; [PubMed: 11667778] (d)Paterson I; Cumming JG; Ward RA; Serge Lambley.*Tetrahedron* 1995, 51, 9393 and references cited therein.
7. Available from Aldrich. For recent application in catalytic Mukaiyama aldol reaction, see, Evans DA; Murry JA; Kozlowski MCJ. *Am. Chem. Soc* 1996, 118, 5815.
8. Paterson I; Osborne S *Tetrahedron Lett.* 1990, 31, 2213 and references cited therein.
9. Bulman Page PC; Marchington AP; Graham LJ; Harkin SA; Wood WW *Tetrahedron* 1993, 49, 10369.
10. Details of the determination of ee's and absolute configuration of **8** will be reported in due course.

11. In a typical procedure, Cu(OTf)₂ (Aldrich, 241 mg, 0.66 mmol) and ligand **9** (264 mg, 0.8 mmol) were stirred together in CH₂Cl₂ (20 mL) at <MI> for 1 h under nitrogen. The resulting deep blue solution (5 mol% catalyst) was cooled to -<MI> and aldehyde **5** (Aldrich, 2 g, 13.3 mmol) in CH₂Cl₂ (1 mL) followed by diene **4** (2.8 mL, 16.28 mmol) were added. The mixture was stirred for 9 h at - and then quenched with aq. NaHCO₃. Standard workup and evaporation of the solvents gave a residue which was stirred with TFA (10 mL) in CH₂Cl₂ (10 mL) at for 1 h. The reaction was quenched carefully with sat. NaHCO₃ solution. Standard workup and chromatography over silica gel afforded **7** (1.8 g, 62% yield) as a colorless oil.
12. Sirsi W; Padias AB; Hall HK, Jr. *J. org. Chem.* 1984, 49, 5424.
13. Toshima K; Miyamoto N; Matsuo G; Nakata M; Matsura SJ. *Chem. Soc. Chem. Commun.* 1996, 1379.
14. Oppolzer W; Kingma AJ *Helv. Chim. Acta* 1989, 72, 1337 and references cited therein.
15. Rubottom GM; Kim CJ. *org. Chem.* 1983, 48, 1550.
16. All new compounds gave satisfactory spectral data. Ketone **2**: ¹H-NMR (400 MHz, CDCl₃) δ: 5.08 (m, 1H), 5.7 (d, 1H, J = 1.2 Hz), 4.63 (s, 2H), 4.3 (br s, 1H), 3.65 (m, 3H), 3.36 (s, 3H), 2.5 (m, 1H), 2.24 (m, 2H), 2.13 (s, 3H), 2.05–1.86 (m, 3H), 1.58–1.23 (m, 3H), 0.92 (d, 3H, J = 6.3 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: 223.3, 129.9, 124.1, 96.4, 69.4, 65.2, 64.4, 55.1, 52.2, 42.8, 34.5, 31.1, 29.6, 26.5, 19.3.

Scheme 1:

(a) K-10, OTBS, CH_2Cl_2 , 0°C , 2 h; (b) NaBH_4 , MeOH, 0°C , 30 min; (c) MOMCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 23°C , 8 h; (d) liq. NH_3 , -78°C , 1 h; (e) MCl , Et_3N , DMAP, CH_2Cl_2 , 0°C , 30 min; (f) $n\text{-Et}_4\text{N}^+\text{CN}^-$, $\text{CH}_3\text{CN-PhH}$ (1:1), reflux, 4 h; (g) Dibal-H, Et_2O , -78°C , 4 h; (h) NaH , THF, 0°C , $(\text{EtO})_2\text{P(O)CH}_2\text{CO}_2\text{Et}$, 1 h; (i) 1 M LiOH , 23°C , 6 h; (j) $\text{Me}_3\text{CCOC1}$, Et_3N , THF, 0°C then N-lithiosultam, -78°C , 2 h; (k) Me_2CuLi , Et_2O , -78°C , 8 h; (m) 1M LiOH , 23°C , 5 h; (n) MeLi , THF, 0°C then TMSCl .

Table 1.Cu(II)-bis(oxazoline) catalyzed Hetero Diels-Alder Reaction at -78°C

Entry	Aldehyde	Ligand	Time(h)	% Yield ^a	% ee ^b	Config. ^c
1.	5	10	9	76	51	2S
2.	5	11	9	72	38	2R
3.	5	9	11	76	85	2S
4.	5	12	9	62	87	2R
5.	6	12	9	46	81C	2S
6.	6	10	10	20	59C	2R

^aAfter silica gel chromatography.^bBy chiral HPLC and comparison of optical rotation.^cBy comparison of optical rotation.