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SYNTHETIC STUDIES OF ANTITUMOR MACROLIDE LAULIMALIDE: ENANTIOSELECTIVE SYNTHESIS OF THE C_3-C_{14} SEGMENT BY A CATALYTIC HETERO DIELS-ALDER STRATEGY

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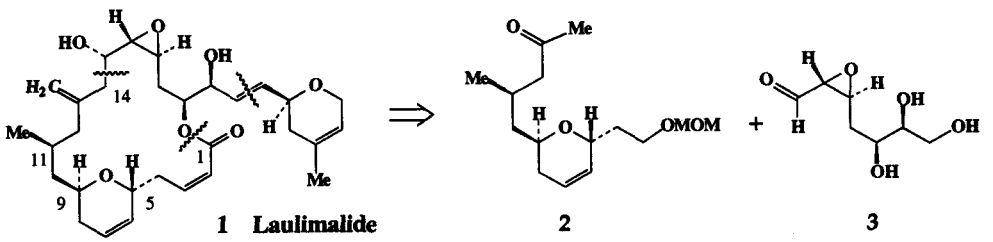
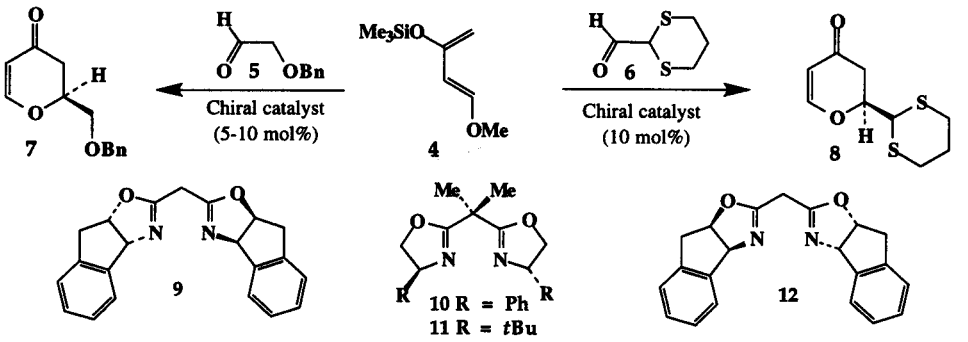
Abstract: The C_3-C_{14} segment of the novel antitumor agent laulimalide has been constructed enantioselectively by utilizing a catalytic asymmetric hetero Diels-Alder reaction of benzyloxyacetaldehyde and Danishefsky's diene followed by Ferrier rearrangement and asymmetric conjugate reaction as the key steps. © 1997 Elsevier Science Ltd.

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 IC_{50} 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 (IC_{50} 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 C_3-C_{14} 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.



1 Laulimalide **2** **3**

Chiral bis(oxazoline)-metal complex catalyzed cycloaddition reactions have received increasing attention in recent years.[3] We recently reported[4] 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 derivatives[6] 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% ee[10] and only 20% isolated yield.

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

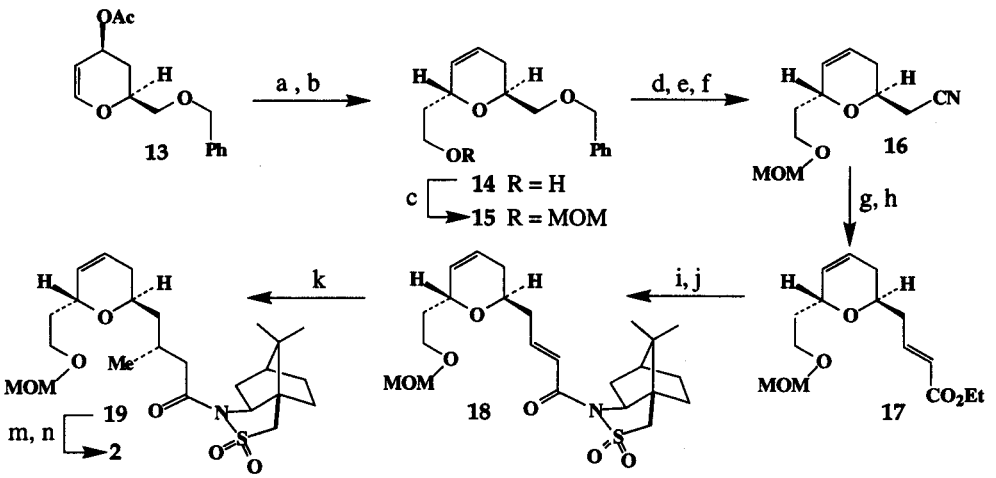
Entry	Aldehyde	Ligand	Time (h)	% Yield[a]	% ee[b]	Config.[c]
1.	5	10	9	76	51	2S
2.	5	11	9	72	38	2R
3.	5	9	11	76	85	2S
4.	5	12	9	62	87	2R
5.	6	12	9	46	81[c]	2S
6.	6	10	10	20	59[c]	2R

[a]After silica gel chromatography. [b]By chiral HPLC and comparison of optical rotation. [c]By comparison of optical rotation.

For synthesis of the C_3-C_{14} 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 Ac_2O and 3 equiv of Et_3N in CH_2Cl_2 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 ether[12] and stoichiometric amount of Montmorillonite clay K-10[13] as the Lewis acid in CH_2Cl_2 at 0°C followed by $NaBH_4$ 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 ^{13}C-NMR). Protection of the alcohol with MOMCl and *i*Pr_2NEt 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 Me_2CuLi in Et_2O 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 Me_2CuLi 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.



Scheme 1: (a) K-10, OTBS, CH_2Cl_2, 0°C, 2 h; (b) $NaBH_4$, MeOH, 0°C, 30 min; (c) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 23°C, 8 h; (d) Na, liq. NH_3, -78°C, 1 h; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0°C, 30 min; (f) n-$Et_4N^+CN^-$, CH_3CN-PhH (1:1), reflux, 4 h; (g) Dibal-H, Et_2O, -78°C, 4 h; (h) NaH, THF, 0°C, $(EtO)_2P(O)CH_2CO_2Et$, 1 h;(i) 1 M LiOH, 23°C, 6 h; (j) Me_3CCOCl, 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.

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 procedure[15] to furnish **2** ($\alpha_D^{23°}$ -55.6; c, 0.18, $CHCl_3$) in 63 % yield.[16]

In summary, the C_3-C_{14} 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.

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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 CH_2Cl_2 (20 mL) at 23ℑC for 1 h under nitrogen. The resulting deep blue solution (5 mol% catalyst) was cooled to -78ℑC and aldehyde **5** (Aldrich, 2 g, 13.3 mmol) in CH_2Cl_2 (1 mL) followed by diene **4** (2.8 mL, 16.28 mmol) were added. The mixture was stirred for 9 h at -78ℑC and then quenched with aq. $NaHCO_3$. Standard workup and evaporation of the solvents gave a residue which was stirred with TFA (10 mL) in CH_2Cl_2 (10 mL) at 23ℑC for 1 h. The reaction was quenched carefully with sat. $NaHCO_3$ solution. Standard workup and chromatography over silica gel afforded **7** (1.8 g, 62% yield) as a colorless oil.
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16. All new compounds gave satisfactory spectral data. Ketone **2**: ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) d: 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.

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